CDC Priorities to Detect, Prevent and Respond to Influenza

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October 7, 2020
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Influenza Division Strategic Priorities

- Improve influenza detection and control
- Improve epidemic and pandemic risk assessment and readiness
- Improve vaccine impact
National Influenza Vaccine Modernization Strategy

• **Objective 1:** Strengthen and Diversify Influenza Vaccine Development, Manufacturing, and Supply Chain

• **Objective 2:** Promote Innovative Approaches and Use of New Technologies to Detect, Prevent, and Respond to Influenza

• **Objective 3:** Increase Influenza Vaccine Access and Coverage Across All Populations
From Infection to Protection: CDC Activities Across the Influenza Spectrum

**DETECT**
- Global and Domestic Surveillance and Epidemiology
- Virus Characterization
- Risk Assessment
- Diagnostic Guidance
- Testing Capabilities
- Forecasting and Predictive Analytics

**CONTROL**
- Antiviral Supply Monitoring
- Resistance Monitoring
- Clinical Management and Antiviral Guidance
- Infection Control Guidance
- Outbreak Intervention
- Community Mitigation
- Travel and Border Intervention

**PREVENT**
- Vaccine Virus Development and Selection
- Vaccine Guidance
- Vaccine Supply
- Vaccine Campaign
- Vaccine Distribution
- Vaccine Effectiveness
- Vaccine Safety
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DETECT: Innovation in Flu Surveillance

- Comprehensive, layered surveillance that captures viral surveillance, ambulatory care, hospitalization, and mortality data
  - Same systems are being used for COVID-19
  - Surveillance in all U.S. States and through 143 laboratories globally

- Expansion for the 2020-2021 season
  - Adding 471 emergency departments to outpatient syndromic surveillance system ILINet
  - Expanding hospitalization surveillance with new mandated flu reporting from ALL hospitals daily
  - Increased Flu Surveillance at LTCFs – Testing COVID-19 specimens collected at LTCFs for flu
  - Adding Commercial Lab Flu Reports for County-level views
  - Adding Real-Time Flu Diagnosis Codes from >4700 EDs for facility-level views
DETECT: Innovation in Flu Diagnostics

**PRIORITY:** Expand global and domestic capacity for whole genome characterization of influenza viruses

**PRIORITY:** Improve CDC’s influenza virus characterization and surveillance monitoring systems to inform influenza vaccine composition

- Expanding global and domestic **next-generation sequencing**
  - Implemented cloud-based computing, storage and analysis
  - Piloting enhanced surveillance in key strategic locations globally
- Real-time sequencing and analysis in the field
  - **Developed a portable flu laboratory “Mia” (Mobile Influenza Analysis)**
  - Sequences the influenza genome and analyze influenza A viruses in real-time in the field during an outbreak
- Use of **new multiplex CDC test** at PHLs will add flu detection to specimens tested for SARS-CoV-2
  - Additional monitoring from direct diagnostic reporting
- Providing **testing guidance** for use of diagnostics for flu and SARS-CoV-2
DETECT: Innovation in Influenza Forecasting and Modeling

• ILI forecasting to support flu control has been in place for several years.

• This fall, CDC will be forecasting influenza hospitalizations for the public and for healthcare providers for planning.

• This forecast will be publicly available on the CDC website when flu has begun circulating.

• CDC maintains several influenza economic and transmission models to help inform prevention and control efforts.

https://www.cdc.gov/flu/weekly/flusight/index.html
DETECT: Influenza Risk Assessment for Emerging Novel Influenza Viruses

- Ten risk elements evaluated to develop a risk score:
  - properties of the virus
  - population immunity
  - animal and human ecology

- Scores determined for
  - Risk to emerge to cause human pandemic
  - Risk to cause significant human illness impact if emerges
From Infection to Protection: CDC Activities Across the Influenza Spectrum

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Influenza
CONTROL: Antiviral Treatment and Monitoring

• **Treatment and Management Guidance:**
  - Updated recommendations for clinicians for treating influenza during SARS-CoV-2 co-circulation
  - Outbreak management guidance on CDC website for state/local health department response
    - Cohorting and infection control
    - Antiviral prophylaxis
    - Vaccination as appropriate

• **Antiviral Medicine Tool:** MedFinder is a free, online service for consumers to search for pharmacy locations that offer anti-influenza drugs

• **Antiviral Monitoring:** Using manufacturer and pharmacy supply and dispensing data, trends in drug availability and use are monitored.
  - Expected 10 M doses available by season start
  - Looking to expand antiviral stocks in LTCFs
CONTROL: An advanced test to find virus drift and drug resistance

High-content Imaging Neutralization Test utilizes automatic digital microscopy

Improvements over traditional microneutralization:

- High-content imaging for accurate counting of virus-infected cells
- Can directly test clinical specimens for antigenic drift and drug susceptibility
- Simplified protocol (a single cycle infection eliminates the need for cell overlay)
- Expedites antigenic analysis by up to 10 days
- Improves sensitivity of antigenic analysis
- High throughput, automated format
CONTROL: Impact of Mitigations in Southern Hemisphere

- Experience from Australia, South Africa, Chile, and other countries in the Southern Hemisphere are seeing very little flu

- Declines attributed to:
  - Changes in the data, as fewer people left their homes to seek medical care for respiratory symptoms
  - Implementation of practices for preventing the spread of SARS-CoV-2, such as school closures, mask wearing, and social distancing

- In the US, there was a 61% decline in the number of respiratory specimens tested for flu, but a 98% decrease in the number testing positive for flu from late February to March

- Given these trends, CDC researchers believe that if there is continued widespread use of COVID-19 prevention strategies, along with seasonal flu vaccination, the impact of flu in the Northern Hemisphere during the upcoming flu season may be reduced

- It is not possible to predict exactly what will happen this fall and winter in the Northern Hemisphere, making it imperative to prepare for circulation of both flu and SARS-CoV-2 viruses

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6937a6-H.pdf
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PREVENT: Improving Vaccine Impact

• **PRIORITY:** Expanding virus characterization and increasing capacity of CDC laboratories to support manufacturers of vaccine
  - Begun a genomic approach for the selection of ideal cell-based candidate influenza vaccine viruses (CVVs) for isolation, characterization and down selection
  - Use of reverse genetics for synthetic virology to develop CVVs

• **PRIORITY:** Enhance evaluation of vaccine effectiveness (VE)
  - Expanded enrollment in outpatient clinics in multiple states to enable the U.S. Flu Vaccine Effectiveness (VE) Network to assess the effectiveness of cell based, recombinant and adjuvanted vaccines

• **PRIORITY:** Enhancing communication to increase vaccination
  - 2020-2021 expanded campaign
  - Focus on reducing disparities in vaccination
  - Discussed on Day 3 of Listening Session
PREVENT: Synthetic Virology Used to Generate Vaccine Viruses at CDC

**Emerging Virus Threat**
- RNA segments sequenced
- RNA Sequence Data Shared Electronically
- DNA synthesis of HA and NA surface antigens
- Create specialized “Reverse Genetics” constructs

**HA/NA**
- Synthetic HA and NA surface antigens
- Transfection mammalian cells
- Amplification
  - Seed stock
  - EID₅₀
  - Sequencing

**High growth virus**
- HA Yield
  - Preparative scale
  - Gradient Purification
  - BCA
  - IDMS/SDS-PAGE

**Reassortant CVV Master Stock**
- HA Yield
- Preparative scale
  - Gradient Purification
  - BCA
  - IDMS/SDS-PAGE
PREVENT: Monitoring Vaccine Effectiveness

Challenges to Vaccine Effectiveness Monitoring

- Universal recommendation: all ages ≥6 months
- Annual vaccination
- 4 vaccine subtypes/lineages
- Frequent vaccine strain updates
- Many vaccine formulations
PREVENT: Annual Estimates of Seasonal Influenza Vaccine Effectiveness, 2008-20

SEASONAL FLU VACCINE EFFECTIVENESS

<table>
<thead>
<tr>
<th>FLU SEASON</th>
<th>PERCENT EFFECTIVE</th>
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<tbody>
<tr>
<td>2008-09</td>
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<tr>
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<td>2018-19</td>
<td>31</td>
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<tr>
<td>2019-20</td>
<td>39</td>
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https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
PREVENT: Monitoring Vaccine Effectiveness

• All CDC affiliated networks are currently enrolling and collecting data on COVID-19 cases

• Outpatient Network – US Flu VE Network
  • 55 ambulatory care clinics, ages >6 months
  • Combined with genomic sequence data for clade-specific VE
  • Allows annual determination of influenza illness averted

• Hospital Networks
  • Hospitalized Adults Influenza VE Network (HAIVEN)
  • New Vaccine Surveillance Network (NVSN)

• ICU Networks of Adult and Pediatric Patients
  • Evaluates VE for severe ICU related outcomes
  • Also used to characterize multi-system inflammatory syndrome (MIS-C)

• Electronic Medical Record (EMR) platforms
  • VISION – Virtual network for VE
  • PREVENT – Pregnancy Influenza Vaccine Effectiveness Network
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Implementing the NIAID Strategic Plan for a Universal Influenza Vaccine

Alan Embry, PhD
Chief, Respiratory Diseases Branch
Division of Microbiology & Infectious Diseases
NIAID, NIH, DHHS
## Adjusted Influenza Vaccine Effectiveness Estimates in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Effectiveness</th>
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<tr>
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<td>10%</td>
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<tr>
<td>2005-06</td>
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<td>41%</td>
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<td>29%</td>
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Source: CDC
# Influenza Pandemics Occur

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtype</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>&gt;50 million</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td>2009</td>
<td>H1N1</td>
<td>~151K-575K</td>
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Source: CDC
Vaccine Lags Behind 2009 H1N1 Influenza Pandemic

Percent of ILI Visits Reported by Sentinel Providers, Weeks 30-50 2009

Children Return to School

6 months after virus isolation (April 2009), first vaccine doses become available

H1N1 Vaccine Doses Available

AS Fauci/NIAID
A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases

EJ Erbelding, D Post, E Stemmy, PC Roberts, A Deckhut Augustine, S Ferguson, CI Paules, BS Graham, AS Fauci
A universal flu vaccine should

- Be at least 75% effective
- Protect against group I and II influenza A viruses
- Have durable protection that lasts at least 1 year
- Be suitable for all age groups
NIAID Universal Influenza Vaccine Strategic Plan

Research Area 1
Improve Understanding of Transmission, Natural History & Pathogenesis

Research Area 2
Precisely Characterize Influenza Immunity & Correlates of Protection

Research Area 3
Support Rational Design of Universal Influenza Vaccines

- Develop and improve animal models & reagents
- Establish longitudinal cohorts
- Expand human challenge study capability and capacity
- Develop and apply systems biology approaches
CIVICs: A Comprehensive Program for Universal Influenza Vaccine Development

Vaccine Centers
- Iterative vaccine design, preclinical testing and in-depth immunologic analyses
- Assay & reagent development

External Advisory Board

Manufacturing & Toxicology Core

Clinical Cores

Statistical, Data Management & Coordination Center (SDMCC)
Multidisciplinary Network to Accelerate Development of Universal Influenza Vaccines
A Broad Spectrum of Approaches

- Recombinant protein
- LAIVs, VLPs
- Nanoparticle
- DNA, RNA
- Microneedle patch
Nanoparticle Platform for Universal Influenza Vaccines

Influenza Virus

Head region

Stem region

HA Stem

Nanoparticle Stem: Group 1 Influenza A

Nanoparticle Stem: Group 2 Influenza A

Nanoparticle HA: Mosaic for Groups 1 & 2

Courtesy of VRC

AS Fauci/NIAID
HA Stem Nanoparticle Phase 1 Underway (VRC 321)

- Phase 1 trial to evaluate dose, safety, tolerability and immunogenicity of influenza H1 stabilized stem ferritin vaccine in healthy adults

- Current status: 52/53 enrolled. Safe and well tolerated.

- Headless group 2 HA stem trimer on ferritin (VRC 323) starting fall 2020
A universal flu vaccine should

- Be at least 75% effective
- Protect against group I and II influenza A viruses
- Have durable protection that lasts at least 1 year
- Be suitable for all age groups

**Vaccine**
- Strain-specific
- Subtype-specific (e.g., H1)
- Multi-subtype (e.g., H1/H2/H5)
- Pan-group

**Coverage**
- Current circulating strains
- All strains within a single HA subtype
- Multiple HA subtypes within single group
- Covering all group 1 or 2
- All influenza A (+/- influenza B)

Courtesy Gary Nabel
NIAID-Supported Clinical Trials Informing Universal Vaccine Strategies

RedeeFlu (M2SR LAIV)
- Phase I H3N2 M2SR prime and IIV4 boost in subjects 9-17 years of age

M-001 Peptide Vaccine
- Phase II M-001 prime and IIV3/IIV4 boost in healthy adults

Adjuvanted Seasonal Vaccines
- Phase 1 study of Fluzone® or Flublok® with or without either AF03 or Advax-CpG55.2™ adjuvant in healthy subjects 18-49 years of age
Expanding Influenza Human Challenge Capacity

- Human challenge study successfully conducted at 4 NIAID VTEU sites
  - H1N1pdm09 strain (Dr. Matt Memoli, NIAID)

- GMP manufacture of 2 new influenza challenge strains
  - H3N2 (Clade 3C3a)
  - H1N1 (Clade 6B.1)

- Dose-finding human challenge study planned for 2021
Advances In COVID-19 Will Inform Influenza Strategies

- Together with USG partners, advancing novel vaccine platforms
- Innovations in diagnostic technologies
- Natural history studies to compare COVID-19 and influenza disease course and immunopathology
- Therapeutic strategies to treat severe disease

Siddiqi and Mehra, J Heart Lung Transplant. 2020 May; 39(5): 405-407
Thank you