World Health Organization

INTERGOVERNMENTAL MEETING ON PANDEMIC INFLUENZA PREPAREDNESS: SHARING OF INFLUENZA VIRUSES AND ACCESS TO VACCINES AND OTHER BENEFITS
OPEN-ENDED WORKING GROUP
Provisional agenda item 3

A/PIP/IGM/WG/3
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Extracts from EB122/5

TERMS OF REFERENCE

WHO Collaborating Centres
WHO H5 Reference Laboratories
National Influenza Centres

This document contains extracts from document EB122/5, Annex 6, the consolidated outcome text of the Intergovernmental Meeting, pages 84–95. The full document was first issued as White Paper 3 (dated 21 November 2007).

Key to document references:

IGM/2 Rev.1 refers to document A/PIP/IGM/2 Rev.1, Reports by the Director-General: Summary progress reports. (The document summarizes actions undertaken and planned in order to implement the following paragraphs of resolution WHA60.28: 2(1) on frameworks and mechanisms, 2(2) on establishing an international stockpile of vaccines, and 2(3) on mechanisms and guidelines for distributing vaccines fairly and equitably.)

IGM/4 refers to document A/PIP/IGM/4, Sharing of influenza viruses and access to vaccines and other benefits: Interdisciplinary Working Group on Pandemic Influenza Preparedness. (The meeting (Singapore, 31 July – 4 August 2007) was convened in accordance with resolution WHA60.28 (paragraph 2(5)) and the document contains a summary of the debate.)

IGM/5 refers to document A/PIP/IGM/5, Annex: Fundamental principles and elements for the development of a new system for virus access and fair and equitable benefit sharing arising from the use of the virus for the pandemic influenza preparedness. (This text was proposed by Indonesia to be considered as a working document for the discussion in the Intergovernmental Meeting on Pandemic Influenza Preparedness, 20–23 November 2007.)

IGM/6 refers to document A/PIP/IGM/6, Annex: A proposal from Thailand for the Intergovernmental Meeting on Pandemic Influenza Preparedness, 20–23 November 2007: Standard Terms and Conditions (STCs) for the transfer and use of influenza biological materials and fair and equitable benefits sharing (between Member States [MS] and WHO Secretariat [WS]).

AFRO refers to document A/PIP/IGM/7, Annex: Standard Terms and Conditions for the transfer and use of influenza biological materials and fair and equitable benefit sharing: A proposal from the African Region for the Intergovernmental Meeting on Pandemic Influenza Preparedness, 20–23 November 2007.

In all cases, the **bold number** immediately following the document number refers to the paragraph in the document.

AFRO ANNEX 3

ANNEX 3 (REVISION TO THE EXISTING TOR)

All activities by the WHO Collaborating Centres for Reference and Research on Influenza under this Terms of Reference will be subject to the Standard Terms and Conditions.

(a) Provide:

- Recommendations to WHO on suitable influenza vaccine viruses for use in seasonal, pre-pandemic and pandemic influenza vaccine development and production;
- Regular and timely surveillance data to WHO, particularly from local and neighbouring geographical regions;
- Advice to the WHO Global Influenza Surveillance Network (GISN)ii National Influenza Centres and other national laboratories designated by the State on laboratory methods for the diagnosis of influenza, the adoption of new diagnostic approaches, the improvement of laboratory practices and on other operational needs;
- Regular and timely reports of virus characterization to WHO and the country contributing the virus and GISN members;
- Expertise, continuous training and laboratory support to WHO Member States in particular developing countries facing influenza outbreaks to conduct influenza outbreak investigation, risk assessment and response activities, including developing candidate influenza vaccine virus.

And response, especially those with pandemic potential; and

- Expertise to assist WHO on the improvement of global surveillance of influenza viruses causing or with the potential to cause human infections, including the development and revision of relevant policies, recommendations and guidelines.

(b) Conduct:

- Isolation and analysis in both embryonated eggs and cell culture of influenza viruses causing or with the potential to cause human infections;
- Complete antigenic and genetic analysis of influenza viruses causing or with the potential to cause human infections, making the information available to WHO and the originating country in a timely manner;
- Antiviral susceptibility testing and analysis of circulating influenza strains and provide a minimum of two reports each year to WHO and the originating country on the findings;
- Active communication and collaboration with other laboratories, especially with the WHO recognized National Influenza Centres, to ensure that high quality clinical specimens and/or virus isolates are received and information is exchanged;

(c) Develop, produce and distribute:

- Antisera against representative influenza viruses causing or with the potential to cause human infections to WHO laboratories involved in influenza vaccine virus selection, development and other WHO activities; and

- Laboratory diagnostic reagents for circulating influenza viruses to GISN members.

(d) Participate in:

- Bi-annual WHO influenza vaccine composition consultations; and

- WHO process to select, develop and distribute candidate influenza vaccine viruses for influenza pandemic preparedness and response.

OR

IGM/4 ANNEX 4

APPENDIX 4

Core Terms of Reference for WHO Collaborating Centres for Reference and Research on Influenza (including WHO Collaborating Centre on Surveillance, Epidemiology, and Control of Influenza)

This document has not been agreed by all IDWG participants.

The title, WHO Collaborating Centre for Reference and Research on Influenza, designates, through a defined WHO application process, centres of excellence on influenza which:

- Meet all core Terms of Reference (TOR) for WHO Collaborating Centres for Reference and Research on Influenza (WHO CCRRI) listed below. This includes the maintenance of Biosafety Level 2 and Biosafety Level 3 laboratory facilities;
- Work under the coordination of the WHO Global Influenza Programme (GIP);[1] and
- Receive adequate long-term governmental and/or other non-commercial financial support to fulfil the core TOR for WHO CCRRI.

The core TOR constitute minimum requirements; an individual WHO Collaborating Centre for Reference and Research on Influenza may have additional functions in its TOR in discussion with and agreed upon with WHO GIP.

Core Terms of Reference

All influenza clinical specimens, candidate influenza vaccine viruses and other influenza viruses will be distributed subject to Standard Terms and Conditions for Transfer and Use of Specimens (STC).

A. Advisory role

1. Provide data and advice to WHO concerning suitable influenza viruses for use in vaccines against seasonal, A(H5N1) and other influenza virus with a potential to cause a pandemic; participate in the development and timely availability of the candidate influenza vaccine viruses;

2. Advise the WHO Global Influenza Surveillance Network (GISN)[2] on laboratory methods for diagnosis of influenza, including the adoption of new diagnostic approaches, the improvement of laboratory practices and other operational needs;

[1] WHO Global Influenza Programme http://www.who.int/csr/disease/influenza/en/.

[2] The WHO Global Influenza Surveillance Network http://www.who.int/csr/disease/influenza/surveillance/en/index.html.

3. Serve as ready technical resources globally to WHO on routine influenza surveillance and influenza emergencies, especially on influenza outbreaks with pandemic potential.

B. Technical performance

1. Strengthening the WHO Global Influenza Surveillance Network

(a) Maintain and strengthen active communication and collaboration with National Influenza Centres (NICs)[1] and other national influenza laboratories to ensure that high quality clinical specimens and/or viruses are received and up-to-date information is exchanged;

(b) Conduct training and provide support to NICs and other national influenza laboratories, especially those in developing countries, on laboratory techniques and skills, including diagnosis, data analyses, risk assessment and other critical capacities;

(c) Develop, update and produce laboratory diagnostic reagents for circulating influenza viruses and distribute to NICs and other national influenza laboratories;

2. Laboratory analyses and other related activities

(a) Isolate in both cell culture and embryonated eggs influenza viruses causing or with the potential to cause human infections;

(b) Develop and produce antisera in ferrets against representative influenza viruses causing or with the potential to cause human infections;

(c) Conduct complete antigenic and genetic analyses of influenza viruses causing or with the potential to cause human infections;

(d) Develop data for recommending appropriate vaccine viruses for use globally, including semi-annual data for seasonal influenza vaccine viruses and, for pandemic preparedness, ongoing data for influenza vaccine viruses with a potential to cause a pandemic;

(e) Participate in the development of candidate influenza vaccine viruses for seasonal influenza semi-annually and for influenza pandemic preparedness;

(f) Conduct antiviral susceptibility testing of circulating influenza strains, as part of routine surveillance, and provide findings to WHO at least twice every year;

(g) Select, maintain and update a group of influenza reference viruses, including seasonal, A(H5N1) and other influenza viruses with pandemic potential, and corresponding antisera if available; update the availability of reference viruses and corresponding antisera, if any, to WHO, which will maintain a web page on the WHO web site;

(h) Actively initiate research on influenza viruses, engaging laboratories providing clinical specimens and/or viruses; rapidly share findings of public health significance with WHO.

[1] WHO designated National Influenza Centers http://www.who.int/csr/disease/influenza/centres/en/index.html.

3. Global influenza response and preparedness

(a) Provide expertise and laboratory support, in coordination with WHO, to Member States to assist in influenza outbreak response, especially those associated with influenza viruses having pandemic potential;

(b) Assist WHO in the development of standards, recommendations and policies concerning the broad areas of influenza surveillance, response and preparedness.

C. Communication and distribution of viruses and/or clinical specimens

1. Laboratory analyses and results

(a) Provide data and/or results timely to originating laboratories/countries providing clinical specimens and/or viruses and to WHO;

(b) Alert WHO and the country from which the specimens were provided on unusual findings, especially those related to seasonal or pandemic influenza risks obtained from the analysis of the specimens.

2. Gene sequences

(a) Seasonal influenza

➢ Upload available sequences of HA and NA genes, and other genes, to a publicly accessible database after each WHO semi-annual vaccine composition consultations, unless otherwise instructed by the laboratory or country providing the specimens.

(b) A(H5N1) and other influenza viruses with pandemic potential

➢ Upload available sequences of HA and NA genes, and other genes, to a publicly accessible database within 3 months after sequencing done, unless otherwise instructed by the laboratory or country providing the specimens. **[Germany: What is the rationale for 3 months?]**

➢

(c) Post a list of virus isolates/specimens analysed but not approved for public use.

(d) (old c) Appropriately acknowledge originating laboratories/countries providing clinical specimens and/or viruses.

3. Scientific presentations and publications

(a) Actively engage scientists from originating laboratories/countries in scientific projects associated with research on specimens from these countries and engage them actively in preparation of manuscripts for presentations and publications;

(b) Appropriately acknowledge in the presentations and publications the contributions of various collaborators, including laboratories/countries providing clinical specimens, viruses or reagents.

4. Influenza clinical specimens and influenza viruses

Share i**nfluenza clinical specimens and influenza viruses, in a timely and unrestricted manner,** with laboratories working in coordination and in collaboration with GIP, including

i. Other WHO CCs for laboratory analyses as defined above;

ii Other laboratories involved in WHO coordinated specialized activities, (e.g. the WHO External Quality Assessment Project for the detection of subtype influenza A viruses using PCR; the WHO influenza PCR primer updating), and other activities whose purpose is to strengthen global influenza surveillance and other risk assessment and risk response; as well as capacity building.

iii Key national regulatory laboratories, including FDA, NIBSC and TGA, which are involved in the WHO process of candidate influenza vaccine virus selection and development, as well as vaccine potency reagent development.

5. Candidate influenza vaccine viruses are selected and developed under the coordination of WHO, for development and production of vaccines against seasonal, A(H5N1) and other influenza viruses with a potential to cause a pandemic. The candidate influenza vaccine viruses include wild type viruses and high-growth reassortant viruses, including those prepared by reverse genetics.

(a) Distribute to appropriate recipients on request, including influenza vaccine manufacturers, diagnostic companies, research institutes and others interested in receiving influenza vaccine viruses;

(b) Report the distribution status to WHO, which will maintain a list of recipients on the WHO web site.

6. Influenza reference viruses are a group of viruses selected, maintained and updated by WHO CCs as antigenically and genetically representative of important groups of viruses, including seasonal, A(H5N1) and other influenza viruses with pandemic potential. These viruses are often used to generate corresponding antisera. Both reference viruses and corresponding antisera will be:

(a) Distribute, on request, to NICs and research institutes for non-commercial activities including surveillance, reference and research; the laboratories/countries providing the original clinical specimens and/or viruses will be notified of the distribution;

7. Distribution of influenza clinical specimens and influenza viruses, for purposes beyond those described above, will require approval from the laboratories/countries providing the original clinical specimens and/or viruses.

AFRO ANNEX 4

ANNEX 4 (REVISION TO EXISTING TOR)

TERMS OF REFERENCE FOR WHO H5 REFERENCE LABORATORIES

In 2004, the WHO H5 Reference Laboratory Network was established, as an ad hoc component of the WHO Global Influenza Surveillance Network (GISN)1, in response to the public health needs arising from avian influenza A(H5N1) infection in humans and influenza pandemic preparedness. The laboratories involved to date2 include the four WHO Collaborating Centres for Reference and Research on Influenza, the WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals and other laboratories with internationally recognized expertise in avian influenza.

The addition of new laboratories to the Network is based on an overall assessment of global public health needs, the ability of candidate laboratories to fulfil the Terms of Reference listed below, and, in particular, the added value that inclusion of candidate laboratories would bring to the Network.

Membership in the WHO H5 Reference Laboratory Network is ad hoc and will be reviewed periodically to ensure the Network's optimum effectiveness in meeting emerging public health risks.

A. Provide

1. accurate laboratory diagnosis of influenza infection in humans to assist in rapid outbreak response, especially those suspected of being associated with avian influenza A (H5) viruses;

2. expertise and laboratory support in response to A (H5) avian influenza outbreaks

3. immediately report to WHO and the originating laboratory the results of laboratory diagnostic tests, especially the detection of A (H5) viruses and any other important findings;

4. feedback to WHO on the use of WHO recommended diagnostic protocols and primers to assist WHO in the update of laboratory diagnostic recommendations.

B. Actively seek approval from the Ministry of Health of the originating laboratory for sharing the A (H5) clinical specimens and/or viruses with any other entity.

OR

IGM/4 APPENDIX 6

APPENDIX 6

Terms of Reference for WHO H5 Reference Laboratories

This document has not been agreed by all IDWG participants.

The title, WHO H5 Reference Laboratory, designates, through a defined WHO process, on an ad hoc basis,[1] a national influenza laboratory which:

- Meets the WHO Criteria for accepting positive results of H5 infection in humans,[2] which ensures that the laboratory conducts reliable diagnosis of influenza A(H5) infection in humans, and that the positive results of A(H5) detection are accepted by WHO as confirmatory without external verification in a WHO Collaborating Center (CC) for Reference and Research on Influenza (RRI); and

- Fulfills the Terms of Reference (TOR) for WHO H5 Reference Laboratories.

Terms of Reference for WHO H5 Reference Laboratories

A. Core functions

1. Provide accurate laboratory diagnosis of influenza infection in humans to assist in rapid outbreak response, especially those suspected of being associated with avian influenza A(H5) viruses; and

2. Provide A(H5) laboratory diagnostic services to its own country and beyond when needed.

B. Technical performance

1. Provide advice to clinics, hospitals and other specimen collection sites on safe and appropriate clinical specimen collection, storage, packaging and shipping;

2. Conduct accurate laboratory diagnosis of specimens received, typing and subtyping influenza viruses, especially the confirmation of A(H5) human infections; and

3. Provide expertise and laboratory support in response to A(H5) avian influenza outbreaks.

[1] WHO maintains an up-to-date list of WHO H5 Reference Laboratories.

[2] Web-link to Criteria.

C. Communication and exchange

1. Report immediately to WHO and the originating laboratory the results of laboratory diagnostic tests, especially the detection of A(H5) viruses and any other important findings;

2. Actively seek approval from the Ministry of Health of the originating laboratory for sharing the A(H5) clinical specimens and/or viruses with WHO for further characterization in the WHO CCRRI; and

3. Provide feedback to WHO on the use of WHO recommended diagnostic protocols and primers to assist WHO in the update of laboratory diagnostic recommendations.

IGM/4 APPENDIX 5

APPENDIX 5

Terms of Reference for National Influenza Centers

This document has not been agreed by all IDWG participants.

The title, National Influenza Center(NIC), recognizes, through a defined WHO process, national influenza laboratories which:

- Function as members of the WHO Global Influenza Surveillance Network (GISN)[1] in coordination with the WHO Global Influenza Programme (GIP);[2]
- Are formally designated by the country Ministry of Health and officially recognized by WHO; and
- Fulfill the Terms of Reference (TOR) for NICs.

The TOR constitutes minimum requirements for a NIC being a member of the WHO GISN; an individual NIC may have additional obligations under the authority of its Ministry of Health.

Terms of Reference for National Influenza Centres as members of the WHO Global Influenza Surveillance Network

D. Core functions

1. Serve as the key reference point between WHO and the country of origin on all issues related to influenza virological surveillance, laboratory diagnosis of influenza infection in humans and sharing of influenza clinical specimens and/or viruses with WHO;

2. Participate actively in WHO global influenza surveillance activities and maintain active communication and collaboration with other members of the WHO GISN, including WHO Collaborating Centers and other National Influenza Centers.

E. Technical performance

4. Collect appropriate clinical specimens from patients year-round and especially during influenza seasons and outbreaks;

5. Act as a collection point for influenza viruses where available from laboratories within the country;

[1] http://www.who.int/csr/disease/influenza/surveillance/en/index.html.

[2] http://www.who.int/csr/disease/influenza/en/.

6. Review, expand and maintain sufficient coverage of influenza virological surveillance in the country;

7. Isolate in cell culture and/or embryonated eggs seasonal/influenza viruses under appropriate laboratory containment;

8. Conduct preliminary characterization of influenza virus type and subtype;

9. Store original influenza positive clinical specimens for at least 18 months at -70 ^{o}C;

10. Provide technical advice and support to other influenza laboratories in the country, on specimen collection and shipment logistics, laboratory diagnosis, laboratory biosafety and other operational procedures related to influenza virological surveillance;

11. Select seasonal/influenza viruses, especially those of geographical and possibly antigenic and genetic representativeness, for further characterization in WHO Collaborating Centers for Reference and Research on Influenza (CC RRI).

F. Communication and exchange

4. Alert WHO GIP immediately on the emergence of unusual outbreaks of influenza or influenza-like illness, the detection/isolation from humans of A(H5) or other influenza viruses with a potential to cause a pandemic, or of influenza viruses that cannot be readily identified with WHO diagnostic reagents provided through the WHO GISN;

5. Report regularly to WHO FluNet,[1] weekly during influenza seasons, the extent of influenza activity in the country, virological surveillance data and other relevant information of public health importance;

6. Provide to national authorities and the general public, information on influenza viruses circulating in the country;

7. At least twice every year make shipments to WHO CCRRI of a selection of representative seasonal influenza virus isolates and all influenza virus isolates which gave low titres in HI tests using WHO diagnostic reagents provided through the WHO GISN:

(a) For northern hemisphere countries, once in November and once in early January;

(b) For southern hemisphere countries, once in June and once in mid-August;

(c) For tropical countries, depending on influenza activity, make shipments of recent virus isolates timely to be included in the next WHO vaccine composition recommendation, either for northern hemisphere or southern hemisphere; and

(d) For all countries, make shipments of any unusual viruses within one week after detection.

[1] http://gamapserver.who.int/GlobalAtlas/home.asp.

8. Initiate shipments to WHO CCRRI of clinical specimens and/or viruses from all suspected/confirmed infections of A(H5) and other influenza in humans, within two weeks after detection or isolation of the virus with potential to cause a pandemic; include in the shipment information of time, geographical, epidemiological and clinical factors associated with the suspected/confirmed human infections, for the purpose of ongoing and rapid WHO global pandemic risk assessment and response, as well as and pandemic preparedness.

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