

Tuberculin skin test and interferon- γ release assay in the detection of latent tuberculosis infection among Polish health care workers

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KEY WORDS

interferon- γ release assay, latent tuberculosis infection, tuberculin skin test

ABSTRACT

INTRODUCTION For many years, Poland has had a mandatory vaccination program against tuberculosis, which recommended repeated vaccinations from birth to adulthood. Therefore, the clinical value of the tuberculin skin test (TST) in diagnosing latent tuberculosis infection (LTBI) in Poland remains unclear.

OBJECTIVES We conducted a study on the usefulness of the TST and QuantiFERON®-TB test (QFT) for the evaluation of the prevalence and risk factors of LTBI among Polish health care workers.

PATIENTS AND METHODS The study group consisted of the Polish health care workers. TST and QFT were performed in each participant. The usefulness of TST and QFT was tested in relation to occupational risk factors.

RESULTS A total of 305 participants were included. A positive TST result was observed in 149 cases (48.9%) and a positive QFT result was observed only in 27 cases (8.9%). In the subgroup that declared contact with tuberculosis ($n = 44$), positive QFT and TST results were found in 20.5% and 63.3% cases, respectively. Past contact with tuberculosis was the only significant variable associated with a positive TST result. Independent variables associated with positive QFT results were older age, lower education level, longer period of work in health care, and previous contact with tuberculosis.

CONCLUSIONS The QFT has a higher diagnostic value than the TST in the assessment of LTBI in Polish health care workers.

INTRODUCTION Tuberculosis still remains one of the most common and, in many cases, lethal infectious diseases in the world. The humanitarian disaster caused by the Second World War led to a tremendously high increase in the mortality rate associated with tuberculosis, with an estimated notification rate in large cities amounting to between 400 and 450 deaths per 100,000 of the Polish citizens.¹ The Polish National Tuberculosis Register was established in 1957, and the first registered notification rate of tuberculosis amounted to 290.4 cases per 100,000 of the Polish citizens. Nowadays, Poland belongs to a group of countries with low incidence of tuberculosis. However, the percentage of latent tuberculosis infection (LTBI) in the Polish society still remains high. Nosocomial infections of the respiratory system are

still a serious clinical problem.^{2,3} In several studies, health care workers appear as a subpopulation with a higher risk of a tuberculosis infection than the remaining population without occupational exposure.³ Currently, 2 methods are available for the evaluation of LTBI: a tuberculin skin test (TST) and interferon- γ release assays (IGRAs). Some data suggest a strong discrepancy between the results of the TST and IGRAs.^{4,5} We decided to conduct a study on the usefulness of the TST and one of the IGRAs, QuantiFERON®-TB test (QFT), to evaluate the prevalence of LTBI among Polish health care workers.

PATIENTS AND METHODS The study was approved by the Ethics Committee of the Military Institute of Medicine (Warsaw, Poland). The study

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TABLE 1 Association between the tuberculin skin test and QuantiFERON®-TB test results

	Negative QFT result	Positive QFT result	Overall results	Kendall's <i>W</i>
all, n (%)				
TST positive	126 (41.31)	23 (7.54)	149 (48.85)	0.38
TST negative	152 (49.84)	4 (1.31)	156 (51.15)	
overall	278 (91.15)	27 (8.85)	305 (100)	
contact with tuberculosis, n (%)				
TST positive	20 (45.45)	8 (18.18)	28 (63.64)	0.39
TST negative	15 (34.09)	1 (2.27)	16 (36.36)	
overall	35 (79.55)	9 (20.45)	44 (100)	
without contact with tuberculosis, n (%)				
TST positive	106 (40.61)	15 (5.75)	121 (46.36)	0.37
TST negative	137 (52.49)	3 (1.15)	140 (53.64)	
overall	243 (93.10)	18 (6.90)	261 (100)	

Abbreviations: QFT – QuantiFERON®-TB test, TST – tuberculin skin test

group consisted of health care workers employed by the Military Institute of Medicine. A written informed consent, a completed questionnaire on the socio-economic, occupational, and medical data, as well as the history of the Bacillus Calmette–Guérin (BCG) vaccination were obtained from each participant. The exclusion criteria were as follows: a history of active tuberculosis, history of acute or chronic infection symptoms, any vaccination during the 6 weeks preceding the study, human immunodeficiency virus infection, pregnancy, treatment with steroids or with any other immunosuppressive drugs during the 12 weeks preceding the study, history of a gastrointestinal or lung resection, diabetes, sarcoidosis, rheumatoid arthritis, silicosis, any malignant disease, and chronic hepatic or renal failure.

Venous blood for QFT was collected from each subject prior to performing the TST. The blood was collected by qualified personnel into 2 heparinized tubes from the kit: one tube with the walls coated with ESAT-6, CFP-10, and TB7.7 antigens and the other containing pure physiological saline with phosphate buffer (negative control). The serum QFT was performed according to the manufacturer's instructions (Cellestis Ltd, Carnegie, Australia) with a cut-off value for the positive result of the interferon- γ concentration of 0.35 IU/ml and higher, as accepted in Poland.⁴ Blood for the QFT was taken by a well-trained nurse. The TST was performed with 2 tuberculin units (0.1 ml) of a purified protein derivative, RT23 (Statens Serum Institute, Copenhagen, Denmark). A TST reaction was scored as positive when the infiltration diameter was 10 mm and higher. The TST was performed and read 72 h later by 2 experienced public health nurses. If there was any inconsistency between the 2 readings with regard to the size of the post-tuberculin infiltration, an experienced pulmonologist was asked for his opinion and the final consensus was reached. Both the laboratory worker performing the QFT and the nurses conducting the TST were blinded to test results.

Based on the previous studies, participants were classified according to occupation, education, and the place of work. Four categories of occupation were distinguished for health care workers: physicians, nurses, auxiliary staff (e.g., therapists, housekeepers, laundry workers, pharmacists, and technicians), and administrative staff (e.g., administrative assistants, librarians, computer specialists, management).^{6–11} Three educational categories were also distinguished: university, secondary or technical, and primary. The place of work was defined as patient-care area (hospital wards, emergency room, radiology unit, etc.) and laboratory or nonpatient-care area (management, laundry, central supply, or any administrative department).

The *t* test was used for the assessment of quantitative variables. In the case of qualitative variables, the χ^2 and Fisher's exact tests (for small numbers) were used for comparisons between the subgroups. The multiple logistic regression model was used for the assessment of variables significantly associated with the risk of latent tuberculosis infection, and odds ratios were calculated for significant variables. The Kendall's coefficient of concordance (Kendall's *W*) was calculated for the results of the QFT and TST. Moreover, odds ratios were compared for the assessment of probability of positive QFT and TST results in participants who have had contact with tuberculosis in the past. The confidence interval was set at 95% for significant differences.

RESULTS A total of 320 health care workers working at the Military Institute of Medicine (about 1000 beds) agreed to participate in the study. We excluded 7 participants because of a history of active tuberculosis and the other 8 because they did not meet other inclusion criteria. Finally, 305 participants (243 women and 62 men) at a mean age of 42.6 \pm 10.8 years were recruited. Each participant was vaccinated in the past against tuberculosis in compliance with the mandatory Polish vaccination program.

TABLE 2 Association between tuberculin skin test and QuantiFERON®-TB test results and participant's age and time of work in health care

Variable	TST results		
	positive n= 149 (48.9%)	negative n= 156 (51.1%)	P value ^a
age, y	42.0 (10.4)	43.2 (11.2)	0.3
time of work in health care, y	17.1 (11.3)	17.1 (11.6)	0.9
time of work at the Military Institute of Medicine, y	11.0 (10.1)	11.9 (10.1)	0.4

Variable	QFT results		
	positive n= 27 (8.9%)	negative n= 278 (91.1%)	P value ^a
age, y	49.0	42.0	0.001 ^b
time of work in health care, y	23.0	16.5	0.004 ^b
time of work at the Military Institute of Medicine, y	15.7	11.0	0.02 ^b

Data are presented as mean \pm standard deviation.

a *t* test

b significant difference

Abbreviations: see [TABLE 1](#)

The average time of work in health care institutions was 17.1 ± 11.4 years, while the average time of work at the Military Institute of Medicine was 11.4 ± 10.1 years. There were no significant differences in the mean age and time of work in health care between men and women (42.2 ± 9.9 vs. 42.7 ± 11.03 years and 15.5 ± 10.1 vs. 17.5 ± 11.7 years, respectively). A positive TST result was found in 149 of the participants (48.9%) while a positive QFT was observed in 27 cases (8.9%) ([TABLE 1](#)). A negative QFT result was noted in 126 of 149 participants (84.6%) with a positive TST result, while a negative TST result was observed in 4 of 27 participants (14.8%) with a positive QFT result. The Kendall's *W* coefficient for both tests was low – 0.38 ([TABLE 1](#)). There were no significant differences in age, sex, and time of work in health care institutions between participants with positive and negative TST results, while participants with a positive QFT result were significantly older and worked longer in health care institutions than those with a negative QFT result ([TABLE 2](#)). There were no significant differences between people with a positive and negative TST result in relation to educational status, place of work in the hospital, and occupation ([TABLE 3](#)).

It was shown that workers with primary school education had a positive QFT result more often than those with secondary, technical, or university education ([TABLE 4](#)).

A positive QFT result was rarely observed among people working in nonpatient-care area or in laboratories ([TABLE 4](#)). The auxiliary staff had a significantly higher probability of a positive QFT result than the administrative staff, nurses or physicians, while nurses were significantly more threatened with LTBI than the administrative staff ([TABLE 4](#)). Of 305 participants, 44 reported a close contact with tuberculosis (38 cases of occupational exposure and 6 cases of family contact). Among them, there were 21 participants (47.7%) who declared contact with a sputum-positive case

of tuberculosis, 7 (15.9%) with a sputum-negative case, and 16 individuals (36.4%) did not know whether they had contact with a sputum-positive or sputum-negative case of tuberculosis ([TABLES 3](#) and [4](#)). A close contact with tuberculosis was declared by 12 of 52 doctors (23.1%), 23 of 116 nurses (19.8%), 8 of 72 auxiliary medical staff workers (11.1%), and 1 of 65 administrative staff workers (1.5%). Health care workers who declared contact with tuberculosis had positive TST and QFT results significantly more often ([TABLES 3](#) and [4](#)). The logistic regression model showed that the previous contact with tuberculosis was the only independent prognostic factor of a positive TST result, while significant independent predictors of positive results of QFT were older age of a participant, longer period of work in health care, lower level of education, and previous contact with tuberculosis ([TABLE 5](#)). The multiple logistic regression model showed the area of work in the hospital and occupation to be weak determinants and nonsignificant independent factors of a positive QFT result. Previous contact with tuberculosis was reported by 28 of 149 participants (18%) with a positive TST result and 9 of 27 participants (33.3%) with a positive QFT result. In the group of 44 participants who had contact with tuberculosis, TST and QFT results were positive in 28 (63.3%) and 44 participants (20.5%), respectively. In the group of people who had no contact with tuberculosis ($n = 261$), TST and QFT results were positive in 121 (46.3%) and 18 cases (6.90%), respectively ([TABLE 1](#)).

DISCUSSION In 1950, tuberculosis was responsible for 9.1% of all deaths in Poland.¹ The Polish National Tuberculosis Register was established in 1957, and the first recorded annual notification rate of tuberculosis amounted to 290.4 cases per 100,000 of inhabitants.^{1,4,12} In 2010, Poland reached a notification rate below 20 cases/100,000 of citizens for the first time and was

TABLE 3 Association between tuberculin skin test results and sex, past contact with tuberculosis, educational status, area of work, and occupation

Variable		TST results		P value ^a
		positive	negative	
sex	women	115 (47.3)	128 (52.7)	0.3
	men	34 (54.8)	28 (45.2)	
past contact with tuberculosis				
yes		28 (63.6)	16 (36.4)	yes vs. no, 0.03 ^b
sputum-positive		13 (61.9)	8 (38.1)	
sputum-negative		5 (71.4)	2 (28.6)	
not known		10 (62.5)	6 (37.5)	
no		121 (46.4)	140 (53.6)	
education				
1. university (n = 192)		101 (52.6)	91 (47.4)	1 vs. 2, 0.08
2. secondary or technical (n = 87)		36 (41.4)	51 (58.6)	1 vs. 3, 0.5
3. primary school (n = 26)		12 (46.2)	14 (53.8)	2 vs. 3, 0.7
area of work				
1. patient care (n = 191)		92 (48.2)	99 (51.8)	1 vs. 2, 0.8
2. nonpatient care (n = 79)		37(46.8)	42 (53.2)	1 vs. 3, 0.3
3. laboratory (n = 35)		20 (57.1)	15 (42.9)	2 vs. 3, 0.3
occupation				
1. physician (n = 52)		28 53.8)	24 (46.2)	1 vs. 2, 0.6
2. nurse (n = 116)		57 (49.1)	59 (50.9)	1 vs. 3, 0.2
3. auxiliary staff (n = 72)		30 (41.7)	42 (58.3)	1 vs. 4, 0.9
4. administrative staff (n = 65)		34 (52.3)	31 (47.7)	2 vs. 4, 0.7
				3 vs. 4, 0.2
				2 vs. 3, 0.3

Data are presented as number (percentage).

a χ^2 test

b significant differences

Abbreviations: see [TABLE 1](#)

among the European countries with low incidence of tuberculosis.¹² Despite the decreasing number of active tuberculosis cases, there are some data on the high prevalence of LTBI in the Polish population, especially estimated with the TST. During mass vaccinations against tuberculosis conducted as part of the International Tuberculosis Campaign from 1948 to 1951, it was estimated that a positive TST result was present in about 88% of the Polish teenagers.¹ From 1955 to 2005, there was an obligatory program of vaccination against tuberculosis with repeated vaccinations from birth to the age of 18 years. Such vaccination calendar could affect a false-positive TST result in the Polish population. Farhat et al.¹³ found that the TST rarely gives positive results at 10 years after vaccination in populations receiving a single vaccination immediately after birth, while a positive TST is present 10 years after vaccination 20 times more often if vaccinations were repeated after the first year of life. Nowadays, it is estimated that a positive TST result (with a cut-off level of 10 mm) is present in 45.8% to 50.3% of the Polish citizens.^{4,14} In our study, we observed positive TST results in 48.9% of the cases, while positive QFT results were present only in 8.9% of

the participants. It was a notably larger percentage of a positive TST result than that in the studies from Germany or United States (18.3% and 31.8% with a cut-off level of ³10 mm, respectively)^{15,16} and rather similar to the prevalence of TST positivity in low- and middle-income countries.³ The percentage of positive QFT results among health care workers in Poland is about 2.5-fold higher than that in other European countries with low incidence of tuberculosis.⁵ In our opinion, the substantial discrepancy between the percentage of positive TST and QFT results from a high percentage of postvaccination positive TST in the Polish society. For many years, the obligatory program of vaccination against tuberculosis in Poland consisted even of 5 BCG injections from birth to the age of 18 years depending on the size of the postvaccination scar after the first year of life and the diameter of post-tuberculin infiltrations at the age of 7, 12, and 18 years. Only since 2006, newborns in Poland are vaccinated only once, at birth, so most adults have a high probability of a postvaccination or “postboosting” positive TST result.

It is well known that health care workers represent a subpopulation threatened with LTBI owing

TABLE 4 Association between QuantiFERON test results and sex, past contact with tuberculosis, educational status, area of work, and occupation

Variable		QFT results		P value ^a
		positive	negative	
sex	women	21 (8.6)	222 (91.4)	0.48
	men	6 (9.7)	56 (90.3)	
past contact with tuberculosis				
yes		9 (20.5)	35 (79.5)	yes vs. no, 0.008 ^b
sputum-positive		4 (19.1)	17 (80.9)	
sputum-negative		4 (57.1)	3 (42.9)	
not known		1 (6.3)	15 (93.7)	
no		18 (6.9)	243 (93.1)	
education				
1. university (n = 192)		12 (6.3)	180 (93.8)	1 vs. 2, 0.3
2. secondary or technical (n = 87)		8 (9.2)	79 (90.8)	1 vs. 3, 0.003 ^b
3. primary school (n = 26)		7 (26.9)	19 (73.1)	2 vs. 3, 0.03 ^b
area of work				
3. patient care (n = 191)		19 (9.9)	17 (20.1)	1 vs. 2, 0.007 ^b
4. nonpatient care (n = 79)		1 (1.3)	(98.7)	1 vs. 3, 0.08
3. laboratory (n = 35)		7 (20.0)	28 (80.0)	2 vs. 3, 0.001 ^b
occupation				
1. physicians (n = 52)		3 (5.8)	49 (94.2)	1 vs. 2, 0.4
2. nurses (n = 116)		10 (8.6)	60106 (91.4)	1 vs. 3, 0.02 ^b
3. auxiliary staff (n = 72)		14 (19.4)	4358 (80.6)	1 vs. 4, 0.09
4. administrative staff (n = 65)		0 (0)	65 (100)	2 vs. 4, 0.01 ^b
				3 vs. 4, 0.0001 ^b
				2 vs. 3, 0.02 ^b

Data are presented as number (percentage).

a Fisher's exact test

b significant differences

Abbreviations: see [TABLE 1](#)

to occupational contact.³ We observed a positive TST result in 63.6% and positive QFT in 20.5% of the health care professionals who declared contact with tuberculosis in the past. The percentage of positive test results in the subgroup without contact with tuberculosis amounted to 46.4% and 6.9%, respectively, and was significantly lower than in contact people. The Kendall's *W* of the QFT and TST in the whole study group and subgroups (with and without contact with tuberculosis) was rather low, which shows that there is little concordance between the tests. In our opinion, low concordance between the tests is primarily the consequence of a high percentage of positive tuberculin reactions. Such overrepresentation of positive TST results in individuals who reported to have previous contact with tuberculosis or not seems to be related to a high number of postvaccination positive TST results in the Polish population. Studies conducted in low- and high-income countries, in which the only vaccination against tuberculosis was obligatory or recommended, revealed that a TST could be a valuable predictor of LTBI and that it correlates with different occupational and nonoccupational risk factors.^{3,6-11} For example, Roth et al.⁹ found that

a positive TST in the group of health care workers is strictly related to older age, lower educational level, work in the patient area, and nursing occupations.⁹ Similarly, according to the Australian data, a positive TST result was associated with more years of health care work, nursing, older age, or foreign birth. However, it was also stressed that the BCG vaccination is an independent predictive factor of TST positivity.¹⁰ In the logistic regression model, we did not find any significant relationship between positive TST results and such variables as age, occupation, level of education, or the place and period of work in the health care field. Only previous contact with tuberculosis significantly increased the probability of a positive result of TST.

On the other hand, positive QFT results were significantly related to some independent occupational and nonoccupational risk factors typical for the Polish health care workers surveyed, such as older age, lower educational level, period of work in the health care field, and previous contact with tuberculosis. Such results provide a more comprehensive explanation for better efficacy of the QFT compared with the TST in detecting LTBI in the Polish society. In

TABLE 5 Predictors of positive QuantiFERON®-TB test and tuberculin skin test results (multiple logistic regression model)

Variable	Dependent variable, QFT (negative vs. positive result) overall <i>P</i> value of the model, 0.003 ^a			Dependent variable, TST (negative vs. positive result) overall <i>P</i> value of the model, 0.24		
	odds ratio	95% CI	partial <i>P</i> value	odds ratio	95% CI	partial <i>P</i> value
age, y	0.86	0.77–0.97	0.01 ^a	0.97	0.94–1.2	0.3
period of work in health care, y	1.15	1.04–1.27	0.005 ^a	1.01	0.98–1.05	0.4
education						
primary school vs. secondary or technical vs. university	2.3	1.16–4.68	0.02 ^a	0.84	0.56–1.26	0.4
place of work						
nonpatient care vs. patient care vs. laboratory	1.6	0.6–4.4	0.4	1.2	0.8–1.8	0.4
occupation						
administrative staff vs. physicians vs. nurses vs. auxiliary staff	1.4	0.73–2.66	0.3	1.01	0.97–1.06	0.4
contact with tuberculosis						
yes vs. no	3.5	1.4–9.0	0.001 ^a	2.6	1.3–5.4	0.008 ^a

^a significant differences

Abbreviations: CI – confidence interval, others – see TABLE 1

summary, despite the fact that Poland is currently a low-incidence country, a high probability of a false-positive TST result due to postvaccination reactions makes the TST a worse diagnostic method for the evaluation of LTBI in the Polish society. These findings seem to be in contrast to those of the American Centers for Disease Control and Prevention guidelines, which do not differentiate clearly between the clinical usefulness of the TST and QFT.¹⁷ However, they are partially similar to the British, Canadian, or German recommendations, which stressed that the TST was less useful than the QFT for diagnosing contact with *Mycobacterium tuberculosis* in low-incidence countries even in a partially vaccinated population.^{18–20} The QFT seems to be a markedly more useful predictor of LTBI than the TST in Polish health care professionals.

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Skórny test tuberkulinowy i test z interferonem γ w wykrywaniu utajonego zakażenia prątkiem gruźlicy wśród pracowników polskiej opieki zdrowotnej

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SŁOWA KLUCZOWE

test z interferonem γ ,
utajone zakażenia
prątkiem gruźlicy,
tuberkulinowy test
skórny

STRESZCZENIE

WPROWADZENIE Przez wiele lat w Polsce obowiązywał kalendarz obligatoryjnych szczepień przeciwko gruźlicy, w którym rekomendowano wielokrotne wakcynacje od urodzenia do dorosłości. W związku z tym kliniczna wartość tuberkulinowego testu skórno (TTS) w wykrywaniu utajonego zakażenia prątkiem gruźlicy (*latent tuberculosis infection* – LTBI) w Polsce jest niejasna.

CELE Przeprowadzono badanie dotyczące przydatności TTS i testu QuantiFERON (QFT) do oceny występowania i czynników ryzyka LTBI wśród pracowników polskiej opieki zdrowotnej.

PACJENCI I METODY Grupę badaną stanowili pracownicy polskiej opieki zdrowotnej. U każdego uczestnika wykonano TTS i QFT. Badano przydatność TTS i QFT w odniesieniu do zawodowych czynników ryzyka.

WYNIKI Do badania włączono ogółem 305 osób. Dodatni wynik TTS stwierdzono w 149 przypadkach (48,9%), a dodatni wynik QFT zaobserwowano jedynie w 27 przypadkach (8,9%). W podgrupie, która zadeklarowała kontakt z gruźlicą ($n = 44$), dodatni wynik QFT i TTS stwierdzono odpowiednio w 20,5% i 63,3% przypadków. Kontakt z gruźlicą w przeszłości był jedynym istotnym czynnikiem związanym z dodatnim wynikiem TTS. Niezależnymi zmiennymi związanymi z dodatnim wynikiem QFT były: starszy wiek, niższy poziom wykształcenia, dłuższy staż pracy w opiece zdrowotnej i wcześniejszy kontakt z gruźlicą.

WNIOSKI QFT ma większą wartość diagnostyczną niż TTS w wykrywaniu LTBI wśród pracowników polskiej opieki zdrowotnej.

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