



Screening Health Care Workers with Quantiferon-Gold: Possible False Negative Results in Individuals with High Pre-Test Probability of Latent Tuberculosis Infection

Nira Pollock, M.D., Ph.D.¹, Alex Sloutsky, Ph.D.², Swati Joshi, Ph.D.², Michael Wong, M.D.¹, and Edward Nardell, M.D.³

(Beth Israel Deaconess Medical Center (BIDMC), Boston, MA (1); Massachusetts State Laboratory Institute, Boston, MA (2); Brigham and Women's Hospital, Boston, MA (3))



Abstract

Introduction. Quantiferon-Gold (QFT-G) is FDA-approved for diagnosis of infection with *M. tuberculosis*. CDC guidelines have supported the use of QFT-G for routine TB screening of health care workers (HCW) and have suggested that QFT-G could be used in place of the PPD. Our goal was to evaluate the proportion of positive and negative QFT-G results in PPD-positive HCW at a large American medical center, particularly in those who were felt to be at highest clinical risk for having LTBI.

Methods. In October, 2006, BIDMC (Boston, MA) began routinely testing all PPD-positive (≥ 10 mm induration) new employees with QFT-G to aid in diagnosis of LTBI. To assess clinical risk factors for LTBI, Employee Health Service and Infectious Diseases Clinic records for all employees tested with QFT-G between October and December 2006 were reviewed. HCW who had at least two of the following risk factors were considered to be at high clinical risk for having LTBI: PPD ≥ 15 mm, abnormal chest X-ray consistent with old TB, regular work exposure (direct daily patient care, either currently or for an extended period in the past), long-term residence (≥ 5 years) in a highly TB-endemic area (incidence rate $\geq 40/100,000$ persons), patient-reported contact with an active TB case, or documented PPD conversion (≥ 10 mm increase). QFT-G results (interpreted per manufacturer's guidelines) for each individual were evaluated.

Results. Of the 143 PPD-positive HCW who received QFT-G testing, 26 (18%) tested positive, 115 (81%) tested negative, and 2 (1%) tested indeterminate. Of the 143 HCW tested, 115 had sufficient clinical information available to allow LTBI risk classification; 82 of the 115 were classified as high clinical risk for LTBI by our criteria. Of the 82 high LTBI risk individuals, 57 (70%) tested negative with QFT-G, suggesting that their QFT-G test results were potentially false negatives. 24 of the 115 clinically evaluable HCW (21%) tested positive by QFT-G, and 23/24 were in the high LTBI risk group (the remaining individual had a 24 mm PPD but spent much of his life in Iran, an area of intermediate TB endemicity (13/100,000) according to our resource table).

Conclusions. Though our results confirm our expectation of high specificity (and positive predictive value) of QFT-G in our HCW (in that 23/24 positive QFT-G tests were in those at high risk for LTBI), the high proportion of negative QFT-G tests in the group with highest clinical pre-test probability of LTBI (57/82, or 70%) raises concern about the sensitivity of the test for detection of LTBI in this population. It is possible that the test is reflecting those at high risk of reactivation rather than all those previously infected, but that interpretation of the results has yet to be proven. In the absence of a gold standard for this diagnosis, our data suggests that we should interpret a negative QFT-G result with some caution.

Introduction

Quantiferon-Gold (QFT-G) is a whole-blood interferon-gamma release assay which is FDA-approved for detection of *M. tuberculosis* infection. Recent CDC guidelines have suggested that this test could be used in place of the PPD for testing of health care workers (HCW) (1, 2). In October, 2006, Beth Israel Deaconess Medical Center (BIDMC, Boston, MA), in collaboration with the Massachusetts State Laboratory Institute TB laboratory, began routinely testing all PPD+ (≥ 10 mm induration) newly hired employees with QFT-G to aid in diagnosis of latent tuberculosis infection (LTBI). This algorithm was designed to take advantage of the high specificity of QFT-G to determine which PPD+ new employees needed further clinical follow-up and potential LTBI therapy. After three months of testing, a quality assurance review of all clinical and QFT-G data was performed. Our goal was to evaluate the proportion of positive and negative QFT-G results in our employee population, and in particular in those employees felt to be at the highest clinical risk for having LTBI.

Methods

Baseline PPD testing of all newly hired hospital employees was done per existing BIDMC guidelines, which in turn follow the recommendations of the CDC (2). All PPD+ (≥ 10 mm induration) new employees were tested with QFT-G. Employees who had received ≥ 1 month of therapy in the past for either active TB or LTBI were excluded from testing. Per existing BIDMC protocol, all PPD+ new employees received a chest X-ray and completed a basic TB screening questionnaire in Employee Health Clinic. A subset of the employees also had evaluation in Infectious Diseases Clinic (either before QFT-G testing became available, or after they tested positive by QFT-G). For the quality assurance (QA) review, clinical records (as available) for all HCW tested with QFT-G between October and December 2006 were reviewed to assess LTBI risk. HCW who had at least two of the following risk factors were considered to be at high clinical risk for having LTBI: PPD ≥ 15 mm, abnormal chest X-ray consistent with old TB, regular work exposure (direct daily patient care, either currently or for an extended period in the past), long-term residence (≥ 5 years) in a highly TB-endemic area (incidence rate $\geq 40/100,000$ persons) per World Health Organization data 2004-2006, as summarized by the Public Health Agency of Canada, http://www.phac-aspc.gc.ca/tbpc-latb/itir_e.html, patient-reported contact with an active TB case, or documented PPD conversion (≥ 10 mm increase). QFT-G results were interpreted per manufacturer's guidelines.

Results

Table 1. Quantiferon-Gold Test Results for PPD-positive New Hospital Employees

	Quantiferon-Gold Result		
	Positive	Negative	Indeterminate
A. All PPD-positive HCW ^a (n=143)	26 (18%)	115 (81%)	2 (1%)
B. HCW at high clinical risk for LTBI ^b (n=82)	23 (28%)	57 (70%)	2 (2%)

^aHCW: health care workers
^bLTBI: latent tuberculosis infection

A. Quantiferon-Gold (QFT-G) test results for 143 PPD+ (≥ 10 mm induration) newly-hired HCW tested as part of a new hospital TB screening algorithm. Approximately 93% reported a definite or probable history of BCG vaccination. B. Of the 143 HCW tested, 115 had sufficient clinical information available to allow LTBI risk classification; 82 of the 115 were classified as high clinical risk for LTBI by our criteria. Of these 82 high LTBI risk individuals, 57 (70%) tested negative, suggesting that their QFT-G test results could be false negatives. 24 of the 115 clinically evaluable HCW (21%) tested positive by QFT-G and 23/24 were in the high LTBI risk group (the remaining individual had a 24 mm PPD but spent much of his life in Iran, an area of intermediate TB endemicity (13/100,000) according to our resource table).

Table 2. Clinical Data for 57 PPD-positive, QFT-G negative HCW Meeting Criteria for High LTBI Risk

Age	PPD(mm)	PPD date	2-step?	BCG?	Birthplace	CXR	Criteria Used for Classification as High LTBI Risk
39	15	Aug-98	N	?	Ukraine	NI	Ukraine ≥ 5 y, PPD
23	17	Feb-04	Y	Y	India	NI	PPD, India ≥ 5 y, ? Conversion
45	24	7-99	N	Y	UK	NI	Contact, PPD, MD
46	15	Aug-06	N	Y	Mexico	NI	MD, PPD
39	15	Oct-06	N	Y	Japan	NI	PPD, MD
36	17	Jul-06	N	Y	England	NI	RN, PPD
35	15	Mar-06	Y	Y	Israel	RUL scarring	CXR, extensive travel, PPD
35	17	Sep-06	N	Y	Greece	NI	PPD, MD
31	7/2	7-97	N	Y	China	NI	China > 5 y, MD
35	15	Apr-06	N	Y	Russia	NI	MD, PPD, Russia > 5 y
38	16	2003	N	?	China	R apical pleural thickening	PPD, China > 5 y, MD, CXR
50	18	Sep-06	N	Y	China	NI	PPD, life in China
39	24	Sep-06	N	Y	Cape Verde	NI	Cape Verde > 5 y, ? Conversion, PPD
27	15	Sep-06	N	Y	Philippines	NI	Nurse, Philippines > 5 y
28	15	May-06	N	?	Taiwan	NI	PPD, Taiwan > 5 y
36	20	Oct-06	Y	Y	Pakistan	NI	PPD, MD, ? > 5 y Pakistan, ? Conversion
27	15	Oct-06	N	Y	Guatemala	Calcified granuloma RML	CXR, PPD
34	14	May-06	N	Y	Philippines	NI	Nurse, Philippines > 5 y
31	15	Aug-06	N	Y	Ireland	NI	Nurse, PPD
49	15	Jun-06	Y	Y	Portugal	NI	PPD, nurse
42	18	Dec-06	N	Y	China	NI	PPD, China > 5 y, MD, apparent conversion
39	16	Jun-06	N	Y	Hungary	NI	PPD, MD
23	20	Sep-06	N	Y	Haiti	NI	PPD, Haiti > 5 y
30	12	Oct-06	N	Y	England	NI	RN, conversion, contact in CCU 4/06
41	12	Sep-06	N	Y	China	NI	MD, China > 5 y
29	15	Sep-06	N	Y	Turkey	NI	ICU nurse, PPD
29	15	Aug-06	N	Y	China	NI	PPD, China > 5 y
23	20	2006	N	Y	Ghana	NI	PPD, Ghana > 5 y, new conversion from 2004
23	10	Jul-00	N	Y	Philippines	NI	RN, Philippines > 5 y
30	15	Nov-06	Y	Y	Russia	NI	Russia > 5 y, PPD, ? Conversion in past 7 mths
44	11	Nov-06	N	?	Thailand	RLL opacity, ?Calcified cartilage	Thailand > 5 y, apparent conversion
37	17	Jul-06	N	Y	Mexico	NI	Mexico > 5 y, PPD
37	15	Nov-06	Y	?	Dominican Rep	NI	Dominican Rep > 5 y, PPD
21	20	Dec-04	N	Y	India	NI	PPD, India > 5 y, can't do conversion
43	14	May-96	?N	Y	China	L hilar granulomatous calcification	CXR, China > 5 y, MD
31	23	Feb-03	N	Y	Pakistan	NI	PPD, MD, Pakistan > 5 y, conversion 2000-2001
25	15	Sep-06	N	Y	Romania	NI	PPD, MD, Romania > 5 y
35	15	Nov-06	N	Y	China	NI	PPD, China > 5 y, MD
46	17	Nov-06	N	N	Ukraine	NI	PPD, Ukraine > 5 y, ? conversion
56	15	Nov-06	Y	Y	India	NI	India > 5 y, PPD
30	14	Mar-06	N	Y	Norway	NI	nurse, apparent contact 2 y ago
53	15	Nov-06	N	N	USA (MA)	NI	PPD, conversion from 2005
40	17	Nov-06	Y	Y	China	NI	China > 5 y, PPD, ? Conversion from 2002
49	17	Jul-05	N	Y	Moldavia	NI	PPD, Moldavia > 5 y, ? Conversion past 2 years
33	18	Nov-06	N	Y	Japan	NI	Nurse, PPD, ? Conversion
43	25	1990	N	Y	Russia	NI	Russia > 5 y, PPD
50	17	Nov-06	N	Y	England	NI	PPD, MD, India > 5 y
26	11	2001	N	Y	Philippines	NI	Philippines, contact
30	>20	2003	N	Y	China	NI	China > 5 y, MD, contacts at work, PPD
30	16	Dec-06	N	Y	China	NI	MD, China > 5 y, PPD
31	20	Jul-06	N	Y	USA	NI	Conversion from 2005, NICU nurse
42	13	Jun-06	Y	Y	India	NI	MICU RN, India > 5 y
49	Hx pos	1994	?N	Y	Haiti	NI	MD, Haiti > 5 y
49	Hx pos	?	?N	Y	Dominican Rep	Small nodule RLL low granuloma	CXR, Dominican Rep > 5 y
30	18	Sep-06	N	?	USA	NI	RN, PPD, ?contact/conversion
35	12	Dec-06	N	Y	China	NI	MD, China > 5 y
34	18	Apr-06	N	Y	Japan	NI	PPD, MD

Conclusions

1. Our results confirm our expectation of high specificity (and positive predictive value) of QFT-G in our HCW, in that 96% of positive QFT-G tests were in those at high risk for LTBI; however,

2. We found a surprisingly high proportion of negative QFT-G tests in the group with highest clinical pre-test probability of LTBI (57/82, or 70%), raising concern about the sensitivity of the test for detection of LTBI in this population.

These data provide important insight into the performance of the QFT-G assay in our hospital population and have implication for other American hospitals planning to use this assay for HCW testing. In particular, our data suggest that it may be problematic to completely replace the PPD with QFT-G for testing of HCW, as a large proportion of individuals who would otherwise be considered to be at high risk for LTBI (and who thus would potentially merit treatment to protect the hospital community) will test negative with QFT-G. It is possible that the test results reflect those at high risk of reactivation rather than all those previously infected, but that interpretation of the results has yet to be proven. In the absence of a gold standard for this diagnosis, our data suggests that in this population we should interpret a negative QFT-G result with some caution.

References

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