Assessing Pandemic Risk and Evaluating US and Global Pandemic Readiness

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APHL Annual Meeting - June, 2018
Influenza Viruses and Pandemics
Influenza Viruses are Constantly Changing

- Surface proteins HA and NA critical for transmission and virulence
- Constantly evolving
- Eight separate gene segments, easily exchanged
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Shift: Reassortment Events Create Pandemic Viruses

• Human-adapted viruses can arise from reassortment to cause efficient and sustained transmission
• Four pandemics in last 100 years
• All have had genes from either avian or swine origin
Influenza A Viruses Since 1918

All three have hemagglutinin genes of avian origin
Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans

Rebecca J. Garten, 1,2 C. Todd Davis, 1,2 Colin A. Russell, 1,2 Bo Shu, 1 Stephen Lindstrom, 1 et al.

10 JULY 2009 VOL 325 SCIENCE
Are We Ready for the Next Pandemic?
Pandemic Readiness

- World more crowded, more connected, and the worlds of humans and animals are increasingly converging

- If 1918 pandemic were to occur today, estimated 105-110 million deaths

- WHO International Health Regulations (IHR) (2005)
  - Agreement with 196 countries for global health security
  - All agreed to build their capacities to detect, assess and report public health events
  - Only about 1/3 of the countries in the world currently have the ability to assess, detect and respond to public health emergencies

WHO. IHR. http://www.who.int/ihr/about/en/; IOM. https://www.nap.edu/read/11150/chapter/1
• **Strengths**
  - Domestic and global distribution of free testing materials via International Reagent Resource (IRR)
  - CDC PCR tests detect H1, H3, B’s, H5, H7 given to >140 labs globally
  - Greatly improved commercial flu assays for fast PCR results

• **Gaps**
  - Limited flu testing and poor lab capacity in developing nations
  - Slower to confirm novel flu
  - Simple, reliable, OTC tests not available
Global Surveillance Readiness

- **Strengths**
  - WHO Global Influenza Surveillance and Response System
    - 153 laboratories in 114 countries
    - Global molecular detection supported with rRT-PCR kits from IRR
  - CDC supports >30 countries for surveillance and novel flu detection
    - Building capacity to detect novel influenza viruses with pandemic potential, other threats

- **Gaps**
  - Lack of geographic and population level representativeness of seasonal viruses
    - ‘Data Deserts’ in Africa and Southern Hemisphere
    - Influenza not a priority in resource poor countries
  - Insufficient surveillance and reporting of influenza in animals
  - Specimen/virus sharing of influenza viruses with pandemic potential is complex which delays timeliness
Sequencing First Changes the Virus Characterization Paradigm

1. Specimen collection
   - Batching & Shipping
   - 1–2 weeks
   - AMD/Genomics
   - Drive
   - Phenotypic analysis
   - N ≈ 10,000/yr

2. Isolate and propagate
   - N ≈ 10,000/yr

3. Phenotypically analyze
   - N ≈ 10,000/yr

4. Genetic analysis: a subset
   - N ≈ 2,000/yr

Advantages
- Faster
- Cheaper
- More samples
- More data
- Better data

1. Specimen collection
   - 1 week
   - N ≈ 10,000/yr

2. Genetic analysis
   - N ≈ 10,000/yr

3. Isolate and propagate
   - N ≈ 2,000/yr

4. Phenotypically analyze
   - N ≈ 2,000/yr

Right-sizing US surveillance enhances ability to detect novel viruses
Domestic Surveillance Readiness: Sequence First and Next Generation Sequencing

Next Gen Sequencing at National Influenza Reference Centers: CA, WI, NY PHLs

APHL Informatics Message Services (AIMS) Cloud: assembly and analysis

Publicly Accessible Sequence Databases
GISAID
Genbank

CDC Technical Staff Monitor:
1) Next Gen Quality
2) Specimen submissions

~6,000 viruses per yr

CDC and National Reference Centers Influenza Genomic Surveillance

Running Total of Samples Sequenced

CDC
National Reference Centers
Influenza Genomic Surveillance

24K
22K
20K
18K
16K
14K
12K
10K
8K
6K
4K
2K
0K


Date Uploaded to GISAID

23,326

Accessed via APHL AIMS Cloud

GISAID
Genbank
Surveillance Readiness: What’s next?

Next Gen Sequencing
Key GISRS sites globally

Cloud assembly and analysis

Publicly Accessible Sequence Databases
GISAID
Genbank

Mobile Sequencing for Outbreaks:
MinION

CDC Technical Staff Monitor:
1) Next Gen Quality
2) Specimen submissions
Response Tools - Domestic

- **Strengths**
  - Risk assessment
    - CDC-Influenza Risk Assessment Tool (IRAT)
      - Used in pre-pandemic phase
  - Severity Assessment
    - CDC-Pandemic Severity Assessment Framework (PSAF)
      - Used when pandemic virus has emerged
      - Transmissibility and clinical severity
    - CDC Community Mitigation
      - New guidelines for non-pharmaceutical interventions

- **Gaps**
  - Need better tools for disease forecasting and operational modeling

Reed EID 2013; Qualls MMWR 2017
• **Strengths**
  - Risk assessment
    - European CDC
    - WHO-Tool for Influenza Pandemic Risk Assessment (TIPRA)
  - Severity Assessment
    - WHO Pandemic Influenza Severity Assessment (PISA) guidance

• **Gaps**
  - Disease surveillance and lab inputs for tools lacking in many countries

ECDC 2017; WHO 2016, 2017
• Strengths
  – HHS Pandemic Influenza Plan updated in 2017
    • Lessons learned from 2009
  – HHS vaccine and antiviral stockpiles
  – Pre-pandemic vaccine clinical trials (H5 and H7) provide knowledge for adjuvant use and dosing
  – CDC pandemic planning resources and tools
    • Updated Preparedness and Response Framework
    • Conducts pandemic response exercises

• Gaps
  – Healthcare infrastructure stressed by seasonal influenza epidemics
    • Saline shortages due to hurricanes
  – Pharmaceutical and non-pharmaceutical intervention components made outside of US
Global Preparedness Planning and Response

• Strengths
  – WHO Pandemic Influenza Preparedness (PIP) Framework, established 2011
    • Improve virus sharing and achieve more efficient and equitable access to benefits from sharing
    • Supports improved surveillance and response efforts in >70 countries
    • Industry partners have committed to provide to WHO:
      – 400 M vaccine doses for next pandemic
      – 10 million doses of antivirals
      – 250K diagnostic kits
  – Country Preparedness
    • WHO Joint External Evaluation (JEE) – peer review of capacity to respond to public health threats
    • Influenza-specific pandemic plans to augment operational readiness

• Gaps
  – Most countries do not have robust pandemic plans and very few exercise response efforts
    • Only 1/3 of countries ready for response based on IHR review
• **Strengths**
  - WHO’s continual risk assessment provides a pipeline for vaccine viruses
  - New vaccine technologies available
    - Synthetic biology for making vaccine viruses
    - Cell-grown vaccines
    - Recombinant protein
  - More manufacturing capacity available now
  - New programs for introducing vaccine for low- & mid-income nations

• **Gaps**
  - Current vaccines do not elicit longer-lasting, broad protection
    - Need to develop “universal vaccines”
  - Low- mid-income countries not prepared for mass vaccination in pandemic
  - Time to produce vaccine is too long
• In 2009, pandemic vaccine was available just after summer/fall peak
  – Decreasing this timeline is critical
• HHS has multiple initiatives
  – Improve yield of candidate vaccine viruses (CVV)
  – Develop alternative vaccine potency assays
• WHO has ongoing consultations with global partners to
  – Identify and solve bottlenecks in vaccine development
    • CVV development, biocontainment, manufacturing processes, clinical trials
  – Develop process, risk assessment for decision on when to switch from seasonal to pandemic vaccine production
Emerging Influenza Viruses with Pandemic Potential
• ~30-fold increase in no. zoonotic influenza cases reported from 1990s to 2000s

• Factors for emerging influenza virus:
  - People
  - Poultry
  - Pigs
  - Passengers

H5NX in Birds Spreads from Asia Globally

Point sizes for each type of bird corresponds to total number of cases. All points are equally transparent to show overlapping reports.
**A(H5N1)**
- 860 laboratory-confirmed cases, including 454 fatal cases in 16 countries
- Case fatality rate in reported cases remains 53%
- Human infections in Egypt (3) and Indonesia (1) in 2017

**A(H5N6)**
- 19 cases (12 fatal) reported to WHO since 2014
- Exposure to poultry main risk factor for H5 subtype human infections
- No sustained human-to-human transmission
H7N9 Cases Increasing Much Faster than H5N1

Cumulative Number of Human Infections of Avian Influenza A(H5N1) and A(H7N9) by Season, Nov 2017

- A(H5N1)
- A(H7N9)

Number of Human Infections

Year (Season)

Human Infections of A(H7N9) – 6 Waves

Epidemic Curve of Confirmed Avian Influenza A(H7N9) Virus Infections of Humans Reported by WHO or in Chinese Provincial or Hong Kong CHP Press Releases, 18 Feb 2013 – 26 Feb 2018 (N=1,567)
Geographic Distribution of Fifth Epidemic Confirmed Avian Influenza A(H7N9) Virus Infections of Humans, Reported by WHO or in Chinese Provincial or Hong Kong CHP Press Releases, October 1, 2016-September 30, 2017 (N=766)

- **Human Infections of A(H7N9) with HPAI mutation reported to WHO**
- **Human Infections of A(H7N9) with HPAI mutation identified by China CDC or Taiwan CDC**

LPAI human infections are by Province of Reporting; HPAI human infections are by Province of Exposure.
Influenza Older Men and Bird Markets – Common in All 5 Waves

- **Age**
  - Median 57 yrs (4 – 93 yrs)
  - In contrast, H5N1 is 19 yrs (5 – 32)
- **Gender**
  - Male 70%
- **Chronic Illness**
  - At least one underlying disease in 53%
- **Exposure**
  - Poultry/live bird market exposure in 90%
- **Severe human infections**
  - Pneumonia 90%; ICU admission 70%
  - Death in 39%
- **Clusters of infection (2 or 3 Persons)**
  - Similar number of clusters in all waves
  - No sustained human-to-human transmission

MMWR CDC and China CDC. Sept 2017; H5 Epi Lai et al Lancet 2016; China Daily/AFP
Yangtze Lineage Dominates Wave 5 – Evades Vaccine

- Yangtze Lineage
  - 97% of all Wave 5 viruses
  - Poor match to stockpiled 2013 vaccine

- HPAI H7N9 viruses first appeared in Wave 5
  - Four amino acid insertion in the cleavage site of the HA protein
  - 28 human cases of HPAI H7N9

- New Candidate Vaccine Viruses developed and in clinical trials
Influenza Risk Assessment Tool - IRAT

• A global public health tool to prioritize pandemic preparedness activities
  – Evaluates risk from novel viruses currently circulating in animals, i.e. in pre-pandemic period
• Assess potential pandemic risk for:
  – Emergence of a novel influenza virus in humans
    • Human-to-human transmission
  – Public health impact
    • Severity
• The IRAT can prioritize readiness activities
  – Diagnostics, reagents, vaccines and antivirals development
  – Stockpiling and deployment
• The IRAT cannot predict the next pandemic strain

CDC. https://www.cdc.gov/flu/pandemic-resources/monitoring/irat.htm
• CDC Influenza Risk Assessment Tool (IRAT)
  - Ten elements of the virus, population, and animal/human ecology are evaluated to develop a score

1. Genomic variation
2. Receptor binding
3. Transmission in Laboratory animals
4. Antivirals and Treatment Options
5. Existing Population Immunity
6. Disease Severity and Pathogenesis
7. Antigenic Relationship to Vaccine Candidates
8. Global Geographic Distribution
9. Infection in Animals, Human Risk of Infection
10. Human Infections and Transmission

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Influenza Risk Assessment using IRAT

- H7N9 in China has maintained the highest emergence and impact score since 2013

H7N9 in China has maintained the highest impact and emergence score since 2013.

Conclusions

• Influenza viruses are constantly changing, requiring ongoing surveillance and frequent vaccine virus changes.

• The number of detected emerging novel influenza viruses is increasing, requiring ongoing laboratory and epidemiologic investigations for risk assessments.
  - H7N9 is greatest risk.

• Many improvements in global and domestic pandemic readiness and response, however, many gaps remain.
Thank You!
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