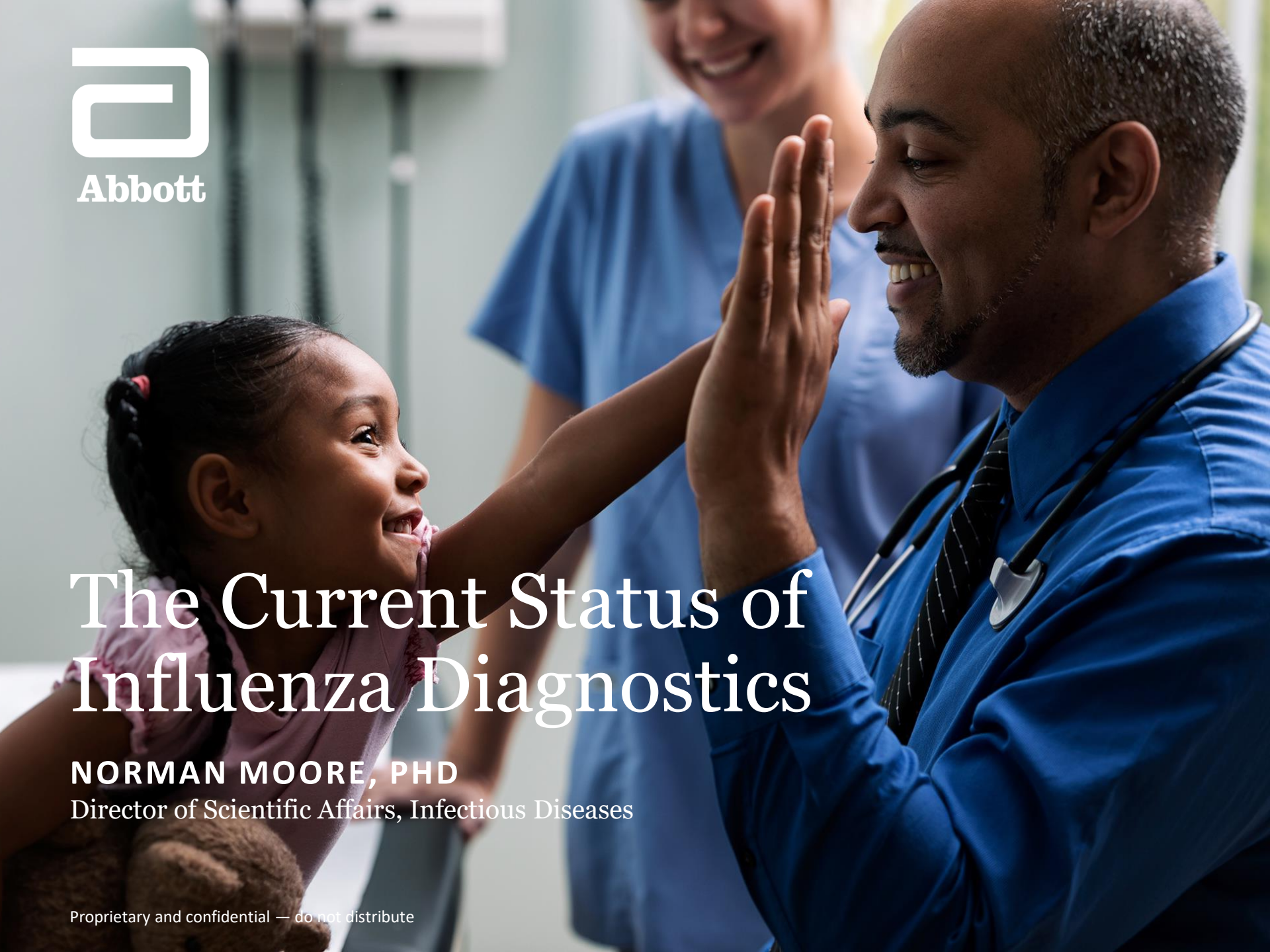


The Current Status of Influenza Diagnostics

NORMAN MOORE, PHD
Director of Scientific Affairs, Infectious Diseases

Objectives

1. Discuss the health impacts of influenza in the US

2. Discuss the diagnostic options available for influenza

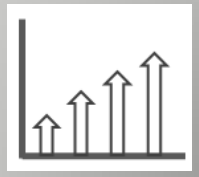
3. Discuss the biology of how an influenza infection can predispose a person to pneumococcal pneumonia

Infectious Disease in the US

William Stewart, the Surgeon General of the Us (1965-9) has been cited as saying the U.S. was "ready to close the book on infectious disease as a major health threat…war on pestilence was won"; modern antibiotics, vaccination, and sanitation methods had done the job. (Some discussion on whether Stewart said this or not, but other leading academia did adopt this belief at the time.)[1]

1970

Infectious disease had again become the third leading cause of death, and the leading cause of premature deaths. Its incidence was growing![2]



1995

- Infectious disease mortality - downward trend in deaths (mainly because of decline in HIV/AIDS mortality)[3]
- In US-"Most infectious disease deaths [about 40%] from 1980-2014 were due to influenza or pneumonia "[3]

2018

1. Spellberg B, Taylor-Blake B. *Diseases of Poverty*. 2013;2:3. doi:10.1186/2049-9957-2-3.]
2. World Health Organization. Press Release 1996. Encyclopedia of World Poverty. doi:10.4135/9781412939607.n765
3. Hansen V, Oren E, Dennis LK, Brown HE. Infectious Disease Mortality Trends in the United States, 1980-2014. *JAMA*. 2016;316(20):2149–2151. doi:10.1001/jama.2016.12423

Average Disease Burden of Influenza A&B in the US[1]

Annual Impact of influenza in the US

- Cases 9,200,000 – 35,600,000
- Hospitalizations up from 140,000 – 710,000
- Deaths between 12,000 – 56,000
- Influenza target population: 188MM in US

5-20% of US population affected by influenza each year

Most deaths affect elderly and young children

- Also affects otherwise healthy individuals

1. Centers for Disease Control and Prevention. www.cdc.gov/flu/keyfacts.htm

Disease Burden : Oct. 2018 – Feb. 2019

CDC estimates that, from **October 1, 2018,** through **February 23, 2019**, there have been:

20.4 million – 23.6 million
flu **illnesses**

9.5 million – 11.1 million
flu **medical visits**

252,000 – 302,000
flu **hospitalizations**

16,400 – 26,700
flu **deaths**

1. CDC. Influenza (Flu). https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

Influenza - Overview

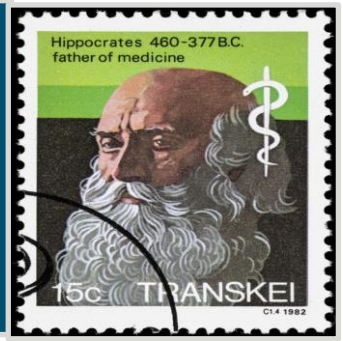
The old thinking. . . “it’s just the flu”

A bit of history

Flu History[1]:

- Flu epidemics: every 1 to 3 years for at least the last 400 years
- Pandemics (worldwide) occur around every 10 to 50 years

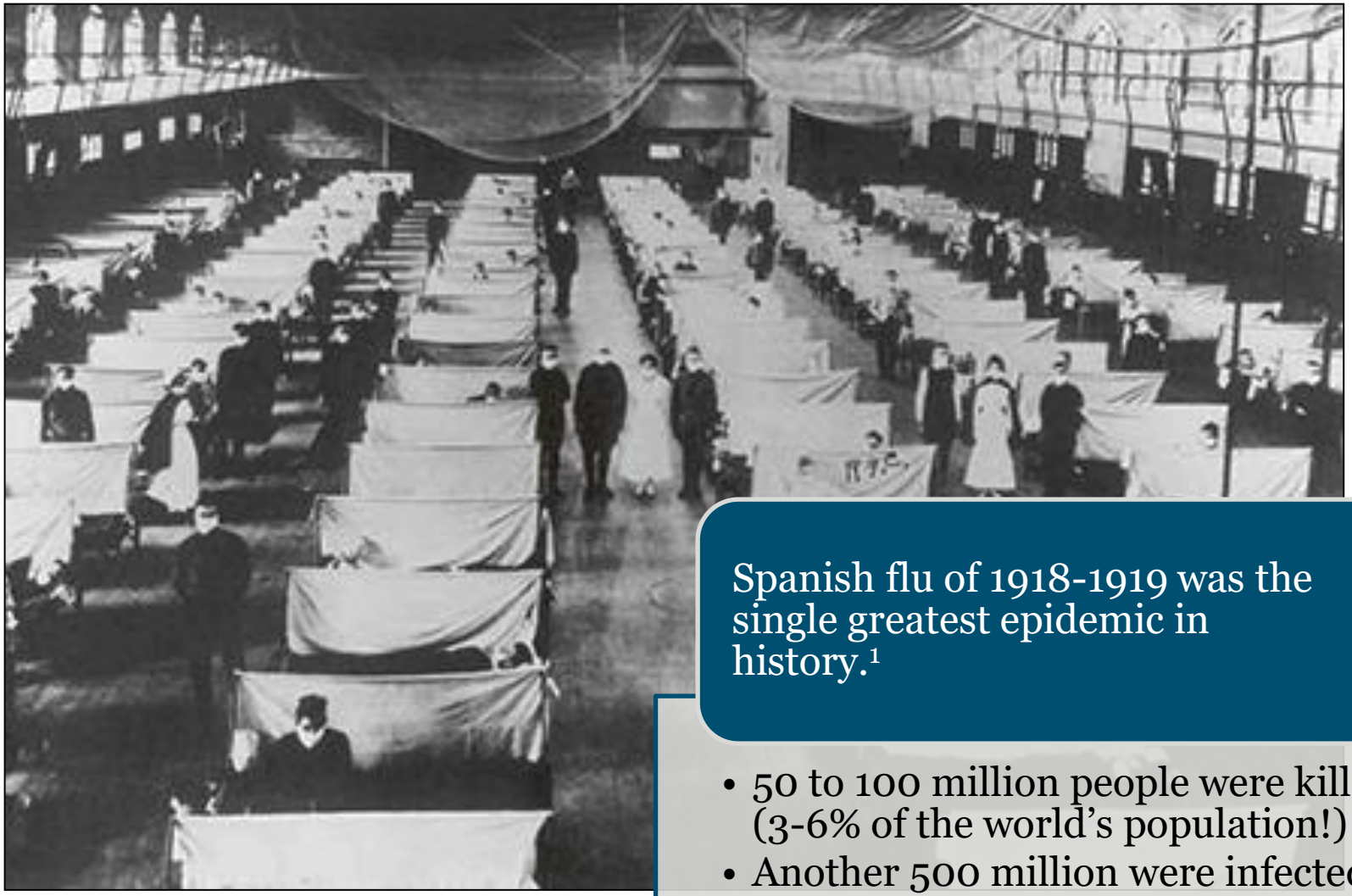
Hippocrates described flu back in the 5th century BC.



Columbus brought a devastating flu on his second voyage to the new world.

1. Saunders-Hastings PR, Krewski D. Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission. Young LS, ed. *Pathogens*. 2016;5(4):66. doi:10.3390/pathogens5040066

1918 Flu Pandemic – Spanish Flu



Spanish flu of 1918-1919 was the single greatest epidemic in history.[1]

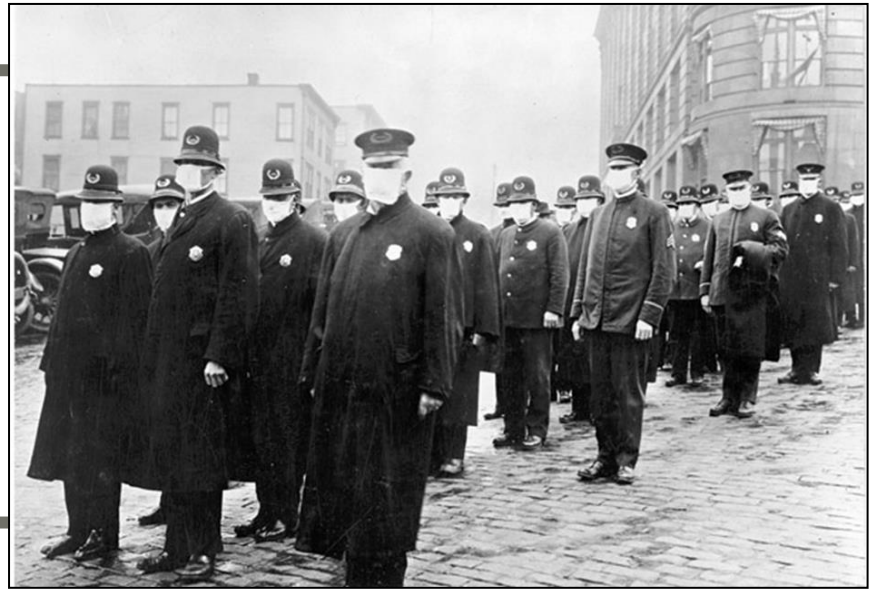
- 50 to 100 million people were killed[1] (3-6% of the world's population!)
- Another 500 million were infected[1] (1/3 of the world's population)

1. CDC. Influenza (Flu). 1918 Pandemic. https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html

1918 Flu Pandemic – Spanish Flu

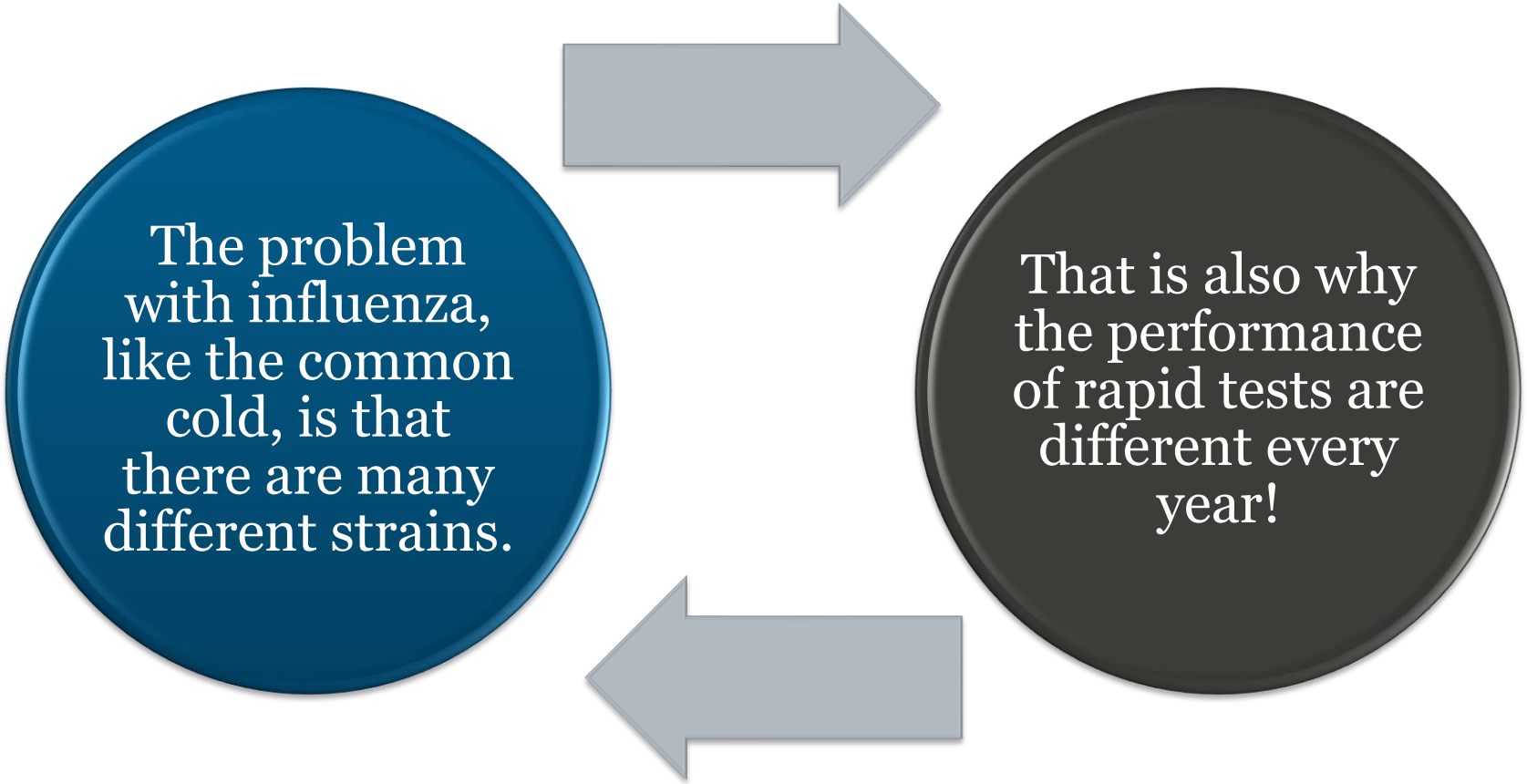
1918 Spanish Flu Pandemic broke out during WWI. Image of WWI soldiers.

Policemen in Seattle wearing masks made by the Red Cross, during the influenza epidemic. December 1918.



National Archives at College Park, MD. Record number 165-WW-269B-25.

Aren’t you supposed to build immunity to influenza?



Influenza A versus Influenza B

Influenza A

- More severe disease than B
- Can cause disease in a wide variety of animals

Influenza B

- Causes a milder flu, usually in the spring months

What Can Increase Cases of Seasonal Influenza?

Vaccine Mismatch

- Vaccine is made by predicting strains for next season so may not be accurate

Multiple strains hitting at the same time

- Can have multiple strains as well as overlap of influenza A and B

Virulence of Strains

- Some strains can cause an extreme immune response

What Makes You Ache When You Have Influenza?

Influenza

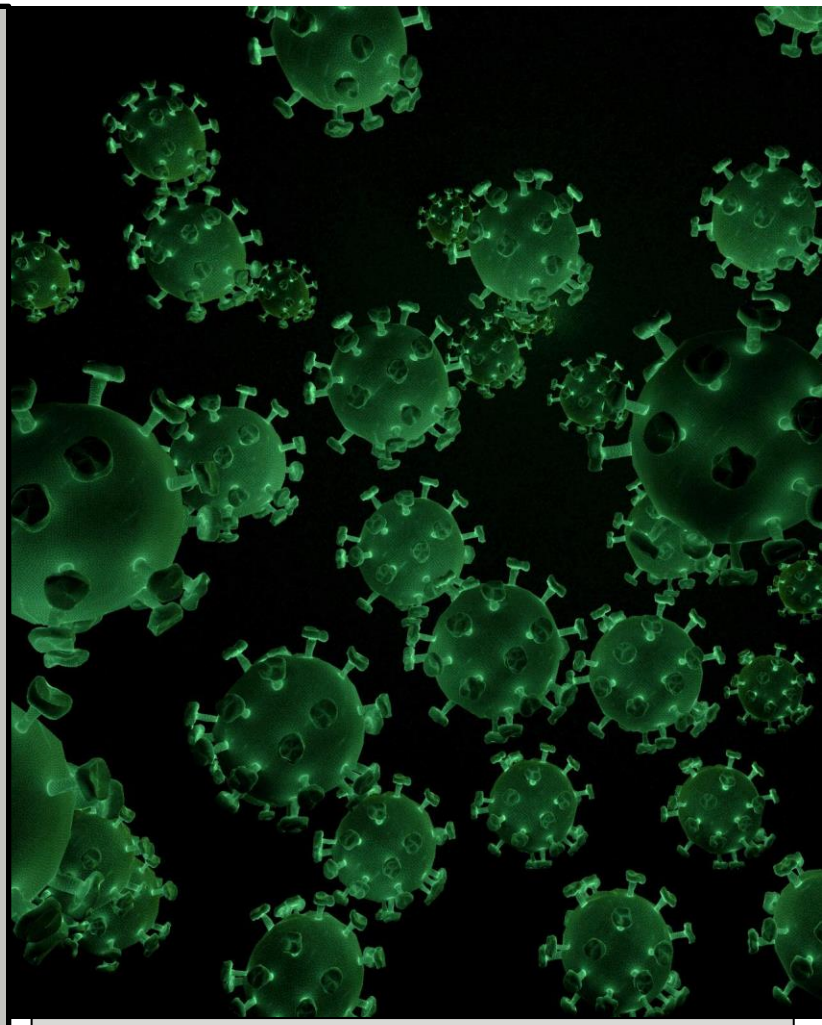
- Is attacking epithelial cells in the nose, throat, and respiratory system

Body's reaction

- Releases histamine which widens the blood vessels near infection
- Allows immune responses like antibodies to get to the infection better
- Histamines also end up in other body parts like muscles
- Cytokines are also released that help coordinate the body's attack on virus

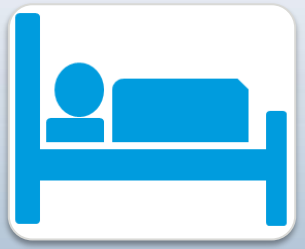
The problem

- Histamines and cytokines can affect pain receptors

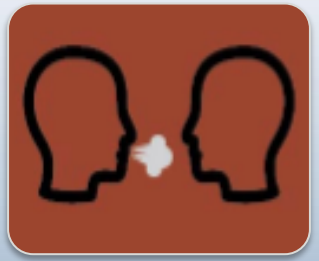


3D rendering of influenza virus.

Hypothesis On Evolution of Feeling Bad When You Are Sick



If a person is sick, he/she will stay in bed



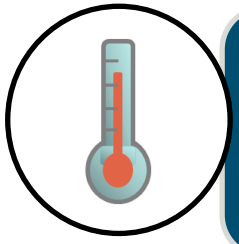
If a person stays in bed, he/she will be less likely to expose other people

Bottom image. CDC. https://www.cdc.gov/flu/resource-center/freeresources/graphics/seasonal-vs-pandemic-flu-infographic.htm

Should You Get the Fever Down?

Why Do You Get a Fever?

- Your immune system releases chemicals called pyrogens
- The hypothalamus portion of the brain get the pyrogens and raises the temperature

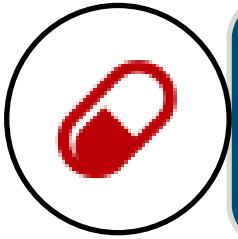


Increased temperature

- Can kill some bacteria
- Can inhibit the replication of some viruses

When you reduce the fever

- Doesn't reduce the amount of virus
- Research is suggesting that tens of thousands of more people can be then infected!



Do you reduce the fever?

- If too high, yes!
- If not too high. . .

Differences Between the Sexes[1]

Women tend to generate stronger immune responses than men

- Helps clear virus faster from the system

The good

- Lower virus can shorten intensity and duration of illness
- Especially important if pregnant

The bad

- More likely to have hyperimmune response so could have higher morbidity/mortality in outbreak or pandemic
- Chronic infections (like HIV) have been linked to accelerating the aging process

1. Klein, SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza pathogenesis. Journal of Leukocyte biology. 2012. Jul: 92(1) 67-73

Results of CDC's 2016-2017 Internet panel survey of pregnant women

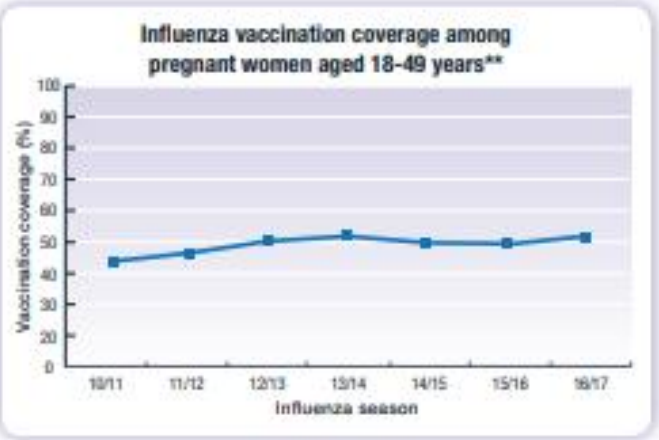
Half of pregnant women protect themselves and their babies against flu. Time to bump it up!

With only half of pregnant moms getting their flu shot, too many remain unprotected.

Flu shots help protect pregnant women and their babies from potentially serious flu illness during and after pregnancy.

During the 2016-2017 flu season, an estimated 50%* of pregnant women in the U.S. protected themselves and their babies from flu by getting a flu shot. While this is a significant improvement since the years before the 2009 pandemic, about half of pregnant women and their babies, still remain unprotected from influenza.

We can do better. All pregnant women need flu shots to protect themselves and their babies.



If you're pregnant, a flu shot:

- is recommended at any time during your pregnancy
- can reduce your risk of getting sick from flu
- can protect your baby from flu for several months after birth

Pregnant women also need a whooping cough (Tdap) shot. Talk to your doctor.

Get vaccinated to protect yourself and your baby.

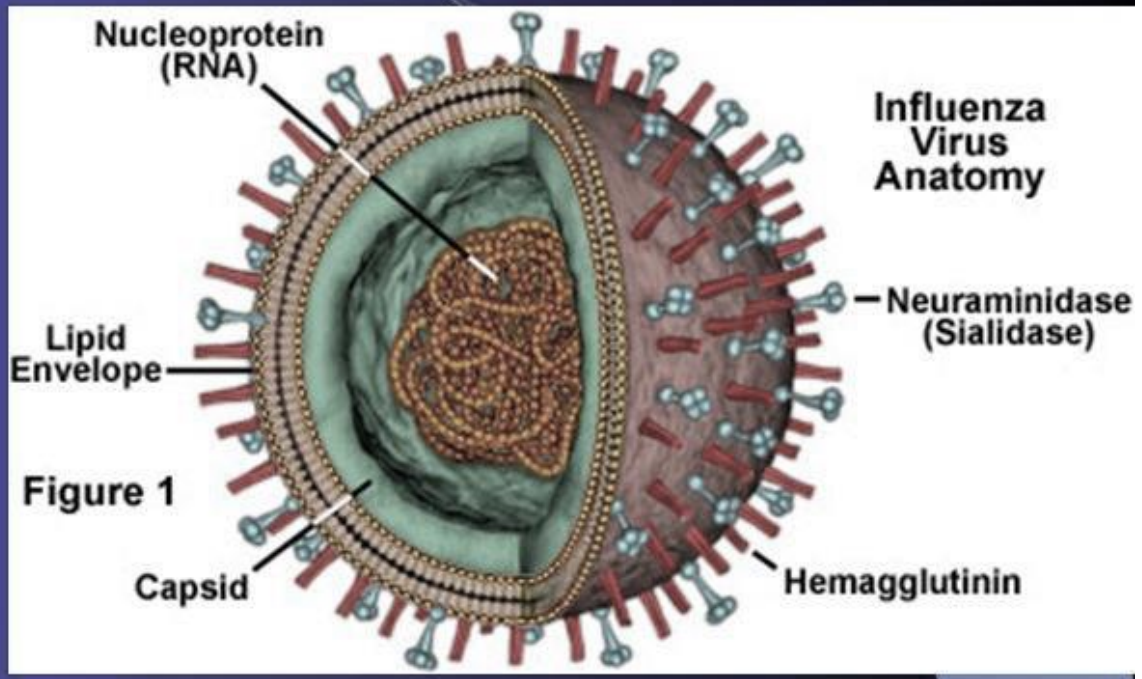
www.cdc.gov/flu/protect/vaccine/pregnant.htm

NCIRDig705 | 10/25/17

*https://www.cdc.gov/flu/fluvaxview/pregnant-women-nov2016.htm **Sources: 2007-2010 BRFSS, 2010-11-2016-17 Internet Panel Survey.

Influenza Virus

- The influenza virus contains ssRNA in its core
- This is surrounded by a matrix protein membrane
- A lipid bilayer envelopes the virus
- The outer layer is studded with prominent glycoprotein spikes



Courtesy of http://micro.magnet.fsu.edu/cells/viruses/influenzavirus.html

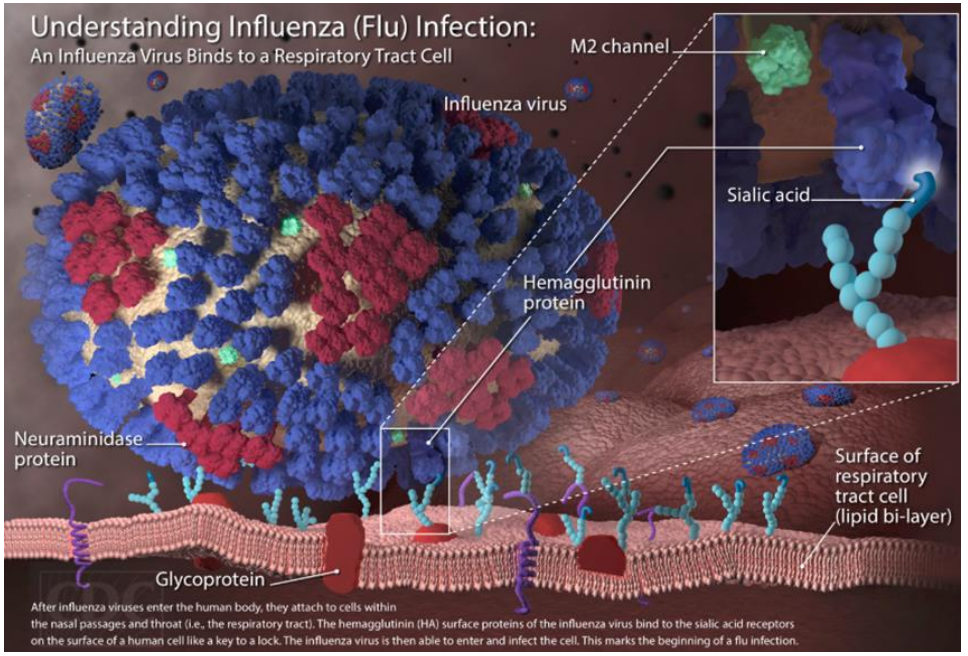
So what is with the H and N?

H stands for hemagglutinin

- **Allows virus to stick to cells**
- **Around 13 types**

N stands for neuraminidase

- **Helps release new virus from cells**
- **Around 9 types**



Influenza A types have designations like H5N1, while influenza B viruses don't

"Novel H1N1" is the same as swine flu

1. CDC. https://www.cdc.gov/flu/resource-center/freeresources/graphics/images.htm

What are the issues of respiratory disease?

The symptoms of respiratory diseases are vague

- Pneumonia symptoms
  - Cough
  - Fever
  - Chills
  - Difficulty breathing
- Influenza
  - Cough
  - Fever
  - Chills
  - Malaise

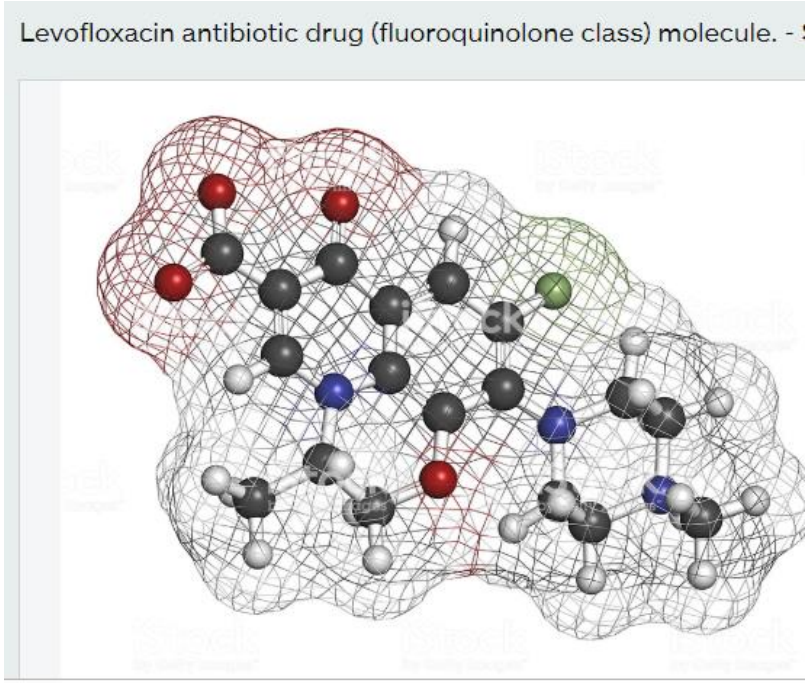
Treatment is different

- Bacteria
  - Broad spectrum antibiotic
  - Narrow spectrum antibiotic
- Influenza
  - Antiviral
  - Treat symptoms only

Complications of mistreatment

- Mistreatment of bacterial etiology
  - May increase morbidity/ mortality
  - May have longer hospital stay
  - May get *C. difficile*
- Mistreatment of influenza
  - May have increased resistance and *C. difficile*

Misuse of Antibiotics Can Lead to Other Medical Issues



Pneumonia may be treated with fluoroquinolone

Disrupts normal intestinal flora

O27 strain of *C. difficile* is specifically resistant to fluoroquinolone

Antibiotics - Microbiome and Influenza

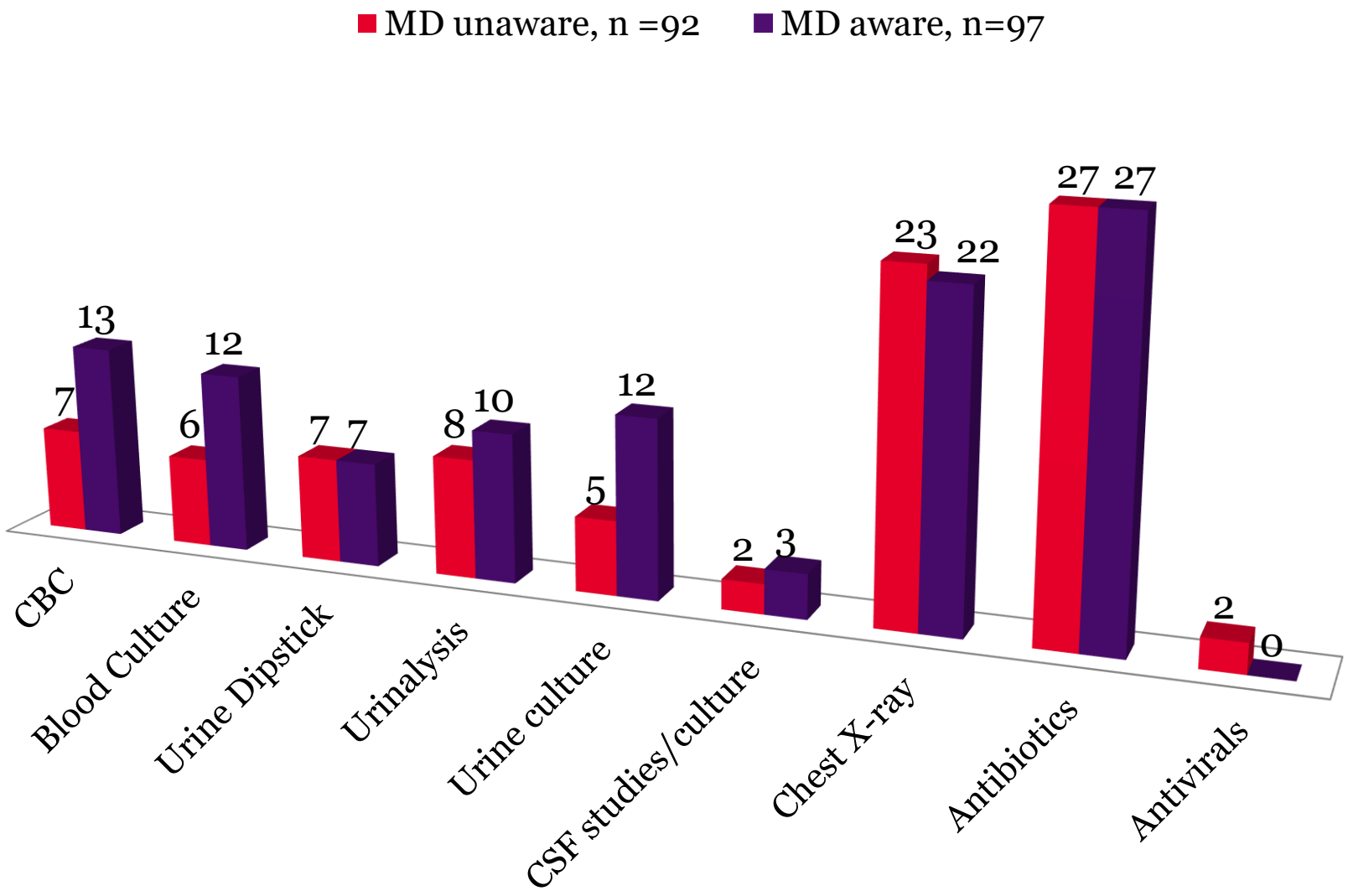
Treating with antibiotics may worsen the effectiveness to respond to influenza

Antibiotics can destroy the natural microbiome

Mechanism

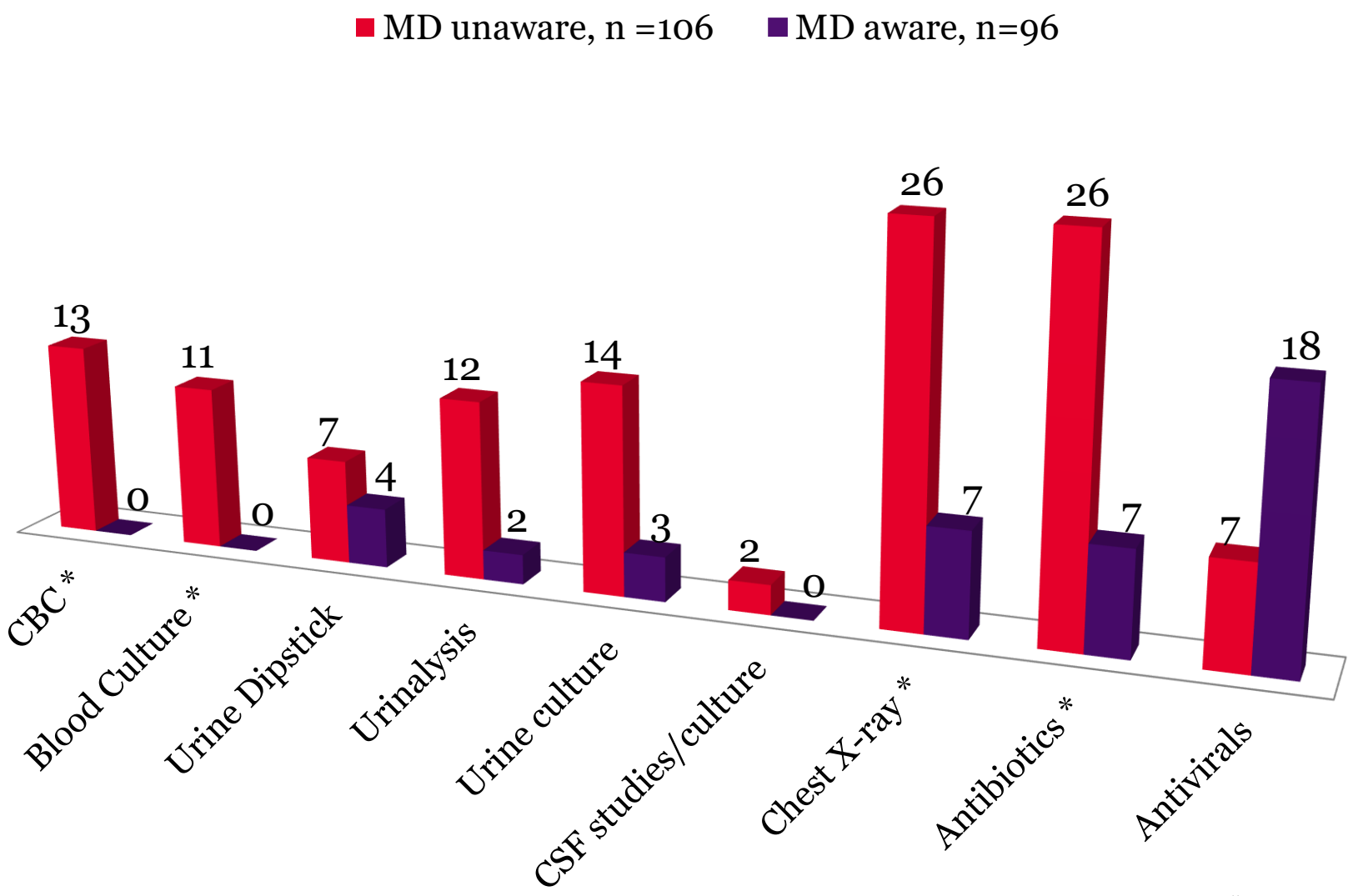
- Microbiota can increase interferon (IFN) signature in lung stroma cells
- Increased IFN can help slow early influenza infection

Results – Flu Negative



Bonner, *et al,* Pediatrics (2003) 112:363-367

Results – Flu Positive



Bonner, *et al*, Pediatrics (2003) 112:363-367

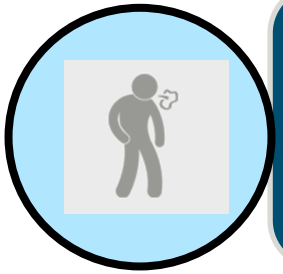
* - p ≤ 0.001

Pediatric Study

CHILDREN WHO WERE POSITIVE BY A RAPID INFLUENZA TEST WERE:

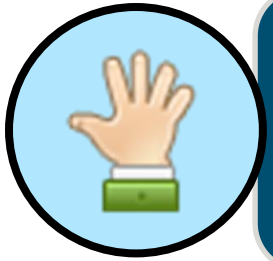
- **More likely to be prescribed an antiviral**
- **Less likely to be prescribed an antibiotic**
  - Jennings et al. "Effect of Rapid Influenza Testing on the Clinical Management of Paediatric Influenza."

Spread of Influenza



Flu is spread person-to-person through coughing or sneezing.

- Quick incubation of around 2 days



Hands can spread influenza if the person then touches their nose.

Healthy adults can infect others one day BEFORE symptoms develop and up to 5-7 days after.

Viral Shedding

Viral Shedding

- Shedding can begin 1 day before sickness
- Peak of the shedding is within first 3 days of illness
- Subsides around 5-7 days
  - Can be longer in children

Treatment

Nothing

Antiviral Treatment

Who gets priority for antiviral treatment?

- People who are hospitalized
- Under the age of 2 or over the age of 65
- Pregnant women
- Particular chronic or immunosuppressive conditions
- People under 19 who are receiving long-term aspirin therapy
- American Indians/ Alsaka Natives
- Extremely obese, BMI ≥40
- Residents of nursing homes

1. CDC. www.cdc.gov/h1n1flu/antiviral.htm
https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Treatment

- Ideally, antivirals should be taken within first 48 hours. Greatest benefit is when started as close to onset as possible.
- Some people do not go in on first day of symptoms.
- Treatment window can be small.
- Some influenza strains are resistant to Tamiflu

Treatment

RECOMMENDED MEDICATIONS FOR TREATMENT OF INFLUENZA:

ANTIVIRALS

- **Oral oseltamivir phosphate – Tamiflu®**
- **Inhaled zanamivir – Relenza®**
- **Intravenous peramivir – Rapivab®**

CAP-DEPENDENT ENDONUCLEASE INHIBITOR

- **Oral baloxavir marboxil – Xofluza®**

RESISTANCE

It is possible that some influenza viruses may become less susceptible or resistant to oseltamivir and peramivir during antiviral treatment with one of these drugs and remain susceptible to zanamivir; this has been reported most often for influenza A(H1N1)pdm09 viruses (Graitcer, 2011; Lackenby, 2011; Memoli, 2010; Nguyen, 2010; Nguyen, 2012) Influenza A(H1N1)pdm09 viruses have also emerged that are resistant to all neuraminidase inhibitors, including zanamivir, in highly immunosuppressed patients on prolonged neuraminidase inhibitor treatment (Tamura, 2015; L'Huillier, 2015). Resistance and reduced susceptibility of influenza viruses to antiviral drugs can also occur spontaneously, with no known exposure to antiviral medications (Hurt, 2011; Takashita, 2013; Takashita, 2014).

1. CDC. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

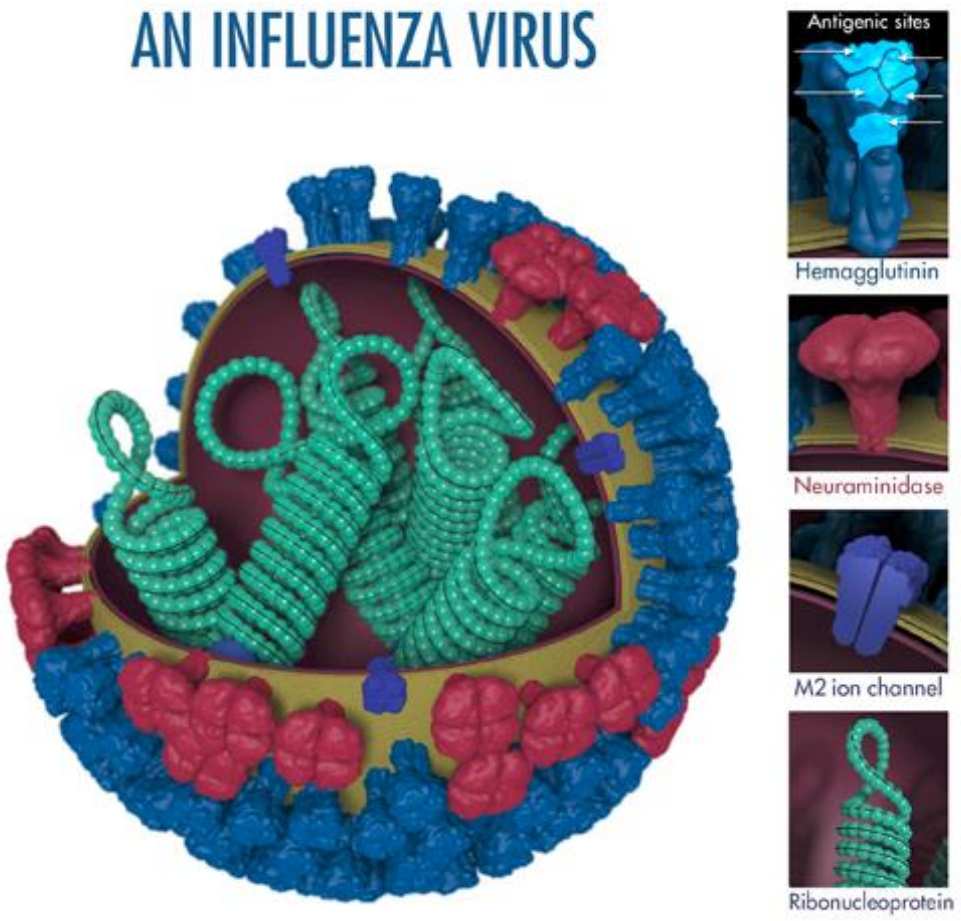
How the virus changes – Shift vs. Drift

ANTIGENIC DRIFT –

Small changes in the virus that happen over time. It allows new strains that can evade the body's immune system.

ANTIGENIC SHIFT –

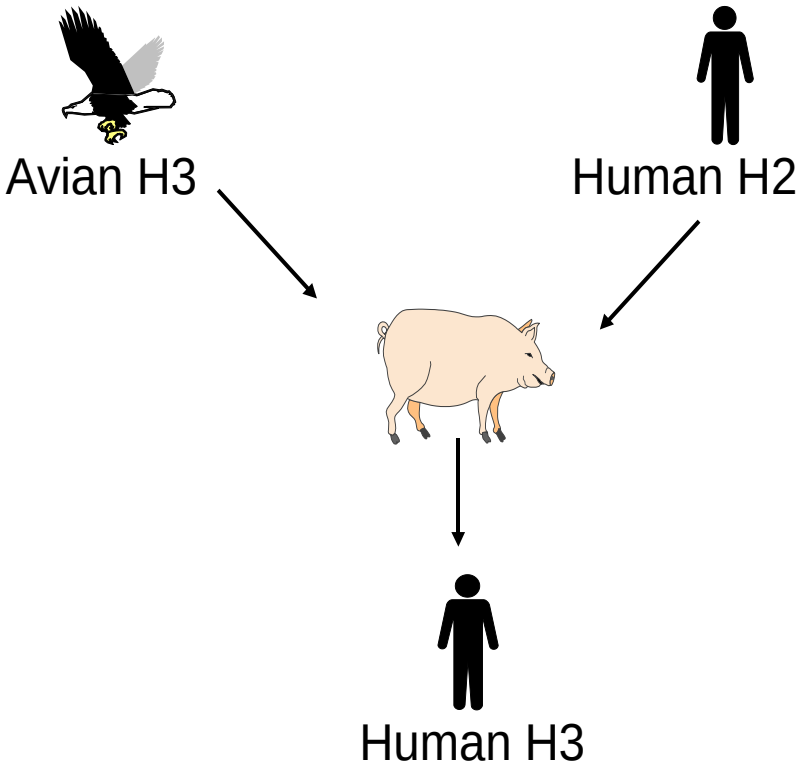
An abrupt, major change that results in a new hemagglutinin and/or new hemagglutinin and neuraminidase protein.



Following influenza infection or receipt of the influenza vaccine, the body's immune system develops antibodies that recognize and bind to "antigenic sites," which are regions found on an influenza virus' surface proteins. By binding to these antigenic sites, antibodies neutralize flu viruses, which prevents them from causing further infection.

1. CDC. https://www.cdc.gov/flu/professionals/laboratory/antigenic.htm
2. Image- Courtesy CDC. . https://www.cdc.gov/flu/images/virus/fluvirus-antigentic-characterization-medium.jpg

How do you make a pandemic flu?



Risk factors for severe disease with novel H1N1 [1]

- Overall, similar to risk factors for seasonal influenza

- Chronic medical conditions including cardiopulmonary disease and immunosuppression

- Pregnancy

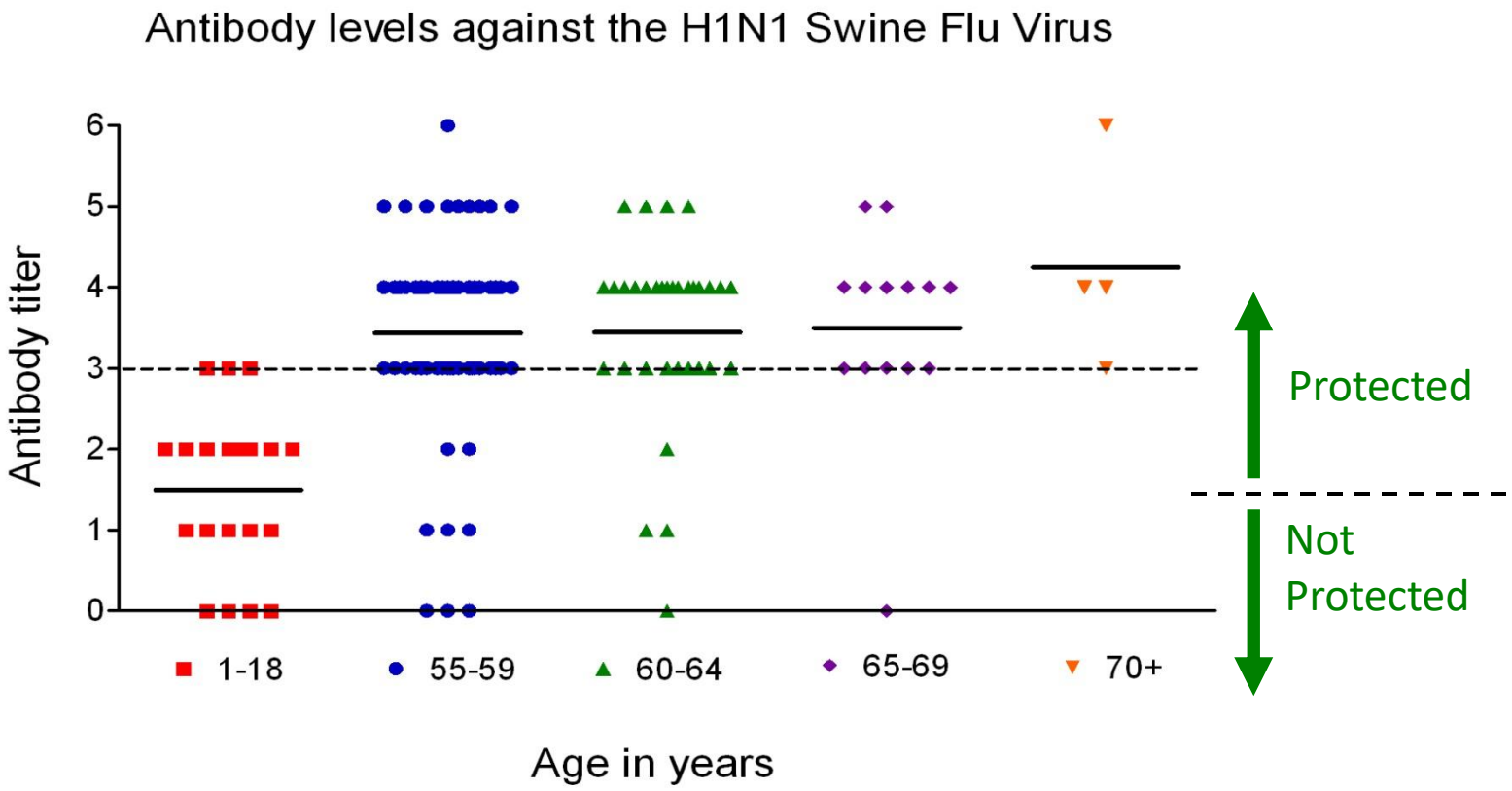
- Neurodevelopmental delay

- Obesity (this is not recognized as a risk factor for seasonal influenza)

- Extremes of age have <u>not</u> been a risk factor for H1N1

1. Courtesy of Jonathan McCullers, Department of Infectious Diseases, St. Jude Children's Research Hospital

Natural protection against H1N1



❖ Older adults have natural protection from H1N1

- **from J.A. McCullers Unpublished research**

Specimen Collection

Influenza Sample Collection

Appropriate specimens

- Nasal wash/aspirate, nasopharyngeal swab, or nasal swab
- Throat swabs have dramatically reduced sensitivity

Samples should be collected within first 24 to 48 hours of symptoms since that is when viral titers are highest and antiviral therapy is effective

Testing can be done immediately with rapids or sample placed in transport media

- Infectivity is maintained up to 5 days when stored @ 4-8°C
- If the sample cannot be evaluated in this time period, the sample should be frozen @ -70°C.

2018 IDSA Guidelines

Who Should be Tested?
Outpatients During Influenza Season[1]

- **High-risk patients like immune compromised**
- **Patients who have acute onset of respiratory symptoms that may or may not have fever or a chronic medical condition if it affects clinical management**
- **Patients not at risk of complications but decisions;**
  - May change antiviral treatment
  - Reduce unnecessary antibiotics
  - Reduce further diagnostic testing
  - Reduce time in the emergency department
  - May influence high-risk household contacts' treatment decisions

1. Uyeki et al. Clinical Practice Guidelines by the IDSA: 2018 Update . https://www.idsociety.org/globalassets/idsa/practice-guidelines/2018-seasonal-influenza.pdf

Who Should be Tested?
Outpatients **Not** in Influenza Season[1]

- May consider testing acute onset respiratory symptoms with/without fever, especially if patients in high risk category or immune compromised

1. Uyeki et al. Clinical Practice Guidelines by the IDSA: 2018 Update . https://www.idsociety.org/globalassets/idsa/practice-guidelines/2018-seasonal-influenza.pdf

Who Should be Tested?
Hospitalized Patients in Influenza Season[1]

- **Test influenza on any admissions of patients with respiratory illness with or without fever**
- **Test on patients that have acute worsening of chronic cardiopulmonary disease such as COPD, asthma, heart failure, or coronary artery disease**
  - Influenza may exacerbate these conditions
- **Test patients with acute onset of respiratory symptoms with/without fever that are immune compromised or at high risk of complications**
  - Influenza in these patients may be less characteristic
- **Test hospitalized patients with acute onset of respiratory symptoms with/without fever when there isn't a clear alternative diagnosis**

1. Uyeki et al. Clinical Practice Guidelines by the IDSA: 2018 Update . https://www.idsociety.org/globalassets/idsa/practice-guidelines/2018-seasonal-influenza.pdf

Who Should be Tested?
Hospitalized Patients **Not** in Influenza Season[1]

- **Test patients on admission with acute respiratory illness with or without fever that have a epidemiological link to person with influenza, an outbreak of influenza, or an outbreak of respiratory illness with uncertain cause, or travel to an area with known influenza activity**
- **Consider testing children and adults who are immune compromised or at risk of complications that have an acute, febrile respiratory tract illness**

1. Uyeki et al. Clinical Practice Guidelines by the IDSA: 2018 Update . https://www.idsociety.org/globalassets/idsa/practice-guidelines/2018-seasonal-influenza.pdf

Sensitivity vs Specificity vs PPV vs NPV

Sensitivity:

Probability test=positive if patient=positive

Specificity:

Probability test=negative if patient=negative

PPV: Probability patient=positive if test=positive

NPV: Probability patient=negative if test=negative

How prevalence can impact perceived test performance

Flu is seasonal. Prevalence of the disease is different in June than in January.

This will impact the perceived performance of the test.

Test 1,000 persons

Test Specificity = 99.6% *(4/1000)*

Prevalence = 10%

True positive: 100 **False positive: 4**

Positive predictive value: 100/104 = 96%

How prevalence can impact perceived test performance

Test 1,000 persons

Test Specificity = 99.6% *(4/1000) P*revalence = 10%
True positive: 100 False positive: 4
Positive predictive value: 100/104 = 96%

Prevalence = 0.4%

True positive: 4 False positive: 4

Positive predictive value: 4/8 = 50%

Diagnostic Methods for Influenza

- Culture
- DFA
- PCR
- Rapid Tests

Viral Culture

Pro

- Highly sensitive as long as sample is properly handled

Con

- Can’t give same day result to help monitor therapy
- High level of difficult/equipment

DFA

Pro

- Usually considered to have high level of sensitivity
- Can usually test for other respiratory pathogens at the same time
- Results can be achieved in same day

Con

- Labor intensive needed experienced users
- Turn-around time from lab usually takes many hours

Rapid Lateral Flow Tests

Pro

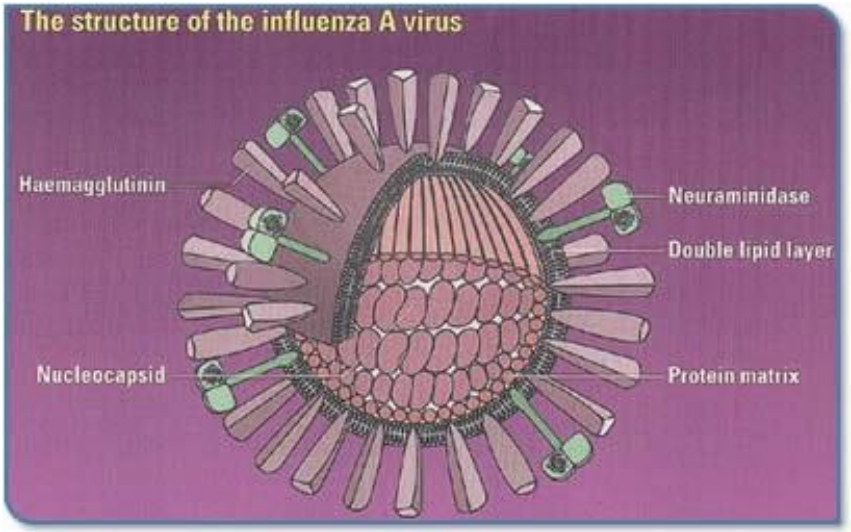
- Tests take minimal time
- Some tests are so simple that they can be CLIA-waived
- Can be used to triage patients
- Positive results can be used to rule out other issues like pneumonia so don't give unnecessary chest x-ray, antibiotics, etc.

Con

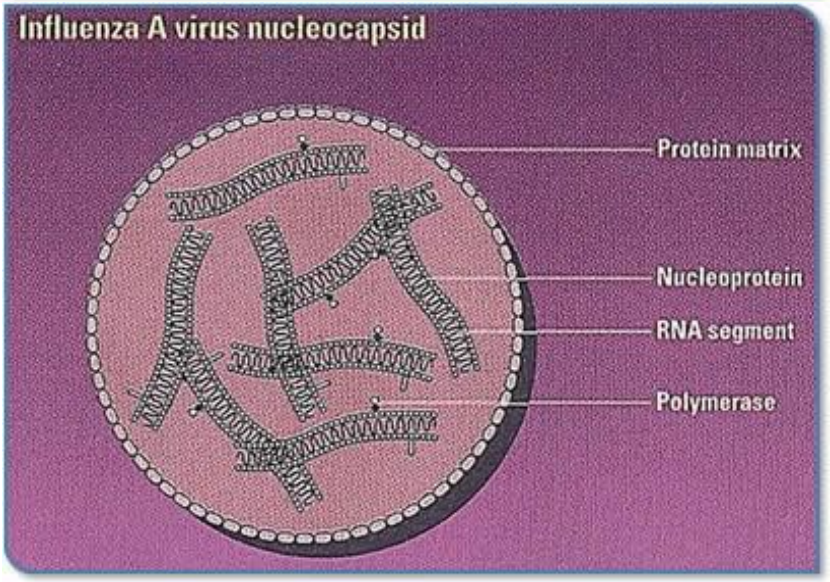
- Performance is not as good as culture, PCR, and DFA

What rapid tests target

Detecting influenza A and influenza B nucleoproteins (Ag)



The nucleoproteins are conserved throughout a given species



Molecular Assays

Pro

- For respiratory specimens, high performance
- Same day results

Con

- Turn around time from lab may be extensive, especially if batching specimens
- Expensive
- May require experienced technicians, labs, dedicated equipment, etc.

Rapid Molecular Tests

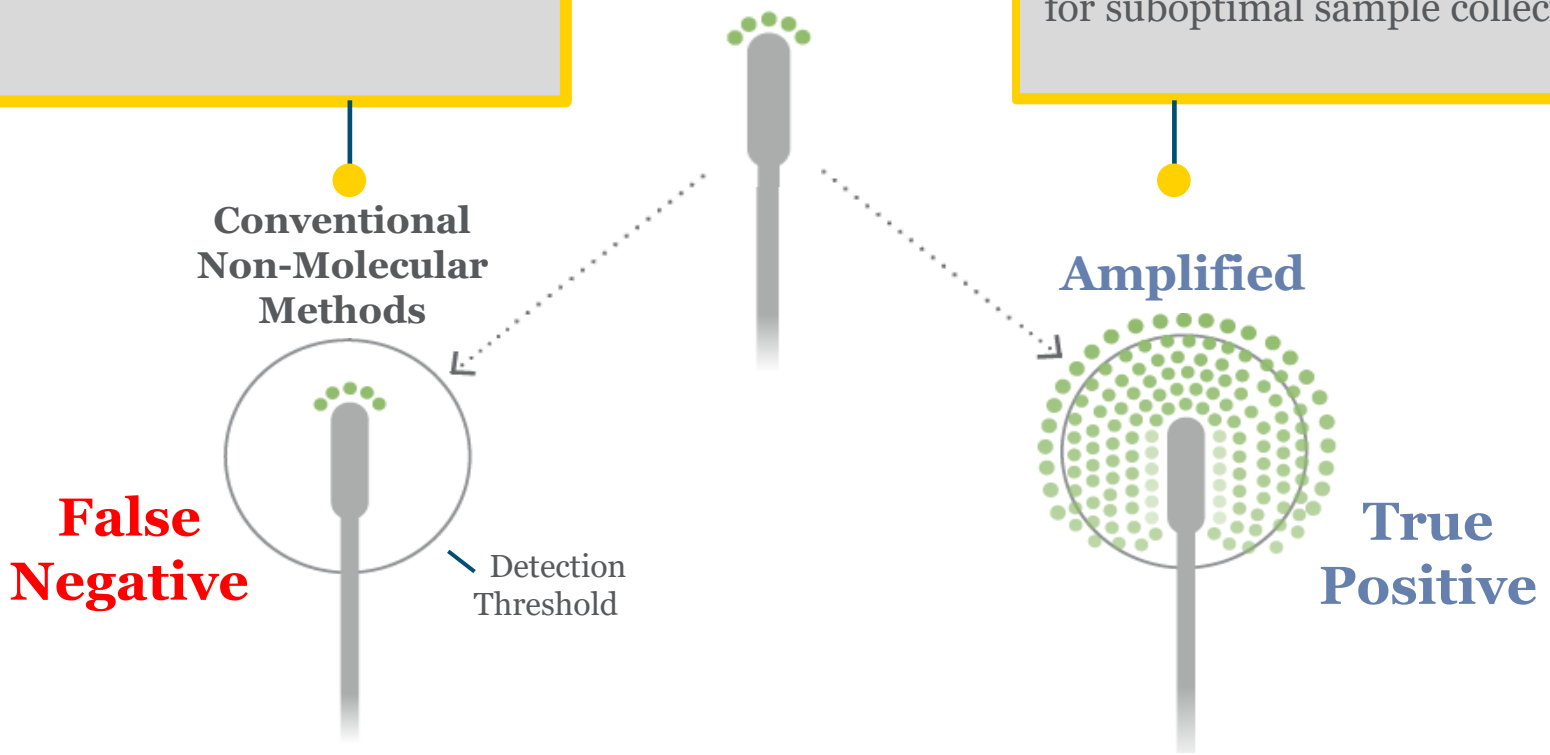
Why molecular?
The power of sample amplification

Conventional **non-molecular** methods can have suboptimal limits of detection.

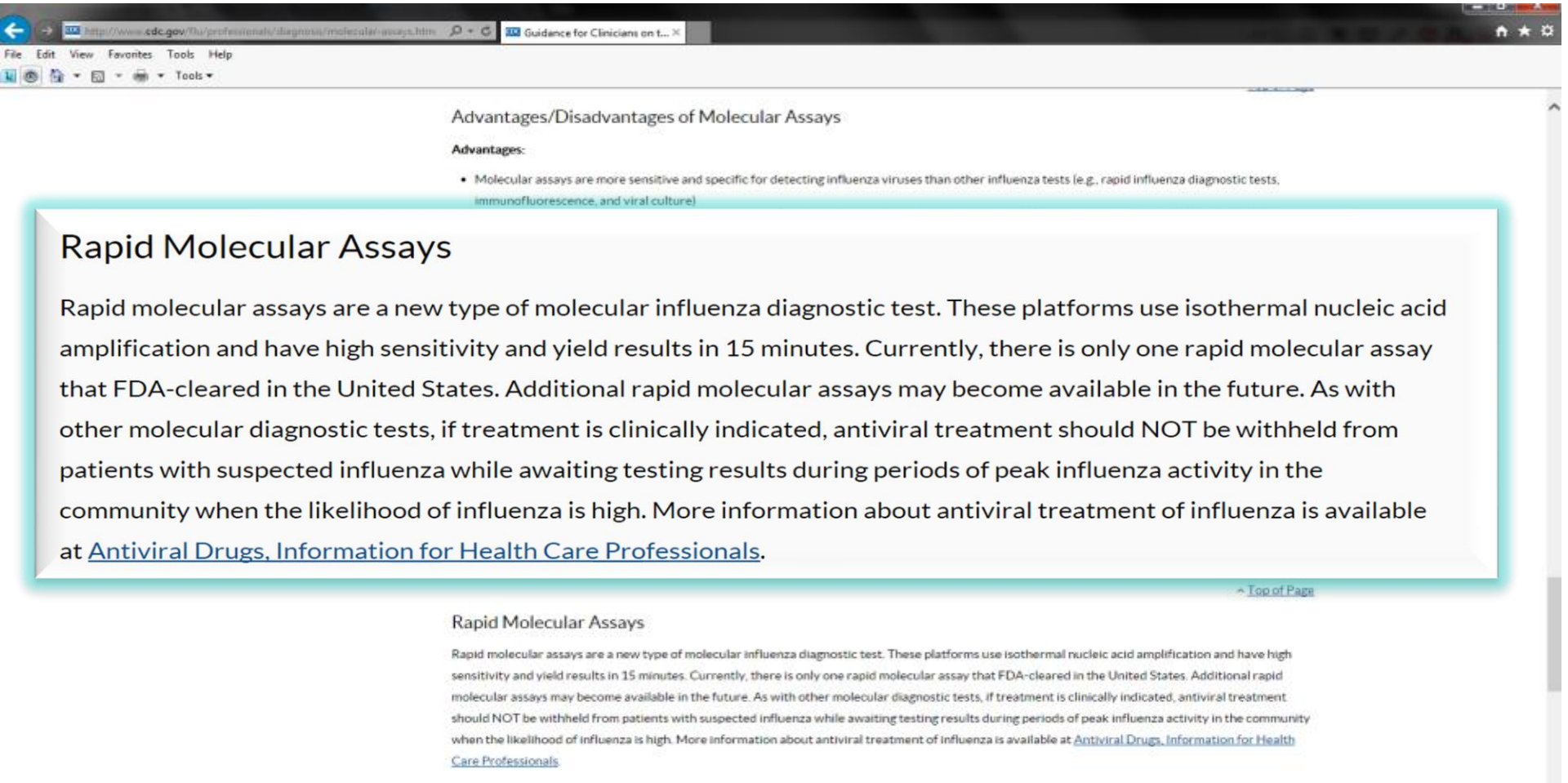
Samples with low viral or bacterial load could result in a false negative.

With **molecular**, even a few hundred infectious particles can be amplified billions of times!

Amplification increases likelihood of detection, and may compensate for suboptimal sample collection.



CDC Website Creates a New Diagnostic Category



Centers for Disease Control and Prevention. Information on Rapid Molecular Assays, RT-PCR, and other Molecular Assays for Diagnosis of Influenza Virus Infection. February 20, 2018. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Technology Comparison

	IMMUNOASSAY		MOLECULAR	
	RAPIDS	LAT FLOW READERS	PCR	Rapid
FAST	✓	✓		✓
CONVENIENT	✓	✓		✓
POC-FRIENDLY	✓	✓		✓
ACTIONABLE RESULTS	✓	✓		✓
REMOVES SUBJECTIVITY		✓	✓	✓
CONNECTED		✓	✓	✓
EXCELLENT PERFORMANCE			✓	✓

Multiplexing Assays[1]

Pros

Able to do multiple pathogens at the same time

- Many pathogens give similar symptoms
- Don't have to do one assay at a time

Cons

Longer time than other rapid molecular

Doesn't do well with commensal bacteria

- *S. pneumoniae* and H. *influenzae*
- *C. difficile*

Not all pathogens are created equally

- Things like influenza, RSV, and hMPV are rare in asymptomatic children and adults
- Rhinovirus and coronavirus can be present in asymptomatic patients and as part of co-infection

1. Self et al. Respiratory Viral Detection in Children and Adults: Comparing Asymptomatic Controls and Patients With Community-Acquired Pneumonia, *The Journal of Infectious Diseases*, Volume 213, Issue 4, 15 February 2016, Pages 584–591, https://doi.org/10.1093/infdis/jiv323

The Connection Between Influenza and *S. pneumoniae*

Statistics of influenza and pneumonia

Influenza pandemics of 1957 and 1968

- Bacterial etiology in roughly 70% of patients with severe pneumonia (life threatening or fatal)[1,2]

Influenza hospitalizations rates (non pandemic)

- 44-57% bacterial pneumonia[3-6]

Approximately 25% of influenza-related deaths have a secondary bacterial pneumonia[7]

1. Hers JFP, Masurel N, Mulder J. Bacteriology and histopathology of the respiratory tract and lungs of fatal Asian influenza. Lancet **1958; 2:1141–3.**
2. Lindsay MI Jr, Herrmann EC Jr, Morrow GW Jr, Brown AL Jr. Hong Kong influenza: clinical, microbiologic, and pathologic features in 127 cases. JAMA **1970; 214:1825–32.**
3. Scadding JG. Lung changes in influenza. Quart J Med **1937; 6:425–65.**
4. Stuart-Harris CH, Laird J, Tyrrell DA, Kelsall MH, Franks ZC. The relationship between influenza and pneumonia. J Hyg (Lond) **1949; 47:** 434–48.
5. Tyrrell DAJ. The pulmonary complications of influenza as seen in Sheffield in 1949. Quart J Med **1952; 21:291–306.**
6. Nicholson KG. Human influenza. In: Nicholson KG, Webster RG, Hay AJ, eds. Textbook of influenza. London: Blackwell Science, **1998:222–3.**
7. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine **1999; 17(Suppl 1):S3–10.**

EID - Predictors of Pneumococcal Co-infection with Pandemic (H1N1)

Study in Spain

July 2009- March 2010

- Looked at adults who had influenza-like illness and sought medical attention and had ≥ 1 risk factor for contracting influenza-related complications

Emerging Infectious Diseases. www.cdc.gov/eid. Vol 17 1475-8.

EID Study- Data Collection[1]

Samples

- Oropharyngeal and nasopharyngeal swab samples
- Urine sample
- Sputum and 2 blood cultures

Assays

- PCR for the detection of influenza
- Blood, urinary antigen, or qualified sputum for *S. pneumoniae*

1. Emerging Infectious Diseases. Predictors of Pneumococcal Co-infection for Patients with Pandemic (H1N1) 2009. Masia, M. et al.Vol 17. 1475-8. https://wwwnc.cdc.gov/eid/pdfs/vol17no8_pdf-version.pdf

EID Study – Results[1]

418 patients were evaluated

- 179 were confirmed H1N1
- In PCR H1N1 negative, 25.1% had pneumococcal disease

Of 100 patients with influenza

- 14% had pneumococcal infection
  - "Infection in more than half these patients would not have been diagnosed if a pneumococcal urinary antigen test had not been performed."

1. Emerging Infectious Diseases. Predictors of Pneumococcal Co-infection for Patients with Pandemic (H1N1) 2009. Masia, M. et al.Vol 17. 1475-8. https://wwwnc.cdc.gov/eid/pdfs/vol17no8_pdf-version.pdf

EID Study
When Coinfection Found[1]. . .

Patients more frequently admitted to the hospital and to the intensive care unit

Had lower oxygen saturation

Had higher axillary temperature

1. Emerging Infectious Diseases. Predictors of Pneumococcal Co-infection for Patients with Pandemic (H1N1) 2009. Masia, M. et al.Vol 17. 1475-8. https://wwwnc.cdc.gov/eid/pdfs/vol17no8_pdf-version.pdf

EID Study – Conclusions[1]

Concurrent infection significantly increased risk of patient complications

If only looking for influenza, pneumococcal pneumonia may be missed or only looking for pneumonia, influenza may be missed.

1. Emerging Infectious Diseases. Predictors of Pneumococcal Co-infection for Patients with Pandemic (H1N1) 2009. Masia, M. et al.Vol 17. 1475-8. https://wwwnc.cdc.gov/eid/pdfs/vol17no8_pdf-version.pdf

H1N1 Pandemic with S. pneumoniae in Argentina[1]

May 2009 – pandemic H1N1 had estimated fatality rate of 0.6%

- Similar to seasonal influenza

July 2009 – Argentina reported fatality rate of 4.5% (137 deaths out of 3056 cases)

- No genetic difference in virus
- *S. pneumoniae* associated with 56.4% of severe disease

1. Palacios G, Hornig M, Cisterna D, Savji N, Bussetti AV, et al. (2009) Streptococcus pneumoniae Coinfection Is Correlated with the Severity of H1N1 Pandemic Influenza. PLoS ONE 4(12): e8540. doi:10.1371/journal.pone.0008540

Proposed Mechanisms

Bacterial adherence after epithelial destruction

- Autopsy evidence in 1918 outbreak with *S. aureus*[1]

Neutrophil apoptosis in presence of influenza and *S. pneumoniae*[2]

Upregulation of molecules that *S. pneumoniae* can use as receptors

- Incubation with cytokines from viral infections[3]

Environmental factors

- High temperature, ATP, norepinephrine

1. JFP Hers, N Masurel, and J Mulder. Bacteriology and histopathology of the respiratory tract and lungs of fatal Asian influenza. Lancet. 1958; 2: 1164-5.
2. G Engelich, M White, and KL Harshorn. Neutrophil survival is markedly reduced by incubation with influenza virus and Streptococcus pneumoniae: role of respiratory burst. J. Leukoc Biol. 2001; 69: 50-6.
3. DR Cundell, NP Gerard, C Gerard, I Idanpaan-Heikkila and EI Tuomanen. Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature. 1995; 377: 435-8.

On The Horizon

- Universal influenza vaccine
- New drugs that are promising to eliminate influenza in a day

Conclusions

Diagnostic technologies for respiratory infections allow more directed therapy

Biological mechanisms do exist which predispose patients with influenza to pathogens such as *S. pneumoniae*

A superinfection with bacterial pneumonia has been shown to increase morbidity/mortality in influenza infections

Testing for both influenza and bacterial pneumonia in select populations can help predict how well patients do

Abbott