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REVIEW ARTICLE

Tuberculin reactivity and the risk of tuberculosis: a review

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SUMMARY

SETTING: Although various studies have examined the association between tuberculin reactivity and the risk of tuberculosis (TB), this evidence has not been collated and examined to determine the strength and consistency of the association across multiple studies.

OBJECTIVE: To review the evidence supporting the association between tuberculin reactivity and the risk of TB.

DESIGN: Prospective studies which included raw data on the incidence of TB according to three or more tuberculin reactor categories were located using electronic search methods. The findings of these studies were recalibrated if necessary and compared.

RESULTS: All 11 studies identified demonstrated that increased tuberculin skin test (TST) reactivity was associated with an increased risk of TB, and several found that low tuberculin reactivity was associated with a protective effect. The magnitude of the association between TST reactivity and the risk of TB varied substantially. The association between tuberculin reactivity and the risk of TB was greater among studies that reported a lower incidence of TB among the smallest tuberculin reactor category.

CONCLUSION: All studies reviewed support a positive association between tuberculin reactivity and the risk of TB. However, this review found a substantial degree of variation in the extent of increased risk associated with larger tuberculin reactions.

KEY WORDS: tuberculin skin test; tuberculosis; risk

THE UNPREDICTABLE but usually long incubation period of tuberculosis (TB) is a notable factor that complicates attempts to control the disease. The success of TB control strategies is highly dependent upon an improvement in targeted preventive therapy among individuals at high risk of TB.[1] The use of preventive therapy among low-risk tuberculin reactors has also been shown to have public health benefits, particularly when considering the reduced secondary transmission to contacts.[2] Early identification and treatment of individuals with subclinical infections significantly reduces the likelihood of progression to overt disease.[3] The tuberculin skin test (TST) is the only routinely available and comparatively cheap method for detecting individuals infected with *Mycobacterium tuberculosis*. The TST is widely used to screen for mycobacterial infection, and is used to provide an indication of the risk of TB. Although many studies have examined the association between the magnitude of the TST reaction and the subsequent risk of TB, this evidence has not been collectively evaluated.

The tuberculin skin test

The TST is based on the development of delayed hypersensitivity to antigenic components of tuberculin in individuals infected with *M. tuberculosis*. Although reactivity to tuberculin is a continuous phenomenon, TST results have traditionally been referred to as positive or negative.[4] In view of evidence indicating the variability of tuberculin reactivity under different conditions[4] and among different populations,[5] the definition of a criterion for a positive TST is problematic. The definition of a positive reaction may also vary with the intent of the tuberculin survey, and the relative importance of sensitivity and specificity in the test situation.

A number of factors may influence the degree of tuberculin reactivity, and must be considered when determining the criterion for a positive reaction. These include the prevalence of non-tuberculous mycobacterial (NTM) infection, previous bacille Calmette-Gúerin (BCG) vaccination, age, exposure to active TB, country of birth, immune-competence, chest X-ray appearance and socio-economic status.[6] Severe illness, particularly in the elderly, may also impair tuberculin reactivity.[7] Infection with NTM or BCG vaccination are important confounding factors in the interpretation of the TST,[5,8] and no reliable method exists to distinguish between reactions induced by infection with *M. tuberculosis* and BCG.[9]

The distribution of reactions to *M. tuberculosis* is defined most accurately in a population free from other causes of mycobacterial sensitisation. This is not the case for most populations. In areas of high

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Table 1 Studies of the tuberculin reaction and the risk of tuberculosis

Study and evidence of association	Study type and sample providing tuberculosis risk data	Main follow-up type* and period	Tuberculin skin test	Induration categories (mm)	Cumulative incidence of TB according to tuberculin reaction (cases/total)	Average yearly incidence of TB per 100 000 according to tuberculin reaction	Comment
Alaskan[3] Weak	Randomised controlled trial of isoniazid prophylaxis. Placebo group: 845 indigenous Alaskan adults and children (>2 months old).	Passive 3.5–6.5 (average 6) years 1957–1964	5 TU PPD-S	0–4 5–9 10–14 15–19 >19	6/275 2/61 9/157 14/215 7/137	364 546 955 1085 852	Isoniazid preventive therapy lessened the likelihood of further new infections. Case rates in the placebo and isoniazid groups decreased over the trial period. Risk of TB was greatest among young adults and positive reactors. Small likelihood of BCG confounding results.
British Medical Research Council[12,19,20] Weak	Controlled trial of BCG. Control group children aged 14–15 years from 3 large UK cities: 15 704 reactors (⩾5 mm to 3 TU), 6253 reactors (⩾5 mm to 100 TU), and 12 867 unvaccinated controls (<5 mm to 3 TU & 100 TU).	Active for the first 9 years 15 years 1950–1967	3 TU Old Tuberculin	<5 5–14 >14 <5 5–14 >14	(0–2.5 years)† 80/19 120 17/8838 64/6866 (10–15 years)† 23/19 120 16/8838 16/6866	(0–2.5 years)‡ 168§ 77 375 (10–15 years)‡ 25§ 37 48	Lowest reactor group comprised of 0–4 mm reactors to 3 TU or 100 TU who were not vaccinated. Low tuberculin reactivity appears protective. Incidence of TB decreased markedly over the follow-up period, and the decrease in TB incidence was greatest in the largest reactor group.
Puerto Rican[13,14] Moderate	Controlled trial of BCG. Children aged between 1 and 19 years in Puerto Rico: direct reactors (⩾6 mm to 10 TU), and 27 338 unvaccinated controls (<6 mm to 10 TU).	Passive 18.1–19.8 years 1949–1969	10 TU PPD RT 19-20-21	<6 6–10 11–15 >15	141/27 338 38/~ 59/~ 222/~	28 46 98 160	Initial testing with 1 TU was discontinued (results not reported). Number of cases among controls and vaccinees decreased over time. High proportion of persons with low-grade sensitivity suggests a significant proportion of reactors may not be infected with TB. Little evidence of a protective effect in individuals with low TB sensitivity.
Muscogee, Georgia & Russell, Alabama[21,22] Moderate	Controlled trial of BCG. 64 136 county residents aged 5 years or over. Estimated midpoint population: 13 390 controls (<5 mm), & 22 027 reactors (⩾5 mm).	Passive 20 years 1950–1970	5 TU PPD RT 19-20-21	0–4 5–9 10–14 15–19 >19	36/13 390§ 77/13 148 88/6234 36/2210 6/435	13 29 71 81 69	Incidence of TB decreased markedly over the follow-up period among reactors. No similar trends were found in controls (0–4 mm induration) or vaccinees, although the number of cases in these groups was small.
South India[23] Strong	Controlled trial of BCG. 260 000 villagers in southern India aged from 1 month to over 65 years: placebo group data. Reactors not excluded from vaccination.	Active 7.5 years 1968–1978	3IU PPD-S	0–7 8–11 12–15 >15	47/~ 19/~ 46/~ 369/~	20 40 150 450	A greater percentage of older adults were tuberculin positive than younger adults. Reactors >15 mm not actively followed after 2.5 years. No information about distribution of cases over time.

Danish[24] Weak	Observational study. Danish aged 15–44 years: 286 250 reactors (⩾6 mm) and who had not been BCG vaccinated, and 10 893 unvaccinated 'non-reactors' (<6 mm) who refused BCG.	Passive 12 years 1950–1964	10 TU PPD RT22	0–5 6–11 12–17 >17	26/10 893 103/~ 443/~ 441/~	20 17 28 35	Controlled for BCG status. Non-reactors and reactors cannot be validly compared. Incidence of TB was higher among younger subjects. Incidence of TB decreased over the study period such that the difference in incidence between small and large reactions diminished. Decrease in incidence less pronounced in older subjects.
Rwanda HIV+ve[18] Weak	Observational study. 289 HIV-infected urban Rwandan women aged 18–39 years who were attending out-patient paediatric or prenatal clinics. Nearly 80% of women had a BCG scar.	Active 1 year 1989–1990	1 TU PPD RT23	0–4 5–9 >9	3/214 0/13 2/62	1402 0 3226	This analysis excluded cases detected prior to or on TST. The risk of TB was significantly associated with a lower income, age ⩾30 years, and a lower body mass index. BCG vaccination was not associated with a significantly lower risk of TB. Incidence of TB among HIV-infected women was 23 times that of non-HIV-infected women.
United States HIV+ve[17] Moderate	Observational study. 1130 HIV-infected patients (without AIDS) aged between 18 and 67 years. Sample predominantly male (87%) and homosexual men (72%).	Active Median 4.5 years 1988–1994	5 TU PPD ~	0 1–4 5–9 10–19 >19	Cases/p-y 17/985 0/56 2/24 3/36 6/34	IR 500 0 2400 2500 5400	Analysis did not exclude participants who may have received treatment before the study. It was reported that exclusion of these cases increased the difference in the incidence of TB according to the magnitude of the PPD response.
Malawi[15] Moderate	Observational study. Approximately 45 000 residents of northern Malawi. Results reported for BCG negative individuals only.	Active Approx 5 years 1980–1989	2IU PPD RT23	0 1–5 6–10 11–15 16–20 >20	Cases/p-y 19/71 055 2/5 442 3/15 059 14/21 561 9/13 488 6/2 801	IR 27 37 20 65 67 214	Controlled for BCG status. A similar increased risk of TB was found among BCG positive and negative individuals who had large reactions >20 mm. Results indicate some protection is associated with low or intermediate levels of tuberculin reactivity.
US Navy recruits[10] Moderate	Observational study. 1 124 883 new recruits aged between 17 and 21 at recruitment.	Passive 3–15 (average 5) years 1958–1972	5 TU PPD-S	0–5 6–11 12–17 >17	384/1 058 122 36/32 649 80/20 932 49/13 180	7 22 76 74	Dual testing with NTM antigens found some small reactions (6–11 mm) were likely to be reflective of infection with NTM, and these men had no more increased risk of TB than non-reactors. Cross-reactions among men who had large reactions were not associated with a significantly lower TB incidence.
Italy HIV+ve[16] Strong	Observational study. 1054 HIV-infected patients aged between 18 and 61 years who were non-anergic at entry. Approximately 79% had asymptomatic HIV infection, and 75% of subjects were men.	Active 3–133 weeks (median 2 years) 1990–1993	5 TU Sclavo-Test PPD	0–1 2–4 5–9 >9	Cases/total 5/802 1/55 5/128 10/69	IR 390 1 150 2 780 10 260	Incidence of TB may be overestimated due to patients lost to follow-up having a higher CD4+ lymphocyte count. Incidence of TB strongly associated with the size of the tuberculin response, and did not appear to be dependent on individual levels of immune suppression.

* Follow-up categorised as predominantly active or passive. Passive methods may have been used in settings that had widespread active case-finding programmes.
† Crude rate not adjusted for population at risk.
‡ Average annual incidence adjusted for population at risk.
§ Estimated midpoint population.
TU = tuberculin units; IU = international units; HIV+ve = human immunodeficiency virus positive; ~ Unable to be precisely determined from publication; NTM = non-tuberculous mycobacteria; IR = incidence rate: per 100 000 p-y of observation; p-y = person-years.

NTM prevalence, the specificity of the TST declines because an increased proportion of positive tests are due to cross-reactions.[10] Cross-sensitivity between tuberculin and NTM has been associated with medium-sized tuberculin reactions which make it difficult to identify *M. tuberculosis*-infected individuals.[11] It is important to consider the possible effect of cross-reactions when deciding on the most appropriate balance between the sensitivity and specificity of the TST.

Screening programmes designed to survey the prevalence of infection or detect disease among large groups generally use a single administration of the TST. Although serial testing and the identification of boosted reactions may be important for an individual case or for specialised applications, such as screening of health workers, it is less relevant in public health terms (e.g., for migrant screening surveys in developing countries), as serial testing and re-screening to identify boosting are expensive and logistically complex. Thus, concerns about the effect of boosting on the interpretation of the TST following serial testing[4,6] do not complicate the use of the TST in most screening situations.

Despite problems with interpretation, the TST remains at present the best method for diagnosing *M. tuberculosis* infection,[6] and TST surveys of the prevalence of *M. tuberculosis* infection have been used to estimate the incidence of new infections.[11] As such, it is important to determine the value of the TST in predicting the risk of TB.

METHODS

Studies that provided data on the association between tuberculin reactivity and the incidence of TB were located through key word searches of the Medline and Current Contents electronic databases, and retrieval of some non-indexed papers cited within located articles. Studies included in this review were required to publish data on the risk of TB according to at least three tuberculin reactor categories. Studies that only published data according to dichotomous groups, indicating no differential magnitude of risk among tuberculin reactors, were excluded. In order to provide a basis for the comparison of the cumulative incidence of TB, all studies included in this review reported a rate of TB in the smallest reactor category of at least 1/100 000. This paper reviews the 11 studies we could identify, published between 1956 and 1999, that provide data on the association between tuberculin reactivity and the risk of TB.

This review sought to limit the inclusion of data based on the administration of multiple TSTs. Consequently, the British Medical Research Council (MRC) study data[12] were based only on testing with 3 tuberculin units (TU) of Old Tuberculin, and not on the subsequent 100 TU testing. For the same reason data based on single administration of 10 TU TSTs were also selectively extracted from the Puerto Rican study.[13,14] Non-reactors to 1 TU who were subsequently re-screened with 10 TU were excluded from this study. The 'non-reactor control group' in the Puerto Rican study was defined as those who had an induration of less than 6 mm to 10 TU. We were unable to identify and exclude a small proportion of this control group that was screened with 1 TU prior to the 10 TU testing.

The non-uniform presentation of TB incidence among studies created some difficulties in comparison of data. Several studies assessed the incidence of TB using person-years of observation,[15–17] although most studies reported cumulative incidence. Cumulative incidence measures which were reported relative to the total duration of follow-up of the study were converted to average yearly rates based on the mean or median period of follow-up reported in the study. As the sample sizes varied considerably between studies, the proportion of error in the estimation of the yearly cumulative incidence of TB per 100 000 individuals is not constant.

The various measures of TB incidence reported in the studies were used to calculate risk ratios of TB using the largest and smallest reactor categories reported in each study. Only in the Rwanda human immunodeficiency virus (HIV) positive,[18] United States HIV-positive,[17] and Malawi[15] studies was the smallest reactor category restricted to non-reactors with an induration of 0 mm. The risk ratio of TB in the largest tuberculin reactors relative to the smallest tuberculin reactors was used to assess the association between tuberculin reactivity and the risk of TB. To facilitate graphic representation of the tuberculin reactor categories according to the size of the reaction, reactor categories were classified according to the midpoint induration size in millimetres. For the final open-ended category, an induration size 2 mm greater than the induration defining the lower bound of the category was used to represent the category midpoint.

RESULTS

The 11 studies identified included observational studies and controlled trials of preventive chemotherapy or BCG vaccination. The main characteristics of the reviewed studies are summarised in Table 1, and the risk ratios for the largest reactor category relative to the smallest reactor category are presented in Table 2. For the purposes of clear graphic representation, the incidence of TB according to tuberculin reactivity is presented separately for studies of non-HIV-infected individuals (Figure 1) and HIV-infected individuals (Figure 2).

Data from the Danish study[24] are not displayed in Table 2 or Figure 1, as the estimated incidence of TB among the smallest reactor category (0–5 mm indura-

Table 2 Risk of tuberculosis among the largest tuberculin reactors relative to the smallest tuberculin reactors

Study	Average yearly incidence of TB per 100 000 for the smallest/largest TST categories	Risk ratio*	Approximate length of follow-up (years)
Medical Research Council[12,19,20]	168/375	2.2	2.5
Alaskan[3]	364/852	2.3	6
Rwanda HIV+ve[18]	1 402/3 226	2.3	1
Muscogee[21,22]	13/69	5.3	20
Puerto Rican[13,14]	28/160	5.8	19
Malawi[15]	27/214	8.0†	5
US Navy recruits[10]	7/74	10.2	5
US HIV+ve[17]	500/5 400	10.8†	4.5
South India[23]	20/450	22.5	7.5
Italy HIV+ve[16]	390/10 260	26.3†	2

* Risk ratios may differ slightly from those calculated on the basis of the average yearly incidence data for some studies due to the use of original incidence data in calculation.
† Rate ratios.

tion) was reported to have questionable validity. This was based on evidence that the group had a higher mortality rate than larger reactors, may have been self-selected and be comprised of a large proportion of false negatives.[24] An inflated estimate of the incidence of TB among this smallest reactor category would underestimate the association between tuberculin reaction size and the risk of TB. Consistent with this hypothesis, the risk ratio of the Danish study comparing the largest and the smallest reactor categories produced an estimate of 1.8, which is lower than that of all other studies reviewed.

In the 10 studies where the largest and smallest reactor categories can be validly compared, the largest reactor category was found to have a greater risk of TB than the smallest reactor category, indicating a positive association between tuberculin reactivity and the risk of TB. The risk ratio of TB among the largest reactors varied from 2.2 to 26.3. Across the 10 studies the largest reactor category had a mean induration size of approximately 19 mm. The risk ratio did not appear to be related to the TST protocol used, the number of tuberculin reactor categories described, the use of active or passive follow-up methods, or

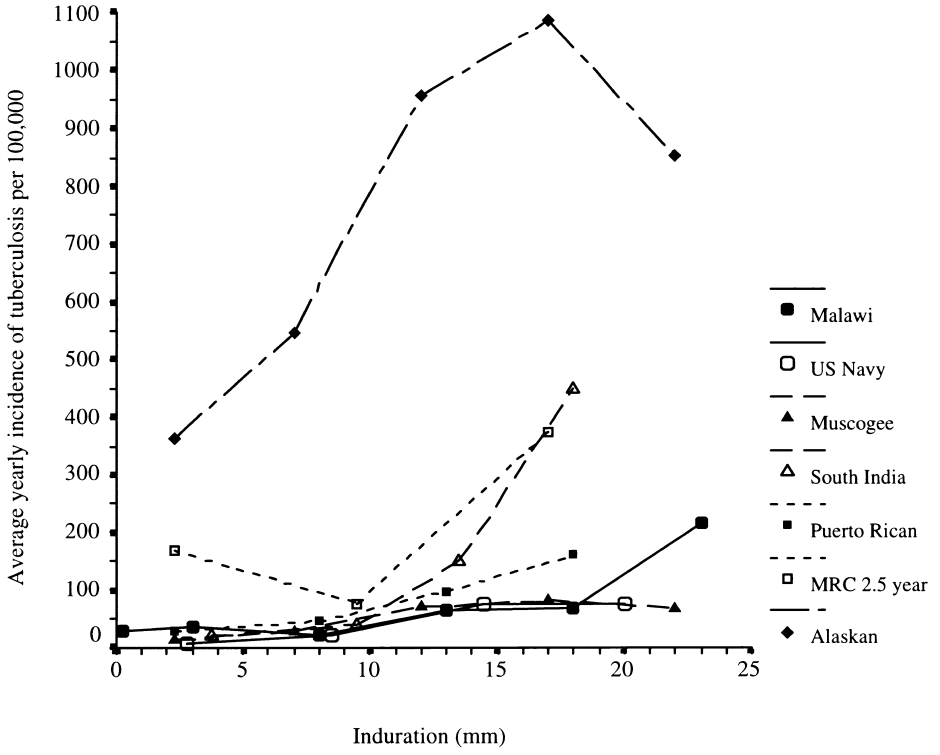

Figure 1 Average yearly incidence of tuberculosis according to the category midpoint induration size in non-HIV-infected individuals.

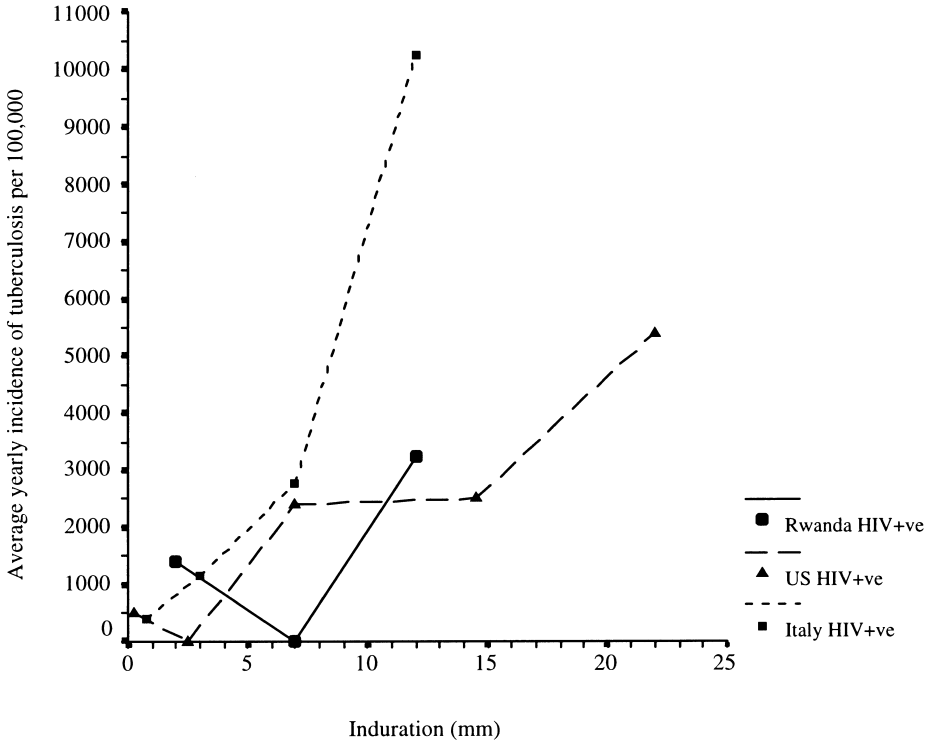

Figure 2 Average yearly incidence of tuberculosis according to the category midpoint induration size in HIV-infected individuals.

whether the study was a controlled trial or an observational study.

Several studies found that the strength of the positive association between tuberculin reactivity and the risk of TB varied according to age. Both the Danish[24] and Alaskan[3] studies sampled individuals across a broad age range, and found that the incidence of TB was greater in early adulthood than in late adulthood. In contrast, the Muscogee study found no significant difference in case rates among whites according to three age groups.[21] Thus the evidence that the strength of the association between tuberculin reactivity and the risk of TB may vary with age is not entirely clear.

Several studies independently noted an association between the duration of follow-up and the strength of the association between tuberculin reactivity and the risk of TB, although no clear association was found across the studies reviewed. The Danish,[24] MRC,[12] and Muscogee[21] studies found that the incidence of TB decreased over time, and that the incidence of TB decreased most rapidly among the largest tuberculin reactors. This effect would weaken the strength of the association between initial tuberculin reactivity and the risk of TB over long periods. A decreased incidence of TB over the study period was also reported in the Puerto Rican[13] and Alaskan[3] studies; however, the authors did not indicate whether the decreased incidence of TB was associated with tuberculin reactivity.

A decreased risk of TB relative to the smallest reactor category was found among those who demonstrated a low level of tuberculin reactivity in the MRC,[12] Rwanda HIV-positive,[18] US HIV-positive,[17] and Malawi[15] studies. This protective effect was found to be present among the observational studies and controlled trials that demonstrated a smaller risk ratio of TB. The low incidence of TB in individuals with an induration of between 5 and 14 mm in the MRC study was suggested to be attributable to the protective effects of NTM infection.[12] Although protection afforded by NTM infection is most likely to explain this result, it is not possible to exclude the potential influence of new transmission among the smallest reactor category. Further evidence of the protective influence of infection with NTM on the risk of TB was provided by the US Navy study.[10] Among the largest tuberculin reactors, the risk of TB only increased as the size of the reaction to PPD exceeded that of the NTM antigens.

The strength of the observed association between tuberculin reactivity and the risk of TB in studies of non-HIV-infected individuals was associated with the incidence of infection among the smallest reactor category. The association between tuberculin reactivity and the risk of TB was generally weaker among studies that reported a comparatively high incidence of TB among the smallest reactor category (Table 2). Findings among HIV-infected individuals were not consistent with those in non-HIV-infected individuals; however, examination of the studies of HIV-infected individuals in isolation suggests that there is

some evidence of a similar association between the incidence of infection among the smallest reactor category and the strength of the association between tuberculin reactivity and the risk of TB.

DISCUSSION

A direct comparison of the results of these studies is difficult in light of the diverse nature of their primary purposes, sample inclusion criteria, follow-up procedures, TST protocols, and use of controls for factors known to be related to the risk of TB. Several potential confounding influences were standardised within studies. These factors included the TST methods used, the duration of follow-up, and the nature and intensity of case detection methods. Although passive case detection methods are more likely to underestimate the presence of disease as disease recognition depends on the intensity of medical investigation,[25] no association was observed between the type of follow-up methods used and the risk of TB according to tuberculin reactivity.

Several confounding influences cannot be assumed to be independent of tuberculin size in all studies, including the influence of previous BCG vaccination, duration of *M. tuberculosis* infection, and the population prevalence of infection with *M. tuberculosis* or NTM. Most studies reviewed controlled for previous BCG vaccination, or stated that BCG vaccination was not prevalent among the population studied, and their findings are unlikely to be appreciably confounded by this factor.

Studies that had a shorter duration of follow-up may provide a more accurate reflection of the risk of clinical disease associated with tuberculin reactivity, as recently infected individuals are more likely to develop disease than those who were infected years ago.[25] In support of this assertion, the Danish,[24] MRC[12] and Muscogee[21] studies reported that a longer period of follow-up had the effect of decreasing the association between tuberculin reactivity and the risk of TB. This decline in the risk of disease over time has been attributed to large reactions occurring among individuals who have been recently infected, and who have an initially high risk of disease that declines rapidly.[24] A large tuberculin reaction is also more likely to reflect infection with *M. tuberculosis*.[6] Although a longer follow-up period has been shown to decrease the apparent risk of TB associated with large tuberculin reactions, no clear association was detected between the period of follow-up and the strength of the association of tuberculin reactivity and the risk of TB across studies in this review. This finding is likely to be associated with other confounding influences across studies, such as the proximity to the date of infection, as well as the small number of studies available for review. Proximity to the date of infection may also be associated with the finding of an increased incidence of TB in early adulthood as compared to late adulthood in the Danish[24] and Alaskan[3] studies.

The association between the incidence of infection among the smallest reactor category and the strength of the association between tuberculin reactivity and the risk of TB among studies of non-HIV-infected individuals suggests that a high prevalence of TB exerts an appreciable risk of infection on previously uninfected individuals. Thus, studies of samples with a high population prevalence of TB are likely to produce weaker estimates of the association between tuberculin reactivity and the risk of TB, depending on the length of follow-up. The small increase in risk associated with a large tuberculin reaction in the Danish study[24] may also be a product of a high prevalence of TB, and conjointly a high risk of disease among those recently infected. In contrast, when the population prevalence of TB is low, most cases of TB infection will occur among individuals already infected.[3]

The altered susceptibility to infection among HIV-infected populations when compared to the general community[15] is thought to be associated with the different findings among studies of HIV-infected individuals. Although only three studies of HIV-infected individuals were reviewed, these studies also suggest that the prevalence of TB infection among the HIV-infected sub-population may influence the association between tuberculin reactivity and the risk of TB.

The decreased strength of the association between tuberculin reactivity and the risk of TB in studies that found a protective effect among small tuberculin reactors is likely to be a product of the observed protective effect applying to some degree across all tuberculin reactors. The protective effect of low levels of tuberculin reactivity has been attributed to variations in susceptibility associated with previous infection with NTM or prior BCG immunisation.[9] NTM infection has been demonstrated to have a protective effect among both smaller and larger tuberculin reactors.[10] Controlling for the magnitude of the protective effect observed within studies may enhance the comparability of findings among the studies reviewed.

Variations between estimates of the risk of TB associated with tuberculin reactivity may be linked in part to variation in the sensitivity of TST methods used to measure and classify tuberculin reactivity. This appears to be particularly important when low levels of tuberculin reactivity are associated with a protective effect. The influence of tuberculin reactivity classification methods on the strength of the association between tuberculin reactivity and the risk of TB is illustrated by the MRC study data used in this review.[12] The use of data that excluded the effect of repeated testing with 100 TU among those who had an induration of less than 5 mm to 3 TU shifted the lower risk of TB present among reactors to 100 TU to the smallest reactor category. This effectively lowered

the observed risk of TB among the smallest reactor category, which in turn increased the apparent magnitude of the association between tuberculin reactivity and the risk of TB. Thus, the sensitivity of methods used to classify tuberculin reactivity is an important consideration in the quantification of the risk of TB when low levels of reactivity may be associated with a protective effect.

This review found, with the exception of protective effects at low levels of reactivity, a positive association between tuberculin reactivity and the risk of TB. The risk of TB is greater among larger tuberculin reactors. This finding is consistent with previous research suggesting that large tuberculin reactions are more likely to indicate infection with *M. tuberculosis* rather than a cross-reaction with NTM or previous BCG vaccination.[6] Although all these studies found a greater risk of TB among the largest reactor group, the degree of increased risk was not consistent. Variability in the risk of TB across studies can be partially attributed to confounding influences, the small number of studies fitting the criteria for this review, and the diverse nature and size of these studies. Thus, although increasing TST positivity predicts subsequent risk of disease, it appears to be only one of several indicators necessary to determine disease risk with any accuracy.

The population prevalence of TB, as indicated by the incidence of TB among the smallest reactor category, was the most important factor associated with variability in the association between tuberculin reactivity and the risk of TB across studies. The presence of a protective effect, possibly due to NTM infection, was also linked to a weaker association between tuberculin reactivity and the risk of TB. The data were less clear as to the effect of time of follow-up on the risk of TB. It is likely that the risk of TB in large tuberculin reactors decreases over time. It is also possible that the effects of time and population prevalence on the risk of TB may interact, resulting in a relatively greater decline in risk over time among large tuberculin reactors in high prevalence settings.

The observed influence of the population prevalence of TB on the risk of TB according to tuberculin reactivity suggests that, in a contemporary context, some risk estimates derived from this review may be conservative. Studies that produced the smallest risk ratios were conducted in times of a substantially higher population prevalence of TB, thus increasing the risk of new infection in a longitudinal study. It is likely that similar contemporary studies in comparatively lower prevalence settings would produce higher risk ratio estimates. The variation in the risk of TB according to population prevalence indicates that the TST is likely to be a more useful predictor of TB in low prevalence settings. The high incidence of new infection among previously uninfected persons and re-activation among previously infected persons in high prevalence settings may undermine the ability of the TST to identify individuals at a significantly higher risk of TB over time. Although imprecise, the TST provides a valuable means of scaling the risk of TB among individuals with high tuberculin reactivity. However, development of a more accurate indicator of the risk of TB, and the determination of factors that significantly affect this risk, is necessary.

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RÉSUMÉ

CADRE : Bien que plusieurs études aient examiné l'association entre la réactivité à la tuberculine et le risque de tuberculose (TB), les faits observés n'ont pas été rassemblés et examinés pour déterminer la puissance et la cohérence de l'association dans de multiples études.
OBJECTIF : Passer en revue les preuves corroborant l'association entre la réactivité tuberculinique et le risque de TB.
SCHÉMA : Par l'emploi de méthodes de recherche électroniques, les études prospectives qui incluaient des données brutes sur l'incidence de la TB en relation avec trois catégories ou davantage de réactions à la tuberculine ont été recherchées. Les observations de ces études ont été recalibrées si nécessaire et comparées.
RÉSULTATS : Toutes les 11 études ont démontré qu'une augmentation de la réactivité du test cutané tuberculinique (TST) était associée à un risque accru de TB, et certaines ont trouvé qu'une réactivité tuberculinique faible était associée à un effet protecteur. L'ampleur de l'association entre la réactivité du TST et le risque de TB varie de manière substantielle. L'association entre la réactivité tuberculinique et le risque de TB est plus élevée dans les études qui font état d'une incidence plus basse de TB au sein de la plus basse catégorie de réaction tuberculinique.
CONCLUSION : Toutes les études passées en revue corroborent une association positive entre la réactivité tuberculinique et le risque de TB. Toutefois, cette revue a trouvé un degré substantiel de variation en ce qui concerne l'étendue de l'accroissement du risque associée avec des réactions tuberculiniques plus fortes.

RESUMEN

MARCO DE REFERENCIA : A pesar de que varios estudios han examinado la asociación entre la reacción tuberculínica y el riesgo de la tuberculosis (TB), esta evidencia no se ha sido cotejada y examinada para determinar la fuerza y la coherencia de la asociación a través de estudios múltiples.
OBJETIVO : Revisar la evidencia que apoye a la asociación entre la reacción tuberculínica y el riesgo de la TB.
MÉTODO : Se localizaron, a través de métodos electrónicos de búsqueda, los estudios prospectivos que incluían datos en bruto sobre la incidencia de la TB de acuerdo con tres o más categorías de reactores tuberculínicos. De haber sido necesario, se recalibraron y compararon los hallazgos de estos estudios.
RESULTADOS : Los 11 estudios identificados demostraron que el aumento de la reacción del test cutáneo tuberculínico (TST) estaba asociado con un aumento del riesgo de la TB y varios de éstos hallaron que una baja reacción tuberculínica estaba asociada con un efecto protector. La magnitud de la asociación entre el TST y el riesgo de la TB variaba de forma substancial. La asociación entre la reacción tuberculínica y el riesgo de TB fue mayor en aquellos estudios que informaron una menor incidencia de TB entre la categoría más baja de reacciones tuberculínicas.
CONCLUSIÓN : Todos los estudios revisados apoyan una asociación positiva entre la reacción tuberculínica y el riesgo de la TB. Sin embargo, esta investigación encontró un grado de variación substancial en la extensión del riesgo aumentado asociado con reacciones tuberculínicas mayores.