World Health Organization

# Terms of Reference for National Influenza Centers of the Global Influenza Surveillance and Response System

## Introduction

The National Influenza Centers (NICs)[1] together with the World Health Organization (WHO) Collaborating Centres for Influenza (WHO CCs)[2], WHO Essential Regulatory Laboratories (ERLs) and H5 Reference Laboratories form the Global Influenza Surveillance and Response System (GISRS) coordinated by the WHO Global Influenza Program (GIP).

WHO GISRS, previously known as the Global Influenza Surveillance Network (GISN) until 2011, was established in 1952. It has been, and is, the primary global mechanism and resource for surveillance and control of influenza. GISN was renamed as GISRS after adoption of resolution WHA64.5 by the Sixty-fourth World Health Assembly in May 2011[3]. The GISRS network continuously monitors the evolution of influenza viruses around the world in the interest of public health, conducts risk assessment and recommends risk management measures. GISRS functions through efficient sharing of influenza viruses and surveillance information, provision of technical support and updated reagents by and to GISRS members, as endorsed by national authorities of host countries of GISRS institutions. The function of GISRS is coordinated by the GIP across the three levels of WHO: headquarters, regional offices and country offices.

NICs are national institutions authorized and designated by their national health ministry and subsequently recognized by WHO for the purpose of participating in the work of GISRS under the applicable WHO terms of reference (ToRs). A NIC may have additional obligations under the national authority of its host country.

## General conditions

*National Influenza Centres:*

- serve as a reference laboratory for influenza in their country;
- serve as a technical resource on influenza-related matters for their national authority;
- serve as a key point of contact to WHO on issues related to influenza in their country;
- adhere to their national and/or international biosafety standards for work with influenza viruses,
- adhere to national and international regulations on the transport of dangerous goods (Class/division 6.2)[4] when shipping clinical specimens and/or virus isolates,
- meet quality requirements of national or international quality standards, as applicable, and participate in external quality assessment programmes (EQAP) provided by WHO to GISRS, and
- maintain a high level of technical proficiency by participating in training provided by GISRS.

[1] http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/list/en/
[2] http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/
[3] http://apps.who.int/gb/ebwha/pdf_files/WHA64-REC1/A64_REC1-en.pdf
[4] http://www.who.int/ihr/capacity-strengthening/infectious-substances/en/

**As part of GISRS, NICs may handle influenza viruses belonging to three categories:**

**Category 1:** human seasonal influenza viruses;

**Category 2:** influenza viruses with human pandemic potential and, therefore, classified as "PIP biological materials" (PIP BM)[5]; and

**Category 3:** other influenza viruses from animal or environmental specimens that are not classified as "human seasonal influenza viruses" or PIP BM.

## When working with human seasonal influenza viruses (Category 1)

- NICs collect influenza viruses either through an established network of physicians, health care centers or other sentinel sites, and/or they solicit influenza virus-positive samples from laboratories providing diagnostic services. Patients included in the surveillance should preferably meet the syndromic case definition of influenza-like illness (ILI)[6], acute respiratory infection (ARI) or severe acute respiratory infection (SARI). If possible, patients of all age groups should be represented in the surveillance system.
- According to available resources, NICs identify influenza viruses by molecular detection methods and/or virus culture and/or immunological methods.
- NICs differentiate between influenza A and influenza B viruses and attempt to identify the subtype of influenza A viruses and the lineage of influenza B viruses. To be assisted in this, NICs can obtain updated reagents from WHO CCs of GISRS.
- Influenza A viruses that cannot be typed or subtyped with updated reagents from the WHO CCs of GISRS, including those without clear-cut results, must be immediately sent to a WHO CC of GISRS.
- NICs report unusual or novel influenza viruses to their national authority according to the domestic and international rules and regulations including the International Health Regulations (IHR) (2005).[7]
- NICs report timely[8], defined virological surveillance information either directly to WHO's FluNet platform[9] or indirectly to a regional platform for uploading into WHO's FluNet platform. Other epidemiological information, if available, is reported to WHO's FluID platform[10] either by the NIC or another focal point as designated by the host country. Reporting should be done weekly during the months when seasonal influenza is commonly observed, but preferably throughout the year.

[5] "PIP biological materials", for the purposes of this Framework (and its annexed Standard Material Transfer Agreements (SMTAs) and terms of reference (TORs)) and the Influenza Virus Tracking Mechanism (IVTM), includes human clinical specimens, virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment. Also included in "PIP biological materials" are RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes.

[6] http://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1

[7] http://www.who.int/ihr/publications/9789241580496/en/

[8] Results for the previous week should be reported the following week by Thursday 12:00 UTC even if incomplete. Already submitted results should be updated when more detailed results, e.g. subtype detection become available.

[9] http://www.who.int/flunet

[10] http://www.who.int/influenza/surveillance_monitoring/fluid/en/

- NICs are required to send representative seasonal influenza virus isolates and/or clinical specimens to one or more WHO CCs of GISRS of their choice[11]. However, it is important to note that the same viruses should not be sent to multiple WHO CCs. Together with the biological material, NICs should also provide associated available virological, clinical and epidemiological background information and if available, also sequence data.
- Shipments should be timed to provide WHO CCs with the most recently circulating viruses for further characterizations to inform decisions made at twice yearly vaccine composition recommendation meetings, according to relevant WHO guidance materials on selecting and shipping of seasonal influenza viruses to WHO CCs of GISRS[12].
- NICs immediately report to their national authorities and to WHO any observation of unusual influenza activity in their country.

## When working with influenza viruses that are "PIP biological materials" (Category 2)

Terms of Reference are described in Annex 5 of the PIP Framework[13] (reproduced in **Annex 1**). NICs share Influenza Viruses of Pandemic Potential (IVPP) according to relevant WHO guidance materials[14].

## When working with other influenza viruses from animal or environmental specimens that are not classified as "human seasonal influenza viruses" or PIP BM (Category 3)

Occasionally, NICs may receive influenza viruses that do not fall in the categories of human seasonal viruses or PIP BM; for example, viruses from animal or environmental specimens.

- NICs follow applicable national and/or international biosafety requirements to avoid cross-contamination with viruses of human origin. Such material should preferably be handled in facilities away from those where human specimens and viruses are investigated.
- NICs share virus samples with WHO CCs of GISRS of their choice to support GISRS risk assessment following national and international rules and regulations. It is the responsibility of the NICs to ensure that appropriate permits and other national/international documents and approvals are in place to facilitate virus-sharing.

[11] http://www.who.int/influenza/gisrs_laboratory/logistic_activities/en/
[12] http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/NIC_virus_sharing_guidance_20171103.pdf?ua=1
[13] http://www.who.int/influenza/resources/pip_framework/en/
[14] http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/IVPP_Sharing_Guidance_20171103.pdf?ua=1

**Annex 1.** Extract (pp 49-52) from Annex 5 of the Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits: National Influenza Centres, Terms of Reference related to work with Pandemic Influenza Preparedness Biological Materials[15]

## National Influenza Centres

### Terms of Reference related to work with Pandemic Influenza Preparedness biological materials

#### Background

The WHO global influenza surveillance and response system (GISRS) serves as a global alert mechanism for the emergence of influenza viruses with important features, including those with pandemic potential. For activities related to pandemic influenza, the WHO GISRS includes four complementary categories of institutions and laboratories: National Influenza Centres, WHO Collaborating Centres, WHO H5 Reference Laboratories and Essential Regulatory Laboratories. The WHO GISRS is coordinated by the WHO Global Influenza Programme. Within each category all institutions and laboratories perform functions defined by core terms of reference. Each laboratory or institution that is formally recognized or designated as a part of the WHO GISRS by WHO has accepted to be bound by the core terms of reference applicable to its category. The following are the core terms of reference applicable to the National Influenza Centres.

National Influenza Centres play a key role in pandemic influenza risk assessment by alerting WHO immediately to outbreaks of H5N1 or other influenza viruses with pandemic potential. National Influenza Centres collect specimens from suspected cases of H5N1 or other unusual influenza viral infection, perform laboratory diagnosis and analysis, and ship in a timely manner, such specimens or viruses isolated from them, to a WHO Collaborating Centre or H5 Reference Laboratory for advanced virological analysis. Efficient pandemic influenza risk assessment and risk response are based on collective efforts from all WHO GISRS members through rapid exchange of biological materials, reference reagents, epidemiologic data and other information.

It is understood that the Guiding Principles, as agreed by the Intergovernmental Meeting and reproduced below, will guide all activities, specific terms of reference or associated functions of the WHO GISRS laboratories when they act in their capacity as a WHO GISRS laboratory. The terms of reference for all WHO GISRS laboratories have been developed under the following overarching Guiding Principles:



[15] http://apps.who.int/iris/bitstream/10665/44796/1/9789241503082_eng.pdf

## Guiding Principles for the development of terms of reference for current and potential future WHO global influenza surveillance and response system (GISRS) laboratories for H5N1 and other human pandemic influenza viruses

1. All activities conducted by WHO GISRS laboratories under their WHO terms of reference will be consistent with the Framework and the Standard Material Transfer Agreement.*
2. The WHO GISRS laboratories will be coordinated by, and provide support to, WHO.
3. The WHO GISRS laboratories will provide a timely summary report of laboratory analyses and on request any other available information on tests conducted, test results and associated risk assessment and risk response as is specified in their terms of reference.
4. The WHO GISRS laboratories will share experience and provide capacity strengthening support to WHO Member States within their resources where necessary.
5. The WHO GISRS laboratories will provide support as specified in their terms of reference for the development of potential pandemic vaccine, pandemic vaccine, diagnostic test materials and pharmaceuticals.
6. If WHO GISRS laboratories conduct research on influenza viruses received for public health surveillance purposes, they will do so in a manner that includes participation of scientists, to the fullest extent possible, from the submitting National Influenza Centre or other authorized laboratory, especially those from developing countries, including through the publication process.
7. The WHO GISRS laboratories will support global public health preparedness and response, especially for urgent situations including international outbreaks and epidemics.
8. The WHO GISRS laboratories will share in a rapid, systematic and timely manner PIP biological materials, using the Influenza Virus Traceability Mechanism as appropriate, including distribution to other qualified laboratories, to facilitate public health risk assessment, risk response activities and scientific research in accordance with the Standard Material Transfer Agreement.*
9. The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.*
10. The originating laboratories which provide the PIP biological materials received by the WHO GISRS laboratories will be given due credit and recognition.

* Editor's note: the reference to "Standard Material Transfer Agreement" is understood to mean "Standard Material Transfer Agreement 1".

## Core terms of reference

National Influenza Centres are laboratories that fulfil the terms of reference listed below. A National Influenza Centre is formally designated by the health ministry of the country concerned and is recognized by WHO. A National Influenza Centre may have additional obligations under the authority of its ministry of health.

### *A. General conditions and activities*

National Influenza Centres:

1. work under the coordination of the WHO Global Influenza Programme and provide support to WHO (Guiding Principles 2, 7);
2. use the WHO Influenza Virus Traceability Mechanism to record the receipt and transfer of PIP biological materials (Guiding Principle 8);
3. comply with the Standard Material Transfer Agreement* of the Pandemic Influenza Preparedness Framework for sharing of influenza viruses and access to vaccines and other benefits (Guiding Principle 1);
4. serve as a key point of contact between WHO and the country of the National Influenza Centre on issues related to surveillance, laboratory diagnosis, and sharing of clinical specimens and/or influenza viruses with pandemic potential, as well as sharing of important related clinical or epidemiological information, when available, with WHO (Guiding Principles 2, 3, 4, 7, 8);
5. participate actively in WHO pandemic influenza surveillance activities and maintain active communication and collaboration with other members of the WHO GISRS (Guiding Principles 4, 7, 8).

### *B. Laboratory and related activities*

National Influenza Centres:

1. collect or process as appropriate clinical specimens from patients suspected to be infected with H5N1 and other influenza viruses with pandemic potential (Guiding Principle 7);
2. act as a collection point for virus isolates of suspected pandemic influenza from laboratories within the country;
3. conduct testing of clinical specimens for influenza viruses and detect influenza viruses that cannot be readily identified with diagnostic reagents provided through the WHO GISRS;
4. ship, within one week, clinical specimens and/or viruses that cannot be readily identified with diagnostic reagents provided through the WHO GISRS to

* Editor's note: the reference to "Standard Material Transfer Agreement" is understood to mean "Standard Material Transfer Agreement 1".

a WHO Collaborating Centre or H5 Reference Laboratory of their choice and include the date the specimen was collected and relevant geographical, epidemiological and clinical information (Guiding Principles 2, 3, 5, 7, 8);

5. attend laboratory training courses provided by the WHO Collaborating Centres in an effort to establish and maintain capacity to recognize influenza viruses that cannot be readily identified (Guiding Principle 4);

6. review, maintain and strengthen influenza surveillance in the country (Guiding Principle 2);

7. provide technical advice and support to other influenza laboratories in the country on specimen collection and shipment logistics, laboratory biosafety and other operational procedures related to influenza surveillance (Guiding Principles 2, 7).

### C. Information and communication

National Influenza Centres:

1. alert WHO immediately when influenza viruses are detected that cannot be readily identified with diagnostic reagents provided through the WHO GISRS or when unusual outbreaks of nonseasonal influenza or influenza-like illness emerge;

2. provide national authorities and the general public with information on H5N1 and other influenza viruses with pandemic potential circulating in the country in a timely manner.

### D. Research, scientific presentations and publications

National Influenza Centres:

1. actively seek the participation of scientists from originating laboratories/countries in scientific projects associated with research on clinical specimens and/or influenza viruses from their countries and actively engage them in preparation of manuscripts for presentation and publication (Guiding Principle 6);

2. appropriately acknowledge in presentations and publications, the contributions of collaborators, including laboratories/countries providing clinical specimens or influenza viruses with pandemic potential or reagents, using guidelines such as those outlined by the International Committee of Medical Journal Editors[1] (Guiding Principle 6).

[1] See http://www.icmje.org/