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Effect of neonatal bacille Calmette-Guérin on the tuberculin skin test reaction in the first 2 years of life

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SUMMARY

SETTING: Latent tuberculous infection (LTBI) is an important reservoir of disease reactivation that is sufficient to generate new cases for decades. The tuberculin skin test (TST) is an important tool to diagnose LTBI; however, neonatal bacille Calmette-Guérin (BCG) vaccination may impact interpretation of TST data.

OBJECTIVES: To analyse the effect of the neonatal BCG vaccine on TST reaction in the first 2 years of life in children with no identified contact with tuberculosis (TB).

DESIGN: This was a cross-sectional study in children up to 2 years of age who received neonatal BCG vaccination. In the absence of baseline comorbidities or contact with the bacillus, the children were given the TST.

RESULTS: Seventy-nine children participated in the study. A decline in TST reactivity was observed in the first 12–24 months of age in patients who had been vaccinated with neonatal BCG but with no contact with TB. After the age of 10 months, no patient showed a TST reaction of >5 mm.

CONCLUSION: BCG had low impact on the TST in children with no TB contact. This finding suggests the need to reassess the cut-off point to 5 mm of induration to improve TST specificity in LTBI identification.

KEY WORDS: *Mycobacterium tuberculosis*; latent tuberculosis; TST; BCG

TUBERCULOSIS (TB) IS A COMPLEX infectious disease caused by *Mycobacterium tuberculosis*, with high rates of morbidity and mortality.[1–4] It is estimated that a third of the world's population is infected with the disease-causing bacillus. Brazil is one of the 22 countries prioritised by the World Health Organization (WHO).[1]

In most situations in which the host comes into contact with *M. tuberculosis*, the body's immune response may be sufficient to prevent the disease, and total destruction of the bacteria or disease latency may occur. In this case, the individual remains infected, but is positive on the tuberculin skin test (TST) and negative on screening tests for mycobacteria.[5–7] Carriers are asymptomatic and are not infectious; however, 5–15% of these cases are likely to progress to the active form of the disease, although the possible occurrence of TB reactivation can be avoided with preventive treatment.[8]

Latent tuberculous infection (LTBI) may be present in any age group, but its presentation in childhood is worrying because of the possible severity of the manifestation.[9,10] Paediatric patients, particularly those aged <5 years, are considered high-risk for disease progression and at a higher risk of severe forms of the disease. Young children are thus one of the main targets for the preventive treatment of LTBI, with accurate and rapid diagnostic methods having an impact on TB control strategies.[11,12]

In Brazil, all children, unless contraindicated, receive the lyophilised bacille Calmette-Guérin (BCG) vaccine in the neonatal period. This consists of live, attenuated and lyophilised BCG from the Moureau-Rio de Janeiro strain, and is administered intradermally at 0.1 ml into the inferior insertion of the right-arm deltoid.[13]

It is well known that previous vaccination can generate false-positive results to the TST, which may lead to inappropriate management of high-risk groups.[14] There is evidence that post-vaccinal TST reactivity declines over time.[15] However, subsequent reactivity can vary depending on dose, manufacturer of the vaccine, age when vaccinated, and the interval between vaccination and testing.

According to the World Health Organization (WHO), the correct diagnosis and treatment of LTBI is crucial for disease control,[15] as it reduces the risk of progression to active disease, particularly in high-risk

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groups such as children aged <5 years, human immunodeficiency virus (HIV) infected patients or those on immunosuppressive therapy.[11] Interferon-gamma release assays (IGRAs) are recommended for the detection of tuberculous infection in children aged >5 years, but have yielded inconsistent results and even lower sensitivity in young children.[16–20] Diagnosis of tuberculous infection in high-risk populations such as young children is thus mainly reliant on the TST.

There is no consensus about the appropriate TST cut-off point in infants.[16–20] The WHO recommends using a TST induration size of ⩾10 mm as positive regardless of BCG status. Brazilian guidelines recommend a TST size of ⩾10 mm in infants who receive neonatal BCG. Guidelines set by the UK National Institute for Health and Care Excellence (NICE) recommend that any TST ⩾5 mm be considered positive and cut-offs recommended by the Infectious Diseases Society of America vary depending on whether subjects are close contacts of TB cases or are immunosuppressed.[16,21]

Most of the studies on which these guidelines are based did not focus specifically on the effect of BCG on the TST in children aged <2 years.[14] Earlier studies described a cut-off of 10–12 mm, but TB contacts were not excluded and this may have led to bias.[22,23] A recent study in the UK assessing different cut-offs of the TST among vaccinated and non-vaccinated children found a high negative predictive value for 5 mm, but IGRAs were considered the 'gold standard' in that study.[24]

Given the importance of accurate diagnosis of tuberculous infection in infants, reliance on the TST for diagnosis in this age group and uncertainty about the best cut-off point to use, we assessed the effect of BCG neonatal vaccination on the TST induration reaction in the first 2 years of life in children with no exposure to TB.

MATERIALS AND METHODS

Design and sampling

A cross-sectional study was carried out between June and November 2016 in the municipality of Santa Cruz do Sul, RS, Brazil. For convenience, study sampling was non-probabilistic. First, inclusion criteria were applied based on an analysis of the records of all births that occurred in Santa Cruz do Sul during the study period; contact was made via telephone, and a paediatric consultation was scheduled.

Children aged up to 2 years who had received the BCG vaccine were included in the study. Exclusion criteria were children of birth weight <2000 g; of HIV-positive mothers; of mothers with bacilliferous TB in the perinatal period; with evidence of primary and/or secondary immunodeficiency; with no BCG vaccine scar; those who were screened for TB, or had symptoms indicative of the disease; and those who lived in neighbourhoods with notified adult cases. People who could not be contacted by telephone were also excluded.

After obtaining written informed consent from parents, children with no health disorders or TB contacts were given the TST.

Procedures

An intradermal TST was given and induration size read after 72 h by the same trained investigator in all patients. Based on the results, participants were classified as non-reactive (0–4 mm), weakly reactive (5–9 mm) or strongly reactive (⩾10 mm).

Data analysis

Data were analysed using SPSS v 22.0 (IBM, Armonk, NY, USA). In the descriptive analysis, mean and standard deviation or median and interquartile ranges were used for quantitative variables, and percentages for qualitative variables. Pearson's χ^2 test or Fisher's exact test were used to assess differences in associations between categorical variables. Single-factor analysis of variance (ANOVA) was used to compare mean values of TST. $P < 0.05$ was considered statistically significant.

Ethics

The study protocol was approved by the Research Ethics Committee of Universidade de Santa Cruz do Sul, Santa Cruz do Sul (1 540 102).

RESULTS

The study sample consisted of 79 children selected purposively from neighbourhoods with no registered TB cases (Figure 1). Infants' ages ranged from 3 to 24 months (median 9.5 months in boys; 11 months in girls). Participants were predominantly White and from middle-income families (Table 1). Data on respiratory symptoms were collected to exclude TB-associated symptoms: 16 patients (20%) had symptoms associated with respiratory viral infection (cough, coryza) in the previous month. No participant (0%) presented with chronic cough or persistent fever (>3 weeks).

Infants received BCG before 28 days of life and were recorded in the BCG registry and/or presented with BCG scar. With regard to the TST reaction, 59 participants (74.9%) were non-reactive, while 20 (25.3%) were classified as weakly reactive (Figure 2).

The sample was divided into three groups according to age: group I comprised children aged 3–9 months, group II, children aged 10–18 months and group III, 19–24 months. On ANOVA, there was a statistically significant decrease in the mean TST reaction with increase in age ($P = 0.041$; Table 2).

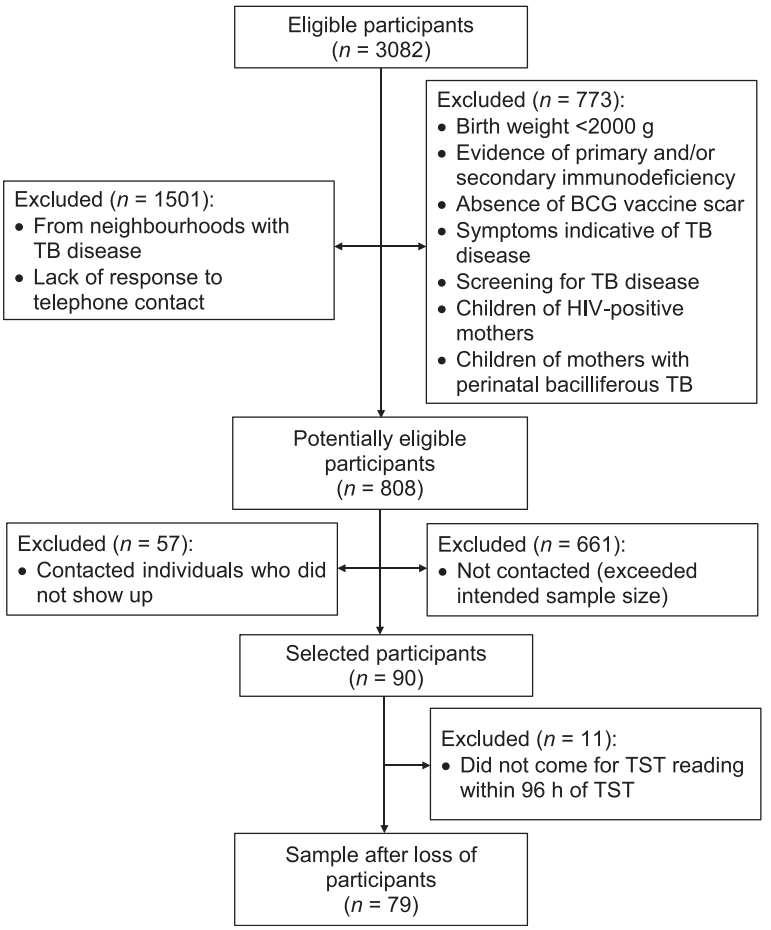

Figure 1 Sample flowchart. BCG = bacille Calmette-Guérin; TB = tuberculosis; HIV = human immunodeficiency virus; TST = tuberculin skin test.

After the age of 10 months, no participants had a TST reaction of >5 mm, which is evidence of the decline in TST reactivity as early as the first year of life. No adverse effects secondary to the TST were recorded during the study period.

Table 1 Characteristics of the study cohort

Variable	*n* (%)
Sex	
Male	42 (53.2)
Female	37 (46.8)
Age, months	
3–9	37 (46.8)
10–18	22 (27.9)
19–24	20 (25.3)
Ethnicity	
White	72 (91.1)
Black	3 (3.8)
Mixed	4 (5.1)
Asian	0
Native Brazilian	0
Family income	
<1 minimum wage	3 (3.8)
1–2 minimum wages	30 (38.0)
3–4 minimum wages	30 (38.0)
⩾5 minimum wages	16 (20.3)
Total	79 (100)

DISCUSSION

According to our findings in children with no adult TB contact, BCG vaccination had little impact on the TST. A decline in TST reactivity was observed in the first 12–24 months of age in healthy, previously BCG-vaccinated patients with no TB contact. In those aged 3–9 months, a greater induration reaction was observed. After the age of 10 months, no patient showed a TST reaction of >5 mm.

Differences in guidelines possibly reflect settings with different burdens and risk perceptions, and

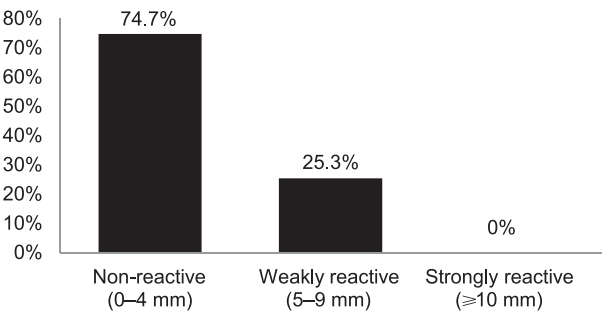

Figure 2 Distribution of patients in terms of TST reactivity. TST = tuberculin skin test.

Table 2 Association between age groups and TST result

Age group, months	*n*	TST result Mean ± SD	*P* value (ANOVA)
I: 3–9	37	3.73 ± 2.874	0.041
II: 10–18	22	2.41 ± 2.482	
III: 19–24	20	2.10 ± 1.917	
Total	79	2.95 ± 2.631	

TST = tuberculin skin test; SD = standard deviation; ANOVA = analysis of variance.

suggest that further research on the effect of neonatal BCG on the TST is required.[25] Several studies have addressed the impact of BCG on the TST in children, but many of them had a different focus. Findings from a 1965 study carried out in the Navajo community in the United States with no BCG vaccination after 1 year of age are very similar to ours; however, as malnourishment rates and comorbidities were not reported, comparisons are difficult.[23]

Two large reviews dealt mainly with the long-term impact of BCG. A meta-analysis involving studies published until 1999 reported an increased risk of a TST reaction ⩾10 mm until 15 years of age among vaccinated children with no known TB contact. Different varieties of tuberculin used as well as the vaccination age may affect the results, with children immunised after infancy showing a longer duration of TST positivity.[26] Interestingly, a recently published study with a long follow-up reported an impact of BCG until 55 years of age when vaccination occurred after infancy.[27] Another large review involving studies published until 2005 reported a rate of 8.5% for ⩾10 mm TST induration in children vaccinated during infancy.[14] However, as many types of tuberculin were compared, these findings cannot be extrapolated to specific settings.

A large study from the United Kingdom recently reported very high sensitivity and negative predictive value for TB using ⩾5 mm as the cut-off point. However, IGRA positivity was considered the gold standard, which is an important limitation. Furthermore, all included patients had previous contact with TB.[24] Nevertheless, we believe that as those possible biases would increase and not decrease TST positivity, those results are in line with our findings.

According to the evidence mentioned above, using TST induration of ⩾10 mm in infants (as recommended by some current guidelines) to diagnose TB may result in the emergence of new TB cases. Changing to a cut-off point of <5 mm could reduce the number of false-negatives, particularly in infants aged <24 months with suspected LTBI. Some authors have questioned the lack of specificity when using lower cut-off points. However, in populations with a higher risk of severe forms of TB and low incidence of isoniazid-related adverse events (e.g., infants), a higher negative predictive value and sensitivity may be more appropriate.[24]

Limitations of our study were the relatively small number of patients, lack of a control group, and convenience sampling. Conversely, as our sample was rigorously evaluated to exclude patients with TB contacts and underlying diseases, the specific effect of BCG in healthy infants could be assessed, although Brazil is a high TB burden country. It is evident that TB prevalence in the setting studied should also be taken into account when assessing the accuracy of a test, and the fact that TST yields more false-positive results in low-prevalence areas.[28] As our sample was selected carefully to exclude close TB contacts, our findings may be more generalisable to low-prevalence settings. However, as mentioned above, false-negatives and not false-positives, are of greater importance in infants.

CONCLUSION

The present study demonstrated little or no effect of BCG on the TST in infants. In this high-risk population, a higher negative predictive value is desirable. Our results, therefore, suggest that the cut-off induration size should be 5 mm in infants, as recommended by NICE guidelines.[21] This re-evaluation of the lower cut-off point in the first 2 years of life may help physicians achieve early and correct diagnoses, prevent paediatric patients from developing severe forms of TB, and avert inappropriate management of TB.

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Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : L'infection tuberculeuse latente (LTBI) constitue un important réservoir de réactivation de la maladie qui suffit à générer de nouveaux cas pendant des décennies. Le test cutané à la tuberculine (TST) est un outil important de diagnostic de la LTBI, mais le bacille Calmette-Guérin (BCG) néonatal est susceptible de modifier son interprétation.

OBJECTIF : Analyser l'effet du vaccin BCG néonatal sur la réaction au TST dans les 2 premières années de la vie des enfants n'ayant pas eu de contact identifié avec la tuberculose (TB).

SCHÉMA : Etude transversale, qui a inclus les enfants jusqu'à 2 ans qui ont reçu un vaccin BCG néonatal. En l'absence de comorbidités de départ ou de contact avec le bacille, les enfants ont été soumis au TST.

RÉSULTATS : Un total de 79 enfants ont participé à l'étude. On a observé un déclin de la réactivité au TST chez les enfants de 12–24 mois sans contact avec la TB qui ont été vaccinés par le BCG en période néonatale. Après l'âge de 10 mois, aucun patient n'a eu de réaction au TST >5 mm.

CONCLUSION : Cette étude montre le faible impact du BCG sur le TST chez les enfants sans contact avec la TB. Ce résultat suggère une réévaluation du seuil de 5 mm d'induration, afin d'améliorer la spécificité du TST dans l'identification de la LTBI, évitant une prise en charge inadéquate des patients pédiatriques.

RESUMEN

MARCO DE REFERENCIA: La infección tuberculosa latente (LTBI) representa un importante reservorio de reactivación de la enfermedad, capaz de generar casos nuevos durante decenios. La prueba cutánea de la tuberculina (TST) es un instrumento primordial en el diagnóstico de la LTBI, pero la vacuna antituberculosa (BCG) neonatal puede influir en la interpretación de sus resultados.

OBJETIVOS: Analizar el efecto de la vacunación neonatal con el BCG sobre la reacción TST durante los primeros 2 años de vida, en los niños sin un contacto conocido con la tuberculosis (TB).

MÉTODO: Fue este un estudio transversal en el cual se incluyeron niños hasta los 2 años de edad, que habían recibido la vacuna BCG neonatal. Se practicó la TST a los niños sin enfermedades subyacentes o contacto con el bacilo de la TB.

RESULTADOS: Participaron en el estudio 79 niños. Se observó una disminución de la reactividad a la TST en los primeros 12 a 24 meses de edad, en los niños sin contacto con la TB que habían recibido el BCG en el período neonatal. Después de la edad de 10 meses, en ningún niño la reacción TST fue >5 mm.

CONCLUSIÓN: En el presente estudio se pone de manifiesto una baja repercusión del BCG sobre la reacción TST en los niños que no han tenido contacto con la TB. Esta observación da motivos para reevaluar el umbral de 5 mm de induración, a fin de mejorar la especificidad de la prueba en la detección de la LTBI y evitar un manejo inadecuado de los pacientes pediátricos.