Viral Disease and Prevention
BioScience in the 21st Century
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Outline

• Case Study – Mystery Illness in 1981
• 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
Case Study -- 1981

• Adult Male walks into the Hospital
• Mid thirties, severe case of community acquired pneumocystis carinii
• Pale, very skinny—evidence of other opportunistic 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 “helper” cells)
• Strange?—Maybe, but its just one patient, right?
Consistent CD4 depletion in group of patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Percent of PBMC*</th>
<th>CD4/CD8 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4⁺</td>
<td>CD8⁺</td>
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<tr>
<td>1</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>52</td>
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<tr>
<td>3</td>
<td>10</td>
<td>57</td>
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<tr>
<td>4</td>
<td>2</td>
<td>47</td>
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<tr>
<td>Mean</td>
<td>3</td>
<td>53</td>
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<tr>
<td>Normal subjects</td>
<td>46</td>
<td>28</td>
</tr>
</tbody>
</table>

*PBMC = peripheral blood mononuclear cells (lymphocytes and monocytes)
The disease spreads...1982-1983

- No one, at this time knows what is causing this illness
- Originally, only seemed to infection Homosexual males
- January 1982, the first clinic for patients with this disorder opened in San Francisco
- September 24th, first time that the term AIDS is used—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—female partners of male AIDS patients
- CDC hosts a meeting to talk about the blood supply—criteria for testing, and no consensus is reached
  - Blood Banks did nothing/were required to do nothing
- 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) ---associated with AIDS patients
  • Professor Luc Montagnier (won the Nobel Prize in 2008)

• In November Dr. Robert Gallo’s lab in the USA also propegates LAV in immune cells (NIH)

• AIDS was caused by a newly discovered virus (LAV then renamed HIV)

• Not uncommon...new viruses jump into the human population frequently
So...What is a Virus?

Discovery, Structure and Replication
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 determined in plants

• **1892** – Dmitri Ivanovskiy, 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”
Discovery of Viruses

• **1889** – Friedrich Loeffler discovered a similar agent was responsible for foot-and-mouth disease (the first proof of a virus infecting humans)

• **1901** – Walter Reed discovered that yellow fever was caused by a virus during construction of the panama canal (mosquito control controlled infection...first proposed by Carlos Finlay)...verified by human testing
Wide Variety of Shapes and Sizes

- Likely that there is a virus that infects every living organism on the planet – animals, plants even bacteria.
- Typically comprised of a protein capsid surrounding nucleic acids (genome).
- Sometimes has a lipid envelope surrounding...
Wide variety of Illness cause by viruses

• Many make people sick and can result in death

• 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 Transmit Viruses...Means of Spread

- **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—Reovirus (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)

- **Zoonotic** – Transmission from animals to humans
  - Swine Flu, Ebola
Basic Viral Replication

How viruses break in, and break your cells to replicate
Basic Replication Overview – Obligate Host Replication
How do viruses infect your cells?

• Cells take in resources from the outside world via a process known as **endocytosis** (protein import)

• All cells do this at all times, this is how cells “drink” or take up “food” particles

• Process is mediated by **receptors** on the cell surface
  • **Receptors** on proteins or “food” attach, and the particles are brought into the cell
  • **Very specific**...think “lock and key”
  • Certain Receptors can see only certain particles

• **Viruses mimic this process to gain entry**
What does this look like...
Viruses use mimicry to get into your cells...

- Many Viruses infect cells in the respiratory tract
- For example: Influenza Hemaglutinin (target) binds to Salic Acid Receptor on cells that line the respiratory tract
  - Delivers viral genome into cells...replication occurs
  - Influenza infects these cells, and causes symptoms of disease
  - Cell is now infected...and virus can replicate spread to other cells

- Interaction between Target and Receptor determines what cell type that viruses infect
Influenza Overview
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
  • Best defense is to get your Flu Shot every year
  • Infect epithelial cells in the reparatoratory tract (tropism)

• Member of the Orthomyxovirus Family
• Genome composed of 8 RNA strands (RNA virus)
Flu Symptoms

Symptoms of Influenza

Central
- Headache

Systemic
- Fever
  (usually high)

Muscular
- (Extreme) tiredness

Joints
- Aches

Nasopharynx
- Runny or stuffy nose
- Sore throat
- Aches

Respiratory
- Coughing

Gastric
- Vomiting
Aerosol or Fomite Transmission of Influenza
Typical Seasonal Influenza Tracking

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System
Data as of October 15, 2015 through week ending September 26, 2015

Epidemic Threshold
Seasonal Baseline

% of All Deaths Due to P&I

MMWR Week

2011 2012 2013 2014 2015
40 50 10 20 30 40 50 10 20 30
Recurring and Frequent Influenza Pandemics
Spanish Flu Pandemic
Spanish Flu Pandemic 1918

- Killed between 20 and 40 million people—more than 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
Notable Flu Strains over time

**Figure**
Recorded human pandemic influenzas since 1885 (early sub-types inferred)

- **H2N2**
  - 1895: Russian influenza (H2N2)
  - 1900: Old Hong Kong influenza (H3N8)
  - 1918: Spanish influenza (H1N1)
  - 1957: Asian influenza (H2N2)
  - 1968: Hong Kong influenza (H3N2)
  - 2009: Pandemic influenza (H1N1)

- **H1N1**
  - 1915-1925: Pandemic (H1N1)
  - 1955-1965: Pandemic (H1N1)
  - 1975-1985: Pandemic (H1N1)
  - 2005-2010: Pandemic (H1N1)

Source: European Centre for Disease Prevention and Control (ECDC) 2009
Reproduced and adapted (2009) with permission of Dr Masato Tashiro, Director, Center for Influenza Virus Research, National Institute of Infectious Diseases (NIID), Japan.
H1N1 Swine Flu: Similar Influenza Symptoms in Pigs
Many animals are infected by Influenza
Influenza Mutates Over Time – Mixing of human and animal flu strains
H1N1 Swine Flu: Result of Antigenic Shift

• 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
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
Ebola

...also has an animal reservoir...
Discovery of Ebola Virus in 1977

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

K. M. Johnson
J. V. Lange

P. A. Webb
F. A. Murphy

Virology Division, Center for Disease Control, Atlanta, Georgia 30333, U.S.A.
Distribution: Ebola Virus Families

- Endemic to regions of Africa; also isolated in Philippines from Non-human primates
  - **Ebola and Sudan viruses:**
    - Congo (1995, 81%; 2007, 71%),
    - Sudan (1976, 53%),
    - Uganda (2000, 2008, 53%),
    - Zaire (1976, 88%) 
  - **Marburg virus:**
    - Uganda (2008, small outbreak),
    - Congo (1988, 83%),
    - Angola (2004, 90%)

Figure and data: CDC
West Africa outbreak of 2014-2015

• 13,540 cases in Guinea, Sierra Leone, and Liberia (data as of Fall 2014; peak epidemic)
  • 4,941 deaths

• Cases in Nigeria, Spain, US, Mali and Senegal

• Additionally, separate outbreak in Dem Rep of Congo
Current treatments for Ebola

• Supportive care:
  • Balancing the patients' fluids and electrolytes
  • Maintaining their oxygen status and blood pressure
  • Treating patients for any complicating infections
  • Death typically results rapidly without supportive care
  • Best treatment is to keep patients hydrated

• Some experimental therapies still working their way through clinical trials
Ebola Treatment 37 years after discovery...not much has changed

1977

2014
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-1
    - Skin (sweat)
    - Saliva
    - Urine
    - Feces
    - Breast milk
    - Semen
    - Vaginal fluid
Zoonotic Cycle and Reservoir...infections likely to continue if animal reservoir is maintained
Also true for mosquito born viruses...zika/dengue/chickungunya/west nile
HIV – How Do we Prevent Viral Infection?

...zoonotic transmission...understanding HIV prevention...
Evidence suggests HIV jumped into the human population from Chimpanzee

- Similar virus in Apes known as Simian Immunodeficiency Virus (SIV)

HIV is a genetically diverse retrovirus

- Three groups: M (Major), N (non-M, non-O), and O (outlier)

Each group represents a distinct cross species transmission of SIV_{cpz} into the human population
Global Infection Rates
What characterizes AIDS?

• Case Study: 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 (Zidovudine)

• 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

• HIV quickly mutated – resistant to antiviral drugs
HAART—triple drug cocktail

- **Highly Active AntiRetroviral Therapy**
- Use three or more drugs at one time to completely stop viral replication
- Drugs are so powerful that they prevent HIV from becoming resistant to therapy
- Taken daily, makes HIV a “chronic condition”
Multiple Drugs Available for HIV Treatment and Prevention
More Limited Options for Influenza Treatment
Antivirals

• Lots of development activities for various infections
• Recent success in some: HIV, HCV (HIV latency still prevents total cure)
• Resistance and limited options in others: Influenza
  • Lack of combinations increases chance of 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?
Vaccines: Gold Standard for the Prevention of Infection
Edward Jenner

• Known as the father of Modern Immunology
• Famous experiment performed 1796
  • Smallpox is the scourge of the 18th century world (kills many in highly populated areas)
  • 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)
However, there has always been backlash against vaccination

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

2017: Nothing new, but still not helpful for human health...
Vaccination is incredible powerful and effective
Importance of Vaccination...how does it work?

- Vaccination and Sanitation have been two of the most important contributions in public health
- Notable achievements in public health over the past century
Herd Immunity

• Basic idea came from groups of animals—hence “herd”

• Basically, farmers could vaccinate a portion of their animals (less cost) and end up with full protection (great!)

• Same principle works in human populations
Power of Vaccines

- 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)
**Childhood Vaccinations: Global Success, vast reduction in childhood diseases**

<table>
<thead>
<tr>
<th>Vaccine given</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>4–6 years</th>
<th>11–12 years</th>
<th>14–16 years</th>
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<tbody>
<tr>
<td>Diphtheria–tetanus–pertussis (DTP/DTaP)</td>
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<tr>
<td>Inactivated polio vaccine</td>
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<tr>
<td>Measles/mumps/rubella (MMR)</td>
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<tr>
<td>Pneumococcal conjugate</td>
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<tr>
<td><em>Haemophilus</em> B conjugate (HIBC)</td>
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<td>Hepatitis B</td>
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<tr>
<td>Varicella</td>
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More work to be done...

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated annual mortality</th>
<th>Estimated annual incidence</th>
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<tr>
<td>Malaria*</td>
<td>1,086,000</td>
<td>300–500 million</td>
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<tr>
<td>Schistosomiasis</td>
<td>14,000</td>
<td>no numbers available</td>
</tr>
<tr>
<td>Worm infestation</td>
<td>16,000</td>
<td>no numbers available</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,498,000</td>
<td>~8 million</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>2,213,000</td>
<td>~4,100 million</td>
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<tr>
<td>Respiratory disease</td>
<td>4,039,000</td>
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<tr>
<td>HIV/AIDS</td>
<td>2,673,000</td>
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<tr>
<td>Measles†</td>
<td>875,000</td>
<td>~44 million</td>
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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 strain results in “brand new viruses”
- Constant battle of evolution of virus and host
- Viral therapy is most effective in combination...reduced chance of mutation

- Zoonotic transmission is a key factor is viral epidemics and pandemics
- Also maintains infection cycles – 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?

DON’T GET THE FLU.
DON’T SPREAD THE FLU.
GET VACCINATED.

cdc.gov/flu