Viral Disease and Prevention

BioScience in the 21st Century

October 2019

Robert Buckheit III, Ph.D

ImQuest BioSciences, Inc.

Robert.Buckheit@imquestbio.com

Outline

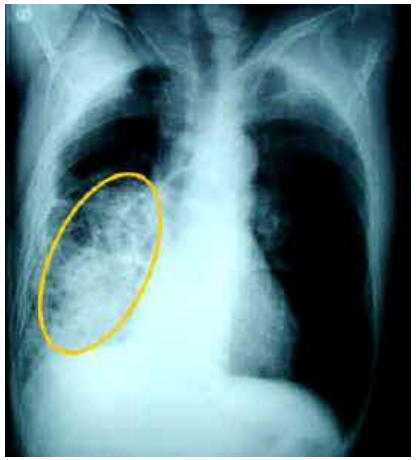
- Case Study – Emergence of a New Virus
- What is a Virus?
  - History and discovery
  - Basic viral replication and transmission
- Influenza: How Do Viruses Change Over Time?
- Ebola: Zoonotic Transmission and Reservoirs
- HIV: Antiviral Drugs and Principle of Combinations
- Vaccination: Principles and Challenges

Mystery Illness -- 1981

- Adult Male walks into the Hospital
- Mid thirties, severe case of community acquired pneumocystis carinii (yeast)
- Pale, very skinny—evidence of other unusual infections

- 2 weeks prior the patients was healthy, no other underlying health factors

- Within 48 hours, patient dies of pneumonia
- Immune system is damaged (No CD4 T cells cells)
- Strange?—Maybe, but its just one patient



Other reports of CD4 Loss in Patients

ORIGINAL ARTICLE

PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN

Evidence of a New Acquired Cellular Immunodeficiency

MICHAEL S. GOTTLIEB, M.D., ROBERT SCHROFF, PH.D., HOWARD M. SCHANKER, M.D., JOEL D. WEISMAN, D.O., PENG THIM FAN, M.D., ROBERT A. WOLF, M.D., AND ANDREW SAXON, M.D.

ORIGINAL ARTICLE

AN OUTBREAK OF COMMUNITY-ACQUIRED *PNEUMOCYSTIS CARINII* PNEUMONIA

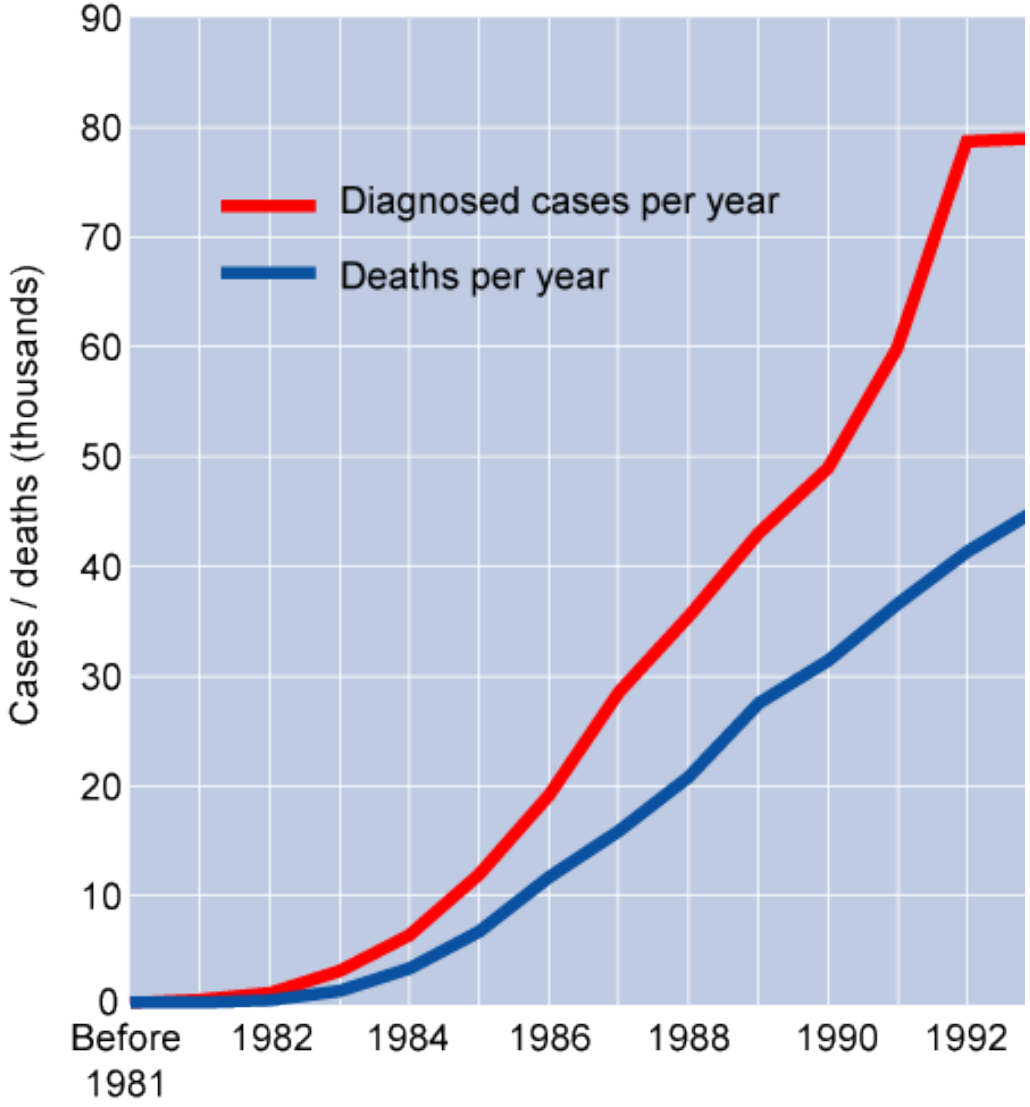
Initial Manifestation of Cellular Immune Dysfunction

HENRY MASUR, M.D., MARY ANN MICHELIS, M.D., JEFFREY B. GREENE, M.D., IDA ONORATO, M.D., ROBERT A. VANDE STOUWE, M.D., PH.D., ROBERT S. HOLZMAN, M.D., GARY WORMSER, M.D., LEE BRETTMEN, M.D., MICHAEL LANGE, M.D., HENRY W. MURRAY, M.D., AND SUSANNA CUNNINGHAM-RUNDLES, PH.D.

The disease spreads…1982-1983

- No one knows what is causing the illness
  - Originally, only seemed to affect Homosexual males
- January 1982, the first clinic for patients with this disorder opened in San Francisco
- September 24th, the term AIDS is coined— **Acquired Immune Deficiency Syndrome**
- December 10th—AIDS described in young infants who received blood transfusions (blood borne illness?)
- First reported cases of women with a syndrome similar to AIDS
- CDC hosts a meeting to talk about the blood supply—criteria for testing, and no consensus is reached
- Also, reports of AIDS in Haitian populations—is AIDS going global?

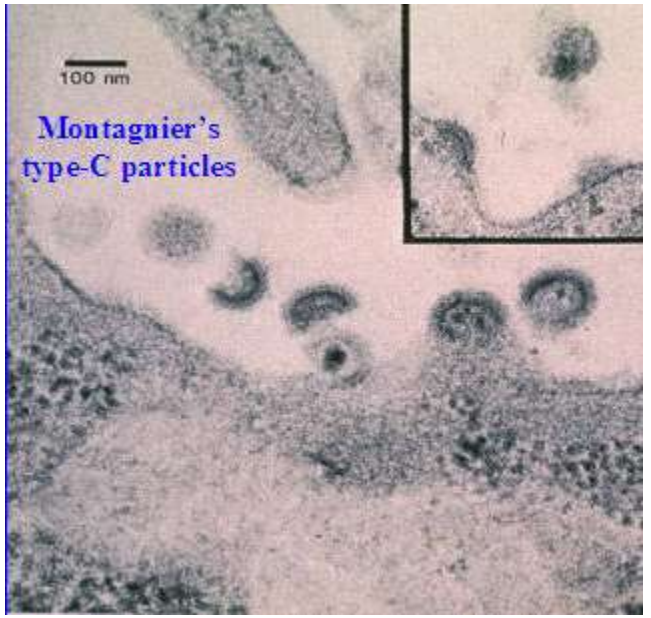
- Many though this disease pattern to be consistent with a infectious agent…mortality rate of infected patients is almost 100%

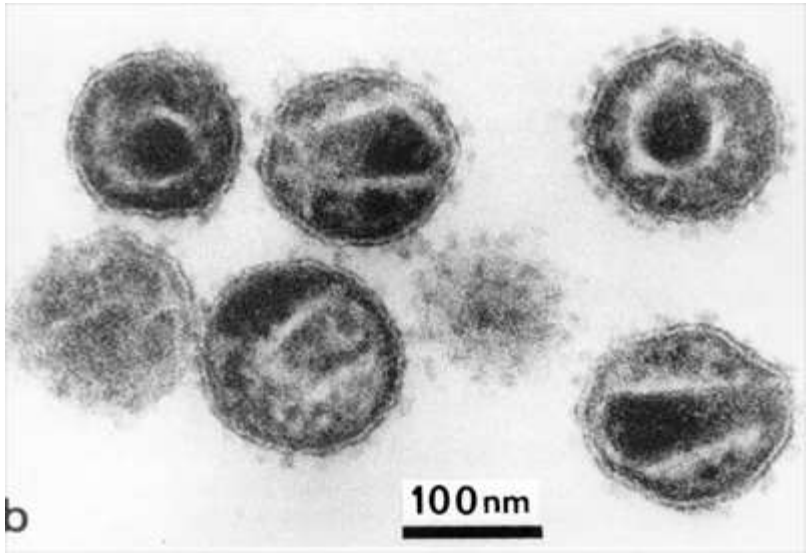


Source: CDC HIV AIDS surveillance report 2003

Discovery of the Causative Agent

- In May 1983--First reports from a French Research group describing Lymphadenopathy Associated Virus (LAV)
  - Professor Luc Montagnier (won the Nobel Prize in 2008)
  - In November Dr. Robert Gallo's lab in the USA also propagates LAV in immune cells (NIH)
- AIDS was caused by a newly discovered virus (renamed HIV)
  - New virus jumped into the human population…not a new phenomenon for humans



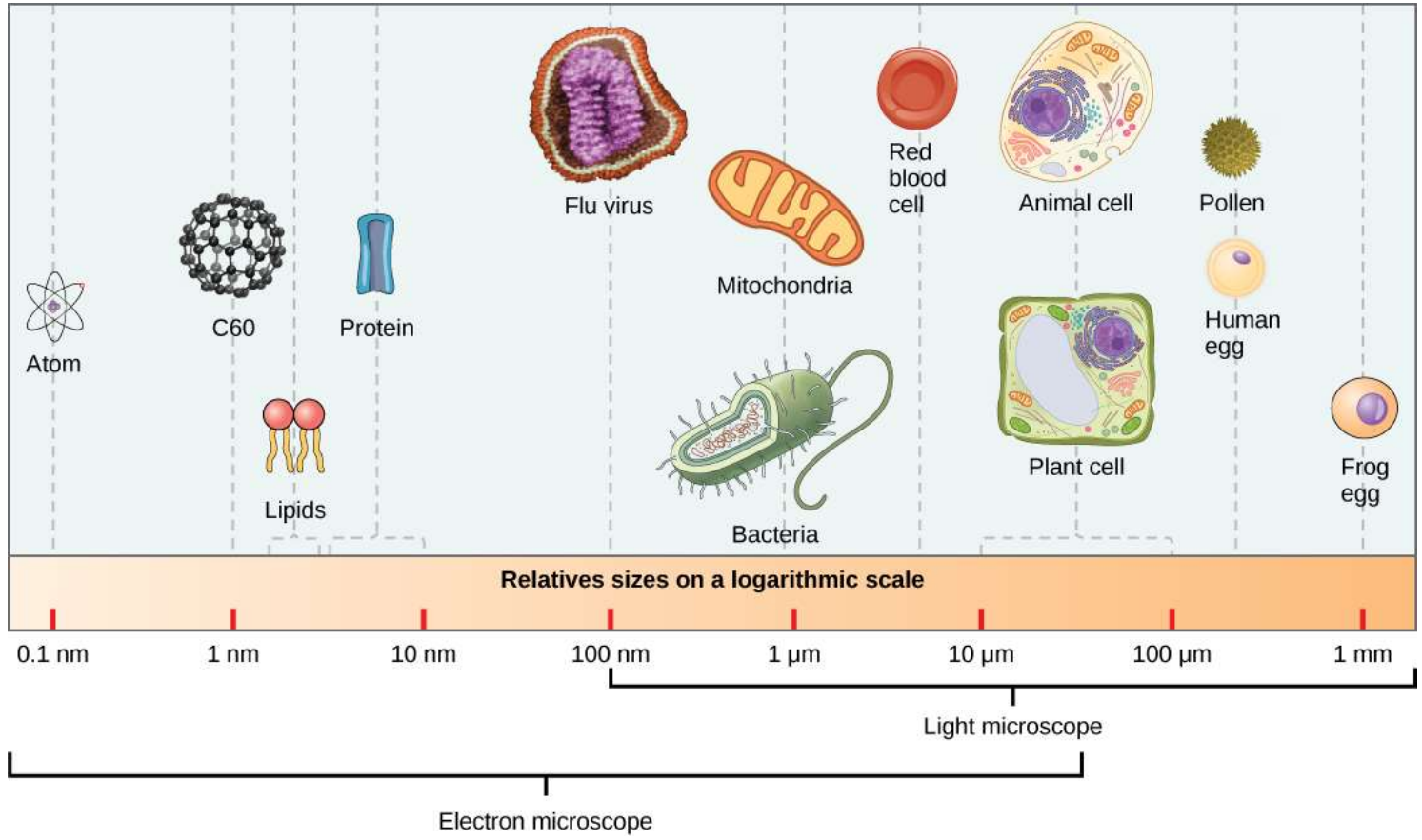


Discovery, Structure and Spread

So…What is a Virus?

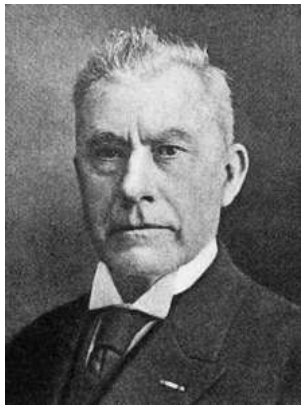
Definition

- “An infective agent that typical consists of a nucleic acid molecule (genome) inside a coat protein, is too small to be seen by light microscopy, and is able to multiple only within the living cells of a host”



Discovery of Viruses – First identified in plants

- **1892** – Dmitri Ivanovsky, studied tobacco mosaic disease, and discovered that the disease causing agent was able to pass through a ceramic filter that trapped all bacteria
  - Thought the agent was a toxin
- **1898** – Martinus Beijerinck confirmed this discovery and terms the causative agent a “contagium vivum fluidum” or “soluble living germ” (not a toxin)

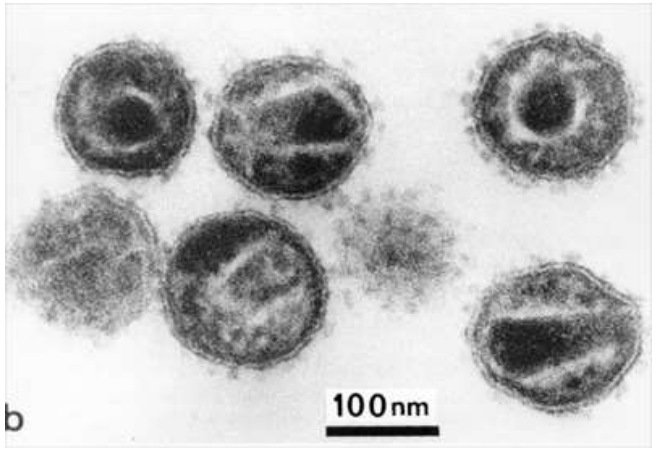


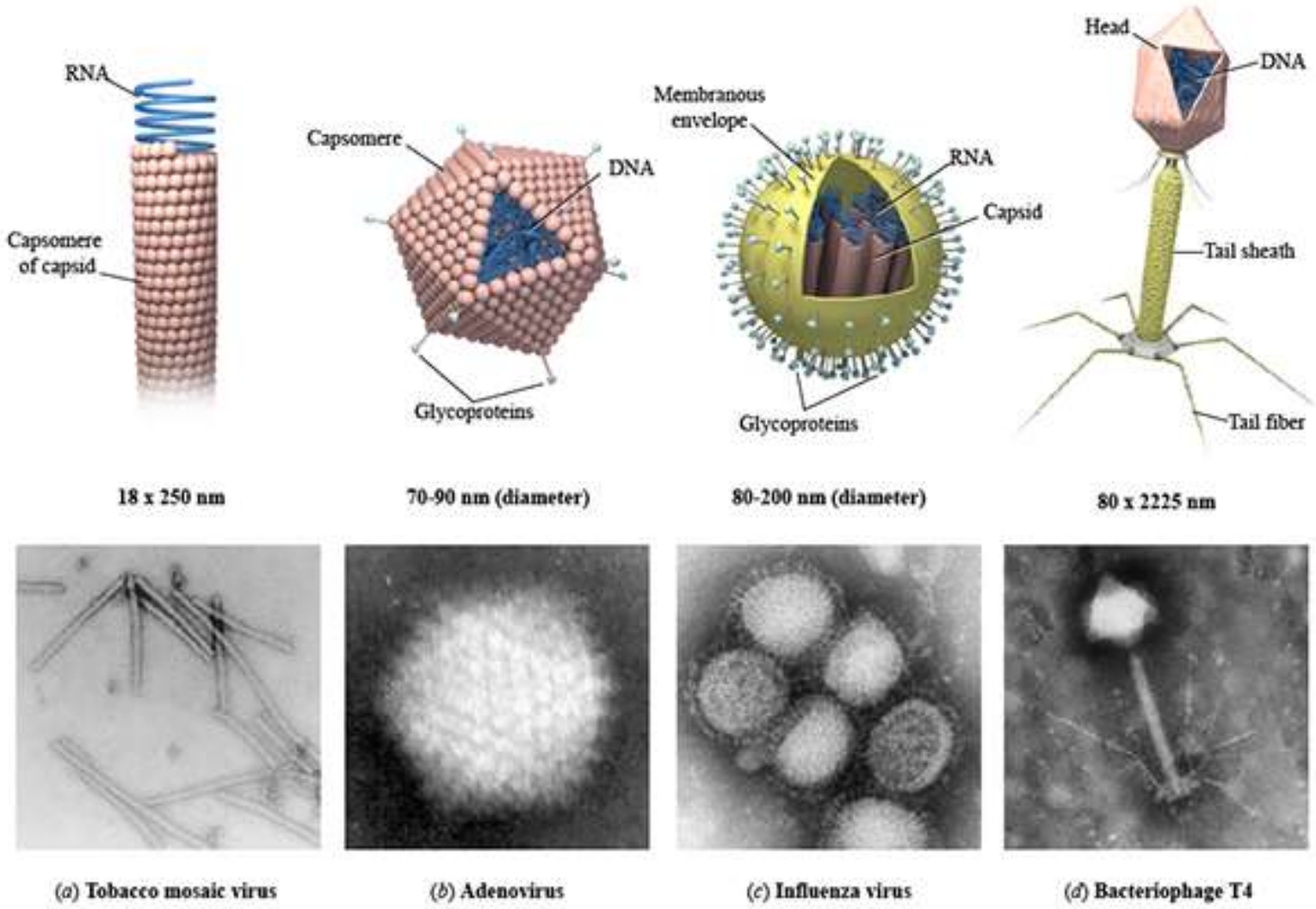
Discovery of Human Viruses

- **1897** – Friedrich Loeffler discovered a similar agent was responsible for foot-and-mouth disease
  - Viruses also infect humans
- **1901** – Walter Reed discovered that yellow fever was caused by a virus passes by mosquitos (panama canal)
  - Mosquito vector theory was first proposed by Carlos Finlay in 1881...verified by Walter Reed Commission (human testing)

Wide Variety of Shapes and Sizes

- Likely that there is a virus that infects every living organism on the planet
- Typically comprised of a protein shell (with or without lipid envelope) surrounding nucleic acids genome.

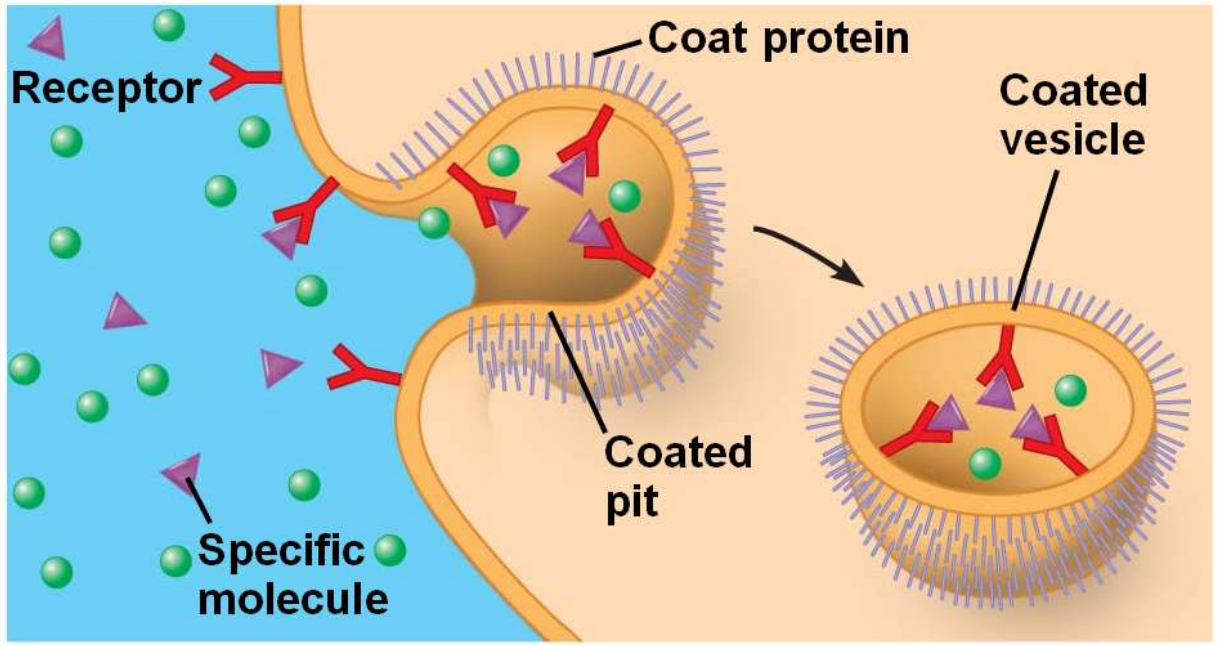


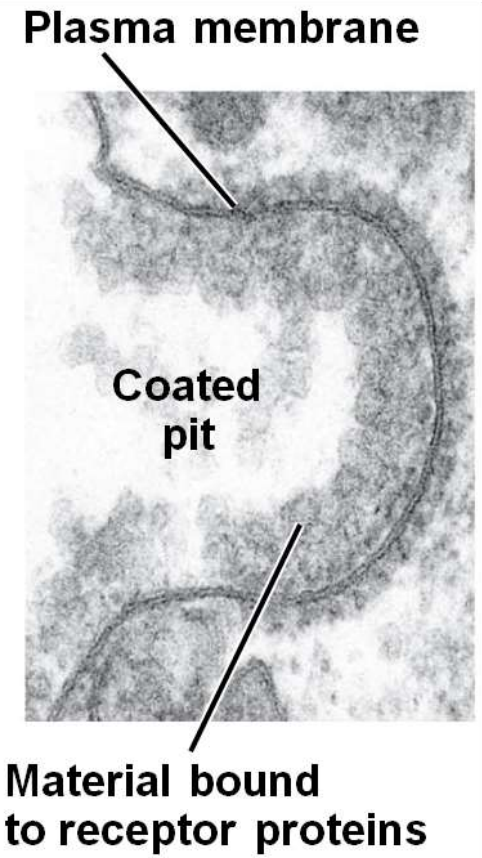


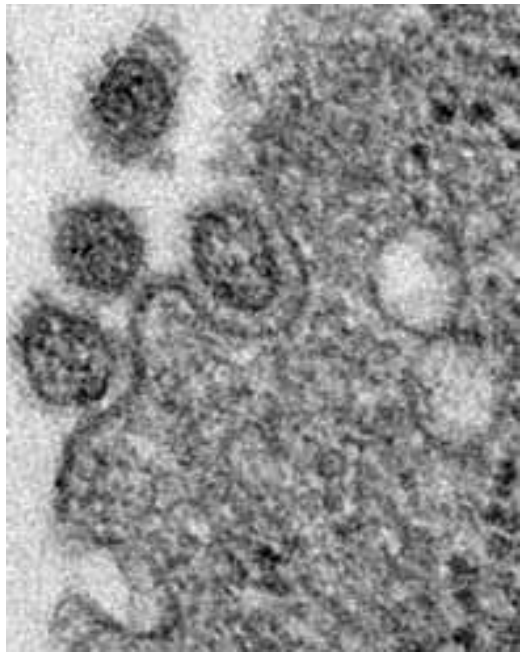
How do viruses infect your cells?

- Endocytosis (protein import): How cells take in resources from the outside world
  - All cell do this at all times, this is how cells “drink” or take up resources
- Process is mediated by **receptors** on the surface of cells
  - **Receptors** on proteins attach to particle and the particle is ingested
  - **Very specific**: “Lock and key”
- **Viruses mimic this process to invade cells**
- Example: Influenza Hemaglutinin **(virus protein)** binds to Salic Acid **Receptor** on respiratory tract cells
  - Virus enters the cell through endocytosis… viral replication occurs
  - Influenza replicates in these cells, makes copies of itself and causes symptoms of disease
  - Cell is now infected… virus can spread to other cells

What does this look like…

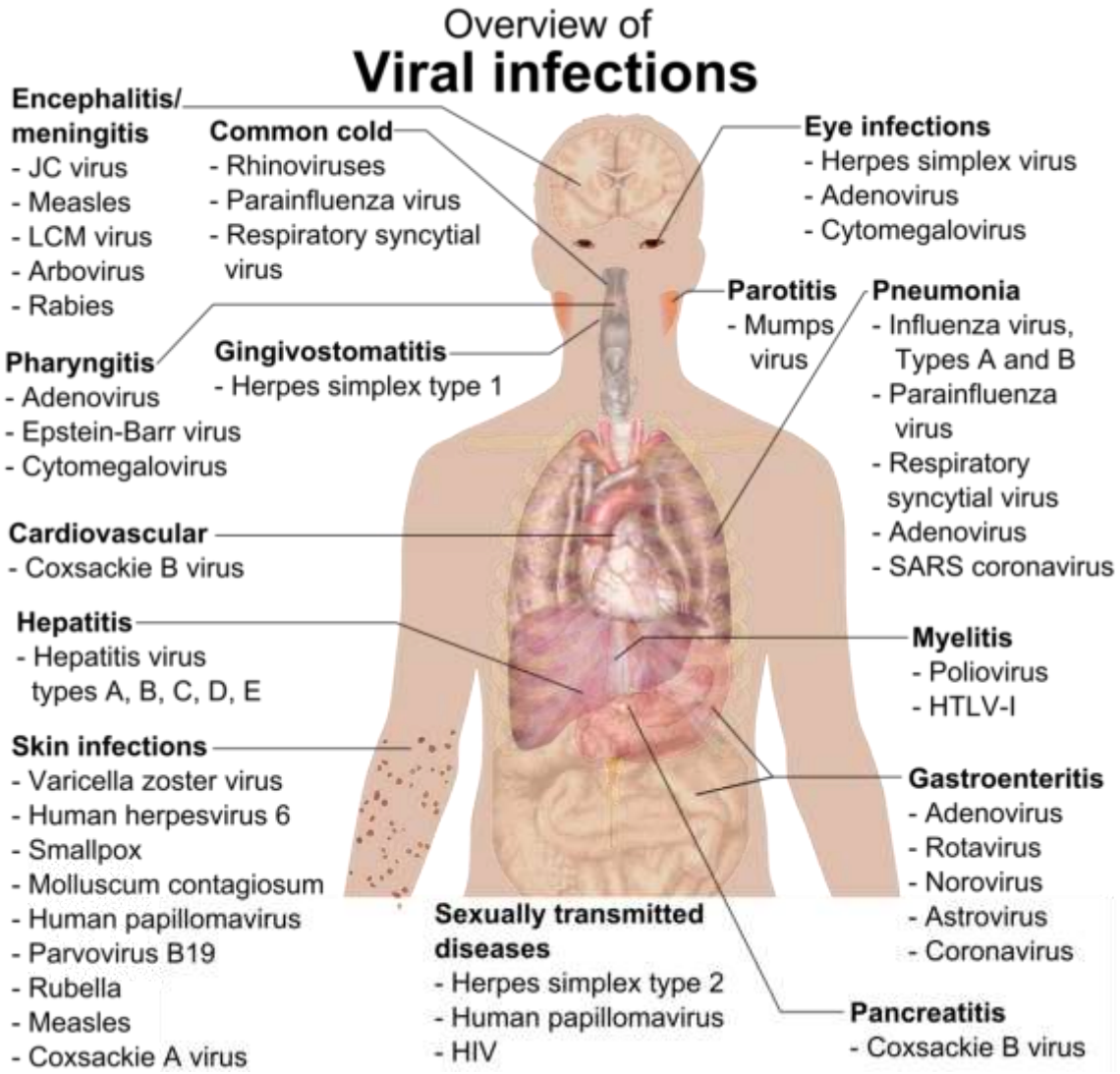






Wide variety of Illness

- Many make people sick and can result in death
- Viruses affect every organ and system in the body
- Why study viruses? – Many cell biology functions have been discovered by studying how viruses manipulate the human body
- Best viruses never cause disease to the host (and never kill the host)



Many Ways to Spread Viruses

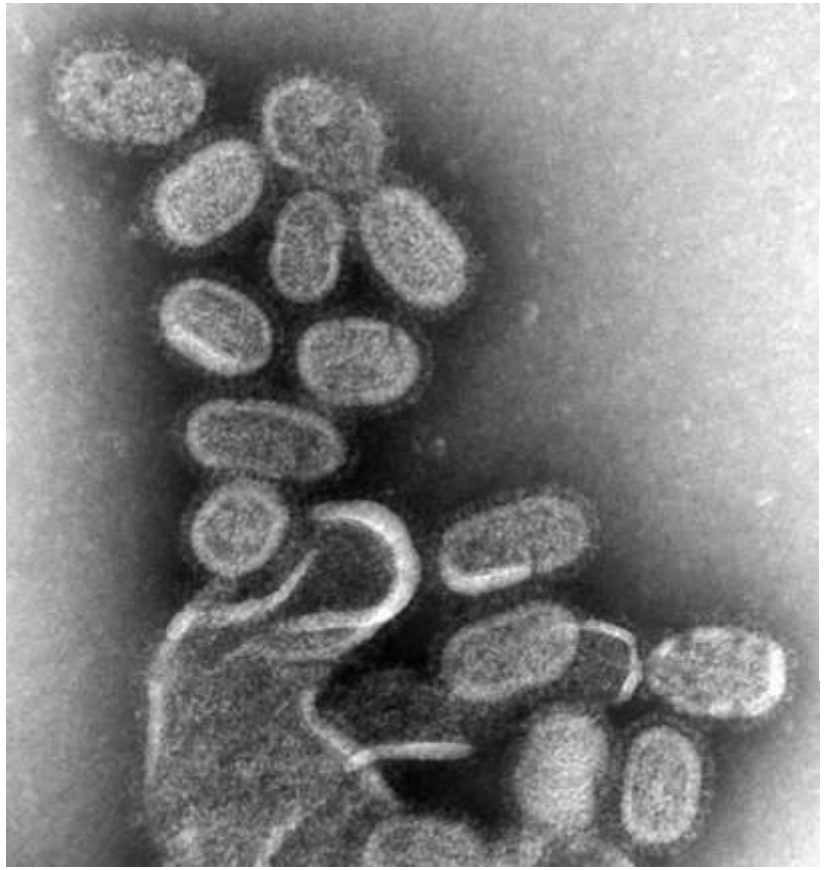
- **Aerosol** – When you sneeze or cough, you make small, tiny water droplets or "aerosols", many viruses and bacteria can fit in these droplets and can be inhaled
  - Influenza, RSV
- **Direct Contact** – bacteria or viruses transmitted by contact or by bodily fluids
  - Ebola (bodily fluids), HIV (bodily fluids)
- **Oral** – transmission by food or other particles entering the mouth
  - Cruise Ship Viruses (Norwalk Virus)—food poisoning
  - Fecal-Oral transmission—Rotavirus (stomach flu, and diarrhea in infants)
- **Fomite** – non-living objects such a bedding, towels toys and barbed wire or nails that can cause disease
  - Biological warfare, also Influenza and childhood diseases (sharing toys in daycare)
- **Zoonotic** – Transmission from animals to humans
  - Swine Flu, Ebola

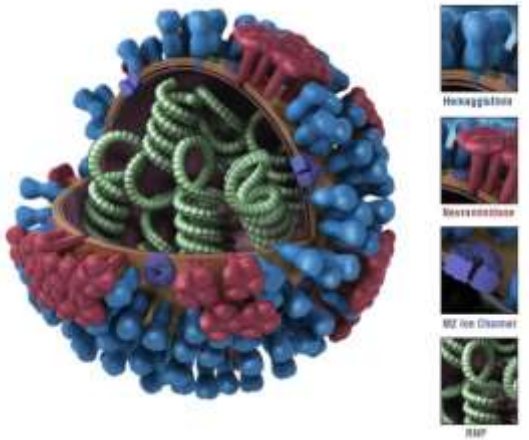
How Do Viruses Change Over Time?

Influenza

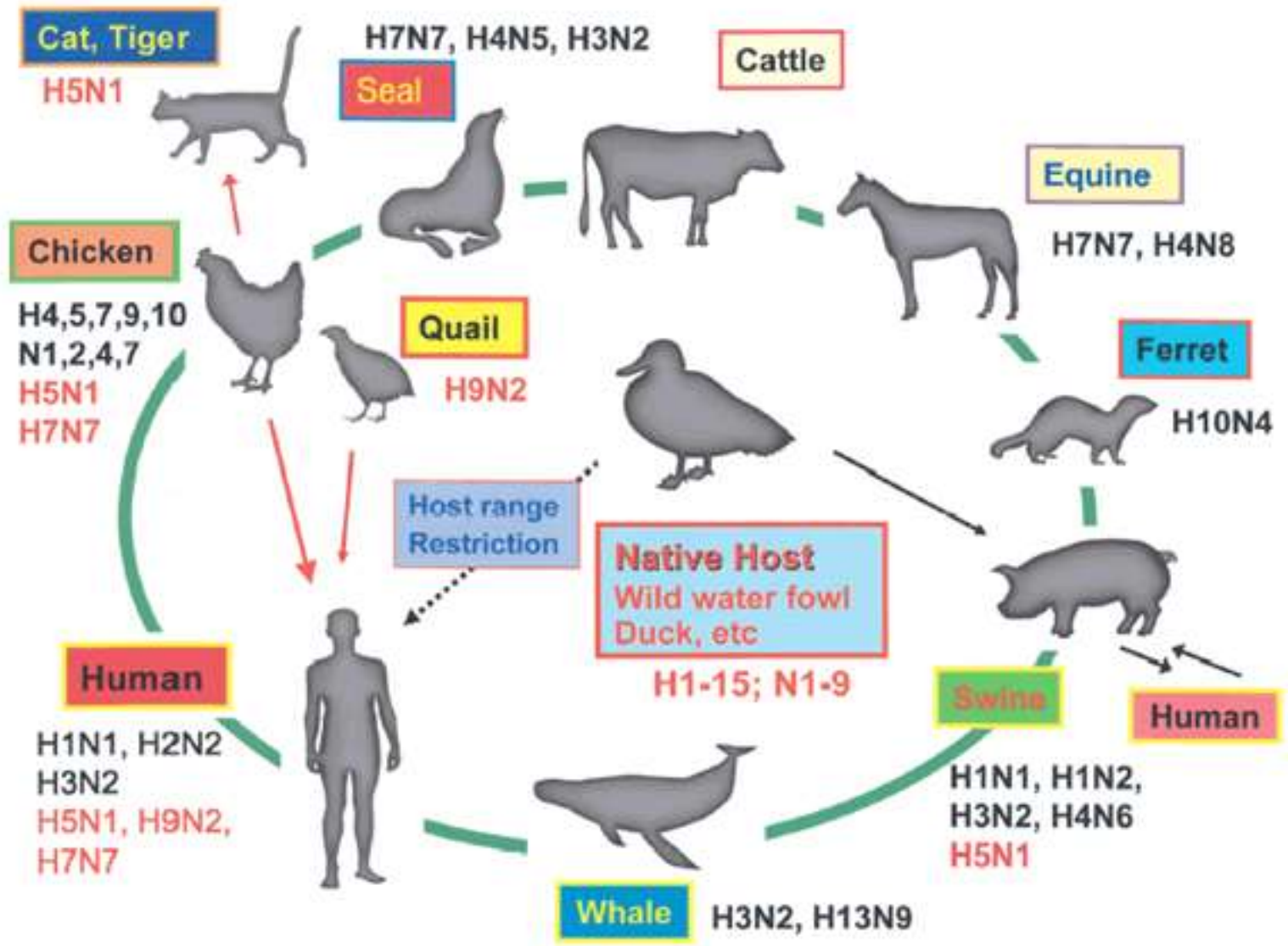
Influenza Virus

- Infectious disease of birds and mammals
  - Causes mild to severe respiratory illness
  - Serious illness results in hospitalization or death
  - Children and older adults are at high risk for flu infection (and death)
  - Best defense is to get a flu vaccine every year
  - Infects cells that line the respiratory tract
- Viral genome composed of 8 pieces of RNA inside a protein coat

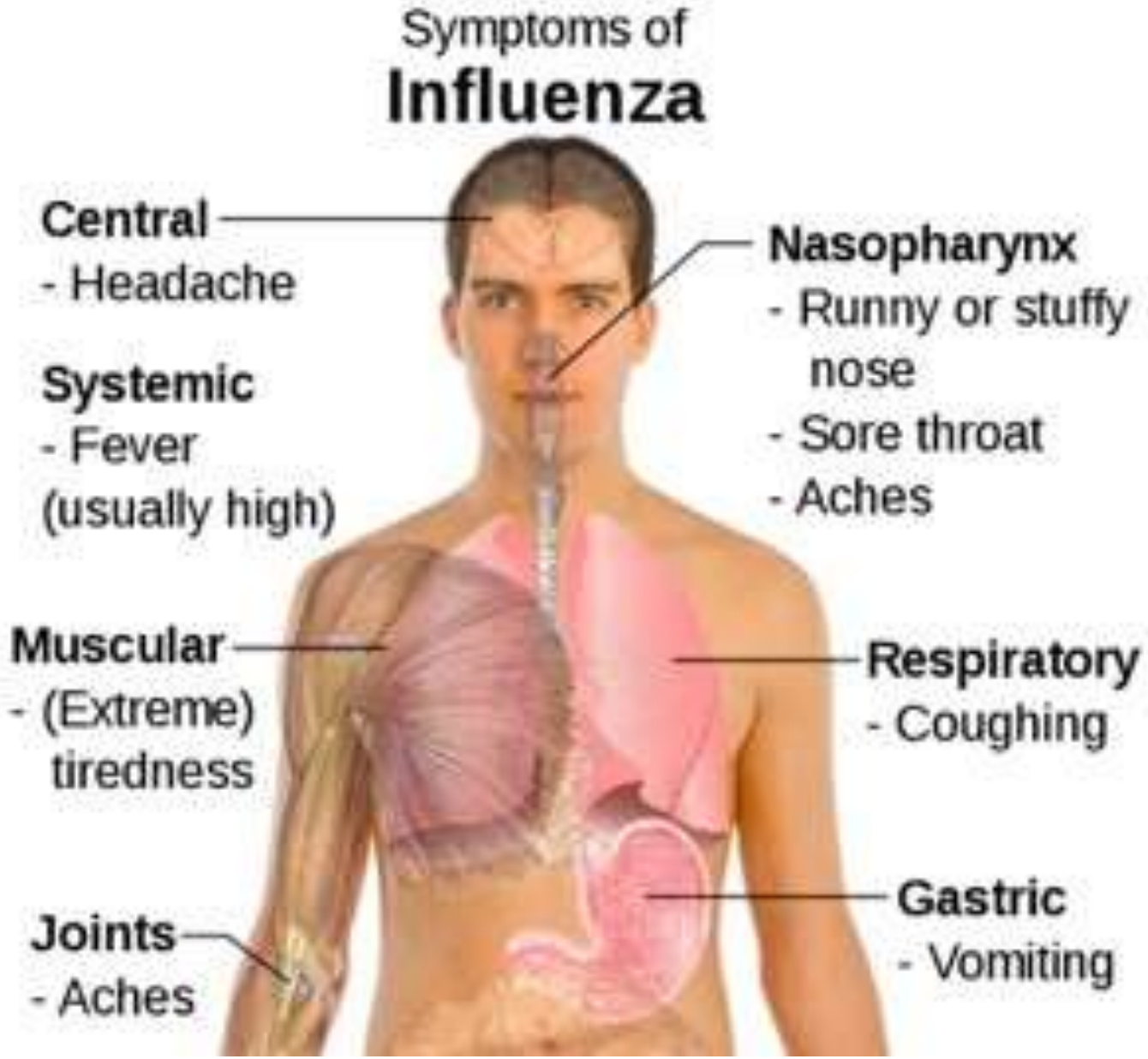




Influenza Infects Many Animals Species



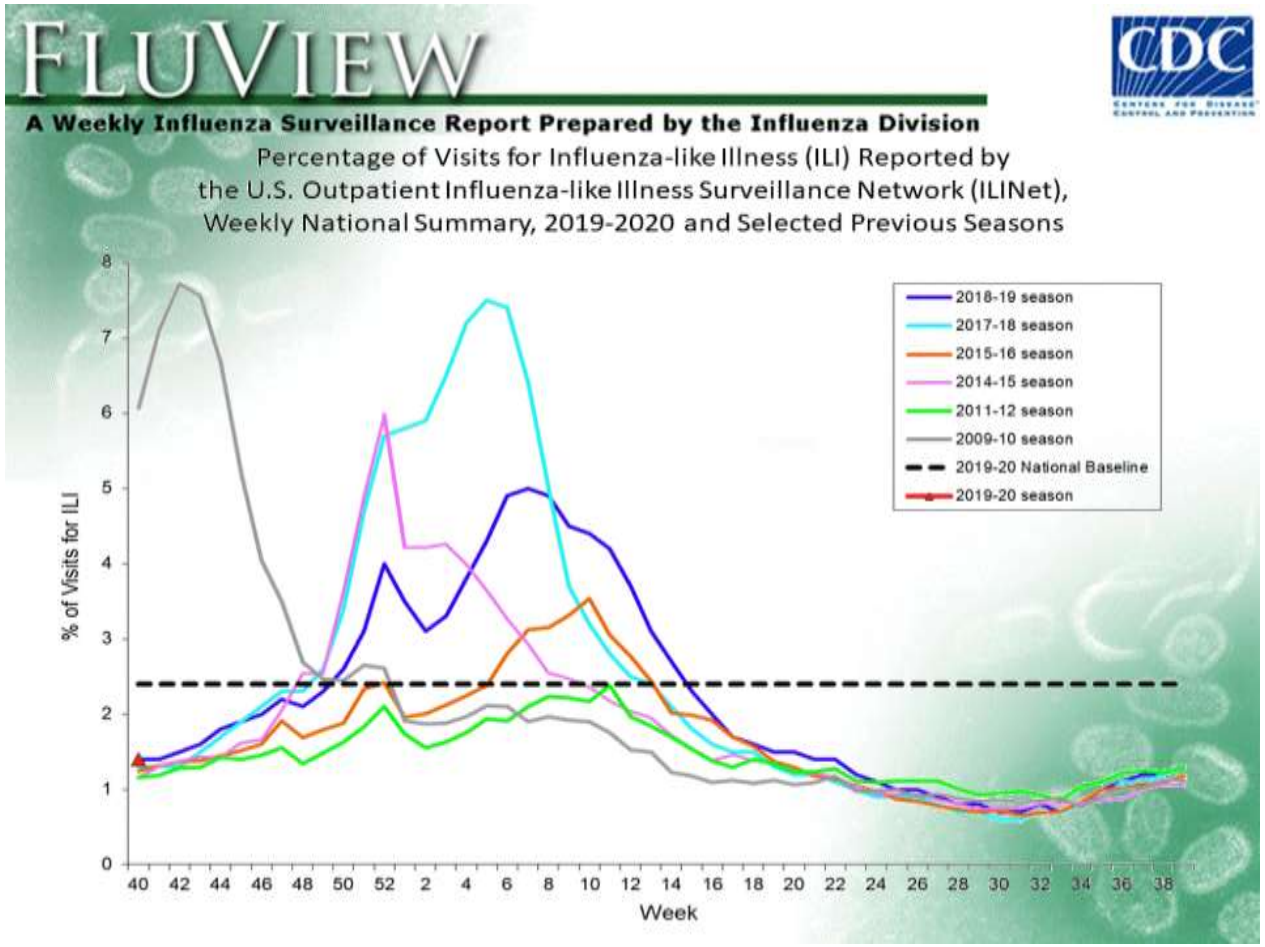
Flu Symptoms

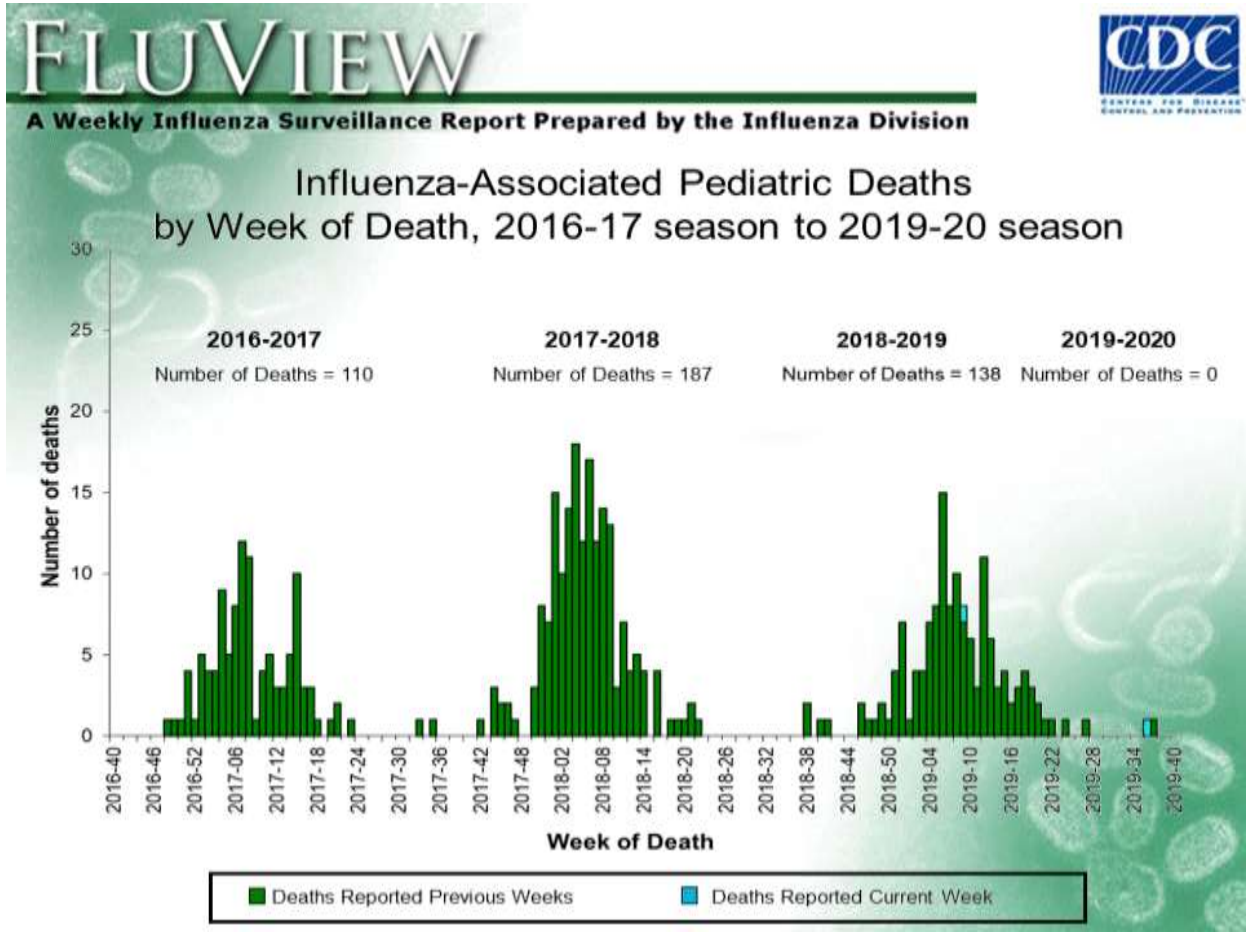


Aerosol or Fomite Transmission of Influenza

Center for Disease Control and Prevention

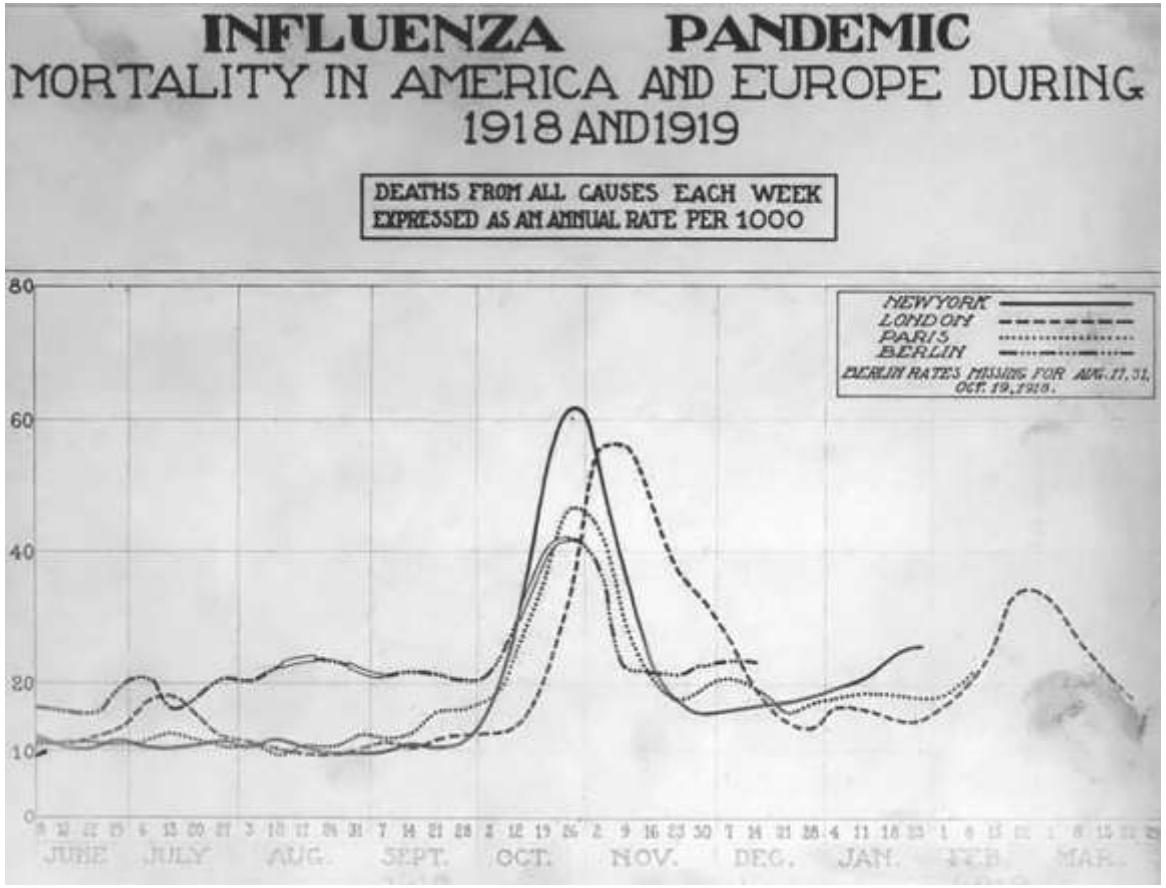
Seasonal Influenza is typical and usual predictable

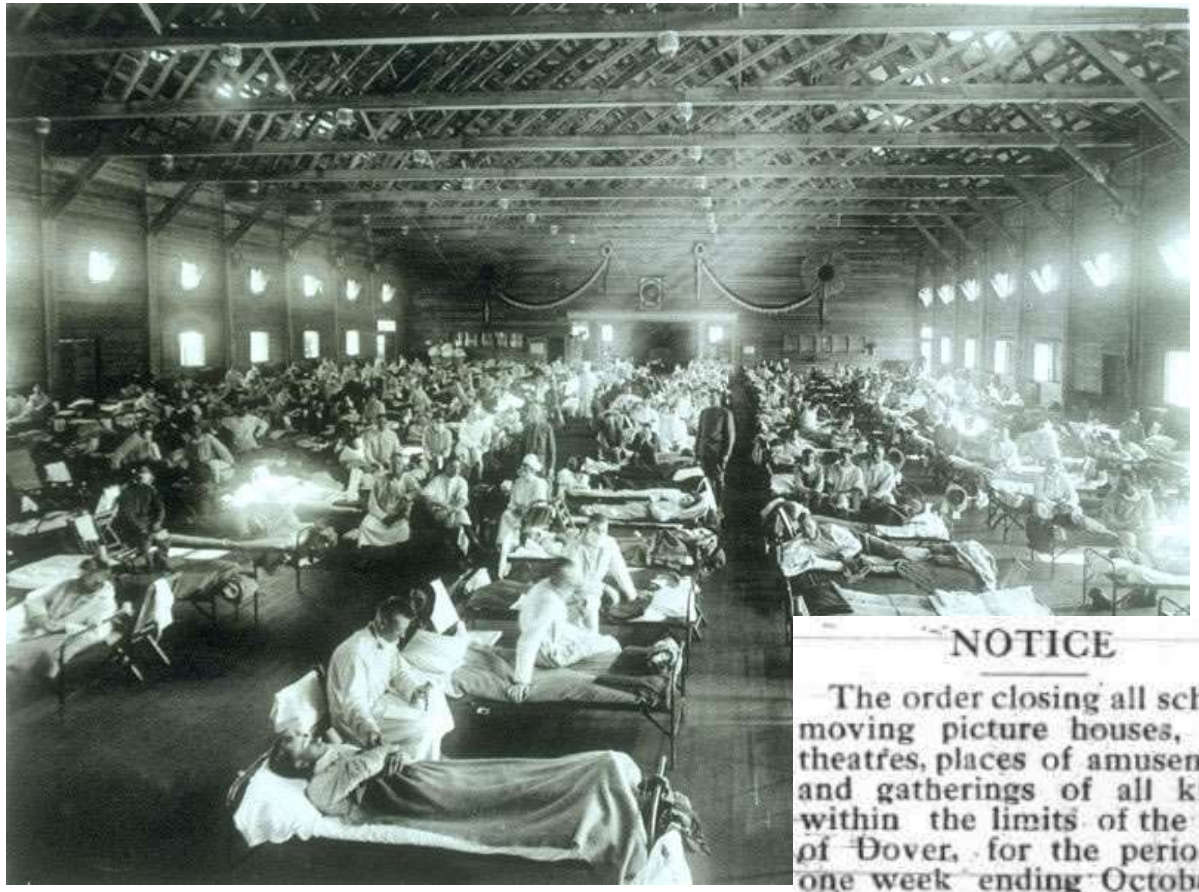




Center for Disease Control and Prevention: Flu Tracker

Recurring and Frequent Influenza Pandemics



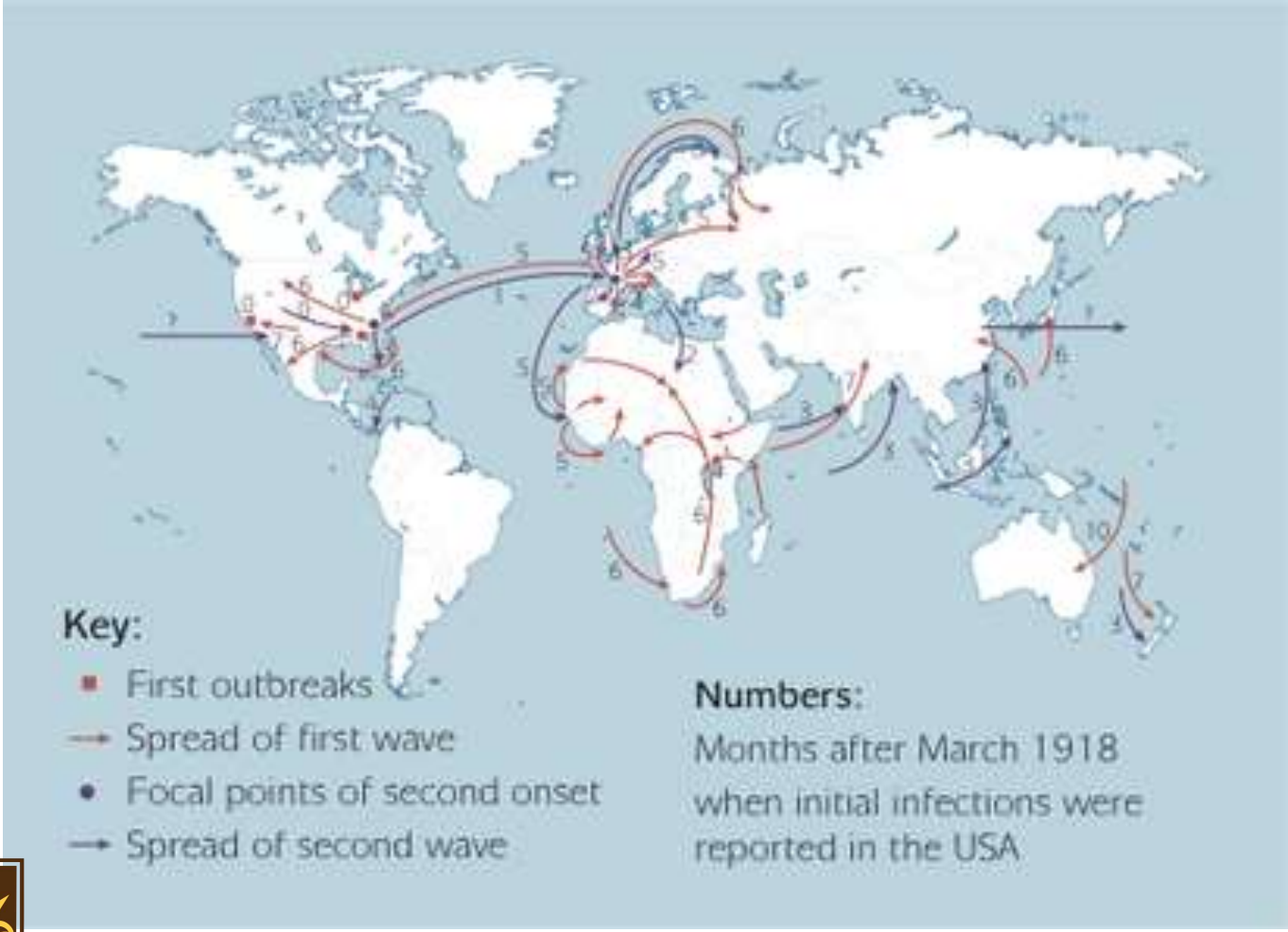


NOTICE

The order closing all schools moving picture houses, also theatres, places of amusement, and gatherings of all kinds, within the limits of the City of Dover, for the period of one week ending October 6, 1918, is hereby extended to ~~12~~ o clock midnight Sunday, Oct. 13. 1918. This order is subject to revocation, should conditions warrant. By order of the Board of Health.

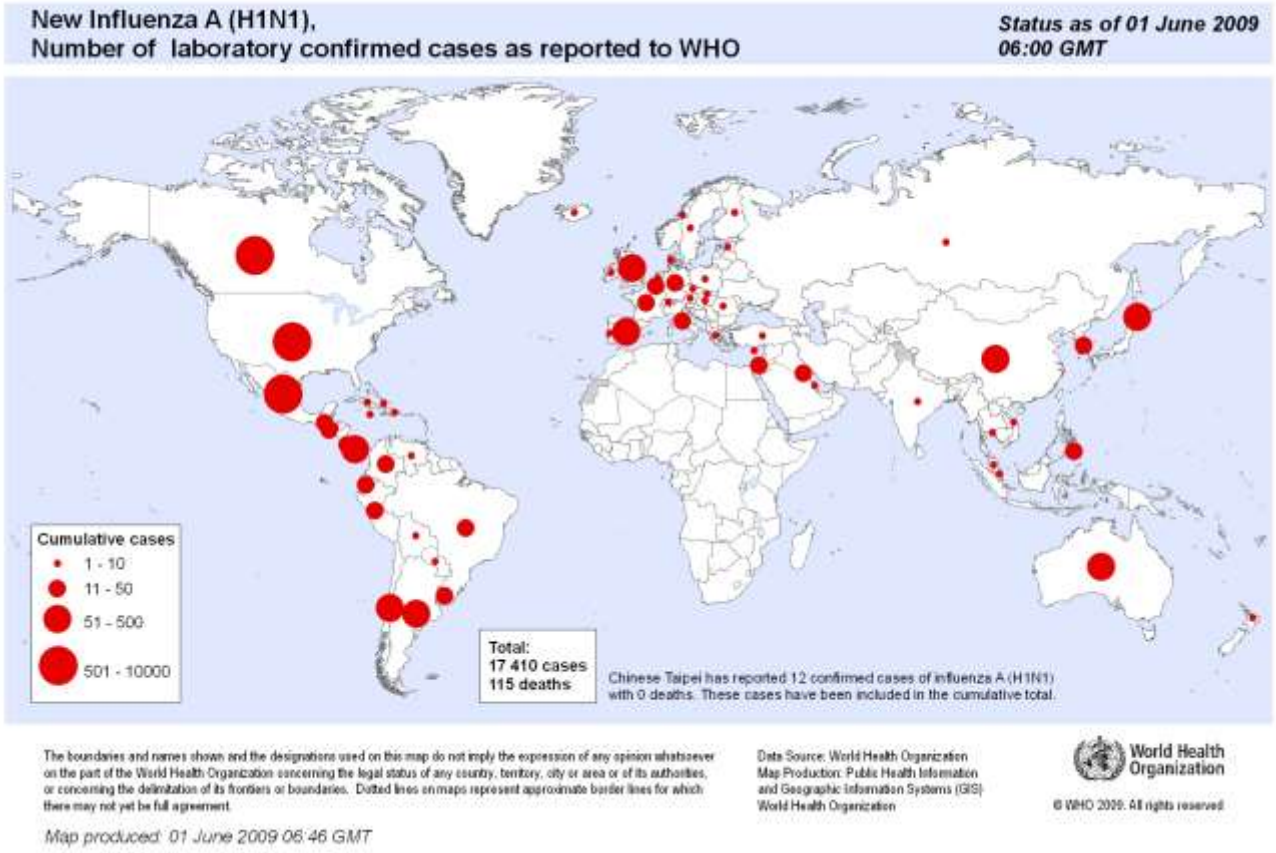
William E. Whiteley Clerk,

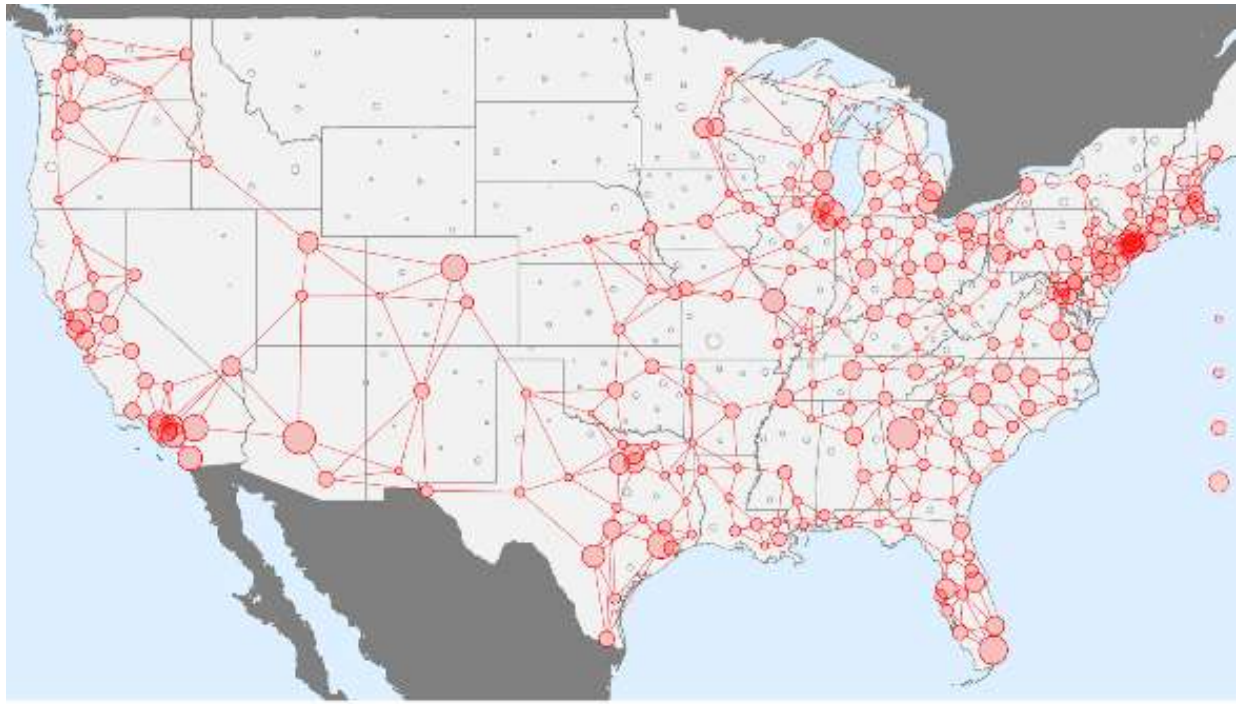
Spanish Flu Pandemic 1918



- Killed between 20 and 40 million people—more then all of the soldiers who died in World War I
- Likely exacerbated by an increase in world travel after WWI
- Infected **28%** of all Americans

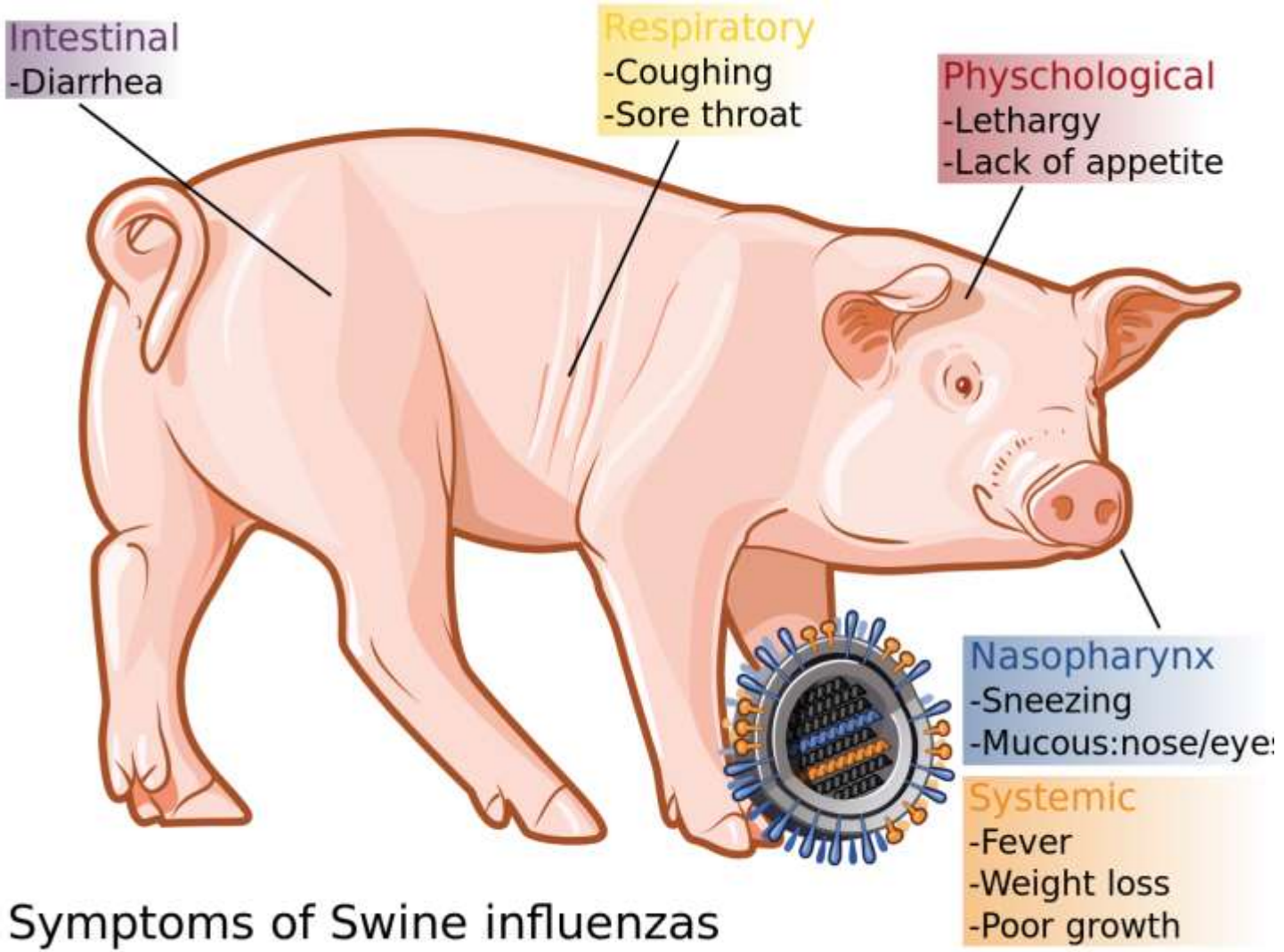
Swine Flu Pandemic of 2009





1.Julia R. Gog, Sébastien Ballesteros, Cécile Viboud, Lone Simonsen, Ottar N. Bjornstad, Jeffrey Shaman, Dennis L. Chao, Farid Khan, Bryan T. Grenfell. **Spatial Transmission of 2009 Pandemic Influenza in the US**. *PLoS Computational Biology*, 2014; 10 (6): e1003635 DOI: 10.1371/journal.pcbi.1003635

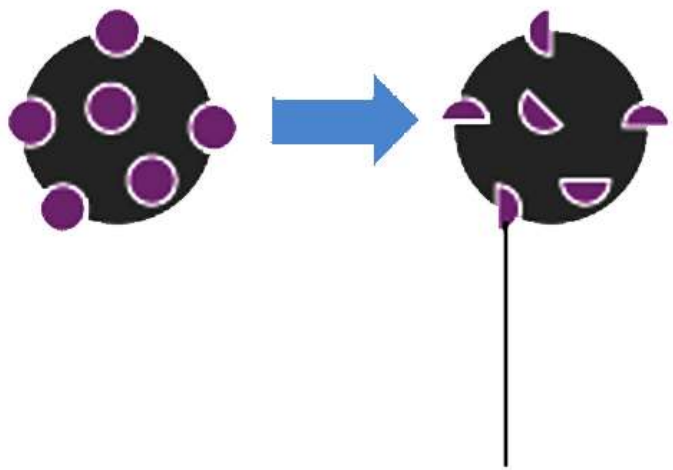
H1N1 Swine Flu: Similar Influenza Symptoms in Pigs



Symptoms of Swine influenzas

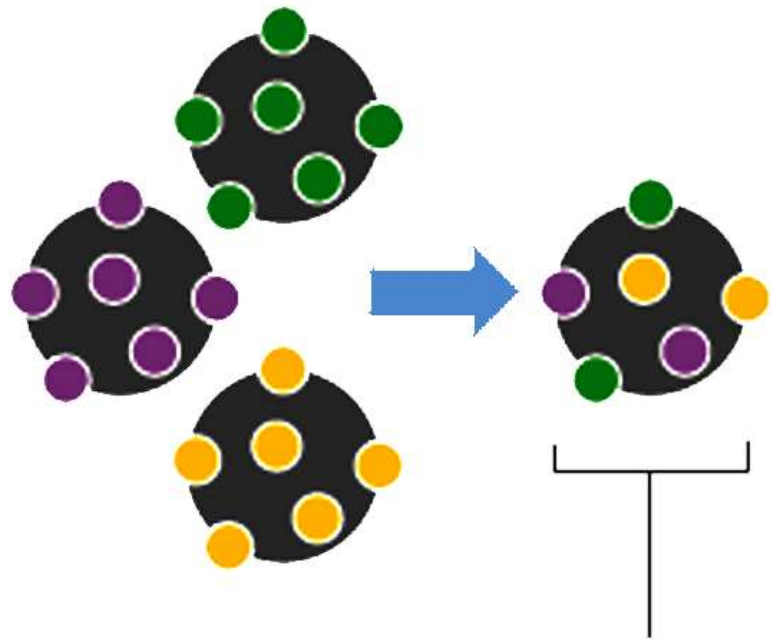
Influenza Mutates/Changes Over Time

Mutation
Antigenic drift



Small Mutations
Seasonal Influenza

Antigenic shift
Mixing Different Animal Strains



New Strain
Pandemic Influenza

H1N1 Swine Flu: Result of Antigenic Shift

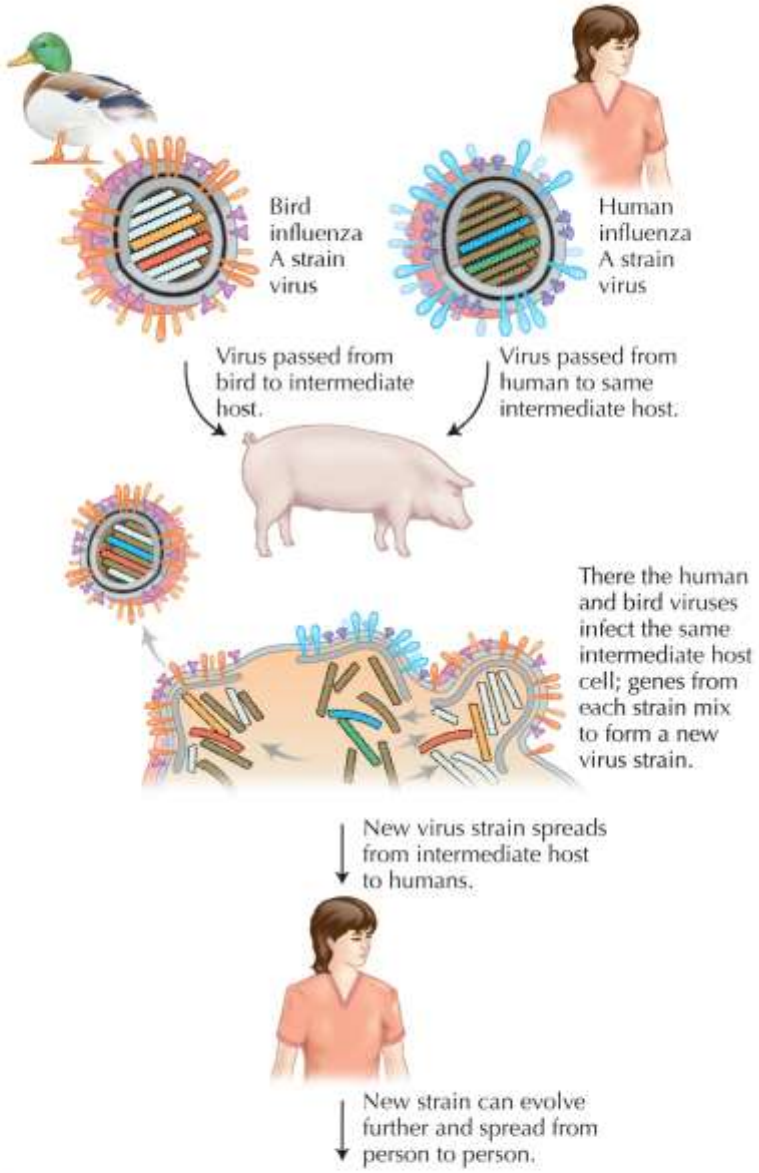
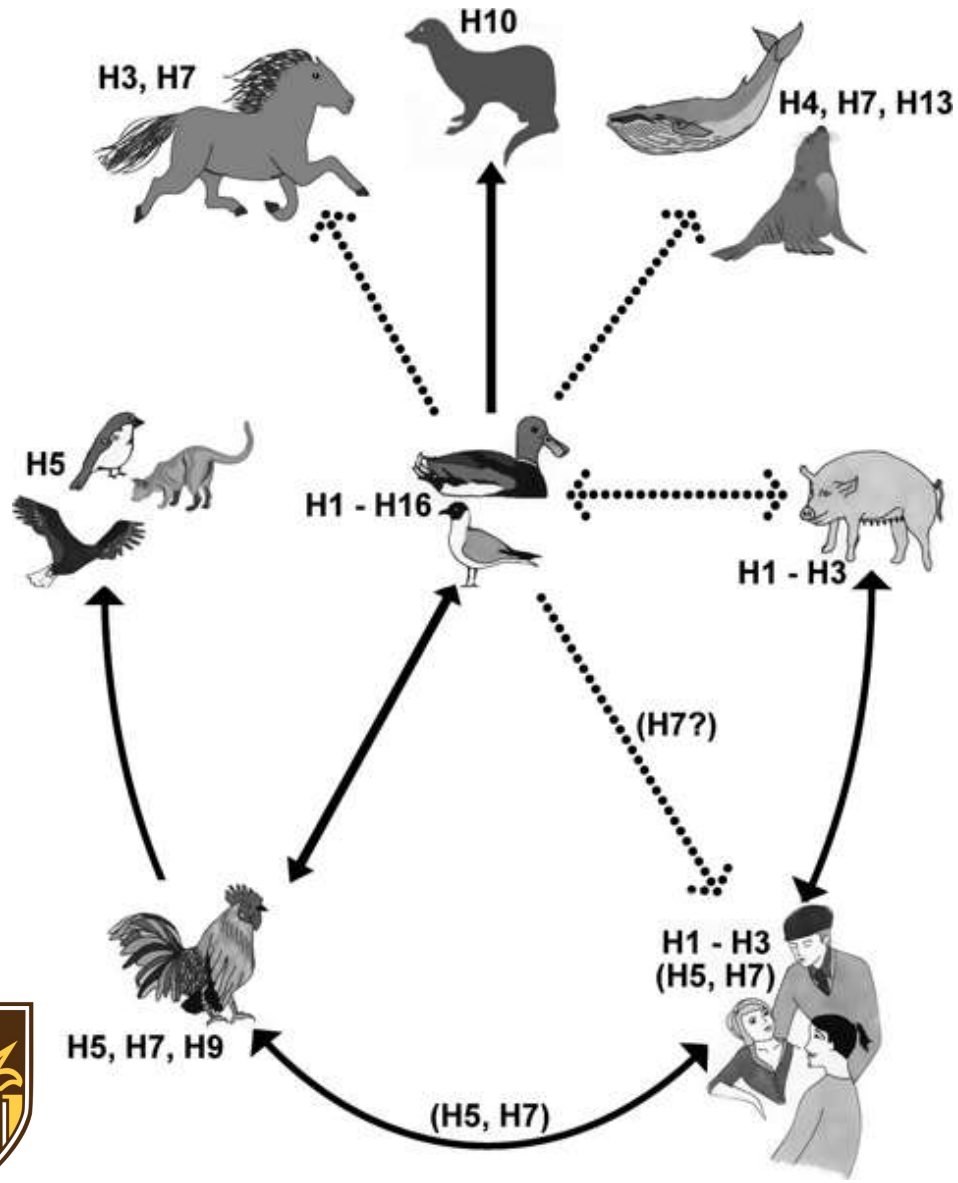


FIGURE 12.25. Antigenic shift in influenza.

12.25, based on http://www3.niaid.nih.gov/news/focuson/flu/illustrations/antigenic/antigenicshift.htm

- Pig (swine) was infected with a avian and human influenza virus at the same time
- Viruses mixed, resulting in a virus with new viral proteins, that could infect humans
- No human had ever seen the combination – no immunity in the population
- Pandemic Influenza is cause by Antigenic Shift – typically much more lethal

Central Role of Water Fowl in Transmission



- Many believe the next deadly pandemic will be a result of avian influenza jumping into the human population
- Avian Influenza assisted the jump from Swine to humans in 2009

- Zoonotic Transmission
  - Disease that is transmitted between vertebrate animals and humans
  - Cross species jump into the human population
    - Often, host species is not affected by virus or acts as a **reservoir**
  - Unless this reservoir is eliminated, the viruses can still be transmitted to humans and cannot be eradicated

Zoonotic Transmission and Reservoirs

Ebola

Discovery in 1977 and Current Distribution

ISOLATION OF MARBURG-LIKE VIRUS FROM A CASE OF HÆMORRHAGIC FEVER IN ZAIRE

S. PATTYN W. JACOB
G. VAN DER GROEN P. PIOT
G. COURTEILLE

University of Antwerp and Institute of Tropical Medicine, Antwerp, Belgium, and Clinique Ngaliema, Kinshasa, Zaire

WE record here our findings in the investigation of the outbreak of severe hæmorrhagic fever in Zaire.

SOURCE AND EXAMINATION OF SPECIMEN

A 42-year-old woman (patient M.E.) fell ill on Sept. 23, 1976, in Yambuku, Equateur Province, Zaire. She was transported by air on Sept. 25 to Kinshasa, where a hæmorrhagic syndrome gradually developed. Clotted blood taken on the 5th day of illness was sent on ice to the Institute of Tropical Medicine, Antwerp. The sample arrived in the evening of Sept. 29 and was kept in the refrigerator.

The next morning serum was inoculated into 6 young adult mice by intracerebral and intraperitoneal routes, into 2 litters

Preliminary Communications

ISOLATION AND PARTIAL CHARACTERISATION OF A NEW VIRUS CAUSING ACUTE HÆMORRHAGIC FEVER IN ZAIRE

K. M. JOHNSON P. A. WEBB
J. V. LANGE F. A. MURPHY

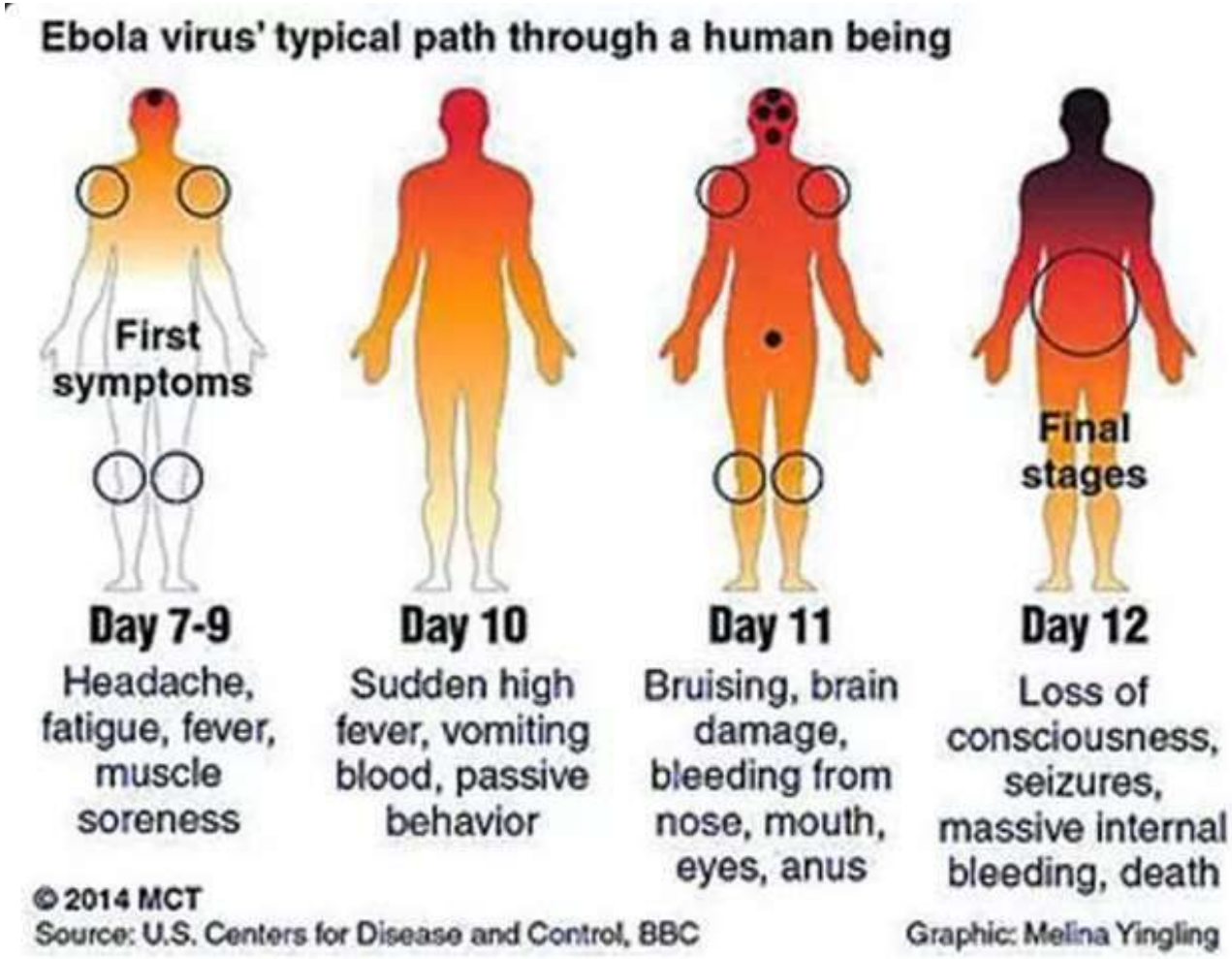
Virology Division, Center for Disease Control, Atlanta, Georgia 30333, U.S.A.

Endemic to regions of Africa; also isolated in Philippines from Non-human primates

Figure and data: CDC

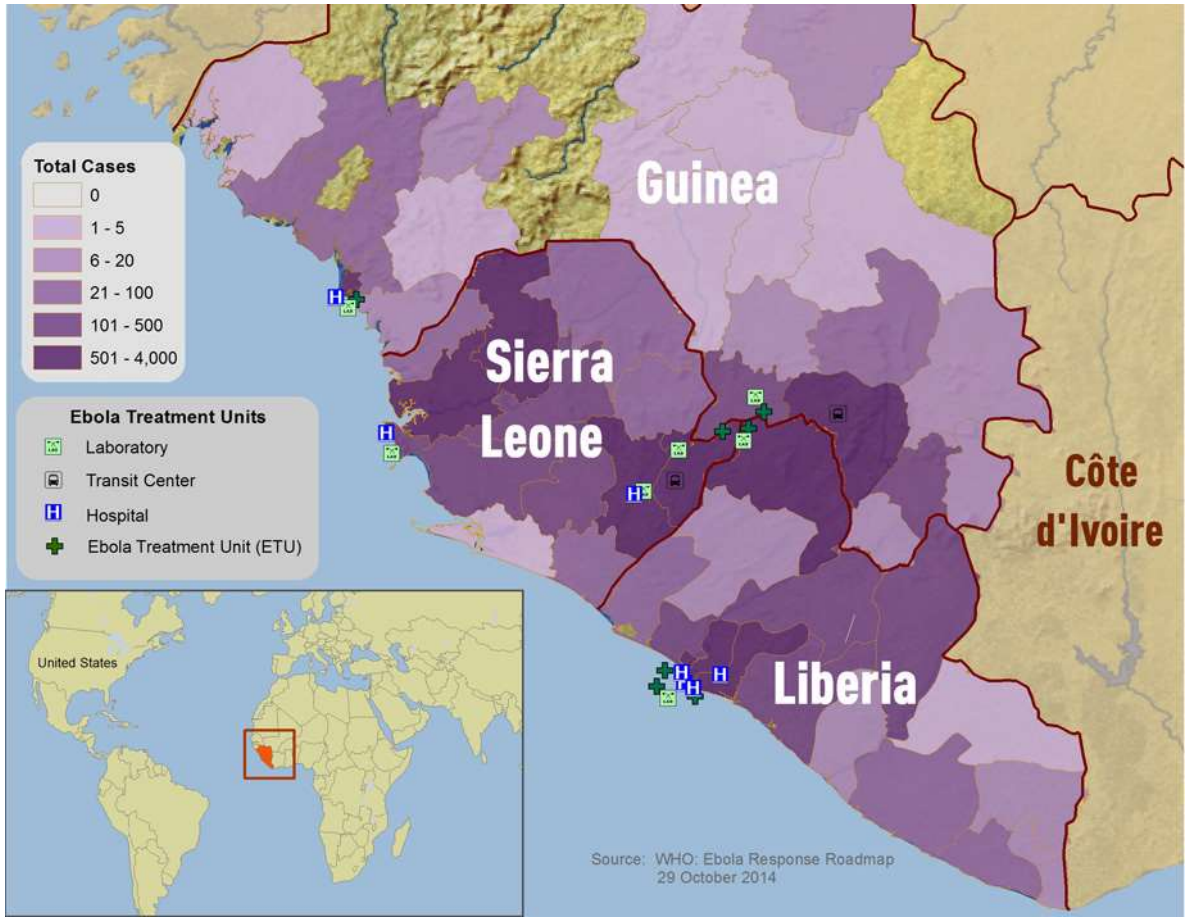
Transmission and Pathogenesis

- Transmission: Bodily fluids and ingestion of infected meat
- Requires direct contact with contaminated fluids
  - Virus has been detected in many body fluids, making transmission easier than for a virus like HIV
    - Skin (sweat)
    - Saliva
    - Urine
    - Feces
    - Breast milk
    - Semen
    - Vaginal fluid



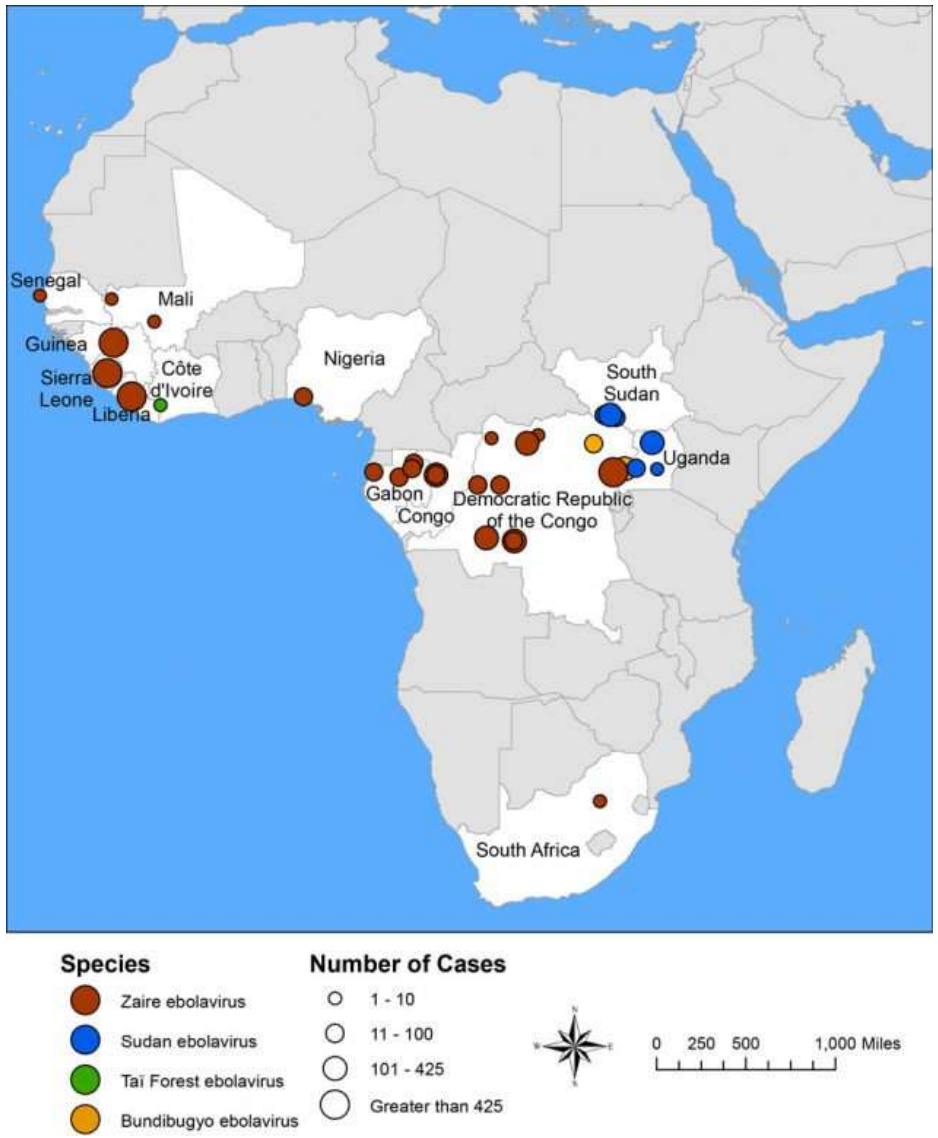
West Africa outbreak of 2014-2015

- First outbreak in a highly populated area
- 28,600 cases in Guinea, Sierra Leone, and Liberia (11,325 deaths)
- Cases in Nigeria, Spain, US, Mali and Senegal
- Additionally, separate outbreak in Dem Rep of Congo



Current Ebola Outbreak (2nd largest in History)

- 3,204 Ebola Cases, 2,142 Deaths since August 2018
  - Outbreak is likely to continue in endemic areas
- Current vaccination of rVSV-ZEBOV is being tested in the field (unknown efficacy)

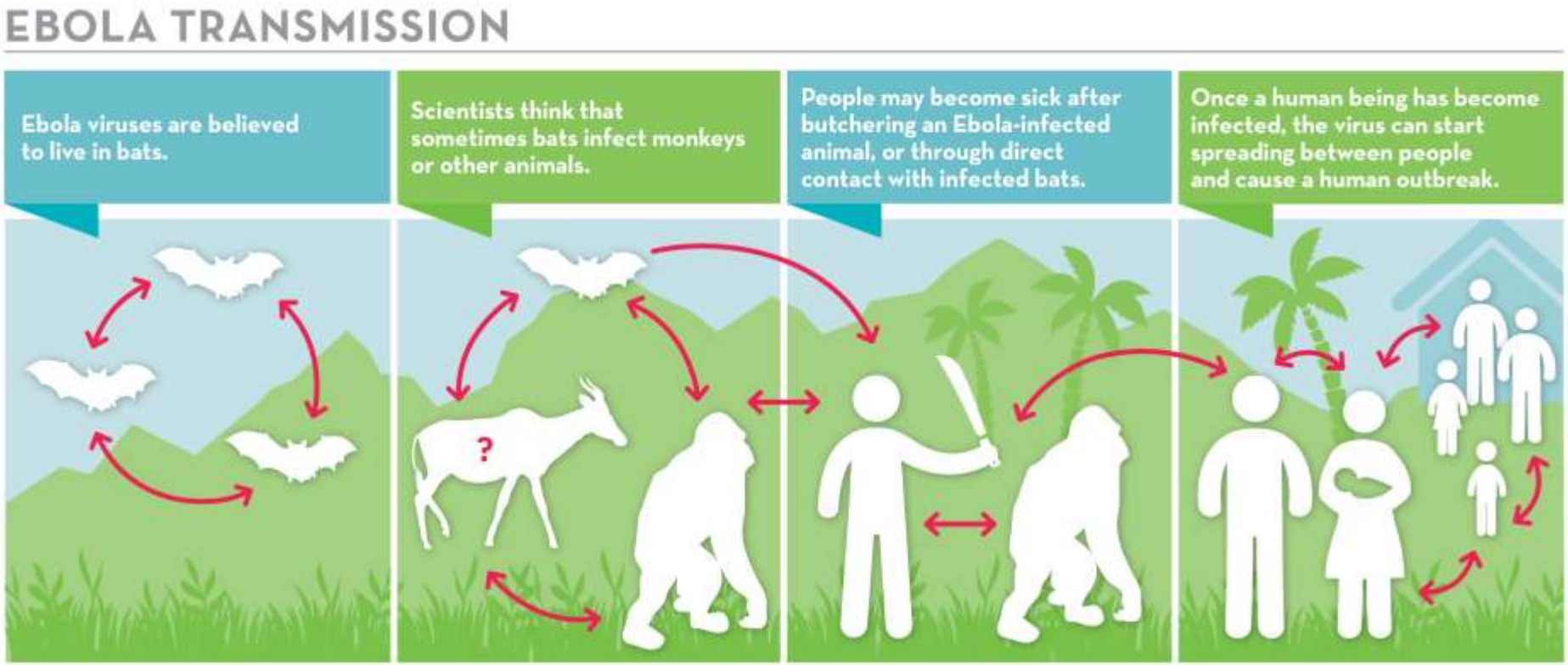


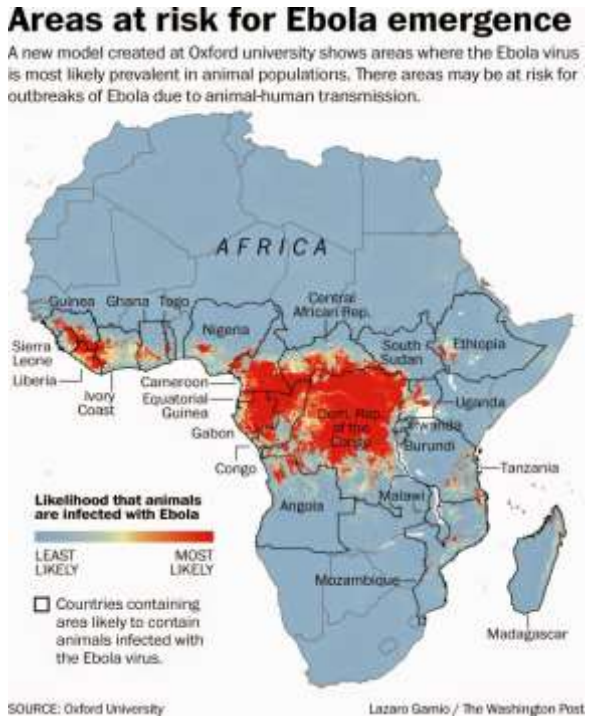
Ebola Treatment 37 years after discovery…not much has changed

1977

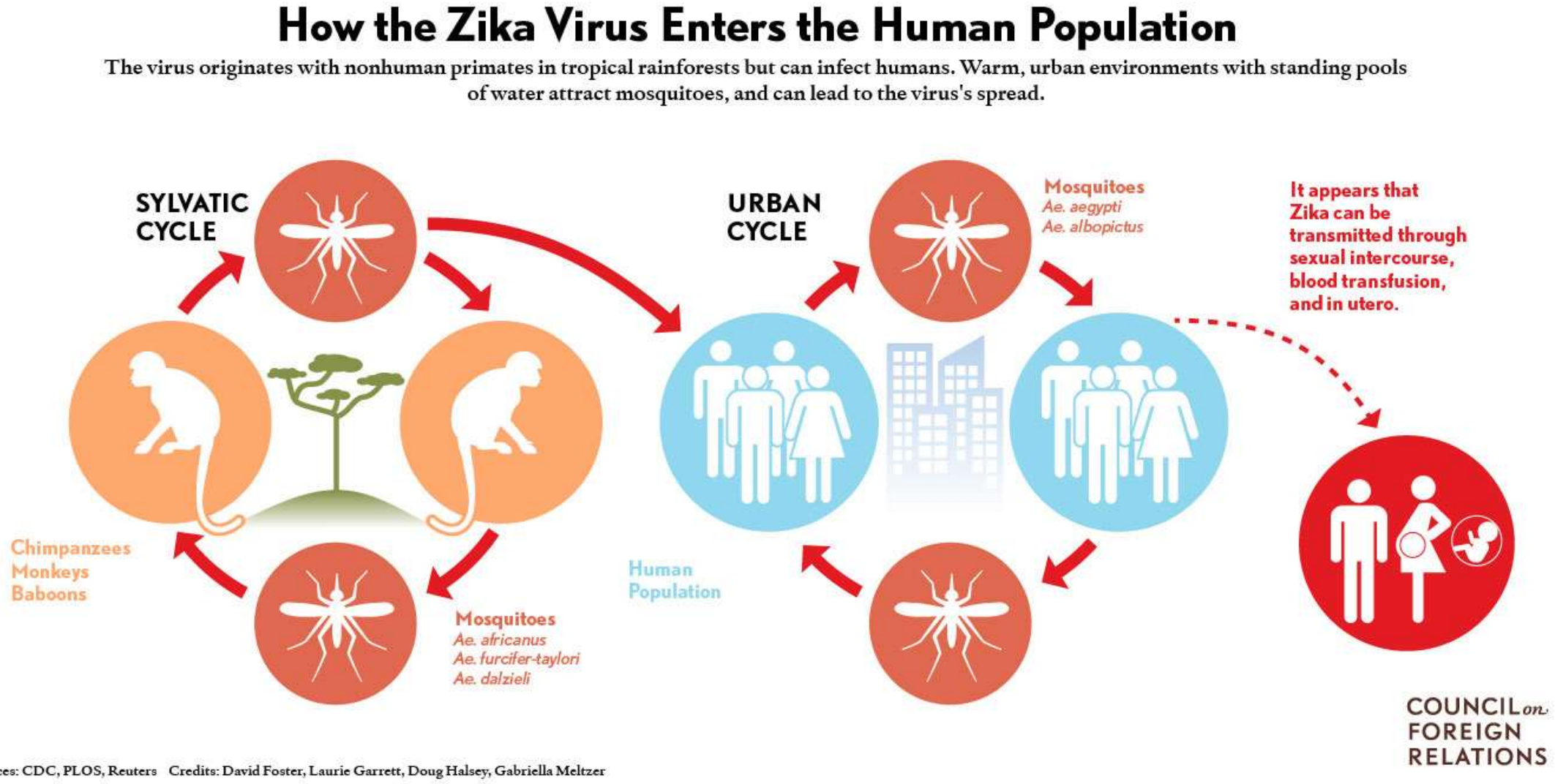
2014

Zoonotic Cycle and Reservoir…outbreaks likely to continue if animal reservoir is maintained





Also true for mosquito born viruses…zika/dengue/chikungunya/west nile



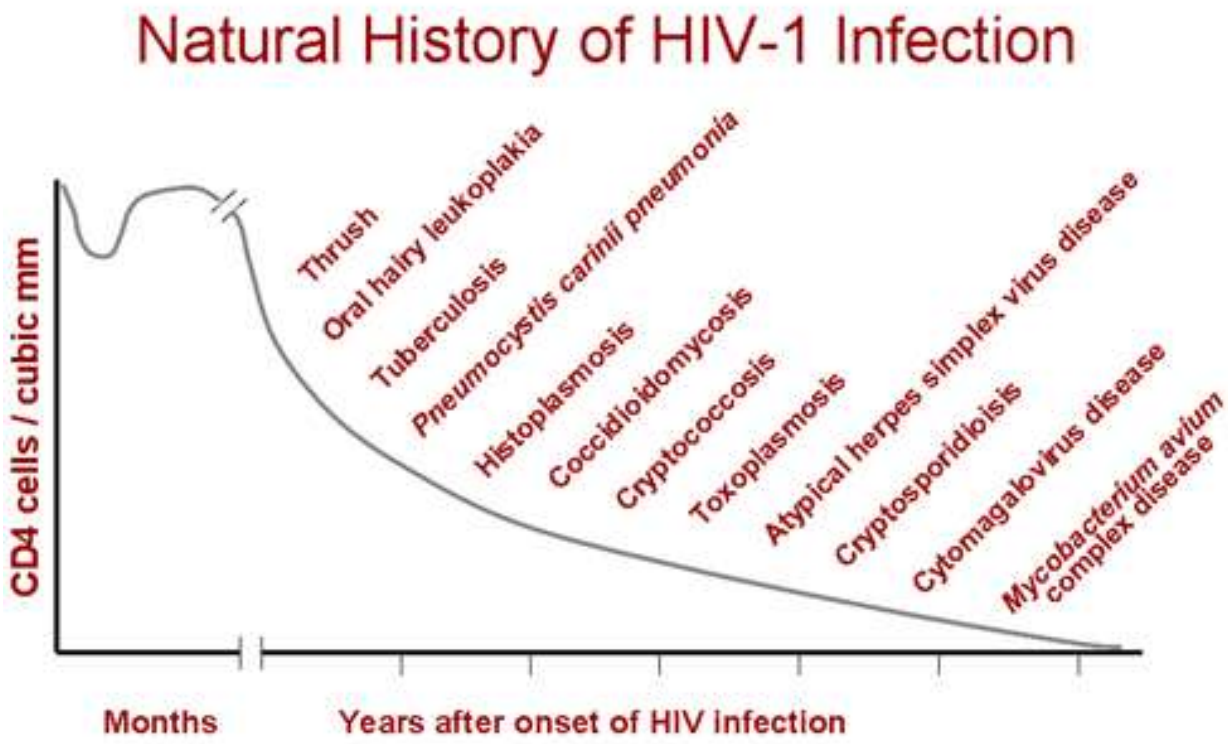
How Do we Prevent Viral Infection?

HIV

What characterizes AIDS?

- Immune system is broken…
- Once your $CD4^+$ T cell count falls well below healthy levels, rise in opportunistic infections
- Infections that arise from pathogens that are normally harmless in healthy individuals
- Your Immune system is no longer functioning

- HIV never actually kills you---other viruses, bacteria and fungus do
- HIV kills your immune system and response to infections



Opportunistic Infections

- Common yeasts, part of normal flora
- Cause of thrush: superficial infection of the oral cavity
- Can be invasive in the GI tract especially in the esophagus making it hard to swallow (dysphagia)

- Non HIV related: Skin Cancer affecting elderly, Jewish men
  - Mainly lesion on the feet, benign
- HIV Pandemic: Severe, aggressive form of the disease
- KSHV or HHV-8 (Human Herpesvirus-8) identified as causative agent in 1994 (also a virus)
- Today, significant morbidity and mortality in subequatorial African countries

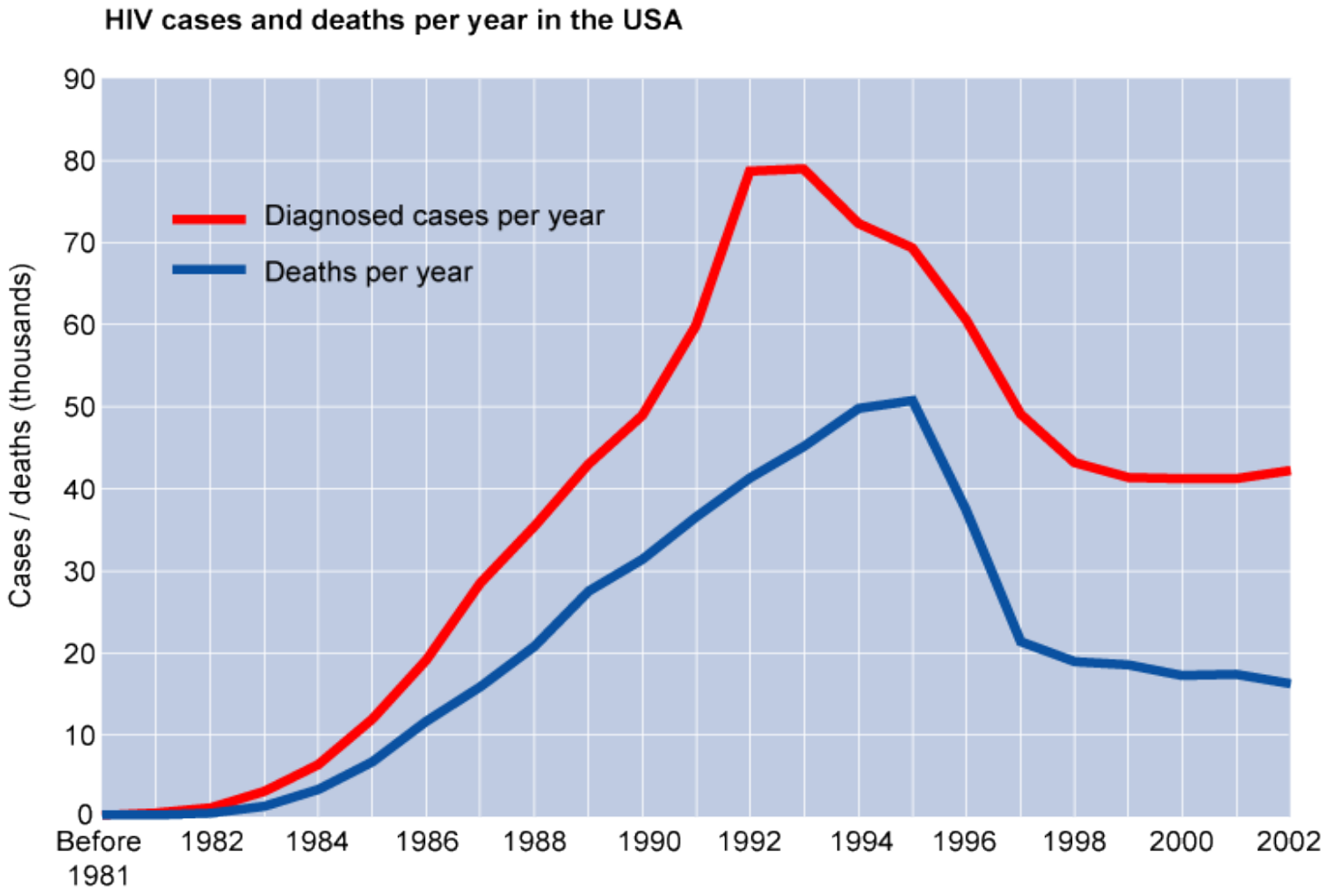
HIV: Discovery of Antiretroviral Drugs

- Earliest Drug was AZT (Zidovodine)
  - Originally a cancer therapeutic, was found to be active against HIV
  - At the original dose, was highly toxic to patients—but did work to control infection for a period of time
- Used alone, only extended life for about a year
  - virus mutated and AZT was no longer effective

- HIV mutates quickly resulting in resistant to antiviral drugs

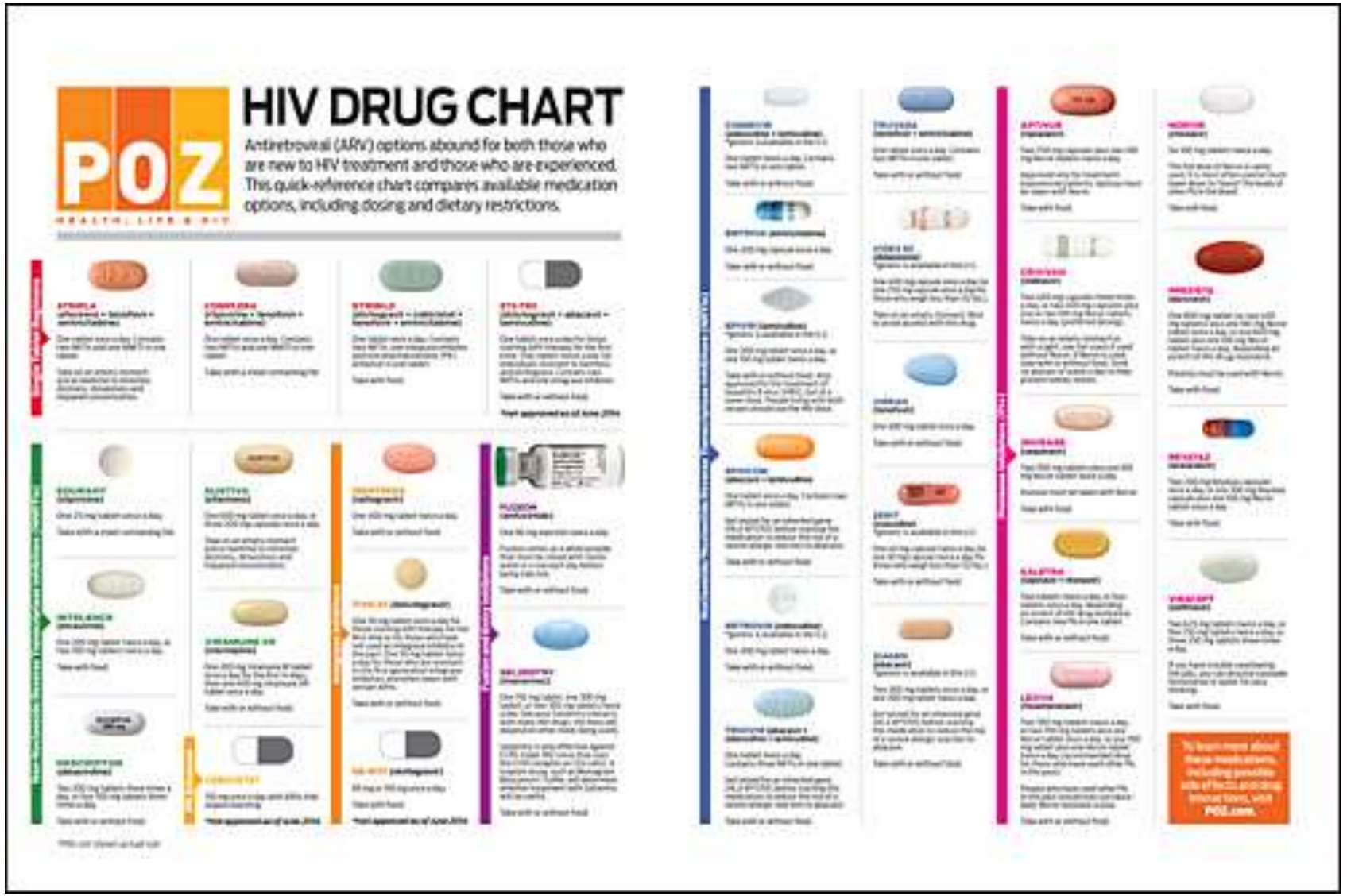
HAART—Combination Antiviral Treatment

- **H**ighly **A**ctive **A**nti**R**etroviral **T**herapy
  - Use three or more drugs at one time to stop viral replication
- Combination drugs are powerful and prevent HIV from mutating and becoming resistant to therapy
- Taken daily, makes HIV a “chronic condition”

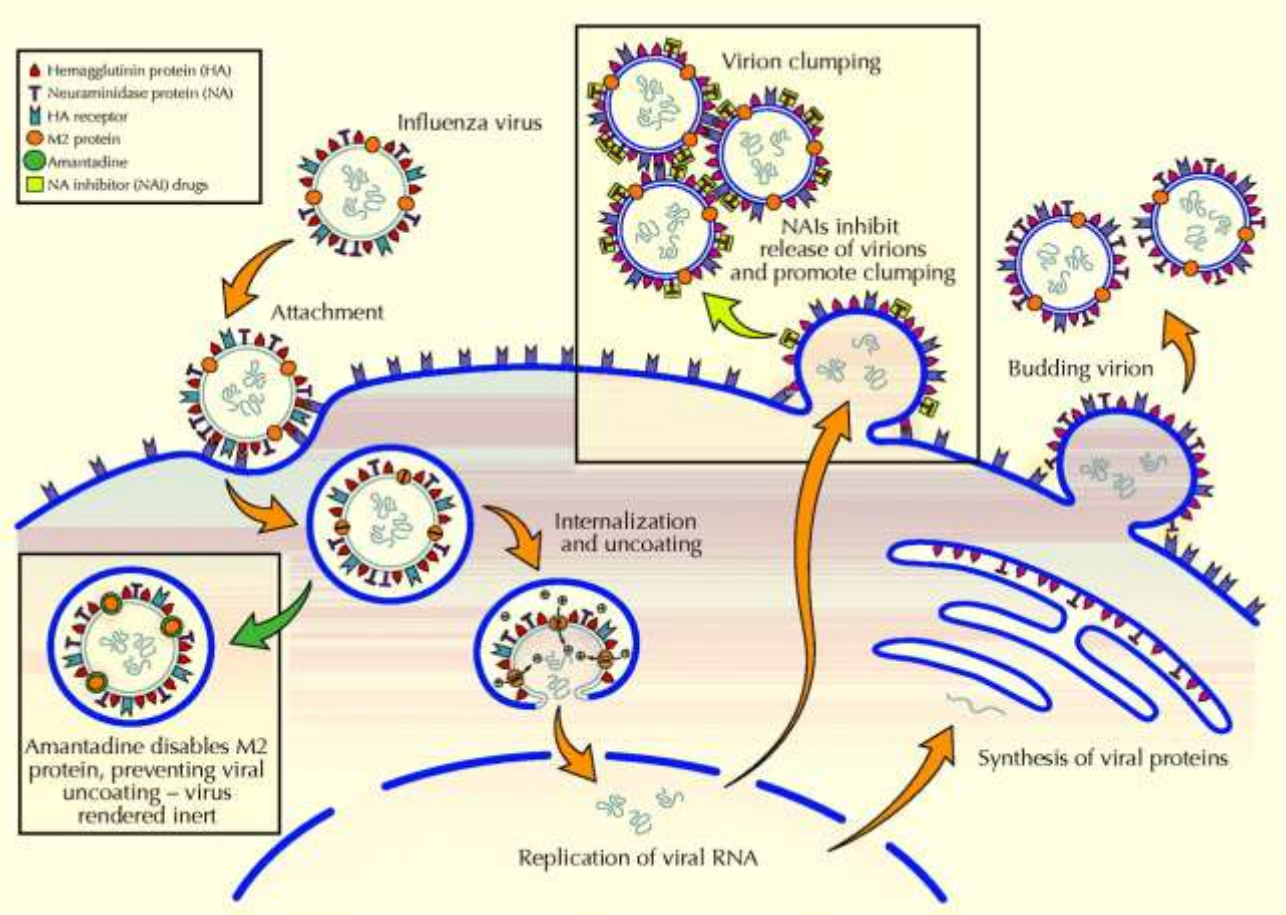


Source: CDC HIV AIDS surveillance report 2003

Multiple Drugs Available for HIV Treatment and Prevention…Prevention is possible…



More Limited Options for Influenza Treatment…but maybe this is changing…



More Evidence That Baloxavir Reduces Flu Symptom Duration

— Investigational antiviral matches or exceeds efficacy of oseltamivir

by Liz Highleyman, Contributing Writer, MedPage Today
October 08, 2018

Baloxavir Reduces Flu Symptoms and Viral Shedding

Diana Phillips
September 05, 2018

Genentech Announces FDA Approval of XOFLUZA (Baloxavir Marboxil) for Influenza

– First and only single-dose oral medicine approved to treat the flu –

– XOFLUZA significantly reduced the duration of flu symptoms compared to placebo –

– First novel proposed mechanism of action to treat the flu in nearly 20 years –

October 24, 2018 01:00 PM Eastern Daylight Time

…But resistance is already occurring one year later…

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Baloxavir and Treatment-Emergent Resistance: Public Health Insights and Next Steps

Larisa V. Gubareva and Alicia M. Fry

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

RAPID COMMUNICATION

Detection of influenza A(H3N2) viruses exhibiting reduced susceptibility to the novel cap-dependent endonuclease inhibitor baloxavir in Japan, December 2018

Emi Takashita[1], Chiharu Kawakami[2], Hiroko Morita[1], Rie Ogawa[1], Seiichiro Fujisaki[1], Masayuki Shirakura[1], Hideka Miura[1], Kazuya Nakamura[1], Noriko Kishida[1], Tomoko Kuwahara[1], Keiko Mitamura[3], Takashi Abe[4], Masataka Ichikawa[5], Masahiko Yamazaki[6], Shinji Watanabe[1], Takato Odagiri[1], on behalf of the Influenza Virus Surveillance Group of Japan[7]

1. Influenza Virus Research Center, National Institute of Infectious Diseases, Tokyo, Japan
2. Yokohama City Institute of Public Health, Kanagawa, Japan
3. Eiju General Hospital, Tokyo, Japan
4. Abe Children's Clinic, Kanagawa, Japan
5. Ichikawa Children's Clinic, Kanagawa, Japan
6. Zama Children's Clinic, Kanagawa, Japan
7. The members of the group are listed at the end of the article

Correspondence: Takato Odagiri (todagiri@nih.go.jp)

Antiviral Drugs

- Lots of pharmaceutical and small biotech development activities for various viruses
  - Recent success in some: HIV, HCV
  - Resistance and limited options in others: Influenza
  - Lack of combinations increases chance of **resistance, new drugs still needed**
  - New drugs may not be as effective as initially thought due to resistance
- Failure in current treatment for many: HBV, Ebola, Dengue/Zika

- Antivirals can only treat you once you are infected, so how can we prevent viral infection in the first place?
- How can we reduce animal reservoirs?

Gold Standard for the Prevention of Infection

Vaccines

Edward Jenner

- Known as the father of Modern Immunology
- Famous experiment of 1796
  - Smallpox is the scourge of the 18th century world
  - Folklore that milkmaids who suffered from cowpox never got small pox
    - Jenner hypothesized that exposure to cowpox prevented smallpox infection
  - Key experiment: exposed 8 year old James Phipps to pus from a cowpox pustule, and then exposed James to small pox (he survived, luckily)
  - Vaccine provided *Protective Immunity*
- First "vaccine"
  - Vaccines were named in honor of Jenner
  - Vacca is cow in latin, hence Vaccine (in honor of the cow pox story)

There has always been backlash against vaccination…

1802: Satirical cartoon implying that those who got vaccinated turned into cows

2018: Nothing new, but still not helpful for human health…

Vaccination is incredible powerful and effective

- Smallpox has been eradicated from the globe
- Polio is undergoing an eradication campaign
- Measles, chickenpox and other childhood diseases are almost non-existent in the United States
  - Unless parents don't vaccinate their children

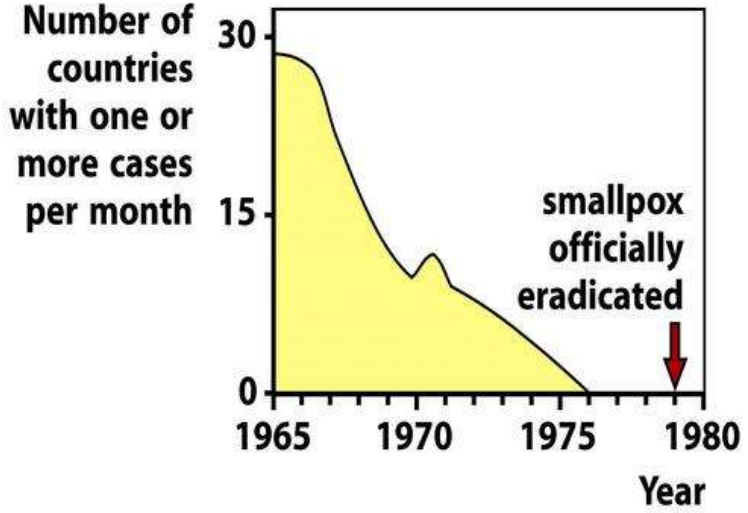
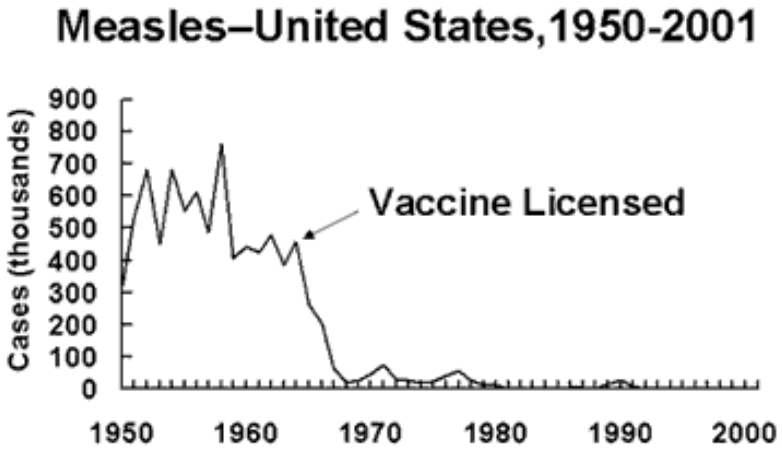
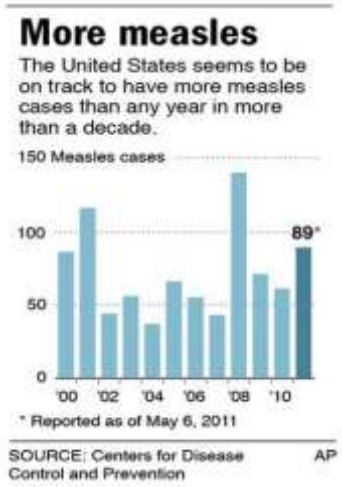


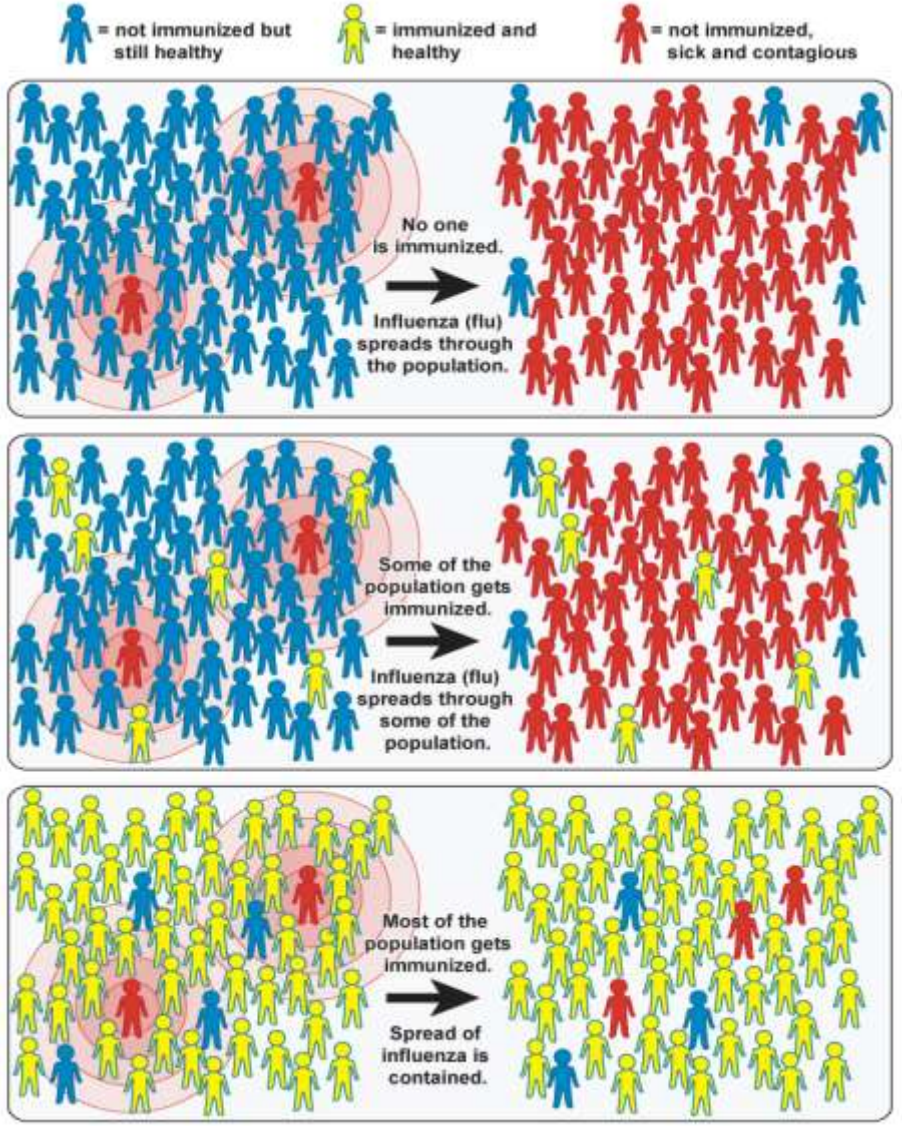
Figure 1-2 Immunobiology, 7ed. (© Garland Science 2008)





How Vaccines Work: Herd Immunity

- Basic idea came from protecting groups of animals—hence “herd”
- Vaccination of a portion of the herd (less cost) and end up with full protection (great)
- Same principle works in human populations (“herds”)



Summary

- Viruses are ancient and infect all organisms on the planet
- All evolve over time as a result of small random mutations
- Mixing of different virus strains results in “brand new viruses”
- Constant battle of evolution of virus and host
- Viral therapy is most effective in combination…reduces chance of mutation

- Zoonotic transmission is a key factor is viral epidemics, pandemics, and maintenance of virus in the population
  - Must eliminate animal reservoir to eliminate jumps back into the human host
- Vaccines are the best protection against infection
  - Can protect you and others from infection (and animals)

Thanks! Any Questions?