SPECIAL ARTICLE

Priorities for the Treatment of Latent Tuberculosis Infection in the United States

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ABSTRACT

BACKGROUND

The prevention of active tuberculosis through the treatment of latent tuberculosis infection is a major element of the national strategy for eliminating tuberculosis in the United States. Targeted treatment for persons who are at the highest risk for reactivation tuberculosis will be needed to achieve this goal. A more precise assessment of the lifetime risk of reactivation tuberculosis, usually estimated at 5 to 10 percent, could help to identify patients who are at the highest risk and motivate them to complete treatment. Currently, the rate of completion of treatment is low.

METHODS

Published reports were reviewed to obtain estimates of the risk of tuberculosis among persons with a positive tuberculin skin test. Using these data, I constructed a model to estimate the lifetime risk of tuberculosis among persons with specific medical conditions.

RESULTS

The lifetime risk of reactivation tuberculosis is 20 percent or more among most persons with induration of 10 mm or more on a tuberculin skin test and either human immunodeficiency virus infection or evidence of old, healed tuberculosis. The lifetime risk is 10 to 20 percent among persons with recent conversion of a tuberculin skin test and among most persons younger than 35 years of age who are receiving infliximab therapy and have induration of 15 mm or more on a tuberculin skin test. The risk is also 10 to 20 percent among children five years of age or younger who have induration of 10 mm or more on a tuberculin skin test.

CONCLUSIONS

Persons with these characteristics should be targeted for intensive efforts to ensure full treatment of latent tuberculosis. Improved rates of completion of treatment among such persons could help to eliminate tuberculosis in the United States.

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Once the transmission of *Mycobacterium tuberculosis* from persons with active tuberculosis has been controlled in a population, the focus of tuberculosis control shifts to the prevention of active tuberculosis among persons with latent tuberculosis infection — those who have a positive tuberculin skin test but no evidence of active disease. Tuberculosis in this subpopulation results from the reactivation of previously controlled infection and is termed reactivation tuberculosis. The prevention of reactivation tuberculosis through the treatment of latent tuberculosis infection is a major goal of the national strategy for eliminating tuberculosis in the United States.[1-3]

Unfortunately, the treatment of latent tuberculosis requires a prolonged course of antibiotic therapy.[4] Both clinicians and patients may perceive the risk of reactivation tuberculosis as low, so that clinicians do not prescribe and patients do not adhere to treatment.[5,6] The rate of completion of a six-month course of self-administered therapy ranges from 3 percent to 60 percent, with rates of 20 to 30 percent in most series.[4,7-11] Completion rates for the currently recommended nine-month course of therapy are likely to be even lower.

The lifetime risk of reactivation tuberculosis for a person with a positive tuberculin skin test is usually estimated to be 5 to 10 percent; this estimate is based on a large body of data that were collected before treatment for latent tuberculosis was routinely recommended.[4] However, this range substantially underestimates the risk for some patients and overestimates the risk for others, because risks vary greatly according to age, the size of the skin-test reaction, and the presence or absence of specific medical conditions. A more precise assessment of the risk of reactivation tuberculosis could help both to identify patients who are at high risk and to motivate such patients to complete a course of treatment. Therefore, I reviewed existing data to obtain estimates of the risk of reactivation tuberculosis. These estimates suggest strategies for improving the treatment of latent infection as a means of eliminating tuberculosis in the United States.

METHODS

DEFINITIONS

A recent conversion of a tuberculin skin test was defined as a positive skin test in a person who was known to have had a negative test within the previous two years or as a positive skin test in a person who was a household contact of a person with active pulmonary tuberculosis. A positive skin test in a person who did not meet the definition of recent conversion was called a nonconversion positive test.

RATES OF REACTIVATION TUBERCULOSIS

Prospective cohort studies of the risk of reactivation tuberculosis in the United States were collected from the literature for the period from 1949 to 2003. Reports were identified through a search of the Medline database and through examination of references to the literature in review articles and book chapters. Studies that provided information on the size of the skin-test response and the age of the subjects and that reported at least five years of follow-up were included. Outbreaks due to a single source case were excluded. Because the cutoffs for skin-test reponses varied among studies, categories of 6 to 10 mm, 11 to 15 mm, and 16 mm or larger were treated as equivalent to categories of 5 to 9 mm, 10 to 14 mm, and 15 mm or larger. Similarly, age groups of 5 to 14 years, 15 to 24 years, and so on were treated as equivalent to age groups of 6 to 15 years, 16 to 25 years, and so on. In studies in which complete information on age or the size of skin-test responses was not provided, cases of reactivation disease were distributed in proportion to the number of persons in the age group and skin-test category. The exact binomial method or Wilson's method, where appropriate, was used to calculate the confidence intervals.[12]

CALCULATION OF LIFETIME RISK OF REACTIVATION TUBERCULOSIS

The lifetime risk of reactivation tuberculosis was assumed to decrease for the first nine years after skin-test conversion and then to continue to decrease at a rate of 10 percent per decade — a rate that is consistent with the reported decreases in skin-test reactivity.[13-15] The lifetime risk of reactivation tuberculosis was calculated with the use of age-group–specific predicted life expectancies for the United States.[16]

RELATIVE RISK OF REACTIVATION TUBERCULOSIS

Prospective cohort studies and case–control studies of the relative risk of tuberculosis among persons with a positive skin test with or without specific medical conditions were collected from the literature for the period from 1949 to 2003. Studies that did not include a control group or that included only controls from the general population were

excluded. The relative risks of reactivation tuberculosis among persons with evidence of old, healed tuberculosis, underweight persons, and persons with untreated human immunodeficiency virus (HIV) infection were calculated with the use of Episheet software, version 6 (www.us.oup.com/us/companion.websites/0195135547/downloads/).

When no studies were available that included a group of skin-test–positive controls who did not have the condition whose contribution to risk was being assessed, the relative risk of reactivation tuberculosis was estimated on the basis of the overall relative risk of tuberculosis as follows. The overall risk of tuberculosis can be expressed as the product of three risks: the risk of exposure times the risk of infection times the risk of disease.[17] The overall relative risk for a group that has a specific medical condition of interest, as compared with a group that does not have that condition, is calculated as the overall risk with the condition divided by the overall risk without the condition, or the relative risk of exposure times the relative risk of infection times the relative risk of disease.

When the analysis is restricted to reports in which the level of exposure can be assumed to be equal for persons with the specific medical condition of interest and persons without that condition, the relative risk of exposure is 1.0, and the overall relative risk equals the relative risk of infection times the relative risk of disease. Since most immunosuppressive conditions that increase the risk of disease are also likely to increase the risk of infection to a similar degree, it is assumed that the relative risk of infection equals the relative risk of disease, and the relative risk of disease equals the square root of the overall relative risk. In addition, immunosuppression is presumed to affect primary disease and reactivation disease equally, so that the relative risk of reactivation can be approximated as the square root of the overall relative risk.

The incidence of tuberculosis was below 10 percent in all groups. Therefore, this analysis treated odds ratios as equivalent to relative risks.[18] When relative risks were provided for specific subgroups, a weighted average risk was calculated, with weighting based on the relative number of persons in each subgroup.

LIFETIME RISK AMONG PERSONS WITH SPECIFIC MEDICAL CONDITIONS

The lifetime risk of reactivation tuberculosis among persons in a given age group and category of skin-test reaction was multiplied by the relative risk of reactivation tuberculosis among persons with a given medical condition in order to estimate the lifetime risk of reactivation tuberculosis among persons with that condition.

RESULTS

RISK AMONG PERSONS WITH A NONCONVERSION POSITIVE TUBERCULIN SKIN TEST

The rates of occurrence of tuberculosis among children with a nonconversion positive skin test who have not received treatment (Table 1) were taken from Comstock et al.[19] Five reports describe the risk of tuberculosis among adults with a nonconversion positive skin test.[19,20,22-24] Three of these studies showed a similar annual rate of reactivation tuberculosis of 0.11 to 0.12 percent.[19,20,23] This rate is the same as that found after nine years of follow-up among persons who had skin-test conversion.[13] Two other reports give slightly different results — one higher, at 0.16 percent,[22] and one lower, at 0.07 percent.[24] Therefore, the report with an average annual rate of 0.11 percent that provided the most detailed information was used to estimate the annual rates among adults in each age group and skin-test category.[13,20]

RISK AFTER SKIN-TEST CONVERSION

Two reports from the United States provide sufficient data about persons with recent *M. tuberculosis* infection.[13,21] Tuberculosis rates during the first nine years after infection, stratified according to age and the size of the skin-test reaction, are shown in Table 1.

LIFETIME RISK

The lifetime risks of reactivation tuberculosis among persons with a nonconversion positive skin test, calculated on the basis of the tuberculosis rates from Table 1, are shown in Figure 1 and Table 2. The lifetime risk in this group varies from 13 percent among children 0 to 5 years of age who have an induration of 15 mm or more on the tuberculin skin test to 2 percent in the oldest cohort. The lifetime risks of tuberculosis among persons with recent conversion of the skin test, also calculated on the basis of the tuberculosis rates from Table 1, are shown in Table 2. The lifetime risk varies from 17 percent among children 0 to 5 years of age who have induration of 15 mm or more on the skin test to 2 percent in the oldest cohort.

Table 1. Annual Risk of Reactivation Tuberculosis.*

Size of Induration on Tuberculin Skin Test	Age				
	0–5 Yr	6–15 Yr	16–35 Yr	36–55 Yr	≥56 Yr
	percent (95 percent confidence interval)				
Persons with nonconversion positive result					
5–9 mm	0.06 (0.03–0.11)	0.04 (0.03–0.06)	0.12 (0.05–0.32)	0.07 (0.03–0.19)	0.07 (0.03–0.16)
10–14 mm	0.19 (0.12–0.28)	0.08 (0.06–0.11)	0.15 (0.08 –0.29)	0.10 (0.05–0.19)	0.10 (0.06–0.17)
≥15 mm	0.24 (0.19–0.30)	0.14 (0.12–0.17)	0.19 (0.10–0.34)	0.12 (0.07–0.21)	0.12 (0.08–0.20)
Persons with recent conversion or contacts of patients with active tuberculosis					
5–9 mm	0.29 (0.08–0.74)	0.06 (0.02–0.18)	0.30 (0.18–0.50)	0.23 (0.10–0.44)	0.12 (0.02–0.44)
10–14 mm	0.37 (0.16–0.71)	0.12 (0.05–0.25)	0.37 (0.26–0.53)	0.28 (0.17–0.45)	0.15 (0.04–0.39)
≥15 mm	0.54 (0.27–0.95)	0.12 (0.07–0.23)	0.56 (0.41–0.76)	0.42 (0.28–0.62)	0.17 (0.05–0.42)

* Data are from Ferebee,[13] Comstock et al.,[19] Ferebee et al.,[20] and Ferebee and Mount.[21] Data for persons with recent conversion or contacts of patients with active tuberculosis represent the average annual rates during the first nine years after exposure.

RELATIVE RISKS AMONG PERSONS WITH SPECIFIC MEDICAL CONDITIONS

Two prospective cohort studies demonstrate that there is a substantially increased relative risk of reactivation tuberculosis among persons with advanced, untreated HIV infection, as compared with controls with a positive tuberculin skin test who are not infected with HIV.[25,26] However, only one of these studies allows for the estimation of the relative risk attributable to HIV infection (Table 3). Only one study addressing the rate of tuberculosis among persons with a positive skin test and a chest radiograph showing the presence of inactive tuberculosis used a group of controls with a positive skin test.[13,20] Two prospective cohort studies have assessed the contribution of being underweight to the risk of reactivation tuberculosis.[22,23] Because these two studies were performed in similar populations with the use of the same protocol, the results were combined to yield the relative risk given in Table 3.

Other persons that have been reported to have an increased risk of tuberculosis are those with silicosis, chronic renal failure, insulin-dependent diabetes, or gastrectomy and those receiving immunosuppressive therapy.[4,34] Persons in these groups are thought to have increased risk because of a decrease in the immune system's ability to prevent infection, progression to primary disease, and reactivation. However, the amount of excess risk of reactivation tuberculosis among persons in these groups that is attributable to the given condition cannot be calculated directly, since none of the studies used a group of controls with a positive tuberculin skin test who did not have the condition under study. Risks of reactivation tuberculosis among persons with these conditions were therefore estimated on the basis of

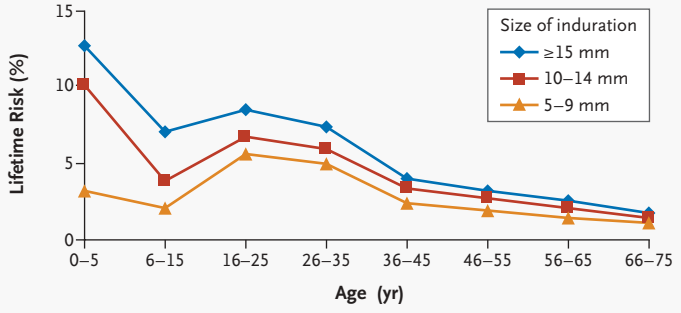

Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Nonconversion Positive Tuberculin Skin Test.

Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.

Table 2. Lifetime Risk of Reactivation Tuberculosis.*

Size of Induration on Skin Test and Age	Nonconversion Positive Skin Test	Recent Conversion of Skin Test	Immunosuppressive Therapy	Old, Healed Tuberculosis	Advanced HIV Infection
	percent (95 percent confidence interval)				
Induration of ≥15 mm					
0–5 Yr	13 (10–16)	17 (12–24)	25 (7–87)	66 (34–100)	100 (88–100)
6–15 Yr	7 (6–8)	8 (6–10)	14 (4–46)	37 (21–67)	70 (52–92)
16–25 Yr	8 (5–15)	13 (8–21)	17 (3–84)	44 (15–100)	83 (39–100)
26–35 Yr	7 (4–13)	12 (8–19)	15 (3–74)	39 (14–100)	73 (35–100)
36–45 Yr	4 (2–7)	7 (5–12)	8 (2–39)	21 (8–57)	40 (20–79)
46–55 Yr	3 (2–6)	6 (4–10)	6 (1–32)	17 (6–46)	32 (16–44)
56–65 Yr	3 (2–4)	3 (1–7)	5 (1–23)	13 (5–33)	25 (14–46)
≥66 Yr	2 (1–3)	2 (1–5)	4 (1–17)	9 (4–24)	18 (10–33)
Induration of 10–14 mm					
0–5 Yr	10 (6–15)	13 (8–21)	20 (4–82)	53 (22–100)	100 (56–100)
6–15 Yr	4 (3–5)	5 (3–7)	8 (2–30)	20 (10–44)	38 (24–61)
16–25 Yr	7 (3–13)	10 (6–17)	13 (2–73)	35 (12–100)	66 (30–100)
26–35 Yr	6 (3–12)	9 (5–15)	12 (2–64)	31 (10–93)	58 (26–100)
36–45 Yr	3 (2–6)	5 (3–9)	7 (1–34)	17 (6–50)	33 (15–68)
46–55 Yr	3 (1–5)	5 (3–8)	5 (1–8)	14 (5–40)	26 (12–55)
56–65 Yr	2 (1–4)	3 (1–6)	4 (1–20)	11 (4–29)	20 (11–39)
≥66 Yr	2 (1–3)	2 (1–5)	3 (1–14)	8 (3–20)	15 (8–28)
Induration of 5–9 mm					
0–5 Yr	3 (2–6)	6 (2–12)	6 (1–31)	16 (6–45)	31 (15–63)
6–15 Yr	2 (1–3)	3 (2–5)	4 (1–17)	11 (5–25)	21 (13–34)
16–25 Yr	6 (2–14)	8 (4–17)	11 (2–79)	29 (7–100)	55 (19–100)
26–35 Yr	5 (2–13)	7 (3–15)	10 (1–69)	25 (6–100)	48 (17–100)
36–45 Yr	3 (1–6)	4 (2–9)	5 (1–34)	12 (3–50)	24 (8–68)
46–55 Yr	2 (1–5)	4 (2–8)	4 (1–28)	10 (3–40)	19 (7–55)
56–65 Yr	2 (1–3)	2 (1–6)	3 (0–18)	8 (2–26)	15 (6–36)
≥66 Yr	1 (0–2)	2 (0–5)	2 (0–13)	6 (2–19)	11 (4–26)

* Data on the risk associated with recent conversion are from studies of household contacts of patients with active tuberculosis and are applicable to situations in which recent infection is likely, such as among persons with recent skin-test conversion, persons living in prison or a homeless shelter, intravenous-drug users, or persons who immigrated from a country with a high incidence of tuberculosis within the previous five years. Data on the risk associated with immunosuppressive therapy are from a study involving patients who were receiving infliximab and are applicable to patients undergoing long-term therapy with other medications that are known to impair cell-mediated immunity. HIV denotes human immunodeficiency virus.

studies that included a control group whose risk of exposure was similar to that among the persons with the condition under study (Table 3).[27-33]

RELATIVE RISK AMONG PERSONS WITH INCREASED RISK OF RECENT INFECTION

Residents of prisons and homeless shelters, intravenous-drug users, and foreign-born persons who come from areas where the prevalence of tuberculosis is higher than 30 cases per 100,000 population and who have been in the United States for five years or less have also been observed to have an increased risk of tuberculosis disease.[4] Persons in these groups are not thought to be at increased risk for progression from latent tuberculosis infection to active tuberculosis; rather, there is an increased likelihood that the nonconversion positive skin test is the result of recent infection (no prior test result is available). Therefore, the maximal lifetime risk of tuberculosis in such groups is the same as that

among persons with recent conversion of the tuberculin skin test (Table 2).

DISCUSSION

This analysis demonstrates that the lifetime risk of reactivation tuberculosis equals or exceeds 20 percent among most persons with induration of 10 mm or more on the tuberculin skin test and HIV infection or evidence of old, healed tuberculosis. The lifetime risk is 10 to 20 percent among most persons 35 years of age or younger with induration of 15 mm or more on the tuberculin skin test who are receiving infliximab therapy or have had recent conversion of the skin test. The risk is also 10 to 20 percent among children five years of age or younger with induration of 10 mm or more on the skin test.

These high-risk groups differ from those that have previously been identified in several ways. First, the estimated risk of reactivation tuberculosis among children five years of age or younger, although substantial, is lower than the risk of 25 to 50 percent that is frequently cited.[35] However, the higher risk includes both primary tuberculosis and reactivation tuberculosis. Since a substantial proportion of tuberculosis disease among children who are household contacts of patients with infectious cases is primary progressive disease and is present on the initial evaluation,[21] it cannot be prevented by skin testing and subsequent treatment of latent infection.

Previous estimates of the lifetime risk of tuberculosis have been based on the assumption that after the initial decade, the lifetime risk of reactivation remains constant.[4] However, in long-term follow-up of persons with positive tuberculin skin tests, roughly 10 percent of adults lose tuberculin reactivity each decade,[13-15] and persons with negative skin tests do not contribute to the group's overall risk of reactivation tuberculosis. Therefore, we calculated lifetime risk by assuming that the risk of reactivation tuberculosis decreases at a rate of 10 percent per decade, rather than remaining constant. This assumption is consistent with Comstock's observation that the risk of tuberculosis in a birth cohort decreases over time.[36] A decrease of 10 percent per decade reduces the lifetime risk by 25 percent in the youngest age group, with less effect on each subsequent age cohort and no effect on the oldest age group (data not shown).

The relative risks of tuberculosis associated with medical conditions that impair the ability of the host's immune system to control *M. tuberculosis* are lower than those previously estimated.[4,34] This difference results from the failure of previous analyses to distinguish among the risk of exposure, the risk of infection, and the risk of reactivation. In making decisions about the need to treat latent tuberculosis in a person with a positive tuberculin skin test, risks other than that of reactivation should not be considered, since these risks cannot be decreased by the treatment of latent infection.

Advanced HIV infection is associated with the greatest relative risk of reactivation — a risk nearly 10 times that of persons without HIV. Untreated HIV infection that is less advanced is associated with a decreased risk of tuberculosis,[30,37] and HIV infection that is treated with effective antiretroviral therapy conveys only 20 percent of the risk of tuberculosis that is associated with untreated HIV infection.[37,38] However, the risk of tuberculosis among persons receiving effective antiretroviral therapy is still twice that of persons without HIV infection, and the failure of antiretroviral therapy results in reversion to the higher level of risk. Therefore, treatment of latent tuberculosis infection is warranted for all HIV-infected persons with a positive tuberculin skin test.

The lifetime risk of tuberculosis among persons with other immunosuppressive conditions is less well defined. The relative risk associated with chronic renal failure is 2.4, and that associated with infliximab therapy is 2.0, but no appropriately controlled

Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.*

Condition	Study	Relative Risk (95% CI)
Advanced HIV infection	Pablos-Mendez et al.[27] Moss et al.[26]	9.9 (8.7–11.3)† 9.4 (3.5–25.1)
Old, healed tuberculosis	Ferebee,[13] Ferebee et al.[20]	5.2 (3.4–8.0)
Chronic renal failure	Pablos-Mendez et al.[27]	2.4 (2.1–2.8)†
Infliximab therapy	Keane et al.[28]	2.0 (0.7–5.5)†
Poorly controlled diabetes	Pablos-Mendez et al.[27]	1.7 (1.5–2.2)†
Silicosis	Cowie[29] Corbett et al.[30] Kleinschmidt and Churchyard[31]	1.7 (1.3–2.1)† 1.3 (1.1–1.7)† 1.2 (1.0–1.5)†
Underweight (≤10 percent below normal)	Palmer et al.,[22] Edwards et al.[23]	1.6 (1.1–2.2)
Gastrectomy	Thorn et al.[32] Steiger et al.[33]	1.4 (1.1–1.9)† 1.3 (1.2–1.4)†

* CI denotes confidence interval, and HIV human immunodeficiency virus.
† The relative risk is estimated, as described in the Methods section.

studies have addressed the risk associated with cancer or long-term treatment with corticosteroids, cyclosporine, or other immunosuppressive agents. Until more data become available, I believe the lifetime risk of tuberculosis associated with the long-term administration of high-dose corticosteroids or other immunosuppressive agents should be assumed to be equivalent to that associated with infliximab therapy. As can be seen in Table 3, the relative risks associated with silicosis and gastrectomy are low; moreover, these conditions are uncommon in the United States. Thus, efforts to target the treatment of latent tuberculosis should not focus on persons with these conditions.

In dealing with individual patients, it is appropriate to evaluate the need for treatment of latent tuberculosis in relation to the lifetime risk. However, from a public health viewpoint, tuberculosis that occurs soon after infection leads to more secondary transmission and thereby expands the epidemic. Decisions that are based only on the individual person's lifetime risk ignore this effect. Therefore, additional efforts to increase the rate of completion of treatment for latent tuberculosis are justified for some groups of contacts of persons with active tuberculosis and for persons with recent conversion on the skin test in order to prevent secondary spread of *M. tuberculosis*.[39] Similarly, special attention should be given to persons whose epidemiologic characteristics suggest that a nonconversion positive tuberculin skin test is likely to represent unrecognized recent conversion. However, a person in such circumstances who is known to have had a previous positive skin test would not, by definition, have recent conversion and would therefore not merit special attention.

This study was limited by a lack of current data to substantiate the assumption that the observed rates still pertain. There is no reason to suspect that the biologic basis of reactivation is different today, but since tuberculosis is less common in the United States now than it was in 1960, it may be less likely now that a skin-test reaction of a given size indicates the presence of latent tuberculosis. Thus, this analysis may overestimate the absolute rates of reactivation tuberculosis.

These results have important implications for tuberculosis control. Persons who are reported to have had a positive tuberculin skin test in the past but whose records do not indicate the size of the reaction, as well as persons whose skin test was read by an untrained reader, should be retested (unless blistering occurred after the earlier test). Such retesting would also identify persons who previously had positive skin tests but have lost their tuberculin reactivity and therefore do not require treatment. Reliable current results of a tuberculin skin test can help clinicians to estimate accurately the risk of reactivation tuberculosis for individual patients. Communication of the existence of a substantial risk will reinforce the importance of adherence to treatment for latent tuberculosis. The population groups that are at the highest risk for reactivation tuberculosis should be targeted with intensive efforts to increase adherence, such as the use of directly observed therapy.[10,11,40] The targeting of such efforts will enhance the likelihood that tuberculosis will be eliminated in the United States.

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