Comstock Lecture 2013

The Place of Children in the Global Epidemiology of Tuberculosis

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Faculty of Medicine and Health Sciences
Stellenbosch University
South Africa
Introduction

• Recent years have seen a concerted effort to ensure the inclusion of children in global efforts to manage TB.

• A number of initiatives to bring childhood TB into the wider TB “family”.
Introduction
An historical approach to the development of our knowledge of the natural history of childhood TB and its implications for research and the global epidemiology and management of TB in children.
Introduction

The North American contribution to our knowledge of childhood TB and its relevance to our current understanding of the epidemiology and management of childhood TB.
Recent data of the Global Epidemiology of TB in Children

• In 2010 approximately 8.8 million people were diagnosed with TB and there were 1.4 million deaths globally including 500,000 women and 64,000 children.

• However it is estimated that close to 1/3rd of cases, including many children, are not detected by health systems.
Recent Global Epidemiology of TB in Children


• Amongst the 22 high burden countries, figures for childhood tuberculosis were not reported by 12.

• It is estimated that children comprise 15-20% of the global childhood tuberculosis burden.
It is also estimated by Stop TB Department, WHO that there were between 490,000 and 550,000 childhood TB cases globally in 2010.

Malawi 1998: 12% of notified cases were children.

South Africa children age < 13 years comprised 14% of the notified TB burden (407/100,000).
The diagnosis of TB and the differentiation of disease and infection

The discovery of *Mycobacterium tuberculosis* by Robert Koch in 1882 made possible the accurate diagnosis of TB.

From approximately 1910 with the aid of tuberculin testing, chest radiology and sputum culture and microscopy it became possible to detect TB infection, to differentiate disease from infection and determine the prognosis after infection.
The diagnosis of TB and the differentiation of disease and infection

• TB infection in childhood was not very often fatal.
• Many children survived infection without any overt signs and only minor symptoms.

**HOWEVER**

• Certain groups of children were, subject to a considerable morbidity and mortality.
The diagnosis of TB and the differentiation of disease and infection

From approximately 1920 a number of centers in North America started long-term studies of children infected with *M. tuberculosis*. Differing criteria used to enroll children in studies.
Wade Hampton Frost. 1880-1938

Qualified in Medicine at the University of Virginia 1903. 1917 diagnosed with TB; spent several months in a sanatorium. 1922. Professor & Chairman of the Department of Epidemiology and Public Health Administration at Johns Hopkins University. Approximately 1928 he began to study tuberculosis.
Wade Hampton Frost 1880-1938

• In 1930 Dr EL Bishop established an epidemiological study of TB in Trenton, Gibson County, Tennessee.
• Dr Bishop consulted Frost a former teacher for guidance in the study of this chronic infectious disease. Defects in the initial study were noted and a second study planned in Kingsport, Sullivan County, Tennessee to test a proposed methodology.
Frost WH. Risk of persons in familial contact with pulmonary tuberculosis. Am J Publ Hlth 1933; 23: 426-432

- The negro population of Kingsport, Tennessee 1930-1931.
- A unit of the Tennessee State Department of Health.
- 132 families and 794 present and former family members.
- Age-specific annual TB death-rates and attack rates were determined. Contacts classified as sputum positive or negative for Mtb.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Contact history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Person years in comparison</td>
<td></td>
</tr>
<tr>
<td>Cases of TB, annual rate/1,000</td>
<td>26</td>
</tr>
<tr>
<td>Deaths from TB, annual rate/1,000</td>
<td>10</td>
</tr>
<tr>
<td>Deaths all causes, annual rate/1,000</td>
<td>28</td>
</tr>
</tbody>
</table>
Frost WH. Risk of persons in familial contact with pulmonary tuberculosis. Am J Publ Hlth 1933; 23: 426-432

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases of TB</th>
<th>Deaths from TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate/1,000</td>
</tr>
<tr>
<td>&lt;1</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>1-4</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>5-9</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>10-19</td>
<td>19</td>
<td>9.9</td>
</tr>
<tr>
<td>20-29</td>
<td>17</td>
<td>7.8</td>
</tr>
<tr>
<td>30-39</td>
<td>18</td>
<td>11.6</td>
</tr>
<tr>
<td>40-49</td>
<td>6</td>
<td>7.8</td>
</tr>
<tr>
<td>50-59</td>
<td>4</td>
<td>13.0</td>
</tr>
<tr>
<td>&gt;60</td>
<td>4</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>8.0</td>
</tr>
</tbody>
</table>
“...the disease is of slow evolution and we cannot assume the risk ... is concentrated within a year or even a decade following establishment of known exposure.”

“...sufficiently large group of people under systematic, exact observation for such length of time is a difficult task...”
“Hence, observation of the exposed group must extend over a sufficient number of years to define the rates of morbidity and mortality prevailing in successive periods throughout the usual span of life.”
Frost WH. The age selection of mortality from tuberculosis in successive decades. Am J Hyg 1939; 30: 91-96

Death rates per 100,000 from TB, all forms, for Massachusetts, 1880 to 1930, by age and sex, with rates for cohort 1880 indicated.
Frost WH. The age selection of mortality from tuberculosis in successive decades. Am J Hyg 1939; 30: 91-96

• “...the curve of mortality from tuberculosis shows a continuous movement either upward or downward...there is perhaps no statistical record which is potentially of more significance...if we could accurately interpret this record we would be well on our way to knowing the epidemiology of tuberculosis.”
Frost WH. The age selection of mortality from tuberculosis in successive decades. Am J Hyg 1939; 30: 91-96

- “...the most striking changes in mortality rate do not correspond to reasonably probable changes of like extent in rate of exposure to infection...

- Constancy of age selection...in successive cohorts suggests rather constant physiological changes in resistance (with age) as the controlling factor.”

- Following the Trenton, and Kingsport studies there was considerable correspondence and planning between Frost and the Tennessee health authorities.

- In December 1931 the Williamson County Study was launched

• The study ran for **24 years**; **19 papers** and **two books** resulted.

• **Initial objectives included:**
  
  • The systematic study of the **familial incidence** of tuberculosis
  
  • Investigation into the **evolution of TB infection in childhood**, especially children who are in close contact with a tuberculous parent

- 767 households investigated.
- Focus on 298 (38.9%) “sputum-positive” index cases.
- 60 new TB cases and 37 TB deaths were recorded amongst 1358 household associates followed for an average of 6.4 years.
New cases of TB and attack rates per 1,000 person years of household associates of white "sputum-positive" index cases by age and sex.

<table>
<thead>
<tr>
<th>Age group yrs</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person yrs</td>
<td>New cases</td>
<td>Rate /1,000</td>
</tr>
<tr>
<td>&lt; 5 yrs</td>
<td>138.25</td>
<td>3</td>
</tr>
<tr>
<td>5-14</td>
<td>583.5</td>
<td>0</td>
</tr>
<tr>
<td>15-24</td>
<td>657.0</td>
<td>5</td>
</tr>
<tr>
<td>25-34</td>
<td>329.0</td>
<td>2</td>
</tr>
</tbody>
</table>
New cases of TB and attack rates per 1,000 person years of household associates of *coloured* “sputum-positive” index cases by age and sex.

<table>
<thead>
<tr>
<th>Age group yrs</th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person yrs</td>
<td>New cases</td>
<td>Rate /1,000</td>
<td>Person yrs</td>
</tr>
<tr>
<td>&lt; 5 yrs</td>
<td>53.3</td>
<td>1</td>
<td>18.8</td>
<td>65.5</td>
</tr>
<tr>
<td>5-9</td>
<td>156.0</td>
<td>1</td>
<td>6.4</td>
<td>185.8</td>
</tr>
<tr>
<td>10-14</td>
<td>219.5</td>
<td>1</td>
<td>4.6</td>
<td>233.5</td>
</tr>
<tr>
<td>15-24</td>
<td>426.0</td>
<td>4</td>
<td>9.4</td>
<td>320.3</td>
</tr>
</tbody>
</table>

• Data related to familial incidence of TB and risk for children collected for 22 years in Williamson County Tennessee.

• Sputum positive TB attack rate amongst children 3.3/1,000 person years, but 1.8 if sputum negative.

• The highest rates seen in those < 5 years age, and 15-24 years.

• Lowest rates in those age 5-15 years

- During household exposure males less than age 5 years and females 15-24 years were particularly liable to develop disease.
- Children exposed to infection during infancy had a short incubation period as did those infected between ages 15-24.
- When exposed to infection between 1-14 years disease often did not develop until age >15 years.
Eugene Lindsay Opie 1873-1971

- Eugene Lindsay Opie attended Johns Hopkins University graduating 1897.

- In 1923 he became the Director of the Phipps Institute for the Study & Treatment of Tuberculosis at Pennsylvania University, Philadelphia.

- The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis was established in 1903 with grant from Henry Phipps a one time business partner of Andrew Carnegie.

• “Investigation of the epidemiology of tuberculosis must include not only clinically manifest disease but infection demonstrable by the tuberculin test and by roentgenographic examination in the absence of symptoms and physical signs…”

• Investigations should be “continued over a period of years corresponding with the chronic course of the disease.”

**Categorised by:**

- Exposure to tubercle bacilli in sputum
- Or no known tubercle bacilli in sputum
- Age group: 0-9 yrs, 10-14 yrs, > 15 yrs
- Time after exposure to manifest tuberculosis (yrs)
- Time after exposure to death (yrs)
Opie EL, McPhedran FM. The organization of a tuberculosis outpatient clinic for epidemiological investigation. Am J Hyg 1935; 22: 539-

Analysis of the records of the Out-Patient Clinic of the Henry Phipps Institute, Univ of Pennsylvania, Philadelphia. Families of which some member suffered from TB.

<table>
<thead>
<tr>
<th>Age</th>
<th>Index sputum</th>
<th>Acquisition of TB over 10-14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>Pos</td>
<td>9.9%</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>10-14</strong></td>
<td><strong>Pos</strong></td>
<td><strong>20.2%</strong></td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>6.86%</td>
</tr>
<tr>
<td>≥15</td>
<td>Pos</td>
<td>9.68%</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>6.86%</td>
</tr>
</tbody>
</table>

0-9 years
Mean frequency of manifest tuberculosis in white persons by years following exposure to tuberculosis with and without tubercle bacilli in the sputum.

**Fig. 4.** Mean frequency of clinically manifest tuberculosis in white persons by years following (a) exposure to tuberculosis with tubercle bacilli in the sputum and (b) exposure to tuberculosis with no known tubercle bacilli in the sputum, beginning between birth and 9 years of age.

0-9 years
Annual death rate after exposure to TB patients with and without tubercle bacilli in the sputum

Fig. 8. Annual death rates from tuberculosis in white persons following (a) exposure to tuberculosis with tubercle bacilli in the sputum and (b) exposure to tuberculosis with no known tubercle bacilli in the sputum, beginning between birth and 9 years of age.
Age 10-14 years
Mean frequency of manifest tuberculosis in white persons by years following exposure to TB with and without tubercle bacilli in the sputum.

**Age 10-14 years**

Annual death rate from TB in white persons following exposure to TB with and without tubercle bacilli in the sputum.
Ch’iu PTY, Myers JA, Stewart CA. The fate of children with primary tuberculosis. JAMA 1939; 112: 1306-1308.

- **Study 1921-1928** at Lymanhurst Health Center, Minneapolis.
- **Childhood contacts** of tuberculous patients or children suspected of tuberculosis disease. Those with obvious disease excluded.
- **Positive tuberculin reactions** in 446 children, negative in 772. The average age at which the tuberculin test was positive was 7 years.
Ch’iu PTY, Myers JA, Stewart CA. The fate of children with primary tuberculosis. JAMA 1939; 112: 1306-1308.

- Followed for a mean of 11.3 (positive TST) and 10.95 (negative TST) years respectively.
- Children located and followed up by public health nurses or seen at the Lymanhurst clinic.

- Of positive reactors 67 (15.02%) developed TB but only 13 (1.68%) amongst negative reactors.
- The average age at which tuberculosis presented was 18.9 years.
- Survival of primary infection did not appear to offer protection from disease.

- Chadwick Clinics, Massachusetts
- 400,000 tuberculin tested 1924-1934
- Follow-up approximately 11 years
- Low TB disease incidence age 6-10 years
- Disease incidence rose rapidly age 10-19 years
- Risk for females twice that for males
Adult type TB X4 as common amongst reactors as non-reactors.

Adult TB incidence higher amongst those whose original CR showed primary TB.

“All of our evidence indicates that in schoolchildren it is the age of the individual ....which determines the time at which tuberculosis develops.”
Miriam Esther Brailey

Miriam Brailey received both her MD (1930) and a doctorate in Epidemiology (1931) from Johns Hopkins. She was one of the first doctoral students in the Dept of Epidemiology, and joined the faculty as its first female member. She taught with Frost. And also served as Director of the TB Bureau of Baltimore City Health Department.
Miriam Esther Brailey

• Long association with Johns Hopkins Hospital
• An outpatient clinic of the Harriet Lane Home conducted from 1928 where children in contact with, or suffering from TB were assessed and followed to age 20 years.
• The introduction of TB into the household documented as accurately as possible by dating the symptom onset of the adult TB contact.
Miriam Esther Brailey

- Brailey ME. Prognosis in white and colored tuberculous children according to initial chest X-ray findings. Am J Publ Hlth 1943; 33: 343-352.

- Limited to children <2 years of age.
- Either with a positive tuberculin test.
- Or familial contact with a sputum smear-positive adult.

- 5 years up to November 1933
- **170** children, mortality presented for 1 year and **5** years

**Chest radiology**

- A. parenchymal lung involvement (67)
- B. nodal enlargement (36)
- C. normal (67)
22 (33%) children in group A were symptomatic; of these 68% died within a year and 82% within 5 years.

<table>
<thead>
<tr>
<th>Findings at 1st examination</th>
<th>N</th>
<th>Within 1 year</th>
<th>Within 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Parenchymal lesions</td>
<td>67</td>
<td>31.5</td>
<td>40</td>
</tr>
<tr>
<td>B. Tracheobronchial nodes</td>
<td>36</td>
<td>5.6</td>
<td>12.7</td>
</tr>
<tr>
<td>C. Normal CR</td>
<td>67</td>
<td>7.5</td>
<td>9.2</td>
</tr>
<tr>
<td>B &amp; C.</td>
<td>103</td>
<td>6.8</td>
<td>11.1</td>
</tr>
</tbody>
</table>

- **TBM** 11, generalized TB 6
- Further 3 miliary TB at PM
- If infected age <6 mths, mortality 33.3% in first year and 78% by end of 5 years

Duration of household contact (months) prior to tuberculin testing.
Deaths in White Children

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>All causes Rate/1,000</th>
<th>TB n</th>
<th>Rate/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>8</td>
<td>47.44</td>
<td>2</td>
<td>11.86</td>
</tr>
<tr>
<td>1-4</td>
<td>14</td>
<td>15.07</td>
<td>4</td>
<td>4.30</td>
</tr>
<tr>
<td>5-9</td>
<td>6</td>
<td>5.03</td>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td>10-14</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>15-19</td>
<td>4</td>
<td>10.5</td>
<td>3</td>
<td>7.54</td>
</tr>
</tbody>
</table>


**Deaths in Coloured Children**

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>All causes Rate/1,000</th>
<th>TB n</th>
<th>Rate/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>16</td>
<td>119.35</td>
<td>8</td>
<td>59.68</td>
</tr>
<tr>
<td>1-4</td>
<td>28</td>
<td>34.62</td>
<td>15</td>
<td>18.55</td>
</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>3.80</td>
<td>4</td>
<td>3.80</td>
</tr>
<tr>
<td>10-14</td>
<td>2</td>
<td>2.77</td>
<td>2</td>
<td>2.77</td>
</tr>
<tr>
<td>15-19</td>
<td>9</td>
<td>24.32</td>
<td>8</td>
<td>21.62</td>
</tr>
</tbody>
</table>

“It seems clear that no period in life suffers so high a case fatality as the first year of life,”
Brailey ME. Prognosis in white and colored tuberculous children according to initial chest X-ray findings. Am J Publ Hlth 1943; 33: 343-352

- The influence of the extent of the chest lesion studied in 1,148 infected children.

- 22% of children age <1 year had severe tracheobronchial node involvement and 47% extensive parenchymal lesions.

- Between age 1-2 years 18% had parenchymal lesions and only 8% if seen when aged >2 years. After age 5 years parenchymal involvement in only 2/168 children.
Mortality if infection age <3 years with parenchymal lesions was 21% within a year rising to 30% by the end of 5 years.

Cause of death if <3 years
- TBM 43.8%, miliary TB 35.6%

Cause of death if 3–15 years
- TBM 25%, miliary TB 16.7%
Edith Maas Lincoln

- Edith Lincoln (1899–1971), one of the most influential American pediatricians to study childhood TB.
- She followed more than a thousand children from time of TB infection into adult life. She was also a clinician and spoke thus with authority regarding the prognosis of childhood TB and its clinical features.

(Donald PR. Edith Lincoln, an American pioneer of childhood tuberculosis. Pediatr Infect Dis J 2013 [Epub ahead of print])
Edith Maas
Lincoln

Photograph courtesy
Ehrman Medical Archives,
New York University.
Langone Medical Center
Edith Maas Lincoln

• Her observations of chemotherapy in children treated with isoniazid led directly to chemoprophylaxis, now of new importance in the management of the human immunodeficiency syndrome.

• In 1922 a Children’s Chest Clinic was started at Bellevue Hospital with Edith Lincoln at its head;

• The clinic was maintained by a municipality, but also an integral part of a university teaching service.
• A long-term follow-up study with the goal of enrolling 1,000 children with chest radiographic evidence of uncalcified primary TB
• Follow up until age 25-years.
• Also followed were children with adult-type TB, extra-pulmonary TB with normal chest radiographs and infants and children under two years of age with positive TST and normal CR.
• Enrollment of children with recent infection was continued; by 1947 the group was 964. By the time of the publication of “Tuberculosis in Children” in 1963, close to 2,500 children with various manifestations of TB had been studied and, more importantly, many of the children were followed long-term.
In July 1940 the last of 1,000 children who were to be followed-up was enrolled; two thirds (622) of the children had recent uncomplicated primary TB at study entry and the remainder were children who had successfully survived primary infection as evidenced by calcification present on chest radiograph.
Frequency of fatal complications among 622 children classified by sex and age at diagnosis of uncalcified primary TB

Frequency of “chronic pulmonary TB” among 471 survivors of primary TB classified by sex and age at diagnosis of uncalcified primary TB

![Bar chart showing the percentage of patients with chronic pulmonary TB by age and sex.](chart.png)

Probability of developing chronic pulmonary TB in each year of life among survivors of primary TB.
There is evidence in this reported series ... that isoniazid may prevent the development of complications of primary tuberculosis, especially meningitis.

**TABLE 1**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>NUMBER OF CASES</th>
<th>TREATMENT</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930–1946</td>
<td>980</td>
<td>No specific therapy</td>
<td>21.5</td>
</tr>
<tr>
<td>1947–1951</td>
<td>421</td>
<td>Streptomycin, PAS, and Promizole used in 35 per cent of cases</td>
<td>5.0</td>
</tr>
<tr>
<td>1952–1953</td>
<td>129</td>
<td>Isoniazid added</td>
<td>1.5</td>
</tr>
</tbody>
</table>

• Beginning in **1944** **six of 9** patients treated with **thiazolsulfone** survived miliary tuberculosis, and none of them developed meningitis.

• **CR cleared slowly** and in 3 of the 6 complications continued to be experienced up to 20 months after treatment.

• **Streptomycin successful...20**\(^{th}\) November 1944

**Fig. 1.** Symptoms of endobronchial disease in relation to age.
George Wills Comstock  
(1915-2007)

Medical degree from Harvard in 1941 and joined the US Public Health Service. Responsible for trials of BCG in Georgia and Alabama (1947-1951) and Puerto Rico; received a Doctorate of Public Health in Epidemiology from Johns Hopkins in 1956 and the Trudeau medal from the American Thoracic Society.


Comstock GW, Shaw LW. Controlled trial of BCG vaccination in a school population. Public Health Reports 1960; 75; 583-594.

- Comprehensive Muscogee County, Georgia 1947 TB studies.
- Evaluation of BCG vaccination amongst school children.
- Tuberculin testing amongst 11,262 children aged 5-19 years (mean 11.4) with 5 TU or 100 TU if the initial test with 5 TU was negative.
Comstock GW, Shaw LW. Controlled trial of BCG vaccination in a school population. Public Health Reports 1960; 75; 583-594.

- Positive reactions to 5TU were obtained amongst 1,492 (13%) children.
- The average annual rate of newly reported cases among the study population was 26/100,000.
- The rate for 5 TU reactors 134/100,000 compared to only 9/100,000 for non-reactors.
Comstock GW, Shaw LW. Controlled trial of BCG vaccination in a school population. Public Health Reports 1960; 75; 583-594.

- Children with a 5 TU reaction of $\geq 10$ mm comprised 7% of children but yielded 54% of cases over a 12 years and 80% during the first 5 years.

- Further 28 of the 35 cases had at least one normal chest radiograph on initial evaluation.
Comstock GW, Shaw LW. Controlled trial of BCG vaccination in a school population. Public Health Reports 1960; 75; 583-594.

“The incidence of new disease was highest in late adolescence and early adult life.”

<table>
<thead>
<tr>
<th>Age group (in years)</th>
<th>Person-years experience</th>
<th>Reactors</th>
<th>New cases</th>
<th>Rate (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>18</td>
<td>134</td>
</tr>
<tr>
<td>5–8</td>
<td></td>
<td>400</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9–12</td>
<td></td>
<td>2,000</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>16–16</td>
<td></td>
<td>4,200</td>
<td>5</td>
<td>120</td>
</tr>
<tr>
<td>17–20</td>
<td></td>
<td>4,100</td>
<td>8</td>
<td>197</td>
</tr>
<tr>
<td>21–24</td>
<td></td>
<td>2,300</td>
<td>3</td>
<td>130</td>
</tr>
<tr>
<td>25–28</td>
<td></td>
<td>500</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

• Puerto Rican children age 1-6 years had a case rate X2 that of older children.

• 10% of cases 1-6 were miliary or meningeal TB.

• Children 7-12 had the lowest subsequent rates.

• Other highlights:
  • Rate of disease was 14% higher in urban residents vs rural residents
  • 18% higher in females than males
  • Children initially 7-12 years had the lowest subsequent case rates
Arnold Rice Rich
(1893-1968)

MD from Johns Hopkins 1919. He remained associated with Hopkins the rest of his career. He was appointed Chairman of the Department of Pathology and pathologist-in-chief of the Johns Hopkins Hospital in 1944, until he retired in 1958.

Mortality from tuberculosis at different age periods in the general population and in the estimated infected portion of the population

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Deaths from Tuberculosis</th>
<th>Estimated Per Cent Infected*</th>
<th>Deaths from Tuberculosis per 100,000 Persons of Each Age Period</th>
<th>Deaths from Tuberculosis per 100,000 Estimated Infected Persons of Each Age Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>496</td>
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<td>90</td>
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<td>95</td>
<td>101.3</td>
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<td>95</td>
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<td>105.4</td>
<td>51.1</td>
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<td>70–74</td>
<td>2,179</td>
<td>95</td>
<td>107.6</td>
<td>62.5</td>
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<td>75 and over</td>
<td>2,057</td>
<td>95</td>
<td>90.3</td>
<td>66.8</td>
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</table>

* Estimated from recent tuberculin surveys. See Table XII and text discussion for limitations.
<table>
<thead>
<tr>
<th>Age</th>
<th>Total Deaths from Tuberculosis</th>
<th>Estimated Per Cent Infected*</th>
<th>Deaths from Tuberculosis per 100,000 Persons of Each Age Period</th>
<th>Deaths from Tuberculosis per 100,000 Estimated Infected Persons of Each Age Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>496</td>
<td>0.5</td>
<td>24.8</td>
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<td>6,243</td>
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<td>52.7</td>
<td>59.7</td>
</tr>
</tbody>
</table>
Chart II. Tuberculosis mortality rates by age and sex for 1900, 1932 and 1940 (United States Census Bureau Statistics)
Beaven PW. Analysis of tuberculosis infection from birth to old age: its relationship to clinical tuberculosis and deaths from tuberculosis. Dis Chest 1950; 17: 280-292

- The author sets TB **morbidity** and **mortality** in relation to the **risk of infection**.
- TB **incidence rates** determined with the calculated number of **infected individuals** as denominator.
- **1942-1944** extensive tuberculin testing in Rochester, New York by the TB and Health Association of Rochester: **9252** adult factory workers and **3,000** children to age 14 years. From these figures the number of infected individuals in the general population is calculated and used to determine TB morbidity and mortality.
Beaven PW. Analysis of tuberculosis infection from birth to old age: its relationship to clinical tuberculosis and deaths from tuberculosis. Dis Chest 1950; 17: 280-292

TB incidence rate amongst those infected

TB mortality rate amongst those infected
Figure 3.2A: The population pyramid for South Africa for 1993, based on the estimated population (Department of Health, 1995). The central open bars show the portion of the population infected by *M. tuberculosis*, assuming an annual risk of infection of 2.5% and that a maximum of 75% of the population will become infected.
Figure 3.2B: The number of tuberculosis notifications in South Africa during 1993 (Department of Health, 1995), illustrated in the form of a population pyramid. Note that the horizontal scale differs from that used in Figure 3.2A.
• Wrote repeatedly about the natural history of tuberculosis
• Distinguished between the response to primary infection and that to endogenous or exogenous re-infection.
• Where Frost held the underlying human physiology responsible for the age and sex related epidemiology of TB, Myers blamed the acquired immune response.

- Experience documented in The Minneapolis Division of Public Health 1921-1941.
- Routine at one time included tuberculin testing, CR, gastric aspirate and sedimentation rate.
- 300 children (mean age 6 yrs girls and 5 yrs boys) seen with primary pulmonary infiltrates or subsequent calcification.
• Mild symptoms, when diagnosed.
• 267 (89%) located after 6,000 person years, mean age approximately 31 yrs.
• 9 (3.4%) cases of death as result of TB recorded. (4 TBM, 1 miliary, 2 pneumonia, 2 adult type TB).
In only one case was the subsequent lesion in the same lung area as the primary lesion.

222 children developed no evidence of subsequent clinical disease.

Had treatment been applied to these children it would have been credited with achieving a “cure”.


A study based on the epidemiology of tuberculosis in Ontario, Canada.

- Records of all active newly reported cases of TB in British Columbia and Saskatchewan 1966-1971.
- All contacts investigated including tuberculin testing and if this was positive a CR.

Contacts designated as close or casual and infected or not infected.

Active TB amongst white infected intimate contacts according to the bacteriological status of the source case. Tuberculin positivity in general population 0.7-2.2%.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Status of source case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sm+</td>
</tr>
<tr>
<td>0-14 years</td>
<td>412</td>
</tr>
<tr>
<td></td>
<td>123</td>
</tr>
<tr>
<td>Active TB</td>
<td>37.7%</td>
</tr>
</tbody>
</table>
Active TB amongst Indian infected intimate contacts according to the bacteriological status of the source case. Tuberculin positivity in general population 0.7-2.2%.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Status of source case</th>
<th>N</th>
<th>Sm⁺</th>
<th>Cult⁺</th>
<th>Sm&amp; Cult⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 years</td>
<td></td>
<td>352</td>
<td>223</td>
<td>88</td>
<td>41</td>
</tr>
<tr>
<td>Active TB</td>
<td>%</td>
<td>85</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

| 0-14 years | 38.1 | 12.5 |
| Active TB  | 9.8  |
“Thus the risk of an infected individual developing tuberculous disease does not only depend on two well established factors – the age of the individual...and time elapsing since infection; it also depends upon the bacteriological status of the source.”
If these findings are true, and if TB infection is caused by a single infected droplet nucleus containing 1-3 bacilli, why should the bacteriological status of the index case affect the likely development of disease in those infected?
Tuberculosis in Adolescents
Tuberculosis in Adolescents


- TB is one of the 5-10 leading causes of death for the 15-44 year olds.
- Infection in adolescents spreads to peers and their own children.
- Emotional problems specifically related to the disease plague the tuberculous adolescent.
- Special outpatient clinic for adolescents held in late afternoon after school.
- Meets peers with the same problems at the clinic.
“The most earnest study should be devoted to an elucidation of the factors which influence the development of progressive tuberculosis at this time of life, for the precise reasons for the disastrous effects observed during in this period... are still for the most part obscure and the problem is one not only of theoretical interest, but of the utmost importance from the standpoint of human welfare.”
Conclusions

The epidemiology of TB, the occurrence of TB disease in children, and the spectrum of disease, occurs following clear, well demarcated patterns that depend upon the age and sex of the individual and is probably influenced by immuno-endocrinological factors that must still be elucidated.

These factors are probably not unique to tuberculosis but rest upon the normal features of human physiology.
Conclusions 2

• These established patterns of infection and subsequent disease can assist in planning interventions.

• High incidence communities with limited resources may be best served by concentrating interventions, like chemoprophylaxis, on the most vulnerable portions of the childhood population.
Conclusions 2

In low incidence communities, looking towards TB elimination, efforts could be focused on tuberculin positive children and those living in sections of the community with a likely higher incidence of TB.
Conclusions 3

These established patterns of infection and subsequent disease should also be kept in mind in interpreting reporting of childhood tuberculosis.
Conclusions 3

Children diagnosed following contact tracing will most often have minimal signs of disease, but will be reported as TB cases in a developed community much more frequently than in a developing community.
Conclusions 4

• Adolescents are a vulnerable group of TB patients. We know relatively little about the success of treatment, compliance, or relapse in these patients or the impact of their disease on their close contacts.

• Does failure to comply with treatment lead to drug-resistance more frequently in adolescence?
Conclusions 4

Now that childhood tuberculosis is firmly established on the tuberculosis “agenda” we need to continue our efforts and advocate the closer study of all aspects of tuberculosis in adolescence.
Conclusions 5

• With regard to immunity to TB (and immunization) we are dealing with a continuously “moving target”.

• If we could better understand this we would be well on our way to designing better vaccines and, possibly, preventing the necrotizing response associated with cavitation that becomes the typical feature of adolescent TB.
Conclusions 5

The widespread development of necrosis and the associated lung cavitation seated in the “vulnerable” apical and sub-apical regions of the lungs during adolescence is of the greatest epidemiological importance. Fully understanding this process would be of considerable aid to the control of tuberculosis.
Conclusions 6

Speculation

• The establishment of infection is clearly associated with the bacteriological status of the index case.

• However the subsequent occurrence of disease may also be influenced by the same factors!
Conclusions 6

Speculation

If infection is indeed caused by single droplet nuclei why should the intensity of infection (sputum smear-positivity) or proximity to the source case influence the development of disease?

• The establishment of infection and the subsequent occurrence of disease may be influenced by the metabolic condition of the infecting organisms.
Conclusions 6

- Those working in developed communities have the opportunity when investigating sporadic epidemics to study the influence of smear-positivity and the proximity to the source case on both infection and the occurrence of disease in contacts.
“There are many contributions which the pediatrician can make to a tuberculosis control program. ... Obviously with a decreasing rate of infection there will be fewer tuberculin conversions. But the pediatrician must continue to be aware of the possibility of tuberculosis.”
“Wherever there are tuberculous adults there are infected children. No one is immune. No child will be even relatively safe from tuberculous infection and some of its dread sequelae until tuberculosis is diminished to the point where it is no longer a public health problem.”
Thank You!