

The Public Health Importance of Timely Sharing of Sequence Data

Nancy J. Cox, Ph.D.

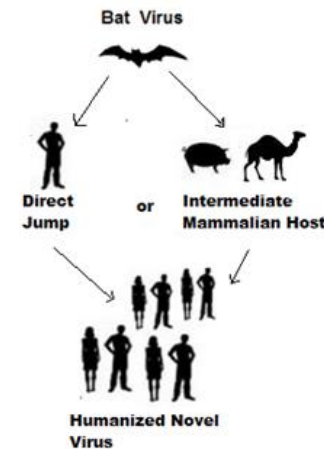
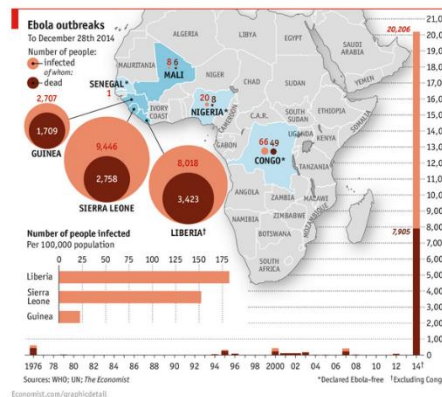
Guest Researcher, Influenza Division

Centers for Disease Control and Prevention

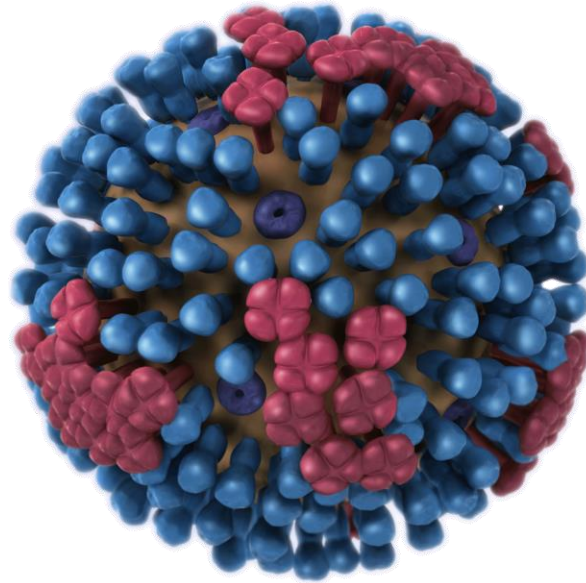
Workshop on Next Generation Sequencing of Viruses

Institute Pasteur, Paris

May 21, 2015



njc1@cdc.gov



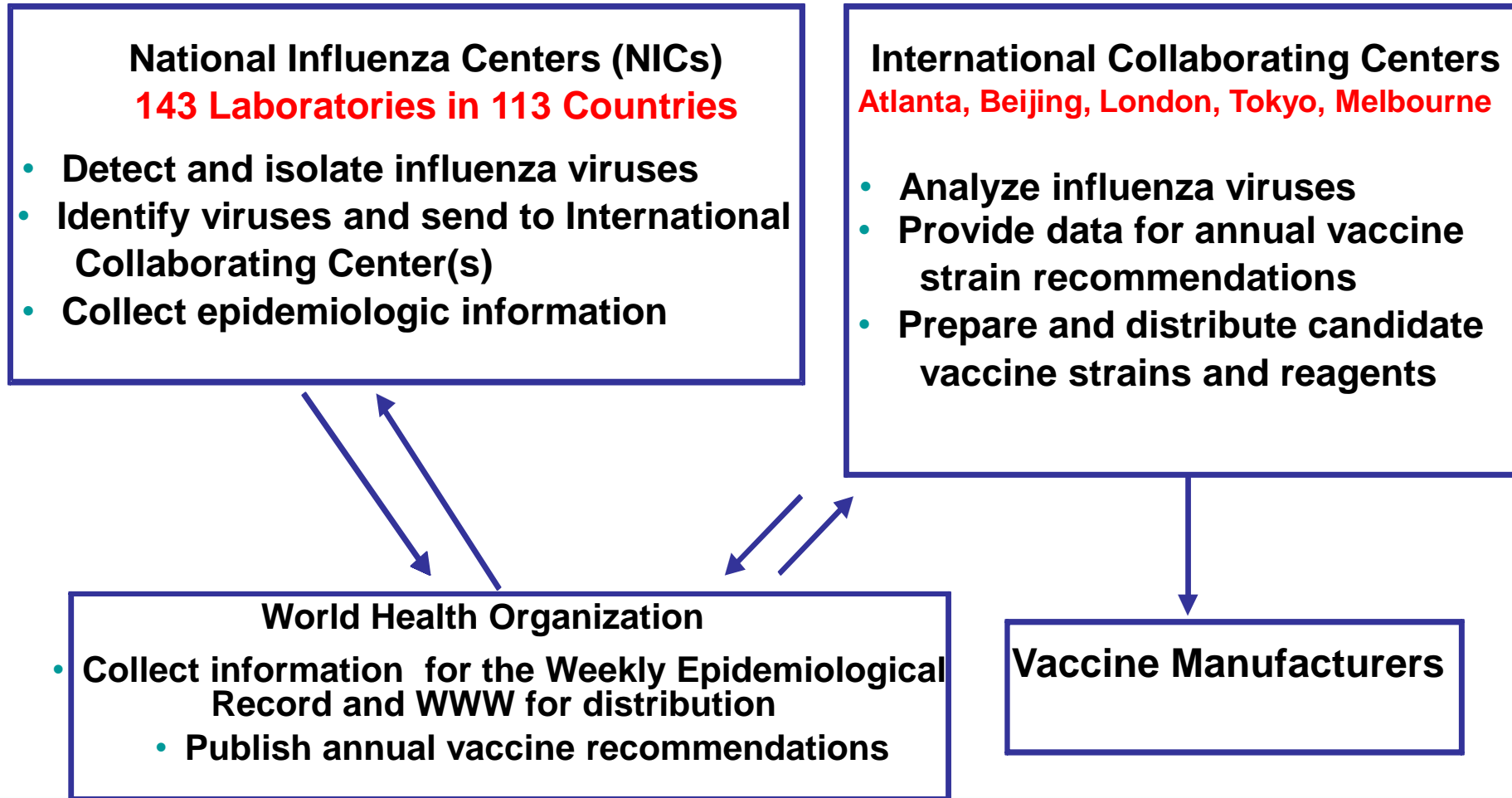
The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Talk Outline

- Influenza virus, benefits and data sharing controversy
 - H5N1 virus sharing debate
 - H1N1 2009 vaccine sharing difficulties
- Influenza virus, benefits and data sharing solutions
 - Pandemic Influenza Preparedness Framework, ratified in 2011
 - GISAID
 - H7N9 data sharing, China
- Looking forward
 - Rapid data sharing is essential
 - GISAID - model for other disease-specific databases

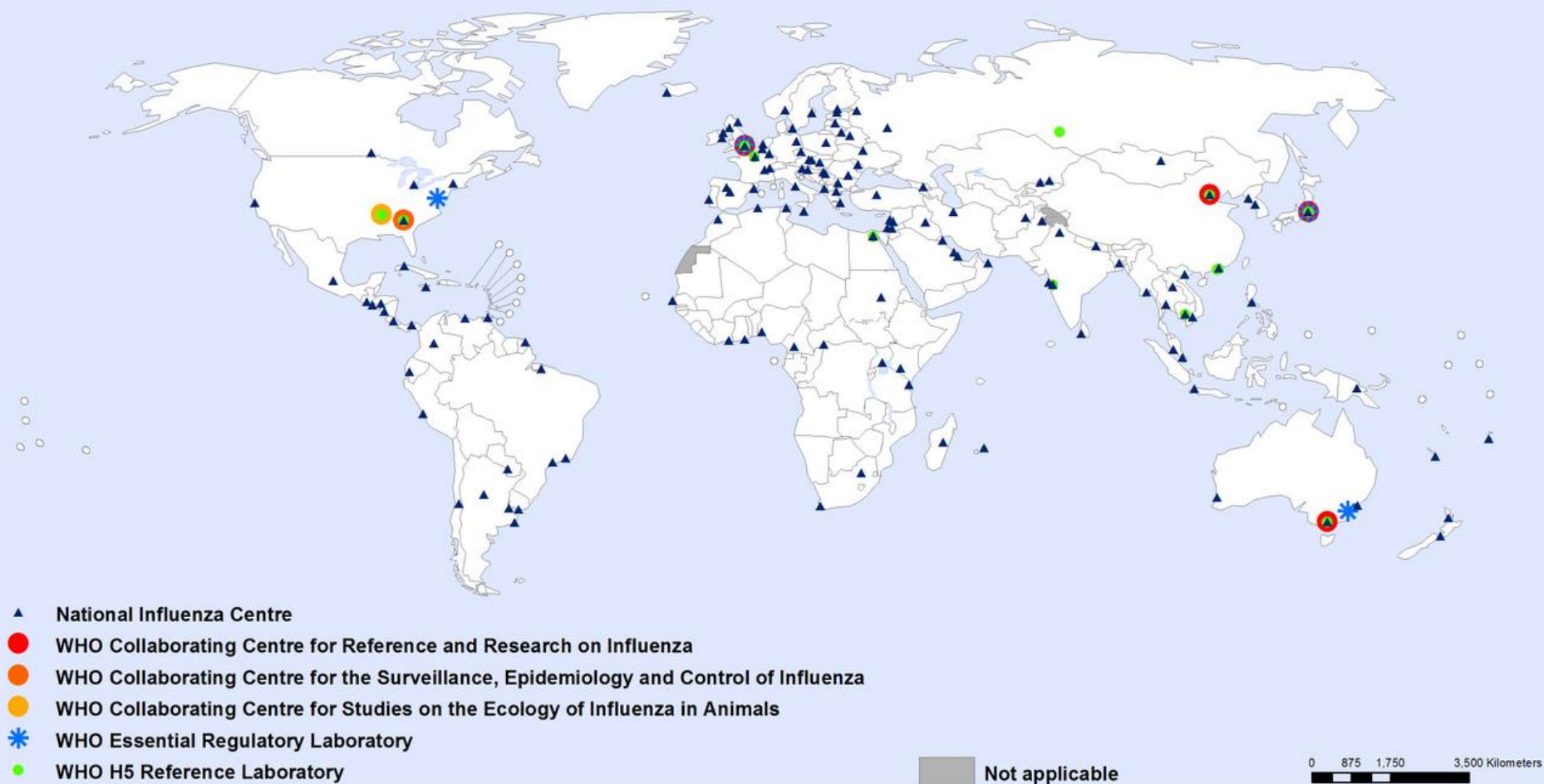


WHO's Global Influenza Surveillance and Response System (GISRS) - 60 + Years Old



WHO Global Influenza Surveillance and Response System

28 November 2014



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Influenza Surveillance and Response System (GISRS), WHO
Map Production: WHO GISRS Team
World Health Organization

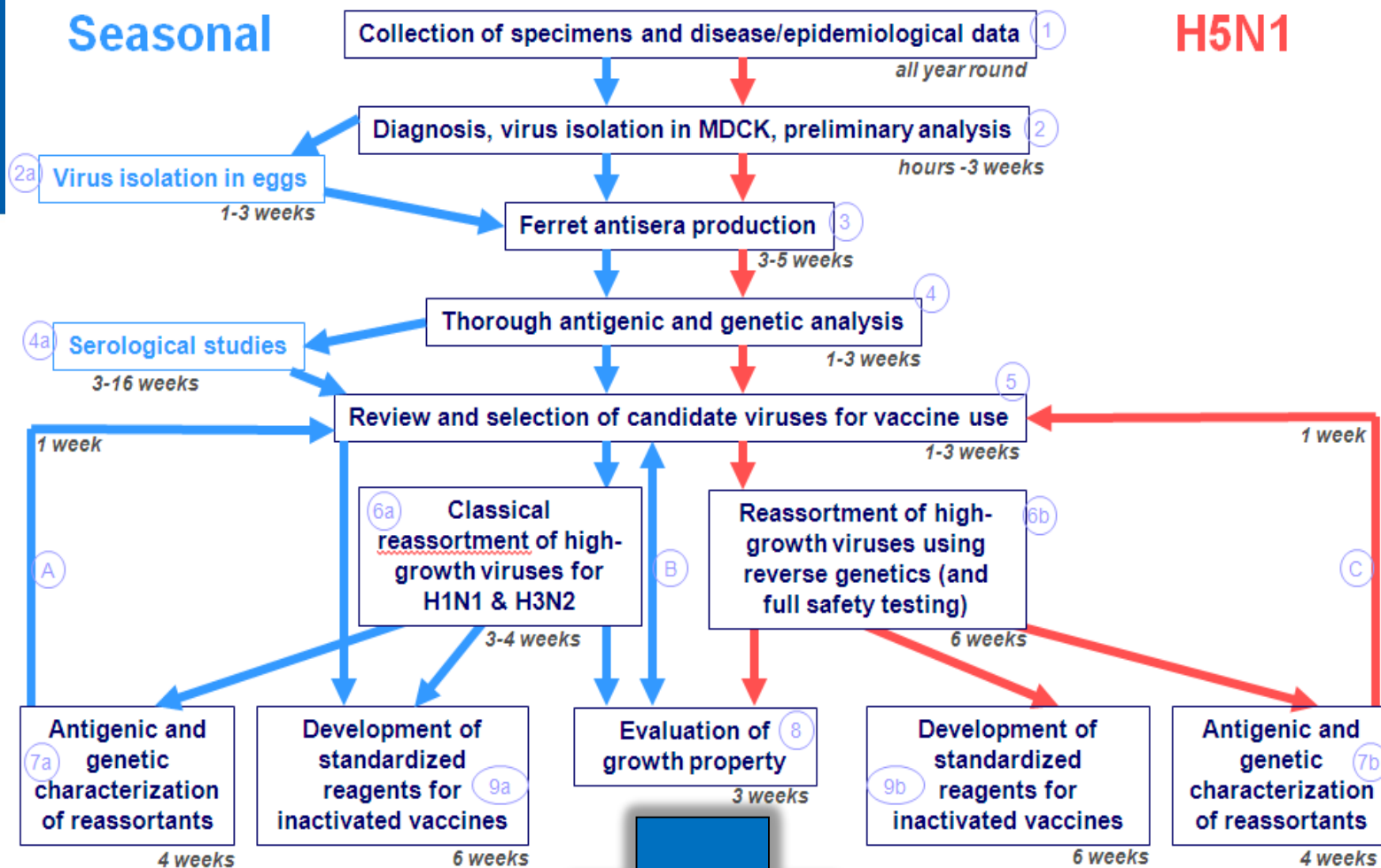


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Seasonal

H5N1



Candidate vaccine viruses and potency reagents available

Vaccine development, production and use



Setting the Scene for The H5N1 Controversy

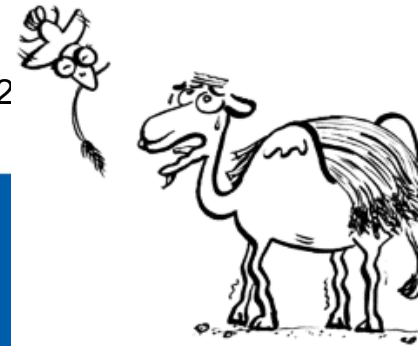
- 1997 – 18 human cases of H5N1 in Hong Kong, SAR, China
- February 2003 – 3 confirmed human cases of HPAI H5N1 in Hong Kong family with travel to mainland China (daughter died)
- 2004 - H5N1 human cases detected in Vietnam and Thailand
- 2005 – H5N1 cases detected in Vietnam, Cambodia, Thailand, Indonesia, and China
- December 2006, 146 H5N1 human cases detected in: Indonesia (74 or 51%), Thailand (24), China (22), Egypt (18), Iraq (3), Turkey (2), Azerbaijan (1) and Djibouti (1)
- International concern about the risk of an H5N1 pandemic peaked at about this time
- January 2007 – Indonesia stopped sharing all H5N1 clinical samples with WHO causing a “crisis in global health¹” because Asia is the believed to be the epicenter for influenza pandemics

1.Fidler DP. Influenza virus samples, international law, and global health diplomacy. *Emerg Infect Dis.* 2008;14(1):88-94.



Why Indonesia Withheld H5N1 Samples

- Virus samples sent abroad; data generated in recipient labs used for scientific meeting presentations without permission and for manuscripts with no/little/late involvement of Indonesian scientists
- Little/no understanding of the purpose, structure and function(s) of the WHO's global influenza program, in spite of country participation in GISRS as a WHO National Influenza Center (NIC)
- Indonesian family cluster of 7 confirmed and 1 probable H5N1 cases led to criticism about lack of seq data sharing; in response MoH Indonesia requested US-CDC and HKU enter data in GenBank
 - US-CDC and HKU happy to oblige; did not previously have permission to do so and feared losing trust of Indonesian counterparts
- Indonesia felt they had capacity to detect cases independently
- “The Final Straw” – Vaccine company developed H5 vaccine using Indonesian virus; too expensive for them²



The Equity and Fairness Argument

- Developing countries provided information and virus samples to the WHO's Global Influenza Program
- Pharmaceutical companies in developed countries obtained free access to samples, “exploited” them, patented methods and sold products for profit
- Developing countries with H5N1 cases could not afford to purchase H5 vaccines and antivirals¹
- Trust in the WHO GIP was broken for Indonesia which asserted that reform was needed in the areas of virus and benefit sharing (access to vaccines). Other low income countries expressed similar concerns.
- In short, Indonesia and similar countries had greatest H5N1 disease burden but could not afford vaccines though they shared viruses from which vaccines were made.

The Legal Argument for Withholding Influenza Specimens

- Indonesia claimed sovereignty over its viruses based on the Convention for Biological Diversity (CBD)³
 - CBD is an international treaty meant to protect indigenous/traditional resources in developing countries (e.g., traditional medicinal plants, etc. often exploited by others)
 - Initial CBC concept not meant to cover HPAI viruses which we would like to eradicate, but this argument gained ground
- Indonesia asserted that the International Health Regulations (IHR) of 2005 [legally binding international law] did not require sharing of biological samples
 - IHR are ambiguous with respect to requirements for sharing samples

After Negotiations Began: The 2009 H1N1 Pandemic and the Nagoya Protocol

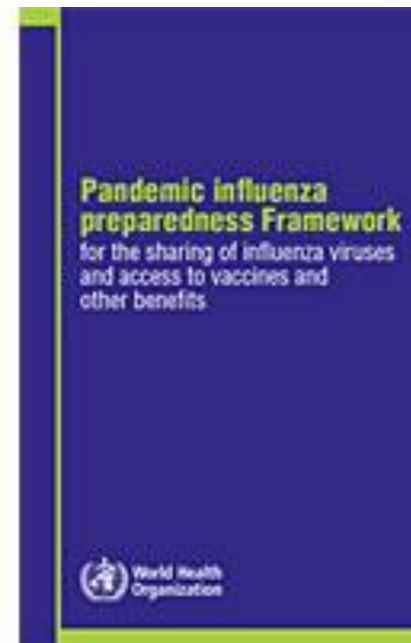
- Developing country mistrust increased in 2009 when H1N1pdm09 vaccine was not “shared equitably” in during the 2009 pandemic
- European and North American Contracts mopped up vaccine
 - US and Canada didn’t share vaccine with other countries (including Mexico) until after domestic market saturation
- October 2010 – Countries that were party to CBD reasserted state sovereignty over biological materials including pathogens by negotiating the Nagoya Protocol⁴ -in effect October 2014
 - Allows countries to assert rights to and negotiate for benefits in return for sharing genetic resources including pathogens
 - Legally binding for countries that are signatories
 - Unknown ramifications for outbreak investigations and responses

⁴ Secretariat of the Convention on Biological Diversity. *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising From Their Utilization to the Convention on Biological Diversity: Text and Annexes*. Montreal, QC: Secretariat of the Convention on Biological Diversity; 2011.



After 4 Years: The Flu Solution was the Pandemic Influenza Preparedness (PIP) Framework

- April 2011 the WHO Director General announced the WHO Pandemic Influenza Framework
- The World Health Assembly approved the PIP Framework in May 2011



The Pandemic Influenza Preparedness Framework

- Why did it take 4 years and millions of dollars to negotiate?
 - The identified problems were complex; equity, fairness and transparency
 - Countries had divergent interests; developed countries value intellectual property rights while developing countries argued for equity in health
- The PIP framework is a landmark in global governance for public health
- The framework governs sharing of H5N1 and other influenza viruses with human pandemic potential and the benefits accruing from them (not seasonal flu)
- Strives to improve pandemic preparedness through WHO's GISRS by sharing viruses and enhancing equitable access to benefits



PIP Framework⁵ (continued)

- Framework principles include acknowledgment of: country sovereignty over biological resources; the ongoing threat of a pandemic; and virus and benefit sharing on an equal footing
- Includes financing mechanisms for equitable access to benefits
- The framework is not legally binding b/c WHO did not exert its constitutional authority to adopt international law
 - Permissive language, e.g., member states should share....
 - Standard Material Transfer Agreements govern movement of viruses into and out of the WHO surveillance system
 - SMTA 1 governs movement of samples within GISRS
 - SMTA 2 governs movement of samples outside GISRS (e.g, to vaccine manufacturers and to researchers outside GISRS)

5. World Health Organization. Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits [advanced unedited]. Geneva, Switzerland: World Health Organization; April 16, 2011. PIP/OEWG/3/4. http://www.who.int/csr/disease/influenza/pip_framework_16_april_2011.pdf. Accessed January 2014.



Virus and Sequence Data Sharing

- Sharing PIP Biological material (viruses) was facilitated by creating a tracing mechanism for their movement, i.e. the IVTM
- Provision of material to a WHO lab under SMTA1 indicates consent to transfer within and outside GISRS
- Member states may share PIP biological materials with other entities if also provided to GISRS
- Genetic sequence data “should be shared with the originating lab and among WHO GISRS labs” for risk assessment
- The framework directs WHO’s DG to strengthen sequence data sharing by addressing access, transparency and other concerns



Benefits Sharing

- Key components of benefit-sharing system in PIP-FW
 - Requires industry to pay for “half” of GISRS’s annual operating costs
 - In return, industry has access to PIP biological materials under SMTA 2s in exchange for providing annual Partnership Contributions (an annual assessment) and other contributions during a pandemic.
 - In effect, the contributions by industry give pharmaceutical companies access to PIP biological materials in exchange for Partnership Contributions that will be used by WHO to assist developing countries with their influenza surveillance and estimation of burden of disease.
 - Companies also sign on to donating vaccines/antivirals during a pandemic or to offer them at reduced prices to developing countries.



PIP Framework Summary

- The PIP Framework seeks to strengthen pandemic surveillance & response and improve global equity
- It emphasizes virus sharing as a norm but does not create legally binding obligations
 - During the H5N1 and H1N1 crises, WHO Member States shared viruses (except Indonesia)
- No major departure from the “custom” for sharing genetic sequence data, but countries expressed concerns about sharing data if first publication by others precluded publication by their scientists
- Greatest outward differences:
 - Transparency for member states on transfer of influenza viruses with pandemic potential through the Influenza Virus Tracking Mechanism and SMTA’s 1 and 2
 - Financial contributions from Industry to WHO provided under SMTA 2; these go to developing countries for improving pandemic surveillance and response



Solution for Sequence Data Sharing

- GISAID established as a mechanism for sharing all influenza virus data in 2008
 - Adopted by the “WHO Collaborating Centers for Influenza” for entering sequence data from samples received from NIC’s
 - Used by NIC in Indonesia for depositing H5N1 sequence data
 - Used for deposit of early 2009 H1N1 pandemic viruses
 - Extremely important for entry of H7N9 sequence data by China
 - Chinese sequence data used for early pandemic risk assessment
 - Sequence data also used for synthesis of HA and NA genes for rescue of candidate vaccine viruses – new era of synthetic biology
 - Synthetic viruses used in some vaccine production for US stockpile



GISAID Data Access and Sharing Principles

- GISAID is the non-profit Global Initiative on Sharing All Influenza Data (influenza sequence and meta data)
 - Hosted by the Federal Republic of Germany
 - Operates the publicly accessible EpiFlu™ database
 - Based on the guiding principle that those using Data **must acknowledge the contributions of those providing the Data and must respect the rights, including pre-existing IP rights**
- Access is free of charge and open to everyone, provided they identify themselves to allow fully transparent access and sharing
 - Used by about 6,000 researchers in 800 institutions around the world
- Data submitted to GISAID are publicly accessible and data submitters don't lose rights to the data they deposit



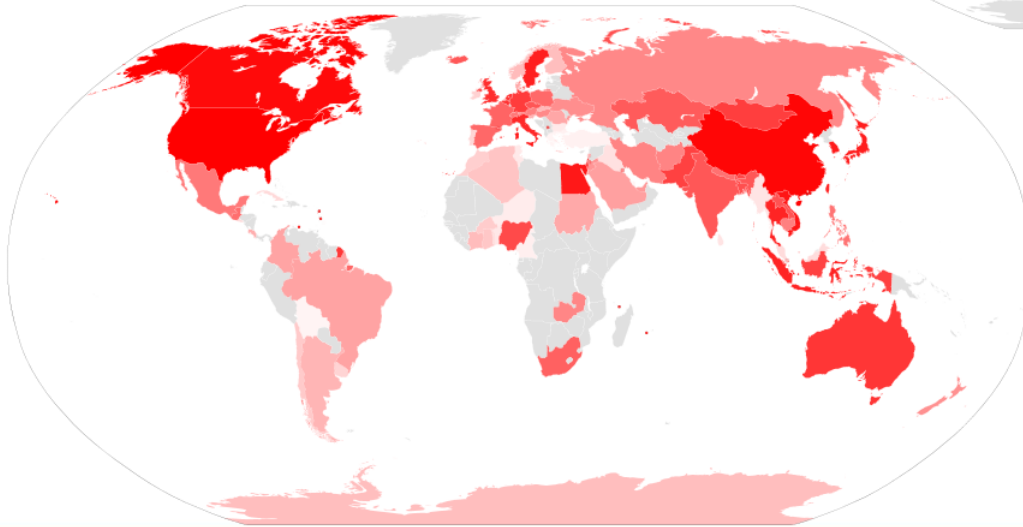
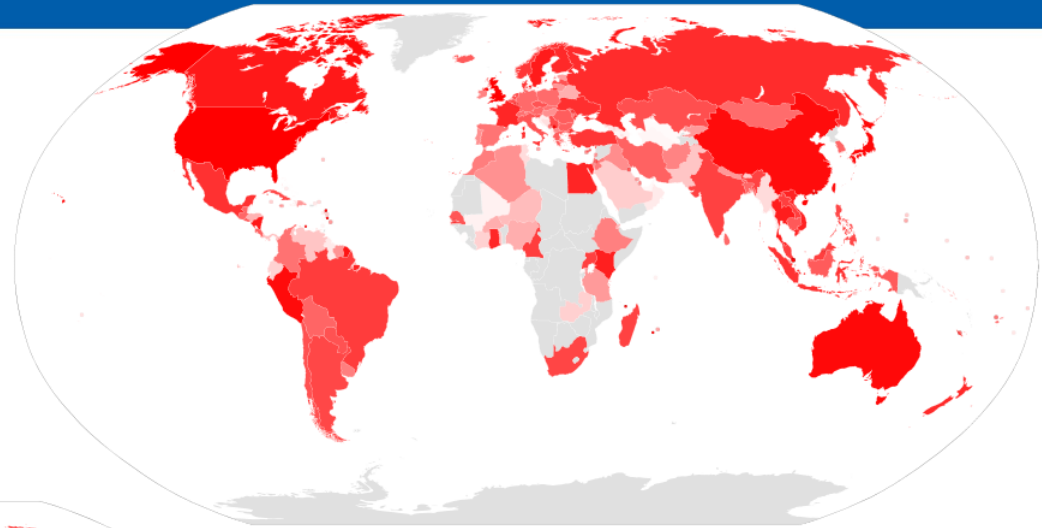
Why Did/Do We Need GISAID

- H5N1 affected countries were sensitive about release and publication of viral sequence data
 - CDC established a “private compartment” for deposit of H5 data with limited access to about 50 influenza researchers to ensure data could be analyzed by multiple groups but also ensure that publication of data from developing countries without permission did not occur
 - H5 data base hosted by Los Alamos National Laboratories (LANL had hosted HIV, HPV and HCV sequence databases without controversy) but unfortunate international “optics”
 - GISAID was a new paradigm for influenza and required adherence to scientific etiquette regarding acknowledgement of contributions by submitters of samples and data by the users of genetic sequence data



Strong and Rising GSD Contributions from Asia

Global distribution of
human host derived
isolates in GISAID




Global distribution of
animal host derived
isolates in GISAID

Countries ranked by number of HA sequences in GISAID in August 2014,
colored by rank percentile from red (most) to white (least), gray (none)



The new GISAID EpiFlu™ 2.0 database



GISAID published: 34,593 viruses with 89,498 Sequences

Total count: 113,361 viruses with 393,536 Sequences

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► Administration
► Registered Users

Number of results: 47 Viruses

☒ Released
 ☐ My released
 ☐ My unreleased
 ✖ Reset Filters
📊 Count Viruses
🔍 Search Results

Search pattern

Type ▲ -

A	<input checked="" type="checkbox"/>	3	<input type="checkbox"/>
B	<input type="checkbox"/>	4	<input type="checkbox"/>
C	<input type="checkbox"/>	5	<input type="checkbox"/>
		6	<input type="checkbox"/>
		7	<input checked="" type="checkbox"/>
		8	<input type="checkbox"/>

Passage Category ▲ -

Cell	<input type="checkbox"/>
Egg	<input type="checkbox"/>
Mixed	<input type="checkbox"/>
Other	<input type="checkbox"/>

Geographic Grouping ▲ -

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Antarctica	<input type="checkbox"/>
Asia	<input checked="" type="checkbox"/>
Europe	<input type="checkbox"/>
North America	<input type="checkbox"/>
Oceania	<input type="checkbox"/>
South America	<input type="checkbox"/>

Country Name

Qatar	<input type="checkbox"/>
Saudi Arabia	<input type="checkbox"/>
Singapore	<input type="checkbox"/>
Sri Lanka	<input type="checkbox"/>
Syrian Arab Republic	<input type="checkbox"/>
Taiwan	<input type="checkbox"/>
Tajikistan	<input type="checkbox"/>
Thailand	<input type="checkbox"/>
Turkey	<input type="checkbox"/>
Turkmenistan	<input type="checkbox"/>
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Uzbekistan	<input type="checkbox"/>
Vietnam	<input type="checkbox"/>
Yemen	<input type="checkbox"/>

Host Group ▲ -

Animal	<input checked="" type="checkbox"/>
Environment	<input type="checkbox"/>
Human	<input type="checkbox"/>
Laboratory derived	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

Host Subgroup ▲ -

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mammals	<input type="checkbox"/>

Host Family ▲ -

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Duck	<input type="checkbox"/>
Eagle	<input type="checkbox"/>
Falcon	<input type="checkbox"/>
Goose	<input type="checkbox"/>
Grouse	<input type="checkbox"/>

Host Species ▲ -

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Host Subspecies

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Collection Date from to

Submission Date from to

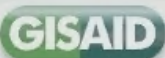
Harvest Date from to

☐ GISAID Viruses only ☐ INSDC Viruses only

Originating Lab ▲ -

[Argentina, Buenos Aires] Instituto Nacional de Enfermedades Infecciosas	<input type="checkbox"/>
[Argentina, Buenos Aires] Malbran	<input type="checkbox"/>
[Argentina, CABA Pcia. de Buenos Aires] Servicio de Virosis Respiratorias INEI-ANLIS Carlos G. Malbran	<input type="checkbox"/>
[Argentina, Capital Federal- Buenos Aires] Servicio de Virosis Respiratorias INEI-ANLIS "Carlos G. Malb...	<input type="checkbox"/>
[Argentina, Mar del Plata] Instituto Nacional de Epidemiologia	<input type="checkbox"/>
[Armenia, Yerevan] Centre for Diseases Control and Prevention	<input type="checkbox"/>

EpiFlu™ 2.0 – New “Publication Embargo Function”



GISAID published: 34.593 viruses with 89.498 Sequences

Total count: 113.361 viruses with 393.536 Sequences

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Viruses

Search in Results

Select All

Deselect All

Virus Name ▲

☐ A/Alaska/21/2014

☐ A/Austria/96/2014

☐ A/chicken/B15/Jiangxi/2014

☐ A/chicken/Italy/13VIR4527-11/2013

☐ A/Chicken/Kumamoto/1-7/2014

☐ A/chicken/Nepal/T-359/2014

☐ A/chicken/77/Jiangxi/2014

☐ A/duck/Jiangxi/95/2014

☐ A/Galicia/1786/2014

☐ A/Madrid/SO12318/2014

☐ A/mallard duck/Shanghai/SH-9/2013

7

A/Mato Grosso/55658/2014

☐ A/Paris/1823/2014

7

A/Sao Paulo/3-26852/2014

☐ A/silky chicken/Hong Kong/1772-...

et

Release Selected Viruses


F	Host	Submitting Lab
	Human	[United States, Atlanta] Cen...
	Human	[Austria, Vienna] Medical U...
	Animal/Avian/...	[China, Beijing] Tsinghua U...
	Animal/Avian/...	[Italy, Legnaro (PD)] Istituto ...
	Animal/Avian/...	[Japan, Tsukuba-shi] Natio...
	Animal/Avian/...	[United Kingdom, New Haw...
	Animal/Avian/...	[China, Beijing] Tsinghua U...
	Animal/Avian/...	[China, Shenzhen] BGI She...
	Human	[Spain, Madrid-Majadahond...
	Human	[Spain, Madrid-Majadahond...
	Animal/Avian/...	[China, Changchun] Institut...
	Human	[Brazil, São Paulo] Instituto ...
	Human	[France, Paris] Institut Past...
	Human	[Brazil, São Paulo] Instituto ...
	Animal/Avian/...	[Hong Kong (SAR), Hong K...


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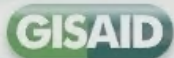
 IVHPP

7

Days of publishing embargo

 Analyze or Export Data

EpiFlu™ 2.0 – New IVHPP function (WHO PIP Framework)



GISAID published: 34.593 viruses with 89.498 Sequences

Total count: 113.361 viruses with 393.536 Sequences

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Viruses

Search in Results

☐ Select All

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☐ Show

Virus Name ▲

Vir

☐ A/Alaska/21/2014

A (H3N

☐ A/Alberta/01/2014

A (H5N

☐ A/Austria/96/2014

A (H3N

☐ A/Cambodia/X0810301/2013

A (H5N

☐ A/chicken/B15/Jiangxi/2014

A (H10

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A (H7N

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A (H5N

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A (H5N

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A (H10

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A (H3N

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A (H5N

☐ A/Jiangxi-Donghu/346/2013

A (H10

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A (H3N

☐ A/mallard duck/Shanghai/SH-9/2013

A (H5N

☐ A/Paris/1823/2014

A (H1N

☐ A/Shanghai/1/2013

A (H7N

☐ A/silky chicken/Hong Kong/1772-...

A (H7N

☐ A/Taiwan/2/2013

A (H6N

You are about to access

Data of an Influenza Virus with Human Pandemic Potential (IVHPP)

The Data provider advises that the use of the IVHPP Data for commercial purposes, including but not limited to manufacture of influenza vaccines, antiviral medicines or diagnostic materials, may be subject to the signing of Material Transfer Agreements.

Use of these IVHPP Data for academic research or fulfilling public health responsibilities are not subject to these special conditions.

If you intend to use the IVHPP Data for commercial purposes, you are strongly advised to [contact the Data provider](#) prior to the use of these genetic sequence Data.

☒ Continue

et

☒ Release Selected Viruses

EF

Host

**

Submitting Lab

Human

[United States, Atlanta] Cen...

Human

[Canada, Winnipeg] Public ...

Human

[Austria, Vienna] Medical U...

Human

[Cambodia, Phnom Penh] I...

Animal/Avian/...

[China, Beijing] Tsinghua U...

Animal/Avian/...

[Italy, Legnaro (PD)] Istituto ...

Animal/Avian/...

[Japan, Tsukuba-shi] Natio...

Animal/Avian/...

[United Kingdom, New Haw...

Animal/Avian/...

[China, Beijing] Tsinghua U...

Animal/Avian/...

[China, Shenzhen] BGI She...

Human

[Spain, Madrid-Majadahond...

Human

[Hong Kong (SAR), Hong K...

Human

[Indonesia, Jakarta] Nation...

Human

[China, Beijing] WHO Chine...

Human

[Spain, Madrid-Majadahond...

Animal/Avian/...

[China, Changchun] Institut...

Human

[France, Paris] Institut Past...

Human

[China, Beijing] WHO Chine...

Animal/Avian/...

[Hong Kong (SAR), Hong K...

Human

[Taiwan, Taipei] Taiwan CDC

 IVHPP

 Analyze or Export Data

Questions?

njc1@cdc.gov

Acknowledgements

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Dave Wentworth

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National Influenza Centers
WHO Collaborating Centers
Essential Regulatory
Laboratories

GISAID Colleagues

Peter Bogner
Anne Puhlman (FLI)
GISAID's TAG and SAC
Alan Hay

