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Interferon-gamma release assays during follow-up of tuberculin skin test-positive contacts

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SUMMARY

SETTING: Following a large-scale contact investigation, individuals with a positive tuberculin skin test (TST) result were offered preventive tuberculosis treatment.

OBJECTIVE: To investigate the effect of isoniazid (INH) treatment and the effect of time on interferon gamma release assay (IGRA) results during follow-up.

DESIGN: TST-positive subjects (n = 122) detected during the large-scale contact investigation were included in the study. Blood was obtained every 6 months over 2 years to perform both tests.

RESULTS: Preventive INH treatment was completed by 36 of the 122 (29.5%) subjects, 71 (58.2%) were followed up with 6-monthly X-ray screening and 15 (12.3%) did not complete INH treatment. The overall percentage of individuals with a positive result remained stable during the 2 years, at approximately 45–50%, but individual responses varied over time. The majority of initially low IGRA results remained below the cut-off value, initially high IGRA results remained positive, while initially intermediate IGRA results were followed by more dynamic patterns.

CONCLUSION: This study showed a highly variable pattern of IGRA responses over time and suggests limited value for their use during follow-up of latently infected individuals. However, the significance of different kinetic patterns observed among subjects with intermediate initial IGRA results warrants further study.

KEY WORDS: follow-up; latent tuberculosis infection; T-SPOT.*TB*; QuantiFERON TB Gold In-Tube

AS *Mycobacterium tuberculosis*-specific interferon-gamma release assays (IGRAs) QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis Ltd, Carnegie, VIC, Australia) and T-SPOT.*TB* (Oxford Immunotec, Abingdon, UK) have become available, numerous studies using these tests have been published.[1–9] They have clarified the main characteristics of these assays, but have also given rise to new questions regarding their use in daily practice.[10–14] The main advantage of IGRA over the tuberculin skin test (TST) is the use of *M. tuberculosis*-specific antigens early secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) (and TB7.7 in QFT-GIT).[10,15,16] The TST, in contrast, uses purified protein derivative (PPD), which is a crude mixture of tuberculosis (TB) antigens and may cause a false-positive TST response due to vaccination with bacille Calmette-Guérin (BCG) or exposure to non-tuberculous mycobacteria (NTM). The lack of false-positive responses is the main advantage of IGRA. One of the unclear issues relates to their value for follow-up during treatment, as has been pointed out previously.[14,17] Thus far, reports on follow-up data during treatment mainly considered patients with active TB, and these have been inconsistent. Thus, it remains unclear whether IGRA can be used to monitor treatment success and what conversions and/or reversions signify.[18]

During a large-scale contact investigation in 2005, more than 400 non-BCG-vaccinated supermarket customers who had been exposed to a highly infectious employee had a positive TST result.[19,20] They were offered preventive treatment consisting of 6 months of isoniazid (INH) treatment or, in persons declining treatment, 2 years of radiographic follow-up as an alternative. In the present study, we aimed to follow up patients diagnosed with latent TB infection (LTBI; TST $\geqslant$ 15 mm) to compare the effect of INH treatment as well as the effect of time on IGRA results. Because most subjects had also participated in the large-scale contact investigation in 2005, pre-treatment IGRA results of these individuals were available.[19]

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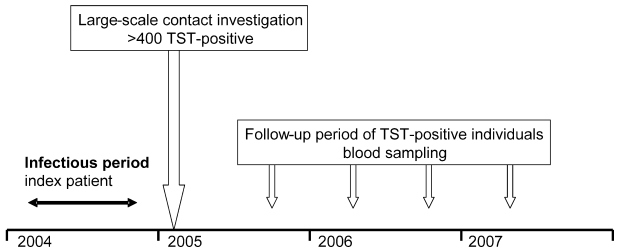

Figure 1 Time line of events of this study. TST = tuberculin skin test.

SUBJECTS AND METHODS

Study design

Individuals with a positive TST (defined as ⩾15 mm[19]) during the large-scale contact investigation in February 2005 were invited to participate in the present study. Blood samples were obtained half-yearly for 2 years starting September 2005 and ending April 2007. Time points are referred to as 0M (time of the previous study during the contact investigation), 6M (6 months later at the start of the present follow-up study), 12M, 18M and 24M (Figure 1). Participants completed a questionnaire regarding frequency of visits to the supermarket and potential exposure to NTM.

The Ethical Review Board of the Leiden University Medical Centre approved the study protocol (Protocol number P05.53). All participants provided informed consent.

Procedures

Blood was drawn at the Municipal Health Authority and transported to Diakonessenhuis in Utrecht for T-SPOT.*TB* and to Leiden University Medical Centre for QFT-GIT. Assays were performed following the manufacturers' instructions, as described in the previous study.[19]

Statistics

Agreement and disagreement between assays were investigated with kappa (κ) statistics and McNemar's test, respectively. Analysis of variance (ANOVA) for repeated measurements was used to determine whether individual IGRA responses varied over time. The paired *t*-test was used to compare results in the T-SPOT.*TB* panels for 6M and 24M. Two-sided *P* values <0.05 were considered statistically significant.

Table 1 Characteristics of the study population

Characteristics	INH		Follow-up chest radiography (n = 71) n (%)
	Completed (n = 36) n (%)	Stopped (n = 15) n (%)	
TST result, mm, mean ± SD	17.8 ± 3.9	19.1 ± 3.4	18.1 ± 5.1
Age, years, mean ± SD	36.9 ± 13.1	43.4 ± 11.8	47.2 ± 12.2
Male sex	9 (25.0)	3 (20.0)	40 (56.8)
Cumulative shopping time, range in min			
1–300	7 (21.2)	5 (38.5)	15 (27.7)
301–600	5 (15.2)	1 (7.7)	4 (7.4)
601–1200	9 (27.3)	1 (7.7)	14 (25.9)
1201–2400	10 (30.3)	6 (46.2)	14 (25.9)
>2400	2 (6.1)	0	7 (13.0)

INH = isoniazid; TST = tuberculin skin test, SD = standard deviation.

RESULTS

Study population

A total of 122 individuals participated in the study. Preventive INH treatment was completed by 36 (29.5%) individuals, 71 (58.2%) were followed up for 2 years by X-ray and 15 (12.3%) had started INH treatment but stopped prematurely because of side effects. When comparing the cumulative shopping time as measure of exposure to the index patient, there were no significant differences between INH-treated individuals and those with radiographic follow-up (P = 0.44). Table 1 shows the characteristics of individuals with and without INH treatment. As of September 2007, none of the participants of this study had developed active TB. The first blood sample was obtained at either 0M or 6M. Seventy-eight (63.9%) individuals

Table 2 IGRA results

Follow-up time points, months	Assay	Positive results/no. tested (%)			
		INH completed (n = 36)*	INH stopped (n = 15)*	Chest radiography (n = 71)*	All (N = 122)*
0	QFT	11/22 (50.0)	4/11 (36.4)	17/45 (37.8)	32/78 (41.0)
	TSPOT	12/22 (54.5)	5/10 (50.0)	21/45 (46.7)	38/77 (49.4)
6	QFT	11/29 (37.9)	7/15 (46.7)	30/65 (46.2)	48/109 (44.0)
	TSPOT	17/29 (58.6)	7/15 (46.7)	32/65 (49.2)	56/109 (51.4)
12	QFT	7/16 (43.8)	5/11 (45.4)	21/43 (48.8)	33/70 (47.1)
	TSPOT	9/16 (56.2)	6/11 (54.5)	20/42 (47.6)	35/69 (50.7)
24	QFT	11/27 (40.7)	5/11 (45.4)	24/49 (49.0)	40/87 (46.0)
	TSPOT	13/27 (48.1)	4/9 (44.4)	23/48 (47.9)	40/84 (47.6)

* Total number of participants in each group. The number of participants differs for each time point.
IGRA = interferon-gamma release assay; INH = isoniazid; QFT = QuantiFERON-TB Gold In-Tube; TSPOT = T-SPOT.*TB*.

Table 3 Individual QuantiFERON-TB Gold In-Tube and T-SPOT.*TB* results in all study participants

No.	Assay	Category*	0M	6M	12M	24M	No.	Assay	Category*	0M	6M	12 M	24 M
1	QFT-GIT	CN	Negative −0.01		Negative 0.00	Negative 0.00	31	QFT-GIT	CN	Negative −0.02	Negative −0.01	Negative −0.01	Negative 0.01
	T-SPOT.*TB*	CN	Negative 1		Negative 0	Negative 2		T-SPOT.*TB*	CN	Negative 0	Negative 0	Negative 0	Negative 2
2	QFT-GIT	CN	Negative −0.01	Negative 0.00	Negative −0.02	Negative 0.00	32	QFT-GIT	CP		Positive 1.45	Positive 1.74	Positive 5.67
	T-SPOT.*TB*	CN	Negative 5	Negative 1	Negative 0	Negative 0		T-SPOT.*TB*	Variable‡		Positive 45	Negative 3	Positive 60
3	QFT-GIT	Reversion†		Positive 1.44	Negative 0.12		33	QFT-GIT	CN	Negative 0.04	Negative 0.10	Negative 0.00	Negative −0.06
	T-SPOT.*TB*	CP		Positive 30	Positive 11			T-SPOT.*TB*	CN	Negative 0	Negative 0	Negative 0	Negative 1
4	QFT-GIT	CP	Positive 2.99	Positive 2.60		Positive 6.75	34	QFT-GIT	CN	Negative −0.09	Negative −0.04		Negative 0.01
	T-SPOT.*TB*	CP	Positive 25	Positive 40		Positive 13		T-SPOT.*TB*	CN	Negative 0	Negative 0		Negative 0
5	QFT-GIT	CN	Negative −0.18		Negative 0.02		35	QFT-GIT	CP		Positive 10	Positive 10	
	T-SPOT.*TB*	CN	Negative 2		Negative 1			T-SPOT.*TB*	CP		Positive 100	Positive 100	
6	QFT-GIT	Reversion	Positive 0.63		Negative 0.16	Negative 0.16	36	QFT-GIT	CN	Negative −0.01	Negative 0.01		Negative 0.01
	T-SPOT.*TB*	Reversion	Positive 9		Positive 8	Negative 2		T-SPOT.*TB*	CN	Negative 0	Negative 0		Negative 0
7	QFT-GIT	Conversion§	Negative 0.15		Positive 0.53	Positive 0.61	37	QFT-GIT	Reversion	Positive 0.45	Negative 0.30		Negative 0.13
	T-SPOT.*TB*	Conversion	Negative 1		Positive 8	Positive 6		T-SPOT.*TB*	Variable	Positive 14	Negative 2		Positive 9
8	QFT-GIT	CN	Negative −0.01	Negative 0.00			38	QFT-GIT	CP	Positive 1.25	Positive 0.49	Positive 0.76	Positive 0.97
	T-SPOT.*TB*	CN	Negative 0	Negative 0				T-SPOT.*TB*	CP	Positive 19	Positive 26	Positive 19	Positive 24
9	QFT-GIT	CN		Negative −0.03	Negative 0.04	Negative 0.05	39	QFT-GIT	CP		Positive 2.42		Positive 2.36
	T-SPOT.*TB*	CN		Negative 0	Negative 0	Negative 2		T-SPOT.*TB*	CP		Positive 39		Positive 16
10	QFT-GIT	CN	Negative 0.00	Negative 0.01		Negative −0.01	40	QFT-GIT	CN	Negative 0.01	Negative 0.06		Negative 0.03
	T-SPOT.*TB*	CN	Negative 1	Negative 3		Negative 0		T-SPOT.*TB*	Reversion	Positive 13	Positive 14		Negative 2
11	QFT-GIT	Conversion	Negative 0.22	Negative 0.32		Positive 0.67	41	QFT-GIT	CP	Positive 2.43	Positive 8.95	Positive 1.80	Positive 2.12
	T-SPOT.*TB*	CP	Positive 27	Positive 38		Positive 29		T-SPOT.*TB*	Conversion	Negative 0	Positive 63	Positive 16	Positive 22
12	QFT-GIT	CP	Positive 0.38			Positive 1.83	42	QFT-GIT	CN	Negative −0.01	Negative −0.02	Negative 0.00	Negative 0.01
	T-SPOT.*TB*	CP	Positive 16			Positive 42		T-SPOT.*TB*	CN	Negative 0	Negative 0	Negative 0	Negative 0
13	QFT-GIT	No FU			Positive 4.71		43	QFT-GIT	CN		Negative −0.02		Negative 0.03
	T-SPOT.*TB*	No FU			Positive 59			T-SPOT.*TB*	CN		Negative 0		Negative 0
14	QFT-GIT	CN	Negative 0.11	Negative 0.05		Negative 0.04	44	QFT-GIT	CP	Positive 0.86	Positive 2.23	Positive 1.54	Positive 3.03
	T-SPOT.*TB*	Reversion	Positive 12	Negative 4		Negative 3		T-SPOT.*TB*	CP	Positive 33	Positive 42	Positive 40	Positive 21
15	QFT-GIT	CP	Positive 3.16		Positive 3.81		45	QFT-GIT	CP	Positive 3.69	Positive 10	Positive 2.67	Positive 2.57
	T-SPOT.*TB*	Reversion	Positive 67		Negative 2			T-SPOT.*TB*	CP	Positive 58	Positive 47	Positive 14	Positive 47
16	QFT-GIT	CP	Positive 0.72	Positive 0.62		Positive 0.53	46	QFT-GIT	CP	Positive 9.73	Positive 10		
	T-SPOT.*TB*	CP	Positive 13	Positive 50				T-SPOT.*TB*	CP	Positive 42	Positive 83		
17	QFT-GIT	CP	Positive 5.78	Positive 10	Positive 10	Positive 10	47	QFT-GIT	Variable	Negative 0.11	Positive 0.56	Negative 0.05	Negative 0.09
	T-SPOT.*TB*	CP	Positive 162	Positive 72	Positive 46	Positive 56		T-SPOT.*TB*	Variable	Negative 5	Positive 9	Negative 5	Positive 7
18	QFT-GIT	CN	Negative 0.03	Negative 0.23		Negative 0.04	48	QFT-GIT	CN	Negative 0.02	Negative 0.06	Negative 0.02	Negative 0.05
	T-SPOT.*TB*	CN	Negative 1	Negative 0		Negative 1		T-SPOT.*TB*	CN	Negative 1	Negative 0	Negative 0	Negative 0
19	QFT-GIT	CP	Positive 1.98		Positive 4.83		49	QFT-GIT	CP		Positive 10	Positive 10	Positive 10
	T-SPOT.*TB*	CP	Positive 69		Positive 56			T-SPOT.*TB*	CP		Positive 100	Positive 92	Positive 100
20	QFT-GIT	CP	Positive 10	Positive 10	Positive 10	Positive 10	50	QFT-GIT	CN	Negative −0.06	Negative 0.01		Negative 0.02
	T-SPOT.*TB*	CP	Positive 95	Positive 15	Positive 44	Positive 100		T-SPOT.*TB*	CN	Negative 1	Negative 0		Negative −2
21	QFT-GIT	CP		Positive 10	Positive 10	Positive 10	51¶	QFT-GIT	CN		Negative −0.01		
	T-SPOT.*TB*	CP		Positive 63	Positive 75	Positive 100		T-SPOT.*TB*	CN		Negative 0		
22	QFT-GIT	CP			Positive 0.84	Positive 0.49	52	QFT-GIT	CN	Negative 0.01	Negative 0	Negative 0.19	
	T-SPOT.*TB*	CP			Positive 27	Positive 24		T-SPOT.*TB*	CN	Negative 0	Negative 0	Negative −1	
23¶	QFT-GIT	CN			Negative −0.01		53	QFT-GIT	CN		Negative −0.03		Negative 0.00
	T-SPOT.*TB*	CN			Negative 0			T-SPOT.*TB*	CN		Negative 0		Negative 0
24	QFT-GIT	CN	Negative 0.01	Negative 0.00			54	QFT-GIT	CN		Negative 0.15	Negative 0.03	Negative 0.02
	T-SPOT.*TB*	CN	Negative 1	Negative 0				T-SPOT.*TB*	CP		Positive 19	Positive 17	Positive 16
25	QFT-GIT	Conversion	Negative 0.25	Positive 1.27	Positive 0.67	Positive 2.13	55	QFT-GIT	CN		Negative −0.30		Negative −0.01
	T-SPOT.*TB*	CP	Positive 28	Positive 28	Positive 21	Positive 22		T-SPOT.*TB*	CN		Negative 0		Negative 0
26¶	QFT-GIT	CN			Negative 0.04		56	QFT-GIT	CN	Negative −0.02	Negative −0.04	Negative 0.02	
	T-SPOT.*TB*	Conversion			Negative 1			T-SPOT.*TB*	Conversion	Negative 1	Negative 0	Positive 10	
27	QFT-GIT	CN	Negative −0.03	Negative 0.02	Negative 0.02	Negative −0.01	57	QFT-GIT	CN	Negative −0.01	Negative −0.01	Negative 0.03	Negative 0.01
	T-SPOT.*TB*	Reversion	Positive 16	Negative 0	Negative 2	Negative 0		T-SPOT.*TB*	CN	Negative 0	Negative 0	Negative 0	Negative −1
28¶	QFT-GIT	CN		Negative −0.03			58	QFT-GIT	CP	Positive 0.38	Positive 4.09	Positive 10	Positive 1.47
	T-SPOT.*TB*	CN		Negative 0				T-SPOT.*TB*	CP	Positive 110	Positive 60	Positive 31	Positive 41
29	QFT-GIT	CP	Positive 1.65	Positive 1.42	Positive 0.44	Positive 0.66	59	QFT-GIT	CP		Positive 1.88	Positive 2.71	
	T-SPOT.*TB*	CP	Positive 20	Positive 40	Positive 7	Positive 46		T-SPOT.*TB*	CP		Positive 65	Positive 7	
30	QFT-GIT	CN		Negative 0.01		Negative 0.00	60	QFT-GIT	CP	Positive 3.98	Positive 3.34		Positive 8.14
	T-SPOT.*TB*	CN		Negative 0		Negative 0		T-SPOT.*TB*	CP	Positive 32	Positive 72		Positive 55

61	QFT-GIT	CP	Positive	7.46	Positive	10	Positive	3.19			92	QFT-GIT	CN	Negative	0.06	Negative	−0.03			
	T-SPOT.*TB*	CP	Positive	13	Positive	72	Positive	32				T-SPOT.*TB*	CN	Negative	1	Negative	1			
62	QFT-GIT	Reversion			Positive	0.35			Negative	0.05	93	QFT-GIT	CN	Negative	−0.01	Negative	0.02			
	T-SPOT.*TB*	CN			Negative	4			Negative	0		T-SPOT.*TB*	CN	Negative	0	Negative	0			
63	QFT-GIT	CP	Positive	0.35	Positive	0.65	Positive	0.45	Positive	0.43	94	QFT-GIT	CN	Negative	0.02	Negative	−0.04			Negative 0.01
	T-SPOT.*TB*	Variable	Positive	16	Negative	3	Positive	11	Negative	3		T-SPOT.*TB*	CN	Negative	0	Negative	0			Negative 0
64	QFT-GIT	CP			Positive	4.95	Positive	2.64			95	QFT-GIT	CN	Negative	−0.02	Negative	−0.03	Negative	−0.01	
	T-SPOT.*TB*	CP			Positive	42	Positive	19				T-SPOT.*TB*	Reversion	Positive	6	Negative	1	Negative	0	
65	QFT-GIT	CN			Negative	−0.01	Negative	−0.02			96	QFT-GIT	CP	Positive	9.19	Positive	10			
	T-SPOT.*TB*	CN			Negative	0	Negative	2				T-SPOT.*TB*	Conversion	Negative	0	Positive	86			
66	QFT-GIT	CN			Negative	0.29	Negative	0	Negative	0.13	97	QFT-GIT	CN			Negative	−0.01			Negative 0.00
	T-SPOT.*TB*	Variable			Negative	1	Positive	7	Negative	3		T-SPOT.*TB*	CN			Negative	4			Negative 0
67	QFT-GIT	Variable			Positive	4.71	Negative	0.18	Positive	0.71	98	QFT-GIT	CN	Negative	−0.01	Negative	−0.02			
	T-SPOT.*TB*	CP			Positive	15	Positive	24	Positive	36		T-SPOT.*TB*	Conversion	Negative	1	Positive	8			
68	QFT-GIT	CP			Positive	8.28	Positive	6.42			99	QFT-GIT	CP			Positive	1.37	Positive	1.58	
	T-SPOT.*TB*	CP			Positive	98	Positive	50				T-SPOT.*TB*	Reversion			Positive	27	Negative	1	
69	QFT-GIT	CP	Positive	10	Positive	5.35			Positive	10	100	QFT-GIT	CN	Negative	0.20	Negative	0.09	Negative	0.02	
	T-SPOT.*TB*	CP	Positive	87	Positive	79						T-SPOT.*TB*	Conversion	Negative	1	Negative	4	Positive	8	
70	QFT-GIT	CN	Negative	−0.02	Negative	−0.02	Negative	0.00			101	QFT-GIT	CP	Positive	3.01	Positive	10	Positive	0.82	Positive 0.59
	T-SPOT.*TB*	CN	Negative	6	Negative	−5	Negative	−1				T-SPOT.*TB*	CP	Positive	48	Positive	39	Positive	13	Positive 16
71	QFT-GIT	CP			Positive	0.48			Positive	1.98	102	QFT-GIT	CN	Negative	−0.02	Negative	−0.04	Negative	0.05	Negative 0.01
	T-SPOT.*TB*	No FU			Positive	65						T-SPOT.*TB*	CN	Negative	0	Negative	1	Negative	−2	Negative 0
72	QFT-GIT	CN	Negative	−0.04	Negative	−0.07	Negative	−0.01	Negative	0.01	103	QFT-GIT	Variable			Positive	1.38	Negative	0.19	Positive 0.52
	T-SPOT.*TB*	CN	Negative	2	Negative	2	Negative	−1	Negative	0		T-SPOT.*TB*	Reversion			Positive	63	Negative	0	Negative 1
73	QFT-GIT	CN			Negative	0.34	Negative	0.33	Negative	0.11	104	QFT-GIT	CN	Negative	0.01	Negative	0.01	Negative	−0.05	Negative 0.00
	T-SPOT.*TB*	Reversion			Positive	25	Negative	0	Negative	2		T-SPOT.*TB*	CN	Negative	1	Negative	0	Negative	0	Negative 0
74	QFT-GIT	No FU			Negative	0.12					105	QFT-GIT	CN	Negative	−0.01	Negative	−0.01			
	T-SPOT.*TB*	No FU			Positive	7						T-SPOT.*TB*	CN	Negative	1	Negative	1			
75	QFT-GIT	CN	Negative	0.13	Negative	−0.23	Negative	−0.03	Negative	−0.01	106	QFT-GIT	CN			Negative	−0.03			Negative −0.01
	T-SPOT.*TB*	CN	Negative	4	Negative	1	Negative	−1	Negative	1		T-SPOT.*TB*	CN			Negative	1			Negative 0
76	QFT-GIT	Conversion			Negative	−0.21			Positive	0.59	107	QFT-GIT	CP	Positive	2.00	Positive	10	Positive	10	Positive 7.67
	T-SPOT.*TB*	CN			Negative	−1			Negative	1		T-SPOT.*TB*	CP	Positive	50	Positive	87			Positive 98
77	QFT-GIT	CN			Negative	−0.03			Negative	0.07	108	QFT-GIT	CP	Positive	7.82	Positive	8.53			Positive 4.46
	T-SPOT.*TB*	CN			Negative	2			Negative	1		T-SPOT.*TB*	CP	Positive	18	Positive	88			Positive 34
78	QFT-GIT	CN			Negative	0.10			Negative	0.01	109	QFT-GIT	CN	Negative	−0.01	Negative	0.08	Negative	0.00	
	T-SPOT.*TB*	CN			Negative	0			Negative	0		T-SPOT.*TB*	CN	Negative	3	Negative	2	Negative	0	
79	QFT-GIT	CN			Negative	0.32			Negative	0.04	110	QFT-GIT	CP	Positive	1.31	Positive	4.83			Positive 4.04
	T-SPOT.*TB*	CN			Negative	4			Negative	2		T-SPOT.*TB*	CP	Positive	43	Positive	44			Positive 18
80	QFT-GIT	CN			Negative	−0.03	Negative	0.06	Negative	0.08	111	QFT-GIT	CP			Positive	5.39			Positive 4.95
	T-SPOT.*TB*	Variable			Positive	26	Negative	0	Positive	23		T-SPOT.*TB*	CP			Positive	78			Positive 92
81	QFT-GIT	CN	Negative	−0.01	Negative	−0.02	Negative	0.03	Negative	0.00	112	QFT-GIT	CP	Positive	10	Positive	10	Positive	7.37	Positive 10
	T-SPOT.*TB*	Variable	Negative	5	Positive	13	Negative	1	Negative	5		T-SPOT.*TB*	CP	Positive	19	Positive	100	Positive	83	Positive 99
82	QFT-GIT	CN			Negative	0.09			Negative	0.02	113	QFT-GIT	CN	Negative	0.06	Negative	0.08	Negative	0.00	Negative 0.09
	T-SPOT.*TB*	CP			Positive	10			Positive	9		T-SPOT.*TB*	Reversion	Positive	7	Positive	11	Negative	4	
83	QFT-GIT	Conversion	Negative	0.14	Positive	0.53					114	QFT-GIT	Reversion			Positive	0.95	Positive	0.63	Negative 0.07
	T-SPOT.*TB*	Conversion	Negative	5	Positive	15						T-SPOT.*TB*	Conversion			Negative	4	Positive	22	Positive 23
84	QFT-GIT	CP	Positive	2.31	Positive	3.56			Positive	1.03	115	QFT-GIT	CP	Positive	6.32	Positive	10	Positive	7.59	
	T-SPOT.*TB*	CP	Positive	28	Positive	74			Positive	100		T-SPOT.*TB*	Reversion	Positive	18	Positive	94	Negative	5	
85	QFT-GIT	CN	Negative	0.01	Negative	−0.07					116	QFT-GIT	CN	Negative	0.00	Negative	0.02	Negative	0.04	Negative 0.00
	T-SPOT.*TB*	CN	Negative	0	Negative	0						T-SPOT.*TB*	CN	Negative	1	Negative	0	Negative	0	Negative 0
86	QFT-GIT	CP	Positive	8.38	Positive	10	Positive	9.7	Positive	10	117	QFT-GIT	CP	Positive	0.37	Positive	3.60	Positive	0.85	Positive 1.44
	T-SPOT.*TB*	Variable	Positive	69	Positive	88	Negative	5	Positive	56		T-SPOT.*TB*	CP	Positive	18	Positive	96	Positive	19	Positive 26
87	QFT-GIT	CN	Negative	0.02	Negative	−0.15			Negative	−0.01	118	QFT-GIT	CP			Positive	9.28	Positive	10	Positive 10
	T-SPOT.*TB*	CN	Negative	1	Negative	0			Negative	1		T-SPOT.*TB*	CP			Positive	64	Positive	56	Positive 50
88	QFT-GIT	CP	Positive	3.62	Positive	10					119	QFT-GIT	CP			Positive	6.16			Positive 3.64
	T-SPOT.*TB*	CP	Positive	68	Positive	78						T-SPOT.*TB*	CP			Positive	63			Positive 18
89	QFT-GIT	Conversion	Negative	−0.08	Negative	0.19	Negative	0.24	Positive	0.42	120	QFT-GIT	Variable	Positive	0.77	Negative	0.31			Positive 1.40
	T-SPOT.*TB*	Variable			Negative	5	Positive	6	Negative	5		T-SPOT.*TB*	CP	Positive	18	Positive	21			Positive 13
90	QFT-GIT	CN	Negative	0.00	Negative	0.09	Negative	0.02	Negative	0.05	121¶	QFT-GIT	CN							Negative −0.01
	T-SPOT.*TB*	Reversion	Positive	10	Negative	1	Negative	0	Negative	3		T-SPOT.*TB*	CN							Negative 0
91	QFT-GIT	CP			Positive	10	Positive	1.70	Positive	9.22	122	QFT-GIT	CN	Negative	−0.01					Negative −0.01
	T-SPOT.*TB*	CP			Positive	41	Positive	14	Positive	38		T-SPOT.*TB*	CN	Negative	5					Negative 0

*Category of kinetics of QFT-GIT and T-SPOT.*TB* results.
†Reversions were defined as change from positive to negative.
‡The variable category was appointed when conversion or reversion was not consistent.
§Conversions were defined as a change from negative to positive according to the manufacturer's instructions (cut-off for QFT-GIT at 0.35 IU/ml; cut-off for T-SPOT.*TB* at 6 spots).
¶These individuals had a follow-up visit after 18M.
0M = 0 months; 6M = 6 months; 12M = 12 months; 24M = 24 months; QFT-GIT = QuantiFERON-TB Gold In-Tube; CP = consistent positive; CN = consistent negative; no FU = missing follow-up data.

had participated at 0M.[19] A total of 109 (89.3%) participants provided blood samples at 6M, 70 (57.4%) at 12M, 49 (40.2%) at 18M and 87 (71.3%) at 24M. Blood was obtained at all four follow-up time points, 6M, 12M, 18M and 24M, from 23 (18.9%) individuals, of whom 15 (12.3%) had also participated during the contact investigation (0M).

QuantiFERON-TB Gold In-Tube

The overall percentage of individuals with a positive QFT-GIT result remained stable over the 2 years, at around 45% (Table 2). Using ANOVA for repeated measurements for the 15 individuals with QFT-GIT results at all time points and for the 23 with results from 6M to 24M, no significant relationship between follow-up time and QFT-GIT responsiveness could be distinguished. When applying McNemar's test to compare the initial test result with the result at 24M, no significant difference was observed. Results were not different between subjects for whom a 0M value was available compared to those who were first included at 6M. All available individual QFT-GIT results are shown in Table 3.

When individual patterns of QFT-GIT results were evaluated, all possible variations were observed. However, common patterns were distinguished when the initial QFT-GIT result was divided into three categories. When the initial QFT-GIT result was low (<0.25 international units [IU]/ml), the majority of follow-up results stayed below the cut-off value of 0.35 IU/ml. When the initial QFT-GIT result was >4 IU/ml, the results remained positive and well above the cut-off value. When the initial QFT-GIT result was ⩾0.25 and ⩽4 IU/ml, more dynamic patterns were distinguished (Figure 2). Moreover, these patterns were similar for the two patient groups with INH and radiographic follow-up.

*T-SPOT.*TB

The overall percentage of positive T-SPOT.*TB* results remained unchanged during follow-up (Table 2). As in the case of QFT-GIT, no significant change in T-SPOT.*TB* results was observed among individuals with T-SPOT.*TB* results at all time points or among subjects with results from 6M to 24M (ANOVA for repeated measurements or McNemar's test). All available individual T-SPOT.*TB* results are shown in Table 3.

The three patterns that were observed for QFT-GIT were also found for T-SPOT.*TB* (Figure 3). Most individuals with low spot counts in the initial T-SPOT.*TB* test (maximum spot count <5) remained negative during the entire follow-up period (*n*/*N* = 24/33);

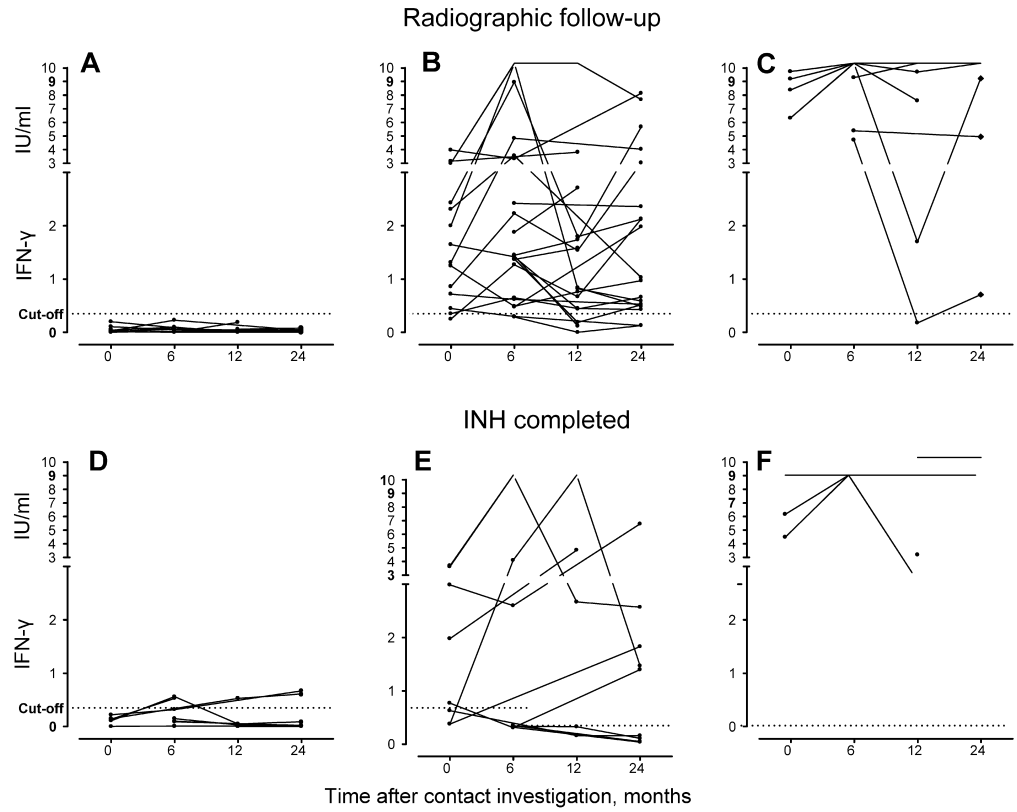

Figure 2 Kinetics of QFT-GIT results during radiographic follow-up or INH treatment. Number on *x*-axis indicates the number of months after the initial contact investigation in February 2005. The figures show the time course of QFT-GIT results in IU of IFN-γ/ml in subjects during radiographic follow-up and INH treatment whose initial QFT-GIT result was <0.25 IU/ml (**A** and **D**); ⩾0.25 and ⩽4.0 IU/ml (**B** and **E**) or >4.0 IU/ml (**C** and **F**). QFT-GIT values ⩾10 IU/ml are shown as 10 IU/ml. IU = international units; IFN-γ = interferon-gamma; INH = isoniazid; QFT-GIT = QuantiFERON-TB Gold In-Tube.

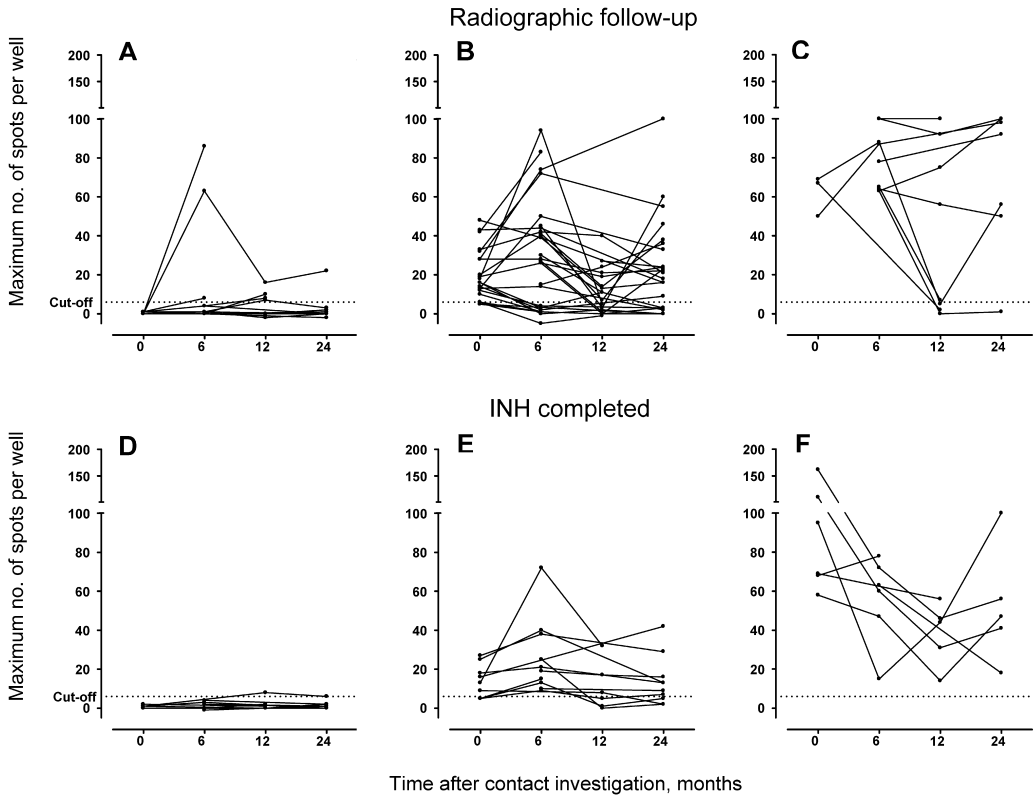

Figure 3 Kinetics of T-SPOT.*TB* results during radiographic follow-up or INH treatment. Number on *x*-axis indicates the number of months after the initial contact investigation in February 2005. The figures show the time course of T-SPOT.*TB* results expressed as the maximum spot count. The course of quantitative T-SPOT.*TB* results is shown for subjects during radiographic follow-up or INH treatment, whose initial response was <5 spots (**A** and **D**), ⩾5 and >50 (**B** and **E**) or ⩾50 spots (**C** and **F**). INH = isoniazid.

only 9/33 converted to a positive result at any later time point. If the first T-SPOT.*TB* result was high (maximum spot count exceeding 50 spots), the assay remained positive during the entire follow-up period in 8/10 subjects, although spot counts were usually lower at the last follow-up time point. Just 2/10 initially high-responding individuals reverted to a negative result at any later time point. Of 35 individuals with an initial T-SPOT.*TB* score of between 5 and 50 spots, most had a stable number of responding T-cells during the follow-up period, although there were some individuals with more dynamic patterns. As was observed for the QFT-GIT, no influence of INH treatment could be distinguished.

Responses to the different antigens of the T-SPOT.*TB* assay were analysed. Of individuals with an initially positive T-SPOT.*TB* result, the majority (31/38) responded positively to both antigens and remained positive for both during follow-up. The response to panel A decreased significantly between 6M and 24M ($P = 0.015$), whereas the decrease in responses to panel B was of borderline significance ($P = 0.051$).

*Agreement between T.SPOT-*TB *and QuantiFERON-TB Gold*

There was a strong correlation between T-SPOT.*TB* and QFT-GIT results at all different time points, with Cohen's κ values between 0.7 and 0.8, independently of the time point and of preventive treatment. There was a positive correlation between the number of spots in the T-SPOT.*TB* assay and the ^{10}log of concentration of interferon-gamma (IFN-γ) produced in the QFT-GIT ($R = 0.6$, $P < 0.001$). This was the case for panel A and panel B separately, but also when the individual maximum number of spots was analysed.

DISCUSSION

This study showed three different kinetic patterns of IGRA response. T-SPOT.*TB* and QFT-GIT remained positive during at least the follow-up in respectively 92% and 90% of the individuals with an initially strongly positive QFT-GIT or T-SPOT.*TB* result, irrespective of whether they had completed preventive INH treatment. This finding is in accordance with other studies reporting that responses remain positive in a proportion of treated individuals.[4,21–23] Moreover, initially very low or very high responses mostly remained in the same range over the 2-year follow-up period, with or without INH preventive treatment. Thus, overall, IGRA appears to be of little clinical value for follow-up.

T-SPOT.*TB* was more frequently positive than QFT-GIT at all investigated time points. The cause of this difference is not known, but it has been suggested that T-SPOT.*TB* is more sensitive than the QFT-GIT for

detection of TB infection.[6,24] On the other hand, T-SPOT.*TB* could be more sensitive in detecting infection that was not recently acquired, as most studies included populations with undocumented exposure history. The present study most likely included individuals with a positive TST due to past infection, because they were identified during mass screening. In the absence of a gold standard for the presence of LTBI, the only method of proving superiority would require follow-up of untreated TST-positive persons with a positive or negative IGRA result, as is currently under way in several clinical-epidemiological settings.[25,26]

An interesting observation was the strong correlation between the number of spots in the T-SPOT.*TB* and the log of the IFN-γ concentration produced in the QFT-GIT, for both antigens and at a low and a high number of spots. This implies that cells responding to ESAT-6 or CFP-10 do not differ at a qualitative level. As a linear increase of spots appears to be responsible for an exponential increase in the concentration of IFN-γ, reflecting total production, this suggests a strong dependence of the QFT-GIT result on the number of peripheral blood mononuclear cells present in the volume of whole blood used for QFT-GIT, and may explain part of the observed discrepancies between the two different IGRA formats. Participants in this study were all healthy immunocompetent individuals. It is therefore unlikely that low cell counts had led to false-negative results. However, in other settings with immunocompromised patients or children, this could be problematic, and false-negative or indeterminate results might be obtained.[8]

Our study shows that it is possible to characterise different kinetic patterns of responses that vary by the initial response. IGRA responses that were either negative or very high at the first measurement most often remained in the same category of responses during the entire follow-up period. In contrast, initially intermediate results were more variable over time, and both conversions and reversions were observed, even within the same individual. The clinical significance of these patterns is unclear, as the positive or negative predictive value of IGRA results for later TB reactivation is as yet unproven. In this regard, the group with initially intermediate responses seems the most interesting category because the changes in responses suggest an ongoing dynamic interaction between host and pathogen. Follow-up of sufficiently large numbers of individuals in each category in a low-prevalence TB setting will provide more definitive information with regard to the relation between IGRA kinetics and risk of progression to TB disease, which would provide a rational basis for therapeutic consequences.

Although all individuals included in this study had a TST induration of ⩾15 mm, half of them were IGRA-negative and remained negative during follow-up. As none of these individuals developed TB, there are three possible explanations. The first option, of false-positive TST results caused by NTM or undetected BCG vaccination, was unlikely, as TST results generally do not exceed 15 mm in that setting. Second, Hill et al. showed that rapid ELISPOT reversion can occur after TB exposure.[27] Because the infectious period of the index patient lasted from February to October 2004, while we first tested in February 2005, it is possible that participants with a positive TST and negative IGRA had already reverted to IGRA-negative.[27] Third, as these individuals were detected during large-scale contact screening, the TST could be positive due to an old infection in association with a reverted IGRA result.

Before concluding that the added value of follow-up IGRA in guiding clinical decisions may be limited, some potential pitfalls need to be taken into consideration. First, data on all time points were available for a limited number of subjects, as a result of the design and the voluntary nature of the study, precluding robust statistical analysis. However, the observed patterns were consistent and the agreement between the QFT-GIT and T-SPOT.*TB* was good at all time points, with a κ of 0.7, independent of preventive INH treatment, in agreement with previous comparative studies.[6,19,24] Second, very few studies have addressed the issue of inter-assay variability and reproducibility of IGRA. The studies reported so far have analysed the inter-assay variability of the QFT-GIT within a short period of time, i.e., with repeated measurements over a maximum interval of 3 months in a population not recently exposed to TB.[28,29] These studies indicate that variability between measurements (i.e., positive or negative) of about 16% can be expected. In our study, data were collected over a much longer period in a population recently exposed to TB, and consistent changes over time may reflect a change in immune reactivity rather than experimental variability of IGRA. Another factor of consideration with regard to repeated measurements is regression to the mean: when very high or low results are obtained first, on subsequent testing it is expected that such outliers are closer to the group average. This can be a cause for variations in test outcome but is without clinical significance. Taking the above into consideration together with the current lack of understanding of the normal kinetics/variability of IGRA, it was not possible to differentiate between test variability and true conversions and/or reversions.

Based on our data, IGRA do not seem to be useful for the follow-up of patients with LTBI in deciding when to stop treatment or identify those at risk of reactivation. The moderate effect of INH treatment on the percentage of positive IGRA responses cannot be regarded as relevant at the individual level for the determination of treatment success. In that regard, our findings were different from those of a follow-up study of patients with TB disease describing consistent conversion to negative results at the end of successful

treatment,[30] but are in part similar to those of another follow-up study using ELISPOT in recently exposed subjects that observed a decrease in responses among treated but not among untreated subjects.[31] Based on our data, repeated testing in individuals with initially negative or very high responses will not yield additional information. Repeating IGRA in individuals with initially intermediate responses might provide useful information with regard to progression to TB disease. In animal models, there was a clear correlation between high ESAT-6 responses and subsequent development of TB disease, as was the case in two human studies.[25,32–35] Because a number of individuals with initially negative results just below the cut-off (>0.25 and <0.35 IU/ml) had dynamic responses, including conversions to positive, it could be useful to repeat the assay in these cases 6 months to 1 year later.

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RÉSUMÉ

CADRE : Après une investigation sur large échelle de contacts, on a offert un traitement préventif de la tuberculose aux individus dont les tests cutanés positifs à la tuberculine (TST) étaient connus.
OBJECTIF : Investiguer à la fois l'effet du traitement à l'isoniazide (INH) ainsi que son effet au fil du temps sur les résultats de deux tests différents de libération d'interféron gamma (IGRA) au cours du suivi.
SCHÉMA : On a inclus dans l'étude les 122 sujets à TST positif détectés au cours de l'investigation des contacts sur une large échelle. On a prélevé pendant 2 ans du sang tous les 6 mois pour la réalisation des deux tests sanguins.
RÉSULTATS : Le traitement préventif à l'INH a été complet chez 36 des 122 individus (29,5%) ; 71 (58,2%) ont été suivis par un dépistage radiologique tous les 6 mois et le traitement à l'INH n'a pas été complété chez 15 (12,3%). Le pourcentage global d'individus dont le résultat positif reste stable au cours des 2 ans est d'environ 45% à 50%, mais les réponses individuelles peuvent varier au fil du temps. La majorité des résultats initiaux faibles d'IGRA reste en dessous des valeurs-seuil. Les résultats d'IGRA initialement élevés restent positifs, alors que les résultats d'IGRA initialement intermédiaires sont suivis de types plus dynamiques d'évolution.
CONCLUSION : Cette étude montre le type fortement variable des réponses IGRA au fil du temps et suggère sa valeur limitée pour son utilisation lors du suivi de sujets atteints d'une infection tuberculeuse latente. Toutefois, la signification de divers types d'évolution observés chez les sujets dont les résultats d'IGRA étaient initialement intermédiaires justifie des études complémentaires.

RESUMEN

MARCA DE REFERENCIA : Tras una investigación en gran escala de contactos de pacientes tuberculosos, se ofreció el tratamiento preventivo a las personas con resultado positivo en la prueba cutánea de la tuberculina (TST).
OBJETIVO : Investigar el efecto del tratamiento con isoniazida (INH) y el efecto del tiempo en la respuesta a las pruebas de liberación de interferón gama (IGRA) durante el seguimiento.
MÉTODO : Se incluyeron los participantes en la investigación de contactos que presentaron una reacción TST positiva ($n = 122$). Durante 2 años se obtuvieron muestras de sangre cada 6 meses, con el fin de realizar ambas pruebas sanguíneas.
RESULTADOS : De los 122 pacientes, 36 (29,5%) completaron el tratamiento preventivo con INH ; 71 (58,2%) tuvieron un seguimiento con examen radiográfico cada 6 meses y 15 (12,3%) no completaron el tratamiento con INH. El porcentaje global de personas con un resultado positivo permaneció estable durante los 2 años, entre 45% y 50%, pero las respuestas individuales podían variar con el paso del tiempo. La mayoría de pacientes con resultados iniciales bajos en la IGRA conservó valores por debajo del límite de significación ; aquellos con resultados iniciales altos permanecieron positivos y en los pacientes con resultados iniciales intermedios se observaron modelos de evolución más dinámicos.
CONCLUSIÓN : En el presente estudio se puso en evidencia una pauta de respuesta sumamente variable en la IGRA con el paso del tiempo, lo cual indica que este ensayo tiene una utilidad limitada durante el seguimiento de pacientes con infección tuberculosa latente. Sin embargo, la significación de los diferentes modelos cinéticos observados en pacientes con una reacción inicial intermedia justifica nuevos estudios.