Emerging New Infectious Diseases

Emerging and New Infectious Diseases
- New pathogens that were previously not identified became widespread after HIV infection (AIDS) due to damaged immune systems.
- Previously known diseases, but less frequent, continue to occur with increased incidence and/or showed changes in their epidemiological characteristics
  - E.g. TB, Cryptococcosis, PCP

Opportunistic Infections with HIV
- The following are the largest contributors to newly emerging infections
  - Tuberculosis: Risk of primary progressive TB and lifetime risk of progressive disease with HIV infection 5x that of without HIV.
  - Cryptococcosis: meningitis with this rare infection became the hallmark of HIV/AIDS
  - Kaposi Sarcoma: Caused by HHV-8 increased dramatically
  - Pneumocystis carinii Pneumonia: Hallmark of AIDS before the discovery of HIV
  - Other Infections: Cytomegalovirus, Varicella Zoster, Mycobacterium avium

Emerging & Re-emerging IDs
- New appreciation for IDs since 1980s
  - AIDS and related diseases (TB)
  - Lyme disease
  - Ebola & Marburg Hemorrhagic Fever
  - Dengue
  - Hantaviruses
  - West Nile-like Encephalitis
  - Avian Flu/H1N1
  - SARS
  - MDR & XDR tuberculosis
  - Cholera
  - Zika

Zika Virus Infection
- Viral infection recently implicated in Microcephaly and Guillain-Barré Syndrome
- Zika virus isolated in 1947 in monkeys in Zika Forest in Uganda
- First recognized in humans in 1952 in Uganda and Zaire; Large outbreak in 2007 in Yap Island in Micronesia
- 1.5 million infected in Brazil with ~5,280 cases of Microencephaly; Epidemiological link is “a smoking gun”
- Thus far, 41 Microcephaly out of 462 confirmed cases (8.87%); Epidemiological link is “a smoking gun”
### Ebola & Marburg Hemorrhagic Fever
- Recently emerging viruses of primates
- High infectivity and mortality rates
  - Ebola in Zaire in 1976 with CFR of 78%
  - MHR in Angola in 2005 with CFR of 88%
  - Ebola in W. Africa in 2014-15 with CFR of 53%
- Human-to-human, recent phenomenon
- Both infection highly transmissible through body fluids, mainly blood
- Infection is reduced by universal precaution
- Immune serum developed from survivors is used to boost immunity after infection

### Hantaviruses
- First noted in Korean war (1951) as KHF
- 3,000 troops infected with CFR of 5%
- Etiologic agent not identified until isolated from striped mouse in 1976
- In 1993, 100 cases were noted in NM, AZ, CO, UT with CFR of 5%
- Disease was characterized by interstitial pneumonitis with pulmonary failure

### Severe Acute Respiratory Syndrome (SARS)
- Epidemic started in 2003 in China
- Caused by the SARS Coronavirus
- Started in live civet cat “wet market” dealers
- Soon 8,450 infected in 26 countries with 850 deaths (CFR=10%)
- Infectious during symptomatic phase only
- Effective PH measures, 1) Isolation of the sick and quarantine of healthy contacts, 2) Universal precautions, and 3) Effective surveillance controlled the epidemic

### Cholera (Example of re-emergence)
- Epidemic occurred in S. America in 1991 after >100 years of absence
- A new strain of cholera, *V. cholera* 0139, emerged with no cross-immunity with the classic *El Tor V. cholera* 01
- Soon >2x10^5 cases occurred in SE Asia and 20x10^3 cases in Africa
- CFR in Africa 60% while in S. America it was 1%, the difference being due to oral hydration and good diagnosis in the latter

### Emerging Infections & Promoters
- Some of the factors favoring emergence
  - **SARS**: Human contact with exotic animals
  - **Anthrax**: Bioterrorism
  - **Hantavirus**: Climate change ↑ mice pop.
  - **Dengue**: ↑ Global travel, Urbanization
  - **Ebola, Marburg**: ↑ Contact with primates
  - **Influenza**: Integrated pig-duck agriculture
  - **E. coli** 0157:H7: Global distributions of food
  - **Malaria**: ↑ Population, ↓ use of insecticide
  - **Cholera**: El Niño climate change
  - **MDR TB**: Rx Misuse, Crowding prisons
  - **Rift Valley Fever (RFV)**: Dams, Irrigation

### Factors in the emergence of IDs
- Population growth
- Speed and ease of travel
- Economic changes
  - Dam building
  - Relocation of animals
  - Expansion into new areas
- Bioterrorism
- Inadequacy of public health infrastructure
- Global climate change
- War and Societal disruption (Swine Flu, 1918-19)
- Increase in Day Care and Nursing Homes
- Antibiotic use and Abuse
Factors in the emergence of IDs
(...continued)
- Increased susceptibility of the human host
  - AIDS, Cancer, Immune-compromising conditions
  - Nutritional deficiencies
  - Chronic diseases
- Construction of Dams (over 75 meters high)
- Agricultural use of antibiotics in animal feed
- Change in the ecosystem from manmade activities
  - Pesticides
  - Deforestation
  - Genetically modified foods

Societal Issues in the emergence of IDs
- Poverty
- Malnutrition
- Unsafe Water
- Aging of population
- Refugee populations
- Human behavior
- Urbanization

Climate Change—Greenhouse Gases (CO₂, CH₄, NO, and water vapor)

PHS Response (IOM, 1991)
- Need for increased surveillance
- Expansion of nosocomial infection surveillance
- Development of computerized database on ID surveillance, vaccine and drug availability
- Increased research on factors leading to emerging disease, expansion of the EIS program
- Funding for program for PH and epi training
- Development of a means of stockpiling vaccines
- Ensuring availability of critical antibiotics
- Licensing and developing new pesticides for IDs
- Focus on education to enhance behavioral changes

Conclusion
- New infectious agents continue to emerge and old ones to re-emerge with brute force due to environmental changes, population growth, and intentional cultivation of organisms for various purposes
- Increased awareness of new infections and efficient public health surveillance are the first line of defense
- Strengthening the public health system and implementing the IOM recommendation is critical for human survival
Healthcare Associated Infections

HAIs in the USA
- Healthcare-associated or Hospital acquired infections (HAI); Also Nosocomial Infection
- Estimated 2 million infections/Yr. (5-10% of persons hospitalized develop HAI)
- 100,000 deaths yearly
- Death occurring in hospitals
  - Contribute to 0.7-10%
  - Cause 0.1-4.4%
- Increased morbidity
  - 4 extra days in LOS & $2,100/patient
  - 6.5 Billion dollars annually

Risk Factors for HAIs
- **Host factors** —compromised immunity
- **Environment** —hospital is where the sick cluster, microorganisms abound, contamination of tools, unwashed hands, etc.
- **Technology** —new portals of entry for organisms (canula, central line, etc.)
- **Human factors** —cut back of highly trained personnel and substitution with less trained ones.

Host factors
- **Extremes of age**
  - 37.4% of infections in adults >60
  - Accounts for 24% of all discharges
- **Underlying conditions**
  - Immunosuppression
  - Diabetes

Environment
- **Proximity to other patients**
- **Inadequate ventilation**
- **Contamination of common equipment**
- **Exposure to contaminated water**
- **Presence of construction and renovation**
- **Unwashed hands of health care workers**

Technology
- **Sophisticated means of monitoring patients**
- **Provide new portals of entry**
  - catheters, ventilators, canula
  - Coag neg staph adhere to prosthetic devices, catheters
- **Altered normal host flora**
- **Increase antibiotic resistance**
Human factors
- Cost saving measures
  - Due to recent cutbacks, the number and skill of health care providers has decreased
- Busy units, omitting simple infection control practices
  - Hand washing, scrubbing
  - Increasing beds per room

Microbiologic factors
- Virulence factors
- Ability to survive in hospital environment
- Antimicrobial resistance
- Less virulent pathogens can cause disease in immunocompromised patients

Extrinsic factors
- Medical treatment and interventions
  - Placement of devices
  - Surgical procedures
  - Chemotherapy which weakens the immune system
  - Equipment with complicated reservoirs
    - Dialysis
  - Use of antibiotics which change normal flora

National Nosocomial Infection Surveillance (NNIS) system
- Established in the 1970s
- Estimates the type and number of infections
- Consists of 231 self-selected hospitals
  - Voluntary participation
  - Data collection using four standardized protocols
- What type of surveillance system?

Case definition
- An infection developing in a patient who has been hospitalized for 48-72 hours and was not incubating at the time of admission
- May be present upon admission if they developed during/prior to admission
- May not be identified prior to discharge

Most common pathogens
- Bacteria account for 90% and 10% by other microorganisms—*Candida albicans*, *Aspergillus*, and viruses.
- Common bacteria in NIs.
  - Staph aureus* 13%  (SSI, LRTI)
  - E coli 12%  (UTI)
  - Coag neg staph 11%  (BSI)
  - Enterococcus 10%
  - Pseudomonas 9%  (LRTI)
- Dependent upon the site of infection
* Red font indicate the most common bacteria by the CDC
Goals of NI Control Programs

- Reduce nosocomial infections
- Reduce the spread of resistant organisms
- Reduce cost of care and LOS
  - Estimated that 1/3rd can be prevented
  - Currently less than 1/10 are prevented

Increasing drug resistant pathogens

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - 1975: 2.4%
  - 1991: 29% in 2013~50%; 2016~60%
  - Life threatening and only respond to Vancomycin
  - Resulting in development of Vancomycin resistant organisms, such as enterococci
  - Currently, *S. aureus* with intermediate vancomycin resistance (VR enterococcus)
  - If fully resistant, there would be no treatment

Factors essential in decreasing nosocomial infections

- Surveillance
- Adequate numbers of trained infection control practitioners
- Reports of infection rates to practitioners
- An effective and trained infection control physician

Measures of Disease Incidence: Rate and Risk

- **Rate** is an instantaneous potential of a given quantity of an event (disease) to occur per unit change in another quantity (time) for a referent constant (K=10,000 people).
  - Varies between 0 to ∞
  - It does not reflect individual experience in the candidate population
    - E.g. Incidence rate of breast cancer in post-menopausal women 55 cases/year/10,000 population

Cumulative Incidence (CI)

\[ CI = IR \times T \]

CI is the proportion of a population at risk that will develop an outcome in a given period of time.

- Takes into account time observed for each person at the interval, i.e., Person-time (PT)
- Provides Incidence Density (ID) = \( \frac{1}{PT} \)

Measures of Disease Incidence: Rate and Risk (...2)

- **Risk** is the probability that a person develops a given health condition over a specified time conditional on not dying from other causes.
  - Varies between 0 and 1
  - It is dimensionless
  - Needs a temporal boundary as a qualifier
    - E.g. 5-year risk of developing breast cancer
Infectious Disease epidemiology BMTRY 713
(Lecture 27) Review Slides for Final Exam
April 26, 2017
Department of Public Health Sciences

Cumulative Incidence (CI) & Risk

In a stable dynamic population, the midpoint of a time interval approximates the midpoint average of that population.

If this assumption stays true, then CI can approximate the Risk for the observed time interval with the following formula.

\[ R_{\Delta t} = 1 - \exp[-ID \times \Delta t] \]

where exponent (e) refers to the mathematical constant 2.71828 indicating growth or decay over time.

Example of ID and Risk

- incidence rate of obstetrical infection after C-Section in Kilinga state over 5-year period

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Observed Cases</th>
<th>Person-Years (PY)</th>
<th>Computed Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Infections</td>
<td>ID (Yr. -1)</td>
</tr>
<tr>
<td>20-24</td>
<td>60,000</td>
<td>90</td>
<td>190,000</td>
</tr>
<tr>
<td>25-29</td>
<td>70,000</td>
<td>168</td>
<td>210,000</td>
</tr>
<tr>
<td>30-34</td>
<td>65,000</td>
<td>215</td>
<td>195,000</td>
</tr>
<tr>
<td>35-39</td>
<td>55,000</td>
<td>227</td>
<td>165,000</td>
</tr>
<tr>
<td>20-39</td>
<td>250,000</td>
<td>700</td>
<td>750,000</td>
</tr>
</tbody>
</table>

The 5-year risk of obstetrical infection in Kilinga State after C-Section is 1.87%.

Nutrition and Infectious Diseases

Malnutrition

- Malnutrition is a broad term commonly used as an alternative to undernutrition; technically it also refers to overnutrition.
- People are malnourished if their diet does not provide adequate calories and protein for growth and maintenance or they are unable to fully utilize the food they eat due to illness (undernutrition).
- They are also malnourished if they consume too many calories (overnutrition).

Malnutrition

- Compromised biological function due to inadequate intake, absorption, storage, and utilization of nutrients
- A syndrome associated with depletion of protein, CHO, and fat stores along with micronutrients (Vitamins & Minerals)
- Vicious cycle of malnutrition, infection, and decreased immunity
Micronutrients and Immunity
- Micronutrients (Vit C and E, Zn, Se) are strong antioxidants, prohibiting free radicals
  - Nutritional immunology
- Vit A –exerts a wide range of effect in the immune system—T&B Lymphocytes, cytokines expression
- Vit D—regulates Ca and P metabolism
- Vit E, Selenium, Iron, Iodine, Zn

Protein
- Protein malnutrition results in decline of albumin and globulin ratio
  - Essential aminoacids are building blocs for cellular structure
  - Antibody levels are inadequate in malnourished individuals and they react poorly to antigenic stimuli (vaccination)—a phenomenon known as anergy or immune unresponsiveness

What malnutrition does...
- Compromises immune function through a variety of mechanisms
- Poor response to therapy
- Increases comorbidities that weaken the body
- Induces cyclical loops of reaction that leads deterioration of the body’s defense system

Effects of ID on nutritional status
- Loss and redistribution of nutrients and micronutrients (e.g. diarrheal diseases)
- Accelerated rates of metabolism amd O₂ consumption
- Appetite suppression triggering catabolic process (i.e., body breaks down protein to energy)
- In prolonged infection, stored N and fat are used up causing wasted cachetic state

Malnutrition on Host Defense
- Affects the T-cell region of the thymus, spleen, and lymph nodes with depletion of T-lymphocytes leading to defect in immune functions
- Compensatory elevation of antibody levels due to high antigenic loads (especially in impoverished areas)
- Appears to have paradoxical roles since T-lymphocytes levels are suppressed that normally regulate antibody production

Malnutrition & Specific IDs
- Diarrheal diseases
  - Accounts for 19% of the global child mortality
  - Immune deficiency associated with malnutrition is a major risk factor for diarrheal diseases
  - Micronutrient deficiency in diarrheal diseases are: Vit A, D, B₁₂, folate, Cu, Fe, Mg, Se, and Zn
  - Some studies show declining mortality with supplementation of Vit A and Zn
Malnutrition & Specific IDs (...2)

- Lower Respiratory Tract Infections
  - Accounts for 19% of the global child mortality
  - Vit A deficiency is associated with pathologic alteration of mucosal epithelium of the respiratory tract (keratinization, loss of ciliated and goblet cells)
  - Epi studies show ↑ LRTI with ↓ Vit A level
  - No clinical improvement in LRTI with Vit A supplement in the short term

Malnutrition & Specific IDs (...3)

- Measles
  - Accounts for 2 million deaths despite effective vaccine (CFR=10-30%)
  - Lapses in immunization schedules, vaccine failure, problems in timing of vaccination are possible causes
  - ↓ Vit A levels are associated with fulminant forms of measles
  - Vit A supplementation reduces mortality of measles by 50%

Malnutrition & Specific IDs (...4)

- Malaria
  - Globally, 400,000,000 people are annually infected
  - Most common reemerging infection around the world due to global warming
  - ↓ levels of Vit A, Zn, Fe, folate attributed to fulminant forms of malaria in a population-based studies
  - Role of micronutrients in malarial infection are neglected in research

Indicators of malnutrition

- Under-five mortality rate (U5MR)
  - Underlying cause for 55% of the deaths in developing countries
  - Wide range in U5MR per 1,000:
    - 211−320 in Afghanistan, Niger, Angola, etc.,
    - 4−8 in Finland, USA, UK
  - 50% of childhood mortality in developing countries could be prevented by improving micronutrient intake
    - Vitamin A and Folate
    - Iodine
    - Zinc

Indicators of malnutrition (...2)

- Low-birth weight (2,500 gm or 5½ lb.)
  - 3–35 x increased perinatal mortality risk
  - Premature gestational age (<37 weeks) and intrauterine growth retardation are major determinants
  - Factors that appear to contribute are
    - Genetic and constitutional factors
    - Demographic factors (Race and Ethnicity)
    - Nutritional status
    - Smoking during pregnancy
    - Morbidity during pregnancy (e.g. malaria)
    - Multiple pregnancy, esp. high-order pregnancy

Indicators of malnutrition (...3)

- Maternal mortality
  - Death of a woman while pregnant or due to the pregnancy within 42 days of termination of pregnancy regardless of gestation
  - Expressed, maternal death/100,000 live birth
  - Major cause include
    - Severe anemia
    - Hemorrhage (Placenta Previa, Abruptio Placenta)
    - Eclampsia
    - Dystocia (difficult birth leading to uterine rupture)
    - Induced abortion (Late or ‘Botched’)
    - Infection and post-partum sepsis
Markers of Malnutrition
- Alterations in growth (stunted growth)
- Lower weight-for-age ratio (2 s.d. below population norm)
- Lower height-to-weight ratio (BMI)
  - \( \frac{\text{Weight}}{\text{height}^2} = \text{Quetelet Index} \)
  - <18.5: Underweight (for adults)
  - 18.5-24.9: Healthy Weight
  - 25.0-29.9: Overweight
  - ≥30.0: Obese
- Head and arm circumference (Age<5)

Tuberculosis
- Caused by *Mycobacterium tuberculosis*
- Suggestive identification in skeletons from 8,000-5,000 BC
- Additional evidence from Egyptian mummies
- Hypothesized it resulted from domestication of cattle

Impact of TB
- 1999, WHO identified TB as among the most serious threats to the world
- \( \frac{1}{3} \) of the population of the world latently infected
- 7-9 million new cases annually
- ~2 million deaths annually
Epidemiology

- Pandemic in occurrence
- Among the top ten leading cause of death in the world
- Second leading infectious cause of death
- 95% of all cases are in the developing world, most victims between 15 and 55

Global variation in disease

- US and Europe
  - Low prevalence
  - Lowest in infancy, increasing with age
- Latin America and Caribbean
  - Higher prevalence, incidence, and mortality
  - Two peaks in incidence and mortality
    - Infancy TB >Males
    - Early adult TB>Females; Age 35 TB >Males

Global variation in disease (2)

- Asia and Africa
  - 60-70% adults have latent infection
  - Two peaks in incidence
    - Infancy TB >Males
    - Late adolescence TB >Females
    - Rates of women exceed men until age 60

The Organism

(see table 14-1 in Nelson et al. for the full list)

- Four are usual human pathogens
  - Mycobacterium tuberculosis (1882 Koch)
  - M. africanum
  - M. canettii (1969; 1997)
  - M. bovis
  - M. kansaii
  - M. leprae—causes leprosy
  - M. avium—opportunistic infection in AIDS

Clinical Manifestations

- Initial latent infection
  - Asymptomatic
- Clinical disease
  - Usually pulmonary (80%)
  - Extrapulmonary
    - Can strike almost any organ system
      - Pericardium, spine, GI tract, skin, kidney, lymph nodes
    - More common in children and immunocompromised

Clinical manifestations (2)

- Active disease
  - Variable intensity
  - Non-specific symptoms
    - Cough, with or without bloody sputum, fatigue, anorexia and weight loss, fever, sweating and/or chills, chest pain
    - Extrapulmonary – fatigue and night sweats, other symptoms specific to organs
Diagnosis

- Latent
  - Asymptomatic, based on clinical tests
  - Tuberculin skin test (TST)—purified protein derivative (PPD, Mantoux test)
    - Intracutaneous injection
    - Diagnosed by the size of the zone on induration surrounding the injection site 48-72 hours
    - >10 mm induration strongly suggestive
    - Identifies disease in 98% of positives, only 5% of negatives
    - BCG vaccine can produce false positive

False negative tests

- Individuals with HIV or cancer
- Malnutrition
- Viral infection, such as measles
- Actively infected may have neg test
- Immune suppresion

Cut points for positive test

- Dependent upon the size of induration, prior probability of infection, and clinical consequences of misreading the result.
- >=5 HIV+, close contact with known case
- >=10 Medical factors increase risk, high prevalence area
- >=15 Low risk

Active disease

- 5-10% with latent infection develop active disease
- Diagnosis is based upon assessment of risk, clinical findings and symptoms, PPD test, chest X-ray, sputum culture
- Where medical tests are unavailable, diagnosis depends upon clinical symptoms and examination of sputum

Current treatment approach

- Slowly progressive disease; longer Rx
- Some drugs only kill actively growing bacteria
- Need to be taken for at least 6 months
- Risk of mutation with single drug therapy
- Usual treatment 2 or more drugs
Patient adherence
- Main hurdle in TB therapy
- If non-adherent there is a risk of an antibiotic resistant strain developing
- Directly observed therapy (DOT)
- 6 month treatment, relapse 5% or less

Natural History & Bacteriology
- Moderately infectious
  - 20%-30% of exposed become infected
  - Can remain dormant for 20-30 years
  - 5%-10% develop active disease, the rest have latent disease
  - 5%-10% of those with latent disease develop active disease (reactivation TB)
    - Facilitated by malnutrition, HIV, other medical

Impact of natural history on population
- Reservoir of latent infection (stage 1)
- Development of active infection (stage 2)
- People with active infection or reactivation transmit disease to others (stage 3)
  - Impacted by prevalence of HIV
  - Average of 10 contacts infected before case is treated
  - 5-10% will develop TB in 12 months
  - Transmit disease to their contacts

Transmission of TB
- Airborne via respiratory tract
- People with active disease discharge minute particles of sputum when coughing, talking, sneezing, singing
- Smaller droplets are suspended in the air for long time periods
- Inhaled by uninfected people

Infectivity of pulmonary TB
- Function of
  - Virulence of the bacteria
  - Frequency of cough
  - Degree of pulmonary infiltration
  - Bacterial load in the sputum

Extrapulmonary TB
- Enters the body through mucous membranes in GI tract, genitourinary tract, conjunctiva, breaks in the skin
- Causes infection at the site of entry which can remain localized or spread to other organs
- Rarer transmission, esp. in developed countries
Risk factors associated with infection
- Severity of disease in the index case is the most important factor
- Social factors
  - Crowding and poverty
  - May be related to probability of exposure
- Risk is a function of exposure

Risk factors associated with development of disease
- 5%-10% of infected become diseased, usually within the first 2 years
  - 1% in the first year
  - 0.07% 8-10 years later
- Age, cohort effect
- Gender
  - Peak in women during reproductive years maybe hormonal
  - Peak in men at older ages a function of decrease immunity due to smoking and drinking

Risk factors associated with development of disease (2)
- Genetics
  - Twin studies – infection of second twin more likely if monozygotic
  - Some correlation of TB response and blood type
    - OR for Types AB and B vs. O and A =3
  - Lean body build
  - SES, but may reflect different exposure

Risk factors associated with development of disease (3)
- Stress (Danish study)
  - Lowest in married men
  - Intermediate in single and widowed men
  - Highest in divorced men
  - Similar results but less dramatic for women
  - Married people developed less severe disease
  - Poverty

Risk factors associated with development of disease (4)
- Nutrition
  - Specific micronutrients
    - Low vitamin A and selenium associated with increased risk of developing disease
  - Malnutrition
    - Higher among malnourished, thinner people
- Occupation
  - Silica in the work site, health care workers

Risk factors associated with development of disease (5)
- HIV infection and AIDS
  - Most potent biologic risk factor for developing TB
    - Reactivation is 3%-14%
    - New infection 40% of HIV + develop Tb within several years
    - Can occur even with relatively high CD4 counts
  - HIV epidemic severely undermines TB control, especially in developing countries
BCG vaccination

- Developed in 1921
- Common in Europe until Lubeck disaster
  - In 1930, 251/412 German children vaccinated contracted TB
  - Accidentally vaccinated with live, virulent culture
  - Decreased usage followed by increase in TB
  - Safe vaccine, efficacy range 22% to 85%
  - WHO standard vaccine, except US and Netherlands

Control strategies

- Case finding and treatment
  - Strong surveillance system, sufficient laboratory components, effective treatments (DOT), reliable supply of drugs
  - Goal is to identify 70% of smear positive patients and to treat 85% successfully
  - Current estimate is 1/3 of cases identified and treated

Epidemiologic basis of control

- Reproductive rate to be <1
- Developing countries
  - BCG vaccination
  - Case detection and treatment
- Preventive therapy
  - Treatment of latent disease reduces the risk by 60%-90%
  - Offering preventive treatment of high risk patients
    - Close contacts, HIV, recent converters

Increasing prevalence of drug-resistant TB

- 1994-1997
  - Patients without prior therapy 9.9%
  - History of therapy 35.6%
- Multi-drug resistance
  - Treatment is more toxic and expensive
  - Hot spots
    - Russia, Dominican Republic, China

Malaria

- Malaria is an intermittent and remittent fever caused by a protozoan parasite that invades the red blood.
- The parasite is transmitted by mosquitoes in many tropical and subtropical regions.
- People with malaria often experience fever, chills, and flu-like illness. Left untreated, they may develop severe complications and die
Population at Risk
- 3.4 billion people live in areas at risk of malaria transmission
- 106 countries at risk
- 207 million clinical episodes in 2012
- 110 million cases reported yearly
- 1-2 million cases are fatal annually
- 91% of the deaths are in Africa

Agent of the disease
- Protozoan parasites of the genus *Plasmodium*
- 5 phases of the life cycle involving the mosquito vector and human host
- Affinity for erythrocytes varies with species
- *P. falciparum* is associated with most virulence and highest mortality in endemic African countries

The female Anopheles mosquito feeding on a human arm

Asexual Life Cycle of Plasmodium
- Saliva of infected Anopheles enters host blood
- Sporozoites mature in the liver and attach to RBC receptor sites
- Lysis of the RBC releases mature sporozoites
- Clinical signs and symptoms are a result of this release of pyrogens
- Asexual division takes 48-72 hours

Sexual Life Cycle of Plasmodium
- Gametocytes are released as RBC’s are digested in the mosquito
- Gametocytes form zygotes which mature into sporozoites
- Migration of sporozoites to salivary glands of mosquito

Life Cycle of Plasmodium
- Extrinsic (sporogonic phase) takes 7-12 days
- Dependent on species and ambient temperature
- As temperature increases, length of developmental cycle decreases
Anopheles Mosquito and Plasmodium Protozoan

- Host feeding preferences
- Digestion rates
- Frequency of blood meals
- Biting and resting habits

Favored habitats for egg laying
Predators/enemies
Density of vectors related to humans
Survival probability of vector during extrinsic incubation

At Risk Host

- Infection depends on parasite transmission and availability of prophylaxis for susceptible
- Immune depends on number of infected
- Susceptible depends on number of immune

Immunity and Endemicity

- Climatic conditions that favor vector and parasite development contribute to a sustained infection rate among the population
- Seasonal climates allow loss of collective immunity

Host Response

- Intense and widespread immunological and cellular response
- Clinical response includes classic shaking chills, fever, sweats
- Childhood picture of P. falciparum include coma and convulsions, along with nonspecific stomach cramps, headache, cough, muscle aches
Host Immunological Response

- Humoral
  - Immunoglobulinemia
  - Antibody dependent cellular inhibition

- Cellular
  - Cytokine cascade defense
  - Reticulocytosis
  - Phagocytosis

Protective Host Factors

- Nutritional deficiencies
  - PABA, Mg., Pyridoxine, Riboflavin, Vit. C & E (Vitamin A supplementation helps combat disease)
  - Protein Energy Malnutrition
  - Iron deficiency anemia (value of treatment is greater than risk of intensifying disease)

- Sickle Cell Trait

Diagnosis

- ELISA/RIA
  - Presence of antibodies lack clinical relevance in endemic areas

- PCR
  - promising in drug trials

- Giemsa Stain
  - Dependent on life cycle at parasite stage
  - False positive in endemic areas

Treatment/Prophylaxis

- Drugs
  - Chloroquine (increasing resistance)
  - Amodiaquine
  - Chloproguanil and Dapsone (antifolates)

- Antimalarials protect against disease, not infection

Environmental Influences

- Climate variables are distant in the web of causation
- Risk assessments are difficult to predict
- Temperature and Rainfall were the only factors considered in this analysis

Temperature Influences

- Mosquito longevity
- Frequency of blood meals
- Incubation period of the parasite
Mosquito Longevity and Survival Probability
- Optimal is 20º-25º (C)
- Threshold is 16º (C)
- Minimum is assumed to be 9º (C)
- 0.90 at 20º (C)
- 0.04 at 40º (C)
- 0.82 at 9º (C)

Frequency of Blood Meals (Human Blood Index)
- Product of frequency and proportion of such meals from humans
- Depends on rate of digestion
- Digestion increases with ambient temperature

Basic Reproduction Rate ($R_0$)
- Average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible
- Measure of an individual parasite's reproductive potential
- $R_0 < 1$: Disease will die out
- $R_0 > 1$: Disease will spread indefinitely
- Allows calculation of critical density threshold of hosts necessary for parasite transmission

Malaria Transmission
- Entomologic Inoculation Rate (EIR)
  - Human host parameter
    - based on landing rate and sporozoite rate
- Vectorial Capacity (VC)
  - Vector parameter
    - based on vector density, blood meals taken, survival probability, and extrinsic incubation
- Epidemic potential
  - is reciprocal of vectors population’s critical density

Rainfall Criterion
- > 80 mm per month
- Minimum of 1.5 mm/day
- 50-60% relative humidity needed to survive
- relationship is poorly defined
Critical Density of Hosts for Malaria Transmission

\[ \left( \frac{N_2}{N_1} \right) = K \left[ \frac{-\ln(p)}{a^2 p^n} \right] \]

- \( N_2/N_1 \) = Number of malaria mosquitoes per human (Critical Density)
- \( p \) = survival probability of mosquito
- \( a \) = frequency of taking human blood
- \( n \) = incubation period in vector
- \( K \) = constant incorporating variables independent of temp.

- **Epidemic Potential** is the reciprocal of the critical density
  
  \[ \left( \frac{N_1}{N_2} \right)^{-1} \]

Other Influences

- Rising populations
- Deforestation
- Health care access
- Drug resistant parasites
- Wars resulting in mass migration
- Agriculture, commerce causing migration of non-immune into endemic areas
- Water development projects

Introduction to Emerging Vector-Borne Infections

- Several occurrence in the last two decades
- Facilitated through unique changes in human activity and the environment such as,
  - Increase ease of global travel
  - Rapid urbanization and density of human population
  - Profusion of nondegradable containers and tires

Emerging Vector-borne Diseases

Major Vectors of Vector Borne Diseases

- *Aedes aegypti* (Dengue, Zika, Yellow fever)
- *Aedes albopictus* (Dengue, Zika, Chikungunya)
- *Culex pipiens* (West Nile, St. Louis Encephalitis, filariasis)
- *Anopheles gambiae* (Malaria)

Introduction of *Aedes albopictus* to US

Tire shipment
West Nile Virus (WNV)
- Mosquito-borne virus that may often cause encephalitis or meningitis
- First isolated in 1937 from a febrile patient in the West Nile district of Northern Uganda
- Spreads to humans by the bite of an infected mosquito
- A mosquito becomes infected by biting a bird that carries the virus
- Hence, birds are the reservoir and amplifying host (increasing pathogen level) of WNV
- In addition to humans, horses are infected

Epidemiology
- WNV is the prototype of the emerging vector-borne infection in the Western Hemisphere
- It has also been recognized in eastern Europe, the Middle East, former Soviet Union, South Asia, and Australia
- Seasonal epidemic in North America

Risk Factors
- Overall low risk
  - <1% of people bitten by mosquitoes
- Spending time outdoors
- People >50 at risk for more severe disease
- Risk from medical procedures is low
- Pregnancy and nursing do not increase risk

Some Possible Pathways of Introduction of WNV in the US
- Infected human host (remote possibility)
- Human-transported vertebrate host
  - Legal/Illegal
- Human-transported vector(s)
- Storm-transported vertebrate host (bird)
- Intentional introduction (terrorist event)

Symptoms and Signs
- 3-14 days after exposure (Incubation)
- No Symptoms in Most People. (80%)
- Mild Symptoms in Some People. (20%)
  - Fever, headache, myalgia, nausea, vomiting, and sometimes swollen lymph glands or a skin rash on the chest, stomach and back, typically lasting a few days
- Serious Symptoms (encephalitis) (0.67%)
  - High fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness and paralysis. These symptoms may last several weeks, and neurological effects may be permanent.
### Transmission
- Bite from infected mosquitoes
  - Basic transmission cycle involves mosquitoes feeding on birds infected with the West Nile virus
  - Infected mosquitoes then transmit West Nile virus to humans and animals when taking a blood meal
- Transfusions and transplants
- Perinatal
  - Vertical transmission
  - Breastfeeding

### Diagnosis
- Clinical symptoms
  - High fever, confusion, muscle weakness, and severe headaches
- Have been in an area where WNV is present
- Antibody test—blood/Cerebrospinal fluid
  - May not be positive when symptoms first occur; however, the test is positive in most infected people within 8 days of onset of symptoms

### Treatment
- No specific treatment
- Seeking clinical support early in the course of the disease may reduce serious complications
- Severe cases, supportive care
  - IV fluids, ventilation, nursing care

### Prevention
- Use insect repellents containing DEET
- Stay indoors at dawn and dusk
- Wear light colored clothes
- Have good screens on windows
- Eliminate breeding sites
- Dead bird alert
  - Report dead birds to local health department
  - Do not touch the bird with bare hand

### Yellow Fever
- The yellow fever virus is in the genus *Flavivirus*, in the family *Flaviviridae*.
- It is transmitted to humans through the bite of infected mosquitoes
- Illness ranges in severity from a self-limited febrile illness to severe hepatitis and hemorrhagic fever
- The disease is diagnosed based on symptoms, physical findings, laboratory testing, and the possibility of exposure to infected mosquitoes.
- There is no specific treatment for yellow fever; care is based on symptoms.

### Epidemiology Yellow Fever
- It is a very rare cause of illness in U.S.
- The last epidemic of yellow fever in North America occurred in New Orleans in 1905
- Many acquire the disease as travelers to endemic areas without being vaccinated
- As in WNV, risk of infection is through the bite of an infected mosquito
Infectious Disease epidemiology BMTRY 713
(Lecture 27) Review Slides for Final Exam

April 26, 2017
Department of Public Health Sciences

Yellow Fever Transmission
- Transmitted in "jungle cycles" between non-human primates and mosquitoes in S. America and sub-Saharan Africa.
- Humans can acquire yellow fever from jungle mosquitoes.
- Peridomestic transmission from humans to mosquitoes, leading to other humans in "urban cycles" causing yellow fever epidemics in cities and towns of tropical America and Africa.
- Currently, yellow fever transmission occurs almost exclusively in areas of sub-Saharan Africa and South America.

Yellow Fever Early Symptom/Signs
- Patients with yellow fever may be viremic for 3 to 6 days before demonstrating symptoms.
- Initial symptoms include fever and chills, severe headache, back pain, general muscle aches, nausea, fatigue, and weakness.
- This phase may be followed by a short period of symptom remission.
- Hepatic coagulopathy produces hemorrhagic symptoms, including hematemesis, epistaxis, gum bleeding, petechial and purpuric hemorrhages.
- Deepening jaundice and proteinuria frequently occur in severe cases.

Late Stages of Yellow Fever
- Hypotension, shock, metabolic acidosis, acute tubular necrosis, myocardial dysfunction, and cardiac arrhythmia. Confusion, seizures, and coma can also occur.
- During epidemics, case-fatality rates 15% to >50% can occur in unvaccinated populations.
- Secondary bacterial infections and kidney failure are complications.
- Symptoms of weakness and fatigue may last several months in people who recover.
- Those who recover from yellow fever generally have lasting immunity against subsequent infection.

Yellow Fever Prevention
- Avoid Mosquito Bites
  - Use Insect Repellent—use an EPA-registered insect repellent (e.g., DEET, picaridin or oil of lemon eucalyptus).
  - Wear Proper Clothing—wear long-sleeves, long pants, and socks when outdoors.
  - Avoid Peak Mosquito Hours—peak biting times for many mosquito species is dusk to dawn, except for Aedes aegypti that bites during daytimes.
- Obtain Vaccine if Recommended
  - Persons aged ≥ 9 months traveling to or living in endemic areas of S. America and Africa should be vaccinated.

Zika Virus Infection
- Aedes aegypti (Dengue, Zika, Chikungunya, Yellow fever)
- Aedes albopictus (Dengue, Zika, Chikungunya)

Zika Virus Transmission Cycles
- Sylvatic (jungle) cycle
- Epidemic (urban) cycle
Zika Virus Epidemiology
- First isolated from a monkey in Uganda in 1947
- Prior to 2007, only sporadic human disease cases reported from Africa and southeast Asia
- In 2007, first outbreak reported on Yap Island, Federated States of Micronesia
- In 2013–2014, >28,000 suspected cases reported from French Polynesia

Zika Virus in the Americas
- In May 2015, the first locally-acquired cases in the Americas were reported in Brazil
- Currently, outbreaks are occurring in many countries or territories in the Americas, including the Commonwealth of Puerto Rico and the U.S. Virgin Islands
- Spread to other countries likely

Zika Virus in the Continental United States
- Local transmission of Zika virus has not been reported in the continental United States
- Since 2011, there have been laboratory-confirmed Zika virus cases identified in travelers returning from areas with local transmission
- With current outbreaks in the Americas, cases among U.S. travelers will most likely increase
- Imported cases may result in virus introduction and local spread in some areas of U.S.

Zika Virus Clinical Disease Course and Outcomes
- Clinical illness usually mild
- Symptoms last several days to a week
- Severe disease requiring hospitalization uncommon
- Fatalities are rare
- Guillain-Barré syndrome reported in patients following suspected Zika virus infection
  - Relationship to Zika virus infection is not known

Zika Virus and Microcephaly in Brazil
- Reports of a substantial increase in number of babies born with microcephaly in 2015 in Brazil; true baseline unknown
  - Zika virus infection identified in several infants born with microcephaly (including deaths) and in early fetal losses
  - Some of the infants with microcephaly have tested negative for Zika virus
- Incidence of microcephaly among fetuses with congenital Zika infection is unknown

What is Microcephaly?
- Clinical finding of a small head when compared to infants of same sex and age
- Measured by head circumference (HC) or occipitofrontal circumference (OFC)
- Reliable assessment of intracranial brain volume
- Often leads to cognitive and/or neurologic issues
- Difficult birth defect to monitor because of inconsistent definition and use of terminology

Diagnostic Testing for Zika Virus
- Reverse transcriptase-polymerase chain reaction (RT-PCR) for viral RNA in serum collected ≤7 days after illness onset
- Serology for IgM and neutralizing antibodies in serum collected ≥24 days after illness onset
- Plaque reduction neutralization test (PRNT) for ≥4-fold rise in virus-specific neutralizing antibodies in paired sera
- Immunohistochemical (IHC) staining for viral antigens or RT-PCR on fixed tissues

Serology Cross-Reactions with Other Flaviviruses
- Zika virus serology (IgM) can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses)
- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus
Lyme Disease

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**Lyme disease Overview**
- Tick-borne zoonosis
- Most common vector-borne illness in US
- 33,097 cases were reported in 2011
- Multisystem, multistage disease
- Early diagnosis and treatment important to prevent future complications
- Currently **vaccine available** but off market

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**Lyme disease**
- Historical
  - 1975 first identified by mothers
  - 12 children diagnosed with juvenile rheumatoid arthritis
  - Sudden onset of pain and swelling of joint, flu-like symptoms
  - Some following a unique skin lesion described as **erythema migrans** (EM), possibly from a tick bite

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**Initial Investigation**
- EM skin rash
  - Occurred primarily in the summer, suggesting a seasonal disease
  - Consistent with the tick bite hypothesis
  - 2.8 cases/1,000 East side of the CT river and 0.1/1,000 on the West (East 28x higher)
  - Patients more likely to have animals
  - Deer tick (**Ixodes scapularis**) more abundant on the **East** than in the West side of town.
Life Cycle of *Ixodes scapularis*

- Complicated lifecycle; 2 years to complete
- Progression through stages:
  - Egg six legged Larval or seed tick
  - Eight legged immature nymph
  - Eight legged mature adult tick
- A blood meal is required at each stage
- Ticks do not fly, hop, or jump, they “quest”

**Life Cycle**

- Eggs are laid in the spring. After hatching as 6-legged larvae, they feed once in the summer.
  - White footed mouse is primary host
  - Other small animals (birds) are possible host
  - Can be infected with *Borrelia burgdorferi.*
  - Matures as 8-legged nymph and stays dormant through fall and winter
  - In the spring it feeds in blood meal on vertebrates and matures to 8-legged adult in fall and feeds on vertebrates and white-tailed deer.
  - Lays eggs in the spring to start lifecycle de novo

† Species name designated to the discoverer, Willy Burgdorfer

**Terminology**

- Reservoir species
  - Are species commonly infected with an organism and remain infectious to a vector for a prolonged period of time
- Vector competence
  - The inherent ability of an arthropod to become infected with an organism subsequently to transmit the infectious agent to a new vertebrate host

**3 Feeds & Patterns of Transmission**

- Larvae (infection free, can acquire it at first feeding, feed on mice)
- Nymph (usually feed on white-footed mice)
- Adult (usually feed on white-tailed deer)
- Vertical transmission is rare
- Importance is order of feeding
  - If Nymph feed before larvae hatches—higher prevalence of infection, NE US
    - Northeast US ↑ Prev. (50%)
    - Southeast US reversed feeding ↓ Prev. (1%)
    - Another factor in SE is bridge vector ticks that feed on lizards

**Borrelia burgdorferi**

- Spirochetes noted in midgut of most ticks
- Also identified in people with Lyme disease but not those without
- Bacteria, maintained in zoonotic cycles
- *Reservoir hosts* are hosts commonly infected and remain infectious for prolonged periods of time
- *White footed* mouse is preferred reservoir host
- *White tailed Deer* is responsible for maintenance of the vector
Clinical Stages of Lyme Disease

- **Early disease**
  - Characteristic skin lesion (Erythema cutaneus migrans)
  - Warm, not painful or pruritic
  - Flu-like symptoms
  - Resolve within 3-4 weeks

- **Secondary disease**
  - 1-6 months after exposure
  - Neurologic disease, including meningitis
  - Carditis,
  - Disseminated lesions

*Erythema Cutaneous Migrans (ECM) skin lesion*

Lyme Disease (2)

- **Late disease**
  - Occurs weeks to months after infection
  - Most common is arthritis, severe joint pain
  - Attacks last weeks to months
  - Can be recurrent
  - Characteristic skin eruption
  - Additional EM rashes
  - Chronic skin disease
  - Neurological and musculoskeletal sx
  - Bell’s palsy
  - Multiple sclerosis
  - Nerve pain, Polymorphic symptoms
  - Difficult to diagnose

Post-treatment Lyme Disease Syndrome (PTLDS)

- Symptoms of Lyme Disease lasting >6 months after completing 2-4 wks. course of antibiotics
  - Sometimes called Chronic Lyme Disease
  - The lingering symptoms are the result of residual damage to tissues and the immune system that occurred during the infection
  - These lingering symptoms might be due to “auto-immune” responses as noted in other infections like Campylobacter (Guillain-Barre syndrome), Chlamydia (Reiter’s syndrome), and Strep throat (rheumatic heart disease)
  - Longer course of antibiotics reduces risk of PTLDS

Diagnosis

- Early phase on signs and symptoms
  - Based upon characteristic clinical presentation, history of tick exposure

- Secondary phase
  - Combination of meningitis and neuropathy
  - Culturing organism, takes days to weeks
  - Antibody may be present but not always

Epidemiology of Lyme disease

- Endemic in several areas in US and Russia
- US
  - Northeast, upper Midwest, northern regions of the Pacific coast
  - Number of cases fluctuates yearly, depending upon acorn production
- Worldwide
  - Russia, north and central Europe
  - Variation in strains of borrelia

Confirmed Lyme disease cases by month of onset
United States, 2001-2010
**Risk Factors**
- Living, working, or vacationing in a woody, rural environment
- Probability of contracting disease in an endemic area – 0.012-0.05
- Transmission is dependent upon how long the tick is attached (at least 36 hours)

**Control measures**
- Control mice (reservoir species)
- Control deer (maintenance of vector)
- Control ticks (vector)
- Prevent exposure to vector
- Immunization against infection

**Vaccine**

**LYMErix vaccination**
- A Lyme disease vaccine is no longer available due to insufficient consumers (Low demand)
- 3 dose IM, initial, one month, 12 months
- Should be timed so 2nd and 3rd doses are administered weeks before transmission season
- Vaccine protection diminishes over time.
- Persons age 15-70
- Safety
  - Local reaction, no serious adverse reactions
- Efficacy “Intent to treat”
  - Against infection 2 doses 49%, 3 doses 76%
  - Against disease 2 doses 83%, 3 doses 100%

**Vaccine (2)**
- Decision to administer based upon the risk
  - Density of vector ticks in environment
  - Prevalence of *B. burgdorferi* in vector ticks
  - Extent of person-tick contact
  - Based upon geographic location and personal activities

**Vaccine (3)**
- Vaccination recommendations
  - Persons who reside, work, or recreate in areas of high or moderate risk
    - Frequent exposure – yes
    - Moderate exposure – possible
    - Low exposure – no
  - Persons who reside, work, or recreate in areas of low risk – no
  - Persons who travel to areas of high or moderate risk – possible
  - Future recommendations
    - Determine the safety and efficacy of the vaccine in children, individuals over 70
    - Identify the need for booster doses

**Viral Hepatitis**
Viral Hepatitis

- Five hepatic viruses, specifically hepatotropic

<table>
<thead>
<tr>
<th>Virus</th>
<th>Acronym</th>
<th>Transmission Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A**</td>
<td>HAV</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Hepatitis B**</td>
<td>HBV</td>
<td>Parenteral, (sex, perinatal)</td>
</tr>
<tr>
<td>Hepatitis C**</td>
<td>HCV</td>
<td>Parenteral, (sex, perinatal)</td>
</tr>
<tr>
<td>Hepatitis D**</td>
<td>HDV</td>
<td>Parenteral, (sex perinatal)</td>
</tr>
<tr>
<td>Hepatitis E*</td>
<td>HEV</td>
<td>Fecal-oral</td>
</tr>
</tbody>
</table>

Risk of chronic illness: * mainly acute; ** High chronicity

Other Viruses Affecting the Liver

- Non-hepatotropic viruses that may affect the liver include the following
- These viruses have other organs as primary target and are not defined as viral hepatitis

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<tr>
<td>Cytomegalovirus</td>
<td>HCMV</td>
<td>Contact w. body fluids</td>
</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>EBV</td>
<td>Contact w. saliva</td>
</tr>
<tr>
<td>Yellow Fever Virus</td>
<td>As is</td>
<td>Mosquito(s)</td>
</tr>
<tr>
<td>Ebola Virus</td>
<td>As is</td>
<td>Blood, body secretions</td>
</tr>
<tr>
<td>Lassa Fever Virus</td>
<td>As is</td>
<td>Mastomy’s rodent excreta</td>
</tr>
</tbody>
</table>

Hepatitis A

- RNA virus
- Transmitted by fecal-oral contact
- Incubation period = 2-4 weeks
- Stable in the environment
  - Remains infectious for 2-4 weeks at room temperature
  - Relatively resistant to free chlorine
- Single serotype, infection confers life-long immunity
- Only humans and non-human primates infected

HAV Clinical Features

- Prodromal constitutional symptoms; anorexia, nausea, abdominal discomfort, diarrhea, fever, jaundice
- No chronicity; yet 2-27% develop fulminant hepatitis in developed countries; 10-15% develop relapse within a few wks of recovery
- Severity of illness directly correlated with age
  - Many children asymptomatic or mild disease
  - Older adults and seniors severe illness
- Dx confirmed by presence of IgM antibodies

HAV Transmission Routes

- Fecal-oral
  - Contaminated food and water
  - Person-to-person
- Household or sexual contact is most commonly reported transmission route (22%)
- Rare via blood transmission
- Common source outbreaks (8%)
  - Food infected by food handlers; raw vegetables
  - Seafood (shellfish, clams, oysters, mussels harvested from sewage-contaminated body of water)
- Day-care centers (15%)
- International travel

HAV Epidemiology

- Based on seroprevalence, three levels of endemicity: High, Intermediate, Low
- High endemicity
  - 90% seroprevalence among adults, most children infected by age 10
  - Individuals of higher SES may not be infected until adolescence or adulthood
  - Africa, Asia, Central and South America, Middle East
HAV Epidemiology (2)
- Intermediate endemicity
  - 80% seroprevalence in adults
  - 20%-30% in children under 10
  - Major increase between ages 10 & 20
  - Italy, Greece, Thailand, Taiwan, Korea
  - Cohort effect, delayed infection increases morbidity

HAV Epidemiology (3)
- Low endemicity
  - Less than 10% in children under 10
  - 30%-50% seroprevalence in adults
  - Low SES is associated with higher rates of infection
  - Europe, US, Japan

HAV Epidemiology (5)
- HAV in US
  - Geographic variation
    - High—Among American-Indian population
    - Intermediate—US/Mexico border
    - Low—General US population
  - Cyclical incidence with 7-10 year peaks
  - Incidence rate highest under age 40

HAV Prevention
- Improved sanitation
- Passive-active immunization
  - Human immunoglobulin (IG) post exposure
  - Effectiveness: 100% if given before; 75-80% if given within 2 wks of exposure
- Active immunization
  - Two types of inactivated HAV Vaccines
  - Both are highly effective
  - Recommended for high risk population

HBV
- Double-stranded DNA virus
- Similar clinical features to HAV
- Individuals more likely to develop serum sickness
- Like HAV, severity of symptoms is directly correlated with age—the older, the worse is the symptom
- Chronicity is inversely related with age
  - Infants 80%, adults 1%-5% to develop chronic hepatitis

HBV and Primary Liver Cancer
- Studies on HBV oncogenic potential
  - Ecologic studies
    - Increased rates of primary hepatic cancer (PHC) with high HBV rates
    - 80% of the global occurrence of PHC is among persons with chronic HBV (WHO)
    - Reduction in liver cancer following immunization
  - Cohort study, 1976-85, Taiwan
    - HBV infection and subsequent liver cancer
      - HBsAg carriers at baseline, RR=104 to noncarriers
      - Synergistic carcinogenic potential w. Aflatoxin, a common contaminant of cereal and oils seeds
    - Analogy
      - Carcinogenesis of other hepadnaviruses
        - Ducks infected with hepadnavirus develop liver ca.
**HBV Diagnosis**

- **HBsAg (surface antigen)**—a glycoprotein coat of HBV circulating independent of the virus
  - Indicates active HBV infection
- **Anti-HBcAg (core antibody)**—Determines recency
  - Indicates past infection; HBcAg doesn’t circulate
- **HBeAg**—Conformational portion of core antigen
  - Assesses the potential infectivity of carriers
- **Anti-HBsAg (surface antibody)**
  - Recovery from acute or post immunization and detect the level of protective antibodies post vaccination

**Hepatic Tumor Marker Tests**

- **Alpha-fetoprotein (AFP) in blood**
  - AFP is found mainly in liver cancer and some germ cell tumors, which are rare
  - Specificity is increased with positive result on liver cancer linked infections HBV/HCV
  - False positive results may occur in pregnancy
- **Human Chorionic Gonadotropin (hCG)**
  - Hormone produced in human placenta that maintains the corpus luteum in pregnancy
  - Increased in cancer of the testicles

**HBV Transmission**

- Percutaneous blood exposure
  - Decreased in blood transfusion
  - Sharing IV needles
  - Acupuncture, tattoos, body piercing
- **Sexual intercourse**
- **Maternal-child transmission**
  - Perinatal period (90% likely infant infected)
  - Prevented by administration of HBV vaccine
- **Household contact**
  - Sharing razors, toothbrushes

**HBV Epidemiology**

- **Areas of high endemicity**
  - 8% or more chronic carriers
  - High rates of liver cancer
  - Account for 45% of the global population
  - China, Southeast Asia, sub-Saharan Africa, several areas in Arctic, including Alaska, Canada, Greenland

**HBV Epidemiology (2)**

- **Areas of intermediate endemicity**
  - Prevalence of carriers ranges from 2%-8%
  - 20%-60% past infection
  - Eastern Europe, Russia, parts of South America, India, North Africa
  - Account for 43% of world’s population

**HBV Epidemiology (3)**

- **Areas of low endemicity**
  - <2% chronic carriers
  - Prevalence 5%-20%
  - Account for 12% of population
  - Developed countries of North America, Western Europe, Australia, some parts of South America
**HBV Risk Factors**
- 41% Heterosexual contact
- 15% Injection drug use
- 9% Homosexual contact
- 2% Household contact
- 1% Health care employment
- 1% Other
- 31% Unknown
- Changing epidemiology to more IVDU

**HBV Prevention**
- Vaccination (HBV Vaccine)
  - Initial targeted strategy, largely ineffective
  - Universal immunization of children
- Post exposure vaccination
  - Used in conjunction with primary immunization for children born to infected moms
  - *Hepatitis B immunoglobulin* used as a post exposure prophylaxis and also as immunization
- Screening of HBV positives for AFP (alpha feto protein)—a tumor marker for liver cancer

**HBV-HIV Coinfection**
- Due to similar modes of transmission, coinfection is very common
- Common in sub-Saharan Africa & Asia
- In the US, chronic HBV infection occur 10-fold more frequently among HIV+
- Indolent HBV infection reactivates after HIV infection
- HBV infection aggravates hepatotoxicity of antiretroviral therapy and ↑ drug resistance

**HDV (Delta Hepatitis)**
- Defective single stranded RNA virus lacking a surface antigen; Hence, co-infection with HBV
- Similar clinical features
  - More severe infection with HBV co-infection
  - High case-fatality rate among pregnant women
- Transmission via blood exposure, sex, IVDU
- Highest prevalence in Columbia, Venezuela, Amazon basin, Africa, Romania, S. Italy
- Higher among drug using populations
- HBV immunization will prevent HDV
- Fulminant type rare, but 10x common with HBV

**HCV (Formerly Non-A Non-B)**
- Single-stranded RNA virus
  - \( \sim 1 \times 10^4 \) die each yr. In the US
- Mostly asymptomatic acute phase
  - Less than 20% show jaundice or sufficient symptoms to seek medical care
  - 85% persistent viremia persisting 10-50 yrs
- Often chronic infections
  - 2-25% develop liver cirrhosis and/or PHC
- Diagnosis
  - HCV antibody using an ELISA test
**HCV Clinical Features**
- Acute is generally asymptomatic
- <1/5 are jaundiced
- 85% have persistent viremia
- 2%-25% develop life-threatening cirrhosis or liver cancer
- Age-adjusted PHC rate in VA discharges show 3-fold increase associated with HCV infection

**HCV Transmission**
- Transfusion
  - Prior to screening, cause of 17% of HCV infections
- Sharing IVDU needles (38%)
- Needle stick injuries 3%-8% exposed to HCV patients
- Tattooing, bites, scarification rituals
- Sexual transmission
- Perinatal transmission 2%-8%
  - Doesn’t appear increased with breastfeeding

**HCV Epidemiology**
- 170 million individuals infected
- Several highly endemic areas
  - Prevalent among >40, uncommon <20
  - Egypt, 10-30%, possibly due to a parenteral schistosomiasis campaign
  - Several areas in Italy and Japan
  - Baltimore MD: 18% ER, 15% STD clinic

**HCV Treatment**
- Recent development
  - Treatment effectiveness depends on:
    - How damaged the liver is.
    - Other health conditions the patients have.
    - How much hepatitis C virus in the body.
    - The genotype of hepatitis C
  - Treatment more effective closer to the infection but most people don’t know they have hepatitis C infection

**HEV Transmission**
- Fecal-oral
  - Especially related to contaminated water
- Epidemics in Asian countries during monsoon season
- Less infectious than HAV

**HEV epidemiology**
- Rare in developed countries
- Endemic in developing countries accounting to 50% of acute Hepatitis
- Increased transmission at age 30
- Prevention
  - Improved sanitation
  - No current vaccines
Influenza

An acute infection with influenza virus
- Affects the upper (nose, throat, larynx) and lower respiratory tract (trachea, bronchi, lungs)
- Acute symptoms affect the entire body that include high fever, myalgia, weakness
- Symptoms are worse on the very young (age <1 yr.), older age ≥65, and persons with poor general health.

Influenza (…2/)

Unique epidemiology
- Annual epidemics
  - Attack rate of 10-30%
- Emerging infection with antigenic change
  - New antigenic variants
  - Causing global pandemics
- Epizootic
  - Avian and animal species
  - Influenza A is from avian species

Influenza virus

Three virus types were isolated and studied
- 1933 first isolated influenza A
- 1940 isolated influenza B
- 1947 isolated influenza C

Structure of A and B
- Contain 8 segments of single stranded RNA
- Codes for 10 proteins

Structure of Influenza C
- Contains 7 RNA segments and single glycoprotein

Proteins—2 types of surface proteins

Hemagglutinin (HA)
- Virulence determinant

Neuraminidase (NA)
- Antigenic determinant

Subtypes of influenza A are determined by these two surface antigens
- H1, H2, H3, ... N1, N2, N3, ...

Nomenclature

Virus strains are named with 5 designations
1) Virus type
2) Geographic site of first identification of the specific virus
3) the strain number from the isolating laboratory
4) the year of virus isolation
5) the virus subtype
- e.g. A Beijing/32/96(H3N2)
Clinical features of disease
- Abrupt onset of fever and respiratory symptoms, including
  - Rhinorrhea, cough, and sore throat
  - Myalgia and headache are common
  - Malaise and prostration
  - GI symptoms
    - Uncommon in adults
    - 50% of children

Clinical Features of Disease (2)
- Self limiting disease
  - 3-5 days
- Complications
  - Children: croup, otitis media
  - Common in elderly persons with chronic disease
  - Viral pneumonia
  - Secondary bacteria infection 2 weeks later

Mode of Transmission
- Respiratory
  - Aerosols of secretions spread by coughing, sneezing, and talking
- Direct contact
  - Kissing
- Indirect contact
  - Virus on inanimate objects
- Incubation 1-4 days
- Infectious one day prior to clinical symptoms - 4th or 5th day of illness

Diagnosis
- Difficulty distinguishing influenza from other respiratory viral infections
- Viral culture or serology

Epidemics and Pandemics
- Annual epidemics
- Three global pandemics in the 20th century, 4th on H1N1 recently.
- Initiation from a single geographic focus
  - Often in Asia or N. America
- Rapid spread along routes of travel
- High attack rates, low case-fatality rates
- Pandemic – multiple waves, infecting different individuals

1918 Spanish influenza
- Attack rate
  - 20-30% in adults
  - 30-45% in children
- Case fatality rate in adults
  - 15-50%
  - High in young adults (unusual pattern)
- 20-40 million people died
- First WW 15 million total deaths
Annual epidemics

- Typical pattern
  - High rates of school and work absences
  - Increase visits to health care facilities
  - Increase pneumonia and flu hospitalizations
  - Increase mortality from flu and pneumonia
- Given locality
  - Begins abruptly, peaks in 3 weeks, ends in 8 weeks
  - Can experience 2 sequential or overlapping epidemics

Geographic variation

- North America → Nov-March
- Southern Hemisphere → May-Sept
  - May be new strain which will infect the Northern Hemisphere the next year
- Tropics
  - May be associated with monsoons
  - Generally associated with winter
  - Lower temperature and humidity
  - Inside crowding

Factors Determining the Size and Impact of Epidemics

- Degree of antigenic variation of new virus
- Virulence of the virus
- Level of protected immunity in the infected population
- Average epidemics
  - Attack rates 10-20%, can be higher in subpopulations

Overall Mortality

- > 20,000 influenza deaths during nine epidemics from 1972 to 1991
- 90% in persons >65
- Average of 148,000 hospitalization

Surveillance Systems

- Sentinel physician network
  - 260 family practice MDs
  - October to May
    - Large number patient visits
    - No. of cases examined with flu by age
    - Report to CDC
  - Clinical case definition
    - Flu-like illness, fever >100°F, cough and sore throat

Surveillance Systems (2)

- Collaborating laboratory surveillance system
  - 70 WHO laboratories, 50 US labs
  - Oct- May
  - Report total number of specimens for respiratory virus testing, and the number positive for the flu
Surveillance systems (3)
- 122 Cities Mortality Reporting System
  - Selected cities with population >100,000
  - Report % deaths listed with pneumonia as underlying cause or associated with the flu
  - Graphically summarized in MMWR

Surveillance Systems (4)
- State and Territorial Epidemiologists Reports
  - Estimated influenza activity
    - No activity
    - Sporadic
    - Regional (outbreaks in counties that total <50% of population)
    - Widespread (outbreaks in counties that are >50% of population)

Antigenic Variation
- Type A causes most epidemics and all 20th century pandemics
- Type B is less severe
- Antigenic drift
  - Minor antigen changes
- Antigenic shift – the genetic change that enables a flu strain to jump from one animal species to another
  - Major genetic and antigenic changes

Antigenic Drift
- Frequent minor antigenic changes in the HA and NA surface antigens
- Due to high rates of spontaneous mutations in RNA viruses
- Approximate 1% annual change in the amino acid composition of HA
- After 10-30 years of circulation of a specific subtype, most members of a population have antibody to that subtype
  - Increases selection pressure for a new shift variant

Antigenic Shift
- Major change in HA, NA, or both
- Creating a new subtype
  - No antibody protection
  - Potential for a pandemic
- Create new variants by random reassortment of RNA segments
  - Co-infection by 2 strains can generate 254 variants
  - Mixing vessel most likely swine, in contact with birds and humans
Most new variants of the flu virus due to antigenic shift don’t have survival advantage and die out. Pandemic ensues when a shift variant, 
- retains ability to replicate well in humans
- efficiently transmissible between humans
- has new surface HA or NA determinants evading existing flu antibody profiles in human population

**Occurrence of Flu Pandemic**

**Pandemics**

- Usually the result of antigenic shift
  - Due to genetic reassortment between human and animal or direct transmission form animal to human
  - 1918 (unknown? swine flu) H1N1
  - 1957 (new avian HA & NA) H2N2
  - 1968 (new avian strain HA) H3N2
  - 1977 (1918-51 H1N1 strain, possibly escaping form a lab, attack rates >50% in people born after 1968)
  - 1997 (Not yet pandemic, new strain H5N1)

Two of the most commonly implicated strains for annual epidemic

**Hong Kong Incident**

- August 1997, CDC tested influenza strain one month after the case
  - 3 year old boy, died
  - H5N1, should not infect humans
  - No human immunity
  - Virus thrives in ducks
- November more cases occurred
- Identified spread among chickens
- Prevention - killing chickens

**Hong Kong 1997-1998**

- Direct transmission from animals to humans
- Human virus only had avian genes
- 18 ill in Hong Kong with 6 deaths
- Inefficient human to human transmission
- Potential for change in infectivity and future epidemic, perhaps new pandemic in the making
- Later this strain was identified as H5N1 and remerged in SE Asia in 2002-04
- Vaccines were developed

**Evolutionary theory**

- Avian influenza strains are the source for all influenza viruses in birds and mammals
- Rate of antigenic drift is low in birds
- Pigs have receptors for avian and human viruses
  - Mixing vessel
- 1918 pandemic thought to be early swine
  - RNA samples from victims buried in permafrost

**Prevention**

- Vaccines—Primarily to prevent infection
  - Early vaccines: Killed virus
  - Current vaccines: inactivated virus derived from virus grown on embryonated hen’s eggs
- Anti-viral drugs—Used prophylactically or for treatment
  - Potency measured by HA antigen content
  - Standard vaccine contains 15-20μg of HA antigen per dose
Vaccines
- Immunogenic in adults after 1 dose, 2 are needed in children
- 50-80% effective in preventing disease when virus matches vaccine strains
- US policy – vaccinate high risk individuals
  - 65+, chronic illness, children 6 mos-18 years on aspirin therapy, women >14 weeks pregnant in winter, health care workers, HIV infected, travelers, anyone who wishes to avoid influenza

Pregnancy
- 1918 excess mortality in pregnant women
- RR = 4.7 for influenza hospitalization of pregnant women in 3rd trimester relative to post-partum women
- 1,000 vaccinations would prevent 1-2 hospitalizations

Vaccines (2)
- Viral mutability from shift and drift
- Need a new vaccine each year
  - January: review circulating viruses
  - Identify the most likely strain
  - Seed viruses sent to manufacturers by Oct
  - 9 manufacturers produce 250 million doses annually

Vaccines (3)
- Impact of vaccination policy
  - Effective in reducing illness/mortality
  - Little impact on overall epidemic
    - Few people are vaccinated
  - Reduces otitis media in children 40%
  - Reduces respiratory illness in adults 20%
  - Policy to vaccinate school aged children to minimize the spread of flu epidemic
- Japan is vaccinating larger population

Vaccines (4)
- Vaccine side effects
  - Inactivated virus, soreness at injection site
  - Occasional fever, malaise, myalgia
  - Rare anaphylactic reactions
  - Slight increase in Guillain-Barre 1/1 million
    - Less risk than flu complications
    - 1976 swine flu vaccination

Vaccines (5)
- Live Attenuated Influenza Viruses (LAIV)
  - Recent development in flu vaccine, as effective as inactivated vaccine
  - Assorted from an epidemic strain and cold-adapted virus
  - 92% protective efficacy on confirmed strains
  - Licensed in 2004 as (FluMist®), administered as nose drops or aerosol
Antiviral Agents (AVAs)

- Two classes of AVAs
  - (Class I) M2 protein inhibitors—Amantadine & Rimantadine, effective only against Type A Influenza
  - (Class II) NA inhibitors—Zanamivir & Oseltamivir (Tamiflu®), effective against both Type A and B Influenza

Prophylactic use

- Class I: 70-90% effective in preventing illness
- Class II: 67-82% effective on any strain of flu

- Begun within 48 hours
- Reduce severity and duration

- Side effects
  - Nervousness, anxiety occasional nausea and anorexia

Preparing for the Pandemic (1)

- Seen as inevitable; Can occur at any time
- As of June 2006 global alert!!
- Estimated that the new virus (A/H5N1) would arrive in the US within 1-6 months of effective person-to-person transmission
- As of 2003, CFR of H5N1~57%
- Inadequate vaccine or drugs
- In the US alone, ~ 200x10^6 cases, 8x10^5 hospitalizations, 3x10^5 deaths in 3-4 months of the pandemic

Preparing for the Pandemic (2)

- 225 human cases of A/H5N1 since 2006
- Was detected in Europe, Middle East, and Africa in addition to SE Asia
- The virus has mutated substantially since 1997, exhibiting new surface antigens with virulence to humans
- The virus still lacks efficient transmissibility to humans and this has yet to happen but difficult to predict

Preparing for the Pandemic (3)

- WHO streamlined and enhanced global flu surveillance system (FluNet) with laboratory in 83 countries
- FluNet identifies human influenza rapidly
- Virologists are developing techniques to adapt newly arising strains of influenza virus for rapid production of virus
- Current strategy relies on speedy response to pandemics due to difficulty of reliable prediction

Preparing for the Pandemic (4)

- Steps to be taken should pandemic occur before sufficient antiviral drugs or specific doses of vaccine are available:
  - Isolation of those with influenza virus
  - Quarantine of their contacts
  - Banning of all public gatherings including schools, workplaces, shopping centers, churches, and bars
- A presidential executive order has already been signed on April 2, 2004 permitting the use of quarantine

Measles
Measles (Rubeola)

- An acute febrile illness resulting from infection with the measles virus
  - Highly contagious virus
  - Acute symptoms include high fever, runny nose, red eyes, followed by generalized rash
  - Left untreated, it can lead to ear infection, pneumonia, and encephalitis
  - May last in 3-4 days

Biology of measles virus

- RNA Virus in the Family of Paramyxoviridae, Genus Morbilivirus
- Closely related to rinderpest (cattle) and canine distemper viruses (CDV), suggesting that measles might have evolved from cattle
- Two membrane envelop proteins—Fusion protein (F) for fusion and Hemagglutinin (H) protein for adsorption of the virus to cells
- The virus is rapidly inactivated by heat and light

Epidemiology of Measles

- One of the oldest child disease, first noted in 1224
- Epidemic reported in Faroe Island in 1846
- 200 million deaths worldwide in 150 years
- Only one antigenic type making it effectively controllable by the vaccine
- Prior to the development of the measles vaccine, there were 30 million cases/year
- Measles is still one of the leading causes of death in young children with 314 deaths every day despite availability of vaccine

Epidemiology of Measles (...2/)

- Susceptibility to measles is universal, with no differences by gender, ethnicity, race, SES, or geography
- Higher incidence in densely populated areas
- Some data suggest higher delayed mortality in females than in males
- Protein-calorie malnutrition aggravates the severity of measles
- Measles in children with vitamin A deficiency leads to severe keratitis, corneal scarring, and blindness

Epidemiology of Measles (...3/)

- Incidence rate of measles is hard to determine because of milder cases
- Complication rate of measles explains regional differences in mortality rates,
  - Death rate in healthy children in developed countries 1%
  - Death rate in healthy children in developing countries 10%
  - Death rate in immune compromised children 30%
- Two most serious complications of measles are encephalitis (1%) and pneumonia.

Epidemiology of Measles (...4/)

- Modes of transmission is droplet infection released during the prodromal stage by sneezing and coughing
- Direct contact with infected sections and contact through fomites or can also transmit the measles infection
- Humans are the only reservoir for measles
- While nonhuman primates are also infected with similar symptoms as in humans, they are not source of human infection
Pathogenesis of Measles

- Respiratory droplets from infected person transferred to URT epithelial cells of the host
- Incubation period is 10-14 days where replication in the local lymph nodes takes place followed by viremia
- Initial pathological changes are seen at the portal of entry (epithelial cells of the buccal cavity)—Koplik’s spots during the prodromal stage
- Virus-specific antibodies appear, first IgM in blood, then IgA in mucosal secretions, followed by IgG in all body fluids after the second week ~ 18-20 days

Pathogenesis of Measles (...2/)

- After intense immune response to measles infection, there is suppression of the immune system lasting several weeks
- Period of infectiousness is difficult to determine, but it is known that infectiousness starts during the prodrome and resolves after a few weeks of resolution of symptoms
- This obscurity in stages of infectiousness hinders the effectiveness of quarantine measures
- Measles outbreak can occur even when <10% of the population is susceptible
- The estimated $R_0 = 12-18$ vs. 5-7 smallpox, 2-3 SARS

Immunity

- Maternally acquired antibody, IgG, protects the infant for the first 9 months
- An active transport mechanism in the placenta is responsible for the transfer of IgG from the maternal circulation to the fetus
- Thus, immunization is not recommended prior to the 9th month after birth
- The patency of maternally acquired immunity depends upon three factors:
  - The level of maternal anti-measles antibodies
  - The efficiency of placental transfer
  - The rate of catabolism of the antibody in the child
- Sufficient number of susceptible is required to maintain infection with 5-10 thousand births/year

Measles Vaccines

- Formalin-Inactivated Measles Vaccine and Atypical Measles
  - Withdrawn because of its tendency to lead to develop atypical measles ~60% of kids
- High-Titer Measles Vaccines
  - High immunogenicity but led to higher mortality than the Standard-Titer Measles Vaccine

Vaccine protection

- Vaccine efficacy (Under ideal condition)
  - $VE = 1 - RR$, Where Relative Risk is the risk ratio in vaccinated group vs. the unvaccinated
  - $VE = \frac{PPV - PCV}{PPV}$, Where PPV is the proportion of the population vaccinated against measles; PCV is the proportion of measles cases among the vaccinated
- Determinants of duration of immunity
  - Evidence of protective antibody titers based on the dose and the strain of the vaccine virus
  - Age of child at vaccine administration
    - 85% at 9 months
    - 90-95% at 12 months

Diarrheal Diseases
Definitions
- **Diarrhea**
  - Three or more liquid stools in 24 hrs
  - Considered terminated if at least 2 days elapse free of diarrhea
- **Persistent diarrhea**
  - A diarrhea that lasts for at least 14 days, not including hereditary syndromes (Celiac disease)
- **Dysentery**
  - Diarrhea which includes blood and mucus

Overview of Diarrheal Diseases
- **Important global problem**
  - High rates of morbidity and mortality
  - 3.3 million deaths per annum, mainly due to dehydration.
  - Very high incidence rate in children < age 5
    - Developing countries—2.6 episodes/child/yr.
    - US: 21-37 million episodes/yr. (0.9 episode/child/yr.)
  - Incidence for all ages in US
    - 0.63 episodes/person/yr.
  - Highest incidence in infants
    - 1.43 episodes/person/yr.

Overview of Diarrheal Diseases (DD)
- **Significant differences between developed and developing countries**
  - In **Developed countries**, DD result from:
    - Outbreaks due to food contaminations
    - Day-care centers
    - Hospitals and Long-term care facilities (C. diff)
  - In **Developing countries**, DD are due to:
    - Poor environmental sanitation
    - Poor hygiene
    - Inadequate water supplies
    - Poverty
    - Limited education

Body Fluid Compartments
- **Total body fluid** represents 45-60% of body weight
- **ICF and ECF balance** is proportional to the ratio of osmotically-active intracellular K⁺ and extracellular Na⁺ maintaining isotonicity.

Overview of Diarrheal Diseases (2)
- **Case Fatality Rate** varies by nations
  - Developing countries—0.1% to 0.5%
  - Developed Countries—very low
- **Impact on** growth
  - Contribute to malnutrition
  - Predisposition to other infectious diseases
- **Impact on** the economy
  - Cost of medical care
  - Lost work

Main Pathology of DD
- **Electrolyte Loss**
  - Mainly potassium
  - Disruption in acid-base balance
  - Metabolic acidosis
- **Severe dehydration, Kidney failure**
- **Direct cellular damage** to intestinal mucosa (Amebic dysentery)
What Overcomes Host Defenses

- **Inoculum Size**—The number of microorganisms that must be ingested to cause disease
- **Adherence**—Ability to adhere to the gastrointestinal mucosa as an initial step in the pathogenic process
- **Toxin Production**—Ability to produce one or more toxins

Host Risk Factors

- **Malnutrition**—causing immune decline
- **Micronutrients deficiency**—Vitamin A and Zinc deficiency
- **Gastric acid**—Hypochlorhydria (Low stomach pH)
- **Genetic factors**—Possible genetic link, Blood Type O higher risk for cholera
- **Immunity**—Immune compromised persons

Specific Pathogens

- **Bacteria**
  - E. coli
  - Campylobacter—most identifiable antecedent infection associated with the development of Guillain-Barré syndrome (GBS)
  - Salmonella
  - Vibrio Cholera
  - Shigella sp.
- **Viruses**
  - Rotavirus — ~40% hospitalization in Age <5
  - Enteric adenovirus
  - Norovirus (Formerly Norwalk)
  - Coronavirus

Specific pathogens (...2)

- **Parasites**
  - Cryptosporidium (Cyclospora)
  - Giardia
  - Trichuris *trichuria* (Whipworm)
  - Entamoeba histolytica—most serious complications with amebic liver abscess and ulcerative colitis

Types of Toxins

- **Enterotoxins**
  - Act directly on secretory mechanisms in the intestinal mucosa (Cause watery diarrhea)
- **Cytotoxins**
  - Act by destroying mucosal cells causing associated inflammatory diarrhea (Amebic dysentery, Shigella shigae)
- **Neurotoxins**
  - Act directly on the central or peripheral nervous system (various symptoms)

Most Common Etiologic Agents in Children in Developing Countries

- **Escherichia Coli** (E. Coli)
  - Most common pathogen (23%)
  - Has both endotoxin, exotoxin, and neurotoxin depending on the strain (O157:H7)
- **Giardia lamblia** (10%)
  - Next most common
  - Inhibits absorption
- **Campylobacter sp.** (8%)
- **Shigella sp.** (5%)
**Escherichia coli (E. coli) GI Infections**

- **3 Types based on virulence properties**
  - *Enteropathogenic E. coli (EPEC)*
    - Attaching and effacing lesions in the intestine mainly by over-colonizing; causing persistent diarrhea. Occurs with immune compromise
  - *Enterotoxigenic E. coli (ETEC)*
    - Colonization by strains capable of producing toxins. Occurs in children and sometimes causes dysenteries
  - *Enterohemorrhagic E. coli (EHEC)*
    - Colonization by strains producing exotoxins that result in hemorrhagic

**Salmonella Infections (Salmonellosis)**

- Important public health problem in US
- Highest risk rate in infants; the elderly and the immunosuppressed are at higher risk
- Poultry is an important animal host that increase risk of human infection
  - *S. enteritidis* colonize the ovaries of egg-laying hens, resulting in infection of the egg *in-vivo*
- In developing countries, nearly all of the salmonellosis is due to food-borne transmission

**Shigella Infections (Shigellosis)**

- Often leads to severe illness with high CFR
- Four serogroups of shigella:
  - *S. flexneri*, is the most common
  - *S. sonnei*,
  - *S. boydii*,
  - *S. dysenteriae*, most severe with hi CFR
- *S. flexneri* and *S. sonnei* are most common types in the US
- Often transmission is oral-fecal route in children predominantly in warm seasons

**Cholera Infections (Cholera)**

- Diarrheal illness caused by *Vibrio cholera* also called *Vibrio comma* due to its shape
- Seventh pandemic with high global impact
  - *V. cholera* biotype *El Tor* resulted in global spread and high mortality
  - Global climate change resulting in algal bloom caused large epidemic in 1991 in S. America
- Seasonal epidemic in Indian subcontinent following the monsoon rain
  - Predominantly affects children age 2-15
  - Confers immunity after initial infection
  - Cause of death is mainly dehydration

**Transmission Routes of Cholera**

- General factors
  - Nearly all enteropathogens result from direct contact with human feces (O-F)
  - Indirect: Through water and food
- Waterborne—for most pathogens, especially *V. cholera* and *Norovirus*
- Foodborne—direct contamination due to food handling and storage or intrinsic to the animal ate (chicken, pork, beef, etc.)
- Vectors and Fomites—Flies, roaches, and unclean utensils
Historical link of Cholera with Epidemiology

- Broadwick Street showing the John Snow memorial and public house.
- The BROAD STREET PUMP associated with Dr. John Snow’s discovery in 1854 that cholera is conveyed by water.

Treatment & Control Strategies

- Appropriate treatment
  - Early hydration (Oral or Intravenous) (Best)
  - Appropriate use of antibiotics as needed
  - Vitamins, mineral supplements (Zinc tablets)
- Water treatment—Potable, safe water
- Excreta disposal—Proper disposal of human and animal waste
- Inspection of food handlers and abattoirs

WHO/UNICEF Recommended formula for ORS

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- Osmolality is the amount of electrolytes dissolved in per kgm of serum
- Osmolarity is the concentration of osmotic solution in liter of serum
- Normal Range 285-295 milli-osmoles per kgm of body weight
- Dehydration is fluid loss that accounts to 5% of the body weight
  - Loss of 6-10% of body weight is severe dehydration with anuria
  - Loss >10% leads to circulatory collapse and death

Control Strategies (...2)

- Oral Rehydration Therapy (ORT)
  - Health individuals secrete 20-30 grams sodium/day and most are reabsorbed
  - In diarrheal disease, sodium rich intestinal secretion are lost without reabsorption
- Home hydration therapy is highly recommended with 6 tsp sugar, 0.5 tsp salt in 1 liter of water
- Best if Oral Rehydration Salt (ORS) constituted per WHO guideline obtained (Pedialyte®, Hydralyte®)
- 1 Zinc tablet/day is very important