Impact & Control of Infectious Diseases
A Clinician’s Perspective

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Portrait of misguided enthusiasm...

In 1969, the US surgeon general, William H Stewart, enthused by success against typhoid, cholera and smallpox, told congress that it was time to...

"close the book on infectious diseases"
Outline

• Importance of Infectious Disease
• Historical Impact of Endemic and Epidemic Infectious Diseases
• What’s happening now
• What might we expect in the future
  – With a mathematically inclined audience in mind!
Infectious Diseases as a group remain the most common cause of death and DALY’s lost globally.
But this burden of infectious morbidity and mortality is not shared equally
Causes of Mortality by Region
Adults 15-59

Deaths/1000 Adults

Lancet '06;367:1747
Deaths/1000. Children Aged 0-4
1990-2001
Alberta Notifiable Disease Summary Sept. 2007

Infectious & Parasitic Diseases Rates in Alberta

Age Specific Rates of IPD among First Nations and Non-First Nations, in Alberta, 2000-2007

[Bar chart showing age-specific rates of infectious diseases for different age groups and regions]
Rich Countries 100 years Ago Resembled Poor Countries Today
The Dramatic Decline in Mortality in the Past Century is Largely Explained by Decreased Mortality from Infection

Figure 2. Crude Mortality Rates for All Causes, Noninfectious Causes, and Infectious Diseases
The history and the great successes of public health have been in infectious disease prevention and control.
Impact of Infectious Diseases: Summary Points

• Infectious diseases are major causes of morbidity and mortality worldwide
• The importance of infectious diseases is greater in poor countries
• The major decline in infectious disease impact in developed countries is public health’s greatest success and indicates the immense potential for improving health globally through control of infectious diseases
Epidemics & Plagues

- Plagues described in biblical & early history—disease entity usually unclear
- Athens 430-29 BC killed ¼ of land army
- Rome 165-70 (Antonine plague) ¼-1/3 population mortality
Historical Examples of Epidemics in the Americas

- Cortes defeated the Aztec empire with 600 men and a smallpox epidemic
- Pizarro defeated the Inca empire with 168 men and extreme duplicity, following loss of the Inca emperor & his successor to smallpox
- Overall estimated 95+% depopulation of Americas post Columbus—”not a virgin continent, but a widow”
The Black Death

• 542, Roman empire: Justinian plague
• 1331 plague started in China
• Traveled to Middle East via trade routes
• 1346 plague introduced at the siege of Caffa (Crimea), → Europe by ship
• Frequent recurrences: last in England 1665, in the Mediterranean 1721
• 1894 epidemic in Hong Kong dispersed to all major ports within 10 years
Plague: impact

- Mortality in Europe 1346-50 est. 33%
- European population continued to decline until mid 1400’s
- Population of China halved 1200-1393
- Contributed to major cultural and social changes: anti-Semitism, possibly undermining of religious authority, decline of serfdom & other social changes
- Most recent outbreak in India 1994
- Still widely endemic in rural rodents
The Cholera Pandemics

- 1\textsuperscript{st} Pandemic started Calcutta 1817
- 13\% population mortality Cairo 1831
- “millions” of deaths world wide 19\textsuperscript{th} century.
- Global dissemination enabled by global sea transport
- Generated a high level of fear
- *Cholera epidemics an important factor in the establishment of boards of health and the development of urban sanitation*
- Recent return to South America after a century of absence
- Remains endemic in S. Asia, recurrently epidemic in Africa
ID’s in Battles & Wars

• “And typhus, with its brothers and sisters,--plague, cholera, typhoid, dysentery,--has decided more campaigns than Caesar, Hannibal, Napoleon….Zinsser

• Typhus & dysentery along with other factors, decimated Napoleon’s troops in Russia

• Distribution of smallpox-infected blankets to Indians, Lord Amherst 1763

<table>
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<tr>
<th></th>
<th>wounded</th>
<th>died of wounds</th>
<th>sick</th>
<th>died of disease</th>
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<td>French</td>
<td>39,869</td>
<td>20,356</td>
<td>196,430</td>
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<td>18,283</td>
<td>4,947</td>
<td>144,390</td>
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<td>Russian</td>
<td>92,381</td>
<td>37,958</td>
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Crimean War: 1854-56
Epidemics are Not Ancien

Polio
• Terrified Canadian parents in the 1950’s
• 50 years later, approaching global eradication

HIV
• Largest impact of any epidemic in human history

Influenza
• Annual epidemics since ?
• 40+ million deaths in 1918
• Pandemic expected any time

West Nile Virus

SARS
HIV Impact; Mortality. A Highly Dynamic Epidemic
Major Historical Developments in Infectious Diseases
History: The ‘Germ’ Theory

- Many diseases we now know to be infectious were recognized in antiquity, e.g. by Hippocrates
- 1546: germ theory proposed by Fracastoro
- 1683 van Leeuwenhoek saw “animalcules” through a microscope
- 19th Century: “Miasma” theory of disease widely popular, “proven” by yellow fever
- 1854 John Snow and the Broad Street pump supported water-borne hypothesis
“Germ theory” cont’d

• 1864 Louis Pasteur disproves spontaneous generation, later discovers bacterial pathogens in silkworms

• 1874 on...discovery of disease-causing bacteria: *M. leprae, P. falciparum, B. anthracis, M. tuberculosis, V. cholerae*

• Faced skepticism
  – Ingestion of a beaker of *Vibrio cholerae* by a German miasmatist, von Pettenkoffer “disproved” its pathogenicity
Insect Transmission

- 1879 Ross demonstrated mosquito transmission of filaria
- 1881 Finlay publicized the role of *Aedes aegypti* yellow fever transmission (led to elimination of yellow fever from Havana in a year)
Measurement of Fever

• 1592 Galileo devised a thermometer
• 1717 Fahrenheit scale
• Boerhaave 1668-1738: first clinical use of thermometry—documented normal temperature and diurnal variation
• Wunderlich 1815-77: Documented importance of fever as a clinical sign
Anti-infective measures

- B.C. era, China: use of *Artemesia annua* (qinghaosu) for malaria (also hemorrhoids)
- 1633 cinchona (quinine) brought to Europe
- 1891 Diphtheria antitoxin
- 1910 Ehrlich: Salvarsan (arsenical) effective against syphilis
- 1932 Domagk: sulfonamides (human 1935)
- 1928 Fleming: Penicillin (1st clinical use 1941)
- 1944 Waksman: Streptomycin (tuberculosis)
- 1989 zidovudine (AZT)
Key People in the Early History of Infectious Diseases
Louis Pasteur 1822-95

- Discovered 2 infectious diseases of silkworms
- Disproved spontaneous generation
- Proved microbial cause of fermentation
- Cultured aerobic and anaerobic organisms;
- developed “pasteurization”
- 1881 Demonstrated vaccination of sheep with attenuated anthrax bacilli
- Developed a rabies vaccine and gave it to a boy bitten by a rabid dog
Robert Koch 1843-1910

• Discovered *B. anthracis, M. tuberculosis, V. cholerae*

• Developed tuberculin
  – Initially as a therapy, now important diagnostic tool

• Developed “Koch’s postulates” – 1st framework for assessing infectious etiology of disease
Koch’s postulates
valuable precedent in establishing criteria for causality, but with many limitations

- 1. The specific organism should be shown to be present in all cases of animals suffering from a specific disease but should not be found in healthy animals.

- 2. The specific microorganism should be isolated from the diseased animal and grown in pure culture on artificial laboratory media.

- 3. This freshly isolated microorganism, when inoculated into a healthy laboratory animal, should cause the same disease seen in the original animal.

- 4. The microorganism should be re-isolated in pure culture from the experimental infection.
Preventive Interventions & Public Health
Successes

• Traditional practices:
  – avoiding pork (Judaism, Islam)
  – boiling water for tea (China)
  – Variolation—widespread in near and far East prior to adoption in West
  – (N.B. many traditional practices had negative health impacts e.g. applying dung to neonatal cord, withholding fluids in diarrhoea, wife inheritance in HIV era, etc.)
Quarantine

• Leprosy isolated under biblical injunction
• 1348 Dubrovnik (former Yugoslavia) during the Great Plague, all immigrants were obligatorily isolated for 40 days
Vaccination

- Starting with Antiquity…variolation
- Vaccinia (small pox vaccine) 1798
Accidental Health Improvements: By-products of development

- Water supply for convenience
- Sewer for esthetic reasons
- Cleanliness, for social & esthetic reasons
- Better nutrition
- Decreased crowding
- Better housing → less rat and insect friendly

**Note:** *most involve improved socio-economic conditions*
Sanitation/Boards of Health

- Largely in response to threat of cholera
- 1832 1st local boards of health (England)
- 1848 Central Board of Health, England
- Edwin Chadwick: Development of urban water and sewer
- 1866 New York Board of Health
- *all prior to general acceptance of contagion theory
- Note: identification of infectious etiology led to a more reductionist “scientific” approach to public health & may have de-emphasized a focus on broader social improvement.
Surveillance: History

John Graunt (1620 - 1674) published
Observations on the Bills of Mortality
January 1662
Some conclusions from the “Bills of Mortality”

- That about one-third of all that were quick die under five years old

- That some diseases and casualties keep a constant proportion whereas some others are very irregular

- Annis 1603, and 1625, about a fifth part of the whole died, and eight times more than were born.
Military Public Health

- Washington & Napoleon mandated smallpox vaccination of armies 1776, 1805
- “Sanitary police” monitoring and controlling yellow fever and malaria mosquitoes enabled construction of the Panama canal
- Russo-Japanese war 1902-4: systematic inoculation & sanitary police ↓ disease mortality to ¼ of battle mortality
- Routine de-lousing stations in western armies in WWI limited typhus
- STI prevention WWII
- Ongoing issues: mandatory vaccination, “Gulf War syndrome, antimalarial drug development, preoccupation with bioterrorism
The Overall Health Impact of War is, of Course, Profoundly Negative

- > 600,000 Iraqi deaths since the war there Burnham et al Lancet. 2006 ;368:1421-8.
- War continues to have a major impact on health including direct trauma, malnutrition, epidemics and loss of public health and curative services
Great Works of Literature with Medical Themes

- The Bible (leprosy & various plagues)
- The Magic Mountain (TB) … Thomas Mann
- La Peste (The Plague) Albert Camus
- Love in the Time of Cholera … Gabriel Garcia Marquez
- La Traviata, La Boheme (TB)
- Philadelphia (& others) HIV
Brief history of modelling

• Daniel Bernoulli (1760) - smallpox
• William Farr (1840) – smallpox
• Hamer (1906) – rate of contact
• Ronald Ross (1908) - malaria
• Kermack & McKendrick (1927)
The future

• “Emerging infectious diseases”
  – Human behaviour
  – Climate change
• Disease eradication
• Drug resistance; the post antibiotic era?
• New tools
  – Vaccines
  – Antimicrobial agents
  – Diagnostic technologies
  – Molecular epidemiology
  – Modelling!
• The old diseases will still be here!
Emerging Infectious Diseases

1976 Ebola virus
1977 *Legionella*
1979 HTLV 1
1982 *Borrelia burgdorferi*
1982 *E.coli 0157:H7*
1983 HIV
1989 Hepatitis C virus
1992 *V. cholerae 0139*

Ebola
Legionaire’s disease
T cell leukemia myelopathy
Lyme disease
hemolytic uremic syndr
AIDS
Hepatitis etc.
Cholera (new strain)
<table>
<thead>
<tr>
<th>Year</th>
<th>Agent Name</th>
<th>Description</th>
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<tr>
<td>1993</td>
<td>Sin Nombre Virus</td>
<td>Hantavirus Pulmonary Syndrome</td>
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<tr>
<td>1994</td>
<td>Sabia Virus</td>
<td>Brazilian Hemorrhagic Fever</td>
</tr>
<tr>
<td>1995</td>
<td>Human Herpesvirus v. 8</td>
<td>Kaposi's Sarcoma etc</td>
</tr>
<tr>
<td>1996</td>
<td>New prion</td>
<td>New Variant Creutzfeld Jakob Disease</td>
</tr>
<tr>
<td>1997</td>
<td>H5N1 avian influenza</td>
<td>Influenza birds &amp; Man</td>
</tr>
<tr>
<td>1999</td>
<td>Nipah virus</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>2001</td>
<td>Metapneumovirus</td>
<td>Respiratory infection</td>
</tr>
<tr>
<td>2003</td>
<td>SARS-associated coronavirus</td>
<td>SARS</td>
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Ebola Virus
Temporal Course of the Bovine Spongiform Encephalopathy Epidemic in Cattle and Subsequent Human nvCJD Epidemic

Estimated 2 Million cattle infected
West Nile Surveillance: 2003

[Image of a map of Canada showing the locations of dead birds submitted and those found positive for West Nile virus]
Our patient is the most northerly reported human HPS.
H5N1 Avian Influenza
First Report of What Turned out to be AIDS
HIV
CURRENT
EPI

Zimbabwe
Disease Eradication—A Rash Idea?
Last wild case Somalia
Oct 26, 1977
Global annual reported polio cases, 1974-2001
Countries Reporting Wild Polio in 2006 and Routes of Viral Spread 2002-6

NEJM 2006;355:2508
Drug Resistance: 
Back to the Future?
*P. falciparum* Cure Rate with Various Drugs, Thailand
CQ=chloroquine, SP=pyrimethamine/sulfadoxine, M=Mefloquine (mg/kg)
Q=quinine, QT=quinine/tetracycline
Trends in malaria mortality in children aged 0–4 years (green) and aged 5–9 (orange), Senegal

2-3 fold increase in deaths and admissions for severe malaria concurrent with spread of chloroquine resistance

Am J Trop Med Hyg 2001;64:12-17
XDR TB
Tugela Ferry, South Africa 2006

- 41% of all cases cultured multidrug resistant (MDR)
- 53 (24% of MDR) are extensively drug resistant (XDR)
- 51% of XDR had had no prior treatment (therefore presumed transmitted)
- 64% hospitalized at some time prior to XDR TB onset (likely site of transmission)
- 44/44 tested HIV+
- 87% isolates molecularly similar
- 98% mortality, median days to death 16
Figure: Dynamics of the emergence and transmission of multiple strains of tuberculosis resistant to a variety of first-line and second-line drugs

Predicted data generated using the Amplifier model and uncertainty analysis. To generate these predictions we assumed that extensively drug-resistant tuberculosis (XDR-TB) cases could not be cured, and that the cure rates of multidrug-resistant tuberculosis (MDR-TB) cases were not increased substantially above their current rates. The figure shows the quantitative relation between the percentage of MDR tuberculosis cases that are XDR tuberculosis and the percentage of MDR tuberculosis cases that are detected and treated. The fitted curve is exponential ($y = 3.912e^{0.0409x}$; $R^2 = 0.76$).
The Old Diseases:
Still Causing Problems
Falciparum malaria
(colour darkness correlates with level of endemicity)

Snow R et al. Nature 05;434:214
Sustained Benefit of Treated Bednets (Kenya)

Lindblade et al. JAMA 2004;291:2571

Malaria Vaccine Trial
entomological inoculation rate (EIR)

- Number of infective bites received/person/day “h = mas” where:
  - m = anopheline density in relation to humans
  - a = average # persons bitten/mosquito/day
  - ma = human landing rate (measured by bait catch techniques)
- s = proportion of mosquitoes with sporozoites in their salivary glands (measured by mosquito dissection)
- Vector capacity (VC) = \( ma^2 p^n / -\log p \) where p= daily survival probability of vector, n= extrinsic incubation period of vector

EIR varies from <1 to > 1000 across Africa
Reported Infectious Syphilis Rates in Alberta and Canada, 1994 to 2006

10 Congenital Syphilis Cases, Alberta, 2002 to 2006

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(April 30/07)
Trypanosomiasis cases reported to WHO BMJ 2002;325:204
Young Man With Fever, Muscle Pain, Headache & Rash on Return from Sri Lanka
Evolving distribution of *Aedes aegypti*
Ascaris

PREVALENCE (%)

AGE (YEARS)

○ >1/10ml
△ >10/10ml
● >100/10ml
□ >1000/10ml
Distinctive Features of Helminth (worm) Epidemiology

- Individual worm burden is the main determinant of disease
- Worm burden is asymmetrically distributed in the population
- Almost all (Strongyloides, Capillaria exceptions) require a stage outside the definitive host in order to reproduce
Hospital Acquired Disease and Infection Control

Childbed Fever – Vienna 1846

![Graph showing maternal mortality over years with intervention point]

- First
- Second

Year:
- 1841
- 1842
- 1843
- 1844
- 1845
- 1846
- 1847
- 1848
- 1849
- 1850

Maternal mortality (%):
- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14
- 16
- 18
New Tools
Molecular Epidemiology
Restriction fragment length polymorphism “RFLP”

Fingerprinting of Mycobacterium tuberculosis
“Family Tree” of HIV viruses

Unrelated viral strains

Sporadic cases from this community

Two closely related “clusters”
Results

- The unusually high female to male rate suggests substantial under-testing in men; many women were diagnosed through routine prenatal testing while a number of male partners have declined HIV testing.

- Using conservative assumptions (male=female and adding 20% for undetected cases), HIV prevalence approaches 1% among adults 15-54 in this rural population.

- This worryingly high prevalence is largely attributable to intra-community heterosexual transmission, with important implications for prevention and control measures.
Summary

- Infectious disease epidemiology has a fascinating past and an exciting future, in which modelling will surely play a growing role.