The Public Health Importance of Timely Sharing of Sequence Data

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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

National Influenza Centers (NICs)
143 Laboratories in 113 Countries
- Detect and isolate influenza viruses
- Identify viruses and send to International Collaborating Center(s)
- Collect epidemiologic information

International Collaborating Centers
Atlanta, Beijing, London, Tokyo, Melbourne
- Analyze influenza viruses
- Provide data for annual vaccine strain recommendations
- Prepare and distribute candidate vaccine strains and reagents

World Health Organization
- Collect information for the Weekly Epidemiological Record and WWW for distribution
- Publish annual vaccine recommendations

Vaccine Manufacturers
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 health” because Asia is the believed to be the epicenter for influenza pandemics

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 them.

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 antivirals
- 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

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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 Protocol\(^4\) -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

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
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)
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.
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.
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)
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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.
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Questions?
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