CONCISE COMMUNICATION

False-Positive Tuberculin Skin Test Results Among Low-Risk Healthcare Workers Following Implementation of Fifty-Dose Vials of Purified Protein Derivative

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Following large declines in tuberculosis transmission the United States, large-scale screening programs targeting low-risk healthcare workers are increasingly a source of false-positive results. We report a large cluster of presumed false-positive tuberculin skin test results in healthcare workers following a change to 50-dose vials of Tubersol tuberculin.

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The Centers for Disease Control and Prevention (CDC) recommends annual tuberculosis (TB) screening for employees working at healthcare facilities with ≥200 beds that diagnose ≥6 cases of active TB disease annually.[1] However, little evidence suggests that current work at a US healthcare facility alone increases the risk of infection with *Mycobacterium tuberculosis*.[2,3] Testing low-risk individuals for latent TB infection (LTBI) increases the risk of false-positive results and is not recommended by diagnostic guidelines jointly issued by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA).[4] Here, we report a significant increase in presumed false-positive tuberculin skin test (TST) conversions among healthcare workers (HCWs) associated with changing from a 10-dose to a 50-dose vial of purified protein derivative (PPD).

METHODS

An increase in TST conversions among HCWs compared to prior years was reported by the Employee Health Service (EHS) at Grady Memorial Hospital in 2014 and 2015. The increase prompted an investigation by the Hospital Epidemiology and Infection Control Departments. Grady Memorial Hospital provided care to 65 and 57 cases of active TB disease in 2014 and 2015, respectively. In accordance with CDC guidelines, all HCWs at Grady Memorial Hospital are screened for TB infection at the time of hire (2-step testing is required at baseline) and annually with a TST using the Mantoux method.[4] Additionally, any HCWs exposed to a patient with pulmonary TB prior to the institution of airborne precautions are evaluated with a postexposure TST.[4] All positive TST results are followed up with a clinical exam and chest radiograph to evaluate for active TB disease.

We performed a retrospective chart review on all 34 HCWs with a TST conversion from 2014 and 2015 to determine whether any shared identifiable risk factors or common epidemiologic links. The HCWs with a TST conversion during this period were subsequently offered a Quantiferon Gold In-Tube Test (QFT) and/or a repeat TST using a 10-dose vial to further evaluate for LTBI. Statistical analyses were performed using R version 3.3.0 software (R Foundation for Statistical Computing, Vienna, Austria). Rates of TST conversion were compared between years using the Fisher exact test. Confidence intervals for annual conversion rates were calculated using a 2-tailed test for population proportion.

RESULTS

Of 9,279 tests performed on HCWs with at least 1 previously negative TST in 2014 and 2015, there were 34 TST conversions (0.37%; 95% confidence interval [CI], 0.26–0.52) compared to 16 TST conversions of 14,842 tests performed in 2012, 2013, and 2016 combined (0.11%; 95% CI, 0.06–0.18). This represented a greater than 3-fold increase in the TST conversion rate ($P < 0.001$) (Figure 1). Of 34 HCWs with a TST conversion from 2014 to 2015, 33 were documented in persons presenting for routine annual testing, while 1 HCW had a TST conversion following an identified TB exposure. All HCWs with a newly positive TST during this period were asymptomatic, and chest imaging findings were unremarkable (Table 1). Of these 34 employees, 20 were retested for LTBI with a QFT and/or TST using the 10-dose vial, and 16 (80%) had negative results.

The epidemiologic investigation revealed that of the 34 HCWs with a new TST conversion, 14 (41%) had job assignments with no patient contact. These HCWs worked in 20 different areas of the Grady Health System, and few shared the same job description or would have been expected to have contact with similar patients. None reported common epidemiologic links in the community, with the 34 affected HCWs listing home addresses in 26 different zip codes.

After failing to find evidence of unrecognized institutional TB transmission or shared community risk factors among the HCWs, we evaluated the TST screening protocol in the EHS to determine whether any protocol changes could account for the increase in TST conversions. This investigation revealed that the EHS started using 50-dose vials of PPD (Tubersol) for TST screening in the second half of 2013 due to a supply shortage of 10-dose vials. No changes in personnel placing and reading TSTs occurred. Positive TST results were seen with 8 lots of PPD and across multiple testing periods. At the end of October 2015, the EHS resumed the use of 10-dose vials, and the annual conversion rate in 2016 declined to 0.12%, which was similar to historic averages.

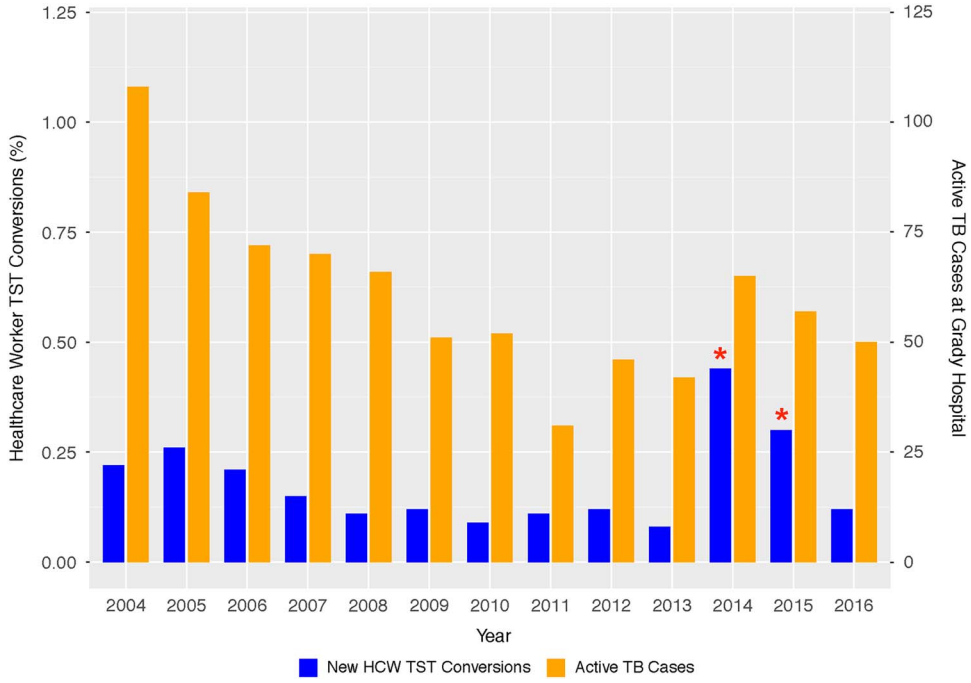

FIGURE 1. Proportion of healthcare workers with a new tuberculin skin test conversion and number of active tuberculosis cases diagnosed each year at Grady Memorial Hospital. NOTE. 50-dose vials of purified protein derivative were used to administer the tuberculin skin tests to healthcare workers at Grady Hospital for 12 months in 2014 and for 10 months in 2015.

DISCUSSION

We describe a significant increase in TST conversions among HCWs in the Grady Health System temporally associated with use of 50-dose vials of Tubersol tuberculin, most of which were presumed to be false-positive results. After switching back to 10-dose vials, TST conversion rates returned to the previous baseline rate. To our knowledge, this is the first report of an increase in TST conversions temporally associated with a change to larger-volume vials of PPD. Although an increase in TB transmission in the Grady Health System and/or surrounding community cannot be entirely excluded, we found no evidence to support occult TB transmission. Similarly, no evidence was found of increased exposure to environmental mycobacteria, which could also potentially lead to false-positive TST reactions. The mechanism for the increase remains unclear, but these results occurred with multiple lots of PPD and is thus unlikely to be a batch effect.

Larger areas of induration following TST administration using larger PPD vials has been reported[5] and could theoretically result from the properties of the vials themselves. There may be less adsorption of PPD in larger glass vials with less contact surface area between glass and solution.[6] Additionally, a vial containing more doses of PPD may have more exposure to air and spend more time at room temperature, both of which have been associated with reduced concentrations of preservative.[7] However, studies examining these factors are decades old, and it is unclear whether any observed differences in PPD potency had a measureable impact on human TST results.

Proponents of annual TB screening programs often cite their ability to recognize TB transmission not identified through other infection control programs. However, as infection control procedures in the United States have improved[8] and the incidence of TB in the United States has declined,[9] serial TB screening programs targeting low-risk HCWs have increasingly become a source of false-positive test results.[3] Annual screening for low-risk HCWs prevents active TB disease at an incremental cost of more than US$1.5 million per case prevented compared to testing only those with known TB exposure.[10] Here, we demonstrate that false-positive TST conversions can result in expenditures of hospital resources beyond the cost of a low-yield LTBI testing and treatment program.[3] An increase in false-positive results occuring over a short period of time in a population with a very low baseline rate of test conversions can give the appearance of institutional TB transmission, leading to unnecessary investigations by hospital epidemiology and infection control personnel.

This study shows the possibility of false-positive TST conversions when using 50-dose vials of Tubersol tuberculin, and our results suggest that using smaller vials may help limit false-positive results. These results also provide another demonstration of the potential pitfalls of serial TB screening in a low-risk population. When the prevalence of a disease in the

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TABLE 1. Characteristics of Employees With a Tuberculin Skin Test (TST) Conversion From 2014 and 2015

Characteristic	Positive TST 2014–2015 (n = 34), No. (%)[a]
Age, median y (IQR)	34 (27–41)
TST result	
10–14 mm	20 (59)
15–19 mm	10 (29)
≥20 mm	4 (12)
Negative chest radiograph	33 (97)[b]
Repeat latent TB testing	
Positive QuantiFERON	4 (12)
Negative QuantiFERON	12 (35)
Negative QuantiFERON and TST[c]	4 (12)
Negative TST[c]	4 (12)
Not Done	14 (41)
Patient contact	20 (59)
Known exposure to infectious TB case	1 (3)
No. of previous negative TST results, median (IQR)	3 (2–4.75)
Job description	
Resident nurse	3 (9)
Nurse assistant	8 (24)
Ancillary services	9 (26)
Paramedic	3 (9)
Administrative assistant	3 (9)
Student	2 (6)
Unit clerk	2 (6)
Other	4 (12)
Vial lot number	
C4515AA	8 (24)
C4546AA	7 (21)
C4585AA	2 (6)
C4513BB	2 (6)
Other	4 (12)
Unknown	11 (32)

NOTE. IQR, interquartile range; TB, tuberculosis; CT, computed tomography.
[a]Unless otherwise specified.
[b]One healthcare worker had an abnormal chest x-ray, but the chest CT was normal.
[c]Repeat tuberculin skin test (TST) was done using a 10-dose vial of purified protein derivative.

population is low (e.g., <1%) and the performance characteristics of screening tests are poor,[4] most positive tests are falsely positive.[3,10] Annual TB screening programs should be modified to eliminate automatic annual LTBI testing for low-risk, previously negative HCWs and could instead be structured to carefully evaluate individual exposure risks and personal health history.

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REFERENCES

1. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Recomm Rep* 2005;54:1–141.
2. Lambert LA, Pratt RH, Armstrong LR, Haddad MB. Tuberculosis among healthcare workers, United States, 1995–2007. *Infect Control Hosp Epidemiol* 2012;33:1126–1132.
3. Blumberg HM, Ernst JD. The challenge of latent TB infection. *JAMA* 2016;316:931–933.
4. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis* 2017;64:111–115.
5. Ruffino-Netto A, Kritski AL, Teixeira EG, Dos Santos-Loredo CC, De Souza DN, Trajman A. Influence of vial size on the results of the tuberculin test. *J Bras Pneumol* 2005;31:144–148.
6. Landi S, Held HR, Hauschild AH, Hilsheimer R. Adsorption of tuberculin PPD to glass and plastic surfaces. *Bull World Health Organ* 1966;35:593–602.
7. Held HR, Landi S. Loss of preservative from a tuberculin solution in rubber stoppered vials fastened with different seals. *J Biol Stand* 1985;13:211–219.
8. Blumberg HM, Watkins DL, Berschling JD, et al. Preventing the nosocomial transmission of tuberculosis. *Ann Intern Med* 1995;122:658–663.
9. Yuen CM, Kammerer JS, Marks K, Navin TR, France AM. Recent transmission of tuberculosis—United States, 2011–2014. *PloS One* 2016;11:e0153728.
10. Mullie GA, Schwartzman K, Zwerling A, N'Diaye DS. Revisiting annual screening for latent tuberculosis infection in healthcare workers: a cost-effectiveness analysis. *BMC Med* 2017;15:104.