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Methodology for the Assessment of Burden of Smear-positive Pulmonary TB and Its Infectivity

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XU QUN*, WU ZHENG-LAI*, LIU XIAO-LIN**, JIN SHUI-GAO***, AND ZHANG LI-XING#

*Department of Epidemiology, School of Basic Medicine, Peking Union Medical College, Institute of Basic Medical Sciences, Chinese Academy of Medical Sicences, Beijing 100005, China; **Department of Preventive Medicine, Jinzhou Medical College, Jinzhou 121001, China; ***Information Center for Public Health, Chinese Academy of Preventive Medicine, Beijing 100050, China; #Beijing Research Institute for TB Control, Beijing 100035, China

Objective The study investigated the burden of smear-positive pulmonary TB and its infectivity using DALY(disability-adjusted life year) as an indicator. **Methods** An assumed cohort of 2 000 cases was set up based on the age-specific incidence of 794 newly registered smear-positive cases in Beijing in 1994. Prognostic trees and model diagrams of infectivity under natural history and DOTS(directly observed treatment, short-course) strategy were established according to the epidemiological evidence. **Results** The results showed that 29. 6% of DALYs would be neglected if the burden caused by the infectivity was not considered. **Conclusion** DOTS strategy may reduce 97.3% of the number of potential cases infected, 92.9% of DALYs related to TB-patients themselves, and 99.9% of DALYs caused by TB's infectivity as well.

Key words: Tuberculosis(TB); Burden of disease(BOD); Disability-adjusted life year(DALY)

INTRODUCTION

Disability-adjusted life year (DALY) is a new measurement of burden of disease (BOD) introduced by C. Murray and his colleagues[1,2]. This measurement consists of years of life lost (YLL) and years lived with disability (YLD). DALY is more reasonable and comprehensive as compared to other traditional indicators in evaluating BOD[3].

Directly observed treatment, short-course (DOTS) is the primary intervention strategy for smear-positive TB (TB). Previously BOD was estimated wothout considering the *infectivity caused by smear-positive cases, though the total BOD associated with TB* would be underestimated[4,5]. The present study explored the methodology of DALY in evaluating the burden of newly registered smear-positive TB cases attributed to their infectivity, in addition to their YLL and YLD, and also compared the BOD of TB in

Biography of the first author: Xu Qun, female, born in Jan. 1969, Ph. D candidate, major in epidemiology and health statistics.

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Beijing under DOTS intervention strategy.

MATERIALS AND METHODS

Subjects

Without losing generality, an assumed cohort of 2 000 cases was set up based on the age-specific incidence of 794 newly registered smear-positive cases in Beijing in 1994 (Table 1).

TABLE 1

Newly Registered Smear-positive Cases in 1994 and the Study Cohort

Sex	Age Group	1994		Study Cohort	
		Population (× 1 000)	Cases No.	Population (× 1 000)	Cases No.
Male	5~	696	1	1365	2
	15~	2848	284	5584	557
	45~	863	84	1692	165
	60~	530	141	1039	276
	Subtotal	4937	510	9680	1000
Female	5~	620	2	2183	7
	15~	2760	190	9718	669
	45~	870	36	3063	127
	60~	562	56	1979	197
	Subtotal	4812	284	16944	1000
	Total	9749	794	26624	2000

Methods

Calculating instantaneous rates of cure or death from the cohort data. A decision tree was drawn to illustrate the transmission of smear-positive cases in later years after infection. Usually, there would be three possible outcomes for those infected[6]: they could die, or could be cured, or remain smear-positive with or without intervention. The simple prognostic tree was structured accordingly(Fig. 1).

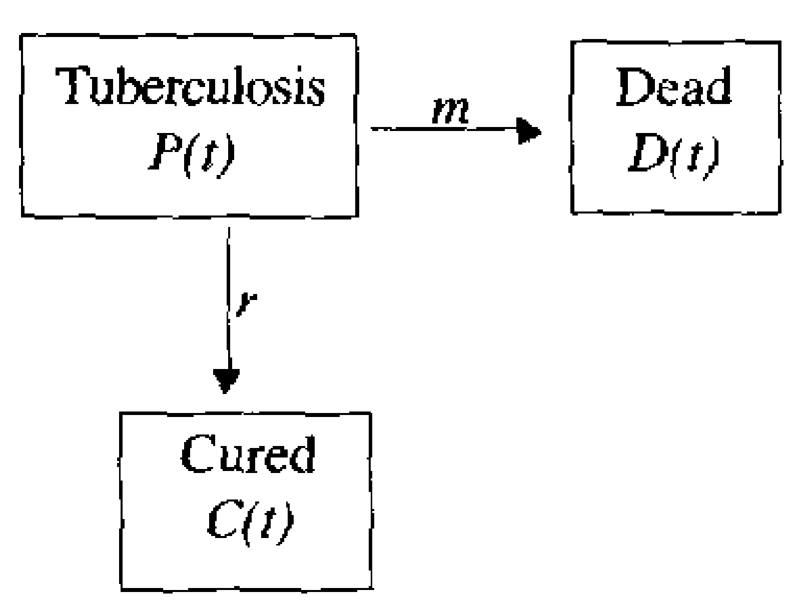

FIG. 1. The simple prognostic tree under natural history.

In Fig. 1, $D(t)$ is the number of the cohort dead at time t. $C(t)$ is the number cured in the study at time t, and $P(t)$ is the number of smear-positive tuberculosis cases left at time t.

By definition, $P(0)$ is the number of individuals in the cohort at the beginning of the period of observation, which in our study is 2 000.

When disease processes are modeled, it is common to make use of mathematical equations that include rates. By definition, these rates are instantaneous rates of cure or death.

The three boxes represent the three possible outcomes: tuberculosis uncured, death, and cure. m is the instantaneous rate at which individuals with tuberculosis die; r is the instantaneous rate at which individuals with tuberculosis are cured. The rates m and r are the instantaneous death and cure rates, respectively. Instantaneous rates can be denominated in any units such as days, months, or years. In this study, we used the unit of year.

The 2 000 cases were assumed to be followed up for a period of 5 years without any intervention. It was anticipated that about half of the patients in the cohort would die, one-fourth would become smear-negative and the rest would remain smear-positive under the natural history[6-8]. Under this situation, the estimation of instantaneous cure and death rates can be calculate according to the following formulas.

The formula for the instantaneous rate of cure for the tuberculosis cases is

$$r=\left[\frac{C(t)}{C(t)+D(t)}\right]\frac{\ln\left[1-\left(\frac{C(t)+D(t)}{P(O)}\right)\right]}{t}$$

and that for the instantaneorus rate of death is

$$m=\left[\frac{C(t)}{C(t)+D(t)}\right]\frac{\ln\left[1-\left(\frac{C(t)+D(t)}{P(O)}\right)\right]}{t}$$

Using the two formulas, the annual cure rate may be calculated as 9.2% and the annual death rate as 18.4%.

Prognostic trees and model diagrams of infectivity under natural history. Epidemiological evidence. The transmission of TB appears to take an extremely regular and stable course in comparison with other infectious diseases such as malaria or cholera[3]. An undiagnosed or untreated smear-positive TB patient would infect on the average 10-14 negative individuals per year. The probability of developing TB, a clinical case for those infected in one's lifetime is about 10 percent, of which half would be smear-positive[7,9]. Among those who would eventually develop clinical TB, about 40% would develop TB in the first year, 10% in the second year, and 5% in each of the third to fifth year. Of the rest, about 35% wold develop TB clinically after the fifth year[9]. To simplify the model, we assumed that the remainder would develop clinical TB in the sixth year. Based on this assumption, it could be easily estimated that an infected person will have 4% chance of developing clinioal TB in the first year, 1% chance in the second year, 0.5% in each of the third to fifth year and 3.5% there after. prognostic trees and model diagrams of infectivity are structured accordingly under natural history (Fig. 2).

Prognostic trees and model diagrams of infectivity under DOTS strategy. Epidemiological evidence. It was reported[10,11] that on the average more than 90% of the new smear-positive cases could be cured under DOTS strategy in Beijing and less than 5% would die of different causes. For retreated smear-positive cases, 80% would be cured under DOTS strategy, and those who failed the treatment would become chronically infectious and carry TB bacterium for 5 years[12]. It is estimated that diagnosis would be delayed for 30 days[10], and so the average duration would be 7 months for cases of initial positive smear, 8 months for retreated cases and 5 years for chronic infectious cases.

While the infectivity of smear-positive cases would rapidly decrease under DOTS strategy, the cases failing the treatment would remain infectious to healthy peolpe[12]. The parameters would be the same as those under natural history as mentioned previously (Fig. 3).

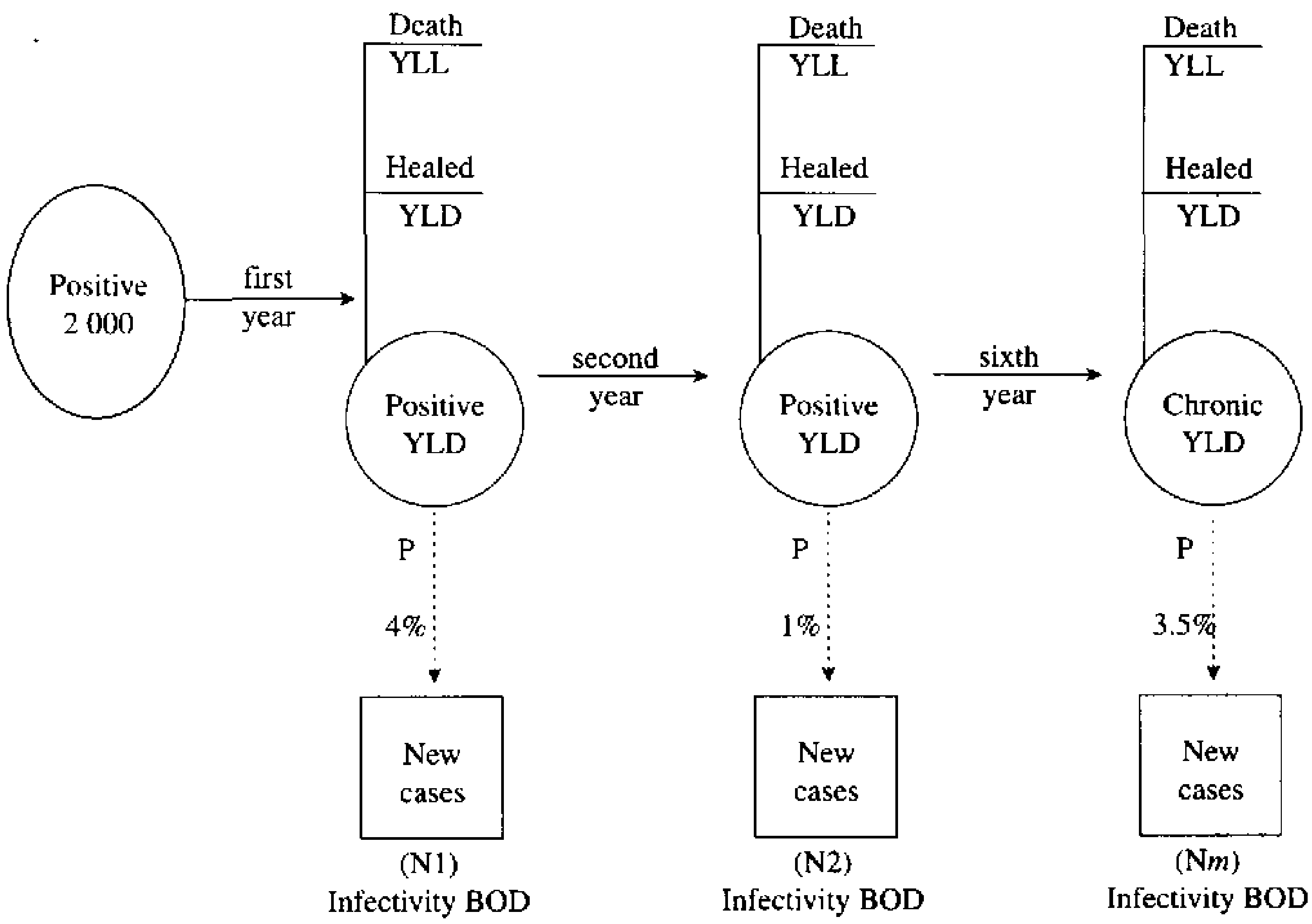

FIG. 2. Prognostic trees and model diagrams of infectivity under natural history.
P : Probability of developing clinical TB in infected individuals.

DALY formulation. We used some recommendations made by WHO and the World Bank(WB) as parameters in our study such as age of the onset, disability weight and average expectation of life[6]. For the average duration, we used different variations for the duration of TB patients under natural history or DOTS according to a large number of epidemiological data collected on the public issues in the study[13].

RESULTS

Tables 2~5 show the potential cases infected and DALY per 100 thousand population estimations under natural history and DOTS strategy. It can be seen that DOTS extensively reduce the burden of TB in three aspects in all of the age groups.

The Number of Death or Cured in the Cohort Under Natural History

Table 2 shows that 1 071 of the 2 000 cases cohort would die in the 5 years under natural history, given no other causes of death to be considered. Five hundred thirty six cases can be cured in the first 5 years owing to good nutrition, air and adequate rest. After the sixth year, 36 cases were cured and 72 cases died. It can be seen that the decerase of the infections is at the cost of labour lost, of which 18.5% occurs in the frist year, 53.6%

in the 5 years, 57.2% after the sixth year. In a world, the life lost for smear-positive TB patients is considerably severe.

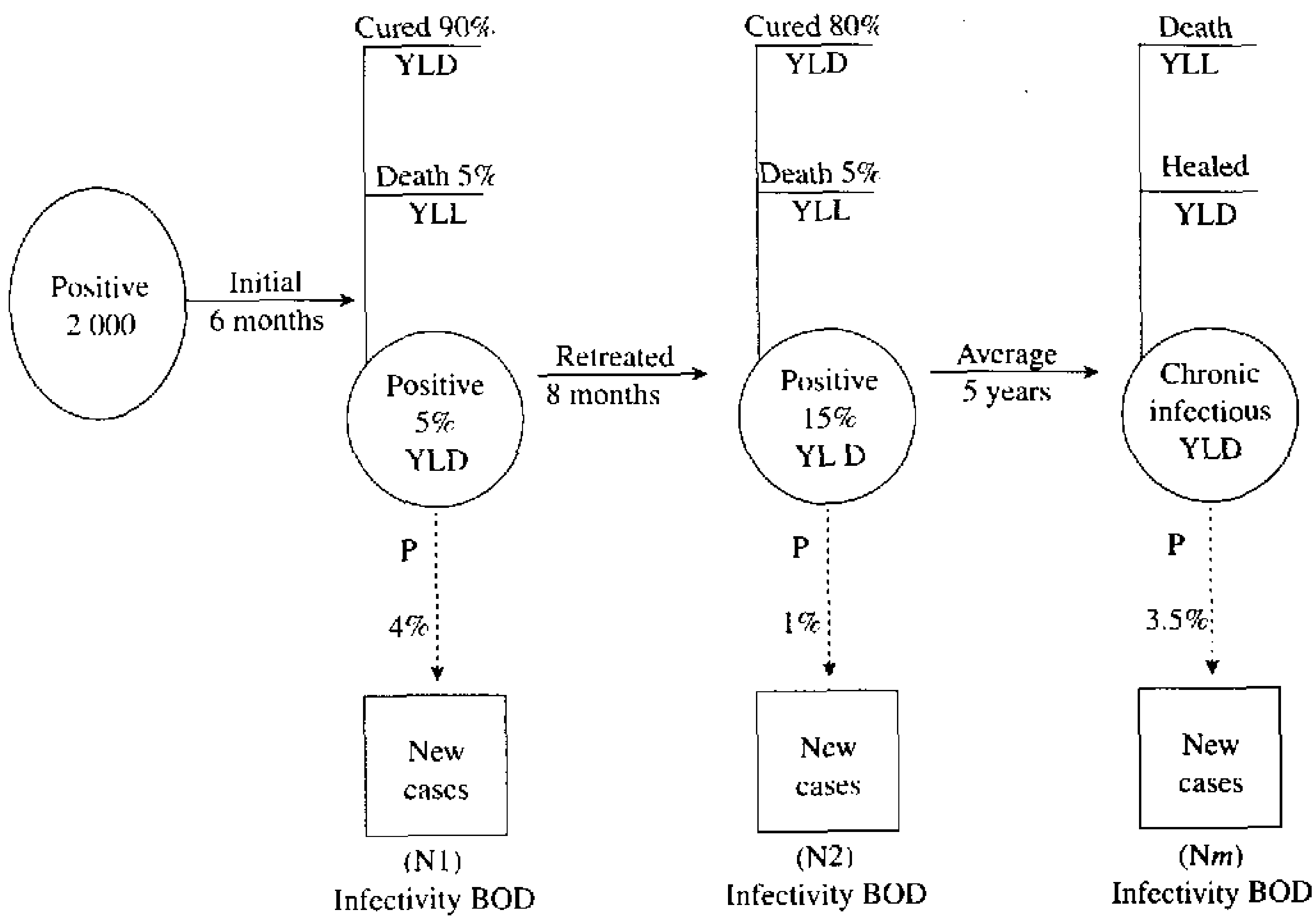

FIG. 3. Prognostic trees and model diagrams of infectivity under DOTS strategy.
P: Probability of developing clinical TB in infected individuals.

TABLE 2

The Number of Cured and Death in the Cohort Study Under Natural History

Following Year	No. of Smear-Positive		No. of Cured		No. of Death	
	Beginning	End	Following Year	Cumulation	Following Year	Cumulation
1	2000	1445	185	185	370	370
2	1445	1044	134	319	267	637
3	1044	754	97	416	193	830
4	754	544	70	486	140	970
5	544	394	50	536	100	1071
6+	394	286	36	572	72	1144

The Number of TB-Infections Under Natural History and DOTS

Table 3 shows that under the natural history, 517 new infections will emerge only if the infectivity of the first generation from this cohort to healthy individual is taken into consideration. Among these 517 new TB cases, 458 cases will become infectious during the first 5 years and the other 59 cases will do so there after. On the contrary, only 14 healthy individuals will be infected if DOTS strategy is adopted, which means that DOTS could prevent 97.3% of the potential infections.

TABLE 3

The Numbers of TB-Infection Under Natural History

Following Year	No. of SP in the Middle of the Year	No. of Infection	
		Following Year	Cumulation
1	1723	345	345
2	1245	62	407
3	900	23	430
4	651	16	446
5	470	12	458
6+	340	59	517

BOD of the Cohort Under Natural History and DOTS Strategy

BOD under natural history. If there is no medical intervention (under natural history), the average DALY per 100 thousand population is 141.48 (Table 4). The highest age-specific DALY per 100 thousand population is found at age 15 to 45 years (199.01 DALYs), and the second highest one is found, at age 60 and above(92.53 DALYs). As shown in Table 4, the total amount of life years lost may reach 141.48 DALYs per 100 thousand population, of which 65.4% (92.55 DALYs per 100 thousand population) can be attributed to death from TB (YLL), 5.0% (7.08 DALYs) to disability (YLD), and the remaining 29.6% to those infected by smear-positive TB cases.

TABLE 4

The DALYs per 100 Thousand Population Under the Natural History

Age Group	YLL	YLD	YLI[a] Caused by Infectivity	Total DALYs
5~	5.45	0.25	2.46	8.16
15~	130.86	8.99	59.16	199.01
45~	56.33	5.07	25.46	86.86
60~	57.79	8.62	26.12	92.53
Total	92.55	7.08	41.84	141.48

[a] The DALYs of the first generation infection of the cohort.

BOD under DOTS intervention strategy. The DALYs per 100 thousand population for the same cohort (2 000 TB cases) declined substantially from 141.48 under natural history to 10.01 under DOTS (Table 5), with the highest at the age 15 to 45 (13.93 per 100 thousand population), and the lowest at age 5 to 15 (less than one per 100 thousand population). Of the total 10.01 DALYs per 100 thousand population, 7.1% will remain without intervention. Among the total 10.01 DALYs per 100 thousand population, 85.0% (8.50) could be attributed to TB death, 14.9% (1.49) to disability, and 0.1% (0.01) to its potential infectivity.

Infectivity BOD

As shown in Table 4, among the DALYs per 100 thousand population, 29.6% (41.84 DALYs per 100 population) could be attributed to those who would be infected by smear-positive TB cases under natural history. This indicates that DALYs would be underestimated if the infectivity of the cohort is not taken into consideration. As shown in Table 5, only

0.1% (0.01 per 100 thousand population) of the total DALY is attributed to its potential infectivity under DOTS strategy. Therefore, it is clear that the implementation of DOTS greatly reduces (99.9%) the potential BOD by reducing infectivity.

TABLE 5

The DALYs of per 100 Thousand Population Under DOTS Strategy

Age Group	YLL	YLD	YLD[a] Caused by Infectivity	Total DALYs
5~	0.50	0.05	0.00	0.55
15~	12.02	1.90	0.01	13.93
45~	5.17	1.07	0.01	6.25
60~	5.31	1 82	0.01	7.14
Total	8.50	1.49	0.01	10.01

[a]The DALYs of first generation infection of the cohort.

DISCUSSION

In this study, we assumed a cohort based on recent data from a large cohort of newly registered smear-positive cases in Beijing in 1994. On the bases of assumed cohort, we tried to explore application of the disability-adjusted life year (DALY) to estimate the burden of smear-positive tuberculosis (TB), and to compare the use of directly observed treatment, short course (DOTS) with the natural course of untreated TB.

The burden of smear-positive TB cases is related not only to death and disabilty, but also to their infectivity. For infection diseases, the burden caused by their infectivity is an important part of BOD. In this study, the burden from infectivity accounted for large proportion of the total burden of TB. At least 30% of total DALYs would be neglected if the burden from the first generation infection was not considered in the cohort under natural history.

Age distribution of smear-positive tuberculosis. The age distribution of DALY per 100 thousand population is important in determining the effect on public health aspects of smear-positive TB, and is the most appropriate means of preventing or controlling TB. Clearly, smear-positive cases are relatively rare in children, smear-positive tuberculosis is concentrated on adults-more than 75.9% of cases occur between the ages of fifteen and sixty, and among workers and leaders of society, according to the data in Beijing in 1994.

This methodology is basically a simple form of risk assessment involving minimal data requirements to estimate and illustrate potential disease burdens and the effect of DOTS intervention. In order to simplify the model in this study, the prognostic trees and model diagrams of infectivity under natural history and DOTS were based on the assumptions that the implications of multidrug resistant TB and other risk factors were not taken into consideration.

Unlike the uniformed average duration of TB patients defined by the World Bank and WHO as 2.4 years, we used different variations for duration of TB patients with or without intervention according to a large number of epidemiological data collected on the public issues in this study. The average duration was defined as 7 months after an initial positive smear (which includes the delayed 30 days) as compared with 8 months with the retreated cases under DOTS intervention[10,11]. However, few reports have referred to the effects of chronic infection except for data reported by Zhang *et al.*[12]. In which those people with chronic infection carried the TB bacillus for 5-8 years on the average[12]. Estimated optimistically, a five-year average duration of chronic infection was defined in this study. If we consider the increase of multidrug resistant TB and the initial smear-positive cases not treated in a timely fashion by DOTS, the number of multidrug resistant individuals would increase. The BOD of smear-positive pulmonary TB and its infectivity would rise as well.

In this study, we used an assumed cohort based on recent data from a large cohort of newly registered smear-positive cases in Beijing in 1994, although it is basically a simply form of risk assessment requiring minimal data to estimate and illustrate potential disease burdens and the effect of DOTS intervention. Our finding may be generalized to different areas, different populations, and different nations in the world. It may be used to evaluate the cost-effectiveness of interventions[14]. But the primary prerequisite is the reliable data of incidence and mortality by age and sex in different areas.

Despite some controversies, the DALY is becoming widely used in international public health community. The BOD of newly registered smear-positive cases remains a complicated issues, and infectious burden is only considered for the first generation of the cohort in this study. Moreover, the BOD of TB which impacts the families, friends, and society at large (e. g. the economic cost. of illness) is not included in this study.

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