Infectious Disease Epidemiology: Basic Principles for Mathematical Modeling

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Goal

- To review concepts necessary for the study and control of infectious diseases
- Become familiar with some commonly used epidemiology terms
- Discuss how these concepts relate to mathematical modeling
Outline

- Part I- Basics of Infectious Disease Epidemiology
  - Epidemiological Triangle
  - Infection Transmission
  - Basic Epi Terms

- Part II- Sources of Epidemiological Data
Goals of Infectious Disease Epidemiology

1. Identify and describe a causative agent
2. Understand the relationship between the host, the agent and the environment
3. Interrupt disease transmission to prevent spread
Goals of Infectious Disease Modeling

1. Better understanding of how disease is spread

2. Predict future course of epidemics
   • medical costs
   • impact of outbreaks

3. How to control the spread of epidemics
   • Education?
   • Immunization?
   • Isolation?

Epidemiological Triangle

- **HOST**
  - Age, gender, genetics
  - Behaviour (smoking, sex, work)
  - Exposures (animal)
  - Immune suppression, vaccination

- **AGENT**
  - Pathogenicity
  - Infectivity
  - Immunogenicity
  - Environmental stability
  - Infective dose

- **ENVIRONMENT**
  - Social
    - crowding
    - “networks”
    - public health
  - Physical
    - urban/rural
    - climate
Biological Classification

- **Bacteria**
  eg. TB, Gonorrhea, syphilis

- **Viruses**
  eg. HIV, Influenza, Measles

- **Fungi**
  eg. Cryptococccus

- **Protozoan**
  eg. Malaria, Giardia

- **Prions**
  eg. “Mad cow” disease
Site of Infection

- Respiratory - eg. cold/flu
- Hepatitis
- Skin Infection/Soft Tissue
- Cardiovascular
- Diarrheal Diseases
- STDs/Genitourinary
- Central Nervous System - eg. Meningitis
- Bone/Joints
Modes of Transmission

- **Contact** - Direct – Skin/Sexual
  - Indirect - eg. Infected blood

- **Airbourne**: eg. TB, chickenpox

- **Vectors** (eg. mosquitos) eg. malaria

- **Foodborne/Waterborne**: eg. cholera

- **Vertical** - Transplacental
  - Perinatal
  - Post-partum (eg. breastfeeding)
Classification by Reservoir in Nature

- **Human**
  - eg. Gonorrhea, HIV, smallpox

- **Environmental**
  - Plants, Soil, Water
  - Cholera, Legionella – Water
  - Tetanus, Botulism - Soil

- **Animals**
  - Zoonoses (animal to human)
  - eg. Bats - Rabies
  - eg. Rodents – Hantavirus, Yersinia pestis
Transmission:

<table>
<thead>
<tr>
<th>Susceptible</th>
<th>Infected</th>
<th>Infectious</th>
<th>Removal</th>
</tr>
</thead>
</table>

Level of Agent in Host

Infection

Min. level for Transmission

Time

Latent

Incubation

Symptomatic

Nelson et al. Infectious Disease Epidemiology p.151
Latent Infection - SLIR (SEIR) Model

Example: TB

- Susceptible
- Latent (Exposed)
- Infectious
- Recovered
Incubation Period

- Incubation period: time from exposure to development of disease
  - Expressed as a range
  - Time can be variable – depending on infection
  - Represents time needed for agent to reach a critical level to create clinical signs and symptoms
  - Can be infectious while being in the incubation period
    - Difficulty in control of spread,
      - eg. Measles, Hepatitis A, Chickenpox, etc.
Figure 2-2 Incubation periods of common bacterial diseases (top panel) and viral diseases (bottom panel).

Incubation Period
Bacterial Diseases
Outcomes of Exposure

Exposure

Infectivity

No Infection

Infection

http://www.nwcphp.org/docs/infectious/attachments/transcript.pdf
Infectivity

The proportion of exposed persons who become infected

\[
\frac{\text{Persons who become infected}}{\text{Exposed persons in the population}}
\]

-Related to dose of agent transmitted - i.e. number of infectious particles transmitted

Examples: Tuberculosis: Low Infectivity

Measles/Smallpox: High Infectivity

* This is related to beta \( (\beta) \) of models, eg.

\[
\frac{dS}{dt} = -\frac{\beta SI}{N}
\]

Outcomes of Exposure

- Exposure
  - No Infection
  - Infection
    - Infectivity
    - Pathogenicity
      - Disease
Pathogenicity

Proportion of infected people who develop clinical disease

Number infected and exhibiting disease
Total number infected

Examples:

Tuberculosis: Low Pathogenicity
Smallpox/Common cold: High Pathogenicity

http://www.nwcpd.org/docs/infectious/attachments/transcript.pdf
Outcomes of Exposure

Exposure → Infectivity → Pathogenicity → Virulence

- No Infection
- Infection
- Disease
- Serious Infection & Severe Disease
Virulence

Proportion of persons with clinical disease who become severely ill or die

\[
\frac{\text{Number with severe disease}}{\text{Total number with disease}} \quad \text{or} \quad \frac{\text{Fatal cases}}{\text{Total cases}}
\]

High virulence
- Ebola
- Smallpox
- Pandemic Flu

Low virulence
- Rhinovirus
## Outcomes of Exposure

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infectivity</th>
<th>Pathogenicity</th>
<th>Virulence</th>
</tr>
</thead>
<tbody>
<tr>
<td>chickenpox</td>
<td>high</td>
<td>high</td>
<td>very low</td>
</tr>
<tr>
<td>common cold</td>
<td>intermediate</td>
<td>intermediate</td>
<td>very low</td>
</tr>
<tr>
<td>leprosy</td>
<td>very low</td>
<td>very low</td>
<td>high</td>
</tr>
<tr>
<td>measles</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>smallpox</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>tuberculosis</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
</tbody>
</table>

http://www.nwcphp.org/docs/infectious/attachments/transcript.pdf
Environment

- Interacts with agent and host
- Allows exposure to occur

- Physical: Geology, Climate, Habitat
  - Biological: Human Populations, Flora, Fauna
    - Sources of Food, Influence on Habitat, Vectors

- Socioeconomic: Occupations, Crowding, Urbanization

- Disasters: Earthquakes, Floods, Wars
Animal-Human Co-Habitation

- Outbreaks of the H5N1 virus (Bird Flu) seen, especially in Asia
  - 330 cases since Nov 2003
  - >50% of cases are fatal
  - direct contact with infected poultry, or surfaces contaminated by their feces
- rural areas: households keep poultry flocks, which often roam freely, enter homes or share outdoor areas where children play

http://www.cdc.gov/flu/avian/gen-info/facts.htm
Conflict and HIV

- Sexual abuse/rape of female civilians
- Large proportion of military infected
  - 2-5X higher than general population
  - 2000, HIV prevalence rates among some South African military units of between 60% and 90%
  - Uganda, 27% of military personnel have tested HIV positive.

- Food insecurity – sex for food or money
- Forced migration
- Loss of Infrastructure
Factors Affecting the Risk of Contracting a Disease
May be Biological, Behavioural or Sociodemographic
Examples
- Age (young/old)
- Immunity
- Genetic Susceptibility
- Socioeconomic Status
- Nutritional status
Example: Immunity / Vaccination

Direct Immunity
- by Infection
  - Protected by being infected again (variable length of time)
  - eg. Measles, Mumps, Rubella, Chickenpox, etc.
    (vs. infections that do not generate long-lasting immunity, eg. Chlamydia)

- By Vaccination
  - Variable Protection – may need multiple doses or boosters
SIR and Immunization

Susceptibles

Infected

Immune
Vaccinations

- 1798 Smallpox
- 1882 Rabies
- 1890’s (Cholera)
- 1890’s Typhoid
- 1920’s BCG
- 1920’s Diphtheria
- 1920’s-90’s Pertussis
- 1930’s Yellow Fever
- 1940’s Influenza
- 1950’s/60’s Polio
- 1960’s Measles
- Mumps, Rubella
- 1970’s Meningococcus
- 1980’s Hemophilus B
- 1970’s Varicella
- 1980’s Hepatitis B
- 1920’s-90’s Pneumococcus
- 1980’s Hepatitis A
- 1990’s Rotavirus
- 1990’s Lyme
- 2002 Papillomavirus
### Impact of Immunization

**Table 312–1** Baseline 20th Century Annual Morbidity and 1998 Provisional Morbidity from Nine Diseases with Vaccines Recommended before 1990 for Universal Use in Children—United States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Baseline 20th Century Annual Morbidity</th>
<th>1998 Provisional Morbidity</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164*</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885†</td>
<td>1</td>
<td>100%‡</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271§</td>
<td>6279</td>
<td>95.7%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1314‖</td>
<td>34</td>
<td>97.4%</td>
</tr>
<tr>
<td>Poliomyelitis (paralytic)</td>
<td>16,316¶</td>
<td>0**</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282‡‡</td>
<td>89</td>
<td>100%‡</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209‡‡</td>
<td>606</td>
<td>99.6%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745§§</td>
<td>345</td>
<td>99.3%</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>823</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B</td>
<td>20,000¶¶</td>
<td>54***</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

Nelson et al. Infectious Disease Epidemiology p.151
Epidemiology of Immunity / Vaccination

- Indirect: Herd Immunity
  - The number of people immune in the population decreases the risk of infection to the susceptible by diminishing the probability of exposure.
  - Related to the proportion of individuals with complete immunity in order to prevent transmission/epidemics
    (e.g. measles & other vaccine-preventable infections)
**Herd Immunity**

- Susceptible
- Immune
- Infected
- Disease transmission

http://www.nwcphp.org/docs/infectious/attachments/transcript.pdf
Basic reproductive rate (or ratio) \( R_0 \)

The number of secondary cases generated from a single infective case introduced into a susceptible population
Basic reproductive rate ($R_0$)

- If $R_0 > 1$, then disease will increasingly spread (epidemic)
- If $R_0 = 1$ then disease will become stable (endemic)
- If $R_0 < 1$ then disease will die out
Level of Immunization to achieve $R_0 < 1$

If $p =$ prevalence of persons immunized

$$p > 1 - \frac{1}{R_0}$$

**Eradication of Measles (WHO):**

- $R_0 = 15$ (western countries)
- to prevent a measles epidemic (herd immunity)
  $$p > 1 - \frac{1}{15} = 0.94 = 94\%$$
Epidemiological Triangle

HOST

AGENT

ENVIRONMENT
Public Health/Prevention Interventions at individual, community or global level

- Improved water supply
- Sanitation
- Hygiene
- Vaccination
- Vector control
- Treatment of infectious cases
- Sexual behaviour change
- Regulatory measures, e.g. quarantine, food standards
- Other, e.g. Antimicrobial prophylaxis, Screening of blood supply
Other Epi Terms

- Incidence vs. Prevalence
- Incidence:
  - Number of New Cases in a given time period
- Prevalence:
  - Number of cases existing at a given time
Incidence Rate

Rates measure disease levels in population.

Incidence Rate

\[
\frac{\text{# of new cases of disease}}{\text{# at risk for the disease}}
\]

http://www.nwcphp.org/docs/infectious/attachments/transcript.pdf
Prevalence

Prevalence

\[ \frac{\text{# of existing cases of disease present at a specified time}}{\text{# at risk for disease at that specified time}} \]
# HIV-Epidemic in Numbers

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Incidence</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>People newly infected with HIV in 2002</td>
<td>5.0 million</td>
<td>4.2 million</td>
<td>2.0 million</td>
</tr>
<tr>
<td>Adults</td>
<td>4.2 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>2.0 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &lt; 15 years</td>
<td>800,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of people living with HIV/AIDS in 2002</td>
<td>42.0 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>38.6 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>19.2 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &lt; 15 years</td>
<td>3.2 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS deaths in 2002</td>
<td>3.1 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>2.5 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.2 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &lt; 15 years</td>
<td>610,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS deaths since the beginning of the epidemic until the end of 2001</td>
<td>21.8 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>17.5 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>9.0 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &lt; 15 years</td>
<td>4.3 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS orphans since the beginning of the epidemic until the end of 2001</td>
<td>14.0 million</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimates of the worldwide HIV epidemic, end of year 2002.
Source: UNAIDS (Joint United Nations Programme on HIV/AIDS)

© AIDS Information Switzerland
Part II: Sources of Epidemiological Data

We have the model -

\[
\frac{dS_N}{dt} = (1 - p)(1 - q)A - \beta_s S_N (I_N + I_D) - \mu S_N
\]

\[
\frac{dI_N}{dt} = q(1 - p)A + \beta_s S_N (I_N + I_D) - (\mu + d)I_N
\]

– now where’s the data?
“And, it was so typically brilliant of you to have invited an epidemiologist.”
Types of Data

- Surveillance Data
- Research Studies
  - Laboratory
  - Medical
  - Epidemiological: Observational Studies
“Public Health Surveillance is the: 
- ongoing,
- systematic collection,
- analysis,
- interpretation and 
- dissemination of health data to help guide public health decision making and action”

**Surveillance is Data for Action**
Functions of Surveillance

1. Estimate the magnitude of a health problem
2. Determine the distribution of illness
3. Detect an epidemic or outbreak
4. Evaluate control measures (eg. vaccines)
5. Monitor changes in infectious agent (eg. drug resistant strains)
6. Facilitate planning and setting priorities
7. Respond to emerging health threats
Notifiable Diseases

- Mandatory reporting of these infections by Physicians and/or Laboratories
- Choice of Diseases are based on factors such as:
  - Incidence
  - Severity
  - Transmissibility
  - Preventability
### Some Notifiable Diseases in Alberta

<table>
<thead>
<tr>
<th>Blood Borne Pathogens</th>
<th>Communicable Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>– HIV/AIDS</td>
<td>– Congenital CMV</td>
</tr>
<tr>
<td>– Hepatitis B</td>
<td>– Congenital Rubella</td>
</tr>
<tr>
<td>– Hepatitis C</td>
<td>– Diphtheria</td>
</tr>
<tr>
<td><strong>STIs</strong></td>
<td>– Leprosy</td>
</tr>
<tr>
<td>– Chlamydia</td>
<td>– Malaria</td>
</tr>
<tr>
<td>– Chancroid</td>
<td>– Measles</td>
</tr>
<tr>
<td>– Gonorrhea</td>
<td>– Mumps</td>
</tr>
<tr>
<td>– Lymphogranuloma Venereum</td>
<td>– Pertussis</td>
</tr>
<tr>
<td>– Syphilis</td>
<td>– Poliomyelitis</td>
</tr>
<tr>
<td></td>
<td>– Rubella</td>
</tr>
<tr>
<td></td>
<td>– Tuberculosis</td>
</tr>
</tbody>
</table>
Reporting Process

1. Detected by Lab
2. Public Health Nurse Assigned to Case and collects information (e.g., sex, age, exposure risks)
3. Province Compiles Data
4. Provincial Data sent to Federal Public Health
5. National Statistics Compiled

Physician
- Treats Patient
Figure 11

Chlamydia in Alberta: Number of Cases and Crude Rate by Year of Diagnosis, 1998 to 2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>5,253</td>
<td>184.1</td>
</tr>
<tr>
<td>1999</td>
<td>5,420</td>
<td>185.4</td>
</tr>
<tr>
<td>2000</td>
<td>6,032</td>
<td>203.2</td>
</tr>
<tr>
<td>2001</td>
<td>6,488</td>
<td>214.6</td>
</tr>
<tr>
<td>2002</td>
<td>7,358</td>
<td>238.4</td>
</tr>
<tr>
<td>2003</td>
<td>7,901</td>
<td>252.1</td>
</tr>
<tr>
<td>2004</td>
<td>8,347</td>
<td>262.6</td>
</tr>
<tr>
<td>2005</td>
<td>8,839</td>
<td>274.3</td>
</tr>
<tr>
<td>2006</td>
<td>10,452</td>
<td>316.9</td>
</tr>
</tbody>
</table>

Source: Communicable Disease Reporting System - Sexually Transmitted Infections Database as of April 30, 2007
Provided by: Disease Control & Prevention and Public Health Surveillance & Environmental Health Branches, Alberta Health & Wellness - May 4, 2007
Syphilis Outbreak - Alberta

Treponema pallidum causes syphilis.
**Figure 19**

Infectious Syphilis in Alberta: Number of Cases and Crude Rate by Year of Diagnosis, 1995 to 2006

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>Cases</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>1996</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>1997</td>
<td>9</td>
<td>0.3</td>
</tr>
<tr>
<td>1998</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>2000</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>2001</td>
<td>23</td>
<td>0.8</td>
</tr>
<tr>
<td>2002</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>2003</td>
<td>37</td>
<td>1.4</td>
</tr>
<tr>
<td>2004</td>
<td>75</td>
<td>2.3</td>
</tr>
<tr>
<td>2005</td>
<td>146</td>
<td>4.5</td>
</tr>
<tr>
<td>2006</td>
<td>218</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Note:** Includes primary, secondary and early latent stages of syphilis. Early congenital cases are excluded.

**Source:** Communicable Disease Reporting System - Sexually Transmitted Disease Database (April 30/07).

**Provided by:** Disease Control & Prevention and Public Health Surveillance and Environmental Health Branches, AHW.
### Figure 20

#### Reported Infectious Syphilis Rates in Alberta and Canada, 1994 to 2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Canada</th>
<th>Alberta</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>95</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>96</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>97</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>98</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>99</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>00</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>01</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>02</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>03</td>
<td>2.9</td>
<td>1.2</td>
</tr>
<tr>
<td>04</td>
<td>3.5</td>
<td>2.3</td>
</tr>
<tr>
<td>05</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>06</td>
<td>5.1</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Note:** Includes primary, secondary and early latent stages. National rates for 2005 and 2006 are preliminary.

**Source:** Surveillance and Epidemiology Section, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada 2006; [http://www.phac-aspc.gc.ca/std-mts/stdcases/casmts/index.html](http://www.phac-aspc.gc.ca/std-mts/stdcases/casmts/index.html)(April 30/07)

**Provided by:** Public Health Surveillance and Environmental Health Branch, AHW.
Figure 32
Rates of Infectious Syphilis by Region, Alberta 2006 and 2000-2006 Combined

Note: Includes primary, secondary and early latent stages of syphilis.

Source: Communicable Disease Reporting System - Sexually Transmitted Disease (STD) Database as of April 30, 2007.
Provided by: Disease Control & Prevention and Public Health Surveillance and Environmental Health Branches, AHW.
Research - As a Source of Data

- Animal Studies
- In-vitro Studies
- Cross-Sectional Studies
- Case-Control Studies
- Cohort Studies
- Randomized Clinical Trials

Laboratory Studies
Cross-Sectional Study

- Also called “prevalence survey”
- Taking a “snapshot” of a population in terms of infection status and exposure risks
- Can give you hints as to causation

Defined Population

Gather Data on Exposure and Disease

Exposed
- Have Disease
- Do Not Have Disease

Not Exposed
- Have Disease
- Do Not Have Disease
Case-Control Studies

- Compare exposures of people with disease (case) and people without a disease (control)
- Can identify exposures associated with an outcome
Cohort Study

- Compare disease status of people with and without exposure
- Follow cohort prospectively, therefore can calculate Incidence
Randomized Clinical Trial

- Population is randomized to two treatments – new and current (or placebo)
- Follow subjects forward in time and determine outcomes
- Used to test hypotheses

Defined Population

- New Treatment
  - Develop Disease
  - Does Not Develop Disease
- Current Treatment
  - Develops Disease
  - Does Not Develop Disease
Male Circumcision and HIV

- Postulated that circumcision will prevent infection (and transmission) of HIV
  - biological reasons
  - positive trends seen in cross-sectional, case-control and cohort studies
- Randomized HIV negative men to circumcision or no circumcision
- Followed up over time and measured HIV incidence
Why Use Modelling?

- conduct conceptual experiments that would be difficult/impossible
  - easier to manipulate than a whole system
  - predict impact of changes on a system
e.g. using simulations
- determine plausibility of epidemiological explanations
- improve understanding of unexpected relationships
- (relatively) low cost
Acknowledgements

- Dr Stan Houston – for his slides!
- References:
  - Giesecke. Modern Infectious Disease Epidemiology.
  - Nelson. Infectious Disease Epidemiology.
  - Gordis. Epidemiology.