

# Comstock Lecture 2013

## The Place of Children in the Global Epidemiology of Tuberculosis

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# 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 **1/3<sup>rd</sup> of cases**, including many children, are not detected by health systems.

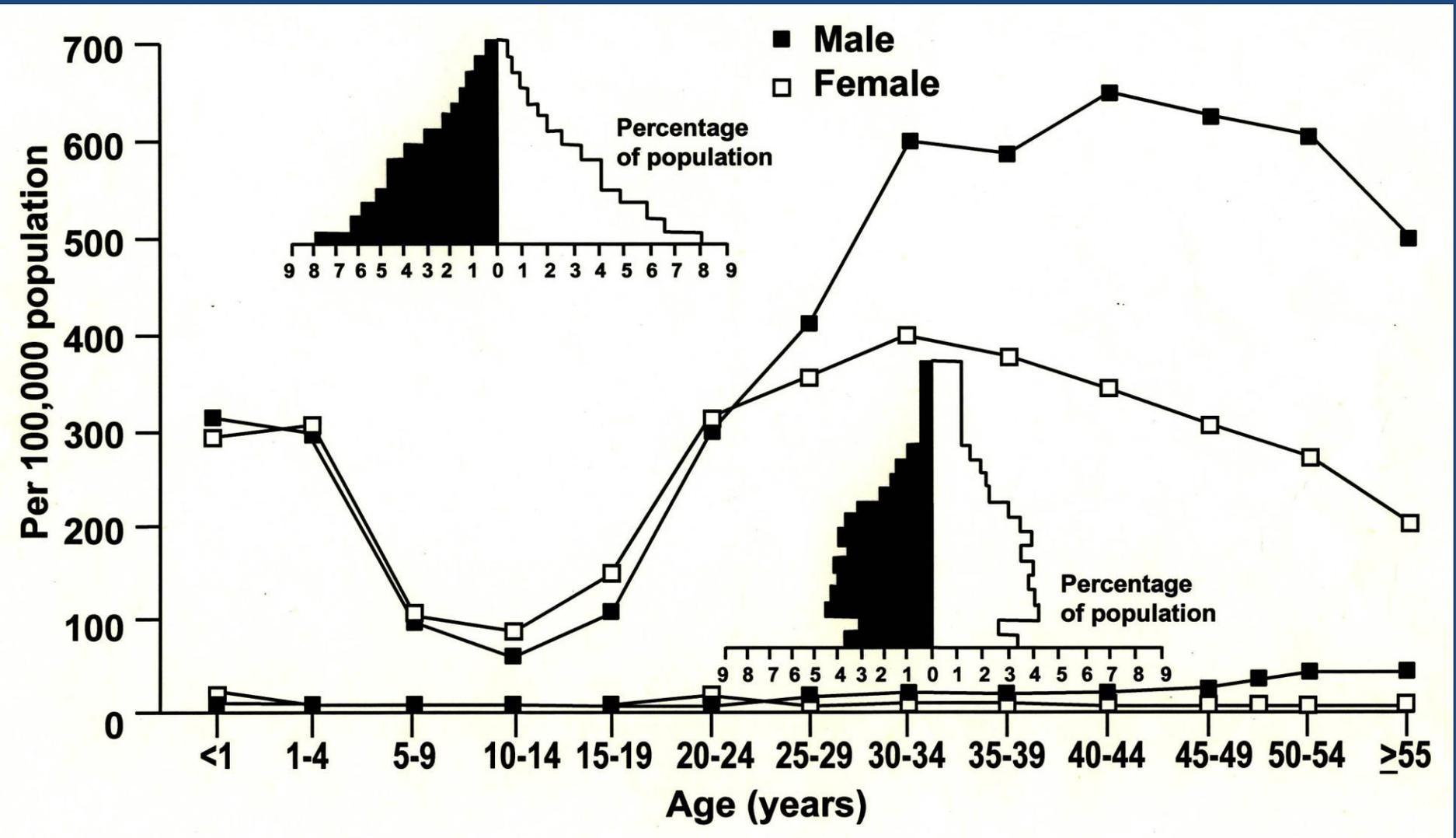
# Recent Global Epidemiology of TB in Children

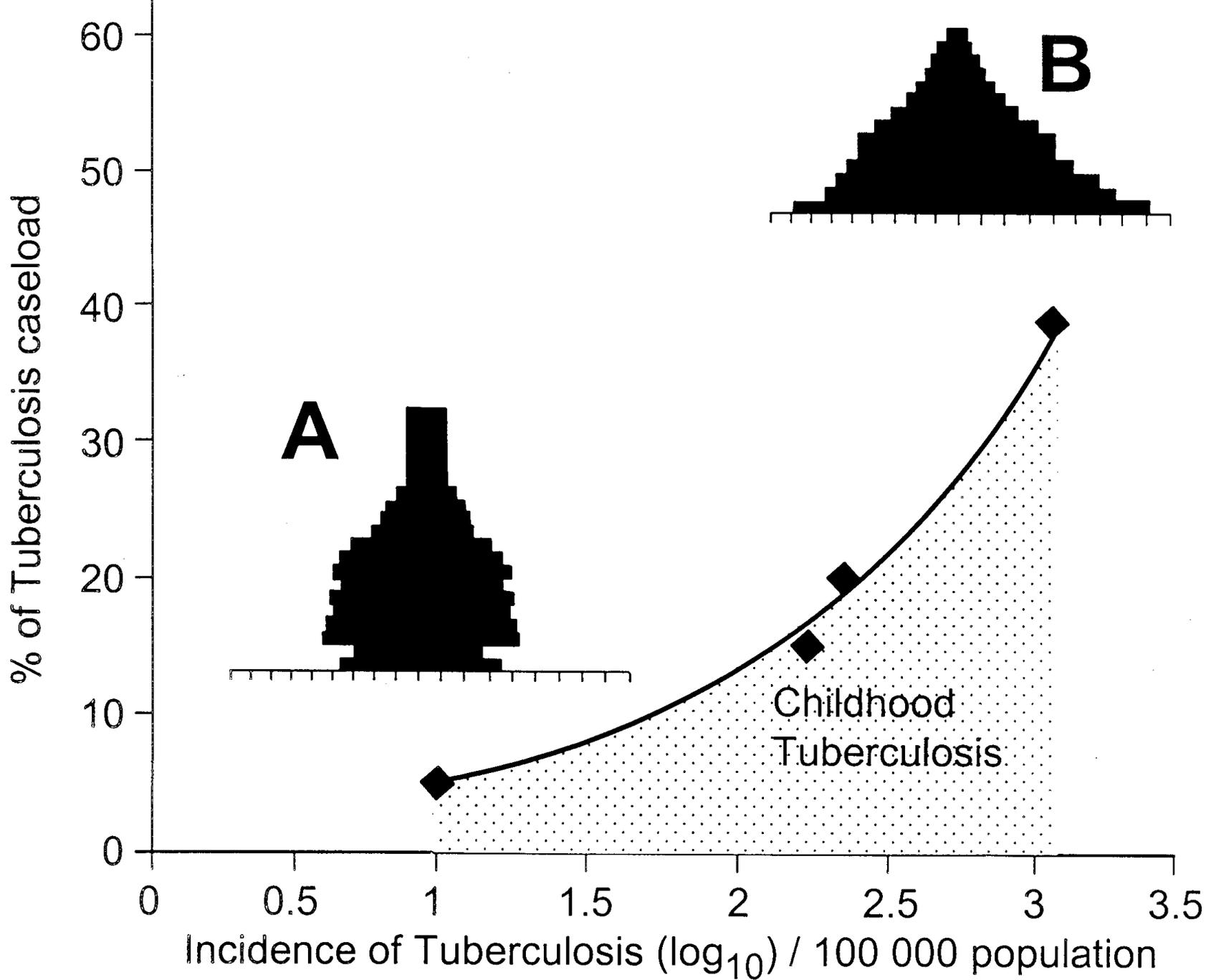
- Getahun et al Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. *J Infect Dis* 2012; 205; S216-227.
- Amongst the 22 high burden countries, figures for childhood tuberculosis were not reported by 12.
- It is **estimated** that children comprise **15-20%** of the global childhood tuberculosis burden.

Getahun et al Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. J Infect Dis 2012; 205: S216-227.

- 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**).

Donald PR. Childhood tuberculosis: the hidden epidemic. *Inter J Tuberc Lung Dis* 2004; 8: 627-629.





# 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.

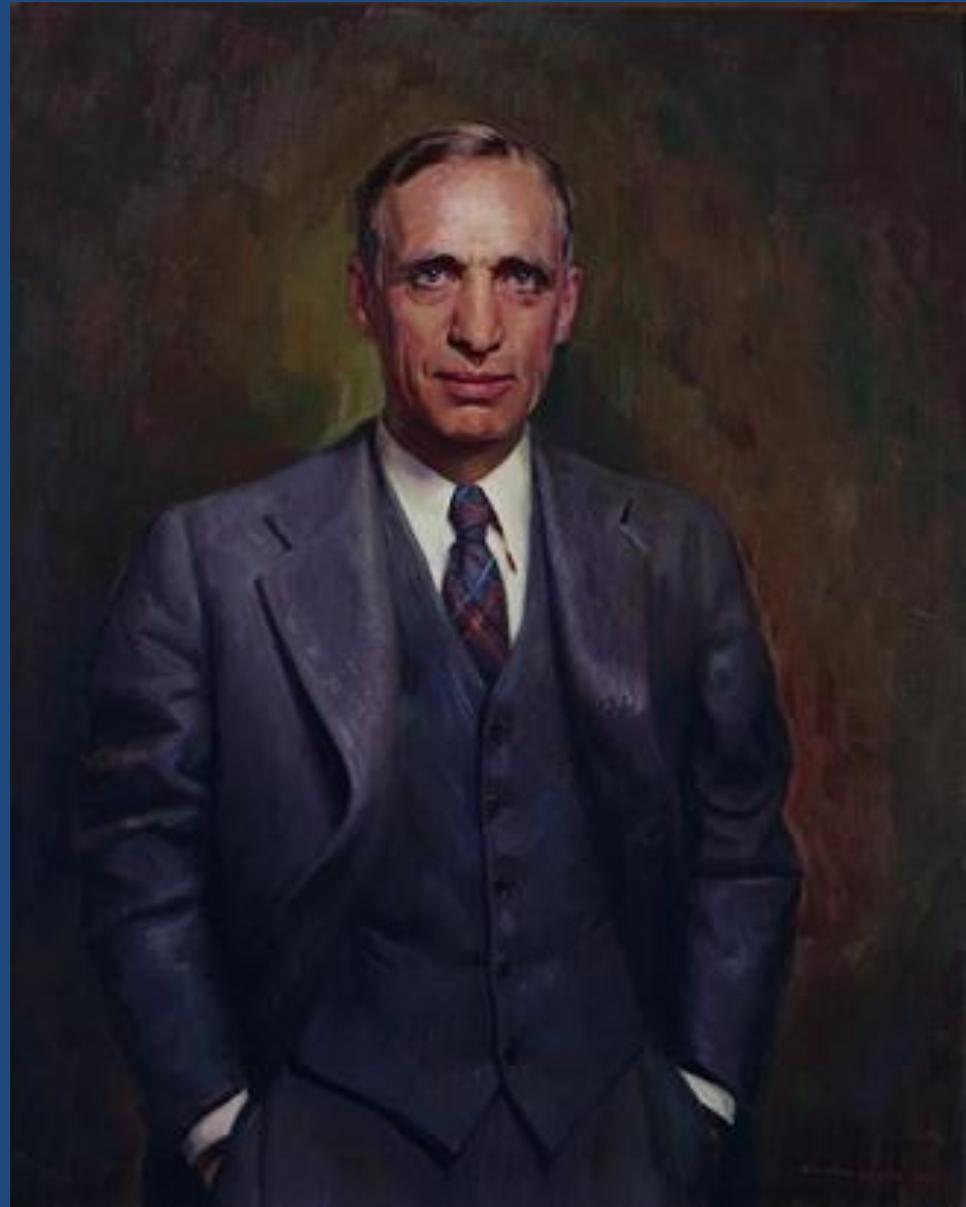
# Wade Hampton Frost. 1880-1938

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.

Comparison	Contact history			
	n	Positive	n	Negative
Person years in comparison	2,199		7,472	
Cases of TB, annual rate/1,000	26	12.9 ± 1.7	51	6.8 ± 0.64
Deaths from TB, annual rate/1,000	10	4.6 ± 1.01	17	2.3 ± 0.38
Deaths all causes, annual rate/1,000	28	12.8 ± 1.62	68	9.2 ± 0.67

Frost WH. Risk of persons in familial contact with pulmonary tuberculosis. Am J Publ Hlth 1933; 23: 426-432

Age	Cases of TB		Deaths from TB	
	n	Rate/1,000	n	Rate/1,000
<1	2	5.8	1	2.9
1-4	2	1.6	1	0.8
5-9	5	4.0	2	1.6
10-19	19	9.9	8	4.2
20-29	17	7.8	7	3.2
30-39	18	11.6	4	2.6
40-49	6	7.8	1	1.3
50-59	4	13.0	2	6.5
>60	4	45.5	1	11.4
	77	8.0	27	2.8

Frost WH. Risk of persons in familial contact with pulmonary tuberculosis. Am J Publ Hlth 1933; 23: 426-432

“...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...”

Frost WH. Risk of persons in familial contact with pulmonary tuberculosis. Am J Publ Hlth 1933; 23: 426-432

- “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.

Age	1880	1890	1900	1910	1920	1930
<i>Males</i>						
0- 4 . . . . .	760	578	309	209	108	41
5- 9 . . . . .	43	49	31	21	24	11
<u>10-19 . . . . .</u>	126	115	90	63	49	21
20-29 . . . . .	444	301	288	207	149	81
30-39 . . . . .	378	368	296	253	164	115
40-49 . . . . .	364	336	253	253	175	118
50-59 . . . . .	366	325	267	252	171	127
60-69 . . . . .	475	346	304	246	172	95
70+ . . . . .	672	396	343	163	127	95
<i>Females</i>						
0- 4 . . . . .	658	595	354	162	101	27
5- 9 . . . . .	71	82	49	45	24	13
<u>10-19 . . . . .</u>	265	213	145	92	78	37
20-29 . . . . .	537	393	290	207	167	92
30-39 . . . . .	422	372	260	189	135	73
40-49 . . . . .	307	307	211	153	108	53
50-59 . . . . .	334	234	173	130	83	47
60-69 . . . . .	434	295	172	118	83	56
70+ . . . . .	584	375	296	126	68	40

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."

The Williamson County tuberculosis study.  
Zeidberg LD, Gass RS, Dillon A, Hutcheson RH. Am  
Rev Respir Dis 1963; 87: 1-88

- 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 Williamson County tuberculosis study.  
Zeidberg LD, Gass RS, Dillon A, Hutcheson RH. Am  
Rev Respir Dis 1963; 87: 1-88

- 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

Puffer RR, Zeidberg LD, Dillon A, Gass RS, Hutcheson RH.  
Tuberculosis attack and death rates of household associates.  
Am Rev Tuberc 1952; 65: 65: 111-127.

- **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**.

Puffer RR, Zeidberg LD, Dillon A, Gass RS, Hutcheson RH.  
Tuberculosis attack and death rates of household associates. Am Rev  
Tuberc 1952; 65: 65: 111-127.

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.

Age group yrs	Male			Female		
	Person yrs	New cases	Rate /1,000	Person yrs	New cases	Rate /1,000
< 5 yrs	138.25	3	21.7	98.0	0	-
5-14	583.5	0	-	462.0	0	-
15-24	657.0	5	7.6	495.8	6	12.1
25-34	329.0	2	6.1	370.0	6	16.2

Puffer RR, Zeidberg LD, Dillon A, Gass RS, Hutcheson RH.  
 Tuberculosis attack and death rates of household associates. *Am Rev Tuberc* 1952; 65: 65: 111-127.

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.

Age group yrs	Male			Female		
	Person yrs	New cases	Rate /1,000	Person yrs	New cases	Rate /1,000
< 5 yrs	53.3	1	18.8	65.5	0	-
5-9	156.0	1	6.4	185.8	1	5.4
10-14	219.5	1	4.6	233.5	7	30.0
15-24	426.0	4	9.4	320.3	4	12.5

Zeidberg LD, Dillon A, Gass RS. Risk of developing tuberculosis among children of tuberculous parents. *Am Rev Tuberc* 1954; 70: 1009-1019

- 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**

Zeidberg LD, Dillon A, Gass RS. Risk of developing tuberculosis among children of tuberculous parents. *Am Rev Tuberc* 1954; 70: 1009-1019

- 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.

Opie EL, McPhedran MR. The organization of a tuberculosis out-patient clinic for epidemiological investigation. *Am J Hyg* 1935; 22: 539-564

- "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."

Opie EL, McPhedran FM. The organization of a tuberculosis outpatient clinic for epidemiological investigation. Am J Hyg 1935; 22: 539-

McPhedran FM, Opie EL. The spread of tuberculosis in families. Am J Hyg 1935; 565-643

Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. Am J Hyg 1935; 22: 644-682.

## 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-

McPhedran FM, Opie EL. The spread of tuberculosis in families. *Am J Hyg* 1935; 565-643

Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. *Am J Hyg* 1935; 22: 644-682.

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.

Age	Index sputum	Acquisition of TB over 10-14 years
0-9	Pos	9.9%
	Neg	2.0%
10-14	Pos	20.2%
	Neg	6.86%
≥15	Pos	9.68%
	Neg	6.86%

Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. *Am J Hyg* 1935; 22: 644-682.

## 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.

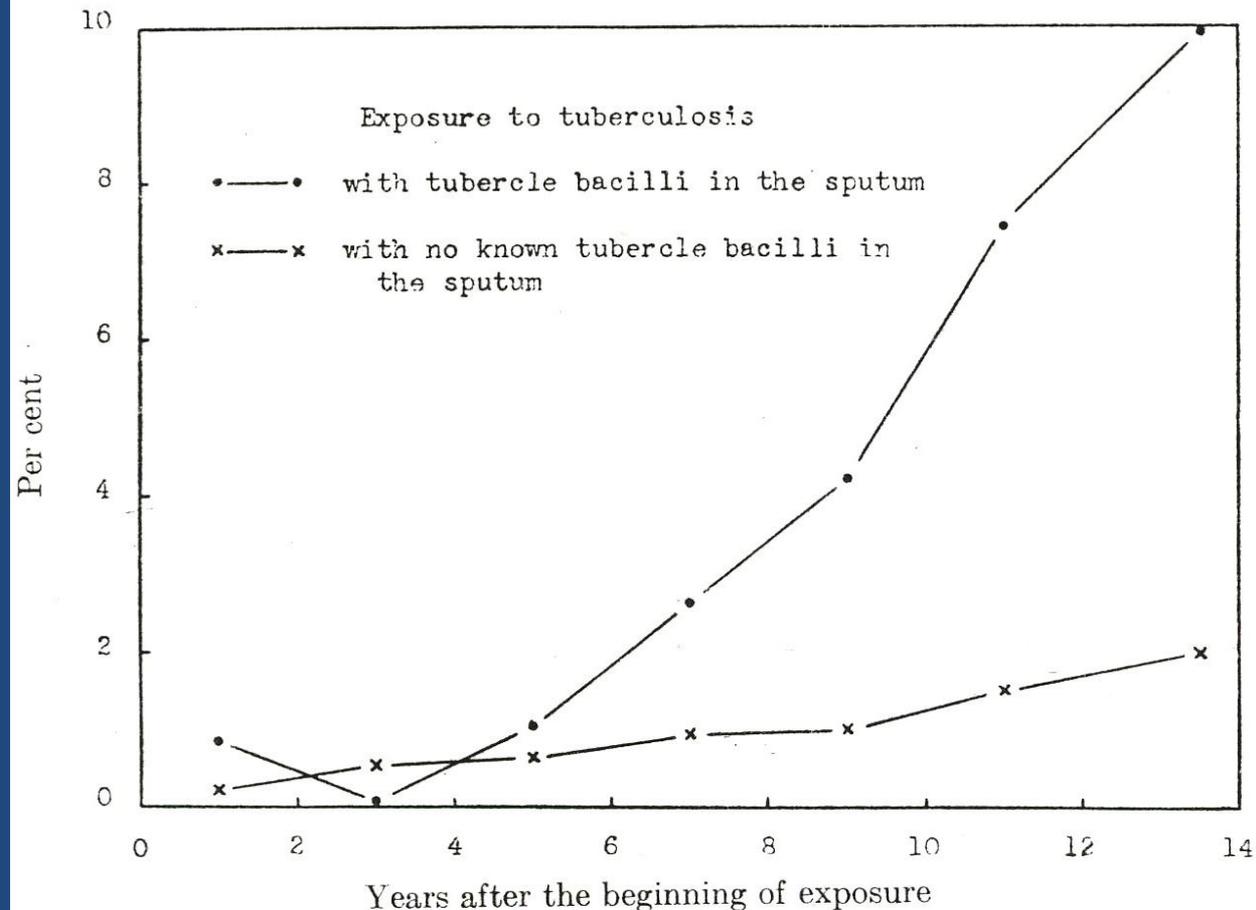


FIG. 4. Mean frequency of clinically manifest tuberculosis in white persons by years following (a) exposure to tuberculosis with tubercle bacilli in the sputum and (b) exposure to tuberculosis with no known tubercle bacilli in the sputum, beginning between birth and 9 years of age.

Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. *Am J Hyg* 1935; 22: 644-682.

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

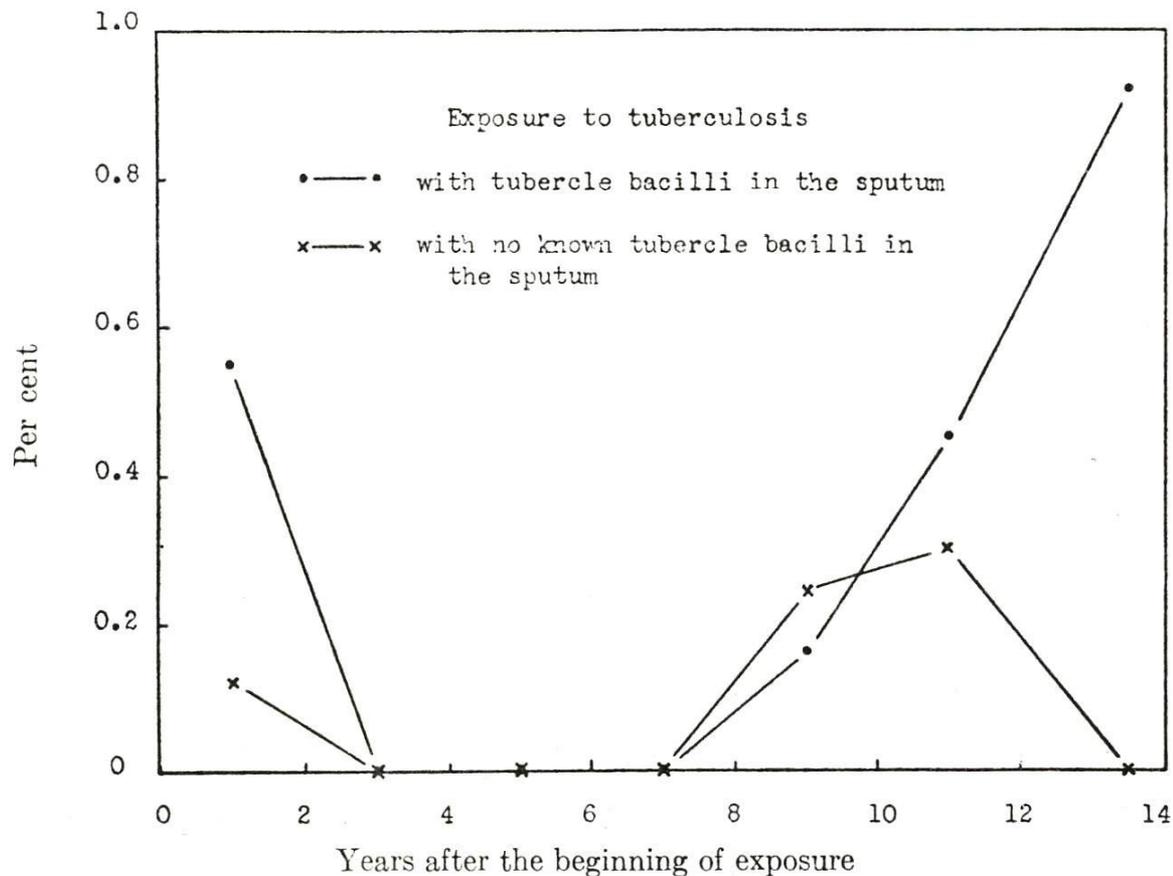
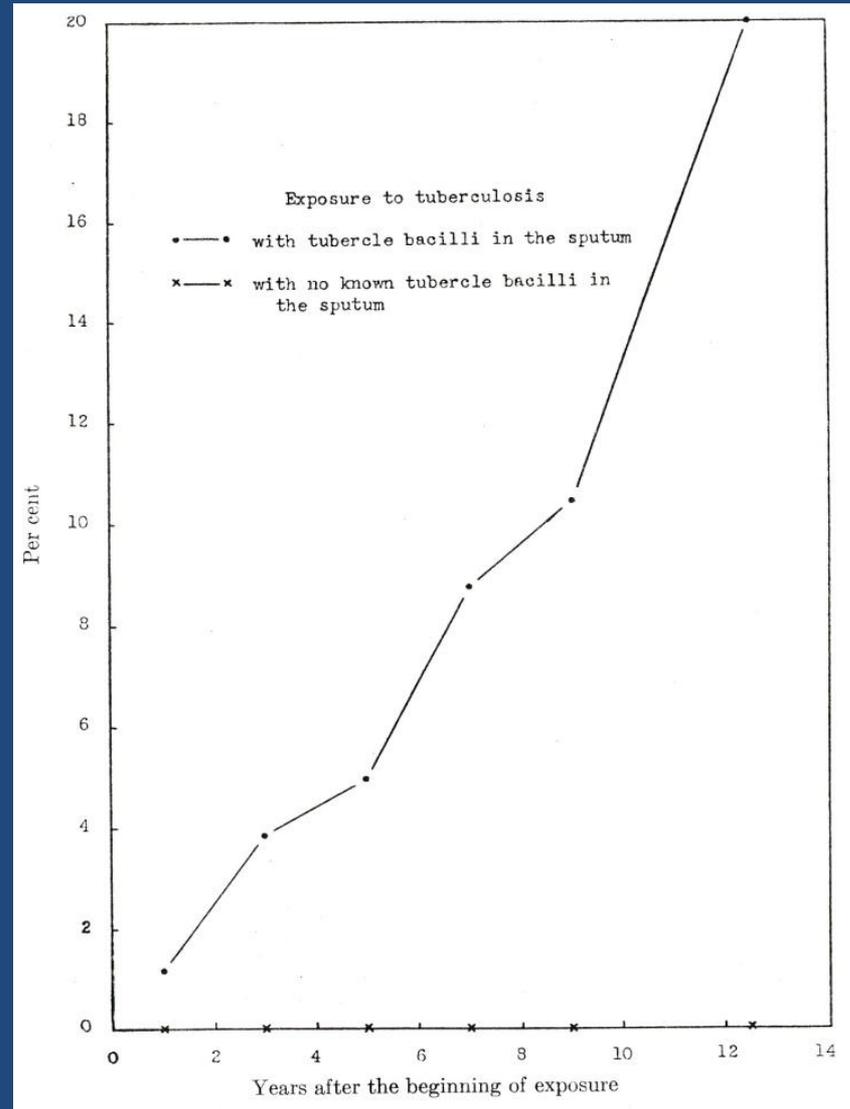


FIG. 8. Annual death rates from tuberculosis in white persons following (a) exposure to tuberculosis with tubercle bacilli in the sputum and (b) exposure to tuberculosis with no known tubercle bacilli in the sputum, beginning between birth and 9 years of age.

Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. *Am J Hyg* 1935; 22: 644-682.

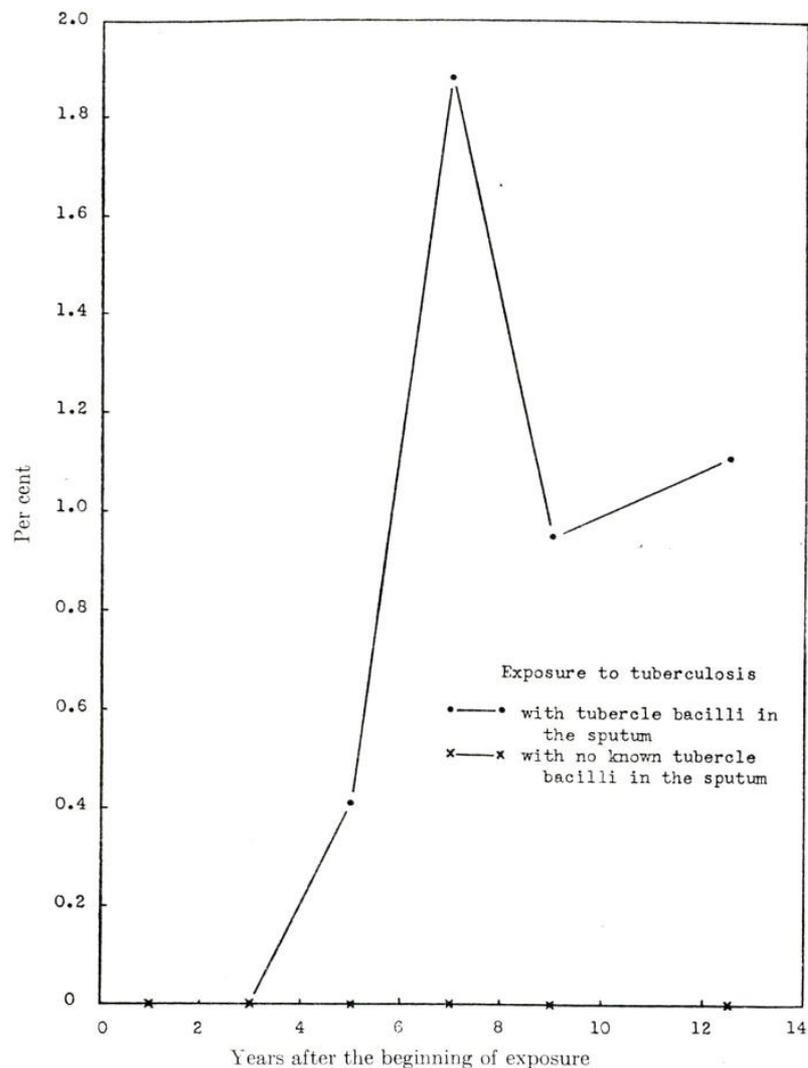
Age 10-14 years  
Mean frequency of **manifest tuberculosis** in white persons by years following exposure to TB with and without tubercle bacilli in the sputum.



Opie EL, McPhedran FM, Putnam P. The fate of persons in contact with tuberculosis: the exogenous infection of children and adults. Am J Hyg 1935; 22: 644-682.

## 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.

Pope AS, Sartwell PE, Zacks D. Development of tuberculosis in infected children. *Am J Publ Hlth* 1939; 29: 1318-1325.

- 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

Pope AS, Sartwell PE, Zacks D. Development of tuberculosis in infected children. *Am J Publ Hlth* 1939; 29: 1318-1325.

- **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 M. Mortality in tuberculin-positive infants. Bull Johns Hopkins Hosp 1936; 59: 1-10.
- Brailey M. A study of tuberculous infection and mortality in the children of tuberculous households. Am J Hyg 1940; 31: 1-43.
- Brailey M. Mortality in the children of tuberculous household. Am J Publ Hlth 1940; 30: 816-823.
- Brailey ME. Prognosis in white and colored tuberculous children according to initial chest X-ray findings. Am J Publ Hlth 1943; 33: 343-352.

Brailey M. Mortality in tuberculin-positive infants.  
Bull Johns Hopkins Hosp 1936; 59: 1-10.

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

Brailey M. Mortality in tuberculin-positive infants.  
Bull Johns Hopkins Hosp 1936; 59: 1-10.

- 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)

Brailey M. Mortality in tuberculin-positive infants.  
Bull Johns Hopkins Hosp 1936; 59: 1-10.

22 (33%) children in group A were **symptomatic**; of these 68% died within a year and 82% within 5 years

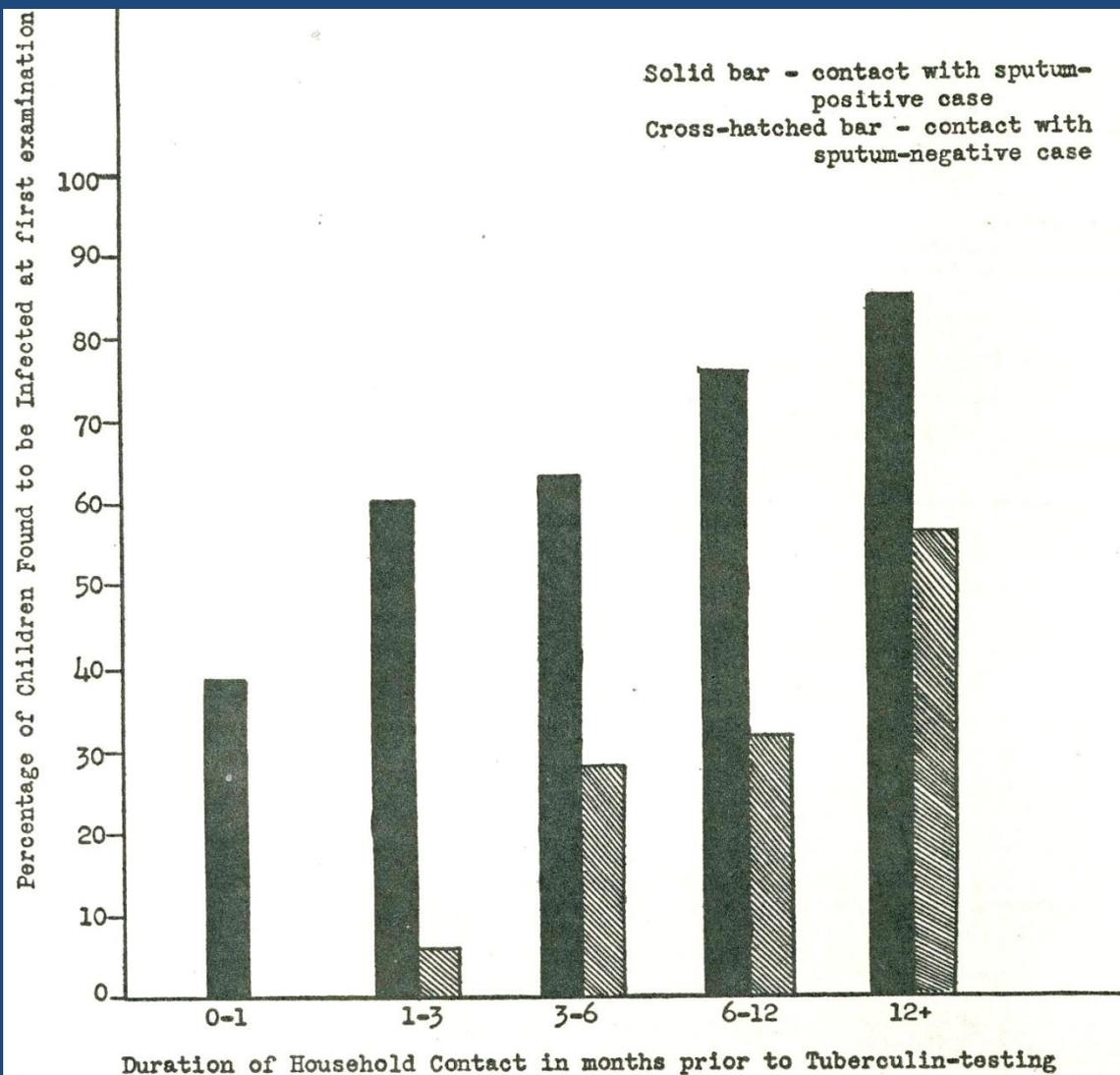
Findings at 1 <sup>st</sup> examination	N	Mortality %	
		Within 1 year	Within 5 years
A. Parenchymal lesions	67	31.5	40
B. Tracheobronchial nodes	36	5.6	12.7
C. Normal CR	67	7.5	9.2
B & C.	103	6.8	11.1

Brailey M. Mortality in tuberculin-positive infants.  
Bull Johns Hopkins Hosp 1936; 59: 1-10.

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

Brailey M. A study of tuberculous infection and mortality in the children of tuberculous households. Am J Hyg 1940; 31: 1-43.

Duration of household contact (months) prior to tuberculin testing.



GRAPH 1. Relation between duration and type of household contact with pulmonary tuberculosis and the proportion of children found to be infected at their first examination for tuberculosis.

Brailey M. A study of tuberculous infection and mortality in the children of tuberculous households. *Am J Hyg* 1940; 31: 1-43.

Brailey M. Mortality in the children of tuberculous household. *Am J Publ Hlth* 1940; 30: 816-823.

## Deaths in White Children

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

Brailey M. A study of tuberculous infection and mortality in the children of tuberculous households. Am J Hyg 1940; 31: 1-43.

Brailey M. Mortality in the children of tuberculous household. Am J Publ Hlth 1940; 30: 816-823.

## Deaths in Coloured Children

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

"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.

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

- 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

# Edith Maas Lincoln

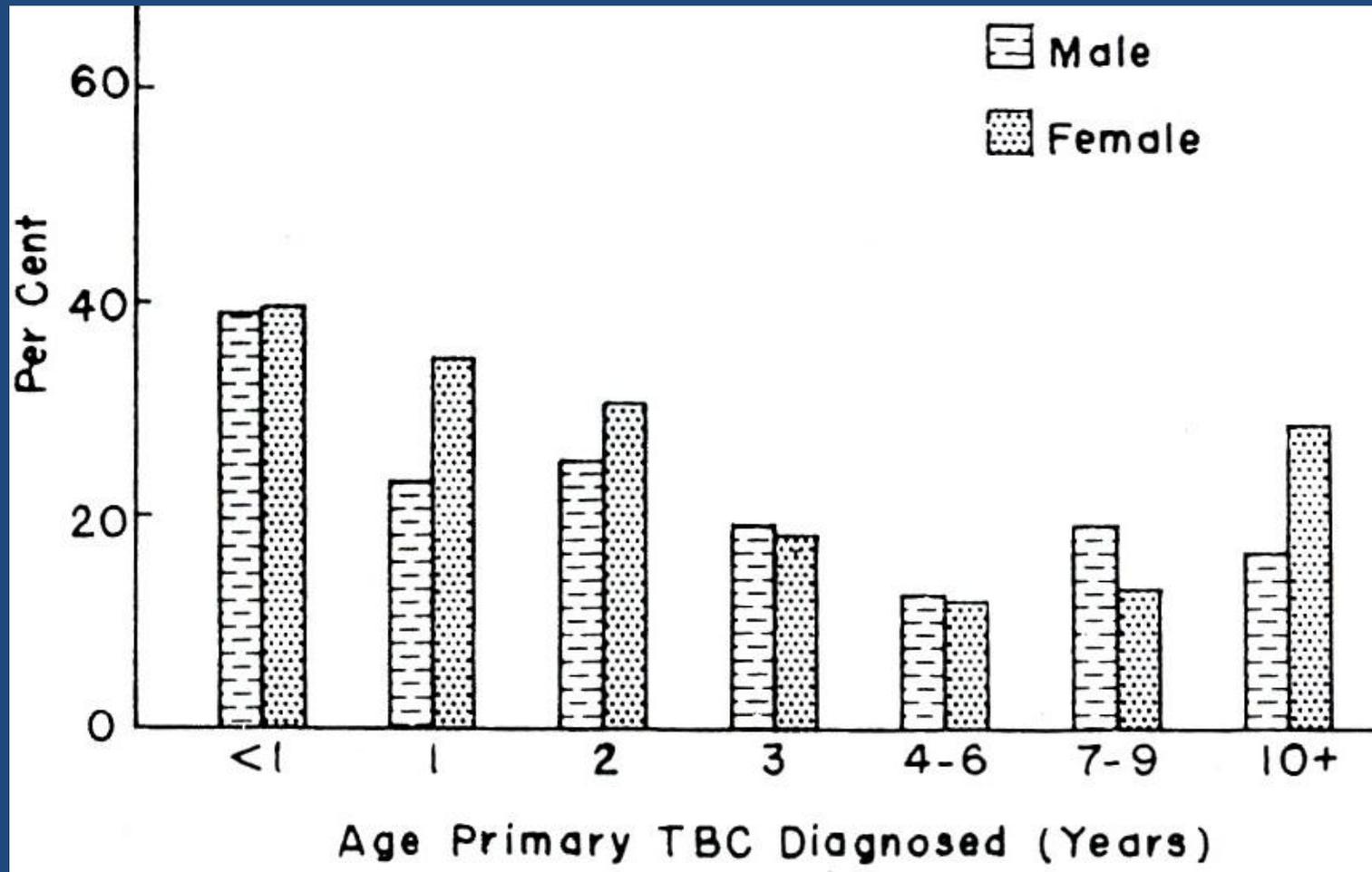
- A long-term follow-up study with the goal of enrolling **1,000 children** with **chest radiographic evidence of uncalcified primary TB**
- Follow up until **age 25-years**.
- Also followed were children with adult-type TB, extra-pulmonary TB with normal chest radiographs and infants and **children under two years** of age with **positive TST** and **normal CR**.

# Edith Maas Lincoln

- 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.

# Edith Maas Lincoln

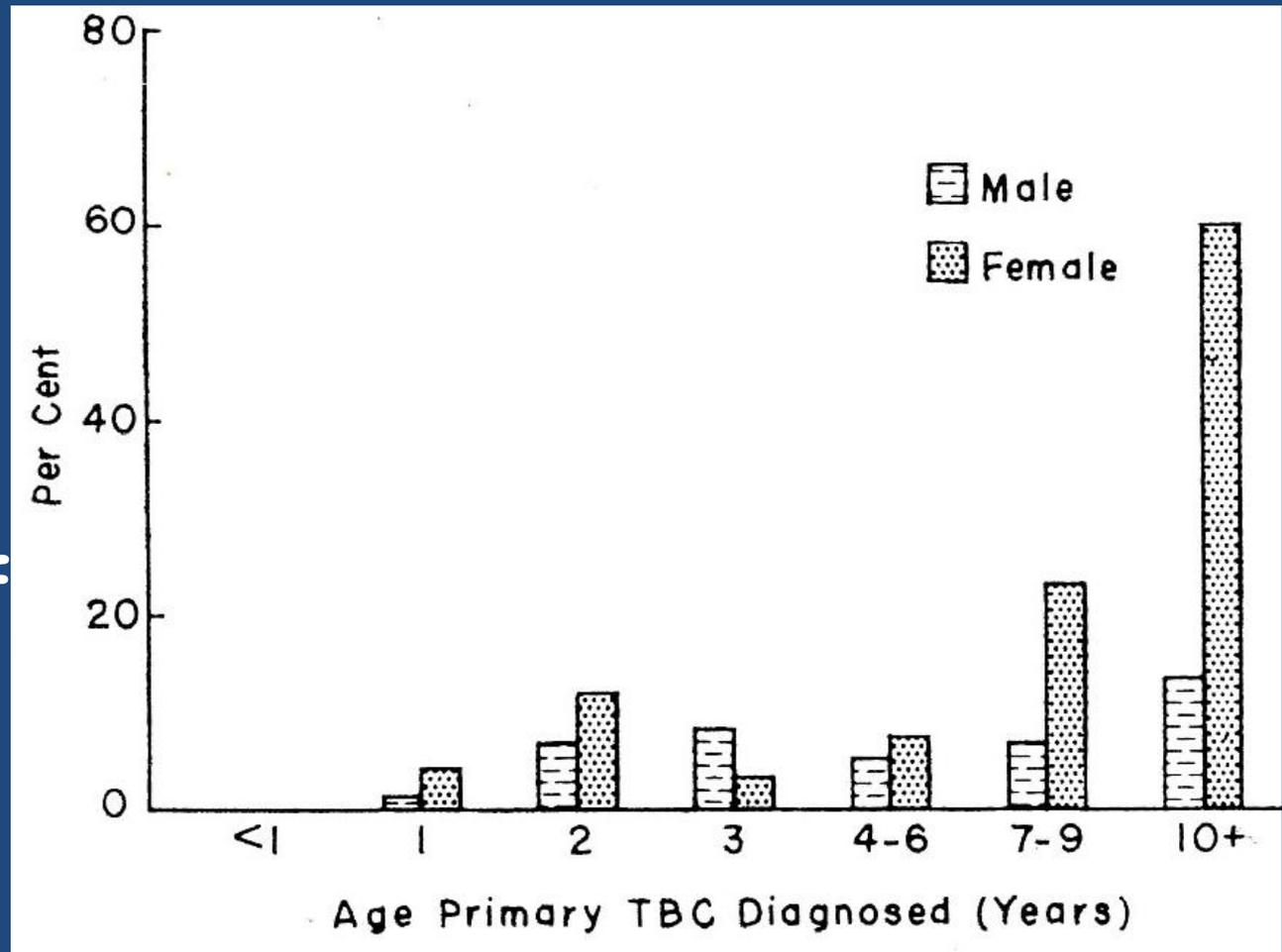
- In July **1940** the last of **1,000** children who were to be followed-up was enrolled; two thirds (622) of the children had recent uncomplicated primary TB at study entry and the remainder were children who had successfully survived primary infection as evidenced by calcification present on chest radiograph.



Frequency of **fatal complications** among 622 children classified by sex and age at diagnosis of uncalcified primary TB

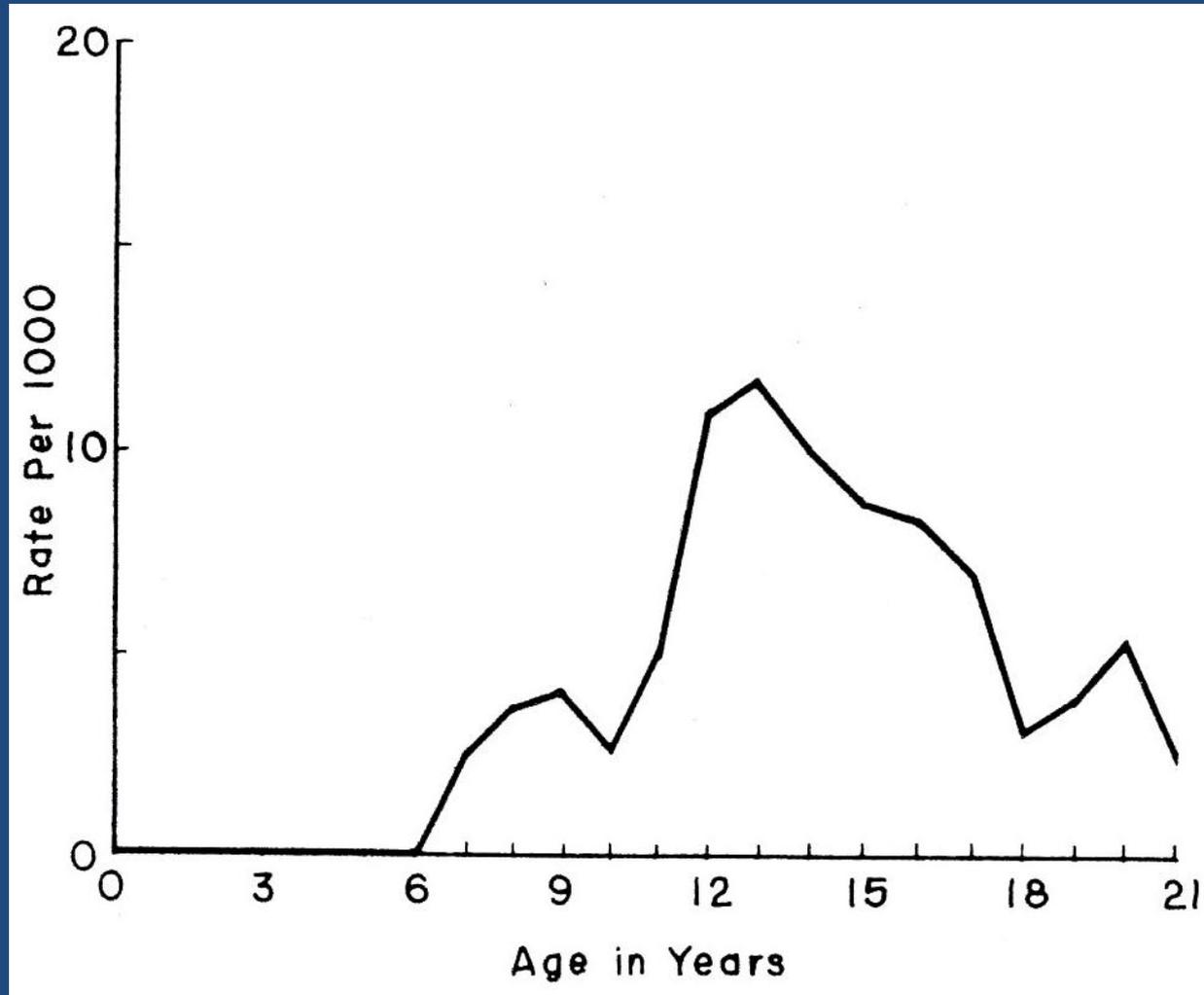
Lincoln EM, Gilbert LA, Morales SM. Chronic tuberculosis in individuals with known previous primary tuberculosis. *Dis Chest* 1960; 38: 473-482.

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



Lincoln EM, Gilbert LA, Morales SM. Chronic tuberculosis in individuals with known previous primary tuberculosis. *Dis Chest* 1960; 38: 473-482.

Probability of developing chronic pulmonary TB in each year of life among survivors of primary TB.



Lincoln EM. The effect of antimicrobial therapy on the prognosis of primary tuberculosis in children. *Am Rev Tuberc* 1954; 69: 682-688

“There is evidence in this reported series ...that isoniazid may prevent the development of complications of primary tuberculosis, especially meningitis.”

TABLE 1

DIMINISHING MORTALITY RATE FROM PRIMARY TUBERCULOSIS IN PATIENTS ON CHILDREN'S TUBERCULOSIS WARD OF BELLEVUE HOSPITAL FROM 1930 THROUGH 1953  
(Decrease Is Apparently Related to Use of Specific Therapy\*)

YEAR	NUMBER OF CASES	TREATMENT	MORTALITY
1930-1946	980	No specific therapy	21.5
1947-1951	421	Streptomycin, PAS, and Promizole used in 35 per cent of cases	5.0
1952-1953	129	Isoniazid added	1.5

- Milgram L, Levitt I, Unna MS. Promizole treatment of miliary tuberculosis. Am Rev Tuberc. 1947; 55: 144-159.
- Lincoln EM, Stone S, Hoffman OR. Treatment of miliary tuberculosis with Promizole. Bull Johns Hopkins Hosp. 1948; 82: 56-75.
- 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<sup>th</sup> November 1944

Lincoln EM, Harris LC, Bovornkitti S, Carretero R. The course and prognosis of endobronchial tuberculosis in children. *Am Rev Tub* 1956; 74: 246-255

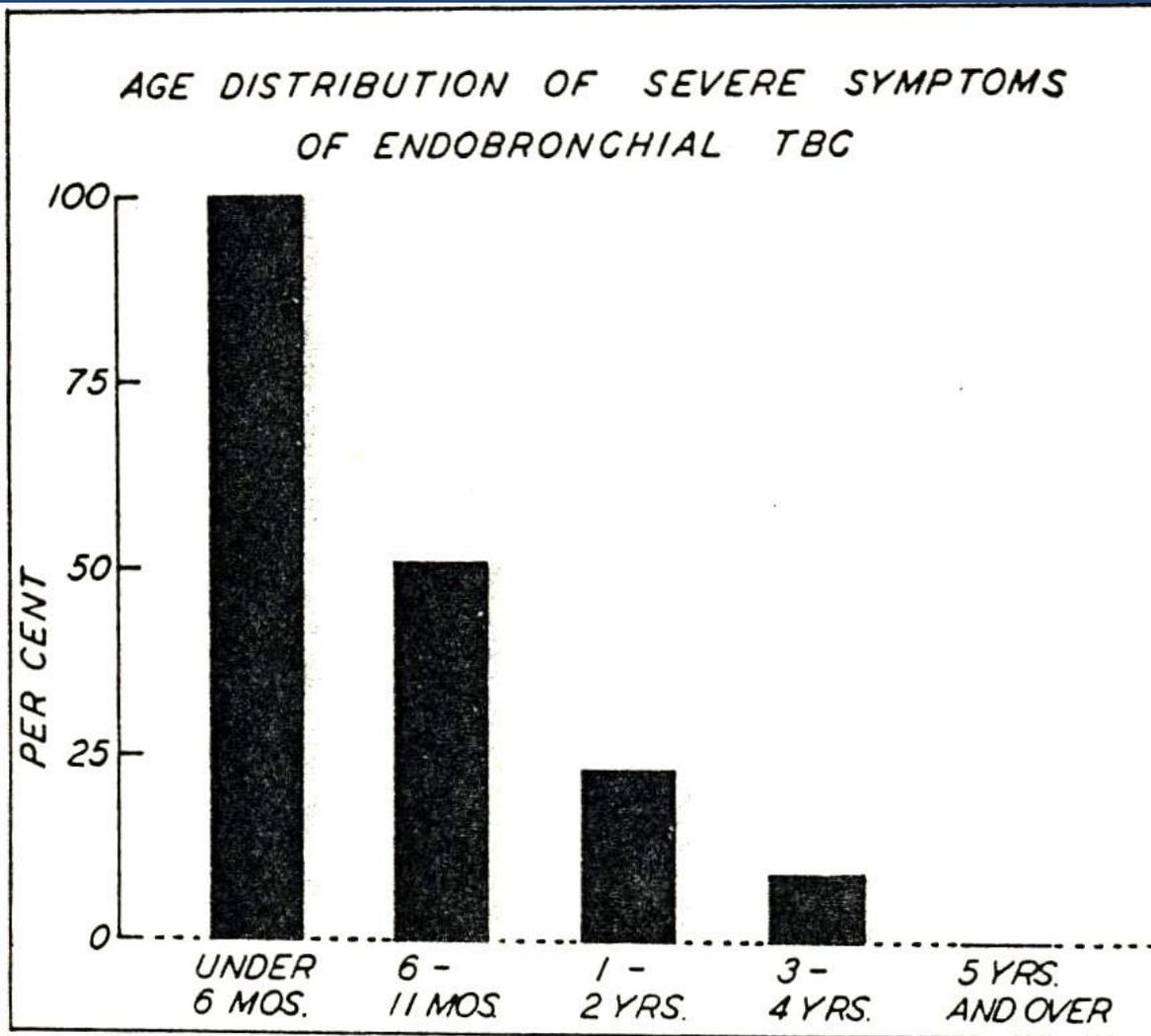
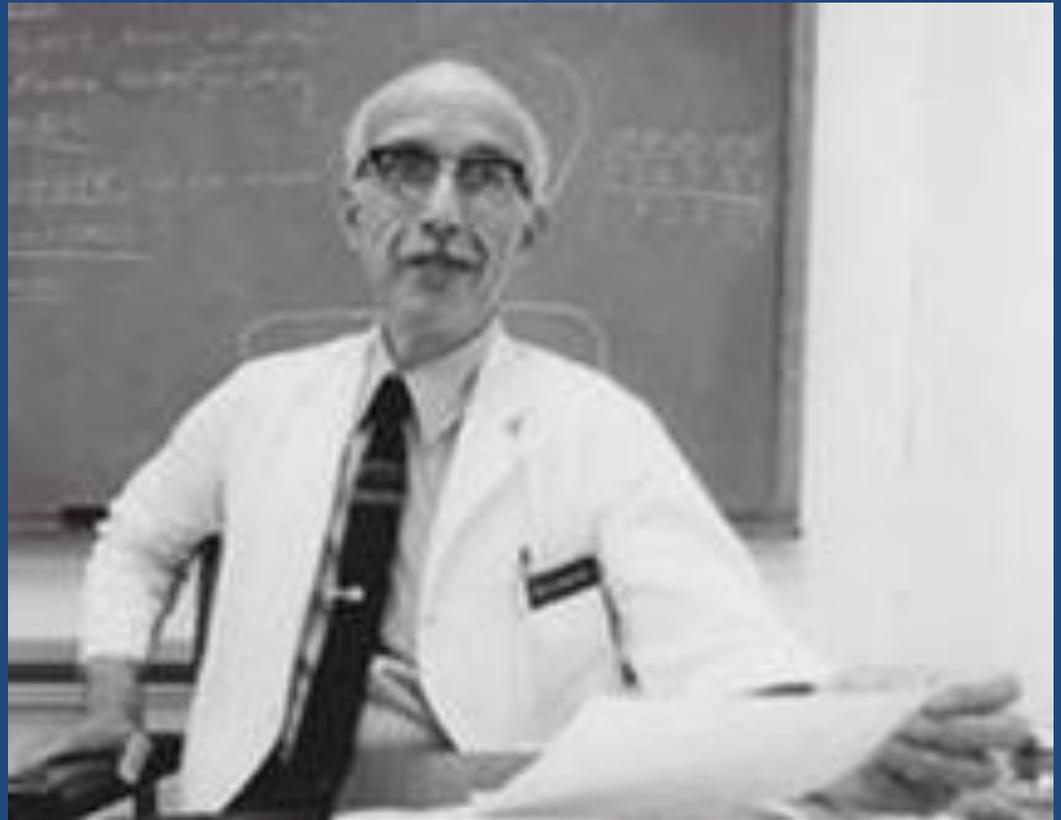


FIG. 1. Symptoms of endobronchial disease in relation to age.

# 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.



Palmer CE, Shaw LW, Comstock GW. Community trials of BCG vaccination. *Am Rev Tuberc Pulmon Dis* 1958; 77: 877-907.

Comstock GW, Edwards PQ. An American view of BCG vaccination illustrated by results of a controlled trial in Puerto Rico. *Scand J Resp Dis* 1972 53: 207-217.

Comstock GW, Livesay VT, Woolpert SF. Evaluation of BCG among Puerto Rican children. *Am J Publ Hlth* 1974; 64: 283-291.

Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; 99: 131-137.

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”

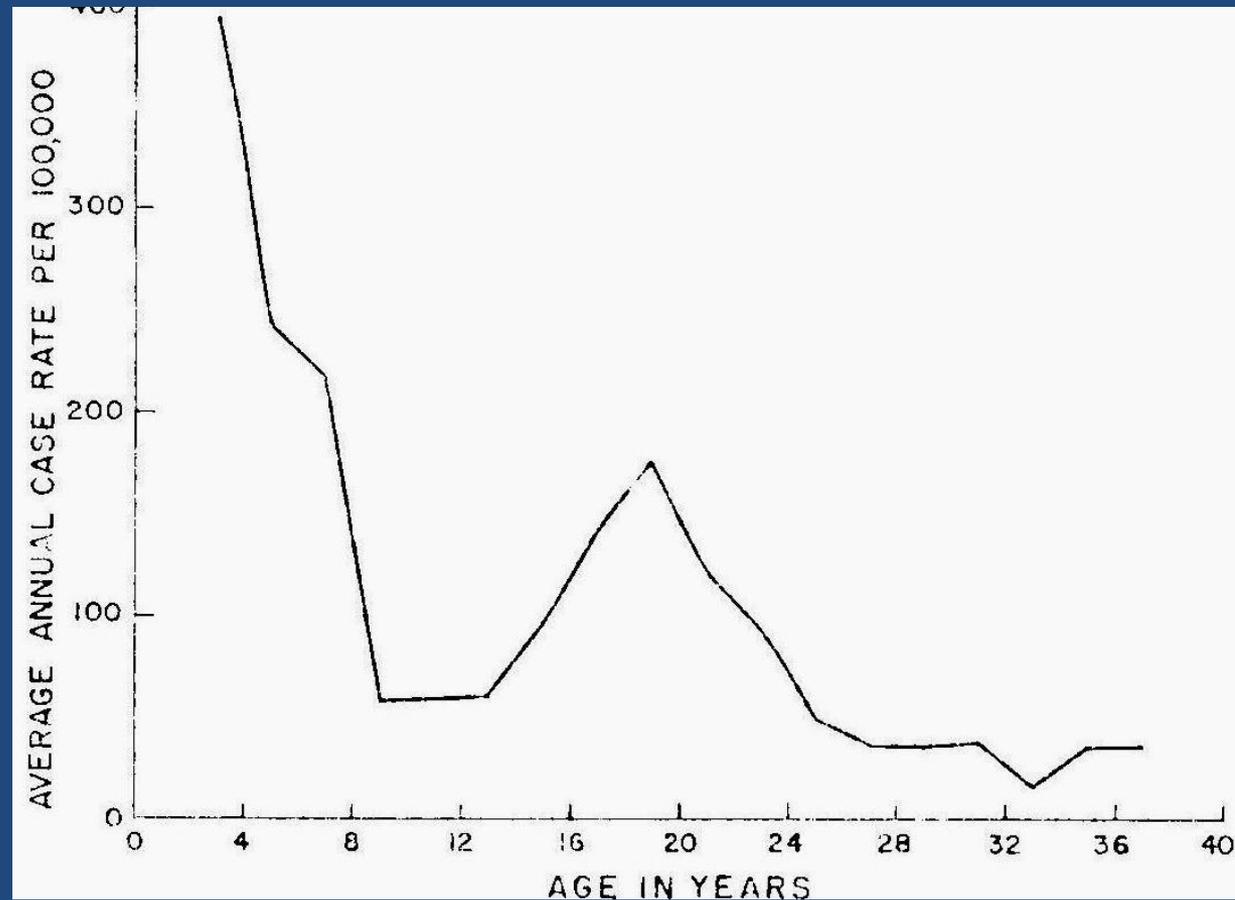
Age group (in years)	Reactors		
	Person-years experience	New cases	
		Number	Rate <sup>1</sup>
Total	13, 400	18	134
5-8	400	0	
9-12	2, 000	2	100
13-16	4, 200	5	120
17-20	4, 100	8	197
21-24	2, 300	3	130
25-28	500	0	

Comstock GW, et al. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; 99: 131-138

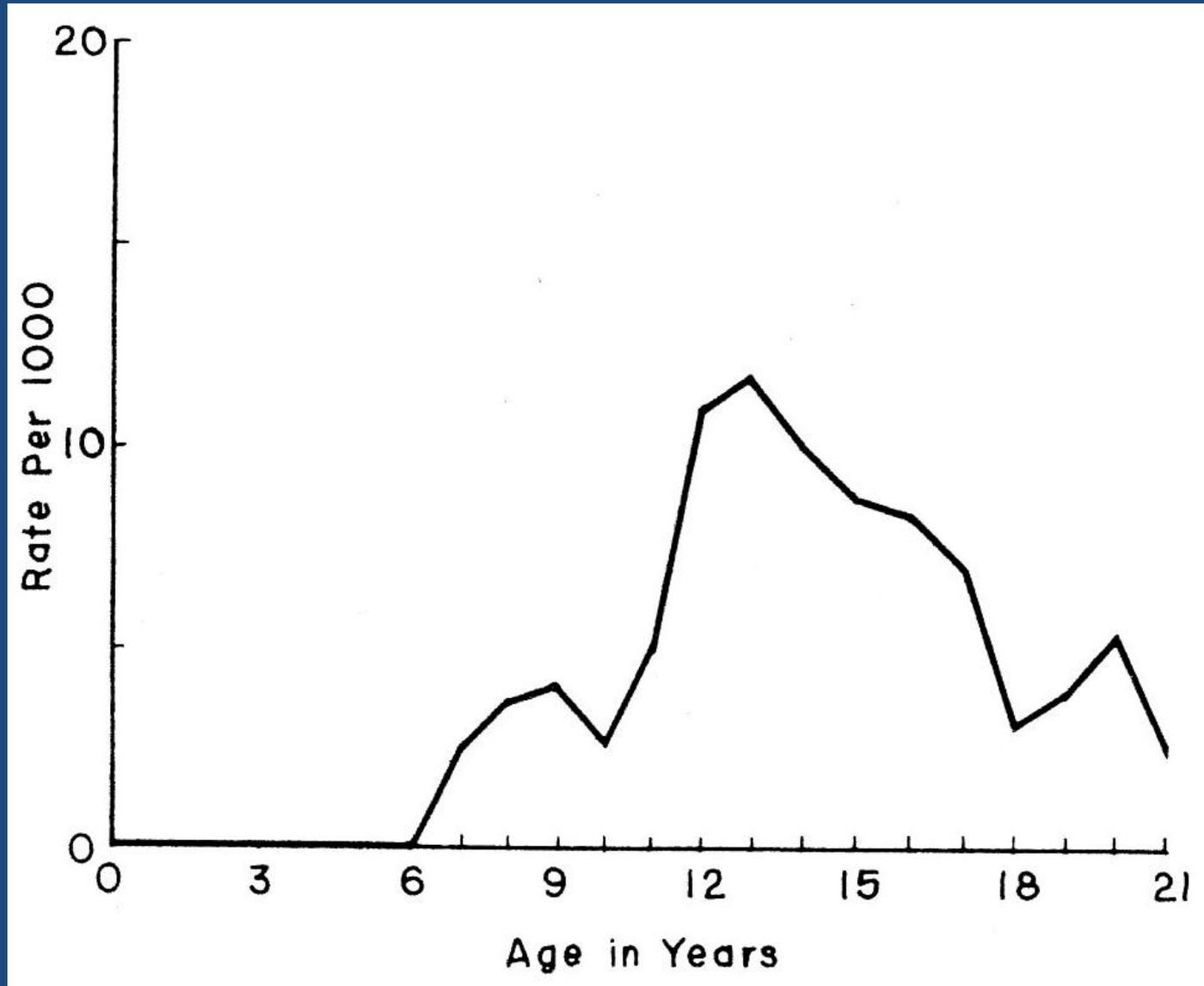
• Puerto Rican children age 1-6 years had a case rate X2 that of older children.

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

• Children 7-12 had the lowest subsequent rates.



Lincoln EM, Gilbert LA, Morales SM. Chronic tuberculosis in individuals with known previous primary tuberculosis. *Dis Chest* 1960; 38: 473-482.



Comstock GW, et al. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; 99: 131-138

- 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.



AR Rich. The Pathogenesis of Tuberculosis. 1<sup>st</sup> Ed. Chap V11:180-248. Table X111.

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

TABLE XIII  
MORTALITY FROM TUBERCULOSIS AT DIFFERENT AGE PERIODS IN THE GENERAL POPULATION,  
AND IN THE ESTIMATED INFECTED PORTION OF THE POPULATION  
(U. S. Registration Area, 1940)

Age	Total Deaths from Tuberculosis	Estimated Per Cent Infected*	Deaths from Tuberculosis per 100,000 Persons of Each Age Period			Deaths from Tuberculosis per 100,000 Estimated Infected Persons of Each Age Period
			Male	Female	Both Sexes	Both Sexes
0-1	496	0.5	24.8	24.3	24.6	4,920
1-4	1,047	10	12.6	12.0	12.3	123
5-9	469	25	4.6	4.2	4.4	18
10-14	775	35	5.0	8.2	6.6	19
15-19	3,375	45	19.7	35.1	27.4	61
20-24	5,752	55	41.5	57.5	49.6	90
25-29	6,243	65	52.7	59.7	56.3	87
30-34	5,775	75	60.3	52.6	56.4	75
35-39	5,448	85	67.0	47.3	57.1	67
40-44	5,438	90	83.2	40.4	61.9	69
45-49	5,222	95	90.6	34.8	63.3	66
50-54	5,058	95	101.3	35.8	69.7	73
55-59	4,409	95	109.9	38.9	75.4	79
60-64	3,641	95	110.3	42.8	77.0	81
65-69	2,975	95	105.4	51.1	78.2	82
70-74	2,179	95	107.6	62.5	84.8	89
75 and over	2,057	95	90.3	66.8	77.8	82

\* Estimated from recent tuberculin surveys. See Table XII and text discussion for limitations.

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15-19	3,375	45	19.7	35.1	27.4	61
20-24	5,752	55	41.5	57.5	49.6	90
25-29	6,243	65	52.7	59.7	56.3	87

AR Rich. The Pathogenesis of Tuberculosis. 1st Ed. Chap V11:180-248. Chart II.

Tuberculosis mortality rates by age and sex for 1900, 1932 and 1940 (United States Census Bureau Statistics)

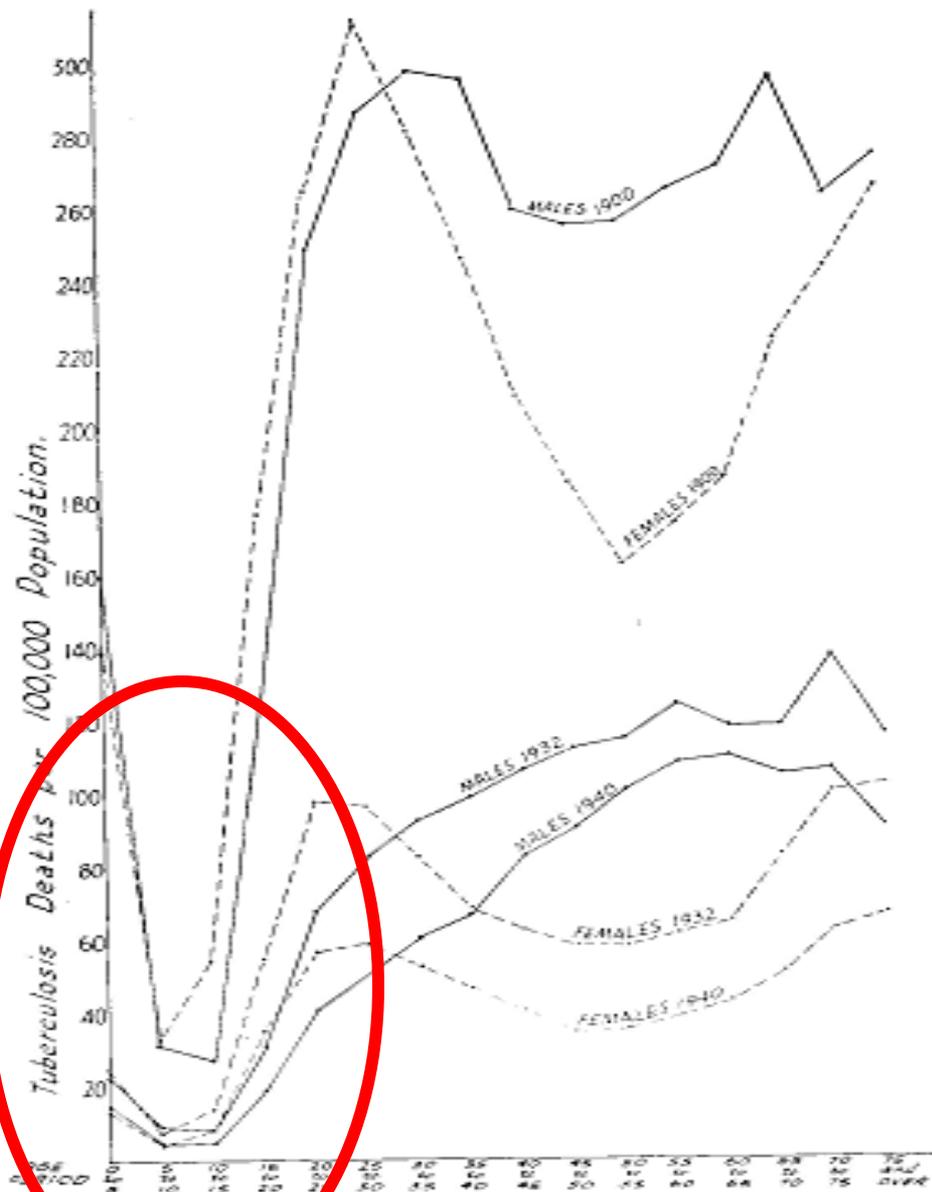


CHART II  
TUBERCULOSIS MORTALITY RATES BY AGE AND SEX FOR 1900, 1932, AND 1940  
(United States Census Bureau Statistics)

Hall S. The prevalence of tuberculosis in FRG Heaf, Ed. A symposium of Tuberculosis. Cassel & co 1957:67-107.

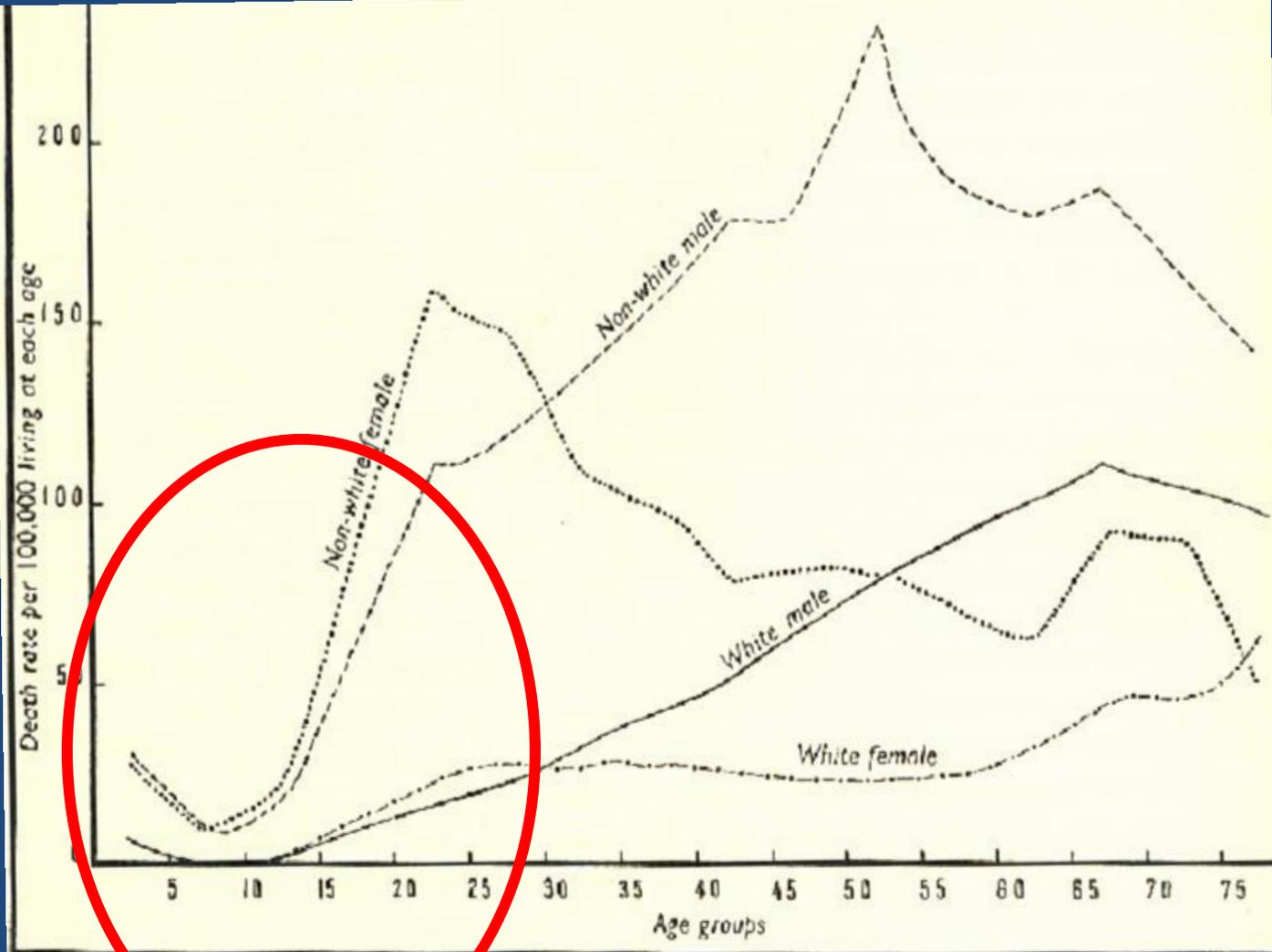
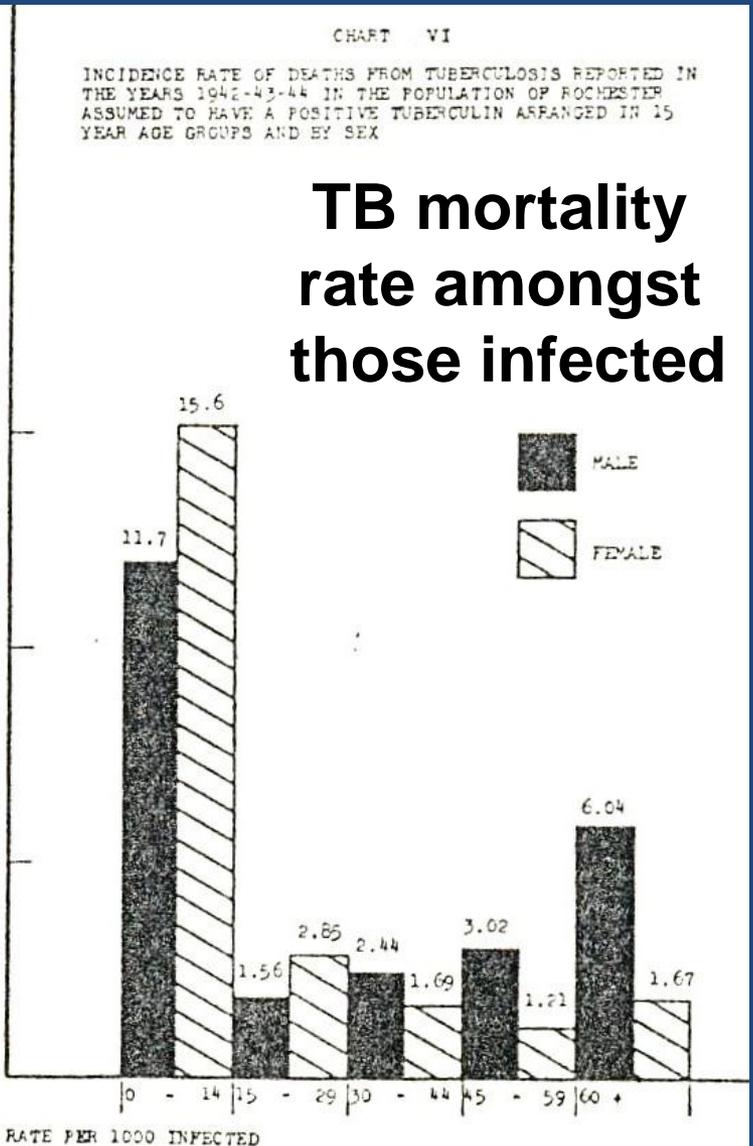
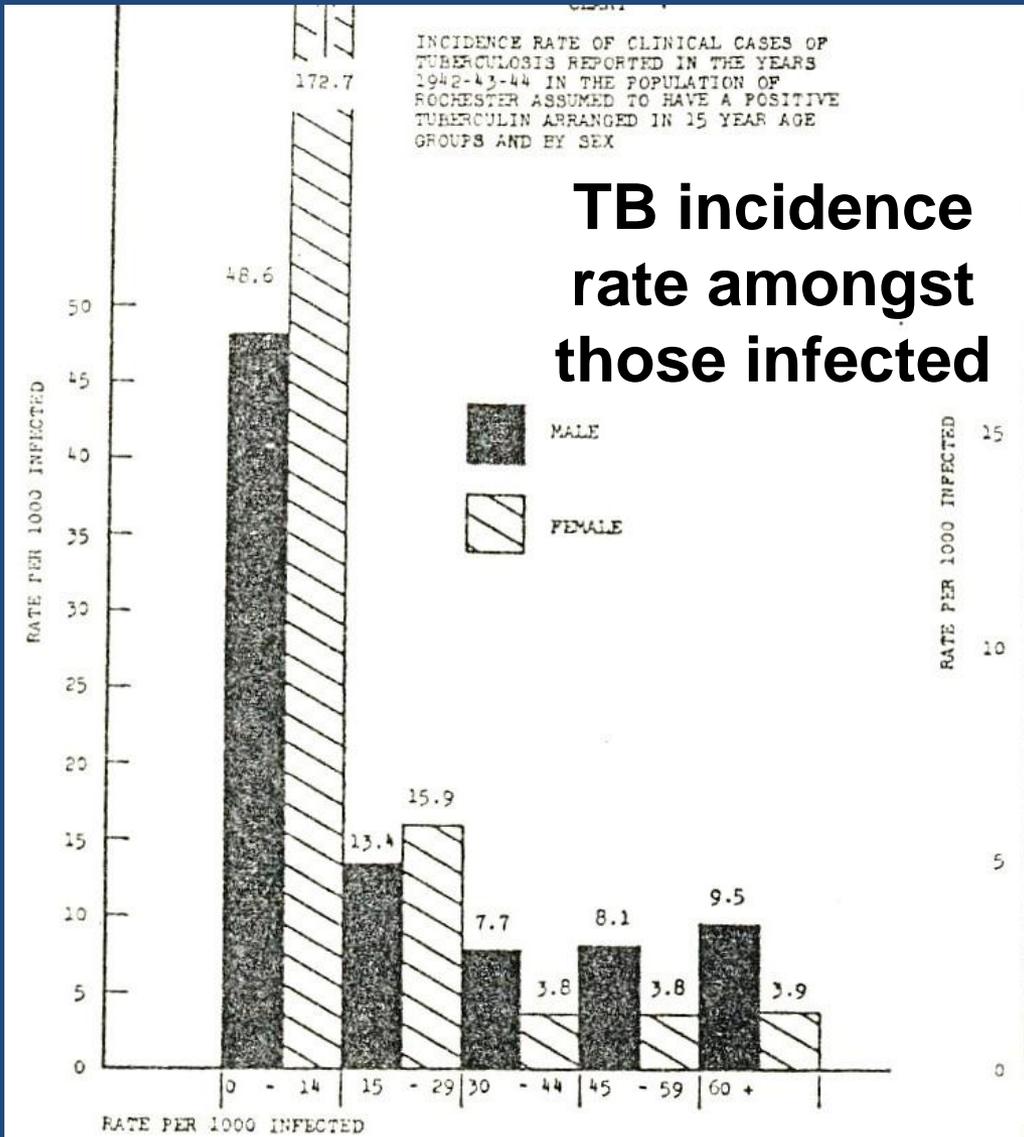


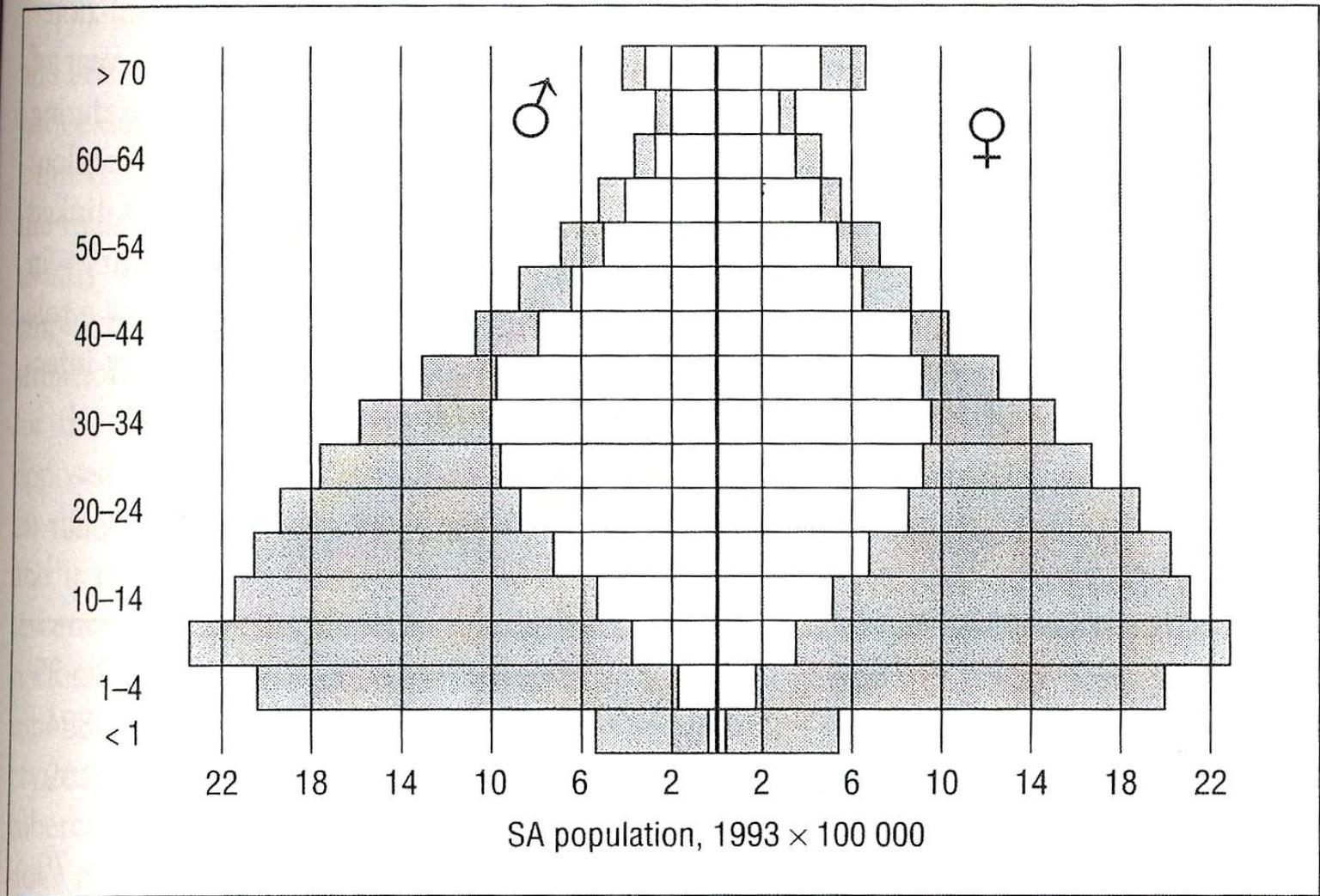
FIG. 9. Manitoba. Tuberculosis (all forms) mortality, whites and Indians, 1927-47.

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

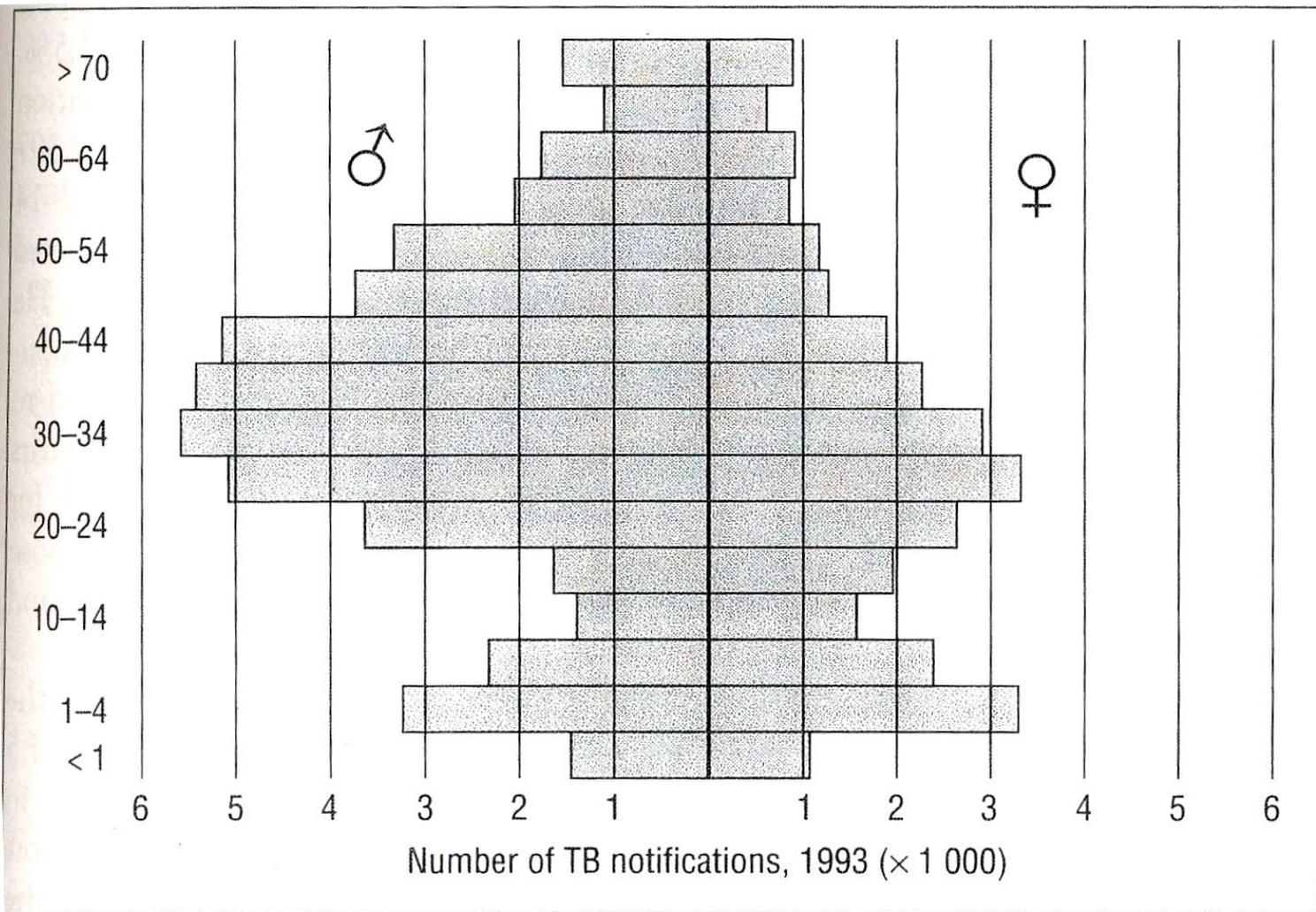
- The author sets TB morbidity and mortality in relation to the risk of infection.
- TB incidence rates determined with the calculated number of infected individuals as denominator.
- 1942-1944 extensive tuberculin testing in Rochester, New York by the TB and Health Association of Rochester: 9252 adult 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





**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.

JA Myers. The natural history of tuberculosis in the human body. 1. The demonstrable primary pulmonary infiltrate. Am Rev Tuberc 1959; 79: 19-30.

- 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**.

JA Myers. The natural history of tuberculosis in the human body. 1. The demonstrable primary pulmonary infiltrate. Am Rev Tuberc 1959; 79: 19-30.

- 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.

JA Myers. The natural history of tuberculosis in the human body. 1. The demonstrable primary pulmonary infiltrate. Am Rev Tuberc 1959; 79: 19-30.

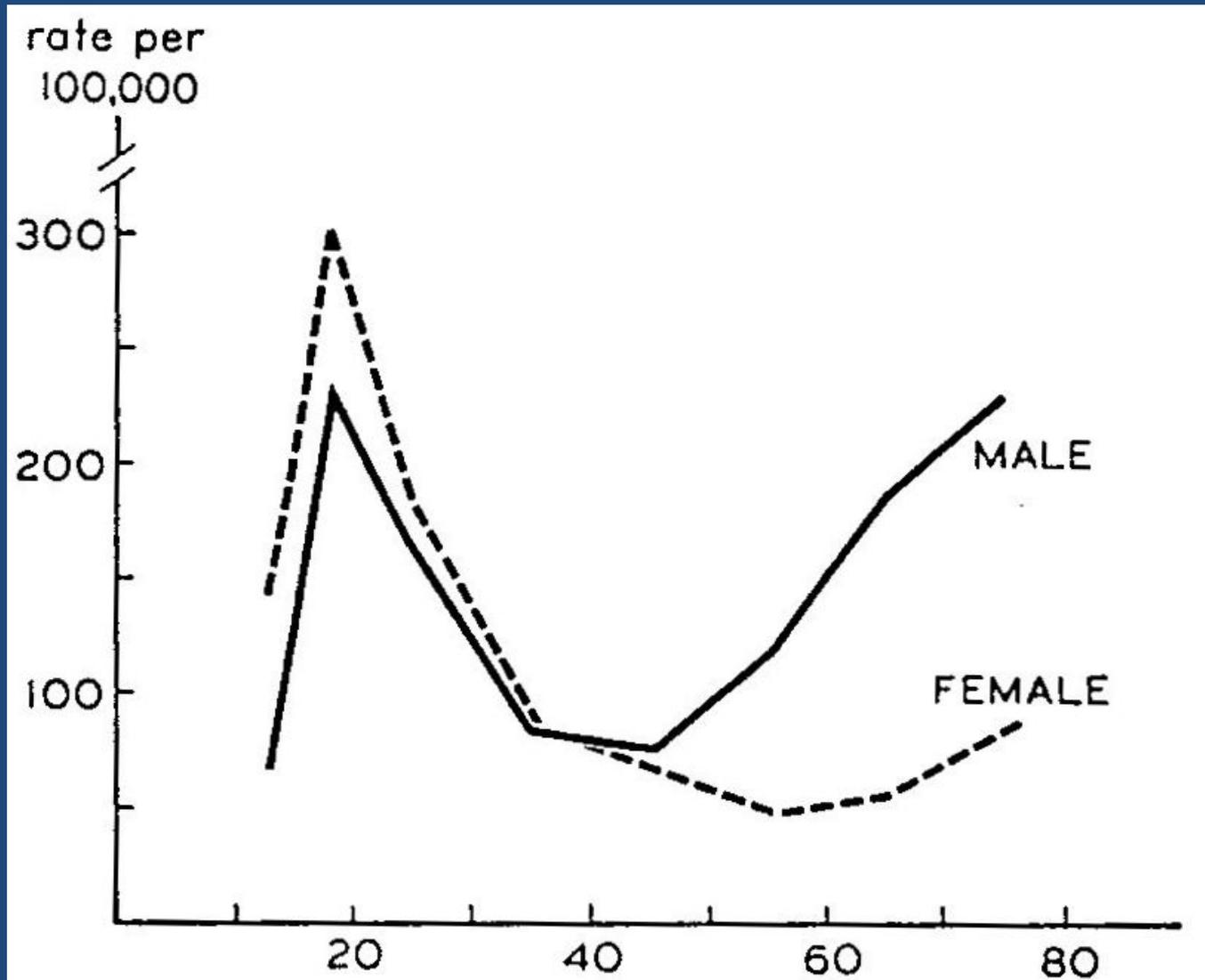
- Mild symptoms, when diagnosed.
- **267 (89%)** located after 6,000 person years, mean age approximately **31 yrs.**
- **9 (3.4%)** cases of death as result of TB recorded. (4 TBM, 1 miliary, 2 pneumonia, 2 adult type TB).

JA Myers. The natural history of tuberculosis in the human body. 1. The demonstrable primary pulmonary infiltrate. Am Rev Tuberc 1959; 79: 19-30.

- 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".

- Myers JA, Bearman JE, Dixon HG. Natural history of tuberculosis in the human body VI. Prognosis among tuberculin reactor children from birth to five years. *Am Rev Respir Dis* 1963; 87: 354-369.
- Myers JA, Bearman JE, Dixon HG. Natural history of tuberculosis in the human body VI. Prognosis among tuberculin reactor children of six to twelve years. *Am Rev Respir Dis* 1964; 90: 359-369.
- Myers JA, Bearman JE, Dixon HG. Natural history of tuberculosis in the human body VIII. Prognosis among tuberculin reactor girls and boys from thirteen to seventeen years. *Am Rev Respir Dis* 1965; 91: 896-908.
- Myers JA. The natural history of tuberculosis in the human body. *JAMA* 1965; 194: 1086-190.

Grzybowski S, Allen EA. The challenge of tuberculosis in decline. *Am Rev Respir Dis* 1964; 90: 707-720  
A study based on the epidemiology of tuberculosis in Ontario, Canada.



Grzybowski S, Barnett, Styblo K. Contacts of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975; 50: 90-106.

- 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**.

Grzybowski S, Barnett, Styblo K. Contacts of active pulmonary tuberculosis. Bull Int Union Tuberc 1975; 50: 90-106

**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%**.

Age group	Status of source case			
	Sm+	Cult+	Sm&Cult-	
0-14 years				
N	412	326	55	31
Active TB	123	10	3	
%	37.7	18.2	9.7	

Grzybowski S, Barnett, Styblo K. Contacts of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975; 50: 90-106

**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%.

Age group	Status of source case			
	Sm+	Cult+	Sm&Cult-	
0-14 years				
N	352	223	88	41
Active TB	85	11	4	
%	38.1	12.5	9.8	

Grzybowski S, Barnett, Styblo K. Contacts of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975; 50: 90-106

“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.”

Grzybowski S, Barnett, Styblo K. Contacts of active pulmonary tuberculosis. Bull Int Union Tuberc. 1975; 50: 90-106

**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

Smith MHD. Tuberculosis in adolescents.  
Characteristics, recognition, management. Clin  
Pediatr 1967; 6: 9-15.

- 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.

# Adolescent Tuberculosis

Arnold Rich. *The Pathogenesis of Tuberculosis*. 2<sup>nd</sup> edition, Charles C Thomas, Springfield, Illinois 1951.

- "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 1

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.

Lincoln EM. Eradication of tuberculosis in children.  
Arch Environmental Hlth 1961; 3: 44-455

- “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.”

Lincoln EM. Eradication of tuberculosis in children.  
Arch Environmental Hlth 1961; 3: 44-455

“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!

