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Pediatrics 2002;109;765
DOI: 10.1542/peds.109.5.765

Evaluation of Young Children in Contact With Adult Multidrug-Resistant Pulmonary Tuberculosis: A 30-Month Follow-up

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ABSTRACT. *Setting.* **The Western Cape Province of South Africa, an area with a high tuberculosis (TB) incidence, where initial multidrug resistance (MDR) among adult TB cases was 1.1% during 1992–1993.**

Objective. **To determine the long-term prevalence of TB infection and disease in children in household contact with adults with MDR pulmonary TB, and to establish the efficacy of chemoprophylaxis in preventing disease in these children.**

Method. **Children <5 years old in contact with 73 MDR TB adults were evaluated. Disease was treated by prescribing at least 2 drugs to which the adult's strain was susceptible. The remaining children were classified as infected or noninfected and received chemoprophylaxis according to the index's strain susceptibility or were followed up and treated when indicated. All were followed up for 30 months.**

Results. **At the initial evaluation 125 children were seen, median age 27.5 months. Of these, 119 were followed up. Fourteen (12%) had disease, 61 (51%) were infected only, and 44 (37%) were noninfected. By 30-month follow-up, 29 (24%) had developed disease and 64 (54%) were infected only. Four adult-child pair *Mycobacterium tuberculosis* isolates were compared by DNA fingerprinting; 3 were identical. All children who developed TB disease were clinically cured. Two (5%) of 41 children who received appropriate chemoprophylaxis and 13 (20%) of 64 who did not, developed TB during follow-up (odds ratio: 4.97).**

Conclusion. **The study confirms MDR TB transmission to childhood contacts. Seventy-eight percent of children were infected or developed disease. Appropriate chemoprophylaxis may prevent disease in these children.** *Pediatrics* **2002;109:765–771; *tuberculosis, multidrug-resistant, children, contacts, follow-up, chemoprophylaxis.***

ABBREVIATIONS. TB, tuberculosis; MDR, multidrug-resistant; CI, confidence interval; HIV, human immunodeficiency virus; ESR, erythrocyte sedimentation rate; RFLP, restriction fragment length polymorphism.

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Received for publication Jul 26, 2001; accepted Dec 20, 2001.

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Tuberculosis (TB) contact tracing has produced a significant yield of new TB cases and newly infected patients in the past.[1] Children in close contact with drug-susceptible adult pulmonary TB have a high risk of becoming infected and developing disease.[2,3] It is generally accepted that 30% to 50% of household contacts of adults with infectious forms of pulmonary TB will become infected.[3] The risk for young children with untreated infection to develop TB is up to 43% in children <1 year of age and about 24% for children 1 to 5 years of age.[3] Little is known, however, about the long-term outcome of children in contact with multidrug-resistant (MDR) adult pulmonary TB cases. Although studies in guinea pigs suggested that isoniazid-resistant strains are less infectious and cause less disease than the drug-susceptible strains, this diminished infectiousness and pathogenicity was not confirmed in human studies.[4,5] The management of adults or children in contact with infectious MDR pulmonary TB cases is still very uncertain and, although many suggestions for different regimens for MDR chemoprophylaxis have been made, there are no prospective studies to verify their effectiveness.[6] Furthermore, the optimal duration of chemoprophylaxis with these drugs is uncertain.[6,7] On the other hand, the implications of not being able to give adequate chemoprophylaxis to children infected with MDR strains of *Mycobacterium tuberculosis* are serious, because about 10% or more of infected children will develop TB disease in their lifetime, and they will have the potential to continue the transmission of MDR TB in future.[8]

Drugs used in the treatment of MDR TB cases are generally much more toxic than first-line drugs. In children, the use of fluoroquinolones is not generally recommended.[9] Although their safety in short and medium treatment have been documented, uncertainty still exists about long-term treatment with the fluoroquinolones.[9,10]

The main purpose of this study was to determine the long-term prevalence of tuberculous infection and disease in young children in household contact with adults with MDR pulmonary TB in a geographical area with a high incidence of TB. An additional aim was to establish whether chemoprophylaxis is effective in preventing active disease in these children.

PATIENTS AND METHODS

Primary resistance was defined as resistance in *M tuberculosis* cultures from patients with no previous TB treatment. Initial re-

sistance is drug resistance in new TB patients but allowing for undisclosed previous TB treatment (ie, primary resistance plus undisclosed acquired resistance). Acquired resistance is resistance found in cultures from patients who have had 1 or more previous TB treatment episodes. MDR is resistance to isoniazid and rifampin with or without resistance to other anti-TB drugs.[11]

A prospective study was conducted between April 1994 and January 2000 in the Western Cape Province of South Africa, an area with a TB incidence of 589 new cases per 100 000 population per year in 1998 (Department of Health: Directorate Health Systems Research and Epidemiology). The rate of initial resistance to isoniazid determined in adult TB cases in the Western Cape Province during 1992–1993, was 3.9% (95% confidence intervals [CI]: 3.3%–4.6%) and initial resistance to both isoniazid and rifampin was found in 1.1% of isolates (95% CI: 0.7–1.4).[12] Human immunodeficiency virus (HIV) seroprevalence in women attending antenatal clinics in the Western Cape Province rose from 1.16% (95% CI: 0.76–1.56) to 5.21% (95% CI: 3.2–7.2) from 1994 to 1998 (Department of Health: Directorate Health Systems Research and Epidemiology).

An index case was defined as an individual >15 years of age with sputum culture positive for *M tuberculosis*, which was resistant to at least isoniazid and rifampin. The sputum specimens were processed by the South African Institute for Medical Research in Cape Town, which is responsible for the mycobacteriology services in the Western Cape. Laboratory procedures for determining drug resistance were described previously.[11] Briefly, Middlebrook 7H12 (Bactec; Becton Dickinson and Company, Sparks, MD) culture medium was used for isolation of mycobacterial strains. The niacin production test was used to identify *M tuberculosis*. Drug susceptibility testing was performed by the indirect proportion method. The following drugs were tested at the indicated concentrations: isoniazid 0.2 μg/mL LJ; rifampin 30.0 μg/mL LJ; streptomycin 5 μg/mL LJ; ethambutol 2 μg/mL LJ; and ethionamide 20 μg/mL LJ. Resistance was defined as 1% or more bacterial growth. Quality assurance for drug susceptibility results is done locally with every batch and quarterly by the national TB reference laboratory.

Index cases were resident in suburbs surrounding the Tygerberg Hospital, a tertiary referral center for the area. Information collected regarding the adult index case included gender and age, their relation to the childhood contact, whether their sputa were smear-positive or smear-negative, the susceptibility pattern of the *M tuberculosis* culture, and the index case's outcome after 30 months.

Childhood contacts were defined as children 5 years of age or less living and sleeping in the same house or group of clustered houses/shacks on the same residential site as the index case for at least 1 month.[11] Parents or guardians were asked to bring these children to hospital for initial and follow-up evaluations, even if the parents considered the child to be asymptomatic. All the children in these households were seen.

Initial evaluation included obtaining a history regarding previous TB chemoprophylaxis or treatment and whether there were other adults in the same house who had or had recently had TB. This information was verified by contacting the local authority health clinics where patients reside. Evidence regarding recent weight loss or failure to gain in weight and documentation of BCG immunization was obtained from the patient's "Road to Health" clinic card or from clinic records.

Each child was subjected to an initial clinical examination, tuberculin skin test (Mantoux test-5TU [0.1 mL] Japanese purified protein derivative by intradermal injection read after 48–72 hours), antero-posterior and lateral chest radiographs, and 2 early morning gastric aspirates for *M tuberculosis* cultures.[11] The erythrocyte sedimentation rate (ESR) was determined and HIV serology with enzyme-linked immunosorbent assay was done in all children with written informed consent and after counseling of the parent. An area of induration ≥15 mm in transverse diameter after Mantoux skin testing was regarded as significantly positive in accordance with World Health Organization criteria and National TB program guidelines as >95% of children in this area receive BCG at birth.[13] Bronchoscopy was performed only when the chest radiograph was persistently abnormal but was not diagnostic of TB. As part of the initial evaluation, children were seen again after 2 months when the relevant results of investigations including cultures and, where indicated, follow-up chest radiograph were available.

Children were classified as noninfected, infected, or diseased. Noninfected children were asymptomatic, had a nonsignificant (<15-mm induration) Mantoux test, normal chest radiograph, and negative cultures for *M tuberculosis*. Children with a Mantoux test of ≥15 mm who were asymptomatic, had a normal chest radiograph or only calcifications in the lung parenchyma or regional lymph nodes on the chest radiograph, and negative cultures were regarded as having infection and not disease.[14] Diseased children were those who on chest radiograph had well-defined hilar or mediastinal adenopathy, miliary TB or endobronchial TB (as evidenced by hilar or mediastinal adenopathy with bronchial compression or segmental/lobar consolidation or both), those with adenopathy compressing airways identified by bronchoscopy, acid-fast bacilli on biopsy histology specimen, or those with a positive culture for *M tuberculosis* from any source. The chest radiograph and bronchoscopy findings could be present with or without a positive (≥15 mm) Mantoux test, and with or without positive cultures for *M tuberculosis*. A cough lasting >2 weeks, weight loss or failure to gain adequately in weight for ≥3 preceding months, and an ESR of >50 mm/hour Westergren substantiated the diagnosis of disease but was not regarded in itself as confirming the presence of tuberculous disease.

All infected children and all children <2 years of age who had received no previous treatment or chemoprophylaxis of any kind for TB were offered chemoprophylaxis with high-dose isoniazid 15 to 20 mg/kg/d, pyrazinamide 25 to 35 mg/kg/d, ethionamide 10 to 15 mg/kg/d and/or ethambutol 15 to 20 mg/kg/d and/or ofloxacin 15 mg/kg/d for 6 months, the latter 2 drugs being included depending on the susceptibility of the MDR *M tuberculosis* strain of the adult index case. Children who had received previous TB treatment or chemoprophylaxis with isoniazid with or without rifampin/pyrazinamide were not routinely prescribed another course of chemoprophylaxis except when it was preferred by the parent rather than follow-up only.

Children who had TB disease received individualized treatment. This consisted of a 4- or 5-drug regimen (isoniazid, pyrazinamide, ethionamide, ethambutol, and ofloxacin) that included at least 2 or 3 drugs to which the adult index case's isolate was susceptible. Prescribed duration of treatment was for 6 to 12 months, determined by extent of disease, eg, hilar adenopathy only was initially treated for 6 months (later 9 months), whereas extensive pulmonary infiltrates were treated for 12 months.

All treatment and chemoprophylaxis was given as directly observed therapy. Caregivers were expected to take the children to the local health clinic daily (5 days a week) where health care workers had to observe the children taking their treatment. When patients did not return for treatment, several home visits were made to motivate caregivers to bring the children for treatment. If despite all efforts (including motivation for hospital admission for treatment) children did not receive any treatment for >1 month, treatment was discontinued. Follow-up visits were, however, continued.

Follow-up visits were arranged for all children at 4 months, 6 months, and 6-monthly thereafter to 30 months. Other evaluations occurred as were clinically indicated. Evaluations at follow-up comprised a clinical examination, Mantoux skin testing if a previous test was not significantly positive, and chest radiographs every 6 months or more often, when clinically indicated. Culture for *M tuberculosis*, lymph node biopsy, and bronchoscopy were done only when clinically or radiologically indicated.

In those cases where cultures of *M tuberculosis* were obtained from both the adult index case and the child contact, isolates were genotyped by restriction fragment length polymorphism (RFLP) analysis using the internationally standardized method (IS6110–3′) and 3 additional probes as previously described.[15,16]

Children older than 5 years of age and adults were not assessed as part of this study, but were referred to the local authority health clinics in their area.

Categorical data were analyzed using the χ^2 test to compare groups and Fisher exact test was applied where appropriate. Statistical analysis was done using Epi Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA).

The study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of Stellenbosch and informed written consent was obtained from the parent or guardian for participation in the study.

RESULTS

Seventy-three index cases and 125 childhood contacts <5 years of age were identified and studied. Two index cases with 3 childhood contacts identified in the original study were excluded because the 1 index case was not culture-positive after the birth of the 2 children, and the second index case was subsequently shown to have a drug susceptible *M tuberculosis* strain.[11]

The median age of the index cases was 30 years (range: 16–63 years; mean: 33.1 years) and the male: female ratio was 1:1.2. Thirteen (18%) index cases had primary drug-resistant TB. At 30-month follow-up, 24 (33%) of the index cases had died, in 2 of whom the cause was not TB-related; 8 (11%) were still smear- and/or culture-positive for MDR *M tuberculosis*; and 5 (7%) were lost to follow-up. Thirty-six (49%) index cases were alive and culture-negative.

There was no significant age difference between the index cases of children who developed disease (median: 32 years old; range: 19–62), had infection only (median: 32 years old; range: 16–63) and those that were not infected (median: 30 years old; range: 17–60).

Forty-one households (56%) affecting 57 (46%) children had >1 adult source case, consisting of additional MDR TB source cases in 38 children (68%), drug-susceptible source cases in 19 children (28%), and cases with unknown susceptibility in 11 children (16%).

At initial evaluation of all 125 childhood contacts there were 58 boys and 67 girls with a median age of 28 months (range: 1–60 months). Of these, 14 (11%) children had tuberculous disease, 66 (53%) were infected only, and 45 (36%) were not infected. Six (5%) children, 5 infected only and 1 noninfected, did not return for any follow-up and were excluded from the analysis.

One hundred nineteen children attended follow-up visits, 116 (97%) of whom were seen at the 30-month appointment. Except for the 4-month follow-up attendance of 71%, all 6-monthly evaluations had an attendance of >90%. The median number of follow-up evaluations per child was 6 (range: 1–16) with only 6 children having <4 follow-up evaluations. Twenty-three (19%) children were followed up beyond 30 months.

On follow-up, an additional 15 children (12%) developed disease by 30 months. Diagnosis at 6-month follow-up evaluations is summarized in Table 1. There was no significant difference in the rate of infection or disease by age. Twelve (80%) of the 15 children that developed disease during the 30-month follow-up, were diagnosed by 12 months, and only 1 child developed disease between 18 and 30 months. Ninety-five (80%) children were in contact with an acid-fast bacilli smear-positive MDR TB index case and 24 with a culture only confirmed index case. Of the smear-positive contacts, 80 (84%) were infected of whom 27 (34%) developed disease and of culture only positive contacts 14 (58%) were infected of whom 2 (14%) developed disease. Infection occurred significantly more in the smear-positive group [$P = .012$; odds ratio 3.81 (95% CI: 1.28–11.36)], but disease among those infected was not significantly more frequent. ($P = .21$) Ten (40%) of 25 noninfected children had a smear-negative adult index case.

Continued contact with the adult index case after the initial evaluation was shorter for noninfected children (median: 2 months; range: 1–7 months) than for infected only ($P = .002$; Kruskal-Wallis test)) and diseased children ($P = .04$; both groups, median: 4 months; range: 1–30 months).

TB was confirmed in 6 (21%) of 29 children with disease, 5 by culture of *M tuberculosis* and 1 by finding acid-fast bacilli on microscopy of a peripheral lymph node biopsy. Drug susceptibility testing was done in 4 cases and these isolates were all MDR. The 1 isolate not tested was contaminated and the histology specimen was regrettably not submitted for culture. RFLP analysis was performed on 4 adult-child pair isolates, 3 of which were identical. In 1 adult-child pair the drug susceptibility pattern and RFLP were dissimilar, but both were MDR and a community infection was likely in the child.[16]

Of the 29 children diagnosed with TB, 27(93%) had hilar lymphadenopathy on chest radiography, 16 of whom had other parenchymal or pleural changes. A Mantoux test of ≥15 mm induration was present in 22 (76%), a cough for >2 weeks in 16 (55%) and documented weight loss or failure to gain weight in 12 (41%). In 3 children hilar lymphadenopathy compressing the airways was confirmed by bronchoscopy. In 1 of these the chest radiograph did not clearly show hilar adenopathy. The ESR was >50 mm/hour in both children who did not have hilar lymphadenopathy on chest radiography. No child had disseminated disease.

At the initial evaluation, calcification was present on chest radiography in 10 (8%) of 119 children, all of whom were tuberculin skin test-positive. Subsequently, an additional 29 (24%) children developed calcification on chest radiograph. In 10 cases, in 2 of whom the Mantoux test remained 0 mm, calcifications developed 6 to 18 months after diagnosis of TB

TABLE 1. Diagnosis at Follow-up Evaluations*

TB Diagnosis	TB Disease	Infected Only	Noninfected	Lost to Follow-up
Initial evaluation	14 (11%)	66 (53%)	45 (36%)	
6-mo evaluation	24 (19%)	58 (46%)	37 (30%)	6 (5%)
12-mo evaluation	26 (21%)	62 (49%)	31 (25%)	6 (5%)
18-mo evaluation	28 (22.5%)	63 (50%)	26 (21%)	8 (6.5%)
24-mo evaluation	28 (22.5%)	65 (52%)	24 (19%)	8 (6.5%)
30-mo evaluation	29 (23%)	64 (51%)	23 (19%)	9 (7%)

* ($n = 125$).

disease. In 4 children with infection only, the diagnosis was based solely on the presence of calcifications on chest radiograph. In 3 of these cases, the Mantoux test showed no reaction and in 1 an induration of 10 mm was found.

Tuberculin skin test results are summarized in Table 2. Only 1 child, whose Mantoux test was 0 mm and was diagnosed as having TB disease, was HIV-infected.

Individualized treatment according to the drug susceptibility pattern of the index case was prescribed in 25 (86%) of 29 children that had disease (Table 3). Fourteen (56%) children completed a 4- to 5-drug regimen of 9 to 12 months, 6 (24%) children defaulted from a 9-month treatment course after 4 to 8 months, and 5 (20%) children, all with only hilar adenopathy on chest radiograph, completed a 6-month treatment regimen. Of the 4 children who did not receive treatment, in 3, one of whom had received previous TB treatment, the diagnosis was made retrospectively. These children were followed up but no treatment was given. The remaining child missed his 6-month follow-up and was diagnosed at the local authority health clinic and received isoniazid, rifampin, and pyrazinamide for 6 months. All 29 children were clinically and radiologically well after 30 months follow-up.

Forty-one children received chemoprophylaxis for MDR TB. Three- or 4-drug combinations for 6 months were prescribed (Table 3). Isoniazid and pyrazinamide were included in almost all regimens together with ethionamide and/or ethambutol or ofloxacin. A comparison between the groups of children that did and those that did not receive appropriate chemoprophylaxis once they were identified as MDR TB contacts is summarized in Table 4. Fifty-seven of these contacts had no other adult source case identified. None of the 29 children who received appropriate chemoprophylaxis and 6 of 28 children who did not, developed disease during follow-up ($P = .01$; Fisher exact). Of the remaining 9 children who developed disease and did have other source cases, 6 source cases had MDR (including both cases in the chemoprophylaxis group), in 2 the source cases' susceptibility patterns were unknown and one child had an additional drug-susceptible contact.

Ethionamide was used in the treatment or prophylaxis of 61 (51%) children. Thirty (49%) children experienced gastrointestinal side effects, and the drug had to be stopped in 4 cases. There was no difference in the occurrence of side effects attributable to ethionamide in children less or more than 2 years of age.

TABLE 2. Mantoux Test Results During 30-Month Follow-up of Children in Contact With Adult MDR Pulmonary TB Cases*

Induration	0–9 mm	10–14 mm	≥15 mm
Initial evaluation	42 (35)	8 (7)	69 (58)
6-mo evaluation	40 (34)	7 (6)	72 (60)
12-mo evaluation	38 (32)	5 (4)	76 (64)
18-mo evaluation	36 (30)	5 (4)	78 (66)
24-mo evaluation	35 (29)	5 (4)	79 (67)
30-mo evaluation	33 (28)	5 (4)	81 (68)

* $n = 119$; % in parentheses.

TABLE 3. List of Regimens Used as Chemoprophylaxis and Treatment

Chemoprophylaxis Regimens	($n = 41$)	(%)
5 d/wk for 6 mo		
H Z Eth	20	(49)
H Z E	9	(22)
H E Eth	4	(14)
E Eth	2	(5)
H Z E Eth	2	(5)
Z E Eth	2	(5)
H Z Eth	2	(5)
Treatment regimens	($n = 25$)	(%)
6 H Z E Eth	4	(16)
6 H Z Eth O	1	(4)
9 H Z E Eth	8	(32)
9 H Z Eth O	2	(8)
9 H Z E Eth O	4	(16)
6 H Z E O / 6 H Z E Eth*	1	(4)
12 H Z E Eth	1	(4)
12 H Z Eth O	1	(4)
12 H Z E Eth O	3	(12)

H indicates isoniazid; Z, pyrazinamide; E, Ethambutol; Eth, Ethionamide; O, ofloxacin.
* Ofloxacin was stopped because of arthralgia.

Ofloxacin, used mainly for treatment, was administered in 15 children for durations of 6 to 12 months. Median age of onset of treatment with ofloxacin was 37 months with a range of 7 to 63 months. In combination with ethionamide, it was not possible to establish whether it caused gastrointestinal side effects. Only 1 child, a girl in whom treatment was started at 19 months old, complained of pain in the knees after 6 months, and ofloxacin was immediately stopped. The arthralgia cleared, but it could not be determined whether ofloxacin was the actual cause. No radiologic studies were done to evaluate potential toxicity in any of these children.

DISCUSSION

Although TB contact tracing has produced a significant yield of new cases in the past, the duration and value of long-term follow-up has been debated.[1,17] Data from previous studies suggest that contacts of smear-positive pulmonary TB and adult pulmonary TB cases in socioeconomically deprived areas should be followed up after the initial examination.[1,17,18] In several retrospective contact tracing studies, 90% or more of TB cases were identified within the first 12 months after identification of the index case.[1,17,19] Furthermore, studies have shown that drug-resistant organisms can be as infectious as drug-susceptible *M tuberculosis*, but no long-term follow-up of childhood contacts of MDR TB index cases could be found.[4,5] In this study, 29 (23%) children developed disease, 90% of whom were diagnosed as diseased by 12-month follow-up. Tuberculous infection with or without disease was present in 78% of children by 30 months, 95% of whom were already infected by 12 months. The low yield after completion of the first 12 months of follow-up is similar to findings in other studies.

It is generally accepted that between 30 and 50% of all household contacts of infectious adults will have a positive tuberculin skin test.[3] In children 0 to 5 years of age this infection rate was reported to be as

TABLE 4. Comparison of Children Who Received and Those Who Did Not Receive Appropriate Chemoprophylaxis During This Follow-up

Characteristic	Appropriate Prophylaxis $n = 41$ (%)	No Prophylaxis $n = 64$ (%)
Age (mo)	Median: 19 (range: 1–60)*; average: 25	Median: 31 (range: 1–60); average: 31.5
Male:female	20:21	27:37
Previous prophylaxis	10 (24)*	32 (50)
Previous TB treatment	2 (5)*	16 (25)
Mantoux first evaluation		
≥15 mm	28 (68)*	33 (52)
5–14 mm	5 (12)	4 (6)
0–4 mm	8 (20)	27 (42)
Adult index case		
Smear-positive	39 (95)*	43 (67)
Duration of contact after first evaluation (mo)	Median: 6 (range: 1–30)*; average: 9.15	Median: 2 (range: 1–30); average: 5.0
Initial diagnosis		
Infected only	28 (68)*	33 (52)
Noninfected	13 (32)	31 (48)
Outcome:		
TB disease†	2 (5)	13 (20)
Confirmed	0	3
Probable	2	10
Infected only	34 (83)	31 (48)
Noninfected	5 (12)	20 (31)

* Group in which more disease is expected.
† $P = .05$; odds ratio: 4.97 (95% CI: 1.06–23.33).

high as 72% in earlier studies.[20,21] The very high infection rate in this study is therefore not unexpected. Possible explanations are that 80% of the children had smear-positive adult index cases, MDR TB usually remains infective for longer periods[4] and 46% of children had >1 adult household source case with active pulmonary TB. Other studies of households with a drug-resistant index case have shown similar high infection rates.[22–24]

Twenty percent of household contacts <5 years of age of mainly drug-susceptible index cases developed TB disease during a 5-year follow-up in India.[2] This is similar to the 15 (14%) cases that developed disease during follow-up in our study. The rate of developing disease was the highest for children <5 years of age, but chemoprophylaxis significantly reduced disease in this age group to 5% in the Indian study.[2] This is similar to the group without appropriate chemoprophylaxis in our study in whom 20% developed disease compared with the 5% who developed disease in the group given appropriate chemoprophylaxis.

The age of the adult index cases of those children who developed disease and those who did not was not significantly different. This is in contrast to the findings of Snider et al[4] where adults with drug-resistant TB causing infection and disease among childhood contacts were significantly younger. Nearly half of the children, however, had >1 adult source case. This may influence results but it is a common problem in communities with a high incidence of TB and complicates the management of these patients.[25,26] Childhood contacts of smear-positive adults were more likely to be infected than contacts of smear-negative adults. This again emphasizes the importance of smear positivity as a determinant of the transmission of infection.

DNA fingerprinting of *M tuberculosis* isolates from 3 of 4 adult-child pairs that were analyzed by RFLP were identical which confirms transmission from adult index case to the child contact.[16]

All 29 children with TB disease had primary disease. It is known that a large proportion of these children will improve even without treatment,[27] but effective treatment remains important to prevent progression of disease especially in the very young child. Furthermore, the eradication of live bacilli may prevent relapse with MDR disease in future, which is an important consideration in the face of the rapidly spreading HIV/AIDS epidemic. The optimal duration of anti-TB treatment in children even in cases of drug-susceptible TB is still uncertain and many children are probably overtreated.[9]

Although directly observed therapy is practiced mainly in the urban areas, it has limitations, as the patients are expected to pay a daily visit to the local clinic. Children are therefore dependent on their caregivers to take them for treatment. Problems arise when this does not happen despite home visits by nursing staff. Resources at clinic level are inadequate to treat children at home and if hospital admission is not possible, treatment is stopped and patient declared a defaulter.

Isoniazid was given to almost all children either as treatment or chemoprophylaxis. There is evidence that about half the patients with primary isoniazid resistance have low-level resistance (minimal inhibitory concentration ≤2.0 μg/mL) and these serum levels are easily achievable in children with a dose of 15–20 mg/kg/d.[28,29] Furthermore, child contacts in this study often had contact with >1 adult source case, of whom a number had either drug-susceptible TB or their susceptibility pattern was unknown.

Ethambutol has been accepted as first-line agent in TB and can even be recommended in children aged 5 years or more for routine treatment. Reviews of clin-

ical trials in children <5 years of age did not reveal any serious ocular complications during treatment with ethambutol at a dose of 15 mg/kg/d.[30,31] It is an essential drug in the treatment of MDR TB cases, even for younger children.[9,30,31]

Of the second-line anti-TB drugs, ethionamide has significant activity against tubercle bacilli but causes considerable gastrointestinal discomfort. It seems to be better tolerated in children than in adults and therefore plays an important role in the treatment of MDR TB in children. About half of the 61 children who received ethionamide in this study experienced gastrointestinal side effects but by dividing the daily dose, drug-induced nausea and vomiting subsided so that it could be continued once again as a single dose in all but 4 patients.

The fluoroquinolones are generally not recommended for use in children because of their possible effect on cartilage growth in immature animals following long-term administration.[9] A number of reports have shown low rates of side effects with arthralgia episodes in only 1.3% to 3.5% of children even when used for periods of 150 to 300 days.[10,32,33] Three women who were receiving ofloxacin treatment became pregnant but no adverse effects were noted in their infants.[34] Ofloxacin has a higher early bactericidal activity of 0.32–0.39 against *M tuberculosis* compared with the early bactericidal activity of 0.205 of ciprofloxacin, and the pharmacokinetic profile of ofloxacin is better than that of ciprofloxacin.[35–37] Ofloxacin is therefore the fluoroquinolone preferred by many experts in the treatment of MDR TB.[34,38] Arthralgia was experienced in only 1 of 15 children receiving ofloxacin for 6 to 12 months in our study. Because of the gastrointestinal discomfort caused by ethionamide, it was difficult to evaluate this side effect of ofloxacin in these children.

Chemoprophylaxis was successfully administered to 41 children, and 64 children received no appropriate chemoprophylaxis. This was, however, not a randomized, controlled study and results should therefore be interpreted with caution. The children who received chemoprophylaxis were clearly the group with the higher risk for developing disease since they were significantly younger, had more sputum smear-positive index cases, had a higher rate of infection and had had previously received treatment or chemoprophylaxis less often (Table 4). Despite the higher risk for disease, they developed significantly less disease than those that did not receive chemoprophylaxis. This is particularly true of the children that had no other adult TB source case. Several combinations have been advocated such as pyrazinamide and ethambutol, pyrazinamide and a fluoroquinolone, a fluoroquinolone alone, and ethionamide and cycloserine.[8,9] We have used several combinations according to the drug resistance pattern of the index case, but most children received a combination of isoniazid, pyrazinamide, and ethionamide with good effect.

The optimal duration of chemoprophylaxis for MDR TB contacts is uncertain. Our experience suggests that 6 months may be adequate if not optimal. Twelve months chemoprophylaxis has been advised in at least 2 official recommendations.[6,7] An alternative strategy to chemoprophylaxis, because of the lack of data, is regular follow-up without chemoprophylaxis, an option which was also offered to our patients.[7] However, with the high incidence of infection and disease in our study we believe that giving chemoprophylaxis should be the preferred management. In areas with a high burden of disease and in poorly resourced countries where treating smear-positive TB cases is the priority, 6 months of directly observed chemoprophylaxis may be more appropriate than giving 12 months of unsupervised chemoprophylaxis to MDR TB contacts.

CONCLUSION

This study confirms the transmission of TB infection from MDR adult index cases to children in close household contact and the subsequent development of disease in these children. The incidence of infection and disease was comparable to that occurring in children in contact with drug-susceptible adult index cases. Our results suggest that in resource limited situations the follow-up of such children with a view to detecting the development of disease can be limited to 12 months, as only a minority of children developed disease after this period. Appropriate chemoprophylaxis, taking into account the resistance profile of the index case, seemed to be effective in preventing the development of disease. There is, however, an urgent need for a multicenter, randomized, controlled trial to identify the most effective drug combinations and the optimal duration of chemoprophylaxis in contacts of MDR pulmonary TB adults.

ACKNOWLEDGMENTS

This study was supported by GlaxoSmithKline International Action TB Research Initiative and the South African Medical Research Council.

We thank Marlein Bosman and the South African Institute for Medical Research staff for information on the index cases' cultures, the clinic nursing staff at the Western Cape local authority health clinics, and Suzanne Verver for statistical advice.

This article was written in partial fulfillment of an MD thesis registered at the University of Stellenbosch.

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NEONATAL BLEEDING IN THE UNITED KINGDOM

"Vitamin K is now given in 4 common, but very different, regimens. In 1993, 1 or 2 units gave no routine prophylaxis, some gave a single oral dose, some gave multiple oral doses, and some gave intramuscular vitamin K to all infants. The relative risk of bleeding in infancy is maximum in the first and minimum in the last of these groups with dramatic differences across the groups; infants given no prophylaxis (including those whose parents have refused it) are 80 times more likely to bleed than those given intramuscular prophylaxis."

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Evaluation of Young Children in Contact With Adult Multidrug-Resistant Pulmonary Tuberculosis: A 30-Month Follow-up

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Pediatrics 2002;109;765
DOI: 10.1542/peds.109.5.765