

Online Data Supplement

Performance of QuantiFERON-TB Gold Plus assays in paediatric tuberculosis – a multicentre PTBNET study

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Table E1. Underlying disorders in the 136 children with pre-existing comorbidities that were part of the study population.

Comorbidities	No. (percentage)
Respiratory disease	24 (17.6)
Cardiovascular disease	21 (15.4)
Neurological disease	20 (14.7)
Premature birth	17 (12.5)
Non-malignant hematological disease	9 (6.6)
Sickle cell disease	8 (5.9)
Malignant hematological disease	9 (6.6)
Rheumatological disease	13 (9.6)
Malnutrition	12 (8.8)
Gastrointestinal disease	10 (7.4)
Immune disorder ^a	57 (42.0)
Immunosuppressive treatment	20 (14.7)
Renal/urological disease	9 (6.6)
Diabetes mellitus	5 (3.7)
Solid organ tumor	4 (2.9)
Other medical conditions	32 (23.5)

^a Includes 8 children with human immunodeficiency virus infection

Table E2. Summary of the test performance of interferon-gamma release assays and the tuberculin skin test (at ≥ 5 mm and ≥ 10 mm cut-offs) in children with microbiologically-confirmed tuberculosis (n=488) according to demographics and clinical characteristics.

	No. of patients with positive test result / No. of patients tested Test sensitivity [95%CI]					QFT-Plus vs. QFT-GIT*	TST5 vs.			TST10 vs.		
	QFT-Plus n=182	QFT-GIT n=285	T-SPOT. <i>TB</i> n=33	TST10 n=268	TST5 n=268		QFT-Plus*	QFT-GIT*	T-SPOT. <i>TB</i> *	QFT-Plus*	QFT-GIT*	T-SPOT. <i>TB</i> *
Male	80/94 85.1 [79.0 – 93.1]	110/133 82.7 [76.3 – 89.1]	12/15 80.0 [51.9 – 95.7]	103/132 78.0 [71.0 – 85.1]	115/132 87.1 [81.4 – 92.8]	0.63	0.66	0.31	0.44	0.18	0.33	0.86
Female	79/88 89.8 [83.4 – 96.1]	133/152 87.5 [82.2 – 92.8]	12/18 66.7 [44.9 – 88.4]	110/136 80.9 [74.3 – 87.5]	122/136 89.7 [84.6 – 94.8]	0.59	0.98	0.55	0.006	0.07	0.12	0.16
Age <1 year	24/28 85.7 [72.8 – 98.7]	39/43 90.7 [82.0 – 99.4]	2/3 66.7 [9.0 – 99.0]	17/29 58.6 [40.7 – 76.5]	24/29 82.8 [69.0 – 96.5]	0.51	0.76	0.32	0.49	0.02	0.0013	0.78
Age 1-5 years	56/62 90.3 [83.0 – 97.7]	97/119 81.5 [74.5 – 88.5]	8/10 80.0 [55.2 – 97.0]	88/110 80.0 [72.5 – 87.5]	99/110 90.0 [84.4 – 95.6]	0.12	0.94	0.06	0.33	0.07	0.77	0.99
Age 6-10 years	28/32 87.5 [76.0 – 99.0]	26/30 86.7 [74.5 – 98.8]	6/7 85.7 [59.8 – 99.6]	35/45 77.8 [65.6 – 89.9]	37/45 82.2 [71.1 – 93.4]	0.92	0.53	0.60	0.82	0.27	0.33	0.63
Age >10 years	51/60 85.0 [77.7 – 95.2]	81/93 87.1 [80.3 – 93.9]	8/13 61.5 [35.1 – 88.0]	73/84 86.9 [79.7 – 94.1]	77/84 91.7 [85.8 – 97.6]	0.71	0.21	0.32	0.002	0.74	0.36	0.02
Respiratory TB	111/121 91.7 [86.8 – 96.6]	157/177 88.7 [84.0 – 93.4]	15/17 88.2 [72.9 – 98.5]	141/171 82.5 [76.8 – 88.2]	153/171 89.5 [84.9 – 94.1]	0.39	0.51	0.81	0.87	0.02	0.09	0.54
Miliary and/or CNS TB	15/19 78.9 [60.6 – 97.3]	35/50 70.0 [57.3 – 82.7]	6/10 60.0 [29.6 – 90.4]	16/36 44.4 [28.2 – 60.7]	26/36 72.2 [57.6 – 86.9]	0.45	0.58	0.82	0.45	0.014	0.017	0.38
Other disease focus †	33/42 78.6 [68.4 – 92.6]	51/58 87.9 [79.5 – 96.3]	3/6 50.0 [10.0 – 90.0]	56/61 91.8 [84.9 – 98.7]	58/61 95.1 [89.7 – 98.9]	0.21	0.010	0.16	0.0002	0.05	0.48	0.002
Pre-existing comorbidities	26/31 83.9 [70.9 – 96.8]	31/44 70.5 [57.0 – 83.9]	5/11 45.5 [16.0 – 74.9]	32/43 74.4 [61.4 – 87.5]	35/43 81.4 [69.8 – 93.0]	0.18	0.78	0.23	0.015	0.33	0.68	0.06
Immunocompromise (including HIV)	13/17 76.5 [56.3 – 96.6]	16/26 61.5 [42.8 – 80.2]	4/8 50.0 [15.4 – 84.6]	15/25 60.0 [40.8 – 79.2]	17/25 68.0 [49.7 – 86.3]	0.31	0.55	0.63	0.35	0.26	0.91	0.62

* Two-sided Wald Chi-square tests with Bonferroni correction ($\alpha=0.017$) to account for multiple comparisons.

† Other disease focus comprised: lymph node, osteoarticular, genitourinary, abdominal, and pericardial TB.

CNS = central nervous system; HIV = human immunodeficiency virus; TB = tuberculosis.

Table E3. Summary of the test performance of interferon-gamma release assays and the tuberculin skin test (at ≥ 10 mm and ≥ 5 mm cut-offs) in children with tuberculosis according to ethnic background.

	No. of patients with positive test result / No. of patients tested Test sensitivity [95%CI]					QFT-Plus vs. QFT-GIT*	TST5 vs.			TST10 vs.		
	QFT-Plus n=358	QFT-GIT n=600	T-SPOT. TB n=58	TST10 n=636	TST5 n=636		QFT-Plus*	QFT-GIT*	T-SPOT. TB*	QFT-Plus*	QFT-GIT*	T-SPOT. TB*
White / Caucasian	136/157 86.6 [80.3 - 91.5]	268/315 85.1 [80.6 - 88.8]	36/42 85.7 [71.5 - 94.6]	257/291 88.3 [84.1 - 91.7]	275/291 94.5 [91.2 - 96.8]	0.65	0.004	0.0001	0.03	0.61	0.24	0.63
Black / African American	36/39 92.3 [79.1 - 98.4]	40/47 85.1 [71.7 - 93.8]	3/8 37.5 [8.52 - 75.5]	35/39 89.7 [75.7 - 97.1]	36/39 92.3 [79.1 - 98.4]	0.29	1.00	0.29	0.0002	0.69	0.52	0.0006
Asian	26/31 83.8 [66.3 - 94.5]	37/38 97.3 [86.2 - 99.9]	2/2 100.0 [15.8 - 100.0]	33/39 84.6 [69.5 - 94.1]	36/39 92.3 [79.1 - 98.4]	0.05	0.27	0.32	0.28	0.93	0.05	0.54
Arab / Berber	25/31 80.6 [62.5 - 92.5]	17/19 89.4 [66.8 - 98.7]	1/2 50.0 [1.26 - 98.7]	26/33 78.7 [61.1 - 91.1]	27/33 81.8 [64.5 - 93.0]	0.41	0.91	0.46	0.27	0.85	0.33	0.35
Hispanic / Latin American	28/34 82.3 [65.5 - 93.2]	19/23 82.6 [61.2 - 95.1]	0/1 0 [0.00 - 97.5]	25/40 62.5 [45.8 - 77.3]	32/40 80 [64.3 - 90.9]	0.98	0.79	0.79	0.06	0.06	0.09	0.21

* Two-sided Wald Chi-square tests with Bonferroni correction ($\alpha=0.017$) to account for multiple comparisons.

Table E4. Comparison of retrospective and prospective study arms regarding demographics, BCG vaccination status, TB confirmation status, site of disease, and test performance of interferon-gamma release assays and the tuberculin skin test (at ≥ 10 mm and ≥ 5 mm cut-offs).

	Retrospective arm (n=607)	Prospective arm (n=394)	Statistical comparison *
Baseline characteristics			
Age (years), median (IQR)	5.5 (2.3 - 12.4)	5.8 (2.6 - 11.6)	0.72
Gender (male) [†]	329 (54.2)	208 (52.9)	0.70
Ethnic background			
White / Caucasian	385 (63.4)	120 (30.5)	<0.001
Black / African American	63 (10.4)	28 (7.1)	
Asian	49 (8.1)	21 (5.3)	
Arab / Berber	20 (3.3)	32 (8.1)	
Hispanic / Latin American	23 (3.8)	34 (8.6)	
Mixed race	4 (0.7)	16 (4.0)	
Unknown	63 (10.4)	143 (36.3)	
Pre-existing comorbidities [†]	81 (13.3)	55 (14.0)	0.77
Underlying immunocompromise			
HIV infection	5 (0.8)	3 (0.8)	0.88
Immunosuppressive treatment	12 (2.0)	8 (2.0)	
Other immune disorder	27 (4.6)	22 (5.8)	
BCG vaccination status			
BCG-vaccinated	138 (22.7)	97 (24.6)	0.79
BCG-unvaccinated	395 (65.1)	251 (63.7)	
Unknown	74 (12.2)	46 (11.7)	
Microbiologically-confirmed TB	316 (52.1)	172 (43.7)	0.009
Site of disease			
Respiratory	457 (75.3)	289 (73.4)	0.50
Miliary and/or CNS	55 (9.1)	33 (8.4)	
Other focus [†]	94 (15.5)	72 (18.3)	
Test sensitivity			
QFT-Plus	119/138 86.2 [80.0 - 92.0]	181/220 82.3 [76.6 - 87.1]	0.25
QFT-GIT	395/455 86.8 [83.3 - 89.7]	118/145 81.4 [74.1 - 87.4]	0.10
T-SPOT.TB	19/27 70.4 [49.8 - 86.2]	26/31 83.8 [66.3 - 94.5]	0.22
TST5	295/317 93.1 [89.7 - 95.6]	277/319 86.8 [82.6 - 90.3]	0.009
TST10	276/317 87.1 [82.8 - 90.5]	254/319 79.6 [74.8 - 83.9]	0.012
* P-values based on two-sided Wald Chi-square tests, except for the age comparison (Mann Whitney <i>U</i> test).			
[†] Other disease focus comprised: lymph node, osteoarticular, genitourinary, abdominal, and pericardial TB.			
BCG = bacille Calmette Guérin; CNS = central nervous system; HIV = human immunodeficiency virus; IQR = interquartile range; TB = tuberculosis; TST = tuberculin skin test.			

Table E5. Detailed breakdown of test results in patients with confirmed TB versus those with unconfirmed TB, and in patients with immunocompromise and those without known immunocompromise.

	Entire cohort n=1001	Confirmed TB n=488	Unconfirmed TB n=513	p	Immuno-compromise * n=77	No Immuno-compromise n= 924	p
QFT-Plus (n=358)	n=358	n=182	n=176		n=24	n=334	
Positive	300 (83.8)	159 (87.4)	141 (80.1)	0.06	18 (75.0)	282 (84.4)	0.22
Negative	47 (13.1)	17 (9.3)	30 (17.0)	0.03	5 (20.8)	42 (12.6)	0.22
Indeterminate	11 (3.1)	6 (3.3)	5 (2.8)	0.80	1 (4.2)	10 (3.0)	0.53
QFT-GIT (n=600)	n=600	n=285	n=315		n=47	n=553	
Positive	513 (85.5)	243 (85.3)	270 (85.7)	0.87	28 (59.6)	485 (87.7)	<0.0001
Negative	66 (11.0)	25 (8.8)	41 (13.0)	0.09	18 (38.3)	48 (8.7)	<0.0001
Indeterminate	21 (3.5)	17 (6.0)	4 (1.3)	0.003	1 (2.1)	20 (3.6)	<0.0001
T-SPOT. TB (n=58)	n=58	n=33	n=25		n=11	n=47	
Positive	45 (77.6)	24 (72.7)	21 (84.0)	0.30	5 (45.5)	40 (85.1)	0.010
Negative	8 (13.8)	6 (18.2)	2 (8.0)	0.26	5 (45.5)	3 (6.4)	0.004
Indeterminate	5 (8.6)	3 (9.1)	2 (8.0)	0.88	1 (9.1)	4 (8.5)	1.00
TST ≥10 mm (n=636)	n=636	n=268	n=368		n=44	n=592	
Positive	530 (83.3)	213 (79.5)	317 (86.1)	0.03	26 (59.1)	504 (85.1)	<0.0001
Negative	106 (16.7)	55 (20.5)	51 (13.9)	0.03	18 (40.9)	88 (14.9)	<0.0001
TST ≥5mm (n=636)	n=636	n=268	n=368		n=44	n=592	
Positive	572 (89.9)	237 (88.4)	335 (91.0)	0.28	30 (68.2)	542 (91.6)	<0.0001
Negative	64 (10.1)	31 (11.6)	33 (9.0)	0.28	14 (31.8)	50 (8.4)	<0.0001

* Immunocompromise includes children with immune disorder (n=57) and children receiving immunosuppressive treatment (n=20).

Table E6. Proportion of agreement and Cohen's Kappa coefficient between categorical tuberculin skin test results (≥ 5 mm and ≥ 10 mm cut-offs) and the categorical results of the three interferon-gamma release assays. Indeterminate assay results were excluded from this analysis.

	TST5		Agreement	Cohen's K	TST10		Agreement	Cohen's K
	Negative	Positive			Negative	Positive		
QFT-Plus								
Negative	16	19	87.3	0.462	20	15	83.7	0.429
Positive	9	177			21	165		
QFT-GIT								
Negative	16	29	87.6	0.343	19	26	84.1	0.301
Positive	17	309			33	293		
T-SPOT.TB								
Negative	1	2	88.6	0.271	1	2	68.6	0.025
Positive	2	30			9	23		