

Trends in mortality from respiratory diseases among the elderly and the influenza vaccine intervention, 1980–2009

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Suggested citation

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ABSTRACT

Objective. To evaluate mortality trends before and after the anti-influenza vaccination campaigns among the elderly in Brazil.

Methods. This was an ecological time-series study of mortality from respiratory diseases among the elderly living in the state of São Paulo, Brazil, in 1980–2009. Mortality rates were calculated using death data from the Ministry of Health's Mortality Information System and population data from the Brazilian Institute of Geography and Statistics. Polynomial regression models were used to evaluate mortality trends by sex and age group (60–69 years; 70–79, and 80 years or older) before and after the beginning of influenza vaccination campaigns.

Results. An increase in the respiratory mortality rates was observed in 1980–1998, mainly among males. The rate and velocity of the increase was higher among the older age groups. In the years following the vaccine campaigns (1999–2009), respiratory mortality rate trends by sex and age stabilized in São Paulo state.

Conclusions. A greater reduction in mortality rates would be observed if vaccinal coverage against influenza were greater and more homogenous. New strategies to increase the uptake of vaccine among the elderly are needed to reach higher coverage levels, especially in municipalities with older and larger populations.

Key words

Mortality, influenza vaccines; influenza, human; respiratory tract diseases; health of the elderly; Brazil.

Patterns of morbidity and mortality have changed with the increased proportion of population in the older age groups, resulting in a significant increase in the demand for health prevention and health care (1, 2). In Brazil, data from the national Mortality Information System (SIM/DATASUS) reveals deaths from respiratory disease among the elderly increased 49% from 1996–2009 (from 59 196 to 88 237 registered deaths). These

figures represent 15.1% and 14.3% of the total number of deaths registered in Brazil between 1996 and 2009, respectively (3).

According to the *International Statistical Classification of Diseases and Related Health Problems* (ICD, 4), respiratory system illnesses are one of the five main causes of death in Brazil and are of greater significance among the elderly. The pathological events that comprise respiratory system illnesses result from the actions of pathogens, allergens, chemical agents, physical events, and traumas, among others. The epidemio-

logical importance of such diseases, and particularly, of acute infections of the respiratory system makes information regarding the frequency, distribution, and tendencies of such diseases among specific population segments essential. Research provides a greater understanding of the phenomenon, as well as facilitating predictions, suppositions about the etiology of the diseases, the implementation of prevention strategies, and evaluation of the possible impact of health care interventions (5, 6).

Infection processes with distinct etiologies are more serious among the el-

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derly and can lead to respiratory, metabolic, and cardiovascular complications, as well as the aggravation of pre-existing chronic illnesses (7, 8). Among the physiological changes of aging are loss of elasticity in the lungs, reduced movement of the cilia, and a reduction in the cough reflex. Dilatation and diminution of the number of alveoli has also been observed, which may reduce total breathing surface. Such alterations may occur simultaneously with cardiovascular changes, affecting cardiorespiratory function (9). Therefore, acute respiratory infections among the elderly increase the probability of decompensation of chronic base conditions, leading to reduced physiological and immune capacity (8, 9).

Vaccination against influenza in Brazil was provided by the Ministry of Health for individuals older than 65 years in 1999, and since 2000, for those 60 years of age or older (7). Since then, heterogeneous coverage has been observed in Brazil through data campaigns and local surveys (10–13). Some studies have found that several factors, such as age, schooling, living with others, chronic illness, lifestyle, use of health services, and mainly, the lack of prompting from medical professionals may interfere with vaccination adherence and explains variation in coverage results (11, 14–19).

Considering that millions of elderly individuals have been vaccinated over more than a decade of annual campaigns, an evaluation of the impact of these mass immunizations on the mortality rate of respiratory illnesses is justified, especially since vaccination is particularly effective in reducing hospitalization and death by viral and bacterial pneumonias, both associated with influenza in the elderly (20–22). The aim of this study was to evaluate mortality trends among elderly residents in the state of São Paulo, Brazil, in 1980–2009, comparing tendencies before and after the provision of anti-influenza vaccination.

MATERIALS AND METHODS

Study design and data sources

This was an ecological time-series study of mortality by respiratory illnesses among the elderly in 1980–2009. An historical series of deaths obtained from DATASUS was built based on the coefficients of a selected set of diagnoses

using a base of 1 000 individuals. Demographic data, including sex and age, for the state of São Paulo was obtained from the Brazilian Institute of Geography and Statistics (IBGE), also available on DATASUS. The populations on 1 July in intercensal years were estimated by IBGE. Considering increasing population survival rates over the last 30 years, these populations were standardized by age using the direct method, and the harmonic mean of the populations as a reference (23).

Data analysis

Deaths were analyzed according to sex and age group (60–69 years, 70–79 years, and 80 years or older). The following diagnoses of underlying cause were used in 1980–1997 by the ICD-9 Chapter VIII: pneumonia and influenza (480–483, 485–487), bronchitis (490, 491), and chronic obstruction of the airways (496); and from 1998 onwards by the ICD-10 Chapter X: pneumonia and influenza (J10, J15, J18, J22), bronchitis (J40, J42), and chronic obstruction pulmonary disease (J44). These diagnoses have been used in recent years to evaluate the influence of influenza on the community (21, 24, 25).

Analysis of diagrams of dispersion between mortality coefficients and calendar year of study were followed by polynomial regression models, considering the mortality coefficients of the selected diagnoses as dependent variables (Y) and year of study as an independent variable (X). To avoid serial correlation between the terms of the regression equation, the variable *year* was transformed into the variable *centralized-year* (year minus midpoint of the historic series), since expressing the independent variable as a deviation from its mean substantially reduces autocorrelation (26). The *centralized-year* variable was selected for the series related to the period 1980–1998, and for the period 1999–2009, after intervention. Therefore, the years 1989 and 2004 were considered the midpoint of the historic series for the period before and after vaccinal intervention against influenza.

The Kolmogorov-Smirnov test was used to verify the adherence of the data series to Normal distribution, and all data series had Normal distribution (data not provided). Next, the modeling began starting with the simple linear

regression model ($Y = \beta_0 + \beta_1 X$). Subsequently, more complex models were tested, such as second degree ($Y = \beta_0 + \beta_1 X + \beta_2 X^2$), third degree ($Y = \beta_0 + \beta_1 X + \beta_2 X^2 + \beta_3 X^3$) and exponential ($Y = e^{\beta_0 + \beta_1 X}$). The choice of best model was based on level of significance (P) and residual analysis. When two models were similar from a statistical point of view, the lower order model was chosen. Significant tendencies were those in which an estimated model obtained a value of $P < 0.05$ (26, 27). In the present study, coefficients of determination for estimated models (r^2) were considered as precision measurements (26).

Calculations of mortality rates and analysis of the historical series tendencies were performed using Microsoft Excel™ (Microsoft Corp., Redmond, Washington, United States) and IBM SPSS Statistics software, version 17 (SPSS Inc., an IBM company, Chicago, Illinois, United States).

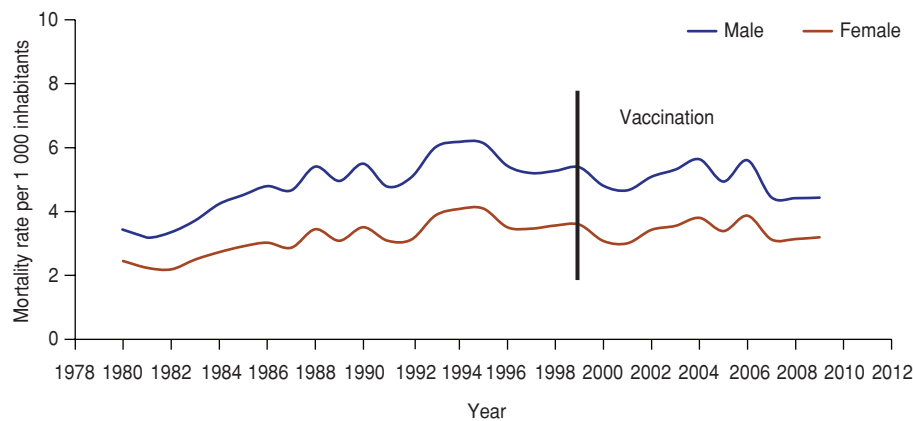
Data of vaccination coverage was supplied by the Epidemiological Surveillance Center of the São Paulo State Health Department (28) for 1999–2010. Vaccination coverage is traditionally calculated by the number of doses applied, divided by the target population. The numerator represented the amount of vaccines given in each of the vaccination units and the denominators were the population estimates. These indicators should, however, be evaluated with caution, as they may include underestimates or overestimates of coverage (29).

RESULTS

During the study period, the standardized mortality rates for respiratory diseases increased for elderly of both sexes in 1980–1999, with a peak of greater magnitude observed in 1993–1995. A rate reduction was observed in 2000 and 2001, followed by an increase and peaks in 2004 and 2006, and then a decrease at end of the period.

Respiratory mortality trends before vaccination

Standardized mortality rates of respiratory illnesses for the selected set of diagnoses for the population 60 years of age and older increased in 1980–1998 (before influenza vaccination) in São Paulo, for both men and women (Figure 1, Table 1), with distinct magni-

FIGURE 1. Standardized mortality rates for selected respiratory diseases (per 1 000 inhabitants) among the population 60 years of age or more, by sex, State of São Paulo, Brazil, 1980–2009**TABLE 1. Number of deaths and standardized mortality ratios (% inhabitants) for selected respiratory diseases, by sex and year, State of São Paulo, Brazil, 1980–2009**

Year	Male		Female	
	No. of deaths	Standard rates ‰ men	No. of deaths	Standard rates ‰ women
1980	2 346	3.41	1 919	2.45
1981	2 306	3.18	1 852	2.24
1982	2 551	3.35	1 932	2.19
1983	2 972	3.72	2 327	2.50
1984	3 535	4.24	2 679	2.73
1985	3 937	4.52	3 007	2.91
1986	4 352	4.79	3 279	3.02
1987	4 397	4.66	3 251	2.87
1988	5 287	5.41	4 072	3.45
1989	5 019	4.96	3 795	3.08
1990	5 751	5.50	4 478	3.51
1991	5 183	4.78	4 108	3.09
1992	5 749	5.07	4 383	3.12
1993	6 725	6.01	5 315	3.87
1994	7 024	6.18	5 683	4.08
1995	7 077	6.14	5 780	4.09
1996	6 946	5.43	5 679	3.51
1997	6 770	5.20	5 704	3.46
1998	6 954	5.27	5 934	3.56
1999	7 185	5.38	6 056	3.59
2000	7 470	4.80	6 315	3.08
2001	7 373	4.66	6 271	3.01
2002	8 177	5.09	7 259	3.43
2003	8 655	5.31	7 625	3.55
2004	9 298	5.63	8 253	3.80
2005	8 368	4.94	7 552	3.39
2006	9 634	5.60	8 764	3.87
2007	9 622	4.44	9 072	3.12
2008	9 772	4.42	9 326	3.14
2009	10 236	4.43	9 917	3.19

tudes according to age group (Figure 2). During the period, the mean coefficient was 5.10 deaths per 1 000 males with a non-constant linear increase of 0.15 per year; and for females, the mean annual coefficient was 3.21 deaths per 1 000, with a non-constant increment of 0.10

per year (Table 2). The mortality rates for the elderly population showed, however, a growing evolution for both sexes in 1980–1998, with peaks in 1988, 1990, and 1993/1995 (Figure 1).

The ratio between standardized male/female rates indicated that respiratory

illnesses were of greater importance among men (data not showed). For the male population more than 70 years of age, the differences observed were more significant, in relation to mean coefficients in the period, denoting a faster growth rate in relation to the female population. The mean annual growth was greater in relation to increased age of groups. In the group over 80 years, there were 21.3 deaths /1 000 and 14.4 /1 000 for men and women, respectively (Table 2).

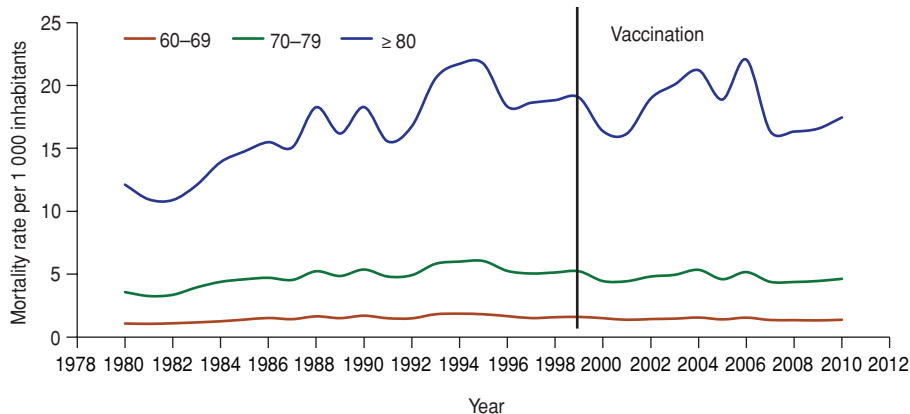
Respiratory mortality trends after vaccination

In relation to the period 1999–2009 (after influenza vaccination), it was found that for both sexes, the mortality coefficients remained stable ($P > 0.05$), with estimated annual means of 5.43/1 000 men and 3.80/1 000 women (Table 2). The tendency, however, peaked in 2004 and 2006 (Figure 1).

When the population was disaggregated according to sex and age group, it was observed that there was a slight, non-constant reduction for mortality coefficients in 1999–2009 ($P < 0.05$) for the male population 60–69 years of age, while for other age groups this tendency remained stable. The tendency for the female population remained stable for all age groups following intervention. Mean coefficients of mortality observed were highly similar to values observed during the earlier period, particularly for the group 70–79 years of age, namely, 6.5/1 000 for men and 3.5/1 000 for women, respectively (Table 2).

In general, mortality coefficients of respiratory illnesses for the selected set of diagnoses varied among the age groups and had different magnitudes among sexes, but behaved similarly with regard to tendencies analyzed during both of the periods analyzed.

Data referring to coverage of vaccination against influenza in the state of São Paulo, obtained from the historical series provided by the Epidemiological Surveillance Center (CVE), revealed that coverage varied from 63.9% in 2000 to 81.9% in 2008 (Table 3). By the end of 2007, the target established by the Ministry of Health was 70%, and in 2008, after updated IBGE population estimates revealed an increase in the elderly population, the target was increased to 80% (7).

FIGURE 2. Specific mortality rates for selected respiratory diseases (per 1 000 inhabitants) among the population 60 years of age or more, according to sex, State of São Paulo, Brazil, 1980–2009**TABLE 2. Analysis of trends of standardized mortality rates for respiratory diseases according to sex and age groups, State of São Paulo, Brazil, 1980–2009**

	β_0	β_1	β_2	P (model)	r^2
Period: 1980–1998					
Male, age (years)					
60–69	2.23	0.05	–0.006	< 0.001	0.82
70–79	6.97	0.18	–0.017	< 0.001	0.87
≥ 80	21.29	0.68	–0.039	< 0.001	0.84
Total	5.10	0.15	–0.011	< 0.001	0.89
Female, age (years)					
60–69	1.03	0.03	–0.001	< 0.001	0.84
70–79	3.65	0.08	–0.006	< 0.001	0.72
≥ 80	14.43	0.43	–0.017	< 0.001	0.78
Total	3.21	0.10	–0.004	< 0.001	0.86
Period: 1999–2009					
Male, age (years)					
60–69	1.99	–0.027	–0.003	0.049	0.529
70–79	6.49	–0.072	0.171	0.197	0.197
≥ 80	22.34	–0.209	0.481	0.057	0.057
Total	5.43	–0.004	0.921	0.001	0.001
Female, age (years)					
60–69	1.02	–0.008	0.230	0.155	0.155
70–79	3.45	–0.005	0.849	0.004	0.004
≥ 80	15.99	0.020	0.914	0.001	0.001
Total	3.80	0.041	0.151	0.215	0.215

DISCUSSION

Main findings

The present study analyzed the historical series of coefficients of mortality by respiratory illnesses for a selected set of diagnoses from 1980–2009 using the elderly population of the state of São Paulo as a reference. Analysis revealed that the mortality coefficients showed a tendency to increase in 1980–1998, and following the vaccinal intervention against influenza, remained stable during 1999–2009, with peaks in 2004 and 2006. In 2004,

there were 11 outbreaks of influenza-like illness in Brazil, in the North (Amazonas), the South East (Minas Gerais and São Paulo), and the South (Paraná, Rio Grande do Sul, and Santa Catarina). The average number of people affected was 22.4%, with an elevated incidence of elderly individuals hospitalized. Data from the Ministry of Health's Surveillance indicated that there was a higher proportion of health visits for influenza-like illnesses in sentinel units in Brazil in 2004, compared to 2002 and 2003. Among nasopharyngeal secretion samples analyzed at these sentinel units, 41.5% iden-

tified the influenza virus, predominantly the A/H3N2 virus (30).

Some studies found a higher rate of seasonal transmission and an excess of mortality by influenza and pneumonia (31) in 2004 and 2006/2007 for all underlying causes (32) associated with the circulation of the Influenza A/H3N2 virus. In Brazil, in 2004, the occurrence of peaks of mortality in different age groups may be associated with the circulation of this viral variant, while the A/Fujian/411/2002 (H3N2) virus was anticipated in the composition of the vaccine for the same year. In 2006, the A/Wisconsin/67/2005 (H3N2) and A/California/7/2004 (H3N2) viruses circulated in Brazil, however only the latter variant was included in the composition of the vaccine for that year (33). Data available in the System of Epidemiological Surveillance for Influenza (Sivep-Gripe) shows that in 2004, in samples collected in the sentinel network positive for influenza A, antigenic characterization identified predominance of the variant A/H3N2 (67%) (34).

It should be stated that in 2009/2010, the circulation of the influenza variant A/H1N1 was globally widespread, although susceptibility to infection decreased with age, possibly generating a small impact on the mortality of the elderly (35, 36), which may also have occurred in Brazil.

While changes in the mortality curve tendency associated with influenza before and after vaccination campaigns for the elderly is evident, a number of factors may be associated with seasonal mortality in this age group, among them, acquired immunity during earlier epidemics, declining immunological response due to age, and the viral variant in circulation during the season, as well as variations in vaccinal cover among different population groups (37, 38).

Access to vaccination

Another relevant aspect is the difference in quality of life among municipalities and within medium- and large-sized municipal regions. Where there is a higher absolute number of elderly individuals, they comprise a higher percentage of the population, and distinct vaccinal coverage profiles may exist that are not reflected in the mean. Additionally, the reproduction

TABLE 3. Doses and influenza vaccination coverage in the population 60 years or more. State of São Paulo, Brazil, 1999–2009

Year	Population	Doses on campaigns (April/May)	Coverage
1999 ^a	1 937 783	1 628 466	84.04
2000	2 974 804	1 901 796	63.93
2001	3 364 622	2 241 059	66.61
2002	3 409 103	2 234 970	65.56
2003	3 451 858	2 575 241	74.60
2004	3 494 555	2 727 952	78.06
2005	3 591 383	2 792 380	77.75
2006	3 640 716	2 920 479	80.22
2007	3 689 623	2 997 183	81.23
2008	3 738 999	3 063 185	81.93
2009	4 535 697	3 455 999	76.20

Source: Adapted from Division of Immunization/CVE/CCD/SES-SP. Updated in March 2012.

^a In 1999, the target population was 65 years or more.

rate of disease in Brazil is highest in the more populous areas as presented in a study comparing geographic areas of the country (39).

A study performed in Campinas in 2008/2009 showed that socioeconomic conditions, lifestyle, and physical mobility do not restrict access to vaccination, denoting the scope of the campaigns, albeit vaccinal coverage of the elderly population had been lower than expected at 62.6% (95% Confidence Interval [95% CI]: 59.3–65.7) (14). Despite being free of charge, vaccination against influenza has not reached desired coverage levels in a number of municipal areas in Brazil (11–14).

Importance of vaccination

Among the limitations of the present study, it should be noted that in working with underlying cause of death, the inclusion of non-respiratory illnesses common among the elderly (e.g., cardiovascular disease) is possible. The quality of diagnosis of underlying cause of death, estimated by the proportional mortality due to ill-defined causes, has generally improved among municipalities in Brazil (40). However, as this is an ecological study using secondary data, its high

quality (by national and international standards) and improved coverage by SIM/DATASUS, must be noted.

As such, the study analysis performed allows for observation of the *contextual effect* of the ecological exposure on individual risk (41), namely, the intervention's effect (vaccination) on the respiratory illnesses investigated (selected set of diagnoses). It should be stated that *contextual effects* are fundamental to the epidemiology of infectious diseases, where the risk of becoming ill depends on the prevalence of the disease in others with whom the individual comes into contact (42).

Vaccination is, historically, a public health intervention (43), and in the context of the Brazilian health system, this intervention is guided by the principals of universality and equality (29). Among the elderly who do not adhere to preventive procedures, considering the vaccine to be unimportant and believing that the vaccine causes a reaction were the main motives identified in some studies in Brazil (14, 15, 44). The recommendation of a physician or other health professional is fundamental to increasing vaccinal coverage (14, 45). In addition improved information regarding the co-circulation of microorganisms that cause clinical respiratory manifestations similar to those of influenza is needed to avoid equivocal interpretations of adverse events of the vaccine.

It should be noted that pneumonia is the principal cause of death by respiratory illness among the elderly, particularly associated with *Streptococcus pneumoniae*. Vaccination against influenza can prevent complications and death by primary viral and bacterial pneumonia, however, the anti-pneumococcal vaccination, with low coverage among this population segment, can significantly contribute to the reduction of mortality caused by these illnesses (46). Vaccination at the time of hospital discharge may represent an effective form of reaching populations vulnerable to pneumonia and its complications.

Conclusions

The present study measured the ecological effect using data from the state of São Paulo, resulting in an evaluation of relevance to preventive procedures implemented and made available to the entire elderly population of Brazil. The stabilizing of mortality tendency after vaccination campaigns suggests that the interventions have had an impact, although other factors may be involved in the excess of risk of death by illnesses associated with influenza. The small number of samples collected in the sentinel units may not reflect viral circulation in the state in a consistent manner, making the interpretation of these tendencies difficult.

The question is whether a greater reduction in mortality rates, for the selected set of diagnoses, would be observed if vaccinal coverage against influenza was greater and more homogenous, particularly in medium and large cities in the state, especially in a populous state such as São Paulo. It is certain that such an intervention would result in the prevention of a large number of deaths among the elderly.

New strategies to extend coverage and to increase homogeneity are necessary, among them: the identification and reduction of missed immunization opportunities, expansion of awareness campaigns to include those beyond the target public (e.g., caregivers and relatives), and improvements to vaccination access, especially among the elderly and dependents. Therefore, the continuation of such campaigns, the broadening of vaccination coverage against influenza, increased homogeneity between and within municipal areas (especially those with a greater absolute number of elderly individuals), and the expansion of anti-pneumococcal vaccine coverage will result in the prevention of deaths from respiratory illnesses. Additionally, the continuous monitoring of the viral variants that circulate in Brazil will support the evaluation of other factors that may affect the severity of disease in each season.

Conflicts of interest. None.

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RESUMEN**Tendencias de la mortalidad por enfermedades respiratorias en ancianos e influencia de la vacuna antigripal, 1980–2009**

Objetivo. Evaluar las tendencias de la mortalidad antes y después de la provisión de la vacuna antigripal a los ancianos del Brasil.

Métodos. Estudio ecológico de series temporales sobre la mortalidad por enfermedades respiratorias en ancianos residentes en el estado de São Paulo, Brasil, llevado a cabo de 1980 al 2009. Se calcularon las tasas de mortalidad a partir de los datos del Sistema de Información sobre Mortalidad del Ministerio de Salud y los datos sobre población del Instituto Brasileño de Geografía y Estadística. Se utilizaron modelos de regresión polinómica para evaluar las tendencias de mortalidad según el sexo y el grupo de edad (60 a 69 años; 70 a 79 años, y 80 años o mayores), antes y después del inicio de las campañas de vacunación antigripal.

Resultados. Se observó un incremento de las tasas de mortalidad por enfermedades respiratorias de 1980 a 1998, principalmente en hombres. Las tasas y la velocidad del incremento fueron más elevadas en los grupos de mayor edad. En los años posteriores a las campañas de vacunación (de 1999 al 2009), las tendencias de las tasas de mortalidad por enfermedades respiratorias por sexo y edad en el estado de São Paulo se estabilizaron.

Conclusiones. Se observaría una mayor reducción de las tasas de mortalidad si la cobertura de la vacunación antigripal fuera mayor y más homogénea. Es necesario adoptar nuevas estrategias para aumentar la aceptación de la vacuna entre los ancianos con objeto de alcanzar mayores niveles de cobertura, especialmente en los municipios con poblaciones más numerosas y de edades más avanzadas.

Palabras clave

Mortalidad; vacunas contra la influenza; gripe humana; enfermedades respiratorias; salud del anciano; Brasil.