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REVIEW ARTICLE

False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria?

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SUMMARY

BACKGROUND: Despite certain drawbacks, the tuberculin skin test (TST) remains in widespread use. Important advantages of the TST are its low cost, simplicity and interpretation based on extensive published literature. However, TST specificity is reduced by bacille Calmette-Guérin (BCG) vaccination and exposure to non-tuberculous mycobacteria (NTM).

METHODS: To estimate TST specificity, we reviewed the published literature since 1966 regarding the effect of BCG vaccination and NTM infection on TST. Studies selected included healthy subjects with documented BCG vaccination status, including age at vaccination. Studies of NTM effect had used standardised NTM antigens in healthy subjects.

RESULTS: In 24 studies involving 240 203 subjects BCG-vaccinated as infants, 20 406 (8.5%) had a TST of 10+ mm attributable to BCG, but only 56/5639 (1%) were TST-positive if tested ⩾10 years after BCG. In 12 studies of 12 728 subjects vaccinated after their first birthday, 5314 (41.8%) had a false-positive TST of 10+ mm, and 191/898 (21.2%) after 10 years. Type of tuberculin test did not modify these results. In 18 studies involving 1 169 105 subjects, the absolute prevalence of false-positive TST from NTM cross-reactivity ranged from 0.1% to 2.3% in different regions.

CONCLUSIONS: The effect on TST of BCG received in infancy is minimal, especially ⩾10 years after vaccination. BCG received after infancy produces more frequent, more persistent and larger TST reactions. NTM is not a clinically important cause of false-positive TST, except in populations with a high prevalence of NTM sensitisation and a very low prevalence of TB infection.

KEY WORDS: tuberculin skin test; latent TB infection; atypical mycobacteria; environmental mycobacteria; non-tuberculous mycobacteria; BCG vaccination

DESPITE CERTAIN DRAWBACKS, the tuberculin skin test (TST) remains in widespread use. The test is inexpensive and simple, facilitating its use in the field and in resource-limited settings. A very important advantage of the TST is the extensive published evidence from numerous cross-sectional and longitudinal studies in different settings and populations. This permits estimation of the likelihood of false-positive and false-negative tests, as well as risk of progression to active disease. However, accurate interpretation of the TST depends upon careful synthesis of this vast evidence, a difficult challenge for most busy clinicians.

New interferon-gamma release assays (IGRA) such as the QuantiFERON-TB Gold (Cellestis, Carnegie, VIC, Australia) and T-SPOT.TB tests, provide attractive alternatives to the TST. These tests are not affected by bacille Calmette-Guérin (BCG) vaccination nor by certain non-tuberculous mycobacteria (NTM), and so should be more specific than the TST.[1] However, their higher cost and requirement for laboratory facilities may limit their adoption. Thus it seems timely to re-evaluate the situations and populations most likely to have false-positive TST reactions, for whom the new IGRA may be more accurate.

We conducted an extensive literature review and meta-analysis to determine the best possible estimates of false-positive TST reactions related to the two most important causes: prior BCG vaccination and exposure to NTM. We also examined factors modifying the effect of BCG vaccination on TST.

METHODS

Literature search

A Medline search was conducted for articles published between 1966 and 2005 using the terms 'tuberculosis', 'atypical mycobacteria', 'atypical mycobacterial infections', 'environmental mycobacteria',

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'non-tuberculous mycobacteria', 'BCG vaccination', and 'skin tests' or 'tuberculin skin tests'. The search was limited to human studies published in the English language. Titles and abstracts of all original articles found were reviewed. If the abstract suggested that the study might meet the review inclusion criteria (see below), the full article was reviewed. The reference lists from these articles, and related reviews, were used to identify further original articles. We contacted the authors of some studies for additional data. Reviewers suggested two additional studies.

Study selection

To be included in the analysis of the effect of BCG vaccination on TST results, studies must have performed tuberculin testing using the Mantoux technique and standardised tuberculin antigens in healthy populations, some of whom had been BCG vaccinated and others who had not (controls). Furthermore, BCG vaccination must have been documented by vaccination records or presence of scar. Age at BCG vaccination had to be known, as age of vaccination and the interval between vaccination and TST are recognised determinants of the effect of BCG on tuberculin reactions.[2–7] The minimum interval between BCG vaccination and TST had to be 1 year, and the type of tuberculin test material had to be specified, as this has been identified as a potential determinant.[8] A total of 400 articles were initially identified; of these, 65 were selected for full review and 31 met the criteria for inclusion for estimate of BCG effect (summarised in Tables 1 and 2).

A number of studies cited in an earlier meta-analysis on this topic[8] were not included in our estimate of effect for the following reasons: BCG was ascertained by history in all or a substantial proportion of subjects,[36–40] age of vaccination was not known or not reported,[36–46] interval was not known or not reported and the interval between TST and BCG was less than 1 year in some of the subjects.[4,47–49] The booster phenomenon was included as a positive TST;[42,43,49] the actual numbers with specific TST reaction sizes were not given,[50] there were very few[51] or no non-vaccinated controls.[4,48,50] Others were not used because repeat vaccination at an older age was given to an unknown number who had been tuberculin-negative.[5,51–53] In the last of these studies,[5] the sub-group that had been vaccinated only in infancy was included.

To be included in the estimate of NTM effect, studies must have: tested healthy populations who were not BCG-vaccinated (or the authors adjusted for BCG), using purified NTM antigens from one of five recognised centres—the US Public Health Service (Atlanta, GA, USA), Statens Serum Institut (Copenhagen, Denmark), Connaught Laboratories (Toronto, Canada), Weybridge Laboratory (London, UK), or the laboratory of Dr Stanford (Royal Free & University College Medical School, London, UK). Studies testing patients with active mycobacterial disease were excluded. A total of 147 studies were identified from the literature

Table 1 Summary of methodology of studies in healthy populations that had received BCG in infancy (up to 1 year old)

Author, year	Setting	BCG vaccine type/source	Methods of verification	TST method*	Age when TST, years	TST in BCG *n* tested	TST in non-vaccinated *n* tested
Eason, 1987[9]	Solomon Island	Unspecified	Scar/records	5 TU PPD-S	1–8	1 425	357
Karalliedde, 1987[10]	Sri Lanka	Japan. UNICEF	Scar	1 TU RT-23	5–11	522	None‡
al-Kassimi, 1991[11]	Saudi Arabia	Many strains were used	Scar	5 TU PPD-S	5–13	1 945	643
el-Kassimi, 1991[12]	Saudi Arabia	Many strains were used	Scar	5 TU PPD-S	5–14	283	44
Menzies, 1992[6]	Montreal	Armand Frappier	Records	5 TU PPD-S	11–17	1 041	3 118
Young, 1992[13]	North Ontario	Connaught (Toronto)	Records	5 TU PPD-S	1–15	522	126
al-Kassimi, 1993[14]	Saudi Arabia	Many strains were used	Scar	5 TU PPD-S	5–14	2 119	681
Menzies, 1994[7]	Montreal	Armand Frappier	Records	5 TU PPD-S	21	381	951
Miret-Cuadras, 1996[5]	Spain	Danish	Scar	5 TU RT-23	20–25	446	887
Bener, 1996[15]	Arab Emirates	Unspecified	Scar	5 TU PPD-S	5–15	544	238
Getchell, 1992[16]	Peru	Unspecified	Scar	5 TU PPD-S	5–25+	251	40
Liard, 1996[17]	Algeria	Unspecified	Scar	2 TU RT-23	5–18	920	315
Schwartzman, 1996[18]	Montreal	Armand Frappier	Records	5 TU PPD-S	36	76	133
Jochem, 1997[19]	Montreal	Armand Frappier	Records	5 TU PPD-S	39	11	52
Bosman, 1998[20]	Kenya	Unspecified	Scar	2 TU RT-23	6–13	25 381	14 984
Chadha, 2000[21]	India	Danish 1331	Scar	1 TU RT-23	5–9	3 165†	2 861§
Chadha, 2001[22]	India	Danish 1331	Scar	1 TU RT-23	6–7	5 653	3 687§
Tanzania TB Survey, 2001[23]	Tanzania	Unspecified	Scar	2 TU RT-23	6–14	161 357	84 599
Chadha, 2003[24]	India	Danish 1331	Scar	1 TU RT-23	5–9	5 542	2 991§
Bierrenbach, 2003[25]	Brazil	Moreau	Scar	2 TU RT-23	7–14	437	633
Lienhardt, 2003[26]	The Gambia	Unspecified	Scar	2 TU RT-23	1–50+	2 314	2 691§
Chadha, 2004[27]	India	Danish 1331	Scar	1 TU RT-23	5–9	24 398	31 476
Hill, 2004[28]	The Gambia	Unspecified	Scar	2 TU RT-23	20	959	985§
Pai, 2005[29]	India	Danish 1331	Scar	1 TU RT-23	22	511	200§

* Positive TST = ⩾10 mm unless otherwise stated. PPD-S = studies using commercial PPD standardised to PPD-S.
† Substantial confounding with age. BCG coverage higher in older children.
‡ Prevalence of LTBI estimated from smear-positive TB incidence (see text).
§ Published information supplemented by data from authors.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test; LTBI = latent tuberculosis infection; TB = tuberculosis; PPD = purified protein derivative.

Table 2 Summary of methodology of studies in healthy populations that had received BCG after the age of 1 year

Author, year	Setting	BCG vaccine type	Methods of verification	TST method†	Age at BCG, years	Age at TST, years	Interval BCG-TST, years	BCG-vaccinated *n* tested	Non-vaccinated *n* tested
Abrahams, 1967[30]*	Australia	Danish	Records	5 TU PPD-S	8–12	13–14	1–5	53	1012
Abrahams, 1968[31]*	Australia	Danish	Records	5 TU PPD-S	8–12	13	1–5	395	374
Comstock, 1971[32]	Southern US	Chicago	Records	5 TU PPD-S	5–12	5–12	8–15	63	66
Horwitz, 1972[33]	Copenhagen	All types	Study	2 TU RT-23	7	12	5	716	None*
Baily, 1980[34]	India	Pasteur, Danish	Records	3 TU PPD-S	5–14	9–18	4	8702	8698‡
Eason, 1987[9]	Solomon Islands	Not specified	Records	5 TU PPD-S	0 and 7	10–19	3–12	1395	80
Menzies, 1992[6]	Montreal	Armand Frappier	Records	5 TU PPD-S	6–8	6–8	7–19	469	3118
Menzies, 1994[7]	Montreal	Armand Frappier	Records	5 TU PPD-S	2–10		10–25	210	951
Ildirim, 1995[3]	Turkey	Danish, Pasteur	Records	5 TU PPD-S	0 and 5	6–12	1–6	470	1518§
Schwartzman, 1996[18]	Montreal	Armand Frappier	Records	5 TU PPD-S	>2	36	20–30	117	133
Jochem, 1997[19]	Montreal	Armand Frappier	Records	5 TU PPD-S	>2	38.7	20–30	39	52
Kang, 2005[35]	South Korea	Pasteur	Scar	2 TU RT-23	0 and 12	20	8	99	None*

* Prevalence of LTBI in non-vaccinated estimated from smear-positive TB incidence (see text).
† Positive TST = 10+ mm unless otherwise stated. PPD-S = studies using commercial PPD standardised to PPD-S.
‡ In this substudy of the Madras BCG trial (see page 60–61 of reference[34]) all participants were TST-negative before vaccination and BCG vaccinees as well as the placebo group were retested after 4 years.
§ Ildirim—two or three scars were interpreted to mean that the child must have received vaccination at least once at the age of 5–6 years.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test; LTBI = latent tuberculosis infection; PPD = purified protein derivative.

Table 3 Summary of methodology of 18 studies measuring prevalence of NTM sensitivity in healthy populations

		Participants			NTM antigens	
Author, year	Setting	Age, years range or mean	*n*	TST methods	Types	Source
Bleiker, 1968[54]	The Netherlands	6–15	3 108	2 TU RT-23	2 U PPD-avian	Weybridge, England
	France	6–15	2 038			SSI, Copenhagen
Jeanes, 1969[55]	Canada	14–22	26 158	5 TU PPD-S	PPDG, B	US Department of Health
			7 583			
Edwards, 1973[56]	US–North*	17–21	573 141	5 TU PPD-S	PPDB, G	US Department of Health
	US–Central†	17–21	268 554			
	US–South‡	17–21	185 475			
Brickman, 1974[57]	Montreal	4–6	567	5 TU PPD-S	PPDA, B, K(Y), G	Connaught Laboratories, Toronto
			473			
Paul, 1975[58]	Kenya	6–17	27	2 TU RT-23	11 reagents	Stanford
			7			SSI, Copenhagen
Ogunmekan, 1977[59]	Nigeria	10–15	509	5 TU PPD-S	PPDG, PL, A, F, Y	US Department of Health
			245			
Baily 1980[34]	India	1–14	101 106	3 TU PPD-S§	PPD-B	Antigen production laboratory (CDC), Atlanta, GA
Wells, 1982[60]	Barbados	3–8	908	5 TU PPD-S	PPD-B	Connaught Laboratories, Toronto
Bahr, 1986[61]	Lebanon	7–17	1 823	No TST	Leprosin A, Vaccin, Scrofulin	Stanford's method
Frappier-Davignon, 1989[62]	Quebec	15–19	1 047	2 TU RT-23	PPDB, K	SSI, Copenhagen
Ly, 1989[63]	Vietnam	12	153	No TST	15 new tuberculins	Stanford
			155			
Menzies, 1989[64]	Montreal	11.6	2 408	5 TU PPD-S	PPD-B	Connaught Laboratories, Toronto
		16.1	983			
Lind, 1991[65]	Sweden	8–9	1 368	2 TU RT-23	*M. avium* RS10, *M. scrofulaceum* RS95	SSI, Copenhagen
			1 451			
von Reyn, 1993[66]	NH	18–65	102	5 TU PPD-S	0.1 ml PPDRS 10 (*M. avium*)	Connaught Laboratories, Toronto
	Boston	18–65	104			SSI, Copenhagen
	Finland	18–45	74			
	Trinidad	18–65	102			
	Kenya	18–65	102			
Osman, 1994[67]	Saudi Arabia	6–12	34	2 TU RT-23	PPDA, G	SSI, Copenhagen
			38			
Fine, 2001[68]	Malawi	20–65	2 623	2 TU RT-23	A, B, G and 12 others	Stanford
			2 886			SSI, Copenhagen
			3 324			
von Reyn, 2001[69]	South US	29	284	5 TU PPD-S	0.1 ml MAS 10/2	SSI, Copenhagen
	North US	29	500			US Department of Health
Bierrenbach, 2003[25]	Brazil	11	170	2 TU RT-23	PPD-A, G, F, K	SSI, Copenhagen
			145			

* Northern: any of the following states: CA, CO, CT, DC, ID, IL, ID, IA, KY, ME, MA, MI, MN, MT, NH, NJ, NY, OH, OR, PA, RI, SD, UT, VT, WA, WI, WY.
† Central states: DE, KS, MD, MO, NE, NV, NM, NC, ND, OK, TN, VA, WV.
‡ Southern states: AL, AZ, AR, FL, GA, LA, MS, SC, TX.
§ For this study, a preliminary study demonstrated that 3TU of the PPD-S used was bioequivalent to 5TU PPD-S. Hence this PPD dose was considered bioequivalent to 5TU PPD-S.[34]
NTM = non-tuberculous mycobacteria; TST = tuberculin skin test; LTBI = latent tuberculosis infection; PPD-S = studies using commercial PPD standardised to PPD-S; PPD = purified protein derivative; SSI = Statens Serum Institute.

search, 46 were reviewed in depth and 18 studies, summarised in Table 3, met the review inclusion criteria.

Effect of BCG on TST

We examined the size of BCG-associated TST reactions, age when vaccinated, interval between vaccination and TST, and type of tuberculin material. Number of BCG vaccinations received could not be assessed, as this was confounded with age when vaccinated and interval since vaccination. Nor could we analyse the effect of BCG vaccine strain because many different strains were used (Danish—eight studies, Armand-Frappier—four, Pasteur—one, Tice—one, Connaught—one, Moreau—one, two strains—three, many strains—four), or the strain was not specified in eight studies. Age at BCG vaccination was categorised into vaccination in infancy (first year of life) or later. This reflects BCG vaccination policy in many countries where it is given just after birth and/or in primary school.[28] Interval was dichotomised into more or less than 10 years, using the average or the midpoint if a range was given.

In each study, we compared the proportion of BCG-vaccinated or non-vaccinated individuals with TST reactions in four categories (0–4, 5–9, 10–14 and ⩾15 mm), three categories (0–4, 5–9 and ⩾10 mm), or two categories (0–9 and ⩾10 mm). For each TST size category, the difference between vaccinated and non-vaccinated was assumed to represent the percentage with false-positive (FP) TST due to BCG (the FP-TST_{BCG}). For each study, the number BCG-vaccinated was multiplied times this percentage to estimate the total number of individuals with FP-TST_{BCG} in that TST size range. These values from all studies were combined in a weighted average FP-TST_{BCG} for each TST size category.

Effect of NTM on TST

Definitions

The following definitions were used to calculate the effect of NTM on TST, and vice versa:

- TST reaction: skin test reaction to antigens (PPD) derived from *Mycobacterium tuberculosis*.
- Positive TST: reaction to PPD of ⩾10 mm.
- NTM reactions: reactions to antigens derived from NTM.
- Positive NTM: reaction to NTM antigens of ⩾5 mm.
- TST or NTM cross-reactions: these could be determined only if dual TST was performed simultaneously with PPD and NTM antigens. If the reaction to one antigen was larger than the other, the smaller reaction was considered a cross-reaction.[56,71,72]
- TST dominant: TST reaction equal to or greater than NTM reaction. In this case, the reaction to the NTM was assumed to be a cross-reaction.
- NTM dominant: reaction to NTM antigen was more than 1 mm larger than the TST reaction (to ensure NTM was truly bigger).[56,71,72]
- FP-TST_{NTM}: false-positive TST due to NTM. When the TST was 10–14 mm and the dual NTM reaction was larger (dominant), then the TST reaction was considered a cross-reaction from NTM sensitivity.[56,71,72] The TST was thus considered false-positive.
- Dual mycobacterial infection: if the TST is ⩾15 mm, the subject is considered to have TB infection (true positive), even if the NTM reaction is larger.[71,72] These persons are believed to have latent TB infection (with *M. tuberculosis*), and sensitisation to an NTM.[71,72]

Calculating the effect of NTM on TST reactions

In the 18 studies reviewed, different definitions of a positive NTM test were used. Five studies provided millimetre by millimetre results. We used these to calculate the ratio between reactions of 2, 4 and 6 mm to reactions of 5 mm (Table 4). We used the same studies to estimate a correction factor to account for false-positive NTM reactions due to larger reactions to TST (Table 4). These two correction factors were applied to 12 studies in which dual testing with TST and NTM antigens was performed. We used these to estimate the rate of false-positive TST per 100 individuals with NTM reactions of 5+ mm—the FP-TST_{NTM}. This rate was applied to the prevalence (standardised and corrected, as above) of NTM in 18 surveys to estimate the absolute rate of false-positive TST related to NTM in different regions and countries of the world.

RESULTS

False-positive TST from BCG

Based on 240 203 vaccinees in 24 studies reviewed, BCG vaccination in infancy caused an overall rate of 8.5 false-positive TST reactions (FP-TST_{BCG}) per 100 vaccinees, with a rate of 2.6 FP-TST_{BCG} per 100 vaccinees for reactions of 15+ mm (Table 5). BCG received by 12 728 subjects after the age of 1 year caused 41.8 false-positive TST reactions (10+ mm) per 100 vaccinees; about half of these reactions measured 15+ mm (Table 6). In the six studies that included persons vaccinated at different ages, BCG vaccination at an older age had a much greater effect on TST than BCG in infancy[4–7] (Figures 1 and 2).

As seen in Table 7, after 10 years (a clinically useful cut-off, although without biological justification), the effect of the BCG received in infancy was virtually nil (1.0 FP-TST_{BCG} per 100 vaccinees). On the other hand, the effect on TST of BCG vaccination after the first year of life seems to persist, although there is significant waning. The distribution of reactions (10–14 mm vs. 15+ mm) is not different in those tested 10+ years after vaccination, compared to those tested sooner.

The prevalence of positive reactions to 5 TU PPD-S, 1 TU RT23 or 2 TU RT23, was similar in subjects who had been BCG vaccinated in infancy (Table 7). Among subjects vaccinated in later childhood, prevalence of

Table 4 NTM size standardisation ratios and correction factor for true TB infection, from five studies with complete data (mm by mm) from dual testing with NTM and *M. tuberculosis* antigens

											Correction factor for NTM reactions due to true TB infection			
		Participants			NTM size standardisation ratios NTM reaction prevalence				Total prevalence of TST reactions		Frequency of non-dominant NTM reactions* when TST is	
Author, year	Setting	Age, years range or mean	*n*	NTM antigen	⩾2 mm %	⩾4 mm %	⩾5 mm %	⩾6 mm %	⩾10 mm %	⩾5 mm %	⩾10 mm %	⩾5 mm %
Bleiker, 1968[54]	Netherlands	6–15	3108	A	21.8	10.0	7.5	5.7	1	4	44	25
	France	6–15	2038	A	9.9	8.1	7.7	7.0	10	12	43	37
Brickman, 1974[57]	Montreal	4–6	554	A	3	3	3	2	1	2	32	28
			567	B	3	3	3	2				
			473	G	6	5	5	5				
Paul, 1975[58]	Kenya	6–17	27	A	n/a	n/a	44	37	14	21	44	41
			7	G			29	29				
Menzies, 1989[64]	Montreal	11.6	2408	B	n/a	9	7	7	5	9	35	31
		16.1	983	B	n/a	17	14	14				
Lind, 1991[65]	Sweden	8–9	1368	A	52.4	37.4	32.3	25.4	1	6	22	27
			1451	G	56.3	42.5	38.2	32.4				
Standardising factors†					0.613	0.856	1.000	1.202				
Average correction factor (of TST causing cross-reacting non-dominant NTM reaction)											39	31

* Non-dominant NTM reaction defined as [NTM ⩾5 mm] and [NTM ⩽TST+1] (see definitions in text).
† Weighted average of ratio of [Prevalence at cut-off = 5 mm]/[Prevalence at cut-off = *n* mm].
NTM = non-tuberculous mycobacteria; TB = tuberculosis; TST = tuberculin skin test.

positive TST was higher in two studies of subjects tested with 2 TU RT23, compared to subjects in 10 studies tested with 5 TU-PPDS. However, test type was confounded with interval: both studies using RT23 involved shorter intervals of 5 and 8 years.

False-positive TST from NTM

As shown in Table 8, based on the 12 studies with 1 169 105 persons who underwent dual TST and NTM testing, 2.0 persons would have a false-positive TST (of 10–14 mm) per 100 persons with NTM reactions of 5+ mm (FP-TST_{NTM}). Using only the five studies of 12 984 persons with detailed data, the absolute rate of FP-TST_{NTM} was 2.7 per 100 NTM-sensitised population. When this higher estimate of FP-TST_{NTM} was multiplied by the prevalence of NTM reactions of 5+ mm in the 18 NTM prevalence surveys reviewed, the absolute prevalence of FP-TST_{NTM} ranged from 0.1% in Montreal or France to a maximum of 2.3% in India (Table 9).

DISCUSSION

The results of this review indicate that the impact of BCG vaccination on TSTs was strongly affected by age when vaccinated and interval since vaccination, but not by type of tuberculin material. Size of reaction was not that helpful in distinguishing BCG-related TST from true infection. False-positive TSTs due to NTM were very uncommon, and thus important only in populations with a low prevalence of true TB infection.

Although the overall estimates of impact of BCG in infancy and at an older age are based on a large number of studies and very large numbers of vaccinees, the sub-group analyses were limited by smaller numbers of studies and vaccinees. Studies with very large numbers would tend to skew results, given our method of weighting estimates by the size of study populations. However, unweighted estimates of the effect of age when BCG-vaccinated and interval since vaccination were similar to the weighted estimates. We calculated the absolute effect of BCG or NTM on tuberculin reactions independently of the prevalence of TB infection. Such estimates should be applicable and useful for calculating positive predictive value in all BCG vaccinated populations with very different prevalences of true TB infection.

This review demonstrates that age when BCG-vaccinated is a critical determinant of subsequent tuberculin reactions. The finding that BCG in infancy has little effect, particularly 10 years or more after vaccination, means that adolescents or adults who were BCG-vaccinated in infancy with a TST of 10+ mm can be assumed to have a true positive TST. This lack of effect is biologically plausible, as the immune response to BCG given in the first few months of life is much less than the immune response to BCG given after 9 months.[73] The prevalence of positive TST has also been correlated with number of BCG scars—a proxy of older age when last vaccinated.[3,74] BCG in older childhood produces more frequent, more persistent and larger TSTs, making this group of vaccinees the most likely to benefit from the application of new, highly specific IGRA tests. However, it might be anticipated that this group will diminish over time, given

Table 5 Details of calculations of effect on tuberculin reactions of BCG in infancy (subtracting TST in non-vaccinated from TST in vaccinated, and deriving weighted estimates)

	TST in BCG				TST in non-vaccinated			Difference in prevalence			Number with FP-TST_{BCG}		
Author, year	*n* tested	5–9 mm %	10–14 mm %	15+ mm %	5–9 mm %	10–14 mm %	15+ mm %	5–9 mm %	10–14 mm %	15+ mm %	5–9 mm *n*	10–14 mm *n*	15+ mm *n*
Eason, 1987[9]	1 425		2.5			2.2			0.3			4	
Karalliedde, 1987[10]	522		3.9			4.4			−0.5			−3	
al-Kassimi, 1991[11]	1 945		11.5			5.1			6.4			125	
el-Kassimi, 1991[12]	283	11.0	18		9.1	4.5		1.9	13.5		5	38	
Menzies, 1992[6]	1 041	7.5	5.0	2.7	1.5	1.1	1.2	6.0	3.9	1.5	62	41	16
Young, 1992[13]	522	3.8	2.2	4.0	2.4	6.0	5.4	1.4	−3.8	−1.4	7	−20	−7
al-Kassimi, 1993[14]	2 119		12.0			5.6			6.4			136	
Menzies, 1994[7]	381		8.1			2.3			5.8			22	
Miret-Cuadras, 1996[5]	446	24.0	20.1	9.0	5.4	6.8	5.2	18.6	13.3	3.8	83	59	17
Bener, 1996[15]	544	8.6	11.8		7.2	7.5		1.4	4.3		8	23	
Getchell, 1992[16]	251	19.5	39.9		2.5	42.5		17	−2.6		43	−7	
Liard, 1996[17]	920	10.0	16.0	9.8	4.0	3.2	1.9	6	12.8	7.9	55	118	73
Schwartzman, 1996[18]	76		33.0			18.0			15.0			11	
Jochem, 1997[19]	11		27.0			23.0			4.0			0.4	
Bosman, 1998[20]	25 381	13.8	10.5	7.4	10.7	5.2	5.3	3.1	5.3	2.1	787	1 345	533
Chadha, 2000[21]	3 165	40.5	21.5	15.2	45.8	17.6	10.3	−5.3	3.9	4.9	−168	123	155
Chadha, 2001[22]	5 653	27.4	12.9	14.4	27.3	8.4	12.1	0.1	4.5	2.3	6	254	277*
Tanzania, 2001[23]	161 357	—	19.1	8.3	—	12.5	5.3	—	6.6	3.0	—	10 621	4799
Chadha, 2003[24]	5 542	15.0	7.8	6.0	11.5	5.9	7.7	3.5	1.9	−1.7	194	116	−94*
Bierrenbach, 2003[25]	437	23.3	12.6	3.2	10.6	6.2	5.4	12.7	6.4	−2.2	55	28	−10
Lienhardt, 2003[26]	2 314	10.2	20.9	8.6	11.2	21.2	12.1	−1.0	−0.3	−3.5	−23	−7	−81
Chadha, 2004[27]	24 398	24.5	12.2	14.1	18.6	7.0	11.6	5.9	5.2	2.5	1439	1269	610
Hill, 2004[28]	959	6.3	10.3	28.0	6.0	13.0	27.0	0.3	−2.7	1.0	3	−26	10
Pai, 2005[29]	511	21.1	18.6	22.7	14.5	17.5	25.0	6.6	1.1	−2.3	34	6	−12
Total number BCG-vaccinated: studies with TST results in four categories (14 studies)							232 646					13 918	6 139
Total number BCG-vaccinated: studies with TST results in three categories (16 studies)							72 367				2 590	20 406	
Total number BCG-vaccinated: all studies. TST results in two categories (24 studies)							240 203						
Mean of effect estimated in each study: four size categories								4.9	4.1	1.2			
Mean of effect estimated in each study: two size categories									4.5				
Average effect – weighted by number of BCG vaccinees in each study: four size categories (14 studies)							232 646				3.6	6.0	2.6
Average effect – weighted by number of BCG vaccinees in each study: 10+ mm only (24 studies)							240 203					8.5	

Summary of calculations of weighted averages:
Reactions of 5–9 mm: 2590/72 367 (16 studies) = 3.6%.
Reactions of 10–14 mm: 13 918/232 646 (14 studies) = 6.0%.
Reactions of 15+ mm: 6139/232 646 (14 studies) = 2.6%.
In total reactions of 10+ mm: 20 406/240 203 (24 studies) = 8.5%.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test; FP = false-positive.

Table 6 Details of calculation of effect on tuberculin reactions of BCG given after the age of 1 year (subtracting TST in non-vaccinated from TST in vaccinated, and deriving weighted estimates)

		TST in BCG-vaccinated		TST in non-vaccinated		Difference in prevalence		Number with $FP_{BCG\ older}$	
Author, year	*n* tested	10–14 mm %	15+ mm %	10–14 mm %	15+ mm %	10–14 mm %	15+ mm %	10–14 mm *n*	15+ mm *n*
Abrahams, 1967[30]	53	19.1	1.9	0.9	1.2	18.2	0.7	5	0.4
Abrahams, 1968[31]	395	10.3	0.8	0.3	0.3	10	0.5	40	2
Comstock, 1971[32]	63	11.1	4.8	1.5	0	9.6	4.8	6	3
Horwitz, 1972[33]	716	15.2	64.8	0.6	0.8	14.6	64	105	458
Baily, 1980[34]	8 702	62.9		20.4		42.5		3 698	
Eason, 1987[9]	1 395	33	11	9	6	24	5	335	70
Menzies, 1992[6]	469	12.8	10.2	1.4	1.6	11.4	8.6	53	40
Menzies, 1994[7]	210	26.2		2.3		23.9		50	
Ildirim, 1995[3]	470	40.9	30.2	6	5	34.9	25.2	164	118
Schwartzman, 1996[18]	117	43		18		25		29	
Jochem, 1997[19]	39	46		23		23		9	
Kang, 2005[35]	99	24	27	7	10	17	17	17	17
Total 10+	12 728							5 314	
10–14, 15+	3 660							725	708

Summary of calculations of weighted averages:
Total TST reactions attributable to BCG:
Reactions of: 10+ mm (12 studies) = 5314/12 728 = 41.8%.
10–14 mm (8 studies) = 725/3660 = 19.8%.
15+ mm (8 studies) = 708/3660 = 19.4%.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test; FP = false-positive.

Table 7 Modification of effect of BCG vaccination on TST by age of BCG vaccination, interval between BCG and TST, as well as type of TST

	BCG in infancy			BCG older (after age of 1 year)		
		Positive TST			*n* positive	
Comparison	*n* subjects (*n* studies)	Criteria mm	*n* (%)	*n* subjects (*n* studies)	Criteria mm	*n* (%)
Overall effect from all studies	240 203 (24)	10+	20 406 (8.5)	12 728 (12)	10+	5 314 (41.8)
By interval						
⩽10 years	234 464 (16)	10	4 930 (8.7)	3 128 (7)	10	5 123 (43.3)
>10 years	5 739 (8)	10	56 (1.0)	898 (5)	10	191 (21.2)
By TST size	71 289 (13)	10–14	3 297 (4.6)	3 660 (8)	10–14	725 (19.8)
		15+	1 340 (1.9)		15+	708 (19.4)
By interval and TST size						
⩽10 years	170 401* (9)	10–14	13 854 (8.1)	3 128* (6)	10–14	649 (20.7)
		15+	6 346 (3.7)		15+	665 (21.3)
>10 years	5 271 (5)	10–14	73 (1.4)	532 (2)	10–14	59 (11.1)
		15+	0 (0)		15+	43 (8.1)
By type of TST						
5TU PPDS	170 401 (13)	10+	15 878 (9.3)	11 913 (10)	10+	4 622 (39.0)*
1TU RT23	39 791 (6)	10+	2 701 (6.8)	—	—	—
2TU RT23	30 011 (5)	10+	2 056 (6.9)	815 (2)	10+	597 (73.3)*

* Of the 10 studies using 5TU PPDS to test subjects vaccinated at an older age, 5 involved average intervals of ⩾10 years between vaccination and TST. On the other hand, both studies using 2TU RT23 involved shorter intervals of 5 or 8 years.
BCG = bacille Calmette-Guérin; TST = tuberculin skin test.

the current World Health Organization recommendations to give BCG only in infancy[75] as there is no benefit of revaccination in older children.[76]

This review did not consider the effect of BCG vaccine strain because six different strains were used in 16 studies, and multiple or unknown strains in 15. The largest number of studies with a single strain was for BCG-Danish, six of which reported results for vaccination in infancy. The average TST-FP_{BCG} effect was 6.6% (compared to 8.5% overall), and ranged from 17.1% (the second largest effect in all 24 studies) to −1.2% (third smallest). No other comparison could be made, given the very small size of the sub-groups. Other evidence is contradictory regarding BCG strain as a determinant of post-vaccinal tuberculin reactions. In one experimental study,[33] there was minimal inter-strain variation in tuberculin reactions after 5 years. Nevertheless, in one review, substantial differences in post-vaccinal tuberculin reactivity were noted,[77] but were not associated with vaccine efficacy. Behr and col-

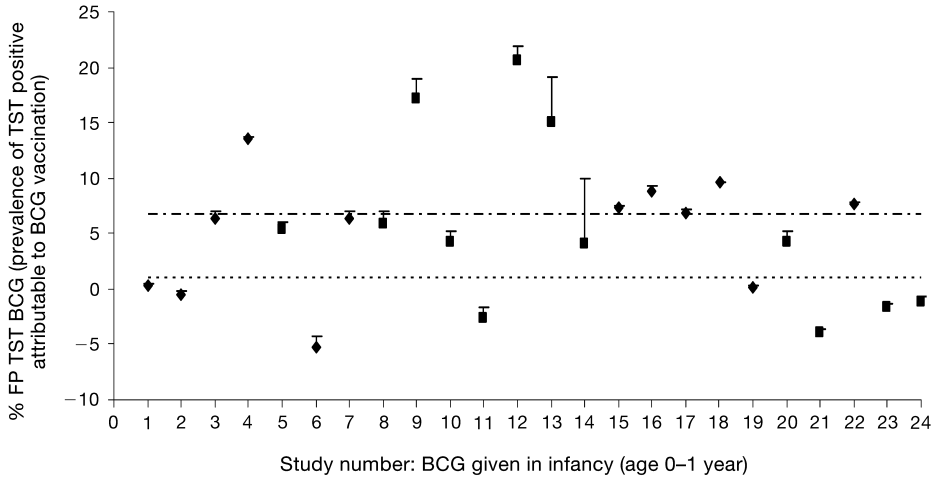

Figure 1 Effect on TST reactions of BCG vaccination in infancy. Dashed line: weighted average effect in studies where the interval from BCG until TST was <10 years. Dotted line: weighted average effect in studies where the interval from BCG until TST was >10 years. Diamonds: point estimates (and SE bars) from individual studies with interval of <10 years. Squares: point estimates from individual studies with interval of ⩾10 years. FP = false-positive; TST = tuberculin skin test; BCG = bacille Calmette-Guérin; SE = standard error. References for studies: 1: Eason,[9] 2: Karalliedde,[10] 3: El Kassimi,[11] 4: El Kassimi,[12] 5: Menzies,[6] 6: Young,[13] 7: El Kassimi,[14] 8: Menzies,[7] 9: Miret,[5] 10: Bener,[15] 11: Getchell,[16] 12: Liard,[17] 13: Schwartzman,[18] 14: Jochem,[19] 15: Bosman,[20] 16: Chadha,[21] 17: Chadha,[22] 18: Tanzania TB Survey,[23] 19: Chadha,[24] 20: Bierrenbach,[25] 21: Lienhardt,[26] 22: Chadha,[27] 23: Hill,[28] 24: Pai.[29]

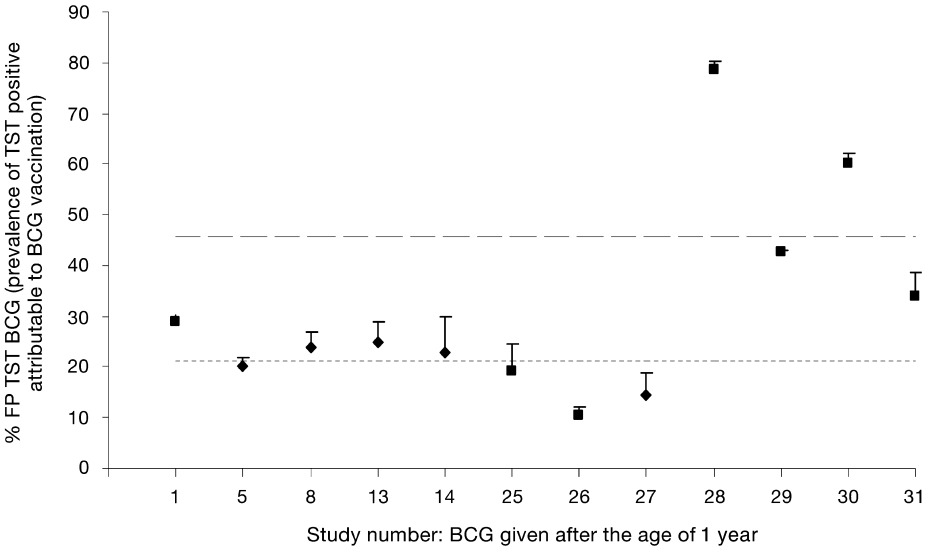

Figure 2 Effect on TST reactions of BCG vaccination given after the age of 1 year. Dashed line: weighted average effect in studies where the interval from BCG until TST was <10 years. Dotted line: weighted average effect in studies where the interval from BCG until TST was >10 years. Diamonds: point estimates (and SE bars) from individual studies with interval of ⩾10 years. Squares: point estimates from individual studies with interval of <10 years. FP = false-positive; TST = tuberculin skin test; BCG = bacille Calmette-Guérin; SE = standard error. References for studies: 1: Eason,[9] 5: Menzies,[6] 8: Menzies,[7] 13: Schwartzman,[18] 14: Jochem,[19] 25: Abrahams,[30] 26: Abrahams,[31] 27: Comstock,[32] 28: Horwitz,[33] 29: Baily,[34] 30: Ildirim,[3] 31: Kang.[35]

Table 8 Using 12 studies with dual testing to estimate the false-positive TST rate per 100 NTM sensitised (FP-TST_{NTM})

Author, year	Setting	Participants		Prevalence of NTM infection		False-positive TST per 100 with NTM dominant (FP TST_{NTM})	
		Age, years range or mean	*n*	Antigen	Standardised and corrected %	10–11 mm	10–14 mm
Studies providing complete data*							
Bleiker, 1968[54]	The Netherlands	6–15	3 108	A	6.4	1.5	4.0
	France	6–15	2 038	A	3.0	4.8	11.3
Brickman, 1974[57]	Montreal	4–6	1 594	A/B/G	3	12	12
Paul, 1975[58]	Kenya	6–17	34	A/G	24	0	5
Menzies, 1989[64]	Montreal	11.6	2 408	B	3	0	1.4
		16.1	983	B	8	7.9	7.9
Lind, 1991[65]	Sweden	8–9	2 819	A/G	34.1	0.7	1.1
Cumulative TST-FP/100 NTM from five studies						1.6	2.7
Studies with categorical data*							
Jeanes, 1969[55]	Canada	14–22	33 741	B/G	6.2	—	3.1
Edwards, 1973[56]	US–North†	17–21	573 141	B/G	16	1.0	1.5
	US–Central‡	17–21	268 554	B/G	28	0.7	1.3
	US–South§	17–21	185 475	B/G	44	0.9	1.3
Baily, 1980[34]	India	1–14	101 106	B	85	2.4	5.7
Wells, 1982[60]	Barbados	3–8	908	B	23	0	0
Frappier-Davignon, 1989[62]	Quebec	15–19	1 047	B	3	0	0
von Reyn, 2001[69]	US	29	784	A	38	1.6	3.6
Bierrenbach, 2003[25]	Brazil	10.9	315	A/G	35	—	8.2
Cumulative TST-FP/100 NTM from all twelve studies						1.1	2.0

* The first five studies provided mm by mm data for all skin test reactions. The remaining six provided categorical data (i.e., reactions of 5–9, 10–14 mm, etc.).
† Northern states include the following: CA, CO, CT, DC, ID,IL, ID, IA, KY, ME, MA, MI, MN, MT, NH, NJ, NY, OH, OR, PA, RI, SD, UT, VT, WA, WI, WY.
‡ Central states: DE, KS, MD, MO, NE, NV, NM, NC, ND, OK, TN, VA, WV.
§ Southern states: AL, AZ, AR, FL, GA, LA, MS, SC, TX.
TST = tuberculin skin test; BCG = bacille Calmette-Guérin; FP = false-positive.

leagues noted that vaccine efficacy appeared to wane over successive BCG strain cultures, but that tuberculin reactivity was maintained,[78] differences that were associated with significant genetic deletions.[79] The authors speculated that this was due to the selection by vaccine manufacturers of strains that produced tuberculin reactivity. This was done to comply with regulatory authorities in many countries, who required proof of post-vaccinal tuberculin reactivity (which was easy to measure), rather than vaccine efficacy (which was not).

Use of the 5 mm cut-off point to define NTM sensitivity was arbitrary. This definition was adopted because the studies of NTM reviewed used cut-off points of 2–6 mm to define NTM sensitivity. The 5 mm definition was thus used to facilitate comparison of the different studies reviewed, and to compare our results with others. This also allows us to calculate the likelihood of false-positive TST in any setting where the prevalence of NTM sensitivity is known. In reality, only NTM reactions of 12+ mm will cause false-positive TST (with PPD-S or equivalent) of 10+ mm, so it is only the prevalence of such reactions that are of interest. However, use of a definition of NTM reactions of 12+ mm could have caused some confusion, as the resultant estimated prevalence of NTM sensitivity would have been much lower than all published estimates.

This review demonstrates that the absolute impact of NTM is surprisingly low, even in populations with a high prevalence of NTM sensitivity. NTM reactions will therefore be important only if the likelihood of true TB infection is very low. For example, in a young adult from the Southern US, the likelihood that a TST of 10–14 mm indicates TB infection will be below 50%, because the expected prevalence of true TB infection in this population is below 1%. On the other hand, in adults from India, Malawi or Brazil, the likelihood that a TST of the same size indicates TB infection exceeds 95%.

CONCLUSIONS

The effect on TST of BCG received in infancy is minimal, and virtually nil 10 years or more after vaccination. BCG given after the age of 1 year produces more frequent, persistent, and larger TST reactions. NTM is not an important cause of false-positive TST, except in populations with a high prevalence of NTM sensitisation and a very low prevalence of TB infection.

Based on this review it can be predicted that new IGRAs will be most useful in populations who have received BCG vaccination after the age of 1 year. In settings where BCG vaccination was not given, or given only in infancy, the specificities of TST and IGRAs should be similar and the selection of TST or IGRA

Table 9 Estimated absolute prevalence of false-positive TST (of 10–14 mm), due to cross-reactions from NTM in a healthy general population sample

		Participants		NTM prevalence*		FP-TST$_{NTM}$ (10–14 mm)	
Author, year	Setting	Age, years	*n*	Antigen	Prevalence %	Lower estimate %	Higher estimate %
Bleiker, 1968[54]	Netherlands	6–15 (boys)	3 108	A	6.4	0.1	0.2
	France	6–15 (girls)	2 038	A	3.0	0.0	0.1
Brickman, 1974[57]	Montreal	4–6	567	B	2	0.0	0.1
			473	G	4	0.1	0.1
Paul, 1975[58]	Kenya	6–17	27	A	22	0.4	0.6
			7	G	29	0.6	0.8
Menzies, 1989[64]	Montreal	11.6	2 408	B	3	0.0	0.1
		16.1	983	B	8	0.2	0.2
Lind, 1991[65]	Sweden	8–9	1 368	A	31	0.6	0.8
			1 451	G	38	0.8	1.0
Edwards, 1973[56]	US–North†	17–21	573 141	B/G	16	0.3	0.4
	US–Central‡	17–21	268 554	B/G	28	0.6	0.8
	US–South§	17–21	185 475	B/G	44	0.9	1.2
	US–Florida			B/G	51	1.0	1.4
Ogunmekan, 1977[59]	Nigeria	10–15	509	A	33	0.7	0.9
			245	G	34	0.7	0.9
Baily, 1980[34]	India	1–14	101 106	B	86	1.7	2.3
Wells, 1982[60]	Barbados	3–8	908	B	23	0.5	0.6
Bahr, 1986[61]	Lebanon	7–17	1 823	G	3	0.1	0.1
Frappier-Davignon. 1989[62]	Quebec	15–19	1 047	B	3	0.1	0.1
Ly, 1989[63]	Vietnam	12	153	AA	15	0.3	0.4
			155	G	6	0.1	0.2
Osman, 1994[67]	Saudi Arabia	6–12	34	A	16	0.3	0.4
			38	G	25	0.5	0.7
Fine, 2001[68]	Malawi	20–65	2 623	A	39	0.8	1.0
			2 886	B	58	1.2	1.6
			3 324	G	58	1.2	1.6
Bierrenbach, 2003[25]	Brazil	10.9	170	A	36	0.7	1.0
			145	G	34	0.7	0.9
Jeanes, 1969[55]	Canada	14–22	26 158	B	4.9	0.1	0.2
			7 583	G	6.6	0.1	0.2
von Reyn, 1993[66]	NH, Boston	18–65	206	A	12	0.2	0.3
	Finland	18–45	74	A	3	0.1	0.1
	Trinidad	18–65	102	A	14	0.3	0.4
	Kenya	18–65	102	A	30	0.6	0.9
von Reyn, 2001[69]	South US	29	284	A	46	0.9	1.2
	North US		500	A	33	0.7	0.9

* NTM prevalence now corrected for TST dominant reactions and standardised to 5 mm cut-off point.
† Northern states: any of the following states: CA, CO, CT, DC, ID,IL, ID, IA, KY, ME, MA, MI, MN, MT, NH, NJ, NY, OH, OR, PA, RI, SD, UT, VT, WA, WI, WY.
‡ Central states: DE, KS, MD, MO, NE, NV, NM, NC, ND, OK, TN, VA, WV.
§ Southern states: AL, AZ, AR, FL, GA, LA, MS, SC, TX.
TST = tuberculin skin test; NTM = non-tuberculous mycobacteria; FP = false-positive.

will depend on other considerations such as cost, feasibility and acceptability.

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RÉSUMÉ

CONTEXTE : Malgré certains inconvénients, le test cutané tuberculinique (TST) reste largement utilisé. Les avantages importants de ce test sont son faible coût, sa simplicité et son interprétation basée sur des publications abondantes dans la littérature. Toutefois, la spécificité du TST est réduite par la vaccination au bacille de Calmette-Guérin (BCG) et par l'exposition à des mycobactéries non-tuberculeuses (NTM).

MÉTHODES : Pour estimer la spécificité du TST, nous avons fait une revue de la littérature publiée depuis 1966 en ce qui concerne les effets de la vaccination BCG et ceux de l'infection à mycobactéries non-tuberculeuses sur le TST. Les études sélectionnées ont comporté des sujets sains dont le statut vaccinal BCG était documenté, y compris l'âge à la vaccination ; pour les études sur les effets des NTM, on a utilisé des antigènes NTM standardisés chez les sujets sains.

RÉSULTATS : Dans 24 études impliquant 240 203 sujets vaccinés au BCG dans la prime enfance, au total 20 406 (8,5%) avaient un TST ⩾10 mm attribuable au BCG, mais 56 seulement parmi 5639 (1%) avaient un TST positif s'ils avaient été testés ⩾10 ans après le BCG. Dans 12 études concernant 12 728 sujets vaccinés après leur premier anniversaire, au total 5314 (41,8%) avaient des TST faussement positifs de ⩾10 mm et 191 sur 898 (21,2%) après 10 ans. Le type de TST ne modifie pas ces résul-

tats. Dans 18 études impliquant 1 169 105 sujets, la prévalence absolue des TST faussement positifs provenant d'une réactivité croisée aux NTM varie de 0,1% à 2,3% selon les régions.

CONCLUSIONS : L'effet sur le TST du BCG appliqué dans la prime enfance est minimal, spécialement ⩾10 ans après la vaccination. Le BCG reçu après la prime enfance produit des réactions du TST plus fréquentes, plus persistantes et plus importantes. Les NTM ne sont pas une cause cliniquement importante de TST faussement positif sauf dans les populations où la prévalence de la sensibilisation aux NTM est élevée et où la prévalence de l'infection tuberculeuse est très faible.

RESUMEN

MARCO DE REFERENCIA : Pese a algunos inconvenientes, la prueba cutánea de la tuberculina (TST) se sigue utilizando en forma generalizada. Entre sus ventajas se cuentan el bajo costo, la sencillez y la interpretación respaldada por una base considerable de artículos publicados. Sin embargo, la vacunación bacille Calmette-Guérin (BCG) y la exposición a las micobacterias atípicas (NTM) reducen la especificidad de la reacción a la TST.

MÉTODOS : Con el fin de estimar la especificidad de la TST se analizaron los artículos publicados a partir de 1966, referentes a las consecuencias de la vacuna con BCG y de la infección por NTM sobre la respuesta a la TST. Los estudios escogidos incluyeron individuos sanos con situación confirmada de su vacunación BCG, incluida la edad a la vacunación. En los estudios sobre las NTM se aplicaron antígenos normalizados en individuos sanos.

RESULTADOS : En 24 estudios que incluyeron 240 203 individuos vacunados con el BCG durante el primer año de vida, un total de 20 406 (8,5%) tuvo una reacción TST de ⩾10 mm atribuible al BCG, pero sólo en 56 de 5639 (1%) la reacción fue positiva cuando se practicó con un intervalo de ⩾10 años después de la vacunación. En 12 estudios de 12 728 individuos vacunados después del primer año de edad, un total de 5314 (41,8%) tuvo una reacción TST falsamente positiva de ⩾10 mm y 191 de 898 (21,2%) con un intervalo de >10 años. El tipo de TST no modificó estos resultados. En 18 estudios que comprendieron 1 169 105 individuos, la prevalencia absoluta de una reacción TST positiva falsa por reacción cruzada con NTM osciló entre 0,1% y 2,3% en diferentes regiones.

CONCLUSIONES : La repercusión de la BCG recibida en la primera infancia sobre el resultado de la TST es mínima, en particular ⩾10 años después de la vacunación. El BCG recibido después del primer año de vida, produce con mayor frecuencia reacciones TST positivas, más persistentes y de mayor magnitud. Las NTM no constituyen una causa importante de reacciones positivas falsas, excepto en poblaciones con una alta prevalencia de sensibilización a las mismas y muy baja prevalencia de infección tuberculosa.