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INFECTIOUS DISEASES

Active community surveillance of the impact of different tuberculosis control measures, Tiruvallur, South India, 1968–2001

R Subramani,[1] T Santha,[1] TR Frieden,[2] S Radhakrishna,[3] PG Gopi,[1] N Selvakumar,[1] K Sadacharam[1] and PR Narayanan[1]*

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Background Tuberculosis is curable, but community surveys documenting epidemiological impact of the WHO-recommended DOTS strategy on tuberculosis prevalence have not been published. We used active community surveillance to compare the impact of DOTS with earlier programmes.

Methods We conducted tuberculosis disease surveys using random cluster sampling of a rural population in South India approximately every 2.5 years from 1968 to 1986, using radiography as a screening tool for sputum examination. In 1999, DOTS was implemented in the area. Prevalence surveys using radiography and symptom screening were conducted at the start of DOTS implementation and after 2.5 years.

Results From 1968 to 1999, culture-positive and smear-positive tuberculosis declined by 2.3 and 2.5% per annum compared with 11.9 and 5.6% after DOTS implementation. The 2.5 year period of DOTS implementation accounted for one-fourth of the decline in prevalence of culture-positive tuberculosis over 33 years. Multivariate analysis showed that prevalence of culture-positive tuberculosis decreased substantially (10.0% per annum, 95% CI: 2.8–16.6%) owing to DOTS after only slight declines related to temporal trends (2.1% annual decline, 95% CI: 1.1–3.2%) and short-course chemotherapy (1.5% annual decline, 95% CI: −9.7% to 11.5%). Under DOTS, the proportion of total cases identified through clinical care increased from 81 to 92%.

Conclusions Following DOTS implementation, prevalence of culture-positive tuberculosis decreased rapidly following a gradual decline for the previous 30 years. In the absence of a large HIV epidemic and with relatively low levels of rifampicin resistance, DOTS was associated with rapid reduction of tuberculosis prevalence.

Keywords Community surveys, mass chest X-ray, epidemiology, rifampicin, disease control, tuberculosis, DOTS

Tuberculosis remains one of the leading infectious causes of death globally, killing nearly 2 million people a year.[1] Tuberculosis control programmes can achieve a high level of treatment success[1] and are associated with a decline in reported disease burden.[2–5] However, there have been very few analyses that included active, population-based surveillance of disease burden before and after implementation of effective tuberculosis control measures and none published, of which we are aware, that specifically evaluated the impact of the WHO-recommended DOTS (Directly Observed Treatment, Short-course) strategy.

In India, DOTS has been implemented as the Revised National Tuberculosis Control Programme (RNTCP) since

[1] Tuberculosis Research Centre, Chennai, India.
[2] Department of Health and Mental Hygiene, New York City.
[3] Institute for Research in Medical Statistics, Chennai, India.
* Corresponding author. Tuberculosis Research Centre, Mayor V.R. Ramanathan Road, Chetput, Chennai, India 600 031. E-mail: nrparanj@md2.vsnl.net.in

1993. The RNTCP expanded rapidly throughout India starting in 1998, with essentially the entire country covered in 2006.[6] Diagnosis is primarily by sputum microscopy. Treatment is standardized and thrice-weekly throughout, with every dose to be directly observed in the initial phase and at least one dose per week to be directly observed in the continuation phase. Medicines are supplied in boxes each containing a full course of treatment for an individual patient. Standardized methods of recording and reporting are used. Policy direction, drugs, and equipment are provided by the central government, with state governments responsible for programme staffing and implementation.[7]

The Tiruvallur area of India provides a unique opportunity to evaluate the rate of tuberculosis prior to and after implementation of DOTS. In 1968, a 15 year Bacillus Calmette-Guerin (BCG) vaccine trial was begun in the area[8]; disease burden in the population was monitored intensively and rigorously through active surveys in the community over the ensuing 15 years. In 1985, short-course chemotherapy with rifampicin-containing regimens was introduced in the area, but without direct observation of treatment or the management interventions of the DOTS strategy. In 1999, a new intervention study was begun based on the DOTS strategy. A baseline survey of disease prevalence among adults was conducted at the start of the DOTS programme and a follow-up survey was conducted after 2.5 years. In all, this analysis represents more than 700 000 mobile X-ray evaluations, most in remote rural areas, and sputum examinations of 40 000 people.

Methods

Sampling

Cases were identified both through presentation at clinics and active community survey. Clinically diagnosed, culture-negative cases were not included in the analyses as there is no gold standard for diagnosis of culture-negative tuberculosis and the great majority of tuberculosis cases are culture-positive. Surveys took 2.5 years. Of ~500 000 people in 218 clusters representing the sampling unit (209 villages and 9 towns) in five different areas, or blocks, each survey between 1968 and 1986 randomly selected 78 clusters (74 villages, 4 towns), and every adult in these areas formed the survey population. For the two surveys between 1999 and 2003 (DOTS period), 53 clusters (50 villages and 3 towns) were selected at random from the 78 surveyed earlier. The total population covered was 83 431 and 84 572 for these two surveys, and population within each cluster ranged from 516 to 5429 for the first survey and 476 to 5649 for the second survey. Thus, there were three periods: prior to use of rifampicin-containing, short-course chemotherapy regimens (pre-SCC, 1968–1986); after introduction of rifampicin-containing regimens (SCC, 1986–1999); and during DOTS implementation (DOTS, 1999–2003). The pre-SCC and SCC periods constitute the pre-DOTS phase of tuberculosis treatment services in this area.

Survey methodology

Survey methods have been described in detail elsewhere.[8–10] All persons in the selected villages/towns were registered by door-to-door census, and adults aged ⩾15 years present at the time were questioned regarding chest symptoms and underwent a chest radiograph (70 mm photofluorogram, postero-anterior view) at a nearby health centre. This radiograph was read independently by two readers and, in case of disagreement, by a third reader. In the community survey, we evaluated both those with radiographic abnormalities suggestive of tuberculosis and those who presented at health facilities in the survey area with symptoms suggestive of tuberculosis who had an abnormal chest X-ray.

In the initial disease surveys, from 1968 to 1986, two sputum specimens were collected from patients who had an abnormal X-ray suggestive of tuberculosis. Sputum samples were subjected to smear and culture examination, with specimens yielding growth subjected to identification tests for *Mycobacterium tuberculosis*. If the smear result was positive for acid-fast bacilli (AFB), one more sputum sample was collected. Patients who had two positive smears, or who were culture-positive, were considered to have tuberculosis and were referred to a health facility for anti-tuberculosis treatment. If only one smear was positive, action was taken based on radiographic results.[11] Patients were categorized and treated as per World Health Organization guidelines.[12] Patients absent for examination were revisited the same day or on subsequent days until at least 90% of patients had provided the required number of sputum specimens.[9] Patients who did not commence treatment despite being reminded by three home visits were considered initial defaulters.

Surveys were repeated every 2.5 years. In the DOTS period (1999–2003), in addition to chest radiography, survey participants were asked about pulmonary symptoms (i.e. cough for ⩾2 weeks, chest pain or fever for 1 month or more, or haemoptysis at any time during the previous 6 months); those with either an abnormal radiograph suggestive of tuberculosis or chest symptoms were asked to submit two sputum specimens.[11] These were examined by fluorescence microscopy and cultured on Lowenstein–Jensen medium.

Numbers and cases in study

For the primary analysis of trends in the prevalence of tuberculosis and the impact of short-course chemotherapy and DOTS, we have restricted the analysis to the cases identified by radiographic screening alone (the number varied from 62 000 to 92 000) as this method was employed uniformly in all the surveys (Table 1).

Case definitions

People with a positive culture for *M. tuberculosis*, regardless of smear, were considered culture-positive cases. People with a positive smear containing more than three acid-fast bacilli (AFB), regardless of culture, were considered smear-positive cases. The policy was to examine each slide for at least 5 min before declaring it to be smear-negative for AFB.

Estimation of prevalence in the community

If *Xi* is the number of eligible persons in the *i*th subgroup (by sex and by age), *xi* is the number assessed (by radiography), *Si* is the number eligible for sputum collection (based on abnormal radiograph), *si* is the number with a sputum examination, and *fi* is the number with a positive finding (culture/smear), the total number of positives in the *i*th

Table 1 Prevalence of tuberculosis (per 100 000), standardized to 1968–1970 population, based on screening by radiography alone (for population in five blocks in South India)

Period of survey	Sample size	Examined by radiography in the survey			Sputum examined		Prevalence		Standardized prevalence[a]	
		No.	%	Abnormal	No.	%	C+ rate[b]	S+ rate[c]	C+ rate[b]	S+ rate[c]
1968–1970	77 089	61 718	80	6646	6143	92	1017	630	1017	630
1971–1973	84 760	70 312	83	4264	3686	86	876	565	894	576
1973–1975	88 213	73 133	83	6115	5310	87	915	586	942	603
1976–1978	94 837	83 242	88	4673	4466	96	857	476	894	498
1979–1981	98 816	87 432	88	4132	3863	93	791	529	820	550
1981–1983	102 999	91 645	89	6237	5975	96	775	579	808	602
1984–1986	104 611	91 881	88	5445	5190	95	671	507	688	519
1999–2001	83 431	75 121	90	3355	3206	96	508	274	510	276
2001–2003	85 472	77 216	90	2768	2616	95	363	232	372	239
Annual decrease (%) in										
Pre-SCC period (years 0–15)							2.3 (1.4 to 3.2)[d]	0.9 (−0.7 to 2.7)[d]	2.1 (1.1 to 3.2)[d]	0.9 (−0.7 to 2.3)[d]
SCC period, pre-DOTS (years 15–30)							1.8	4.1	2.1	4.1
DOTS programme (years 30–32.5)							12.5	6.5	11.9	5.6

[a] Standardized with reference to 1968–1970 survey population.
[b] Prevalence of culture-positive tuberculosis (per 100 000), smear either positive or negative.
[c] Prevalence of smear-positive tuberculosis (per 100 000), culture either positive or negative.
[d] Range in brackets denotes 95% CI.

subgroup is conventionally estimated as $(fi/si) \times (Si/xi) \times Xi = Ci$, assuming that the findings in those not examined would be the same as in those assessed.[9]

In this study, however, the number of sputum-positive cases among those that did not have sputum collected was estimated from the nature of the radiographic abnormality by utilizing the probability of a positive finding in the appropriate radiographic category[8,9]; within each category, it was higher in those with chest symptoms than in those without. Thus, eligible subjects who did not have a sputum examination (~4% in the 1999–2001 survey) were classified into 16 categories (4 by radiography × 2 by symptom status × 2 by sex), and the number in each group was multiplied by the culture-positive probability, to estimate the number of missed culture-positive cases, and multiplied by the smear-positive probability, to estimate the number of missed smear-positive cases.[9]

To estimate the number of cases among those with no radiograph, the relative risk (RR) of a person having chest symptoms (compared with that of a person with a radiograph) was taken as a proxy for the RR of a person without a radiograph having tuberculosis (compared with a person with a radiograph); this did not appear to be influenced by age and was 0.6 for males and 0.4 for females.[8,9] The number of missed cases owing to non-coverage by radiograph or sputum examination was added to the observed number of cases, and overall estimates of culture-positive and smear-positive tuberculosis were obtained (for both sexes and all ages combined) by pooling of appropriate categories.[9]

Statistical analysis

A cluster sampling design was used for each survey. The required sample size was estimated to be 82 000 adults aged ⩾15 years for precision of 20% at a 95% confidence level, proportion examined (coverage) of 90%, and a design effect of 2.[9] Statistical methods employed were the Chi-square test for equality of proportions, linear regression analyses for determining rate of decline over time, and standardization by the direct method.

Prevalence was estimated for each survey and age–sex standardized to the population of the 1968–1970 survey. A weighted multivariate regression analysis of log prevalence on time was undertaken, including rifampicin and DOTS as dummy variables; the weight was the inverse of the sampling variance of the prevalence estimate.

Ethical considerations

The institutional ethics committee of the Tuberculosis Research Center, Indian Council of Medical Research, approved the project.

Programme implementation and performance

During the pre-SCC period, the average proportion of the estimated annual incident smear-positive cases detected and treated in the programme was reported to be 30% of total estimated new smear-positive cases, and only 30% of those starting treatment completed treatment.[13] During the SCC period, the detection rate increased slightly to ~45% of the estimated total new smear-positive cases and treatment completion also increased to ~50%.[14] The government of Tamil Nadu implemented the DOTS strategy in this area in May 1999.

In the pre-SCC period, non-rifampicin-based regimens were used almost exclusively. In the SCC period, many patients, particularly those who were AFB smear-positive, received rifampicin-containing regimens but entirely under

self-administration. In the DOTS period, nearly all patients received rifampicin-containing, thrice weekly regimens, with medication administration that was to be directly observed thrice weekly (i.e. all doses) in the initial 2–4 month treatment period and at least once per week in the follow-up treatment period. National policies, treatment regimens, and results of DOTS implementation have been described elsewhere.[7] Diagnosis in clinical facilities was largely based on radiological examination in the pre-SCC period, single AFB smear and radiological examination in the SCC period, and three AFB smears, if negative, followed by empiric antibiotic treatment and then radiological examination in the DOTS period.

Results of DOTS implementation in the project are as follows. Against an estimated 85 new smear-positive cases per 100 000 population, the average case detection rate between 1999 and 2003 was 86% in the study area (range 65–94%; WHO global target $\geqslant$70%[1]). The average treatment success rate for new smear-positive patients was 77% (range 71–80%; WHO global target $\geqslant$85%[1]). Case detection in the project area is somewhat higher, and treatment success somewhat lower, than in the rest of the national programme.[7] Throughout the survey period, all diagnosed cases were referred to the nearest governmental health facility for further management. Patients were treated on an ambulatory basis, with drugs supplied for self-administration during pre-SCC and SCC periods. During the DOTS period, directly observed treatment was given by either governmental or community providers; attempts were made to involve the private sector, and sensitization programmes were conducted for the private sector, village officers, and the community. Virtually all private practitioners, although only a minority of private laboratories, participated and referred patients with symptoms of tuberculosis. No enablers or incentives were used at any time.

Results

During the pre-SCC period, there was a small decline of 2.1% per annum in the prevalence of culture-positive tuberculosis (95% CI: 1.1–3.2%), from 1017 per 100 000 in 1968–1970 to 688 per 100 000 in 1984–1986 (Table 1, Figure 1). The annual rate of decline was the same in the SCC period, with prevalence decreasing to 510 per 100 000 in 1999–2001, but the rate of decline accelerated substantially after DOTS implementation to 11.9% per annum, with prevalence decreasing to 372 per 100 000 in 2001–2003.

Smear-positive tuberculosis prevalence declined by 0.9% per annum during the pre-SCC period (Table 1, Figure 1) and by 4.1% annually during the SCC period (from 519 per 100 000 to 276 per 100 000), with an overall decline of 2.5% per annum prior to DOTS implementation (95% CI: 1.1–3.8%). After DOTS implementation, the rate of decline accelerated to 5.6% per annum, with prevalence declining to 239 per 100 000 in 2001–2003.

The decline during the DOTS period was similar in males and females for both culture-positive (10.9 vs 12.3%, respectively) and smear-positive cases (4.7 vs 3.2%, respectively).

For the entire pre-DOTS period, including both pre-SCC and SCC periods, the annual rates of decline in culture-positive and smear-positive tuberculosis were 2.3 and 2.5%, respectively. In the DOTS period, the annual rate of decline of culture-positive tuberculosis increased to 11.9% (from 510 to 372 per 100 000) and for smear-positive tuberculosis to 5.6% (from 276 to 239 per 100 000).

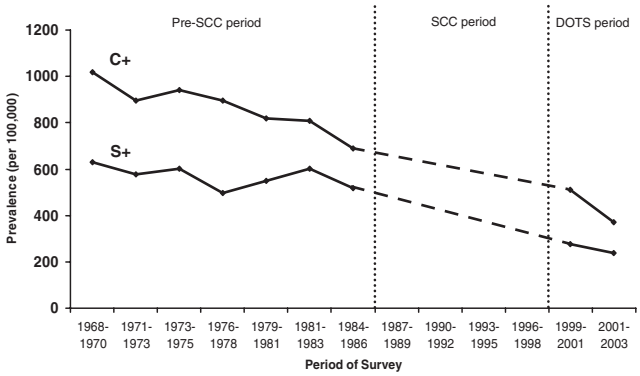

Figure 1 Trends in prevalence of culture-positive (C+) and smear-positive (S+) tuberculosis in South India, 1968–2001. Age–sex standardized with reference to 1968–1970 survey population

Considering all cases identified by both symptom and radiographic screening, the annual decline observed for culture-positive tuberculosis was 1.4% (from 1039 to 827 per 100 000 population) during the pre-SCC period, 2.1% during the SCC period (from 827 to 608 per 100 000), and 11.3% (from 608 to 450 per 100 000) during the DOTS period. The corresponding annual declines for smear-positive tuberculosis were: pre-SCC: 0% (646–636 per 100 000); SCC: 4.3% (636–328 per 100 000); and DOTS: 9.0% (328–259 per 100 000).

Restricting the analysis to the 53 sampled clusters (of the 78 total), which were surveyed during both the DOTS and the pre-DOTS periods, very similar decreases in rates were observed.

A multivariate linear regression analysis of the data with time, rifampicin (short-course chemotherapy), and DOTS as dummy variables showed that the annual decrease in prevalence of culture-positive tuberculosis over time was 2.1% (95% CI: 1.1–3.2%), short-course chemotherapy was associated with an additional 1.5% annual decrease in prevalence (95% CI: −9.7 to 11.5%), and DOTS was associated with an additional 10.0% annual decrease (95% CI: 2.8–16.6%).

For the entire community, the absolute decrease in prevalence over the 33 years was 645 per 100 000 for culture-positive tuberculosis (i.e. from 1017 to 372 per 100 000). Of the decrease, 21% occurred after just 2.5 years after implementation of DOTS, as against the 8% (2.5/33 years) that would have occurred if the decrease over time had been uniform.

During the period of DOTS implementation, a decreasing proportion of cases was diagnosed through active disease survey and an increasing proportion through the routine diagnostic and treatment system. The proportion detected through community surveys decreased from 18.8% in 2000 and 2001, the first 2 full years of DOTS implementation, to 8.1% in 2002 and 2003 (379 of 2011 vs 159 of 1969, $P < 0.00001$); similar trends were seen among both new and re-treatment patients.

Discussion

We have demonstrated a substantial annual decline in the prevalence of culture-positive (11.9%) and smear-positive

(5.6%) pulmonary tuberculosis cases after introduction of the DOTS strategy. In the survey area, we were able to measure the association of tuberculosis prevalence with tuberculosis control programmes in various periods (i.e. pre-SCC and SCC, which together constitute the pre-DOTS period, and the DOTS period). We observed the same annual decline in culture-positive tuberculosis (2.1%) during the pre-SCC and SCC periods; however, the decline became far more rapid after implementation of the DOTS strategy (11.9%). Similarly, this project recently documented a significant decline in tuberculosis infection during the DOTS period after no significant decrease during either the pre-SCC or SCC periods.[15] The 5.8% decline in annual risk of tuberculosis infection documented[15] was similar to the 5.6% decrease in smear-positive prevalence reported here. The prevalence of smear-positive tuberculosis should, on a theoretical basis, correlate well with annual risk of infection, since most infections are spread by smear-positive prevalent cases.

Use of rifampicin-containing SCC regimens appears to have been associated with a slight hastening of the long-term gradual decline in tuberculosis prevalence in this area. However, only when DOTS was implemented did a rapid decrease in tuberculosis prevalence occur. Thus, changing recommended drug regimens alone does not appear to adequately control tuberculosis. It is essential that there be a management system in place to ensure that patients take medication regularly. The importance of direct observation of treatment has been emphasized by the Tuberculosis Research Centre for nearly 50 years.[16]

The rapid increase in the proportion of cases identified through the diagnostic and treatment system in this area, from 81% during the first 2 years of DOTS implementation to 92% in the next 2 years, is encouraging. This provides evidence to support what has been described as a 'recruitment effect' of good quality care, whereby improved treatment systems draw patients into the system of care.[17] In addition to recognition on the part of patients that the programme was reliably curing those in care, the increased case detection through the DOTS programme may also reflect rational economic decisions of patients. Cost per patient in the study area dropped by more than two-thirds after DOTS was implemented, from Rs 4588 (~US $109) before DOTS was implemented to Rs 1398 (~US $32).[18] In addition, this finding suggests that monitoring disease trends by monitoring case notifications may, in the presence of an effective control programme with a good notification system, provide a reasonable approximation of the epidemiology of tuberculosis in an area.

Comparison with other studies

Although our analysis is, to our knowledge, the first to employ systematic community disease surveys to monitor the impact of the WHO-recommended DOTS strategy, several systematic surveys have documented declines in tuberculosis case rates in the context of sound diagnosis and treatment. In Kolín, former Czechoslovakia, prior to establishment of the global DOTS strategy, an intensive surveillance and treatment programme employing direct observation of anti-tuberculosis treatment in a population of 100 000 reduced the prevalence of bacteriologically (smear or culture) confirmed tuberculosis by 10% annually, from 150 per 100 000 in 1960 to 91 per 100 000 in 1964; however, no historical comparison data were available.[5] In Korea, nationwide prevalence surveys between 1965 and 1995 found a 5% annual decline in bacteriologically confirmed cases (from 940 per 100 000 in 1965 to 219 in 1995).[4]

Investigators in Beijing, China, reported an annual decline of 17.2% (from 127 per 100 000 in 1979 to 16 per 100 000 in 1990) in prevalence of smear-positive pulmonary tuberculosis based on results for Beijing of three nationwide tuberculosis prevalence surveys conducted in 1979, 1984–1985, and 1990.[19] A strategy similar to DOTS was implemented in Beijing in 1978, and the decline was attributed to the increase in programme coverage from 10% in 1978 to 90% in 1990. As their community survey methods are not fully described, it is not possible to make detailed comparisons. The annual decline reported was nearly twice the 9.0% observed in our area, although in the first 5.5 years of their implementation the annual rate of decline was lower (13.8%) than in the last 5.5 years (20.4%). The fact that our programme did not meet the global target of 85% treatment success (77% treatment success in our area vs the $\geqslant$85% global target and $>$90% success in Beijing) probably resulted in less than the full potential impact of DOTS implementation. Direct observation in the continuation phase is once-weekly in the programme in India. In addition, our baseline survey overlapped with initial DOTS implementation, which could result in an underestimation of the impact of DOTS.

Other reports on the impact of DOTS on tuberculosis have been based on case notification.[20,21] Thus, Peru had reported a decline of ~6% per year during 1993–2000, following a stationary phase up to 1991 and an increase between 1991 and 1993 owing to improved case detection after DOTS implementation.[20] The decline was observed even though case detection efforts increased and was attributed to successful implementation of the DOTS strategy. New York City reported that cases of tuberculosis tripled between 1978 and 1992, then declined 9.3% annually through 1994 among culture-positive pulmonary tuberculosis cases notified, despite the presence of HIV.[22] This decrease was attributed to improved tuberculosis control, including standardization of short-course treatment, direct observation of treatment, systematic monitoring of all treatment outcomes, and reduction of nosocomial spread of tuberculosis among HIV-infected persons. The rate of decline observed in these two reports was similar to what we obtained in our area based on community survey.

Limitations

A limitation of our study is that we estimated the rate of decline during the DOTS period from the findings of two surveys only. However, the surveys were based on random sampling and the magnitude of the decline is substantially greater than the decline that occurred in the previous 3 decades. Because survey participation was high, it is unlikely that there were either selection or surveyor bias. Another limitation is that we assessed the impact of DOTS by comparing the decrease in prevalence with temporal changes in the past in the same population. While it would have been ideal to compare it with the changes in a similar area without DOTS over the same period, this was not ethically feasible as DOTS had been

designated the national policy of care for tuberculosis. We have also not considered socioeconomic changes in the community due to non-availability of accurate information; there have been, however, no apparent significant socioeconomic changes in the years covered by the survey. Our study may have over-estimated the impact of SCC and under-estimated the impact of DOTS; this is because the baseline survey, which lasted for 2.5 years, was begun at around the same time DOTS implementation began and could, consequently, have yielded a lowered prevalence due to the impact of DOTS. Finally, our findings are not generalizable to areas of the developing world with a high prevalence of HIV infection, as <1% of tuberculosis patients in the survey area were infected with HIV (Tuberculosis Research Centre, unpublished data), or to areas with high prevalence of rifampicin-resistant tuberculosis strain; rifampicin resistance in previously untreated patients in this area was <2%.[23]

Conclusion

Implementation of DOTS enables effective clinical and public health management and resulted in a much more rapid decline in culture-positive tuberculosis prevalence than the decline that occurred in this area for more than 30 years previously. These results suggest that, in the absence of a large epidemic of HIV and with relatively low levels of rifampicin resistance, DOTS can result in rapid control of tuberculosis as measured through a sharp decline in prevalence and a significant reduction in the annual risk of tuberculosis infection.[15] Future surveys will determine the long-term impact on tuberculosis prevalence and the effect on incidence.

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KEY MESSAGES

- Anti-tuberculosis treatment without the management package known as DOTS does not adequately control tuberculosis, even in the absence of a high prevalence of HIV infection or anti-tuberculosis drug resistance.
- DOTS appears to result in rapid reduction of tuberculosis prevalence in areas without a large HIV epidemic and with relatively low levels of rifampicin resistance.
- Implementation of DOTS increases the proportion of patients who present to governmental health care facilities.

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