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ORIGINAL ARTICLE

Antituberculosis chemoprophylaxis in a public hospital - study of 100 children

Solange G. David,[1] Clemax C. Sant'Anna,[2] Anna M. Marques[3]

Abstract

Objective: to evaluate the recommendations of the Brazilian National Tuberculosis Control Program for antituberculosis chemoprophylaxis in children and in special cases, such as very young children, BCG vaccinated children with a positive tuberculin skin test, and recent or current exposure to infected cases.

Methods: a retrospective cross-sectional study of 100 children submitted to isoniazid chemoprophylaxis at a public hospital in Rio de Janeiro was carried out. The variables analyzed were gender, age, BCG vaccination, nutritional status, tuberculin skin test, tuberculin test conversion, source of tuberculous infection, adherence to preventive treatment, evolution to tuberculosis, and isoniazid side effects.

Results: the study population consisted of 57 boys and 43 girls; 62% were younger than 5 years of age; previous BCG vaccination was reported in 92%, malnutrition in 28% and recent tuberculin test conversion in 9% of the cases. Parents were the source of infection in 60% of the cases. There was adherence to preventive treatment in 73%, chemoprophylaxis failure in 1%, and isoniazid side effects in 1% of the cases.

Conclusion: control Program guidelines were followed strictly in 15% of the cases, including the 9 cases of recent tuberculin test conversion; 85% of the indications for chemoprophylaxis were associated with coverage of groups at high risk for developing the disease.

J Pediatr (Rio J) 2000; 76(6): 413-20: tuberculosis, chemoprophylaxis, tuberculin test.

Introduction

Antituberculosis chemoprophylaxis is concerned with the prevention of tuberculosis (TB) using a specific antituberculosis drug. The use of a specific antituberculosis drug dates back to the 1950s. Studies conducted by the U.S. Public Health Service showed a reduction of 88% in the cases of tuberculosis in patients who were submitted to therapy with isoniazid (INH) in comparison with those who received placebo.[1]

Despite its effectiveness to prevent and reduce the risk for TB, chemoprophylaxis is not yet widely used in Brazil. Current Brazilian rules restrict the recommendation of chemoprophylaxis to certain groups, which include asymptomatic, non-BCG-vaccinated children younger than 5 years of age, with normal chest x-rays and a positive tuberculin skin test (TST).[2]

1. Pulmonary service, Hospital Municipal Jesus.
2. Associate Professor of Pediatrics, Universidade Federal do Rio de Janeiro (UFRJ) School of Medicine. Pulmonary service, Instituto de Puericultura e Pediatria Martagão Gesteira, UFRJ.
3. Pulmonary Service, Hospital Municipal Jesus. Pulmonary Department, Brazilian Pediatric Society.

The 1st Brazilian Consensus on TB (1997) suggests the extension of chemoprophylaxis to previously underprioritized groups. Individuals who are in close contact with the active form of the disease, having a TST result equal to or higher than 5 mm, regardless of age or previous BCG vaccination, are currently considered to be at higher risk and more likely to require chemoprophylactic treatment.[3]

This study aims at evaluating antituberculosis chemoprophylaxis recommendations for children at a public hospital in Rio de Janeiro, based on the Brazilian Ministry of Health standards,[2] in addition to recommendations for special cases, including very young, BCG-vaccinated children with a positive tuberculin skin test and in contact with infected adults.

Patients and methods

A retrospective cross-sectional study of 100 consecutive cases of antituberculosis chemoprophylaxis was conducted with children treated at the pulmonary clinic of Hospital Municipal Jesus (HMJE) in Rio de Janeiro between January 1st, 1991, and December 31st, 1996. This hospital, located in the Vila Isabel district, has earned the respect of the municipal health system for its 64 years of solid work in the field of pediatrics, serving (among other populations) the economically underprivileged population of Baixada Fluminense, who seek medical care at that institution either spontaneously or on a referral basis.

Patient information was obtained from medical records through standardized forms. The analyzed variables were gender, age, BCG vaccination, nutritional status, tuberculin skin test, tuberculin test conversion, source of tuberculous infection, adherence to preventive treatment, evolution to tuberculosis and side effects of the treatment.

The x-ray examination of the total study population was carried out at Hospital Municipal Jesus radiology service. The children presented normal chest x-rays before they were submitted to chemoprophylaxis.

Chemoprophylaxis was recommended according to the standards for tuberculosis control established by the Ministry of Health[4]: a) children younger than five years of age, non-BCG-vaccinated, asymptomatic, with normal chest x-rays, presenting weak or strong reaction to tuberculin skin test, in contact with the active form of the disease; b) recently infected individuals; c) special clinical situations, in which individuals are at a greater risk for infection, as in diseases that cause immune system depression during therapy with immunosupressants or long-term corticotherapy. In addition to these recommendations, chemoprophylaxis was used in special situations, for instance, very young, BCG-vaccinated children with a positive tuberculin skin test and in contact with infected adults. One of the goals of this paper is to evaluate this study and the criteria that were used.

Out of the 119 children with chemoprophylaxis recommendation, 100 (84%) were studied within a period of 6 years; there was, however, a 16% loss of the total. 19 cases were ruled out due to missing medical records or inability to fill in 70% of the forms used for data collection. Five age groups were considered: younger than 6 months of age; 7 to11 months; 1 to 5 years; 6 to 10 years, and older than 11 years.

BCG vaccination was confirmed by the vaccination control booklet or by the scar found in the deltoid region of the child's arm reported on the medical record. For nutritional status evaluation, the National Center for Health Statistics (NCHS) reference standard was used.

The Mantoux test with PPD-RT23 was used for tuberculin testing. The interpretation of results was based on the size of induration: nonreactive if less than 5 mm, weakly reactive when induration was between 5 and 9 mm, and strongly reactive if above 10mm.[5]

Some children were submitted to a second tuberculin skin test as they were in close contact with tuberculous adults, and since their first test resulted nonreactive or weakly reactive. The cases of tuberculin test conversion, as they are one of the reasons for chemoprophylaxis recommendation,[4] were studied separately, following the same criteria applied to the other children, assessing the time period between both tests and the size of induration obtained by each of them.

The tuberculosis positive epidemiological history was obtained from the information provided by the child's family member. The fact that the child's family members admitted the contact of at least one tuberculous individual with the child was characterized as source of infection. When the source of infection occurred in the same home, it was called household contact, and blood relations were specified. We tried to identify the source of infection, for instance, mother, father, brother and uncle, and the presence of one or more sources of infection in contact with the child. When the infectious individual was known but did not live with the child, there was out-of-home contact. The epidemiological history of tuberculosis was considered negative when family members denied the contact of tuberculous individuals with the child. We ignored all the information that was unknown.

We considered that patients had total adherence to chemoprophylaxis when they completed the preconized 6 months of INH. The time of discontinuation was determined by the length of time during which antituberculosis drugs were used. Primary discontinuation was considered when patients had an indication for chemoprophylaxis and did not return for treatment (it was impossible to know whether or not the drug was administered). In the other discontinuation cases (considering the length of time during which medication was used, expressed in months), we determined the time according to the date of the last medical consultation.

Drug side effects included vomiting, jaundice, and skin rash. In these cases, patients were urged to suspend medication and return for consultation, when the physician would decide to maintain or suspend medication.

Since the study was retrospective, it did not influence chemoprophylaxis recommendation in the study population, and no ethical rules were violated.

The Epi-Info 5 software was used to analyze the frequency and the percentage of the variables under consideration.

Results

The study population included 57 (57%) boys and 43 (43%) girls. Chemoprophylaxis recommendations were more frequent among infants under the age of 5, amounting to 75% of the total. The distribution of chemoprophylaxis cases according to age is shown in Table 1.

BCG vaccination was confirmed in 92 cases, and only 6 children had not received the BCG vaccine. The history of BCG vaccination could not be tracked down in 2 children.

According to the reference standard, 69 (71.8%) of the children were eutrophic, and 27 (28.1%) suffered from malnutrition. The nutritional status of 4 children (4%) could not be assessed since their weight had not been registered on their medical record.

In regard to tuberculin test reaction, 79 (81.4%) children were strongly reactive, 1 was weakly reactive, and 6 (6.1%) were nonreactive to the test. In 11 children (11.3%), the test was not performed, and such information was absent in 3 cases. Table 2 shows the intensity of tuberculin test in 79 strongly reactive patients, in which reactivity ranged from 10 and 14 mm to +15 mm.

Nine BCG-vaccinated children were submitted to a second tuberculin test, after a considerable time interval, as they were in close contact with tuberculous adults, and also because 6 out of 9 children were weakly reactive or nonreactive in their first test. In 3 children, even though their first test showed a reaction of 10 mm, a second test was performed, probably due to their higher risk for tuberculosis infection. The correlation between the intensity of the first and second reactions, the time elapsed between them, in addition to gender, age, nutritional status, BCG vaccination and source of infection are shown in Table 3.

Table 1 - Distribution of chemoprophylaxis cases according to age

Age group	n	%
0-6 months	5	5
7-11 months	8	8
1-5 years	62	62
6-10 years	21	21
>11 years	4	4
Total	100	100

Table 2 - Results of tuberculin test in 79 strongly reactive patients

Tuberculin test (mm)	n	%
10-14	23	29.1
>15	56	70.8
Total	79	100

A survey on the source of infection in patients submitted to chemoprophylaxis showed household contact in 75 individuals (75%), out-of-home contact in 18 (18%), no contact in 5 (5%), and undetermined infection source in 2 (2%). Whenever household contact was observed, the blood relation with the child was checked (Table 4).

Figure 1 shows the correlation between household contact with tuberculous patients and age group in the evaluated children.

As to out-of-home contact, 12 out of 18 children were between 1 and 5 years of age, and the other 6 were between 6 and 10 years old.

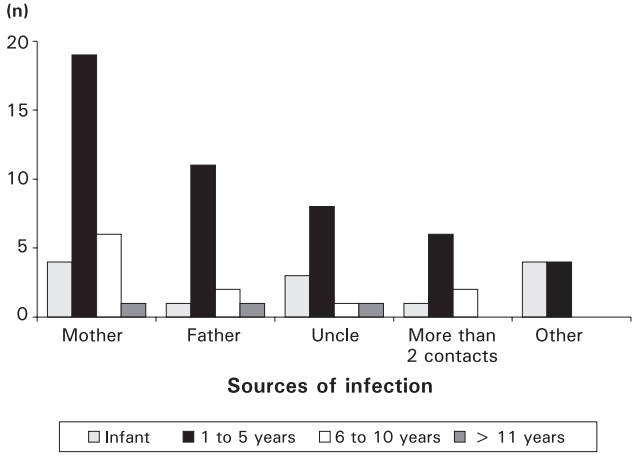

Figure 1 - Correlation between household contact and age group in 75 children

Table 3 - Summary of the nine cases of tuberculin test conversion

Case	Gender	Age	Nutrition (years)	Test 1	Time (mm)	Test 2 (months)	Contact (mm)
1	M	1 to 5	eutrophic	10	6 m	22	AH
2	M	1 to 5	malnourished	10	7 m	26	OH
3	M	1 to 5	eutrophic	0	6 m	13	OH
4	F	1 to 5	eutrophic	2	8 m	10	AH
5	M	1 to 5	eutrophic	7	6 m	14	AH
6	M	1 to 5	malnourished	0	4 m	15	AH
7	F	6 to 10	malnourished	10	2 m	17	OH
8	M	6 to 10	eutrophic	0	7 m	20	AH
9	F	6 to 10	eutrophic	0	1 m	13	AH

AH = at home; OH = out of home; M = male; F = female

The 72 cases that followed the preconized 6 months of medication were considered to have finished chemoprophylaxis. The time of drug discontinuation was analyzed in 27 children who, as they did not turn up for therapy during a variable time period, were regarded as cases of discontinuation from chemoprophylaxis (Table 5). One child, regarded as a discontinuation case for not following the preconized 6 months of therapy, had the medication suspended due to side effects. There were 16 cases of primary discontinuation .

Table 4 - Blood relation concerning household contact in 75 cases of chemoprophylaxis

Blood relation	n	%
One relative		
Mother	30	40
Father	15	20
Uncle	13	17.3
Other	8	10.6
More than 2 relatives	9	12
Total	75	100

One child had to be treated with the MMR vaccine, which replaced monotherapy in the second month of preventive therapy. In this case, cervical lymph node tuberculosis was detected.

Out of the 100 studied cases, only 3 patients presented side effects. Vomiting after isoniazid intake was observed in 2 children (2%), and jaundice related to drug intake was observed in 1 child (1%).

Discussion

The use of well-known preventive actions against any disease that is potentially avoidable should be encouraged so that unnecessary human suffering can be averted.

Children, as they are seldom infectious, do not play a vital role in the epidemiology of tuberculosis transmission. The prevention of tuberculosis in this age group has no immediate epidemiological impact; however, it prevents children from being infected or becoming potential carriers of the disease.

Children younger than 5 years of age represented 75% of the total chemoprophylaxis recommendations during the study period (Table 1), following the standards of the Brazilian National Program for the Control of Tuberculosis promoted by the Ministry of Health, which prioritizes preventive treatment for this age group[21]. The recommendation of children older than 5 years for preventive therapy, representing 25% of the cases, was based on the patient's individual evaluation and on the risk factors presented by each case. Curiously enough, 18 children (72%) in this age group were strongly reactive to tuberculin (> 15 mm) and 14 children (56%) presented household contact with the disease.

Table 5 - Moment of chemoprophylaxis discontinuation in 27 children

Time (months)	n	%
Primary discontinuation (<1)	16	59.2
1	2	66.6
2	4	81.4
3	3	92.5
4	2	99.9
Total	27	100

Schaaf et al.,[6] after reviewing 258 cases of tuberculosis, concluded that age influences the morbidity and mortality of the disease. They observed that infants younger than 3 years, and especially younger than 1 year, easily disseminate the disease and, depending on the local epidemiological situation, the presence of infection may be an indication for MMR vaccination in children younger than 1 year, and for isoniazid prophylaxis in older children (age 7 or 8). This recommendation is not followed by current Ministry of Health standards.[5]

Udani[7] reports a study of 3,000 economically underprivileged children suffering from tuberculosis in the south of India, in which 91% were younger than 9 years and 57% were younger than 5. Half of them presented severe forms of tuberculosis, including meningitis and miliary tuberculosis.

In the present study, infants younger than one year accounted for 13% of the total secondary chemoprophylaxis recommendations (Table 1). In Brazil, primary chemoprophylaxis, which is concerned with the protection of uninfected individuals, is highly recommended for newborns. Tuberculosis is aggravated in 15% of women during puerperium, and pregnant women when untreated or under irregular treatment, develop severe forms of the disease, making newborns and breast-feeding infants more vulnerable to infection and tuberculosis.[8,9] The use of INH, right after birth, would protect infants from developing the disease if they were infected. The Brazilian National Program for the Control of Tuberculosis preconizes that after using the drug for three months, tuberculin testing is indicated. If tuberculin testing yields negative results, vaccination should be performed. If the result is positive, medication should be maintained for three more months.[5] Primary chemotherapy was not recommended for any of the breast-feeding infants studied, since all of them had received BCG except one.

Considering that 92% of the children studied had received BCG, we suppose they would be protected against severe cases of tuberculosis if they were infected. Whether or not recommend chemoprophylaxis for such cases is a clinical decision as the probability that tuberculous infection would develop into disease depends on several factors, which are related not only to the amount of bacilli involved in transmission but also to the individual characteristics of the person exposed and to the duration of infection. Recently infected individuals are more likely to develop the disease.[10]

Notwithstanding, it is known that BCG vaccination may not prevent primary pulmonary infection. The vaccine wards off infection and reduces hematogenic dissemination as T cells in BCG-vaccinated children are highly sensitive; therefore, even in the presence of infection in the lungs and lymph nodes, the possibility of dissemination of the disease is negligible.[11]

Tuberculin reactivity after BCG vaccination ranges between 3 and 9 mm, and the intensity of the reaction decreases with time. Thus, a tuberculin test result higher than 10 mm probably indicates *M. tuberculosis* infection, especially if the test is performed some years after BCG vaccination.[12]

As a rule, it is recommended that children younger than 5 years of age, who have not received BCG, presenting normal clinical and radiological examination, and who are nonreactive to tuberculin skin test, receive BCG vaccination. The 1st Brazilian Consensus on TB (1997)[3] suggests that vaccination should only be administered after performing a second tuberculin skin test within 4 to 8 weeks, depending on nonreactive results.

Out of 86 children submitted to tuberculin skin test, 80 presented a positive reaction to Mantoux test. The test was not performed in 11/100 children due to operational problems or young age.

Among the 80 BCG-vaccinated children, submitted to Mantoux test, only one was weakly reactive, and six were nonreactive. TST reaction higher than 15 mm in BCG-vaccinated children, or higher than 10 mm in children who did not receive BCG or who did so more than two years ago, in children who are in contact with sources of tuberculous infection, asymptomatic, and with normal chest x-rays, could be a case for chemoprophylaxis recommendation.[13] In our study population, 70.8% of the patients who were strongly reactive to TST presented a reaction higher than 15 mm, and 29.1%, a reaction between 10 and 14 mm. The high percentage of strongly reactive individuals in a population with positive epidemiological history of tuberculosis, despite large BCG coverage, may justify a recommendation for chemoprophylaxis.

It is not possible to distinguish between a tuberculin reaction caused by BCG and that caused by natural infection with *M. tuberculosis*.[14] Tuberculin reaction postvaccination is affected by the vaccine power, infectious dose of bacilli the vaccine contains, form of vaccine administration, and the age at which the vaccine is administered and also the interval between BCG vaccination and tuberculin skin test. In addition, TST reaction decreases very quickly in the first 5 years after vaccination.[15]

The disappearance of positive TST reaction postvaccination is referred by several authors. On average, allergic reaction to BCG lasts for 2 years, reducing after this period.[16] A strong reaction to TST in children who received BCG by the intradermal route more than 2 years ago may be interpreted as infection with *M. tuberculosis*.[17]

Sarinho et al.,[17] in Recife, state of Pernambuco, in a prospective study of 371 eutrophic children who received BCG in their first month of life and who were submitted to tuberculin skin test at different ages, showed that 71.4% of BCG-vaccinated children were nonreactive to the test; there was no significant difference between those who received the vaccine and those who did not. The authors state that TST is recommended for diagnosing tuberculous infection in children younger than 2 years who received BCG in the neonatal period.

It was concluded that TST is useful even for BCG-vaccinated children, considering that a reaction equal or higher than 10 mm suggests natural exposure to *M. tuberculosis*.[18]

In 1974, the American Thoracic Society defined as cases of TST conversion individuals presenting an induration of 10 mm or higher in a second test, with an increase of at least 6 mm between the first and the second tests.[19]

Recent conversion to PPD is one of reasons for chemoprophylaxis recommendation in Brazil.[29] Individuals whose TST results converted from negative to positive in the 2 previous years are at a high risk for tuberculosis.[20]

According to this criterion, nine children were considered recent TST converters in our study. Skin hypersensitivity takes 2 to 10 weeks to develop. Therefore, a recently discovered contact with nonreactive or weakly reactive test, as found in 6 of the nine children, should not be regarded as free of infection.

The boost or potentializing response to TST should be considered in recently infected individuals. This phenomenon consists of apparent conversion, interpreted as a new infection, when a second tuberculin skin test is carried out in a patient who presented previous tuberculin sensitivity.[21]

Skin sensitivity to tuberculin, caused by any microbacterium species or by BCG vaccination, disappears in some patients over the years, triggering negative reactions.[21] However, a second tuberculin skin test may induce to hypersensitivity, and could be misinterpreted as TST conversion.

The boost effect seldom occurs in childhood, usually increasing with age, especially in individuals over 50 years of age.[22]

The implications of an underprivileged socioeconomic situation for the incidence and prevalence of tuberculosis are well-known. Chapman and Dyerly,[23] in a study of 187 families in Texas (USA) in 1963, showed how social and environmental factors are related to the transmission of the disease, pointing out that overpopulated homes and poor living standards favor the inhalation of tuberculosis-infecting particles. Social factors, combined with the environment, predispose the transmission of tuberculous infection.

The assessment of infection risks implies knowledge about the degree of transmission of the index case and closeness of the contact. Transmission is enhanced when bacilli are identified on direct sputum examination. If the sputum examination result is negative, the risk is much lower, even if individuals share the same environment. Individuals in contact with patients who suffer from extrapulmonary tuberculosis are at an even lower risk for infection.[24]

In the present study, 18% of tuberculosis cases showed out-of-home or occasional contact. Risk was admittedly lower under these circumstances, except for too young children or immunodepressed patients.[24] There was no positive epidemiological history in just 5 cases, probably because family members did not know their relatives or friends were infected with the disease.

There was a predominance of household contact in all age groups, probably because children shared the environment with adults. Remarkably, all breast-feeding infants and 77.4% of children between 1 and 5 years of age were infected at home. The percentage was lower for the ages between 6 and 10, accounting for 52.3% of children. Older children do not often stay home and have a larger social circle than breast-feeding infants and younger children; therefore, they are more exposed to infection outside the home.

A considerable percentage (60%) of tuberculosis index cases presented fathers as the source of infection. Mothers represented 40% of the source of infection. Nemir and O'Hare,[25] in a three-decade (1953 to 1981) study of 863 tuberculous patients younger than 10 years of age, related the severity of the disease to younger children and to their closeness to the infection source; mothers were the major source of infection found in that study. In our study population, uncles were the source of infection in 17.3% of the cases, enhancing the importance of adults as carriers of the disease, infecting the children who share the same environment (Table 4). The expressive percentage of infected mothers may help them to accept their condition, urging them to seek health centers, thus increasing the chance that they will have their disease detected.

Health care providers are aware of the difficulty in tracing down parents since they do not show up at clinics, probably due to cultural and economic problems. The fact that uncles are an important source of infection for children can be explained through economic matters, which force adults and close relatives into sharing the same home.

The use of long-term therapeutic and preventive treatments by patients is a problem to health care providers. As far as chemoprophylaxis is concerned, the challenge is even stronger, since it is aimed at healthy individuals, with no symptoms of the disease. In the literature, discontinuation from therapy ranges between 9 and 80% and seems to be proportional to age and length of chemoprophylactic therapy.[26] The huge variation in discontinuation rates may be due to the methodology of studies and to the length of preconized preventive therapy. Discontinuation rates are directly proportional to the length of chemotherapy.

In our study, 72% of the children followed the proposed treatment, whereas 27% gave up. Discontinuation was higher in the first month of treatment, that is, 16 out of 27 cases of discontinuation did not return after therapy was introduced. One child was advised to discontinue medication due to intolerance of the drug. The time of discontinuation was not related with the time elapsed since the beginning of the treatment; the higher rates of discontinuation occurred before the first month of chemoprophylaxis (Table 5). By correlating age and time of discontinuation , we observed that children aged 1 to 5 were more likely to discontinue

treatment, probably due to a larger number of individuals in this age group.

Given the adherence cited in the literature and the regular, monthly medical appointments, differently from other studies which reported quarterly medical appointments,[26] the 72% adherence obtained in our study may be considered satisfactory.

A eutrophic, BCG-vaccinated two-year-old who was strongly reactive to tuberculin skin test (14 mm), with household source of infection (father and grandfather), shifted to MMR vaccination scheme in the second month of chemoprophylaxis. The child was diagnosed with cervical lymph node tuberculosis.

Nolan,[27] in a study conducted in North Carolina (USA), reports that 14% of the 235 cases of tuberculosis notified between 1977 and 1981 occurred during the prophylactic scheme. The author concluded that failure was probably due to individual biological factors and not the INH chemoprophylactic treatment. Hsu[28] estimates the failure rate to be 0.3%. The major cause is probably the nonadherence to the prophylactic scheme.

INH chemoprophylaxis is not recommended for patients who presented previous reaction to the drug or who have severe liver disease. The risk for hepatitis increases with age, and peripheral neuritis occurs in less than 1% of adults submitted to the drug. These effects are rare in childhood.[29]

A retrospective study of 564 children submitted to chemoprophylaxis at a pediatric hospital in New York within a period of 10 years (1978 to 1987) carried out by Naksjo et al.[30] showed an INH-induced hepatotoxicity rate of 0.18%.

In our study, only 3% of the children developed signs or symptoms that could be attributed to the drug. Two infants, one aged 6 months and the other 14 months, presented vomiting after drug intake. The symptom vanished after medication was discontinued for a few days. A tem-year-old presented vomiting and jaundice after drug intake. Lab exams showed an increase in bilirubins and transaminases; there was, however, positive result for the hepatitis virus. Medication was suspended since it was impossible to neglect a possible adverse reaction to the drug.

Based on a study of 100 children carried out at a public hospital in Rio de Janeiro, we conclude that the criteria of antituberculosis chemoprophylaxis recommendations according to the Ministry of Health standards5, strictly applied to 15% of the studied patients, including 6 children who did not receive BCG and 9 cases of recent TST conversion. Eighty-five percent of the study population were recommended for chemoprophylaxis based on special situations specified by the Brazilian National Program for the Control of Tuberculosis standards. These special situations included young children, reactive to tuberculin testing, in contact with tuberculous adults, who received BCG.

The 1st Brazilian Consensus on TB (1997) recommended the expansion of chemoprophylaxis as a strategy to fight tuberculosis. The coverage of high-risk groups extends the Brazilian National Program for the Control of Tuberculosis standards. The Consensus advocates the intense advertisement of chemoprophylaxis among specialists so that it can become a routine in a larger numbers of health centers.[3]

Our study, conducted before preventive therapy recommendations were amplified, corroborates and reinforces the suggestions made at the 1st Brazilian Consensus on TB.

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Correspondence:
Dr. Solange Gonçalves David de Macêdo
Rua Ari Parreiras, 684/904 - Icaraí
CEP 24230-321 Niterói, RJ, Brazil
Phone/fax: +55 21 711.7868