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Tuberculosis fatality rates in the city of Campinas - São Paulo, Brazil, from 2001 to 2009

Taxas de letalidade por tuberculose na cidade de Campinas, São Paulo, Brasil, de 2001 a 2009

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ABSTRACT: *Introduction:* The mortality rate among tuberculosis patients (TB fatality) has been attributed to irregular chemotherapy, delay in diagnosis, multidrug resistance, and HIV coinfection. *Objective:* To analyze TB fatality rates by sex, clinical presentation and HIV coinfection in Campinas, São Paulo, Brazil. *Methods:* Cohorts of residents in the city of Campinas who either died during treatment for tuberculosis or had the disease confirmed after death were divided into three intervals: 2001–2003, 2004–2006, and 2007–2009. Data were obtained from the database of the Tuberculosis Surveillance System of the University of Campinas, and notifications were gathered through TB-WEB Health São Paulo Secretary. Statistical significance was determined using a chi-square test, considering $p < 0.05$. *Results:* Between 2001 and 2009, 3,416 TB patients were diagnosed: 2,827 (82.8%) were new TB cases and 589 (17.2%) were retreatments. Between the first and second triennium, the number of new patients decreased by 18%, and 23% among retreatments. Between the second and third intervals, the reduction was 5% and 21%, respectively. General case fatality rate declined from 11.4% to 9.9% across intervals, and was most significant among patients that had previously abandoned treatment (17.3% to 5.1%). Fatality rates among patients coinfecting with TB-AIDS were 2–3 times that of patients not infected with TB-AIDS throughout the intervals. Fatality between the first and third triennium among TB-AIDS co-infected patients declined (24.8% to 19.5%), while increasing slightly among non-AIDS TB patients (7.3% to 8%) during this period. *Conclusion:* Though mortality among TB-AIDS patients declined from 2001–2009, rates among non-AIDS TB remained stagnant. Improved TB diagnosis and treatment is needed to further decrease TB mortality in Campinas.

Keywords: Tuberculosis. AIDS. Case fatality rate. Comorbidity. Treatment. Mortality.

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RESUMO: *Introdução:* A letalidade por tuberculose tem sido atribuída à quimioterapia irregular, à demora no diagnóstico, à multidrogarresistência, à coinfeção com o vírus da imunodeficiência humana (HIV). *Objetivo:* Analisar letalidade por tuberculose segundo sexo, apresentação clínica, presença da coinfeção pelo HIV, em Campinas, São Paulo, Brasil. *Metodologia:* Foram verificadas coortes de residentes em Campinas que morreram durante tratamento para tuberculose e aqueles notificados após óbito, agrupados em três intervalos: 2001–2003, 2004–2006 e 2007–2009. As informações foram obtidas no Banco de Dados para Vigilância da Tuberculose da Universidade Estadual de Campinas (UNICAMP), com captação das notificações no Sistema de Notificação e Acompanhamento de Casos de Tuberculose da Secretaria Estadual de Saúde de São Paulo. A significância estatística foi verificada pelo teste χ^2 considerando $p < 0,05$. *Resultados:* Entre 2001 e 2009, foram diagnosticados 3.416 pacientes com tuberculose: 2.827 (82,8%) sem tratamento anterior e 589 (17,2%) com retratamentos. Entre o primeiro e o segundo triênio, o número de pacientes novos diminuiu 18% sem tratamento anterior e 23% entre retratamentos. Entre o segundo e o terceiro intervalo, a redução foi de 5 e 21%, respectivamente. A letalidade geral declinou de 11,4 para 9,9%, diferença mais significativa entre os que haviam abandonado tratamento anteriormente (17,3 para 5,1%). A letalidade entre pacientes com coinfeção tuberculose-síndrome da imunodeficiência adquirida (Aids) foi 2–3 vezes maior que entre tuberculose sem aids durante todo o período estudado. A letalidade entre o primeiro e o terceiro triênio declinou no grupo com tuberculose-aids (24,8 para 19,5%), enquanto teve ligeiro aumento entre tuberculose sem aids (7,3 para 8%). *Conclusão:* Embora a mortalidade entre pacientes com tuberculose-aids tenha diminuído de 2001–2009, as taxas no grupo tuberculose sem aids permaneceram estagnadas. Melhorias no diagnóstico e no tratamento são necessárias para a redução da mortalidade entre pacientes com tuberculose em Campinas.

Palavras-chave: Tuberculose. Aids. Letalidade. Comorbidade. Tratamento. Mortalidade.

INTRODUCTION

Brazil still remains on the World Health Organization's list of 22 high-burden tuberculosis (TB) countries, although the country has successfully met the Stop TB Partnership target of a 50% reduction in the mortality rate by 2015¹.

The emergence of the HIV epidemic in the 1980s led to global changes in the epidemiologic trend of tuberculosis morbidity and mortality, reversing decades of declining rates. Prior to the HIV epidemic, TB surveillance and control programs were shortchanged as resources were shifted from the TB program to other programs², thus setting the stage for a reemerging epidemic in the late 1980s^{3,4}. The advent of antiretroviral treatment (ART) programs in the mid 1990s helped to decrease TB mortality among TB-AIDS patients in Brazil⁵, particularly because Brazil took the bold step of paying for ART for patients in need⁶. Furthermore, the expansion of the WHO's DOTS strategy significantly impacted TB mortality worldwide⁷.

In Campinas, a large industrial city in the state of São Paulo, the richest in the country, a reduction in case fatality rates was observed between 1993 to 2000 from 18.1% to 13.5%. This reduction was determined to be related to the introduction of ART⁵. The Campinas health care system is well organized, and at present, primary care is offered at 65 clinics. As in all of Brazil, TB and HIV/AIDS laboratory exams and treatment are free. Treatment of

drug sensitive pulmonary tuberculosis with standard anti-tuberculosis drugs is highly efficacious, though some patients receiving these drugs still die. We set out to determine mortality trends in Campinas, specifically, to describe TB case fatality rates by sex, clinical presentation and presence of HIV co-infection in the period of 2001 to 2009, stratified by triennium.

METHODS

TB morbidity and mortality data were abstracted from local registries for residents of Campinas city (the State of São Paulo, Brazil) from January 1, 2001 through December 31, 2009. The analysis included patients that died during treatment and those that were diagnosed after death. Prisoners and all patients with non-tuberculosis mycobacterium were excluded from the study.

Pulmonary TB cases were defined by a sputum positive smear and/or culture for mycobacteria (BK), or suggestive radiology images with respiratory complaints. Extra-pulmonary TB was defined by a positive smear/culture for BK in any secretion, liquid or tissue sample, from radiology, histology or laboratory analysis.

Since 1993, a TB Surveillance Data Bank has been kept by the State University of Campinas. Data were retrieved from the National Notification System (SINAN) administered by the Health Ministry through 2006, and since 2007 from the TB-WEB, run by the São Paulo Health Secretary.

The TB Surveillance Data Bank includes all variables registered in the case notification form, including registration date, smear and culture results, radiology and laboratory analysis, date treatment began, anti-tuberculosis drugs and treatment outcomes. TB-AIDS was defined by the assistant doctor and registered in the comorbidity item of the notification form.

The main demographic variables included in this analysis were sex, age, and primary health unit that reported the case. Health variables included type of entrance in the notification system — new case or history of previous treatment (relapse, dropout or failure), clinical presentation (pulmonary and extra-pulmonary), laboratory exams (smear, culture, HIV), presence of other diseases (AIDS, diabetes, alcoholism, etc.), and treatment outcome (cure, county transfer, dropout, death, failure). Thus death data registered in SINAN or TB-WEB underwent confirmation and eventual correction using SIM. The later was used to verify under-notification.

Data tabulation of new cases, relapse, dropout and failure among cases and deaths, calculation of case-fatality rates by period, and stratification by sex, period and clinical form was performed using Epi Info 6.04d and Microsoft Excel 2007 for three periods 2001–2003, 2004–2006 and 2007–2009. Statistical significance among proportions was determined using the chi square test ($p < 0.05$). Trends were analyzed using the chi square test for linear trends by Epi Info Statcalc, version 6.04.

The project was approved by the Ethics Research Committee of the School of Medical Sciences at the State University of Campinas.

RESULTS

Between 2001 and 2009, 3,416 TB cases were diagnosed. Of these, 2,827 (82.8%) were newly diagnosed TB cases and 589 (17.2%) were retreatment cases. Across the first 3-year intervals, new cases diminished 18%, while retreatment cases declined 23%. The decline was 5 and 21%, respectively, between the second and third intervals. General case fatality rate had a slight but not significant decline from 11.4 to 9.9% between the first and third triennium. Prior treatment dropout was the only group where fatality rate diminished significantly, from 17.3 to 5.1%. There was a decreasing linear trend for retreatment cases vs new cases ($p = 0.038$), and the same occurred for deaths ($p = 0.038$) (Table 1).

Table 1. Tuberculosis patients, deaths, and fatality rates in the city of Campinas-SP-Brazil, 2001 to 2009.

Variables	2001–2003		2004–2006		2007–2009		p-value
	n	%	n	%	n	%	
Entrance							
New case	1088	81.4	891	82.4	848	84.9	0.087
Relapse	111	8.3	92	8.5	69	6.9	0.336
Previous dropout	133	10.0	95	8.8	79	7.9	0.198
Failure	4	0.3	3	0.3	3	0.3	0.994
Total number of cases	1336	100	1081	100	999	100	
Deaths							
New case	116	76.3	94	81.0	86	86.9	0.117
Relapse	13	8.6	14	12.1	8	8.1	0.528
Previous dropout	23	15.1	8	6.9	4	4.0	0.007
Failure	0	0	0	0	1	1.0	-
Total number of deaths	152	100	116	100	99	100	
Fatality rate							
New case	10.7		10.5		10.1		0.929
Relapse	11.7		15.2		11.6		0.701
Previous dropout	17.3		8.4		5.1		0.014
Failure	-		-		33.3		-
General	11.4		10.7		9.9		0.526

Statcalc linear trend for retreatment patients vs new patients $p = 0.038$; Statcalc linear trend for retreatment deaths vs new patient deaths $p = 0.038$.

During the whole study period, 687 (20.1%) patients were notified to have TB-AIDS and 2,729 (79.9%) did not have the coinfection (Table 2). Males constituted the vast majority of cases (68.4%) and deaths (74.1%), both among TB-AIDS and non-AIDS TB patients. The case fatality rate was more than double for TB-AIDS patients compared to non-AIDS

Table 2. Tuberculosis patients with and without AIDS, according to sex, death and fatality rates. Campinas, SP, Brazil, 2001 to 2009.

Variables	2001–2003		2004–2006		2007–2009		p-value
	n	%	n	%	n	%	
TB-AIDS							
Patients (N = 687)							
Female	80	25.7	61	29.5	55	32.5	0.269
Male	231	74.3	146	70.5	114	67.5	
Total	311	100	207	100	169	100	
Deaths (N = 160)							
Female	17	22.1	19	38.0	11	33.3	0.134
Male	60	77.9	31	62.0	22	66.7	
Total	77	100	50	100	33	100	
Fatality rate							
Female	21.3		31.1		20.0		0.283
Male	26.0		21.2		19.3		0.318
Total	24.8		24.2		19.5		0.406
non-AIDS TB							
Patients (N = 2,729)							
Female	348	33.9	285	32.6	251	30.2	0.250
Male	677	66.1	589	67.4	579	69.8	
Total	1,025	100	874	100	830	100	
Deaths (N = 207)							
Female	19	25.3	18	27.3	11	16.7	0.303
Male	56	74.7	48	72.7	55	83.3	
Total	75	100	66	100	66	100	
Fatality rate							
Female	5.5		6.3		4.4		0.615
Male	8.3		8.2		9.5		0.658
Total	7.3		7.6		8.0		0.876

Statcalc linear trend for TB-AIDS male patients vs non-AIDS TB male patients $p < 0.0001$; Statcalc linear trend for TB-AIDS male death vs non-AIDS TB male deaths $p < 0.001$.

TB patients in the first (24.8 and 7.3%) and last triennium (19.5 and 8.0%). In the first triennium, among TB-AIDS patients, male fatality rate was the highest (26%). In the second triennium, the highest was among female (31.1%). Non-AIDS TB men had higher fatality rates than women in all the trienniums. Male TB-AIDS patients compared to non-AIDS TB patients had a decreasing linear trend for cases and deaths ($p < 0.001$) (Table 2).

TB-AIDS patients had nearly twice or more than three times the fatality rate of non-AIDS TB patients, depending on the clinical form and period (Table 3). In 2001–2003, the

Table 3. Deaths and fatality rates among tuberculosis patients according to clinical presentation and AIDS comorbidity. Campinas, SP, Brazil, 2001 to 2009.

Variables	2001–2003		2004–2006		2007–2009		p-value
	n	%	n	%	n	%	
I. New cases							
Pulmonary presentation							
Patients							
TB-AIDS	176	18.9	92	12.5	97	13.5	< 0.001
non-AIDS TB	757	81.1	642	87.5	624	86.5	
Total	933	100	734	100	721	100	
Deaths							
TB-AIDS	43	44.8	22	31.0	16	22.9	0.010
non-AIDS TB	53	55.2	49	69.0	54	77.1	
Total	96	100	71	100	70	100	
Fatality rate							
TB-AIDS	24.4		23.9		16.5		0.288
non-AIDS TB	7.0		7.6		8.7		0.517
Total	10.3		9.7		9.7		0.892
Extra-pulmonary presentation							
Patients							
TB-AIDS	51	32.9	39	24.8	33	26.0	0.237
non-AIDS TB	104	67.1	118	75.2	94	74.0	
Total	155	100	157	100	127	100	
Deaths							
TB-AIDS	9	45.0	13	56.5	9	56.2	0.708
non-AIDS TB	11	55.0	10	43.5	7	43.8	
Total	20	100	23	100	16	100	

Continue...

Table 3. Continuation.

Variables	2001–2003		2004–2006		2007–2009		p-value
	n	%	n	%	n	%	
Fatality rate							
TB-AIDS	17.6		33.3		27.3		0.225
non-AIDS TB	10.6		8.5		7.5		0.728
Total	12.9		14.7		12.6		0.855
II. Retreatment							
Pulmonary presentation							
Patients							
TB-AIDS	69	31.5	62	36.7	32	23.0	0.035
non-AIDS TB	150	68.5	107	63.3	107	77.0	
Total	219	100	169	100	139	100	
Deaths							
TB-AIDS	22	66.7	12	63.2	8	61.5	0.936
non-AIDS TB	11	33.3	7	36.8	5	38.5	
Total	33	100	19	100	13	100	
Fatality rate							
TB-AIDS	31.9		19.4		25.0		0.260
non-AIDS TB	7.3		6.5		4.7		0.684
Total	15.1		11.2		9.4		0.241
Extra-pulmonary presentation							
Patients							
TB-AIDS	15	51.7	14	66.7	7	58.3	0.572
non-AIDS TB	14	48.3	7	33.3	5	41.7	
Total	29	100	21	100	12	100	
Deaths							
TB-AIDS	3	100	3	100	0	-	-
non-AIDS TB	0	-	0	-	0	-	-
Total	3	100	3	100	0	-	-
Fatality rate							
TB-AIDS	20.0		21.4		-		0.417
non-AIDS TB	-		-		-		-
Total	10.3		14.3		-		0.404

Statcalc linear trend for new pulmonary TB-AIDS patients vs non-AIDS TB patients $p = 0.001$; Statcalc linear trend for new pulmonary TB-AIDS deaths vs non-AIDS TB deaths $p = 0.002$.

highest fatality rate was among TB-AIDS retreatment cases with a pulmonary presentation (31.9%) (Table 3). From 2004 onwards, the highest fatality rates were among TB-AIDS new cases with an extra-pulmonary form (33.3 and 27.3% respectively) (Table 3).

There were 488 new TB-AIDS patients, 365 (74.8%) of which had a pulmonary presentation. This proportion was 86.5% among the 2,339 non-AIDS TB patients. Comparing the third with the first triennium, these cases decreased by 44.9% among TB-AIDS patients and 17.6% among non-AIDS TB patients. A decreasing linear trend was observed for new cases of pulmonary TB-AIDS and deaths when compared with non-AIDS TB cases ($p = 0.001$ and $p = 0.002$) (Table 3).

DISCUSSION

In Campinas, the total number of TB patients has diminished in relation to the annual mean of the first years (1997–2000)⁵ with Highly Active Antiretroviral Therapy (HAART) both among male and female patients with and without HIV.

Fatality rates in the period from 2001 to 2009 were lower than in the period from 1997–2000 among TB non-AIDS patients⁵. No consistent differences in the trend of fatality rates were observed among the sexes.

The predominance of the male sex among both TB non-AIDS and TB-AIDS patients is a fact observed by many authors^{8,9} and also previously described in the city⁵.

Before HAART in Campinas, the number of TB-AIDS patients represented 28.7% of all TB cases⁵. This proportion dropped to 24.6% after HAART was introduced⁵. In the years covered by this study, it gradually decreased to 23.3% (2001–2003), 19.1% (2004–2006) and 16.9% (2007–2009).

In consonance with several studies¹⁰ performed in Campinas, TB-AIDS cases presented much higher fatality rates (19.5 to 24.8%) than TB non-AIDS cases (7.3 to 8.0%). Similar fatality rates were observed in 2000–2006 in the State of Espírito Santo, Brazil (28.8% among TB-AIDS patients and 5.9% among non-AIDS TB patients)¹¹. In a sample of 2,473 hospitalized patients in the city of São Paulo, Brazil in 2001, fatality rates were similar for TB-AIDS cases (24%) but much higher among non-AIDS TB cases (15.1%), which can be explained by the severity of the clinical presentation of patients that need hospital care, considering that disseminated TB that killed 66% of the patients with this clinical form¹². In a cohort of 887 pulmonary TB patients followed for two years in a Tanzanian city¹³, fatality among the TB-AIDS cases (29.7% in 471 patients) was similar to that in Campinas, and quite lower among non-AIDS TB cases (3.6% in 416 patients). In spite of this later fatality¹³, it can be argued that important efforts need to be done in Campinas to reduce fatality among pulmonary TB patients without HIV.

The lack of significant reduction in the fatality rates of TB-AIDS in Campinas denotes no real improvement in treatment. On the other hand, the reduction in the proportion of patients with TB-AIDS represents an advancement in the prevention and control of AIDS,

since less people become ill with TB-AIDS. In New York City, between 1995 and 2004, the fatality rate of TB-AIDS decreased from 26% to 14%¹⁴. In Cambodia, a study of 490 non-AIDS TB patients and 339 TB-AIDS patients treated in TB clinics, observed a case-fatality rate of 37% in 2004 when HAART had not been implemented, and a 18% rate in 2005, when it was used along with anti-TB treatment¹⁵. In the same years, among non-AIDS TB patients, the fatality rate remained at 5%¹⁵. As observed by Lawn et al.¹⁶, to reduce mortality among AIDS patients, early diagnosis and ARV treatment must be improved, because mortality is associated with low CD4 cell count, less than 50 cells/ μ l, and an advanced stage of the disease. In Rio de Janeiro, Brazil, the proportion of AIDS patients with tuberculosis diagnosed annually decreased from 24.4% in 1995 to 15.2% in 1998, but from 1995 to 2004, there was no further improvement. Pacheco et al.¹⁷ pointed out that to reduce TB incidence among AIDS patients, earlier HIV/AIDS diagnosis and ART initiation is needed.

Although extra-pulmonary TB is more difficult to diagnose than pulmonary TB, in Campinas, their fatality rates were not significantly different among new and retreatment cases, and among non-AIDS TB and TB-AIDS cases. Since clinical presentation does not contribute to differences in fatality rates, it may be observed that once extra-pulmonary presentations are diagnosed, they are adequately treated.

In essence, treating patients with a previous history of TB might be more difficult than treating new cases, because of immunologic deficiencies among relapse patients, resistance to adherence among dropouts, or multidrug resistance among failures. Nevertheless, in Campinas, a significant reduction in fatality rates among patients with previous dropout ($p < 0.014$) was observed. This data points to better management of retreatment patients, with a provable improvement in the quality of management, resulting in higher adherence to treatment.

Most conditions related to higher TB incidence and TB fatality are poor living conditions, being homeless, unhealthy lifestyle (smoking and alcoholism)¹, all of which are in some degree related to poor schooling^{18,19}. Health Education is an important issue in the management of TB. It has been observed that people that have a general knowledge about TB have better care-seeking behavior and understand the need of daily and prolonged treatment²⁰, having higher adherence to treatment. In Rio de Janeiro, in populations living in slums, it was observed that when community health workers were engaged in Directly Observed Treatment Short-courses (DOTS), the patients adherence to treatment was higher²¹. These professionals are able to communicate with efficiency among poor people, reducing social inequalities in health.

Interrupting treatment during the intensive phase has been associated with increased risk of death²², and it represents lack of adherence. In Campinas, as in all of Brazil, DOTS is considered to be present when 24 doses are supervised in the first 60 days of treatment²³. This lower number of supervised doses might be a point to be improved in order to reduce morbidity and mortality. In Rio de Janeiro, patients' engagement in DOTS conducted by community health workers resulted in higher cure rates and lower fatality, when compared to self-administered therapy²¹.

Some limitations of this manuscript, with secondary data, include lack of information to track dropouts and transfers. As such, our fatality rates may be underreported. Also, the lack of information from DOTS at an individual level impairs the possibility of evaluating the importance of this factor. In TB-AIDS cases, the lack of clinical severity variables, such as CD4 cell count, is a barrier in understanding the degree in which it contributes to fatality rates.

CONCLUSION

Although the absolute number of cases, mainly those with a pulmonary presentation and with TB-AIDS, decreased in Campinas, non-AIDS TB and TB-AIDS fatality rates have not diminished, except for previous dropouts, which remain much higher than in other countries or cities reported in this paper. Epidemiological surveillance has an important role in evaluating the adequate registration of the compulsory notification form and in monitoring TB cases reported in a municipality.

Considering that TB is curable, and thus deaths from this disease are avoidable, the quality of the diagnosis process — treatment initiation and adequate quality of treatment, including direct supervision according to the terms defined by the WHO and patient follow-up — must be constantly revised in order to decrease fatality rates in Campinas.

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