

THE PROGNOSIS OF A POSITIVE TUBERCULIN REACTION IN CHILDHOOD AND ADOLESCENCE

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Comstock, G. W. (Training Center for Public Health Research, Box 2067, Hagerstown, Md. 21740), V. T. Livesay and S. F. Woolpert. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 99: 131-138, 1974.—In the course of a controlled trial of bacillus of Calmette and Guerin vaccination among Puerto Rican children in 1949-1951, 82,269 reactors to 1 or 10 tuberculin units of purified protein derivative were identified. During the 18 to 20 years after initial testing, 1400 cases of tuberculosis were identified among these tuberculin reactors. The major risk factor was age. Children under four years of age had the highest tuberculosis rates and the most serious disease. A secondary peak of incidence was observed at about 20 years of age. At all ages, children with the strongest sensitivity to tuberculin had the highest rates of subsequent tuberculosis. The risk for females and for urban residents was slightly greater than for males and rural residents. Essentially no difference in tuberculosis risk was found between white and black reactors. Because the risk of tuberculosis among infected persons appears to persist for a lifetime, the need for preventive treatment is highly dependent on age, and to a considerable but lesser extent on degree of tuberculin sensitivity.

BCG vaccination; tuberculin reactors, epidemiology, prognosis; tuberculosis

A major difficulty in understanding the epidemiology of tuberculosis stems from the frequent failure to take account of the fact that the development of tuberculous disease is a two-stage process. To develop tuberculosis, one must first become infect-

ed. Then, following infection, there must be sufficient multiplication of the infecting organisms to overcome host resistance and to produce disease. Tuberculosis is not unique in this respect, for the development of any infectious disease can be broken down into similar stages. What does distinguish tuberculosis from the acute communicable diseases is the low risk of becoming infected on exposure to an infectious case and its very long and unpredictable incubation period.

Although there are occasional instances of tuberculosis epidemics resulting from brief and intense exposures, most infections occur only after prolonged exposure. Only 51 per cent of children ages 5-19, living in the households of sputum-positive cases in rural Tennessee in the 1930's were infected by the time the case was diag-

Abbreviations: BCG, bacillus of Calmette and Guerin; PPD, purified protein derivative (of tuberculin); TU, tuberculin unit.

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Carroll E. Palmer would have been the senior author of this paper, but for his untimely death. He was primarily responsible for the concept, design and execution of this trial and its emphasis on epidemiologic principles.

nosed (1). In the early 1960's, the percentage of infected persons of all ages among household contacts of active cases from 39 health departments was 48 per cent (2). Even if one makes the extreme assumption that the sole source of infection was the index case, the rate of infection per hour or day of exposure must have been exceedingly low. This is in sharp contrast to many acute infectious diseases where it is usual for nearly all susceptible contacts to become infected after a much shorter exposure.

Following infection, the incubation period of tuberculosis ranges from a few weeks to a lifetime. Both the length and variability of the incubation period are tremendously greater than for nearly all other infectious diseases.

Because of the long average periods of time between exposure and infection and between infection and disease, there is considerable opportunity for a variety of "risk factors" to play a part in determining both infection and disease. Most of the known determinants of tuberculous infection are extrinsic: the likelihood of coming into contact with an infectious case (3), the infectiousness of the case (4), and the treatment status of the case (5). In contrast, the major known determinants of the development of disease following infection are intrinsic: age (1), sex (6, 7), body build (8, 9), the presence of diabetes (10), and the use of immunosuppressant therapy (11).

The development of disease among infected persons can now be effectively prevented by isoniazid, albeit at the cost of occasional drug reactions. Consequently, it is becoming increasingly important to map out the risk factors for both conditions, so that the safest possible course for infected persons can be plotted between the Scylla of tuberculosis and the Charybdis of drug reactions. This paper will attempt to add a few more details to the pilot charts of Scylla.

Much of what we know about the fate of infected persons has been deduced from the study of tuberculosis contacts whose infection status was usually unknown. In Williamson County, Tennessee, for the period 1931 to 1955, children exposed to tuberculosis before the age of three years had a high risk of developing disease within a short period of time (1, 12). After this age, the risk was low until about age 11, following which it rose to a peak at about age 18. Among children exposed after the age of three years, the incidence tended to follow a similar curve, the risk being low under 11, and again increasing to a peak at about age 18. The same general pattern was observed among a group of tuberculin converters in Norway (13).

The first solid indication of the prognosis for children found to be infected on routine examinations came from the Chadwick Clinics in Massachusetts (14). More than 400,000 school children, tuberculin-tested by the von Pirquet method, were followed for periods up to 11 years. The incidence of tuberculosis among tuberculin reactors was low between the ages of six and 10, but rose rapidly from 10 to 19, the oldest age for which data were available. The risk for girls was approximately twice that for boys. Among 14- to 15-year-old children found to be reactors to an intermediate dose of tuberculin on entry to the controlled trial of bacillus of Calmette and Guerin (BCG) vaccination conducted by the British Medical Research Council, the incidence of disease was high during the first 2½-year period and fell thereafter to a relatively low level from ages 22 to 30. Tuberculosis rates among females were approximately 20 per cent higher than among males throughout this period (15).

In a controlled trial of BCG vaccination conducted among Puerto Rican children by the US Public Health Service in cooperation with the Puerto Rico Department of Health, it was not possible to study the first stage, the development of tuberculous

infection after the start of the trial, because serial tuberculin testing was not done. However, information is available about the second stage in the pathogenesis of the disease. Cases of tuberculosis developing among the study population were carefully recorded, not only among nonreactors to tuberculin who were eligible for vaccination, but also among reactors, a group presumably already infected at the onset of the trial (16).

MATERIAL AND METHODS

Descriptions of the trial have been published previously (16, 17). Briefly, during a two-year period in 1949 to 1951, an attempt was made to enroll all Puerto Rican children between the ages of one and 19. Owing largely to unfavorable publicity related to political opposition, this ambitious goal was not achieved. Only a quarter of the children of school age and 5 per cent of younger children participated. Nevertheless, the study population comprised 191,827 children from all parts of the island and from all walks of life.

The trial was conducted as similarly as possible to the mass BCG campaigns of that time. Pre-vaccinal screening consisted only of exclusion of obviously ill children in addition to routine tuberculin testing. The tuberculin was purified protein derivative (PPD) (RT 19-20-21) obtained from the Statens Serum Institut, Copenhagen, Denmark. Because it was feared that severe reactions to tuberculin might be common, the first dose was originally only 1 tuberculin unit (1 TU = 0.00002 mg). Nonreactors to this dose were given a second test containing 10 TU. Later in this program, it was found that it was not necessary to give the 1 TU dose, and the initial test then contained 10 TU of PPD. Persons with an area of induration 6 mm or more in diameter after either the 1 or 10 TU dose were classified as reactors. Among the nonreactors to 10 TU, there were a considerable number who asked not to be vaccinated;

they were called refusals. The remaining non-reactors were tested with 100 TU of PPD. Allocation to control or vaccinee group depended on year of birth. For each three consecutive birth years, the children born in the central year were controls, and the children born in the other two years were vaccinated with BCG.

No publicity was given to the follow-up aspects of the trial. Tuberculosis cases were recognized by matching death certificates, tuberculosis case reports, and reports of admissions to tuberculosis hospitals and clinics to the records of the study population, according to clearcut rules and procedures. An estimate of emigration from Puerto Rico was obtained from individual follow-up of participants in a later trial of isoniazid prophylaxis. Because it was found that approximately one-half of the emigrants had gone to New York City, a search of that city's tuberculosis case registers was conducted in 1966. Records of persons with Spanish names and in the appropriate age range were matched against the study file in Puerto Rico.

Follow-up was discontinued as of June 30, 1969, nearly 19 years after the midpoint of the intake into the trial. Some individuals could have been observed for slightly more than 20 years, others for as little as 18 years.

RESULTS

A total of 82,269 children reacted to either the 1 or 10 TU dose of PPD with induration that measured 6 mm or more in diameter. The demographic characteristics of these tuberculin reactors are shown in table 1. There were somewhat more urban than rural residents, and slightly more males than females. Over three-fourths were classified as white. Less than 4000 were between the ages of one and seven years, a result both of lower prevalence of tuberculous infection and poorer coverage in the pre-school age group.

During the follow-up period, 1400 cases

of active tuberculosis were reported among children who were tuberculin reactors at the start, an overall case rate of 90.2 per 100,000 initial population per year. This is also shown in table 1. The rate was 14 per cent higher among urban residents than among rural residents, and 18 per cent higher among females than among males. The rates were almost the same for whites and blacks. The most marked differences

were observed between the age groups. Children who were one through six years on entry had a case rate twice that of older children. Children initially aged seven through 12 years had the lowest subsequent case rate. Adjusting the rates for the effects of the other three variables yielded results that were virtually identical with the crude rates.

A better indication of the risk of tuberculous disease among reactors as they passed through early life is given in figure 1. To produce this figure, cases were entered in a table according to the age and calendar year in which they were diagnosed, together with the population, reduced according to known deaths and estimates of emigration. Although the method of presentation in figure 1 confounds the effects of age and the other changes that occurred with the passage of time, the latter effect was small and inconstant compared with the effect associated with age. The case rates were highest under the age of four years, fell rapidly to age eight, rose again after age 12 to a peak at age 19, and fell again to a relatively stable low rate at age 24.

A risk factor second only to age in this study population was the degree of tuber-

TABLE 1
Average annual tuberculosis case rates per 100,000 tuberculin reactors on entry to trial, by demographic characteristics

Characteristics	Persons	Cases	
		No.	Rate*
Residence			
Urban	47,021	844	95.1
Rural	35,248	556	83.7
Ethnic group			
White	67,184	1,152	90.9
Black	15,085	248	87.1
Sex			
Male	43,100	674	82.9
Female	39,169	726	98.2
Age on entry (years)			
1-6	3,906	119	164.8
7-12	35,869	520	77.0
13-18	42,494	761	94.6
Total	82,269	1,400	90.2

* The mean observation period for reactors for 18.87 years varies slightly among some subgroups because of the scheduling of the trial.

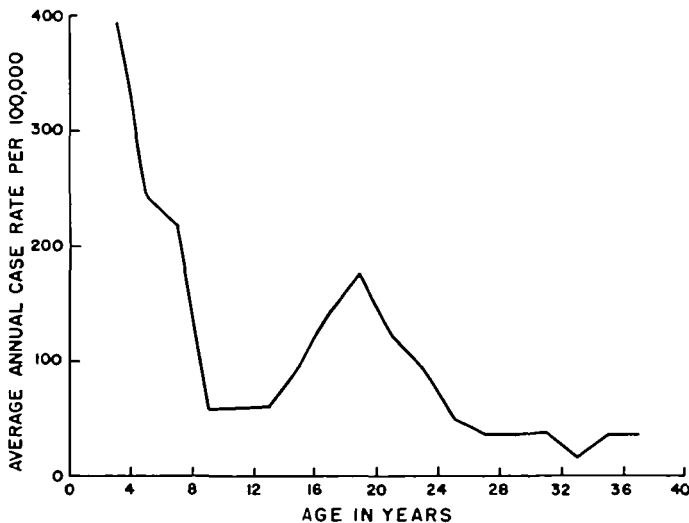


FIGURE 1. Incidence of tuberculosis among initial reactors to tuberculin, by age when tuberculosis was first diagnosed.

culin sensitivity. Its association with subsequent case rates is shown in table 2. In this table, screened reactors are those who were tested early in the program when it was believed desirable to give the 10 TU dose of tuberculin only to children who had been classified as negative reactors to the 1 TU dose. Direct reactors are children tested later in the program when the 10 TU dose was used for the initial testing. For each age group, the subsequent risk was greatest among reactors who were initially most sensitive to tuberculin. The risk was approximately five times greater for those whose reactions to 1 TU of PPD measured more than 15 mm in diameter than for those whose reactions to 10 TU were only 6 through 10 mm in diameter. A young child with more than 15 mm of induration to the 10 TU dose had almost a 5 per cent chance of developing active tuberculosis some time during the next two decades.

The type of tuberculosis that developed subsequently also differed with age. Table 3 shows the tuberculosis cases according to

the most serious diagnosis that was reported. All deaths ascribed to pulmonary tuberculosis were classified as far advanced disease. The proportion of cases reported as pulmonary varied from 80 per cent in the youngest age group to nearly 95 per cent in the oldest group. The most marked difference between the age groups was noted in the category of primary tuberculosis. Nearly a third of the cases in the youngest group were given this diagnosis, contrasted with less than 1 per cent among the oldest age group. Marked age differences were also noted with respect to miliary and meningeal tuberculosis. Ten per cent of the cases in the group initially aged one through six were miliary or meningeal in character, whereas this category comprised only 0.4 per cent of the cases in the oldest age group.

Case fatality rates also varied considerably with age. There were 15 deaths among the group initially aged one through six, 32 among those aged seven through 12, and 53 among those aged 13 through 19 on entry.

TABLE 2
Average annual tuberculosis case rates per 100,000 tuberculin reactors on entry to trial, by age and initial tuberculin status

Tuberculin status (induration size in mm)	No. of cases				Average annual rate			
	Age (years)				Age (years)			
	Total	1-6	7-12	13-18	Total	1-6	7-12	13-18
Screened								
1 TU								
16+	211	1	77	133	162.0		133.0	186.1
11-15	248	1	97	150	107.8		93.6	119.8
6-10	417	4	154	259	89.8		76.9	99.1
10 TU								
16+	43	0	21	22	81.8		85.3	79.5
11-15	69	0	30	39	60.7		63.1	59.5
6-10	93	1	36	56	33.2		28.6	37.1
Direct								
10 TU								
16+	222	79	70	73	159.9	238.1	123.4	149.2
11-15	59	22	21	16	98.2	186.2	88.8	65.1
6-10	38	11	14	13	45.7	59.0	40.0	44.0
Total	1400	119	520	761	90.2	164.8	77.0	94.6

TABLE 3
*Classification of most serious form of tuberculosis occurring among persons who were
 tuberculin reactors on entry to trial, by initial age group*

Classification	Age (years)					
	1-6		7-12		13-18	
	No.	%	No.	%	No.	%
Pulmonary	95	79.8	474	91.2	717	94.2
Far advanced	24	20.2	119	22.9	201	26.4
Moderate advanced	17	14.3	170	32.7	279	36.7
Minimal	18	15.1	147	28.3	224	29.4
Primary	35	29.4	32	6.2	6	0.8
Not stated	1	0.8	6	1.2	7	0.9
Nonpulmonary	22	18.5	42	8.1	38	5.0
Meningeal, miliary	12	10.1	5	1.0	3	0.4
Pleurisy with effusion	0		5	1.0	8	1.1
Adenitis	6	5.0	22	4.2	20	2.6
Bone and joint	4	3.4	5	1.0	3	0.4
Genitourinary	0		4	0.8	4	0.5
Gastrointestinal	0		1	0.2	0	
Not specified	2	1.7	4	0.8	6	0.8
Total	119	100.0	520	100.0	761	100.0

The corresponding case fatality ratios were 12.6 per cent, 6.2 per cent, and 7.0 per cent.

DISCUSSION

Not all tuberculin reactors to an intermediate dose of PPD have been infected with tubercle bacilli (18). This fact undoubtedly accounts in large measure for the increasing risk of subsequent tuberculous disease with increasing size of reaction observed in this and other populations. The simplest basis for this phenomenon, and hence by Occam's razor the most attractive one, is that the proportion of tuberculin reactions caused by tubercle bacilli increases as the reactions get larger.

In the material presented in this paper, it may be that the definition of a tuberculin reactor was not sufficiently rigorous. If the current definition of a positive tuberculin reaction, namely 10 mm or more of induration to 5 TU of PPD, had been accepted at the time of the study, the number of reactors would have been decreased consid-

erably and the rate of tuberculosis among them increased even more. However, there is no indication that the pattern of tuberculosis by demographic characteristics would have been altered appreciably.

Most physicians know that tuberculous infections occurring in early childhood and in adolescence carry a high risk of tuberculosis. It is not so commonly realized that infected children who pass unscathed through the risks of childhood face another period of high risk in adolescence. Even less commonly is the risk of tuberculosis among tuberculin reactors assessed as potentially lifelong. Although the risk for older people is not as well known as it is for younger persons, it is clear that it is far from negligible (19).

In estimating the need for preventive treatment of tuberculin reactors with isoniazid, life expectancy becomes an important parameter. The lifetime risk for a young child who is a strongly positive reactor may run as high as 10 per cent.

Even a young adult found to be a tuberculin reactor on a routine examination may have a lifetime risk of developing tuberculosis on the order of 1 to 3 per cent. On the other hand, the lifetime risk for an elderly person is bound to be less, regardless of the average annual risk, merely because life expectancy is shorter.

Now that it is apparent that preventive treatment with isoniazid carries a small but definite risk of hepatitis (20), it is increasingly important to delineate the factors associated with this side-effect. At present, it appears that age is also related in an important way to isoniazid-associated hepatitis (21). The risk of this side-effect below the age of 30 is exceedingly low; above 40, it may approach 1 per cent.

If these rough estimates are confirmed, it would appear wise to base the indications for preventive treatment of routinely detected tuberculin reactors largely on age, being hesitant to treat such persons who are over 40. If, however, a tuberculin reactor has additional risk factors, such as evidence of recent tuberculous infection, recent household exposure to an infectious case, a chest lesion suggestive of tuberculosis, diabetes, or treatment with immunosuppressive drugs, the risk of tuberculosis is likely to exceed the risk of hepatitis at any age (22).

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