Terms of Reference for National Influenza Centers and GISRS

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Objectives:

- To review the history and function of GISRS
- To describe the Terms of Reference for National Influenza Centers
Global influenza virus surveillance has been conducted through the WHO Global Influenza Surveillance and Response System (GISRS) for over half a century.

- Global Influenza Surveillance Network (GISN) was established in 1952
- GISN was renamed GISRS in 2011

Robust laboratory diagnostics and timely surveillance are essential for the early detection of:
- the continuous evolution of influenza viruses
- the pandemic potential of non-seasonal influenza viruses
The laboratory network comprises:

- **6 WHO Collaborating Centres** (CCs),
- **4 Essential Regulatory Laboratories** and
- **143 institutions** in **113** WHO Member States recognized by WHO as National Influenza Centres (NICs).
- **ad hoc groups** set up to address specific emerging issues
Function of GISRS

- monitors seasonal and zoonotic influenza worldwide

Specimen transport and virus sharing
  - Workshops for handling infectious substances
  - Shipment fund project

Providing electronic platforms for information gathering and sharing

shares influenza viruses for consideration for seasonal and pandemic vaccines

provides surveillance information
  - ILI and SARI sentinel surveillance
    - Early warning
    - Investigation and risk assessment guidance.
    - recommends risk management measures
Function of GISRS

Reporting and information dissemination

- FluNet: real time lab data sharing since 1997
- FluID: real time epi data sharing since 2010
- GISRS Information Centre: EzCollab

![Global circulation of influenza viruses](image_url)
Function of GISRS

- provides technical support and reagents-
  - RT- PCR Expert WG
  - Antiviral Susceptibility Surveillance Expert WG

- enhances pandemic influenza preparedness
  - supports the Pandemic Influenza Preparedness (PIP) Framework

- supports capacity building

- Implements and monitors quality assurance
  - Influenza EQA Project for detecting influenza viruses by PCR
The Terms of Reference for NICs
(overview)

- **Definition:**
  - NIC
  - Categories of viruses

- **General conditions for NICs**
  - Work with human seasonal influenza viruses (Category 1)
  - Work with influenza viruses that are “PIP biological materials” (Category 2)
  - Work with other influenza viruses from animal or environmental specimens that are not classified as “human seasonal influenza viruses” or PIP BM. (Category 3)

- **Core terms of reference**
  - A. General conditions and activities
  - B. Laboratory and related activities
  - C. Information and communication
  - D. Research, scientific presentations and publications
General requirements for NICs

- NICs serve as:
  - a **reference laboratory** for influenza in their country;
  - a **technical resource** on influenza-related matters for their Ministry of Health.
  - a **key point of contact to the WHO** on issues related to the prevailing influenza situation in their country.
  - NICs also **adhere to their national and international biosafety regulations** for work with influenza viruses.
General requirements for NICs (continued)

- NICs meet quality requirements of national or international quality standards and participate in Quality Assurance Programmes provided by WHO.

- maintain a high level of technical proficiency by participating in training provided by GISRS.

- 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.
Three categories of viruses handled by NICs

- **Category 1**: Human seasonal influenza viruses
- **Category 2**: Influenza viruses with human pandemic potential and therefore are classified as “PIP biological materials” BM
- **Category 3**: other influenza viruses from animal or environmental specimens that are not classified as “human seasonal influenza viruses” or PIP BM.
Work with human seasonal influenza viruses (Category 1)

- NICs collect influenza viruses;
  - 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 should preferably meet the syndromic case definition of influenza-like illness (ILI), acute respiratory infection (ARI) or severe acute respiratory infection (SARI).

- If possible, patients of all age groups should be represented in the surveillance system.

- NICs identify influenza viruses by;
  - molecular detection methods,
  - virus culture (encouraged) and
  - immunological methods.

- NICs differentiate between influenza A and influenza B and
  - attempt to identify the subtype of influenza A viruses and
  - the lineage of influenza B viruses.

- updated reagents are available from the WHO CCs of GISRS.

- Influenza A viruses – untypable and viruses without clear-cut results must be immediately sent to a WHO CC of GISRS.
Work with human seasonal influenza viruses (Category 1) (continued)

- NICs report unusual or new viruses to their national authority according to the domestic and international rules and regulations including the International Health Regulations (IHR) (2005).

- NICs report to the WHO FluNet platform via regional platforms on:
  - the number of clinical specimens tested for influenza
  - the number of influenza-positive specimens
  - geographic spread of influenza and epidemiological information, if available, reported to the FluID platform.
  - Weekly reporting during the months when seasonal influenza is commonly observed, but preferably throughout the year.

- 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.
  - The SAME viruses should NOT be sent to multiple WHO CCs.
  - also provide 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 detailed characterizations to inform decisions made at twice yearly vaccine composition recommendation meetings.
Work with influenza viruses that are “PIP biological materials” (Category 2)

- **Category 2:** Influenza viruses with human pandemic potential and therefore are classified as “PIP biological materials” BM

- Terms of Reference are endorsed by the WHA 64.5 (Annex 1) and are described in Annex 5 of the PIP Framework\(^1\,\!\!^2\)

1. [http://apps.who.int/iris/bitstream/10665/44867/1/9789243503080 spa.pdf](http://apps.who.int/iris/bitstream/10665/44867/1/9789243503080 spa.pdf)
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
A. General conditions and activities (NICSs)

- NICs work under the coordination of the WHO Global Influenza Programme and provide support to WHO (Guiding Principles 2, 7);

- NICs use the WHO Influenza Virus Traceability Mechanism (IVTM) to record the receipt and transfer of PIP biological materials (Guiding Principle 8);

Special conditions for work with Category 2 viruses

- NICs 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);

- NICs serve as a key point of contact between WHO and the country of the NIC
  - 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);

- NICs 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 (NICs)

- NICs 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);

- NICs act as a collection point for virus isolates of suspected pandemic influenza from laboratories within the country;

- NICs 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;

- NICs ship, within one week, clinical specimens and/or viruses that cannot be readily identified with diagnostic reagents provided through the WHO GISRS to
  - 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);
B. Laboratory and related activities (continued)

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

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

- NICs 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 (NICs)

- NICs 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 non-seasonal influenza or influenza-like illness emerge;

- NICs 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 (NICs)

- NICs 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);

- NICs 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 (Guiding Principle 6).
Summary

- GISRS is the key laboratory network for global influenza surveillance
- National Influenza Centres are a primary component of GISRS
- Revised Terms of Reference will facilitate standardization and the continued improvements in the quality and function of GISRS
- Continued strong epi and virology surveillance to respond quickly to outbreaks is needed
- Global surveillance has strengthened over recent years
  - Continued implementation of guidelines and the development of strategic plans will address gaps identified
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- WHO Regional Offices
4.1 Pandemic influenza preparedness biological materials or PIP biological materials

“PIP biological materials”,¹ 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,² 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 GISSRS 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.¹
5.4 Standard Material Transfer Agreements

5.4.1 The Standard Material Transfer Agreement 1 (SMTA 1) in Annex 1 will be used to cover all transfers of PIP biological materials within the WHO GISRS for the duration of its applicability.

5.4.2 The Director-General will, using the Standard Material Transfer Agreement 2 (SMTA 2) in Annex 2, enter into agreements with entities outside the WHO GISRS. Such agreements will cover all transfers of PIP biological materials to recipients for their duration.
The PIP Benefit Sharing System will operate to:

(i) provide pandemic surveillance and risk assessment and early warning information and services to all countries;

(ii) provide benefits, including, where appropriate, capacity building in pandemic surveillance, risk assessment, and early warning information and services to Member States.

(iii) prioritize important benefits, such as and including antiviral medicines and vaccines against H5N1 and other influenza viruses with human pandemic potential as high priorities, to developing countries, particularly affected countries, according to public health risk and needs and particularly where those countries do not have their own capacity to produce or access influenza vaccines, diagnostics and pharmaceuticals. Prioritization will be based on assessment of public health risk and need, by experts with transparent guidelines;

(iv) build capacity in receiving countries over time for and through technical assistance and transfer of technology, skills and know-how and expanded influenza vaccine production, tailored to their public health risk and needs.
Article 4. Rights and obligations of the Provider

4.1 The Provider undertakes the following with respect to the Materials:

4.1.1. To comply with its respective WHO global influenza surveillance and response system (GISRS) terms of reference.

4.1.2. To ensure that the Materials are handled in accordance with applicable WHO guidelines and national bio-safety standards.¹

4.2. The Provider agrees to the onward transfer and use of the Materials, to all members of the WHO GISRS, on the same terms and conditions as those provided in Standard Material Transfer Agreement within the WHO GISRS (SMTA 1).

4.3 The Provider consents to the onward transfer and use of the Materials to entities outside the WHO GISRS on the condition that the prospective recipient has concluded a Standard Material Transfer Agreement outside the WHO GISRS (SMTA 2).

4.4 The Provider shall inform the WHO of shipments of Materials to entities inside/outside the WHO GISRS by recording in the Influenza Virus Tracking Mechanism (IVTM).
Article 5. Rights and obligations of the Recipient

5.1 The Recipient undertakes the following with respect to the Materials:

5.1.1 To comply with its respective WHO GISRS terms of reference.

5.1.2 To ensure that the Materials are handled in accordance with applicable WHO guidelines and national bio-safety standards.

5.1.3 To inform WHO of shipments of Materials to entities inside/outside the WHO GISRS by recording in the IVTM.

5.1.4 In the event of further transfers within the WHO GISRS, to do so in accordance with SMTA 1.

5.2 The Recipient shall actively seek the participation of scientists to the fullest extent possible from originating laboratories and other authorized laborato-
Article 10. Acceptance and Applicability

10.1 Recipients or Providers in the WHO GISRS at the time of the adoption of the Framework by the World Health Assembly: Acceptance by such laboratories of their WHO terms of reference, as contained in the Framework, constitutes acceptance of SMTA 1.

10.2 Recipients or Providers that join the WHO GISRS after adoption of the Framework by the World Health Assembly: Acceptance of designation or recognition by WHO to become a WHO GISRS laboratory will constitute acceptance of SMTA 1.

10.3 Applicability: SMTA 1 shall cease to be applicable only upon suspension or revocation of designation or recognition by WHO or upon formal withdrawal by the laboratory of its participation in the WHO GISRS or upon mutual agreement of the WHO and the laboratory. Such a suspension, revocation or withdrawal shall not relieve a laboratory of pre-existing obligations under SMTA 1.