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ORIGINAL PAPER

QuantiFERON-TB Gold Plus Test in Diagnostics of Latent Tuberculosis Infection in Children Aged 1–14 in a Country with a Low Tuberculosis Incidence

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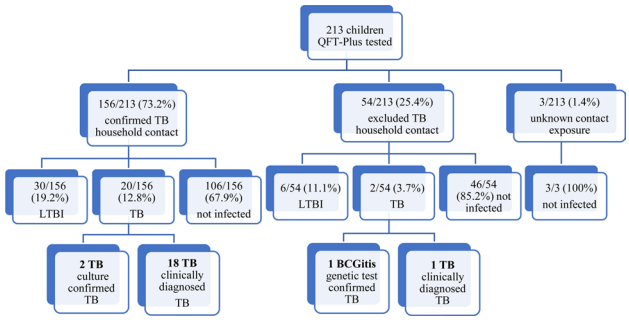
Abstract

The aim of the study was to evaluate the QuantiFERON-TB Gold Plus (QFT-Plus) test usability in the identification of latent tuberculosis infection (LTBI) in children and the determination of features associated with tuberculin skin test (TST) and QFT-Plus-positive results concerning LTBI. Two-hundred thirteen children aged 1–14 were screened for LTBI due to household contact with TB, suspected TB, or were qualified for biological therapy. The objective of this study was to evaluate the QFT-Plus affectivity as a diagnostic test in the absence of a gold standard (GS) test for the diagnosis of LTBI. The children were diagnosed with QFT-Plus, TST, and culture of TB. The QFT-Plus results were analyzed depending on the children's age, TST size, and type. In children aged 1–4, the positive predictive value of QFT-Plus was 1, the negative predictive value was 0.94, QFT-Plus sensitivity was 75%, and specificity was 100%. It was observed that in children aged 5–14 years, the level of agreement decreased to the substantial, i.e., 87.2%. Moreover, the negative predictive value was 0.83. QFT-Plus sensitivity was 64%, and specificity



was 100%. Statistical analysis of QFT-Plus and TST results showed substantial and almost perfect agreements. Our study suggests that QFT-Plus is helpful in a pediatric practice showing good sensitivity and specificity for LTBI. The BCG vaccine, infections, and concomitant morbidities do not affect QFT-Plus results.

K e y w o r d s: QuantiFERON-TB Gold Plus, tuberculin skin test, latent tuberculosis infection, tuberculosis, children

Introduction

The latest WHO data indicate that about 1 million children become infected with tuberculosis (TB) every year. In 2018, 233,000 children died due to this potentially possible to avoid and cure infectious disease (WHO 2018a; 2018b; 2019).

For most children the source of *Mycobacterium tuberculosis* infection is an adult immediate family member living in the same household: the closer and longer contact with a TB patient, the higher risk of *M. tuberculosis* infection. In small children, a threatening aspect of tuberculosis is its fast progression, usually in the first year of infection. It is contrary to adults, in whom LTBI may persist for many years without progression to active TB (Kampmann et al. 2018). The risk of tuberculosis infection is affected mainly by a child's age, and the youngest children are most at risk due to insufficient immune system mechanisms. It has been found that the two-year accumulated risk of tuberculosis in children younger than five years old was approximately 20% (Martinez et al. 2020). The WHO recommends isoniazid preventive treatment for at least six months in all children less than five years old who had recent contact with TB patients (WHO 2018a; 2018b; 2019; Sterling et al. 2020).

Tuberculosis incidence in Poland in 2019 was 13.9 and was lower by 2.8% compared to 2018, ranking Poland as a low TB burden country. Eighty-one TB cases in children under 14 years old were reported, which was

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1.5% of the total incidence. Bacteriological confirmation was obtained in 34.6% (Korzeniewska-Koseła 2020).

LTBI diagnostics should be performed if a child has been in close contact with a TB patient, was scheduled for immunosuppressive or anti-TNF-α treatment, was infected with HIV, or presented symptoms indicating tuberculosis. The TB incidence in pediatric population corresponds with the epidemiological TB situation in adults. The incidence of new cases in children indicates a recent transmission of mycobacteria in the environment and loss of control over the disease (Augustynowicz-Kopeć and Zwolska 2008).

For many years the only diagnostic tool to diagnose LTBI was TST, a simple and no expensive test. It is characterized by low specificity due to false-positive results in patients after Bacille Calmette-Guérin (BCG) vaccination or infected with nontuberculous mycobacteria (NTM) (Auguste et al. 2017). For 15 years, the Interferon-Gamma Release Assays (IGRA) have been used as a more specific alternative for TST.

QuantiFERON-TB Gold Plus (QFT-Plus; Qiagen, Hilden, Germany) is a fourth-generation test for IFN–γ measurement in two populations of CD4+ and CD8+ T-lymphocytes. It was designed to enhance the sensitivity of detecting immune responses to *M. tuberculosis* in children, HIV-infected persons, or patients recently infected with TB. So far, it has exhibited similar properties to QFT-GIT in adults (Qiagen 2018; Kay et al. 2019; Pourakbari et al. 2019; Primaturia et al. 2020). Although IGRA are more expensive and technically more demanding to perform, they require only one patient's visit. TST requires the measurement of induration after 48–72 hours. The second visit for TST evaluation ranged from 12% to 72% (Verhagen et al. 2014). It is particularly distressing when TST is used as an auxiliary tool for TB diagnosis since it may result in underdiagnosis.

Our analysis evaluated QFT-Plus action compared with TST in Polish children aged 1–14 at risk of *M. tuberculosis* infection, often in their household. The studies aimed to evaluate QFT-Plus usability in identifying LTBI in children and determine features associated with TST and QFT-Plus positive results regarding LTBI.

Experimental

Materials and Methods

The analysis involved 213 children aged 1–14 who underwent QFT-Plus between January 2018 and June 2020 at the Mazovian Treatment Centre of Tuberculosis and Lung Diseases in Otwock. The tests were conducted at the National Tuberculosis and Lung Diseases Research Institute in Warsaw. LTBI/TB diagnostics was performed due to household contact with TB patients, qualification for biological treatment, or as a part of the examination for tuberculosis with clinical or radiological symptoms. Demographic features, TB exposure, clinical history, and BCG vaccination status (confirmed by vaccination history review and scar presence) were recorded (Table I). The TST interpretation depended not only on the size and type of reaction but also on the child's age, the risk of contact with a TB person, BCG vaccination, immunological status, and comorbid diseases. Children's TST ≥ 10 mm was considered positive following national guidelines (Table II) (Augustynowicz-Kopeć et al. 2013; Bielecka et al. 2018a; 2018b).

Table I
Characteristics of the study population (n = 213 children).

Characteristics	Number (n = 213)	%
Sex		
Male	98	46
Female	115	54
Age (years)		
1–4	83	39
5–14	130	61
Nationality		
Polish	205	96
English	2	1
Danish	2	1
Ukrainian	4	2
BCG vaccination		
the second day of life	208	97.5
6 years	1	0.5
no BCG vaccination	4	2
Exposure to tuberculosis (children groups)		
1: confirmed TB household contact[a]	156	73.2
2: excluded TB household contact	54	25.4
3: unknown contact exposure	3	1.4

[a] – close contact: household contact, staying with a sputum culture-positive, high risk of LTBI/TB

Blood samples were incubated immediately after collection in a laboratory as specified by the QFT-Plus manufacturer's instructions. Serum was stored at 4°C following incubation until examination, and the tests were conducted 1–2 times weekly. QFT-Plus results (IU/ml) were interpreted following the manufacturer's criteria (Qiagen 2018). In case of radiological or clinical suspicion of tuberculosis diagnostic, the procedures were continued, including microscopy (auramine and Ziehl-Neelsen staining), PCR, and culture of the clinical specimens (gastric washing). LTBI was defined as the presence of a positive TST and/or QFT-Plus test and a normal chest X-ray in the absence of symptoms of tuberculosis. Active tuberculosis was

Table II
Interpretation criteria of a positive TST[a] in investigated TB contacts.

Risk of TB infection	Patient groups
High (close contact with a smear-positive TB patient)	
≥ 15 mm	Immunocompetent, BCG-vaccinated > 12 months of age
≥ 10 mm	Immunocompetent, non-BCG-vaccinated or BCG-vaccinated in the first year of life
≥ 5 mm	non-BCG-vaccinated
Low (other contacts of TB patient)	
≥ 15 mm	Immunocompetent, non-BCG-vaccinated or BCG-vaccinated in the first year of life, TST is not recommended for those vaccinated after 12 months of age
≥ 10 mm	HIV and other factors of increased risk of developing TB, regardless of BCG vaccination

[a] – Translation from "Recommendations for the management of tuberculosis in children – KOMPASS TB. Part 1: Tuberculosis prevention" of the Polish Society of Pediatric Pulmonology and National Consultant of Pediatric Pulmonology by the group of experts-TB Team (2018) (Bielecka et al. 2018a).

confirmed microbiologically and/or clinically. The data was analyzed using our modules based on the available Python libraries, particularly scipy.stats. The agreement of TST and QFT-Plus tests was calculated using Cohen's kappa coefficient.

Results

The study was performed on 213 children aged 1–14 years (median age: 5). Eighty-three children (39%) were under five years old. There were 98 boys (46%) and 115 girls (54%). The majority of children (205; 96%) were of the Polish nationality. There were 31 siblings of two persons and 6 siblings of three persons among children studied. The results were analyzed in three groups: 1) 156 children with a confirmed household contact with a TB patient (73.2%); 2) 54 children without c contact with a TB patient (25.4%) and 3) children who did not provide any data regarding the contact (1.4%). Two hundred and nine children (98%) were vaccinated with BCG (Table I).

Over 73% of children were screened for LTBI/TB due to a confirmed household contact with a TB infected person. The remaining children were tested because of an abnormal X-ray or CT images, cough, dyspnea, allergies, bronchial asthma, and rheumatic diseases (juvenile idiopathic arthritis, lichen nitidus, juvenile dermatomyositis, spherocytosis, or discoid lupus) often before being qualified for the biological treatment.

QFT-Plus results were obtained for 213 children. There were 42 (19.7%) positive, 170 (79.8%) negative and 1 (0.47%) indeterminate results. Simultaneously, 204 children underwent TST, and 87 children had parallel bacteriological TB tests (Table III).

In Group 1 of 156 children with a confirmed TB household contact, QFT-Plus test results were obtained for all children, TST results for 98% of them, and microbiological examinations were ordered for 66 (42.3%) subjects. The positive results were recorded for 41 QFT--Plus and 48 TST assays, and only two cases were confirmed microbiologically by culture. In 40 children, an agreement of QFT-Plus/TST positive results was observed, and for 105 children, the agreement between QFT-Plus/TST negative results was noted. For eight (5%) children, a disagreement between QFT and TST negative results was demonstrated. LTBI was diagnosed in 30 (19.2%) children, TB in 20 (12.18%), and for 106 (67.9%) children both LTBI and TB were excluded (Fig. 1, Table III). Twenty-seven per thirty LTBI children received prophylactic treatment, and for three per thirty children, the data were not available.

Among 20 TB children, the microbiological confirmation was obtained only for two subjects (10%); in 17 (85%), microbiological results were negative, and for one child (5%) received no tests. All 20 children obtained anti-tuberculosis treatment (Table III).

Group 2 consisted of 54 children, in whom household TB contacts were excluded, QFT-Plus results were obtained for all children, TST results were obtained for 48 (89%), and microbiological examinations for tuberculosis were ordered for 20 (37%) subjects. There was one QFT-Plus positive result, 13 positive TST results, and one microbiological confirmation of tuberculosis. Agreement of positive results of QFT-Plus/TST was observed for one child (2%), and of QFT-Plus/TST negative results for 35 children (73%). As many as for 12 children (25%) the results of QFT-Plus/TST assays did not agree. LTBI was diagnosed in six (11%) children, TB in two (4%), and LTBI/TB were excluded in 46 (85%) subjects.

In group 3, consisting of children with no data available on TB contacts, LTBI and TB were excluded for all subjects. The children had negative results fromboth tests. Only one of three children was ordered microbiological examinations that were negative (Fig. 1, Table III).

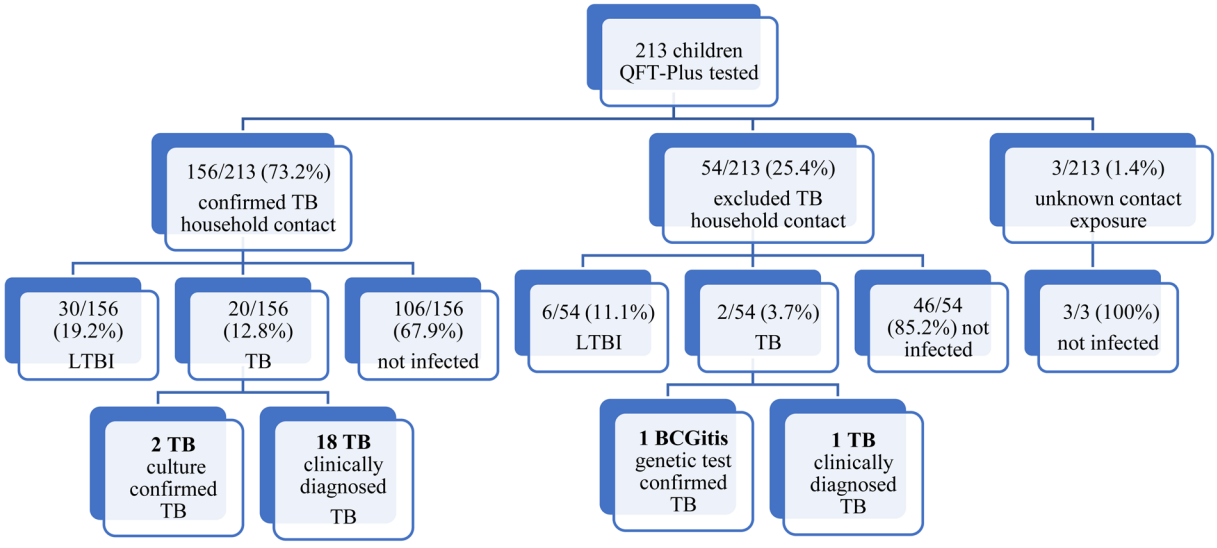

Fig. 1. Flow diagram of exposure to tuberculosis and final diagnosis.

LTBI was diagnosed in 17% (36/213) and TB in 10% (22/213) of children. Based on clinical studies, the diagnoses were confirmed as follows: pulmonary tuberculosis, tuberculosis of intrathoracic lymph nodes, primary respiratory tuberculosis with no records regarding bacteriological or histological confirmation, and tuberculous pleurisy for 18 subjects in the TB group. The microbiological confirmation of pulmo-

Table III
QFT-Plus, TST, and microbiological examinations results of all children (n = 213). Final diagnosis divided into three groups regarding the exposure to *Mycobacterium tuberculosis*.

Children n = 213		QFT-Plus			TST			Bacteriological tests[a]		
		+	–	Indeter-minate	+	–	No order	+	–	No order
Group 1 confirmed TB household contacn = 156	LTBI n = 30	24			24				23	1
			6		5	1			5	1
	TB n = 20	16			16			1	15	
		1					1	1		
			2		2				2	
			1			1				1
	no LTBITB n = 106		1		1					1
			2				2			2
			103			103			19	84
Group 2 excluded TB household contact n = 54	LTBI n = 6	1			1				1	
			3		3				3	
			2		2					2
	TB n = 2		1		1			1		
			1		1				1	
	no LTBI/TB n = 46		5		5				2	3
			5				5		1	4
			35			35			10	25
				1			1		1	
Group 3 no known contact exposure n = 3	no LTBI/TB n = 3		3			3			1	2
Total	213 (100%)	42 (19.7%)	170 (79.8%)	1 (0.47%)	61 (28.6%)	143 (67.1%)	9 (4.2%)	3 (1.4%)	84 (39.4%)	126 (59.1%)

[a] – bacterioscopy (auramine and Ziehl-Neelsen staining), molecular testing (PCR), and the sample culture (gastric washing)

Table IV
QFT-Plus and TST (mm) results in two age groups: 1–4 (n = 83) and 5–14 (n = 130) years old.

Children		QFT-Plus n = 213			TST n = 204			
Age	Number	+	–	Indeterminate	Number	(≥ 10 mm)	(< 10 mm)	No order
1–4	83	13 (15.7%)	70 (84.3%)	0	79	17 (21.5%)	62 (78.5%)	4
5–14	130	29 (22.3%)	100 (76.9%)	1 (0.77%)	125	45 (36%)	80 (64%)	5
Total	213	42 (19.7%)	170 (79.8%)	1 (0.46%)	204	62 (30.4%)	142 (69.6%)	9

nary tuberculosis was *M. tuberculosis* culture; BCG-itis was confirmed genetically for three children. For the remaining 155 (73%) children, both LTBI and TB were excluded (Fig. 1, Table III).

The correlation between QFT-Plus and TST results was analyzed. The final comparative analysis involved the results of 104 children because in 9/213 children from this group, TST was not performed, or tuberculin reaction was not measured.

The children were divided into two age groups: 1–4 (79/204) and 5–14 (125/204) years old. In the younger group, the positive QFT-Plus results were noted in 15.7% and negative results in 84.3% of children. In the 5–14 age group, there were 22.3% positive results, 76.9% negative, and 0.77% indeterminate ones. TST positive results accounted for a higher percentage than positive results of QFT-Plus; 21.5% *vs.* QFT-Plus 15.7% in the 1–4 years old group, respectively, and 36% *vs.* QFT-Plus 22.3% in older children, respectively (Table IV).

Statistical analysis of QFT-Plus and TST results of 204 children showed almost perfect (Kappa test 0.83) and substantial (Kappa test 0.7) agreement between both tests in the 1–4 and 5–14 years old groups, respectively.

In 4/79 children of the 1–4 years old group, there was a disagreement between QFT-Plus/TST results. LTBI and TB and post-vaccinal type III reactions were excluded from children. One child was diagnosed with BCG-itis. The number of the observed agreements between QFT-Plus and TST was 75/79 (94.94%). QFT-Plus results ensured good classification for 79 samples (Kappa test 0.83, 95% confidence interval 0.66–0.99). Assuming TST results as the reference, a positive predictive value of QFT-Plus was 1, a negative predictive value was 0.94, QFT-Plus sensitivity in identifying children with *M. tuberculosis* was 75%, and specificity was 100% (Table V).

When analyzing 125 children aged 5–14, the level of agreement decreased to substantial (Kappa test 0.7, 95% confidence interval 0.57–0.83) with 109/125 (87.2%) agreements, a negative predictive value of QFT-Plus was 0.83. QFT-Plus sensitivity was 64%, and specificity was 100%. For 16/125 (12.8%) children, a disagreement between negative results of QFT-Plus/TST was noted; 2/16 had a post-vaccinal reaction, 13/16 a post-infection reaction, and in one child, the type of reaction was not classified. LTBI was diagnosed in nine and TB in three cases, and LTBI and TB were excluded for four children (Table V). No disagreements of QFT-Plus/TST results were found. In the LTBI group, the results of QFT-Plus/TST agreed. Concerning QFT-Plus/TST results, an agreement was observed in 15 and disagreement in four children with TB.

When comparing QFT-Plus and TST results, it was observed that in the 1–4 age group, a 75% positive result of QFT-Plus correlated with very high ≥ 15 mm tuberculin reactions, always of I and II type, and never III or IV type, like the case of BCG. In the remaining 25% of children (3/12) with a positive QFT-Plus result, a 10–14 mm diameter reaction was noted, which was also considered positive. Only 6% of the children (4/67) with a negative QFT-Plus result had a 10–14 mm tuberculin reaction. In 63 children with a negative QFT-Plus result, the diameter of tuberculin reaction was 0–9 mm (Fig. 2).

In the 5–14 age group comprising125 children, all subjects with a positive QFT-Plus result had a positive result of TST; almost 76% (22/29) of children had tuberculin reaction diameter larger than 15 mm. Over 83% (80/96) of children had an agreement of QFT-Plus and TST negative results, and only in 8.3%, TST was of a 5–9 mm diameter. However, in about 17% (16/96) of children with negative results of QFT-Plus, TST was equal to or larger than 10 mm (Fig. 3).

Table V
Comparison of TST and QFT-Plus in two groups: 1–4 (n = 79) and 5–14 (n = 125) years old.

1–4 age (n = 79)				5–14 age (n = 125)			
QFT--Plus	TST			QFT--Plus	TST		
	+	–	Total		+	–	Total
+	12[a]	0	12	+	29[b]	0	29
–	4	63[a]	67	–	16	80[b]	96
Total	16	63	79	Total	45	80	125

[a] – Number of observed agreements between QFT-Plus and TST: 75[a] samples (94.94% of the observations).
Kappa test 0.83, 95% confidence interval 0.66 to 0.99.
[b] – Number of observed agreements between QFT-Plus and TST: 109[b] samples (87.2% of the observations).
Kappa test 0.7, 95% confidence interval 0.57 to 0.83.

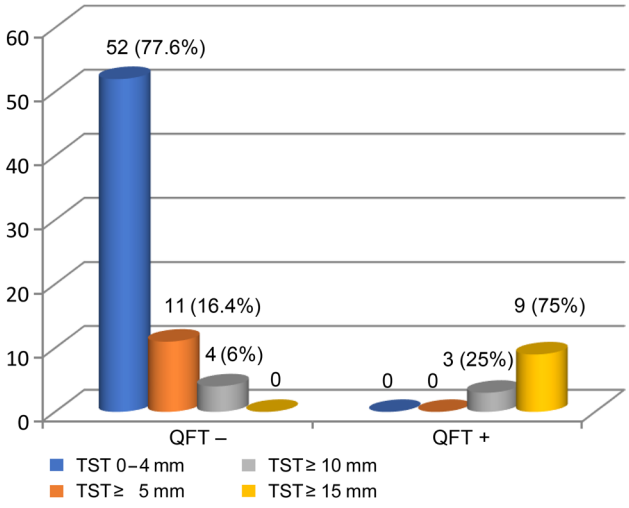

Fig. 3. Distribution of QFT-Plus and TST results depending on the size of induration (mm) in the group aged 5–14 years (n = 125).

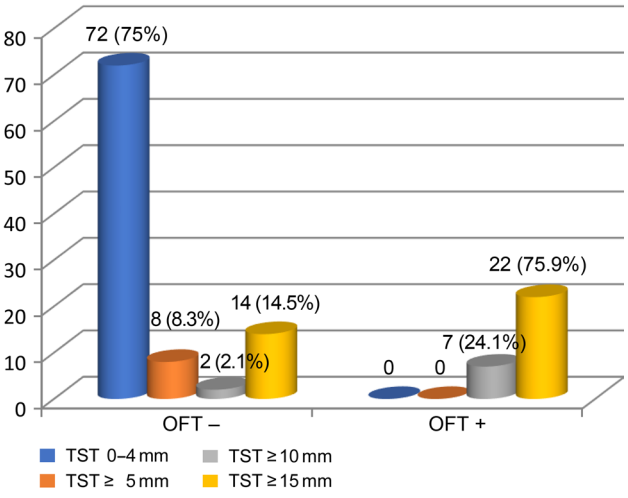

Fig. 2. Distribution of QFT-Plus and TST results depending on the size of induration (mm) in the group aged 1–4 years (n = 79).

Discussion

Our study evaluates the diagnostic application of the QFT-Plus test in Polish children aged 1–14. Quick diagnostics of LTBI before developing fully symptomatic disease is crucial to commence preventive treatment and inhibit disease transmission regarding TB household contacts, particularly in children under five years old (Benjumea-Bedoya et al. 2019). For LTBI diagnosis, WHO advocates the performance of TST or IGRA. Simultaneous performance of these tests might be considered as increasing the diagnostic sensitivity in children from TB high-risk group. Following a positive result of any of the above-mentioned tests, a chest X-ray must follow. Abnormalities indicating tuberculosis compel further diagnostic investigations that involve bacteriological tests (Bielecka et al. 2018a; 2018b). According to The Polish Respiratory Society, children with TB contact should be treated even if TST and IGRA results are negative (Augustynowicz-Kopeć et al. 2013). Over 73% of the analyzed group were children who remained in close household contact with TB patients. Over 19% of children were diagnosed with LTBI and 12% with active TB. Tuberculosis was bacteriologically confirmed only in three per 22 children. Therefore, it appears crucial to detect LTBI in children and prevent tuberculosis development. It is estimated that in children under five years old, active tuberculosis usually develops within two years of infection (Kozińska and Augustynowicz-Kopeć 2016). More numerous positive results were obtained in the analyzed group in TST: 61/204 (29.4%) than in IGRA: 41/204 (20.1%). The disagreement between the results of QFT-Plus and TST was noted in both age groups, but the vast majority of children had been BCG-vaccinated. In the group of 20 children with the described above disagreement, four subjects were found with TB, and 10 with LTBI. In the remaining six children, further diagnostics excluded LTBI/TB, and three children had immunological disorders. Antigens present in tuberculin or the low ability of small children to produce IFN-γ in response to bacilli antigens could have effected such a result distribution (Tebruegge et al. 2010; Borkowska et al. 2011; Seddon et al. 2016; Lombardi et al. 2018a; 2019b). The agreement of QFT-Plus and TST tests was 95% in the 1–4 age group and 87% in children aged 5–14 years old. In the study of Primaturia et al. (2020), the results were opposite, and the authors observed more numerous positive results of QFT-Plus than TST. The study group included children aged 5–18 years on immunosuppression and BCG-vaccinated. Kappa coefficient was only 0.345. QFT-Plus yielded more specific results than TST. This assay is based on ESAT-6 and CFP-10 antigenic proteins that have no cross-reactivity with a BCG vaccine (Borkowska et al. 2017). The authors claimed that the QFT-Plus test was more sensitive than TST for the population of children on immunosuppression. Benachinmardi et al. (2019) obtained more positive results with IGRA test (E TB-feron) than with TST, and the Kappa coefficient was 0.4753. Our results are similar to these from Belgium, the country with a low TB incidence: 8.6/100,000. Debulpaep et al. (2019) concluded that disagreement between the results of QFT-Plus and TST was related to TST false-positive results in subjects BCG-immunised recently. Seddon et al. (2016) observed that BCG vaccination affected TST response in children aged < 5 years with a negative IGRA result, but the effect disappeared with age. In Poland, to improve the sensitivity of LTBI diagnostics in children, two tests are used: TST and IGRA (QFT or T-SPOT.TB) (Augustynowicz-Kopeć et al. 2013; Bielecka et al. 2018a; 2018b). Importantly, Buonsenso et al. (2020) reported

that QFT-Plus could be particularly useful for the evaluation of children with suspected LTBI, giving only a 2.5% rate of indeterminate results in pediatric group. Therefore, QFT-Plus is effective in children and can be a good alternative to TST (Buonsenso et al. 2020). This rate is much lower than that reported from previous studies on QFT assay (Lombardi et al. 2018; 2019; Kay et al. 2019; Primaturia et al. 2020) but higher than in this study (0.47%; 1/213). Indeterminate results mostly concerned the children with acute infections (pneumonia) and did not occur in TB children (Lombardi et al. 2018; 2019). The young age of patients did not adversely affect IGRA response, and QFT-IT positive versus negative results were not age-related (Critselis et al. 2012). The study by Jenum et al. (2014) showed that malnourishment of children had a greater impact on indeterminate results than their age. In our studies, in which the vast majority of children were BCG-vaccinated, an increasing number of positive QFT-Plus results correlates with a growing value of a TST diameter. About 75% of positive QFT-Plus results were noted in children with the reaction exceeding 15 mm (Fig. 2 and 3). Analyzing the test results and assuming TST results as the reference and a 10 mm cut-off point, a negative predictive value in the youngest children was 0.94 and 0.83 in the group of older children aged 5–14. The sensitivity was 75% and 64%, respectively, with 100% specificity (Table V). Seddon et al. (2016) proved that BCG vaccination affected TST response in children aged < 5 years with a negative IGRA result, but not in older ones. In the case of BCG-vaccinated children, a 10 mm cut-off point ensured a high negative predictive value, and the positive predictive value increased in a correlation with a child's age (Seddon et al. 2016). This study evaluated fourth generation QFT-Plus, which was considered more sensitive for patients with decreased immunity (Hoffmann et al. 2016; Petruccioli et al. 2017; Qiagen 2018; Ryu et al. 2018; Pourakbari et al. 2019).

Our analysis has certain limitations. Firstly, due to the lack of a gold standard in LTBI diagnostics, TST was assumed to be the reference point. Such choice was not ideal in a BCG-vaccinated population, susceptible to NTM infections and concomitant morbidities. Secondly, there were no children under one year of age in the study group due to inconveniencies related to the collection of 4 ml of blood for the QFT-Plus test and immaturity of their immune system. Thirdly, there was a low number of relevant studies to compare the results with.

Conclusions

Our study suggests that the QuantiFERON-TB Gold Plus is helpful in pediatric practice, showing good sensitivity and specificity for LTBI. The age has not appeared to determine unspecified IGRA results, considering that our analyzed group did not include children younger than 12 months. The BCG vaccine, infections, and concomitant morbidities did not affect QFT-Plus results. Undoubtedly, QFT-Plus is a valuable tool and should be applied in diagnostics of LTBI in children aged 1–14, but the ultimate diagnosis needs to be based on a vast array of examinations and not only on a single test result.

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Conflict of interest
The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Literature

Auguste P, Tsertsvadze A, Pink J, Court R, McCarthy N, Sutcliffe P, Clarke A. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. BMC Infect Dis. 2017 Mar 9;17(1):200. https://doi.org/10.1186/s12879-017-2301-4

Augustynowicz-Kopeć E, Demkow U, Grzelewska-Rzymowska I, Korzeniewska-Koseła M, Langfort R, Michałowska-Mitczuk D, Rowińska-Zakrzewska E, Zielonka TM, Ziołkowski J, Zwolska Z. [Guidelines of Polish Respiratory Society concerning diagnosis, treatment and prevention of tuberculosis in adults and in children] (in Polish). Pneumonol Alergol Pol. 2013;81(4):323–379.

Augustynowicz-Kopeć E, Zwolska Z. [Epidemiology of tuberculosis in children and some problems in microbiological diagnostics] (in Polish). Post N Med. 2008;9:569–577.

Benachinmardi KK, Sangeetha S, Rao M, Prema R. Validation and clinical application of interferon-gamma release assay for diagnosis of latent tuberculosis infection in children. Int J Appl Basic Med Res. 2019 Oct–Dec;9(4):241–245. https://doi.org/10.4103/ijabmr.ijabmr_86_19

Benjumea-Bedoya D, Marín DM, Robledo J, Barrera LF, López L, del Corral H, Ferro BE, Villegas SL, Díaz ML, Rojas CA, et al. Risk of infection and disease progression in children exposed to tuberculosis at home, Colombia. Colomb Med (Cali). 2019 Dec 30; 50(4):261–274. https://doi.org/10.25100/cm.v50i4.4185

Bielecka T, Augustynowicz-Kopeć E, Gonerko P, Gruszczyński P, Korzeniewska-Koseła M, Krasińska M, Krenke K, Lange J, Pankowska A, Popielarz M, et al. Recommendations for the management of tuberculosis in children – KOMPASS TB. Part 1: Tuberculosis prevention. Adv Respir Med. 2018a;86(3):149–157. https://doi.org/10.5603/ARM.2018.0023

Bielecka T, Komorowska-Piotrowska A, Krenke K, Feleszko W, Kulus M. Is secretion of IFN-gamma in response to *Mycobacterium*

tuberculosis antigens in youngest children sufficient to play a role in TB diagnostics? Pediatr Pulmonol. 2018b Feb;53(2):181–188. https://doi.org/10.1002/ppul.23910

Borkowska D, Napiórkowska A, Brzezińska S, Kozińska M, Zabost A, Augustynowicz-Kopeć E. From latent tuberculosis infection to tuberculosis. News in diagnostics (QuantiFERON-Plus). Pol J Microbiol. 2017 Mar 30;66(1):5–8. https://doi.org/10.5604/17331331.1234987

Borkowska D, Zwolska Z, Michałowska-Mitczuk D, Korzeniewska-Koseła M, Zabost A, Napiórkowska A, Kozińska M, Brzezińska S, Augustynowicz-Kopeć E. [Interferon-gamma assay T-SPOT.TB for the diagnosis of latent tuberculosis infection] (in Polish). Pneumonol Alergol Pol. 2011;79(4):264–271.

Buonsenso D, Delogu G, Perricone C, Grossi R, Careddu A, De Maio F, Palucci I, Sanguinetti M, Valentini P, Sali M. Accuracy of the QuantiFERON-TB Gold Plus test in the diagnosis of *Mycobacterium tuberculosis* infection in children. J Clin Microbiol. 2020 May 26;58(6):e00272-20. https://doi.org/10.1128/JCM.00272-20

Critselis E, Amanatidou V, Syridou G, Spyridis NP, Mavrikou M, Papadopoulos NG, Tsolia MN. The effect of age on whole blood interferon-gamma release assay response among children investigated for latent tuberculosis infection. J Pediatr. 2012 Oct;161(4): 632–638. https://doi.org/10.1016/j.jpeds.2012.04.007

Debulpaep S, Corbière V, Levy J, Schelstraete P, Driessche KV, Mascart F, Mouchet F. Contribution of QuantiFERON-TB Gold-in-Tube to the diagnosis of *Mycobacterium tuberculosis* infection in young children in a low tb prevalence country. Front Pediatr. 2019 Jul 18;7:291. https://doi.org/10.3389/fped.2019.00291

Hoffmann H, Avsar K, Göres R, Mavi SC, Hofmann-Thiel S. Equal sensitivity of the new generation QuantiFERON-TB Gold plus in direct comparison with the previous test version QuantiFERON-TB Gold IT. Clin Microbiol Infect. 2016 Aug;22(8):701–703. https://doi.org/10.1016/j.cmi.2016.05.006

Jenum S, Selvam S, Mahelai D, Jesuraj N, Cárdenas V, Kenneth J, Hesseling AC, Doherty TM, Vaz M, Grewal HM. Influence of age and nutritional status on the performance of the tuberculin skin test and QuantiFERON-TB gold in-tube in young children evaluated for tuberculosis in Southern India. Pediatr Infect Dis J. 2014 Oct;33(10):e260–e269. https://doi.org/10.1097/inf.0000000000000399

Kampmann B, Seddon JA, Paton J, Nademi Z, Keane D, Williams B, Williams A, Liebeschutz S, Riddell A, Bernatoniene J, et al. Evaluating UK national guidance for screening of children for tuberculosis. A prospective multicenter study. Am J Respir Crit Care Med. 2018 Apr 15;197(8):1058–1064. https://doi.org/10.1164/rccm.201707-1487OC

Kay AW, DiNardo AR, Dlamini Q, Kahari J, Mndzebele T, Mtetwa G, Ustero P, Maphalala G, Mandalakas AM. Evaluation of the Quanti FERON-Tuberculosis Gold Plus assay in children with tuberculosis disease or following household exposure to tuberculosis. Am J Trop Med Hyg. 2019 Mar;100(3):540–543. https://doi.org/10.4269/ajtmh.18-0674

Korzeniewska-Koseła M. Tuberculosis and lung diseases in Poland in 2019. Warsaw (Poland): National Tuberculosis and Lung Diseases Research Institute; 2020.

Kozińska M, Augustynowicz-Kopeć E. Transmission of drug-resistant TB among family members. Pneumonol Alergol Pol. 2016; 84(5):271–277. https://doi.org/10.5603/PiAP.2016.0034

Lombardi G, Pellegrino MT, Denicolò A, Corsini I, Tadolini M, Bergamini BM, Meacci M, Garazzino S, Peracchi M, Lanari M, et al. QuantiFERON-TB performs better in children, including infants, than in adults with active tuberculosis: a multicenter study. J Clin Microbiol. 2019 Sep 24;57(10):e01048-19. https://doi.org/10.1128/jcm.01048-19

Lombardi G, Petrucci R, Corsini I, Bacchi Reggiani ML, Visciotti F, Bernardi F, Landini MP, Cazzato S, Dal Monte P. Quantitative analysis of gamma interferon release assay response in children with latent and active tuberculosis. J Clin Microbiol. 2018 Jan 24; 56(2):e01360-17. https://doi.org/10.1128/jcm.01360-17

Martinez L, Cords O, Horsburgh CR, Andrews JR; Pediatric TB Contact Studies Consortium. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet. 2020 Mar 21;395(10228):973–984. https://doi.org/10.1016/S0140-6736(20)30166-5

Petruccioli E, Vanini V, Chiacchio T, Cuzzi G, Cirillo D, Palmieri F, Ippolito G, Goletti D. Analytical evaluation of QuantiFERON-Plus and QuantiFERON-Gold In-tube assays in subjects with or without tuberculosis. Tuberculosis. 2017 Sep;106:38–43. https://doi.org/10.1016/j.tube.2017.06.002

Pourakbari B, Mamishi S, Benvari S, Mahmoudi S. Comparison of the QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube interferon-γ release assays: a systematic review and meta-analysis. Adv Med Sci. 2019 Sep;64(2):437–443. https://doi.org/10.1016/j.advms.2019.09.001

Primaturia C, Reniarti L, Nataprawira HMN. Comparison between the interferon γ release Assay-QuantiFERON Gold Plus (QFT-Plus)-and tuberculin skin test (TST) in the detection of tuberculosis infection in immunocompromised children. Pulm Med. 2020 May 10;2020:7159485. https://doi.org/10.1155/2020/7159485

Qiagen. QuantiFERON-TB Gold Plus (QFT-Plus) Package Insert. Germantown (USA): QIAGEN; 2018 [cited 2021 Jun 22]. Available from https://www.quantiferon.com/us/wp-content/uploads/sites/13/2018/09/QFT-Plus-ELISA-IFU-L1095849-R04.pdf

Ryu MR, Park MS, Cho EH, Jung CW, Kim K, Kim SJ, Oh HY, Huh W, Jang HR, Koh WJ, et al. Comparative evaluation of Quanti-FERON-TB gold in-tube and QuantiFERON-TB gold plus in the diagnosis of latent tuberculosis infection in immunocompromised patients. J Clin Microbiol. 2018 Oct 25;56(11):e00438-18. https://doi.org/10.1128/JCM.00438-18

Seddon JA, Paton J, Nademi Z, Keane D, Williams B, Williams A, Welch SB, Liebeschutz S, Riddell A, Bernatoniene J, et al. The impact of BCG vaccination on tuberculin skin test responses in children is age dependent: evidence to be considered when screening children for tuberculosis infection. Thorax. 2016 Oct;71(10):932–939. https://doi.org/10.1136/thoraxjnl-2015-207687

Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, Menzies D, Horsburgh CR Jr, Crane CM, Burgos M, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020 Feb 14;69(1):1–11. https://doi.org/10.15585/mmwr.rr6901a1

Tebruegge M, Connell T, Ritz N, Bryant PA, Curtis N. Discordance between TSTs and IFN-γ release assays: the role of NTM and the relevance of mycobacterial sensitins. Eur Respir J. 2010 Jul;36(1):214–215. https://doi.org/10.1183/09031936.00025510

Verhagen LM, Maes M, Villalba JA, d'Alessandro A, Perez Rodriguez L, España MF, Hermans PWM, de Waard JH. Agreement between QuantiFERON-TB Gold In-Tube and the tuberculin skin test and predictors of positive test results in Warao Amerindian pediatric tuberculosis contacts. BMC Infect Dis. 2014 Jul 11;14:383. https://doi.org/10.1186/1471-2334-14-383

WHO. Global tuberculosis report. Geneva (Switzerland): World Health Organization; 2019.

WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva (Switzerland): World Health Organization; 2018a.

WHO. Roadmap towards ending TB in children and adolescents. Geneva (Switzerland): World Health Organization; 2018b.