Impact of influenza vaccination on mortality by respiratory diseases among Brazilian elderly persons

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Abstract

Objective
Respiratory diseases, especially infectious ones, are becoming increasingly representative in the morbidity and mortality patterns of elderly persons. The aim of the present study was to analyze trends in the mortality by respiratory diseases and to observe the impact of influenza vaccination on mortality rates.

Methods
The study was carried out between 1980 and 2000. Subjects were elderly persons living in the State of São Paulo, and mortality data were obtained from the Mortality Information System of the Brazilian Ministry of Health. This is an ecological time-series study. We analyzed the time trends of standardized mortality rates by infectious diseases, according to age group (60-64, 65-69, 70-74, 75-79, and 80+ years) and sex, using polynomial regression. We estimated confidence intervals for the mean expected response in the years following the intervention.

Results
Rates increased for both sexes among the elderly population. After the intervention, we observed a declining trend with respect to mortality indicators. For older males, the mean rate in the 1980-1998 period was 5.08 deaths per thousand men, with a linear, non-constant increase of 0.13 per year; in 2000, the rate observed was 4.72 deaths per thousand men. The mean annual rate among women over 60 years was 3.18 deaths per thousand women, with a non-constant increase of 0.08 per year; in 2000, the rate observed was 2.99 deaths per thousand women. There was also a significant reduction in mortality rates in all age groups.

Conclusions
Data indicate the importance of respiratory diseases among the elderly population and suggest that specific protection against influenza has a positive effect on the prevention of mortality due to these diseases.

INTRODUCTION

Respiratory tract diseases, infectious ones especially, are an important cause of morbidity and mortality among the elderly population worldwide.[4,7,10]

In Brazil, data from the *Sistema de Informações sobre Mortalidade* (Mortality Information System) indicates the growing importance of hospital admissions and deaths due to respiratory diseases among the elderly, even considering the ageing of the population.[6] In 1995, in São Paulo State, the proportional rate of mortality due to pneumonia among persons older than 70 years was 9%, with a specific mortality of 594.03 per 100,000 population. In the 60-70 years age group, 1,676 deaths were registered, with a proportional mortality of 4.75% and a specific rate of 101.39 per 100,000 population.[6,20]

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Influenza epidemics happen more frequently during winter. Such epidemics account for a mean 20,000 yearly deaths in the United States.[21] Influenza outbreaks are associated with increases in hospital admissions and deaths, mostly due to complications of the disease and to chronic subjacent ilnesses.[2,3]

Vaccination has been the major method for preventing influenza and its more severe complications. When vaccine composition coincides with circulating viral strains, vaccine efficacy can be as high as 70-90% in healthy adults. Among persons older than 60 years, however, efficacy falls to the 30-40% range.[2,8,10]

Even considering the greater physiological and immunological susceptibility of elderly persons to infection, influenza vaccination has a positive effect on the prevention of severe influenza, pneumonia, and mortality in this risk group.[4,8-10,17]

The aim of the present study is to analyze trends in mortality by respiratory diseases among elderly persons and to observe the impact of influenza vaccination on mortality indicators.

METHODS

This is an ecological time-series study, based on the mortality records of the *Sistema de Informações sobre Mortalidade do SUS* (Mortality Information System of the Brazilian Unified Healthcare System - SIM/SUS) for São Paulo State, between the years 1980 and 2000. Estimates of the elderly population living in the State were obtained from the *Instituto Brasileiro de Geografia e Estatística* (Brazilian Institute for Geography and Statistics - IBGE).* Elderly persons were divided into five age groups: 60 to 64 years, 65 to 69 years, 70 to 74 years, 75 to 79 years, and 80 years and older.

We analyzed diagnoses referring to pneumonias and influenza (until 1997, ICD-9 classifications 480-483 and 485-487 were used), bronchitis (490 and 491) and chronic airway obstruction (496). For 1998, ICD-10 classifications were used (J10 to J15, J18, J22, J40 to J42, and J44). These classifications have been used by a number of authors attempting to measure the impact of influenza on the community.[7,17,22] We chose to include chronic obstructive pulmonary disease (COPD) in light of its intimate relationship with pulmonary infection among the elderly.[22]

We calculated standardized mortality rates using the harmonic mean of the populations in the 1980-1998 period as a standard population.[13]

We calculated the annual ratio between standardized male/female rates and evaluated changes in this relationship throughout the years using simple linear regression models. We considered p-values above 0.05 as indicative of an absence of change in this ratio within the studied period.[11]

Initially, we built scatter plots opposing mortality rates and calendar years in order to better visualize the function that might better express the relationship between these variables. Based on the functional relationship observed, we estimated polynomial regression models, which, in addition to being statistically powerful, are easy to elaborate and interpret.[12,15]

During the modeling process, we considered the rates of mortality due to selected diagnoses as the dependent variable (Y) and calendar years as the independent variable (X). The transformation of variable *year* into variable *centralized year* (year minus the midpoint of the time series) was required, since, in polynomial regression models, the terms in the equation are often self-correlated.[15]

As a measure of the model's precision, we used the coefficient of determination (r^2). We verified adherence to normal distribution using the Kolmogorov-Smirnov test; all series were normally distributed. Residual analysis confirmed the assumed homocedasticity of the model.[11,15]

We tested the simple linear regression model ($Y=\beta_0+\beta_1X$) and then second degree ($Y=\beta_0+\beta_1X+\beta_2X^2$), third degree ($Y=\beta_0+\beta_1X+\beta_2X^2+\beta_3X^3$), and exponential ($Y=e^{\beta_0+\beta_1X}$) models. In light of the statistical similarity of two of the models, we chose that of lower degree. We considered as significant trends whose estimated models obtained p-values below 0.05.[11]

In these models, β_0 is the mean yearly rate, b_1 is the linear effect coefficient (speed), and b_2 is the quadratic effect coefficient (acceleration). We considered 1989 as the midpoint of the time series.

For some of the age groups, variations in the series were smoothed using a moving average centered on three terms. In this process, the smoothed rate of year i (Y_{ai}) corresponds to the arithmetic mean of the coefficients of the previous year ($i-1$), of the year itself (i) and of the following year ($i+1$):

$$Y_{ai} = \frac{Y_{i-1}+Y_i+Y_{i+1}}{3}$$

Based upon the models we estimated using data from the 1980-98 period, we calculated confidence intervals for the mean expected response, i.e., the mortality rates referent to the two subsequent years (1999 and 2000). In addition to models and confidence intervals, we also present the rates obtained after vaccination.

We calculated mortality rates and generated graphs using Microsoft Excel (Version 7.0 for Windows 95) spreadsheets. We performed trend analyses using SAS (Statistical Analysis System) Version 8.0 software.

RESULTS

Standardized mortality rates by selected respiratory diseases increased among the population 60 years and older in São Paulo State between 1980 and 1998. This was true for both men and women (Figure 1). Among men, the mean rate in the period was 5.08 deaths per thousand men, with a linear non-constant increase of 0.13 per year. Among women, the mean annual rate was 3.18 deaths per thousand women, with a non-constant increase of 0.08 per year. The male to female standardized mortality rate ratio did not change with time (p=0.338). This ratio remained in average 1.55 men for each woman, showing the greater importance of respiratory diseases among men.

An analysis of trends in separate age groups showed that, for men and women alike (Table 1, Figure 2), the older the age group, the greater the magnitude of the annual increment.

The annual linear non-constant increase (β_1) was greater among older males. In the 75-79 years age group, this increase was as much as three times that of the female population in the same age group. In both sexes, the population 80 years and older is distinguished by
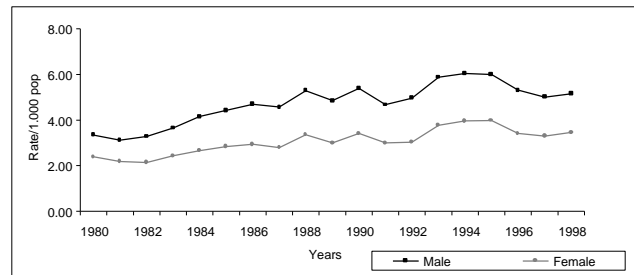
	Male	Female
Model	$Y = 5.08 + 0.13.(year - 1989) - 0.012.(year - 1989)^2$	$Y = 3.18 + 0.08.(year - 1989) - 0.004.(year - 1989)^2$
Trend	Increasing (p<0.001; r^2=0.85)	Increasing (p<0.001; r^2=0.79)

Figure 1 - Standardized mortality rates by selected respiratory diseases (‰ pop.) among the elderly population, according to sex. Sao Paulo State, 1980 to 1998.
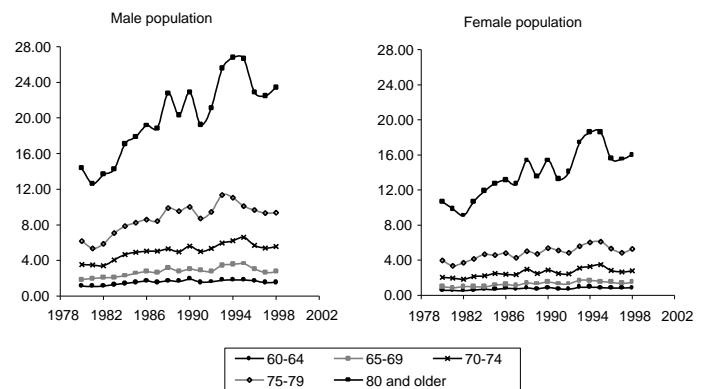

Figure 2 - Mortality rates by selected respiratory diseases (‰ pop.) among the elderly population, according to sex and age group. Sao Paulo State, 1980 to 1998.

the magnitude of the mean annual rate (β_0) (Table 1).

An analysis of mortality rates after the vaccine intervention shows that, in 1999, there was a significant reduction in these rates among women in the 70-74 years age group. In 2000, there was a steep decline in rates among men in the 70-74 and 80+ years groups, along with a significant reduction in rates among the female population in all age groups (Table 2).

For the population over 60 years as a whole, with-

Table 1 - Regression coefficients and statistical significance of trends in mortality rates by selected respiratory diseases, according to sex and age groups. São Paulo State, 1980 to 2000.

Sex	β_0	β_1	β_2	p (F)	r^2
Male					
60 a 64[a]	1.70	0.03	-0.005	<0.001	0.93
65 a 69[b]	2.96	0.08	-0.007	<0.001	0.87
70 a 74[c]	5.36	0.14	-0.011	<0.001	0.85
75 a 79[d]	9.56	0.26	-0.029	<0.001	0.95
80 and older[e]	21.29	0.68	-0.039	<0.001	0.84
Female					
60 a 64[f]	0.79	0.02	-0.001	<0.001	0.82
65 a 69[g]	1.35	0.04	-0.002	<0.001	0.76
70 a 74[h]	2.68	0.07	-0.003	<0.001	0.86
75 a 79[i]	5.05	0.10	-0.007	<0.001	0.74
80 and older[j]	14.43	0.43	-0.017	<0.001	0.78

Note: (c, e, f, g, i, j) original series; (a, b, d, h) smoothed series
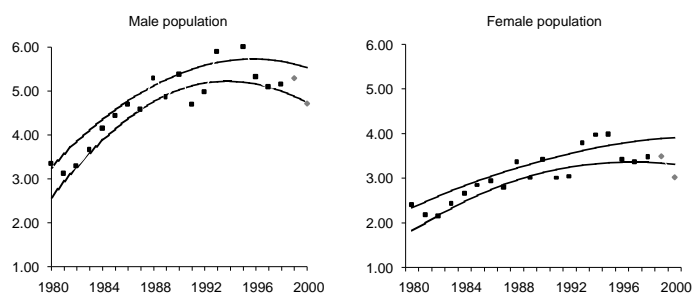
Figure 3 - Confidence intervals and standardized mortality rates by selected respiratory diseases (‰ pop.) among the elderly population, according to sex. Sao Paulo State, 1980 to 2000.

In the present study, we found that the trends in mortality by selected respiratory diseases showed a real increase between 1980 and 1998 in São Paulo State, even after controlling for the age composition in the period by using standardized rates. However, the increase in such indicators was asymmetric with respect to sex and age groups, with a greater annual increase among males and older groups. Respiratory diseases were confirmed as an important cause of death among the elderly, corroborating the findings of other authors.[6,7,19]

out distinction of age group, standardized mean mortality rates by selected respiratory diseases fell within the expected interval for both male and female populations in 1999. In 2000, however, there was a significant reduction in rates, i.e., rates fell below the lower limit of the confidence interval (Table 2, Figure 3).

Among the male population, the absence of impact of vaccination in the years following the intervention was observed only in the 60-64 years group, whereas the remaining groups showed a decreasing trend. In the female population, the decreasing trend is clearer, especially among the 70-74 and 75-79 age groups (Table 2).

DISCUSSION

Mortality information registries cover the vast majority (95%) of deaths in São Paulo State, and thus have sufficient explanatory power for the construction of satisfactorily reliable mortality indicators.[18]

Ecological studies of time series are capable of showing the evolution of disease rates in a given geographically defined population, as well as of evaluating the impact of healthcare interventions, being, therefore, an adequate design for examining trends in mortality rates with time.[5,11,14]

Generally speaking, mortality rates by selected respiratory diseases usually differ between the sexes in the age groups studied, but behave similarly in terms of trends throughout the period.

The peaks in mortality in 1988, 1990, and 1994/95, seen in Figures 1 and 2, could not be explained by the present study. Some hypotheses can be offered for later investigation, including the greater circulation of virulent strains, the circulation of other etiological agents, and climactic factors.

The reduction in mortality rates following vaccine implementation may be due to reductions in the number of cases or in the incidence of more severe cases after vaccination, to the greater sensitivity of healthcare services in the early diagnosis of severe pulmonary conditions, or to an improvement in the specific treatments administered.

When evaluating the impact of influenza vaccination, one must consider also that virus and bacteria of different etiologies may be involved in respiratory conditions leading to the hospitalization and death of elderly persons,[2,3] especially during cold and dry seasons, this being a worldwide phenomenon.[1]

Table 2 - Regression models and confidence intervals of mortality rates by selected respiratory diseases, according to sex and age groups. Sao Paulo State.

Age grups	Model	Conf. Int. $Y_{Est.1999}$	$Y_{Obs.1999}$	Conf. Int. $Y_{Est.2000}$	$Y_{Obs.2000}$
Male					
60-64	$Y = 1.70 + 0.03.X - 0.005.X^2$	1.42-1.56	1.60	1.34-1.49	1.59
65-69	$Y = 2.96 + 0.08.X - 0.007.X^2$	2.80-3.21	2.84	2.71-3.15	2.73
70-74	$Y = 5.36 + 0.14.X - 0.011.X^2$	5.31-6.05	5.39	5.20-5.99	4.79
75-79	$Y = 9.56 + 0.26.X - 0.029.X^2$	8.88-9.68	10.24	8.50-9.37	8.66
80 and older	$Y =21.29 + 0.68.X -0.039.X^2$	22.39-26.16	23.74	22.11-26.18	20.52
60 and older	$Y = 5.08 + 0.13.X - 0.012.X^2$	4.88-5.62	5.29	4.74-5.53	4.72
Female					
60-64	$Y = 0.79 + 0.02.X - 0.001.X^2$	0.82-0.94	0.85	0.81-0.94	0.80
65-69	$Y = 1.35 + 0.04.X - 0.002.X^2$	1.41-1.67	1.50	1.39-1.68	1.30
70-74	$Y = 2.68 + 0.07.X - 0.003.X^2$	2.87-3.24	2.76	2.85-3.25	2.27
75-79	$Y = 5.05 + 0.10.X - 0.007.X^2$	4.98-5.76	5.30	4.89-5.74	4.45
80 and older	$Y =14.43 + 0.43.X -0.017.X^2$	15.64-18.42	16.42	15.60-18.60	14.13
60 and older	$y = 3.18 + 0.08.X - 0.004.X^2$	3.34-3.89	3.49	3.31-3.90	2.99

Note: x = (year - 1989)

Our data show that mortality rates in São Paulo State were lower in 2000 for both sexes. Repeated yearly vaccination is associated with greater levels of immunological protection and with reduced mortality compared to the first immunization.[1,2] Even considering the weak immune response of elderly persons to vaccination, a perspective study conducted in the Netherlands in 1994[8] showed that vaccination can reduce clinical and serological influenza by one-half in non-institutionalized elderly persons.

Nichol et al[16] (1994), in a cohort study carried out in the United States between 1990 and 1993 with 25 thousand subjects aged 65 years and older, found an impact on the prevention of hospital admissions due to pneumonia and influenza (48% to 57%) and to all acute and chronic respiratory conditions (27% to 39%). In a meta-analysis study, Gross et al[9] (1995) confirmed the reduction in respiratory diseases, hospital admissions, and death among institutionalized elderly persons following vaccination.

The results of the present study also indicate a reduction in mortality by selected respiratory diseases, varying according to sex and between different age groups. Nevertheless, a number of factors must be considered when evaluating the protective effect of influenza vaccination, including vaccine immunogenicity, the agreement between the vaccine's antigen content and circulating viral strains,[8,9] the prevalence of chronic diseases in the community, and previous exposure to the Influenza virus. These factors vary between the seasons, as well as between different regions.

Apart from these considerations, it is likely that the investments in healthcare directed towards specific anti-influenza immunization of elderly persons in the State of São Paulo are having a positive effect on this populational segment.

In the present study, we sought to draw a general picture of the behavior of mortality due to respiratory tract diseases among elderly persons in the last decades. Continuous evaluation of this trend in years to come may provide more consistent evidence of the impact of successive wide-coverage vaccination campaigns on the Brazilian elderly population.

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