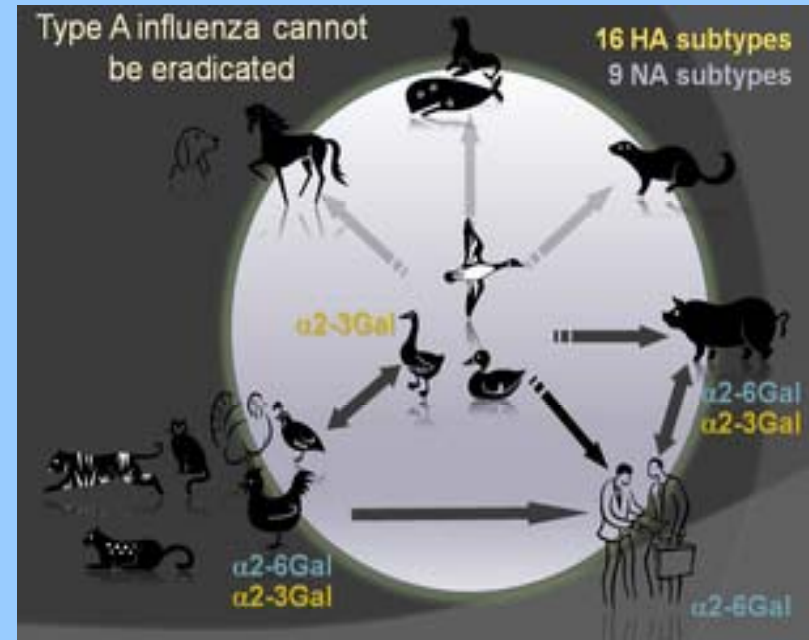
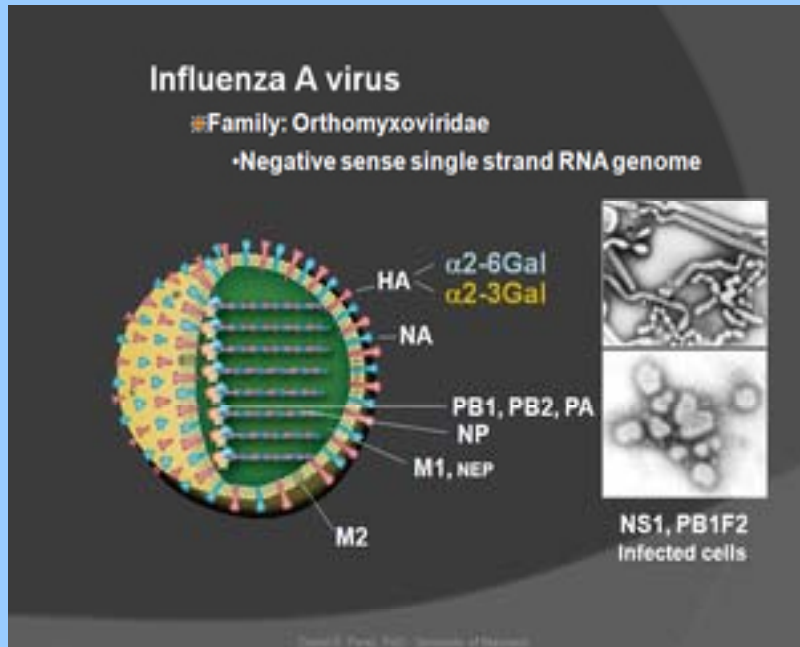


H1N1: An Overview



Thomas Neal, MD, MPH
Chief Physician, Health Systems
MITRE Corporation

Report Documentation Page

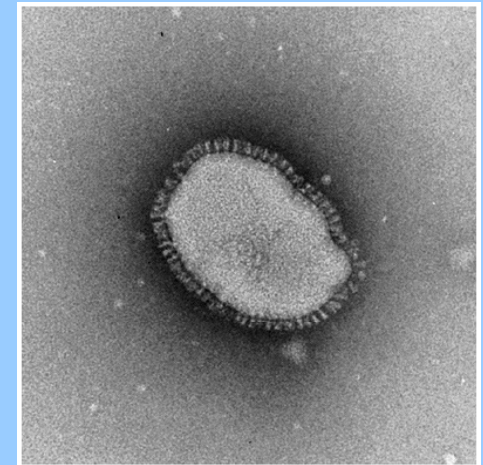
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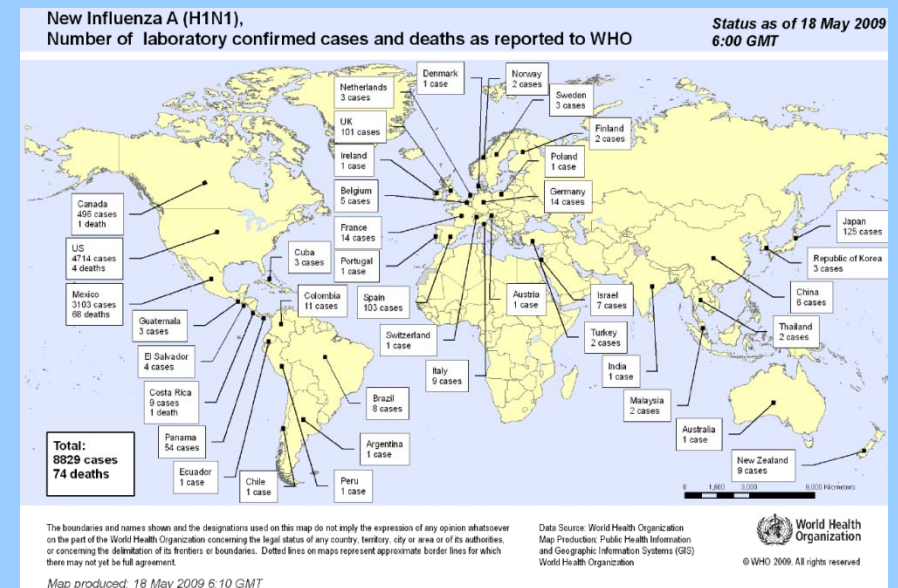
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Overview

- Introduction, ROE, Disclaimers, Acknowledgements
- The Human Health Story
- **The Agent:** Influenza A
- **The Disease:** “You and Me”
 - » Clinical Medicine
- **The Epidemic:** “The Herd”
 - » Population Health
- Prevention, Preparation and Mitigation
 - » Seasonal Influenza
 - » Pandemic Influenza



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Introduction, ROE, Disclaimers, Acknowledgements

Goals:

- A broad appreciation of the medical, biological, epidemiological and public health challenges in managing seasonal influenza and pandemics
- Emphasize some practical individual health strategies and planning that may protect employees and their families during the fall influenza season and beyond

ROE:

- Questions at anytime

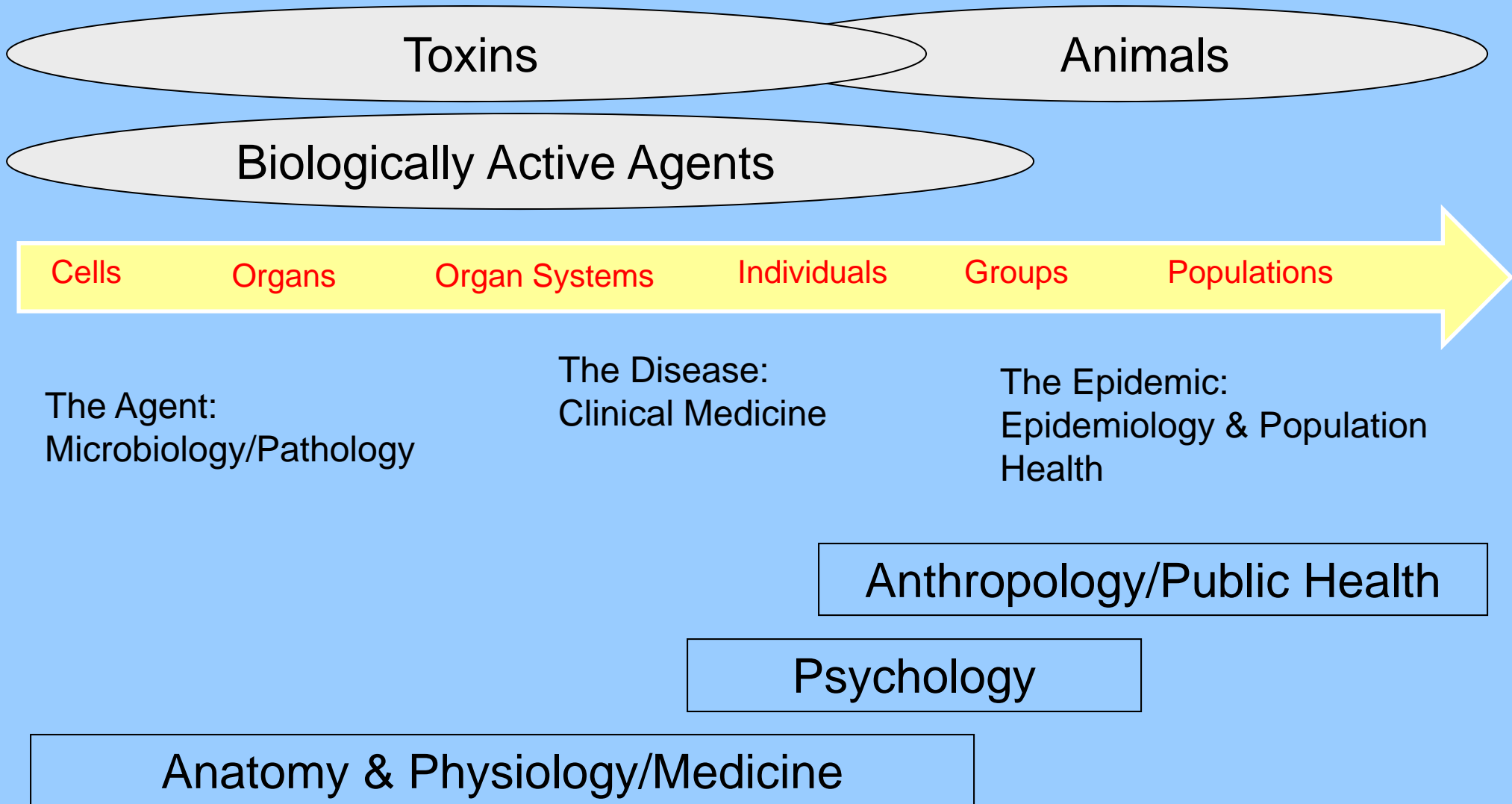
Disclaimers:

- Individual medical advice = Your primary care advisor
- MITRE Health Services, Business Continuity Program Office

Acknowledgements:

- NEJM, May 7, 2009, multiple articles (Triple Reassortment, Novel H1N1)
- Dori Reissman, MD, MPH; CDC
- Jean Otto, DrPH: Armed Forces Health Surveillance Center
- David Siegrist, PhD; Lynn Cooper, PhD; MITRE

The Human Health Story

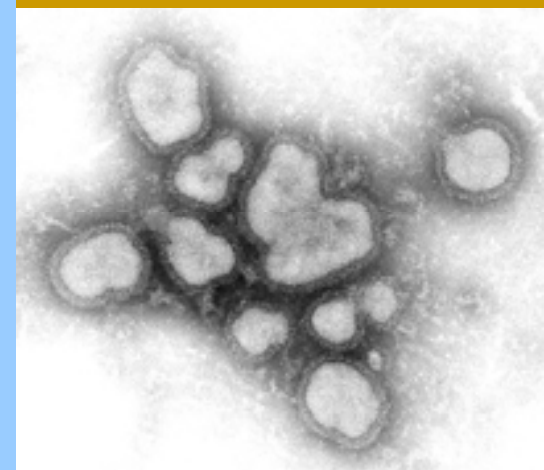


The Agent: Influenza A

- Influenza, also known as Flu, is a respiratory disease caused by the influenza A, B or C virus.
 - » Virus: obligate parasite, not “alive” and must “invade” a host, RNA/DNA strands
- Flu is contagious (H1N1: RNA Polymerase—PB2) and can be a mild, severe or, at times, deadly disease.
- In most hosts, the viral point of entry is the upper respiratory tract (nose, throat) and the primary target is the columnar epithelium of the airway (trachea, bronchi, bronchioles), H1N1: Alpha 2-6 Glycan Receptors.
- Epidemiology (Seasonal Flu):
 - » Between 5-20% of the U.S. population each year
 - » 200,000 hospitalizations
 - » 36,000 US deaths and 250,000 Global deaths



Transmission Electron Micrograph of influenza A virus



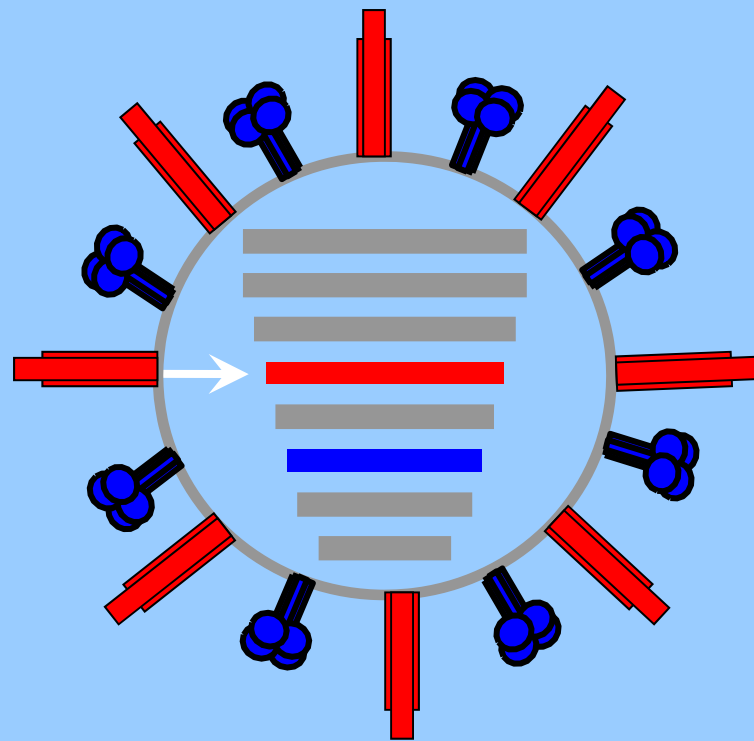
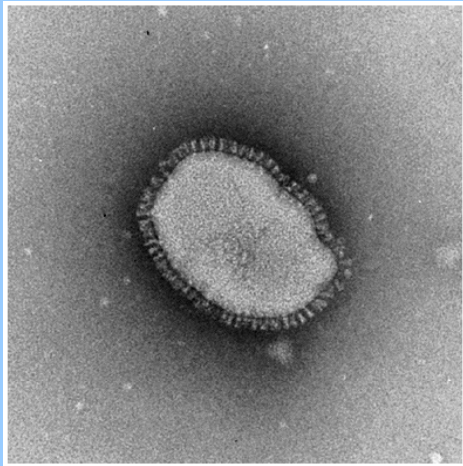
Negative stain of the influenza virus

Source: CDC

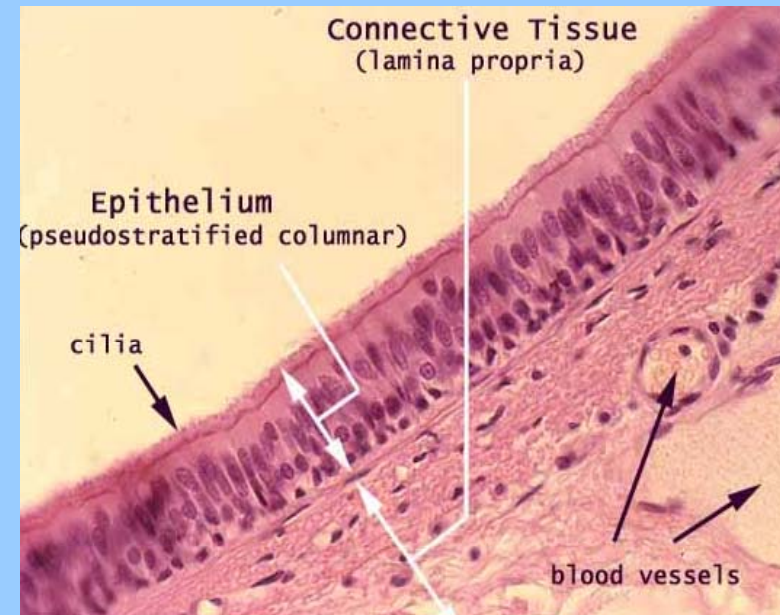
The Agent: Influenza A

Entry Key: HA, Receptor Binding Site

Hemagglutinin



8 Gene
Segments



Circulating Human Strains

H3N2 since 1968

H1N1 (human) since 1977

H1N1 (swine) ? 2009

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Source: Dr. Juan Arroyo, MITRE

The Agent: Influenza A & Viral Diversity

- There are 16 distinct HA* types and 9 distinct NA types; all are found in aquatic birds
- Aquatic birds are natural reservoir for diversity, virus is non-pathogenic for waterfowl
- New combinations of HA and NA as well as the other six genes occur during dual infections, random process
- Certain combinations are successful, others don't
- Pigs are susceptible to human and avian flu viruses, long thought to be the viral "mixing bowl" from which new human strains emerge
- Swine & poultry often co-located, particularly in Asia

** H5 and H7 inclined to turn highly pathogenic in poultry*



Source: Dr Dave Siegrist, Dr Lynn Cooper, MITRE

The Agent: Influenza A & Reassortment

Entry Key Varieties (subtypes)

H1 bird human pig

H2 bird human

H3 bird human pig

H4 bird

H5 bird



H16 bird



Exit Key Varieties (subtypes)

N1 bird human pig

N2 bird human pig

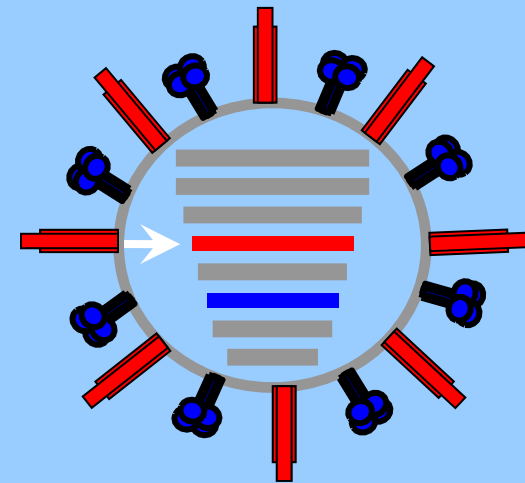
N3 bird



N9 bird

H1N1 } Seasonal flu
H3N2 }

H5N1 Avian flu

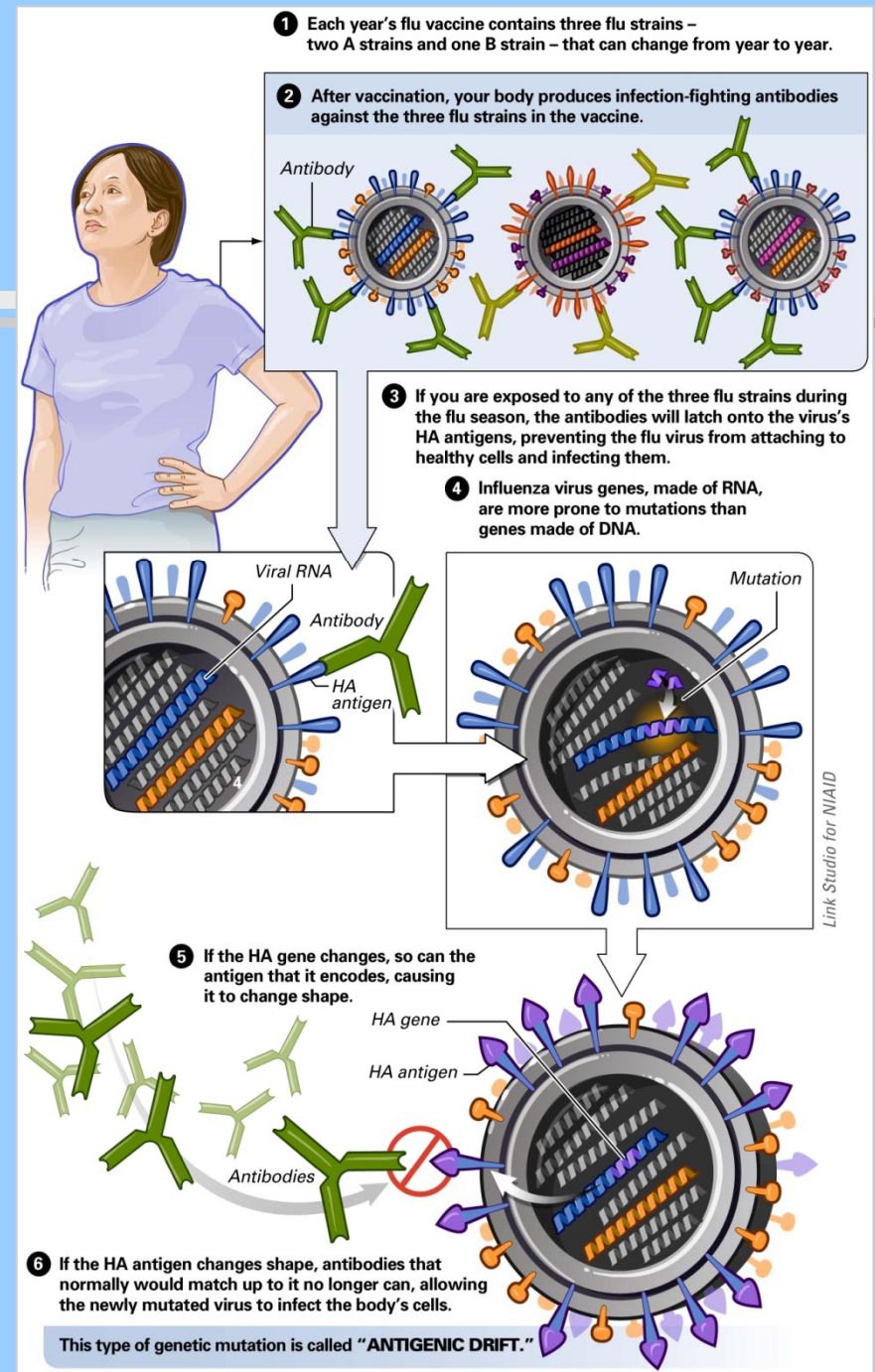


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The Agent: Change Mechanisms

Antigenic “drift”

- » Small errors (mutations) occur during the copying of genetic information.
- » Flu A viruses are unable to repair errors.
- » Small changes make the virus look new to the immune system.
- » Immunity against previous strains does not protect against the new version.

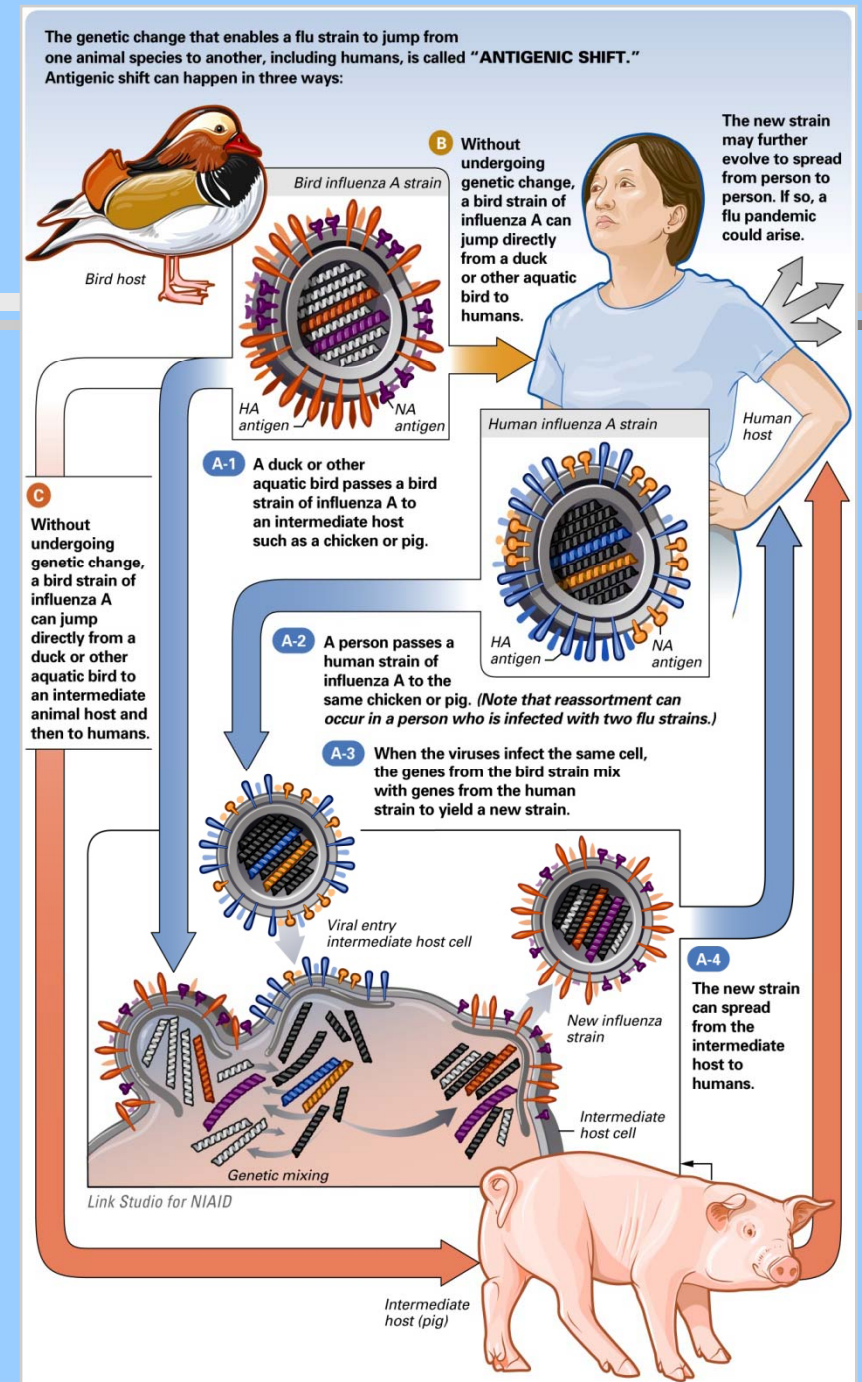


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NIAID/NIH

The Agent: Change Mechanisms

- **Antigenic “shift”**
 - » Drastic change in the composition of a virus.
 - » Influenza A viruses can exchange genetic material with other subtypes.
 - » This process results in new combinations of H and N subtypes.
 - » Hong Kong flu resulted from the emergence of a new H3N2 combination.



The Agent: Influenza A

Recently Discovered Evidence of a Significant Human/Swine Interaction



Source: Dr Lynn Cooper, MITRE

The Agent: The Current H1N1 “Swine” Flu Reassortment Summary

First swine flu virus isolated in 1930 – H1N1 descendant of the 1918 pandemic strain called classical swine viruses

Classical swine flu viruses (H1N1) circulated widely; common in pigs in US, Mexico, Canada, SA, Europe,, Kenya, Mainland China, Taiwan, and Japan

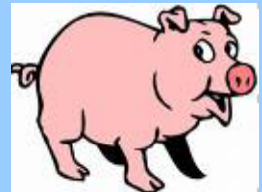
Caused rare human cases ~1 per year; usually associated with underlying chronic condition and/or contact with pigs

Swine are susceptible to human strains, avian strains and swine strains – mixing bowl concept

In late 1990s new triple-reassortant swine strains emerged in US combinations of swine, avian, and human genes: H3N2 with HA, NA, PB1 (human seasonal), PA and PB2 (avian), other 3 genes swine origin; H1N2 triple-reassortants; H1N1 classic swine triple-reassortants

Current H1N1 outbreak strain*:

- HA H1 swine origin gene of a lineage midway between Eurasian and North American
- NA + M genes are Eurasian swine new to North America
- PA + PB2 avian from North American from a triple reassortant swine virus
- PB1 human seasonal H3N2 from a North American triple reassortant in swine



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* Source: Science Insider, 29 APRIL; interview with Ruben Donis – CDC Atlanta, Dr Dave Siegrist, MITRE

The Disease: “You and Me”

- Who? Where?: Humans, all ages, anterior nares, nasopharynx
- Modes of Transmission (fomites)
 - » Virus laden droplets in the breathing zone---cough, sneeze
 - » Contaminated Surfaces, Viral Survival: 8-12 hrs (paper), 24-48 hrs (glass), may vary with change in temperature or humidity---touch, cough, sneeze
- Symptoms: sudden onset of high fever, headache, sore throat, non-productive cough, muscle aches, GI upset and fatigue.
- Contagious Period:
 - » Adults—24 hrs prior and up to 7 days post symptoms onset
 - » Children—24 hrs prior and up to 14 days post symptoms onset
- Individual Treatment:
 - » Judicious use of antivirals (Tamiflu—Oseltamivir, Relenza—Zanamivir) x 5 days, Chemoprophylaxis 5-7 days post exp
 - » Vaccination (if available and appropriate)
 - » Symptomatic Treatment
- Complications can include bacterial pneumonia, dehydration, and worsening of chronic medical conditions.

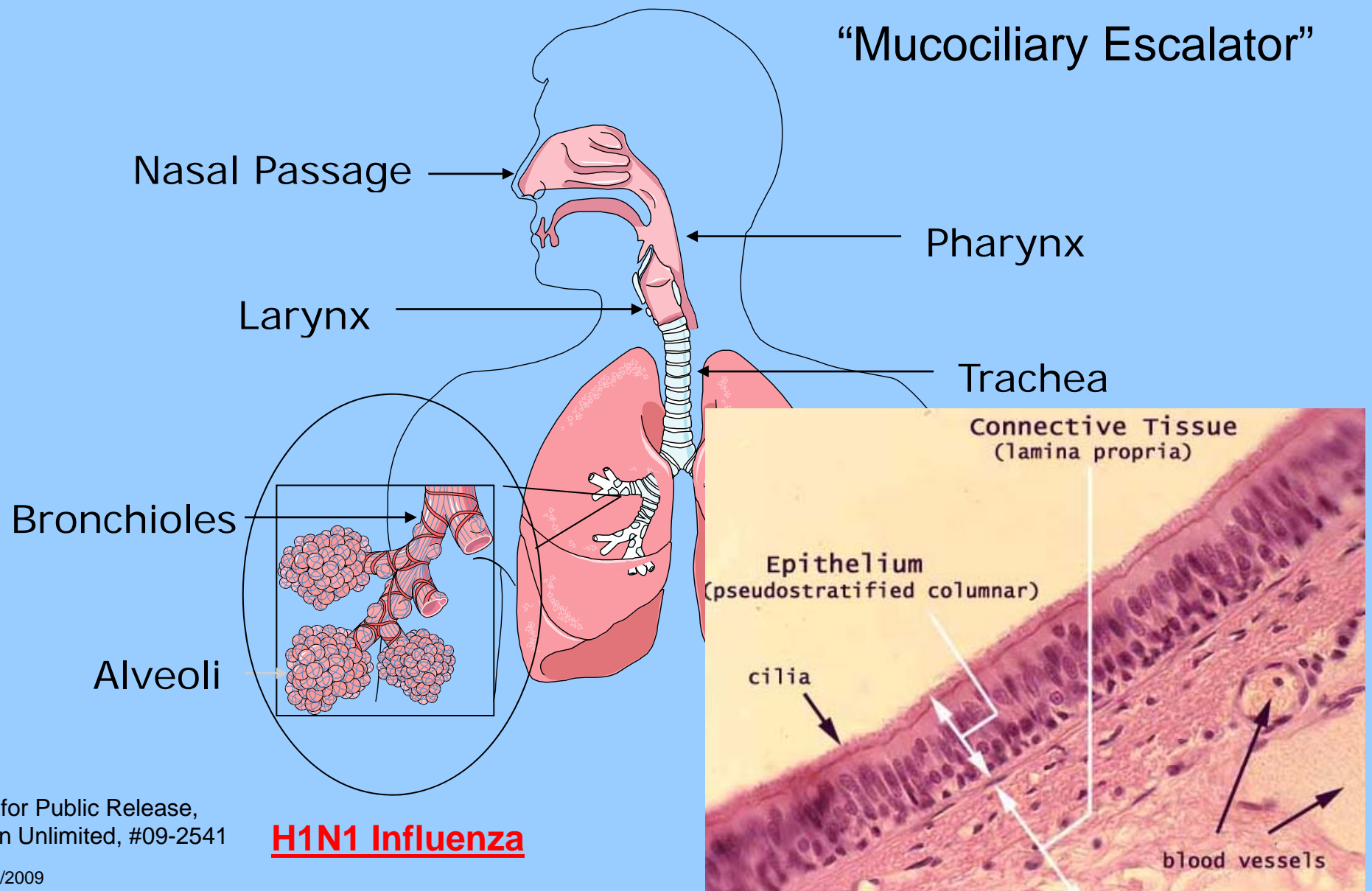


Influenza germs spread through the air when someone coughs.

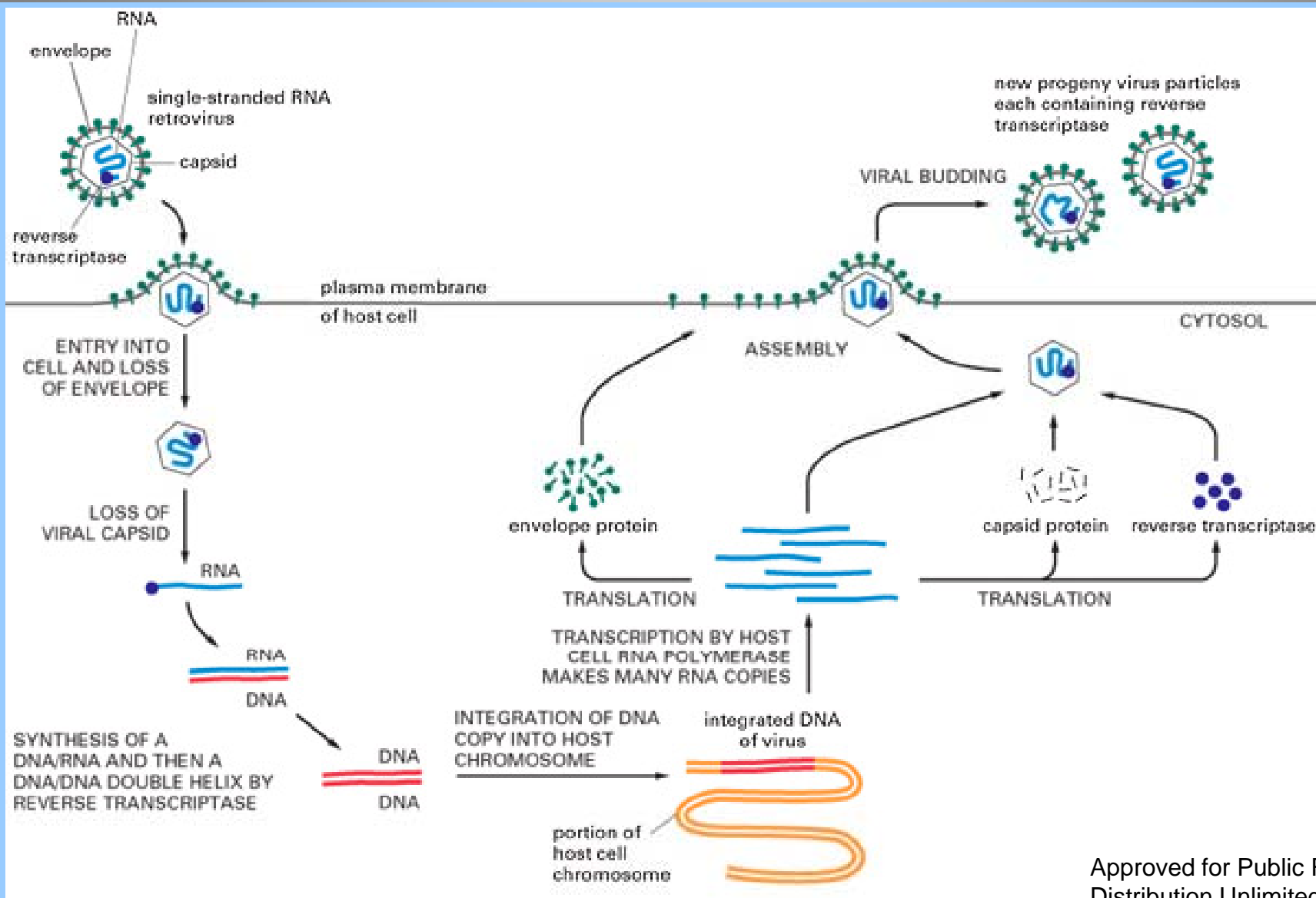


Emergency hospital during the 1918 influenza epidemic, Camp Funston, Kansas

The Disease: "You and Me"

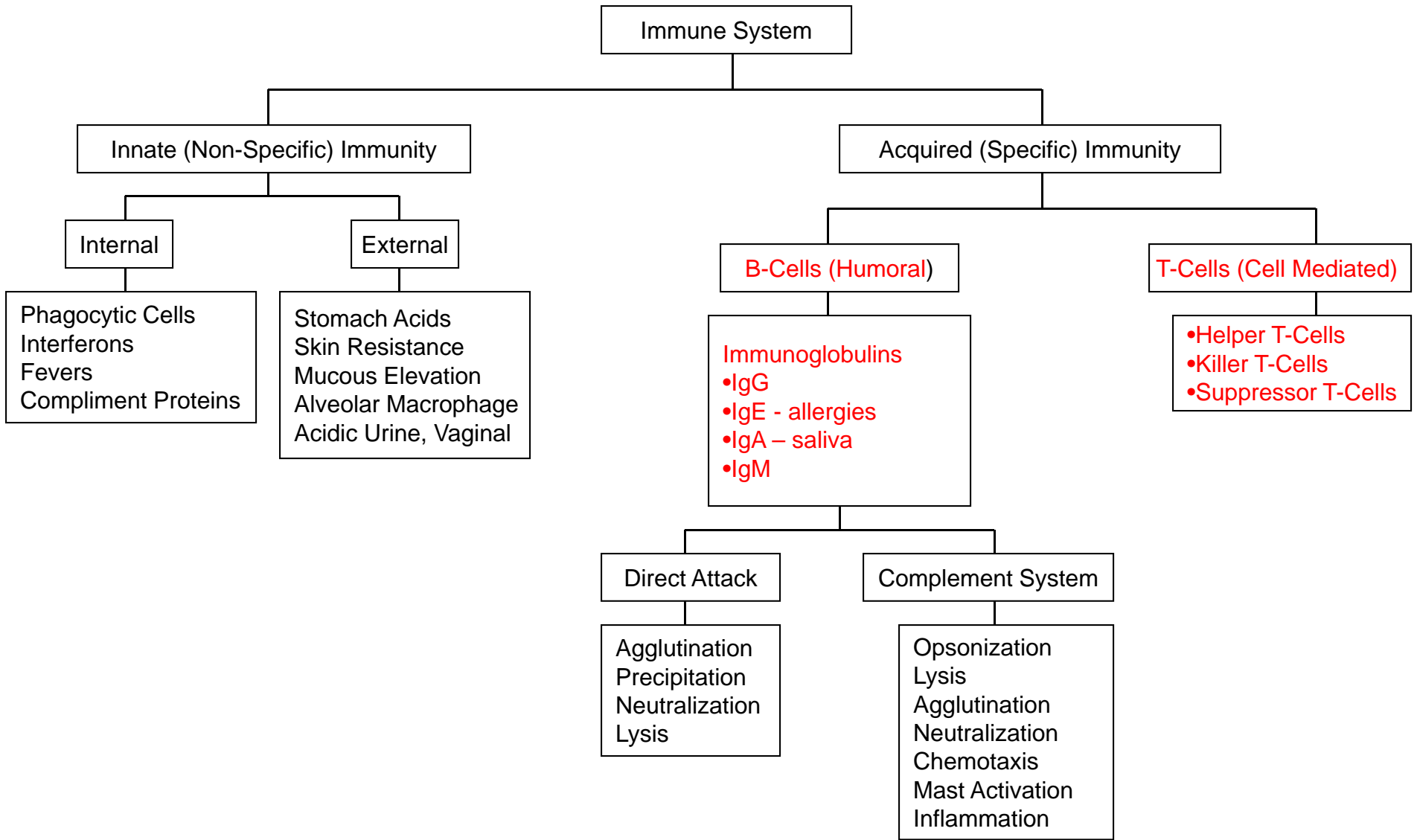


The Disease: "You and Me"

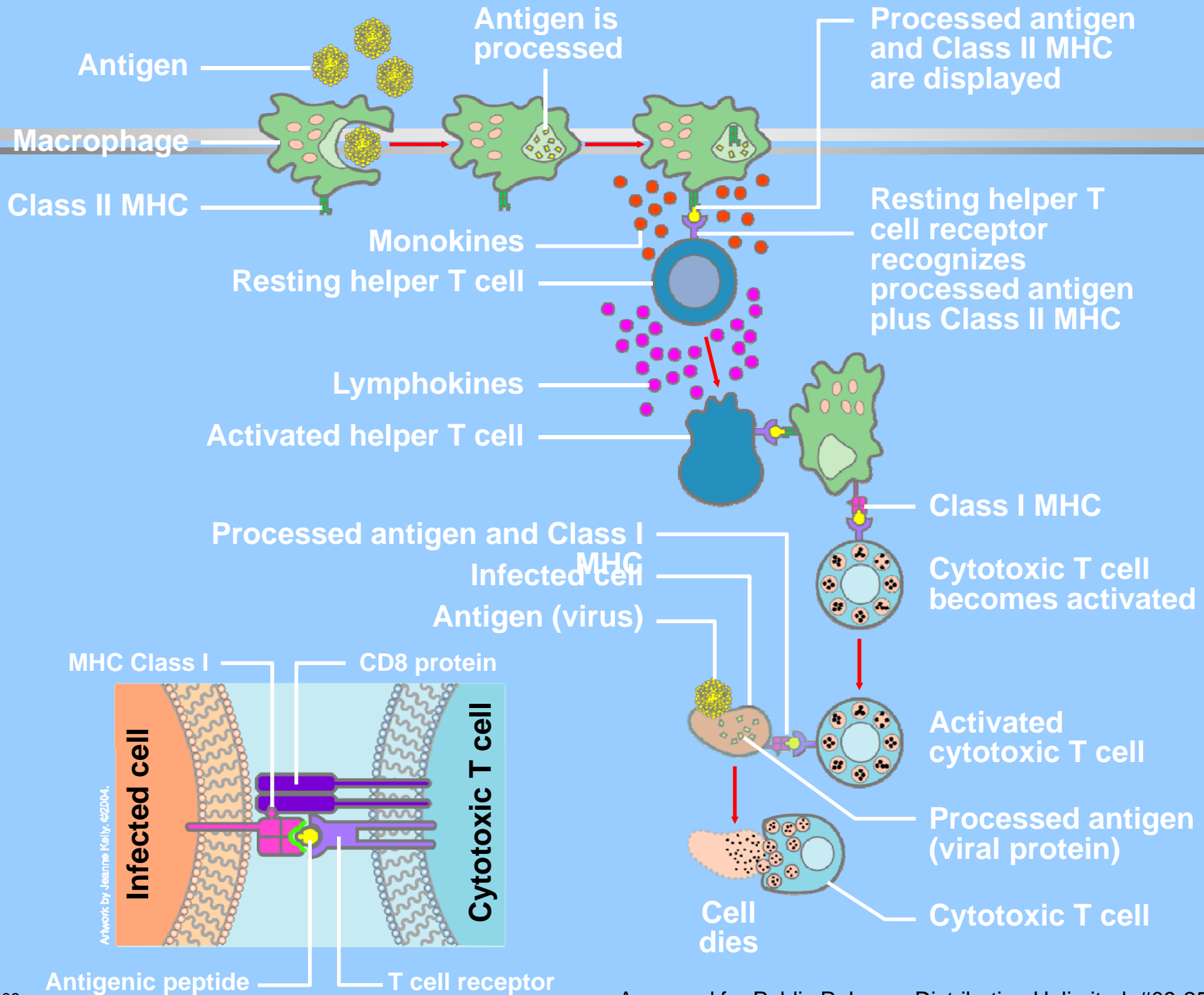


Respiratory Epithelium

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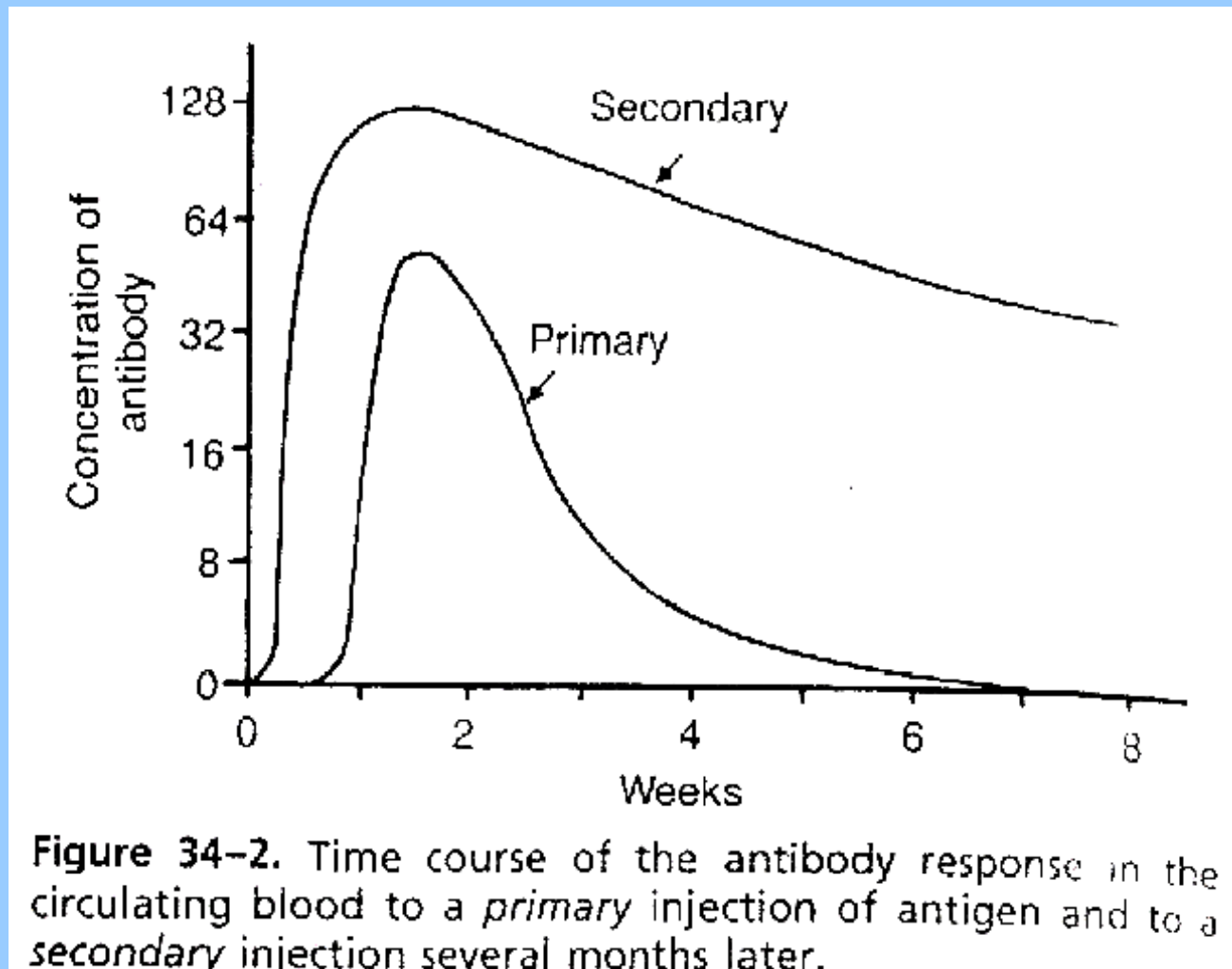


T-Cell Activation: Cell Mediated Immunity



The Disease: “You and Me”

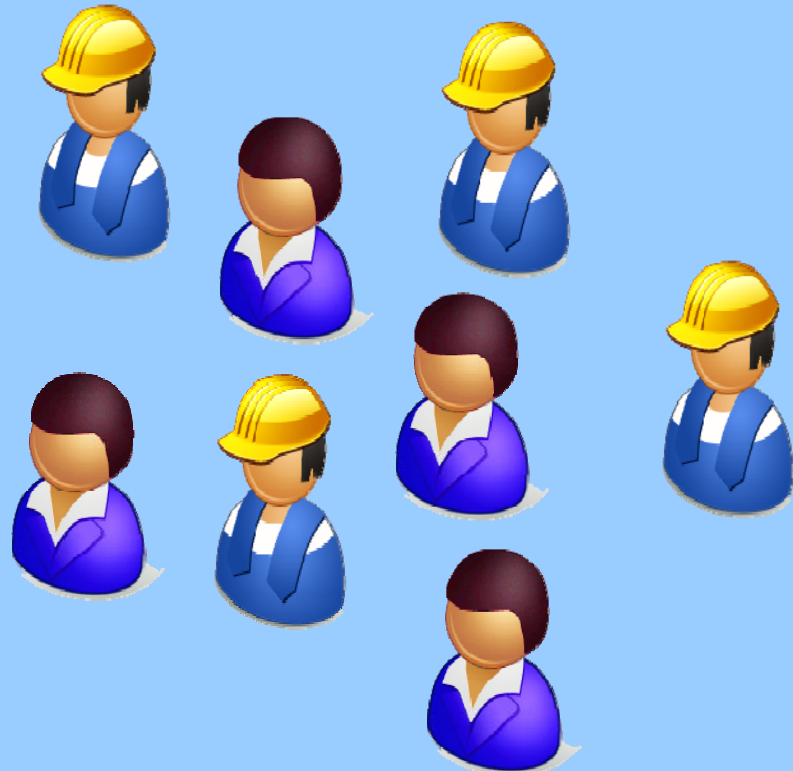
The Immune System Response



Individuals to Groups (ESE)

Pandemics:

Test our global political,
econ & social fabric



- Education/ Preparation
- Intervention(s)
 - NPI—Social Distancing
 - Vaccination/Pharm
- Communicating/Managing Risk

The Epidemic: “The Herd”

Epidemiologic Terms

- Population Health = Population Resilience
- Epidemiology: “The Study of the distribution and determinants of disease and injuries in human populations”
- Infectious Disease Epidemiology: Host-Parasite Interaction, Mechanisms of Transmission, Type of Epidemic, Epidemic Control Mechanisms
- Agent Assessment: Pathogenicity—Attack Rate, Virulence, CFR, Reservoirs—human/animal
- Epidemic Type: Common Source (John Snow—cholera) vs Propagated (index case, secondary attack rate- “Waves”)
- Herd Immunity > 90% immune (vaccinated or previous infection)
- High risk cohorts: elderly, young children, pregnant women, and people with certain health conditions
- Pandemic: A Global Epidemic

Influenza germs spread through the air when someone coughs.



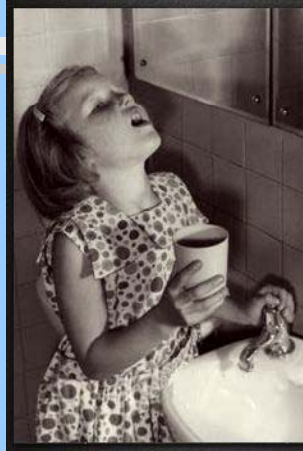
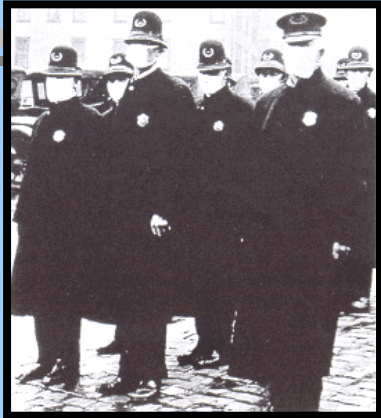
Emergency hospital during the 1918 influenza epidemic, Camp Funston, Kansas

Global Epidemic = Pandemic

- An influenza pandemic is a global outbreak of disease that occurs when a **new influenza A virus appears or “emerges” in the human population**, causes serious illness, and then spreads easily from **person to person** worldwide.
- Pandemics are different from seasonal outbreaks or “epidemics” of influenza. Seasonal outbreaks are caused by subtypes of influenza viruses that are already in existence among people, whereas **pandemic outbreaks are caused by new subtypes or by subtypes that have never circulated among people or that have not circulated among people for a long time.**
- Past influenza pandemics have led to **high levels of illness, death, social disruption, and economic loss.**

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Pandemics in 20th Century



1918: "Spanish Flu"

1957: "Asian Flu"

1968: "Hong Kong Flu"

20-40 million deaths

1 million deaths

1 million deaths

H1N1

H2N2

H3N2

1920

1940

1960

1980

2000

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Source: Dr Dave Siegrist, Dr Lynn Cooper, MITRE

The Next Pandemic: Elevated Risk

Global Scientific, Technical, Social, Political and Economic Issues that put us at increased risk of a PI event:

- New/Novel Strain Appearance (e.g. herd immunity low)
- Difficult Initial Identification (inter mixing of seasonal vs new)
- Increased World Population & Density
- Increased World Travel/Mixing
- Antiviral resistance
- Vaccine Development Technology Limitations (egg vs cell based)
- Traditional Screening Tools (POE's) Less Valuable
- Significant Chronic Disease Population Vulnerability

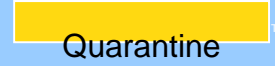
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Estimates of the Impact of an Influenza Pandemic by Severity



[Approx 800 K hospital beds in US, w/ 2/3 staffed]



	Category 2 (Similar to a 1957 pandemic)	Category 4/5 (Similar to a 1918 pandemic)
Illness	90 million (30%)	90 million (30%)
Outpatient medical care	45 million (50%)	45 million (50%)
Hospitalization	865,000	9,900,000
ICU care	128,750	1,485,000
Mechanical ventilation	64,875	745,500
Deaths	209,000	1,903,000

Infectious Disease Control/Mitigation Interventions

- Measures directed against the agent reservoir (H1N1, H5N1...)
 - » Culling
 - » Isolation—imposed on individual for maximum incubation period
 - » Quarantine—imposed on groups for maximum incubation period
 - » **Social Distancing**
- Measures that interrupt the transmission of Organisms
 - » Hospital: **Medications**—tamiflu, relenza, etc., Universal Precautions & Ventilation Systems--laminar flow rooms, Infection Control
 - » Community: Medications, **PPE/T**--N95 Mask, Social Distancing
- Measures to reduce host susceptibility
 - » **Vaccination**
 - » **Intact Immune System**
- Disease Surveillance
 - » Screening
 - » Data base analysis and reporting tools
- Historical Probability & Scientific Interconnectedness



Non-pharmacological Interventions used in the 1918 “Spanish Flu”

- Making influenza a reportable disease
- Isolating sick individuals
- Quarantine of households with sick individuals
- School closure
- Protective sequestration of children or adults
- Cancellation of worship services
- Closure of public gathering places [e.g., saloons, theatres, etc.]
- Staggered business hours to decrease congestion on trams, etc.
- Mandatory or recommended the use of masks in public
- Closing or discouraging the use of public transit systems
- Restrictions on funerals, parties, and weddings
- Restrictions on door-to-door sales
- Community-wide curfew measures and business closures
- Social distancing strategies for those encountering others
- Public health risk communication measures
- Declaration of public health emergency



Historical Data on Non-pharmacological Interventions (NPI)*

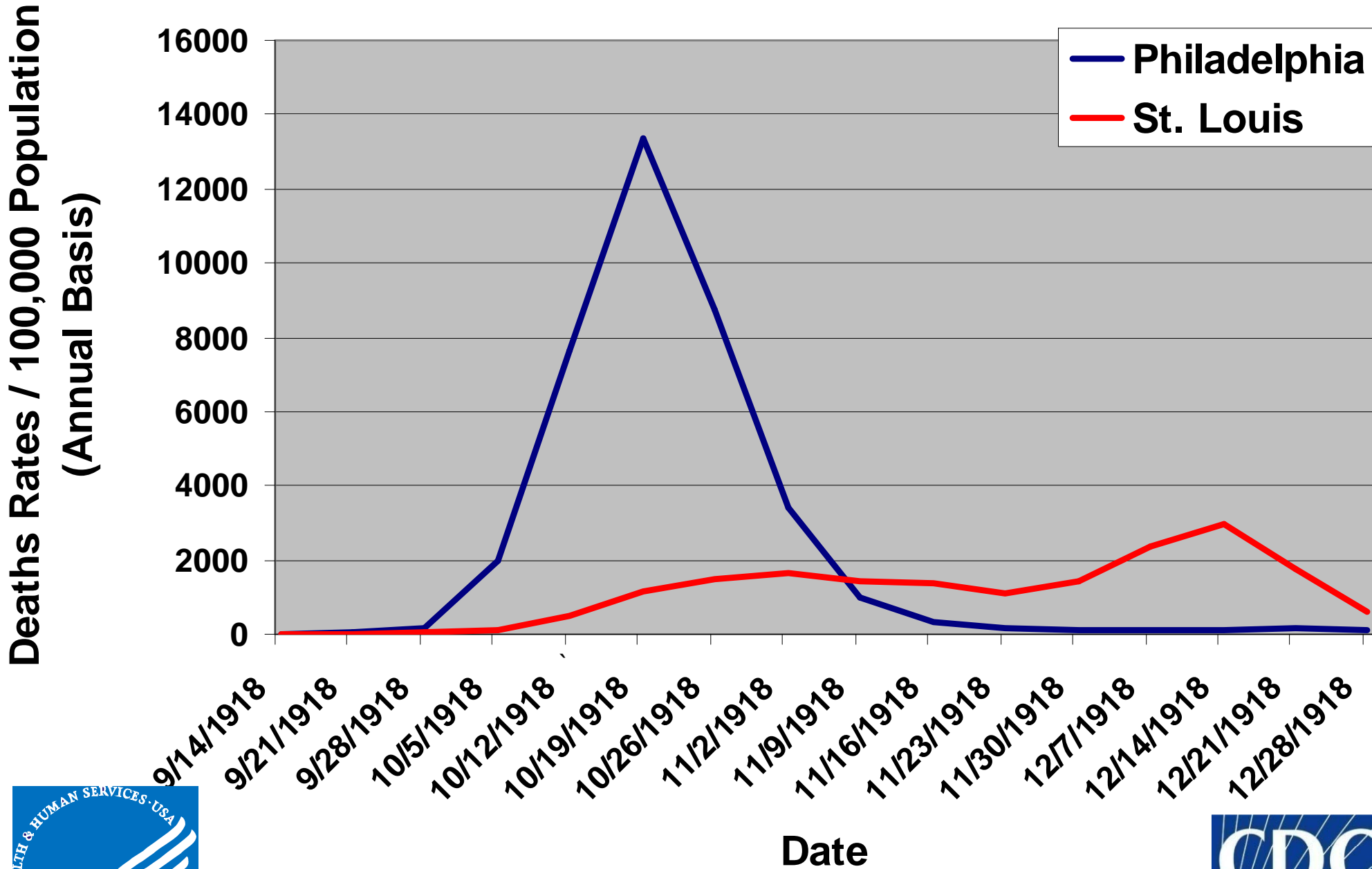
- Review of 17 US cities, 1918 pandemic, US
- Cities that implemented multiple NPIs early in the pandemic, lower death rates
 - » 50% lower peak death rate
 - » 20% lower cumulative death
- Releasing NPIs early resulted in increased death rates

Richard J. Hatchett *, Carter E. Mecher , and Marc Lipsitch.

Public health interventions and epidemic intensity during
the 1918 influenza pandemic, PNAS, April 2007



1918 Death Rates: Philadelphia v St. Louis





Who Infects Whom?

Glass, RJ, et al. Local mitigation strategies for pandemic influenza.
 NISAC, SAND Number: 2005-7955J

	To Children	To Teenagers	To Adults	To Seniors	Total From
From Children	21.4	3.0	17.4	1.6	43.4
From Teenagers	2.4	10.4	8.5	0.7	21.9
From Adults	4.6	3.1	22.4	1.8	31.8
From Seniors	0.2	0.1	0.8	1.7	2.8
Total To	28.6	16.6	49.0	5.7	

Likely sites of transmission

-  School
-  Household
-  Workplace

Demographics

- Children/Teens 29%
- Adults 59%
- Seniors 12%

Communicating Risk

- Technical Expert's definition
 - » Hazard + probability = risk assessment
 - » Relies upon research and statistics
 - » Characterized by health risk assessments
- Public's definition
 - » Consequences of hazards
 - » Individual feelings about likelihood that something bad will happen to them



Risk is about **FEAR**

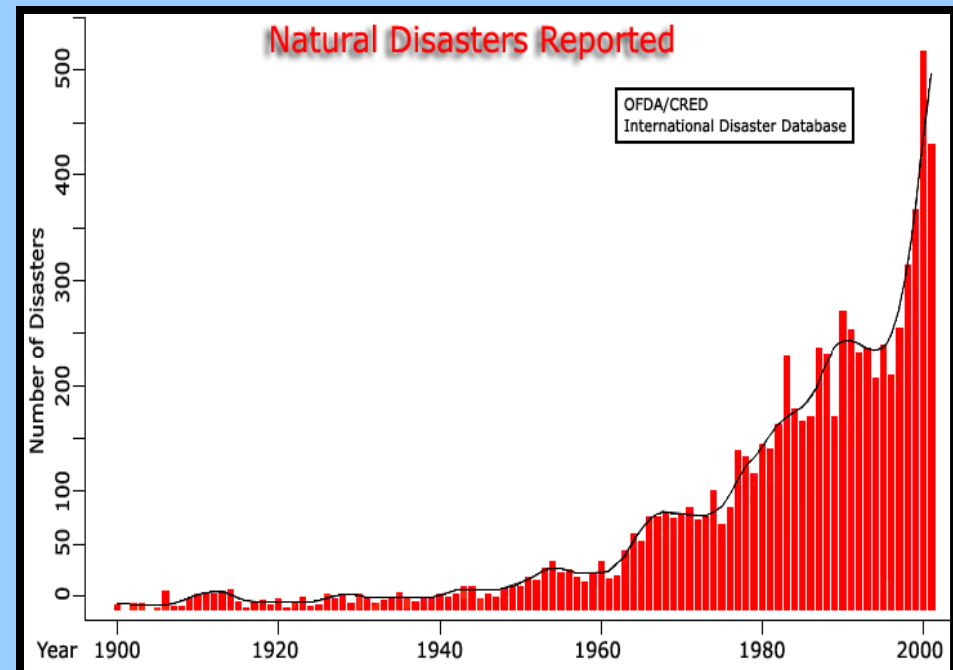
- Public versus Expert “gap”

Risk is about **DANGER**

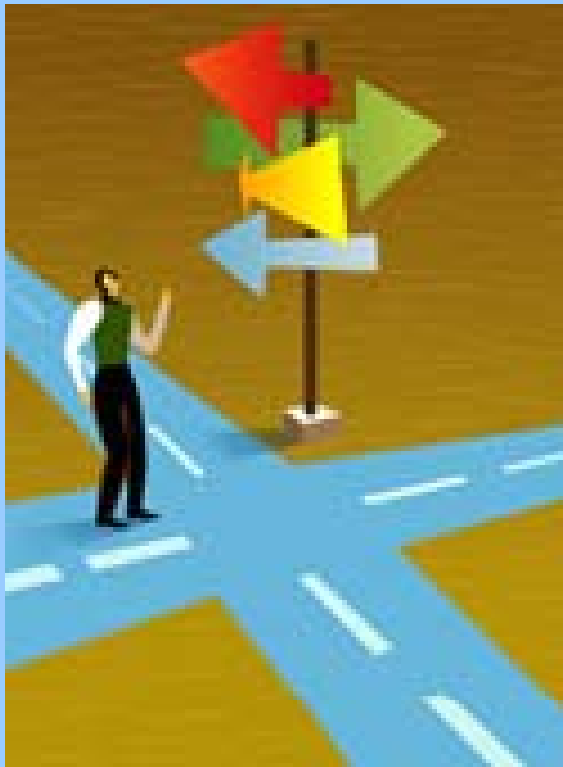
- Emotional
- Contentious

Risk is about **SURVIVAL**

- Disagreement can be fierce



OK, so now what doctor?



Know the Enemy: Differences Between Pandemic Influenza and Seasonal Influenza

- **Seasonal Influenza**

- » Occurs in cooler parts of year (winter in USA)
- » **Affects 10%** of population
- » **Usually mild** and **not life threatening**
- » Very young and very old are at highest risk
- » **Vaccine is available and usually protective**
- » Antiviral drugs (Tamiflu, Relenza) are available to treat those few people at special risk

- **Pandemic Influenza**

- » Historically pandemics have occurred about every 10-40 years, at any time of year
- » **May affect >50%** of population
- » Illness can be more **serious**
- » Cases may come in waves
- » All age groups at risk
- » **Specific vaccine not yet available, and unlikely to be widely available early in outbreak**; may take six months to develop and distribute
- » Large number of affected people will create large demand; supportive care and potentially limited supply of antiviral drugs

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OK, So now what doctor?



U.S. Army Camp Hospital No. 45, Aix-Les-Bains, France, Influenza Ward No. 1, 1918.

Photo by Dr. Al Jenny

- Stay or Get Informed
http://www.cdc.gov/h1n1flu/#stay_healthy
- Vaccination
 - » Flu shot or nasal flu spray
 - » Recommended for “at-risk” groups
 - » Given during flu season, starting in October
- Good health habits
 - » Have an N95 Mask available
 - » Wash hands
 - » Avoid touching nose, mouth, and eyes
 - » Cover mouth and nose when coughing or sneezing
 - » Avoid close contact with infected individuals
 - » Avoid public areas when infected
- Develop a family EP&R Plan
 - » Communicate about Finances, Legal, Health
 - » At the “End of the Day”.....



Questions

Definitions

- *Isolation*
 - » Separation of ill persons with contagious diseases
 - » Often in a hospital setting, could be at home
- *Quarantine*
 - » Restriction of persons who are not ill but presumed exposed, usually in the home or a designated facility
- *Social Distancing*

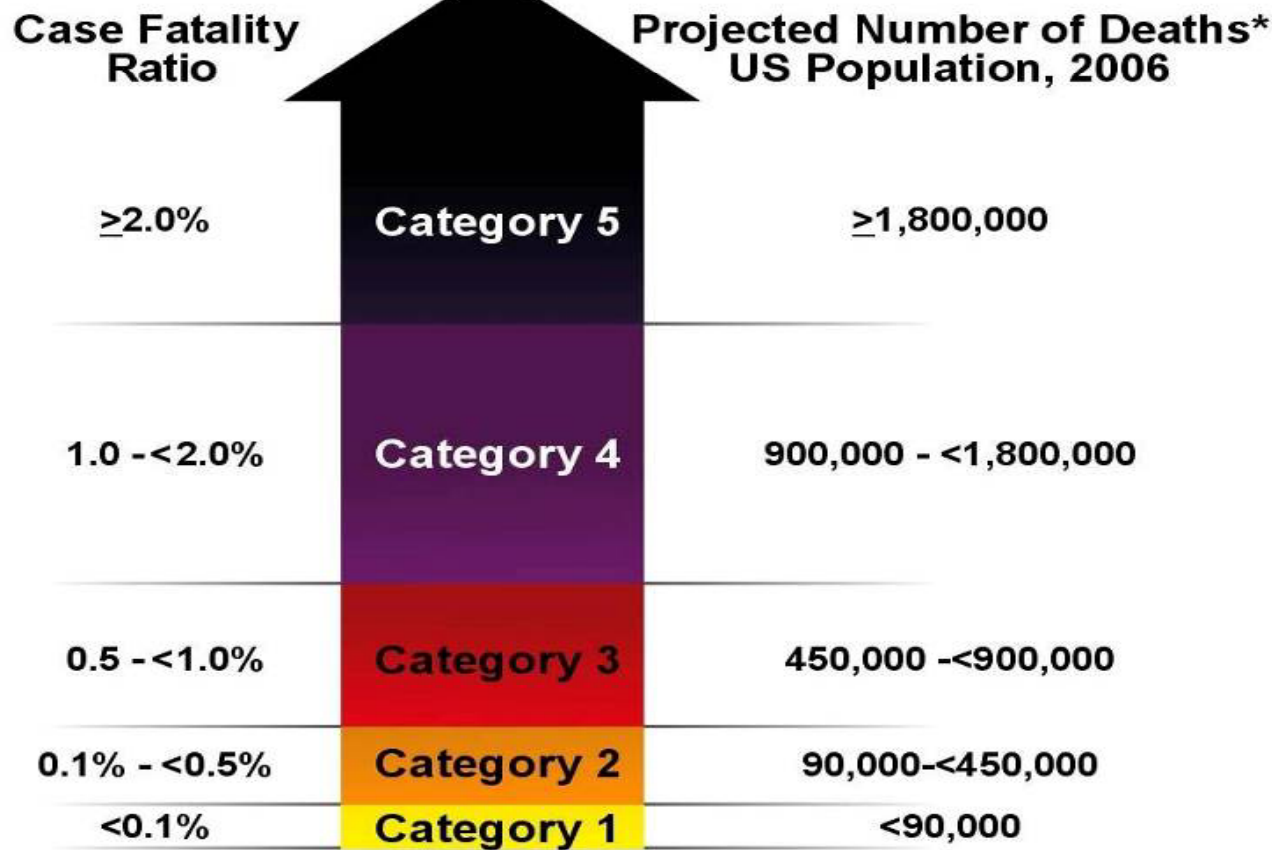
“social measures to decrease the frequency of contact among people in order to diminish the risk of spread from communicable diseases”
- *Infection Control*

“hygienic measures to decrease spread of infectious pathogens”



CDC Pandemic Severity Index

Pandemic Severity Index



* Assumes 30% Illness Rate



A Virus With Pandemic Potential

HOW THE FLU VIRUS MUTATES

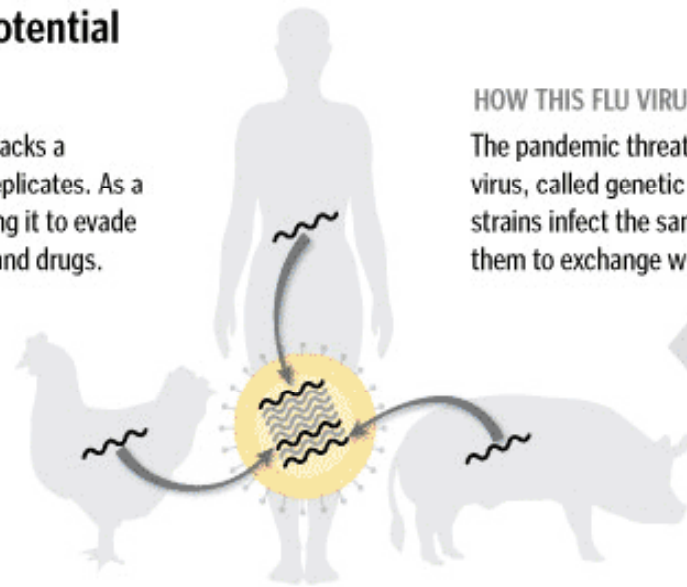
The genetic machinery of the flu virus lacks a mechanism to correct errors when it replicates. As a result, it mutates at a high rate, allowing it to evade the body's natural defenses, vaccines and drugs.

Seasonal flu strains that circulate every winter generally have minor changes from those of the previous year. But people who have been exposed to flu in the past usually retain a measure of immunity.

HOW THIS FLU VIRUS IS DIFFERENT

The pandemic threat arises from another trick of the flu virus, called genetic reassortment. When different strains infect the same host at the same time, it allows them to exchange whole sections of their genetic code.

Scientists think the current virus strain combines genetic material from pigs, birds and humans. Segments from the three different viruses have created a reassorted virus that has not been seen before.

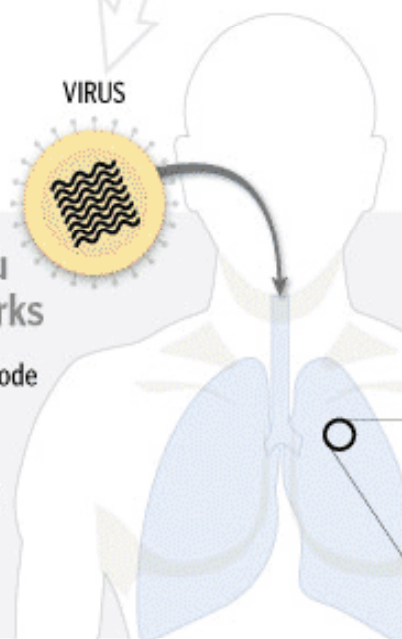


Why is this virus killing healthy people?

One theory is that the virus triggers an excessively aggressive immune response that destroys the throat and lung tissue. Those with robust immune systems may be especially vulnerable.

How a flu virus works

The genetic code of the flu is contained in eight strands of RNA.

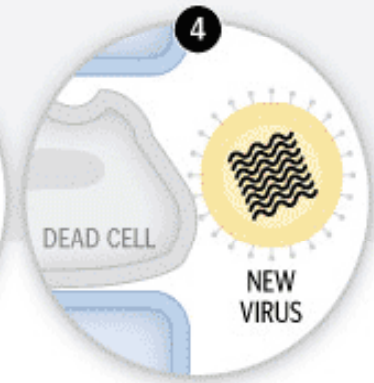
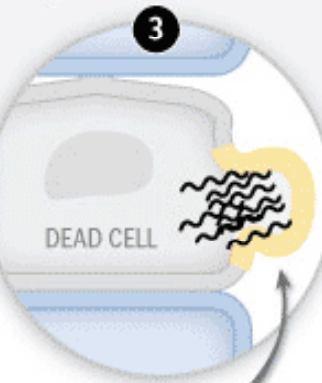
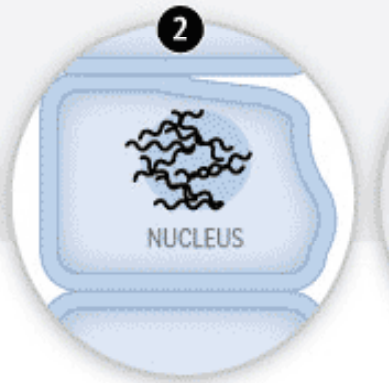
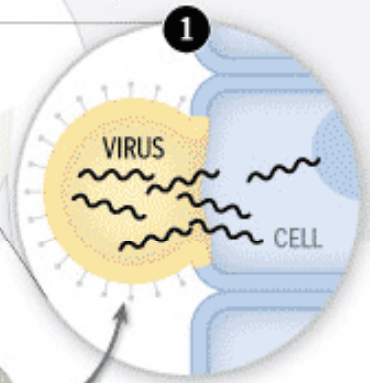


A protein on the virus binds to receptors on healthy cells in the airways and lungs, causing the virus to open and release its RNA.

The RNA moves to the cell nucleus, where it is incorporated in the cell's machinery, directing the cell to make copies of the virus.

Another protein on the virus punches a hole in the cell, killing it and releasing the replicated virus. . .

. . . either into the airway to find another cell to infect or ejected by a cough or sneeze and launched to find a new host.



Fighting the Flu

PREVENTION: VACCINE

Vaccines teach the body's immune system to make antibodies to kill the virus. A weakened form of the virus is grown in hens' eggs, purified and killed with a chemical. Creating a new vaccine takes at least six months and requires hundreds of millions of eggs.

INTERRUPTION: ANTIVIRAL DRUGS

Relenza and Tamiflu, both shown to be effective against this current virus, stop it from budding out of the cell if administered soon after symptoms appear. Antivirals can also be given to people in contact with an infected person to prevent the disease from spreading.



Vaccines, from the Washington Post

Staying the course for now

Vaccine manufacturers are just beginning production for next winter's regular influenza vaccine, which protects against three human flu strains. Until more is known about the current virus, the World Health Organization said Monday that factories should continue as planned and not change the formula for the seasonal vaccine.

Time-consuming mission

Creating and distributing a new vaccine typically takes at least 6 months and requires hundreds of millions of eggs.

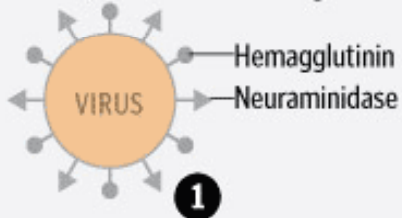
The Center for Disease Control and Prevention reported yesterday that scientists have been able to grow the virus in eggs but found the growth to be unusually slow.

It may take several months before any shots are available for the first required safety testing in volunteers.

Then manufacturers would get the strain to start their own production supply, which could take another two months.



Using samples of the new swine flu taken from people who fell ill in Mexico and the United States, scientists must engineer a strain that will trigger the immune system without causing illness.



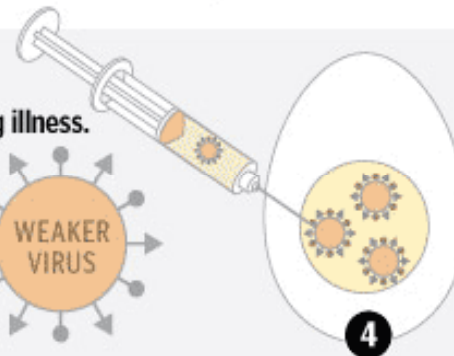
The virus carries two proteins on its surface called hemagglutinin (HA) and neuraminidase (NA). HA helps the virus enter healthy cells; NA helps the virus exit cells after it has replicated many times over.



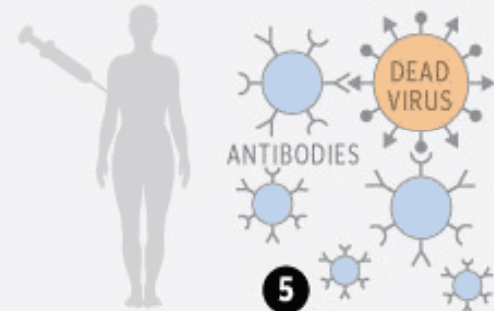
These proteins give flu strains their main identity, and scientists must use a technique called **reverse genetics** to match the HA and NA components to form the basis of a vaccine.



To create a "seed virus," these components are combined with segments taken from another, weaker flu strain that is known to grow well in hens' eggs.



The seed virus is inserted into hens' eggs so that it can multiply. From each egg will come one dose of vaccine.



The new vaccine is chemically inactivated ("killed") and then injected into humans, prompting the creation of swarms of antibodies that recognize the proteins and can fight the virus.

Some manufacturers are studying production options. A cell-based technology* in which viruses are harvested in cell cultures, not eggs, may produce vaccines more rapidly.

*Currently, no cell-based vaccines are approved in the United States.

Community-Based Interventions

1. Delay disease transmission and outbreak peak
2. Decompress peak burden on healthcare infrastructure
3. Diminish overall cases and health impacts

