Can Social Interventions Prevent Tuberculosis?
The Papworth Experiment (1918–1943) Revisited

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***Rationale*: There is consensus on the need to address social determinants of tuberculosis (TB) to achieve TB control, but evidence based on interventions is lacking.**

***Objectives*: We reanalyzed data from the sociomedical experiment performed at the Papworth Village Settlement in England, where the impact of stable employment and adequate housing and nutrition on the incidence of TB infection and disease in children living with parents with active TB was documented during 1918–1943.**

***Methods*: Information on 315 children of patients, who lived at Papworth, was abstracted from a published monograph. Overall and age-specific occurrence of TB infection, disease, and deaths among children born in the settlement (village-born cohort) were compared with those of children born outside and admitted later (admitted cohort) to Papworth.**

***Measurements and Main Results*: The annual risks of infection in the village-born and admitted cohorts were 20 and 24%, respectively. Of 24 children who developed TB disease, only one was village-born. Among children 5 years of age or less, there was zero incidence of TB in the village-born, compared with five cases (1,217/100,000 person-years) among children born outside Papworth. In the admitted cohort, among children 13 years of age and older, the incidence of TB before admission to Papworth was 5,263/100,000 person-years, whereas it was 341/100,000 person-years while living in Papworth.**

***Conclusions*: At Papworth social interventions including adequate nutrition did not reduce TB transmission but did reduce the incidence of TB disease in children living with parents with active TB. These results are relevant today for prevention of TB in children of patients with active TB, particularly with multidrug-resistant TB in high-burden settings.**

Keywords: tuberculosis; epidemiology; prevention and control

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Current decline in tuberculosis (TB) incidence in developing countries is slow. There is consensus that to achieve global TB control targets, action on social determinants of TB should complement traditional approaches to TB control, but evidence for the impact of social interventions is lacking.

What This Study Adds to the Field

This study provides evidence that social interventions may reduce TB disease risk even in a vulnerable group of close contacts with a high prevalence of TB infection. Residence of TB-affected families in the Papworth Village Settlement during the prechemotherapy and pre–bacillus Calmette-Guérin (BCG) era (1918–1943), where stable employment was provided together with adequate housing and nutrition, reduced substantially the incidence of TB disease in child contacts.

In developing countries, the incidence of tuberculosis (TB) remains high, with a current decline of less than 1% per year (1). The epidemic of drug-resistant TB poses a major challenge to traditional TB control efforts, based primarily on the use of antibiotics to treat disease and latent infection. There is consensus that social determinants including poverty, undernutrition, poor housing, and substance use are drivers of the TB epidemic and should be addressed to achieve TB control targets (2–6). There is, however, a lack of studies documenting the effects of social interventions on *Mycobacterium tuberculosis* transmission and TB incidence (5, 7).

The Papworth Village Settlement was founded in 1918 by Sir Pendrill Varrier-Jones (8). This was started as a sociomedical experiment for the rehabilitation of working-class patients with TB discharged from a sanatorium (8, 9). Patients with TB were provided assured employment, adequate nutrition and housing, and close medical supervision (9, 10). Attempts to limit TB transmission included strict implementation of cough etiquette, use of sputum flasks containing disinfectants, adequate ventilation, and separate rooms for infectious patients (10, 11). A medical team closely monitored the health status of children at a weekly clinic, provided advice on nutrition, and conducted evaluations for TB-related outcomes (11). In 1938 the settlement consisted of a 200-bed hospital, a sanatorium, laboratories, a research unit, numerous industries, and a residential area with 142 cottages, schools, and recreational facilities for patients and their families (11). *The Lancet* described it as the "the most comprehensive single effort to deal simultaneously with every aspect of the tuberculosis problem" (12).

Beginning in 1937, a survey was conducted to document the outcomes of TB infection and disease in children who had lived in the settlement during 1918–1938 (11). The results were

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published as an article (13), and a detailed 674-page monograph (11). The survey compiled data from patients' files, Papworth clinic records, and the X-ray records of each family (11). Every effort was made to follow up each family until 1938, and the status of children was updated until 1943 (11). We reanalyzed data on 315 children from 135 TB-affected families that lived in the settlement between 1918 and 1943, as reported in the monograph (11), using current epidemiologic and statistical methods. Our objective was to estimate the effect of residence within the Papworth settlement on the incidence of TB infection and disease in child household contacts of patients with TB.

METHODS

Study Population and Data Collection

After a period of sanatorium treatment, patients with active TB were admitted to the Papworth settlement, and their families then joined them, including their children. We studied 315 children who lived with a parent with active TB at Papworth during 1918–1943. This included children who died of TB before the family was admitted to the settlement, but excluded surviving children who never resided in Papworth, and children of healthy staff members.

We abstracted detailed information from the monograph on the Papworth families (11). This included years of birth, admission, evaluation, and discharge from the Papworth settlement or death. Clinical, microbiologic, and radiologic information about the source case, as well as results of clinical, microbiologic, and radiologic evaluation in the children, TB disease characteristics, and causes of death were also retrieved.

Definition of Outcomes

The following outcome definitions were used (11):

- Normal—No clinical or radiologic abnormalities.
- TB infection—Absence of clinical symptoms with one of the following radiologic abnormalities: Ghon focus, calcified foci, radiologic evidence of primary infection, transient perifocal reactions (transient radiologic densities that appeared and resolved completely). Tuberculin skin testing was done in 136 child contacts, using Moro's tuberculin ointment. However, X-rays were used to diagnose TB infection, perhaps due to completeness of data, and issues of sensitivity and interpretation of the Moro's test (14).
- TB disease—Presence of clinical symptoms with sputum smear and gastric lavage examinations positive or radiologic abnormalities documented on serial X-rays. This was classified as childhood tuberculosis (pulmonary and extrapulmonary) or adult-type (cavitary) pulmonary TB.

Data Analysis

We compared outcomes in two groups of child contacts, based on their place of birth (as was done in the original study). The village-born cohort included all children born within the settlement. The admitted cohort included children born outside Papworth, who were later admitted with their families. Both groups of children lived in the same house as their parent with active TB at Papworth. We analyzed outcomes in the two cohorts during different time periods defined as follows:

- The *pre-Papworth period*, applied only to the admitted group, and extended from the year of TB diagnosis in the source case to the year of admission to Papworth.
- The *Papworth period* began with the year of birth (village born) or the year of admission to Papworth (admitted), and extended to the year the child left, or to the end of the study period (1943).
- The *post-Papworth* period was the same for both cohorts, and extended from the year of leaving to the year of reevaluation at Papworth; this could be analyzed only for those later reevaluated. However, all those discharged were evaluated and were known to be free of disease at the time of discharge.

For each period, we calculated the total person-years of exposure of each child within three age groups: 0–5 years, 6–12 years, and 13 years and older.

The prevalence of TB infection and the annual risk of infection in the village-born and admitted cohorts were compared in a series of analyses: The village-born children were exposed to TB since birth; hence the duration of exposure to TB at the time of assessment for TB infection was equal to their age. For the admitted cohort, their exposure was estimated in three ways: Analysis 1: The duration of household exposure to TB at the time of assessment was considered as the age at assessment minus their age when TB was first diagnosed in their parent. Analysis 2: The age at assessment was considered as the duration of exposure, which incorporated both household and community exposure to TB. Analysis 3: The analysis was restricted to the subset of children in the admitted cohort who were exposed to TB since birth, in whom the duration of exposure was equal to their age at the time of assessment for TB infection. This analysis was considered the most comparable to that in the village-born children.

The annual risk of infection (ARI) per year of exposure was calculated according to the formula $ARI = 1 - (1 - P)^{1/A}$ (15, 16), where P is the mean prevalence of infection, and A is the weighted mean duration of exposure.

TB incidence rates were estimated in the two cohorts of children, the three age groups, and in the three time periods. Incidence rate ratios were calculated to compare disease incidence in the two cohorts, and between time periods. Confidence intervals (CIs) for incidence rates were calculated using the Poisson distribution. Ninety-five percent confidence intervals were calculated, unless explicitly stated otherwise. Confounding was assessed using *a priori* criteria and stratified analysis. All data were analyzed with STATA 11.1 (StataCorp LP, College Station, TX).

RESULTS

The 315 child contacts consisted of 84 children in the village-born cohort, and 231 children in the admitted cohort. Figure E1 (in the online supplement) provides an overview of all families and children, while Figure 1 describes the number of child contacts in the pre-Papworth, Papworth, and post-Papworth periods. In 135 families, the fathers alone were the source cases, while in 15 families; the fathers plus additional family members had active TB. Source cases spent a median of 1 year (interquartile range [IQR], 1–2 yr) in the sanatorium before admission to the settlement. The median age of the source cases was 33 years (IQR, 28–38). Among the source cases, 64% had sputum smear-positive TB, of whom 44% died after their admission to the settlement (Table E1). Proportions of children in contact with sputum smear–positive cases were similar among the two cohorts (Table 1). The children's stay in the settlement totaled 2,980 person-years and was similar in both cohorts (median stay, 9 yr; $P = 0.09$); a high proportion (272; 87.2%) resided in the settlement for more than 3 years.

Children in both cohorts underwent detailed clinical evaluation on admission and at regular intervals, or on suspicion of TB disease. The number of evaluations was similar in the two cohorts, such as the number of X-rays per child. Table 2 describes the prevalence of TB infection based on radiologic abnormalities and estimated annual risk of infection in the two cohorts on the basis of analyses 1–3. The age-specific prevalence of infection in the two cohorts including the subset of admitted children exposed to TB since birth was similar. The estimated ARI was high in both cohorts with no significant difference (Table 2).

Table 3 describes the incidence and TB disease characteristics in children before they were admitted to Papworth. The

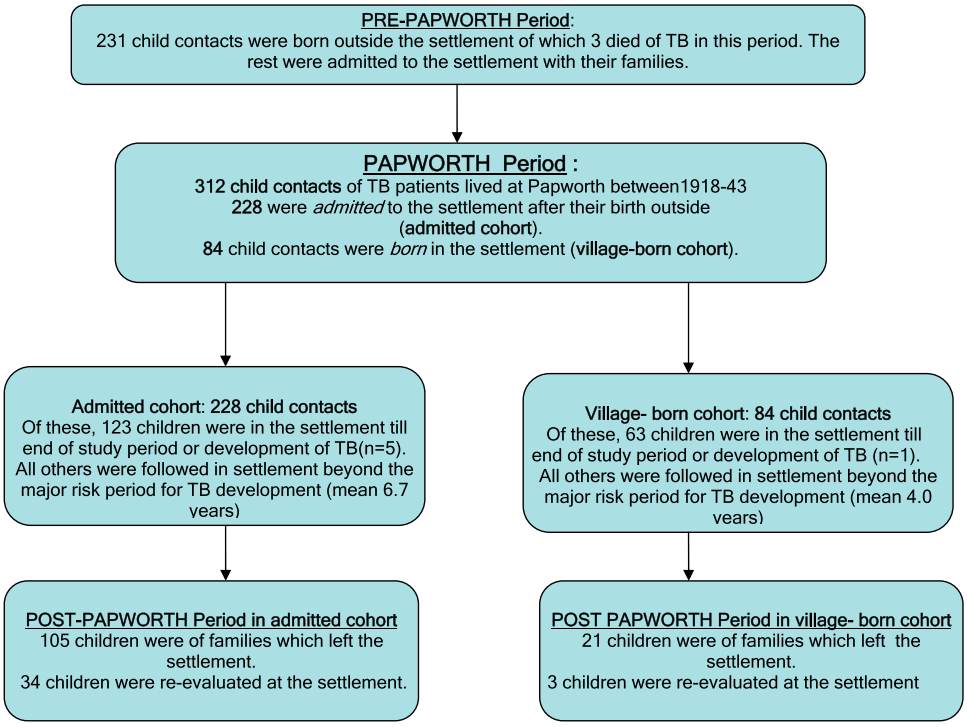

Figure 1. Summary of children in the village-born and admitted cohorts before admission to Papworth, while living in Papworth, and after discharge. TB = tuberculosis.

median age of disease onset was 11 years (range, 2–25 yr). Calculated incidence rates were 578/100,000 person-years (95% CI, 70 to 2,088) in the 6–12 age group, 1,217/100,000 person-years (95% CI, 395 to 2,839) in the 0- to 5-year age group, and 5,263/100,000 person-years (95% CI, 1,931 to 11,456) in children who were 13 years and older. Six deaths occurred in children whose active TB began before admission to Papworth. Of these three deaths occurred before admission to Papworth (one of which was due to disseminated TB in an infant), and three deaths occurred after admission.

TB incidence, disease characteristics, and mortality data for the Papworth period are described in Table 4. Most of the cases,

TABLE 1. CHARACTERISTICS OF CHILDREN IN ADMITTED AND VILLAGE-BORN COHORTS FROM PAPWORTH VILLAGE SETTLEMENT (1918–1943)

Characteristic	Admitted Cohort (*n = 228*)*	Village-Born Cohort (*n = 84*)
Demographic		
Age of children at time of admission to Papworth (yr), median (IQR)	7 (3, 11)	At birth
Females, %	52%	53%
No. of children 5 yr of age and younger at time of admission to Papworth	99	84
Medical status of parents		
Smear-negative pulmonary TB, %	34%	40%
Smear-positive pulmonary TB, %	66%†	60%†
Other characteristics related to exposure to TB		
Age when first exposed to at least one parent with active TB, %		
0–4 yr	72%	100%
⩾5 yr	28%	
No. of child contacts of smear-positive TB	151	50
No. of child contacts of smear-negative TB	77	34
Before admission to Papworth	n = 231	
Total person-years of observation before admission to Papworth	881	Not applicable
Median (IQR) person-years of observation	3 (2, 5)	Not applicable
While living in Papworth	n = 228	n = 84
Total person-years of observation in Papworth‡	2,215	765
Person-years of observation, median (IQR)	9 (5, 14)	9 (5, 13.5)
Child contacts with ⩾ 3-yr stay in Papworth, n (%) and [95% CI]	199 (87) [82, 91]	70 (83) [73, 91]
After discharge from Papworth	n = 34	n = 3
Number of child contacts who left the settlement	105	23
Number reevaluated (percentage of those who were discharged)	34 (32)	3 (13)
Person-years of observation after discharge from Papworth	221	23
Person-years of observation, median (IQR)	6.5 (3, 10)	9 (5, 9)

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; TB = tuberculosis.

*Three children who died before admission to Papworth are not part of this analysis.

† $P > 0.2$ (chi-squared test).

‡ Person-time of stay in Papworth extended from year of admission to either 1943 (for those who continued to live in the settlement), or to year of leaving the settlement (for those who left the settlement). In cases in which the child died, this period extended from year of admission to year of death.

TABLE 2. PREVALENCE OF INFECTION AND ESTIMATED ANNUAL RISK OF INFECTION IN VILLAGE-BORN AND ADMITTED COHORTS, USING DIFFERENT METHODS OF ANALYSIS

		Admitted Cohort*†		
	Village-Born Cohort* (*n* = 69)	Analysis 1‡ (*n* = 196)	Analysis 2§ (*n* = 196)	Analysis 3‖ (*n* = 89)
Prevalence of TB infection in 1.0–3.9 yr	0.44	0.82	0.5	0.38
Prevalence of TB infection in 4.0–6.9 yr	0.71	0.84	0.82	0.79
Prevalence of TB infection in 7.0–9.9 yr	0.94	0.86	0.88	0.9
Prevalence of TB infection in ⩾10 yr	1	0.84	0.87	0.83
Prevalence of infection, mean (95% CI)	0.68 (0.56, 0.79)	0.84 (0.78, 0.89)	0.84 (0.78, 0.89)	0.80 (0.70, 0.88)
Weighted mean of duration of exposure, yr	5.1	6.8	10.1	6.9
Annual risk of infection, mean (95% CI)	0.20 (0.15, 0.26)	0.24 (0.20, 0.28)	0.17 (0.14, 0.20)	0.21 (0.16, 0.26)

Definition of abbreviations: CI = confidence interval; TB = tuberculosis.

* Forty-seven children (15 in the village-born cohort and 32 in the admitted cohort) were not evaluated by X-rays and their status regarding infection cannot be ascertained.

† Assessment for infection was done only after admission to Papworth, and there were no data for the pre-Papworth period.

‡ Analysis 1: All admitted children. Duration of exposure = (age at assessment) – (age of child when TB was diagnosed in parent).

§ Analysis 2: All admitted children. Duration of exposure = age at assessment. (Some admitted children had only community levels of exposure for some years, before the parent was diagnosed with TB.)

‖ Analysis 3: Restricted to admitted children exposed since birth. Duration of exposure = age at assessment.

and all the TB-related deaths, occurred in the admitted cohort. In the village-born cohort only a single case of active TB developed, which was cervical lymphadenitis in a 10-year-old girl (Table 4). No cases of TB disease were diagnosed in the age group of 5 years and under, and no serious forms of extrapulmonary disease occurred in the village-born cohort. The median age at TB diagnosis in the admitted cohort was 15 years (range, 12–19 yr). The incidence rate of the admitted cohort during the Papworth period was significantly lower than in the pre-Papworth period. The reduction in incidence rate in those aged 13 years and older was also significant. There was no significant difference in the overall incidence rates of the village-born and admitted cohorts, while living in Papworth. There were a number of neonatal deaths in the village-born group, and deaths unrelated to TB in both cohorts. Excluding neonatal deaths, there was no significant difference in the all-cause mortality rate in the two cohorts.

TABLE 3. MORTALITY AND MORBIDITY IN ADMITTED COHORT, BEFORE ADMISSION TO PAPWORTH

	Admitted Cohort
No. of children at risk	231
Total no. of children with TB disease	13
Types of disease	PTB, 8 (smear positive, 5; smear negative, 3) EPTB, 5 (disseminated TB, 1; TB peritonitis, 1; articular TB, 1; mediastinal lymph node, 2)
Deaths among children with TB disease	6 (PTB smear positive, 3; PTB smear negative, 1; EPTB, 2)
Estimated PYAR*	871
Overall TB incidence rate per 100,000 PYAR, 95% CI	1,493 (795, 2,552)
Age-specific incidence of active TB (morbidity)	
Age group ⩽ 5 yr	
No. of children with disease	5
PYAR	411
TB incidence rate per 100,000 PYAR,* 95% CI	1,217 (395, 2,839)
Age group 6–12 yr	
No. of children with disease	2
PYAR	346
TB incidence rate per 100,000 PYAR,* 95% CI	578 (70, 2,088)
Age group ⩾ 13 yr	
No. of children with disease	6
PYAR	114
TB incidence rate per 100,000 PYAR,* 95% CI	5,263 (1,931, 11,456)

Definition of abbreviations: CI = confidence interval; EPTB = extrapulmonary tuberculosis; PTB = pulmonary tuberculosis; PYAR = person-years at risk; TB = tuberculosis.

* PYAR, denoting person-years at risk for a child in the pre-Papworth period, extends from the year of exposure to either the year of admission to the settlement or the year of diagnosis of TB. Of the six deaths, three occurred before admission, and three occurred after admission to Papworth. But in all six cases the onset of disease was in the period before admission to Papworth.

Of the admitted cohort, 105 were discharged from Papworth, of whom 34 (32%) were reevaluated, compared with 3 of the 21 (14%) of the village-born group who were discharged from the settlement. As seen in Table 5, of those who left Papworth five persons were diagnosed to have active TB at a median age of 23 years (range, 13–26 yr). All five cases occurred in the admitted cohort, although only three village-born children were reevaluated. Person time was contributed only by those who returned for reevaluation after discharge. If we assume that all diseased children reported back to Papworth, whereas those who did not return remained healthy, then the incidence rate in the post-Papworth period would have been lower (Table 5).

Table 6 provides a summary of disease characteristics and TB incidence calculated for the various time periods. A total of 24 cases of active TB were seen. Most TB cases (20 of 24; 83.3%) were contacts of sputum smear-positive disease cases and the majority (17 of 24; 70.8%) developed pulmonary manifestations. Cases were most common during the pre-Papworth period, followed by the Papworth and post-Papworth periods. The original report of the Papworth study had mentioned 14 cases of active TB in the period from 1918 to 1938 (13), but our reanalysis included 7 cases that occurred during the period 1938–1943, and 3 cases in children who had died of TB before admission to Papworth.

DISCUSSION

The Papworth experiment documented the impact of social interventions on TB infection and disease in child TB contacts monitored closely over an extended time period. The prevalence of TB infection and estimated ARI were high, but were similar in

TABLE 4. MORTALITY AND MORBIDITY IN ADMITTED AND VILLAGE-BORN COHORTS WHILE LIVING IN PAPWORTH

	Admitted Cohort	Village-Born Cohort	Total
No. of children at risk	n = 218	n = 84	302
Morbidity (development of active TB) while in Papworth			
Total no. of children who developed active TB	5	1	6
Type of disease	PTB smear positive, 3; PTB smear negative, 1; EPTB, 1	EPTB, 1	PTB, 4; EPTB, 2
Mortality (TB related, and other) while in Papworth			
Deaths due to TB disease	2 (PTB smear positive)	0	2
Death rate related to TB, per 1,000 person-years	0.9 (0.1, 3.4)	0	
Neonatal deaths due to non-TB causes, neonatal death rate (non-TB)	Not applicable	448/1,000 births	
Nonneonatal deaths due to non-TB causes	2*	4†	
Death rate (non-TB cases, excluding neonatal deaths) per 1,000 person-years	0.9 (0.1, 3.4)	5.3 (1.4, 13.5)	
Estimated PYAR	196	354	550
Overall TB incidence rate per 100,000 PYAR,‡ 95% CI	235 (76, 547)	132 (3, 737)	208 (76, 452)
Age-specific incidence of active TB (morbidity)			
Age group ⩽ 5 yr			
Children who developed active TB	0	0	0
Person-years at risk	196	354	550
TB incidence rate per 100,000 PYAR, 95% CI	0 (0, 1,882)§	0 (0, 1,042)§	0 (0, 671)
Age group 6–12 yr			
Children who developed active TB	1	1	2
Person-years at risk	764	303	1,067
TB incidence rate per 100,000 PYAR, 95% CI	131 (3, 729)	330 (8, 1,839)	187 (22, 677)
Age group ⩾ 13 yr			
Children who developed active TB	4	0	4
Person-years at risk	1,172	99	1,271
TB incidence rate per 100,000 PYAR, 95% CI	341 (93, 874)	0 (0, 3,726)	315 (86, 806)

Definition of abbreviations: CI = confidence interval; EPTB = extrapulmonary tuberculosis; PTB = pulmonary tuberculosis; PYAR = person-years at risk; TB = tuberculosis.

* Causes of death: pneumonia (1), road accident (1).

† Causes of death: diphtheria (1), laryngismus (1), diabetes (1), road accident (1).

‡ PYAR denotes person-years at risk: person-time in years that a child was at risk for TB during the Papworth period. This was measured from year of admission to the year of the end of study (1943) in those who remained in the settlement. In children who left the settlement, this was measured from the year of admission to the year of leaving the settlement. In children who developed the disease, it was measured from year of admission to the year of diagnosis.

§ One-sided 97.5% confidence interval.

the two cohorts of children. There was, however, a marked difference in incidence of disease in two high-risk age groups (17) associated with the period of residence at Papworth. Among young children (⩽5 yr), none of the village-born cohort developed TB in the Papworth period, compared with five children in the same age group who developed TB before admission to Papworth (incidence rate, $1{,}217/10^5$ person-years at risk). In the admitted cohort aged 13 years or older, the incidence rate of

TABLE 5. MORTALITY AND MORBIDITY IN ADMITTED AND VILLAGE-BORN COHORTS AFTER DISCHARGE FROM PAPWORTH

	Admitted Cohort*	Village-Born Cohort	Total
No. of children evaluated at least once, after discharge from Papworth	n = 34	n = 3	37
No. of children with TB disease	5	0	5
Type of disease	PTB smear positive, 4; PTB smear negative, 1	0	PTB, 5
Deaths among children with TB	4 (all PTB smear positive)	0	4
PYAR†	214	23	237
Overall TB incidence rate per 100,000 PYAR, 95% CI	2,336 (759–5,452)	0 (0–16,039)‡	2,110 (685–4,923)
Age-specific incidence of active TB (morbidity)			
Age group ⩽ 5 yr			
Children with TB	0	0	0
PYAR	0	2	2
Age group 6–12 yr			
Children with TB	0	0	0
PYAR	9	14	23
Age group ⩾ 13 yr			
Children with TB	5	0	5
PYAR	205	7	212
TB incidence rate per 100,000 PYAR, 95% CI	2,439 (792–5,692)	0 (0–52,698)‡	2,358 (766–5,504)
Best-case scenario§ for post-Papworth period			
PYAR, best-case scenario	795	239	1,034
TB incidence rate per 100,000 PYAR, 95% CI	629 (258–1,855)	0 (0–1,543)‡	484 (157–1,128)

Definition of abbreviations: CI = confidence interval; PTB = pulmonary tuberculosis; PYAR = person-years at risk; TB = tuberculosis.

* Only 25% of the contacts in the admitted cohort were less than 18 years of age at reevaluation.

† PYAR, or person-years at risk, was estimated as number of years between leaving the settlement and reevaluation/admission at Papworth.

‡ One-sided 97.5% confidence interval.

§ The best-case scenario for the post-Papworth period would assume that all the children who developed active TB after leaving the settlement returned to Papworth for evaluation, and that all the children who did not undergo reevaluation were healthy.

TABLE 6. SUMMARY OF TUBERCULOSIS INCIDENCE RATES IN ADMITTED AND VILLAGE-BORN COHORTS BEFORE ADMISSION TO, WHILE LIVING IN, AND AFTER DISCHARGE FROM PAPWORTH

	Admitted Cohort	Village-Born Cohort	Total
No. of children at risk	n = 231	n = 84	315
PYAR	3,217	779	3,996
Annual risk of infection per year of exposure, 95% CI	0.24 (0.20, 0.28)	0.20 (0.15, 0.26)	
No. of children with disease in all periods	23	1	24
Smear status of source case			
Smear-positive pulmonary TB	20	0	20
Smear-negative pulmonary TB	3	1	4
TB disease characteristics			
Site			
Pulmonary	17	0	17
Extrapulmonary TB	6	1	7
Median age at onset of TB, yr	15	10	15
Deaths due to TB	12	0	12
Pre-Papworth	No. at risk = 231		
No. with disease	13	NA	13
Overall incidence rate per 10^5 PYAR, 95% CI	1,493 (795, 2,552)	NA	1,493 (795, 2,552)
Incidence rate in ⩽5-yr age group per 10^5 PYAR, 95% CI	1,217 (395, 2,839)	NA	1,217 (395, 2,839)
Incidence rate in 6- to 12-yr age group per 10^5 PYAR, 95% CI	578 (70, 2,088)		578 (70, 2,088)
Incidence rate in ⩾13-yr age group per 10^5 PYAR, 95% CI	5,263 (1,931, 11,456)		5,263 (1,931, 11,456)
Papworth	No. at risk = 218	No. at risk = 84	
No. with disease	5	1	6
Overall incidence rate per 10^5 PYAR, 95% CI	235 (76, 547)	132 (3, 737)	208 (76, 452)
Incidence rate per 10^5 PYAR in children ⩽ 5 yr, 95% CI	0 (0, 1,882)*	0 (0, 1,042)*	0 (0, 671)
Incidence rate in 6- to 12-yr age group per 10^5 PYAR, 95% CI	131 (3, 729)	330 (8, 1,839)	187 (22, 677)
Incidence rate in ⩾13-yr age group per 10^5 PYAR, 95% CI	341 (93, 874)	0 (0, 3,726)*	315 (86, 806)
Post-Papworth	No. at risk = 34	No. at risk = 3	
No. with disease	5	0	5
Overall incidence rate per 10^5 PYAR, 95% CI	2,336 (759, 5,452)	0 (0, 16,039)*	2,110 (685, 4,923)
Incidence rate in ⩾13-yr age group per 10^5 PYAR, 95% CI	2,439 (792, 5,692)	0 (0, 52,698)*	2,252 (766, 5,504)
Incidence rate (best-case scenario) per 10^5 PYAR, 95% CI	629 (258, 1,855)	0 (0, 1,543)*	484 (157, 1,128)
Comparison of TB incidence rates in various periods			
IRR: Papworth vs. pre-Papworth period, 95% CI	0.16 (0.04, 0.47)	NA	0.14 (0.04, 0.39)
IRR: Post-Papworth period vs. Papworth period, 95% CI	10 (2.3, 43.3)	0 (0, 1,282)	10.2 (2.5, 40)
IRR: Post-Papworth period vs. Papworth period (best-case scenario), 95% CI	2.7 (0.6, 11.7)	0 (0, 123)	2.3 (0.6, 9.2)

Definition of abbreviations: CI = confidence interval; IRR = incidence rate ratio; NA = not applicable; Papworth = while living in Papworth; post-Papworth = after discharge from Papworth; pre-Papworth = before admission to Papworth; PYAR = person-years at risk; TB = tuberculosis.

*One-sided 97.5% confidence interval.

disease was 16-fold higher before admission to Papworth, compared with while living in Papworth. Overall only 1 of 84 (1.2%) village-born children developed TB, whereas nearly 10% of children born outside the settlement developed TB; the majority of these disease episodes started before admission to Papworth. There were 12 deaths related to TB, all in the admitted cohort.

The monograph on the Papworth survey offered the following explanations for the reduced incidence of TB in children at Papworth: adequate food supply, decreased stress, and reduced intensity of TB exposure through implementation of hygienic precautions and provision of improved housing (11). Interestingly, the results indicate that conditions at Papworth did not reduce the risk of TB infection, although some infection control measures may have reduced the intensity of exposure. Rather, the Papworth experiment was associated with a substantially reduced risk of disease and related deaths. Systematic reviews have underscored the role of undernutrition as a risk factor for progression of TB infection to TB disease (18, 19). In 22 high TB burden countries, 5.2–62.6% (weighted average, 26.9%) of TB cases were attributable to undernutrition (2), and in a cohort of childhood contacts of TB it was found to be strongly associated (hazard ratio, 37.5) with TB disease risk (20).

Ensuring adequate nutrition was given high priority at Papworth. One of the children, who entered the village settlement in 1929, observed in 2011: "There was always enough to eat" (P. Pattle, personal communication). Because weights were not reported we can only speculate that adequate nutrition likely played a significant role in the prevention of TB disease at Papworth. The significant independent effect of nutrition on TB incidence, under similar conditions of housing and stress, was illustrated in ecologic studies from the prechemotherapy era (21, 22). In prisoner of war camps in Germany, TB incidence in British soldiers receiving a 1,000-calorie/day Red Cross supplement in addition to the camp diet of 1,600 calories/day was 1.2%, whereas the incidence of TB in Russian prisoners who subsisted on the camp diet alone was 19% (risk ratio, 0.06; 95% CI, 0.03 to 0.14) (21). The even greater protection from TB seen in the village-born cohort could perhaps reflect early life influences on immune and thymic function, consequent to birth under conditions of better nutrition (23, 24).

A comparison of the results at Papworth with other reports from the same period shows comparable rates of TB infection. Annual risk of infection in children aged 0–10 years, estimated from a 1930 study tuberculin skin test survey, was 0.16 (95% CI, 0.12 to 0.22) in TB contacts and 0.04 (95% CI, 0.03 to 0.05) in children not living with an adult patient with TB (25). Interestingly the incidence of TB disease in the admitted cohort before admission to Papworth period was comparable to rates reported elsewhere in that era, but rates in children while living in Papworth were significantly lower. The incidence rate of TB in family contacts reported from four studies in the United States in the same era showed incidence rates in the range of 1,030–1,330 per 100,000 person-years (26). A notable feature in the Papworth period was the complete absence of severe disease manifestations in young children, although their numbers were

limited. Young children living in contact with patients with TB in the prechemotherapy and pre–bacillus Calmette-Guérin (BCG) era were particularly susceptible to developing tubercular meningitis, which was a major cause of TB-related mortality in this age group (25, 27).

This study has important limitations. It involved mostly child contacts of men with moderately advanced pulmonary TB; contacts of women with TB or bedridden patients with advanced TB were underrepresented. The definition of TB infection was based on the absence of symptoms and the presence of radiologic signs suggestive of infection rather than results of tuberculin skin tests. This could have resulted in an underestimation of TB infection prevalence, or misclassification. However, the main finding relates to reduced risk of TB disease progression, for which case detection methods were similar to what is in use today. There would have been no blinding to the child's birth status—village born or otherwise—but there is no indication that this may have biased the results. The intensity of exposure to TB may have differed in the two cohorts, because village-born children were exposed to source cases after sanatorium "treatment," and occurred under conditions that may have reduced the intensity of exposure. However, the estimated risk of infection was similar in the two groups, suggesting that exposure was similar. Many children were lost to follow-up after they left the settlement, and so estimates of disease risk in the post-Papworth period are much less certain.

Strengths of this reanalysis include the documented experience of more than 300 childhood contacts with close to 4,000 person-years at risk. The two cohorts had comparable characteristics, TB exposure (at least during their stay in Papworth), and were assessed for study outcomes in a similar manner. The diagnosis of TB disease was based on chest radiography and clinical signs similar to those used today, although cultures were not performed. TB incidence estimates for the Papworth period were reliable because of the completeness of data and close medical supervision. There appeared to be no confounding by sputum status of the source case. Differences in a child's age at exposure, or assessment, were handled by restricted and age-stratified analyses. The results of the analyses suggest that unmeasured community exposure to TB in the admitted cohort is unlikely to have influenced the outcomes of TB infection and disease in this study, especially in the case of young children.

This study is of particular relevance to the present problem of child contacts living with patients with multidrug-resistant (MDR) TB in high-burden settings. Their current predicament is reminiscent of that of patients with TB and their child contacts in the prechemotherapy era. Patients often lack access to effective chemotherapy and remain infectious over long periods. Children are at high risk (28) of developing a potentially fatal disease without the benefit of protection by chemoprophylaxis. The World Health Organization (Geneva, Switzerland) does not currently recommend chemoprophylaxis with second-line drugs, suggesting careful clinical follow-up of child contact with initiation of MDR TB treatment should they develop signs consistent with TB disease (29). Ensuring adequate nutrition seems a feasible and necessary intervention in such child contacts in settings where childhood undernutrition is highly prevalent (30). For example, the prevalence of severe undernutrition in child contacts was 31.0 and 26.7% in reports from South Africa and India, respectively (31, 32).

The Papworth experiment suggests that even in the absence of BCG vaccination or chemoprophylaxis, social interventions were associated with reduced incidence of TB disease, despite high rates of infection in highly vulnerable child contacts. Trials evaluating the efficacy and feasibility of such interventions (including adequate nutrition) in child contacts of patients with drug-resistant TB should be conducted as a priority.

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