# Using Modern Technology to Surveil, Monitor, and Diagnose Infectious Disease

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December 18, 2017

# Agenda

- Surveillance
- History
- CDC's Traditional Approaches
- Digitally-based Systems
- Biosensor Program and NSSP
- Influenza
- Using RADTs with Wireless Capability for Surveillance
- Password-enable User Access to Transmitted Data
- Mobile App
- Comparison of RADT Performance to Dept. Of Health PCR
- RADT Use for Surveillance
- Future
- Conclusion

# Notice

Influenza has traditionally been considered a model system for surveillance and modeling.

For this reason, I will use influenza predominantly as the example for discussing the development and use of quickly changing surveillance technology.

Simonsen, L. et alia. J. Infect. Dis. 214 (suppl 4): S380-S385.

# Surveillance

# **Public Health Infectious Disease Surveillance Goals**

- Provide meaningful, actionable information on circulating pathogens
- Do so in a manner that is timely and can facilitate public health intervention

# Surveillance

### Important attributes

- Demographic information
- Representative of population
- Should be representative of special or geographic settings
- Clinical information quality (severity; recovery time; treatment)
- Epidemiology
- Assays' qualities (sensitivity and specificity and availability)
- Validation of outputs (often historical)
- Timeliness (close to real-time?)
- Cost

Temte, J. et alia. "Real Time Influenza Surveillance in Primary Care" J. Am. Board of Fam. Med., vol. 30 (5) 615-623 (2017) Simonsen, L. et alia. J. Infect. Dis. 214 (Suppl 4) S380-S385. (2016)

# Surveillance

### <u>Traditional Weaknesses</u>

- Dependent on sentinel site detection (voluntary)
- Dependent on Laboratory Reporting (not standardized; not timely)
- Often dependent, as well, on clinical observations
- Shortcoming of mechanistic tools specificity (e.g. Google Flu Trends)
- Inadequate dissemination of observations
- <u>Timeliness</u> is the number one short coming.

J. Temte et alia. "Real Time Influenza Surveillance in Primary Care" JABFM, vol. 30 (5) 615-623 (2017)

# **Surveillance Utility and Applications**

- 1. Helps public health officials prepare for unusual disease activity
- 2. Promotes timely vaccination campaigns
- 3. Improce risk assessments
- 4. Stimulates hospital and laboratory human resource planning
- 5. Triggers hospital and laboratory materials resource assessments
- 6. Enables issuance of warnings and educational notices for public
- 7. Facilitates pharmacy resource planning and allocations
- 8. Forecast time of arrival and geographic spread
- 9. Predict surge demand
- 10. Access to specimens for antigenic and molecular characterization and vaccine planning, as well as capabilities of existing diagnostic assays.

Yang et al. BMC Infectious Diseases (2017) 17:332 From: Nancy Cox, Ph.D., CDC, Options IX for Control of Influenza. Walsh, M. et alia. U.S. Pharmacist 42 (4): 32-36. 2017

# U.S. History

# **United States Public Health Service**

# 1798

John Adams, the second president of the United States, signed into law the "Act for the Relief of Sick and Disabled Seamen." A year later, Congress extended the Act to cover every officer and sailor in the U.S. Navy. The Act led to the gradual creation of a network of marine hospitals along coastal and inland waterways.



**President John Adams** 

# U.S PHS Public Health Service

History

**Founded: 1798** 

**Original mission:** 

- a. Protecting against spread of disease by sailors from foreign ports
- b. Checking and maintaining health of immigrants to our country

**<u>Restructured</u>**:

a. 1944, 1953, and became division of HHS in 1979

Mission today:

- a. Protect, promote, and advance the health and safety of the United States
- b. Responsible for NIH, CDC, FDA, HRSA, AHRQ, BARDA, ASPR et alia

### Origins of Food & Drug Administration

### Harvey Wiley



Division of Chemistry Dept. of Agriculture 1887 to 1902

### **1913 Movie Poster**



Upton Sinclair's Novel "The Jungle" Published in 1906

### **Government in Action**

### President Theodore Roosevelt



Signed the Wiley Act aka Federal Food & Drug Act 1906

### President Franklin Roosevelt



Signed the Food, Drug and Cosmetic Act 1938

### **FDA**

### **Food and Drug Administration**

History

Founded: 1906

**<u>Restructured</u>**:

a. 1927, 1940, 1953, and became division of HHS in 1980

**Mission today:** 

- Promote public health by assuring the safety, efficacy and security of human drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- b. Speed innovations to new medicines /devices that are safer and more effective
- c. Provide public accurate, science-based information need to use medicines to improve health
- d. Regulate manufacturing, marketing and distribution
- e. Provide industry with predictable, consistent, transparent and efficient regulatory pathways



Joseph Mountin 1891-1952 Founder of CDC 1946



Alexander Langmuir 1910-1993 1<sup>st</sup> Epidemiologist at CDC (first disease surveillance, 1949)



### **Centers for Disease Control and Prevention**

### History

Founded: on July 1, 1946

Original mission: field investigations, training, and control of communicable diseases.

**<u>Original Staff</u>: mostly entomologists and engineers (400 people)** 



### **Centers for Disease Control and Prevention**

### TODAY

<u>Mission</u>: To protect Americans from health, safety and security threats either of foreign or domestic origin, including chronic or acute disease human error, or deliberate attack

### **Strategic Areas**:

- 1. Support State and Local health Depts.
- 2. Improve global health
- 3. Implement measures to decrease leading causes of death
- 4. Strengthen surveillance and epidemiology
- 5. Reform health policies
- Staff: About 10,900 full time employees and ~3,000 consultants and part time support personnel.

https://www.cdc.gov/about/default.htm

### **2017 Budgets**

	Agency	Budget
FDA		\$5.1 billion
CDC		\$7.0 billion
	Total	\$ 12.1 billion

These programs represent a subset of activities aimed at helping to improve and secure good health for our citizens. And they all have very significant impact on surveillance and monitoring and diagnosis of our model disease—influenza. CDC's Traditional Programs

# **Overview of Influenza Surveillance** in the United States



### **CDC: Outpatient Influenza-like Illness (ILI) Surveillance**



"The number of specimens tested and % positive rate vary by region and season based on different testing practices....therefore it is not appropriate to compare magnitude of positivity rates or the number of positive specimens between regions or seasons."

### CDC: Outpatient Influenza-like Illness (ILI) Surveillance ILI-Net State Activity Indicator Map



Based on the number of outpatient visits to health care because of Influenza-like illness (ILI). "It does not measure extent of geographic spread within a state" and can be influenced by high levels in one city. Region to region comparisons are only rough estimates.

### **CDC: Outpatient Influenza-like Illness (ILI) Surveillance** Geographic Spread as Assessed by State and Territorial Epidemiologists



Data from state Depts. of Health are comprised of ILI patient visits to healthcare facilities and/or laboratory confirmed cases of influenza. The programs for each state are not standardized and vary significantly from state to state.

### **Pneumonia and Influenza Mortality Surveillance**



"Based on National Center for Health Statistics mortality surveillance data available on Nov. 30<sup>th</sup>, 5.7% of deaths ending on <u>Nov. 11</u> were due to P&I. This is below the epidemic threshold of 6.5%." There is a backlog of data requiring manual entry and this estimate is likely low.

### **CDC:** Influenza Hospitalization Surveillance Network



Rates are based on weeklycollected hospitalizations data that also report influenza positives by viral culture, DFA/IFA, PCR, and RIDT. "Rates are probably underestimated..."

From FluView Week 47, ending Nov. 27

Based on data collected from only 13 States.

### **CDC: Influenza-Associated Pediatric Deaths**



Similar data are not routinely presented for other high risk groups—pregnant, >65 yrs. of age, etc. in FluView.

### **CDC: U.S. Virologic Surveillance**



"The percentage of positives is not shown because PHLs usually get samples that have already tested positive. The actual incidence of influenza and the actual percentage positive is not available".

### CDC: U.S. Virologic Surveillance (cont'd.)



Detail about the types of circulating influenza types and strains is reliable. However, one cannot estimate actual positivity rate and prevalence in any region confidently.

# **U.S. CDC Surveillance Limitations**

- Passive system with delayed reporting (often 1-3 weeks)
- Compliance (voluntary) and poor
- Lacks standardization
- Costs impair reporting
- Does not collect incidence data
- Limited feedback mechanisms
- Trends not linked to demographics
- Problems with connectivity
- Sentinel sites do not calculate % positives
- Broader geographical spread needed

- Faster turn around needed
- More graphics and mapping features desired
- Missing epidemiological information
- Influenza-like-illness is often NOT influenza
- Traditionally based on numbers of patients' clinical visits.
- Collecting information from clinical records takes time and resources.

New Approaches Digitally-based Systems

# **Improving Data Access and Quality**

- 1. CDC is expanding the use of laboratory results from State Departments of Health
  - a. Results nearer to real-time
  - b. Enhanced efforts to get state participation and standardized systems
- 2. Supporting FDA's reclassification of rapid antigen detection tests for influenza
  - a. Improving the quality and clinical accuracy of RADTs for influenza (effective Jan. 12, 2018)
  - **b.** Ensuring performance versus emerging viruses

# **Overcoming Shortcomings of Traditional Methods Digital Influenza Surveillance**

<u>Problem</u>: traditional methods are slow, taking 1 to 3 weeks

<u>Goal</u>: The earlier the warning provided by surveillance, the sooner preventive and other control measures can be taken.

**Digital disease surveillance**: has been attempted and/or is being used to attempt to address this shortcoming.

Four categories of digitally-based systems:

- 1. Participatory Surveillance Systems
- 2. Internet News Data Systems
- 3. Search Query Systems
- 4. Social Media Systems

E. Nsoesie and J. Brownstein. Cell Host Microbe 2015 March11; 17(3) 275-278

# **Participatory Digital Surveillance Systems**

### Participatory Surveillance Systems

- 1. Consortium of registered members who voluntarily report how they feel; data are subsequently collated and disseminated to members, e.g. weekly.
- 2. <u>Challenges</u>: accuracy of reported data; lack of standardization; inadequate geographic coverage; reliability of participants.
- 3. Flu Near You is example.

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Voluntary Participation (you report how you've been feeling)



Crowdsourced Data (thousands of participants per week)



Visualized Map (thousands of participants per week)

# **Internet News Data Digital Surveillance Systems**

### **Internet News Data Systems**

- 1. Data procurement directly from Internet primarily with subsequent analyses to detect trends; analysis of data by time and geography; dissemination to public health and other entities
- 2. <u>Challenges</u>: unstructured sources of data complicate collation and analysis; huge amounts of unrelated data can hide important data
- 3. HealthMap is example



Online news aggregators, eyewitness reports, expertcurated discussions and validated official reports, to achieve a unified and comprehensive view of the current global status of disease.

# **Search Query Digital Surveillance Systems**

### **Search Query Systems**

- 1. Data procurement also directly from Internet, using key words and massive web data
- 2. <u>Challenges</u>: Key word changes can have profound effect; web user behavior between truly ill persons and those simply seeking information about a particular illness; requires frequent validations; specificity
- 3. Google Flu Trends is example.



Google Flu Trends is no longer publishing current estimates of Flu based on search patterns...Academic research groups interested in working with Google can approach them.

# **Social Media Digital Surveillance Systems**

### **Social Media Systems**

- 1. Based on individual reports of influenza or flu-like-illness, e.g. on Twitter, Facebook, and Google. Large amounts of data must be extracted and filtered and analyzed. Often use third party data as well, when available.
- 2. <u>Challenges</u>: The nature of the source of data introduces biases based on distribution across geographic location, age, race, and other demographics.
- 3. Sickweather is an example. It combines self-reported data as well as that extracted from social media systems.



"Sickweather scans social networks for indicators of illness, allowing you to check for the chance of sickness as easily as you can check for the chance of rain."
## Limitations Digital Surveillance Systems

#### Limitations

- 1. Differentiating signal from noise (specificity)
- 2. Biases due to representation of individuals in different locations or of different race, ethnicity, income, etc.
- 3. Differences between information and analysis of Internet-sourced data versus traditional, scientifically sound surveillance systems that are well-established (but need improvement)
- 4. Maintenance of privacy of individual's health data.
- 5. Paucity of published controlled studies

E. Nsoesie and J. Brownstein. Cell Host Microbe 2015 March11; 17(3) 275-278

Biosense Program and NSSP

# **CDC's BioSense Program**

### Launch

 Launched in 2003 in response to Public Health Security in Bioterrorism Preparedness Act of Congress in 2002

### Goals

- Improve capabilities for near real-time information and situational awareness
- Advance analytics for diagnostic data
- Increase sharing of data between federal, state and local PH agencies
- Promote standards and specifications to facilitate such integration

## CDC's BioSense Program (Cont'd.) NSSP

- Name Change
  - 2014, National Syndromic Surveillance Program (NSSP)
- Status
  - Over 4,000 hospitals report ED visit data
  - Represents 55% of all ED visits nationally
- Renewed Goals
  - Increase data availability and representativeness of ED visits regionally and nationally
  - Improve data quality
  - Facilitate use of data for situational awareness and response to hazardous events and disease outbreaks

# **Syndromic Data for NSSP**

- Patient Encounter Data
  - Emergency departments
  - Urgent care centers
  - Ambulatory Care
  - In-patient Healthcare
  - Pharmacies
  - Laboratory Data
  - School and Business Absentee Data
  - Social Media
- Use
  - Monitored in near "real-time" as indicator of an event or disease outbreak
  - Information shared between public health agencies

# Influenza as a Model

Why?

### Why Influenza?

United States		Global Impact		
Deaths	3-49К		250-500K	Deaths
Hospitalization	54-430K		3-5 million	Severe Cases
Cases/Year	15-60 million		>700 million	Cases/year

- The overall annual costs for influenza in the United States ranges from \$50 billion to \$87 billion dollars per year.
- Direct costs alone exceed \$10 billion/year.
- The virus undergoes antigenic drift constantly.
- The vaccines are only partially effective and must be remodeled and produced each year.
- A large percentage of our U.S. population is at high risk from influenza
- In 1918, 1957, 1968, and 2009 the virus underwent antigenic shift, causing pandemics, causing 766 thousands deaths in the U.S. alone.

From Nancy Cox, Ph.D., CDC, Options IX for Control of Influenza.

### **Individuals at High Risk from Influenza**

- Pregnancies/yr: 6,000,000
- Organ Transplants/yr: ~30,000
- Bone marrow transplants/yr: ~22,000
- Heart disease: 85.6 million
- Respiratory impairments (COPD and asthma) : 37.6 million
- Population > 65 years of age: 43 million
- Infants < 2 years of age: 8 million
- Diabetes and metabolic impairments: >>30 million
- American Indians and native Alaskans: 2.9 million
- Morbidly obese

#### This is a disease at need of the best possible surveillance.

#### **Rational for early detection of Influenza**



CDC. Community Mitigation Guidelines to Prevent Pandemic Influenza — United States, 2017. MMWR Recommendations and Reports 2017;66(1):1-32.

Using RADTs with Wireless Connectivity for Surveillance

### **RADT Data**

The following several slides show the use of results obtained with a CLIA-waived immunofluorescence-based lateral flow assay.

The result interpretation is obtained with an FDA-cleared, CLIA-waived instrument within 3 to 15 minutes, depending on virus level.

Interpretation is objective, automated, and can be wirelessly transmitted by an instrument.

CLIA-waived lateral flow cassette is inserted into Analyzer. It transmits ALL test results within 3-15 minutes.

Results are transmitted within seconds to minutes

Data are HIPAA compliant.

Data are encrypted.

Analyzer w/ Transmitter

#### **Surveillance Clouds**







2015-2016 season 238,000 patient results.. Peak positivity rate for A+B was March 7, 2016 at 34%.

2016 -2017 season 684,791 ILI patient results. Peaked February 9<sup>th</sup> at 35%.

This system has wirelessly conveyed results every night at midnight to CDC for over two years (>922,000 ILI patient results as of 9/1/17).





#### ~4,500 Transmitting Systems

>18,500 instruments

12-14-17

### **USA Influenza Status**

Sept. 1, 2016 to Dec. 16, 2017



Influenza positivity rate is 22.7% as of yesterday in the U.S. 5,410 patient results transmitted per day.

### **Arizona Influenza Status**

Sept. 1, 2016 to Dec. 16, 2017



Influenza A and B positivity rates are 33.1% and 3.3%, respectively! 255 tests transmitted per day. Strong onset!

### **Massachussets Influenza Status**

Sept. 1, 2016 to Dec. 16, 2017



Influenza positivity rates is only 4.7%. 71 tests/day. No Influenza YET. Password-Enabled User Access to Preprogrammed Analyses of Wirelessly Transmitted Data

### **User's Specific Access to Transmitted Data**

- Website confidential, password-enabled access to an organization's data.
- Analyzes facility's or facilities' test results using preprogrammed analytics and graphic capabilities.
- Allows monitoring trend in one's community, county, state and nation.
- Website data are updated automatically on a <u>daily</u> basis.
- These are <u>near real-time data</u> based on actual test results not on physician assessments that are based on signs and symptoms.
- Only HIPAA compliant, patient de-identified information is
- Data are available within seconds or minutes via a private, confidential password.

### **User Selects**

Pre-programmed Analyses, Charts, and Graphs

Patients by Assay Patients by Facility & Assay Patients by Facility & Result Patients by Result Patient Result Trends Percent Positive Results Quality Control Report Test Volume by Type (Influenza, RSV, Strep, etc.) Regional Mapping

Results are automatically update daily at midnight.

#### Texas: Influenza Status by (By MONTH) 1-1-17 to 12-1-17





In ten seconds, I was able to make the request and get the information above. The positivity rate has ramped quickly since October 15<sup>th</sup>

#### Texas: Influenza Status Patients By Run Date (By DAY) 9-1-17 to 12-1-17



Tests per day can be viewed historically and give advice on resource planning.

#### **Texas: Influenza Status by Mapping Feature**





11/1/17 to 12-1-17

#### DALLAS County: Influenza Status Patients By Run Date 12-1-16 to 12-1-17



You can look at trends in your country, states, and even facilities over durations of interest and selected by you.

#### **DALLAS COUNTY: Influenza Results by Facility**

#### **ONE WEEK'S RESULTS**

#### Nov. 24, 2017 to Dec. 1, 2017



There were 50 different sites transmitting results in Dallas County. User's can get real-time updates for one or more facilities for which they are responsible. User can review performance daily for all sites for which he/she is responsible.

Using wirelessly transmitted data for mobile app

# **Mobile App for Telephone**

## **Public Service App**

- Uses wirelessly-transmitted data on a daily basis
- Presents a near real-time influenza status (Map) for community, state, or nation by zipcode or county name
- Educates the public
  - What is influenza?
  - What are its symptoms?
  - How is it spread?
  - Who is at greatest risk?
  - Where can you get vaccinated
  - Where can you be tested?
  - Are there treatments?
  - How can influenza be prevented?



And if it's easy to **get** the flu, that means it's really easy to **give** the flu to others.



**Comparison of RADT's** wireless surveillance to Wisconsin's Surveillance

#### **EXAMPLE: Locations of Real-Time Influenza Surveillance Network**



J. Temte et al. "New method for real time influenza surveillance in primary care". JABFM (2017) 30 (5): 615-623

## Surveillance Population (N=1,133 ARI and/or ILI patients)



J. Temte et al. "New method for real time influenza surveillance in primary care". JABFM (2017) 30 (5): 615-623

## **Epidemic Curve**



### Comparison between Real-Time and WSLH PCR laboratory Network



RT-PCR data were delayed 1 to 2 weeks compared to near real-time result with this CLIA-waived RADT. N = 1,119 ILI or ARI patients.

### Comparison between Real-Time and WSLH PCR laboratory Network



### RADT Use for Surveillance
# Why RADTs?

- 1. In respiratory season, moving patients through the clinic quickly is important. Time for busy physicians, nurses and assistants comes at a premium.
- 2. Some RADTs give results within 3 minutes

3. The sooner antiviral therapy, e.g. oseltamivir or zanamivir, can be administered the better. Most effective within 48 hours of onset of illness.

4. Early treatment reduces virus production, secreted levels of virus, and risk of spreading disease in a community.

5. Early treatment diminishes symptomatic period by 1 to 2 days, reduces numbers of admissions, and reduces morbidity and mortality, especially in elderly and high risk groups.

#### Why RADTs (Cont'd.)

- 6. For hospitalized patients, increases antiviral use by 3x to 9X
- 7. For hospitalized patients, decreases antibiotic use by over 50% (antibiotic stewardship)
- 8. Invariably accompanied by reduction in other laboratory tests
- 9. Decreases length of stay in hospital
- 10. For hospitalized patients, early antiviral treatment reduces mortality
- 11. Recent guidelines recommend nonpharmacologic management and neuraminidase inhibitors (most effective within 48 hours)
- 12. Performance versus PCR can be excellent, depending on assay, time after onset of disease, proper sample collection

Blaschke, A. et alia. J. Pediatr Infect. Dis.Soc. 2013;doi:10.1093/jpids/pit071
Semret, M. et alia. J. Infect. Dis. 2017 vol. 216: 937-944
Appiah, G., et alia. Clinical Infectious Diseases, Volume 64, Issue 3, 364-367. 2017
Bonner, A., et alia. Pediatrics. 112: 363-367. 2003
J. Temte et alia. JABFM (2017) 30 (5): 615-623
Schweiger B. & Lehmann H., Robert Koch-Institut, National Reference Centre for Influenza, Berlin, Germany.

# **RADTs' Performance for Influenza Surveillance**

#### • <u>Limitations</u>.

- Clinical sensitivity and specificity. Must meet new FDA reclassification performance requirements.
- Geographic coverage
- Use in different settings sometimes limited

#### • Advantages

- Turn around Time
- Ease of Use
- Cost
- Used at different types of sites
- Automatic, objective result interpretation\*
- Wireless transmission within seconds to minutes\*
- Excellent sensitivity for samples taken within 48 hours of onset of symptoms\*

# Using RADTs with wireless connectivity, By Accessing Internet with Password, you can:

- Track arrival of influenza in your State, County, and community by Sofia and, now, by Solana.
- Anticipate staffing and inventory needs.
- Monitor test results in your organization and across your facility networks.
- Monitor and document QC results by operator and facility.
- Support operator/technical staff training initiatives.
- Provide Laboratory Director ready access to instrument and kit useage, testing frequency, resource needs—across your entire network of facilities.
- Facilitate forecasting (historical comparisons)
- Generate reports, charts, and graphs---all at one's finger tips.

# RADT, like the one I described, is of Value to Hospital and Healthcare Staffs

- Places medical director, ER physicians, pharmacy and hospital staff on early notice that influenza (or RSV or Strep A) is arriving in their community.
- Enables official notices to nurses, physician assistants and physicians that influenza is in the community
- Enables resource planning, e.g. antiviral needs
- Forecasts emergency room burden and resource needs
- Anticipates potential surge in hospital admissions
- Facilitates proper diagnosis of patients with ILI



# **Characteristics of Infectious Disease Surveillance Systems**



Data volume, complexity, or amount of preprocessing required

"Hybrid systems combining traditional surveillance with big data streams fall in the desirable zone associated with high information return and high data volume".

*From:* Simonsen, L. et alia. "Infectious Disease Surveillance in the Big Data Era: Towards Faster and Locally Relevant Systems. J. Infectious Dis. 214 (Suppl 4), S380-S385. (2016)



# Conclusion

- There is a long history of development and maturation of infectious disease surveillance in the United States, starting with President John Adams in 1798
- After 125 and 150 years, respectively, came creation of the FDA and CDC, respectively, in the 20<sup>th</sup> century.
- The CDC has led the way to develop reliable and useful surveillance to help ensure the public health and safety
- They have struggled with difficult-to-overcome impediments.
- The advances in diagnostic technology and digital communications bring new, exciting opportunities to the 21<sup>st</sup> century.

#### Conclusion (Cont'd.)

- Because they are new, they carry their own advantages and uncertainties, and these are only now being recognized, analyzed and addressed.
- The application of RADT assay(s) with wireless technology is one of the new capabilities that shows promise for surveillance and monitoring disease. Some molecular methods, not discussed, are already available as well.
- The future of surveillance will likely use some combination of all that has preceded, giving us a hybrid system that employs data from a wide breadth of sources.
- It is an exciting time, but needs a great deal of work and <u>investment</u> to validate the potential of the new methods---as well as of the anticipated hybrids of the new with the old.
- Government investment will be critical to achieving their potential.

