BIOMEDICAL AND ENVIRONMENTAL SCIENCES 13, 140-147(2000)

Estimation of Burden of Disease for Smear-Positive Pulmonary TB and its Infectivity

XU QUN*, JIN SHUI-GAO**, AND ZHANG LI-XING△

*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*

The study investigated the burden of smear-positive pulmonary TB and its infectivity, using DALY (Disability-Adjusted Life Year) as an indicator. An assumed cohort of 2000 cases was set up based on the age-specific incidence of 794 newly registered smear positive cases of TB in Beijing in 1994. Prognostic trees and model diagrams of infectivity under natural history and DOTS (Direct Observed Treatment, Short-course) strategy were established according to the epidemiological evidence. The results show that 29.6% of DALYs would be neglected if the burden caused by the infectivity was not considered. The results also show that 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.

INTRODUCTION

Disability-Adjusted Life Year (DALY) is a new measurement of burden of disease (BOD) introduced by C. Murray and his colleagues (Murray, 1994; Murray and Lopez, 1994). 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 (Murray, 1996).

Directly Observed Treatment, Short-course direct observed treatment (DOTS) is the primary intervention strategy for smear-positive TB (TB). Previously BOD was estimated without considering infectivity caused by smear-positive cases, though the total BOD associated with TB would be underestimated (Anand and Hanson, 1997; Chen, 1998). The present study explores 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 to compare the BOD of TB in Beijing under DOTS intervention strategy.

MATERIALS AND METHODS

Subjects

Without losing generality, an assumed cohort of 2000 cases was set up based on the age-specific incidence of 794 newly registered smear-positive cases in Beijing in 1994 (Table 1).

0895-3988/2000
CN 11-2816

TABLE 1

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

Sex	Age Group	1994		Study Cohort	
		Population	Cases	Population	Cases
		(×1000)	No.	(×1000)	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

Prognostic trees and model diagrams of infectivity

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 (Murray and Lopez, 1996): they could die, or could be cured, or remain smear-positive with or without intervention. Prognostic trees and model diagrams of infectivity was structured accordingly (Fig. 1).

Epidemiological evidence

Natural history. The 2000 cases are assumed to be followed up for a period of 5 years without any intervention. It is anticipated that about half of the patients in the cohort will die, one-fourth will become smear-negative and the rest remain smear-positive under the natural history (Murray and Lopez, 1996; Styblo, 1984; Murray, Styblo and Rouillon, 1996). Under this situation, the estimation of annual cure and death rates will be 9.2% and 18.4% respectively (Table 2).

The transmission of TB appears to take an extremely regular and stable course in comparison with other infectious diseases such as malaria or cholera (Murray, 1996). An undiagnosed or untreated smear-positive TB patient would infect an average of 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 (Zhang and Kan, 1975; Styblo, 1984). 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%, would develop TB clinically after the fifth years. (Zhang and Kan, 1975). To simply the model, we assumed that remainder developed clini-

cal TB in the sixth year. Based on this assumption, it could be easily estimated that an infected person will have 4% chance of developing clinical 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.

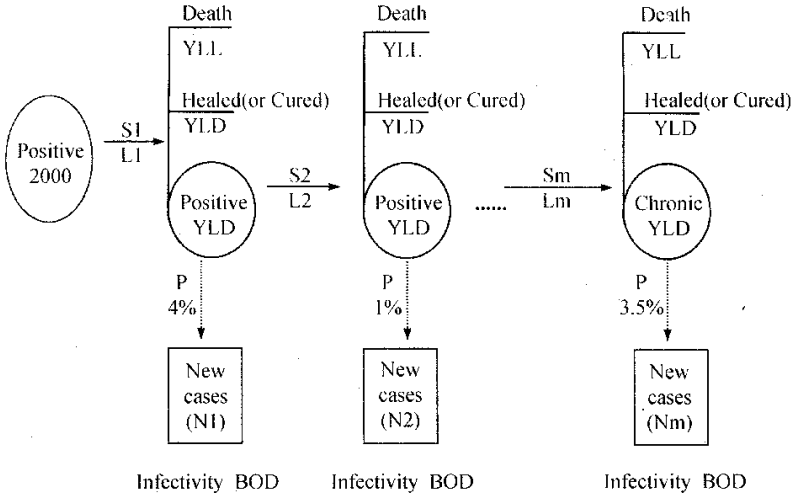

FIG. 1. Prognostic Trees and Model Diagrams of Infectivity. S, strategy, whether adopting DOTS or not; L, duration; P, probability of developing clinical TB in infected individuals.

Epidemiological evidence under DOTS strategy. It is reported (Duanmu *et al*. 1997; Raviglione *et al*., 1997) that on average more than 90% of the new smear-positive cases could be cured by employing the DOTS strategy in Beijing and less than 5% would die for different causes (Table 2). For retreated smear-positive cases, 80% would be cured under DOTS strategy, and those who fail the treatment would become chronically infectious and carry the TB bacterium for 5 years (Zhang and Wu, 1979). It is estimated that diagnosis would be delayed for 30 days (Duanmu, Song and Yue 1997), and so the average duration of the clinical infection would be 7 months for cases with an 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, the cases failing the treatment would remain infectious to healthy people (Zhang and Wu, 1979). The parameters would be the same as those with a natural history of infection as mentioned previously.

TABLE 2

Epidemiological Parameters With Natural History and DOTS Strategy

Intervention	Patient	Healed (Cured) Rate(%)	Death Rate (%)	Positive Rate(%)
Natural history		9.2	18.4	72.4
DOTS	NSP[a]	90.0	5.0	5.0
	Retreated	80.0	5.0	15.0

[a] NSP, new smear-positive.

DALY formulation

In order to estimate DALY, 4 parameters (Murray, 1994; Murray and Lopez, 1994) are essential: standard expected years of life lost, comparing time lived with non-fatal health outcomes with time lost due to premature death, age weight and time discount. DALYs are calculated by using a standard expectation of life at each age. The Coale and Demeny Model Life Table West Level 26 is used for females. The biological difference in the expectation of life for males is 2.5 years, therefore, life expectancy for males is 80 years and that for females is 82.5 years. Disability weights are defined as 7 classes. To facilitate sensitivity analysis the age weight formula: ($Cxe^{-\beta x}$) is changed to a more general form of age-weighting: $KCxe^{-\beta x} + (1 - K)$. We have incorporated a 3% discount rate into the calculation of DALYs. By combining discounting and age-weight, the following is the DALY formula:

$$\begin{aligned} \text{DALY} &= \int_{x=a}^{x=a+l} D\left[KCxe^{-\beta x} + (1-k)\right] e^{-r(x-a)}\,dx \\ &= \frac{KDCe^{-\beta\alpha}}{(\beta+r)^2}\left[e^{-(\beta+r)l}(1 + (\beta+r)(l+a)) \right. \\ &\quad \left. - (1 + (\beta+r)a)\right] + \frac{D(1-K)}{r}(1 - e^{-rl}) \end{aligned}$$

In this equation, D is the disability weight (0 means health and 1 means death), a is the age of onset of the disability or death, L is the duration of disability or the duration of lost life (either potential or expected), r is the discount rate ($r = 0.03$), β is age-weighting factor ($\beta = 0.04$), K is the age-weighting modulation factor ($K = 1$), and C is the adjustment constant necessary because of unequal age-weights ($C = 0.1658$).

We adopted some recommendations made by WHO and the World Bank (WB) as parameters in our study (Murray and Lopez, 1996) (Table 3).

TABLE 3

DALY Parameters Recommended by WHO and the World Bank

Sex	Age Group	Average Expectation of Life (L)	Average Age of Onset (a)	Disability Weight (D)
Male	5 ~	70.40	10.2	0.294
	15 ~	50.51	33.0	0.264
	45 ~	30.99	53.3	0.274
	60 ~	13.58	69.7	0.274
Female	5 ~	72.99	9.8	0.294
	15 ~	53.27	31.9	0.264
	45 ~	33.99	53.3	0.274
	60 ~	12.28	71.3	0.274

RESULTS

Tables 4-6 show the potential cases infected and DALY estimations by two different

strategies (with and without intervention). It can be seen that DOTS extensively reduce the burden of TB in three aspects in all of the age groups.

The Number of TB-Infections Under Natural History and DOTS

Table 4 shows that with a non-intervention strategy, 517 new infections will emerge only if the infectivity of the first generation from this cohort to healthy individual is taken into consideration (Table 4). 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 4

The Numbers of TB-Infection Under Natural History

Following Year	No. of SP in the Middle of the Year	No. of Infection	
		Following Year	Cumulate
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 total amount of life years lost may reach 37667.1 DALYs (Table 5), of which, 65.4% (24641.3 DALYs) can be attributed to death from TB (YLL), 5.0% (1885.9 DALYs) to disability (YLD), and the remaining 29.6% to those infected by smear-positive TB cases.

TABLE 5

DALYs Under the Natural History Cohort

Age Group	YLL	YLD	YLL[a] Cause by Infectivity	Total DALYs
5~	193.3	8.7	87.4	289.4
15~	20025.3	1376.1	9053.1	30454.5
45~	2678.6	241.1	1210.9	4130.6
60~	1744.1	260.0	788.5	2792.6
Total	24641.3	1885.9	11139.9	37667.1

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

BOD under DOTS intervention strategy

The total DALYs for the same cohort (2000 TB cases) under DOTS strategy would decrease to 2663.6 (Table 6), 7.1% of which will remain without intervention. Among the total 2663.6 DALYs, 85.0% (2263.2) could be attributable to TB death, 14.9% (397.8) to disability, and 0.1% (2.6) to its potential infectivity.

TABLE 6

DALYs of the DOTS Cohort

Age group	YLL	YLD	YLD[a] Caused by Infectivity	Total DALYs
5 ~	17.7	1.8	0.0	19.5
15 ~	1839.3	290.2	1.9	2131.4
45 ~	246.0	50.9	0.3	297.2
60 ~	160.2	54.9	0.4	215.5
Total	2263.2	397.8	2.6	2663.6

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

Infectivity BOD

As shown in Table 5, among the total of 37667.1 DALYs, 29.6% (11139.9) 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 6, only 0.1% (2.6) 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.

DISCUSSION

This study describes the application of the disability adjusted life year (DALY) methodology to estimate the burden of smear-positive tuberculosis (TB), specifically comparing the use of direct observed treatment short course (DOTS) vs the natural course of untreated TB. An assumed cohort was prepared based on recent data from a large cohort of newly registered smear-positive cases in Beijing in 1994.

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

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 different interventions. We try to delineate the assumptions well, including the pilot data on which the population distributions and outcomes are based. In order to simplify the model in this study, the prognosis trees and model diagrams of infectivity under natural history and DOTS are based on assumptions that without considering the implications of multiple resistant TB and other risk factors.

Unlike the uniform average duration of TB patients implied by the World Bank and WHO of 2.4 years, we adopt different variations 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 is defined as 7 months after an initial positive smear (which includes the delay of 30 days) as compared with 8 months with the retreated cases under DOTS intervention (Duanmu, Song and Yue, 1997; Raviglione *et al.*, 1997). However, there are few reports that refer to the effects of chronic infection referring to instead data reported by Zhang *et al.* in 1979, in which those people with chronic infections carried the TB bacillus for 5 to 8 years on average (Zhang and Wu, 1979). Estimated optimistically, a-five-year average duration with a chronic infectious is defined in this study. If we consider the increase of multiple drug resistant TB and the initial smear-positive cases not treated in a timely fashion by DOTS, the number of multiple resistant individuals would increased. At the same time, the number of chronically infected cases would increase. The BOD of smear-positive pulmonary TB and its infectivity would increase 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 inquiring minimal data to estimate and illustrate potential disease burdens and the effect of different interventions. The finding is generalized to different areas, different population, and to different nations in the world. It may be used to evaluate the cost-effectiveness of interventions. But, the primary prerequisite is the reliable data of incidence and mortality by age and sex in different areas. We believe that this study will provide a rationale for the importance of active TB surveillance with DOTS.

Although somewhat controversial the use of DALY is growing particularly in international public health applications. The BOD of newly registered smear-positive cases is still a complicated issues, and infectious burden was only considered as for the first generation of the cohort in this study. Moreover, the BOD of TB which impacts the family, friends, and society at large (e.g. the economic cost of illness) was not included in this study. But, according to the International Burden of Disease Network proceedings of the first meeting in Stowe, Vermont, USA, in December 1998, the use of DALY will be much more open-ended and all-inclusive than the traditional methods.

REFERENCES

Chen, Ying-Yao (1998). Evaluation of the methodology on world development report. *Chinese Health Economics* **17** (9), 56 – 58. (in Chinese)

Duanmu, Hong-Jin, Song, Wen-hu, and Yue Shu-min (1997). Tuberculosis surveillance in China (1986-1995). *Bulletin of the Chinese Anti-Tuberculosis Association* **19**(3), 109-111. (in Chinese)

Murray, C. J. L. and Lopez, A. (1996). Using cost-effectiveness and burden of disease to define national control priorities and essential packages of care. Burden of Disease Unit, Harvard Center for Population and Development Studies, workbook 3, pp. 101-105. Kennebunkport, Maine, USA.

Murray, C., Styblo, K., and Rouillon, A. (1996). TB. *Disease Control Priorities in Developing Countries*, pp. 233 – 259. Oxford University Press.

Murray, C. J. L. (1994). Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bulletin of the World Health Organization* **72** (3), 429-445

Murray, C. J. L. and Lopez, A. D. (1994). Global and regional cause-of-death patterns in 1990. *Bulletin of the World Health Organization* **72**(3), 447-480.

Murray, C. J. L. and Lopez, A. D. (1994). Quantifying disability: data, methods and results. *Bulletin of the World Health Organization* **72**(3), 481-494.

Murray, C. J. L., Lopez, A. D., and Jamison, D. T. (1994). The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bulletin of the World Health Organization* **72**(3), 495-509.

Murray, C. J. L. (1996). Rethinking DALY. *Global Burden of Disease and Injury Series* Vol. 1: *The Global Burden of Disease*, pp. 1-98. Harvard University Press. Boston, USA.

Mario C Raviglione, Christopher Dye, Sonja schmidt and Arata Kochi (1997). Assessment of worldwide tuberculosis control. The WHO global surveillance and monitoring project. *The Lancet* **350**, 624-629.

Murray, C. J. L. and Lopez, A. D. (1996). Annex Table 3. Age-specific disability weights for untreated and treat forms of sequel include in global burden of disease study. *Global Burden of Disease and Injure Series* Vol. 1. *Global Burden of Disease*, p. 110. Harvard University Press, Boston, USA.

Murray, C. J. L. and Lopez, A. D. (1996). Epidemiology Table. *Global Burden of Disease and Injure Series* Vol. Ⅱ. *The Global Burden of Disease*, p. 114. Harvard University Press, Boston, USA.

Sudhir Anand, Kara Hanson. (1997). Disability-adjusted life years: a critical review. *Journal of Health Economics* **16**, 685-687.

Styblo, K. (1984). *Epidemiology of Tuberculosis*. VEB Gustav Fischer Verlag Jena. The Netherlands.

Zhang, Li-Xing, and Kan, Guan-Qing. (1975). Problems on tuberculosis infectivity. *Foreign Medical Science* (*Internal Medicine*) **10**, 440-443. (in Chinese)

Zhang, Li-Xing and Wu, Ji-Cheng. (1979). Analysis on chronic infectious of pulmonary tuberculosis in rural. *Chinese Journal of Tuberculosis and Respiration Disease* **2**(4), 204-206. (in Chinese)

(*Received January* 21, 2000 *Accepted May* 9, 2000)