The Dynamics of Tuberculosis in Response to 10 Years of Intensive Control Effort in Peru

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Improved tuberculosis (TB) case detection and cure rates are expected to accelerate the decline in incidence of TB and to reduce TB-associated deaths. Time series analyses of case reports in Peru showed that the per capita TB incidence rate was probably steady before 1991. Case reports increased between 1990 and 1992 as a result of improved case detection. Although diagnostic efforts have continued to increase since 1993, the incidence of new pulmonary TB cases has declined in every department of the country, with a national rate of decline ⩾5.8% per year (range, 1.9%–9.7%). This elevated rate of decline suggests that 27% (19%–34%) of cases (158,000) and 70% (63%–77%) of deaths (91,000) among smear-positive patients were averted between 1991 and 2000. This is the first demonstration that a significant number of TB cases can be prevented through intensive short-course chemotherapy in a high-burden country.

When tuberculosis (TB) control programs improve case detection and patient cure rates, we expect to see an accelerated decline in incidence and a reduction in the number of TB-related deaths. This expectation is based largely on theory [1] and on data from developed countries [2]. There is scant evidence on what can be achieved in developing countries when control programs reach World Health Organization (WHO) targets of 70% case detection and 85% patient cure. Although 127 of 171 countries reporting to the WHO had adopted the DOTS (directly observed treatment, short-course) strategy for TB control by the end of 1999, only 7 were judged to have met the targets [3]. Peru was among them.

Peru has one of the highest TB incidence rates in the Americas (estimated as 228 per 100,000 population in 1999 [4]) and is one of 23 countries accounting for 80% of new TB cases worldwide each year. Three percent of the population of the Americas, but 15% of TB patients, live in Peru [3, 4]. The prevalence of human immunodeficiency virus (HIV) infection is low in Peru (0.56% in adults), especially when compared with high TB burden countries in Africa (adult prevalence, 4%–26% [5]). In August 1990, the National Tuberculosis Control Program (NTP) in Peru was revised, and the revised NTP (RNTP) follows the WHO DOTS strategy. A huge increase in case detection and diagnostic effort led first to an increase in reported cases and then to a decline. Our principal goal in this study was to learn what part of the drop in incidence over the past decade was attributable to the RNTP.

The data underpinning our analysis are from routine reports of a national control program, not from a randomized controlled trial. Although data from national control programs lack the deductive power of a formal experiment, they have the twin compensations of countrywide coverage and of providing large quantities of information. The databases used in this study include >400,000 TB cases throughout Peru reported between 1991 and 2000, with treatment results for >200,000 patients. Our strategy was to compare the rate of decline in TB incidence before and after the intervention, making a conservative estimate of the difference between these two rates. To argue that this difference is attributable to the revised program, we relied on the timing of the fall in incidence, the consistency of the rate of decline with theory and with previous observation, and the absence of any alternative explanation. The estimate of the difference allowed us to evaluate the number of cases and deaths prevented by the RNTP since its introduction.

Methods

TB control program in Peru. The main tenets of TB control under the RNTP are early case detection and diagnosis, followed by DOT of patients. All components of the service are free of charge and were available in nearly all health facilities (99.8% of 6552 units) in 2000. Health facilities first identify persons with respiratory symptoms (productive cough for ⩾2 weeks) and examine sputum smears. This is usually done by nursing staff or trained auxiliary personnel and need not involve a physician. Patients with negative smears and persistent respiratory symptoms are given a medical examination, supported by radiology and culture for *My-*

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Table 1. Values and distributions of variables used in calculations of number and fraction of tuberculosis (TB) cases and deaths averted.

Variable	Best estimate	Range or SE	Distribution	Source
Incidence of TB cases per 100,000, 1997				
Pulmonary	167	150–183	Triangular	This study
Smear positive	119	107–131	Triangular	[4]
Rate of decline in incidence without RNTP, % per year				
Pulmonary and smear positive	3.9	0.4	Normal	This study
Rate of decline in incidence with RNTP, % per year				
Pulmonary	7.5	0.8	Normal	This study
Smear positive	5.8	0.8	Normal	This study
CFR for untreated patients	0.7	0.6–0.8	Uniform	[9, 10]
CFR:treatment ratio in each of 4 treatment outcomes[a]				
Treated successfully	0.15	0.1–0.2	Uniform	Assumed; no data
Defaulted	3.0	2.0–4.0	Uniform	Assumed; no data
Failed treatment	3.0	2.0–4.0	Uniform	Assumed; no data
Transferred	1.05	1.0–1.1	Uniform	Assumed; no data

NOTE. CFR, case fatality rate; RNTP, revised national tuberculosis program.
[a] Treatment CFR = (patients dying during treatment)/(patients successfully treated + treatment failures + patients dying during treatment), varying from year to year [6, 7].

cobacterium tuberculosis, to confirm or exclude TB or other respiratory diseases.

DOT is provided by nursing staff in special areas within health facilities reserved for this purpose. Patients are encouraged to come for treatment by being given food packages and employment support (e.g., training in handicrafts), and their transport costs are paid. In rural or other areas with difficult access to the service, local leaders are identified to carry out health promotion (school teachers, religious leaders, or community association leaders) and are instructed in the administration and follow-up of TB treatment. These health promotion agents are supervised by nursing staff and are given nonfinancial incentives for their collaboration (training, certificates leading to public recognition, or invitations to participate in meetings).

Data. The analysis was done with 5 datasets and used standard case definitions [3], as follows: (1) total pulmonary TB cases reported to the NTP by the Ministry of Health during 1958–1987; (2) the number of new and relapsed TB cases reported by each of the 25 Peru health departments to the NTP in 1987–2000 and stratified by age and type of TB (pulmonary, extrapulmonary, sputum smear positive, and sputum culture positive) [6]; data from departments that were administratively divided during this period, reaggregated to provide continuous time series (between 1992 and 1995, the RNTP reported new cases and relapses together; we estimated the numbers of new cases [smear positive or all pulmonary] for these years by interpolating on the known ratios of new cases to relapses for 1990, 1991, 1997, and 1999); (3) treatment outcomes collected as part of an evaluation of the NTP before its revision [7] plus routine RNTP data for 1991–1999, including numbers of patients treated successfully (smear converted or treatment completed) and the number in whom treatment failed (remained culture-positive at 5 months) and those who defaulted (missed treatment for ⩾30 consecutive days), died during treatment, or were transferred and lost to follow-up [6]; (4) the number of deaths attributed to pulmonary TB in the civil register during 1943–1998 (this register has always been independent of the TB control program); and (5) estimated departmental and national population sizes obtained from the Ministry of Health (before 1989) and from the United Nations Population Division (1990 onward) [8]. These data were used to convert case numbers to per capita rates.

Analysis. We compared the estimated rates of decline in TB incidence (expressed as percentage per year) before and after revision of the control program by using linear regressions of the $\log_e$ time series. The absolute numbers of new smear-positive and all pulmonary cases in each year were calculated by anchoring the incidence series to the rate estimated for 1997, which was derived by considering reported cases to be 95% (range, 86%–106%) of the total in that year [3, 4] (table 1). The number of cases prevented in each year since 1991 is the difference between the estimated number of cases with and without the revised program.

Similarly, the number of TB deaths prevented was calculated by subtracting the total under the RNTP (1991–2000) from the total expected without the revised program. The analysis was restricted to new smear-positive patients, because there were few data on

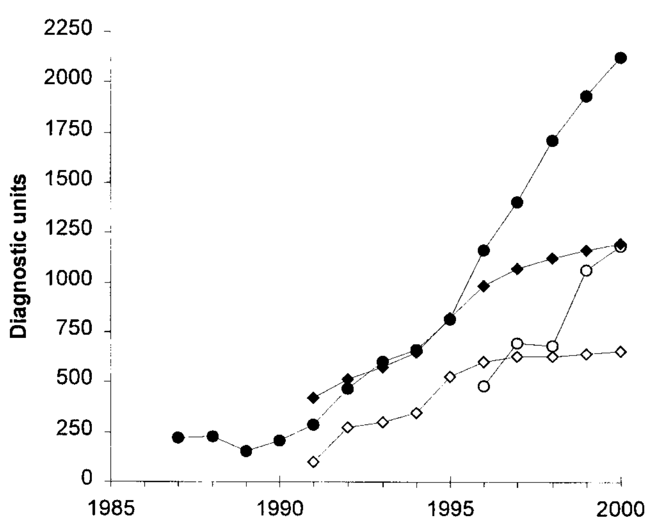

Figure 1. Increased diagnostic effort in Peru, 1987–2000. Thousands of sputum smears examined for diagnosis (●), hundreds of sputum cultures examined (○), tens of health centers participating in the national tuberculosis control program (◇), and nos. of laboratories with microscopy services (◆).

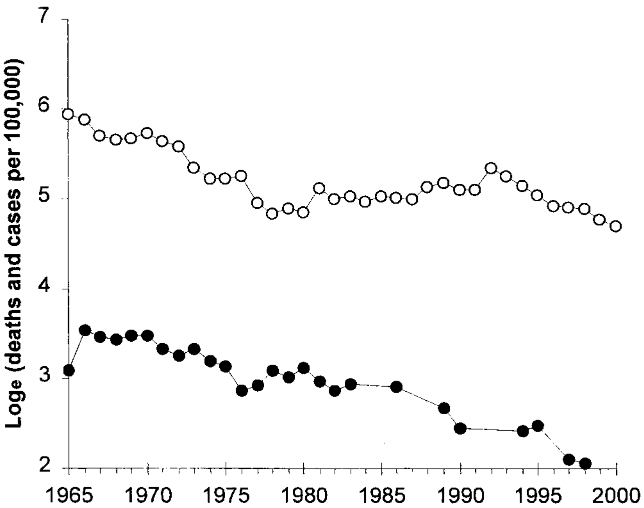

Figure 2. Registered deaths from (●) and reported new cases of (○) pulmonary tuberculosis per 100,000 population in Peru.

treatment outcomes for smear-negative patients. The total numbers of deaths with and without the RNTP were estimated in 3 steps. The first was to calculate the number of treated and untreated patients among the estimated total number of smear-positive patients in each year. We assumed that all reported patients were treated and that the number of untreated patients was the difference between those reported and the estimated total. The number of patients who would have been reported and treated without the RNTP was calculated by applying the average case detection rate for 1987–1990 to the estimated incidence for 1991–2000. The second step was to use data on treatment outcomes to determine how many patients were successfully treated, the number in whom treatment failed, plus those who failed, died, defaulted, or transferred to another reporting center [6, 7]. Finally, we applied case fatality rates (table 1) to each category of treated patients and to untreated patients, to calculate the number who died in each category with and without the RNTP.

For uncertainty and sensitivity analyses, all of the above rates were given appropriate frequency distributions (normal, triangular, or uniform) with point (best) estimates and ranges or SE, as in table 1. Each number or percentage of cases and deaths prevented is the median of 2000 Latin Hypercube samples run in @Risk (Palisade Decision Tools), with bounds at the 5th and 95th percentiles. The relative sensitivity of results to uncertainties in the underlying rates was measured by rank correlation coefficients (RCCs).

Results

Trends in effort, reported cases, and deaths. Effort given to diagnosis and case detection increased massively in Peru during the 1990s (figure 1). The number of health centers participating in the RNTP rose from 977 (24%) in 1991 to 6539 (99.8%) in 1999 (~2500 were new health centers). The number of laboratories capable of doing sputum microscopy increased from 307 in 1989 to 1200 in 2000. During 2000, the RNTP cultured >100,000 sputum samples and microscopically examined >2 million sputum smears from >1 million symptomatic patients [6].

The number of reported pulmonary TB cases per capita remained roughly steady between 1976 and 1990 after an earlier decline (figure 2). The arrested decline in incidence between 1976 and 1990 could be real, but surveillance was poor before the RNTP, and it is conceivable that incidence continued to fall at up to the same rate as deaths, which declined, on average, 3.9% per year (95% confidence interval, 3.2%–4.7%) in 1966–1990. The case report rate increased sharply between 1990 and 1993, coincident with the improvement in diagnostic effort. Since 1993, reported new smear-positive cases have declined in all departments of the country (figure 3*A*). Nationally, the average rate of decline in reporting new pulmonary cases since 1993 has been 7.4% per year (5.9%–8.9%; figure 3*B*), that is, halving every 9.4 years. The reported incidence rate in 2000 (134/100,000) was well below the rate observed in 1990 (170/100,000), before diagnosis and case detection were improved. The average rates of decline of all new cases and of new smear-positive cases have been somewhat lower: 6.4% (5.1%–7.7%) and 6.3% per year (4.7%–7.9%), respectively. The average rates

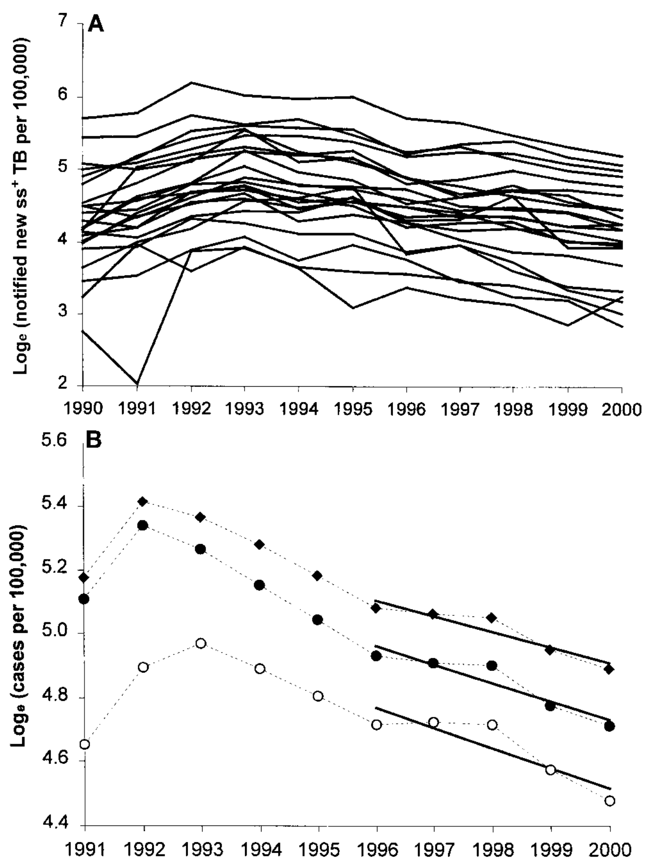

Figure 3. *A,* Case report rates of new sputum smear (ss)–positive tuberculosis (TB) cases per 100,000 population in 25 departments of Peru, plotted on a $\log_e$ scale. *B,* National case report rates of all new TB cases (♦), new pulmonary cases (●), and new smear-positive cases (○). Lines were fitted by regressions for the years 1996–2000.

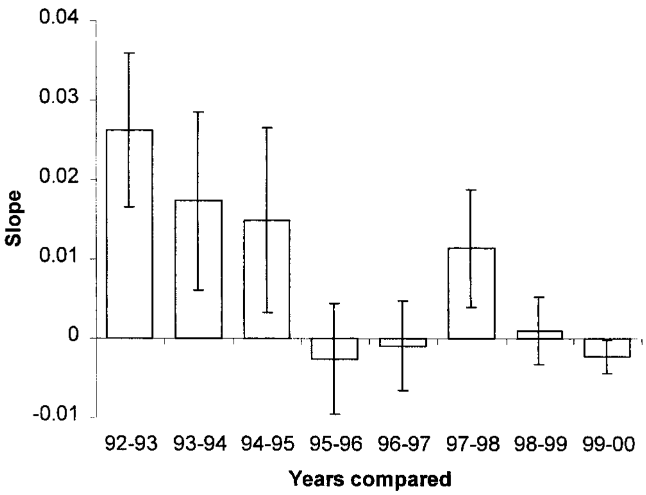

Figure 4. Diminishing returns on increased diagnostic effort. *Open bars,* regression coefficients (slope) of graphs of year-on-year differences for new sputum smear–positive case report rates against year-on-year differences in no. of sputum smears examined per capita for diagnosis in 25 departments of Peru. *Error bars,* 95% confidence intervals.

of decline of all new cases and new pulmonary cases, but not smear-positive cases, were slower after 1996 (figure 3*B*). For pulmonary cases, the rate was 5.8% per year (1.9%–9.7%).

The true rates of decline might be faster than observed because of the steady growth in diagnostic effort (figure 1). To investigate this possibility, we plotted the difference in reported cases in consecutive years (e.g., 1992–1993, 1993–1994) against the difference in sputum smear examinations. The regression coefficient of this graph diminished in magnitude between 1992–1993 and 1999–2000, suggesting that returns on increased sampling effort were significant up to 1994–1995, but not afterward (figure 4).

When TB incidence falls because transmission is reduced, we expect to see a higher proportion of cases among older people. Between 1991 and 2000, there was no trend in the ratio of the incidence rate in children to that in adults (t, −0.36; df, 6; P = .73). There was, however, a geographic association between incidence and mean ages of patients in 1999. The ratio of the per capita incidence rate in children to that in adults was greater in regions of Peru that reported more TB cases per capita (t, 5.3; df, 15; $P < .001$; figure 5).

Treatment outcomes. In all, 207,166 smear-positive patients were successfully treated between 1991 and mid-2000, 77% of the number registered and 88% of the number evaluated. The proportion of patients successfully treated increased dramatically during the decade (figure 6), due principally to a reduction in the default rate, but the RNTP also steadily reduced the numbers of transfers lost to follow-up and TB deaths and treatment failures.

Cases and deaths averted. To obtain a somewhat conservative estimate of the number of cases averted, we assumed that TB incidence was stationary before 1991 (figure 2) and that the impact of the program is reflected in slower rates of decline from 1996 onward (figure 3). In this scenario, the incidence rate of pulmonary TB was 44% (5th–95th percentiles, 31%–54%) lower in 2000 than it would have been had the rate of decline in incidence not increased. Consequently, 158,070 (98,835–232,021) pulmonary cases were prevented during 1991–2000, or 27% (19%–34%) of the number expected. If we assume, still more cautiously, that the annual incidence rate was falling at 3.9% per year from 1976 to 1990, similar to the death rate (figure 2), and would have continued to fall at the same rate, then the program prevented only 44,766 (−2887 to 105,993), or 9.4% (−0.7% to 19%) of, pulmonary cases. Over the same interval, 91,009 (71,614–114,684), or 70% (63%–71%) of, deaths were averted among smear-positive patients (figure 7). The per capita death rate in 2000 was 73% (59%–84%) lower than it would have been without the RNTP.

Estimates of the percentage of cases prevented are those most sensitive to uncertainty in the rate of decline in incidence under the RNTP (RCC >.89). Estimates of the percentage of deaths prevented are those most sensitive to uncertainty about the true incidence rate in 1999 (RCC ⩽.98).

Discussion

This study provides evidence that intensive implementation of short-course chemotherapy can reduce transmission of TB and accelerate the decline of TB incidence in a country with a very high burden of TB and a low prevalence of HIV infection.

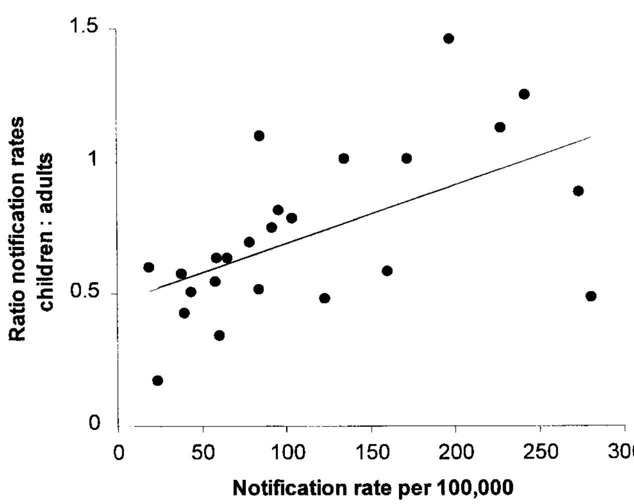

Figure 5. Geographic covariation by age and case report rate of new tuberculosis (TB) cases for 24 departments of Peru in 1999. *Vertical axis,* per capita case report rate for new cases in children <15 years old divided by the rate in adults ⩾15 years. *Horizontal axis,* case report rate in all age groups. One department (Arequipa; case report rate, 130/100,000; child : adult ratio, 1.9) was excluded, because TB was probably overdiagnosed in children.

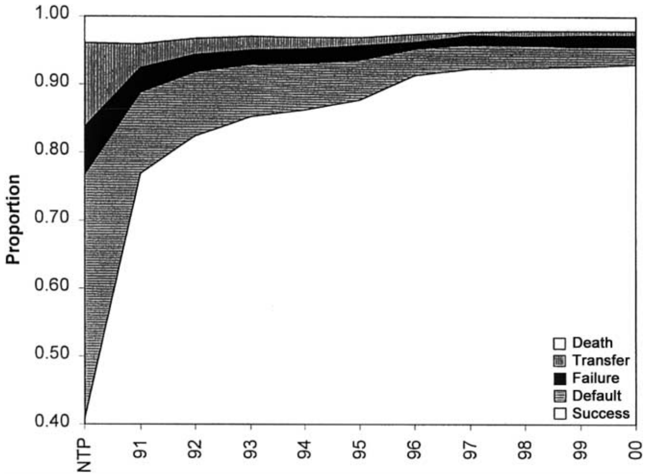

Figure 6. Improved outcomes of treatment for smear-positive cases under revised national tuberculosis control program (NTP; 1991 to mid-2000) vs. control program before revision. Denominator is no. of cases evaluated, which is less than no. registered for treatment.

In the most likely scenario, a stationary incidence rate of TB before 1991 was converted to a decline of ~6% per year. The consequences of this accelerated decline, coupled with improved case detection and treatment outcomes, are that Peru prevented ~158,000 pulmonary cases and ~91,000 deaths (smear-positive cases) between 1991 and 2000. If TB incidence continues to fall at this rate, it will be halved between 2000 and 2012.

We attribute this change to the RNTP for several reasons. First, it happened shortly after the NTP was revised (allowing a brief increase in reported cases, due to improved case detection and diagnosis). Second, the rate of decline is consistent with theory and with previous experience that TB incidence can be expected to fall at 5%–10% per year in moderate-to-good programs that provide standardized short-course chemotherapy [1, 2]. We are not aware of other obvious explanations (there was no evidence of any sudden improvement in social and economic conditions) [11, 12].

There are two reasons why our assessment of impact could be conservative. First, we assumed that the relatively quick rate of decline in pulmonary TB incidence between 1991 and 1995 (>7% per year) was partly attributable to the program that found and removed the backlog of undetected cases. We therefore adopted the lower rate of a 6% annual decline since 1996. Second, we assumed that this 6% annual decline was not offset by increasing diagnostic efforts after 1996. This second assumption is based on our analysis of saturating diagnostic effort and leads to a recommendation on smear examination. If the point of vanishing returns was reached by 1995–1996, there is little reason to increase the number of sputum smears examined beyond the present 2 million each year.

Although the average age of patients is expected to rise as incidence falls, this is a slow process in TB epidemiology. For example, as TB incidence declined relatively quickly in Finland, the median age among men with new respiratory cases increased by only 0.5 years, on average, each year between 1960 and 1990 [13]. It is, therefore, unsurprising that there was no discernible trend in Peru over the short period of 1991–1999; however, there was a strong geographic relationship between age and incidence, probably because the large regional differences in incidence have been stable for decades.

Our analysis of impact of the RNTP on mortality suggests that ~91,000 deaths were prevented between 1991 and 2000, (i.e., 70% of the number that would otherwise have occurred). Despite the uncertainties behind this calculation, the estimate is relatively tightly bounded between 63% and 77%. The result is also insensitive to the calculated impact on incidence. Even if we assume that the revised program had no effect on incidence, about the same fraction of deaths would have been prevented, because deaths were prevented mainly by reducing the case fatality rate, rather than by reducing the number of new cases arising each year. Although 70% may seem high, there is reason to think that the true fraction of deaths prevented was higher. Our calculations assume that the NTP treated all reported patients before 1991, but records from the 1980s suggest

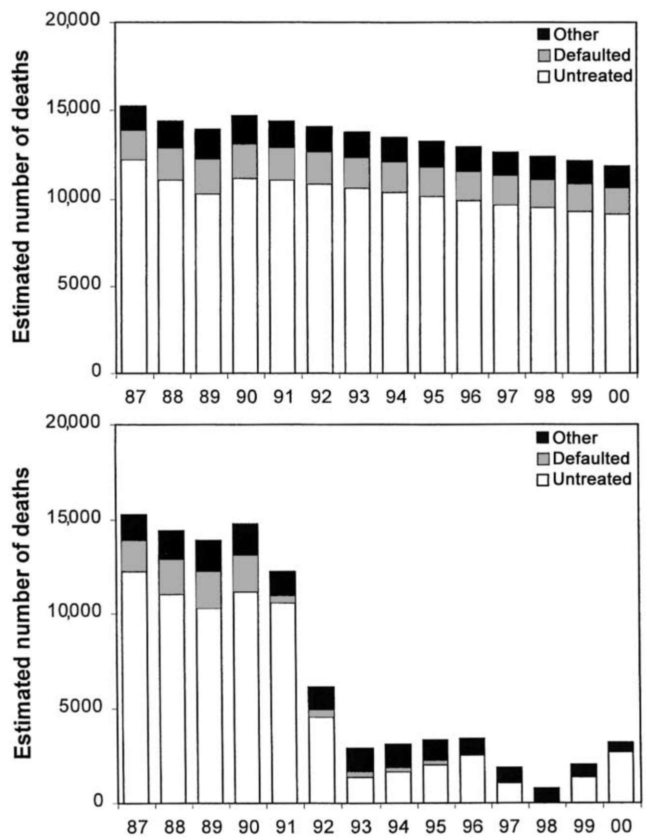

Figure 7. Estimated no. of deaths from new smear-positive tuberculosis (TB) without *(top)* and with *(bottom)* revised national control program that began in 1990.

that treated patients were fewer than the number diagnosed [6]. If so, the death rate before 1991 would have been higher and the estimated impact greater. This analysis also excluded deaths prevented among smear-negative cases.

In conclusion, the RNTP has made a significant impact on the TB epidemic in Peru. The factors underlying this success include the governmental decision to establish TB control as a health and social priority, sustained political and financial commitment by the government at all levels, a high level of coordination between different components of the health service, and continuous improvement of program quality through an effective system of information, training, monitoring, and evaluation.

The program has been a model of DOTS implementation with regard to reaching the WHO targets of 70% case detection and 85% cure [3]. It can now also be held as an example among high-burden countries of what is feasible in terms of reducing numbers of cases and deaths. A selection of countries around the world has made plans to reduce TB prevalence and mortality by 2010 to 50% of those in 2000 [14]. Peru appears to have cut the number of TB deaths by more than half during the 1990s. With sustained effort, the RNTP should be able to repeat that result in the coming decade.

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