GLOBAL INFLUENZA PROGRAMME

GISRS

End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance

REVISED INTERIM GUIDANCE

31 JANUARY 2022

World Health Organization

End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance: Revised interim guidance, 31 January 2022

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

WHO/2019-nCoV/Integrated_sentinel_surveillance/2022.1

Contents

Supplementary Tables

Annexes

Acknowledgements

WHO acknowledges the experts and countries who contributed to the development of this revised interim guidance. Thanks are due to the chair, Rahman Mahmudur, and co-chairs, Cheryl Cohen and Maria Zambon, and to Harry Campbell who served as rapporteur of the 2nd WHO Global Consultation on the Integrated Sentinel Surveillance of Influenza and SARS-CoV-2 and the Development of GISRS Plus held virtually from 12 to 14 October 2021.

WHO acknowledges experts contributing to the guidance review: Romela Abovyan, Cornelia Adlhoch, Hanan Al-Khindi, Ivy Asante, Sikiru Badaru, Nune Bakunts, Christina Bancej, A-Lan Banks, Ian Barr, Silvia Bino, Leon Biscornet, Lynnette Brammer, Myrna Charles, Simon Cottrell, Theresa Enkirch, Rodrigo Fasce, Nada Ghosn, Jean-Michel Heraud, Runa Jha, Erik Karlsson, Catherine Moore, Jim McMenamin, Angeliki Melidou, Joshua Mott, Josie Murray, Richard Njouom, Muesse Tadesse, Binay Thapa, Carla Voto, Sibongile Walaza and Richard Webby.

WHO acknowledges the institutions contributing data and analyses: Ministry of Health, Argentina; Departamento de Epidemiología, de la División de Planificación Sanitaria del Ministerio de Salud de Chile, Hospitales Centinelas para la vigilancia de IRAG y el Instituto de Salud Pública, Chile; Ministerio de Salud de Costa Rica, INCIENSA, CCSS, Costa Rica; National Influenza Centre, National Institute of Virology, Indian Council of Medical Research, India; Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand; Andrew Hayward, Institute of Epidemiology and Health Care, University College London, United Kingdom; and the Usher Institute, University of Edinburgh, United Kindgom.

The following WHO staff and consultants are gratefully acknowledged for their contributions to the development and finalization of the revised interim guidance: Hala Abou-Elnaja, Lubna Al Alariqi, Maya Allan, Amal Barakat, Isabel Bergeri, Silvia Bertagnolio, Sylvie Briand, Chris Chadwick, Paula Couto, Vanessa Cozza, Janet Diaz, Hien Doan, Amgad A. Elkholy, Julia Fitzner, Elizabeth Ann Frodeman, Aspen Hammond, Michala Hegermann-Lindencrone, Belinda L. Herring, Siddhivinayak Hirve, Francis Inbanathan, Jorge Jara, Sandra Jackson, Wasiq Khan, Angie Lackenby, Juliana Leite, Maja Lievre, Bikram Maharjan, Awandha Mamahit, Marco Marklewitz, Khadimul Anam Mazhar, Marie-jo Medina, Ann Moen, Piers Andrew Nicholas Mook, Karen Nahapetyan, Phuong Nam Nguyen, Boris Pavlin, Richard Pebody, Dmitriy Pereyaslov, Angel Rodriguez, Holly Sadler, Gina Samaan, Magdi Samaan, Hirve Siddhivinayak, Ronaldo Silvia, Stefano Tempia, Soe Soe Thwin, Katelijn A.H. Vandemaele, Maria Van Kerkhove, Andrea Vicari, Andrea Patricia Villalobos, Pushpa Wijesinghe, Xiyan Xu and Wenqing Zhang.

The threat of influenza epidemics and pandemics persists. It is imperative for the GISRS to maintain meaningful surveillance of influenza worldwide and for countries to remain vigilant while adapting to meet COVID-19 surveillance objectives.

End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance

REVISED INTERIM GUIDANCE

KEY POINTS

- **End-to-end integration** is the inclusion of influenza and SARS-CoV-2 into all the components or stages of the surveillance process, from the procedures done at the sentinel site to the eventual sharing of sequence data.
- Quality, representativeness, sustainability and country ownership are the guiding principles for end-to-end integration of SARS-CoV-2 and influenza sentinel surveillance.
- Integration of SARS-CoV-2 testing and sequencing should occur without compromising influenza surveillance
- WHO severe acute respiratory infection (SARI)/influenza-like illness (ILI) case definitions should be used in integrated surveillance.
- At least 50, and ideally 150, specimens, should be tested per week by the National Influenza Center for influenza and SARS-CoV-2 with multiplex real-time reverse transcription-polymerase chain reaction (rRT-PCR) assays.
- Surveillance should be conducted year-round wherever feasible.
- A shortfall of sentinel specimens can be bridged by sourcing from non-sentinel sites with adherence to ILI/ARI/ SARI case definition criteria and representativeness.
- Results should be reported separately according to sentinel or non-sentinel surveillance source.
- Timely uploads of influenza and SARS-CoV-2 genetic sequence data to publicly accessible databases, such as GISAID, are recommended to ensure completeness of metadata.

End-to-end integration is the inclusion of influenza and SARS-CoV-2 into all the components or stages of the surveillance process, from the procedures done at the sentinel site to the eventual sharing of sequence data.

Introduction

This interim guidance is an update and replaces two previous documents: Maintaining surveillance of influenza and monitoring of SARS-CoV-2 (published 8 November 2020) (*1*) and Operational considerations to expedite genomic sequencing component of GISRS surveillance of influenza SARS-CoV-2 (published 16 February 2021) (*2*). It complements the Guidance for surveillance of SARS-CoV-2 variants (published 9 August 2021) (*3*) and the Public health surveillance for COVID-19 (interim guidance, published 16 December 2020) (*4*). The interim guidance will continue to be reviewed in the context of anticipated scientific, technical, epidemiological and operational developments over the next nine to 12 months.

It is intended for public health professionals involved in disease and laboratory surveillance at the national level. It is also a guide for WHO staff involved in influenza and COVID-19 sentinel surveillance integration. It provides interim guidance for the integration of SARS-CoV-2 and influenza virologic and genomic surveillance, from sentinel site case enrolment and sampling to the eventual sharing of the virus sequence data, a process known as end-to-end surveillance.

Rational for the update and what's new?

This guidance builds on experiences and lessons learned as countries adapted their influenza surveillance systems in the context of the COVID-19 pandemic and reviews new evidence to provide guidance on end-to-end surveillance. A repeat systematic review of recent evidence on the clinical characteristics of COVID-19 and analysis of surveillance data suggests that ILI and SARI surveillance combined with virologic confirmation are well positioned to detect influenza and COVID-19 cases. The guidance includes new algorithms and strategies to adapt sentinel systems to make them resilient and agile for addressing global and national surveillance needs for influenza and COVID-19. It highlights the need to link sentinel surveillance systems to inform policy and adjust the national public health response to the COVID-19 pandemic. It incorporates inputs from Member States and international experts solicited before and during a virtual consultation in October 2021.

Background

Since the emergence of SARS-CoV-2, GISRS and its network of public health laboratories (National Influenza Centers (NICs), WHO H5 Reference Laboratories, WHO Collaborating Centers (CCs)) in 125 countries, national influenza laboratories (NILs) and national COVID-19 laboratories have been at the forefront of a concerted global and national response for the detection and containment of SARS-CoV-2 transmission. The International Health Regulations (2005) (IHR) Emergency Committee for COVID-19 recommends monitoring disease trends using severe acute respiratory infection (SARI) and influenza-like illness (ILI) surveillance systems and for State Parties to share with WHO all data (including SARI and ILI where available) necessary to conduct global risk assessments through data platforms, such as the GISRS and the IHR mechanism (*5*). It further recommends increasing global genomic sequencing capacities and encourages rapid sharing of sequence data and meta-data; and for WHO to actively support countries to strengthen systematic genomic surveillance by leveraging the Global Influenza Surveillance and Response System (GISRS) and other relevant networks (*6*).

WHO global external quality assessment programs (EQAP) for COVID-19 were built on GISRS mechanisms. Multiplex real-time reverse transcription-polymerase chain reaction (rRT-PCR) diagnostic kits for influenza and SARS-CoV-2 were developed by the WHO Collaborating Centre for influenza at the United States Centers for Disease Control and Prevention of (CDC),

and 50 kits (2500 tests) were made available in November 2020 through the International Reagent Resource (IRR). Production of multiplex diagnostic kits was ramped up to provide 500 kits (25 000 tests) at no cost to GISRS laboratories. Sharing of genetic sequence data of SARS-CoV-2 to publicly accessible databases, such as the Global Initiative on Sharing All Influenza Data (GISAID) was facilitated worldwide based on the trust, experiences and sharing mechanisms established by GISRS for influenza viruses over the years. The GISRS infectious substance shipping mechanism was used for the shipping of SARS-CoV-2 virus materials to WHO COVID-19 reference laboratories.

Early in the pandemic, influenza surveillance systems faced significant disruptions as resources were repurposed to meet the surge in demand for testing of suspected COVID-19 cases for diagnosis, treatment, contact tracing, screening of travellers for containment of outbreaks and control of spread of COVID-19. In many countries, weekly reporting of influenza surveillance data was delayed, infrequent or ceased altogether. In countries that were able to test and report, influenza activity was low and below the epidemic threshold throughout 2020-2021 compared to past years. More recently, regional influenza outbreaks have been detected in Western Africa and South and Southeast Asia.

The threat of influenza remains, and it is essential for countries to be vigilant for the emergence of non-seasonal influenza viruses of pandemic potential and prepare for the 2021-2022 northern hemisphere influenza season. Despite challenges, the COVID-19 pandemic provides an opportunity to strengthen core surveillance capacities that can deliver public health benefits during and well beyond this emergency. Surveillance capacities built by countries during the pandemic would serve to develop resilience in systems that can respond more effectively and rapidly to public health threats in the future.

Objectives for sentinel surveillance

Sentinel surveillance systems should be based on clear objectives that guide data collection and site selection. Sentinel surveillance systems may also include additional objectives in some countries or regions where local capacity, policy needs, and available resources make them desirable. Core and optional objectives of integrated sentinel surveillance are listed in Table 1.

Table 1: Objectives

Core influenza/SARS-CoV-2 sentinel surveillance objectives for all Member States

- Signal the onset and offset of influenza/SARS-CoV-2 activity at defined thresholds
- Describe the seasonality of influenza and SARS-CoV-2 where feasible and relevant
- Establish historic levels of activity for illness and severe disease with which to evaluate the impact and severity of each season/epidemic period and of future pandemic events
- Provide descriptive epidemiology of influenza and SARS-CoV-2-associated ILI/ARI or SARI cases
- Monitor locally circulating virus types/subtypes or lineages/sub-lineages and their relationship to global and regional patterns.
- Provide candidate viruses for influenza vaccine composition and production and risk assessment activities.

Optional influenza/SARS-CoV-2 sentinel surveillance objectives for some Member States

- Identify and monitor groups at high risk of severe disease and mortality
- Assist in developing an understanding of the relationship of virus strains to disease severity
- Generate data that can be used during focused studies to estimate influenza disease and economic burden and help decision-makers prioritize resources and plan public health interventions
- Provide a platform to evaluate vaccine effectiveness and possibly other interventions for both influenza and SARS-CoV-2
- Monitor viruses for susceptibility to antiviral drugs
- Describe the genetic and antigenic characteristics of circulating influenza viruses and monitor circulation of SARS-CoV-2 variants of concern and variants of interest by PCR-based assays and/or sequence analysis
- Detect unusual and unexpected events such as outbreaks or epidemiologic clusters that may indicate a change in virus characteristics
- Define and characterize pathogens associated with ILI/ARI/SARI cases beyond influenza viruses and SARS-CoV-2.

The purpose of routine sentinel surveillance systems is to detect a subset of ILI, ARI or SARI cases from representative sentinel sites and to test for influenza and SARS-CoV-2. Separately, universal/exhaustive surveillance to identify all suspected COVID-19 cases meeting the WHO COVID-19 case definition (*7*) is recommended by the WHO public health guidance for COVID-19 surveillance (*4*) and has its own distinct objectives. Early detection of cases for isolation, testing, contact tracing, quarantine and rapid control of clusters and outbreaks are not the primary objectives of sentinel surveillance systems (*8*). Rather, sentinel surveillance complements other non-sentinel-based systems such as event-based surveillance, outbreak investigations, contact tracing and participatory surveillance by providing insights into the circulation patterns of influenza and SARS-CoV-2 and virologic characteristics of circulating viruses in the community.

Several countries use other surveillance systems to monitor trends for influenza, such as monitoring of International Classification of Diseases (ICD) codes for acute respiratory diseases, excess mortality surveillance and participatory surveillance. Countries also implement early warning systems, notifiable disease surveillance systems, environmental and other surveillance systems to identify outbreaks of epidemic and pandemic potential. However, these surveillance systems are not discussed in this guidance.

Case definitions for integrated influenza and COVID-19 surveillance

Determining optimal thresholds for sensitivity and specificity for an integrated surveillance case definition should be balanced with needs and objectives of surveillance for influenza, COVID-19 and other respiratory infections with similar and non-discriminatory clinical characteristics (*9*). A non-sensitive case definition could result in the failure to detect activity or incorrectly estimate disease impact or severity. By contrast, an overly sensitive case definition, if also non-specific, may signal false alerts for the onset of the epidemic due to a higher number of false positives from other causes, and consequently demand more resources that may make the surveillance system unsustainable over time (*10*).

ILI, ARI and SARI case definition performance for influenza

ILI and SARI case definitions, as defined in WHO global epidemiological surveillance standards for influenza (8), are commonly used by national influenza surveillance systems worldwide, although sometimes with minor adaptations (Box 1). An ARI case definition is also used in some countries for influenza and other respiratory virus surveillance and is included in the WHO Regional Office for Europe guidance for influenza surveillance in humans (*11*).

Box 1: Influenza surveillance case definitions

ILI

- *symptoms onset within past 10 days AND*
- *measured fever of 38˚C or more AND*
- *respiratory infection (cough)*

ARI

- *at least one of cough, sore throat, shortness of breath, runny nose with or without fever AND a clinician's judgement that the illness is due to an infection*

SARI

- *severe (hospitalization) AND*
- *acute (symptoms onset within past 10 days) AND*
- *fever (reported or measured 38˚C or more AND*
- *respiratory infection (cough)*

The ILI case definition has high specificity (85 – 95%) but lower sensitivity (45 – 55%) for detecting influenza in primary care consultations (12). By contrast, the broader ARI case definition is more sensitive (94%) but less specific (27%) for influenza than the ILI case definition. Similarly, the SARI case definition has a specificity and sensitivity for influenza that ranges between 45 and 70% (*13, 14*).

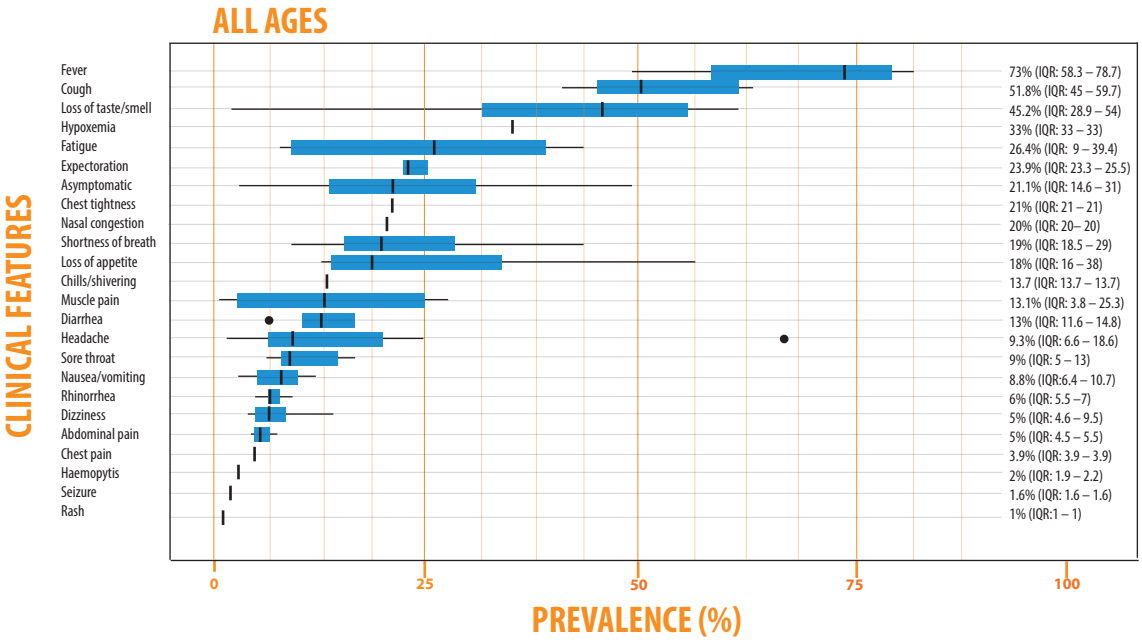
These case definitions have been demonstrated to be suitable for monitoring virologic characteristics and seasonal trends for influenza over time. Special studies (for example, to comprehensively estimate burden of disease in specific subpopulations) may require broader case definitions, but such studies may also need to be time-limited or undertaken separately from the sentinel surveillance system to maintain sentinel system sustainability over time.

ILI, ARI and SARI case definition performance for COVID-19

In October 2020, WHO evaluated the performance of various case definitions for the detection of COVID-19 using data sourced from surveillance and research studies collected between March and September 2020. This review found fever (83%) and cough (60%) to be the most common symptoms associated with COVID-19 followed by loss of smell or taste (41%), fatigue (31%) and loss of appetite.

A more recent review of 14 studies that evaluated 19 clinical features of COVID-19, undertaken in September 2021, showed that fever (73%) and cough (52%) continued to be most prevalent among symptomatic patients followed by recent loss of taste or smell (45%), fatigue (26%) and shortness of breath (19%) (see Fig. 1) (*15*).

Figure 1: Clinical features of COVID-19 (all ages)



A review of surveillance data from 14 countries showed a specificity for ILI that ranged from 60%-90% and a sensitivity that ranged between 20%-51% to detect COVID-19 cases. For SARI the range of specificities and sensitivities were 33%-60% and 40%-55%, respectively. By contrast, ARI case definition had a high sensitivity (86%) but low specificity (23%) for detecting COVID-19 cases (*1*).

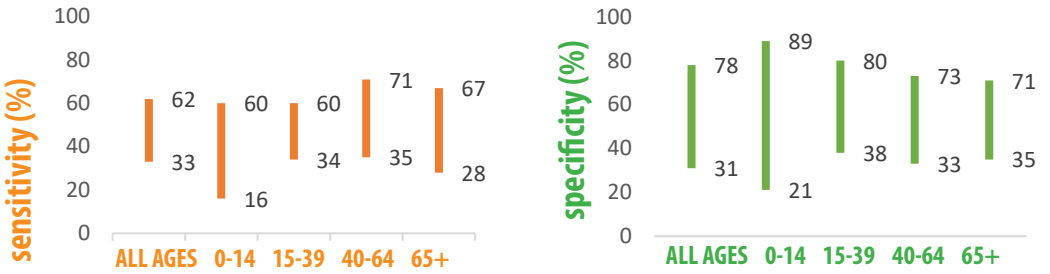
An updated evaluation of the ILI, ARI and SARI case definition performance using more recent surveillance and observational cohort data collected during 2020-2021 and sourced from 6 countries (Table 2; further details in Supplementary Tables S2 to S5) was conducted in 2021.

Table 2: Summary of performance characteristics of ILI, ARI and SARI case definitions for influenza and COVID-19

	Influenza		COVID-19 (2020 assessment)		COVID-19 (2021 assessment)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
ILI	45 – 55%	85 – 95%	20 – 51%	60 – 90%	20 – 55%	38 – 90%
ARI	94%	27%	86%	23%	60 – 96%	10 – 45%
SARI	45 – 70%	45 – 70%	40 – 55%	33 – 60%	33 – 62%	31 – 77%

The specificity of ILI for detecting COVID-19 ranged between 38 and 90% and that for SARI between 31 and 77%. The sensitivity ranged from 20 – 55% for ILI and 33 – 62% for SARI. The ARI case definition had a high sensitivity (range 60 – 96%) but low specificity (range 10 – 45%) for detecting COVID-19 (Table 2). There were no significant age group differences in the sensitivity and specificity of ILI, ARI or SARI case definitions.

Figure 2: Sensitivity (left panel) and specificity (right panel) of SARI case definition for detecting COVID-19, by age group categories (surveillance data sourced from 6 countries)



The data are limited by their heterogeneity and bias towards symptomatic individuals who seek medical care. The range of the ILI and SARI case-definition performance parameters to detect COVID-19 is, as a result, somewhat wider compared to their performance detecting influenza virus infections. The core objectives of sentinel surveillance should be met using the ILI/ARI/SARI case definitions and minimum weekly sample sizes discussed later in this document. If a Member State chooses to revise the WHO ILI and SARI case definitions to achieve additional objectives in sentinel surveillance, the sustainability of the system must be carefully considered.

For the present, GISRS should continue to use existing WHO ILI and SARI case definitions in their sentinel surveillance for influenza and COVID-19. These case definitions are not intended to capture all cases of influenza or COVID-19. Countries with high testing capacities may continue to use the more sensitive but less specific ARI case definition.

Adapting sentinel surveillance systems

In the context of integrating surveillance for influenza and SARS-CoV-2, influenza sentinel networks may need to adapt to ensure that adequate numbers of appropriate specimens and complete clinical and epidemiological information are available to GISRS laboratories for meeting core objectives. Sentinel systems for influenza, respiratory syncytial virus (RSV), Middle East respiratory syndrome coronavirus (MERS-CoV; in the context of the country's risk), and other respiratory diseases should be agile, flexible and resilient, yet stable.

Expansion of the ILI, ARI and/or SARI sentinel systems should not compromise surveillance standards, including quality of specimens and epidemiological information. Good-quality specimens and data with timely reporting, even from fewer sites, are more useful than a large volume of poor-quality specimens and data not reported in a timely manner. Before establishing more sites, it is important to assess whether they can be effectively managed, monitored and sustained, considering increased human and financial resources and technical and operational assistance that may be required. Countries should continue surveillance year-round, wherever feasible. If broader case definitions are implemented for any period, only data from ILI/ARI or SARI cases should be reported to WHO FluNet and FluID to allow for historical within-country and across-countries comparisons. Following an evaluation of the sentinel system, if it is decided to expand the sentinel sites, consideration should be given to increasing the geographical representativeness of the surveillance system, with the goal of improving detection and monitoring transmission of SARS-CoV-2 and influenza in those areas or population groups not yet covered in the sentinel surveillance system.

Sentinel systems should include health facilities where patients presenting for care are representative of the population seeking care. The choice of type and location of sentinel site should be based on collecting data on patients from different demographic and socioeconomic groups, different geographical and climatic areas (especially in large, geographically diverse countries where there may be variation in subnational mitigation/control programs). Sentinel sites can also be selected to reach special population groups (such as cross-border travellers, long-term care facility inhabitants or migrants).

Sampling strategies

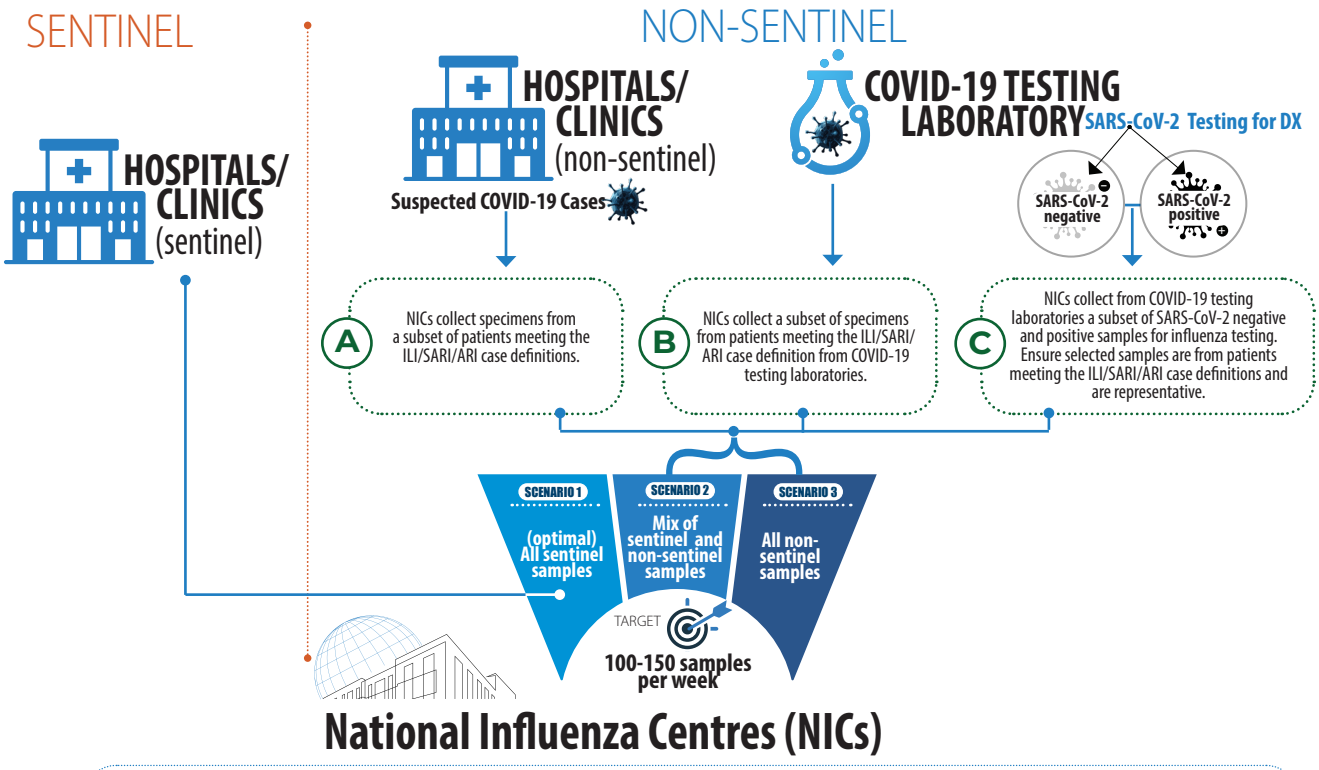
Sampling strategy and sample size considerations

Sampling strategies may need to be adapted to ensure adequate sourcing of specimens for virologic surveillance. GISRS should continue to source specimens from patients seeking care at sentinel health facilities including primary care providers, emergency rooms, outpatient clinics, hospital wards and intensive care units. To meet the core surveillance objectives, it is recommended to obtain at least 50 specimens from sentinel sites, ideally 150 specimens per week per NIC/NIL, all year round for influenza and SARS-CoV-2. Aside from practical considerations based on capacities and resources, this sample size estimate will detect at least one positive specimen from a virus prevalence of around 1 – 2% within the catchment areas of the sentinel sites. Where feasible, specimens should be selected using a sampling strategy that minimizes bias and should represent all age groups (0 to <2 years, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years and ≥65 years) and important geographic regions of the country.

If the minimum or ideal sample size cannot be sourced from sentinel sites, NICs/NILs may source specimens from non-sentinel sites such as COVID-19 testing or treatment centres and other surveillance systems to bridge the shortfall and achieve the required sample size (Fig. 3). NICs/NILs can collect specimens from a subset of ILI/ARI/SARI patients at non-sentinel sites and process them for influenza and SARS-CoV-2 testing. When sourcing non-sentinel specimens to test for influenza and SARS-CoV-2, priority should be given to specimens from patients with symptoms consistent with the ILI/ARI/SARI case definitions and representing the broader population seeking health care.

Alternately, NICs/NILs can collect a subset of specimens from patients suspected of having COVID-19 who meet the ILI/ARI/SARI case definition from COVID-19 testing laboratories and process them both for influenza and SARS-CoV-2 testing. Sourcing only SARS-CoV-2 negative specimens for influenza testing is not recommended, as this will result in biased results, making comparisons across countries difficult. This approach would also impede monitoring the relative co-circulation of the two viruses in the community.

Figure 3: Sourcing Specimens



When specimens are sourced from non-sentinel sites, regardless of the case definition used, test results for influenza and SARS-CoV-2 should be reported as non-sentinel data. Moreover, there is a potential for diagnostic selection in specimens sourced from non-sentinel sites compared to specimens sourced from sentinel sites.

Laboratory considerations for sentinel surveillance specimens

Clinical specimens

Types of clinical specimens recommended for the detection of influenza and SARS-CoV-2 viruses include:

- nasopharyngeal swab
- combined nasopharyngeal and throat (oropharyngeal) swabs; acceptable alternative: nasal and throat (oropharyngeal) swabs
- nasal swab
- oropharyngeal swab
- nasal washes
- nasopharyngeal aspirates
- endotracheal aspirates (for lower tract respiratory infections)
- bronchoalveolar lavage (for lower tract respiratory infections).

Generally, upper respiratory tract specimens have been shown to be suitable for the molecular detection of influenza and SARS-CoV-2, especially during the first week of symptom onset for COVID-19. Nasopharyngeal and oropharyngeal swabs placed into the same respiratory specimen collection vial or directly into a centrifuge tube containing 2–3 ml of virus transport medium remain the specimen types of choice for influenza and SARS-CoV-2 detection (*16-20*). Although current peer-reviewed literature indicates that lower respiratory specimens may be best for the molecular detection of SARS-CoV-2 if collected later in the course of COVID-19 (*20*), the sample collection procedure tends to be invasive for patients and may also generate aerosols, as is the case with bronchoalveolar lavages, and is difficult for patients to produce (*21-23)*. Therefore, strict adherence to infection prevention and control (IPC) procedures during sample collection is required.

Saliva, oral fluid, and sputum samples have been explored as alternative samples for the detection of SARS-CoV-2 (*24-27*). However, the suitability of these alternative sample types for the detection of influenza and SARS-CoV-2 remains uncertain, and further research is needed into alternative sampling strategies. At this time, WHO does not recommend the use of saliva as the sole specimen type for SARS-CoV-2 diagnostics (*20*). Until convincing scientific information is available, alternative respiratory and non-respiratory samples should not be used routinely for the surveillance of influenza and SARS-CoV-2. If a nonstandard collection method is being considered, it must pass the appropriate validation procedure.

In the interest of preserving RNA extraction reagents and avoiding increased personnel workload, specimens for influenza testing should be the same ones used to detect SARS-CoV-2 and vice versa (*28*).

Storage of clinical specimens at the sentinel site

If specimens from sentinel sites cannot be transported immediately to the laboratory, they can be stored at refrigerator temperature (4°C) for up to 72 hours. If longer storage periods are necessary, specimens must be kept frozen at -70°C or below. **Note: DO NOT store clinical specimens at –20°C**. Where possible, **specimens should not be repeatedly frozen and thawed,** because this results in degradation of the virus, reducing detectability and viability for further isolation/ characterization.

Specimens collected for the purpose of surveillance from sentinel sites should be stored in viral transport medium (VTM) to facilitate the sharing of specimens for subsequent virus isolation. The use of inactivating sample collection buffers (e.g., RNA preservative buffers) is not recommended for specimens collected as part of sentinel surveillance unless access to a cold chain is unavailable or unreliable.

Transport of clinical specimens to the laboratory

Transportation of clinical specimens to the laboratory follows national and international transport regulations. WHO recommends (29) that authorities transport patient specimens that potentially may contain human seasonal influenza viruses or SARS-CoV-2 as UN 3373, Biological substance, Category B.

Handling of clinical specimens in the laboratory

Aside from standard practices for handling influenza clinical specimens, special precautions need to be taken when handling such specimens in the laboratory (*30*), since respiratory specimens may also contain SARS-CoV-2 and zoonotic influenza viruses. For culture of influenza viruses, please see the biosafety and biosecurity section of this document. Efforts must be made to confirm the absence of SARS-CoV-2 and zoonotic influenza viruses in specimens intended for influenza virus culture. Virus isolation and passage of samples containing SARS-CoV-2 and zoonotic influenza viruses must currently be done in a containment laboratory with inward directional airflow and other risk control measures, as deemed appropriate by an institutional risk assessment (*30, 31*).

Laboratory techniques for the detection of influenza virus and SARS-CoV-2

Real-time reverse transcription-polymerase chain reaction (rRT-PCR) is the gold standard for detection of influenza and SARS-CoV-2 viruses in GISRS laboratories. PCR is a highly sensitive and specific method for the detection of pathogens in clinical specimens (*32-34*). Primers and probes can quickly be adapted when mutations in critical sites of the pathogens' nucleic acid are recognized; required reagents are available in high quality from many different sources; and the procedure for extracting viral nucleic acids will inactivate viruses in clinical specimens, which allows for their safe use for other tests. For GISRS laboratories, the International Reagent Resource (IRR) (*35*) of the WHO Collaborating Centres (CC) for the Surveillance, Epidemiology and Control of Influenza at the United States Centers for Disease Control and Prevention (CDC) has been the primary source for influenza PCR reagents and kits.

Rapid sharing of sequence data following the emergence of SARS-CoV-2 allowed the design of suitable primers and probes for the specific detection of this novel virus. Suggested protocols for molecular detection of SARS-CoV-2 are published on the WHO website (*20*).

Multiplex assays for the identification of more than one pathogen in the same PCR reaction allows for a more resourceful use of reagents, consumables and hands-on time. Multiplex PCR formats for the simultaneous detection of influenza A and B viruses have been available for several years, and for many GISRS laboratories these are the primary approaches to influenza surveillance.

In 2020, the WHO CC for Surveillance, Epidemiology and Control of Influenza at the CDC developed the rRT-PCR Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay (*36, 37*) for simultaneous detection of RNA from influenza A virus, influenza B virus and SARS-CoV-2 in upper and lower respiratory tract specimens. This quadruplex rRT-PCR assay for surveillance testing for influenza virus and SARS-CoV-2 is available to order by GISRS laboratories registered with the International Reagent Resource (IRR) free of charge. The CDC Flu SC2 Multiplex Assay instructions for use (*38*) and the sequence information for primers and probes (*39*) are publicly available for reference in the development of a diagnostic test based on the CDC design. In addition to the multiplex assay developed by CDC, other test formats, including several commercial tests, are available and have been described elsewhere (*40*).

Whatever singleplex or multiplex test format is to be used for influenza and SARS-CoV-2 surveillance, it is of utmost importance to ensure the highest sensitivity and specificity for the targeted pathogens. Also, well-characterized positive and negative controls must be included in each test run. To assess their performance, laboratories should regularly participate in the GISRS external quality assessment programmes provided by the WHO Global Influenza Programme (GIP) and other sources (e.g. Quality Control for Molecular Diagnostics or Royal College of Pathologists of Australia Quality Assurance Programs).

Algorithms for testing for influenza and SARS-CoV-2

During the ongoing COVID-19 pandemic, national authorities in many countries have requested their GISRS laboratories to serve as SARS-CoV-2 testing sites for primary clinical diagnosis, national reference laboratory service or virological surveillance. This has presented challenges to many laboratories on technical and programmatic fronts.

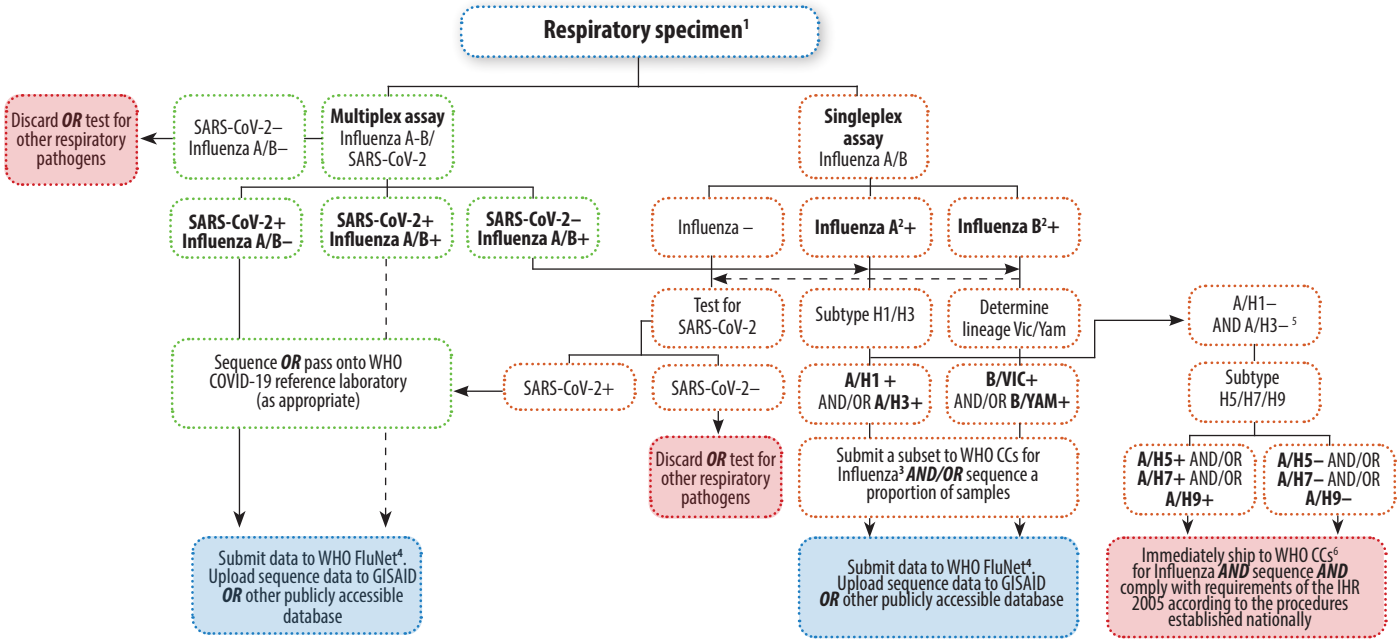
To address the need for both influenza and COVID-19 surveillance, a straightforward strategy is needed to 1) ensure optimal quantity and quality of all sentinel specimens from ILI/ARI, and SARI patients, and 2) test these specimens for **both** influenza virus and SARS-CoV-2.

Single-plex PCR assays for influenza and SARS-CoV-2 detection should ideally be run in parallel, or multiplex influenza/SARS-CoV-2 assays can be utilized to reduce the need for reagents, consumables and staff time. However, it is understood that parallel testing might not always be possible.

The testing algorithms below are for two alternate preferential testing situations: with influenza as the first testing preference (Fig. 4A), or with SARS-CoV-2 as first preference (Fig. 4B). The decision on the first preference should be made based on the epidemiological situation for COVID-19, available resources and relevant national guidance.

The testing algorithms enable the monitoring of the potential co-circulation of these respiratory viruses and the detection of co-infections with SARS-CoV-2 and influenza or other respiratory viruses. The algorithms could be adapted to include testing for other respiratory viruses, such as MERS-CoV in certain countries with a known risk, especially when influenza and SARS-CoV-2 are excluded. Some SARS-CoV-2-infected individuals shed virus or viral RNA over extended periods. Therefore, test results must be carefully interpreted and combined with clinical history.

Figure 4A: Testing algorithms when influenza is first testing preference



[1] Specimens from the sentinel surveillance site meeting specific surveillance case definition (ILI/ARI/SARI). Nasopharyngeal swab, combined nasopharyngeal and throat (oropharyngeal) swabs; acceptable alternative: nasal and throat (oropharyngeal) swabs are suitable clinical specimens for the detection of both influenza viruses and SARS-CoV-2 in clinical specimens.

[2] The dashed line indicates that influenza-positive specimens should, if resources allow, be shown to be SARS-CoV-2 negative prior to submitting to a WHO CC.

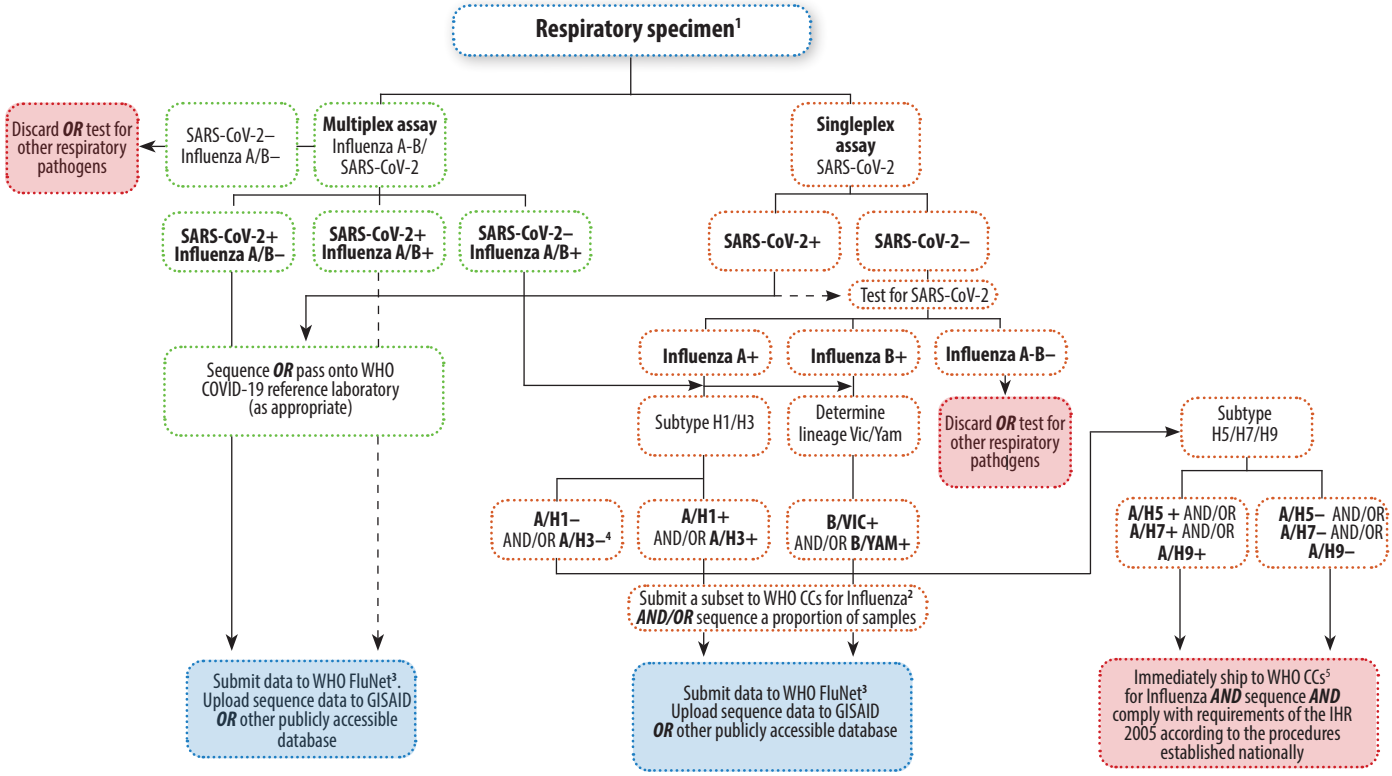
[3] Follow the Operational guidance on sharing seasonal Influenza viruses with WHO CCs under the GISRS (*42*).

[4] The summary results of testing should be shared with WHO through the global database FluNet or through WHO regional databases linked with FluNet.

[5] If an influenza A virus cannot be subtyped as either H1pdm09 or H3, but has the influenza A (matrix) gene detected at a concentration that usually allows subtyping (i.e. with a real-time RT-PCR cycle-threshold (Ct) value of <30), then this maybe due to a zoonotic influenza infection

[6] Follow the Operational guidance on sharing Influenza Viruses with Human Pandemic Potential (IVPP)under the Pandemic Influenza Preparedness (PIP) framework (*43*)

Figure 4B: Testing algorithms when SARS-CoV-2 is first testing preference



[1] Specimens from the sentinel surveillance site meeting specific surveillance case definition (ILI/ARI/SARI). Nasopharyngeal swab, combined nasopharyngeal and throat (oropharyngeal) swabs; acceptable alternative: nasal and throat (oropharyngeal) swabs are suitable clinical specimens for the detection of both influenza viruses and SARS-CoV-2 in clinical specimens.

[2] The dashed line indicates that influenza-positive specimens should, if resources allow, be shown to be SARS-CoV-2 negative prior to submitting to a WHO CC.

[3] Follow the Operational guidance on sharing seasonal Influenza viruses with WHO CCs under the GISRS (*42*).

[4] The summary results of testing should be shared with WHO through the global database FluNet or through WHO regional databases linked with FluNet.

[5] If an influenza A virus cannot be subtyped as either H1pdm09 or H3, but has the influenza A (matrix) gene detected at a concentration that usually allows subtyping (i.e. with a real-time RT-PCR cycle-threshold (Ct) value of <30), then this maybe due to a zoonotic influenza infection

[6] Follow the Operational guidance on sharing Influenza Viruses with Human Pandemic Potential (IVPP)under the Pandemic Influenza Preparedness (PIP) framework (*43*)

Selection of influenza positive clinical specimens and influenza virus isolates to forward to a WHO CC

With the continued circulation of SARS-CoV-2, the WHO GISRS CCs prefer to receive influenza-positive clinical specimens and influenza virus isolates derived from clinical specimens that are negative by rRT-PCR for SARS-CoV-2 from NICs and other laboratories. It is suggested that influenza isolates be grown only from influenza virus-positive samples that are negative for SARS-CoV-2. For SARS-CoV-2-positive specimens that require laboratory confirmation, WHO has established a network of COVID-19 reference laboratories (*41*) providing confirmatory testing for COVID-19.

If it is not possible for a laboratory to screen influenza-positive samples for SARS-CoV-2 before shipping to a WHO GISRS CC, the submission sheet should indicate that these samples have NOT been screened for SARS-CoV-2, which should also be noted in corresponding emails with the WHO CC receiving the samples.

Sharing influenza isolates or clinical specimens that are positive for influenza in a timely manner is critical to the functioning of GISRS. Follow the Operational guidance on sharing seasonal influenza viruses with WHO CCs under the GISRS (*42*). Select a subset of recently collected viruses or specimens representing currently circulating subtypes of influenza A viruses and lineages of influenza B viruses.

If an influenza A virus cannot be subtyped as either H1pdm09 or H3, but has the influenza A (matrix) gene detected at a concentration that usually allows subtyping (i.e. with a real-time RT-PCR cycle-threshold (Ct) value of <30), then this may be due to a zoonotic influenza infection. In this case, alert a WHO CC without delay and send the samples as soon as possible (*43*).

GISRS laboratories need to be reminded that the selection of influenza vaccine viruses is dependent on the availability of virus isolates, and they are encouraged to continue sending influenza isolates and/or original clinical specimens to WHO CCs for culture and full characterization of influenza viruses.

Biosafety and Biosecurity

The diagnosis of respiratory virus infection can rarely be established based only on clinical symptoms. Patients presenting with ILI/ARI or SARI may be infected with an influenza virus, SARS-CoV-2, one of many other respiratory viruses, bacteria, fungi or simultaneously infected with two or more pathogens. Health workers are at high risk for contracting infections in clinical settings. Doctors, nurses and other staff who interact with patients suspected of having influenza or COVID-19 are at especially high risk.

Health workers in this category and laboratory workers handling clinical specimens from such patients must be protected with appropriate training and adequate personal protective equipment (PPE) based on a thorough risk assessment. Every year, health care workers should be encouraged to receive both the seasonal influenza vaccine and COVID-19 vaccine as available. Health care workers and laboratory workers must be immediately tested for influenza and SARS-CoV-2 if respiratory symptoms occur.

Biosafety practices recommended for seasonal or zoonotic influenza virus isolation are described in the WHO Manual for the laboratory diagnosis and virologic surveillance of influenza (*17*).

Biosafety practices and guidelines for handling SARS-CoV-2 infectious material are described in the Laboratory biosafety guidance related to coronavirus disease (COVID-19), Interim guidance, published 28 January 2021 (*30*). A careful risk assessment must be conducted for each work step, from collecting clinical specimens to transport to the laboratory to all procedures in the laboratory. All laboratory workers must be properly trained in the use of PPE and required safety procedures (*17, 30, 31*).

It is unlikely that SARS-CoV-2 will replicate in cell lines or embryonated hens' eggs commonly used for the isolation of influenza viruses, although this cannot be completely excluded (*44*). However, laboratories attempting virus isolation from influenza A(H1)pdm09 or A(H3) or B-positive clinical specimens should first confirm samples are SARS-CoV-2-negative. When attempting to culture SARS-CoV-2, heightened bio-risk control measures (similar to BSL-3) must be observed. A "sequence first" approach could be used to determine which specimens are selected for culture and would be particularly useful in the case of influenza and SARS-CoV-2 co-infections where culture at BSL3 could be restricted to specimens that warranted further investigation.

All clinical specimens are regarded as potentially infectious until proven otherwise.

Genetic characterization

This section provides practical guidance to GISRS laboratories (*45*) on genomic sequencing of influenza and SARS-CoV-2 PCR-positive materials obtained from sentinel surveillance. Operational aspects addressed here include sample selection for sequencing, the number 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 response by achieving the following objectives:

- improve the geographic and demographic representativeness and timeliness of influenza and SARS-CoV-2 genetic sequence data in publicly accessible databases, such as the Global Initiative on Sharing All Influenza Data (GISAID) (*46*)

- monitor the trend and prevalence (proportions) of existing and emerging (co-) circulating genetic variants (clades) among samples from sentinel sites.

To achieve these objectives, laboratories should aim for genetic characterization of at least 10% of the influenza and the SARS-CoV-2-positive specimens originating from sentinel sources by performing Whole Genome Sequencing, or sequencing of the haemagglutinin (HA) gene of influenza virus and spike (S)-gene of the SARS-CoV-2 virus. Laboratories with limited or no sequencing capacity should aim for referring these influenza and SARS-CoV-2-positive specimens in a timely and regular manner to the WHO CCs for reference and research on influenza or WHO COVID-19 Reference Laboratories, respectively for genetic characterization and further analysis (*47, 48*).

Operational considerations for GISRS laboratories with established sequencing capacity

Sample selection in countries performing sentinel surveillance of ILI/ARI/SARI
In general, specimens with a rRT-PCR cycle-threshold (Ct) value of ≤25 of the SARS-CoV-2 ORF gene or influenza HA gene will likely allow for generating good quality genetic sequences of whole genomes. Samples with Ct values above 30 may not give whole genome sequence results; however, these samples can be sequenced to determine influenza subtype/lineage and SARS-CoV-2 lineage/variant, at a minimum.

Unless laboratories conduct genomic sequencing of **all** influenza or SARS-CoV-2 PCR-positive sentinel specimens, selection should prioritize the quality of the specimens, and the representativeness of the sampled patients as outlined below.

Selection of influenza and 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.

Sample selection in countries not performing sentinel surveillance of ILI/ARI/SARI

The 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 (*49*).

Number of viruses to be sequenced

- 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** influenza or SARS-CoV-2 PCR-positive sentinel specimens with a rRT-PCR Ct value of ≤30.
  - Otherwise, try to sequence a minimum of **15** influenza or SARS-CoV-2 PCR-positive sentinel specimens per week. If there are insufficient numbers of good quality specimens that can be selected 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 subse***t (ideally ≥10% as an indication), but at least a **minimum** of 15 influenza or SARS-CoV-2 PCR-positive *sentinel specimens* with a rRT-PCR Ct value of ≤30 *per week*.

Operational considerations for GISRS laboratories without established sequencing capacity

One of the critical roles of NICs within the GISRS is to share a subset of representative influenza virus-positive specimens or influenza virus isolates in a timely and regular manner with WHO CCs for reference and research on influenza. Through this mechanism, data can be derived from viruses in time to be fully utilized in the biannual vaccine composition recommendations to contribute to the selection of best suitable candidate viruses for use in vaccine development. NICs/NILs should follow the Operational Guidance on Sharing Seasonal Influenza viruses with WHO CCs under the GISRS (*42*).

When NICs and H5 Reference Laboratories detect an unsubtypeable influenza A virus or an H5, H6, H7, H9, H10 or other non-seasonal influenza virus including H1 and H3 variant viruses (*50*), they are expected to send virus-positive clinical specimens and/or isolates to WHO CCs following the Operational guidance on sharing Influenza Viruses with Human Pandemic Potential (IVPP) under the Pandemic Influenza Preparedness (PIP) framework (*43*).

GISRS laboratories should consider referring some SARS-CoV-2 PCR-positive specimens that have Ct value of ≤30 and reflect the representativeness described above for genomic sequencing to WHO COVID-19 Reference Laboratories (*41*) following an agreement with them.

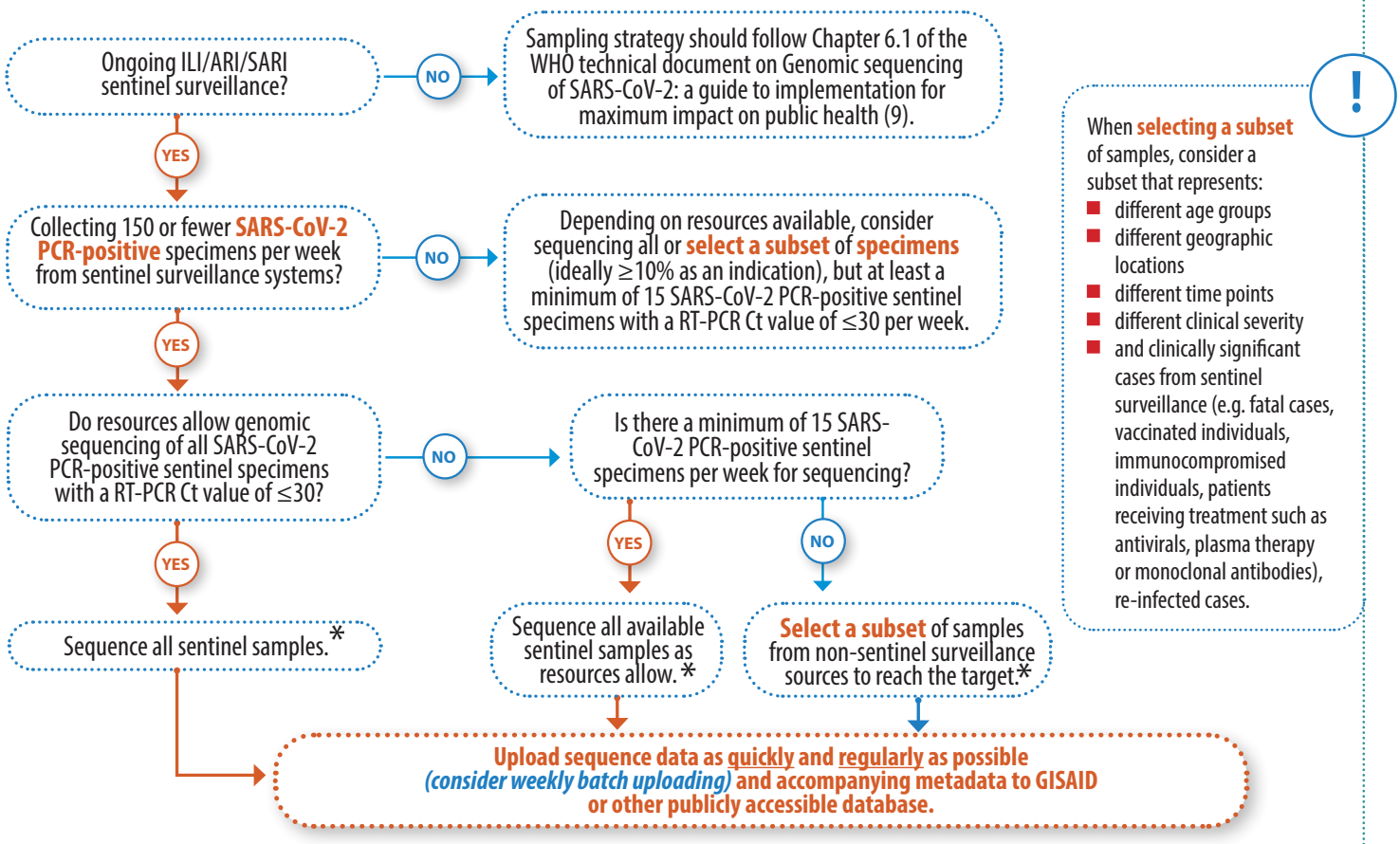
- For countries performing sentinel surveillance of ILI/ARI/SARI: consider referring all or a subset, but ideally, a minimum of 15 SARS-CoV-2 PCR-positive sentinel specimens, including all clinically significant cases, per week, with Ct value of ≤30 for genomic sequencing.

- 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 (published 8 January 2021) (*49*).

Shipments of specimens to WHO CCs for reference and research on influenza or WHO COVID-19 Reference Laboratories can be expedited through a WHO shipment mechanism (*51, 52*).

For countries planning to establish national genomic sequencing capacity (*51, 53, 54*), it is recommended to consider building capacity in their NICs, which can then address current needs for SARS-CoV-2 and other respiratory viruses of public health importance, such as influenza and RSV.

Figure 5: Selecting surveillance specimens for genomic sequencing of SARS-CoV-2



* If no capacity for sequencing, use WHO Shipment Fund to send samples to WHO COVID-19 reference laboratory.

SARS-CoV-2 genetic sequence data sharing

Metadata to accompany genome sequences

Metadata are essential to enabling the best use of GSD. Whenever possible, laboratories should include metadata when sharing or publishing GSD, including date of collection, location and sampling strategy (sentinel/non-sentinel) of specimen collection; age, sex and clinical status of the patient; and other information concerning outbreak/clinical management/vaccination context. Table 3 lists the metadata requested when uploading sequence data in GISIAD.

Table 3: Metadata requested when uploading SARS-CoV-2 sequence data in GISAID *(46)*

GISAID METADATA	NOTES
VIRUS DETAIL	
VIRUS NAME	Format: hcov-19/Country/Sample Identifier/2021
ACCESSION ID	Provided by GISAID upon upload
TYPE	Default: betacoronavirus
PASSAGE DETAILS/ HISTORY	Example: Original, Vero
SAMPLE INFORMATION	
COLLECTION DATE	
LOCATION	Format: continent/ country or territory/ region
ADDITIONAL LOCATION INFORMATION	Example: travel history, residence, cruise ship, etc.
HOST	Example: human, environment, etc.
ADDITIONAL HOST INFORMATION	Example: underlying health conditions, etc.
OUTBREAK DETAIL	Example: date, place, cluster
SAMPLING STRATEGY*	Choices: baseline surveillance, active surveillance, clinical trial, outbreak investigation, research – specific population, same-patient sampling strategy, sentinel surveillance (ILI, ARI, SARI, other), wastewater testing, other
GENDER	
PATIENT AGE	
PATIENT STATUS	Choices: hospitalized, released, live, deceased, unknown
SPECIMEN SOURCE	Choices: alveolar lavage fluid, blood, cloacal swab, faeces, mid-turbinate swab, nasopharyngeal swab, organ, oropharyngeal swab, sewage, stool, tracheal swab, urine, other
LAST VACCINATED	
TREATMENT	Drug name and dosage
SEQUENCING TECHNOLOGY	Examples: Illumina, MiSeq, Sanger, Nanopore MinION, Ion Torrent, etc.
ASSEMBLY METHOD	Example: CLC Genomics Workbench 12, geneious 10.2.4, SPAdes/MEGAHIT v1.2.9, UGENE v 33, etc.
COVERAGE	Example 70x, 1000x, 10000x (average)

Table 3: Metadata requested when uploading SARS-CoV-2 sequence data in GISAID *(46)*

GISAID METADATA	NOTES
INSTITUTE INFORMATION	
ORIGINATING LAB	Where the clinical specimen or virus isolate was first obtained
ORIGINATING LAB ADDRESS	
SAMPLE ID GIVEN BY THE ORIGINATING LAB	
SUBMITTING LAB	Where sequence data have been generated and submitted to GISAID
SUBMITTING LAB ADDRESS	
SAMPLE ID GIVEN BY THE SUBMITTING LAB	
AUTHORS	
SUBMITTER INFORMATION	
SUBMITTER	Default: Name of person signed into GISAID
SUBMISSION DATE	Default: Date of upload
ADDRESS OF SUBMITTER	
SEQUENCE	
CONFIRMATION OPTIONS	Default: Notify me about ALL DETECTED FRAMESHIFTS in this submission for reconfirmation of affected sequences. Other choices
SEQUENCE	upload FASTA sequence

**The Sampling strategy variable should be reported by GISRS laboratories in addition to the mandatory variables.*

Timeliness for sharing GSD through existing sequence-sharing platforms.
WHO encourages GISRS laboratories to sequence influenza and SARS-CoV-2-positive samples in a timely manner and share GSD with accompanying metadata through publicly accessible databases such as the GISAID EpiFlu and EpiCoV databases (*46*). 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

WHO Collaborating Centers for Reference and Research on Influenza & Essential Regulatory Laboratories (ERLs) provide technical support to NICs/NILs on implementation of genomic sequencing of influenza viruses.

The WHO COVID-19 Reference Laboratories (*41*) provide technical support to countries on implementation of genomic sequencing of SARS-COV-2. The WHO Global Influenza Programme (*55*) coordinates the functioning of GISRS. Other practical information can be found on the WHO COVID-19 website (*56*).

Data reporting and analysis

Collection and timely reporting of denominator data (total specimens tested or total specimens negative for each of the viruses reported separately) for specimens collected in sentinel surveillance should be prioritized for data reporting and analysis at all levels. Countries should establish systems to link epidemiological and virologic surveillance data.

Data collection

- The minimum data set for integrated influenza and SARS-CoV-2 sentinel surveillance is included in Annex 1.
- Additional variables could be incorporated into the individual case reporting forms in use at sentinel sites depending on intended surveillance objectives, such as assessing the burden of influenza disease (*57*) or assessing COVID-19 vaccine effectiveness *(58*).
- The benefits of adding new variables or data to collect should be balanced against the potentially increased burden on sentinel site staff when deciding to change the sentinel site case reporting form. Data collection should be designed to meet information needs of public health decision-makers, the public and health workers.

Duplication of efforts (e.g. multiple case report forms, databases) should be avoided wherever possible by adding a variable indicating the COVID-19/ILI/ARI/SARI case definition to the case reporting and specimen submission form so that there is one form in use to indicate which test should be performed and allow separation by case definition. Collecting information on which case definitions reflect the patient's condition would also be useful for retrospective analyses. If one case reporting form is used, ensure that all variables required for weekly aggregated reporting on COVID-19 surveillance to the global level are included.

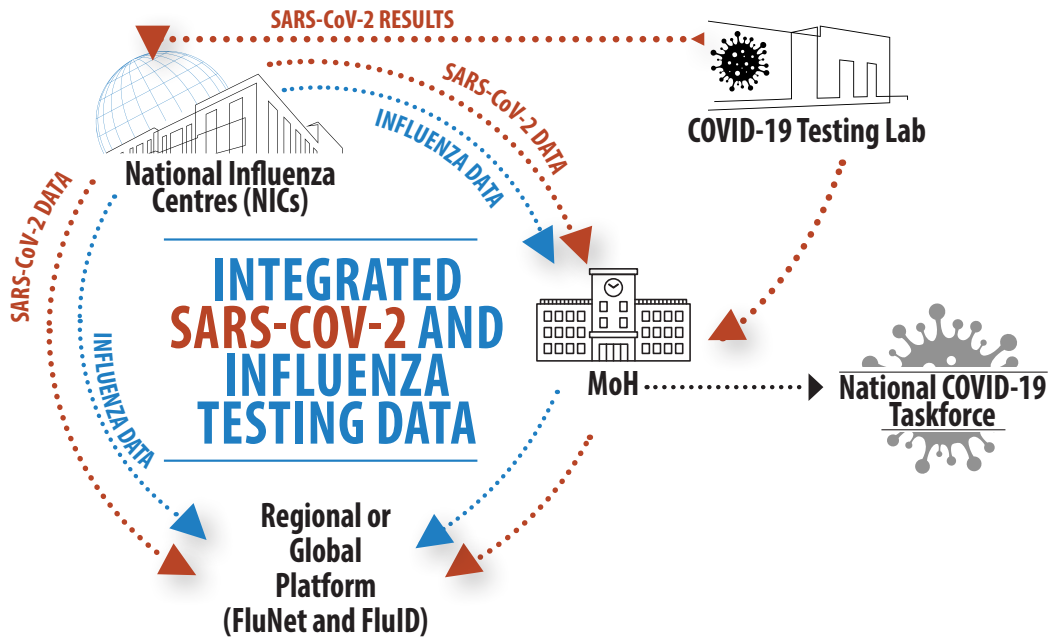
Data reporting and analysis at the national level

Timely and regular analysis and reporting of national sentinel surveillance data helps to ensure that the information is available to policymakers and health care providers and will also improve the data quality and consistency of reporting from sentinel sites. Whenever feasible, such reports should be available to the public on the national surveillance website and fed back to the sentinel sites. Reports should include a summary interpretation with graphs, if possible, to support the interpretation.

To facilitate the collation and analysis of data at the national level, countries may consider establishing or strengthening electronic data platforms that link epidemiological and virologic data and sentinel and non-sentinel surveillance systems and are accessible to stakeholders.

Procedures for routinely reporting the analysis results to respiratory disease surveillance focal points should be in place, as should procedures and actions to be taken when a SARS-CoV-2 or novel influenza virus is detected in a sentinel sample (Fig. 6). This information should be reported to primary care providers, the national COVID-19 task force and other authorities responsible for isolation, contact tracing or other public health actions.

Figure 6: Reporting data



Data reporting to Regional and global levels

Global/regional reporting for influenza and SARS-CoV-2 to FluMART, either directly or via WHO Regional platforms, is important to monitor influenza and COVID-19 trends and compare them with other respiratory diseases. FluMART (*59*), the global data reporting platform that houses the FluNet and FluID datasets, allows the uploading of any user-defined data files in their own format and transforms them into standardized data. FluNet and FluID have been configured to collect COVID-19 data from sentinel surveillance. Outputs from the reporting of integrated surveillance for influenza and SARS-CoV-2 surveillance data to FluMART are available on WHO's website (Integrated sentinel influenza SARS-CoV-2 dashboard). The visualizations aggregate data to the global level or the WHO Region and can be seen separately for sentinel site and non-sentinel site data.

The interpretation of epidemic and seasonal trends in illness over time requires the reporting of data from a stable number of sentinel sites that use standardized case definitions and sampling procedures. Countries should therefore endeavour to separate virologic test results by specimen source – i.e., those specimens from sentinel sites or those from non-sentinel sites, when reporting to FluMART or regional platforms. Laboratory data from sentinel surveillance sites implies the use of a standardized case definition and sampling strategy when obtaining specimens from patients . Laboratory testing of samples collected from individuals associated with respiratory disease outbreaks or for clinical diagnosis or management or from screening of asymptomatic individuals, where a standard case definition (like ILI/ARI/SARI) is not used in selecting patients to sample, should be reported as non-sentinel surveillance data. If surveillance sites have been added temporarily, data from these sites should also be reported as non-sentinel surveillance data, even if these sites are implementing ILI/ARI/SARI case definitions. Non-sentinel data may be biased towards reflecting virus activity in certain populations other than the general population and difficult to compare to historical trends. Data from samples collected as part of universal testing for SARS-CoV-2 and not part of routine sentinel or non-sentinel influenza surveillance do not have to be reported to FluMART. Reporting requirements for universal SARS-CoV-2 surveillance can be found in the WHO public health guidance for COVID-19 surveillance (*4*).

What to report:

- **Influenza test results:** continue timely reporting of aggregated influenza surveillance data weekly to Regional and global levels. At a minimum, this should be the number of samples processed for influenza testing, the number of samples positive for influenza and the number of samples tested and/or samples negative for influenza. Ideally, these data should be reported separately for samples from sentinel sites and non-sentinel sites.
- **COVID-19 test results:** countries are requested to report weekly aggregated COVID-19 results in the same format and frequency as they have been reporting influenza surveillance data. Virologic data (such as the number of samples testing positive and negative for SARS-CoV-2) from cases sampled in existing sentinel and non-sentinel or syndromic surveillance systems should be reported weekly to Regional and global levels. Again, ideally these data should be reported separately for samples from sentinel sites and non-sentinel sites.
- **Co-infections with influenza and SARS-CoV-2:** reporting the detection of co-infections with SARS-CoV-2 and influenza or other respiratory viruses to FluMART is possible. If reporting is done with an Excel file upload, modifications to the routine reporting template would allow the reporting of the number of co-infections per week by combination of viruses detected (e.g., the number of detections of influenza A/SARS-CoV-2 or influenza B/SARS-CoV-2 co-infections). Contact flumart@who.int or the WHO Regional Office focal point for further instructions on reporting co-infections.
- **Syndromic surveillance data:** continue reporting the ILI and SARI data with age breakdown and where possible by influenza type and SARS-CoV-2 testing status, with the denominators. Where established, ARI or pneumonia data should be continuously reported.

How to report:

- For countries uploading data directly to FluMART, please contact flumart@who.int for assistance in modifying the routine reporting influenza template to include COVID-19 data and for assistance in uploading.
- For countries reporting influenza and COVID-19 surveillance data to Regional platforms, this should be done through existing platforms and WHO contact persons. Please include flumart@who.int in all messages.

When to report:

- Routine timely reporting of influenza and COVID-19 data should continue on a weekly basis as long as surveillance is continued (ideally year-round) for influenza. Specific requirements for COVID-19 are provided in the WHO public health guidance for COVID-19 surveillance (*4*). For direct reporting to global platforms, data should be reported by Thursday of the following week. Deadlines for reporting to Regional platforms may differ.

See Annex 2 for more information on how and what to report.

Monitoring and evaluating sentinel surveillance systems

Monitoring is the ongoing review of data entered into the system, and an evaluation is a more comprehensive process, where all parts of the surveillance system are thoroughly examined and checked for performance (*8*). Monitoring should cover data quality, completeness and consistency of reporting. Monitoring tools should not overburden the surveillance team and draw on the information systems and relevant surveillance databases. Table 4 summarizes the characteristics of monitoring and evaluation in the context of this guidance.

Table 4: Characteristics of monitoring and evaluation

	WHAT	HOW	WHEN
MONITORING	Ongoing review of the data for completeness, timeliness, and aberrations or unexpected patterns should be performed at all levels of the surveillance system.	Assess functioning of surveillance during season or period under evaluation and identify disruptions that need to be addressed.	Develop monitoring plan and targets before start of surveillance and then perform weekly to biweekly for data timeliness, completeness and quality.
EVALUATION	All parts of the surveillance system (including each sentinel site) are examined for performance in achieving objectives. Critical domains to assess at sentinel site include case selection, case definitions used, specimen collection, storage and shipment; personal protective equipment, and swabbing techniques; and data reporting, management, analysis and quality.	Assess functioning of surveillance, disruptions, adaptations; review SOPs and implementation at all levels; assess training needs. and check deviations from operational procedures.	On a regular basis when time and resources allow, review changes implemented in the system. Evaluations may need to be done more frequently during the COVID-19 pandemic or other outbreaks to assess surge capacities and protocols. In outbreaks, a rapid assessment to assess short-term opportunities and disruptions is preferable.

Specific operational considerations on the monitoring and evaluation of surveillance systems, and influenza surveillance systems specifically, are covered in detail in existing guidance and protocols (*8, 60-62*). This guidance includes additional considerations for monitoring and evaluation in the context of the COVID-19 pandemic, the integration of SARS-CoV-2 surveillance into existing systems and expanding sentinel surveillance systems to meet the objectives presented earlier in the guidance (see also Annex 3).

Translating surveillance intelligence into action and policy

Countries have typically established incident management teams (IMT) to coordinate the national response to COVID-19 pandemic. A designated focal point for respiratory disease surveillance should be a member of this IMT and act as a liaison with routine respiratory disease surveillance programs. Information from the routine respiratory disease sentinel surveillance programs should inform the risk assessment of acute respiratory infections in the country. Routine sentinel surveillance should be one of many important sources of information to analyse and assess the situation and guide the prevention and control measures for COVID-19 and influenza or any other respiratory pathogen. Sentinel surveillance data should continue to be triangulated with other sources of data (e.g. event-based surveillance, non-sentinel surveillance, mortality surveillance) and used in pandemic influenza severity assessments (PISA) (*63*) and influenza special studies and investigations (iPSS) (*64*), recognizing that changes to surveillance standards may alter baselines and interpretations.

Risk assessment and communication

Risk assessments for SARS-CoV-2 are now integrated into the biweekly influenza risk assessment reports and can be accessed in Influenza updates. Weekly epidemiological updates for COVID-19 are available in COVID-19 Situation Reports. Various tools and training courses are available to assess the severity of seasonal and pandemic influenza PISA.

One-way risk communication, even if evidence-based, is ineffective. Building and maintaining trust requires community engagement and social mobilization. All countries should develop core capacities in risk communication including community engagement and social mobilization to respond to a potential threat of seasonal and pandemic influenza and COVID-19. Training courses in risk communication for influenza events are available at OpenWHO.org. It is critical to know when to communicate the risk and whom to alert and inform. It is equally important to adapt material for target audiences and to communicate with empathy.

Policy

There is a need to communicate the scope, objectives, strengths, and limitations of sentinel surveillance systems and their complementary value to policymakers. Sentinel surveillance systems should build on existing relationships and intersectoral linkages to inform policy. Countries should evaluate the strength and limitations of sentinel surveillance data and make measured conclusions when informing policy. Information collated from different surveillance systems should be used to inform public health decisions on mitigation, prevention and control measures including vaccination, mask use, physical distancing, restriction of mobility and for reviewing public health policy and practice. Surveillance data could be used to assess impact on health systems including the need to scale up capacities, increase the number of critical care beds and maintain and inform the organization of essential health services.

Process and methodology

Two systematic reviews on the clinical symptoms of COVID-19 and case definition performance, and case definition performance analysis of surveillance data sourced from countries, conducted in September 2020 provided the basis for the interim guidance published in November 2020. These reviews and analysis were repeated to include new evidence for this update.

Revisions to this interim guidance are based on:

- Systematic review of the clinical symptoms of COVID-19: Considering the numerous reviews published timely which covered most individual studies, the September 2021 systematic review limited its scope to published systematic reviews only (Annex 4) (*15*). Of the 149 systematic reviews screened, 14 systematic reviews that adhered to PRISMA guidelines and reported pooled estimates for clinical symptoms with laboratory confirmation of COVID-19 by RT PCR or rapid diagnostic tests, had appropriate study design were included in the current review. The quality of the 14 systematic reviews included were assessed using the Joanna Briggs Institute (JBI) critical appraisal tool. Six of the 14 reviews were considered high quality (score of eight or greater) and eight reviews as moderate to low quality (score of seven or less). All the included reviews tested for heterogeneity, publication bias, and assessed quality of individual studies with commonly used tools such as the Newcastle Ottawa scale and others (Annex 5). The purpose of this review was to ascertain the prevalence of COVID-19 symptoms that were part of the existing influenza surveillance case definition. The pooled prevalence was calculated as the median and interquartile range of the point estimates for each symptom reported by the reviews that were included. A potential bias in ranking the most prevalent clinical symptoms due to varying number of symptoms reported by different reviews, was ruled out by a sensitivity analysis of reviews that reported five or more clinical symptoms compared to including all reviews. Another potential bias due to the inclusion of the same primary study several times within the included reviews, was ruled out with a sensitivity analysis that compared the ranking of each clinical symptom from all reviews to the ranking obtained by selecting only the most recent review.
- Systematic review of the performance of COVID-19 surveillance based on existing influenza surveillance: There were no studies that formally evaluated the sensitivity and specificity of influenza case definitions for detecting laboratory confirmed COVID-19.
- Case definition performance analysis: Syndromic surveillance data with laboratory results for influenza and COVID-19 was sourced from several countries. Details of the data source and heterogeneity are provided in supplementary table 1. Patients were categorized as SARI / ILI and ARI based on their clinical features. Sensitivity, specificity and predictive value was estimated for SARI, ILI and ARI case definitions for detecting laboratory confirmed COVID-19.
- Review and synthesis of best practices collected from countries on the integration of SARS-CoV-2 testing in influenza sentinel surveillance
- Inputs were solicited during the 2nd WHO global consultation on the integrated sentinel surveillance of influenza and SARS-CoV-2 and the development of the Global Influenza Surveillance and Response System (GISRS) Plus (12-14 October 2021, virtual meeting), which was attended by experts from the (GISRS) (*65*) network, national disease surveillance programs and partner institutions.

Limitations

The rapid review on clinical characteristics of COVID-19 focused solely on already published systematic reviews. The information on asymptomatic cases did not differentiate pre-symptomatic and asymptomatic and we are not able to comment if the asymptomatic cases went on to develop symptoms. Other limitations include lack of information on the clinical characteristics by variant type.

With new variants being reported, it is possible that clinical symptoms may vary that might impact the performance of these case definitions. Lastly, we have pooled results of prevalence which have been estimated in specific unknown subpopulations (e.g., only hospitalized cases).

For the rapid review of the performance of existing influenza surveillance case definitions for detection of COVID-19, limitations include low sample size (<1000) in two studies, and that most studies were conducted in Europe. The ILI and SARI case definition performance was assessed using data from syndromic surveillance with virologic confirmation and needs to be further evaluated for sensitivity, specificity with focused studies using broader case definitions as reference.

Plans for updating

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance will expire one year after the date of publication.

Declaration of interests

In accordance with WHO policy, experts completed the WHO form for Declaration of Interest before they were invited to the WHO Consultation. The interests declared were reviewed by WHO and determined not to present a conflict with the objective of the WHO Consultation which led to the development of the guidance.

Funder

Funded by WHO

Further Reading

- Extensive guidance on surveillance during an influenza pandemic is available, and much of the content in that guidance is relevant in the current situation. See https://apps.who.int/iris/bitstream/handle/10665/259886/9789241513333-eng.pdf?sequence=1 for more information and background.
- For more information on the Pandemic Influenza Severity Assessment, see the WHO guidance: https://www.who.int/influenza/surveillance_monitoring/pisa/en/.
- More information on implementing SARI surveillance is included in the WHO Global Epidemiological Surveillance Standards for Influenza: https://apps.who.int/iris/handle/10665/311268
- Detailed guidance on monitoring and evaluation of sentinel surveillance systems for influenza is included in the Global Epidemiological Surveillance Standards for Influenza: https://apps.who.int/iris/handle/10665/311268, and in the U.S. CDC Field Guidance Overview of Evaluating Surveillance Systems: https://www.cdc.gov/globalhealth/healthprotection/fetp/training_modules/12/Eval-Surv-Sys_FieldG_Final_09262013.pdf.
- Generic protocols for special investigations and studies Influenza Special studies and investigations (iPSS) https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/pandemic-influenza-special-investigations-studies-pss

References

1. World Health Organization. Maintaining surveillance of influenza and monitoring SARS-CoV-2: adapting Global Influenza Surveillance and Response System (GISRS) and sentinel systems during the COVID-19 pandemic: interim guidance, 8 November 2020. Geneva, Switzerland: World Health Organization; 2020 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/336689.
2. World Health Organization. Operational considerations to expedite genomic sequencing component of GISRS surveillance of SARS-CoV-2, 16 February 2021 Geneva, Switzerland: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/339676.
3. World Health Organization. Guidance for surveillance of SARS-CoV-2 variants: Interim guidance, 9 August 2021. Geneva, Switzerland: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/rest/bitstreams/1361901/retrieve.
4. World Health Organization. Public health surveillance for COVID-19: interim guidance, 16 December 2020. Geneva, Switzerland: World Health Organization; 2020 [20 October 2021]. [Available from: https://apps.who.int/iris/rest/bitstreams/1323058/retrieve.
5. Statement on the fourth meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of coronavirus disease (COVID-19), 1 August 2020 [website]. Geneva, Switzerland: World Health Organization; 2020 [29 October 2020]. Available from: https://www.who.int/news/item/01-08-2020-statement-on-the-fourth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-coronavirus-disease-(covid-19)
6. Statement on the sixth meeting of the International Health Regulations (2005) Emergency Committee regarding the coronavirus disease (COVID-19) pandemic Geneva, Switzerland: World Health Organization; 2021 [1 November 2021]. Available from: https://www.who.int/news/item/15-01-2021-statement-on-the-sixth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic.
7. World Health Organization. WHO COVID-19: case definitions: updated in public health surveillance for COVID-19, published 16 December 2020. Geneva, Switzerland: World Health Organization; 2020 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/337834.
8. World Health Organization. Global Epidemiological Surveillance Standards for Influenza. Geneva, Switzerland: World Health Organization; 2014 [20 October 2021]. Available from: http://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf.
9. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ. 2018;96(2):122-8.
10. Penttinen P, Pebody R. Influenza case definitions - optimising sensitivity and specificity. Euro Surveill. 2015;20(22):21148.
11. WHO Regional Office for Europe guidance for sentinel influenza surveillance in humans, May 2011. Copenhagen: WHO Regional Office for Europe; 2011 [29 October 2020]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0020/90443/E92738.pdf.
12. Jiang L, Lee VJ, Lim WY, Chen MI, Chen Y, Tan L, et al. Performance of case definitions for influenza surveillance. Euro surveill. 2015;20(22):21145.

13. Murray EL, Khagayi S, Ope M, Bigogo G, Ochola R, Muthoka P, et al. What are the most sensitive and specific sign and symptom combinations for influenza in patients hospitalized with acute respiratory illness? Results from western Kenya, January 2007-July 2010. Epidemiology and infection. 2013;141(1):212-22.
14. Hirve S, Chadha M, Lele P, Lafond KE, Deoshatwar A, Sambhudas S, et al. Performance of case definitions used for influenza surveillance among hospitalized patients in a rural area of India. Bulletin of the World Health Organization. 2012;90(11):804-12.
15. Kulkarni D, Ashcroft T, Lee B, Nundy M, Hartnup K, Bhattacharyya U, et al. A rapid review update - case definitions for surveillance integrated for influenza and COVID-19. 2021.
16. Wang X, Tan L, Liu W, Lu Y, Cheng L, Sun Z. Comparison of nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 detection in 353 patients received tests with both specimens simultaneously. Int J Infect Dis. 2020;94:107-9.
17. World Health Organization. Manual for the laboratory diagnosis and virological surveillance of influenza. Geneva, Switzerland: World Health Organization; 2011 [20 October 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44518/9789241548090_eng.pdf?sequence=1.
18. World Health Organization. Global Epidemiological Surveillance Standards for Influenza. Geneva, Switzerland: World Health Organization; 2014 [29 October 2020]. Available from: https://apps.who.int/iris/handle/10665/311268.
19. World Health Organization. COVID-19 clinical management: living guidance, 25 January 2021. Geneva, Switzerland: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/338882.
20. World Health Organization. Diagnostic testing for SARS-CoV-2, 11 September 2020 Geneva, Switzerland: World Health Organization; 2020 [20 October 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/334254/WHO-2019-nCoV-laboratory-2020.6-eng.pdf.
21. Bwire GM, Majigo MV, Njiro BJ, Mawazo A. Detection profile of SARS-CoV-2 using RT-PCR in different types of clinical specimens: A systematic review and meta-analysis. J Med Virol. 2020.
22. Lin C, Xiang J, Yan M, Li H, Huang S, Shen C. Comparison of throat swabs and sputum specimens for viral nucleic acid detection in 52 cases of novel coronavirus (SARS-Cov-2)-infected pneumonia (COVID-19). Clin Chem Lab Med. 2020;58(7):1089-94.
23. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9.
24. Wehrhahn MC, Robson J, Brown S, Bursle E, Byrne S, New D, et al. Self-collection: An appropriate alternative during the SARS-CoV-2 pandemic. J Clin Virol. 2020;128:104417.
25. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a Noninvasive Specimen for Detection of SARS-CoV-2. J Clin Microbiol. 2020;58(8).
26. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, et al. Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2. N Engl J Med. 2020;383(13):1283-6.
27. McCormick-Baw C, Morgan K, Gaffney D, Cazares Y, Jaworski K, Byrd A, et al. Saliva as an Alternate Specimen Source for Detection of SARS-CoV-2 in Symptomatic Patients Using Cepheid Xpert Xpress SARS-CoV-2. J Clin Microbiol. 2020;58(8).
28. Hanson KE, Barker AP, Hillyard DR, Gilmore N, Barrett JW, Orlandi RR, et al. Self-Collected Anterior Nasal and Saliva Specimens versus Healthcare Worker-Collected Nasopharyngeal Swabs for the Molecular Detection of SARS-CoV-2. J Clin Microbiol. 2020.

29. World Health Organization. Guidance on regulations for the transport of infectious substances 2021-2022: applicable as from 1 January 2021. Geneva, Switzerland: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/339825.

30. World Health Organization. Laboratory biosafety guidance related to coronavirus disease (COVID-19): interim guidance, 28 January 2021. Geneva, Switzerland: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/339056.

31. World Health Organization. Laboratory biosafety manual, 4th ed. Geneva, Switzerland: World Health Organization; 2020 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/337956.

32. Matheeussen V, Corman VM, Donoso Mantke O, McCulloch E, Lammens C, Goossens H, et al. International external quality assessment for SARS-CoV-2 molecular detection and survey on clinical laboratory preparedness during the COVID-19 pandemic, April/May 2020. Euro Surveill. 2020;25(27).

33. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3).

34. Wu J, Liu J, Li S, Peng Z, Xiao Z, Wang X, et al. Detection and analysis of nucleic acid in various biological samples of COVID-19 patients. Travel Med Infect Dis. 2020:101673.

35. International Reagent Resource (IRR) [website]. [29 October 2020]. Available from: http://www.influenzareagentresource.org.

36. Balakrishnan VS. In preparation for a COVID-19-influenza double epidemic. The Lancet Microbe. 2020;1(5):e199.

37. Shu B, Kirby MK, Davis WG, Warnes C, Liddell J, Liu J, et al. Multiplex Real-Time Reverse Transcription PCR for Influenza A Virus, Influenza B Virus, and Severe Acute Respiratory Syndrome Coronavirus 2. Emerging infectious diseases. 2021;27(7):1821-30.

38. Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay, 21 September 2020. Atlanta: Centers for Disease Control and Prevention; [29 October 2020]. Available from: https://www.fda.gov/media/139743/download.

39. Research Use Only CDC Influenza SARS-CoV-2 (FluSC2) Multiplex A.ssay Real-Time RT-PCR Primers and Probes [website]. Atlanta: Centers for Disease Control and Prevention; [29 October 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/multiplex-primer-probes.html.

40. COVID-19 Diagnostics & Testing [website]. FIND; [29 October 2020]. Available from: https://www.finddx.org/covid-19/.

41. WHO reference laboratories providing confirmatory testing for COVID-19, 19 April 2020. Geneva: World Health Organization; 2020 [1 November 2021]. Available from: https://www.who.int/publications/m/item/who-reference-laboratories-providing-confirmatory-testing-for-covid-19.

42. World Health Organization. Operational Guidance on Sharing Seasonal Influenza viruses with WHO Collaborating Centres (CCs) under the Global Influenza Surveillance and Response System (GISRS), 31 October 2017. Geneva, Switzerland: World Health Organization; 2017 [29 October 2020]. Available from: https://apps.who.int/iris/handle/10665/259400.

43. World Health Organization. Operational guidance on sharing Influenza Viruses with Human Pandemic Potential (IVPP) under the Pandemic Influenza Preparedness (PIP) framework Geneva, Switzerland: World Health Organization; 2017 [20 October 2021]. Available from: https://apps.who.int/iris/handle/10665/259402.

44. Barr IG, Rynehart, C., Whitney, P., Druce, J. SARS-CoV-2 does not replicate in embryonated hen's eggs or in MDCK cell lines. Euro surveill. 2020;25(25).

45. Global Influenza Surveillance and Response System (GISRS). Geneva: World Health Organization; [29 October 2020]. Available from: http://www.who.int/influenza/gisrs_laboratory/en/.

46. GISAID [29 October 2020]. Available from: http://www.gisaid.org.

47. World Health Organization. WHO Collaborating Centres & Essential Regulatory Laboratories (ERLs) Geneva: World Health Organization; [21 October 2021] Available from: https://www.who.int/initiatives/global-influenza-surveillance-and-response-system/who-collaboration-center-erl.

48. World Health Organization. WHO reference laboratories providing confirmatory testing for COVID-19, 19 April 2020. Geneva, Switzerland: World Health Organization; 2020 [1 November 2021]. Available from: https://www.who.int/publications/m/item/who-reference-laboratories-providing-confirmatory-testing-for-covid-19.

49. World Health Organization. Genomic sequencing of SARS-CoV-2: a guide to implementation for maximum impact on public health, 8 January 2021 Geneva: World Health Organization; 2021 [20 October 2021]. Available from: https://apps.who.int/iris/rest/bitstreams/1326052/retrieve.

50. World Health Organization. Standardization of terminology for the influenza virus variants infecting humans: Update, 30 January 2014 Geneva: World Health Organization; [15 November 2021]. Available from: https://www.who.int/publications/m/item/standardization-of-terminology-for-the-influenza-virus-variants-infecting-humans-update.

51. Guidance for laboratories shipping specimens to WHO reference laboratories that provide confirmatory testing for COVID-19 virus, 31 March 2020. Geneva: World Health Organization; 2020 [1 November 2021]. Available from: https://apps.who.int/iris/rest/bitstreams/1273647/retrieve.

52. World Health Organization. Shipping & logistics Geneva: World Health Organization; [20 October 2021]. Available from: https://www.who.int/initiatives/global-influenza-surveillance-and-response-system/virus-sharing/shipping-and-logistics-activities.

53. Next-generation sequencing of influenza viruses - General information for national influenza centres. Geneva: World Health Organization; [1 November 2021]. Available from: https://cdn.who.int/media/docs/default-source/influenza/global-influenza-surveillance-and-response-system/related-documents/ngs_guidance_for_nics.pdf?sfvrsn=b24248b6_8.

54. SARS-CoV-2 genomic sequencing for public health goals: interim guidance, 8 January 2021 Geneva: World Health Organization; 2021 [1 November 2021]. Available from: https://apps.who.int/iris/handle/10665/338483.

55. Global Influenza Programme Geneva: World Health Organization; [1 November 2021]. Available from: https://www.who.int/teams/global-influenza-programme.

56. Country & Technical Guidance - Coronavirus disease (COVID-19) [website]. Geneva, Switzerland: World Health Organization; [29 October 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance.

57. World Health Organization. A manual for estimating disease burden associated with seasonal influenza. Geneva, Switzerland: World Health Organization; 2015 [20 October 2021]. Available from: https://apps.who.int/iris/rest/bitstreams/803697/retrieve.

58. World Health Organization. Evaluation of COVID-19 vaccine effectiveness: interim guidance, 17 March 2021. Geneva, Switzerland: World Health Organization; 2021 [29 October 2020]. Available from: https://apps.who.int/iris/handle/10665/340301.

59. World Health Organization. FluMart [website]. Geneva, Switzerland: World Health Organization; [29 October 2020]. Available from: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring.

60. Centers for Disease Control and Prevention. Overview of evaluating surveillance systems. Atlanta, Georgia, United States of America: Centers for Disease Control and Prevention; 2013 [29 October 2021]. Available from: https://www.cdc.gov/globalhealth/healthprotection/fetp/training_modules/12/eval-surv-sys_fieldg_final_09262013.pdf.

61. European Centre for Disease Prevention and Control. Data quality monitoring and surveillance system evaluation. Stockholm, Sweden: European Centre for Disease Control and Prevention; 2014 [October 29 2021]. Available from: https://www.ecdc.europa.eu/en/publications-data/data-quality-monitoring-and-surveillance-system-evaluation-handbook-methods-and.

62. World Health Organization. Regional Office for Africa. Protocol for national influenza sentinel surveillance. Brazzaville, Republic of Congo: World Health Organization, Regional Office for Africa; 2015 [29 October 2021]. Available from: https://apps.who.int/iris/handle/10665/187121.

63. World Health Organization. Pandemic influenza severity assessment (‭PISA‬) : a WHO guide to assess the severity of influenza in seasonal epidemics and pandemics Geneva, Switzrland: World Health Organization; 2017 [29 October 2021]. Available from: https://apps.who.int/iris/handle/10665/259392.

64. World Health Organization. Pandemic Influenza Special Investigations & Studies (PSS) Geneva, Switzerland: World Health Organization; [29 October 2021]. Available from: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/pandemic-influenza-special-investigations-studies-pss.

65. World Health Organization. Global Influenza Surveillance and Response System (GISRS) [website]. Geneva, Switzerland: World Health Organization; [29 October 2020]. Available from: https://www.who.int/initiatives/global-influenza-surveillance-and-response-system.

Supplementary Table S1: Source and heterogeneity of newly available data analysed to estimate performance characteristics for ILI, ARI and SARI case definitions for COVID-19

	ARGENTINA	CHILE	COSTA RICA	INDIA	THAILAND	THAILAND Community cohort	UNITED KINGDOM
Data source	ILI/SARI surveillance	SARI surveillance	ILI/SARI surveillance	ILI/SARI surveillance	ILI/SARI surveillance	Community cohort	Community cohorts
Type of surveillance	Sentinel/non-sentinel	Sentinel/ non-sentinel	Sentinel/ non-sentinel	Sentinel/ non-sentinel	Sentinel/ non-sentinel	—	—
Patient source	Hospitals, clinics	Hospitals	Hospitals, clinics	Hospitals, clinics	Hospitals, clinics		Clinics
Total patients	ILI: 308 059 SARI: 31 159	SARI: 13 063	ILI: 179 843 SARI: 11 706	ILI: 24 778 SARI: 16 781	ILI: 3287 SARI: 1744	222	ILI: 1912
Age groups (years)	0-14, 15-39, 40-64, 65+	0-14, 15-39, 40-64, 65+	0-14, 15-39, 40-64, 65+	0-4, 5-14, 15-44, 45-59, 60+	0-14, 15-39, 40-64, 65+	0-14, 15-39, 40-64, 65+	0-14, 15-39, 40-64, 65+
Symptoms evaluated	Fever, cough, sore throat, breathing difficulty, runny nose, tachypnoea, shortness of breath	Fever, cough, shortness of breath, anosmia, dysgeusia, odyno-phagia	Fever, cough, breathing difficulty, anosmia, runny nose	Fever, cough, breathlessness, sore throat, runny nose, GI symptoms, chest pain	Fever, cough	Fever, cough, sore throat, runny nose, dyspnoea, diarrhoea, anosmia, dysgeusia	Fever, cough, sore throat, runny nose
Males	ILI: 47% SARI: 52%	SARI: 56%	ILI: 51% SARI: 52%	ILI: 59% SARI: 60%	ILI: 49% SARI: 55%	27%	50%
Diagnostic test	RT-PCR IFT	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR

Supplementary Table S2: Influenza like illness (ILI) performance characteristics for COVID-19

	COUNTRY	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
All ages	Argentina	6.6 (6.5 – 6.6)	98 (97.9 – 98)	57.7 (57.2 – 58.2)	71.3 (71.2 – 71.3)	0.52
	Costa Rica	31.1 (30.5 – 31.7)	75 (74.6 – 75.5)	51.6 (50.8 – 52.4)	56 (55.5 – 56.5)	0.53
	India	16.4 (15.6 – 17.3)	90.1 (89.6 – 90.5)	38 (36.2 – 39.8)	74.3 – (73.8 –75.0)	0.56
	Thailand (cohort)	20 (6.8 – 40.7)	82.6 (75.9 – 88.1)	15.2 (5.1 – 31.9)	86.9 (80.5 – 91.8)	0.51
	Thailand	55 (43.5 – 66.2)	37.9 (35.4 – 40.5)	4.7 (3.4 – 6.3)	93.8 (91.5 – 95.6)	0.46
	United Kingdom	33 (30.7 – 35.4)	92.4 (91.9 – 92.9)	37.4 (34.8 – 40.1)	91 (90.4 – 91.5)	0.63
0 – 14 years	Argentina	6.4 (6 – 6.9)	94.7 (94.5 – 94.9)	21.1 (19.8 – 22.5)	82.2 (81.8 – 82.5)	0.51
	Costa Rica	19.1 (16.8 – 21.5)	72.2 (70.4 – 73.9)	23.1 (20.4 – 25.9)	67.1 (65.3 – 68.8)	0.46
	India[1]	13.5 (7.9 – 22.1)	89.7 (86.8 – 92.1)	18.8 (11.1 – 30.0)	85.5 (82.3 – 88.3)	0.52
	Thailand (cohort)	0 (0 – 41)	7.1 (52.7 – 88.9)	0 (0 – 41)	74.1 (53.7 – 88.9)	0.37
	Thailand	62.5 (24.5 – 91.5)	27.2 (23.7 – 30.8)	1.1 (0.4 – 2.5)	98.3 (95 – 99.6)	0.45
	United Kingdom	17.7 (11.6 – 25.4)	86.3 (84.5 – 88)	9.6 (6.2 – 14.1)	92.7 (91.3 – 94)	0.52
15 – 39 years	Argentina	6.3 (6.2 – 6.4)	98.1 (98.1 – 98.1)	58.6 (57.9 – 59.4)	71.1 (71 – 71.2)	0.52
	Costa Rica	29.7 (28.9 – 30.4)	75.4 (74.7 – 76)	49.1 (48 – 50.2)	57.2 (56.6 – 57.9)	0.53
	India[1]	16.9 (15.8 – 18.0)	89.7 (89.3 – 90.3)	37.2 (35.1 – 39.3)	75.1 (74.4 – 75.8)	0.56
	Thailand (cohort)	28.6 (3.7 – 71)	85.9 (76.2 – 92.7)	15.4 (1.9 – 45.4)	93.1 (84.5 – 97.7)	0.57
	Thailand	43.2 (27.1 – 60.5)	45 (40 – 50.2)	7.1 (4.1 – 11.2)	89.1 (83.8 – 93.1)	0.44
	United Kingdom	33 (28.5 – 37.8)	92 (90.8 – 93.1)	43.3 (37.8 – 48.9)	88.2 (86.8 – 89.4)	0.63
40 – 64 years	Argentina	7 (6.8 – 7.1)	98.4 (98.3 – 98.4)	65.9 (65.1 – 66.8)	69.9 (69.7 – 70)	0.53
	Costa Rica	35.2 (34.2 – 36.2)	74.9 (74 – 75.8)	60 (58.6 – 61.3)	52 (51.1 – 52.9)	0.55
	India[1]	16.06 (14.22 – 18.09)	90.63 (89.6 – 91.6)	43.19 (39 – 47.5)	70.88 (69.5 – 72.3)	0.57
	Thailand (cohort)	37.5 (8.5 – 75.5)	80 (66.3 – 90)	23.1 (5 – 53.8)	88.9 (75.9 – 96.3)	0.59
	Thailand	64 (42.5 – 82)	46 (40.1 – 51.9)	9.4 (5.5 – 14.8)	93.6 (88.1 – 97)	0.55
	United Kingdom	35.8 (32.3 – 39.4)	93.6 (92.9 – 94.3)	44.5 (40.4 – 48.6)	91.1 (90.3 – 91.9)	0.65
>65 years	Argentina	6.2 (5.9 – 6.5)	98.5 (98.3 – 98.5)	64 (62.1 – 65.9)	70.1 (69.8 – 70.4)	0.52
	Costa Rica	29.8 (27.9 – 31.9)	76.4 (74.5 – 78.3)	56.4 (53.4 – 59.3)	51.6 (49.8 – 53.4)	0.53
	India[1]	16.5 (13.8 – 19.67)	89.07 (87.2 – 90.7)	42.37 (36.2 – 48.8)	68.65 (66.3 – 70.9)	0.56
	Thailand (cohort)	––	––	––	––	––
	Thailand	70 (34.8 – 93.3)	50.7 (42 – 59.4)	9.5 (3.9 – 18.5)	95.8 (88.3 – 99.1)	0.60
	United Kingdom	32.8 (27 – 39)	94.4 (93.4 – 95.4)	40.3 (33.5 – 47.4)	92.5 (91.3 – 93.5)	0.64

[1] INDIA – age groups (years): 0-4, 5-14,15-44, 45-59, 60+

Supplementary Table S3: ARI performance characteristics for COVID-19

	COUNTRY	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
All ages	Argentina	30.5 (30.3 – 30.6)	85.5 (85.4 – 85.6)	47.1 (46.9 – 47.3)	74.4 (74.3 – 74.5)	0.58
	Costa Rica	60.9 (60.3 – 61.5)	45.2 (44.6 – 45.8)	48.8 (48.2 – 49.3)	57.4 (56.8 – 58.1)	0.53
	India	67.8 (67.0 – 68.6)	22.8 (22.4 – 23.2)	26.86 (26.4 – 27.3)	63 (62.1 – 63.8)	0.45
	Thailand (cohort)	96 (79.6 – 99.9)	9.9 (5.8 – 15.6)	14.2 (9.3 – 20.4)	94.1 (71.3 – 99.9)	0.53
	United Kingdom	79.4 (77.3 – 81.4)	38 (37.1 – 38.9)	14.9 (14.2 – 15.7)	93.1 (92.3 – 93.8)	0.59
0 – 14 years	Argentina	23.5 (22.8 – 24.3)	82.8 (82.5 – 83.1)	23.1 (22.4 – 23.9)	83.1 (82.8 – 83.4)	0.53
	Costa Rica	37.3 (34.5 – 40.2)	51.8 (49.9 – 53.7)	25.3 (23.3 – 27.5)	65.4 (63.3 – 67.4)	0.45
	India[1]	65.5 (61– 69.9)	22.3 (20.9 – 24.2)	16.8 (15.1 – 18.6)	72.9 (69.1 – 76.5)	0.44
	Thailand (cohort)	100 (59 – 100)	11.1 (2.4 – 29.2)	22.6 (9.6 – 41.1)	100 (29.2 – 100)	0.56
	United Kingdom	70.8 (62.2 – 78.4)	24.7 (22.6 – 26.9)	7.2 (5.8 – 8.7)	91.1 (88 – 93.6)	0.48
15 – 39 years	Argentina	30.3 (30.1 – 30.6)	84.9 (84.8 – 85)	46.1 (45.8 – 46.4)	74.1 (74 – 74.2)	0.58
	Costa Rica	60.3 (59.5 – 61.2)	45.1 (44.4 – 45.9)	46.8 (46.1 – 47.6)	58.7 (57.9 – 59.5)	0.53
	India[1]	65.3 (64.2 – 66.3)	23.0 (22.4 – 23.5)	24.5 (24.0 – 25.1)	63.2 (62.1 – 64.3)	0.44
	Thailand (cohort)	85.7 (42.1 – 99.6)	11.5 (5.4 – 20.8)	8 (3 – 16.6)	90 (55.5 – 99.7)	0.49
	United Kingdom	80.1 (76 – 83.9)	34.3 (32.3 – 36.3)	18.4 (16.6 – 20.2)	90.3 (88.2 – 92.2)	0.57
40 – 64 years	Argentina	31.7 (31.4 – 32)	86.2 (86 – 86.3)	51.1 (50.7 – 51.5)	73.5 (73.3 – 73.6)	0.59
	Costa Rica	64.8 (63.7 – 65.8)	43.9 (42.8 – 45)	55.2 (54.2 – 56.2)	53.9 (52.7 – 55)	0.54
	India[1]	69.1 (67.5 – 70.7)	22.6 (21.52 – 23.6)	32.3 (31.25 – 33.5)	57.6 (55.64 – 59.7)	0.46
	Thailand (cohort)	100 (63.1 – 100)	6 (1.3 – 16.5)	14.5 (6.5 – 26.7)	100 (29.2 – 100)	0.53
	United Kingdom	80.3 (77.2 – 83.1)	42.9 (41.6 – 44.3)	16.7 (15.5 – 18)	93.9 (92.8 – 94.8)	0.62
>65 years	Argentina	28.8 (28.3 – 29.4)	89.1 (88.8 – 89.3)	54.2 (53.3 – 55)	73.6 (73.3 – 74)	0.59
	Costa Rica	61 (58.9 – 63.2)	42.4 (40.3 – 44.6)	52 (50 – 54)	51.6 (49.2 – 54)	0.52
	India[1]	75.5 (73.7 – 77.3)	20.6 (19.3 – 21.9)	35.1 (33.8 – 36.5)	59.6 (57– 62.3)	0.48
	Thailand (cohort)	100 (29.2 – 100)	16.7 (0.4 – 64.1)	37.5 (8.5 – 75.5)	100 (2.5 – 100)	0.58
	United Kingdom	80.2 (74.6 – 84.9)	39.9 (37.9 – 42)	13.2 (11.6 – 15.1)	94.6 (93 – 96)	0.60

[1] INDIA – age groups (years) 0-4, 5-14, 15-44, 45-59, 60+

Supplementary Table S4: SARI performance characteristics for COVID-19

	COUNTRY	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
All ages	Argentina	3.3 (3.2 – 3.3)	99.2 (99.2 – 99.2)	54.9 (53.9 – 55.8)	76.9 (76.8 – 77)	0.51
	Costa Rica	50.5 (49.2 – 51.8)	52.9 (51.5 – 54.3)	54.5 (53.1 – 55.9)	48.9 (47.5 – 50.2)	0.52
	India	33 (31.4 – 34.7)	67.9 (66.5 – 69.3)	43.1 (41.1 – 42)	58 (56.6 – 59.3)	0.50
	Thailand	37.1 (35.8 – 38.4)	77.7 (76.9 – 78.4)	43.6 (42.2 – 45.1)	72.6 (71.8 – 73.4)	0.58
	United Kingdom	62.2 (44.8 – 77.5)	31.3 (18.4 – 34.2)	3.2 (2 – 4.8)	95.8 (93 – 97.7)	0.47
0 – 14 years	Argentina	2.5 (2.1 – 2.9)	97.9 (97.8 – 98.1)	17.4 (15.1 – 19.8)	85.1 (84.8 – 85.4)	0.50
	Costa Rica	44.1 (41.2 – 47.2)	52 (48.6 – 55.5)	54.2 (50.8 – 57.5)	42 (39 – 45.1)	0.50
	India[1]	22.4 (13.1 – 34.2)	59.1 (53.4 – 64.6)	10.6 (6.1 – 16.9)	77.8 (71.9 – 82.9)	0.41
	Thailand	15.8 (10.2 – 23.6)	89.2 (86.5 – 91.4)	20.7 (13.5 – 30.4)	85.6 (82.7 – 88.0)	0.53
	United Kingdom	60 (14.7 – 94.7)	21.6 (17.9 – 25.7)	0.8 (0.2 – 2.4)	98 (93 – 99.8)	0.41
15 – 39 years	Argentina	2.3 (2.2 – 2.4)	99.5 (99.5 – 99.5)	57.1 (55.3 – 58.8)	77.1 (77 – 77.3)	0.51
	Costa Rica	60.7 (56.7 – 64.5)	38.5 (34.8 – 42.4)	48.5 (45 – 52.1)	50.6 (46.1 – 55.1)	0.50
	India[1]	34 (31.3 – 36.7)	69.2 (67.1 – 71.2)	39.6 (36.6 – 42.6)	63.8 (61.8 – 65.8)	0.52
	Thailand	34.5 (32.6 – 36.5)	80.2 (79.1 – 81.2)	40.7 (38.5 – 42.9)	75.7 (74.5 – 76.7)	0.58
	United Kingdom	50 (21.1 – 78.9)	51.6 (43.5 – 59.6)	7.3 (2.7 – 15.2)	93.1 (85.6 – 97.4)	0.51
40 – 64 years	Argentina	3.6 (3.5 – 3.8)	99.4 (99.3 – 99.4)	64.8 (63.2 – 66.4)	76 (75.9 – 76.2)	0.51
	Costa Rica	55.6 (53.5 – 57.7)	48.2 (45.7 – 50.7)	59.3 (57.1 – 61.4)	44.5 (42.1 – 46.9)	0.52
	India[1]	35.5 (32.8 – 38.2)	69.8 (67.2 – 72.3)	53.4 (49.9 – 56.8)	52.6 (50.2 – 55)	0.53
	Thailand	40.9 (38.4 – 43.4)	73.0 (71.2 – 74.7)	48.2 (45.4 – 50.9)	66.8 (64.9 – 68.6)	0.57
	United Kingdom	71.4 (41.9 – 91.6)	33.2 (26.5 – 40.3)	7.3 (3.6 – 13)	94 (85.4 – 98.3)	0.52
>65 years	Argentina	6.3 (6 – 6.7)	97.9 (97.8 – 98)	53.4 (51.4 – 55.4)	73.5 (73.2 – 73.8)	0.52
	Costa Rica	44.5 (42.2 – 46.9)	62.1 (59.8 – 64.2)	51.6 (49 – 54.1)	55.2 (53.1 – 57.3)	0.53
	India[1]	28.5 (25.3 – 31.8)	65.1 (61.7 – 68.3)	42.3 (37.9 – 46.7)	50.3 (47.3 – 53.3)	0.47
	Thailand	40.5 (38 – 43.1)	71.2 (69.3 – 73)	47.0 (44.3 – 49.8)	65.5 (63.6 – 67.3)	0.56
	United Kingdom	66.7 (22.3 – 95.7)	35.2 (28.8 – 42)	2.8 (0.8 – 7.1)	97.4 (90.9 – 99.7)	0.51

[1] INDIA – age groups (years) 0-4, 5-14, 15-44, 45-59, 60+

Annex 1. Minimum data set for integrated influenza/SARS-CoV-2 sentinel surveillance (adapted from WHOs Global epidemiological surveillance standards for influenza (8))

MINIMUM DATA SET

- Unique identifier (to link laboratory and epidemiological data, and for tracking patient if necessary)
- Patient name and contact information
- Date of form completion
- Sex
- Date of Birth
- Age in years
- Measured fever at admission/consultation
- History of fever in past ten days
- Date of symptom onset
- Date of first presentation to health care system
- Date of presentation to sentinel site
- Hospitalization status (yes/no; and indication of general ward vs. ICU admission)
- Date of hospitalization (for SARI patients)
- Date of specimen collection
- Type of specimen collected
- Pregnancy status and trimester
- Presence of chronic pre-existing medical illness(es):
  - chronic respiratory disease
  - asthma
  - cancer
  - cerebrovascular disease
  - chronic cardiac disease
  - chronic kidney disease
  - chronic neurological or neuromuscular disease
  - dementia
  - diabetes
  - hematologic disorders
  - hypertension
  - immunodeficiency, including human immunodeficiency virus (HIV)
  - mental disorders
  - obesity
- Exposure to influenza or SARS-CoV-2 antiviral medications in past 14 days, and name of medications
- COVID-19 vaccination status, including dates of each dose received in past year and manufacturer of COVID-19 vaccine received

Additional data to consider depending on the needs of the program include signs and symptoms of illness (including those specifically associated with SARS-CoV-2 or indications of pneumonia); smoking history; infection with HIV or Acquired Immune Deficiency Syndrome (AIDS) as a category separate from immunodeficiency; infection with tuberculosis and status of infection (i.e. latent or active); other infections that may be co-infections in a local context (e.g. malaria or dengue fever); height and weight (to determine body mass index); specific haematological disorders such as sickle cell disease or thalassemia major; belonging to a disadvantaged minority group; date of the current year's influenza vaccination; whether the patient received an influenza vaccine the previous year; and patient outcome in the hospital and/or at a later time point (death, survival).

Member States wishing to estimate the population-based burden of influenza or SARS-CoV-2 may have additional case definition, sample size or data collection requirements. These data are discussed further in the Global epidemiological surveillance standards for influenza (*8*) and the Manual for estimating disease burden associated with seasonal influenza (*57*).

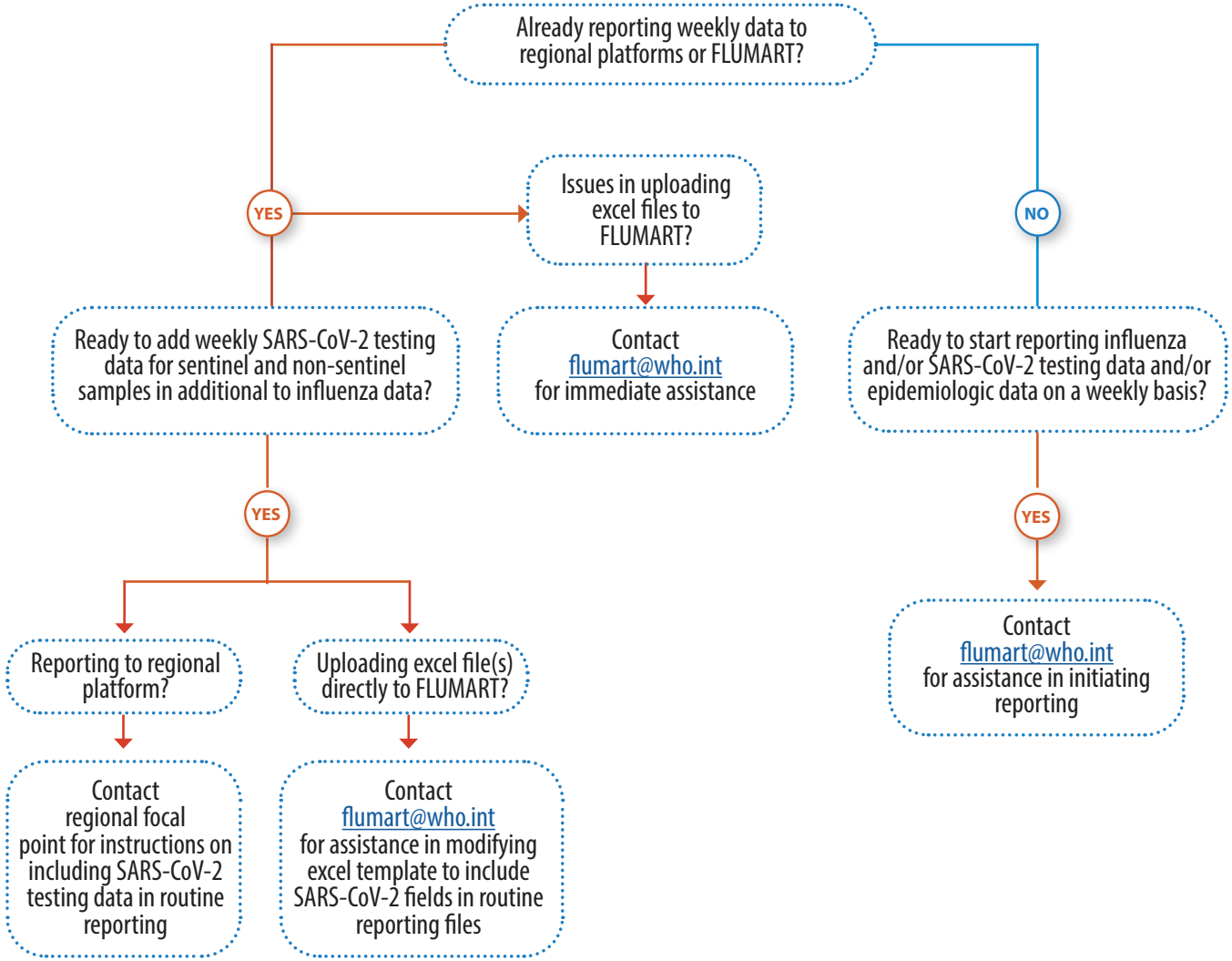
Annex 2. How and What to report

WHAT TO REPORT TO FLUMART (FluNet and/or FluID)

- Depending on the data collected in the country, the following data can be reported on a weekly basis:
  - number of samples tested for influenza (from sentinel sites)
  - number of samples tested for influenza (from non-sentinel sites)
  - number of samples tested for SARS-Cov2 (from sentinel sites)
  - number of samples tested for SARS-Cov2 (from non-sentinel sites)
  - number of samples positive for influenza, SARS-CoV2, RSV and other respiratory viruses if available (from sentinel sites)
  - number of samples positive for influenza, SARS-CoV2, RSV and other respiratory viruses if available (from non-sentinel sites)
  - number of co-infections from sentinel sites (please contact flumart@who.int for further instructions on reporting co-infections)
  - number of co-infections from non-sentinel sites (please contact flumart@who.int for further instructions on reporting co-infections).
  - data from ILI sentinel sites (outpatient facilities)
  - data from ARI sentinel sites (outpatient facilities)
  - data from SARI sentinel sites (inpatient facilities)
  - data from pneumonia sentinel sites (inpatient facilities)
  - mortality (all-cause mortality or pneumonia and influenza [PNI] mortality)
  - number of ILI specimens tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
  - number of ARI specimens tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
  - number of SARI specimens tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
  - number of pneumonia cases tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
  - number of ICU admissions tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
  - number of deaths among people tested for influenza, SARS-CoV-2, RSV and other respiratory viruses if available and number of those positive
- Any of the above can be done by age groups and gender, and the denominator can be reported either by population or by outpatient visits or inpatients.
- Comments: please note any changes to your case definition, sample collection, or other changes to your routine surveillance.
- The number of samples testing negative can also be reported.
- The number of specimens with an indeterminate result can also be reported if available.
- Comment field: Please note which specimens are being tested for SARS-CoV-2 (e.g. all specimens received for respiratory virus testing or only influenza-negative specimens or a subset of influenza-negative specimens) as this may change over time.

Annex 2. How and What to report

HOW TO REPORT TO FLUMART (FluNet and/or FluID)



Annex 3. Considerations for monitoring and evaluation (adapted from WHOs Global epidemiological surveillance standards for influenza (*8*))

PERFORMANCE CONSIDERATION	DESCRIPTION	EVALUATION CONSIDERATIONS	MONITORING INDICATORS
Accuracy	How well do sentinel surveillance data reflect the influenza or SARS-CoV-2 situation as reported in other surveillance systems?	Do the data being collected and reported reflect the true observed situation? Are numbers of ILI/ARI/SARI consultations/admissions abnormally low? Which of the systems best reflects the situation in the country? Are cases being counted appropriately and not being underreported? Are the case definition and sampling strategy consistently applied?	
Completeness	Monitoring the completeness of data is performed for both completeness of sites reporting and the completeness of data entered	Are case reporting forms filled out completely and entered into databases? Are there specific data elements that are most frequently left incomplete/blank? What percentage of sentinel sites continue to report syndromic surveillance data to national level at each reporting interval? What percentage of sentinel sites continue to collect and ship samples for symptomatic patients to the laboratory?	In addition to those listed in existing guidance and protocols, consider: • No. (%) of lab samples correctly identified as coming from sentinel, non-sentinel and unidentified sources? • No. (%) of influenza positive samples shared with WHO CCs? • No. (%) of sequenced samples with full epidemiological data • No. (%) of samples undergoing sequencing • No. (%) sequenced samples with whole genome data uploaded to GISAID or other publicly accessible database
Consistency	Changes that might represent either problems with reporting or a change in behaviour of the disease. Any sudden or unexpected change in the observed pattern of the data should be investigated.	Has the case definition for monitoring respiratory syndromes changed? Has the sampling strategy of patients meeting the case definition changed? How many of the sentinel sites have been reporting every week? Have there been changes in the number of samples received by the labs? Have there been changes in the number of samples processed by the labs? Are the numbers of ILI/ARI/SARI consultations/ admissions abnormally low? Have there been changes in health care seeking behaviour?	Look for aberrations in data compared to historical trends, considering time of year and other potential influencing factors. More guidance and protocols can be found in the references.

Annex 3. Considerations for monitoring and evaluation (adapted from WHOs Global epidemiological surveillance standards for influenza (*8*)) [continued]

PERFORMANCE CONSIDERATION	DESCRIPTION	EVALUATION CONSIDERATIONS	MONITORING INDICATORS
Timeliness	Describes the success of the programme in meeting targets for several different time intervals in the surveillance and reporting process.	Are data submitted, entered, analysed, and reported in a timely manner? Are laboratory specimens collected, tested and are the reports issued in a timely manner? Are specific data elements barriers to timely collection and reporting? How often does a site achieve its target for timeliness? What is the average number of days for each interval over time for each site? How frequently does the system report data to WHO systems and FluMart? Are data included in WHO weekly reports?	In addition to those listed in existing guidance and protocols, consider: • time from sample collection (or illness onset) to uploading of whole genome sequence data to database • time from sample collection (or illness onset) to reporting to those who need the output for actions (case managers, public health decision-makers, etc.).
Representativeness	This can give an indication if the surveillance system accurately describes the occurrence of disease over time and among the population under surveillance.	What proportion of the population or subnational units is covered by sentinel sites? Are specific risk or other population groups represented?	
Acceptability	This can give an indication of the acceptability and sustainability of the system to local stakeholders.	How do sentinel sites contribute and feel about the system? How do the national authorities contribute and feel about the system? Does the MOH own and operate this system? What is the contribution of external partners?	
Flexibility	This may give an indication of flexibility/agility with regard to adding new pathogens.	Has the system been used to monitor for SARS-CoV-2 during the pandemic and is it flexible enough to do so? Were additional pathogens monitored in the sentinel system prior to the pandemic? Why or why not? What would be involved in adding new data elements to monitor SARS-CoV-2 and influenza or other important pathogens to meet revised objectives in the future? How quickly has the system was responded to changes if SARS-CoV-2 or other respiratory viruses were included? What were the barriers to quickly adapting the system?	

Annex 3. Considerations for monitoring and evaluation (adapted from WHOs Global epidemiological surveillance standards for influenza (*8*)) [continued]

PERFORMANCE CONSIDERATION	DESCRIPTION	EVALUATION CONSIDERATIONS	MONITORING INDICATORS
Simplicity	This gives an indication of the structure and ease of operation of the surveillance system.	How is the surveillance system structured? What are the operational procedures? How do different reporting systems operate and how are they linked?	
Usefulness	This gives an indication of how the surveillance system contributes to improved understanding and response to the events under surveillance.	Can national stakeholders articulate how data are used to inform local situational awareness and policy decisions? Have data from the sentinel system been used to advocate for resources? Does the sentinel system play a supporting role to meet IHR core capacities? Do senior stakeholders in the MOH receive reports of sentinel data and trends? Do the sentinel sites receive feedback on the occurrence of disease in their area?	
Stability	This can give an indication of resilience in terms of continued functioning of the system in the face of difficulties.	How severe and long were any disruptions to sentinel surveillance systems? How severe and long were any disruptions to supplies at sentinel sites? How many/what percentage of sentinel sites continued functioning (collecting samples, transporting samples, reporting data)? How many/what percentage of sentinel sites lacked dedicated, trained person for enrolling patients and collecting samples? How many/what percentage of sentinel site staff changed in the course of one year?	
Context and policies from policy documents and surveys	These can be a useful for interpreting evaluation results.	Because of changes in health care delivery, are patients with respiratory symptoms: • referred to seek care at sites other than routine outpatient sites /general practitioners, and since when has this policy been in place? • admitted to designated COVID-19 hospitals as SARI patients? • referred to special screening centres (and since when has this policy been in place)? Have there been changes in health care-seeking behaviour? Have there been changes to sentinel sites and staff, and what proportion of sentinel sites and staff have been repurposed to COVID-19 response?	

Annex 3. Considerations for monitoring and evaluation (adapted from WHOs Global epidemiological surveillance standards for influenza (*8*)) [continued]

PERFORMANCE CONSIDERATION	DESCRIPTION	EVALUATION CONSIDERATIONS	MONITORING INDICATORS
Level of digitalization and IT infrastructure	These can be a useful for interpreting evaluation results.	System might be digitalized in different levels. Have there been improvements in the IT infrastructure for data collection and management and reporting that could be leveraged for sentinel syndromic surveillance?	
Systems and processes	This can be a useful for interpreting evaluation results.	Have there been changes to the systems and processes to collect and report data on ILI/ARI/SARI and lab results? How are the data aggregated and reported and to whom are they reported?	

Annex 4. Methods for the systematic review of the clinical symptoms of COVID-19

This review focused solely on existing systematic reviews on the clinical characteristics of COVID-19. Reviews were extacted from the collection of "clinical characteristics" indexed by the "COVID-19 evidence review" website (www.covid19reviews.org/index.cfm). The reviews were screened according to the eligibility criteria below.

INCLUSION CRITERIA

- Systematic review/rapid review that reported clinical features of polymerase chain reaction (PCR) or rapid diagnostic test (RDT) confirmed COVID-19 infection within the general population; AND
- Systematic reviews reporting the pooled estimate of the prevalence of clinical characteristics; AND
- Reviews added to the database from 19th August 2020 to 19th August 2021.

EXCLUSION CRITERIA

- Reviews not reporting a pooled estimate for clinical features or reporting non-specific clinical symptoms (e.g., gastrointestinal manifestations); OR
- Reviews not limiting their study population to PCR or RDT confirmed COVID-19 cases, OR
- Reviews focussing on sub-groups or patients with special medical conditions (e.g., patients with comorbidities, pregnant women, etc.); OR
- Non-systematic or narrative reviews; OR
- Reviews that focused on particular syndromes that may be sequelae of COVID-19 (e.g., Multisystem inflammatory syndrome in children (MIS-C), Guillain-Barre syndrome and acute respiratory distress syndrome); OR
- Studies published in languages other than English

Annex 5: Results of quality assessment of reviews included in the systematic review of clinical characteristics of COVID-19

					①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	
AUTHOR (YEAR)	**No. of studies included**	**PRISMA guidelines adhered**	**Publication bias**	**Quality of studies assessed**	**Is the review question clearly and explicitly stated?**	**Were the inclusion criteria appropriate for the review question?**	**Was the search strategy appropriate?**	**Were the sources and resources used to search for studies adequate?**	**Were the criteria for appraising studies appropriate?**	**Was critical appraisal conducted by two or more reviewers?**	**Were there methods to minimize errors in data extraction?**	**Were the methods used to combine studies?**	**Was the likelihood of publication bias assessed?**	**Were recommendations for policy and/or practice supported by the reported data?**	**Were the specific directives for new research appropriate?**	**Total (yes)**
Akin,2020	44	Not stated	Not stated	Not stated	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	7
Aziz M 2021	83	Yes	Assessed - funnel plot - Egger's regression test	Assessed - QUIPS tool	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	7
Badal S; 2020	20	Yes	Assessed - funnel plot - Egger's regression test	Assessed - New Castle Ottawa scale	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Christophers B; 2020	22	Yes	Not stated	Assessed - Oxford Evidence based Medicine Schema	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	7
Chua TH;2020	48	Yes	Not stated	Not stated	Yes	Yes	No	No	No	No	No	Yes	No	No	No	3
Gaythorpe 2021	29	Yes	Assessed - funnel plot - Egger's regression test	Assessed - NIH quality assessment tool for observational cohort and cross-sectional studies	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	6
Ghimire S;2021	38	Yes	Assessed - funnel plot - Egger's regression test	Assessed - Tool not stated	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	7
Hasani H; 2020	30	Yes	Assessed - funnel plot - Egger's regression test	Assessed - Modified Appraisal tool for cross sectional studies (AXIS)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	9
Hashan MR 2021	49	Yes	Assessed - funnel plot - Egger's regression test	Assessed - Meta Quality Appraisal Tool (MetaQAT)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11

Annex 5: Results of quality assessment of reviews included in the systematic review of clinical characteristics of COVID-19

					①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪	
AUTHOR (YEAR)	**No. of studies included**	**PRISMA guidelines adhered**	**Publication bias**	**Quality of studies assessed**	**Is the review question clearly and explicitly stated?**	**Were the inclusion criteria appropriate for the review question?**	**Was the search strategy appropriate?**	**Were the sources and resources used to search for studies adequate?**	**Were the criteria for appraising studies appropriate?**	**Was critical appraisal conducted by two or more reviewers?**	**Were there methods to minimize errors in data extraction?**	**Were the methods used to combine studies?**	**Was the likelihood of publication bias assessed?**	**Were recommendations for policy and/or practice supported by the reported data?**	**Were the specific directives for new research appropriate?**	**Total (yes)**
Kim H;2021	80	Yes	Assessed - Egger's regression test	Assessed - Hayden tool - Egger's regression test	Yes	Yes	Yes	Yes	Yes	Yes	**No**	Yes	Yes	**No**	Yes	9
Mutiawati E; 2021a	107	Yes	Assessed - funnel plot - Egger's regression test	Assessed - New Castle Ottawa scale	Yes	Yes	Yes	Yes	Yes	**No**	**No**	Yes	Yes	**No**	**No**	7
Mutiawati E 2021b	78	Yes	Assessed - funnel plot - Egger's regression test	Assessed - New Castle Ottawa scale	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Syangtan G; 2021	16	Yes	Assessed - funnel plot - Egger's regression test	Assessed - New Castle Ottawa scale	Yes	Yes	Yes	Yes	Yes	Yes	**No**	Yes	Yes	Yes	NA	9
Xie J;2021	90	Yes	Assessed - Begg's test	Assessed - Methodological Index for Non-Randomized Studies (MINORS)	Yes	Yes	**No**	Yes	Unclear	Yes	Yes	Yes	Yes	**No**	Unclear	7

World Health Organization

Avenue Appia 20
1211 Geneva 27
Switzerland
www.who.int

influenza@who.int

31 JANUARY 2022