The utility and interpretation of tuberculin skin tests in the Middle East

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Tuberculin skin test (TST) interpretation can be confounded by Bacillus Calmette-Guérin (BCG) vaccination and infection with nontuberculosis mycobacteria (NTM). However, a wealth of epidemiologic information has allowed the formulation of recommendations for reasonably informed interpretation of the TST in most clinical situations. In the Middle East, the TST remains a useful test. BCG vaccination is given at birth, which should have minimal effect on TST reactions in adolescents or adults. In countries of the Middle East with moderate to high incidence of active smear-positive pulmonary TB (>20 per 100,000 per year), a positive TST will almost always indicate true TB infection. However, in Middle East countries with very low incidence of active TB (<10 per 100,000 per year), a positive TST will more likely be false positive because BCG vaccination is still routinely given; until BCG vaccination is abandoned, the TST will be less useful in these countries. These findings are applicable to countries in other regions of the world, and the utility TST will also be increased where the likelihood of TB infection is higher and lowered where TB infection is unlikely, yet BCG vaccination is still given. (Am J Infect Control 2005;33:151-6.)

Over the last century, the tuberculin skin test (TST) has been refined and used extensively in epidemiologic surveys in different populations throughout the world.[1-5] As a result of the information generated, it is a widely used clinical test for the diagnosis of latent mycobacterium tuberculosis infection (LTBI).[6,7] However, infection with nontuberculosis mycobacteria (NTM) or vaccination with the Bacillus Calmette-Guérin (BCG) also cause reactions to TST. This complicates the interpretation of the TST because tuberculin reactions caused by BCG or NTM cannot be distinguished with absolute certainty from those caused by latent TB infection. However, the wealth of epidemiologic information has allowed formulation of recommendations for reasonably informed interpretation of the TST in most clinical situations.[6,7] Despite this, many practitioners remain reluctant to use the TST and therefore do not give therapy for latent TB infection, even in patients at high risk for reactivation. In this article, we review the epidemiology and tuberculin survey results pertinent to the Middle East region and present our recommendations regarding the utility and interpretation of the TST in this region.

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THE TUBERCULIN SKIN TEST

The idea for a TST was conceived by Robert Koch, who observed that infection with *Mycobacterium tuberculosis* caused cutaneous reactivity to tuberculin material that had been derived from heat-killed cultures of *M tuberculosis*.[8] The TST was first introduced for clinical use in 1908 by Von Pirquet, and the intradermal technique was introduced by Mantoux in 1913.[9] By the late 1940s, preparation of purified protein derived from heat-killed cultures of *M tuberculosis* was highly standardized.[4] A single, large standard lot was prepared, which has become the international standard against which all manufactured tuberculin material is compared.[5]

Administration of TST requires proper technique by trained professionals. A standard tuberculin syringe with a 27-gauge needle should be used to inject 0.1 mL (5 tuberculin units) purified protein derivative (PPD) intradermally. Usually, the volar or inner surface of the forearm is used. The area of the skin selected for testing should be free from any cutaneous or subcutaneous lesion that could interfere with interpretation. The injection should be intradermal and neither too deep nor too shallow. A small, wheel-like area, measuring approximately 5 mm in diameter, should be seen at the time of injection. If incorrect administration is suspected, a second test dose can be given immediately at a site at least 5 cm from the first site.[6,7,10-13] As a result of its tendency to be adsorbed by glass and plastics, tuberculin materials should never be transferred to secondary containers. In addition, tuberculin should be administered as soon as feasible

Table 1. Estimated HIV seroprevalence in adults

Country	Estimated adult HIV seroprevalence
Algeria	0.1
Bahrain	0.3
Djibouti	2.8
Egypt	<0.1
Kuwait	0.12
Lebanon	0.09
Iran	<0.1
Iraq	<0.1
Jordan	<0.1
Libyan Arab Jamahiriya	0.2
Morocco	0.1
Oman	0.1
Qatar	0.09
Saudi Arabia	–
Somalia	1.0
Sudan	1.6
Syria	0.01
Tunisia	0.06
United Arab Emirate	0.18
Yemen	0.01

Source of data: Jenkins and Robalino.[13]

after filling the syringe, ideally within 20 minutes. Long-term storage of prefilled syringes is not recommended. Tuberculin material should be kept refrigerated and, most importantly, protected from light. It should not be frozen.[12]

The tuberculin reaction is a classic, delayed-type hypersensitivity immune reaction. This means that reactions begin within 24 hours, are maximal between 48 and 72 hours after injection, and then gradually wane over the next few days. Reading therefore should be done between 48 and 72 hours after administration. The transverse diameter of induration, but not erythema, should be demarcated using the ball-point technique. The induration should be measured and recorded in millimeters. If no reaction occurs, the size should be recorded as 0 mm not simply as ''negative.'' Similarly, readings of ''doubtful'' or ''positive'' are discouraged, particularly in individuals in whom repeated testing is done (see below).[6,7]

Adverse reactions to TST are uncommon. Local allergic reactions to tuberculin or its components can occur in 2%-3% of patients. These usually present as a rash on the arm, although, occasionally, generalized rash can be seen. These reactions begin shortly after injection and disappear within 24 hours. Severe blistering can be seen, for which topical steroids are frequently given, although there is no evidence of their efficacy. The blistered area should be covered with a dry dressing and the patient advised to keep the area clean and avoid scratching.[6,7]

INTERPRETATION OF THE TST

False-negative TST

A large number of factors can cause false-negative tests. These include viral, bacterial, or fungal infections. The most important cause of false-negative TST is HIV infection. In HIV-infected persons, the likelihood of false-negative TST is inversely proportional to the CD4 count–uncommon at CD4 counts above 500/mL and almost universal when the CD4 count is less than 200/mL. In the Middle East, HIV infection is very uncommon, as seen in Table 1, so this is not an important cause of false-negative TST in this region.[13] It is important to remember that patients with active TB can have false-negative tests at the time of diagnosis, particularly with more advanced disease.[6,7] Other causes of false-negative TST include live virus vaccination within the past 2 months, metabolic derangement, protein depletion, concurrent use of corticosteroids or immunosuppressants, very young or very old age, and stress, including surgery, or burns or graft versus host reactions. In addition, technical factors can lead to a false-negative TST. These include defective antigens because of improper storage or manufacturing, and errors in administration such as injection of too little material, too superficial, or too deep; or prolonged storage within the syringe before administration. These technical factors are largely avoidable, although the biologic factors obviously are not.[6,7,12,14,15]

Anergy testing with control antigens to which most normal adolescents and adults should react, such as mumps and Candida, have been used to determine whether persons have true or false-negative tuberculin reactions. However, among HIV-infected persons, anergy testing is not recommended because of convincing evidence that it is unreliable.[6,7]

False-positive TST

BCG VACCINATION

Many different BCG vaccines are available worldwide. All currently used vaccines are live vaccines derived from the original *Mycobacterium bovis* strain; they differ in their characteristics when grown in culture and in their ability to induce a protective immune response to TB.[16-18] These variations may be caused by differences in techniques of production or by genetic changes that occurred in the bacterial strains over time.[18,19] Since it was first administered to humans in 1921, billions of individuals worldwide have received BCG vaccine.[20,21] The BCG vaccination policy and coverage in Middle East countries is summarized in Table 2.[22]

One of the most controversial aspects of BCG is the protective efficacy of this vaccine (in fact, if BCG vaccine were highly effective, there would be no need to perform TST in vaccinated subjects). Most vaccine studies have been restricted to newborns and young children; few studies have assessed vaccine efficacy in persons who received initial vaccination as adults. The largest community-based controlled trial of BCG vaccination was conducted in southern India. No protective efficacy in either adults or children was demonstrated 5 years after vaccination. These vaccine recipients were reevaluated 15 years after BCG vaccination, at which time the protective efficacy in persons who had been vaccinated as children was 17%; no protective effect was demonstrated in persons who had been vaccinated as adolescents or adults.[23,24] Given the lack of evidence of benefit of BCG revaccination, this is not recommended by the World Health Organization (WHO).[25]

Estimates of the protective efficacy of BCG vaccines might have been affected by the methods and routes of vaccine administration and by the environments and characteristics of the populations in which BCG vaccines were studied.[26,27]

A case control study in Saudi Arabia to determine the protective effect of BCG vaccine utilizing the same BCG strain (freeze-dried glutamate BCG, Japan Laboratory, Tokyo, Japan) revealed 82% protective effect in a 5-14 years age group and no protective effect 25 years after vaccination.[28]

Two metaanalyses have been published of the efficacy of BCG vaccination for preventing TB. The first of these metaanalyses included data from 10 randomized clinical trials and 8 case control studies published since 1950.[29] This analysis estimated a 75% to 86% protective effect of BCG against meningeal and miliary TB in children, but the protective efficacy of BCG against pulmonary TB varied so widely between studies that a protective efficacy could not be reasonably calculated.[29] A second metaanalysis reviewed the results of 14 clinical trials and 12 case control studies and estimated the overall protective effect of BCG vaccine to be 51% in the clinical trials and 50% in the case control studies.[30] Vaccine efficacy rates were higher in studies in which subjects were vaccinated during childhood compared with studies in which persons were vaccinated at older ages. The efficacy of BCG vaccination in health care workers is not clear because studies have been limited by small size and methodologic problems.[30] Following BCG vaccination in infancy, tuberculin reactivity wanes rapidly so that by the age of 5 years there is little discernible effect. However, those vaccinated at a later age have larger TST reactions that wane more slowly, with 15% to 25% of reactions persisting beyond 10 years.[31-35] Studies show that a substantial number of BCG-vaccinated individuals convert to a positive TST, but this number appears to be surprisingly low and highly variable (7.4% in a study of Mexican children and 49% in a study of Swedish children).[36-37] While 42% of infants in Singapore who were vaccinated at birth were TST positive, only 12% remained positive at 6 years of age.[38]

Table 2. BCG coverage rate and time of vaccination in the Middle East region

Country	1980 Coverage, %	2002 Coverage, %	Age when vaccinated
Algeria	86 (1985)	98	At birth
Bahrain	–	20	At birth
Djibouti	5 (1982)	52	At birth
Egypt	50	98	Up to 3 months
Kuwait	–	–	4-5 years
Lebanon	NA	NA	NA
Iran	95	99	At birth
Iraq	76	93	At birth
Jordan	32	29	At birth
Libyan Arab Jamahiriya	88	99	At birth
Morocco	50 (1993)	90	At birth
Oman	51	98	At birth
Qatar	4	99	At birth
Saudi Arabia	33	98	At birth
Somalia	–	60	At birth
Sudan	73	68	At birth
Syria	35	99	At birth
Tunisia	88	97	At birth, and 6 years
United Arab Emirate	15	98	At birth
Yemen	9	74	At birth

Current policy does not include repeating BCG vaccine at preschool age or performing TST test post-BCG vaccine.
Source of data: World Health Organization.[22]

The overall proportion of individuals with a prior BCG vaccination who have a positive TST result has been reported to vary from 0% to 90%.[14,35,39-44] Some of the variation between studies may be accounted for by differences in the ages of BCG vaccination, the vaccine manufacturer, the dose, and the method of administration.[19]

Reports from Quebec,[44] Botswana,[45] Sir Lanka,[40] and Singapore[38] have demonstrated that the most useful cut point in persons vaccinated in infancy is a reaction of 10 mm size or greater.[14] A recent meta-analysis of 26 studies of the effect of BCG vaccination on TST concluded that BCG vaccination given more than 15 years previously should usually be ignored as a cause of a TST of 10+ mm and definitely be ignored if the induration is ≥15 mm.[46] This supports our recommendations that TST is useful in BCG-vaccinated individuals in the appropriate clinical setting.

NTM are another major cause of false-positive TST.[6-7,10-12,14] The prevalence of NTM varies considerably

Table 3. Incidence of total and smear positive pulmonary TB cases per 100,000 population and corresponding incidence and prevalence of TB infection

Country	Incidence of total TB cases per 100,000*	Incidence of smear-positive cases per 100,000*	Annual risk of infection,† %	Prevalence of LTBI†	
				At 10 years, %	At 20 years, %
Algeria	52	23	0.47	4.6	9
Bahrain	45	20	0.41	4.0	8
Djibouti	952	402	8.2	58	82
Egypt	29	13	0.27	2.7	5.3
Kuwait	26	12	0.24	2.5	5
Lebanon	14	6	0.12	1.3	2.6
Iran	29	13	0.27	2.7	5.3
Iraq	167	75	1.53	14.3	26.5
Jordan	5	2	0.04	0.4	0.8
Libya	21	9	0.18	1.8	3.6
Morocco	114	51	1.04	10	19
Oman	11	5	0.10	1.1	2.2
Qatar	60	27	0.55	5.4	10.5
Saudi Arabia	42	17	0.35	3.4	6.7
Somalia	405	181	3.69	31.4	53
Sudan	217	96	1.95	18	32.7
Syria	44	20	0.41	4.1	8
Tunisia	23	10	0.20	2.0	4
United Arab Emirates	18	8	0.16	1.6	3.2
Yemen	92	42	0.85	8.2	15.8

*Source of Data: WHO REPORT 2004.[49]

†Annual risk of infection, calculated from incidence of smear positive pulmonary TB, as suggested by Styblo.[47] Prevalence of latent TB infection calculated from age and ARI, as suggested by Styblo.

between regions and countries and even within countries. In general, NTM are less common in colder climates and also less common in desert climates. There are few studies of the prevalence of NTM in the Middle East. Disease because of NTM is variable–ranging from 0.004% to 9%.[35,47] In one of the few studies from the region, NTM accounted for only 82 cases among 6472 suspected cases of tuberculosis in Tehran (Iran).[48]

PREVALENCE OF LTBI (TRUE POSITIVES)

Given that false-positive reactions can occur in almost all populations, the most important determinant of the utility of a TST is the expected prevalence of true latent TB infection. As shown in Table 3, the incidence of smear-positive cases of pulmonary tuberculosis varies widely among countries in the Middle East region.[49] Based on the observation by Styblo[50] of the relationship between incidence of smear-positive pulmonary TB and annual risk of TB infection (ARI), one can calculate the ARI, and, from this, the expected prevalence of latent TB infection in persons of a given age. In countries such as Algeria or Bahrain, between 8% to 10% of 20-year-old adults can be expected to have latent TB infection (Table 3). If the expected prevalence of false-positive TST from NTM or BCG is less, a TST of 10+ mm can be interpreted as most likely indicating latent TB infection. In the setting of close contact or an abnormal x-ray, the expected prevalence of latent TB infection is higher, and therefore the likelihood that a positive TST represents true infection is greater. On the other hand, in countries with very low incidence of TB, such as Jordan, Oman, and Lebanon, the expected prevalence of true infection is less than 3% in 20-year-old adults. In these countries, a positive TST will be less likely to indicate true infection and more likely a false-positive reaction. However, even in these countries, in the situation of recent contact of an active case or if a granuloma is seen on chest x-ray, then a positive TST will most likely mean *true* infection.

Al-Kassimi et al[35] conducted the first comprehensive and nationwide tuberculin survey in Saudi Arabia with urban/rural stratification. Using a definition of a positive tuberculin test of 10 mm or more, overall, 33% of subjects had positive TST and 56% of those aged 45 years and older. The average prevalence in children was 6%, which places Saudi Arabia into the middle prevalence (2%-14%) category. Studies from other Middle East countries showed variable prevalence of positive TST: in BCG vaccinated, 13% to 23% in Ethiopian population to 1.4% in Bahraini population, whereas the prevalence of positive TST in nonvaccinated varies from 2.7% to 26%.[50-53]

SERIAL TUBERCULIN TESTING (CONVERSION OR BOOSTING)

In some clinical situations, it may be necessary to repeat the TST, even on a periodic basis. These situations include contact investigations in which the initial TST is negative but was performed soon after the contact ended, so there may not have been enough time for TST conversion, which usually occurs in 3 to 8 weeks after actual infection. Another situation is for persons entering an environment in which there might be a risk of exposure to TB. These include travellers from low TB incidence countries going to high TB incidence countries and workers or students entering professions with increased risk of occupational exposure such as health care or prisons.[6,54]

When repeated tuberculin testing has been performed, a substantial number of individuals may manifest an increased tuberculin reaction on their second test in the absence of any obvious exposure. It is now understood that this reflects an anamnestic response, whereby immunity resulting from past exposure that has waned is restimulated.[55] This phenomenon, termed ''boosting,'' results from any previous mycobacterial exposure including remote BCG vaccination, NTM exposure, or remote infection with M tuberculosis.[6,54,55] The boosting phenomenon is therefore seen more commonly in older populations or where NTM and/or BCG vaccination is common.[56]

It is important to distinguish boosting from the phenomenon of tuberculin conversion, which occurs after initial tuberculin infection. This is because the risk of developing active tuberculosis in persons who manifest the ''boosting'' phenomenon is actually lower than in those with an initial positive TST and *much* lower than in persons with tuberculin conversion. In persons with conversion, the risk of disease is between 5% and 20% over the next 2 years alone. It is difficult to distinguish the 2 phenomena simply on the basis of size, although if the second reaction is $\geq$15 mm, it is more likely conversion. The most important criteria are epidemiologic. If the second TST is performed soon after the first, and there is no intervening exposure, then boosting is more likely. If the second test is performed months to years after the first *and* there has been exposure to M tuberculosis (such as contacts of active cases), conversion is more likely.

In persons who will undergo repeated tuberculin testing, the 2-step protocol is recommended. For example, persons about to enter an environment with increased risk of exposure (travellers, health care workers, or medical students) should have a baseline TST. If the initial TST is negative ($<$10 mm), a second test should be performed 1 to 4 weeks later to elicit the booster phenomenon.[55] Boosting can be seen after intervals of as much as 2 years, but this phenomenon is maximal if the 2 test are between 1 and 4 weeks apart, and a shorter interval is more practical. If the second tuberculin test is negative ($<$10 mm), the individual can be considered truly negative. If on subsequent retesting the tuberculin test is now positive, this can be considered a true conversion and is strong evidence of new infection.[55]

CONCLUSIONS

In the Middle East, the tuberculin skin test is likely to be a useful test in most countries. This is because, in these countries, BCG vaccination has been given in infancy, which is unlikely to affect TST reactions in adolescence or adult life. HIV seroprevalence is very low, so it is not likely to be an important cause of false-negative tests. In countries with moderate to high incidence of active smear-positive pulmonary TB ($>$20 per 100,000 per year), a positive TST can be considered to indicate true infection with confidence. In countries with very low incidence of active TB ($<$10 per 100,000), a positive TST is more likely to be false positive, and, hence, the utility of the TST in these countries is reduced. However, if the likelihood of TB infection is higher, such as following exposure to an active TB case, a positive TST is more likely to indicate real infection; and, if 2-step tuberculin testing is done and is negative, subsequent conversion of a TST on retesting to a positive result is highly likely to indicate new TB infection.

These conclusions are also applicable to countries in other regions of the world. The utility of the TST will be greater in countries with higher rates of TB disease and thus higher risk of TB infection. In countries with low incidence of active TB and low rates of TB infection, the TST will be more difficult to interpret, particularly if BCG vaccination is still given routinely.

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