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Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China

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Background	Tuberculosis (TB) is still amongst the most important causes of human morbidity and mortality, killing approximately two million people each year. Standard short-course chemotherapy (SSCC) can rapidly control illness and dramatically reduce the chance of death, but the impact of treatment has rarely been evaluated in these terms.
Method	We developed a mathematical model that makes use of routinely-collected data to calculate the number of deaths directly prevented by TB treatment (i.e. excluding those due to reduced transmission). The method was applied to the world's largest TB control programme covering over 500 million people in 12 provinces of China.
Results	Counties which had been enrolled in the programme since 1991 were, by 1997, preventing at least 46% (37–56%) of the TB deaths that would otherwise have occurred. If replicated across the entire TB control programme area, this would amount to 30 000 (range 26 000–59 000) deaths directly prevented each year.
Conclusions	Short-course chemotherapy has substantially reduced TB mortality in half of China. The analytical method described here could be applied to TB control operations in many other countries, and should help to quantify the true burden of tuberculosis alleviated by SSCC.

Keywords	Disease burden, epidemiology, mathematical modelling, standard short-course chemotherapy, TB
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The ultimate goal of tuberculosis (TB) control is to reduce incidence to zero. This cannot, however, be a short-term aim given the huge reservoir of infection which currently exists in highly-endemic areas (about one in three people are infected worldwide[1]). It may even be unrealistic to expect detectable falls in incidence within 5 years, unless a control programme is supremely efficient. By contrast, it should be possible to rapidly demonstrate the impact of good control on illness and death in a community. In a perfect control programme, every new case would be detected immediately and properly treated and then the burden of illness and death (though not the economic burden) would immediately be reduced almost to zero, even if incidence was undiminished. All programmes are imperfect, but it is possible that many have had, or are having, a substantial impact on the burden of disease. That impact has not yet been adequately quantified.

In China in 1990, TB accounted for about half of all deaths due to communicable diseases.[2] In 1991, the country adopted the WHO TB control strategy (DOTS, directly-observed treatment, short-course) as part of a broader Infectious and Endemic Disease Control (IEDC) Project. Over the past 7 years, this has expanded to become the largest DOTS Programme in the world, covering 1200 counties with over 500 million people. Free diagnosis is provided for all patients with symptoms of TB, and free treatment for those with sputum smear-positive disease. The data collected include reported cases (smear-positive or negative) seeking treatment and re-treatment, as well as the outcomes of short-course chemotherapy (completed treatment, cured, failed treatment, defaulted, died, transferred between health facilities).[3] Individual patient records are even richer in information about the history of illness and treatment, including time and place of treatments, as well as personal data on age, sex, occupation and address.

To assess the impact of TB control, Styblo (ref. 3; Styblo K, World Health Organization, unpublished document) suggested

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calculating the ratio of re-treatment/new smear-positive cases (T/N, or alternatively the re-treatment proportion, $R = T/(T + N)$). This is a simple and easily measurable indicator which falls in value in a good control programme because, properly-treated, drug-susceptible cases infrequently require more than a single course of drugs. But it has the major weakness that it cannot be directly related to the change in illness and death. For example, a fall in prevalence will be reflected by a fall in T/N, but we expect both T and N to change as a result of intervention, so we cannot calculate the change in prevalence knowing only the ratio. The general problem is that we do not yet have a formal description of the properties of this potentially useful index, so its precise meaning remains unclear.

Beginning with the notion that the re-treatment proportion provides a useful measure of the impact of TB control, our aim is to develop a more comprehensible method of measuring how effectively control programmes have reduced illness and deaths due to TB. The latter accounts for most of the burden in terms of years of healthy life lost. This paper concentrates on cases cured and deaths averted, using data from the first 7 years (1991–1997) of the Chinese DOTS Programme.

Methods

A treatment-re-treatment model of tuberculosis control

The outcome of treatment for patients in the Chinese Programme is well known: county data show treatment success (demonstrable smear conversion, or treatment completion) rates of over 90% and death rates of typically 2% or less.[3,4] However, these results refer only to patients observed in cohorts; we want to measure success with respect to the whole populations of counties and provinces enrolled in the Programme.

Figure 1 depicts a simple model of the process of treatment and re-treatment for cases producing sputum smears that contain microscopically visible acid fast bacilli. New incident cases enter at the top of the diagram, and we assume that the rate at which they appear is constant through time. Most of these cases are presumed to seek treatment inside or outside the Programme, but some may die before being treated. A proportion of those who are treated will be cured (negative smear, or treatment completion), and the proportion depends on whether they are treated inside or outside the Programme. The rest fail, i.e. they have a persistently positive smear, they default (interrupt treatment), are transferred to another treatment facility, or die. Failures who do not die are likely to seek re-treatment, either inside or outside the Programme, and a proportion of these will also be cured. Again, the cure rate depends on the source of treatment, but re-treatment is generally less successful than primary treatment, partly because poor treatment selects for drug-resistant bacilli.[3,4]

Figure 1 describes the fate of all TB patients, wherever they are treated. In practice we see only new cases and failures seeking treatment from the Programme, and the associated cure and death rates of patients under observation. We do not see, directly, what happens outside the Programme, but we can make some inferences based on the relative numbers of treatment and re-treatment cases. For example, if the cure rate of new smear-positives is nearly 100%, then most re-treatment cases, if they are numerous, must have first been treated elsewhere. This

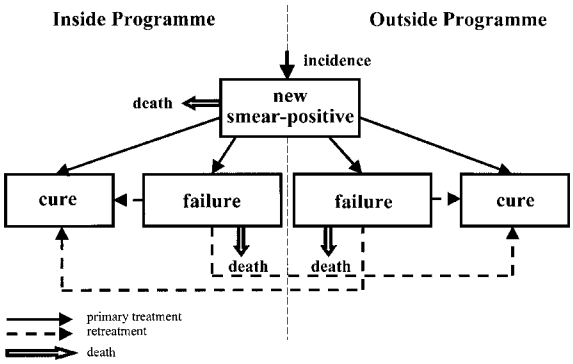

Figure 1 Flow chart of the treatment-re-treatment model, which is described formally in the Appendix

implies that we can use such data to estimate the proportion of new smear-positive cases detected and treated by the Programme. The Appendix shows formally how we can calculate the following important indicators of Programme success: (1) The fraction of all new smear-positive cases seeking treatment that is detected by the Programme (i.e. excluding cases that die before being treated). (2) The incidence rate of new smear-positive cases (lower limit). (3) The overall cure rate of smear-positive cases, with and without the Programme. (4) The fatality rate of smear-positive cases, with and without the Programme. (5) The number of TB deaths directly prevented by the Programme, i.e. excluding those due to reduced transmission.

Sources of data

Technical details of the Chinese TB control Programme, and the epidemiological background, have been described elsewhere.[2,3] The Programme provides, for each enrolled county in each quarter, the numbers of smear-positive cases reporting for primary treatment or re-treatment, and the numbers of these which are cured (negative smear after treatment completion), and which completed treatment, failed (positive smear after treatment completion), defaulted or died. Some cases deemed to have been cured as a result of the first course of treatment will later relapse. In the China control Programme, relapses have been recorded separately from 'other re-treatment' cases; relapses have been excluded from this analysis because they do not reflect Programme performance. These and all other case definitions within the Programme conform to WHO standards.[3,4] Treatment success and case fatality rates outside the Programme have been estimated previously.[2,3]

Results

The results are laid out following the logic of the Appendix. There is strong annual periodicity in the quarterly case reports (Figure 2), so we carried out all statistical analysis on aggregated annual data. Central to the analysis are the numbers of new and re-treatment cases reported through time. Figure 3 presents this information as the re-treatment proportion (R) for the whole of the Programme from 1991–1997. The data include reports for a total of 706 354 patients (503 356 new, 202 998 re-treatment), and counties have been aligned so that 'year 1' is the year of enrolment for each county. Although the total numbers of cases

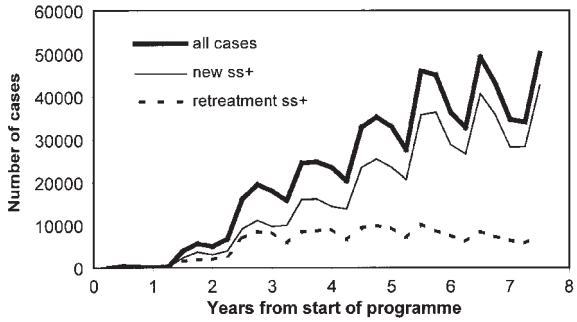

Figure 2 Numbers of smear-positive (ss+) cases reporting for primary treatment and re-treatment, by year from the start of the Programme

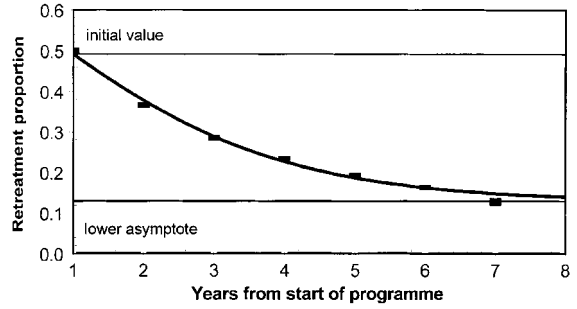

Figure 3 Re-treatment proportions for the IEDC Programme. Counties have been aligned from the date of enrolment in the Programme. Error bars are 95% CI. Horizontal lines mark the positions of initial (upper, estimate of *a*) and final (lower, estimate of *b*) retreatment proportions. Parameter values for the fitted line are in Table 1

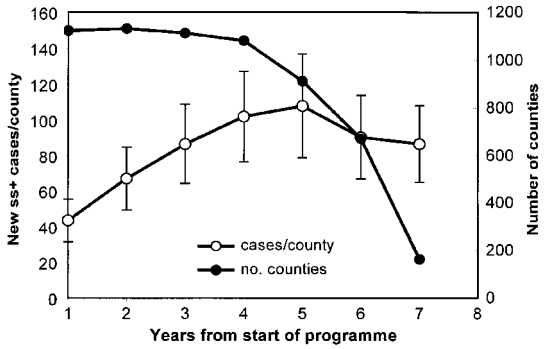

Figure 4 The number of counties, and the reported number of new smear-positive cases per county, with time since enrolment. Counties have been aligned as in Figure 3. Error bars are 95% CI

have continued to grow as the Programme has expanded (Figure 2) there is evidence, albeit equivocal, that the number of cases/county has peaked and is now in decline (Figure 4). Counties have participated in the Programme for different lengths of time: 1132 counties reported cases for at least one year, and 163 (14%) for 7 years (Figure 4). The aligned data for the various counties show the re-treatment proportion falling exponentially from its pre-Programme value towards a new, lower asymptote (Figure 3).

With the data in Figure 3 we can estimate three parameters (with standard errors) by maximum likelihood fitting: the initial (*a*) and final (*b*) values of the re-treatment proportion, and the

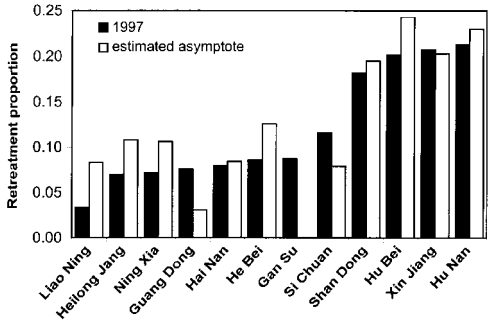

Figure 5 Measured (1997, filled bars) and estimated equilibrium re-treatment proportions (parameter *b*, open bars) for the 12 provinces participating in the control Programme. No estimate of *b* could be obtained for Gan Su Province because the re-treatment proportion has not declined exponentially

Table 1 Input data, including fitted model estimates for the data in Figure 3. Entries are means (with SD) or modes (with ranges)

Variable	Mean or Mode (SD or range)
From Programme data:	
Treatment success rates (%)	
New ss+[a] in Programme (κ_{S_p})	97 (0.03)
Re-treatment ss+ in Programme (κ_{F_p})	92 (0.06)
New ss+ outside Programme (κ_{S_o})	50 (35–65)
Re-treatment ss+ outside Programme (κ_{F_o})	30 (10–50)
Ratio mortality/re-treatment rate (μ/r)	0.40 (0.10–0.70)
By model fitting:	
Initial re-treatment percentage (*a*)	0.49 (0.13)
Asymptotic re-treatment percentage (*b*)	0.13 (0.17)
Transition rate/year (*c*)	0.58 (0.22)

[a] Smear-positive cases.

rate of transition between the two (*c*). The estimates of *a*, *b* and *c* reflect the weighted average performance of all 12 participating provinces (Figure 5, Table 1). The solid line in Figure 3 shows the maximum likelihood fits to the data for the whole Programme. The average re-treatment proportion in 1997 was lower than the predicted asymptote, *b*, because it was lower in 8 out of 12 provinces (Figure 5).

Appendix equations 5–7 show how *a*, *b* and *c* can be interpreted in terms of case detection and cure rates. By rearranging these equations (Appendix, equation 8 onwards), and by using independent estimates of cure and case fatality rates in and out of the Programme, we can calculate values of the five indicators listed above. The cure and completion rates of 608 879 new (425 666) and re-treatment cases (183 213) within the Programme exceed 90% (Table 1). Cure rates outside the Programme have been measured less accurately,[3] and we have accordingly allowed wider bounds on estimates. The ratio, μ/r, is derived from the case fatality rate μ/(μ+r), again allowing a wide range for uncertainty.[2] The entries in Table 1 are the inputs needed to obtain the estimates of indicators given in Table 2.

Among the cases that ever sought treatment from the Programme, 77% (67–100%) were detected as smear-positives seeking primary treatment (fraction p_{Sp}) (Table 2). The notification rate of smear-positive cases was 25/100 000/year which,

Table 2 Impact of the tuberculosis control Programme: estimates derived from the treatment-re-treatment model. Adjusted values are based on a smear-positive (ss+) incidence rate taken from ref. 1

Variable	Mode (5^{th}–95^{th} centiles)	Adjusted mode (5^{th}–95^{th} centiles)
Reported incidence new ss + /100 000/year	25	25
New ss + seeking treatment inside the Programme (p_{Sp}, %)	77 (67–100)	49 (36–51)
Estimated incidence new ss + /100 000/year (Λ)	32 (25–37)	51 (49–70)
Re-treatment rate/year (r)	0.076 (0.01–0.41)	0.076 (0.01–0.41)
Average cure rates (%)		
New cases ($\bar{\kappa}_S$)	85 (82–98)	65 (63–77)
Re-treatment cases ($\bar{\kappa}_F$)	75 (71–93)	50 (48–66)
Improvement due to Programme ($\kappa_S - \kappa_{S_0}$)	36 (28–52)	17 (15–27)
Case fatality rate (%)		
Without Programme	30 (21–49)	30 (21–49)
With Programme	6 (0.6–9.4)	15 (11–26)
Reduction due to Programme	24 (19–42)	15 (9–25)
Population covered (millions)	564	564
Deaths (000s)		
Without Programme	38 (29–69)	67 (56–133)
With Programme	9 (0.8–13)	37 (27–79)
Averted by Programme	30 (26–59)	30 (26–59)
Averted (%)	81 (77–98)	47 (37–56)

together with a case detection rate of 77%, implies a total smear-positive incidence rate of 32/100 000/year (25–37/100 000/year), assuming that all cases eventually seek treatment from the Programme.

The overall cure rate of smear-positive cases on first treatment increased from 50% (35–65%) before the Programme to 85% (82–98%) after the Programme had become established. The fatality rate of smear-positive cases decreased from 30% (21–49%) to 6.1% (0.6–9.4%) over the same period. If performance were maintained at this level throughout the IEDC Programme area (in 1997, covering 564 million people living in half the country), the number of TB deaths would be reduced from 38 000 (29 000–69 000) per year to 8600 (800–13 000) per year. In other words, 30 000 (26 000–59 000) or 81% (77–98%) of deaths would be averted each year.

The assumption that all patients eventually seek treatment from the Programme is almost certainly incorrect, and means that p_{Sp} gives an overestimate of the case detection rate. A recent review[1] of TB epidemiology in China estimated the country-wide smear-positive incidence rate to be 51/100 000/year (range 49–70/100 000/year) in 1997. Using this higher estimate gives the adjusted Figures in the final column of Table 2. The case detection rate (p_{Sp}) falls to 49% (36–51%), and the overall cure rate from primary treatment to 65% (63–77%). The fatality rate of smear-positive cases falls from 30% before the Programme to 15% (11–26%) in 1997; that is, an estimated 47% (37–56%) of deaths were prevented, revised downwards from 81%, though the number prevented remained the same.

Sensitivity analysis[5,6] reveals that the estimated number of deaths averted is most influenced by uncertainty over b, the equilibrium value of the re-treatment proportion (partial rank correlation coefficient 0.77), and by c, the rate at which that equilibrium is reached (PRCC 0.49). The estimated number of deaths averted was much less sensitive to other components of the model, including the ratio μ/r which ranged widely in value from 0.1–0.7 (Table 1).

Discussion

Our method of calculating the number of TB deaths averted is an extension of, and provides a formal explanation for, Styblo's use of the retreatment proportion (R) for monitoring the impact of a control programme. It is an example of the way in which mathematical modelling can be used to extract further information about the impact of an intervention from routine data, outside the ambit of a randomized controlled trial. The principal result is that the 14% of counties enrolled in China's IEDC Programme since 1991 were, by 1997, probably saving over half of the deaths that would otherwise have occurred due to TB. If this performance were maintained throughout the 12 provinces, covering 564 million people in 1997, we conservatively estimate that the Programme would be averting 30 000 (26 000–59 000) deaths/year.

There are four important qualifications to be attached to this finding. First, our analysis assumes that the re-treatment proportion has, following the introduction of the Programme in 1991, settled to a new, lower steady value (b). To achieve this, the Programme must impose an immediate change in the quality of TB control, and that change must have been in place long enough for a new equilibrium to be established. The data in Figure 3 indicate that counties which joined the Programme in 1991 are now close to equilibrium. However, model fitting has overestimated b for most provinces (8 out of 12 in Figure 5) and across the whole Programme. In other words, our analysis is cautious and, for this reason, tends to underestimate the fraction of deaths averted.

Second, the new equilibrium value of R is most strongly influenced by data from the counties that have been enrolled in

the Programme since 1991. The estimated number of deaths that could be saved by the whole Programme assumes that the same result on average will be obtained from all 1200 counties in the 12 IEDC provinces. There is no reason to believe that counties which enrolled earlier are different from the rest, but this remains to be seen. The number of cases found each year is still rising across the 12 provinces.

Third, our treatment-re-treatment model assumes that all smear-positive TB cases that are not cured will eventually seek treatment from the Programme—the model assigns to each patient a fixed probability of doing so after each treatment failure. However, there are certain to be some patients that will never be seen by the Programme. For this reason, the smear-positive case detection rate is probably lower than 77%. On the other hand, it is likely to be higher than the 49% obtained by applying the recent nationwide estimate of 51 new smear-positive cases/100 000/year. The reason is that incidence may have declined within the control Programme area since 1991, so that it is now less than the national average. Whatever the true case detection rate, it has no direct influence on the estimated number of deaths prevented: the 30 000 are either a small fraction of a large number, or a large fraction of a small number.

Fourth, the bigger question about falling incidence, if it is falling, is the extent to which it is due to reduced transmission. Our analysis calculates only the direct epidemiological benefits of treatment, and not the indirect benefits gained by preventing deaths of secondary cases. Dynamic transmission models[7,8] could, in principle, be used to evaluate these extra, indirect benefits for China.

The re-treatment proportion could in principle be reduced to zero but it appears, across the 12 provinces (now 13, since the creation of Chongqing Municipality), to be settling to a lower value of about 13%. Since cure rates within the Programme are close to 100%, this implies that a proportion of smear-positive cases is first treated outside the Programme. In one county, Changshou (Chongqing Municipality), for which b = 19%, we examined the record cards of 288 patients seeking retreatment between 1994 and 1998. The majority (162/288, 58%) received primary treatment outside the county, 91 (33%) were first treated inside the county but outside the Programme, and 25 (9%) were first treated by the Programme. The re-treatment proportion therefore markedly understates the performance of the Programme within this county. Retreatment cases were mostly itinerant patients who were officially residents of Changshou, but who were living or working elsewhere at the time they became ill. They may have returned to Changshou because they were entitled to free treatment in their home county. It is doubtful that they could have been detected as new smear-positive cases, no matter how good the Programme in Changshou. Whether TB patients are usually charged for treatment away from their home counties, and whether patients who pay are more likely to default, are questions now under further investigation.

Having established here another measure of the effectiveness of the Chinese Programme—adding deaths prevented to the patient cure rate[3]—we need to know the cost of achieving this success. The Programme was stimulated, in part, by a $55 million loan from the World Bank, matched by counterpart funds provided within China. However, the overall cost/death prevented, and the relative contributions of external and internal funding, have not yet been assessed. It is vital that the economics of this Programme are better understood as external funding comes to an end in the year 2000. The costs and cost-effectiveness of short-course chemotherapy against tuberculosis in China need to be compared with estimates from other TB control programmes,[9] and from other health interventions,[10] so that TB control can be assigned the correct priority and properly-financed within China.

Finally, China is not alone in reporting the numbers of TB cases seeking treatment and re-treatment, and our method for estimating deaths prevented can in principle be applied to control programmes in other countries. Although the impact of control operations on tuberculosis burden is potentially large it has rarely been quantified; wider application of the technique described here would help to measure the effectiveness of TB control in a variety of different settings.

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Appendix

Treatment-re-treatment model

Our approach is fundamentally a perturbation analysis of the re-treatment proportion, $R = T/(T + N)$. It makes use of the observation that TB control forces R to move between two

equilibria. The first is the status quo achieved with poor treatment (high failure rates) prior to the introduction of the new control Programme; the second is the steady state to which the system settles after the new Programme has been operating for several years with maximum effect. The processes in Figure 1 can be written as follows. New smear positive cases, S, are assumed to arise at a constant rate Λ, and are lost by death (at per capita rate μ) or detection (per capita rate δ) leading to treatment:

$$S^{\bullet} = \Lambda - (\mu + \delta)S \qquad 1$$

where $\bullet$ indicates differentiation with respect to time (following Newton rather than Leibniz). Some cases fail treatment ($1-\kappa$, the proportion cured), outside (subscript o) or inside the Programme (subscript p), and are thereby recruited to two classes of failures, F_o and F_p. They remain here until they successfully seek retreatment (per capita rates $r\kappa$), or die. The (weighted) average proportion of failures that is successfully treated inside and outside the Programme is $\bar{\kappa}_F = p_{F_p}\kappa_{F_p} + p_{F_o}\kappa_{F_o}$. Therefore,

$$F_o^{\bullet} = \delta p_{S_o}(1 - \kappa_{S_o}) - (r\bar{\kappa}_F + \mu)F_o \qquad 2$$

$$F_p^{\bullet} = \delta p_{S_p}(1 - \kappa_{S_p}) - (r\bar{\kappa}_F + \mu)F_p \qquad 3$$

Cure is a dead-end state in this model (Figure 1), and is implicit to equations (1)–(3).

When solving these equations we can set $S(0) = 1$ by letting $\Lambda = \mu + \delta$, since we will only be concerned with ratios in model fitting. The Programme measures T, the rate at which treatment failures present themselves:

$$T = r(F_o + F_p)p_{F_p} \qquad 4$$

and N, the rate at which new smear positive cases present themselves:

$$N = \delta p_{S_p} \qquad 5$$

Note that T and N are rates (incidences) while S and F are numbers (prevalences). Initial and asymptotic values are obtained by setting equations 2 and 3 to zero and noting that, at time zero, immediately before the Programme starts, $p_{S_p} = p_{F_p} = 0$. This gives

$$F_o(0) = \frac{\delta(1 - \kappa_{S_o})}{r\kappa_{F_o}} \qquad 6$$

$$F_p(0) = 0 \qquad 7$$

$$F_o(\infty) = \frac{\delta p_{S_o}(1 - \kappa_{S_o})}{r\bar{\kappa}_F + \mu} \qquad 8$$

$$F_p(\infty) = \frac{\delta p_{S_p}(1 - \kappa_{S_p})}{r\bar{\kappa}_F + \mu} \qquad 9$$

Because the equations for F_o and F_p are independent of each other and we are assuming that $S(t)$ is constant, we can solve for $F_o + F_p$ analytically. Summing equations 2 and 3,

$$F^{\bullet} = F_o^{\bullet} + F_p^{\bullet} = \delta\left[1 - p_{S_o}\kappa_{S_o} - p_{S_p}\kappa_{S_p}\right] - (r\bar{\kappa}_F + \mu)F \qquad 10$$

Then, defining $\bar{\kappa}_S = p_{S_p}\kappa_{S_p} + p_{S_o}\kappa_{S_o}$, we use equations 4 and 10 to get

$$T^{\bullet} = rp_{F_p}\delta\left[1 - \bar{\kappa}_S\right] - (r\bar{\kappa}_F + \mu)T \qquad 11$$

Solving equation 11 gives

$$T = rp_{F_p}\delta\left\{\frac{1 - \kappa_{S_o}}{\kappa_{F_o}}e^{-(r\bar{\kappa}_F + \mu)t} + \frac{1 - \bar{\kappa}_S}{\bar{\kappa}_F + \frac{\mu}{r}}\left(1 - e^{-(r\bar{\kappa}_F + \mu)t}\right)\right\} \qquad 12$$

and thus,

$$\frac{T}{N} = \frac{p_{F_p}}{p_{S_p}}\frac{1 - \kappa_{S_o}}{\kappa_{F_o} + \frac{\mu}{r}}e^{-(r\bar{\kappa}_F + \mu)t} + \frac{p_{F_p}}{p_{S_p}}\frac{1 - \bar{\kappa}_S}{\bar{\kappa}_F + \frac{\mu}{r}}\left(1 - e^{-(r\bar{\kappa}_F + \mu)t}\right) \qquad 13$$

Due to the introduction of a new control programme, the ratio T/N converges exponentially (equation 13) from an initial value of a,

$$a = \frac{p_{F_p}}{p_{S_p}}\frac{1 - \kappa_{S_o}}{\kappa_{F_o} + \frac{\mu}{r}} \qquad 14$$

to an asymptote b,

$$b = \frac{p_{F_p}}{p_{S_p}}\frac{1 - \bar{\kappa}_S}{\bar{\kappa}_F + \frac{\mu}{r}} \qquad 15$$

at a rate c,

$$c = r\bar{\kappa}_F + \mu \qquad 16$$

By fitting the data to an exponential curve with a non-zero asymptote we can estimate the three parameters a, b and c.

Epidemiological interpretation of the estimated parameters

In equations 14 and 15 we have seven parameters: two probabilities p_{S_p} and p_{F_p} (which determine p_{S_o} and p_{F_o}), four proportions κ_{S_p}, κ_{F_p}, κ_{S_o} and κ_{F_o}, and μ/r, the ratio of the mortality rate to the retreatment rate. With two equations we need a further five constraints. By fixing the four proportions and the ratio μ/r we can solve for p_{S_p} and p_{F_p}:

$$p_{S_p} = \frac{\left(a\left(\kappa_{F_o} + \frac{\mu}{r}\right) - b\kappa_{F_o}\right)\left(1 - \kappa_{S_o}\right)}{a\left(\kappa_{F_o} + \frac{\mu}{r}\right)\left(\kappa_{S_p} - \kappa_{S_o} + b\kappa_{F_p} - b\kappa_{F_o}\right)} \qquad 17$$

$$p_{F_p} = a_{p_{Sp}}\left(\kappa_{F_o} + \frac{\mu}{r}\right)\Big/\left(1 - \kappa_{S_o}\right) \qquad 18$$

From equation 16,

$$r = \frac{cb}{a}\frac{1 - \kappa_{S_o}}{\left(\kappa_{F_o} + \frac{\mu}{r}\right)}\frac{1}{\left[1 - \kappa_{S_o} + p_{S_p}\left(\kappa_{S_o} - \kappa_{S_p}\right)\right]} \qquad 19$$

The procedure for parameter estimation is then: (1) Fit an exponential curve to the data using equation 4 to calculate T/N in terms of the three coefficients a, b and c. (2) Use this to calculate $T/(T + N)$. (3) Fit the curve $T/(T + N)$ to the data by maximum likelihood[11] in order to determine the values and covariance matrix of a, b and c.

A Monte Carlo procedure, carried out with *@Risk* software (Palisade Corporation), was used to determine the sampling distributions of p_{S_p}, p_{F_p} and r allowing: (1) a and b (and for the estimation of r, c also) to follow bivariate normal distributions based on the estimated values and covariances, (2) κ_{S_p} and κ_{F_p}

to follow independent normal distributions based on Programme estimates, (3) κ_{S_o} and κ_{F_o} to follow triangular distributions derived from knowledge of their likely values.

The overall proportion of cases that is cured once the Programme has reached a steady state is:

$$P_{prog} = \bar{\kappa}_S + \frac{\left(1-\bar{\kappa}_S\right)\bar{\kappa}_F}{\bar{\kappa}_F + \frac{\mu}{r}} \quad 20$$

and the proportion cured before the Programme has started is:

$$P_{no\,prog} = \kappa_{S_o} + \frac{\left(1-\kappa_{S_o}\right)\kappa_{F_o}}{\kappa_{F_o} + \frac{\mu}{r}} \quad 21$$

In terms of the fitted parameters:

$$P_{prog} = \bar{\kappa}_S + b\bar{\kappa}_F \frac{p_{S_p}}{p_{F_p}} \quad 22$$

$$P_{no\,prog} = \kappa_{S_o} + a\kappa_{F_o} \frac{p_{S_p}}{p_{F_p}} \quad 23$$

Again Monte Carlo methods can be used to determine each of these and their sampling distributions, noting that $1 - P$ is the proportion of the initial smear positive cases that dies (the case fatality rate) under each scenario. Each point estimate obtained by Monte Carlo methods is the mode of a distribution obtained from 10 000 simulations, with 5th and 95th centiles used as lower and upper bounds.