Homeland Defense & Security
Information Analysis Center

Influenza and the Department of Defense

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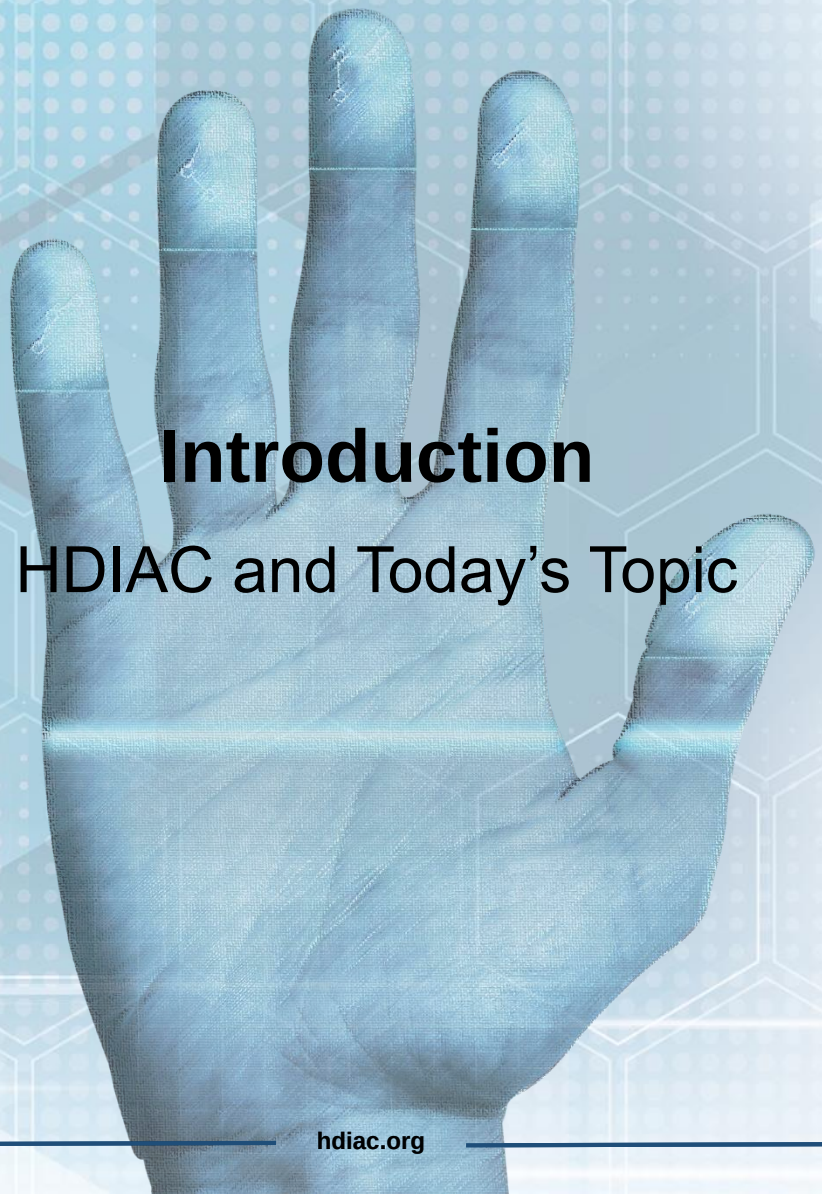
HDIAC Subject Matter Expert

February 28, 2018



Introduction

HDIAC and Today's Topic

HDIAC Overview

What is the Homeland Defense & Security Information Analysis Center (HDIAC)?

One of three Department of Defense Information Analysis Centers

Responsible for acquiring, analyzing, and disseminating relevant scientific and technical information, in each of its eight focus areas, in support of the DoD and U.S. government R&D activities

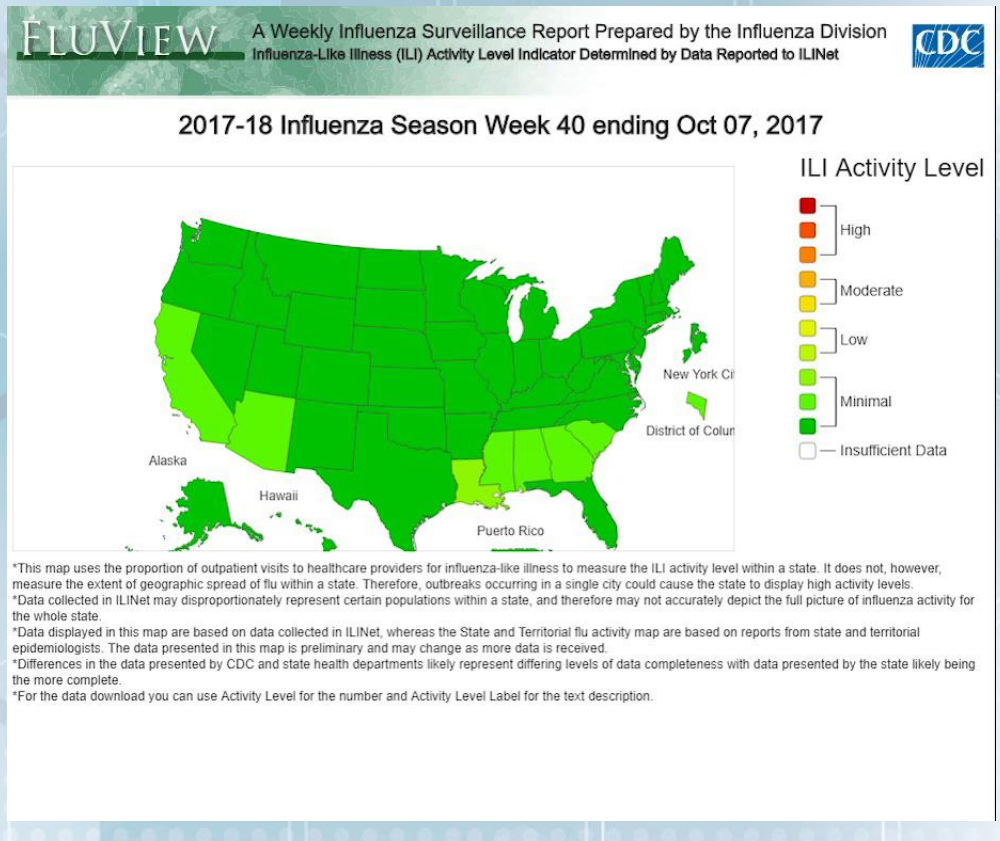
HDIAC's Mission

To provide authoritative, responsive solutions by generating, acquiring, processing, analyzing, and disseminating relevant information and analysis to our customers

Why the Flu? Why Now?

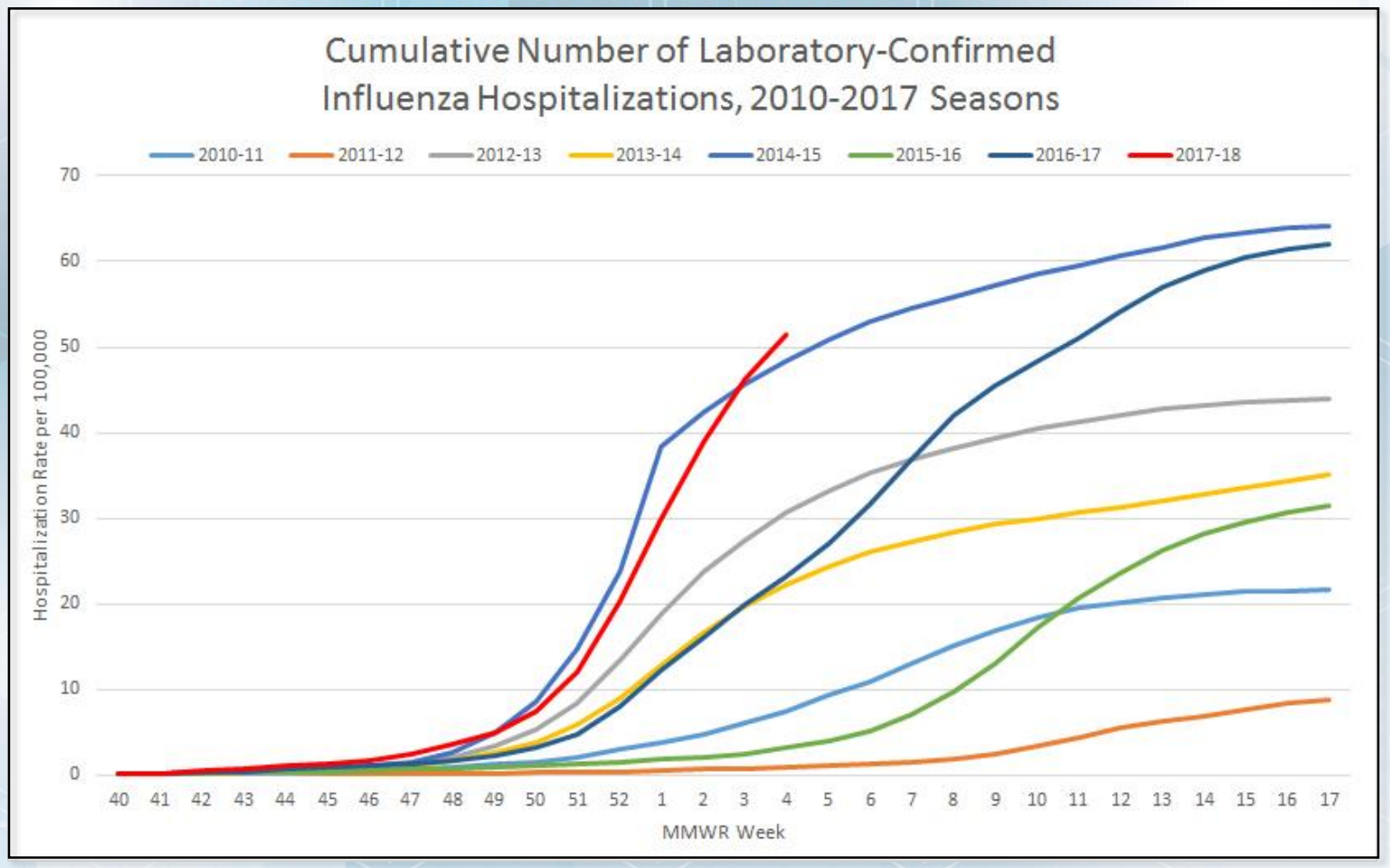
- **Particularly bad season (more to come)**
- **Flu can cause pandemic illness**
  - Obvious health concerns
  - National security issue
  - Economic issue
- **Disease is an old enemy of the military**
- **100 years since the beginning of the 1918 pandemic**
- **Persistent challenges**
  - Vaccine efficacy
  - Logistics
  - Diagnostic accuracy

State of the Current Flu Season



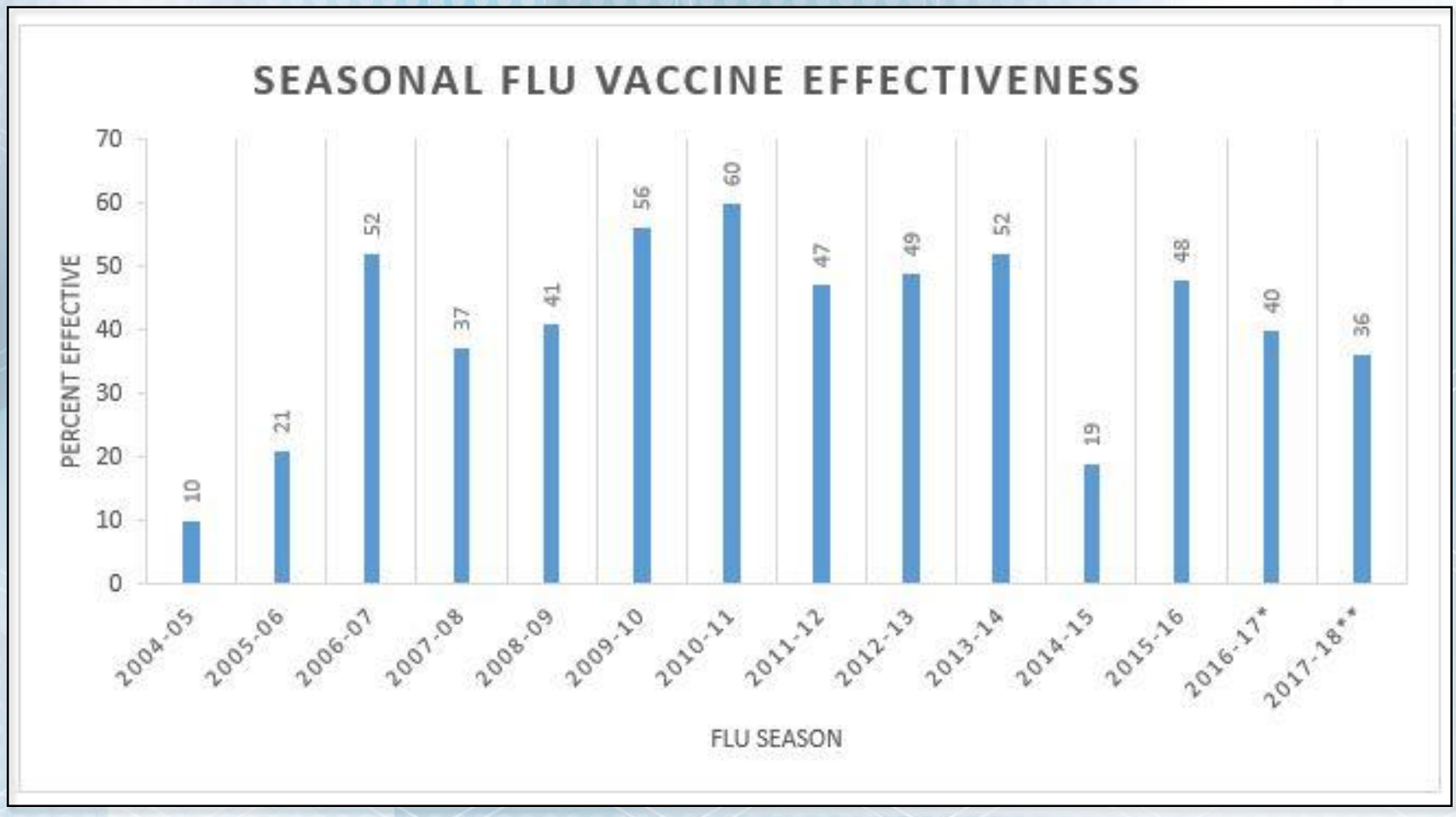
1. Centers for Disease Control and Prevention. (2018, February 23). Weekly U.S. Influenza Surveillance Report: 2017-2018 Influenza Season Week 7 ending February 17, 2018. Retrieved February 27, 2018 from https://www.cdc.gov/flu/weekly/index.htm

Lab-confirmed Influenza Hospitalizations
(as of 2/2/2018)



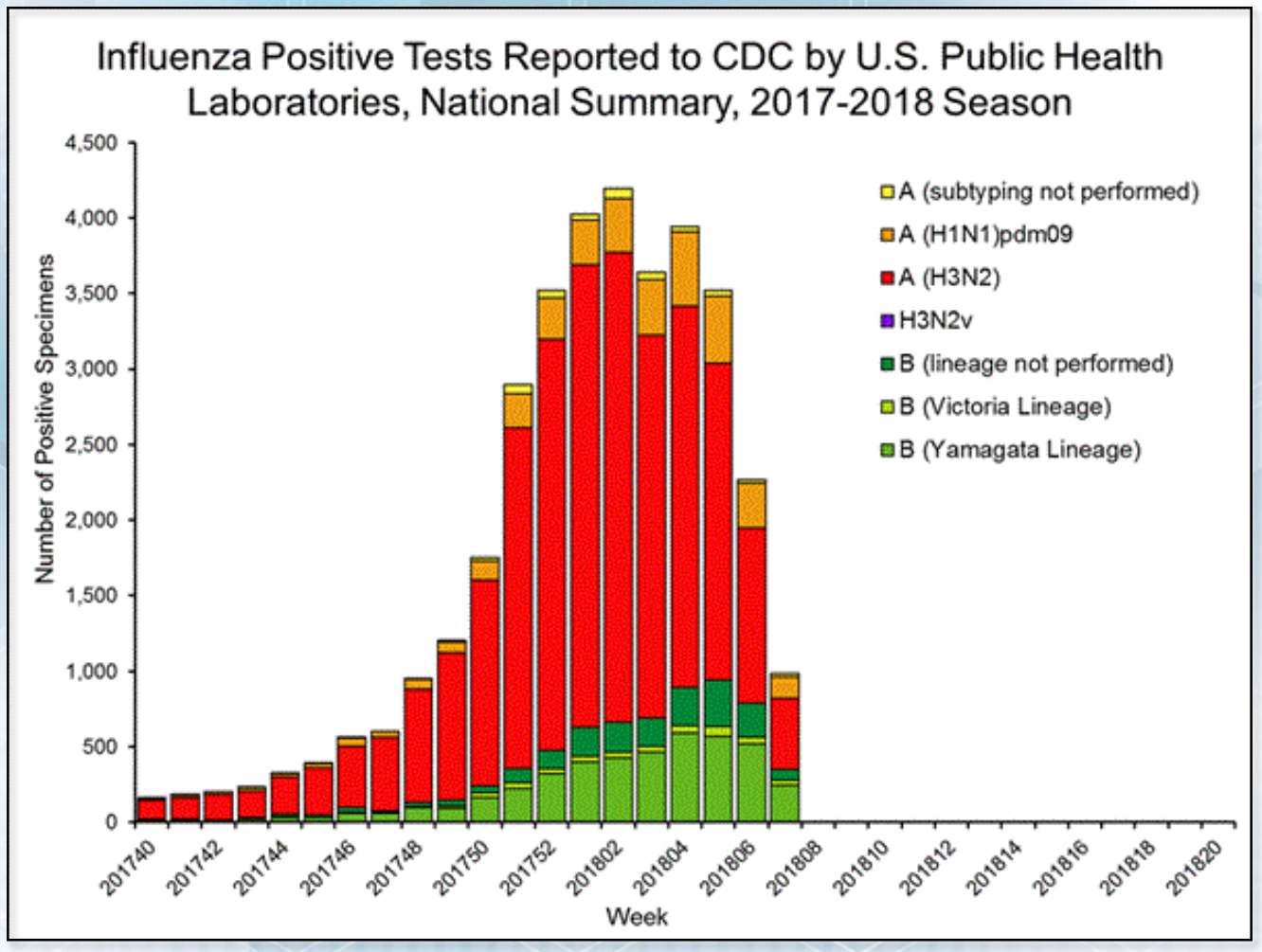
1. Centers for Disease Control and Prevention. (2018, February 5). Transcript for CDC Update on Flu Activity. Retrieved February 27, 2018 from https://www.cdc.gov/media/releases/2018/t0202-flu-update-activity.html

Seasonal Flu Vaccine Effectiveness (2004-2018)



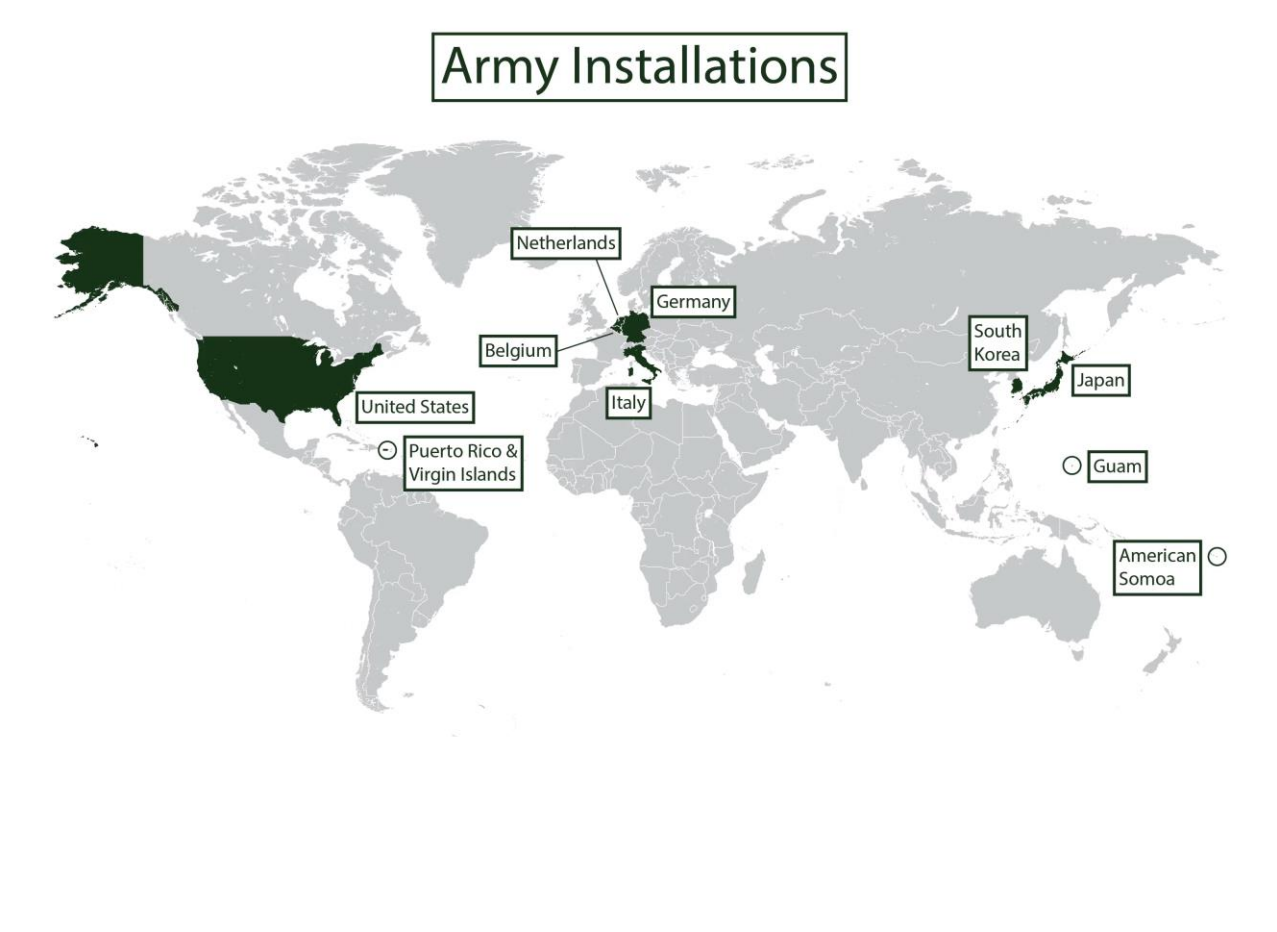
1. Centers for Disease Control and Prevention. (2018, February 15). Seasonal Influenza Vaccine Effectiveness, 2005-2018. Retrieved February 26, 27, 2018 from https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

Positive Flu Tests by Subtype for 2017-2018 Season [1]



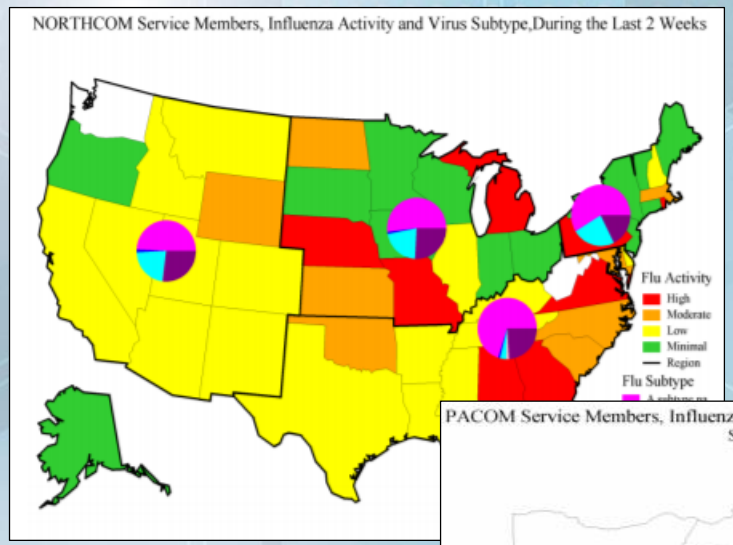
1. Centers for Disease Control and Prevention. (2018, February 23). Weekly U.S. Influenza Surveillance Report: 2017-2018 Influenza Season Week 7 ending February 17, 2018. Retrieved February 27, 2018 from https://www.cdc.gov/flu/weekly/index.htm

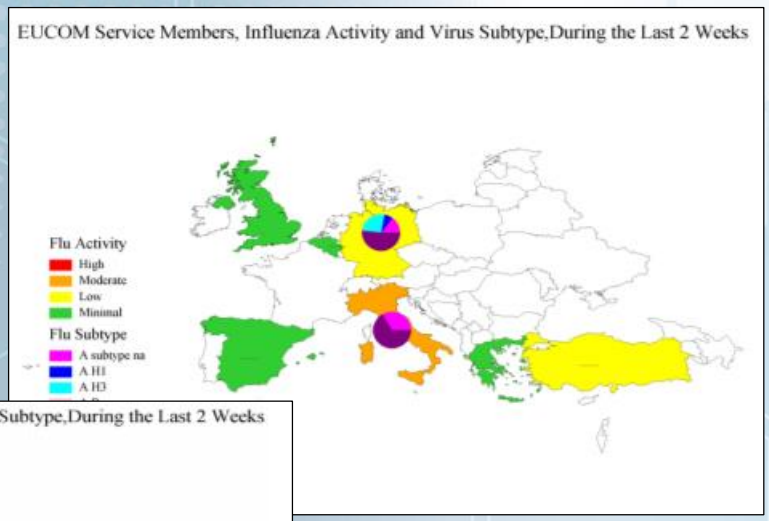
DoD Installations Around the World [1]

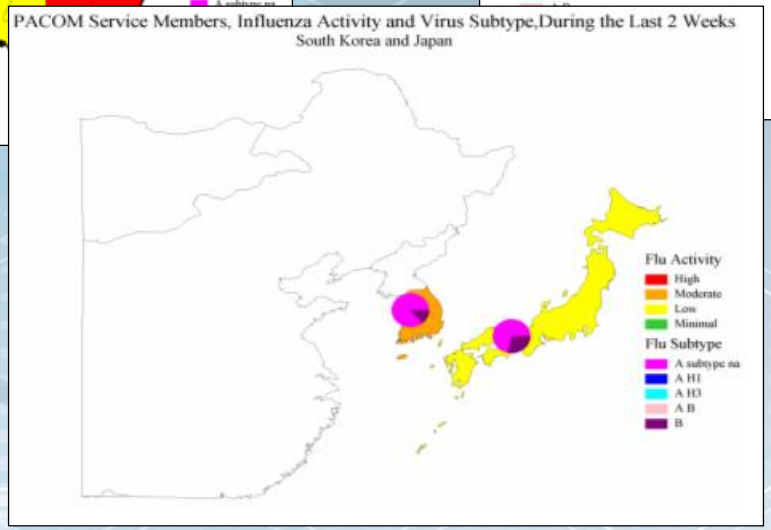


1. Image created by HDIAC with information collected by the Department of Defense, Military OneSource, and the U.S. Navy. Retrieved February 27, 2018 from https://www.defense.gov/About/, http://www.militaryinstallations.dod.mil/MOS/f?p=MI:ENTRY:0, http://www.navy.mil/navydata/nav_legacy.asp?id=146

DoD Seasonal Flu Surveillance [1]







1. DoD. (n.d.). Seasonal Influenza Surveillance Summary – Week 07 (11 Feb-17 Feb 2018). Retrieved February 27, 2018 from https://health.mil/Reference-Center/Reports/2018/02/21/Seasonal-Influenza-Summary-Feb-21-2018.

Background

All About Influenza

What is the Flu? [1]

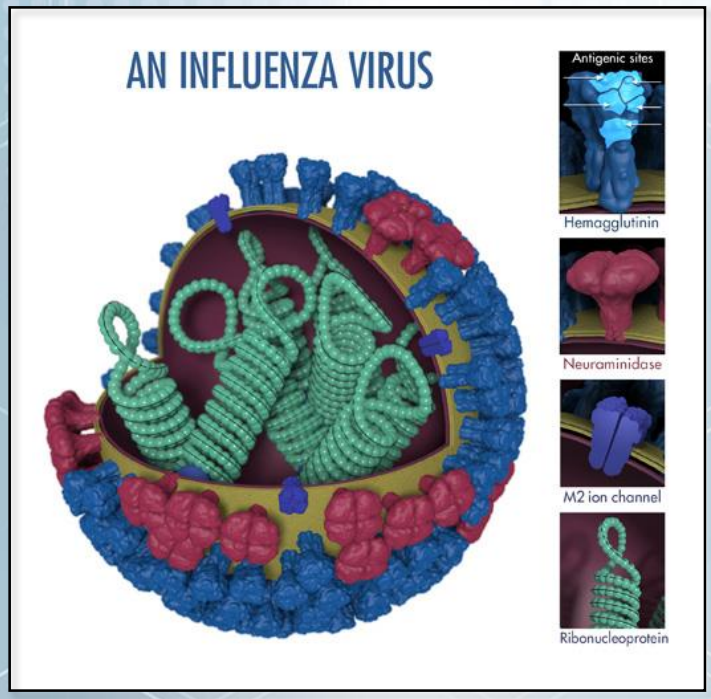
- **Respiratory illness caused by the influenza virus**
- **Symptoms include:**
  - Fever/chills
  - Cough
  - Sore throat
  - Runny or stuffy nose
  - Muscle or body aches
  - Headaches
  - Fatigue
- **Spread by droplets during sneeze or cough**
- **Incubation period – average of 2 days**
- **Can cause seasonal and pandemic illness**

1. Centers for Disease Control and Prevention. (2017, October 3). Retrieved February 17, 2018 from https://www.cdc.gov/flu/keyfacts.htm

Structure, Types, and Subtypes

Types of Influenza	Description
Influenza A Viruses	Classified into subtypes hemagglutinin neuraminidase Only type known to cause pandemics
Influenza B Viruses	Broken down into lineages
Influenza C Viruses	Not detected often Cause mild symptoms
Influenza D Viruses	Primarily affect cattle Not known to cause illness in humans

Classification of influenza viruses [1]



Features of the influenza virus [2]

1. World Health Organization. (2018, January). Influenza (Seasonal). Retrieved February 27, 2018 from http://www.who.int/mediacentre/factsheets/fs211/en/
2. Centers for Disease Control and Prevention. (2017, September 27). Antigenic Characterization. Retrieved February 27, 2018 from https://www.cdc.gov/flu/professionals/laboratory/antigenic.htm

Epidemiology of Influenza

Deaths

Global: 290,000-650,000 [1]

U.S.: 12,000-56,000 [2]

Cases

Global: 3-5 million "severe" [3]

U.S.: 9,200,000-35,600,000 [4]

Hospitalizations

U.S.: 140,000-170,000 [5]

DoD: 37 service members,

171 "other beneficiaries" [6]

Influenza transmission zones [7]

1. World Health Organization. (2018, January). Influenza (Seasonal). Retrieved February 22, 2018, from http://www.who.int/mediacentre/factsheets/fs211/en/
2. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory. (2018, February 21). Disease burden of influenza. Retrieved February 22, 2018, from https://www.cdc.gov/flu/about/disease/burden.htm
3. World Health Organization. (2018, January). Influenza (Seasonal). Retrieved February 22, 2018, from http://www.who.int/mediacentre/factsheets/fs211/en/
4. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory . (2018, February 21). Disease burden of influenza. Retrieved February 22, 2018, from https://www.cdc.gov/flu/about/disease/burden.htm
5. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory . (2018, February 21). Disease burden of influenza. Retrieved February 22, 2018, from https://www.cdc.gov/flu/about/disease/burden.htm
6. *Seasonal Influenza Surveillance Summary.* (2018, February). Department of Defense Armed Forces Health Surveillance Branch.
7. http://www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf

Influenza Pandemics

1918 Spanish Flu [1]

(H1N1)

- From March 1918 to Summer 1919
  - 20-40 million deaths worldwide

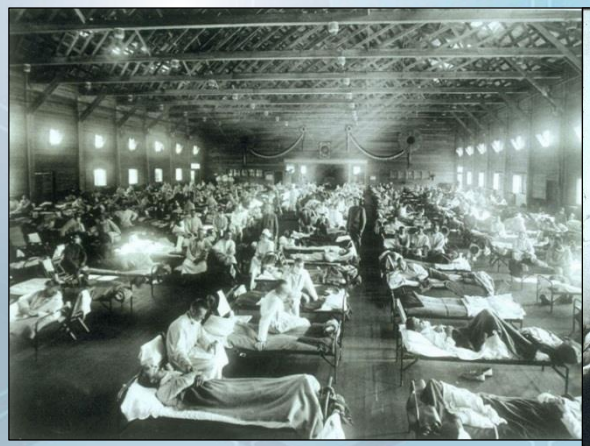
2009 Swine Flu Outbreak [2]

(H1N1pdm09)

- From April 12, 2009 to April 10, 2010
- CDC estimated that there were
  - 60.8 million cases (range: 43.3-89.3 million)
  - 274,304 hospitalizations (195,086-402,719)
  - 12,469 deaths (8868-18,306) in the United States due to the (H1N1)pdm09 virus

1. Billings, M. (2005, February). The Influenza Pandemic of 1918. Retrieved February 22, 2018, from https://virus.stanford.edu/uda/
2. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. (2017, November 02). Past pandemics. Retrieved February 22, 2018, from https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html

1918 Pandemic

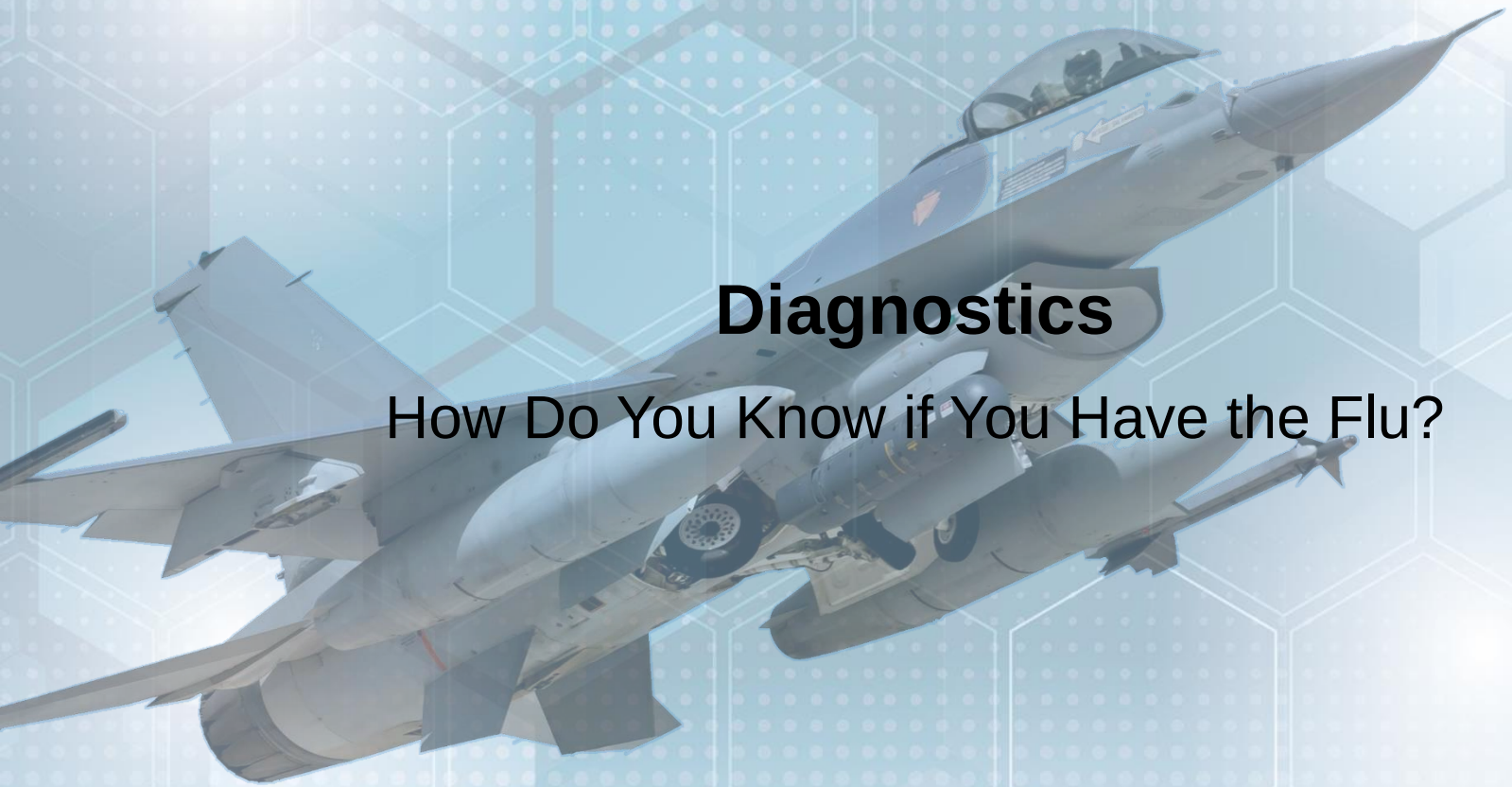


Soldiers ill with Spanish influenza at Fort Riley, Kansas [1]

American Expeditionary Force victims of the flu pandemic at U.S. Army Camp Hospital no. 45 in Aix-les-Bains, France, in 1918 [2]

Influenza ward at Walter Reed Hospital during the Spanish flu pandemic of 1918–1919 [3]

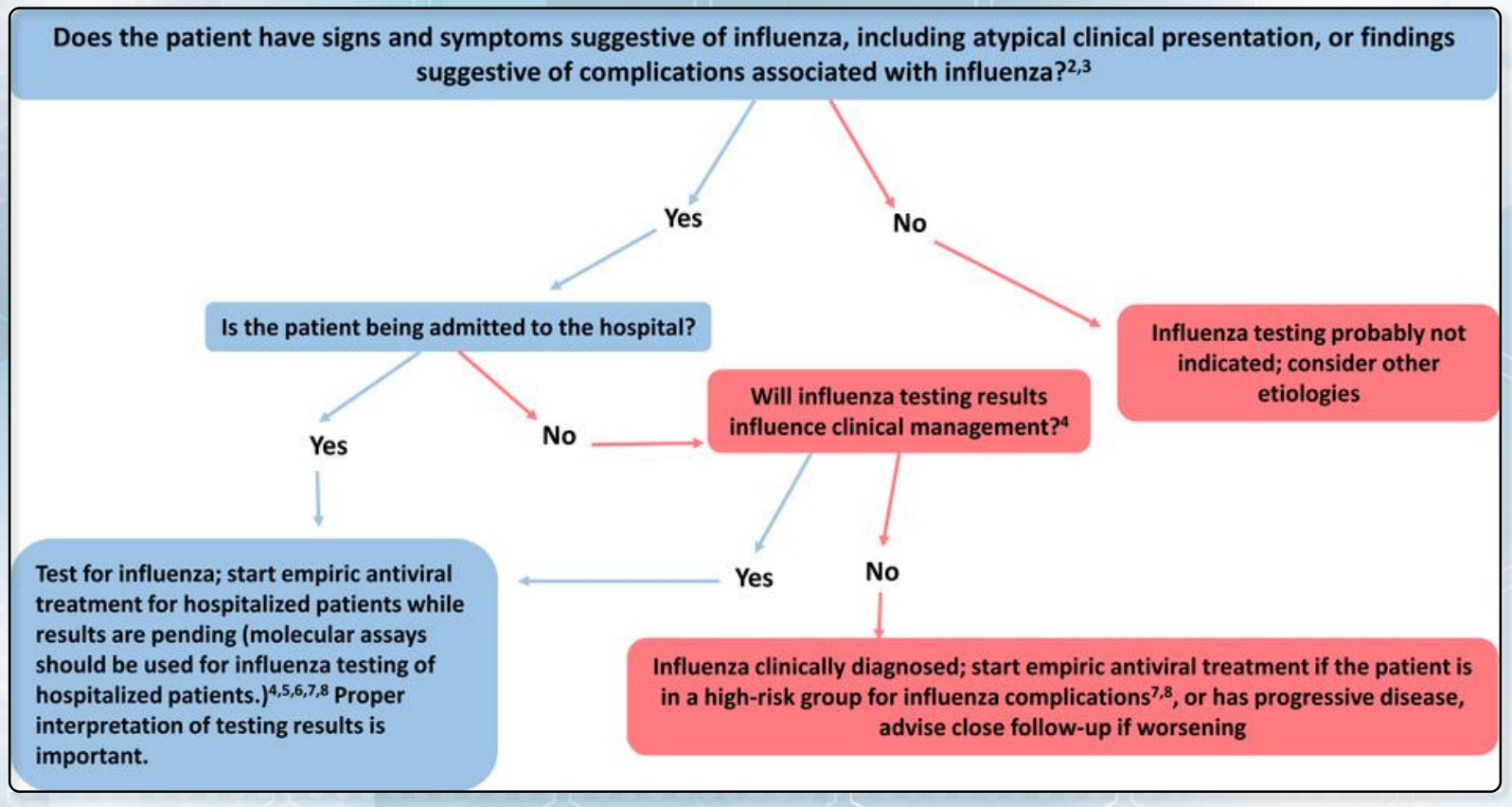
1. *NCP1603* [Photograph found in National Museum of Health and Medicine]. (n.d.). Retrieved from http://www.medicalmuseum.mil/index.cfm?p=exhibits.virtual.1918killerflu.index
2. *U. S. Army Camp Hospital No. 45, Aix-les-Bains, France: Influenza ward No. 1 (NLM Unique ID: 101399244)* [Photograph found in Digital Collections, U.S. National Library of Medicine]. (n.d.). Retrieved from https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101399244-img
3. *Walter Reed Hospital Flu Ward (Reproduction Number: LC-DIG-hec-14088)* [Photograph found in Prints and Photographs Division, Library of Congress, Washington, D.C.]. (n.d.). Retrieved from http://www.loc.gov/pictures/resource/hec.14088/



Diagnostics

How Do You Know if You Have the Flu?

Influenza Testing Decision Tree [1]



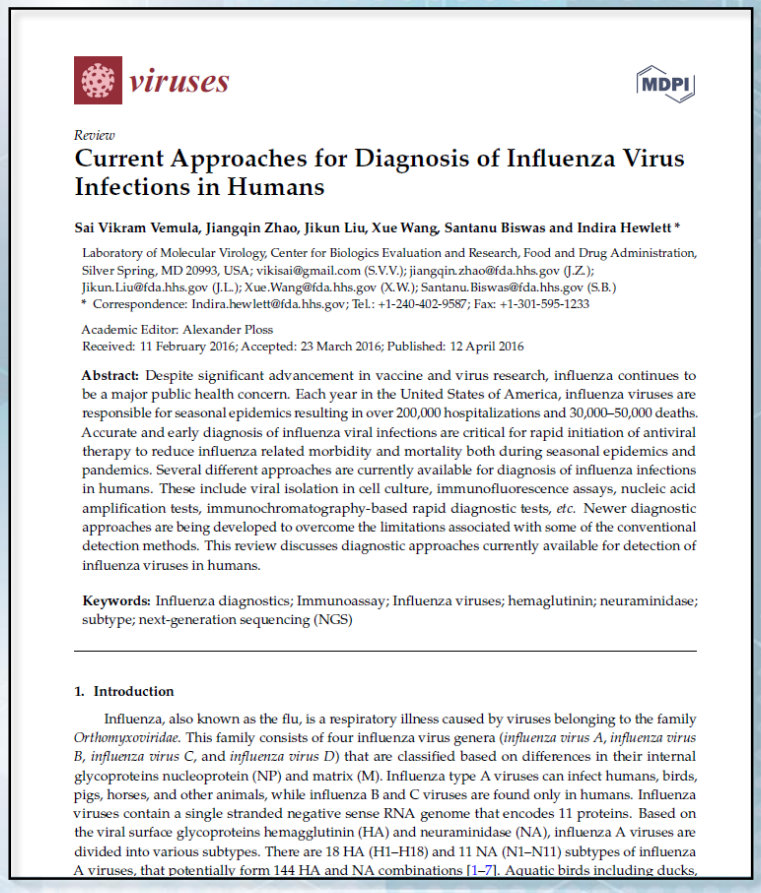
1. Centers for Disease Control. (2018, February 20). Guide for considering influenza testing when influenza viruses are circulating in the community. Retrieved February 27, 2018 from https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm

Testing Methods [1]

Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Rapid Influenza Diagnostic Tests[4] (antigen detection)	A and B	NP[5] swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	<15 min.	Yes/No
Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, nasal swab	15-30 minutes[6]	Yes/No[6]
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining [antigen detection]	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[7] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (1 to 8 hours, varies by the assay)	No
Rapid cell culture (shell vials; cell mixtures; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum; (specimens placed in VTM[8])	1-3 days	No
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in VTM8)	3-10 days	No

1. Centers for Disease Control and Prevention. (2018, February, 20). Influenza Virus Testing Methods. Retrieved February 27, 2018 from https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm

Testing Methods (cont.)



viruses MDPI

Review

Current Approaches for Diagnosis of Influenza Virus Infections in Humans

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Academic Editor: Alexander Ploss
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Abstract: Despite significant advancement in vaccine and virus research, influenza continues to be a major public health concern. Each year in the United States of America, influenza viruses are responsible for seasonal epidemics resulting in over 200,000 hospitalizations and 30,000–50,000 deaths. Accurate and early diagnosis of influenza viral infections are critical for rapid initiation of antiviral therapy to reduce influenza related morbidity and mortality both during seasonal epidemics and pandemics. Several different approaches are currently available for diagnosis of influenza infections in humans. These include viral isolation in cell culture, immunofluorescence assays, nucleic acid amplification tests, immunochromatography-based rapid diagnostic tests, *etc.* Newer diagnostic approaches are being developed to overcome the limitations associated with some of the conventional detection methods. This review discusses diagnostic approaches currently available for detection of influenza viruses in humans.

Keywords: Influenza diagnostics; Immunoassay; Influenza viruses; hemaglutinin; neuraminidase; subtype; next-generation sequencing (NGS)

1. Introduction

Influenza, also known as the flu, is a respiratory illness caused by viruses belonging to the family *Orthomyxoviridae*. This family consists of four influenza virus genera (*influenza virus A*, *influenza virus B*, *influenza virus* C, and *influenza virus D*) that are classified based on differences in their internal glycoproteins nucleoprotein (NP) and matrix (M). Influenza type A viruses can infect humans, birds, pigs, horses, and other animals, while influenza B and C viruses are found only in humans. Influenza viruses contain a single stranded negative sense RNA genome that encodes 11 proteins. Based on the viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), influenza A viruses are divided into various subtypes. There are 18 HA (H1–H18) and 11 NA (N1–N11) subtypes of influenza A viruses, that potentially form 144 HA and NA combinations [1–7]. Aquatic birds including ducks,

Current Approaches for Diagnosis of Influenza Virus Infection in Humans [1]

1. Vemula, S., Zhao, J., Liu, J., Wang, X., Biswas, S., & Hewlett, I. (2016). Current Approaches for Diagnosis of Influenza Virus Infections in Humans. *Viruses, 8*(12), 96. doi:10.3390/v8040096

Flu Diagnostics R&D 1

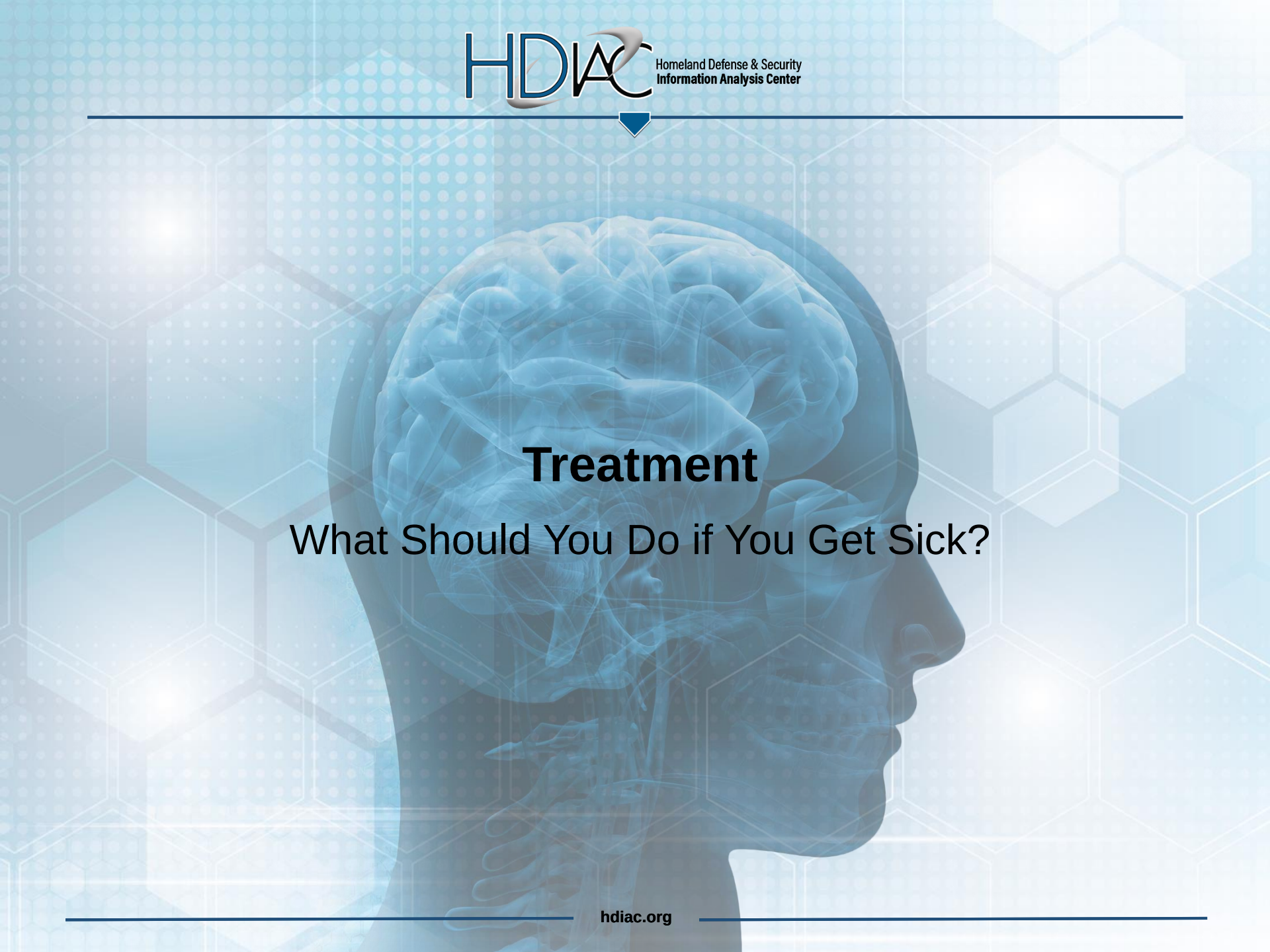
Assay	Description	Developer
Lab-in-a-Tube (Liat) influenza A/B assay	Detect and differentiate influenza A and B strains within 20 minutes	Massachusetts-based IQuum; Roche acquired the company in 2014
FilmArray diagnostic system (respiratory panel)	Uses PCR to detect viruses, bacteria, yeast and parasites in an hour	BioFire Diagnostics, LLC, based in Utah
Xpert Flu A/B diagnostic	Rapidly detect and differentiate flu type A from flu type B and identify the 2009 H1N1 flu strain	Sunnyvale, CA-based Cepheid
QuickVue Influenza Test	Detects and differentiates flu type A and flu type B	San Diego-based Quidel

Clinical assays to determine whether influenza viruses are sensitive to neuraminidase inhibitors, a class of antiviral drugs that inhibit release of influenza virus from infected cells [1]

1. National Center for Immunization and Respiratory Diseases. (2018, February 13). Influenza diagnosis. Retrieved February 22, 2018, from https://www.niaid.nih.gov/diseases-conditions/influenza-diagnosis

Paper-based Assays

1. https://projectreporter.nih.gov/project_info_description.cfm?aid=9136027&icde=31749906&ddparam=&ddvalue=&ddsub=&cr=13&csb=default&cs=ASC
2. Anderson, C. E., Holstein, C. A., Strauch, E., Bennett, S., Chevalier, A., Nelson, J., . . . Yager, P. (2017). Rapid Diagnostic Assay for Intact Influenza Virus Using a High Affinity Hemagglutinin Binding Protein. *Analytical Chemistry, 89*(12), 6608-6615. doi:10.1021/acs.analchem.7b00769
3. Jauset-Rubio, M., Svobodová, M., Mairal, T., Mcneil, C., Keegan, N., Saeed, A., . . . O´sullivan, C. K. (2016). Ultrasensitive, rapid and inexpensive detection of DNA using paper based lateral flow assay. *Scientific Reports, 6*(1). doi:10.1038/srep37732
4. Holstein, C. A., Bennett, S., Strauch, E., Chevalier, A., Fu, E., Baker, D., & Yager, P. (2014). Development of a paper-based diagnostic for influenza detection. *2014 IEEE Healthcare Innovation Conference (HIC)*. doi:10.1109/hic.2014.7038933
5. Wu, D., Zhang, J., Xu, F., Wen, X., Li, P., Zhang, X., . . . Qiu, X. (2017). A paper-based microfluidic Dot-ELISA system with smartphone for the detection of influenza A. *Microfluidics and Nanofluidics, 21*(3). doi:10.1007/s10404-017-1879-6



Treatment

What Should You Do if You Get Sick?

Antiviral Treatment and Resistance [1,2]

Antiviral	Influenza A Viruses		Influenza B Viruses
	2009 H1N1	H3N2	
Amantadine	Resistant	Resistant	No activity
Rimantadine	Resistant	Resistant	No activity
Oseltamivir	Susceptible	Susceptible	Susceptible
Peramivir	Susceptible	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible

1. Centers for Disease Control and Prevention. (2018, February 2). Influenza (Flu) Antiviral Drugs and Related Information. Retrieved February 27, 2018 from https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm#shortage
2. Fiore, A., Fry, A., Shay, D., Gubareva, L., Bresee, J. & Uyeki, T. (2011). Antiviral agents for the treatment and chemoprophyaxis of influenza. *MMWR. 60*(1), 1-25.

Antiviral R&D Pipeline [1]

DAS 181-novel host-based antiviral agent

- NIAID works closely with the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA)
- New class of antiviral therapeutic candidate that inhibits the influenza virus from attaching to host cells

Broadly reactive monoclonal antibodies (MAbs) CR6261 and CR8020

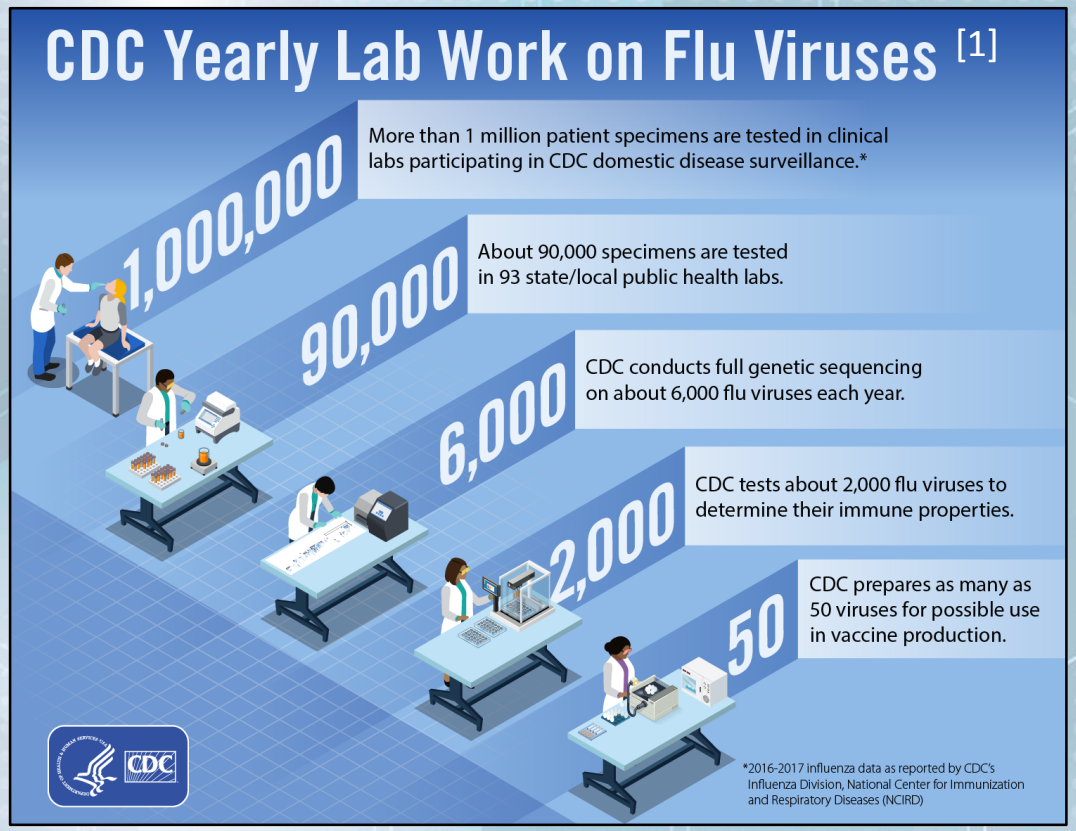
- These candidate immunotherapeutics target the stem region of influenza HA glycoprotein were discovered and developed by Crucell and supported by NIAID contract funding
  - CR621 targets the Flu A Group 1 HA stem, which includes flu types H1, H2, H5 and H9
  - CR8020 targets the Flu A group 2 HA stem, which includes H3, H7 and H10 flu subtypes
- Phase 1 studies were completed in 2013

1. National Institute of Allergy and Infectious Diseases. (n.d.). Influenza Treatment. Retrieved February 27, 2018 form https://www.niaid.nih.gov/diseases-conditions/influenza-treatment

Prevention

How to Minimize Your Chances of Contracting the Flu

Vaccine Selection



Antigenic Characterization

- Whether vaccine will protect against circulating influenza viruses [2]

Genome Sequencing and Genetic Characterization

- Compare the genes of currently circulating influenza viruses with the genes of older influenza viruses and viruses used in vaccines [3]

1. Centers for Disease Control and Prevention. (2017, September 7,). CDC Yearly Lab Work on Flu Viruses Infographic. Retrieved February 27, 2018 from https://www.cdc.gov/flu/resource-center/freeresources/graphics/infographic-lab-work.htm
2. Centers for Disease Control and Prevention. (2017, September 27,). Antigenic Characterization. Retrieved February 27, 2018 from https://www.cdc.gov/flu/professionals/laboratory/antigenic.htm
3. Centers for Disease Control and Prevention. (2017, November 15). Influenza Virus Genome Sequencing and Genetic Characterization. Retrieved February 27, 2018 from https://www.cdc.gov/flu/professionals/laboratory/genetic-characterization.htm

Types of Vaccines

Trivalent

- Trivalent vaccines include one influenza A (H1N1) virus, one influenza A (H3N2) virus, and one influenza B virus [1]
- For the 2017-2018 season, U.S. trivalent influenza vaccines contain:
  - An A/Michigan/45/2015 (H1N1)pdm09–like virus;
  - An A/Hong Kong/4801/2014 (H3N2)–like virus; and
  - A B/Brisbane/60/2008–like virus, which is from the Victoria lineage of B viruses [2]

Quadrivalent

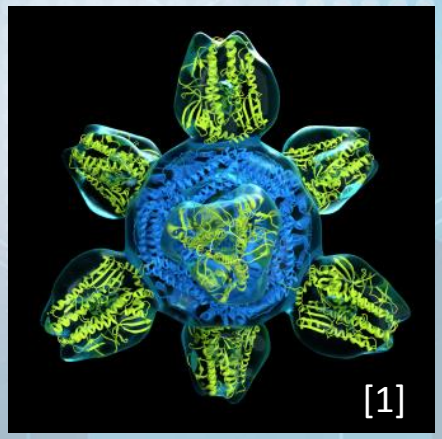
- The quadrivalent flu vaccine is designed to protect against four different flu viruses; two influenza A viruses and two influenza B viruses [1]
- Quadrivalent vaccines will include an additional vaccine virus strain, a B/Phuket/3073/2013–like virus from the Yamagata lineage [2]

1. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. (2018, February 13). Quadrivalent influenza vaccine. Retrieved from https://www.cdc.gov/flu/protect/vaccine/quadrivalent.htm
2. Grohskopf, L. (2017, September 20). 2017-2018 Influenza vaccination recommendations. Retrieved from https://www.medscape.com/viewarticle/885567

Vaccine Challenges [1]

Manufacturer	Trade Name (vaccine abbreviation)[2]	Presentation	Mercury (thimerosal) mcg Hg/0.5 mL	Ovalbumin mcg/0.5 mL	Age Group	CVX	CPT
Seqirus, Inc.	Afluria®[1,5] (IIV3)	0.5 mL single-dose syringe	0	< 1	≥ 5 yrs	140	90656
		5 mL multi-dose vial[4]	24.5	< 1		141	90658
	Afluria®[1,5] (IIV4)	0.5 mL single-dose syringe	0	< 1	≥ 5 yrs	150	90686
		5.0 mL multi-dose vial[4]	24.5	< 1		158	90688
	Fluad®[1,6] (aIIV3)	0.5 mL single-dose syringe (latex in tip caps)	0	< 0.4	≥ 65 yrs	168	90653
	Flucelvax®[1] (ccIIV4)	**0.5 mL single-dose syringe**	0	††	≥ 4 yrs	171	90674
		5 mL multi-dose vial	25	††		186	90756
	Fluvirin®[1] (IIV3)	0.5 mL single-dose syringe (latex in tip caps)	≤ 1	≤ 1	≥ 4 yrs	140	90656
		5 mL multi-dose vial	25	≤ 1		141	90658
GlaxoSmithKline	**Fluarix®[1] (IIV4)**	**0.5 mL single-dose syringe[3]**	0	≤ 0.05	≥ 6 mos	150	90686
	FluLaval®[1] (IIV4)	**0.5 mL single-dose syringe[3]**	0	≤ 0.3	≥ 6 mos	150	90686
		5 mL multi-dose vial[3,4]	< 25	≤ 0.3		158	90688
Sanofi Pasteur, Inc.	Fluzone®[1] (IIV4)	0.25 mL single-dose syringe	0	§§	6-35 mos	161	90685
		0.5 mL single-dose syringe	0	§§	≥ 3 yrs	150	90686
		0.5 mL single-dose vial	0	§§		150	90686
		5 mL multi-dose vial (0.25 mL dose)	12.5	§§	6-35 mos	158	90687
		5 mL multi-dose vial (0.50 mL dose)	25	§§	≥ 3 yrs	158	90688
	Fluzone® Intradermal[1,8] (IIV4-ID)	0.1 mL single-dose microinjection system[9]	0	§§	18-64 yrs	166	90630
	Fluzone® High-Dose[1,7] (IIV3-HD)	0.5 mL single-dose syringe	0	§§	≥ 65 yrs	135	90662
Protein Sciences Corp.	FluBlok®[1] (RIV3)	0.5 mL single-dose vial	0	0	≥ 18 yrs	155	90673
	FluBlok®[1] (RIV4)	0.5 mL single-dose syringe	0	0		185	90682
MedImmune	FluMist®[1,10] (LAIV4)	0.2 mL single-use intranasal sprayer	0	≤ 0.024	2-49 yrs	149	90672

1. DHA. (n.d.). Influenza vaccine product list and age groups: United States, 2017-2018 Season. Retrieved from https://health.mil/.../01/.../Influenza-Vaccine-Product-List-and-Age-Groups-2017-18



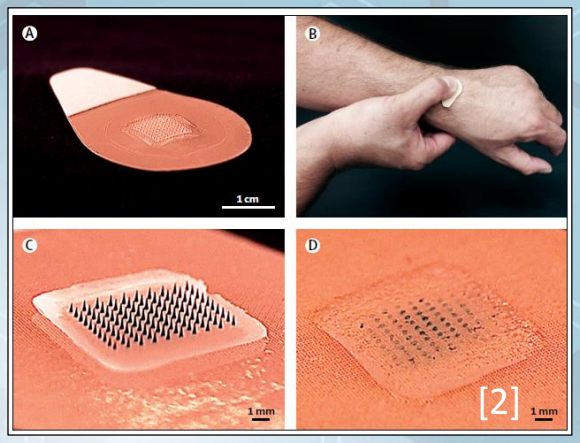
Vaccine R&D

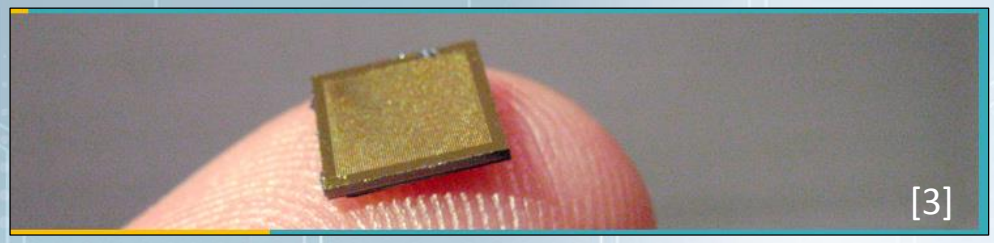
Universal vaccine [1]

Microneedle patches

- TIV-MNP 2015 [2]
- Vaxxas [3]

Single-dose, longer-lasting vaccine





1. NIAID. (n.d.). Colorized structure of a prototype for a universal flu vaccine. Retrieved from https://www.niaid.nih.gov/diseases-conditions/influenza
2. Rouphael, N. G., Paine, M., Mosley, R., Henry, S., Mcallister, D. V., Kalluri, H., . . . Nesheim, W. (2017). The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. *The Lancet, 390*(10095), 649-658. doi:10.1016/s0140-6736(17)30575-5
3. Vaxxas. (n.d.). Overview of Vaxxas. Retrieved from http://www.vaxxas.com/about-vaxxas/overview/

National Security Implications

Economic, Security, and Homeland Defense Aspects

Economic/Productivity Consequences

Seasonal influenza "…costs an estimated $10.4 billion a year in direct medical expenses and an additional $16.3 billion in lost earnings annually." [1]

"A pandemic influenza outbreak could result in GDP losses of $45.3 billion without vaccination and $34.4 billion with vaccination" [2]

1. Flu Prevention. (n.d.). Retrieved February 22, 2018, from https://www.cdcfoundation.org/businesspulse/flu-prevention-infographic#challenges_anchor
2. Prager, F., Wei, D., & Rose, A. (2017). Total economic consequences of an influenza outbreak in the United States. Risk Analysis, 37(1), 4-19.

Security Impact

National Intelligence Council report from 2000 on the national security threat of infectious diseases, including influenza [1]:

- "As a major hub of global travel, immigration, and commerce with wide-ranging interests and a large civilian and military presence overseas, the United States and its equities abroad will remain at risk from infectious diseases."
- "Infectious diseases are likely to continue to account for more military hospital admissions than battlefield injuries. US military personnel deployed at NATO and US bases overseas, will be at low-to-moderate risk. At highest risk will be US military forces deployed in support of humanitarian and peacekeeping operations in developing countries."
- "Infectious disease-related embargoes and restrictions on travel and immigration will cause frictions among and between developed and developing countries."
- "Infectious diseases are likely to slow socioeconomic development in the hardest-hit developing and former communist countries and regions. This will challenge democratic development and transitions and possibly contribute to humanitarian emergencies and civil conflicts."

1. Gannon, J. C. (2000, January). The global infectious disease threat and its implications for the United States. (Rep. NIE 99-17D). National Intelligence Council. Retrieved February 22, 2018, from https://fas.org/irp/threat/nie99-17d.htm

CDC/HHS Role

Updated Preparedness and Response Framework for Influenza Pandemics outlines a framework with six intervals [1]:

- Investigation: Investigation of novel influenza A infection in humans or animals
- Recognition: Recognition of increased potential for ongoing transmission of a novel influenza A virus
- Initiation: Initiation of a pandemic wave
- Acceleration: Acceleration of a pandemic wave
- Deceleration: Deceleration of a pandemic wave
- Preparation: Preparation for future pandemic waves

HHS issues the national _Pandemic Influenza Plan_ with seven domains [2]:

- Surveillance, Epidemiology, and Laboratory Activities
- Community Mitigation Measures
- Medical Countermeasures: Diagnostic Devices, Vaccines, Therapeutics, and Respiratory Devices
- Health Care System Preparedness and Response Activities
- Communications and Public Outreach
- Scientific Infrastructure and Preparedness
- Domestic and International Response Policy, Incident Management, and Global Partnerships and Capacity Building

1. Centers for Disease Control and Prevention. (2014, September 26). *Updated preparedness and response framework for influenza pandemics.* Retrieved February 22, 2018, from https://www.cdc.gov/flu/pandemic-resources/pdf/mmwr-rr6306.pdf
2. US Department of Health and Human Services. (2017). *Pandemic influenza plan.* Retrieved February 22, 2018, from https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf

DoD Role in Pandemics

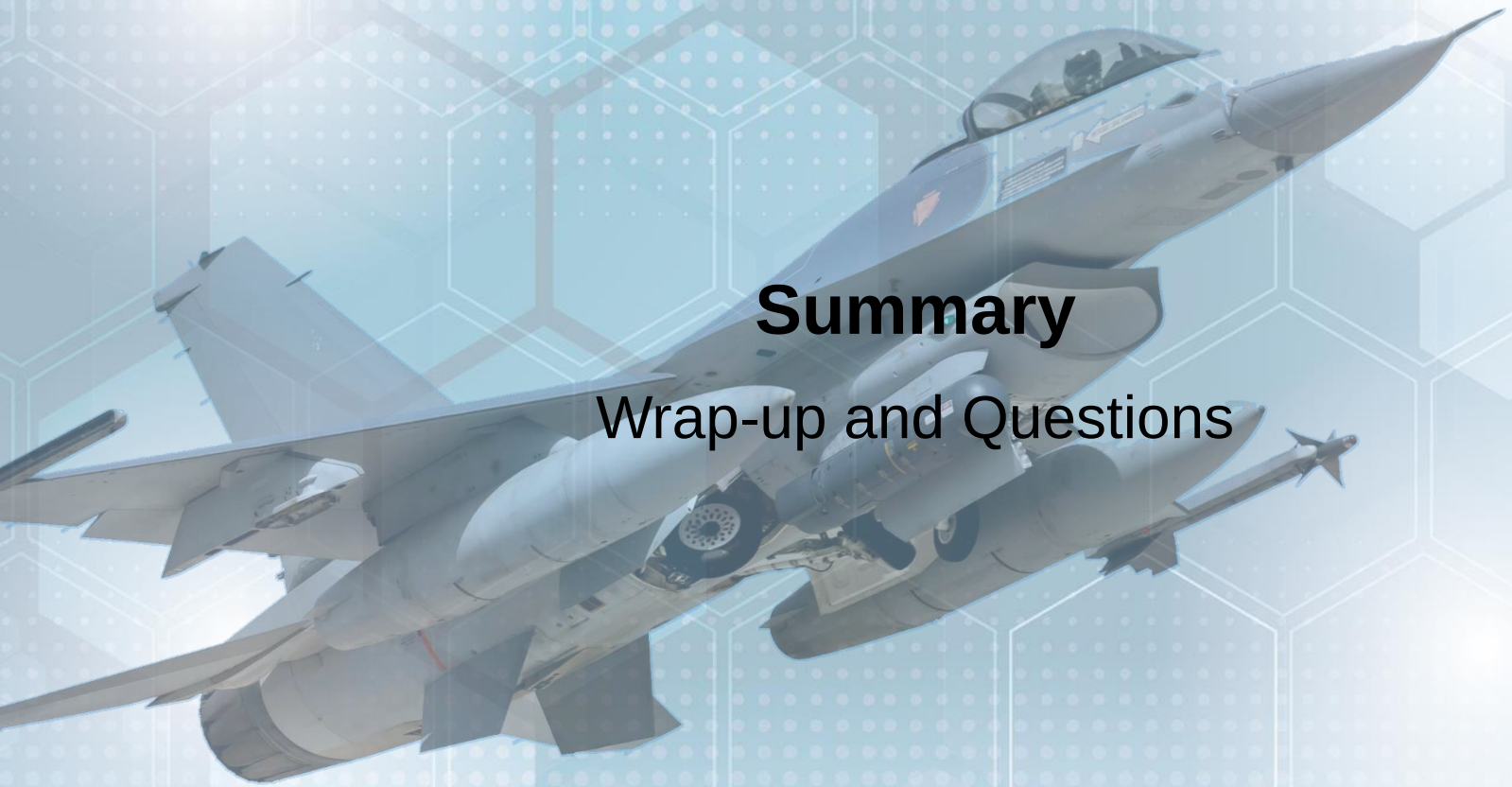
- DoD's mission is to preserve U.S. combat capabilities and readiness, and support U.S. government efforts to save lives, reduce human suffering and slow the spread of infection." [1]
- From the DoD Implementation Plan for Pandemic Influenza: "Under the National Implementation Plan, department and agencies focus on four areas: (1) protection of the health and safety of personnel and resources, (2) determination of essential functions and services and the maintenance of each in a pandemic influenza outbreak, (3) support to Federal, State, and local governments, and (4) effective communications. The DoD plan will include a fifth area – support to international partners and international stability and security." [2]
- DoD Medical Countermeasures Directorate, "develops clinical guidelines for vaccines, diagnostics and antiviral policies that ultimately serve to protect department-wide military and civilian personnel and beneficiaries living abroad or at home." [3]

1. Military Health System. (n.d.). Pandemic influenza watchboard. Retrieved February 22, 2018, from https://health.mil/Military-Health-Topics/Health-Readiness/Pandemic-Diseases/Pandemic-Influenza-Watchboard
2. *Department of Defense implementation plan for pandemic influenza* (Rep.). (2006). Department of Defense.
3. Military Health System. (n.d.). Pandemic influenza watchboard. Retrieved February 22, 2018, from https://health.mil/Military-Health-Topics/Health-Readiness/Pandemic-Diseases/Pandemic-Influenza-Watchboard

Flu as a Weapon?

- Genetic characterization of the 1918 influenza pandemic (H1N1) [1]
- Genomic characterization of the Plague that destroyed Europe in the 14th century [2]
- More virulent strain of bird flu (H5N1) engineered [3,4]
- Recreation of 1918 influenza strain (H1N1) using various strains of bird flu (H5N1) [5]
- Improved horizontal gene transfer demonstrated with the influenza virus [6,7]

1. Tumpey, T. M., Basler, C. F., Aguilar, P. V., Zeng, H., Solórzano, A., Swayne, D. E., . . .García-Sastre, A. (2005, October 7). Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. Science, 310(5745), 77-80. Retrieved from http://science.sciencemag.org/content/310/5745/77 (accessed January 27, 2017).
2. Bos, K. I., Schuenemann, V. J., Golding, B., Burbano, H. A., Waglechner, N., Coombes, B. K., . . .Krause, J. (2011, October 27). A draft genome of Yersinia pestis from victims of the Black Death. Nature, 478(7370), 506- 510. Retrieved from http://www.nature.com/nature/journal/v478/n7370/full/nature10549.html (accessed January 27, 2017).
3. Yong, E. (2012, June 21). Second mutant-flu paper published: Just five mutations allow H5N1 to spread between ferrets. Nature. Retrieved from http://www.nature.com/news/second-mutant-flu-paper-published-1.10875 (accessed January 27, 2017).
4. Yong, E. (2012, May 3). Mutant-flu paper published: Controversial study shows how dangerous forms of avian influenza could evolve in the wild. Nature, 485(7396), 13- 14. Retrieved from http://www.nature.com/news/mutant-flu-paper-published-1.10551 (accessed January 27, 2017).
5. Wahlberg, D. (2014, June 11). UW-Madison scientist creates new flu virus in lab. Wisconsin State Journal. Retrieved from http://host.madison.com/wsj/news/local/health_med_fit/uw-madison-scientist-creates-new-flu-virus-in-lab/article_4cedeb40-efdc-5d2e-a02d-ffb301a84b53.html (accessed January 27, 2017).
6. Herfst, S., Schrauwen, E. J., Linster, M., Chutinimitkul, S., Wit, E. D., Munster, V. J., . . . Fouchier, R. A. (2012). Airborne transmission of influenza A/H5N1 virus between ferrets. *Science, 336*(6088), 1534-1541. doi:10.1126/science.1213362.
7. Imai, M., Watanabe, T., Hatta, M., Das, S. C., Ozawa, M., Shinya, K., . . . Kawaoka, Y. (2012). Experimental adaptation of an influenza H5 HA confers respiratory droplet

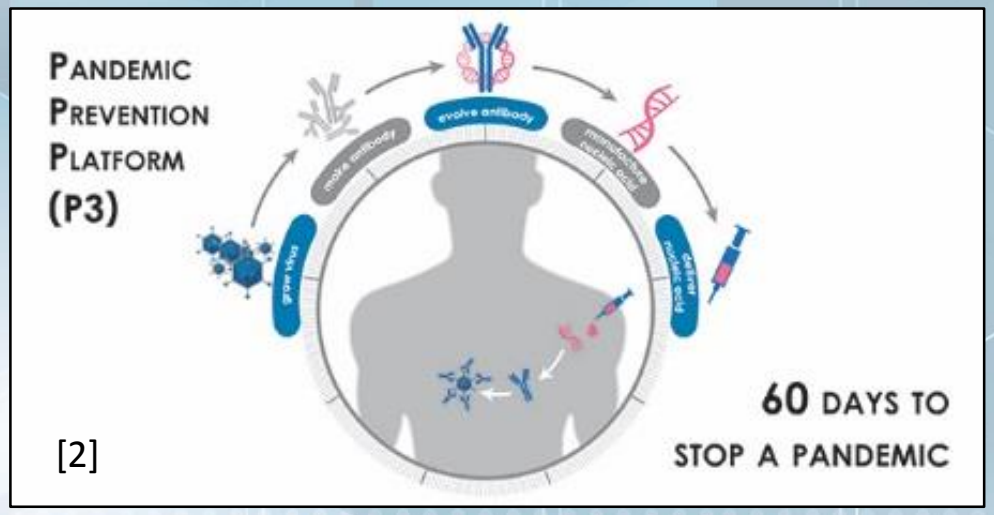


Summary

Wrap-up and Questions

What's Next?

- **Next flu season**
- **Human infection with avian influenza A(H7N4) virus [1]**
- **DARPA [2]**



[2]

1. World Health Organization. (2018, February 22). Human Infection with avian influenza A(H7N4) virus – China. Retrieved February 27, 2018 from http://www.who.int/csr/don/22-february-2018-ah7n4-china/en/
2. Defense Advanced Research Projects Agency. (2018, February 22). DARPA Names Researchers Working to Halt Outbreaks in 60 Days or Less. Retrieved February 27, 2018 from https://www.darpa.mil/news-events/2018-02-22

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Technical Inquiry Service

- HDIAC provides up to 4 free hours of information services:
  - Literature searches
  - Product/document requests
  - Analysis within our eight focus areas – Alternative Energy, Biometrics, CBRN Defense, Critical Infrastructure Protection, Cultural Studies, Homeland Defense and Security, Medical, Weapons of Mass Destruction

Core Analysis Task (CAT)

- Challenging technical problems requiring more than 4 hours of research, can be solved by initiating a CAT:
  - Pre-competed, pre-awarded, contract vehicles
  - Work can begin on a project approximately two months after the statement of work has been approved
  - Cap of $500,000
  - Must be completed in less than 12 months

For more information: https://www.hdiac.org/technical_services