Operational Guidance on Sharing Seasonal Influenza viruses with WHO Collaborating Centres (CCs) under the Global Influenza Surveillance and Response System (GISRS)

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ABBREVIATIONS

ARI	Acute Respiratory Infections
CC	Collaborating Centre of GISRS
CDC	Centers for Disease Control and Prevention
Ct	Cycle Threshold
GIP	WHO Global Influenza Programme
GISRS	Global Influenza Surveillance and Response System
ILI	Influenza-Like Illness
NIC	National Influenza Centre of GISRS
(PIP)	Framework Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
VCM	Vaccine Consultation Meeting
WHO	World Health Organization

Introduction

One of the critical roles of National Influenza Centres (NICs) within the Global Influenza Surveillance and Response System (GISRS) is to share seasonal influenza viruses in a timely manner with one of the WHO Collaborating Centres[1] for Reference and Research on Influenza (WHO CCs) in Atlanta (United States), Beijing (China), London (United Kingdom), Melbourne (Australia) or Tokyo (Japan) (**Annex 1**).

NICs receive clinical specimens collected from patients with influenza-like illness (ILI) or severe acute respiratory infections (SARI) and perform initial identification for the presence of influenza virus and subsequently attempt virus isolation. NICs are expected to select a subset of representative influenza virus-positive specimens or virus isolates to share with WHO CCs, where detailed antigenic and genetic characterization of the viruses is conducted. Any unsubtypeable influenza viruses associated with human infection should also be shared with WHO CCs.

The importance of sharing seasonal influenza viruses

The objectives of virus-sharing with the WHO CCs of GISRS are to:

1. monitor the evolution of influenza viruses to inform epidemic risk assessment associated with evolving strains;
2. make recommendations on the composition of influenza vaccines for use in the relevant subsequent season;
3. assess and monitor antiviral drug susceptibility and adjust risk measures;
4. update diagnostic reagents and protocols for global virus detection; and
5. maintain and strengthen global virus surveillance and response capacity for emergencies, including pandemic response.

Timeliness is critical with regards influenza virus-sharing.

Current vaccines, being the primary intervention to reduce morbidity and mortality of influenza, have to be updated in a timely manner in order to be effective. WHO issues biannual vaccine composition recommendations through vaccine consultation meetings (VCMs). These recommendations are used by the national vaccine regulatory agencies and pharmaceutical companies to develop, produce and license influenza vaccines. These WHO meetings, discussing the composition of influenza vaccines, are held from February to March and September to October for use in the northern and southern hemisphere influenza season respectively. **Timely** sharing of seasonal influenza virus-positive specimens and/or seasonal influenza virus isolates with a WHO CC under GISRS is essential so that data can be derived from viruses in time to be

[1] http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/

fully utilized in these biannual VCMs to contribute to the selection of best suitable candidate viruses for use in vaccine development.

Immediate sharing of any unsubtypeable viruses with a WHO CC will help the rapid identification of any emerging influenza viruses, assess associated risk and guide risk mitigation measures in a timely fashion.

Selecting influenza virus-positive specimens and/or virus isolates for shipping to a WHO CC under GISRS (Annex 2)

Ideally, up to 40 influenza virus-positive clinical specimens or virus isolates representing different types/subtypes or lineages of circulating viruses, collected within 4-8 weeks prior to shipping, should be selected per shipment. At least **two shipments** per year are **required**, and four shipments per year are encouraged.

Should virus isolates, influenza virus-positive clinical specimens, or both be submitted?

1. NICs are encouraged to perform virus culture, but this is not routinely performed in many NICs. Therefore, influenza virus-positive clinical specimens should be submitted to a WHO CC.

2. If NICs do perform virus culture, it is valuable to ship both the virus isolates and their respective clinical specimens (i.e. isolate and specimen pairs).

3. The reasons for this are that:
    a. the provision of influenza virus-positive clinical specimens assists WHO CCs in isolating viruses in tissue culture for antigenic and genetic characterizations, and in attempting isolation of viruses in embryonated hen's eggs or qualified cell cultures, thereby generating egg isolates or qualified cell isolates that could potentially be used as vaccine seed strains;
    b. the provision of virus isolates increases the likelihood of WHO CCs culturing the virus further, as virus culture is not always successful from influenza virus-positive clinical specimens; and
    c. if NICs are having difficulty isolating certain viruses (e.g. A(H3N2)), sharing of the influenza-positive clinical specimen enables genetic characterization by sequence analysis.

What are the criteria for selecting viruses for shipment?

1. The viruses below MUST be included in a shipment if detected:
    a. Any influenza A virus that is unable to be subtyped using the GISRS updated assays, could indicate novel viruses or substantial antigenic or genetic changes. Therefore, these viruses must be sent to a WHO CC **without delay**.

2. Viruses selected for shipment should include recently collected (within 4-8 weeks) specimens and also reflect the proportions of each type/subtype circulating in the corresponding period of time and, if available, include samples from:
    a. different age groups;
    b. different geographical locations within the country;
    c. Severe Acute Respiratory Inflection (SARI) cases;
    d. Acute Respiratory Infection (ARI) cases;
    e. atypical pneumonia cases;
    f. unusual outbreaks (e.g. cases identified outside the expected season such as during summer months in temperate countries); and
    g. clinically significant cases (e.g. fatal cases, vaccinated patients, immunocompromised patients, patients receiving antiviral treatment, viruses known to be resistant to antiviral drugs).

3. Clinical samples with a high viral load (i.e. with a real-time reverse transcription polymerase chain reaction (RT-PCR) cycle-threshold (Ct) value of ≤ 30) should be selected, as virus isolation is typically unsuccessful when specimens have a Ct value much above 30. Good storage of specimens (-80 °C is recommended) within the laboratory is encouraged as it further increases the likelihood of successfully yielding a virus isolate.

4. Same viruses should not be sent to multiple WHO CCs

What is best timing to ship influenza viruses to WHO CCs?

It is important that the maximum possible data on the most recently circulating influenza viruses are available for consideration at each of the VCMs in February and September. To enable this, virus isolates or influenza virus-positive specimens should be shipped **4-8 weeks prior to the VCM to allow WHO CCs to handle the viruses and generate the essential data in time.**

The recommended timing of the four shipments is as follows:

1. Shipment #1: between December and mid-January (at the latest)
2. Shipment #2: between July and mid-August (at the latest)

3. Shipments #3 and #4: The timing of these shipments is more flexible and could be based on the timing of the local influenza season and any unusual events that may occur. For example, these shipments could include samples from:
    a. early in the influenza season (April-May for early southern hemisphere season; September-October for early northern hemisphere season);
    b. late in the season,(April-May for late northern hemisphere season; September-October for late southern hemisphere season); or
    c. any unusual events (such as institutional outbreaks, severe cases, etc.).

Who pays the bill of shipping influenza viruses to WHO CCs?

WHO's Global Influenza Programme (GIP) is able to cover the cost of **four shipments per year**[2] of seasonal influenza viruses or influenza virus-positive specimens from NICs to WHO CC. Additional shipments **can be supported** by contacting WHO's GIP at gisrs-whohq@who.int or fusterc@who.int, WHO regional offices or WHO CCs that will receive the shipment. (**Annex 3**).

NICs can choose any WHO CC under GISRS as recipients of their shipments. However, WHO GIP or regional offices may suggest other recipient WHO CCs for logistical or other reasons.