

Pulmonary Perspective

Interpretation of Repeated Tuberculin Tests Boosting, Conversion, and Reversion

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The tuberculin skin test is one of the few tests developed in the 19th century that is still in present use in clinical medicine. The first tuberculin test material was prepared by Robert Koch (1); its use for detection of tuberculosis (TB) infection was first described in 1907 by von Pirquet (2). Given such a long history of use, it may seem surprising that aspects of interpretation of this test remain controversial. However, this reflects changes in the populations affected with tuberculosis and their relative frequency of true positive tests from TB infection, and false-positive tests associated with bacillus Calmette-Guèrin (BCG) vaccination, or nontuberculous mycobacteria, as well as the recent human immunodeficiency virus (HIV) epidemic.

Particular problems have arisen with use of repeated tuberculin tests to detect new infection in high-risk populations such as initially tuberculin-negative contacts of active cases, and workers with occupational exposure. This has revealed that tuberculin reactions may decrease in size (reversion) or increase in size because of: (1) random variability from differences in administration, reading, or biologic response; (2) immunologic recall of preexisting delayed type hypersensitivity to mycobacterial antigens (boosting); or (3) new infection (conversion).

This review has been undertaken to provide information regarding factors causing changes in the size of repeated tuberculin reactions.

RANDOM VARIABILITY IN TEST RESULTS

Differences in administration of tuberculin tests can increase variability of results; this problem is greater with multipuncture techniques (such as the Tine test) than the Mantoux technique (3, 4). Reading is a much greater source of variation. Inter-reader variability results in standard deviations of readings of 2.3 mm (5) or 2.5 mm (6). Variability is less within the same reader (intra-reader) but, nevertheless, standard deviations of 1.3 to 1.9 mm are still seen (7) although misclassification is only 1 to 2% (4). Biologic variation is remarkably little given the inherent variability resulting from administration and reading (4, 8). Biologic variation in response, and differences in administration and reading, will result in an overall stan-

dard deviation of less than 3 mm (4–6, 8). This means that when repeated tuberculin tests are given, chance variation should result in differences of less than 6 mm (representing 2 standard deviations) in 95% of subjects. This supports the adoption of 6 mm as a criterion to distinguish increases in reaction size due to random variation alone from true biologic phenomena, which could be either conversion or boosting.

The criterion of an increase of at least 6 mm to define boosting or conversion is useful when studying the clinical, epidemiologic, or pathophysiologic correlates of these two phenomena. However, use of this same criterion in day-to-day practice can result in management dilemmas. For example, what should be done for an individual whose first tuberculin test measured 7 mm and the second measured 12 mm? The most pragmatic approach is to consider this individual to have a positive test, refer him or her for radiographic and medical evaluation, and ensure that this individual does not undergo further tuberculin testing in future. The clinician evaluating such an individual must bear in mind the possibility that the increase in reaction size may simply reflect random variation rather than conversion, and therefore that the risk of tuberculosis is relatively low.

THE BOOSTER PHENOMENON

The phenomenon of increased tuberculin reactions upon retesting in the absence of new infection, is believed to result from recall of waned cell-mediated immunity, akin to the anamnestic serologic response. Boosting is maximal if the interval between the first and second test is between 1 and 5 wk (9, 10) and is much less frequent if the interval is only 48 h (11) or more than 60 d (9), although boosting can be detected one or more years after a first negative tuberculin test (11, 12). As summarized in Table 1, the prevalence of boosting is correlated with, although generally lower than, the prevalence of initial tuberculin reactions, so is common in foreign-born, elderly, or BCG-vaccinated populations (9, 11, 13–27). Among subjects vaccinated in infancy, and tested after an interval of 5 yr or more, prevalence of initial tuberculin reactions is the same in vaccinated and nonvaccinated reference populations (26, 28), but prevalence of boosting was 7% higher in vaccinated than nonvaccinated (13). Among subjects vaccinated at an older age, such as at entry to primary school, tuberculin reactions wane more slowly. If tuberculin tested after an interval of 10 yr or more, only 15 to 25% will remain positive on an initial tuberculin test (26, 29). Boosting will be seen in a similar proportion of subjects (13, 27), the proportion being lower if the interval is longer (13).

Sensitivity to nontuberculous mycobacterial (NTM) antigens is common in populations resident in warmer climates although not in colder climates (30, 31). Because the mycobac-

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TABLE 1
PREVALENCE OF POSITIVE INITIAL AND SECOND TEST (TST) IN TWO-STEP TESTING

Population	Setting	Subjects Undergoing T ₁ (n)	Percent with PPD-T1* (%)	Positive Test PPD-T2 [†] (%)	References
Health care workers	USA, Canada	3,776	3.3	1.4	11, 13–15
Nursing home residents	USA, Holland	2,870	29.4	13.8	16–19
Foreign-born	USA, Canada	3,316	37.2	31.0	9, 20, 21
IVDU					
HIV (–)	USA	900	13 [‡]	12 [‡]	22
HIV (+)		95	13	8	
BCG-vaccinated					
In infancy	USA, Canada	380	3	8	13
5 and older	Canada, Europe	3,159	43	18	13, 23–27
NTM					
Sensitive [§]	USA, Canada	128	1.7	13	13, 14
Not sensitive		362	2.1	1.4	

Definition of abbreviations: IVDU = intravenous drug user; NTM = nontuberculous mycobacteria; TST = tuberculin skin test.

* PPD-T1 considered positive if ≥ 10 mm in all studies except Reference 22.

[†] PPD-T2 considered positive in all studies if PPD-T2 > 10 mm and increase of at least 6 mm except Reference 22.

[‡] PPD-T1 or PPD-T2 considered positive if ≥ 5 mm (22).

[§] Sensitive means reactions ≥ 10 mm to antigen from *Mycobacterium intracellulare* (13), or *Mycobacterium scrofulaceum* (14).

terial antigens are similar, individuals sensitive to NTM may demonstrate cross-reactivity when tested with antigens from *Mycobacterium tuberculosis* such as RT-23, purified protein derivative–standard (PPD-S), and purified protein derivative–tuberculin (PPD-T) (32). These cross-reactions are smaller and only 2 to 5% of individuals sensitive to NTM antigens will have sufficient cross-reactivity to *M. tuberculosis* antigens that they will have a false-positive initial tuberculin test of 10+ mm (13, 31, 33). This means that the impact on initial tuberculin reactions is relatively minor except in areas where sensitivity to NTM is common and prevalence of tuberculosis infection is very low, such as in the Southern United States (30). On the other hand, 12 to 13% of individuals who react to NTM antigens will demonstrate boosting on two-step testing with PPD-T compared with approximately 1% of those not sensitive to the same NTM antigens (13, 14). Given the association of boosting with remote TB infection, NTM sensitization, and BCG vaccination in cross-sectional studies, it would appear that boosting is a nonspecific response to any prior mycobacterial exposure.

CONVERSION

Conversion is defined as the development of new delayed type hypersensitivity to mycobacterial antigens following new infection with *M. tuberculosis*, nontuberculous mycobacteria, or BCG vaccination. In Great Britain, among adolescents randomized to not receive BCG vaccination, 2,170 had documented tuberculin conversions during the time of follow-up. Of these, 5.2% developed active tuberculosis—80% within 2 yr. Incidence was higher in those who were younger or, as seen in Table 2, had larger reactions (34). In a second study of contacts of active cases with documented conversion, 7% developed active TB in the first year and another 7.5% developed TB over the next 3 yr (35). When tuberculin tests were repeated after 1 yr in initially tuberculin-negative individuals, the risk of active disease associated with a reaction of 5+ mm was six times higher in a population of household contacts assumed to have tuberculin conversion, compared with a population without known exposure and assumed to have boosting (10). There is little other information from longitudinal studies regarding risk of TB in those with boosting, although in one study, radiographic abnormalities such as granulomata were half as frequent in young adults whose second tuberculin

test measured 10+ mm compared with those whose first test was 10+ mm (13). This suggests that the prognosis of the two phenomena is very different, providing the rationale to distinguish them as accurately as possible.

REVERSION

Serial tuberculin testing has also revealed that tuberculin reversion may occur. Among 179 submarine sailors treated with isoniazid (INH) after tuberculin conversion, the majority later demonstrated reversion (36), although some of those considered to have tuberculin conversion may have actually manifested the booster phenomenon. Among South African schoolchildren with tuberculin reactions of 14 mm or larger who were retested three times over the next 3 yr, average reaction size was slightly smaller (reflecting some random variation with regression to the mean) but more than 95% of reactions remained greater than 10 mm on all occasions (37). Of 346 children with tuberculin reactions of 10+ mm who were treated for primary tuberculosis in Houston between 1953 and 1960 and were retested 3 to 10 yr later, only 29 (8.4%) reverted (38).

Reversion is more common in older adults, estimated at 8% per year (39), or those with initial tuberculin reactions in the 5 to 9 mm (38), or 10 to 14 mm (36, 40, 41) range, or in those manifesting the booster phenomenon (14, 41). Reversion is even more likely if boosting is seen only after a third sequential tuberculin test (41).

The phenomenon of reversion emphasizes that once a tuberculin reaction reaches 10 mm or greater, results of further testing become uninterpretable. For example, if the tuberculin reaction were to revert to negative then become positive again, there is no clinical or epidemiologic information available to allow interpretation of such a phenomenon.

DISTINGUISHING BOOSTING FROM CONVERSION

There are three possible methods to distinguish these two phenomena: the clinical situation; the size of second test reactions (or increase from first to second); and the predictive value of a positive second test.

Clinical

Boosting is best distinguished from conversion on clinical grounds. One can attribute an increase in reaction size to

boosting when the increase in reaction is seen after an interval of 1 to 5 wk during which there has been no possibility of exposure, such as preemployment testing of a health care worker. Conversion can be confidently stated to have occurred when a previously tuberculin-negative individual becomes tuberculin test positive after receiving BCG vaccination, or following significant exposure such as during an outbreak or as a result of close contact with a highly contagious index case. An increased reaction is more likely because of new mycobacterial infection (i.e., true conversion) if several prior tuberculin tests were negative, particularly if baseline two-step tuberculin testing was performed (12).

Size

The most frequently recommended criteria to distinguish these phenomenon is to use the absolute size of the second reaction and/or the increase in size. Conversion has been defined as a second reaction of 10+ mm and an increase of at least 6 mm (42), but alternate criteria have been suggested, including increases of 10 mm (42, 43), 12 mm (44, 45), 15 mm (43), or 18 mm (46). The last three criteria were based on studies in populations with high prevalence of boosting (44–46).

As shown in Table 2, in longitudinal studies incidence of active TB was higher if the tuberculin reactions were larger, whether first or second reactions (10, 34, 47–49). However, the difference between series is much greater than the difference between different size reactions within the same series. This suggests that risk of disease is more strongly affected by the clinical situation and risk factors than size of tuberculin reaction alone. Additional evidence is that among Arkansas nursing home residents, incidence of disease was approximately 1% per year if the increase from a first to second tuberculin test was less than 12 mm, compared with 2.5 to 4% if the increase was 12 mm or more (44, 45; and Dr. William Stead, personal communication). In this population as well, there is higher risk with larger reactions but even with smaller increases, the annual incidence of disease of 1% was still very high.

To further understand the two phenomena, it can be helpful to examine the frequency distributions of boosted and conversion tuberculin reactions from cross-sectional studies in different populations. As shown in Figure 1, the mean, mode, and pattern of initial and boosted tuberculin reactions among young health professionals (average age 27), and among elderly nursing home residents were similar. In both populations, the boosting reactions had a single mode and a right skewed distribution. The pattern of conversion reactions, available only among the elderly, was significantly different from the pattern of boosting reactions with a mode at larger reactions sizes.

If these patterns are found in all populations, then as the size of reaction to a second tuberculin test increases, the likelihood that this represents true conversion (not boosting) will increase. However, it is difficult to recommend any one cutpoint to define conversion. Use of a higher cutpoint to define a conversion reaction will be more specific and would be appropriate in populations where boosting is common such as elderly or BCG-vaccinated individuals, or those living in areas endemic for nontuberculous mycobacteria. However, based only on the data shown in Figure 1, a criterion of 15 mm would have sensitivity of less than 70%. To increase sensitivity, the criterion for conversion should be lower among those with increased risk of disease such as young children or adolescents, close contacts, and immunocompromised individuals. The cutpoint should also be lower if there have been two or more negative tuberculin tests in the past, particularly if prior two-step testing has been negative.

Estimating Positive Predictive Values

Table 3 summarizes the predictive value of a positive second tuberculin test performed as part of a contact investigation or annual screening of health care workers. Figures used in this table were derived as follows: (1) The effect of BCG vaccination on initial reactivity from populations where prevalence of infection with MTB and NTM were low (e.g., Northern Europe or Canada). (2) The effect of BCG vaccination on boost-

TABLE 2
OCCURRENCE OF ACTIVE TB BY SIZE OF TUBERCULIN REACTION

	Author (Ref. No.)							
	Comstock (47)	Ferebee (10)		Ferebee (10)		MacIntyre (48)	Narain (49)	Sutherland (34)
Population								
Country	USA	USA		USA		Australia	India	England
Type	Army recruits (whites)	Mental institutions*		Household contacts*		Contacts	General population	Adolescents*
Age range, yr	18–22	18–65		0–55+		0–65+	0–65+	14–20
Number	1.1 million	12,236		13,945		454	22,973	29,000
Tuberculosis disease								
Measure	Incidence	Incidence		Incidence		Incidence	Prevalence	Incidence
Follow-up years	4	10		10		2	N/A [†]	2
Tuberculin testing								
Number of tests	1	2		2		1	2	2
Interval, yr	—	1		1		—	1.5	N/A
Test (T1 or T2)	T1	T1	T2	T1	T2	T1	(T2–T1)	T2
Size								
0–4 mm	5	28	19	65	17	0	240	N/A
5–9 mm	13	82	66 [‡]	192	369 [‡]	450	420	1,160
10–14 mm	50	122 [‡]		294 [‡]		350	310	2,080 [§]
15–19 mm	100					1,050	2,120 [‡]	2,080 [§]
20+ mm	80					1,725		3,400

* Placebo group in randomized controlled trials.

[†] Estimates of TB disease prevalence at time of PPD-T2. All other studies excluded prevalent disease at time of skin testing.

[‡] Incidence shown is for all reactions in that size range and larger.

[§] Estimates represent overall average for all tuberculin skin test reactions of 5+ mm since data available only for 5–9 and 20+.

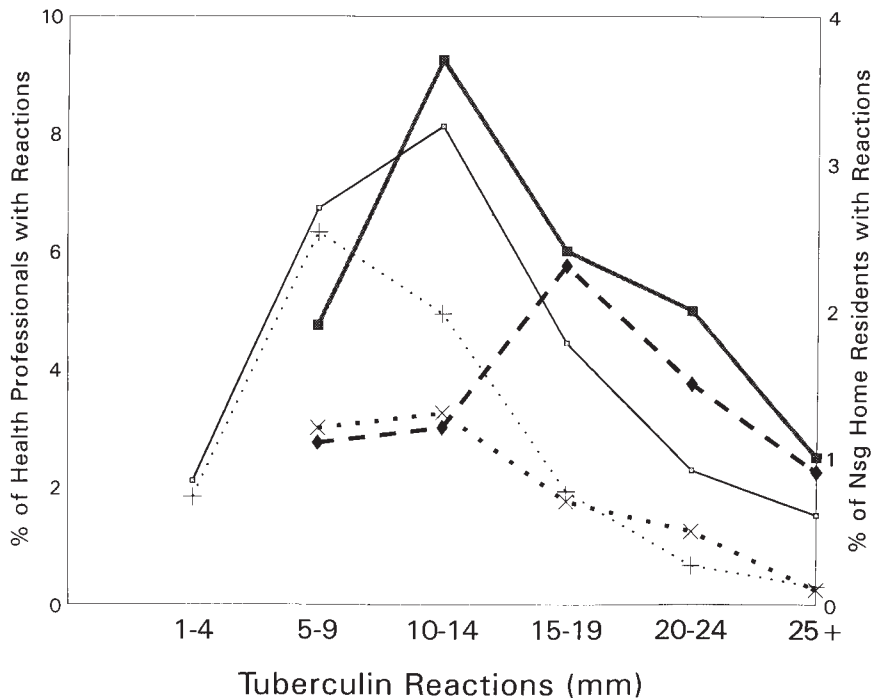


Figure 1. Initial, booster, and conversion tuberculin skin test reactions in Canadian health care students and workers, and Arkansas nursing home residents. (Arkansas data courtesy of Dr. W. Stead.) *Thin solid line:* PPD-T1 in health professionals. *Thin dotted line:* PPD-T2 in health professionals. *Thick solid line:* PPD-T1 in nursing home residents. *Thick dotted line:* PPD-T2 in nursing home residents. *Thick dashed line:* conversion reaction in nursing home residents.

ing from studies of populations with documented BCG vaccination and reference nonvaccinated populations. (3) Effect of NTM on boosting was derived from two studies where dual testing was performed initially and a second tuberculin test was repeated after 1 to 4 wk. (4) Likelihood of boosting if in-

fectured with MTB from studies in North American nonvaccinated health care workers studied preemployment or preexposure, and from nursing home residents in North America and Europe. In these studies, the prevalence of boosting was approximately one-third the prevalence of initial tuberculin

TABLE 3
LIKELIHOOD THAT A POSITIVE TEST FROM SECOND SEQUENTIAL TEST REPRESENTS CONVERSION
(CONTACTS AND HEALTH CARE WORKERS—20-YEAR-OLD ADULTS)

	Mycobacterial Exposure		Likelihood of:		Positive Predictive Value for Conversion (%)	Risk of Disease (per 100,000) [†]		
	BCG (given)	NTM (prevalence) (%)	M. TB (prevalence) (%)	Boosting* (%)		Conversion [‡] (%)	High Estimate (from Ref. 34)	Low Estimate (from Ref. 10)
Household contact								
Northern USA/Canada	None	10	1	1.5	18	92	1,919	345
Southern USA	None	50	1	6.5	18	77	1,617	299
Africa/Asia (ARI 2%)	Infancy	50	33	23	18	49	1,052	214
Western Europe	Older	10	1	19.5	18	53	1,133	227
Eastern Europe (ARI 1%)	Older	10	18	24	18	48	1,033	211
Casual contact								
Northern USA/Canada	None	10	1	1.5	4.5	75	1,577	293
Southern USA	None	50	1	6.5	4.5	42	912	193
Africa/Asia (ARI 2%)	Infancy	50	33	23	4.5	17	408	118
Western Europe	Older	10	1	19.5	4.5	19	449	124
Eastern Europe (ARI 1%)	Older	10	18	24	4.5	16	388	114
Health care worker								
Northern USA/Canada	None	10	1	1.5	1 [§]	40	872	187
Southern USA	None	50	1	6.5	1	13	328	105
Western Europe	Older	10	1	19.5	1	5	166	81

Definition of abbreviation: ARI = annual risk of infection.

* Likelihood of boosting from figures in Table 1.

[†] Likelihood of conversion for second tuberculin test repeated 8 to 12 wk after end of exposure from (10, 53).

[‡] Calculated as [(pos. pred. value for conversion) × (incidence of TB if conversion from (34) or (10))] + [(1 - pred. value for conversion) × (incidence of TB if booster from (10))].

[§] Conversion of 1% after 1 yr of work based on ARI of 1% in population.

reactions. This was assumed to represent remote TB infection as these populations were not likely to have received BCG vaccination although prevalence of NTM sensitivity was not measured in all studies. (5) Prevalence of infection among the foreign-born has been calculated using approximate estimates of annual risk of infection for each region. (6) Prevalence of initial TB infection of 40% among household contacts and 10% among casual contacts was taken from studies summarizing results of contact investigations, which included reference nonexposed populations (50–52). (7) Incidence of conversion of 18% was taken from two studies of initially tuberculin-negative household contacts tested after 1 yr (10, 53). (8) Given that the prevalence of initial tuberculin reactions among casual contacts is approximately 25% that of household contacts (50, 52), the incidence of conversion of initially tuberculin-negative casual contacts was also assumed to be 25% that of household contacts, or 4.5%.

Based on these figures, probabilities were estimated that a positive second test represented conversion and, from this, risk of disease was calculated using higher (34) and lower (10) published estimates of disease. These estimates (10, 34) were based on a definition of conversion as any new reaction of 5+ mm, so the estimates of disease incidence shown in Table 3 may underestimate risk for those with reactions of 10+ mm.

As seen in Table 3, in different clinical situations and populations, the predictive value of a positive second test varies markedly as does the associated risk of disease. The likelihood that a positive test represents true conversion is very low among casual contacts who are foreign-born, BCG-vaccinated, or from the Southern United States where NTM are endemic. The predictive value is even lower among health care workers even though the average annual risk of infection in their hospital was assumed to be 1% annually—considered a very high risk of infection for this population. When the predictive value of a new positive test is low, the corresponding risk of disease and benefit of preventive therapy will also be low. Figures in Table 3 are for 20-yr-old adults. In older adults, the prevalence of boosting will be higher, while the incidence of conversion should be similar, so the likelihood that a positive test represents conversion will generally be lower.

The interval between initial infection and manifestation of delayed type hypersensitivity to specific mycobacterial antigens, known as the “window period,” is variable. The maximum interval has been considered to be 12 wk on the basis of which it is currently recommended that all contacts of active cases who are initially tuberculin negative, should have repeat tuberculin tests 12 wk after the end of exposure (42, 43). However, all available evidence points to a shorter interval or window period. Following BCG vaccination, all but one of 120 recipients had tuberculin reactions greater than 11 mm within 6 wk (54). In a separate group of 163 BCG vaccine recipients, all had tuberculin reactions greater than 5 mm within 4 wk (54). After inadvertent vaccination with *M. tuberculosis* (the Lubbeck disaster), tuberculin reactions were positive in all children within 3 to 7 wk (55). As shown in Figure 2, in 127 cases where the time of exposure was precisely known, the interval from exposure to development of a positive tuberculin test averaged 37 d and ranged from 19 to 57 d (56–58).

If the interval from infection to conversion is never more than 8 wk, then the window period for contact investigation could be shortened to 8 wk. This would mean that new conversions among high-risk contacts would be detected 1 mo sooner. In most situations the lower risk casual contacts are identified and initially tuberculin tested between 4 to 8 wk after the end of exposure. Following current recommendations, tuberculin testing is then repeated 12 wk after the end of ex-

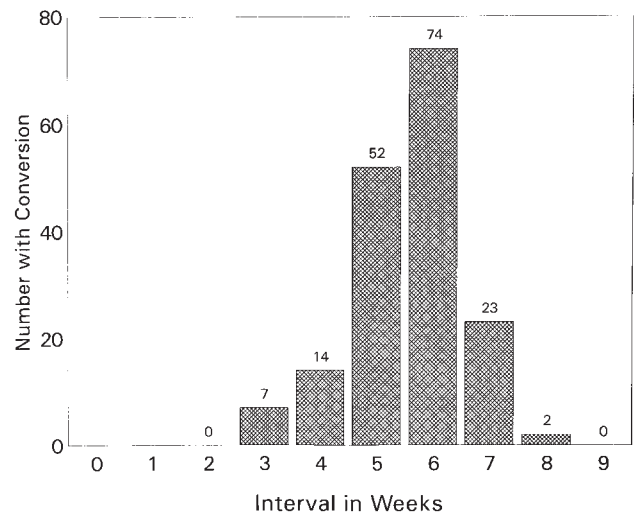


Figure 2. Interval from primary infection to tuberculin skin test conversion in 172 persons with known time of infection. (Data taken from References 57 and 58.)

posure. As shown in Table 3, among casual contacts who are foreign-born, BCG-vaccinated, or from NTM endemic areas, a positive result on this repeat test is much more likely to be the result of boosting than conversion. Because all tuberculin conversions will have occurred by 8 wk after the end of exposure, a single tuberculin test at that time would be sufficient to detect all low-risk casual contacts with new infection. As demonstrated in Table 3, among low-risk casual contacts, the majority of new reactors detected with a second sequential tuberculin test will have boosting, not conversion. Performing only a single test in this group would avoid the difficulties created by the boosting phenomenon and avoid unnecessary medical and radiologic evaluation, as well as therapy. As well, the resultant overestimate of conversion could result in further extension of contact investigations.

Waiting for 8 wk to perform a single test would not be appropriate for contacts who are young children and/or immunocompromised such as HIV-infected populations. In these groups, false-positive results from boosting are of less concern and development of active TB following new infection is much more frequent and rapid.

CONCLUSIONS

Biologic variability in response as well as differences in administration and reading will result in increases (or decreases) of less than 6 mm in 95% of subjects. Therefore, increases of 6 mm or more should be considered to represent a true biologic phenomenon; this may be boosting or conversion. Tuberculin reversion is associated with smaller reactions as well as boosting. The phenomenon of reversion means that the dictum “once positive, always positive” is incorrect, although the corollary “once positive, no longer useful” is still correct.

The boosting phenomenon is common in many populations as it is roughly correlated with prevalence of initial tuberculin reactions, and is nonspecific as it is associated with remote TB infection, nontuberculous mycobacterial sensitivity, and BCG vaccination. The risk of future development of tuberculosis among those demonstrating the booster phenomenon appears to be lower than for individuals from the same population with a positive initial tuberculin test. If repeated tuberculin testing is planned, it is essential therefore to perform initial

two-step testing. The greater expense and complexity of initial two-step testing is easily justified given that otherwise unnecessary evaluation and treatment of individuals with false conversions will occur.

The interval from infection with *M. tuberculosis* to tuberculin skin test conversion is less than 8 wk. Therefore, for low-risk (healthy) casual contacts of active cases, it would be preferable from an individual and public health point of view to wait until 8 wk after the end of exposure and perform a single tuberculin test. This would detect all such contacts with new infection and minimize the likelihood of falsely diagnosing tuberculin conversion among those who actually manifest the booster phenomenon.

The tuberculin test seems ideal because it is so simple, safe, and inexpensive to administer; unfortunately, management of tuberculin reactors is not as simple. Interpretation of tuberculin reactions should not be unidimensional, i.e. focused only on size, but rather "three-dimensional." This means that in addition to size, the predictive value and risk of disease should be considered for each individual with a positive result.

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