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SEKISUI DIAGNOSTICS

“100 Years since the 1918 Spanish Flu Pandemic.
Current Standards for Flu Pandemic Preparedness”

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LEARNING OBJECTIVES

- Discuss the importance of having reliable, high performing diagnostic tests, especially for higher risk patients
- Describe how the FDA monitors compliance with the recently updated performance standards for rapid flu tests
- Explain how to determine whether a test meets FDA-required sensitivity and specificity
- Identify the most suitable tests for different testing scenarios
- Review the pros and cons of molecular and serological tests, plus manual and automated platforms

TOPICS TO BE COVERED TODAY

- Are we better prepared for the next Influenza A Pandemic?
- Improved tools for surveillance, therapy, vaccines and diagnostic tests
- The importance of reliable, high–performance diagnostic tests for influenza
- FDA's reclassification of influenza RIDTs update
- Different tests for different testing scenarios

INFLUENZA A VIRUS PANDEMICS

1918 Pandemic **H1N1**
(1918-1920)
Estimated US Deaths*= 675,000

1957 Pandemic **H2N2**
(1957-1960)
Estimated US Deaths*= 116,000

1968 Pandemic **H3N2**
(1968-1972)
Estimated US Deaths*= 100,000

2009 Pandemic H1N1 (H1pdmA)
(2009)
Estimated US Deaths**= 12,500

All four pandemics in last 100 years have had some genes that originated from avian influenza viruses

The 1918 Pandemic

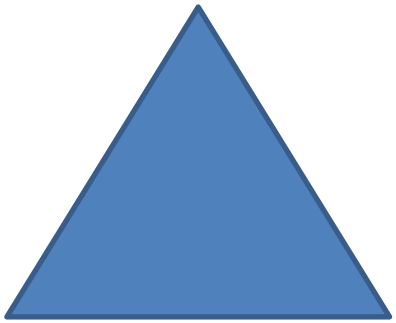
*Glezen WP. Epidemiol Rev. 1996. **Shrestha SS. Clinical Infectious Diseases 2011.

WHY MULTIPLE DEATHS IN 1918?

- Cause of influenza attributed wrongly to a bacillus- *Heamophilus influenz*ae, transmission poorly understood
- Few vaccines- cholera ,typhoid, plague
- Therapies used- aspirin,quinine, beef tea, opium
- Severe shortages of health care personnel- 30% physicians and many nurses deployed overseas (WW I)
- What has changed since then?

INFLUENZA: STILL A SIGNIFICANT ANNUAL BURDEN

12,000 –56,000
140,000 –710,000
9.2M –35.6M



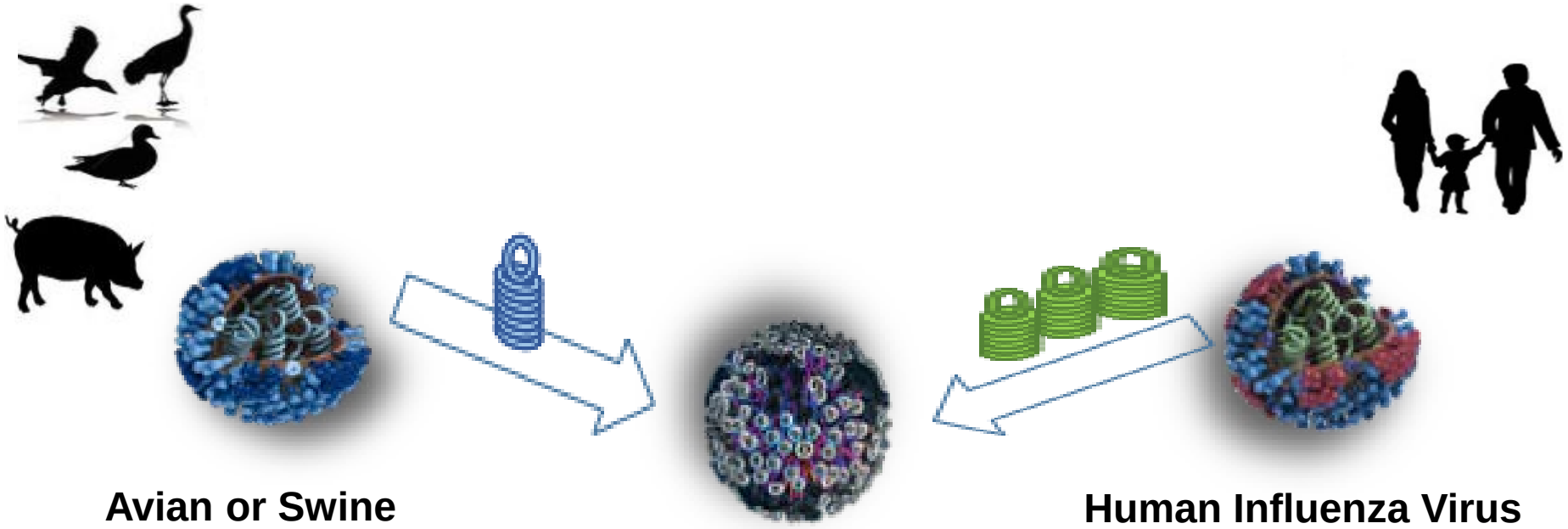
Deaths
Severe Cases
Hospitalization
Cases

2017-18- 80,000 deaths / A-H3N2

291,000 –646,000
3M to 5M
1.0 B

https://www.cdc.gov/flu/about/disease/2015-16.htm; http://www.who.int/immunization/topics/influenza/en/; Iuliano et al Lancet 2017

Cause: INFLUENZA VIRUS REASSORTMENT



Avian or Swine Influenza Virus

Human Influenza Virus

Reassorted Influenza Virus with Pandemic Potential

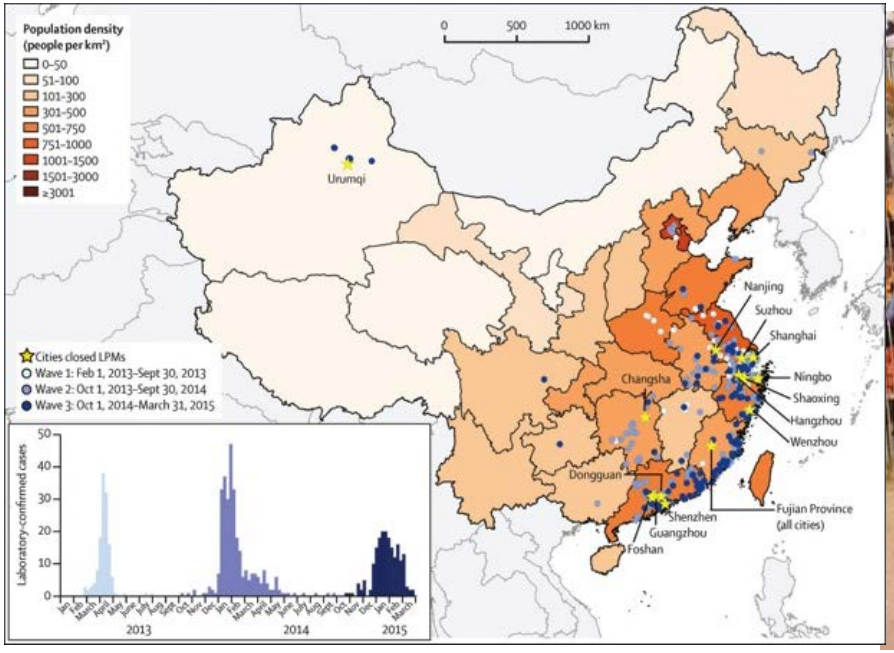
Human-adapted viruses can arise from reassortment to cause efficient and sustained transmission**. >30 fold increase in novel influenza A infection from 1990's to 2000's**

From: Influenza Division CDC

Next Threat: AVIAN INFLUENZA A (H7N9)?

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 66 / No. 35
September 8, 2017

Update: Increase in Human Infections with Novel Asian Lineage Avian Influenza A(H7N9) Viruses During the Fifth Epidemic — China, October 1, 2016–August 7, 2017



2018: ARE WE BETTER PREPARED ?

Issue: The world is more crowded and connected and habitat of animals and humans converging

Key Roles:

- Improved surveillance tools…CDC/PHL
- Improved therapy…CDC/NIH/Industry
- Improved diagnostic tests…FDA/CDC/ Industry

IMPROVED SURVEILLANCE TOOLS

Expanded global and domestic surveillance.CDC using sequencing technology to-

- Detect emerging novel or reassortant viruses
- Inform vaccine strain selection
- Detect and monitor antiviral resistance

Specimens/isolates received from → PHL → NIRC→ CDC and national clinical labs worldwide

General public awareness- CDC collaboration with 4H clubs *e.g. "Junior Disease Detectives*"

Gaps: Inadequate bird and swine screening.
Areas of world where no active collaboration

IMPROVED THERAPY

- Increased availability of antivirals
  - Oseltamivir, Zanamivir, Peramivir, Laninamivir
  - Stockpiled for use in emergency

- New vaccine technologies
  - Synthetic biology for making vaccine viruses
  - Cell-grown vaccines
  - Recombinant protein vaccines
  - More manufacturing capacity available

Gaps: Too long to make vaccine for pandemic response

Need a “universal” vaccine

Resistant viral strains

Shortages of ventilators

IMPROVED *In-vitro* DIAGNOSTIC TESTS

Currently Available:

- Traditional cell culture
- Molecular (RNA) & serological (antigen) tests - high complexity labs/trained users (result >30 min)
- Rapid molecular & serological tests (<30 min)
  - high/ medium complexity labs/ trained users
  - low complexity/ primary care /untrained users
- Manual or automated “walk-away” modes

Future Availability: “over the counter” /self testing?

- January 2018 FDA puts in place new performance requirements for all commercial antigen RIDTs

WHY NEW PERFORMANCE STANDARDS?

- Rapid antigen influenza diagnostics *were* regulated as Class I, did not all meet the needs of patients, physicians, or public health resulting in misdiagnosis and increased mortality. Reclassified to Class II devices with Special Controls
- Needed to mitigate known risks associated with poor performance due to viral antigenic changes
- To establish and maintain minimum performance criteria for RIDT's throughout their product life cycle
- To promote the development of new reliable, high performance influenza tests, especially for higher-risk patients

SPECIAL CONTROLS FOR CLASS II ANTIGEN RIDTs: IMPACT ON MANUFACTURERS

1. Minimum clinical performance criteria requirement demonstrated using a currently appropriate and FDA accepted comparator method.

2. Requirement for annual reactivity testing and results reporting

3. Provision for testing in a declared emergency or potential emergency once viral samples are available

MINIMUM CLINICAL PERFORMANCE CRITERIA & REFERENCE/COMPARATOR MEHOD

Specificity

All influenza antigen detection devices should demonstrate specificity with a lower bound of the 95% CI > 90% for Flu A and Flu B

Sensitivity

When compared to viral culture as the reference method:

- Flu A - Point estimate of 90%; 95% CI lower bound 80%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

When compared to a molecular comparator method:

- Flu A - Point estimate of 80%; 95% CI lower bound 70%
- Flu B - Point estimate of 80%; 95% CI lower bound 70%

2. ANNUAL REACTIVITY TESTING AND RESULT REPORTING

Manufacturers of Class II antigen RIDTs need a post-market test plan for annual reactivity testing with contemporary circulating viruses following a standardized protocol.

This will enable comparability between RIDTs

- These viruses are available each year from CDC
- Annual results recommended to be posted on manufacturer's web site

3. Any new emerging influenza strain will be available if a public health emergency is declared

WHAT IS UNCHANGED FOR DIAGNOSTIC MANUFACTURERS?

- Compliance with Good Manufacturing GMP regulations
- 510(k) submission to FDA for all new RIDTs, whether antigen or molecular, manual or reader result-based
- The requirement for all RIDTs to conduct clinical and analytical performance studies
- A CLIA waiver submission is required if intended use is POC
- Manufacturer’s responsibility to ensure reliable performance throughout the device's "Total Product Life Cycle”

FDA RIDT RECLASSIFICATION: Follow up

What is the status today of FDA's efforts to improve RIDT influenza antigen performance through reclassification?

RIDT RECLASSIFICATION: IMPLICATIONS FOR PHYSICIANS & LABORATORY FACILITIES

- Some manufactured and distributed influenza antigen RIDTs did not achieve the new Special Controls performance criteria and were withdrawn from the market January 12th, 2018
- Some locations experienced a shortage of RIDTs during last Influenza season due to the high incidence of cases Was this due to a lack of available antigen RIDTs?
- According to the FDA's belief there was no shortages of CLIA-waived rapid influenza tests. A February 2018 FDA web site Fact Sheet listed 6 antigen RIDTs that met the new performance criteria and 7 rapid molecular tests.

http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM596063.pdf

RIDT RECLASSIFICATION: IMPLICATIONS FOR PHYSICIANS & LABORATORY FACILITIES (cont.)

- When purchasing new influenza antigen RIDTs, physicians and laboratories are apparently checking test labeling claims and manufacturer's websites before ordering to see if a manufacturer conforms with the FDA's Special Controls for performance and strain detection

RECLASSIFICATION: IMPLICATIONS FOR DISTRIBUTORS OF ANTIGEN RIDTs

- After January 12, 2018, FDA did have the ability to take actions, pursuing seizure of Influenza RIDTs held by a distributor that do not meet the Special Controls

- Although a low FDA priority ,distributors should manage their inventory so that they only possess and distribute devices that meet the Special Controls

DIFFERENT INFLUENZA TESTS FOR DIFFERENT TESTING SCENARIOS (Pros.& Cons.)

- Viral Culture:

  Pros. Still considered as a reference method

  Cons. Losing skill set, variability between users

- Standard Antigen and Molecular Tests:

  Pros. Run in quality controlled lab with experienced technicians ,high throughput capability, reliable reagent storage conditions, part of large instr. menu

  Cons. Lab. space issues, costly investment, maintenance, longer time to result, not close to patient

DIFFERENT INFLUENZA TESTS FOR DIFFERENT TESTING SCENARIOS (Pros. and Cons)

- Rapid Antigen Tests:

Pros. Low cost, simple, manual or automated/minimum equipment, use in low resource settings, remote rural areas, physician's offices, or outpatient clinics

Have high positive predictive value, improved sensitivity, short time to results leads to appropriate treatment decisions, reducing use of antibiotics and timely administration of anti-virals and length of hosp. stay or doctor's office visit = isolate patients quicker

Cons. Lack of proficiency testing/competency assessment in low resource settings. Additional testing may be required to differentiate whether Flu A or B

DIFFERENT INFLUENZA TESTS FOR DIFFERENT TESTING SCENARIOS (Pros. and Cons.)

- Rapid Molecular Tests:

Pros. Can detect small amounts of genetic material using conserved gene targets, decreased hands on time, high sensitivity and specificity regardless of disease prevalence

Short time to results contributing to appropriate treatment decisions, e.g. reducing use of antibiotics and timely administration of anti-virals etc.

Cons. Some tests, (not all), have longer turnaround times than serology tests ,higher cost per test, high-complexity instrumentation may be required

Reader vs. Manual Results: Easier for record keeping

ADDITIONAL TIPS WHEN TESTING FOR INFLUENZA INFECTION

- Follow manufacturer's instructions, including all limitations
- Sample types cleared by FDA: Not always same for a 510(k) / CLIA waived device. Only CDC has claim for lower respiratory samples
- Quality of sample collection, storage and transport. Very important!
- Note limitations if testing in summer - more false positives when low prevalence of influenza
- Whole blood and mucus in a specimen can interfere with result
- Children shed more virus than adults
- Window for treatment success = less than 4 days after illness onset for molecular tests , best within 3 days for serological tests

WHY CONTINUE TO USE INFLUENZA ANTIGEN & MOLECULAR RIDTs?

All FDA cleared and CLIA waived antigen–based RIDTs that conform to the new FDA Special Controls reclassification requirements and all molecular–based tests will continue to be valuable tools for diagnosing influenza especially for high risk patients

IN SUMMARY:

- In preparing for future influenza pandemics we can avoid a tragedy & promote a healthier influenza season through improved diagnostic testing, surveillance, therapy & vaccines

1918

2018

Questions?