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Late boosting phenomenon in TST conversion among health care workers

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Background	Available information is insufficient to guide determination of whether tuberculin skin test (TST) conversions of health care workers (HCWs) within 2 years of two-step testing are related to occupational exposures or to other causes, including late boosting.
Aims	To describe the epidemiologic factors of TST conversion in HCWs, comparing early TST conversion (≤2 years after two-step testing) with late conversion to possibly distinguish late boosting phenomenon from occupational TST conversion.
Methods	Retrospective analysis of a database of TSTs of HCWs from 1 January 1998, through 31 May 2014, in the United States Midwest.
Results	In total, 40 142 HCWs had 197 932 tests over the 16 years, with 123 conversions (conversion rate: 0.3%; 95% CI 0.3–0.4%). Among 61 HCWs with a negative two-step TST, 30 (49%) were found to have early TST conversion within 2 years; 31 (51%) had late conversion, with likely occupational exposure but no identifiable community risks. Persons with early conversion were more likely to be born outside the USA (89% versus 57%; $P < 0.05$), had a higher rate of prior bacille Calmette-Guérin (BCG) vaccination (89% versus 52%; $P < 0.05$) and had no identifiable risk factors for conversion (63% versus 58%; $P < 0.05$).
Conclusions	Early conversions among HCWs after negative two-step TST are associated with various nonoccupational factors, including international birth and BCG vaccination history. Therefore, conversion is not a reliable indicator of recent tuberculosis contact in this population, and two-step TST is insufficient to discount a delayed boosting response for HCWs.
Key words	Boosting phenomenon; health care workers; latent tuberculosis; skin test.

Introduction

Health care workers (HCWs) are at increased risk of acquiring and spreading *Mycobacterium tuberculosis* infection [1–3]. The Centers for Disease Control and Prevention have published guidelines for tuberculosis (TB) surveillance in health care settings, recommending assessment of overall risk of TB transmission in the institution and subsequent formulation of a TB control plan [4–6]. Many health care institutions require serial, routine surveillance testing for HCWs, and despite evolution of guidelines recommending transition to interferon gamma release assays (IGRAs), many of these institutions continue to rely on tuberculin skin test (TST) [7]. When persons have not had recent TST before enrolment in TST surveillance, a two-step test is used [4].

The two-step TST is an important component of TB surveillance programmes and is used to enhance identification of latent TB infection (LTBI) or immunologic recall of pre-existing delayed-type hypersensitivity to mycobacterial antigens [1–3]. A positive TST result on serial surveillance testing after a negative baseline two-step TST result is assumed to represent conversion due to occupational or community exposure. In the occupational setting, *conversion* is generally defined as an increase in skin test induration, or absolute induration of ≥10 mm. In surveillance programmes that use an IGRA, conversion is defined as a change in IGRA result from negative to positive [4,8].

Multiple occupational and nonoccupational factors contribute to a conversion event [2,9,10]. Delayed immune boosting is reported as a reason for TST conversion within the first 2 years of serial surveillance after a negative two-step TST [11,12]. Delayed boosting occurs when a person has past exposure to TB, when TST has not been performed in the recent past and when the initial two-step skin test, performed over 2 weeks, fails to create sufficient immune boosting to produce a positive TST. With time and additional immune stimulation from subsequent serial surveillance tests, a late boost-positive TST can occur.

TST continues to be used in health care TB surveillance programmes where conversions are infrequent. Interpretation of the test is challenging because of factors such as administration variability, interpretation of biologic response, false-positive skin test response to other mycobacterial antigens or nonmycobacterial disease, new infection (i.e. conversion) and immunologic recall of pre-existing delayed-type hypersensitivity to mycobacterial antigens (i.e. boosting) [13–16]. The extent to which delayed boosting phenomena affect presumed occupational conversion reports is unclear in health care surveillance systems [17,18].

In the present study, we sought to understand the extent to which TST conversions reflect late immune boosting and the identifiable factors that suggest a conversion represents late boosting. Such information can be critical for the systematic response to a possible occupational exposure, in assessing the risk of reactivation, and for the shared decision making that engages HCWs who are contemplating chemoprophylaxis.

Methods

This study was a retrospective analysis of a TST database of HCWs from 1 January 1998 to 31 May 2014, at a large US academic medical centre in the Midwest. Mayo Clinic in Rochester, MN, is a tertiary care hospital, outpatient clinical practice and research institution that employs >34 500 HCWs. It is located in an area of low TB prevalence (annual TB rate: 1 case/100 000 persons) [19] and has a low institutional TB admission rate (3 admissions/100 000).

Most of the latent TB in Minnesota is identified in non-native born persons. Mayo Clinic has great diversity of staff, students and visitors who come from other countries to practice, learn and receive health care. In addition, Rochester and Olmsted County, where the city is located, actively participate in sponsoring refugees for resettlement, which contributes to both diversity and TB risk.

We studied all HCWs enrolled in the TST database from January 1998 through May 2014 and who met inclusion criteria. Study criteria were participation in TST routine surveillance, TST conversion during the routine surveillance period and conversion data available in the TST database as of 31 May 2014.

The HCWs' TST database was used to collect data related to TB surveillance and TST conversion events. Data were verified with employee occupational electronic health records. The dataset had demographic data and clinical data, including age at TST conversion, sex, location of employment, employment duration, description of job duties, education level, history of two-step TST, country of birth, age at immigration if born outside the USA, history of bacille Calmette-Guérin (BCG) vaccination and history of travel. When available, data collected included known LTBI, laboratory results (TST induration size, TB test used [QuantiFERON – QFT; Qiagen] and liver function test findings), chest radiographs, history and date of last negative TB test, reported reason for conversion, chronic disease, smoking status, family history of TB, treatment acceptance, treatment adherence and self-reported rate for latent TB after diagnosis.

The described job duties of HCWs were divided into five categories: clinical, high-risk (e.g. respiratory therapist, *M. tuberculosis* laboratory personnel, intensive care unit personnel), laboratory, nonclinical and research and administrative. BCG vaccination status was determined on the basis of self-report and immunization records, or the BCG World Atlas database [20]. Reason for conversion was categorized as nonoccupational exposure (community risk factors identified), occupational known exposure (part of an occupational contact tracing investigation or close occupational contact with a known TB patient) and possible occupational exposure (no community risk factors identified).

Skin tests were read with the institution's standard processes. During TST, an intradermal dose of 0.1 ml (or 5 tuberculin units) purified protein derivative is injected into the forearm's anterior surface. The TST reaction is read 48–72 h after injection. The transverse diameter of the induration is recorded in millimetres [5,17]. For the study, a positive result was defined as an induration of ≥10 mm. A two-step TST was defined as negative when two TSTs were done 1–4 weeks apart with both test reactions read as <10-mm induration [4,5]. Late boosting was defined as the conversion of previously negative skin test within 2 years after a two-step TST in the absence of an identifiable exposure risk.

Statistical analysis of data was performed using Stata 14 (StataCorp LLC) [21]. Data were summarized as mean and SD for continuous variables and absolute and relative frequencies for categorical variables. Fisher exact test was used to compare differences between groups, with P <0.05 as the cut-off point for significance. The study was approved by the Mayo Clinic Institutional Review Board.

Results

During January 1998 through May 2014, 40 142 employees underwent 197 932 TST procedures, of whom 16% underwent a two-step test on initiation of employment. In

total, 123 (0.3%) had TST conversion during this study period (Figure 1). Table 1 lists the characteristics of HCWs with TST conversion. Mean age was 35 years; routine surveillance was the reason for testing in 89%. A history of prior BCG vaccination was present in 40%, and 37% were born outside the USA. The majority of HCWs (57%) had nonclinical duties, and 44% accepted treatment for LTBI. Baseline two-step test data were documented for 61 employees who converted, of whom 48% were foreign born and 54% reported prior BCG vaccination. Most converters underwent confirmatory IGRA test. Of the 91 converters with IGRA test data, 31% had a positive result.

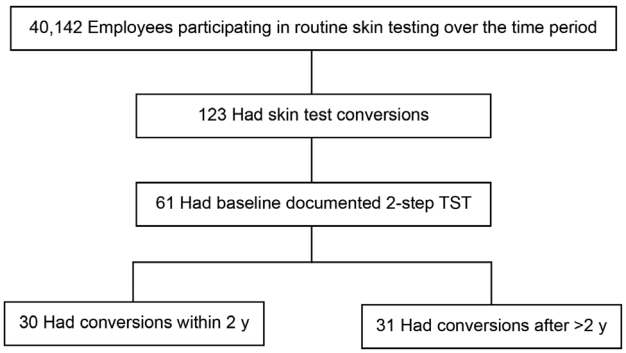

Figure 1. Description of study cohort.

Early conversion (≤2 years after two-step TST) occurred in 49% of the 61 HCWs after a mean duration of 14 months, versus 66 months for late conversion (>2 years). Compared with HCWs with conversion after >2 years (hereafter called *late converters*), the early conversion group (*early converters*) was more likely to be born outside the USA (89% versus 57%; $P < 0.05$) and had a higher rate of prior BCG vaccination (89% versus 52%; $P < 0.05$). Early converters were more likely to have no identifiable risk factors for conversion than late converters (63% versus 58%; $P < 0.05$) (Tables 1 and 2). Early converters were over six times more likely to be born in a foreign country (odds ratio [OR] 6.5 [95% CI 1.2–35.1]; $P < 0.05$) and nearly eight times more likely to have received a BCG vaccination (OR 7.8 [95% CI 1.5–41.7]; $P < 0.05$).

Table 1. Demographic characteristics of HCWs with TST conversion following initial two-step TST

Characteristic[a]	Conversion within 2 years ($n = 30$)	Conversion after >2 years ($n = 31$)	P value
Age at conversion, mean (SD), years	33.3 (10.4)	34.2 (6.7)	NS
Male sex	15 (65)	19 (50)	NS
Country of birth[b]			<0.05
USA	2 (11)	10 (43)	
Other	17 (89)	13 (57)	
Education level			NS
High school graduation	3 (10)	1 (4)	
2 years of college	3 (10)	4 (13)	
4 years of college	4 (14)	10 (33)	
Postgraduate studies	19 (66)	15 (50)	
Job classification			NS
Clinical jobs	14 (47)	10 (32)	
Nonclinical jobs	16 (53)	21 (68)	
Job description			NS
Clinical task	10 (33)	5 (16)	
High risk	0 (0)	2 (6)	
Administration	0 (0)	5 (16)	
Research	10 (33)	9 (29)	
Laboratory	4 (14)	3 (3)	
Nonclinical	6 (20)	7 (23)	
History of BCG vaccination			<0.05
Yes	17 (89)	12 (52)	
No/missing data	2 (11)	11 (48)	
Recent travel			NS
Yes	11 (37)	9 (29)	
No/missing data	19 (63)	22 (71)	
Recent contact with person who had TB			NS
Yes	1 (3)	0	
No	29 (97)	26 (81)	
Not sure/missing data	0	5 (19)	
Two-step TST at hire	23 (100)	38 (100)	

[a]Values are presented as number and percentage of patients unless specified otherwise.
[b]Data about country of birth were reported for 42 HCWs.

Table 2. TST and follow-up data of HCWs who had conversion

Variable[a]	Conversions within 2 years (n = 30)	Conversion after >2 years (n = 31)	P value
Reason for testing			NS
Routine	29 (97)	28 (90)	
Exposure	1 (3)	0 (0)	
Symptom	0 (0)	3 (10)	
TST induration, mm[b]			NS
10–14	16 (53)	14 (45)	
15–19	13 (43)	14 (45)	
≥20	1 (4)	3 (10)	
QFT result			NS
Positive	11 (37)	9 (26)	
Negative	19 (63)	23 (74)	
Quantitative QFT[b]			NS
<1.11	20 (83)	21 (81)	
≥1.11	4 (17)	5 (19)	
Chest radiograph			NS
Normal	25 (83)	27 (87)	
Abnormal findings with no suggestion of active disease	5 (17)	4 (13)	
Treatment acceptance[b]			NS
Yes	4 (15)	7 (23)	
No	22 (85)	24 (77)	
Treatment adherence[b]			NS
Yes	3 (75)	6 (86)	
No/missing data	1 (25)	1 (14)	

NS, non-significant.
[a]Values are presented as number and percentage of patients unless specified otherwise.
[b]Data about treatment were reported for 57 patients of the total population.

Discussion

This study found that overall TST conversion among HCWs working at a large tertiary academic setting in the US Midwest (an area with low prevalence of TB) was rare. Early converters were more likely to be born outside the USA, have a higher rate of prior BCG vaccination and have no identified occupational or community risk factors for conversion. They were also more likely to decline TB treatment.

Despite the technical challenges and limitations, use of TST in regular surveillance for TB infection among HCWs continues in many institutions because of TST feasibility, availability and potential cost benefits [13–16]. Our study suggests that the two-step TST is not sufficient to reliably rule out a booster response in all HCWs. These results are consistent with Kraut *et al.* [17] and Casas *et al.* [18] in suggesting an association between country of birth or history of previous BCG vaccination and a late boosting phenomenon after negative two-step TST at hire. Although the risk of TST conversion was significantly higher in the total population of HCWs (early and late conversion group) who perform nonclinical duties (i.e. research, administration work, housekeeping and food services), our study reported no significant difference in job description between the early and late conversion group. Other investigators have previously described TST conversion in similar nonclinical jobs [22–24].

This study indicates that early conversion among HCWs, even after negative results of two-step TST, can represent delayed boosting. Therefore, evaluation of conversion events, particularly those within the first 2 years of initial two-step testing, must consider that they could represent boosting rather than actual conversion. This understanding is helpful in determining how aggressive to be with contact tracing and other evaluations of such conversion events. In addition, in counselling of persons undergoing clinical evaluation due to a newly positive skin test, clinicians need an understanding that the cause of the newly positive test may not be a new exposure. This understanding allows a clinician to offer a more balanced discussion of the benefits and risks of latent TB treatment.

Despite the larger number of HCWs included in this study than in other studies, the number of TST converters was small because of low prevalence, which led to imprecise estimates. Additionally, the power of this study remains a limitation with a possibility of type II error (or of false-negative findings). Selection bias is a possibility since our data are derived from a low prevalence, primarily Caucasian population in the Midwest. However, a large proportion of our cohort were foreign born and we

believe that our results are likely generalizable to HCWs in facilities with low TB prevalence. Lastly, it is well known that nontuberculous mycobacteria infection can lead to false-positive TST [25]. The positive predictive value of TST (using QFT >1.11 as confirmatory test) was <20% in both early and late converters, suggesting non-TB or expanded BCG reactions. This is a known limitation of TST that should be considered when interpreting the test in HCWs.

Accreditation standards and state licensure of health care facilities mandate TB control standards. Occupational surveillance in low prevalence circumstances creates a quandary, due to the high risk of false-positive results of highly sensitive tests [26]. However, in these settings, tolerance for missing active transmission is exceedingly low. This quandary will continue to worsen as we again approach eradication of TB in some settings.

Among a population of HCWs in an area with low prevalence of TB, TST conversion overall is rare. Early conversions among HCWs, even after negative results of two-step TST, can be due to various nonoccupational factors, including delayed immune boosting, foreign birth and history of BCG vaccination. Therefore, we suggest that conversion may not always be caused by recent TB contact, and initial two-step TST at the start of employment may not be sufficient to identify the booster response in all HCWs.

Key points

- Two-step tuberculin skin testing is insufficient to account for all instances of boosting and may result in a delayed boosting response for health care workers.
- Early conversions among health care workers after negative two-step tuberculin skin test are less likely to be the result of workplace tuberculosis exposure and more likely to be associated with nonoccupational factors.
- Among a population of health care workers in an area with low prevalence of tuberculosis, tuberculin skin test conversion events are rare.

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Conflicts of interest

None declared.

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