Infectious Disease Epidemiology BMTRY 713 (A. Selassie, DrPH)

March 7, 2016
Lecture 17
Reviews & Recaps

Learning Objectives
1. Review key fundamental concepts of IDs
2. Identify unique indices and measures of IDs
3. Describe key features of ID Epidemiology

The 20th Century in the U.S.
- A decrease in death rates, especially infant and child mortality
- A corresponding increase in life expectancy
- A shift away from infectious diseases and toward chronic diseases
- This reflects the "Epidemiologic Transition," which is occurring worldwide in developing countries.

Epidemiology of IDs
- Major causes of human suffering
  - A third of all deaths around the world
  - 43% of the deaths in developing world
  - Lack of access to safe water is main cause
- Changing picture of ID
  - 40+ new pathogens since 1970
  - Changes in virulence (natural, manmade)
  - Changes in population at risk (aging)
  - Changes in the environment (warming)

Leading Causes of Death, U.S., 1900 vs. 2000

<table>
<thead>
<tr>
<th></th>
<th>1900</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Influenza &amp; Pneumonia</td>
<td>Heart Disease</td>
</tr>
<tr>
<td>2</td>
<td>Tuberculosis</td>
<td>Cancer</td>
</tr>
<tr>
<td>3</td>
<td>Heart Disease</td>
<td>Stroke</td>
</tr>
<tr>
<td>4</td>
<td>Stroke</td>
<td>COPD</td>
</tr>
<tr>
<td>5</td>
<td>Diarrhea/Enteritis</td>
<td>Unintentional Injury</td>
</tr>
<tr>
<td>6</td>
<td>Nephritis</td>
<td>Diabetes</td>
</tr>
<tr>
<td>7</td>
<td>Cancer</td>
<td>Influenza &amp; Pneum.</td>
</tr>
<tr>
<td>8</td>
<td>Unintentional Injury</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>9</td>
<td>Diphtheria</td>
<td>Nephritis</td>
</tr>
<tr>
<td>10</td>
<td>Diseases of Early Infancy</td>
<td>Septicemia</td>
</tr>
</tbody>
</table>

Pneumonia and Influenza mortality rates by age during certain epidemic years. (Centers for Disease Control, 1972)

New modes of disease transmission have been created by progress

Technological Progress
- Ventilation systems
- Blood transfusion
- Centrally processed food
- Air travel
- Economic development & Suburbanization
- Antimicrobial agents
- Modern medical treatments (e.g. bone marrow transplant, chemotherapy, renal dialysis)

Problem
- Legionnaires’ Disease
- HIV, Hepatitis C
- Salmonella, E. coli 0157:H7
- Rapid disease spread
- Exposure to new vectors & Lyme disease/rabies
- Drug-resistant organisms
- Opportunistic infections

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm#tabbox3
Differences between basic, clinical, and public health science research

<table>
<thead>
<tr>
<th>Markers</th>
<th>Basic</th>
<th>Clinical</th>
<th>Public Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>What/Who is Studied or Targeted</td>
<td>cells, tissue, animals</td>
<td>sick patients</td>
<td>populations</td>
</tr>
<tr>
<td>Research Goals</td>
<td>disease mechanisms</td>
<td>improve diagnoses and treatments</td>
<td>prevention, health promotion</td>
</tr>
<tr>
<td>Examples</td>
<td>toxicology, immunology</td>
<td>internal medicine, pediatrics, etc.</td>
<td>epidemiology, environmental health sciences</td>
</tr>
</tbody>
</table>

Infectious Disease (ID) Epidemiology
- ID – transmissible illness from an infectious agent or its toxic products
- Establishes relationship between agent, host, and the environment
- Purpose – prevention of ID by breaking the chain of transmission
  - Find the weakest link
  - Design rational measures of prevention

Infectious Disease Epidemiology: how it differs from other applications
- What makes infectious disease different from other health concerns?
  - Multiple infectious agents
  - Heterogeneous infectious agents
    - Not only different types of organisms—viruses, bacteria, fungi, parasites, etc.—but within each type, still further types and categories. Each one must be studied and treated uniquely
  - There are organisms which cause acute, chronic, or both acute and chronic diseases
  - Symptomatic and asymptomatic diseases
  - Multiple modes of transmission
  - Dynamic, not static
  - Infectious agents constantly emerging, re-emerging, evolving (e.g., resistant strains)

Features unique to infectious diseases:
1. A case may also be a source.
2. People may be immune.
3. A case may be a source without being recognized.
4. There is often a need for urgency.
5. Preventive measures often have good scientific basis.

Biologic characteristics of the organism
- Infectivity
- Pathogenicity
- Virulence
- Immunogenicity
- Inapparent infections
- Carrier states
Haddon Matrix: A search for the weakest link in ID transmission

<table>
<thead>
<tr>
<th>Level/Stage of Prevention</th>
<th>Agent</th>
<th>Intermediate Host (Vector/ Vehicle)</th>
<th>Final Host</th>
<th>Physical/ Social Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-event (Primary Prevention)</td>
<td>Plasmodium vivax in Sick person with malaria</td>
<td>Female mosquito</td>
<td>Healthy susceptible host</td>
<td>Swampy poor neighborhood</td>
</tr>
<tr>
<td>During the event (Secondary)</td>
<td>Malaria density surveillance</td>
<td>Entomological surveillance to assess vector competence</td>
<td>Treatment with Antimalarial therapy</td>
<td>Pesticide spray; Drainage of swamps; Social mobilization</td>
</tr>
<tr>
<td>Post-event (Tertiary)</td>
<td>Genetic modification of the parasite</td>
<td>Genetic changes in mosquitoes to disable asexual cycle of parasite</td>
<td>Prophylactic treatment; Vaccine development</td>
<td>Environmental modification - Drainage of swamps, etc.</td>
</tr>
</tbody>
</table>

Infectivity
- Ability of the agent to cause infection in susceptible host (Attack Rate)
- Two measures
  - Minimum number of infectious particles required to establish infection
  - Proportion of susceptible individuals who develop infection after exposure

Pathogenicity
- Ability of a microbial agent to induce disease
  - *Helicobacter pylori* with vac A and cag A alleles are much more pathogenic than *helicobacter pylori* infections without these characteristics
  - Proportion of cases who develop disease

Virulence
- Severity of the disease after infection
- Best measured by
  - Case-fatality rate
  - Proportion of clinical cases who develop severe disease

Host Defense
- Nonimmunologic
  - Integument (Skin, Membranes)
  - Secretions (Tears, Mucus, Gastric juice)
  - Peristalsis
- Immunologic
  - Cell mediated—Phagocytic cells
  - Humoral (Antibody)—Immunoglobulins

Immunogenicity
- The property that endows a substance with the capacity to provoke an immune response
Types of immunogenicity

- High, life-long immunity (Active)
  - Measles, polio
- Weak, reinfection is common (Passive)
  - Rhinovirus Infection (Common cold)
  - Plasmodium falciparum (Malaria)
- Nonprotective, deleterious to the host
  - Streptococci infection resulting in glomerulonephritis or rheumatic fever

Inapparent infections

- Infection that can be documented by the isolation of the organism by culture, identification by PCR, or through a specific immune response but the person remains asymptomatic
- Measure of low pathogenicity, e.g. polio
- Rare in some diseases, e.g. measles, smallpox, hanta virus

Carrier state

- An individual who is asymptomatic but capable of transmitting disease to others
  - HBV infection is acquired perinatally
  - "Typhoid Mary"
  - HIV has a long carrier state, average approximately 10 years

Classification of IDs

- Clinicians – use clinical manifestations or organ systems
- Microbiologists – by agent
- Epidemiologists – 2 common methods
  - Reservoir of organism—zoonoses
  - Means of transmission—STD, food-borne

Classification by reservoir

- Human (Anthroponosis)
- Animal (Zoonosis)
- Soil
- Water
R is the reproductive number that indicates the number of secondary cases expected to be caused by a single, typical infected individual in a population with some level of susceptibility. E.g. R<sub>z</sub>, where 0 < R < 3 for the disease to die out.

1 - \( R_0 \) is sometimes referred to as the Vaccination Threshold (V).

Transmission methods of IDs

- **Direct**
  - Person-to-person (e.g., Gonorrhea)
  - Vertical (Perinatal)
    - Intrauterine (e.g., Rubella)
    - Parturient (e.g., Herpes simplex virus)

- **Indirect**
  - Vector borne (e.g., Malaria, Lyme disease)
  - Vehicular
    - Common (e.g., food, water, milk, etc.)
    - Mechanical (e.g., fomites, door-knobs, etc.)
Infections transmitted by more than one means

- Anthrax
  - Contact with infected animals
  - During butchering — cutaneous disease
- Foodborne
  - Consumption of meat from an infected animal
  - GI anthrax, higher mortality rate
- Inhalation
  - Inhaling spores — pulmonary anthrax, usually fatal

Study design

- Two fundamental tenets
  - Human diseases do not occur at random
  - Existence of causal and preventable factors
- Stochastic vs. Deterministic approaches
  - Stochastic: process with randomness
  - Deterministic: process by which event is determined by proportionality
- How you sample determines the study design and analysis

Epidemiologic triangle

- Three factors
  - Host
  - Agent
  - Environment
- Biologic variation in either the host or agent can influence the natural history of disease
- Environment can effect transmission

Basic distinctions of epi designs

- Three factors
  - Sampling method
    - By disease status—Case-control
    - By exposure status—Cohort
    - By fixing the total sample size—Cross-sectional
    - By event randomness|fixed time—Poisson
  - Timing of occurrence of disease/exposure
    - Time elapsing from exposure to outcome
    - Degree of “control” the design accords
    - Random allocation of subjects

Sampling scheme & design

- What is fixed a priori determines the study

- Fix n₁ and n₂ first = Case-control study
- Fix m₁ and m₂ first = Cohort study
- Fix N first = Cross-sectional study
- Fix N|t = Poisson process
Various designs
- Descriptive: case reports
- Ecological
- Cross-sectional
- Case-control
- Cohort
- Clinical trial (Experimental)
- Variations: nested studies, serial cross-sectional, etc.

Case Reports
- Rabies
- What was the significance of the two case reports presented?
  - 1) child and duck vaccine
  - 2) spelunker
- What should be the next step?

Case series
- AIDS cluster
  - Identification of men in NYC with Pneumocystis carinii pneumonia and men with Kaposi’s sarcoma in San Francisco
    • Pharmacy aid
  - What was the importance of this case series?

Cross sectional studies
- Identification of disease and exposure at the same time
  - HAV and household characteristics on US/Mexico border
- Serial cross-sectional studies to determine trends
  - e.g., Newborn screening for HIV

Case-control studies
- Participants identified on the basis of disease status
- Outbreak investigations
  - Able to test for multiple associations
- Can also test a specific hypothesis
  - Good for rare diseases or diseases with a long latency period

Cohort studies
- Participants identified on the basis of exposure status
- Follow individuals over time
  - Prospective
  - Retrospective
- Best suited for rare exposures, shorter latency periods
Infectious Disease epidemiology BMTRY 713 (Lecture 17)
Midterm Reviews and Recaps

March 7, 2016

Selassie AW (DPHS)

### Types of Cohort Studies

<table>
<thead>
<tr>
<th>Cohort Design</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past</td>
</tr>
<tr>
<td>1. Concurrent</td>
<td>E</td>
</tr>
<tr>
<td>(Prospective)</td>
<td></td>
</tr>
<tr>
<td>2. Nonconcurrent</td>
<td>E</td>
</tr>
<tr>
<td>a) Historical</td>
<td></td>
</tr>
<tr>
<td>(Retrospective)</td>
<td></td>
</tr>
<tr>
<td>b) Mixed</td>
<td>E</td>
</tr>
<tr>
<td>(Ambispective)</td>
<td></td>
</tr>
</tbody>
</table>

Reference: Szklo, M & Nieto, F.J. Epidemiology beyond the basics, 2000
Gordis, L. Epidemiology, 3rd Ed. 2004
Schneider D. Supercourse Lecture on Cohort Studies, UP

### Clinical trials (Experimental)

- Generally used to evaluate a treatment or preventive measure, e.g. vaccination
  - Randomization
  - Blinding
- Most conclusive

### Measures of association

<table>
<thead>
<tr>
<th>Design/ Sampling</th>
<th>Measures of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>✓</td>
</tr>
<tr>
<td>Case-control</td>
<td>✓</td>
</tr>
<tr>
<td>Prospective</td>
<td>✓</td>
</tr>
<tr>
<td>(Cohort)</td>
<td></td>
</tr>
</tbody>
</table>

### Special study designs

- Transfusion-transmission of HIV
  - Novel way to determine viral differences
- Twin studies
  - Comparison of identical (monozygotic) vs fraternal (dizygotic)
- Genetic studies
- Vaccine probe

### Bias

- Selection bias
  - Hospital cases are more severe
  - Differences in enrollment between groups
- Information bias
  - Response-bias
  - Recall bias

### Confounding

- A factor that distorts the apparent magnitude of the effect of a study factor on risk
- Determinant of the outcome of interest and unequally distributed among the exposed and unexposed
- AIDS and “poppers”
**ID Causality (Nelson, p348-9)**

- **Koch’s postulates**—derived from an infectious disease model 1880s
  - Causative agent consistently isolated in ill
  - Not present in those without disease
  - Disease can be induced if organism is inoculated in a healthy individual
  - Organism can be grown in a lab

**Bradford Hill Criteria for Causality**

- Temporal association ↑↑↑↑
- Removing exposure results in reduction of disease (Experiment) ↑↑↑
- Dose-response relationship ↑↑
- Strength of association ↑
- Biologic plausibility ↑
- Consistency ↑
  - (Specificity↓, Analogy↓, Coherence↓)

**Nested Case-Control Studies**

(Incidence Density Sampling, Riskset)

- This also reconciles the benefits of cohort and case-control designs
- Time and cost efficient
- Control selected randomly from cohort at every event among the controls

**Hierarchy of epi designs**

<table>
<thead>
<tr>
<th>Design</th>
<th>Traditional Evaluation</th>
<th>Potential Context sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case History</td>
<td>No Controls</td>
<td>Speculative</td>
</tr>
<tr>
<td>Aggregate</td>
<td>Group Unit</td>
<td>Possibly suggestive</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>No Temporal information</td>
<td>Somewhat suggestive</td>
</tr>
<tr>
<td>Case-control</td>
<td>Retrospective information</td>
<td>Moderately suggestive</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Retrospective information</td>
<td>Strongly suggestive</td>
</tr>
<tr>
<td>Randomized Clinical Trial</td>
<td>Experimental</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from Ibrahim, 1985

**Desirable properties of a surveillance system**

- Simplicity
- Flexibility
- Acceptability
- Timeliness
- Sensitivity
- Predictive Value Positive
- Representativeness
- Cost effectiveness

**Priority indicators for surveillance of diseases**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Flu</th>
<th>Giardia</th>
<th>Hepa C</th>
<th>Rabies</th>
<th>Polio</th>
</tr>
</thead>
<tbody>
<tr>
<td>High communicability</td>
<td>✓</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>✓</td>
</tr>
<tr>
<td>High morbidity</td>
<td>✓</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>High mortality</td>
<td>✓</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>High case fatality rate</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>✓</td>
<td>○</td>
</tr>
<tr>
<td>High preventability</td>
<td>✓</td>
<td>○</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>High long term disability</td>
<td>○</td>
<td>○</td>
<td>✓</td>
<td>○</td>
<td>✓</td>
</tr>
<tr>
<td>High Economic impact</td>
<td>✓</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>✓</td>
</tr>
</tbody>
</table>
Sources of data
- Morbidity Report—ED, Hospital, OPD
- Mortality—Death certificates
- Laboratory Report—Pathology, etc.
- Epidemic/Outbreak reports
- Nosocomial infection surveillance
- Animal disease surveillance
- BRFSS
- Targeted disease reporting

Uses of surveillance
- Monitor trends of diseases and deaths
- Monitor behavior putting people at risk
- Identify outbreaks of high urgency
- Evaluate program effectiveness
  - E.g. Vaccine Efficacy (VE)
    \[
    VE = \frac{(AR_U - AR_V)}{AR_U} \times 100
    \]
  - \(AR_U\) = Attack Rate; \(V\) = Vaccinated, \(U\) = Unvaccinated

Types of surveillance systems
- Passive
  - Submission of reports by mail, phone, or fax to health dept
- Active
  - Researcher actively collects data
- Sentinel
  - Following an identified population over time to monitor trends, specific diseases

Benefits and Disadvantages of Passive Surveillance
- Benefits
  - Inexpensive
  - Cover a large area, e.g. CDC reportable diseases are in all states
- Disadvantages
  - Subject to data quality issues, timeliness

Potential biases in passive surveillance data
- Underreporting
  - Concerns about confidentiality
  - Inactivity of the health dept
  - Underdiagnosis
  - Relevance of the disease
- Reporting delays
  - Regional differences
  - Variation by risk groups

Benefits and Disadvantages of Active Surveillance
- Benefits
  - More control over data quality
  - Data are more timely
- Disadvantages
  - Expensive
  - Usually limited to a smaller number of participants
**Sentinel Health Event**

- A condition which can be used to assess the stability or change in health levels of a population, usually by monitoring mortality statistics
- Preventable disease
  - E.g., polio

**Benefits and Disadvantages of Sentinel Event Surveillance**

- **Benefits**
  - Early warning system
  - Low cost
  - Dependent upon correct diagnosis and timely reporting to the authorities
- **Disadvantage**
  - May miss event

**Assessing Data Quality**

**Example 1: Assessment of PVP and Sensitivity using Medical record Review when prevalence of TBI is 93%**

<table>
<thead>
<tr>
<th>SHDDS Label (800,801,803,804,850-954)</th>
<th>Medical Record Review (Diagnosis narrative, symptoms, signs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for TBI</td>
<td>485</td>
</tr>
<tr>
<td>Negative for TBI</td>
<td>7</td>
</tr>
<tr>
<td>Positive for TBI</td>
<td>3</td>
</tr>
<tr>
<td>Negative for TBI</td>
<td>30</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{485}{(485+7)} \)
Specificity = \( \frac{30}{(3+30)} \)
PV(P) = \( \frac{485}{(485+7)} \)
Prevalence = \( \frac{485+7}{485+7+3+30} \)

**Example 2: Assessment of PVP and Sensitivity using Medical record Review when prevalence of TBI is 43%**

<table>
<thead>
<tr>
<th>SHDDS Label (800,801,803,804,850-954)</th>
<th>Medical Record Review (Diagnosis narrative, symptoms, signs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for TBI</td>
<td>114</td>
</tr>
<tr>
<td>Negative for TBI</td>
<td>3</td>
</tr>
<tr>
<td>Positive for TBI</td>
<td>600</td>
</tr>
<tr>
<td>Negative for TBI</td>
<td>114</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{114}{(114+247)} \)
Specificity = \( \frac{486}{(600+486)} \)
PV(P) = \( \frac{114}{(114+247)} \)
Prevalence = \( \frac{114+247}{114+247+3+30} \)

**Example 3: Assessment of Sensitivity & Specificity when surveillance data source fixes marginal totals and prevalence of TBI is 26%**

<table>
<thead>
<tr>
<th>SHDDS Label (800,801,803,804,850-954)</th>
<th>Medical Record Review (Diagnosis narrative, symptoms, signs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for TBI</td>
<td>289</td>
</tr>
<tr>
<td>Negative for TBI</td>
<td>361</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{483}{(483+483)} \)
Specificity = \( \frac{453}{(289+453)} \)
PV(P) = \( \frac{483}{(483+483)} \)
Prevalence = \( \frac{483+483}{483+483+289+361} \)
Assessing Data Quality (4)

Example 4: Assessment of Sensitivity & Specificity when surveillance
Gold Standard fixes marginal totals and prevalence of TBI is 26%

<table>
<thead>
<tr>
<th>SHDDS Label</th>
<th>Medical Record Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>(800,801,803, 804,850-954)</td>
<td>(Diagnosis narrative, symptoms, signs)</td>
</tr>
<tr>
<td>Positive for TBI</td>
<td>Negative for TBI</td>
</tr>
<tr>
<td>87</td>
<td>274</td>
</tr>
<tr>
<td>80</td>
<td>209</td>
</tr>
<tr>
<td>167</td>
<td>483</td>
</tr>
</tbody>
</table>

Sensitivity = \frac{87}{167} = 0.52

Specificity = \frac{209}{483} = 0.43

Prevalence = \frac{167}{650} = 0.26

PVP = \frac{87}{167} = 0.52

Pos = \frac{209}{483} = 0.43

Outbreak epidemiology

- Study of a disease cluster or epidemic in order to control or prevent further spread of disease in a population
- It is a specific form of descriptive epidemiology intended to identify immediate threat to public health
- Requires urgent action

Special Considerations

- Tracking infectious diseases
  - Epidemic disease, one case may be a signal to action if event is unexpected
    - e.g. Success story (Smallpox eradication)
  - Epidemicity vs. Endemicity
    - Measles in North Carolina (Epidemic)
    - Malaria in sub-Saharan Africa (Endemic)

Terminology

- Outbreak—a small localized cluster of cases, usually an infectious disease
- Epidemic—the occurrence of cases of a condition in a population in a number greater than expected for a given period of time
- Endemic—a constant presence of a communicable disease in a population
  - Holoendemic: high proportion of children affected, conferring immunity in adults. (e.g. malaria)
  - Hyperendemic: constant presence in all ages
- Pandemic—an epidemic that transcends national boundary extending to much of the world

Types of epidemics

- Common source
  - Single source of contamination
  - Single vehicle
    - Consider distribution patterns
- Point epidemics
  - Common source, everyone exposed at the same time
- Propagated epidemics
  - Transfer from one host to another
  - Bimodal with secondary cases
  - Overlapping secondary cases
- Mixed
  - Include both
**Means of transmission**
- **Contact**: direct or indirect
- **Food- or water-borne**: ingestion
- **Airborne**: inhalation of contaminated air
- **Vector-borne**: living organism
- **Perinatal**: during pregnancy or at time of delivery

**Identification of an epidemic**
- Increase in cases of a disease currently reported to CDC
- Reports from doctor’s office, hospitals, nursing home, laboratory
- May be reported by an individual

**Temporal trends in IDs**
- **Seasonal variation**: Vector-transmitted diseases
- **Annual variation**: Dependent upon the number of susceptible individuals in the community
- **Variation over decades**: Decrease in incidence and mortality in some
  - Large number of new infections occurring

**Outbreak investigations**
- Usually conducted by facilities or at the local or state public health level
- CDC is consulted for multi-state outbreaks or those requiring special expertise
### Steps in conducting an outbreak investigation

<table>
<thead>
<tr>
<th>Identify investigative team members and their roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm the existence of an outbreak</td>
</tr>
<tr>
<td>- Compare rates with background levels</td>
</tr>
<tr>
<td>- Rule out &quot;spurious&quot; factors (Improved surveillance)</td>
</tr>
<tr>
<td>- Verify diagnoses</td>
</tr>
<tr>
<td>- Some diseases are so serious that a single case is investigated</td>
</tr>
<tr>
<td>- Anthrax, human rabies, botulism, polio, bubonic plague</td>
</tr>
</tbody>
</table>

### Steps in conducting an outbreak investigation (2)

<table>
<thead>
<tr>
<th>Select a case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>- May include time and place of exposure, laboratory findings, and clinical symptoms.</td>
</tr>
<tr>
<td>- Initial case definition has a greater emphasis on sensitivity than specificity</td>
</tr>
<tr>
<td>- Subsequent case definitions may have greater specificity</td>
</tr>
<tr>
<td>- Classify cases as confirmed and probable</td>
</tr>
</tbody>
</table>

### Steps in conducting an outbreak investigation (3)

<table>
<thead>
<tr>
<th>Identification of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Case finding techniques reviewing existing surveillance data, surveying hospitals, asking existing cases if they know others who may have been exposed</td>
</tr>
<tr>
<td>Identification of population at risk</td>
</tr>
<tr>
<td>- Range from very few to many</td>
</tr>
<tr>
<td>- Those with a common exposure</td>
</tr>
</tbody>
</table>

### Determine study design

<table>
<thead>
<tr>
<th>Based upon size and availability of the exposed population, the speed with which results are needed, and available resources.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Small enumerable exposed groups</td>
</tr>
<tr>
<td>- Large enumerable exposed groups</td>
</tr>
<tr>
<td>- Groups where exposure can be identified but groups cannot be enumerated</td>
</tr>
<tr>
<td>- Exposed population is unknown</td>
</tr>
</tbody>
</table>

### What is a mathematical model?

<table>
<thead>
<tr>
<th>It is an explicit mathematical description of the simplified dynamics of a system. Models approximate events.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A model can be simple or complex</td>
</tr>
<tr>
<td>- Simple model (e.g. Bernoulli model)</td>
</tr>
<tr>
<td>[ P (X=1) = P ; \quad P (X=0)=1-P ]</td>
</tr>
<tr>
<td>- Complex Model (e.g. Logistic model)</td>
</tr>
<tr>
<td>[ P(D) = \frac{1}{1+e^{-\hat{\beta}_0-\hat{\beta}_1 x_1-\cdots-\hat{\beta}_p x_p}} ; \quad \hat{R}_0 = \left[1+\exp(-\hat{\beta}_0)\right]^{-2} ]</td>
</tr>
</tbody>
</table>

### What is a mathematical model? (...continued)

<table>
<thead>
<tr>
<th>Humans use models to approximate how things work. Two common formats:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mental common sense (Mental model)—subjective explanation of the operations of a phenomenon. Often ambiguous and difficult for others</td>
</tr>
<tr>
<td>- Mathematical model—assumptions based explanation of a complex phenomenon that could be tracked and repeated</td>
</tr>
</tbody>
</table>
Why mathematical modeling?
- Think of staging immunization activity to control ID in community with 50k people.
- Limited role of specialized areas of ID to contemplate the feasibility of the activity
  - Microbiology—biochemical/genetics
  - Clinical—natural hx and pathology
  - Epidemiology—rates and risk factors
  - Vaccine—its efficacy against agent
- To extrapolate the effect of immunization activity in 50K people accounting for all factors, need mathematical modeling.

Uses and Functions of models
- Help in determining biological plausibility of epidemiological explanations
- Provide understanding by demonstrating unexpected interrelationships among empirical observations
- Predict the impact of changes on the dynamics of a system
- Allow integration of theoretical strategies in explaining trends

Components of ID modeling
- ID modeling blends various fields like
  - Pop. biology
  - Ecology
  - Demography
  - Genetics
  - Mathematics
  - Statistics
- Time of transition from being infected to spreading the infection (Latency) is a complex interplay of clinical microbiology, host immunity, and epidemiology

Why study modeling of IDs?
- Epidemiologists frame the questions
  - Describe the incidence
  - Describe the transmission methods and the risk characteristics
  - Describe the dynamics of the referent population
- Computational biologists design the computer model
  - Describe sequential and iterative approaches based on laid assumptions

Simple illustration
- Let, $A_c$ = Agent characteristics
  - $R_t$ = Risk of transmission
  - $V_e$ = Vaccine efficacy
  - $I_d$ = Incidence of diseases
  \[ I_d = f(A_c, R_t, V_e) \]
- This can be modeled using complex computer calculations taking into account all the parameters of the model under different values.

Primary purpose of mathematical modeling in ID
- Mathematical models in ID deal with the transmission of infectious agents.
- Transmission ($T_m$)—Direct (person-to-person)
  - Indirect (when vector-borne)
  \[ T_m = \begin{cases} 1 & (\text{if } T_m = \text{True}) \\ 0 & (\text{if } T_m = \text{False}) \end{cases} \]
  - $A_c$ = Agent characteristics ($A_+ \text{ or } A_-$)
  - $i_1, i_2, \ldots, i_n$ = individuals at risk
  \[ i = \begin{cases} 1 & (\text{if } i_{AC+} \Leftrightarrow i_{AC+} ) \\ 0 & (\text{otherwise}) \end{cases} \]
Primary purpose of mathematical modeling in ID (…continued)

- Endemicity is when transmission ($T_m$) is maintained in a population
  \[ \text{Endemicity} = 1 \left\{ i_{IAc} \leftrightarrow i_{2Ac} \cdots i_{nAc} \right\} = N \mid T_m, r_e \]
  - Endemicity is eliminated when $T_m$ is interrupted in a population due to:
    1. Environmental and social condition may no longer support the agent
    2. Rx may eliminate the agent from host or population may get immunity
    3. Herd immunity may get high in the population

Terminology

- Infection—the stage of ailment that begins with entry of the agent in the susceptible host till recovery or death (sometimes subclinical level may linger for a long time)
- Disease—the stage in which the host exhibits clinical manifestations of the infection
- Incubation Period—time from infection to onset of symptoms or clinical manifestations
- Latent Period—time from infection to threshold of infectivity (i.e., the point at which the causative agent reaches effective level for transmission)

Stages of Infection (SIR Model)

- Susceptible
- Infectious
- Infected
- Doubly Infectious
- Removed
- Recovered

Kermack-McKendrick Threshold Theorem

- Specifies that an epidemic can only be established in a population if the initial susceptible population size is large than some critical value, which depends on the parameters governing the spread of disease.
  - $X(t)$=number of susceptible at time $t$
  - $Y(t)$=number of infectious at time $t$
  - $Z(t)$=number of removals at time $t$

What is GIS?

- A procedure to input, store, retrieve, manipulate, analyze, and output data to which spatial attributes are associated.
- The structure of GIS is composed of computer hardware, software, geo coded data, and users.
Role of GIS in ID Epidemiology

- Ease of demonstrating the interplay of host, agent, and environment (vector and reservoir density).
- Good way to summarize the complex relationships associated with disease transmission.
- John Snow’s classic study of cholera transmission around Broad Street pump and its relationship to locations of sick.

Classic Examples of GIS Use

- Schistosomiasis in Egypt
  - Irrigation canals with snail data
  - Villagers with parasite density
- STD in Baltimore
  - Rate diluted when GC incidence was calculated for the city
  - Rate distribution by census tract identified the specific loci with high transmission rates.

Structural Determinants of Pathogenicity & Virulence Factors

- Pathogenicity is determined by
  - Cellular structures
  - Products and toxins
- Virulence factors allow organisms to
  - Colonize
  - Evade host defense mechanisms
  - Invade and disseminate
  - Example: E.coli O157:H7 is a virulent strain

Host Defenses

- Mechanical barriers
  - Skin, mucus and ciliated membranes
  - Washing actions of tears and urine
  - Chemicals—fatty acids, lysozyme, HCl
- Cellular defenses
  - Phagocytic cells (macrophages, neutrophils, monocytes, eosinophils)
- Specific Immunity
  - Humoral—antibody mediated B-cells (IgG, IgE, IgM, etc)
  - Cellular—T-lymphocyte mediated functions

Taxonomy of microorganisms

- Early classification depended on the presence of true nucleus (Eukaryocytes) or absence (Prokaryocytes)
- Modern classification scheme
  - Mainly uses family, genera, and species
  - Phenotype and morphology (Gm-ve cocci)
  - Genetic characteristics using DNA and RNA homology are current breakthroughs that are important for epidemiologic studies

Viruses

- The smallest of infectious agents except prions—agent of CJD (“mad cow”)
- Size ranges 20-200nm
- Contain a single form of nucleic acid—DNA or RNA, the genomic structure
- Depending on their level of complexity, viruses may contain lipids and glycoproteins
- Are obligate intracellular parasites
- Replication is host-cell dependent, directed by their DNA or RNA
Viruses (…continued)
- Infection with viruses is always host-cell specific (surface receptors)
- Outcome of infected cells are:
  - Rapid lysis (e.g. influenza)
  - Continued growth and replication with in cells and shedding new virus particles (e.g. adenovirus)
  - Integrating their nucleic acid into the host cell genome establishing latency (e.g. herpes virus)

Viruses (continued…)
- Classification depends on the following
  - Like other organisms, have families, genera, species
  - Rarely have binomial nomenclature
  - Classification depends on
    - Viral genome—DNA or RNA morphology like double-stranded, segmented, etc.
    - Size and shape of the capsid (shell)
    - Method of replication
    - Pathophysiology of the virus—tropism
    - Physical and chemical features to solvents
  - A Virion is a complete infectious virus

Bacteria
- Much larger than viruses
- Classification uses binomial scheme with genera and species names included
  - Eg. Staphylococcus aureus, Bacillus anthracis, Escherichia coli, Mycobacterium tuberculosis
- Further subdivision by subspecies, serotypes
- Recent genetic methods utilize DNA homology of entire chromosome or cloned or amplified portions of the genome

Bacteria (continued…)
- Further subdivision by subspecies, serotypes
- Classification scheme mainly use staining, morphologic, and biochemical characteristics
  - Shape: cocci (round and spherical), bacilli (rod-shaped), curved, spiral forms
  - Staining technique: Gm +ve—staining blue/purple; Gm-ve—staining red/pink.
  - Arrangement: diplococci (in pair); staphylococci (in cluster)

Fungi (Mycosis)—Medical mycology
- Much larger than viruses and bacteria
- Ranges from microscopic yeasts to macroscopic mushrooms
- Over 100,000 different species, yet a few are medically important—yeasts and molds
- Classification is mainly by morphology, type of sexual reproduction, and locus of infection
  - Superficial mycoses—skin, hair, etc
  - Cutaneous and subcutaneous—moniliasis
  - Systemic—internal organs

Fungi (Mycosis)—Medical mycology (…continued)
- Medically important fungi
  - Pneumocystis carinii—opportunistic infection of the lung among immunocompromised persons
  - Candida albicans—causes vaginitis and oral thrush
  - Cryptococcus neoformans—systemic mycoses
- Pathogenic fungi have two growth forms, existing as either molds (environmental) or yeasts (infectious). This phenomenon is described as dimorphism
Parasites—Protozoa

- Neither plant nor animal (subkingdom)
- Oval, spherical, or elongated cells ranging from 5-10 μm to 1-2mm
- Small subsets are obligate parasites
- Medically important protozoa include
  - *Entamoeba histolytica*—amebiasis
  - *Giardia lamblia*—Giardiasis
  - *Trichomonas vaginalis*—T. vaginitis
  - *Plasmodia* (4s)—Malaria
  - *Trypanosoma* (3s)—Trypanosomiasis
  - *Leishmania* (3s)—Leishmaniasis

Parasites—Helminths

- These are worms that parasitize humans
- Two main phyla
  - Platyhelminthes—flat worms (e.g. Cestodes)
  - Aschelhelminthes—roundworms (e.g. Ascaris)
- Many live in intestinal tracts sharing foods and nutrients from the host
- Medically important include
  - *Cestodes* (3s)—Beef, Pork, Fish tapeworms
  - *Trematodes*—Schistosomiasis, fasciolopsis
  - *Nematodes*—Ascariasis, Trichuriasis, Pinworms, Hookworm, Filariasis, Loa loa

Diagnostic steps in ID organisms

- Microscopy—Light, Florescent, Electron
- Culture—cultivation method outside the host in an artificial culture media
  - Blood agar and Chocolate agar
  - Brain-heart infusion broth, etc.
- Diagnostic immunology
  - Antigen-antibody agglutination (clumping)
  - Complement fixation (lysis)
  - Enzyme immunoassay (ELISA)& Radioimmunoassay
  - Phage typing for sub typing
- Molecular diagnostics—hybridization with DNA or RNA; amplification with PCR

Molecular tests detect…

- Genomes (DNA, RNA)
- Transcripts (mRNA)
- Proteins
- Metabolites

Molecular tests can tell us

- If infectious agent is present
- How much is present
- Whether it has been there in the past

**Terminology**

- A probe is a single-stranded sequence of DNA or RNA used to search for its complementary sequence in a sample genome.
- In molecular biology, nucleic acid hybridization is the process of joining two complementary strands of DNA.
- Signal Amplification is the use of specific detection methodologies to directly increase the signal in proportion to the amount of target in the reaction.
  - Eg: the use of branched DNA probes that contain a reporter group or enzyme amplification.
How to tell an infectious agent is present

- Grow the organism (culture)
- Detect genetic material of the agent (DNA, RNA)
- Detect products made by agent (metabolites, toxins)
- Detect products made by the host in response (metabolites, antibody)

How to tell infectious agent has been there

- Detect specific antibody
- Detect DNA fingerprint

Pulsed-field gel electrophoresis (PFGE)

- A highly discriminative molecular typing technique that is used in epidemiological studies worldwide.
- It is based upon the variable migration of large DNA restriction fragments in an electrical field of alternating polarity.

Vaccines (…continued 1)

- Two major reasons attributable for the decline of ID morbidity and mortality worldwide are:
  - Vaccines
  - Sanitation of the environment
- The greatest public health achievement of global eradication of smallpox in 1977 is due to an effective smallpox vaccine.

Conferral of immunity

- Two types of immunity can be elicited through vaccination
  - Passive immunity—host gets protection through transfer of animal or human products (immunoglobulin).
    - Advantage—naturally available (e.g., maternal)
    - Disadvantage—short-lived (wanes fast)
  - Active immunity—protection due to host-invoked immunity after exposure to an antigen.
    - Antigens are foreign proteins alien to the host
    - Such antigens are usually congeneric to the pathogenic form or are attenuated through chemical deactivation.

Characteristics of ideal vaccine

1. Single dose results in cell-mediated or humoral immunity similar to natural infection
2. Elicits protection against clinical diseases
3. Elicits longer protection, preferably lifetime
4. Minimal adverse effects or mild disease
5. Induced immunity protects multiple strains
6. Easy to administer, acceptable to target pop.
7. Vaccine doesn’t require special handling
8. No significant interference with immune response to other vaccines given simultaneously
9. Cost-benefit ratio outweighs costs and risks of natural infection
Determinants of immune response
- Type and dose of the antigen
- Route of administration (IM, subcut., oral)
- Presence or absence of maternal antibody, and host factors (age, immunosuppression, genetic factors, etc.)
- Timing of vaccine administration (must take place before natural infection occurs).
  - If outbreak has occurred, passive immunization offers shorter but faster protection (e.g., Hepatitis A outbreak and gamma globulin)

Types and forms of vaccines
- Two main groups
  - 1) Attenuated live organisms (e.g., BCG)
  - 2) Inactivated form the organism that is either whole or fractioned components (e.g., Protein or polysaccharide components)
- Recombinant vaccines—live or inactivated vaccines developed by gene manipulation.
- While many vaccines are designed to prevent infection, some are designed to minimize consequence of infection.

New frontier in vaccination
- Vaccination against ID related cancers
  - Hepatitis B and liver cancers
  - Human papilloma virus (HPV) and cervical cancer
- Future plan of vaccines include antitumor vaccines to boost host immune response.

Live attenuated vaccines (LAV)
- Bacteria and viruses rendered nonpathogenic through
  - Laboratory culture and serial passaging
  - Genetic manipulation
- LAV organisms must replicate to induce maximum immune response
- Often elicit stronger and lifelong immune response than do inactivated vaccines due to immunologic memory.

LAV (...continued1)
- Have the advantage of inducing humoral and cell-mediated immunity.
  - Humoral—refers to antibody immunoglobulin (Ig) production after recognition of the antigen by B and T lymphocytes.
    - Primary humoral response yields IgM
    - Delayed humoral response yields IgG
  - Cell-mediated—direct attack against invading organisms with phagocytes, cytotoxic T cells, and complement.

LAV (...continued2)
- Another potential advantage includes horizontal transmission
  - Amplification effect of vaccine coverage
  - However, potential for LAV to revert to virulence due to failure to differentiate between wild-type and attenuated form
  - Requires careful monitoring and surveillance
  - Sometimes antibodies derived from LAV can be rendered ineffective by circulating antibodies that cross-react with attenuated organisms
  - LAV often require appropriate measure to protect from environmental factors (cold chain)
Inactivated Vaccines

- “Killed” organisms with heat or chemicals
- Components include:
  - Toxoid—inactivated toxin (e.g. Tetanus)
  - Polysaccharides—derived bacterial cell-wall. Often elicit short-lived IgM and are not consistently immunogenic (in age extremes)
  - Conjugates—polysaccharides chemically linked with proteins to amplify response
- Have fewer adverse effects and require less stringent handling procedures.

Disadvantages include:
- Immune responses are typically humoral
- Several doses are required to boost the specific antibody, else effect wanes
- Titer levels of antibody are frequently measured before subsequent doses
- At times, when antigenic components of organism can’t be isolated, the whole inactivated organism form the vaccine.
- These organisms often induce adverse effects, and are referred as reactogenic.

Recombinant vaccines

- Live or attenuated vaccines generated through genetic manipulation
- Three major approaches
  - Clonal expression of the primary immunogen in other cells (HBsAg in yeast)
  - Deletion/modification of genes of known pathogenicity (Oral typhoid vaccine)
  - Insertion of gene from one organism to another (Canarypox virus expressing HIV glycoprotein)

DNA Vaccines

- Vaccines from naked DNA of a pathogenic organism injected directly into the body.
- Advantages include,
  - Production of immunized protein takes place in the cells of the vaccinated host eliminating risk of eliciting an infection
  - Capable of eliciting wide range humoral and cell-mediated long-term immune responses.
  - Are stable and can be stored w.o “cold chain”
- Main shortcomings are,
  - Limited immune response to protein structures
  - Safety concerns—carcinogenesis, etc.

Terminology

- Vaccine efficacy—the degree to which the vaccine confers protection against the infectious agent under idealized conditions with carefully selected populations and with optimal resources
- Vaccine effectiveness—the protection achieved against the infectious agent by the use of vaccine in a target population under practical challenges and resource constraints

Vaccine Effectiveness (VE_{ss})

\[
VE_{ss} = \frac{I_{unv} - I_{vac}}{I_{unv}}
\]

\[
VE_{cy} = \frac{I_{ctl} - I_{vac}}{I_{ctl}}
\]
Role of vaccines in ID eradication

- Evan’s postulate (AJE 1985;122(2):200+)
  - Factors associated with the disease
    - E.g., Ease of Dx and Rx; Long-term immunity
  - Factors associated with the agent
    - E.g., No animal reservoir/vector; short incubation
  - Factors associated with the host/target pop
    - E.g., No reservoir state; No reinfection
  - Factors associated with the vaccine
    - E.g., Confers long-term immunity; Easy handling and storing; Low cost; Minimal adverse effects

Definition

- STDs are diseases transmitted through sexual intercourse—a sexual contact which includes vaginal, oral, or rectal intercourse
  - Heterosexual or homosexual sex
  - Risk may be dependent upon specific activities
  - Receptive rectal and vaginal intercourse are the highest risk activities
  - Dependent upon behavioral factors

Determinants of STD Transmission

- Probability of coming into contact with an STD-infected partner
- Susceptibility of the host
- Efficiency of the transmission

Epidemiology

- Incidence is highest in adolescents and young adults
- >95% of gonorrhea and Chlamydia cases occur between ages 15 and 39
- Highest rates in women ages 15-19 and men ages 20-24
- Correlated with multiple sexual partners, high risk partner

Risk factors for STDs

- Age at first intercourse
- Number of partners
  - Serial monogamy vs. multiple concurrent partners
- Use of barrier contraceptives, e.g., condoms
- Other comorbidities
  - Drug use, SES, commercial sex work, travel to areas with endemic STDs

Impact of SES on STDs

- Higher rates of STDs in impoverished areas
- Increased rate of STDs
  - Decrease in preventive services
  - Increase in fees for services
  - Urbanization in developing countries
    - Men work in cities, frequent sex workers, give spouses STDs
    - Illicit drug use
    - Increased STDs among minorities
Gonorrhea
- Caused by Neisseria gonorrhoeae, a gram neg coccus
- Symptoms
  - Men discharge or dysuria within one week 5-10% asymptomatic
  - Women cervicitis, which if untreated can cause PID

Pelvic Inflammatory Disease
- Lack of prospective studies
- Occurs in approximately 30% of women with untreated gonorrhea
- 1988 estimated 500,000 cases, 200,000 hospitalizations
- Increased risk of ectopic pregnancy, infertility

Control strategies
- Partner notification very ineffective
  - Short incubation period
- Screening strategies, especially among women have been utilized
- Current urine screening test

Chlamydia
- Most common STD in the US
- 4 million cases annually
- Symptoms similar to gonorrhea but less acute, incubation 7-14 days
  - Men urethritis, more than 30% asymptomatic,
  - Women cervical infection, 50% asymptomatic, untreated 30% develop PID

Chlamydia (…continued/2)
- Reported infection more common in women
  - Test conducted at a routine exam
- Rates have increased since 1984
  - Results from increased screening and reporting
  - 1985 fewer than 10 states required reporting, now it is 40
  - Difficulty in identifying trends
- Risk factors
  - Multiple partners, new partner, low SES, young age, poor predictive value and only identify 1/3 of cases

Syphilis
- Cause by bacterium
- Three clinical stages
  - Primary
  - Secondary
  - Late (tertiary and late benign syphilis)
- Latent syphilis
  - Inapparent symptoms
  - Early (<1 year) and late (> 1 year)
Epidemiology of Syphilis

- Risk factors
  - Multiple sex partners
    - Bath houses, crack epidemic
  - Predominately in minority communities, especially in the South
  - 1996, N=11,387 cases (lowest number)

Changing epidemiology of Syphilis

- Since WW II, steady decline
- 1976-81 50% increase predominately among gay white men,
- 1981-84 large decrease, >90% among gay men
- 1984-89 >100% increase in minority heterosexual transmission
- Male:female ratio changed from 4:1 to 1:1
- 1989-1990 large increase in congenital syphilis
- Trends have decreases since then except for Baltimore and a variety of counties in the Southeast

Clinical course of syphilis

- Infection with *Treponema pallidium* with sexual contact involving a mucousal membrane
- Incubation period 10-30 days
- Transmission is relatively inefficient
  - 20% per sexual contact
- Latency period of 3 weeks prior to symptoms
  - Non-infectious
  - Antibiotic use will prevent transmission
  - Widely used to control the spread of syphilis

Clinical course of syphilis (…2)

- Development of initial genital ulcerative lesion (chancre)
  - Painless
  - Patient becomes infectious
  - Systemic disease even in primary syphilis
    - 10-15% have cerebral spinal fluid abnormalities
    - Concern for patients with HIV
    - Left untreated, chancre will heal within 2-3 weeks

Clinical course of syphilis (…3)

- If untreated 4-8 weeks, secondary syphilis develops
  - Systemic vasculitis with high levels of *T. Pallidium* in the blood
  - Dermatological symptoms
    - Palmar or plantar rash, alopecia, mucousal lesions
  - Resolves within 1-2 months of onset

Clinical course of syphilis (4)

- Late complications
  - Develop 10-20 years after early syphilis
  - Earlier with patients with HIV infection
  - Neurosyphilis, cardiovascular syphilis
**Congenital syphilis**
- Transmission rate is > 60%
  - Increased stillbirth rates
  - Clinical syndromes at birth
    - Bone abnormalities
- Transmission occurs transplacentally
  - Screening during 1st and 3rd trimester
  - Treatment during pregnancy
  - Considered a sentinel event
  - Risk factors
    - No prenatal care, crack cocaine use
  - Difficult to diagnose in newborn due to passively acquired maternal antibody

**Intervention**
- After treatment, patient is non-infectious
- Long latency offers opportunity to reduce secondary spread
  - Partner notification and screening
  - Presumptive treatment of partners
- Inexpensive test allows widespread screening
- Treatment during pregnancy prevents vertical transmission
  - Establishment of screening and treatment programs

**Epidemiology of chancroid**
- Most common genital ulcer disease in developing countries
- US, epidemics of heterosexual transmission but no homosexual epidemics
- Related to travel to endemic countries
- Prevention is difficult
  - Difficulty in diagnosis
  - Aggressive partner notification and presumptive TX

**Genital herpes infection**
- Life-long infection, latency and recurrences
- Almost exclusively sexually transmitted
  - 90% HSV-2
  - 10% HSV-1
- Acute infection follows inoculation of the virus to mucosal site

**Clinical features of herpes**
- Primary - Ulceration develops 5-10 days after exposure
  - Systemic signs, fever, myalgia, headache
  - Often asymptomatic
- Recurrent – May develop at any time after primary
  - Prodrome, tingling or itching
- Clinical first episode vs. first clinical episode of recurrent disease
  - Many have serologic evidence of prior infection

**Clinical features of herpes (2)**
- Symptomatic recurrences
  - Less symptomatic and heal faster than primary episode
  - Recurrences more frequent within the first year
  - Risk factors for recurrence
    - Not well defined, physical and psychologic stress
  - Asymptomatic shedding
    - Major role in transmission
    - Occurs about 1% of time
    - Increased with HIV
    - Impact of control strategies
Epidemiology of herpes

- Widely prevalent in the adult population
  - Approximately 1 in 6 of married sexually active Americans (40 million) is infected
  - Difficult to enumerate
  - First-office visits used as a surrogate
    - Increasing since 1970s
  - Higher rates in African Americans

Herpes simplex in pregnancy

- Problem if lesions are present in the birth canal at the time of delivery
- Routine culture at parturition
  - If positive, infant can be started on prophylactic antiviral therapy
- Major risk factor is developing primary herpes during the last trimester
  - 33% neonatal herpes syndrome – fatal or leads to disability
- Caesarian section used to prevent transmission if viral shedding is present

Intervention strategies

- Factors associated with increased transmission
  - Asymptomatic viral shedding
  - Misclassification
  - 11% transmission per year among monogamous partners
  - Independent risk factor for HIV transmission

Human Papillomavirus (HPV)

- RNA virus, more than 80 subtypes
- Majority of infections are asymptomatic
- 3 month incubation period
- Small proportion will develop genital warts (1% of sexually active US population)
- Associated with the development of epithelial cancer
  - Cervical cancer most common
  - Focus is on preventing cancer not HPV infection

PAP smears for Cx Ca Dx

- Long latency and slow progression of cervical cancer
  - Screening is effective
  - Recommendations every 3 years
  - If abnormalities are identified
    - Colposcopy or biopsy

Vaginal infections

- Trichomonas
  - 3 million women annually
  - Large number of asymptomatic patients
  - Treatment with metronidazole
    - May be used during pregnancy
  - Can contribute to PROM in pregnancy
**Control of STDs**
- Many STDs are associated with HIV transmission
- Based on reproductive rate
- $R_0 = \beta CD$
  - $\beta =$ transmission coefficient
  - $C =$ turnover of partners
    - Number of different partners
    - Number of exposures with each partner
  - $D =$ duration of infection

**Intervention strategies**
- Promoting condom use
- Partner notification
- Screening
- Core group targeting
  - Social networks
  - GIS screening

**Condoms and STDs**
- June 2000 NIH/CDC/USAID convened a workshop to evaluate male latex condoms and STDs
- Overall recommendations:
  - Abstinence and long term mutually monogamous relationships are the best ways to prevent STDs
  - Latex condoms can reduce the rate of STDs but are not 100% effective

**Condoms and STDs**
- Two types of transmission
  - Infected semen or vaginal fluids contact mucosal surfaces
    - Discharge diseases: HIV, gonorrhea, chlamydia, trichomoniasis
  - Primarily transmitted through contact with infected skin or mucosal surfaces
    - Genital ulcer diseases: genital herpes, syphilis, chancroid, HPV

**HIV/AIDS**
- Most deadly STD
- More comprehensive research on effectiveness of condoms in preventing HIV/AIDS
- Lab data shows condoms provide an impermeable barrier to particles the size of STDs
- Theoretical basis prevents exposure to semen and vaginal fluids
- Epi studies: one partner infected and the other not show a high degree of protection

**Genital Ulcer disease and HPV**
- Infections can occur in both male and female areas that are and are not covered by condom. Can reduce the risk of herpes, syphilis and chancroid only when the infected area or site of potential exposure is protected.
- Condom use has been associated with a lower rate of cervical cancer.
Genital Ulcer disease & HPV (2)
- Lab studies: Latex condoms provide an impermeable barrier to particles the size of STDs
- Theoretical basis: Depends upon the site of the sore/ulcer or infection. Consistent and correct use would protect against some but not all transmissions

Genital Ulcer disease & HPV (3)
- Epi studies: Inconsistent findings. No conclusive studies have specifically addressed the transmission of chancroid and condom use. Although several studies have found reduced rate of genital ulcers in settings where chancroid is a leading cause of genital ulcers.

Genital Ulcer disease & HPV (4)
- Inconsistent findings of condoms and HPV
- HPV infection is intermittently detected
- Association between condom use and HPV-associated diseases: genital warts, cervical dysplasia, and cervical cancer.
- Reason are unknown. Co-infections with other STDs increase the chance that HPV will lead to cancer. More research is needed.

HIV & Acquired Immunodeficiency Syndrome (AIDS)
- First recognized in the US in 1980-81 among men who have sex with other men (MSM); intravenous drug users (IVDU); and hemophiliacs
- Rare fungal infection of the lung (PCP) and Kaposi sarcoma, heretofore found in immune compromised persons, in young healthy men alerted epidemiologists (Figure)
- Contact tracking indicated chain of transmission suggestive of unique pattern of infection and perhaps new etiologic agent

Epidemiological milestones
- 1981
  - Increase in PCP and KS among young homosexual men
  - PCP among children of injection drug users
- 1983
  - Recognized in hemophiliacs
  - HIV isolated
    - Detected in 99% of AIDS patients

The HIV Virus
- Virus was discovered in 1984, four years after the epidemic, by Robert Gallo (NIH) and Luc Montagnier (Pasteur Institute)
- Serological sample stored in Zaire in 1959 was later discovered to have evidence of HIV leading to speculation of the origin of the virus in chimpanzees
- Another HIV, HIV-2, was later discovered in green monkeys in West Africa
Acquired Immunodeficiency Syndrome (AIDS)

- 1980s – epidemic; 1984 HIV discovery
- 1990’s – pandemic
- Deaths through end of 1997 (in millions)
  - 5.1 ♂; 3.9 ♀; 2.7 children
- Same as malaria deaths in 1997
- Disproportionate burden in sub-Saharan Africa with adult prevalence ↑ 7%
- Estimated worldwide prevalence among adults is 1.1%

Impact of AIDS Epidemic

- Reduced life expectancy of its victims by 20 or more years
- Main cause of death in many sub-Saharan African countries
- Higher rates among adolescents, leading to death at the prime of life
- Catastrophic effect in many societies and economies

Current Facts and Figures

- More than 25 million people have died of AIDS since 1981
- By December 2005 women accounted for 46% of all adults living with HIV worldwide, and for 57% in sub-Saharan Africa
- Young people (15-24 years old) account for half of all new HIV infections worldwide - more than 6,000 become infected with HIV every day.
- Of the 6.5 million people in developing and transitional countries who need life-saving AIDS drugs, only 1 million are receiving them.

AIDS in the developed countries

- Among the leading causes of death in the age group 25-44 in the US. Leading cause between from 1992 through 1995.
- In Europe, homosexual/bisexual transmission was leading cause for contracting HIV. Superseded by IDU since 1990.
- In developing countries transmission is mainly heterosexual

Characteristics of the agent

- HIV is a lentivirus of retrovirus subfamily
- Inserts itself into host’s DNA—provirus
- Remains latent in resting lymphocytes
- Transcription and translation occurs when cells are activated resulting in assembly of viral proteins to form virions
- Attacks and weakens immune system
- High replication rate (10x10^9 viral particles/day) and a high mutation rate (as high as 3x10^6 per day)
Types of HIV

- **HIV-1** and HIV-2
  - Some genetic differences
  - Same mode of transmission
  - HIV-1
    - Worldwide transmission
    - Increased perinatal transmission 20-35%
    - Younger age group (20-34)
    - Classified into 10 genetic subtypes
  - HIV-2
    - Primarily West African and India
    - Perinatal transmission 0-4%, mean age 45-55

HIV Genotypes

- Three groups (strains) of HIV-1
  - M has 11 genetic subtypes
    - A, B, C, D, E, F, G, H, I, J, K
      - Viral recombination has been recognized, which occur by packaging RNA different subtypes into the same viral particles resulting in recombinant HIV in coinfect patients.
      - Reombinant forms are either:
        - Circulating recombinant forms (CRF)—If same recombinants are found commonly circulating
        - Unique recombinant forms (URF)—If recombinants are found only in a few individuals
  - N
    - Geographically limited to W. Africa
  - O

Host Susceptibility & Infectivity

- Determined by
  - **Host factors**—genetic polymorphism (see page 801 of Nelson textbook)
  - **Viral genotype**—Subtypes C and E have higher replication rates compared to B; recombinant forms AC, AD, BE have higher infectivity and rapid progression
  - **Environmental**—Parasitic infections, STDs, malaria, TB, nutritional deficiencies, and other environmental insults that result in chronic immune activation contribute to HIV infection rate and rapid progression of to fully blown AIDS

HIV natural history

- Three phases
  - **Acute**
    - High HIV levels, active immune response, symptoms of viral disease
  - **Clinical latency**
    - No clinical symptoms, viral replication
  - **Chronic infection**
    - Progressive symptomatic, clinical disease, non-AIDS defining conditions, AIDS
      - AIDS: PCP and TB most common

Manifestations of acute infection with HIV

- Constitutional symptoms of viremia characterized by:
  - Fever, malaise, joint pains, etc.
  - Macropapular rash
  - Penile ulcers in males

Manifestations of HIV infection with progressive decline of immunity

- Aggravation of latent illnesses
  - CD4 count is 300-400
    - Herpes zoster
    - Tuberculosis
    - Oral Candidiasis
    - Kaposi Sarcoma
HIV detection
- ELISA identifies presence of HIV
- Western blot confirmatory test
- The two tests are applied in series
- Staging of infection
  - Plasma viral load
  - CD4 counts

Disease progression predictors
- The level of viral load at a set point
- Immunological insult due to comorbid infections
- Host genetic polymorphism
- Staging of infection
  - Plasma viral load
  - CD4 counts

Is there immunity to HIV?
- May be there is ...
  - Genetic mutation in some people
    - Delta32 is a gene mutation the keeps CCR5 from latching to the surface of the CD4 T-cells preventing the HIV from infecting the cell, i.e., "door remains closed".
    - 1% of Northern Europeans have it and it is believed to be mutation from surviving the massive epidemic of bubonic plague.
    - It is a recessive gene and for protection, both parents must pass the mutation to the offspring.

Screening test with Elisa

<table>
<thead>
<tr>
<th>Elisa Test</th>
<th>HIV Status</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>HIV +</td>
<td>HIV -</td>
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<tr>
<td>Positive</td>
<td>980</td>
<td>9900</td>
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<tr>
<td>Negative</td>
<td>20</td>
<td>89100</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>99000</td>
</tr>
</tbody>
</table>

\[\text{Sensitivity} = \frac{980}{1000} = 98.0\%
\]

\[\text{Specificity} = \frac{89100}{99000} = 90.0\%
\]
Infectious Disease epidemiology BMTRY 713 (Lecture 17)  
Midterm Reviews and Recaps  

Screening with Western Blot

<table>
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<tr>
<th>Western Blot test</th>
<th>HIV Status</th>
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</thead>
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<td>HIV +</td>
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<tr>
<td>Positive</td>
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<td>950</td>
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<tr>
<td>Negative</td>
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<td>98150</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>99000</td>
</tr>
</tbody>
</table>

Sensitivity $\Rightarrow \frac{900}{1000} = 90.0\%$

Specificity $\Rightarrow \frac{98150}{99250} = 99.0\%$

Series Testing with Western Blot of those tested positive with Elisa (N=10,880)

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<th>Western Blot test</th>
<th>HIV Status</th>
<th>Total</th>
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</thead>
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<td>HIV +</td>
<td>HIV -</td>
</tr>
<tr>
<td>Positive</td>
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<td>40</td>
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<tr>
<td>Negative</td>
<td>80</td>
<td>9860</td>
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<tr>
<td>Total</td>
<td>980</td>
<td>9900</td>
</tr>
</tbody>
</table>

Sensitivity $\Rightarrow \frac{900}{980} = 91.8\%$

Specificity $\Rightarrow \frac{9860}{9900} = 99.6\%$

Parallel Testing with Elisa (El) and Western Blot (WB)

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<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV +</td>
<td>HIV -</td>
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<tr>
<td>EL +</td>
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<td>9800</td>
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<tr>
<td>WB +</td>
<td>40</td>
<td>4850</td>
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<tr>
<td>EL+ &amp; WB+</td>
<td>760</td>
<td>100</td>
</tr>
<tr>
<td>EL- &amp; WB-</td>
<td>10</td>
<td>84250</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>99000</td>
</tr>
</tbody>
</table>

Sensitivity $\Rightarrow \frac{990}{1000} = 99.0\%$

Specificity $\Rightarrow \frac{84250}{99000} = 85.1\%$

Testing Summary

<table>
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<th>Test Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Elisa alone</td>
<td>98.0</td>
<td>90.0</td>
</tr>
<tr>
<td>WB alone</td>
<td>90.0</td>
<td>99.0</td>
</tr>
<tr>
<td>Series +</td>
<td>91.8</td>
<td>99.6</td>
</tr>
<tr>
<td>Parallel +</td>
<td>99.0</td>
<td>85.1</td>
</tr>
</tbody>
</table>

Modes of transmission

Sexual behavior (75-80% of HIVs)

- Unprotected receptive anal intercourse is the most risky behavior (♂ to ♀ | ♀ to ♀)
- Lowest risk among ♀ to ♀
- Heterosexual moderate risk
- Partner studies
  - Infected ♂ to uninfected ♀ $\approx 20\%$
  - Infected ♀ to uninfected ♂ $\approx 1.4-12\%$
- Multiple sexual partners

Injection drug use (15-20%)

- Higher in cocaine than heroin
  - Shorter half life and more frequent injections
- Sharing needles
  - Social institution
  - Lack of access to clean needles
Modes of transmission (3)

- Perinatal transmission
  - Estimated 65-80% of transmission during delivery
    - Risk reduction with C/Sections OR=0.43
    - AZT administration reduces incidence by 67%
    - Breast feeding (12-15% of vertical)

Modes of transmission (4)

- Blood transfusion
  - Infrequent in developed countries
  - Historically very high among hemophiliacs (>90%)
  - Estimated acquisition from false negative is 26 per 1 million transfusion

Modes of transmission (5)

- Transmission to health care workers
  - HIV seroconversion from needle stick injury 0.4%
  - Greater risk with exposure to high quantities of blood

Impact of antiretroviral therapy on epidemicity

- Natural history of AIDS - death 2 years
- 17 years of treatment
  - 1987 AZT developed
  - 1990s triple combination
    - Viral suppression
      - 95% adherent 81%
      - 70-80% adherent 35%
      - <70% adherent 6%
  - Mortality declined by nearly 6 fold with triple combination therapy

Prevention

- “Safe sex”
- Reduce needle sharing
- Identify and treat HIV+ mothers
- Screening of blood products
- Universal precautions

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 increase 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**: Cytomeaglovirus, 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; Epi link is “a smoking gun”.
- Thus far, 41 Microencephaly 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%.
- 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.

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

**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

**Pulsed-field gel electrophoresis (PFGE)**

- A highly discriminative molecular typing technique that is used in epidemiological studies worldwide.
- It is based upon the variable migration of large DNA restriction fragments in an electrical field of alternating polarity.

**Bioterrorism Basics**

*What makes the use of biological agents so attractive to the terrorist?*

- **Ease of Acquisition**
  - Information readily accessible on World Wide Web
  - Ingredients are not difficult to attain
- **Ease and Economy of Production**
  - Only basic microbiology equipment necessary
  - Small labs require no special licensing
  - Investment to cause 50% casualty rate per sq. km:
    - (Conventional weapon $2000, nuclear $800, anthrax $1)
- **Lethality**
  - 50 kg aerosolized anthrax = 100,000 mortality
  - Sverdlovsk experience, former USSR, April 2, 1979

*What makes the use of biological agents so attractive to the terrorist? (…continued)*

- **Stability**
- **Infectivity**
  - Weaponized agents may be easily spread
  - Clinical symptoms days to weeks after release
- **Low Visibility**
- **Ease and Stealth of Delivery**
  - Remote, delayed, undetectable release
  - Difficult/impossible to trace origin of agent
Infectious Disease epidemiology BMTRY 713 (Lecture 17)
Midterm Reviews and Recaps

March 7, 2016

Selassie AW (DPHS)

**Bioterrorism Basics**

**Routes of Delivery of Biological Agents**

1. **Aerosol** is most likely method of dissemination
   - Easy, silent dispersal
   - Maximum number of victims exposed
   - Inhalation is most efficient portal of an infectious agent
2. **Food/Water-borne dispersal** less likely
   - Less stable, ineffective for some agents
   - Inefficient compared to aerosol

**Bioterrorism Basics**

**Events Suggesting Release of a Bio weapon**

- Multiple people ill at the same time (epidemic)
- Previously healthy persons affected
- High morbidity and mortality among affected individuals
- Identification of diseases and pathogens unusual to a particular region
- Recent terrorist claims or activity
- Unexplained epizootic of sick or dead animals

**Bioterrorism Basics /...2**

- CDC has defined and categorized bioterrorism agents into three categories
  - **Category A**: agents with both a high potential for adverse public health impact and that also have a serious potential for large-scale dissemination
  - **Category B**: Agents are moderately easy to disseminate and have low mortality rates.
  - **Category C**: Pathogens that might be engineered for mass dissemination because they are easy to produce and have potential for high morbidity or mortality (examples: nipah virus, hanta virus, and multi-drug resistant Tuberculosis (MTB)).

Further Reading: [http://www.bt.cdc.gov/bioterrorism/overview.asp](http://www.bt.cdc.gov/bioterrorism/overview.asp)  
[http://emergency.cdc.gov/agent/agentlist.asp#r](http://emergency.cdc.gov/agent/agentlist.asp#r)

**Agents of Bioterrorism**

**Bacterial Agents**

1. **Bacillus anthracis** (Anthrax)
2. **Yersinia pestis** (Plague)
3. **Francisella tularensis** (Tularemia)
4. **Brucella spp.** (Brucellosis)
5. **Coxiella burnetii** (Q Fever)
6. **Burkholderia mallei** (Glanders)
7. **Vibrio cholerae** (Cholera)

**Viral Agents**

1. **Variola virus** (Smallpox)
2. **Venezuelan Equine Encephalitis Virus** (VEE)
3. **Hemorrhagic Fever Viruses**: Ebola, Marburg, Lassa
4. **Argentine and Bolivian Hemorrhagic Fever Viruses**
5. **Hantavirus**
6. **Congo-Crimean Virus**
7. **Rift Valley Fever Virus**
8. **Yellow Fever Virus**
9. **Dengue Virus**
Agents of Bioterrorism

Biological Toxins

1. Botulinum Toxins
2. Staphylococcal Enterotoxin B
3. Ricin [http://emergency.cdc.gov/agent/ricin/]
4. Mycotoxins (T2)—ergot, aflatoxin

Anthrax

- Caused by contact with spores of Bacillus anthracis, a spore-forming, gram-positive rod
- Three distinct forms of clinical illness:
  - Cutaneous by inoculation of skin lesions with spores; common, easily recognized and treated
  - Inhalation by inhalation of spores into the lower respiratory tract; rare, difficult to recognize, > 80% mortality (classic description = Woolsorter’s disease)
  - Gastrointestinal by ingestion of spores in contaminated meat; rarely encountered but highly lethal

Smallpox

- Worst-case scenario biological agent
  - Highly contagious once rash present (not before)
  - World’s population is largely susceptible
  - Up to 30% case fatality rate in non-immune
  - Secondary attack rate of 25-40% (10-20 secondary cases can be expected per index case)
  - No specific treatment available
  - Globally very few physicians currently practicing have seen actual cases
  - Virus has been weaponized by Soviets, uncertain who exactly owns viable stocks

Smallpox

- Caused by Variola virus (Orthopox virus)
- Virus is stable in environment
- Spread primarily by respiratory droplets, also by contact, fomites
- Two distinct types of smallpox:
  - Variola Minor (Alastrim): diminutive lesions and mild systemic toxicity
  - Variola Major: Ordinary (subtypes discrete, semi-confluent, confluent), Modified, Flat, Hemorrhagic

Smallpox

Clinical Presentation

- 7-17 day incubation period
- Prodromal phase: 2-4 days of malaise, fever, rigors, headache, backache, delirium
- Rash then develops on face, hands, forearms and legs, including palms and soles (centrifugal distribution is important distinguishing feature).
- Initial rash is maculopapular. In 1-2 days, lesions become vesicular, then evolve into round, tense pustules deeply imbedded in the dermis. Crusts form on 8th to 9th day of rash
- Crusts separate to form depressed, hypo pigmented scars

Bioterrorism Basics

What we do as Healthcare Professionals

- Maintain a high index of suspicion by including biological agents in differential diagnoses
- Learn to recognize historical and physical examination findings suggestive of bioweapon exposure
- Stay informed of local, regional and national epidemiologic trends
- Be knowledgeable about treatment and prophylaxis of patients exposed to biological agents
- Know whom to report suspected biological agent exposures and illnesses to (Police, State Intelligence agency, Infectious Disease Specialists, Local and State Health Officials)