The Indicators of Treatment Outcomes for Tuberculosis Recommended by World Health Organization

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Abstract

Treatment outcomes of tuberculosis (TB) are one of the essential performance indicators in evaluating the performance of national TB control program. It is important to use standardized indicators for outcome analysis, which not only ensure that the performance of TB control programs could be tracked over time but also enable comparison of the performance across countries. The objective of this article is to introduce the definitions of outcome indicators for TB recommended by World

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Health Organization, and the procedure used in carrying out such an analysis. Cohort analysis was recommended in outcome analysis. Outcome of a patient is determined by the event that first occurs during the course of treatment and should not be modified or changed if another event occurs at a later point in time during the follow-up period. The classification of treatment outcome of new and retreatment TB patients is based on the results of sputum smear for acid-fast bacilli, while the classification of treatment outcome of multidrug-resistant tuberculosis (MDR-TB) patients is mainly based on the results of sputum culture for *M. Tuberculosis*. Outcome of new and retreatment tuberculosis patients is determined at 12 months after the close of the cohort and that for MDR-TB, at 36 months. It is important to regularly evaluate treatment outcomes of TB and to identify constraints for the improvement of national TB control programs, in order to achieve the impact target of halving the mortality and prevalence of TB by 2015, as compared with that in 1990.

Keywords: tuberculosis, treatment outcomes, indicators, World Health Organization

Introduction

Target 8 of Goal 6 of the United Nations Millennium Development Goals is to halt and reverse the trend of tuberculosis (TB) incidence by 2015. To ensure that the goal can be achieved efficiently, World Health Organization (WHO) has set up detailed performance indicators [1,2]. Indicator 24 is to calculate the proportion of TB cases detected and cured under directly observed treatment, short-course (DOTS) strategy [2]. The cure rate is one of outcome indicators for TB.

The standardized indicators of treatment outcomes for TB can be

tools not only to evaluate the long-term performance of TB control programs, but also to compare performance across countries in order to increase the sharing and exchanging of successful prevention strategies [3]. Therefore, this article introduces the definitions of outcome indicators for TB recommended by WHO. It also decribes the procedures of cohort analysis to apply those indicators to clinical and public health practice.

Definitions of Treatment Outcomes

Because the denifitions of the indicators of treatment outcomes distinguish drug-susceptible TB patients, susceptible to all antituberculosis drugs, from multidrug-resistant tuberculosis (MDR-TB) patients, the denifitions of the indicators are described in two separate parts as follows:

1.Drug-susceptible TB patients:

According to the descriptions in 'Treatment of tuberculosis: guidelines for national programs' published by the WHO, the definitions of the indicators of treatment outcomes for drug-susceptible TB patients are [4,5]:

(1)Cured :

(A)A patient has completed the course of TB treatment; AND

(B)A patient has initially positive smears but has negative smears in the last month of treatment and on at least one previous occasion.

(2)Completed treatment:

A patient has completed antituberculosis treatment but does not meet the definition for cure or failure. This definition could apply to pulmonary TB patients initially smear-positive and smear-negative and to extrapulmonary TB patients.

(3)Died:

A patient dies for any reason, whether TB or not, before or during the course of TB treatment.

(4)Failed:

A patient whose sputum is still smear-positive at five months or after during treatment.

(5)Defaulted:

A patient whose treatment was interrupted for two or more consecutive months.

(6)Transferred out:

A patient was transferred to another reporting units, and whose outcome is unknown.

(7)Treatment success:

A patient is classified as ‘cured’ or ‘completed treatment’.

2.MDR-TB patients:

The definitions of the indicators of treatment outcomes for MDR-TB patients are [6]:

(1)Cured:

(A)A patient has completed the course of MDR-TB treatment; AND

(B)A patient has at least five consecutive negative cultures collected at least 30 days apart in the last 12 months of treatment; OR

(C)A patient has one positive culture followed by at least three consecutive negative cultures collected at least 30 days apart, and has no concomitant clinical evidence of deterioration.

(2)Completed treatment:

(A)A patient has completed the treatment; AND

(B)A patient has no bacteriological evidence meeting the definition for 'cured'.

For example, a patient is considered as 'completed treatment' when having completed treatment and having only two negative cultures collected at least 30 days apart in the last 12 months of treatment.

(3)Died:

A patient dies of any reason, whether MDR-TB or not, during treatment.

(4)Failed:

(A)A patient has two or more positive cultures of the five cultures in the last 12 months of treatment; OR

(B)A patient has one positive culture of the final three cultures; OR

(C)A patient whose treatment was terminated due to poor response or adverse events.

(5)Defaulted:

A patient whose treatment was interrupted for two or more consecutive months.

(6)Transferred out:

A patient was transferred to another reporting units and whose outcome is unknown.

(7)Treatment success:

A patient is classified as 'cured' or 'completed treatment'.

In summary, the treatment outcomes for drug-susceptible TB patients are determined by the results of sputum smears for acid-fast bacilli, whereas those for MDR-TB patients are determined by the results of

sputum cultures for *M. Tuberculosis* [3].

Procedures of Cohort Analysis

WHO recommends using 'cohort analysis' to determine the treatment outcomes for TB. The cohort analysis is to choose a cohort, a group of patients registered and treated during a certain period, and to evaluate the treatment outcomes of each patients in that cohort after following a certain period. The procedures of cohort analysis are described below for two groups: drug-susceptible TB patients and MDR-TB patients.

1.Drug-susceptible TB patients:

(1)Definition of a cohort:

A cohort is a group of people who are diagnosed and treated with antituberculosis drugs during a certain period [4,5]. For example, all patients diagnosed and treated with antituberculosis drugs from January 1, 2007 to March 31, 2007 could be regarded as the cohort of the first quarter in 2007. The number of a defined cohort as reported by WHO would be the denominator of outcome indicators. In the annual report of Global Tuberculosis Control, WHO only evaluates the treatment outcomes of pulmonary TB patients with positive smears or cultures [5].

(2)Time of analysis performed:

Outcome analysis of a cohort should be performed at 12 months after the last patient received TB treatment [7].

(3)Classification of treatment outcomes:

The classification of treatment outcomes is shown in figure 1 [7]. The

outcome "first" satisfied the definition is the treatment outcome of a patient, which is not reclassified or modified even though another outcome is also met during the follow-up period [7]. A patient had completed the course of treatment at 6 months and died at 9 months; the treatment outcome of this patient should be 'completed treatment', not 'died'. Besides, a patient had positive smears at 6 months, interrupted TB treatment at 9 months, resumed TB treatment at 12 months; the outcome of this patient should be classified as 'failed', not 'defaulted'.

In addition, the outcome of a patient should be classified as 'not evaluated' if this patient continued TB treatment (still on treatment) at 12 months and completed TB treatment at 15 months. The patient whose outcome is 'not evaluated' would still include in the denominator of outcome indicators in the cohort analysis. However, WHO excludes those patients not registered and treated with antituberculosis drugs from the cohort analysis of treatment outcomes.

(4)Calculation of outcome indicators:

The calculating formula of outcome indicators is

$$\frac{\text{The number of patients in a treatment outcome}}{\text{The number of patients registered for TB treatment in the cohort}} \times 100\%$$

The denominator of this formula, the number of patients registered for TB treatment in the cohort, should be the same as the number of notified TB patients in that cohort year since all notified TB patients

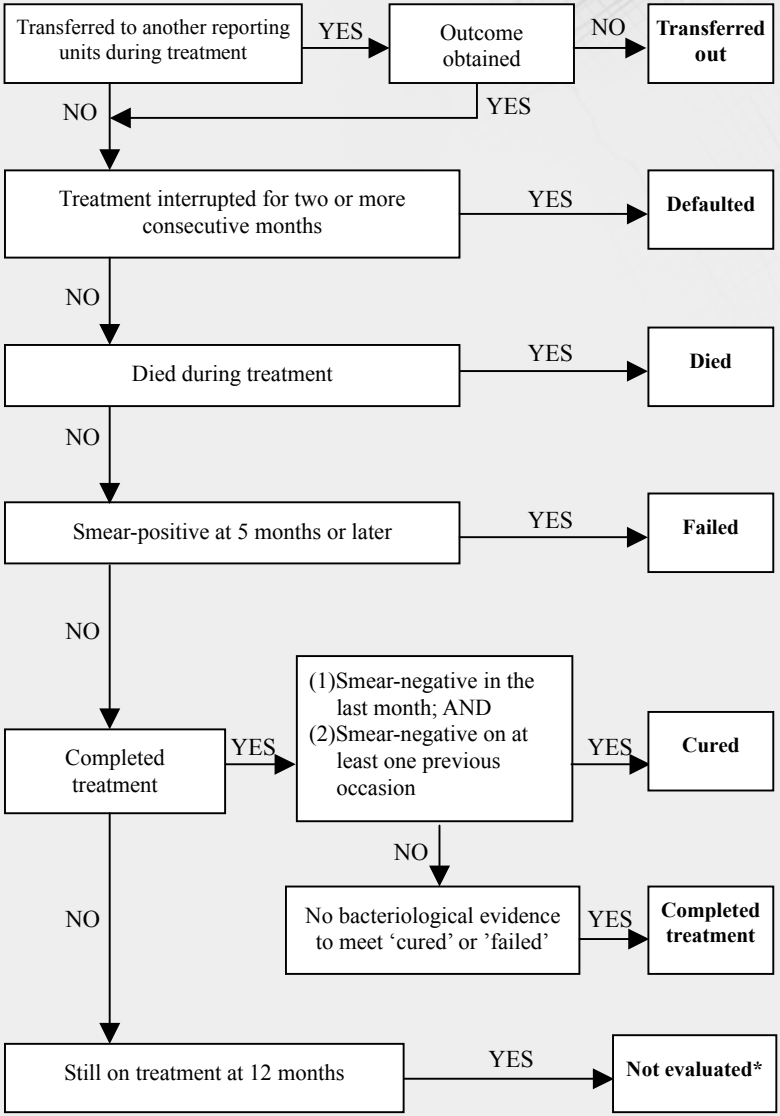

Figure 1. Classification of treatment outcomes for drug-susceptible TB patients [7]

*These patients still count in the denominator of outcome indicators.

should be registered for TB treatment [5]. WHO takes the number of notified TB patients in the cohort year as the denominator of the calculating formula if the number of patients registered for treatment is unavailable. The sum of patients in each treatment outcome would be the denominator of the formula supposing the sum is greater than the number of notified or treated TB patients [5].

2.MDR-TB patients:

(1)Definition of a cohort:

A cohort is a group of people who are diagnosed as MDR-TB being treated with second-line antituberculosis drugs [6]. For instance, all patients diagnosed as MDR-TB and treated with second-line antituberculosis drugs from January 1, 2006 to March 31, 2006 could be considered the cohort of the first quarter in 2006.

(2)Time of analysis performed:

Outcome analysis of a cohort should be performed at 24 and 36 months after the last patient received MDR-TB treatment [6]. At 24 months, the treatment outcomes could be assessed preliminarily, especially for cure rate, because most patients have completed treatment. The 36-month outcome is final outcome of MDR-TB treatment [6].

(3)Classification of treatment outcomes:

The classification of treatment outcomes for MDR-TB patients is shown in figure 2. The outcome “first” satisfied the definition is the treatment outcome of a patient, which is not reclassified or modified even though another outcome is also met during the follow-up period

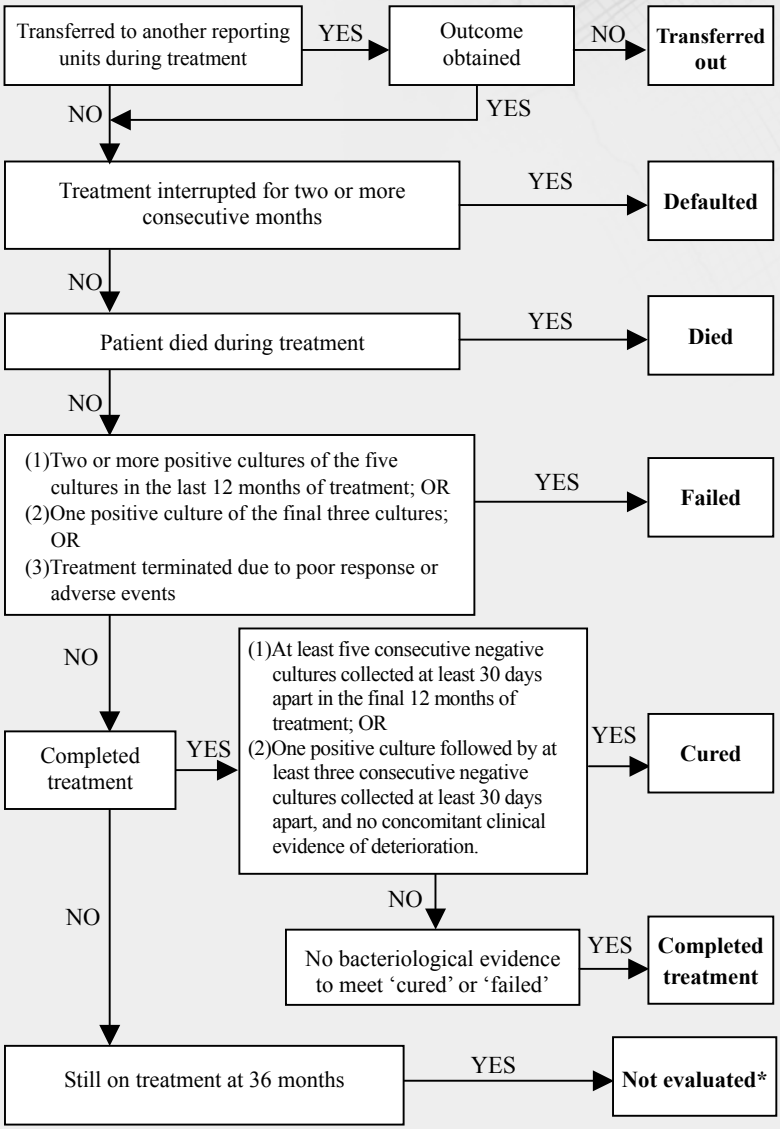

Figure 2. Classification of treatment outcomes for MDR-TB patients

*These patients still count in the denominator of outcome indicators.

[3,6]. A patient had interruptted MDR-TB treatment for more than two months in the first cohort, continued treatment after 14 months, and was cured in the second cohort; the treatment outcome of this patient should be classified as 'defaulted' in the first cohort and 'cured' in the second cohort [6]. The outcome of a patient still on treatment at 36 months is considered 'not evaluated' and described in the supplement [6]. In addition, MDR-TB patients should be followed for two years after finishing the final evaluation of treatment outcomes to know whether the patients have relapses or not [3].

(4)Calculation of outcome indicators:

The calculating formula of outcome indicators is

$$\frac{\text{The number of patients in a treatment outcome}}{\text{The number of patients registered for MDR-TB treatment in the cohort}} \times 100\%$$

The denominator of this formula, the number of patients registered for MDR-TB treatment in the cohort, should be the same as the number of notified MDR-TB patients in that cohort year since all notified MDR-TB patients should be registered for MDR-TB treatment [6]. WHO takes the number of notified MDR-TB patients in the cohort year as the denominator of the calculating formula if the number of patients registered for treatment is unavailable. The sum of patients in each treatment outcome would be the denominator of the formula supposing the sum is greater than the number of notified or treated MDR-TB patients [6].

Discussion

Generally speaking, some factors may affect the treatment outcomes for drug-susceptible TB and MDR-TB patients [8,9].

1.The prevalence of HIV/AIDS

In the areas with high prevalence of HIV/AIDS, patients would have high probability of death and low probability of cure during the course of treatment in spite of effective TB control programs.

2.The prevalence of drug resistance

Patients could hardly be cured after completing the whole treatment in the areas with high prevalence of drug resistance. On the other hand, higher probability of default patients have, and higher probability of drug resistance patients have.

3.The supply of antituberculosis drugs

Patients must acquire a continual supply of antituberculosis drugs to cure TB or MDR-TB effectively. In resource-limited areas, many MDR-TB patients could not get sufficient second-line antituberculosis drugs to complete the whole treatment, which loses control of epidemics [10].

4.The access to medical resources

Patients would interrupt treatment as they have to spend much time and money seeking health care and compling with treatment. In Africa, some patients that live in remote villages often take several days' walk to arrive at the nearest clinic for treatment.

5.The implementation of DOTS program

Patients probably have successful treatment in the areas where DOTS program is implemented well and effectively. The effective

implementation of DOTS program could affect some factors: whether the Government has powerful commitment to enforce the program, whether the District has sufficient staffs to perform the program, whether the patient has strong will to adhere the program.

6.The quality of reported data

The treatment outcomes of patients being irregularly recorded and reported, poor outcomes—low treatment success or low cure rate—would occur in areas with good quality of treatment. Besides, if treatment success was low percentage, understanding which outcomes were high percentages is necessary to identify the problems of national TB control program.

According to the annual report of Global Tuberculosis Control, the cure rate for new smear-positive cases under DOTS was 77.6% in 2005 [11]. The rate of treatment success for new smear-positive cases under DOTS was 84.7% in 2005, which was very close to the 85% target [11]. The rate of treatment success was low in the Europe (71%), the Africa (76%), and the Americas (78%). Patients in Europe and Africa had poor outcomes mainly because of high prevalence of HIV/AIDS, high prevalence of drug resistance, poor quality of medical services [11]. In fact, the death rate for TB patients was as high as 8.3% in Europe owing to high prevalence of drug resistance (eastern Europe) and the aging of population (western and central Europe) [11].

In the United Kingdom, the reason why the elders with TB terminate treatment was death, mainly other than TB [12]. The rate of treatment success in the Netherlands was 63.9% for TB patients more than 65 years

of age [13]. The death rate among that group was 23.7%, and their cause of death was usually other than TB (65%) [13]. Hong Kong, in the Western Pacific Region, also had similar results: the rate of treatment success was 65.2% for elder patients, and the death rate was 11.5% for elder patients, which was usually caused by other than TB (61.9%) [14].

The rate of treatment success for MDR-TB patients was high in Latvia (70%), Germany (63%), and Brazil (60%) in 2003 [11]; whereas, the rate of treatment success was low in Romania (26%) and Lithuania (36%), which had high death and failed rates in 2003 [11].

The treatment outcomes of pulmonary TB patients with smear-positive are one of the essential indicators in evaluating the performance of national TB control program. New pulmonary TB patients differ from retreatment pulmonary TB patients in characteristics and treatment outcomes of patients [4]; accordingly, WHO evaluates the treatment outcomes with separate cohorts: new smear-positive patients with pulmonary TB under DOTS (Table), new smear-positive patients with pulmonary TB under non-DOTS, smear-positive pulmonary TB patients with retreatment after relapse under DOTS [11]. To monitor the effectiveness of treatment for TB patients, WHO recommends that new smear-positive patients with pulmonary TB should collect two or more (ideally three) sputum specimens at 2 months, 5 months, and last month of treatment [4]. Cohort analysis of treatment outcomes for TB patients should be performed every 3 months and at the end of the year [4].

WHO recommends that MDR-TB patients should preliminarily assess the treatment outcomes at 6 months after the start of treatment [6]. Except for the treatment outcomes of MDR-TB patients, many countries

Table. Treatment outcomes for new pulmonary TB patients, 2005 cohort [11]

Region	Country	New smear-positive TB patients (under DOTS)								New smear-positive TB patients (under non-DOTS)							
		Treatment outcomes (%)							% Treatment success	Treatment outcomes (%)							% Treatment success
		Cured	Completed	Died	Failed	Defaulted	Transferred	Not evaluated		Cured	Completed	Died	Failed	Defaulted	Transferred	Not evaluated	
Americas	Canada	8	59	9	0	1	1	21	68	-[a]	-	-	-	-	-	-	-
	U.S.A.	-	64	8	-	2	3	24	64	-	-	-	-	-	-	-	-
Europe	U.K.	-	-	-	-	-	-	-	-	0	68	7	0	1	2	22	68
	Denmark	44	39	6	1	2	3	5	83	-	-	-	-	-	-	-	-
	Netherlands	9	75	7	0	1	4	4	84	-	-	-	-	-	-	-	-
East South Asia	India	83	2	5	2	7	1	0	86	-	-	-	-	-	-	-	-
	Thailand	70	5	8	2	7	3	6	75	-	-	-	-	-	-	-	-
West Pacific Oceans	Australia	12	68	9	-	2	9	0	80	14	68	18	-	-	-	0	82
	New Zealand	0	60	6	0	1	6	27	60	-	-	-	-	-	-	-	-
	Japan	38	22	11	3	1	-	26	60	24	21	4	5	2	-	44	46
	Hong Kong	74	3	5	11	3	2	1	77	3	1	3	1	0	0	93	3
	Singapore	-	83	14	0	2	1	1	83	-	-	-	-	-	-	-	-
	South Korea	81	2	1	1	4	11	0	83	-	-	-	-	-	-	-	-
	Vietnam	90	2	3	1	1	2	0	92	-	-	-	-	-	-	-	-
	Philippines	82	7	2	1	4	2	0	89	-	-	-	-	-	-	-	-
	Cambodia	89	4	3	0	2	2	0	93	-	-	-	-	-	-	-	-
	Malaysia	69	1	9	0	5	6	10	70	-	-	-	-	-	-	-	-

-[a]: missing.

adopt the following indicators to assist in evaluating the control programs [6].

1.The number of patients with "smear conversion":

Initial sputums must be collected within 30 days before or 7 days after the start of treatment [6]. "Smear conversion" is defined that two consecutive negative smears were collected at least 30 days apart, and there were no positive smears followed [3,6].

2.The time to "smear conversion":

The time to "smear conversion" is computed by subtracting the date of the start of treatment from the date of smear conversion, which refers to the date of the first negative smear collected [3,6].

3.The number of patients with "culture conversion":

Patients with " culture conversion" must have two negative consecutive cultures collected at least 30 days apart, and have no positive cultures followed [3,6].

4.The time to "culture conversion":

The time to "culture conversion" is computed by subtracting the date of the start of treatment from the date of culture conversion, which refers to the date of the first negative culture collected [3,6].

5.The number of patients with reversion to positive smears or cultures:

The number of patients with reversion to positive smears or cultures should be monitored at 6, 12, and 24 months after the start of treatment [3].

These above indicators are mainly about smear or culture conversions. WHO recommends that sputum examinations should be performed every month or at least every 2 months, and that the criteria of inclusion and exclusion should be explained explicitly in the cohort analysis [3,6].

Conclusion and Recommendations

The treatment outcomes for TB are an important tool to evaluate the performance of TB control programs. It could identify probable problems and institute appropriate actions to improve the performance of the programs. In the past, many papers on treatment outcomes for TB were published, and they indeed afford valuable information in clinical and public health practice. However, Taiwan now works towards 'halving TB in ten years', and consequently the treatment outcomes for TB should be evaluated in routine and standardized procedures, which benefits from comparisons across population and countries. Therefore, we recommend that: 1) the treatment outcomes recommended by WHO should be performed regularly to enable comparison with other countries; 2) cohort analysis should be conducted every 3 months for drug-susceptible TB patients and at 6 months for MDR-TB patients, and sputum conversion also be monitored to timely modify prevention strategies; 3) the date of initial sputums should be monitored regularly to make sure whether initial sputums were collected within 30 days before or 7 days after the start of treatment; 4) the proportion of drug susceptibility tests performed should be investigated to estimate the real epidemiology of drug resistance for culture-positive pulmonary TB patients.

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