Tuberculosis in the twentieth century: time-series mortality in São Paulo, Brazil, 1900-97

A tuberculose através do século: séries temporais para a mortalidade em São Paulo, Brasil, 1900-97

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Abstract *The objective of this study was to characterize tuberculosis mortality trends in the Municipality of São Paulo, Brazil, from 1900 to 1997. Standardized tuberculosis mortality rates and proportional mortality ratios were calculated and stratified by gender and age group based on data provided by government agencies. These measures were submitted to time-series analysis. We verified distinct trends: high mortality and a stationary trend from 1900 to 1945, a heavy reduction in mortality (7.41% per year) from 1945 to 1985, and a resumption of increased mortality (4.08% per year) from 1985 to 1995. In 1996 and 1997 we observed a drop in tuberculosis mortality rates, which may be indicating a new downward trend for the disease. The period from 1945 to 1985 witnessed a real reduction in tuberculosis, brought about by social improvements, the introduction of therapeutic resources, and expansion of health services. Recrudescence of tuberculosis mortality from 1985 to 1995 may reflect the increasing prevalence of* Mycobacterium *and HIV co-infection, besides loss of quality in specific health programs.*
Key words *Tuberculosis; Mortality; Time Series; Epidemiology*

Resumo *Com o objetivo de caracterizar tendências da mortalidade por tuberculose no Município de São Paulo, Brasil, 1900-1997, foram calculados e estratificados por gênero e grupo etário os coeficientes padronizados de mortalidade e as razões de mortalidade proporcional, por intermédio de dados providos por agências governamentais. Esxas medidas foram ainda submetidas à análise de séries temporais. Foram verificadas diferentes tendências: de 1900 a 1945, alta mortalidade e tendência estacionária; de 1945 a 1985, forte redução na mortalidade (7,41% por ano); e de 1985 a 1995, retomada do crescimento da mortalidade (4,08% por ano). Em 1996 e 1997, a redução observada nos coeficientes de mortalidade pode estar indicando um novo perfil descendente para a enfermidade. Os anos de 1945 a 1985 marcaram período de acentuada queda para a tuberculose, produzida por melhorias sociais, pela introdução de recursos terapêuticos e pela ampliação da cobertura dos serviços de saúde. O recrudescimento da tuberculose, de 1985 a 1995, pode estar refletindo a crescente prevalência da co-infecção por* Mycobacterium *e por HIV, além da virtual perda de qualidade em programas específicos de controle da endemia.*
Palavras-chave *Tuberculose; Mortalidade; Séries de Tempo; Epidemiologia*

Introduction

"Brazilians are spitting less, I would say. As for our women, they don't even spit at all. However, in the days of cutaway coats and corsets, people in the city expectorated much more. I remember the old bronchitis, the coughing of long ago, the nostalgic asthma. In Belle Époque drawing rooms there was an obligatory ornamental figure – the porcelain spittoon decorated with flowers in relief (and colored petals)" (Rodrigues, 1995:17).

The quote emphasizes an almost forgotten cultural aspect of the ubiquitous presence of tuberculosis in the larger Brazilian towns in the early 20th century. The presence of spittoons in public places harks to a time when the risk of contagion was so great that everyone worried about the transmission of bacilli through freely eliminated sputum. Furthermore, the chronicler reflects the great change in the profile of urban dissemination of tuberculosis in Brazil, with a heavy reduction of indicators for the disease from the mid-century onward, as confirmed by the mortality rates calculated in the present study.

Since the early 1980s the increased dissemination of tuberculosis, especially in Asia and Africa, led the World Health Organization (WHO, 1993) to declare the disease a global emergency. Folley & Miller (1993) stated that the white plague was on the rise and were the first to record its association with AIDS in Europe. In the United States, since 1989, the Advisory Committee for the Elimination of Tuberculosis has recommended that HIV-infected individuals be screened for tuberculosis and latent tuberculosis infection. In addition, individuals with tuberculosis or a positive tuberculin skin test should be evaluated for HIV infection to allow for appropriate counseling and treatment (CDC, 1993). At present, as deaths from tuberculosis continues to increase worldwide, the WHO (1996, 1997) has emphasized the importance of local studies and measures in the global fight against the disease. However, in most developing countries there are no studies drawing on available data to evaluate the disease's magnitude.

São Paulo was the first city in Latin America to develop an industrial base, subsidized by the State's affluent coffee-growing market. Concentration on single cash-crop agriculture fueled urban growth: people were forced to move to the cities to survive, since foodstuffs were no longer produced on the farms. Booming industry and trade attracted two major migratory waves to the cities in search of better living conditions. Europeans and Asians made up the first wave, from the late 19th century to the mid-1930s; the second wave, after the late 1920s, brought people from poorer areas of the country, mainly the Northeast. Civil registries and censuses from these periods recorded such demographic shifts in a reasonably regular and reliable manner. Moreover, these data files have not yet been sufficiently explored for public health studies.

We contend that the data generated by recording and interpreting demographic trends associated with tuberculosis can help control the disease and its recent recrudescence in Brazil. We are confident that such information can also help prevent the revival of the social fears that used to be associated with the use of spittoons in large Brazilian cities.

The purpose of this study was to characterize trends in tuberculosis mortality in order to reconstitute the history of the disease in the municipality of São Paulo, Brazil, for the period from 1900 to 1997. Another objective was to highlight the usefulness of applying time-series methodology to relevant measures in the health field.

Methods and data sources

a) Data sources

We surveyed the General Population Censuses from 1890, 1900, 1920, 1940, 1950, 1960, 1970, 1980, and 1991, published by the Brazilian Institute of Geography and Statistics (IBGE), as well as the 1934 São Paulo State Census and the 1996 Population Count. Based on these data, we estimated the population of the municipality of São Paulo year by year, adjusted to the middle of each period (July 1), in order to calculate the relevant population rates. Mortality data were collected from the Statistical Yearbooks. However, due to the irregular publication of this information, we were forced to retrieve original registers kept on file at the São Paulo State Data Analysis and Statistics System.

When working with civil registries, a critical examination of sources is necessary, since several types of errors can be associated as factors in mortality statistics in the study period.

First, different levels of medical training and scientific knowledge were available at each time for diagnostic clarification of causes of death recorded on death certificates. In addition, there is a different risk of under-reporting due to deficiencies in recording the available data for each period. To deal with both sources of error, Mascarenhas (1949a, 1949b, 1950) proposed using the proportion of deaths due to ill-defined causes as an indicator of quality in the death registration service. Observation of this indicator's temporal evolution suggests three different consecutive periods. The first, from 1900 to 1930, with higher proportions, showed a mean ratio close to 6%, with higher values at times, reaching 10% for the first years of the century. The second, from 1930 to 1960, showed a sharp drop in this indicator, with a mean of about 0.7%. In contrast, the third period, from 1960 onward, indicated a slight rise in the mean parameter to about 2%, with lower values for the more recent period.

Second, the occurrence of a sharp "mortality invasion" is posited, whereby the State Capital, with its greater supply of medical care facilities, attracted tuberculosis patients from nearby municipalities. As a quantitative indication of this "mortality invasion", Nussenzveig & Certain (1953) observed that 11.62% of deaths from tuberculosis in the municipality of São Paulo in 1946 were non-residents. This ratio was estimated at 11.27% in 1947 and 10.14% in 1948. However, beginning in the 1970s this source of error became irrelevant, since the system began recording deaths by place of residence.

Third, population growth in the city was not progressive during the inter-census periods, as one would be led to believe by the population estimates employed for analysis, since large neighboring townships were either incorporated into the city over the course of the years, (e.g., Santo Amaro in 1934) or split off (e.g., Osasco in 1958).

Despite the above provisos, this study attempts to systematically arrange existing data while it is still available, emphasizing the effort made each year to gather it and keeping in mind that the natural deterioration of printed matter may prevent further similar surveys in the near future. The study is thus based on the premise that despite the above-mentioned limitations, existing data help identify general trends in the study measures. Moreover, records kept in the past allow for a dialogue with the specialized literature devoted to this topic over the course of this century.

b) Methods

The time-series for pulmonary tuberculosis mortality rates and ratios were delineated, as were the time-series for extrapulmonary tuberculosis mortality rates. Mortality rates were stratified by both gender and four age groups (under 5 years, 5-19 years, 20-49 years, and 50 years or older) in order to better characterize the disease's epidemiological profile. Mortality rates and ratios were calculated and standardized by conventional biostatistical methods, as described by Daniel (1995) and Zar (1996). Individuals aged 5 to 19 years were not highlighted in this study because of their heterogeneous death profile, with low measures for the group aged 5 to 14 years and intermediately high values for individuals aged 15 to 19 years.

Statistical processing of time-series was performed using the SPSS 8.0–1997 software. Measurements were first plotted for a visual determination of their time behavior and then log transformed to reduce the heteroscedasticity (non-uniform pattern of variation) present in the original series. For local determination of the stationary, increasing, or decreasing trend of the measures we performed generalized least squares regression analysis. We also delineated the correlogram of the time-series studied, which both confirmed its structural trend and helped to determine the intensity of the autoregressive movement present in each sequence.

To estimate the regression parameters with control of first-order autocorrelation, we used the Cochrane-Orcutt procedure, according to the methodology described by Johnston (1991). For configuration of the time-series models with control of higher order autocorrelation, we used generalized least squares regression analysis, as described by Hamilton (1994). For the tuberculosis death rate forecast we used the method of Box and Jenkins, Autoregressive Integrated Moving Average – ARIMA (1,1,1) model – as described by several authors, such as Hamilton (1994), Gaynor & Kirkpatrick (1994), and Harvey (1993).

Selection of models and their fit to each time-series analyzed were based on the need to filter the strong autocorrelation observed in the original sequences, a peculiarity common to diverse magnitudes of social order. The Kendall-Stuart (Johnston, 1991) and Goldfeld-Quandt (Chow, 1983; Johnston, 1991) tests were applied for control purposes and for the dimensioning of heteroscedasticity in the distribution of regression residues. The Kolmogorov-Smirnov goodness-of-fit test (Daniel, 1995) was applied to evaluate the normality of this distribution, and the Durbin-Watson indicator (Gaynor & Kirkpatrick, 1994; Frees, 1996) to test the values' autocorrelation.

Results

Tuberculosis mortality followed three reasonably uniform patterns over the course of the century in the municipality of São Paulo: excessively high mortality and a stationary trend between 1900 and 1945, a marked decline of 7.41% per year from 1945 to 1985, and a strong inflection of this tendency between 1985 and 1995, with an exponential growth of 4.08% per year. In the last two years (1996 and 1997), the observed decline in tuberculosis mortality rates may indicate a new downward trend for the disease in the city.

Figure 1 shows the time-series for all forms of tuberculosis mortality rates (in decimal and log linear scales) in the municipality of São Paulo from 1900 to 1997, after standardization of the age distribution recorded in the 1996 Population Count. Figure 1 also shows the trend forecast for 1998-2002 (*ex ante* forecast) and the trend forecast before the reverse of the decreasing trend in the mid-century (1986-97 *ex post* forecast) obtained by ARIMA in an effort to visually emphasize the excess tuberculosis mortality in recent years.

Tables 1 and 2 show the estimates of generalized least squares regression analysis for the time-series delineated, before and after log transformation of original values for each period shown by the partial trends indicated.

Forecast analysis of standardized tuberculosis mortality rates was performed by diagnosis of an ARIMA (1,1,1) model, whose estimates and closeness-of-fit indicators are shown in Table 3. Reliability of prognosis can also be verified on the basis of forecasts made for the *ex post* period (Table 4). As indicated by visual inspection of the time-series, one may state, relying upon the computed forecasts, that tuberculosis mortality will acquire a new profile of declining rates (-4.07% per year) or at least stabilize in the immediate future, although at a significantly higher level than in the early 1980s.

The percent analysis of pulmonary tuberculosis (in proportion to all forms of tuberculosis) shows a slightly downward overall trend throughout the century, with a ratio of early decrease reaching -5.870 x 10-2% (90% CI: -0.117% to -2.026 x 10-4%). All registers oscillated closely around the mean value of 85.940% (95% CI: 84.644% to 87.236%). This very slightly downward trend may be ascribed to the progressive development of diagnostic resources, fostering the detection of a larger number of cases, mainly at extrapulmonary sites.

Figure 2 shows the time-series for the proportional mortality ratio due to pulmonary tuberculosis, stratified by age group. Figure 3 shows the shifting age structure of pulmonary tuberculosis deaths in São Paulo throughout the century.

Visual inspection of the trends highlights the increasing participation of the oldest age group in tuberculosis deaths after the 1930s. In contrast, the 20-49-year age group only decreased until the early 1980s, when it rebounded to an increasing share in tuberculosis deaths. As for the youngest age group, graphic display indicates increasing shares in the 1950s and 60s, with a later decrease. We also verified a suggestive acceleration of the descending trend in mortality for this age group, a fact that may be interpreted as a favorable indicator of intradermal BCG vaccination. From 1964 to 1976, the ratio of yearly decrease reached -9.463% (95% CI: -16.912/-1.346), while during the following period, from 1976 to 1985, it was -18.159% (95% CI: -20.423/-15.831).

Figures 4a and 4b show age-specific pulmonary tuberculosis mortality rates for selected years: 1935, 1945, 1955, 1965, 1975, 1985, and 1995. The graph illustrates the high social cost of tuberculosis mortality, since rates for the adult age group remained almost as high as those for elderly people over time. It should also be emphasized that in 1995, rates for the 20-49-year age group were greater than those recorded in 1985, once again reflecting the impact of HIV co-infection.

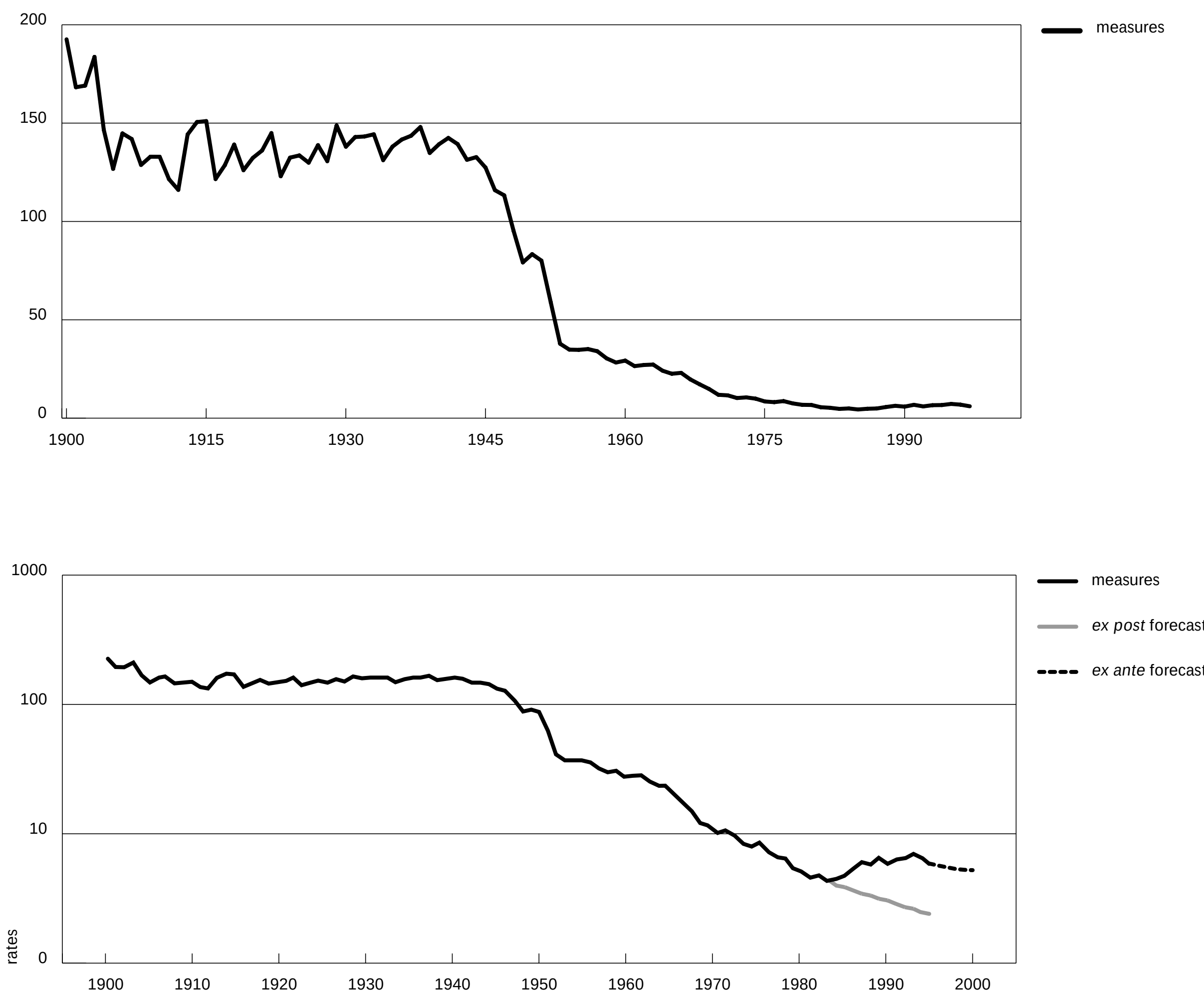
Finally, Table 5 shows the time-series analysis for pulmonary tuberculosis mortality rates, with measures stratified by gender and age group to elucidate the disease's epidemiological profile. For each period, gender, and age group, the table indicates the ratios of yearly increase or decrease in tuberculosis mortality, as estimated by the Cochrane-Orcutt procedure of generalized least squares regression analysis. It also states in table form the mean, minimum and maximum values for each time-series segment.

Discussion

Log transformation of original measures is a conventional tool used to reduce heteroscedasticity in the decimal linear scaled series, as shown in the upper right in Figure 1 (the former period, with higher values, also displays greater variance in the measure). Besides, using this data transformation, one can easily deduce ratios of yearly increase or decrease for

Figure 1

Time-series for standardized tuberculosis mortality rate (all forms, log scale, per 100,000 inhabitants) in São Paulo, Brazil: 1900-97, ARIMA (0,1,1)-ex *post* rate forecast (1986-97) and ARIMA (1,1,1) *ex ante* rate forecast (1998-2002). At top, measures in a linear scale (1900-97).



the respective mortality values, as presented in Tables 2 and 5. Log transformation also improves visual characterization of the stationary trend of values throughout the former period (1900-45). As for the period with a downward trend, from 1945 to 1985, which appeared to be divided into two linear stages (1945-53, with a major decrease, and 1954-85, with less marked reduction of values), log transformation shows that this is a model of exponential decrease with remarkably better indicators of goodness-of-fit to the generalized least squares regression analysis. Finally, for 1985 to 1995, log transformation improves visual characterization of the local trend of a strong and exponential increase in the rates.

Analysis of data in Tables 1 and 2 enhances the historical characterization of the disease's magnitude in the city and fosters an interesting discussion with medical researchers who studied this subject in the past. Initial emphasis should be placed on the fact that the apparent reduction of indicators in the first two decades of this century, defined by Mascarenhas (1953) as a trend towards "intense decline", is not supported by the application of contemporary time-series analytical techniques. In particular, delineation of the sequence correlo-

Table 1

Time-series analysis for standardized tuberculosis mortality rates (all forms, linear scale, per 100,000 inhabitants) in São Paulo, Brazil, 1900-97. Generalized least squares regression estimates.

Period Trend	**1900-20** stationary	**1921-45** stationary	**1900-45** stationary	**1945-53** decrease	**1953-85** decrease	**1985-97** increase
b_1 (year-1900)	-1.256	0.040	-0.121	-10.239	-0.832	0.238
standard error b_1	0.900	0.224	0.231	1.250	0.209	0.039
p b_1	p = 0.181	p = 0.860	p = 0.603	p < 0.001	p < 0.001	p < 0.001
b_0 (intercept)	152.296	136.135	140.289	589.801	73.570	-15.464
standard error b_0	11.326	7.683	6.273	61.917	16.152	3.540
p b_0	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.01
R^2	0.103	0.002	0.007	0.818	0.354	0.841
R^2 adjusted	-0.003	-0.094	-0.041	0.801	0.309	0.795
F	1.449	13.907	11.469	65.443	184.851	86.241
Standard error	13.727	7.062	10.485	8.098	1.307	0.401
Durbin-Watson	1.611	1.915	1.714	1.632	1.887	1.847

Table 2

Time-series for standardized tuberculosis mortality rates (all forms, natural log scale, per 100,000 inhabitants), São Paulo, Brazil, 1900-97, and ARIMA (1,1,1) *ex ante* forecast, 1998-2002. Ratios of yearly increase (percentage) and 95% confidence intervals were estimated by the Cochrane-Orcutt regression analysis procedure, with mean, maximum, and minimum rates (decimal linear scale) for each period.

Period Trend	**1900–1945** stationary	**1945–1985** decrease	**1985–1995** increase	**1995–2002*** decrease
b_1 (year-1900)	$7.722x10^{-4}$	$-7.703x10^{-2}$	$3.994x10^{-2}$	$-4.152x10^{-2}$
standard error b_1	$1.600x10^{-3}$	$5.446x10^{-3}$	$8.094x10^{-3}$	$7.857x10^{-3}$
p b_1	p=0.632	p<0.001	p<0.01	p<0.01
b_0 (intercept)	4.939	8.004	-1.819	5.888
standard error b_0	$4.348x10^{-2}$	$3.789x10^{-1}$	$7.332x10^{-1}$	$7.742x10^{-1}$
p b_0	p<0.001	p<0.001	p<0.05	p<0.01
Ratio of early increase	+0.077%	-7.414%	+4.075%	-4.067%
95% confidence interval	-0.245/+0.400	-8.429/-6.388	+2.187/+5.998	-5.894/-2.205
Mean	139.896	32.808	5.920	6.037
Maximum and minimum	192.59/116.05	127.36/4.42	7.23/4.42	7.23/5.36
R^2	$5.516x10^{-3}$	0.844	0.777	0.848
R^2 adjusted	$-4.184x10^{-3}$	0.835	0.713	0.787
F	11.779	321.042	77.754	46.940
standard error	$7.440x10^{-2}$	$9.670x10^{-2}$	$8.094x10^{-2}$	$3.872x10^{-2}$
Durbin-Watson	1.747	1.567	1.826	1.391

* Prais-Winsten estimates.

Table 3

ARIMA (1,1,1) estimates and closeness of fit indicators for standardized tuberculosis mortality rates (all forms, log scale, per 100,000 inhabitants) in São Paulo, Brazil, 1900-97.

	Estimate	Standard Error	t	p
autoregressive term	$8.881x10^{-1}$	$1.511x10^{-2}$	5.878	p < 0.001
moving average term	$7.887x10^{-1}$	$2.022x10^{-2}$	3.899	p < 0.001
constant	$-1.440x10^{-2}$	$8.295x10^{-3}$	-1.736	p < 0.1
residual mean	$4.740x10^{-4}$	$1.055x10^{-2}$	$4.494x10^{-2}$	p > 0.45
R^2		> 0.999		
Box-Pierce lags 6, 12, 18, 24		p > 0.17		
Ljung-Box lags 6, 12, 18, 24		p > 0.12		
Akaike information criterion		-322.719		
Schwartz Bayesian criterion		-314.994		
mean absolute percent error		5.534%		
log likelihood		164,359		
standard error		$4.512x10^{-2}$		

Table 4

Forecast evaluation for standardized tuberculosis mortality rates (all forms, linear scale, per 100,000 inhabitants) by the ARIMA (1,1,1) model, in São Paulo, Brazil, 1993-97 and 1998-2002.

Period	Forecast tuberculosis mortality rates	Confidence interval (95%)	Measured tuberculosis mortality rates	Absolute percentage error
Ex Post 1993	5.673	4.611-6.979	6.587	13,88%
1994	6.367	5.175-7.833	6.656	4,34%
1995	6.512	5.293-8.012	7.233	9,97%
1996	7.186	5.841-8.841	6.862	4,72%
1997	6.817	5.541-8.387	6.036	12,94%
Ex Ante 1998	5,911	4.805-7.272		
1999	5,781	4.244-7.874		
2000	5,647	3.796-8.400		
2001	5,511	3.414-8,897		
2002	5,373	3.078-9.379		

gram and the generalized least squares regression analysis (p = 0.181) suggest the indicator's stationary nature. On this basis, the explanatory power of the hypothesis mentioned by this author to explain the virtual decrease of tuberculosis mortality during that period is reduced. According to this researcher, the increasing supply of medical professionals in the city of São Paulo probably accounted for the more accurate diagnosis of the disease, with a consequent reduction in "occasional diagnoses", i.e., cases previously classified as tuberculosis were reallocated to the mortality rates from indeterminate causes.

The precariousness of this hypothesis has been pointed out by Almeida (1990), who deduced it from the social characterization of the period, but without justifying it from a statistical perspective. Indeed, the source of this error was the application of ordinary least squares regression analysis to an autocorrelated time-series segment (Durbin-Watson = 0.928).

Figure 2

Time-series for proportional tuberculosis mortality ratio (pulmonary form, log scale, per 100 deaths in the same age group), stratified by age group, in São Paulo, Brazil: 1900-97.

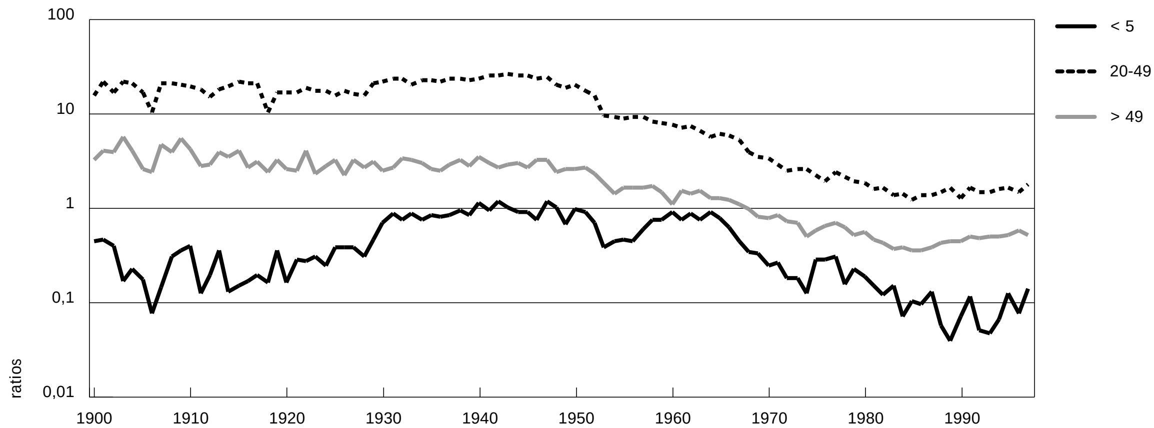
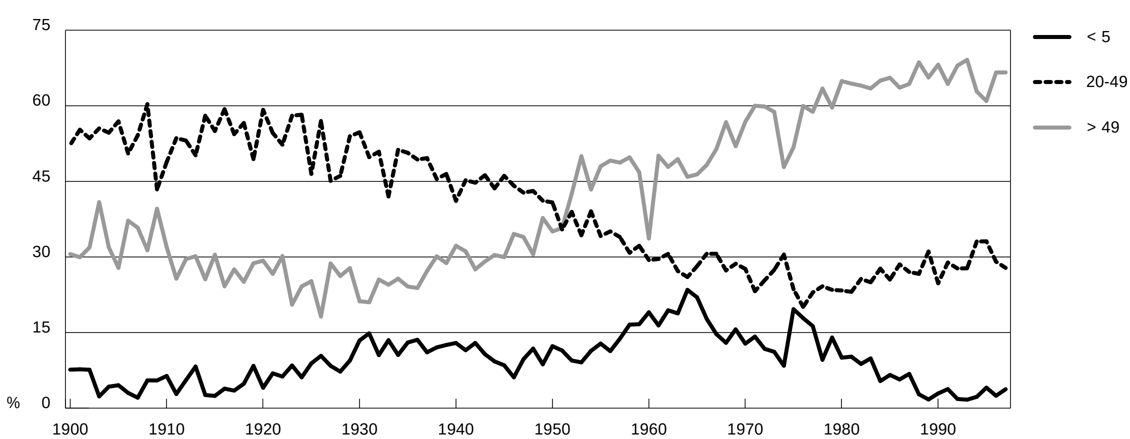


Figure 3

Shifting age structure of tuberculosis deaths (pulmonary form) in São Paulo, Brazil: 1900-97.



With regard to the 1920-1945 period, as well as the overall 1900-1945 period, the time-series showed a stationary trend, supporting the "stability of the epidemic" hypothesis proposed by Nussenzveig & Certain (1953), who observed that the disease persisted at a considerably high level.

Throughout this initial period, the city received an intense flow of immigrants consisting of Europeans and Asians attracted by the expansion of coffee-growing in the interior and the city's early industrialization. Morse (1970) points out that half the foreigners returned to their home countries after some time. Thus, the migratory process was peculiarly heterogeneous, with more affluent population contingents being replaced by less privileged ones, since arriving immigrants needed financial backing for the trip, while those who returned home did so at their own expense. This had a

Figure 4a

Age-specific tuberculosis mortality rates (pulmonary form), São Paulo, Brazil, for selected years (1935, 1945, 1955 and 1965).

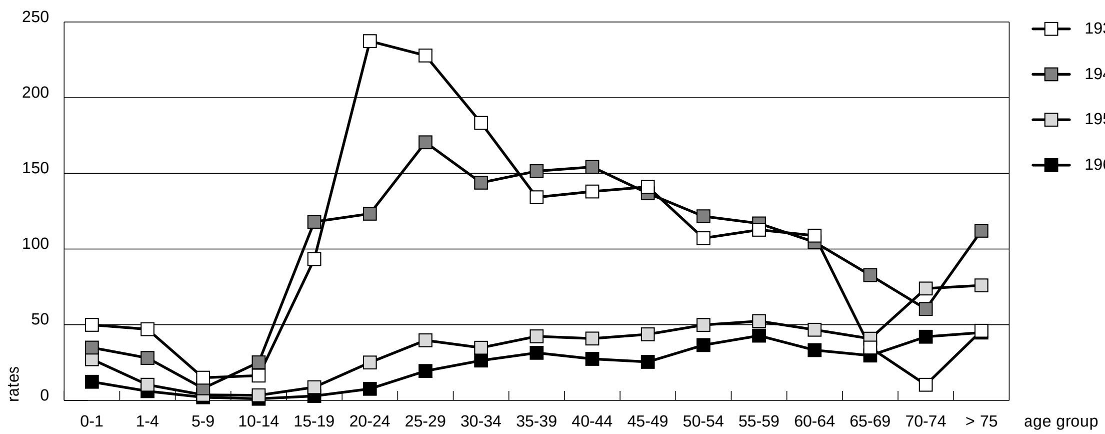
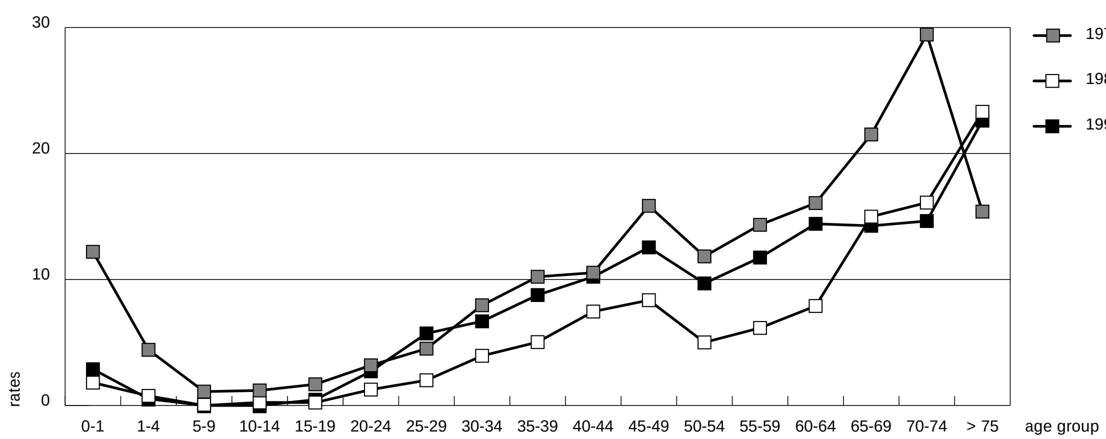


Figure 4b

Age-specific tuberculosis mortality rates (pulmonary form), São Paulo, Brazil, for selected years (1975, 1985 and 1995).



definite impact on the persistently high mortality rates throughout the first half of the century (Antunes, 1998).

However, beginning in the mid-1930s this process was virtually interrupted when government subsidized immigration stopped. With the international financial crisis following the crash on the New York stock exchange, coffee prices plummeted at a time when Brazil already had huge coffee bean reserves to regulate prices. Still, the population flow into the city of São Paulo continued, especially with the arrival of contingents from the Northeast, driven off the land by drought and dire living conditions.

The relevance of this rural exodus for maintaining high tuberculosis rates in the city of São Paulo was also the subject of some controversy among scholars at the time. In a comparative analysis of counties from the interior of the State receiving migrants and others that did

Table 5

Time-series for tuberculosis mortality rates (pulmonary form, per 100,000 inhabitants) stratified by gender and age group, São Paulo, Brazil, 1900-97. Ratios of yearly increase (percentage) and 95% confidence intervals were estimated by the Cochrane-Orcutt regression analysis procedure for each period.

Age group	Period	Females	Males	Total
under 5 years old				
	1900-42	+3.693%	+4.136%	+4.060%
		+2.059 / +5.352	+2.437 / +5.863	+2.363 / +5.785
	1942-53	-10.613%	-6.582%	-8.224%
		-18.328 / -2.169	-13.677 / +1.096	-14.844 / -1.089
	1953-64	+5.805%	+4.526%	+5.162%
		+3.016 / +8.670	+2.468 / +6.625	+3.523 / +6.827
	1964-85	-11.320%	-11.636%	-11.393%
		-13.846 / -8.720	-14.883 / -8.264	-14.248 / -8.442
	1985-97	Stationary trend	-10.467%	Stationary trend
			-14.240 / -2.197	
20 to 49 years old				
	1900-46	Stationary trend	Stationary trend	Stationary trend
	1946-85	-9.189%	-8.260%	-8.294%
		-10.040 / -8.331	-9.396 / -7.111	-9.352 / -7.224
	1985-95	+5.835%	+5.148%	+4.686%
		+1.323 / +11.863	+3.219 / +7.113	+2.848 / +6.557
50 or more years old				
	1900-46	-0.768%	Stationary trend	Stationary trend
		-1.455 / -0.076		
	1946-85	-6.054%	-5.599%	-5.717%
		-6.401 / -5.706	-6.384 / -4.843	-6.343 / -5.087
	1985-97	+7.462%	+2.083%	+2.708%
		+2.196 / +13.000	+0.775 / +3.407	+1.301 / +4.134

not, Mascarenhas (1949a, 1949b,1950) showed that domestic migration was not related to the evolution of mortality due to tuberculosis. Almeida (1990), however, pointed out that even without importing new infectious foci, migrants were more susceptible to tuberculosis, since most of them came from rural areas, and even in the city they faced severe food and housing problems and unhealthy working conditions. Thus, each new wave of migrants contributed to the overall mortality, maintaining the stability of the tuberculosis curve at a high level.

A sharp decline in tuberculosis mortality occurred from 1945 to 1985 (-7.41% per year). This trend partly reflects the overall drop in mortality in the city of São Paulo resulting from the demographic transition phenomenon. However, it also indicates the disease's reduced case fatality, resulting from the introduction of preventive and therapeutic measures. Authors agree in ascribing this trend mainly to the effect of streptomycin use in clinical practice, but the creation of medical and social care facilities also played a role in the city's declining tuberculosis rates. Another possible factor in this reduction was reported by Sant'Anna & Bethlem (1988): by the middle of the century, extension of milk pasteurization had virtually eliminated *Mycobacterium bovis* transmission to humans in cities (a problem emphasized by bacteriologists since the beginning of the century) (Antunes et al., 1992).

The highly uniform trend towards an exponential decline throughout this period can be appreciated based on the high indicator of goodness-of-fit in the regression analysis for the log transformed series (R^2 adjusted = 0.835; F = 321.042). However, this contrasted with the graphic and analytical arrangement of the time-series on a decimal linear scale, which suggested a division of this period into two stages, 1945-1953 and 1954-1985, the former showing a much more marked downward trend than the latter. Interestingly, this interpretation, proposed by Almeida (1990), allows one to associate the period of highest decline in mortality with that immediately following the adoption of streptomycin in clinical practice in 1947 (Wünsch-Filho, 1985). Still, this is not the most satisfactory model, since it yields two time-series segments with worse indicators of goodness-of-fit for generalized least squares regression analysis (Tables 1 and 2).

In contrast, during the period from 1985 to 1995, there was a marked upward trend in the series, a factor partly attributable to the association of tuberculosis with HIV. However, new studies are needed to quantify this association as to the possible reduced effectiveness of therapeutic and preventive resources for tuberculosis in Brazil. This concern is shared by Surdre (1992), highlighting the global magnitude of tuberculosis as reflecting the inadequacy of tuberculosis control programs worldwide.

Dolin (1994) proposes a ratio of 10% for both morbidity and mortality due to tuberculosis associated with AIDS worldwide. He also states that by the year 2000, HIV-attributable cases of tuberculosis will account for almost 15% of all tuberculosis deaths. In a preliminary estimate, Ruffino-Netto (1995) quotes an even higher figure, i.e., that 17.7% of tuberculosis morbidity in Brazil in 1992 involved HIV-attributable cases. Such figures become even more striking when one considers the persuasive evidence reported by Murray (1997), that in the presence of HIV infection, recent tuberculosis infection will progress rapidly to clinically significant disease. According to the same author, the probability of reactivation of latent tuberculosis infection in such cases increases enormously. He also points out that the accelerating and expanding influence of HIV infection also contributes to the increasing incidence of disease involving multidrug-resistant strains of *Mycobacterium tuberculosis*.

Such researchers as Guimarães (1978) and Wünsch-Filho (1985) ascribe the strong decline in tuberculosis mortality mainly to the disease's reduced case fatality, resulting from new therapeutic and social assistance resources. Thus, the study of mortality would be of less interest after this period, indicating only the effectiveness of the programs directed against the disease. Nevertheless, these same investigators did not take into account precisely the analysis of this more recent period, which appears to renew interest in the study of tuberculosis mortality in various cities and countries, where the emergence of AIDS radically altered the disease's overall epidemiological profile (Bernardo, 1991; Brawn et al., 1993; Raviglione et al., 1993; Watson et al., 1993; Dolin et al., 1994; Liard et al., 1994; WHO, 1996).

A forecast analysis of standardized tuberculosis mortality rates using an ARIMA (1,1,1) model indicated a virtual downward trend from 1995 to 2002 (-4.07% per year). This hypothesis also includes stabilization of rates at a higher level than in the early 1980s. In fact, both possibilities hinge on a drop in tuberculosis mortality rates for 1996 and 1997 and may be interpreted as compatible with the sharp decrease in AIDS deaths in São Paulo since 1995, as reported by Waldvogel & Morais (1998).

The present study appears to support Reichman's proposal of a U-shaped curve describing the history of tuberculosis in the 20th century (Reichman, 1991). However, the prediction and early quantification of the upward trend in tuberculosis in Brazil may help to reverse the latest stage in this U-shaped curve, requiring a decisive revitalization of tuberculosis control programs.

Visual inspection of the time-series related to the pulmonary tuberculosis proportional mortality ratio, stratified by age group (Figure 2), supports the conviction that children under 5 years of age suffered the highest rise in tuberculosis mortality over time, a phenomenon that persisted until the mid-1960s. This may be explained by the increasing ability of health care facilities to detect the disease in this age group, although the observed trend in proportional tuberculosis mortality ratios may only be reflecting variations in deaths due to other causes.

A graph of this time-series shows that the period of declining tuberculosis rates in children under 5 years began long before the widespread administration of intradermal BCG vaccine to infants from 1976 to 1979 in the city of São Paulo (Wünsch-Filho, 1985). However, as indicated, ratios of the annual drop in mortality rates for this age group were greatly accelerated from 1964-76 to 1976-85. After 1985, rates recorded for the under-5 age group remained stable, although with a high variance in the measures, which may reflect the small number of pulmonary tuberculosis deaths in this age group. Despite this last observation, the accelerating downward trend should be considered a favorable indicator of intradermal BCG vaccination and its impact on tuberculosis mortality in this age group.

In the remaining age groups there was a decline in proportional mortality rates beginning in the 1950s, with a less marked trend than for those recorded in the time-series for mortality rates. The decrease in tuberculosis mortality during this period thus appears to have accompanied, at least in part, the decline in overall mortality, a factor ascribed to the demographic transition occurring during the same period in the city of São Paulo.

Several comments are at hand on the study of time-series related to tuberculosis mortality rates, stratified by gender and age group, as quantified in Table 5. The general feature of the time-series for overall rates is maintained in almost all the new series. The downward trend in the intermediate period was more marked for the 20-49-year age group than for the over-50 group for both sexes, as noted previously by Vranjac (1980), using other graphic devices. Reporting of tuberculosis deaths remained higher for males in the adult and older age groups, and to a lesser extent among children under 5 years. This observation may be tempered by studies reporting greater under-reporting of the disease among females (Connolly & Nunn, 1996), although there are no such observations on record for Brazil.

Women aged 20 to 49 years experienced a sharper downward trend in tuberculosis death rates than men of the same age in the intermediate period. The same was true for women over 50 years, but with a less marked contrast. Tuberculosis mortality rates were highest among people over 50 years throughout almost the entire century. In recent years this contrast has become even sharper. Thus, this is the age group most susceptible to the disease, despite having lower proportional tuberculosis mortality rates than adults aged 20 to 49 years throughout the century, as shown in Figure 2. This observation does not contradict the realization that tuberculosis mortality still remains high among adults aged 20 to 49 years, involving a high social cost, as indicated in Figures 4a and 4b.

There is still an intriguing observation about the period of decreased tuberculosis mortality in children under 5 years. From 1940 to 1953 and from 1964 to 1985, mortality rates for pulmonary tuberculosis dropped more in this age group than in others, with a regular intensity, i.e., -8.22 and -11.39% a year, respectively. However, from 1953 to 1964 this trend stopped, with a sharp inflection in the mortality curve, which began to display a local tendency towards an annual growth of +5.16%. As an additional indication of social instability during this period, these records should motivate new studies specifically focused on this phenomenon, especially to clarify its relation to the increased migratory process in the 1950s and the increase in infant mortality rates in the 1960s (Leser, 1975; Zuñiga & Monteiro, 1995).

The upward trend in tuberculosis mortality after the early 1980s was more marked for people aged 20 to 49, paralleling the trend in the Aids epidemic, an observation calling for further research on the association between tuberculosis and the Aids epidemic, the declining quality of public health programs for tuberculosis control and treatment, and the aggravation of social inequality in Brazil, as the main causes of resurgent tuberculosis mortality.

Final comments

Tuberculosis was one of the main causes of death in São Paulo throughout the first half of the 20th century, accounting for over 10% of all deaths in the city in the 1930s and 40s. In the historical health records, mortality from tuberculosis greatly exceeded that caused by typhoid fever, measles, diphtheria, and syphilis, other traditional health problems highly prevalent in the city. The high tuberculosis rates led researchers to characterize the disease as being in the "epidemic phase, in the stage of stabilization" (Nussenzveig & Certain, 1953). During the same period, the city of Rio de Janeiro displayed even more dramatic tuberculosis mortality rates, ranging from 300 to 500 annual deaths per 100,000 inhabitants (Penna, 1988).

Beginning in the mid-1940s, mortality from tuberculosis declined sharply in a relatively regular trend that lasted until the early 80s. This phenomenon resulted from the introduction of preventive and therapeutic measures, the creation of health services focused specifically on the disease, and social improvements and other factors related to the demographic and epidemiological transition in the city, which also had repercussions on overall changes in health and social development indicators (Antunes, 1998).

Since the early 1980s there has been a sharp turnaround, with tuberculosis again displaying an exponential increase in death rates. Tuberculosis is still the leading cause of death attributable to a single pathogen, and its incidence is feared to continue to increase worldwide because of the interaction between the disease and the HIV epidemic. Still, at the local level one cannot overlook either the declining quality of health programs for the treatment and control of this disease or the deepening social differences in recent years, as leading causes of the renewed expansion of tuberculosis.

Time-series analysis of epidemiological indicators has proven to be efficient in many ways: improving the use of statistical methodology in the health sciences; bypassing the difficulties inherent to the characteristics of these values (autocorrelation, heteroscedasticity, collinearity, and non-normality of forecast error distribution); integrating quantitative analysis with the historical interpretation of the study phenomena; projecting estimates of future trends in the behavior of variables; and systematizing methodology for application in future social research.

Use of time-series methodology allowed for the development of an interesting analysis of the epidemiological profile of tuberculosis in the city of São Paulo. In addition to providing a description and quantification of the upward and downward trends in the disease's social indicators, this analytical tool fostered a discussion of various hypotheses concerning the disease's behavior in each population segment studied. The present study was thus intended to encourage application of this method to other relevant social measures in collective health.

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