Pediatric Tuberculosis: What Needs to be Done to Decrease Morbidity and Mortality

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ABSTRACT. *Objective.* Tuberculosis (TB) control programs have been less successful among children than among adults in the United States. Between 1992 and 1997, the rate of decline of TB cases among 0- to 14-year-old children was less than the rate of decline among any other age group of US-born persons. Because of the higher prevalence of active TB among adults and their higher infectivity, most programs for TB in the United States have targeted adults. The inherent assumption has been that by targeting adults, from whom children may become infected, TB morbidity and mortality among children also will be reduced effectively.

Methods. Using a semi-Markov model that divided the US population into age groups <15 years old and ≥15 years old and into 18 clinical states based on the risk for or presence of TB and human immunodeficiency virus infection, we developed a computer-based simulation model to examine the effect of a range of potential TB control strategies on projected TB cases and deaths in children. We compare the impact of interventions targeted at children with the impact of interventions targeted at adults on pediatric morbidity and mortality.

Results. After 10 years, a 5% increase in the number of adults with TB who enter treatment would only lead to a .05% decline in TB cases among children, compared with predicted cases without this intervention. Improving treatment efficacy among those adults who are already receiving treatment for their TB leads to a smaller decline in cases among children of only .003%. In contrast, a 5% increase in the number of children who enter treatment leads to a 25% decline, after 10 years, in the number of TB cases among children and a 16% decline in the number of TB deaths. In the presence of immigration of tuberculin-positive children, the benefit of targeting programs directly at children is magnified.

Conclusions. Marginal changes in programs targeted directly at children are significantly more effective at further reducing pediatric TB morbidity and mortality than the same changes in programs targeted at adults with the indirect goal of reducing spread to children.

Marginal increases in the number of children who enter treatment are far more effective at decreasing morbidity and mortality than equivalent marginal increases in treatment effectiveness. Unfortunately, declining insurance coverage and increasing restrictions on services to immigrants have made it harder for those who are at greatest risk of TB to get medical care. Marginal increases in preventive therapy rates substantially reduce future pediatric TB cases and deaths among children with TB infection and human immunodeficiency virus. *Pediatrics* 2000;106(1). URL: http://www.pediatrics.org/cgi/content/full/106/1/e1; *pediatric tuberculosis, tuberculosis control, tuberculosis prevention, computer simulation models.*

ABBREVIATIONS. TB, tuberculosis; HIV, human immunodeficiency virus.

Tuberculosis (TB) control programs have been less successful among children than among adults in the United States. In Boston and New Jersey, the percentage of school-aged children with a positive tuberculin skin test result substantially increased between 1985 and 1993.[1] The epidemic of TB that occurred in the United States between 1985 and 1993 resulted in 64 000 excess cases of active TB with costs in excess of $1 billion.[2,3] Even when TB control efforts reversed the rising incidence of TB and led to a decline in US TB cases, children at risk for TB did not share proportionally in the gains. TB cases in US-born children continued to rise for 2 years longer than in adults.[4] Between 1992 and 1997, the rate of decline of TB cases among 0- to 14-year-old children was less than the rate of decline among any other age group of US-born persons.[5] Microepidemics of TB among children continue to occur.[6–8] Furthermore, even with recently intensified measures, we are failing to meet national goals set in 1989 for decreasing the incidence of TB.[9,10]

Specific groups of children have been particularly hard hit. Children infected with human immunodeficiency virus (HIV) are at high risk for developing TB.[11,12] The percentage of TB cases occurring in foreign-born individuals continues to increase[13]; in New York City, 62% of TB cases occurring in children <5 years old during a 6-month period in 1992 were born outside the US or had foreign-born caretakers.[14]

Because of the higher prevalence of active TB among adults and their higher infectivity, most programs for TB in the United States have targeted adults. The implicit assumption has been that by targeting adults from whom children may become infected, TB morbidity and mortality among children also will be reduced effectively. Treatment of adult active cases has been the foundation for most national policies to control the spread of TB, including in children.[15–17] Because TB case rates have not de-

clined as markedly in children as they have in adults, it is appropriate to reevaluate this strategy.

We developed a computer-based simulation model to examine the effect of a range of potential TB control strategies on projected TB cases and deaths in children. We measured the impact on pediatric morbidity and mortality of interventions targeted at children in comparison with interventions targeted at adults. We modeled the impact of increasing the number of individuals who receive chemoprophylaxis, increasing the number of individuals who receive prompt treatment, and increasing the effectiveness of treatment. Finally, because a high number of cases occur among foreign-born and HIV-infected children, we modeled how immigration and HIV influence what policy approaches will be most effective in eliminating TB among children.

METHODS

This study uses a computer simulation model to follow the US general population for 10 years and project the impact of TB control measures on morbidity and mortality in children. To assess the impact of different interventions currently used in the United States, a series of strategies are introduced, singly and in combinations in children or adults. The interventions include increasing the percentage of patients with active TB who start treatment by 5%, increasing treatment effectiveness by 5%, and increasing the proportion of tuberculin-positive persons who receive isoniazid chemoprophylaxis by 5% (Table 1). The 5% value was chosen based on earlier work that suggested that this level of improvement was both realistic and obtainable. Sensitivity analyses were conducted varying the level of improvement in TB control interventions from 2.5% to 7.5%. The relationship among the different interventions was the same, although 2.5% improvements were, as expected, less effective than 5% improvements, and 7.5% improvements were more effective. Only the results with 5% improvements in TB control interventions are reported.

The modeled outcomes are the prevalence of children <15 years old with active TB (separated into drug-sensitive and multiple-drug–resistant disease), and deaths (separated into tuberculous and nontuberculous) as a function of the public health measures taken to control and to eliminate TB. The effectiveness of marginal changes in control strategies was calculated as the percentage difference between pediatric TB cases or TB deaths after 10 years with and without the changes.

The simulation model is based on a semi-Markov process. Briefly, the population is divided into 2 age groups: <15 years old and ≥15 years old. (Because of limits in data availability, children were not subdivided into narrower age categories.) Each age group is subdivided into 18 nonoverlapping, completely exhaustive clinical states based on TB and HIV status (Table 2). (Completely exhaustive is a modeling concept that means that everyone in the model population can be placed in a category or state.) Examples of TB states in the model include no TB infection, latent TB infection, and active TB. The states are linked by transition equations developed from decision trees. These equations determine the likelihood that individuals remain in 1 state, for example, HIV- and TB-uninfected, or move to another, for example, HIV- and TB-infected, from 1 period to the next. In all analyses, 1 period equals 1 year. This structure is reproduced to allow for 10 periods of observation of health outcomes.

US population data for 1995 are used to calculate the initial population in each risk state. Transition probabilities are derived from the following sources: published literature, Centers for Disease Control and Prevention data on TB epidemiology and control program participation rates and results, US population data from the Department of Commerce, immigration data from the Justice Department, and World Health Organization data on Bacille Calmette-Guérin vaccination rates (Table 3). In each period, the population is supplemented by live births with and without HIV infection, and immigrants with and without TB infection and Bacille Calmette-Guérin vaccination.

The accuracy of the baseline model was checked using national TB data for 1996 and 1997. The annual number of TB deaths reported by the Centers for Disease Control and Prevention for these years were 1336 in 1996 and 1194 in 1997.[18] The 1995 baseline model predicted these deaths within 1.3%; the model predicted 1341 TB deaths in 1996 and 1209 in 1997.

A sensitivity analysis of the impact of interventions was conducted by varying all transition probabilities simultaneously over defined ranges. The model was run 500 times using Latin hypercube sampling[19–21] (Decisioneering Crystal Ball, Denver, CO) to create projected distributions for each baseline outcome. The transition probabilities corresponding to an intervention or combination of interventions were adjusted and the model was rerun 500 times using the same method to generate a new set of projected TB cases and deaths. The projected TB cases and deaths with and without the intervention were compared.

Ranges used in the sensitivity analysis were derived from the literature (Table 3). Quality of parameter estimates was assessed by examining original research studies; sample size, study design, reliability, validity, and generalizability were all taken into account. In a number of cases, best parameter estimates were found to occur close to the high or low end of the range used for sensitivity analyses. Because of this, best estimates of the impact of interventions may lie close to the high or low values of sensitivity analyses in some cases.

RESULTS

For every intervention or combination of interventions studied, control strategies targeted at children were significantly more effective in reducing pediatric TB cases over 10 years than the same increase in interventions in adults (Fig 1).

Therapeutic Interventions Targeted at Adults

A 5% increase in the number of adults with TB who enter treatment led to essentially no change in the prevalence of pediatric TB cases and deaths after 10 years, compared with the number projected without this intervention. TB cases in children declined .05%.

Marginal improvement in treatment effectiveness among adults already receiving TB therapy also had little effect on TB in children, compared with baseline strategies. Projected pediatric TB cases dropped .003% after 10 years compared with the baseline.

A combination of these 2 strategies targeted at adults was similar to the results from increased treatment rates alone in adults. The absolute change in

TABLE 1. TB Control Strategies Assessed in Computer Simulations

Child Intervention Strategy	Description
Increase treatment	5% increase in the percentage of people with TB starting anti-TB treatment
Improve treatment	5% improvement in the cure rate of TB, 5% decrease in TB mortality, and 5% decrease in ongoing active TB among treated patients
Increase and improve treatment	5% increase in the percentage of people with TB starting anti-TB treatment; 5% improvement in the cure rate of TB, 5% decrease in TB mortality, and 5% decrease in ongoing active TB among treated patients
Increase chemoprophylaxis	5% increase in isoniazid chemoprophylaxis among groups for whom it is currently recommended

TABLE 2. Initial Population Prevalence for Each Clinical State Based on HIV Status and Risk for TB

Clinical State	Number of Individuals		
	No Known HIV Infection	HIV-Seropositive	AIDS
No known infection	240 million	900 000[15,34,35]	67 000[34–36]
High risk for active TB†	29 000	3300	1600[37,38]
Low risk for active TB‡	9.1 million[39]	22 000	3400
Drug-sensitive active TB	1500	§	240
Drug-resistant active TB	170[40]	§	170[41]
Nontuberculosis deaths	2.3 million[42]	43 000[43]	46 000[44]
Death attributable to TB	800	§	540

AIDS indicates acquired immunodeficiency syndrome.
* Calculated by subtracting the number of persons with HIV infection, *Mycobacterium tuberculosis* infection, or both from the US population.
† Risk attributable to recent *M tuberculosis* infection or partially treated active TB.
‡ Risk attributable to long-standing *M tuberculosis* infection or partially completed chemoprophylaxis.
§ HIV-infected persons with active TB have AIDS by 1993 Centers for Disease Control and Prevention criteria.

TABLE 3. Baseline Annual Rates and Ranges for TB Strategies per 10 000 Population

Description of Probability	Value (Range†) by HIV Status and Age		
	HIV-Seronegative	HIV-Seropositive	AIDS
TB in the general population			
Children <15 y of age	.18 (.11–.45)	13	13 (10–38)
Adults 15–44 y of age	.36 (.25–.75)	1.0 (.5–5.0)	10 (5–17)
Adults ≥45 y of age	.89 (.63–1.90)	4 (2–6)	10 (5–15)
TB among recent tuberculin converters (<2 y)	138[45] (70–330)	3570[46] (3000–3700)	3700[47] (2000–3900)
TB among persons with latent *Mycobacterium tuberculosis* infection (>2 y)	7.30[48] (3.70–12.00)	790[49] (100–1200)	790[49] (400–2300)
Annual risk of *M tuberculosis* infection			
Children <15 y of age	.36 (0–.54)	1.20 (.62–1.80)	1.20 (.62–1.80)
Adults 15–44 y of age	.48 (.24–.72)	.48 (.24–.72)	.48 (.24–.72)
Adults ≥45 y of age	.80 (.40–1.20)	.80 (.40–1.20)	.80 (.40–1.20)
Likelihood of multiple drug resistance in recently acquired TB	180[40] (0–520)	*	970 (350–1900)[50]
Likelihood of multiple drug resistance in reactivated TB	80[51] (0–160)	*	80[51] (40–160)
TB mortality in treated multiple drug-resistant TB	400 (200–400)[52–55]	*	2800 (1800–5000)[52,55,56]
TB mortality in treated drug-sensitive TB	90 (60–120)	*	600[57] (300–1800)
Ongong TB despite treatment for drug-resistant TB	200 (0–700)[52–55]	*	100 (0–700)[52,55,56]
Drug-resistant TB after treatment for drug-sensitive TB	5 (2.5–7.5)	*	10 (5–15)
Ongoing TB despite treatment for drug-sensitive TB	200 (0–300)[58,59]	*	100[57] (0–100)
Patient cured with treatment for drug-resistant TB	8000[55] (5500–8500)[52–54]	*	4000[52,55]
Patient cured with treatment for drug-sensitive TB	9000[58–60] (5500–9200)	*	6550[57]
Isoniazid mortality	6[61,62] (3–9)	42‡	42‡

* HIV-infected persons with active TB have AIDS by 1993 Centers for Disease Control and Prevention criteria.
† Ranges used in sensitivity analyses.
‡ Adjusted to be greater than the baseline value for non-HIV-infected persons.

the prevalence of pediatric TB cases and deaths by the introduction of the above adult TB control strategies was <1 case and 1 death after 10 years.

Pediatric Therapeutic Interventions

A 5% increase in the number of children who enter treatment leads to a 25% decline in the number of TB cases among children and a 16% decline in the number of TB deaths after 10 years, compared with the baseline predicted without this intervention. Although increasing treatment efficacy among children is less effective than increasing the number of children who enter treatment, it remains more effective in reducing future pediatric cases and deaths than therapeutic interventions among adults. Improving treatment efficacy leads to a 1.7% decline in pediatric TB cases and a 1.3% decline in pediatric deaths (Fig 2).

The results of sensitivity analyses for targeted pediatric TB control strategies are shown in Table 4.

Preventive Measures Targeted at Adults

Increasing chemoprophylaxis among adults did not lead to substantial declines in pediatric TB cases or deaths after 10 years, compared with baseline projections. Increasing the probability that TB-infected adults receive chemoprophylaxis by 5% led to a .001% decline in pediatric TB cases and a .01% decline in pediatric TB deaths (Fig 1).

Preventive Interventions Targeted at Children

Increasing preventive chemoprophylaxis among children with positive tuberculin skin test results led to a 1.2% decline in projected pediatric TB cases and
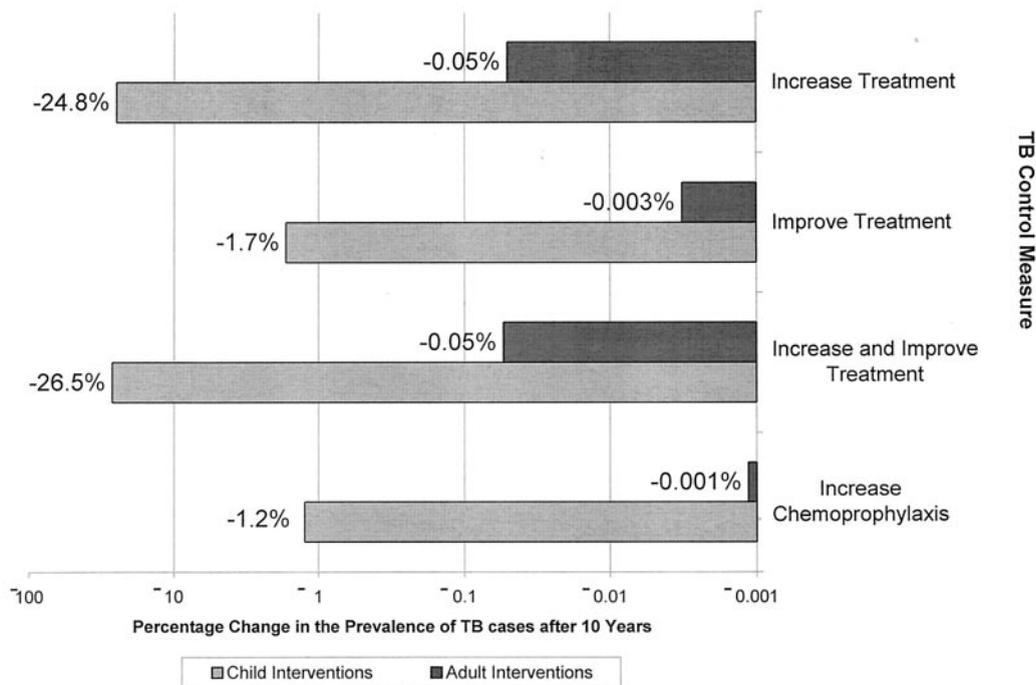
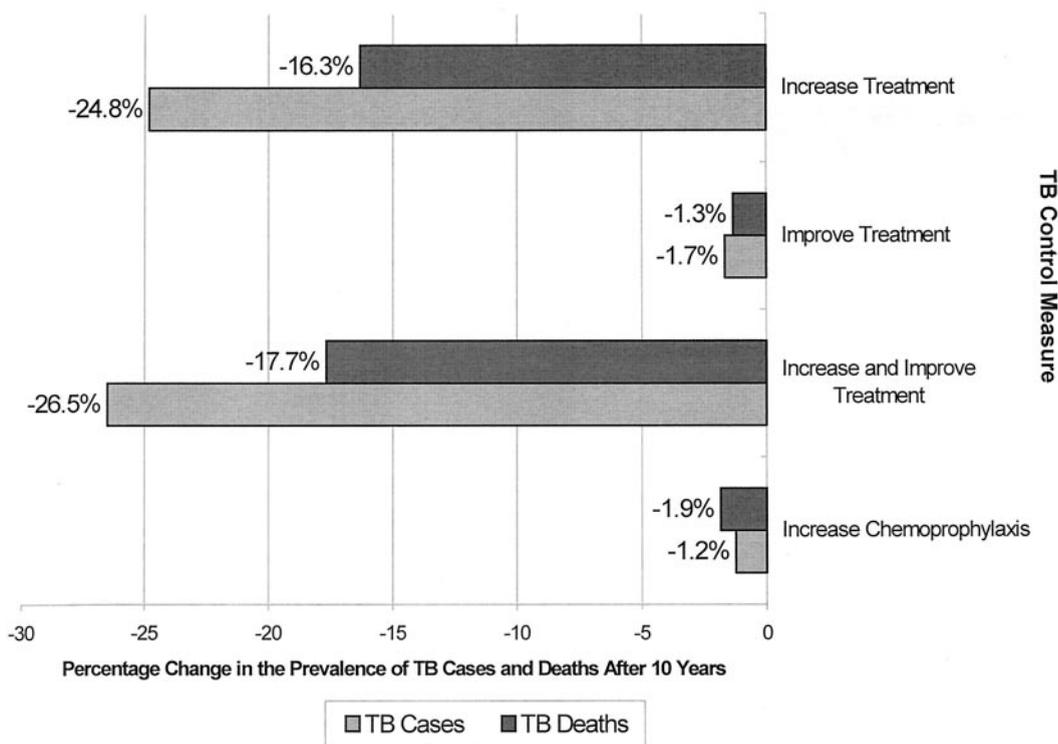**Fig 1.** Comparison of effectiveness of adult and child interventions.

Fig 2. Percentage change in pediatric TB cases and deaths with the introduction of 1 or more control measures targeted at children.

a 1.9% decline in TB deaths after 10 years (Fig 2). Increasing preventive chemotherapy use in skin test-positive children was even more effective at reducing acquired immunodeficiency syndrome-associated pediatric TB cases and deaths over 10 years (7% decline in TB cases and 4% decline in TB deaths among children with HIV) than pediatric TB cases (1.2% decline) and deaths (.9% decline) among children without HIV.

TABLE 4. Sensitivity Analysis Providing Latin Hypercube Estimate of Range of Impact

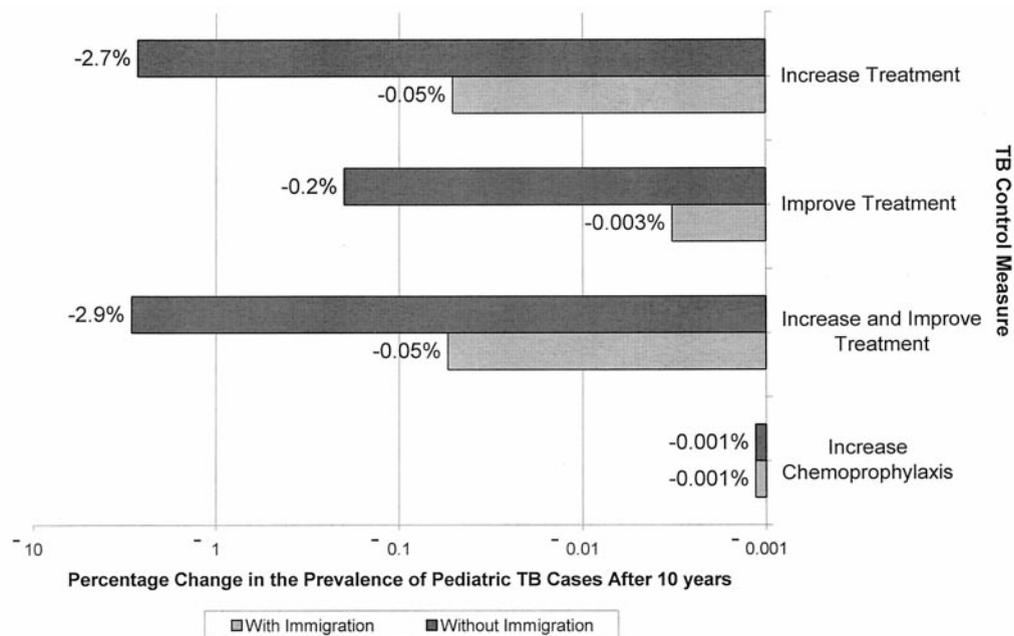| Child Intervention Strategy	TB Cases (%)	TB Deaths (%)
Increase treatment	−29.5 to −8.0	−20.7 to −12.6
Improve treatment	−2.6 to −1.1	−2.4 to −1.1
Increase and improve treatment	−26.8 to −13.3	−22.0 to −14.9
Increase chemoprophylaxis	−4.4 to −1.2	−5.8 to −1.2

Fig 3. Impact of immigration of children with positive skin test results on the effectiveness of TB control measures targeted at adults.

Understanding the Limited Effectiveness of Adult Interventions at Reducing Pediatric Cases and Deaths

Assumptions that improvements in US TB control programs targeted at adults would lead to effective elimination of TB among children rely on the supposition that infectious adults have access to these programs before transmission of TB to children occurs. This assumption may not be valid for children immigrating to the United States from countries with high TB prevalence rates.

All adult TB control strategies were rerun with the assumption that there was no immigration of tuberculin skin test-positive children into the US population. The effectiveness of TB control strategies targeted at adults at reducing TB cases and deaths in children increased by over 50-fold, compared with the results predicted when immigration of tuberculin skin test-positive children occurred (Fig 3). However, even under these extreme assumptions, strategies targeting adults remained less effective at reducing pediatric cases and deaths than the same intervention targeting children.

DISCUSSION

The results of this simulation model have important implications for reducing the morbidity and mortality from TB among children in the United States. First, programs and policies directly targeting children have a critical role to play. Both in the presence and in the absence of immigration, additional programs targeted directly at children are significantly more effective at reducing pediatric TB morbidity and mortality than are additional programs targeted at adults with the indirect goal of reducing spread to children. In the presence of immigration of tuberculin-positive children, the benefit of targeting programs directly at children is magnified many-fold.

The proportion of US TB cases among the foreign-born population continues to increase. In 1991, >1 827 000 immigrants were admitted to the United States; ~148 400 were children <15 years old.[22] The vast majority came from TB endemic countries, such as Mexico, the Philippines, the former Soviet Union, and Vietnam.[22] Treating adults with TB protects children only when it prevents transmission from occurring. When transmission has already occurred, then further reductions in the TB burden in adults has little impact on TB case rates in children.

Second, marginal increases in the number of children who enter treatment are far more effective at decreasing morbidity and mortality than marginal increases in treatment effectiveness. This result is probably due to the already high level of efficacy of current treatment programs. Although a great deal of appropriate attention has been paid to improving the effectiveness of TB treatment in the United States, far less attention has been paid to the availability of treatment. Unfortunately, several national trends have made it harder for those who are at greatest risk of TB to get medical care. The number of Americans who lack health insurance has continued to rise. A total of 10.7 million children in the United States lacked health insurance in 1997.[23] The health care available to immigrants, who are at higher risk for TB, has been impeded by legislation limiting access among both documented and undocumented immigrants to state and federally funded services.[24–28] Third, marginal increases in preventive therapy rates substantially reduce future pediatric TB cases and deaths among children with TB infection and HIV. Well-prepared models may predict the effectiveness of proposed interventions to control TB before such data exist from population-based trials.[29–33] However, it is important to validate model results with ongoing clinical studies and epidemiologic surveillance.

In 1989, the United States set a goal of TB elimina-

tion. Although increased efforts have led to declines in TB caseloads, we are not currently meeting the goals set for reducing the burden of this preventable and treatable disease. Reductions in TB morbidity and mortality have been slower among children than among adults, undoubtedly reflecting the focus on adult interventions and their relative ineffectiveness in reducing pediatric illness and death. Improving the quality of existing adult treatment programs will not be enough. If 1 of our national goals is to reduce the burden of TB in children, we will need to aim interventions directly at children. TB programs that increase children's access to diagnosis and treatment need to be developed and implemented, particularly as the TB burden among non-US-born individuals rises. These programs, targeted at children, will be far more effective than the same interventions aimed at adults, with the hope that children will benefit indirectly.

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