SA Journal of Child Health

Prevalence of Mantoux test positivity among apparently healthy children in Maiduguri, Nigeria

Modu Gofama Mustapha, *MB BS, FWACP*
Ashir Mohammed Garba, *MB BS, FWACP*
Adamu Ibrahim Rabasa, *MB BS, FWACP*
Mohammed Suleman Gimba, *MB BS*
Department of Paediatrics, University of Maiduguri Teaching Hospital, Maiduguri, Nigeria
Corresponding author: *M G Mustapha (mgofama@yahoo.com)*

Background. The impact of tuberculosis (TB) is highest in the developing countries of Asia and Africa, especially among children, in whom the diagnosis is challenging. Periodic skin testing by the Mantoux method is recommended in children living in regions of high TB prevalence.

Objective. To determine the prevalence of Mantoux test positivity among bacille Calmette-Guérin (BCG)-vaccinated and non-vaccinated children aged under 5 in Maiduguri, Nigeria.

Method. The study was descriptive and cross-sectional, conducted in 500 apparently healthy children aged 3 - 59 months and attending the child welfare clinics of the University of Maiduguri Teaching Hospital and two primary health care centres in Maiduguri, Nigeria, from May to August 2008. All children who fulfilled the inclusion criteria were evaluated for a history of BCG vaccination and Mantoux tested.

Results. It was possible to perform a Mantoux reading in 78.0% (390/500) of the children. Of these 201 (51.5%) were males and 189 (48.5%) females (male/female ratio 1.1:1). Thirty-one of the 390 children (7.9%) had a positive Mantoux reaction, 27 (87.1%) with an induration of 10 - 14 mm and the remaining 4 (12.9%) with an induration of 15 - 20 mm. The prevalence of Mantoux positivity was higher among vaccinated than non-vaccinated children (10.1% v. 1.1%, p=0.0034). Differences were also observed between the sexes (p=0.087) and between different age groups (p=0.159), but these were not significant.

Conclusion. Although a positive Mantoux response is usually attributed to TB infection, the effect of previous BCG vaccination on Mantoux test reactivity, especially in children, should be taken into consideration when interpreting Mantoux test responses.

Tuberculosis (TB) is a major public health problem globally, with the highest incidence recorded in the African sub-region.[1] The World Health Organization TB control programme aims at case-finding and treatment, with priority given to sputum smear-positive infectious cases, improvement in living standards and bacille Calmette-Guérin (BCG) vaccination at birth.

Although the burden of TB is high in children, the diagnosis remains challenging because of the nonspecific clinical presentation and laboratory findings. For example, the identification of *Mycobacterium tuberculosis* in clinical specimens (the gold standard for diagnosis of TB in adults) is seldom possible in children.[2,3] Periodic skin testing by the Mantoux method is recommended in children living in regions of high TB prevalence[4] and should be done at intervals based on the epidemiology of TB in the region. This study was undertaken to determine the prevalence of Mantoux test positivity among BCG-vaccinated and non-vaccinated children aged under 5 in Maiduguri, Nigeria.

Methods

A descriptive cross-sectional study was conducted among apparently healthy 3 - 59-month-old children attending the child welfare clinics of the University of Maiduguri Teaching Hospital (UMTH) and two primary health care centres and selected by a simple random method. A lower age limit of 3 months was decided on because tuberculin conversion occurs from 3 weeks to 3 months after contact with mycobacteria.[3] Children vaccinated with BCG at a later date (not at birth) were recruited only if at least 3 months had elapsed since vaccination (also to allow for tuberculin conversion).

Inclusion criteria. Apparently healthy children were defined as children with: (*i*) absence of fever (axillary temperature <37.5°C) or skin rash, as fever and/or skin rash with or without other symptoms could be a manifestation of an infection such as varicella, influenza, measles, malaria, HIV, etc., which are known to lower tuberculin skin test reactivity;[3] (*ii*) no abnormal findings on general physical examination, including the spine, and absence of significant peripheral lymphadenopathy;[5] (*iii*) no abnormal findings in the chest, abdomen, ears and throat; (*iv*) normal weight (>80% of expected weight for age);[6] and (*v*) normal length or height (>90% of expected height for age).[6] For a child to be included, informed consent had to be obtained from the parents or guardians.

Exclusion criteria were: (*i*) children who did not meet the criteria of apparent health (as indicated above); (*ii*) recent vaccination with live attenuated vaccine, e.g. measles, oral

polio vaccine, etc., as these vaccines temporarily suppress the delayed-type hypersensitivity response to the Mantoux test[7] until at least 6 weeks after administration;[8] (*iii*) past or present treatment for TB; (*iv*) concurrent treatment with steroids or cytotoxic agents; (*v*) a recent Mantoux test (less than 1 year), to avoid boosting effect;[9] (*vi*) age <3 months or >59 months; and (*vii*) non-consent of parent or guardian.

Ethical approval for the study was obtained from the Ethical Committee of the University of Maiduguri Teaching Hospital and informed consent was obtained from the parents or guardians of each child before recruitment.

Children who fulfilled the inclusion criteria were Mantoux tested. Purified protein derivative-Siebert (PPD-S) stabilised in Tween 80 (0.005%) (BB-NCIPD Ltd, Sofia, Bulgaria), batch number 4240106, was used in all children studied.

The injection of PPD and the reading of the reaction were done by one of the authors (MGM) after undergoing 1 week of training under the head of the Immunology Department at UMTH, where Mantoux testing is routinely done. The investigator's Mantoux readings were validated and found to be highly reproducible, with a 98% degree of concordance. The diameter of the induration was measured along the transverse axis of the forearm 48 - 72 hours after injection of the PPD[4,8] with a plastic transparent meter rule and also using the 'ball point pen' technique of Sokal,[10] which helps to make measurements more accurate. Reading of the reaction was done in a good light, and an induration of 10 mm and above was considered positive. The Mantoux reactions of the subjects were stratified into (modified from Egbagbe *et al.*[11]): (*i*) negative, induration 0 - 4 mm; (*ii*) borderline, induration 5 - 9 mm (intermediate); (*iii*) positive, induration 10 - 14 mm; (*iv*) moderately positive, induration 15 - 20 mm; and (*v*) strongly positive, induration 21 - 30 mm.

Children with a positive Mantoux test were followed up and managed appropriately.

Data were entered into a computer and analysed using SPSS version 13.0. Results were presented in percentages and frequencies were compared using the chi-square test or Fisher's exact test, as appropriate. A *p*-value of <0.01 was considered significant.

Results

A total of 500 children aged 3 - 59 months were Mantoux tested at the three health facilities between May and August 2007. Of these 390 (78.0%) were brought back so that the reaction could be read 48 - 72 hours after the test. The remaining 110 did not return at the appropriate time, giving a default rate of 22%. The study group consisted of 201 males (51.5%) and 189 females (48.5%) (male/female ratio 1.1:1). The age and gender distribution of the study population is shown in Table I.

Thirty-one of the 390 children in the study had a positive Mantoux reaction, giving a Mantoux positivity prevalence of 7.9%. Of these children 58.0% were males (male/female ratio 1.4:1). No significant statistical difference for Mantoux positivity was observed between the sexes (p=0.087) or between the different age groups (p=0.159). Twenty-seven of the 31 children (87.0%) had indurations of 10 - 14 mm and the remaining 4 (13%) had indurations of 15 - 20 mm. Table II shows the age and gender distribution of the children with positive Mantoux reactions.

The prevalence of Mantoux positivity among the vaccinated children was 10.1% (30/296) and that among the non-vaccinated children 1.1% (1/94). There was a significant difference in the overall prevalence of Mantoux positivity (≥10 mm) between BCG-vaccinated and non-vaccinated children (p=0.0034). Further analysis showed that among the children with a moderately positive Mantoux reaction (15 - 20 mm) there was no significant difference between the BCG-vaccinated and non-vaccinated children (p=1.0). However, in the children with an induration measuring 10 - 14 mm a significant difference was observed between the BCG-vaccinated and non-vaccinated groups (p=0.0007). No child had an induration of ≥20 mm.

Discussion

The importance of Mantoux testing both in the clinical and the epidemiological settings has been highlighted.[2,3,8] The prevalence of Mantoux test positivity among apparently healthy BCG-vaccinated and non-vaccinated 3 - 59-month-old children in Maiduguri is documented in this study.

The significant effect of BCG on the prevalence of Mantoux positivity (≥10 mm) seen in this study is similar to the observation made in validation of a risk assessment questionnaire of targeted testing of children for TB[12] conducted in northern California, where a history of BCG vaccination was observed to have the

TABLE I. AGE AND GENDER DISTRIBUTION OF THE STUDY POPULATION

Age groups (mo.)	Gender		Total	%
	Male	Female		
3 - 11	116	99	215	55.1
12 - 23	15	20	35	9.0
24 - 35	12	15	27	6.9
36 - 47	18	21	39	10.0
48 - 59	40	34	74	19.0
Total	201	189	390	100

TABLE II. AGE AND GENDER DISTRIBUTION OF THE CHILDREN WITH POSITIVE MANTOUX REACTIONS

Age groups (mo.)	Mantoux reaction (mm)				Total
	10 - 14		15 - 20		
	Male	Female	Male	Female	
3 - 11	14	5	0	3	22
12 - 23	4	0	0	0	4
24 - 35	0	0	0	0	0
36 - 47	0	2	0	1	3
48 - 59	0	2	0	0	2
Total	18	9	0	4	31

highest odds ratio of all factors studied. Similar observations of a higher prevalence of Mantoux positivity among BCG-vaccinated subjects compared with non-vaccinated subjects have been reported by workers in Africa as well.[13,14] However, other studies[15-17] showed no significant difference in Mantoux positivity between BCG-vaccinated and non-vaccinated subjects. This variability may be explained by vaccine-related factors, for example dosage, age at immunisation, time since immunisation, type of BCG vaccine used, and prevalence of TB infection and type of BCG vaccine used in the community.[18,19] Different BCG vaccines have been documented to give rise to widely varying tuberculin conversion rates, depending on the strain used to prepare the vaccine.[17,18] Another factor that may be responsible for the variability of the Mantoux results is exposure to non-tuberculous mycobacteria,[8,17] but the subjects in this study were young children and the likelihood of such exposure is therefore remote.

The lack of a significant difference in the prevalence of positive Mantoux reactions between the various age groups in this study is corroborated by the findings of Ifezulike *et al.* in Nnewi, south-eastern Nigeria.[20] Similar observations were also made in Botswana and Uganda.[15,21] However, other studies have shown an increased prevalence of Mantoux positivity with increasing age.[22,23] Differences in Mantoux positivity with age may be due to the different age groups studied. While our study was limited to children younger than 5 years, the studies that showed an increased prevalence with age included older children. The increase in prevalence with age in these studies may be because of cumulative exposure to various mycobacterial antigens with age, especially among BCG-vaccinated subjects.[13]

The lack of a difference in Mantoux positivity between the genders observed in this study corresponds with other reports.[15,20,21] However, Fine *et al.*[13] reported a higher prevalence of Mantoux positivity among males after puberty, which was attributed to increased exposure of males to *M. tuberculosis*, in addition to adult males having a greater tendency than females to develop hypersensitivity to mycobacterial antigens. Lack of a difference between males and females in this study and the others reported may be due to the younger age of the subjects.

The lack of a significant difference between the BCG-vaccinated and non-vaccinated children with moderately positive Mantoux reactions (15 - 20 mm induration) in this study is similar to the findings of Fine *et al.* in Malawi.[13] However, Chadha *et al.*[22] found significant differences between BCG-vaccinated compared with non-vaccinated children with Mantoux indurations of 15 - 19 mm. This was attributed to BCG vaccination, although the possibility of TB infection was also considered. Similarly, the Tanzanian Tuberculin Survey Collaboration[14] also reported a higher proportion of children with Mantoux reactions of 5 - 22 mm among BCG-vaccinated children compared with non-vaccinated children. It is unfortunate that Mantoux reactivity to BCG cannot be distinguished from reactivity due to true infection with *M. tuberculosis*, but data support the conclusion that children from countries with high case rates of TB disease are more likely to have a positive Mantoux test from TB infection than from BCG immunisation.[2] These findings further support the fact that in interpreting Mantoux test reactions the age of the subjects, the epidemiological and clinical characteristics of TB in the community and the BCG status of the subjects, especially children, should be taken into consideration. Depending on the risk factors for TB, children with identical Mantoux test reactions should be evaluated individually. The physician managing children needs to have a clear understanding of TB in his or her community.

References

1. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle* 1991; 72: 1-6.
2. Munoz FM, Strake JR. Tuberculosis (*Mycobacterium tuberculosis*). In: Behrman RE, Kheigamn RM, Jerson HB, eds. *Nelson Textbook of Paediatrics*. 17th ed. Philadelphia: Saunders, 2004: 958-972.
3. Shennan DH, Kibel AM. Tuberculosis. In: Stanfield P, Brueton M, Chan M, Parkin M, Waterson T, eds. *Diseases of Children in the Subtropics and Tropics*. 4th ed. London: Edward Arnold, 1991: 519-552.
4. American Academy of Pediatrics, Committee on Infectious Diseases. Screening of tuberculosis in infants and children. *Pediatrics* 1994; 93: 131-134.
5. Kelly CS, Kelly RE jr. Lympadenopathy in children. *Pediatr Clin North Am* 1998; 45 (4): 875-888.
6. Waterlow JC. Some aspects of childhood malnutrition as a public health problem. *BMJ* 1974 1-502.
7. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; 161: 221-247.
8. American Academy of Pediatrics. Pediatric Tuberculosis Collaborative Group: Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics* 2004; 114: 1175-1201.
9. Lordi GM, Reichman LB. Tuberculin skin testing. In: Schlossberg D, ed. *Clinical Topics in Infectious Disease*. Tuberculosis. 2nd ed. New York: Springer-Verlag, 1988: 33-38.
10. Sokal JE. Measurement of delayed skin test responses. *N Engl J Med* 1975; 293: 501-502.
11. Egbagbe EE, Iyawe VI, Awotedu AA. Value of Mantoux test in the diagnosis of pulmonary tuberculosis in Nigeria. *Niger J Med* 2000; 38(1): 11-13.
12. Hervey F, Lynn MA, Pius AM and the Pediatric Tuberculosis Study Group of Kaiser Permanente, Northern California. Targeted testing of children for tuberculosis: Validation of a risk assessment questionnaire. *Pediatrics* 2001; 107: 54-61.
13. Fine PE, Bruce J, Ponnighaus JM, Nkhosa P, Harawa A, Vynnycky E. Tuberculin sensitivity: conversions and reversions in a rural African population. *Int J Tuberc Lung Dis* 1999; 3: 962-975.
14. Tanzania Tuberculin Survey Collaboration. Tuberculosis control in the era of the HIV epidemic: risk of tuberculosis infection in Tanzania, 1983-1998. *Int J Tuberc Lung Dis* 200; 5: 103-112.
15. Lockman S, Tappero JW, Kenyon TA, Rumisha D, Huebner RE, Binkin NJ. Tuberculin reactivity in a pediatric population with high BCG vaccination coverage. *Int J Tuberc Lung Dis* 1999; 3: 23-30.
16. Janet RS, Barbara SH, Robert MB, Jane MV. Outcomes of annual tuberculosis screening by Mantoux test in children considered to be at high risk: Results from one urban clinic. *Pediatrics* 1997; 99: 529-533.
17. Al-Kassimi FA, Abdullah AK, al-Orainey IO, *et al.* The significance of positive Mantoux reactions in BCG-vaccinated children. *Tubercle* 1991; 72: 101-104.
18. Horwitz O, Bunch-Christensen K. Correlation between tuberculin sensitivity after 2 months and 5 years among BCG vaccinated subjects. *Bull World Health Organ* 1972; 47: 49-58.
19. Comstock GW, Edwards LB, Nabangxang H. Tuberculin sensitivity eight to fifteen years after BCG vaccination. *Am Rev Respir Dis* 1971; 103: 572-575.
20. Ifezulike CC, Ezechukwu CC, Egbonu I, Chukwura JO. Tuberculin reaction among healthy BCG vaccinated primary school children in Nnewi, South Eastern Nigeria. *Nigerian Journal of Clinical Practice* 2005; 8(1): 4-9.
21. Mudido PM, Guwatudde D, Nakakeeto MK, *et al.* The effect of bacille Calmette-Guérin vaccination at birth on tuberculin skin test reactivity in Ugandan children. *Int J Tuberc Lung Dis* 1999; 3: 891-895.
22. Chadha VK, Jaganath PS, Kumar P. Tuberculin sensitivity among children vaccinated with BCG under Universal Immunization Programme. *Indian J Paediatr* 2004; 71(12): 1063-1068.
23. Cuisia-Cruz ESS, Alcaneses MRS. Significance of tuberculin testing using Mantoux test and Monovacc test among Grade I students in a Makati primary public school. *Phil J Microbiol Infect Dis* 2000; 29(2): 61-67.