The Struggle with Infectious Disease

Lecture 4
Polio

• Heine-Medin’s disease
• Infantile paralysis
• Poliomyelitis
  • polios = grey
  • myelos = marrow
• Enteric (intestinal) viral infection
• Slightly in throat and tonsils
Poliovirus

- RNA genome
  - 7500 nucleotides
- Protein capsid
- No envelope
- 30nm diameter

- Smallpox
  - 186,000 nucleotides
  - 300nm diameter

One of the simplest viruses
Polio

• Transmission
  – Infected feces
  – Person to person contact
  – Mucus & phlegm

• Incubation time typically 7-14 days

• Usually results in
  – Mild fever
  – Sore throat
  – Headache
• 1 in 100 becomes serious
• Leaves intestinal tract into blood and lymph
• Infects motor neurons that cause muscles to contract
• Extent of paralysis is difficult to predict
• Highly seasonal: 35 X as many cases in August as April

• Other than paralysis, survivors are healthy
History

- Historically no epidemics or pandemics
- 1500 BC stone carving
- Mentioned by Hippocrates
- Mid 1800’s: small clusters in Europe and America
- Usually isolated communities in summer
- ~ a dozen cases in a short time
Polio Distribution
Polio Epidemics

• First US epidemic Otter valley near Rutland Vermont 1894

• 1916 Epidemic in New York: 8,900 cases
  – Largely children/young adults
Polio Epidemics

• 1917 Outbreak in Vermont

• Plotted and reported by Dr Charles Caverly
  – Cause was not known
  – 123 cases, 18 dead, 50 permanent paralysis
  – Mostly male
  – Appeared in clusters

• Limited public gatherings
  – Particularly Chataqua meetings
Polio Epidemics

• 1905 Epidemic in Sweden
• Ivar Wickman (Sweden) identified non-symptomatic carriers through epidemiology
  – Small village of Trästena
  – Traced progress along streets and railway lines
  – Identified a school as a prominent role
• Noted that poliomyelitis and infantile paralysis were stages of the same disease
Polio Epidemics

• Named the disease Hiene-Medin’s Disease
  – After his mentors who had done the original work in Stockholm

• Papers were published in German
  – Not readily available to American researchers
Epidemics Developed

- By 1907 epidemics had spread widely
- 1916 major epidemic in NE United States particularly New York
- Most affected was Staten Island, one of the richest boroughs
- 27,000 infected: 7,000 deaths
- First major epidemic in Canada: 1927 – 1932
  - West to East in 2 year increments
A Suburban Disease

- Areas with good infrastructure and sanitation were hardest hit. Less common in slums
- Made no sense in terms of common public health practice.

- We now know polio is/was endemic in areas of poor sanitation
- Resulted in a typical ‘childhood illness’
What Causes Poliomyelitis?

• Most infectious diseases of the time which were treatable with vaccines were bacterial:
  – Typhoid, Typhus, Cholera,
  – Pasteur and other institutes had become skilled in bacteriology

• Several vaccines e.g. smallpox were made by diluting obvious sources

• Virus as an infective agent had not been identified
What Causes Poliomyelitis?

• Karl Landsteiner 1908
  – Isolated spinal cord from recently deceased boy
  – Filtered mixture (to remove bacteria)
  – Injected into stomach of Rhesus monkey which became ill
  – Followed Koch’s principles
  – Not bacterial
Foundations

• Rockefeller Foundation:
  • Initial splash with meningitis vaccine
  • Studied polio in monkeys (1911)
  • Determined infection route was respiratory (wrong)
  • Only RH moneys can catch polio they used new world monkeys
  • Lots of money and star power
    – State of art facilities
    – High stature lead scientists
Foundations

• 1921 Franklin Roosevelt contracts polio
• Found hot springs helped his recovery
  – Founded the Warm Springs Foundation
• 1938 FDR established the National Foundation for Infantile Paralysis (March of Dimes)
  – Established the model for all following medical foundations
  – Funded most polio vaccine research
Discovery of a Cause

• 1938: Fecal/oral route of transmission was established (remember 1911)
• 1949: Existence of three strains of polio were established
• IgG therapy was demonstrated to work in animals in the 1930s
• Because of vaccine failures in the 1930’s IgG did not gain widespread use in humans until the late 1940’s
• Supply of ‘convalescent serum’ was limited
Therapy

- Immunoglobulin is an older term for antibodies, usually when they are in plasma.
- Immunoglobulin G (IgG) is the most common form (75%).
- They are extracted from one patient and injected in another in hope that some of the antibodies are appropriate.
Treatment

• Polio causes paralysis and atrophy due to nerve loss
• Initial treatment involved bracing and immobilization for support
• Respiratory paralysis required ‘iron lung’ developed in 1927 by Philip Dinker
Therapy

• During epidemics iron lung centres were required
  – First intensive care facilities

• Kenny therapy was introduced into US and Canada in late 1940’s
  – Sister Elizabeth Kenny
  – Repatterning
Therapy
Vaccine Development
Vaccine Development

• The science of modern virology had to be developed in order to develop a polio vaccine

• 1948: Polio virus cultured in monkey kidney tissues (first in *vitro*)

• Two approaches to vaccines were available
  – Live attenuated oral vaccine (Sabin)
  – Killed virus injected vaccine (Salk)
  • Was ready for trials first
Clinical Trials

• Ethical and social issues over vaccine trials
  – There had been a lot of bad vaccine tried on people: more complex than bacterial vaccines
  – These resulted in side effects and death
  – Questions regarding use of children from foundlings homes

• First clinical trial Feb 24, Watson Elementary Home for Children in Pittsburgh

• Followed a slightly stepwise trial ending with 1.8 million children across the US
The Vaccine

• Results of the field trial were announced on April 12, 1955.

• National vaccination began in 1955
  – 35,000 cases in 1953
  – 2,000 cases in 1957
  – 161 cases in 1961
Canada’s Contribution

• 1947: Polio research program established at Connaught Labs/U of T
  – Funded by
    • Canadian Life Insurance Companies
    • Federal Government
    • March of Dimes (quietly)

• 1949 Enders developed culture method (Vero Cells) but difficulty with yield
Canada’s Contribution

• Connaught scientists tried a growth medium they had been using for cancer cells
• ‘Medium 199’ worked extremely well and was the breakthrough to commercial scale production
• Culture method was developed which allowed growth of polio cultures
• Prepared over 3000l for US clinical trial
Canada’s Contribution

• As ‘acknowledgement’ NFIP offered some ‘left over’ vaccine to Canada for a clinical trial but it was late in the season.

• Plans proceeded for a large scale trial in Canada in 1955 (following year)

• Connaught labs prepared vaccine which was tested twice
  – At Connaught labs
  – In Ottawa Hygiene Lab
Cutter Incident

- After the 1955 announcement there was a clamour for vaccine
- Five companies were licenced to produce the vaccine and rushed it to market
- Cutter Labs was a primarily vet vaccine company with Gov’t contracts for antibiotics
- 149 confirmed cases of polio from vaccination all were traced to Cutter vaccine
Cutter Incident

• Immediate investigation indicated that procedures were being followed, however complete inactivation was not achieved
• Three other companies had smaller scale problems with inactivation
  – production cannot be directly transferred
• Vaccination was halted in the United States
• NIH was reprimanded for lack of oversight and excessive trust of NFIP
Canadian Response

- Canada was about to start the major clinical trial
- Pressure to stop trial but serious outbreaks in previous 2 summers
- Paul Martin Sr., minister of Health had to make decision: suspend or proceed
Factors to consider

- US clinical trial had no problems
- Connaught had been involved in vaccine prep
- There were reports that safety results had been ignored in rush to get vaccine to market in US
- Cutter facility was definitely substandard
- Canadian vaccine was tested routinely by company and government scientists
- Minister Martin trusted his scientific advice
Canadian Response

- Despite concerns from the PM, trials went ahead
- No incidents, no problems with inactivation
- Provided some confidence for the US in the Salk vaccine
Canadian Response

Canada Has Vaccine
To Aid 1,500,000

Ottawa, April 12 — (Staff Special) — The Dominion Government today set its seal of approval on the Salk anti-polio vaccine.

“Thus substantial additional supplies will be available to Canadian physicians and health agencies,” he added.

Mr. Martin pointed out that provincial health agencies now
# Culture Media

## Formulation for Eagle’s Minimum Essential Medium (EMEM) ATCC® 30-2003

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Oral Polio Vaccine

• 1955: Salk announces successful vaccine
• Albert Sabin develops Oral Polio Vaccine
• Prepared for clinical trials
  – No real interest in the US because Salk vaccine had been demonstrated to work
Oral Polio Vaccine

• Oral Polio Vaccine (OPV) has several advantages
  – Provides immunity in the gut where the virus first attacks
  – IPV provides immunity at the level of the nervous system
  – Does not require a sterile syringe

• Supported by the scientific community
Oral Polio Vaccine

• The virus was rendered unable to cause disease in the nervous system by culture in non-human cells at sub-physiological temperatures
  – 7 passages to render virus completely nonfuctional
  – 3 passages were used initially
Oral Polio Vaccine

• Three competing vaccines:
  – Sabin (Vero Cells)
  – Cox (eggs)
  – Koprowski (chimp kidney)

• Sabin ran trials in Russia
  – Reported no problems

• Cox vaccine had caused cases of polio
Oral Polio Vaccine

- WHO was convinced of relative merit of OPV
  - Evaluated data available
  - Selected Sabin’s vaccine
- Cold war politics became involved
- Reticence regarding IPV after Cutter Incident
Oral Polio Vaccine

- Problems
  - Reversion
  - OPV diseases due to shed virus
  - VAPP
    - Vaccine Associated Paralytic Poliomyelitis
  - Monkey viruses (SV40)
    - Now test for specific viruses
- No longer used in most countries where polio has been eradicated
Polio Eradication Program

• Program adopted by WHO in 1988
• Led by WHO, UNICEF and Rotary Foundation
  – 2.5 billion children
  – 200 countries
  – 20 million volunteers
  – $8 billion
Polio Eradication Program

• By 2006:
  – Reduction in cases by 99%
  – Remained endemic in only four countries
    • Nigeria
    • India
    • Afghanistan
    • Pakistan

• The last 1% is elusive
# Polio Eradication Program

## Polio
- Transmitted through feces
- 1/100 clinical
- Carriers common
- 3 serotypes
  - Reversion and drift
- $0.10/dose

## Smallpox
- Transmitted person to person
- Few if any sub-clinical cases
- Few, if any carriers
- Only 1 serotype
- More expensive
The last 1 percent

- 2006: 4 countries
- 2010: re-established in Chad, Angola and Democratic republic of Congo
  - breakdown in infrastructure
  - Politics and war
- Recent flare-up in Egypt
  - From Pakistan
The last 1 percent

- Currently 3 countries with endemic polio:
  - Afghanistan
  - Pakistan
  - Nigeria

- Localized outbreaks in:
  - Chad Lake basin
  - Laos
  - Guinea (2015)
Polio Eradication Program

• Provided inspiration for Gates foundation
  – Inexpensive vaccine
  – Global coordination

“The fight to eradicate polio is a proving ground, a test. Its outcome will reveal what human beings are capable of, and suggest how ambitious we can be about our future.”
Vaccine Questions

• MMR/autism (fraud)
• Thimerosal (mercury in vaccines) ... not
• Neurologic disorders with flu & flu vaccine
• Aluminum in vaccines
  – Role of adjuvants
• Risk-Benefit calculation
• ‘monkey virus’ contamination: SV 40
Reference Slides
(Dr. Christopher Rutty)

Key Global & Canadian Public Health Foundations, 1882-1910

1882 - Ontario Provincial Board of Health (1st in Canada)

1886 - Ontario Smallpox Vaccine Farm established in Palmerston
Conquering The Crippler:
Connaught & Polio Vaccines
Connaught & Polio Vaccines:
Key Global & Canadian Research Foundations

• 1908 – Poliovirus first isolated
• 1910 – First major polio epidemic year in Canada
• 1927-32 - Major polio epidemics begin in B.C. and then in turn strike Alberta, Manitoba, Ontario, Quebec
• 1928 – Connaught prepares polio convalescent serum from blood of recovered cases in hopes of minimizing paralysis in new cases
• 1937 – Ontario’s worst polio epidemic - 2,456 cases, 110 deaths (more than 4,000 cases across Canada)
• 1938 – National Foundation for Infantile Paralysis (March of Dimes) founded by US President F.D. Roosevelt
• 1939-43 – Connaught conducts epidemiological studies into non-paralytic poliovirus strains supported by NFIP grants
Connaught & Polio Vaccines:  
Key Global & Canadian Research Foundations

- **1947** - Dr. A.J. Rhodes (right) launches a comprehensive research program at Connaught Laboratories to investigate the virology, epidemiology and clinical diagnosis of polio.

- **1949** - Hopes for a polio vaccine raised when a research team in Boston, led by Dr. J. Enders, discovered a way to grow poliovirus in a test tube using non-nervous tissues.
“Medium 199”: The 1st Synthetic Media & Connaught’s Breakthrough Coincidence

- **1949** - Connaught research team develops the first chemically defined “Medium 199,” originally for nutritional studies of cancer cells using tissue cultures
- “Medium 199” a precise mixture of more than 60 ingredients
“Medium 199”
The Key to Poliovirus Growth

- 1950-51 - Using Ender’s methods, Rhodes was growing poliovirus in test tubes, but reliant on traditional animal-based tissue culture sera

- 1951 - Through his friendship with one of the “Medium 199” discoverers (Morgan), a member of Rhodes’ research team, Dr. A.E. Franklin, tried the new synthetic medium for cultivating poliovirus in tissue cultures

- The use of this medium vastly improved the yields and purity of poliovirus cultures.
Dr. Jonas E. Salk: Vaccine Pioneer @ University of Pittsburgh

- In the meantime, by 1951, Dr. Jonas Salk had shown that an inactivated poliovirus vaccine could prevent polio in monkeys.

- News of Connaught’s serum-free “Medium 199” and its successful use by Rhodes’ team for poliovirus cultivation, opened the door for Salk to develop and test an inactivated poliovirus vaccine that was safe for use in use in human children.

- However, Salk could only make his vaccine on a small scale.
“The Toronto Method”
Facilitating Large Scale Poliovirus Production

- **1952** - Recognizing Connaught’s experience in developing large scale vaccine and biologicals production technologies (i.e. insulin, diphtheria toxoid, penicillin), the NFIP financed a major pilot project at the Toronto Labs to cultivate poliovirus in large quantities.

- **1953** - Building on her experience with ‘deep culture’ pertussis and other vaccines, Dr. Leone N. Farrell successfully developed a method to mass produce poliovirus using Medium 199 in large Povitsky bottles incubated on special rocking machines.

Dr L.N. Farrell and prototype “Toronto Method” bottle rocking machine, 1953
Salk Polio Vaccine Field Trial: Connaught Supplies Poliovirus Fluids

- **July 1953** - In the wake of the worst polio epidemic year in U.S. history (and the start of Canada’s worst), and encouraged by Salk’s progress and Connaught’s “Toronto Method,” the NFIP asked the Labs to provide all of the poliovirus fluids required to conduct an unprecedented national field trial of Salk’s inactivated polio vaccine.

- **1953-54** - Connaught produced over 3,000 litres of poliovirus fluids for the U.S. trial

- Large bottles of poliovirus fluids were shipped to U.S. by station wagon to Park Davis in Detroit and Eli Lilly in Indianapolis for inactivation and processing into the finished vaccine

- **1954-55** - Connaught then focused on full preparation of vaccine for eventual Canadian use
April 12, 1955: “V-Day”
Salk Vaccine Trial Results Announced

- **April 12, 1955** – Unprecedented media attention to announcement of field trial results in Ann Arbor, Michigan
- Salk vaccine 60-90% effective against the three types of poliovirus
- Vaccine immediately licensed in U.S. and Canada
- In Canada, Salk vaccine distributed through federal-provincial free program for children and subjected to further study of its effectiveness

- Canadian distribution of Connaught’s Salk vaccine continued without interruption despite suspension of U.S. immunizations after 79 polio cases linked to incompletely inactivated vaccine lots produced by Cutter Laboratories in California.