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

31 October 2017
ACKNOWLEDGEMENTS

The World Health Organization (WHO) wishes to acknowledge the contributions of experts from WHO Collaborating Centres (WHO CCs) of the Global Influenza Surveillance and Response System (GISRS), Dr Aeron Hurt, WHO CC, Australia, and WHO regional offices who participated in the peer review of this guidance.
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.

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\(^2\) The maximum number of shipments per year is subject to adjustment as per available financial resources.
Annex 1: Contact details of the WHO Collaborating Centres

**Jacqueline Katz**
WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza Centers for Disease Control and Prevention (CDC)
National Center for Immunization and Other Respiratory Diseases
Influenza Division
1600 Clifton Road, A-20
Atlanta, Georgia 30329
United States of America
Fax: +1 404 639 0080
Email: influenzavirussurveillance@cdc.gov
http://www.cdc.gov/flu/

**Kanta Subbarao**
WHO Collaborating Centre for Reference and Research on Influenza
Victorian Infectious Diseases Reference Laboratory
Peter Doherty Institute for Infection & Immunity
792 Elizabeth Street
Melbourne VIC 3000
Australia
Fax: +613-9342 9329
Email: whoflu@influenzacentre.org
http://www.influenzacentre.org/

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WHO Collaborating Centre for Reference and Research on Influenza
Chinese National Influenza Center (CNIC)
National Institute for Viral Disease Control and Prevention. Chinese Center for Disease Control and Prevention (CDCD)
155 Changbai Road, Changping District
Beijing, 102206
China
Fax: +86 10 5890 0851
Email: whocc-china@cnic.org.cn
http://www.cnic.org.cn
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The Francis Crick Institute
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1 Brill Place
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United Kingdom
Tel: +44 203 796 1520 (JMcC), 203 796 2444 (RD), 203 796 0563 (WIC)
Email: whocc@crick.ac.uk
https://www.crick.ac.uk/research/worldwide-influenza-centre/

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WHO Collaborating Centre for Reference and Research on Influenza
National Institute of Infectious Diseases (NIID)
Influenza Virus Research Center
4-7-1 Gakuen
Musashi-Murayama-shi
Tokyo 208-0011
Japan
Fax: +81 42 561 6149 or +81 42 565 2498
Email: whocc-flu@nih.go.jp
Operational Guidance for Sharing Seasonal Influenza Viruses

Annex 2. Practical diagram for selecting and shipping viruses to WHO CCs of GISRS

Selecting viruses to ship to a WHO Collaborating Centre (CC)

Ideally, no more than 40 viruses should be included per shipment. Four shipments per year would result in a maximum of 160 viruses being sent per year.

What are the criteria for selecting influenza viruses for shipment?

- **Recent seasonal viruses**
  - Where possible the viruses shipped should reflect the proportions of each type/subtype circulating recently
- **Influenza A viruses that cannot be sub-typed**
- **Viruses that are low-reacting in an HI or virus neutralisation test**
  - Where possible, include viruses from:
    - Different genders, age groups and locations
    - Different regions
    - SARI, ARI and atypical pneumonia cases
    - Unusual outbreaks
    - Clinically significant cases

Ship representative isolates and/or clinical specimens to WHO CCs wherever possible

VIRUS ISOLATES
- Help WHO CCs to further isolate the viruses that are received, enabling analysis in HI and NA inhibitor susceptibility assays and genome sequencing

CLINICAL SPECIMENS
- Help WHO CCs to generate vaccine seed viruses (in eggs and cell based candidate vaccine viruses in qualified cells) and genome sequencing

Where possible, ship specimens with a CT <30, and avoid multiple freeze-thaw cycles

The WHO shipment process

Complete and email the booking form

World Courier and WHO

World Courier will contact the NIC to arrange collection of the shipment within one week, assist with documentation and will provide packaging, labelling and dry ice upon request.

Contact WHO CC

Complete the sample submissionsheet (provided by WHO CC) and email the form to the CC to inform of the shipment

Prepare the shipment

Label sample tubes well, package them according to international regulations and include the sample submission form with the shipment.

Where possible, provide 0.5–1.0 ml of clinical specimen and 1.0–2.0 ml of viral isolate

Timely shipment of viruses to a WHO CC

WHO now funds 4 shipments a year to WHO CCs

To enable influenza viruses to be analysed in time for updated vaccine composition recommendations twice every year, shipments should be sent 4–6 weeks prior to the two WHO consultations, i.e. in:

- December and mid-January
- July to mid-August
- April–May for later northern hemisphere (NH) or early southern hemisphere (SH) season samples*
- September–October for later SH or early NH samples*

The most recent samples you have are the most relevant for developing vaccine composition recommendations.

* The timing of the last two shipments is flexible e.g. early or late in the influenza season or after unusual events
Annex 3: Shipping Process

World Courier is the company that has been contracted by WHO GIP to transport virus isolates or influenza virus-positive specimens from NICs to WHO CCs. All designated NICs can access WHO funds and the service of World Courier for the transportation of influenza viruses to the WHO CCs of GISRS. If a laboratory is not designated as a NIC of GISRS, or has no access to World Courier within their country, they should contact either their corresponding WHO regional office or WHO GIP at gisrs-whohq@who.int (attn. Christian Fuster at fusterc@who.int) to discuss the use of WHO funds or to resolve related problems of shipments to a WHO CC.

How to book a shipment

To book a shipment, NICs should complete and submit the booking form (Annex 4) to the World Courier Office in Geneva and WHO’s GIP (email addresses are listed on the booking form). Please complete all required information in order to avoid any delays, including contact information for the person to be contacted for the pick-up.

A local World Courier agent will contact the NIC to arrange collection of the shipment within one week. The courier will assist with the consignment note, custom forms and commercial invoice required for shipping. The Word Courier agent will also provide all relevant packaging, labelling and dry ice upon request.

NICs should contact the WHO CC to inform them of their intention to ship samples. Most WHO CCs have specific sample submission forms to provide virological, epidemiological and patient related information for specimens to be shipped. Sample submission forms are available from WHO CCs upon request. Once completed, the sample submission form should accompany the shipment and be emailed to WHO CC prior to shipping the samples.

Sample preparation and packaging

Sample tubes should be clearly labelled using non-erasable ink or printed labels, sent on dry ice and packaged according to international regulations for the transport of infectious substances\(^3\) (triple packaging system). The completed sample submission form should be included with the shipment.

Virus isolates and influenza virus-positive specimens should be stored at -70 °C to -80 °C, which is why they are shipped on dry ice. Shipping or storage of viruses at -20 °C or 2-8 °C will result in degradation of the virus and is not recommended. Where possible, specimens should not have been repeatedly frozen and thawed as this also results in degradation of the virus and will limit the ability of WHO CC to isolate the virus. It is recommended that 0.5–1.0 ml of clinical specimen and 1.0–2.0 ml of viral isolate supernatant is shipped.

\(^3\) [http://www.who.int/ihr/capacity-strengthening/infectious-substances/en/]
Annex 4: Booking Form

WHO Influenza Shipment Fund Project

**BOOKING FORM**
(One form per shipment)

*PLEASE FILL IN THIS FORM CAREFULLY*

<table>
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<th>Information of Booking Form Sending</th>
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<table>
<thead>
<tr>
<th>TO: World Courier Geneva (Switzerland) SA</th>
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<tbody>
<tr>
<td>Email: <a href="mailto:opsgva@worldcourier.ch">opsgva@worldcourier.ch</a> Fax: + 41-22-827.30.70</td>
</tr>
<tr>
<td>Email: <a href="mailto:fusterc@who.int">fusterc@who.int</a> Email: <a href="mailto:gisrs-wholq@who.int">gisrs-wholq@who.int</a> Fax: + 41-22-791.48.78</td>
</tr>
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<table>
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<tr>
<th>CC: World Health Organization - Global Influenza Program, Mr. Christian Fuster</th>
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<th>Requested Date of Pick-up:</th>
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WHO Influenza Shipment Fund Project

DETAILS OF SHIPMENT:

WHO ACCOUNT: #696002 STUDY / PROTOCOL: WHO

Please click on the relevant(s) box(es)

☐ Biological substance, category B, (UN3373): [Dry ice]
☐ Infectious substance affecting humans, category A, (UN2814): [Dry ice]
☐ Other:

Number of Vials and MLs:

Number of inner packaging and size (if available):

NOTE: LOCAL WORLD COURIER OFFICE OR HIS AGENT WILL PROVIDE DRY ICE, ADEQUATE PACKAGING MATERIALS AND PAPER WORKS (House Air Waybill, DG forms) FOR YOUR SHIPMENT.

Comments:

KIND REGARDS

1. This box should be ticked when you are shipping diagnostic specimens containing A(H5N1) or diagnostic seasonal influenza A(H1N2), A(H1N1), B specimens or seasonal influenza A(H5N1), A(H1N1), B virus isolates.
2. This box should be ticked ONLY when you are shipping virus isolates (Highly pathogenic avian influenza virus (cultures only)) of A(H5N1).
3. This box should be ticked when you are not shipping on the dry ice (-70°C). Please indicate the category (A or B) and temperature conditions: repacks (0°C to +4°C) or RT-room temperature (18°C to 25°C) or Dry shipper (-20°C to -155°C).

If you are not sure which box to tick, please contact infectious@who.int BEFORE sending the form.

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