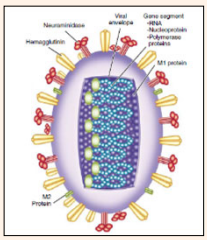
Update on Influenza Vaccination

Overcoming Barriers and Tailoring Vaccine Selection

1

Influenza: The Virus

- Orthomyxoviridae virus
- Key components
  - Hemagglutinin
    - Viral attachment to cell
    - Membrane fusion
  - Neuraminidase
    - Facilitates virus movement
    - Prevents aggregation of newly-formed virus particles

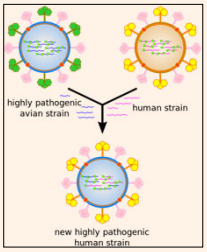


Treanor JT. Influenza. In: Mandell GL, ed. *Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier; 2010: 2265-2288.

2

Epidemiological Terms

- Antigenic drift
  - Amino acid point mutations in hemagglutinin or neuraminidase
  - Seasonal epidemics
- Antigenic shift
  - Large genetic changes lead to emergence of serologically new viruses to which population has no immunity
  - Pandemic flu



CDC. *MMWR Recomm Rep.* 2013; 62(7): 1-43.
Treanor JT. Influenza. In: Mandell GL, ed. *Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier; 2010: 2265-2288.

3

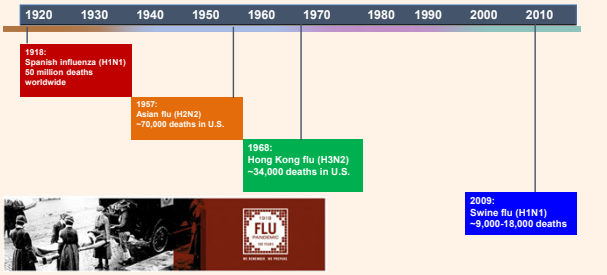
Influenza Transmission

- Spread by contact with respiratory secretions
- Virus attaches to and penetrates columnar epithelial cells of respiratory tract
- Incubation period of 18–72 hours
- Virus remains detectable for 5–10 days

Treanor JT. Influenza. In: Mandell GL, ed. *Principles and Practice of Infectious Diseases*. Philadelphia, PA: Elsevier; 2010: 2265-2288.

4

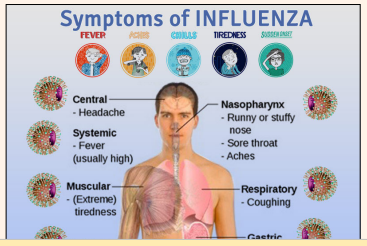
Major Influenza Pandemics



The College of Physicians of Philadelphia. Influenza Pandemics. Available at: https://www.historyofvaccines.org/index.php/content/articles/influenza-pandemics.

5

Symptoms of INFLUENZA



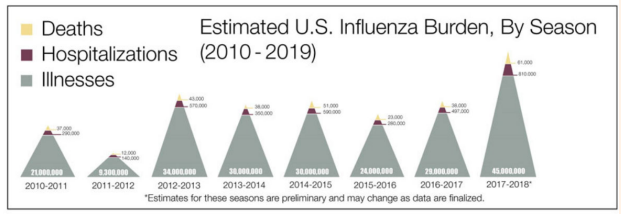
CDC. Flu Symptoms & Complications. Available at: https://www.cdc.gov/flu/consumer/symptoms.htm.

Is it Flu or COVID-19?

Some of the symptoms of flu and COVID-19 are similar, making it hard to tell the difference between them based on symptoms alone. Diagnostic testing can help determine if you are sick with the flu or COVID-19.

6

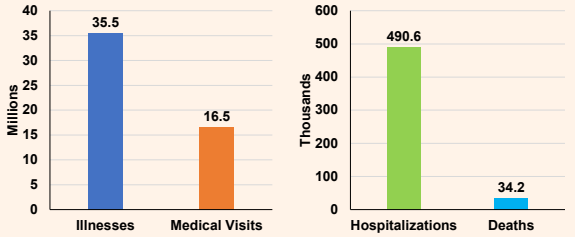
Impact of Influenza



CDC. Available at: https://www.cdc.gov/flu/about/burden/index.html.

7

2018-2019 Influenza Season



CDC. Available at: https://www.cdc.gov/flu/about/burden/2018-2019.html.

8

Influenza Vaccine Priorities

- **ALL 6+ MONTHS WANTING TO PREVENT INFLUENZA**
- **HEALTHCARE WORKERS**
  - High risk for disease (symptomatic and asymptomatic)
  - High risk for transmission
  - If sick, not available to provide healthcare…
- **PATIENTS @ Highest Risk (severe illness/spread)**
  - Pregnant women
  - Newborns and children
  - Elderly
  - "Medical Comorbidities"
  - Household contacts of high-risk
  - Long-term care, institutionalized, crowded living conditions

Does this sound like your patients? That's why YOU need a vaccine.

CDC. Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w.

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Patients at High Risk for Influenza Complications

- Adults 65+
- Children <2yo
- Asthma
- Neurologic conditions
- Blood disorders
- Chronic lung disease
- Endocrine disorders
- Heart diseases
- Kidney diseases
- Liver disorders
- Metabolic disorders
- Obesity (BMI>40 kg/m^2)
- Weakened immune system
- Pregnant women
- Native Americans/Alaska Natives
- Nursing home residents
- Long-term care residents

CDC. Available at: https://www.cdc.gov/flu/highrisk/index.htm.

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Consequences and Complications

- Increased work/school absenteeism
- Fever, cough, myalgia
- Laryngotracheobronchitis
- **Secondary Bacterial Pneumonia:**
  - Uncomplicated influenza illness followed by 4–14 days of improvement
  - Recurrence of fever, cough, sputum production
  - New consolidation on chest X-ray
  - Likely pathogens: *S. pneumoniae, H. influenzae,* ***S. aureus***
- Myositis: elevated creatine kinase and myoglobinuria
- Myocarditis and pericarditis
- Reye's syndrome: post-viral encephalopathy that occurs in children
- Hospitalization and death

Treanor JT. Influenza. In: Mandell GL, ed. *Principles and Practice of Infectious Diseases.* Philadelphia, PA: Elsevier; 2010: 2265-2288.
Cate TR. *Am J Med.* 1987;82:15-19.

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Annals of Internal Medicine — ORIGINAL RESEARCH

Acute Cardiovascular Events Associated With Influenza in Hospitalized Adults

A Cross-sectional Study

Eric J. Chow, MD; Melissa A. Rolfes, PhD; Alissa O'Halloran, MSPH; Evan J. Anderson, MD; Nancy M. Bennett, MD;

- 80,261 adults with confirmed flu & complete medical record abstraction
- Median age 69 (IQR 54 – 81)
- 11.7% with an acute cardiovascular event
  - aHF 6.2%, aIHD 5.7%
- Increase risk with:
  - Age, tobacco use, previous CV disease, diabetes, renal disease

aHF, acute heart failure; aIHD, acute ischemic heart disease
Chow EJ, et al. *Ann Intern Med.* 2020;doi: 10.7326/M20-1509 [Online ahead of print].

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The Journal of Infectious Diseases

MAJOR ARTICLE

Prevention of Influenza Hospitalization Among Adults in the United States, 2015–2016: Results From the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN)

Jill M. Ferdinands,[1] Manjusha Gaglani,[2] Emily T. Martin,[3] Don Middleton,[1] Arnold S. Monto,[3] Kempapura Murthy,[1] Fernanda P. Silveira,[4] H. Keipp Talbot,[4]

- 236 cases, 1231 controls, mean age 58 years, H1N1 year
- 90% with 1 or more comorbidities
- Vaccination **halved** the risk of influenza-associated hospitalization

Ferdinands JM, et al. *J Infect Dis.* 2019;220:1265. https://doi.org/10.1093/infdis/jiy723.

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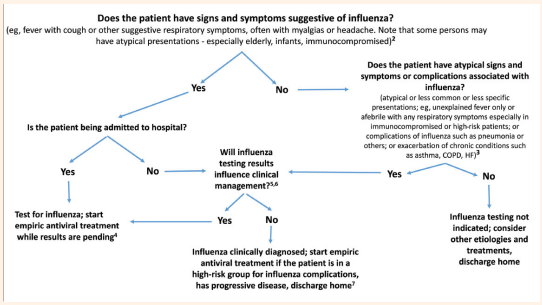
Moderate to Severe Influenza Complications

- Pneumonia
- Myocarditis
- Encephalitis
- Myositis, rhabdomyolysis
- Multi-organ failure
- Sepsis
- Exacerbation of chronic medical conditions

CDC. Available at: https://www.cdc.gov/flu/symptoms/symptoms.htm#complications.

14

Testing



Uyeki TM, et al. *Clin Infect Dis.* 2019;68:e1-e47.

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Influenza Testing Methods

Table 6. Influenza Diagnostic Tests for Respiratory Specimens

Testing Category	Method	Influenza Viruses Detected	Distinguishes Influenza A Virus Subtypes	Time to Results	Performance
Rapid molecular assay	Nucleic acid amplification	Influenza A or B viral RNA	No	15–30 minutes	High sensitivity; high specificity
Rapid influenza diagnostic test	Antigen detection	Influenza A or B virus antigens	No	10–15 minutes	Low to moderate sensitivity (higher with analyzer device); high specificity;
Direct and indirect immunofluorescence assays	Antigen detection	Influenza A or B virus antigens	No	1–4 hours	Moderate sensitivity; high specificity
Molecular assays (including RT-PCR)	Nucleic acid amplification	Influenza A or B viral RNA	Yes, if subtype primers are used	1–8 hours	High sensitivity; high specificity
Multiplex molecular assays	Nucleic acid amplification	Influenza A or B viral RNA, other viral or bacterial targets (RNA or DNA)	Yes, if subtype primers are used	1–2 hours	High sensitivity; high specificity
Rapid cell culture (shell vial and cell mixtures)	Virus isolation	Influenza A or B virus	Yes	1–3 days	High sensitivity; high specificity
Viral culture (tissue cell culture)	Virus isolation	Influenza A or B virus	Yes	3–10 days	High sensitivity; high specificity

Uyeki TM, et al. *Clin Infect Dis.* 2019;68:e1-e47.

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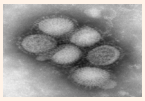
The Seasonal Influenza Vaccine Changes Annually

- Egg-based vaccine production: ~9 months
- Strain choice (Feb) reflects antigenic drift
  [Prior season + Southern Hemisphere]
- US Vaccination season: Vaccine available to 'disease passed'…



CDC. Available at: https://www.cdc.gov/flu/season/faq-flu-season-2020-2021.htm

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The Seasonal Influenza Vaccine Changes Annually

- 2020-2021 trivalent **egg-based vaccines** are recommended to contain:
  - A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus (updated)
  - A/Hong Kong/2671/2019 (H3N2)-like virus (updated)
  - B/Washington/02/2019 (B/Victoria lineage)-like virus (updated)
- Quadrivalent **egg-based vaccines**, add B/Phuket/3073/2013-like (Yamagata lineage) virus.
- For 2020-2021, **cell- or recombinant-based** vaccines are recommended to contain:
  - A/Hawaii/70/2019 (H1N1)pdm09-like virus (updated)
  - A/Hong Kong/45/2019 (H3N2)-like virus (updated)
  - B/Washington/02/2019 (B/Victoria lineage)-like virus (updated)
  - B/Phuket/3073/2013-like (Yamagata lineage) virus

CDC. Available at: https://www.cdc.gov/flu/season/faq-flu-season-2020-2021.htm.

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Available Influenza Vaccine Types

- Inactivated (IIV)
  - Quadrivalent (IIV4)
    - Standard dose egg based
    - High dose egg based
    - Adjuvanted (aIIV4)
  - Trivalent (IIV3)
    - Adjuvanted (aIIV3)
- Inactivated cell culture-based
  - Quadrivalent (ccIIV4)
- Recombinant
  - Quadrivalent (RIV4)
- Live Attenuated
  - Quadrivalent (LAIV4)

CDC. Available at: https://www.cdc.gov/flu/professionals/acip/summary/summary-recommendations.htm#timing.

19

Influenza Vaccine Regular Dose

IIV4: 'Killed', injectable

- 6 months and older– Quadrivalent (IIV4)
- FDA-indicated ages may vary by manufacturer:
  - Practically speaking, these vaccines are for anyone who doesn't have a contraindication to influenza vaccine

IIV, Inactivated Influenza vaccine

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Influenza Vaccine High Dose

IIV4, high-dose (Fluzone® High-Dose)

- Contains 60 mcg each of the 4 influenza antigens (compared to 15 mcg each for regular IIV4)
  - Slightly higher rate of MILD reactions
- Indications: Patients ≥65 years
- Clinical trial had shown high-dose vaccine was 24.2% more effective in preventing influenza in adults ≥65 than the standard vaccine.

Fluzone High-Dose (Influenza Vaccine) Prescribing Information. Sanofi Pasteur Inc. Swiftwater, PA. July 2020.
DiazGranados CA, et al. *N Engl J Med.* 2014;371:635-45.

21

Influenza Vaccine Adjuvanted Vaccine

aIIV4, adjuvanted vaccine (Fluad®)

- Quadrivalent inactivated influenza vaccine plus a proprietary adjuvant that is proposed to recruit immune cells at the site of injection and enhance antigen uptake
  - Results in potentially greater immunogenic response in elderly patients
- Indication: Patients ≥65 years
- Clinical trials show non-inferiority with IIV3 based on seroconversion and geometric mean titers
  - No data yet available that demonstrate decrease in influenza disease

Fluad® (influenza vaccine, adjuvanted) Prescribing Information. Sequiris, Inc., Holly Springs, NC. June 2020.
Fluad® Quadrivalent (influenza vaccine, adjuvanted) Prescribing Information. Sequiris, Inc., Holly Springs, NC. June 2020.

22

Influenza Vaccine
Cell-Cultured and Recombinant Vaccines

- **ccIIV4 (Flucelvax® Quadrivalent)**
  - In place of chicken eggs, uses animal cells (Canine Kidney) as host (reference strain obtained from virus originally grown in eggs); quadrivalent
  - Approved for ages ≥4 years
- **RIV4 (Flublok®)**
  - Recombinant vaccine— egg-free hemagglutinin influenza vaccine produced by recombinant DNA technology using a baculovirus (a virus that infects insects) that produces virus-like particles, hemagglutinin (vaccine of choice for true egg allergy)
  - Approved for ages **≥18 years**
- Adverse events similar to other inactivated vaccines

Flucelvax® Quadrivalent (influenza vaccine) Prescribing Information. Sequiris, Inc., Holly Springs, NC. July 2020.
Flublok® (influenza vaccine) Prescribing Information. Protein Sciences Corp., Meriden, CT. September 2020.

23

Live Attenuated Influenza Vaccine (LAIV4; FluMist®)

- Cold-adapted nasal vaccine; quadrivalent
- Licensed only for healthy people 2 through 49 years
- Approved by ACIP for 2020–21 flu season
  - Not recommended for 2016–17 and 2017–18 flu seasons
- Once again recommended as a first-line vaccine by American Academy of Pediatrics

FluMist® Quadrivalent (influenza vaccine live, intranasal) Prescribing Information. MedImmune, LLC, Gaithersburg, MD. August 2020.

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Alphabet Soup of Influenza Vaccines

- **IIV4:** Quadrivalent Inactivated Influenza Vaccine (standard and high dose)
- **ccIIV4:** Cell culture-based
- **aIIV3 & 4** Tri & Quadrivalent Adjuvanted Inactivated Influenza Vaccine
- **RIV4** Recombinant Influenza Vaccine
- **LAIV4** Live Attenuated Influenza Vaccine

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Vaccination: ACIP Recommendations

- **6 mos – 3 yrs**
  - FluLaval Quadrivalent
  - Fluarix Quadrivalent
  - Fluzone Quadrivalent
  - Afluria Quadrivalent
- **Pregnant Women (any trimester)**
  - IIV or RIV4
  - No LAIV
- **Immune Compromised**
  - No LAIV
- **Older Adults**
  - Get the vaccine
  - Which one? It's complicated…

CDC. Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w.

26

Vaccination: What About Egg Allergy?

- Not a contraindication to any product
- Recommendation
  - Any history of severe allergic reaction to eggs warrants vaccination in a medical setting under the supervision of "a health care provider who is able to recognize and manage severe allergic conditions."
  - A previous severe reaction to any influenza vaccine is a contraindication.

CDC. Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w.

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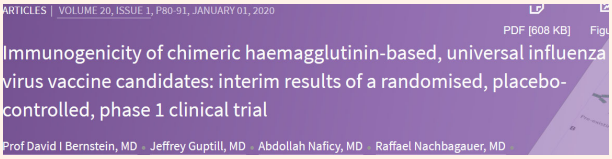
EDITORIAL | VOLUME 18, ISSUE 5, P475, MAY 01, 2018

PDF [57 KB]

Plotting a route to a universal influenza vaccine

The Lancet Infectious Diseases

Published: May, 2018 · DOI: https://doi.org/10.1016/S1473-3099(18)30235-4 · Check for updates


ARTICLES | VOLUME 20, ISSUE 1, P80-91, JANUARY 01, 2020

PDF [608 KB]

Immunogenicity of chimeric haemagglutinin-based, universal influenza virus vaccine candidates: interim results of a randomised, placebo-controlled, phase 1 clinical trial

Prof David I Bernstein, MD · Jeffrey Guptill, MD · Abdollah Naficy, MD · Raffael Nachbagauer, MD

28

Brainstorming and Audience Participation

- How do you choose a vaccine type?
- Does it matter?

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Prepare Yourself: The Pregnancy/Vaccine Questions are Coming

- Study published in the September 25, 2017 issue of *Vaccine*
- Case-control, covered two influenza seasons (2010–11 and 2011–12)
- Spontaneous abortion was associated with receipt of influenza vaccination in the previous 28 days (adjusted OR 2.0 [95% CI, 1.1–3.6])
- No causal relationship established due to study size
- What has been established is the risk of *severe influenza-related consequences* to mother and fetus

Donahue JG, et al. *Vaccine.* 2017;35:5314-22.

30

Influenza Vaccine Supply

- Many issues in prior years
- Current 2020-21 season projection
  - 194–198 million doses
  - Approximately 87% of doses will be thimerosal-free
  - Approximately 99% of doses will be quadrivalent
  - Approximately 80% of doses are produced with eggs

CDC. Available at: https://www.cdc.gov/flu/prevent/vaxsupply.htm.

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Yes, vaccines may cause adverse effects

- But the most common thing they cause is…

Adults

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Case Exercise 1
Which vaccine for:

A 67-year-old man with type 2 diabetes mellitus and no history of egg allergy?

1. IIV4, standard
2. IIV4, high-dose (Fluzone High-Dose)
3. LAIV4
4. ccIIV4 (Flucelvax)
5. Any of the above
6. 1, 2, or 4

33

Case Exercise 1
Which vaccine for:

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3. LAIV4
4. ccIIV4 (Flucelvax)
5. Any of the above
6. 1, 2, or 4

34

Case Exercise 2
Which vaccine for:

A 27-year-old woman with well-controlled asthma and hive-form reaction to eggs?

1. No vaccine
2. IIV4, standard
3. aIIV3 (Fluad)
4. RIV3 (Flublok)
5. 2, 3 or 4
6. 2 or 4 only

35

Case Exercise 2
Which vaccine for:

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1. No vaccine
2. IIV4, standard
3. aIIV3 (Fluad)
4. RIV3 (Flublok)
5. 2, 3 or 4
6. 2 or 4 only

36

Case Exercise 3
Which vaccine for:

A 17-year-old with history of severe allergic reaction (i.e., respiratory distress) to flu vaccine?

1. IIV4, standard
2. LAIV4
3. RIV3 (Flublok)
4. ccIIV4 (Flucelvax)
5. No vaccine/refer to specialist
6. 3 or 4 only

37

Case Exercise 3
Which vaccine for:

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1. IIV4, standard
2. LAIV4
3. RIV3 (Flublok)
4. ccIIV4 (Flucelvax)
5. No vaccine/refer to specialist
6. 3 or 4 only

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Case Exercise 4
Which vaccine for:

A 25-year-old woman in second trimester of pregnancy?

1. IIV4, standard
2. LAIV4
3. No vaccine until after birth
4. 1 or 2

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Case Exercise 4
Which vaccine for:

A 25-year-old woman in second trimester of pregnancy?

1. IIV4, standard
2. LAIV4
3. No vaccine until after birth
4. 1 or 2

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