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Multiple-causes-of-death related to tuberculosis in the state of São Paulo, Brazil, 1998

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ABSTRACT

Objectives

The goal of this paper is to investigate mortality related to tuberculosis in the state of São Paulo, southeastern Brazil, according to multiple causes of death and their interrelation with other underlying causes.

Methods

The study investigated deaths related to tuberculosis that occurred in the state of São Paulo in 1998. Data were obtained from the Fundação Sistema Estadual de Análise de Dados (State System for Data Analysis Foundation – SEADE) database. Causes of death by clinical forms of TB were coded in block A15-A19, and by its sequelae in category B90, according to the guidelines proposed by the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems. Tabulador de Causas Múltiplas (Multiple Cause Tabulator - TCM) software was used for processing

associated causes of death. Statistical analysis included analysis of variance, Student's t-distribution, and chi-squared tests.

Results

TB was the underlying cause of 1,644 deaths, a 4.6/100,000 population mortality rate. Main associated causes were respiratory failure (46.9%), pneumonias (16.5%), other specified symptoms and signs involving circulatory and respiratory systems (13.9%), cachexia (12.9%), diseases of the circulatory system (10.3%), conditions due to alcohol use (8.4%), septicemias (7.2%) and malnutrition (7.1%). Tuberculosis occurred as an associated cause in another 1,388 deaths. The mortality rate including TB as a both underlying and associated cause was 8.9/100,000 population, practically twice the classical rate. Deaths whose associated cause was reported as being TB had as underlying causes: AIDS (65.3%), diseases of the circulatory system (8.9%), neoplasms (7.5%), and diseases of the digestive system (4.8%). Clinical forms of nervous system and miliary TB were more frequent as a cause associated with AIDS than with other underlying causes ($p < 0,001$).

Conclusions

Total reports of TB-related death practically doubled its mortality rate as an underlying cause. The increase in TB mortality was demonstrated to be influenced by the AIDS epidemic.

Keywords

Tuberculosis. Mortality. Cause of death. Acquired immunodeficiency syndrome. Aids-related opportunistic infections. Underlying cause of death. Mortality rate. Multiple-cause-of-death.

INTRODUCTION

Causes of death can be assessed through the information registered by physicians in death certificates.

Of the various causes registered, primary death statistics are based on the "underlying cause of death", defined by the World Health Organization (WHO) as "(a) the disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury".⁸ The underlying cause has been considered as the most efficacious way of preventing death. During the last half of the Twentieth Century, however, the growing demand for full descriptions of death – including all causes mentioned in the death certificate – determined the presentation of mortality data using the so called "multiple causes of death". Thus any complications of the underlying cause, as well as contributing conditions, designated as associated causes of death, were added to the underlying cause in mortality statistics as multiple causes.¹¹

Tuberculosis (TB) mortality showed an ascending trend in many countries since the onset of the AIDS epidemic in the 1980's.^{1,2,17} This increase was also due, among other factors, to modifications in

control and assistance programs, and to population growth.³ However, despite the increase registered, the importance of TB to population-wide mortality is not completely reflected by statistics presented according to underlying cause of death. TB occurs as an associated cause in a large number of deaths in which demise is attributed to a different underlying cause. In the United States, of all death certificates that included mentions of TB, death was attributed to another underlying cause in 56% in 1980 and 57% in 1990.¹⁸ In the state of São Paulo, southeastern Brazil, in 1983, this proportion was 22%.¹¹

Co-infection by TB and AIDS is an important factor for premature mortality and human suffering. Studies on multiple-cause mortality provide wide-ranging information about the magnitude of the impact of AIDS on the TB epidemic as recommended by the World Health Assembly¹⁹. In 1998, in the state of São Paulo, TB was mentioned as an associated cause of death in 19.6% (907/4,619) of AIDS deaths.¹⁵

The Fundação Sistema Estadual de Análise de Dados (State System for Data Analysis Foundation – SEADE) compiles multiple causes in the state of São Paulo since 1983, allowing for investigations of both underlying and associated causes of death. With the exception of the United States, the state of São Paulo was the first to employ the ACME system until 1995. Along with the implementation of the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), in 1996, the Sistema Declarações de Óbito de São Paulo (São Paulo Death Certificate System – DOSP/SCBX), was also implemented, and the first decision tables for automatic processing of AIDS-related deaths were constructed.⁹

The present study is aimed at investigating tuberculosis-related mortality in the state of São Paulo according to multiple causes of death, showing its importance as underlying and associated cause as well, and in this latter form, their interrelation with other underlying causes, especially AIDS.

METHODS

Data on deaths and estimated population in the state of São Paulo in 1998 were obtained from SEADE. Mortality files included fields which reproduced variables included in the death certificates used by the Mortality Information System, coordinated by the Ministry of Health. The underlying cause of death was registered in a separate field. Another string field included all conditions, injuries, external causes, and medical procedures mentioned in the International Form of Medical Certificate of Cause of Death. Additional fields were included in the original death data file structure in order to facilitate processing. These included a numerical field for mean age at death calculation. The proportion of men and women over age 75 years, in five-year groupings, obtained from the recount carried out by the Fundação Instituto Brasileiro de Geografia e Estatística (Brazilian Institute for Geography and Statistics – IBGE Foundation), was applied to the corresponding population estimated by SEADE in order to discriminate TB mortality among these age groups and avoid data distortion.

The underlying cause of death was construed according to WHO criteria, and remaining causes were referred to as associated causes of death.^{8,11} Thus associated causes include both terminal and intervening causes – also known as consequential causes, and considered as resulting from the underlying cause –, as well as contributing causes – which have no relation to the pathological process that lead directly to death. The set including both underlying and associated causes was referred to as “multiple causes of death”.¹¹ All causes registered in the death certificate were computed – even those characterized by WHO as “the mode of dying”, such as “respiratory failure”,⁸ due to their importance in the natural history of TB. Causes of death were identified according to ICD-10 recommendations, processed using DOSP/SCBX⁹ software, and reviewed in case AIDS was mentioned in the death certificate, or in case causes of death were ill-defined. TB as a cause of death corresponded to the clinical forms included in the “Tuberculosis” grouping, codified as A15 to A19, and

to the "Sequelae of tuberculosis" category, coded as B90.⁷ The expressions "deaths by" or "due to" a given condition refer to the underlying cause of death, and the expression "deaths with mention of" refer to the presence of a given cause, be it underlying or associate, in the death certificate.

Demographic and medical variables were processed using dBASE III Plus, version 1.1 (Ashton-Tate, 1985,1986), Epi Info ,version 6.04b/c, 1997, and Excel 97 SR-1. Computer program "Tabulador de Causas Múltiplas de Morte (Multiple Cause of Death Tabulator – TCM) (version 2.0, 25/08/99) was used for the study of mentions, associations, and mean number of causes of death.¹⁴ Special tabulation lists were prepared in order to identify causes of death related to the natural histories of TB and AIDS, and also other causes most frequently mentioned. Cause duplications, presented according to abbreviated tabulation lists, were eliminated. The number of associated causes depends on the amplitude of the class in which these causes are included. This was done in order to eliminate from the count cause duplication/multiplication. Only one cause was included per class (category, group, or chapter of ICD -10) in case two or more causes belonging to the same class were recorded in the same death certificate.¹⁴ Computer program Separador de Registros de Mortalidade (Mortality record separator – SRM_DBF) was used for recovering records for which there was an interest in a given associated cause, in order to study eventual relationships with TB.

Mortality rates per 100,000 population were calculated, according to sex and age groups, for classical underlying causes, and for total number of deaths with mention of TB as both an underlying and an associated cause of death.

Using Epi Info software, variance analysis was carried to test differences in mean age at death, Student's t test for differences in mean number of causes informed in death certificates, and chi-squared test for differences in proportions of associated causes of death when TB and AIDS were presented as the underlying cause. Deaths in which patient age was ignored were not included in mean age at death calculations. Significance level was established at 1%. Mean age at death and number of causes are presented with their respective standard deviations.

RESULTS

In 1998, 232,806 deaths occurred in the state of São Paulo, of which 1,644 had TB as the underlying cause, corresponding to a 0.7% proportional mortality. This share included 1,226 men and 418 women; respective mortality rates were 4.6 per 100,000 population, 7.0 per 100,000 men, and 2.3 per 100,000 women. TB was mentioned as an associated cause in another 1,388 deaths, of which 1,008 were men and 380 were women. Mortality rates calculated based on total mentions, including both underlying and associated causes, were 8.6 per 100,000 population, 12.8 per 100,000 men, and 4.5 per 100,000 women. Ratios between rates based on mentions and on underlying cause were 1.9, 1.8, and 2.0 for total, male, and female deaths, respectively. Of the 3,032 deaths in which TB was mentioned, only 14 were of São Paulo State nonresidents – a number considered as small –, which were studied together with the remainder. Figure 1 shows TB mortality rate distribution among men and women, according to age.

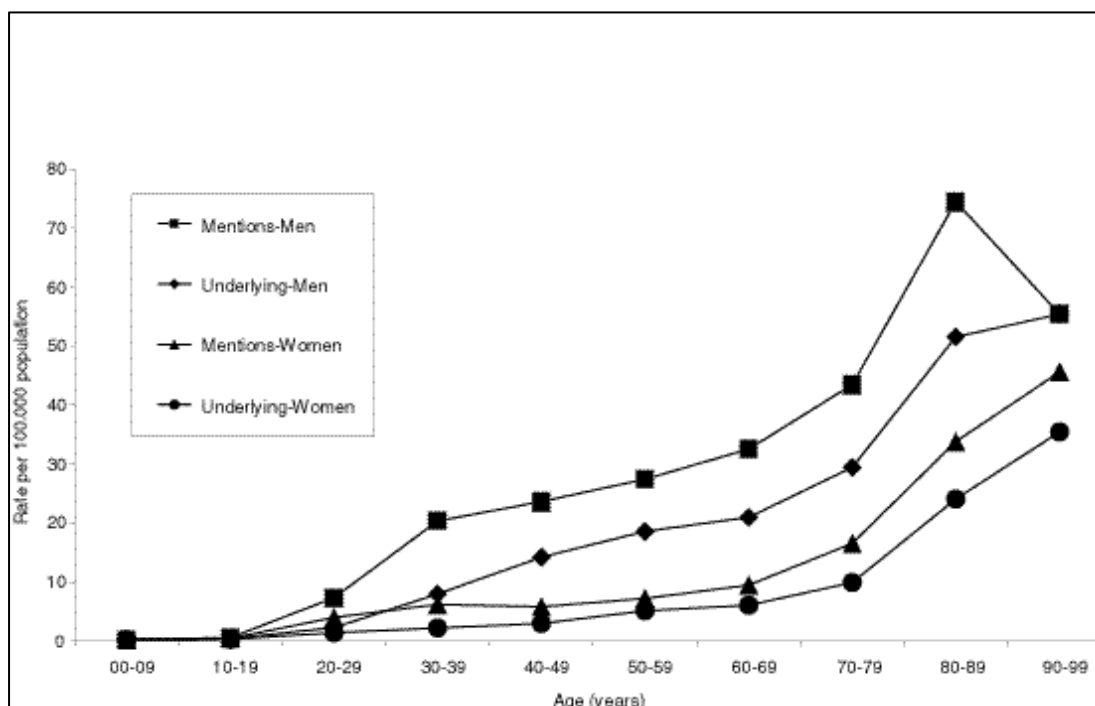


Figure 1 - TB mortality rates, underlying causes, and total mentions, by age and sex, São Paulo State, Brazil, 1998.

Of the 1,644 deaths by TB as an underlying cause, 1,326 (82.5%) were due to TB of the respiratory tract, 26 (1.6%) of the nervous system, 23 (1.4%) of other organs, 124 (7.5%) to miliary TB, and 115 (7.0%) to TB sequelae.

Associated causes in TB deaths are presented in Table 1. Most of these causes may be considered as terminal. This category includes respiratory failure, pneumonias, conditions included in category R09 – concerned with other symptoms and signs involving the circulatory and respiratory systems in the chapter “Symptoms, signs, and abnormal clinical and laboratory findings” –, septicemias, and renal failure. Cachexia and malnutrition proportions together add up to as much as 19.7% of deaths by TB. The greater proportions of circulatory system diseases among women, and of mental disorders due to psychoactive substance use among men were significant ($p < 0.001$). Of the 138 deaths associated to psychoactive substance use, 130 (94.2%) were alcohol related.

Table 1 – Number and percentage of deaths due to TB*, according to associated causes of death and sex, São Paulo State, Brazil, 1988.

Associated causes of death **	Men		Women		Total	
	(deaths =1,226)		(deaths =418)		(óbitos =1,644)	
	N	%	N	%	Nº	%
Respiratory failure (J96)	575	46.9	196	46.9	771	46.9
Pneumonias (J12-J18)	186	15.2	86	20.6	272	16.5
Other symptoms/signs involving circ. & resp. systems(R09)	170	13.9	59	14.1	229	13.9

Cachexia (R64)	160	13.1	52	12.4	212	12.9
Diseases of the circulatory system (I00-I99)***	109	8.9	61	14.6	170	10.3
Rem. resp. tract (J00-J11, J20-J39, J60-J68, J70-J95, J98)	115	9.4	44	10.5	159	9.7
Mental disord. Due to psychoactive subst. use (F10-F19)***	128	10.4	10	2.4	138	8.4
Septicemias (A40-A41)	88	7.2	30	7.2	118	7.2
Chronic lower respiratory diseases (J40-J47)	81	6.6	36	8.6	117	7.1
Malnutrition (E40-E46)	87	7.1	25	6.0	112	6.8
Diseases of liver (K70-K77)	67	5.5	16	3.8	83	5.0
Diabetes mellitus (E10-E14)	52	4.2	20	4.8	72	4.4
Hemorrhage from respiratory passages (R04)	38	3.1	13	3.1	51	3.1
Remaining dis. of the digestive system (K00-K66, K80-K92)	36	2.9	11	2.6	47	2.9
Anemia, unspecified (D649)	23	1.9	14	3.3	37	2.3
Renal failure (N17-N19)	25	2.0	9	2.2	34	2.1
Remaining associated causes of death	182	14.8	75	17.9	257	15.6
Total	2,122	NC	757	NC	2,879	NC

Source: Fundação Sistema Estadual de Análise de Dados database

*Active tuberculosis and its late effects (A15-A19, B90)

**Rubrics and codes of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

***Difference in proportions between men and women ($p < 0.001$)

% Percentages calculated in relation to the number of deaths.

NC = not calculated.

AIDS was the main underlying cause in 65.3% (907/1,388) of deaths in which TB was mentioned as an associated cause (Table 2) and in 85.9% (828/964) of those in the 20-49 years age group. As to the total number of deaths with mention of TB, corresponding percentages were 29.9%, (907/3,032) and 47.6% (828/1,738). Diseases of the circulatory system, neoplasms – including malign neoplasm of the bronchi and lungs –, and diseases of the respiratory system followed AIDS in order of importance as underlying causes (Table 2).

Table 2 – Number and percentage of deaths in which TB is an associated cause, according to underlying cause of death and sex, São Paulo State, Brazil, 1998.

Underlying causes of death*	Men		Women		Total	
	N	%	N	%	N	%
Certain infectious and parasitic diseases (A00-B99)	678	67.3	262	68.9	940	67.7
Human immunodeficiency virus [HIV] disease (B20-B24)	658	65.3	249	65.5	907	65.3
Neoplasms (C00-D48)	76	7.5	28	7.4	104	7.5
Malign neoplasm of bronchus and lung (C34)	21	2.1	9	2.4	30	2.2
Endocrine, nutritional, and metabolic dis. (E00-E90)	18	1.8	7	1.8	25	1.8
Diabetes mellitus (E10-E14)	12	1.2	6	1.6	18	1.3
Mental and behavioural disorders (F00-F99)	11	1.1	3	0.8	14	1.0

Mental disorders ... due to use of alcohol (F10)	9	0.9	2	0.5	11	0.8
Diseases of the circulatory system (I00-I99)	88	8.7	36	9.5	124	8.9
Ischemic heart diseases (I20-I25)	19	1.9	12	3.2	31	2.2
Heart failure (I50)	16	1.6	6	1.6	22	1.6
Diseases of the respiratory system (J00-J99)	68	6.7	17	4.5	85	6.1
Chronic lower respiratory diseases (J40-J47)	46	4.6	11	2.9	57	4.1
Diseases of the digestive system (K00-K93)	50	5.0	17	4.5	67	4.8
Alcoholic liver disease (K70)	12	1.2	0	0.0	12	0.9
Other liver disease (K71-K77)	22	2.2	9	2.4	31	2.2
Other causes (**)	19	1.9	10	2.6	29	2.1
Total	1,008	100.0	380	100.0	1,388	100.0

Source: Fundação Sistema Estadual de Análise de Dados database

*Rubrics and codes of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

**Diseases of the blood and blood & blood forming organs and certain immune disorders (D50-D89), Diseases of the nervous system (G00-G99), Diseases of the musculoskeletal system and connective tissue (M00-M99), Diseases of the genitourinary system (N00-N99), Pregnancy, childbirth, and puerperium (O00-O99), and external causes of morbidity and mortality (V00-Y98).

Clinical forms of nervous system and miliary TB were more frequent as associated causes in deaths due to AIDS, whereas TB sequelae were mostly associated with other causes of death ($p < 0.001$) (Table 3).

Table 3 – Number and percentage of deaths due to AIDS and other causes, according to clinical forms of TB as associated causes of death, São Paulo State, Brazil, 1998.

Associated causes of death*	AIDS		Other causes		p-value
	(deaths =907)		(deaths =481)		
	N	%	N	%	
Respiratory TB (A15-A16)	708	78,1	363	75,5	0,274
TB of nervous system (A17)	65	7,2	2	0,4	<0,001
TB of other organs (A18)	36	4,0	16	3,3	0,548
Miliary TB (A19)	127	14,0	21	4,4	<0,001
Sequelae of TB (B90)	1	0,1	81	16,8	<0,001
Total	937	NC	483	NC	

Source: Fundação Sistema Estadual de Análise de Dados database

*Rubrics and codes of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

% Percentages calculated in relation to the number of deaths.

NC = not calculated.

Considering all deaths with mention of TB, and according to the respective underlying causes of death, the differences in mean age of death by AIDS ($36,2 \pm 9.3$ years), TB (51.1 ± 18.0 years), and other causes (58.6 ± 9.3 years) were statistically significant ($p < 0.001$). Figure 2 shows mortality rates by age group for TB as an underlying cause, and for AIDS and other underlying causes with TB as an associated cause. Mean age at death in the 137 deaths by TB associated with psychoactive substance use was approximately 5.6 years lower (46.4 ± 11.7 years) than the 1,490 deaths by TB without this association (52.1 ± 17.6 years) ($p < 0.001$).

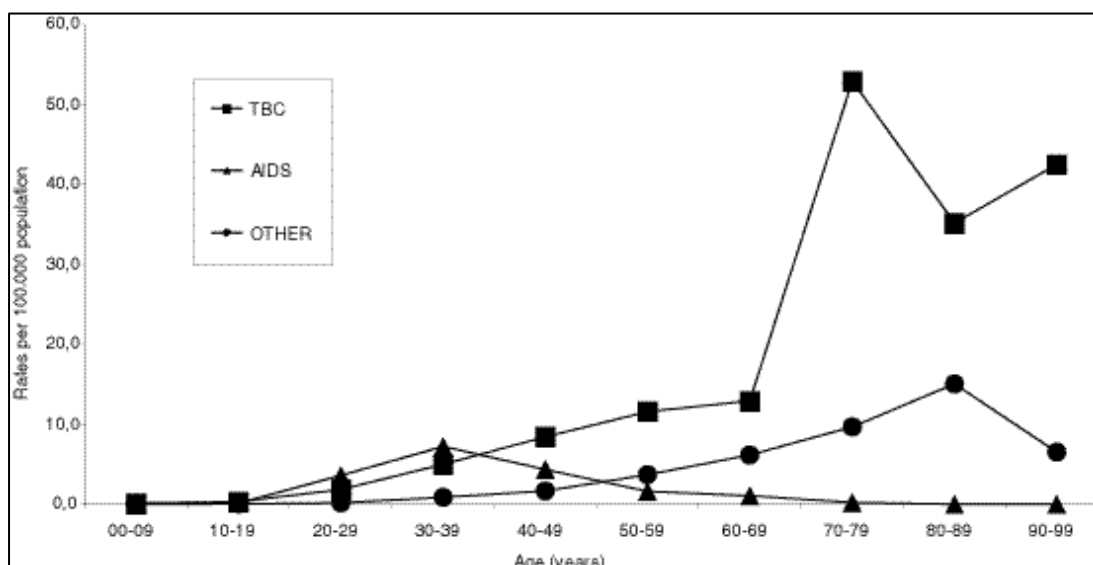


Figure 2 - Mortality rates for TB as an underlying cause and for AIDS and OTHER causes with TB as an associated cause, by age, São Paulo State, Brazil, 1998.

Mean number of causes registered per death certificate was significantly different between the 1,644 deaths due to TB (2.8 ± 1.1), the 907 deaths due to AIDS (3.7 ± 1.0), the 481 deaths due to other causes (4.0 ± 1.1), and the total 232,806 deaths registered in the state of São Paulo in 1998 (2.7 ± 1.3) ($p < 0.001$). Approximately 59.2% (937/1,644) of deaths by TB had three or more causes recorded in the death certificate.

DISCUSSION

The present study verified that the investigation of TB mortality was better and more inclusive when based on multiple causes of death, previous rates being almost doubled after the adoption of this procedure. In the state of São Paulo, in 1983, about 78% (1,043/1337) of all mentions of TB as a cause of death in death certificates had this disease as the underlying cause,¹¹ whereas in the present study this value was 54.2% (1,644/3,032). The smaller proportion of TB as an underlying cause in 1998 is partly due to the recommendations introduced by ICD-10 – which incorporate current knowledge about the etiopathogeny of AIDS – which favor HIV disease as an underlying cause.^{8,12,15} Among such recommendations, that which interprets infectious diseases, especially opportunistic ones, as consequences of AIDS determined the shifting of TB to the status of associated cause in

deaths in which AIDS was present. For this reason, in the state of São Paulo in 1998, AIDS was identified as the underlying cause in 98.2% (4,619/4,702) of deaths in it was mentioned.¹⁵

Associated causes for deaths in which TB was reported as the underlying cause included characteristics of consumptive disease and of the natural history of TB. Respiratory failure, when the main reason for admission to specialized hospitals, is related to greater fatality.⁵ The natural history of TB includes, as consequential causes, pneumonias, septicemia, malnutrition, anemia, and, generally speaking, the conditions included in the ICD-10 chapter on ill-defined causes. Among contributing causes, the association of TB with alcoholism is important in Brazil, especially among men, as a determinant for non-adherence to treatment and disciplinary hospital discharge.⁵ These associated causes must be taken into consideration so as to prevent their influence on the determination of death by TB.

Any eventual differences in associated cause distribution, in deaths for which TB was identified as the underlying cause (Table 1) when compared to the 1983 distribution, may be explained, among other factors, by the update in the ICD version used at the time. However, this is not the case with underlying cause distribution in deaths for which TB was an associated cause (Table 2). In 1983, only 5.4% of these deaths were attributed to infectious and parasitic diseases,¹¹ whereas this value rose to 67.7% in 1998, and 65.3% were related to AIDS (Table 2). The relative importance of the remaining underlying causes decreased noticeably, as in the case of diseases of the circulatory system – from 26.9% to 8.9% – and neoplasms – from 15.3 to 7.5% –, between 1983 and 1998, respectively.¹¹

The association between AIDS and TB may occur through the reactivation of the latter, through rapid progression of a primary infection, and through reinfection (exogenous) at any stage of HIV infection. The risk of primary and reinfection among HIV-positive patients is considerably high. The progression of HIV disease is aggravated by TB. Co-infection by HIV and TB duplicates the risk of demise in relation to infection by HIV alone.

The importance of co-infection was characterized by the clinical forms of TB associated with AIDS.¹⁶ Nervous system and miliary clinical forms of TB are found with greater frequency in HIV-positive patients than in others. Central nervous system TB occurs in 5-10% of HIV-positive patients.¹⁶

In 1990, of all deaths in patients infected by TB, 4.6% were attributed to HIV infection. In the present study, this value was 29.9% (907/3032) of all deaths with mention of TB, more than doubling the 14% estimated for the year 2000.¹⁰

Graphic representation of TB mortality distribution by age before the AIDS epidemic was unimodal in shape, rising along with age. The first studies to investigate this pattern for the AIDS/TB co-infection describe a bimodal curve, with peaks between 24 and 45, and above 60 years.^{2,18} These studies, however, studied TB and AIDS deaths jointly, without a hierarchical distinction between underlying and associated causes. This was due to their being conducted at a time when the defining diseases of AIDS might have been identified as the underlying cause instead of AIDS itself. In the present study, only curves plotted according to total mentions had a slight trend towards elevation between 30 and 44 years among men and 25 and 39 years among women. Graphic representation of deaths due to underlying causes with TB as an associated cause shows that the elevation detected at this younger age is due to AIDS deaths, a hypothesis corroborated by the respective mean age at death. On the other hand, the slight rise detected in the TB-related mortality curve among younger age groups was partly ascribed to deaths due to alcohol or another psychoactive substance abuse.¹⁸ The present study detected an association between alcohol use and TB mortality at younger-than-normal age.

Mean number of diagnosis registered in death certificates is used as an indicator for the quality of mortality data.^{11,15} It can be inferred that at least three causes of death will be described in the lines in

Part I of any correctly filled death certificate, in which the pathological sequence leading to death includes underlying, intervening, and terminal causes. When necessary, one or more contributing causes may be added in Part II of the death certificate. The greater the number of causes registered, the greater our knowledge about the natural history of the disease, and consequently the greater the possibilities of preventing similar deaths. Mean number of causes per certificate for deaths by TB was greater than the correspondent number for the total deaths in the state. The 2.8 causes per certificate obtained was adequate for the study of multiple-cause mortality. However, it was lower than the mean number of causes registered for deaths for which AIDS was selected as the underlying cause, which may reflect the greater importance given to this syndrome by physicians when filling death certificates. The 907 deaths due to AIDS with mention of TB had a greater mean number of causes (3.7 ± 1.0) than the 3,712 deaths without (3.1 ± 1.1) in the State of São Paulo, in 1998.¹³

The present study presents the usual limitations of mortality studies based on secondary data from death certificates forwarded to the Civil Register.¹¹ Although quantitative limitations imposed by under-reporting of deaths in the state are negligible, qualitative limitations should not be neglected, especially those related to the inadequate filling of death certificate items. This situation has been improving in the last few years, however, due to greater knowledge on the part of physicians concerning the statistical and legal importance of this document for public health and for the deceased's family. The 6.6% share of deaths attributed to ill-defined causes in São Paulo State in 1998 was one of the lowest in Brazil. Such improvement is partly due to the progressive increase in the mean number of causes reported per death certificate, which is attributed to the addition of a fourth line to Part I of the International Form of Medical Certificate of Cause of Death.⁸ On the other hand, the advantages of this type of study are greater than the above-mentioned limitations. TB death coverage is greater than that of epidemiological surveillance case notification. A comparison between mortality data and compulsory case notification showed that in São Paulo State in 1980, and in São Paulo City, from 1986 to 1995, respectively 67.5% and 64.2% of TB cases were not reported.^{4,6} In addition, multiple-cause mortality data unite, in a single register, deaths related to TB, AIDS, and other causes, allowing for the evaluation of the impact of any given cause and of its lethal associations.

The study of mortality adds a valuable contribution to TB epidemiology. The results of the present study show that mortality rates almost doubled when deaths with mention of TB as an associated cause – of which, in roughly two-thirds of cases, AIDS was reported as the underlying cause – were added. They also show that information including all registered causes of death allow for a partial reconstruction of the natural history of TB, and for the recommendation of adequate preventive and therapeutic measures.

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