Epidemiol. Infect. (2013), **141**, 1731–1740. © Cambridge University Press 2012
doi:10.1017/S0950268812002221

Influenza-associated excess mortality in southern Brazil, 1980–2008

F. T. M. FREITAS[1]*, L. R. O. SOUZA[1], E. AZZIZ-BAUMGARTNER[2], P. Y. CHENG[2], H. ZHOU[2], M. A. WIDDOWSON[2], D. K. SHAY[2], W. K. OLIVEIRA[1] AND W. N. ARAUJO[1]

[1] *Health Surveillance Secretariat, Ministry of Health, Brasilia, Brazil*
[2] *Centers for Disease Control and Prevention, Atlanta, GA, USA*

Received 5 February 2012; Final revision 4 August 2012; Accepted 5 September 2012; first published online 8 October 2012

SUMMARY

In order to estimate influenza-associated excess mortality in southern Brazil, we applied Serfling regression models to monthly mortality data from 1980 to 2008 for pneumonia/influenza- and respiratory/circulatory-coded deaths for all ages and for those aged ⩾60 years. According to viral data, 73·5% of influenza viruses were detected between April and August in southern Brazil. There was no clear influenza season for northern Brazil. In southern Brazil, influenza-associated excess mortality was 1·4/100 000 for all ages and 9·2/100 000 person-years for persons aged ⩾60 years using underlying pneumonia/influenza-coded deaths and 10·0/100 000 for all ages and 86·6/100 000 person-years for persons aged ⩾60 years using underlying respiratory/circulatory-coded deaths. Influenza-associated excess mortality rates for southern Brazil are similar to those published for other countries. Our data support the need for continued influenza surveillance to guide vaccination campaigns to age groups most affected by this virus in Brazil.

Key words: Brazil, epidemiology, influenza.

INTRODUCTION

Influenza is a respiratory infection annually associated with significant morbidity and mortality [1, 2] and quantifying this burden is critical to guide influenza vaccination policy [3]. Nevertheless, estimates of deaths attributable to influenza are difficult to estimate because influenza infections are often not laboratory confirmed or documented on hospital discharge forms and deaths certificates. Furthermore, a proportion of influenza-associated deaths occur because of pneumonia and bacterial co-infections [4, 5] or as a result of exacerbations of chronic disease such as congestive heart failure and chronic obstructive pulmonary disease, when the influenza virus is no longer detectable through routine clinical testing [6–8].

Statistical models based on time-series of mortality data have been used mainly in temperate and/or high-income countries to quantify the burden of influenza epidemics [9–12]. Data from tropical Singapore and subtropical Hong Kong estimated influenza-associated excess mortality rates in persons of all ages to be 2·9/100 000 and 4·1/100 000 person-years for underlying pneumonia/influenza deaths and 11·9/100 000 and 12·4/100 000 person-years for underlying circulatory/respiratory deaths [13, 14].

* Author for correspondance: Dr F. T. M. Freitas, Ministerio da Saude, Coordenação Geral de Doenças Transmissiveis, Unidade de Doenças Respiratorias e Imunopreviniveis, Setor Comercial Sul, Quadra 4, Bloco A, 2° andar, CEP: 70304-000, Brasilia-DF, Brazil. (Email: felipe.freitas@saude.gov.br)

These estimates are comparable to estimates in temperate countries, such as the USA (2·4 and 9·0 influenza-associated deaths/100 000 person-years, for pneumonia/influenza and respiratory/circulatory outcomes, respectively) [15], despite differences in the timing of influenza seasons.

Nevertheless, it is not known if influenza-associated excess mortality rates in these high-income countries are comparable with rates from large, middle-income countries with multiple climate zones and spanning several latitudes. There is a paucity of data on the burden of seasonal influenza in tropical and subtropical areas of different income strata, especially in South America [16, 17]. Brazil is the largest country in South America, extends across more than 35° of latitude, and encompasses the equatorial Amazon rain forest in the north to subtropical and temperate zones in the south.

The Brazilian Government started influenza vaccination campaigns in 1999, targeting persons aged ⩾65 years because most of the influenza-associated mortality burden documented in temperate countries was concentrated in the elderly. In addition, vaccination campaigns targeted other groups vulnerable to complications of influenza infection (e.g. transplant patients, people living with HIV/AIDS, and patients with chronic pulmonary, cardiovascular, and renal diseases) and health professionals. In 2000, the Brazilian Government extended vaccine recommendations to persons aged ⩾60 years. During April–May, Brazil annually administers the Southern Hemisphere composition of the influenza vaccine free of charge throughout the country. The annual vaccine coverage in the elderly, the largest group targeted, ranged from 68% to 89% during 1999–2010 [18].

In this study, we use the Brazilian mortality statistics from 1980 to 2008 to estimate influenza-associated excess mortality during influenza epidemics for the southern region of Brazil.

METHODS

Influenza viral data

The Brazilian Ministry of Health initiated influenza surveillance in 2000. The national influenza surveillance system consisted of a network of sentinel sites (i.e. general care facilities and emergency departments) that collected an average of five clinical respiratory samples (nasopharyngeal aspirates or throat and nasal swabs) each week from patients with influenza-like illness. Samples were tested for influenza and other respiratory viruses at each state's public health laboratory through indirect immunofluorescence assay (IFA) for detection of respiratory viruses including influenza A and B. The influenza-positive samples and 10% of the negative IFA samples were further retested in one of the three Brazilian National Influenza Centres (NICs) by reverse transcription–polymerase chain reaction and samples which again tested positive for influenza were subtyped and sequenced. We analysed the monthly number of IFA-positive influenza samples from the states' public health laboratories database during 2000–2008 to describe the seasonal pattern of respiratory virus activity in southern and northern Brazil and to determine the time periods when excess pneumonia/influenza and respiratory/circulatory deaths could be attributed to influenza illness.

Geographical division

For the analyses, we divided Brazil into northern and southern regions which correspond to the 15° S latitude demarcating the different influenza seasonal patterns in tropical *vs.* subtropical/temperate Brazil [19] (Fig. 1). Southern Brazil included the mid-west, southeast and south; in 2010, this region had a population of 121 809 395 (11·5% aged ⩾60 years) and a mean population density of 39·1 persons/km². Southern Brazil is where the country's major economics centres are located, with 91% of the population living in urban centres and a *per capita* GDP of US$12 768 [20]. The mean annual temperature in southern Brazil ranges between 14 °C and 24 °C and the annual rainfall ranges between 1250 mm and 2000 mm [21]. Northern Brazil included the north and northeast; in 2010, this region had a population of 68 946 404 inhabitants (9·5% aged ⩾60 years) and a mean population density of 12·7 persons/km². Northern Brazil is less developed with 73% of the population living in urban centres and a *per capita* GDP of US$5058 [20]. The mean annual temperature in northern Brazil ranges between 20 °C and 28 °C and the rainfall can exceed 3000 mm during the first 6 months (January–June) of the year in parts of the Amazon [21].

National mortality and population data

The National Vital Statistics Department of the Brazilian Ministry of Health provided national

Fig. 1 [*colour online*]. Political division of Brazil and study stratification into northern and southern Brazil.

mortality data on pneumonia, influenza, respiratory, and cardiac-coded deaths [22]. Data were collected throughout the year using a standard form and database for the whole country. We categorized mortality data collected during 1980–1995 according to International Classification of Diseases, Ninth Revision (ICD-9) codes [23] and data collected during 1996–2008 according to Tenth Revision (ICD-10) codes [24]. We modelled two death categories according to the underlying cause of death: pneumonia/influenza mortality codes (i.e. ICD-9 codes 480–487 and ICD-10 codes J10–J18) and respiratory/circulatory mortality codes (i.e. ICD-9 codes 390–519 and ICD-10 codes I00–99 and J00–99). We used the census projections estimated in the first year of every decade for each subsequent year by the Brazilian Institute of Geography and Statistics to determine annual population denominators [20]. No visible change in annual pneumonia/influenza and respiratory/circulatory deaths was observed during the transition from ICD-9 to ICD-10, thus no adjustment was needed.

Statistical analyses

We applied Serfling regression models [25, 26] to monthly mortality data for persons of all ages and for those aged $\geqslant$60 years, the main target group for influenza vaccination. The Serfling regression model is a linear regression model that includes terms for time trends and harmonic terms to model seasonal fluctuations in the number of deaths. It assumed a distinct influenza season and used only the monthly number of deaths that occurred outside the influenza season (defined by viral surveillance data) to estimate the seasonal pattern of deaths that were not associated with influenza. In these models:

$$Y_i = \beta_0 + \beta_1(t_i) + \beta_2(t_i^2) + \beta_3[\sin(2t_i\pi/12)] + \beta_4[\cos(2t_i\pi/12)] + e_i,$$

where Y_i represents the number of deaths in a particular month i, β_0 represents the intercept, β_1 represents a coefficient for the linear time trend, β_2 represents a coefficient for the quadratic time trend, β_3 and β_4 represent the coefficients associated with

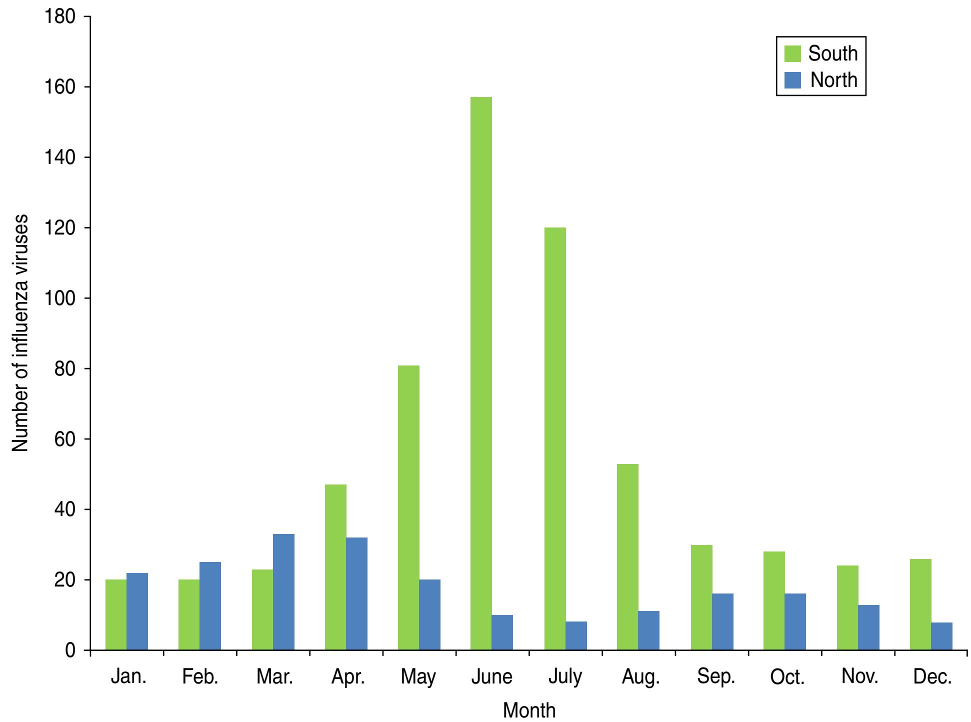

Fig. 2 [*colour online*]. Number of influenza viruses identified through routine surveillance in southern and northern Brazil during 2000–2008.

the seasonal fluctuations in deaths, and e_i represents the error term. Ninety-five percent confidence intervals (CIs) were generated for the prediction for the entire linear regression line which is larger than the estimated variance of the mean response. We defined the 'epidemic months' for each season as those months for which deaths exceeded the upper 95% confidence limit of deaths predicted by the model during the influenza season. The influenza-associated excess of deaths was determined by subtracting the observed deaths from the predicted deaths for the 'epidemic months'. The annual rate of influenza-associated mortality/100 000 person-years was calculated by dividing the annual cumulative number of excess deaths during the influenza season by the sum of the annual mid-year population estimate for the period for all ages and in those aged ⩾60 years.

RESULTS

Timing of influenza activity in Brazil

During 2000–2008, 841 influenza viruses were detected, 627 (75%) in southern Brazil and 214 (25%) in northern Brazil. Influenza was detected throughout the year in southern and northern Brazil. In southern Brazil, most positive samples (73·5%) were found during April–August (Fig. 2). Therefore, we considered the period of April–August as the epidemic season for southern Brazil in our model. In northern Brazil, however, there was insufficient viral data to clearly define the influenza season to the extent necessary for our Serfling models and we excluded this region from our analysis.

Deaths by age group in southern Brazil

In southern Brazil, the annual median of pneumonia/influenza deaths in all ages was 27 419 (range 23 342–35 439) and in persons aged ⩾60 years it was 15 408 (range 6775–27 790). The annual median proportion of underlying pneumonia/influenza deaths in all decedents aged ⩾60 years was 55% (range 24% in 1980 to 78% in 2008). The annual median of underlying respiratory/circulatory deaths was 264 014 (range 208 023–300 707) and in persons aged ⩾60 years it was 185 464 (range 118 941–233 376). The annual median proportion of underlying respiratory/circulatory deaths in all decedents aged ⩾60 years was 70% (range 57% in 1980 to 78% in 2008).

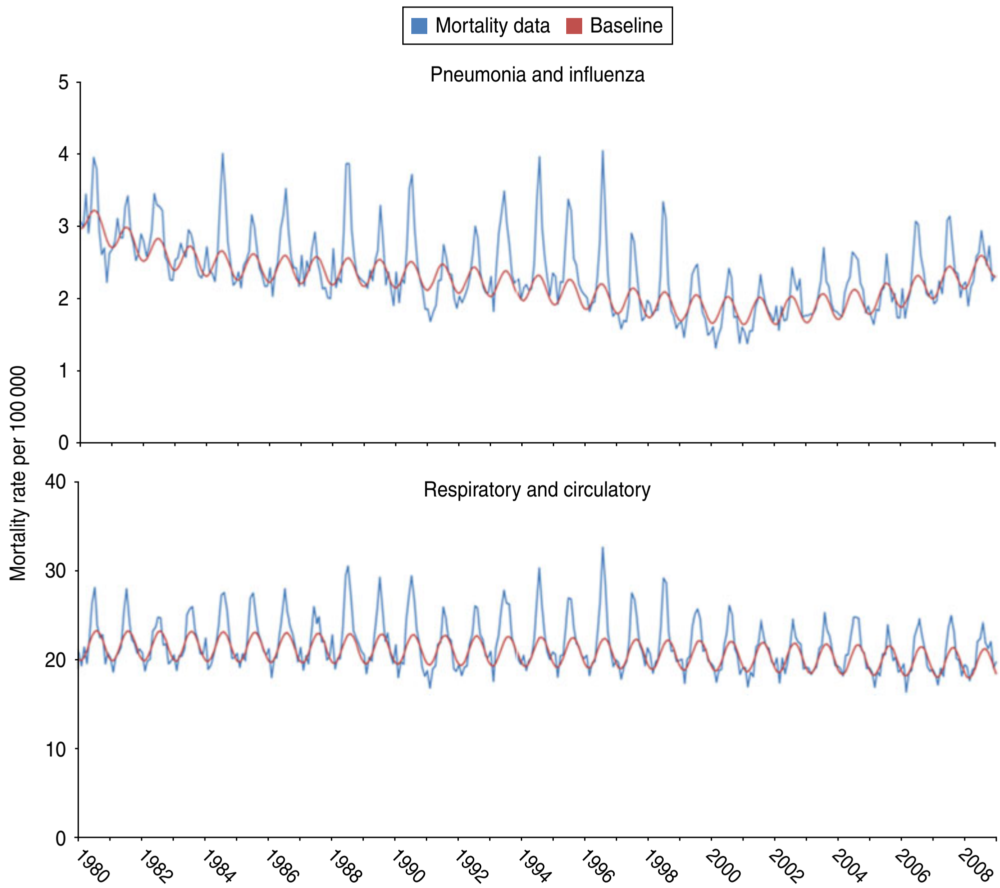

Fig. 3 [*colour online*]. Serfling models of excess mortality during the influenza season in southern Brazil for all ages during 1980–2008.

Influenza-associated excess mortality rates in southern Brazil

The models fitted the data well, especially for respiratory/circulatory data, $R=0{\cdot}81$ for all ages and $R=0{\cdot}83$ for persons aged $\geqslant 60$ years. For pneumonia/influenza data, $R=0{\cdot}76$ for all ages and $R=0{\cdot}68$ for persons aged $\geqslant 60$ years (Fig. 3). In southern Brazil, the annual median number of influenza-associated excess deaths estimated using underlying pneumonia/influenza data was 1035 [interquartile range (IQR) 445–2365] during the influenza season. These influenza-associated excess pneumonia/influenza deaths represented 1–12 % of all pneumonia/influenza deaths coded each year. The annual rate of influenza-associated excess pneumonia/influenza mortality was 1·4 deaths/100 000 person-years [95 % confidence interval (CI) 0·7–2·1 deaths/100 000 person-years] (Table 1). In persons aged $\geqslant 60$ years, the annual median number of influenza-associated excess pneumonia/influenza deaths was 498 (IQR 0–1495). The annual rate of influenza-associated excess pneumonia/influenza mortality for this age group was 10·0 deaths/100 000 person-years (95 % CI 4·9–15·1 deaths/100 000 person-years) (Table 2).

The annual median number of influenza-associated excess deaths in all ages estimated using underlying respiratory/circulatory data was 7377 (IQR 5633–12 926) during the influenza season. These influenza-associated excess deaths represented 1–7 % of all respiratory/circulatory deaths coded each year. The annual rate of influenza-associated excess respiratory/circulatory mortality was 9·2 deaths/100 000 person-years (95 % CI 4·5–13·9 deaths/100 000 person-years) (Table 1). In persons aged $\geqslant 60$ years the annual median number of influenza-associated excess respiratory/circulatory deaths was 5761 (IQR 3088–12 345). The annual rate of influenza-associated excess respiratory/circulatory mortality for this age group was 86·6 deaths/100 000 person-years (95 % CI 41·6–131·7 deaths/100 000 person-years) (Table 2).

Table 1. *Total and excess deaths, and influenza-associated excess mortality (pneumonia/influenza and respiratory/circulatory) for all ages, 1980–2008 in southern Brazil*

	Pneumonia and influenza					Respiratory and circulatory				
Year	Total number of deaths	Excess number of deaths	95% CI	Excess death rate/100 000	Excess deaths/total deaths (%)	Total number of deaths	Excess number of deaths	95% CI	Excess death rate/100 000	Excess deaths/total deaths (%)
1980	28 661	1035	408–1661	1·3	3·6	209 424	6465	3349–9582	8·3	3·1
1981	27 419	347	40–654	0·4	1·3	209 393	5633	2508–8758	7·1	2·7
1982	27 305	1633	387–2878	2·0	6·0	208 023	0*	0–0	0·0	0·0
1983	25 604	0*	0–0	0·0	0·0	217 097	6000	1177–10 824	7·3	2·8
1984	27 481	2418	1449–3388	2·9	8·8	226 344	6955	3695–10 215	8·3	3·1
1985	25 710	466	135–797	0·5	1·8	229 221	7377	4031–10 724	8·7	3·2
1986	27 416	2012	674–3349	2·3	7·3	232 928	8354	3271–13 437	9·6	3·6
1987	25 267	0*	0–0	0·0	0·0	231 983	2986	1249–4723	3·4	1·3
1988	29 127	2726	1689–3763	3·0	9·4	252 554	18 821	11 804–25 838	21·0	7·5
1989	26 362	678	326–1030	0·7	2·6	244 139	10 850	5 504–16 197	11·9	4·4
1990	28 265	2524	1453–3595	2·7	8·9	249 017	16 395	9149–23 641	17·7	6·6
1991	24 270	0*	0–0	0·0	0·0	236 055	2898	1050–4745	3·1	1·2
1992	26 438	963	230–1696	1·0	3·6	246 826	5968	2248–9689	6·2	2·4
1993	29 902	3589	1724–5454	3·7	12·0	264 014	18 881	9400–28 362	19·4	7·2
1994	30 246	3353	2217–4489	3·4	11·1	264 868	15 281	9506–21 055	15·5	5·8
1995	29 463	2650	1495–3805	2·7	9·0	263 994	11 858	5986–17 729	11·9	4·5
1996	28 251	3473	2307–4640	3·4	12·3	274 042	20 409	14 484–26 333	20·2	7·4
1997	24 862	1440	645–2236	1·4	5·8	267 580	12 524	6502–18 546	12·2	4·7
1998	26 362	2365	1558–3171	2·3	9·0	276 137	17 090	10 961–23 219	16·4	6·2
1999	24 044	445	37–852	0·4	1·8	272 745	12 926	4674–21 179	12·2	4·7
2000	23 342	426	4–847	0·4	1·8	272 251	7365	3116–11 613	6·7	2·7
2001	24 000	0*	0–0	0·0	0·0	271 459	2678	508–4848	2·4	1·0
2002	26 274	445	12–879	0·4	1·7	276 835	2928	728–5127	2·6	1·1
2003	27 586	724	285–1164	0·6	2·6	283 182	3886	1657–6116	3·4	1·4
2004	29 936	1661	325–2997	1·4	5·5	293 393	13 538	4514–22 562	11·8	4·6
2005	28 124	479	19–938	0·4	1·7	280 627	2905	576–5233	2·5	1·0
2006	33 469	1759	825–2694	1·5	5·3	293 384	9767	2655–16 880	8·1	3·3
2007	34 808	1623	672–2573	1·3	4·7	295 916	7832	3005–12 659	6·4	2·6
2008	35 439	0*	0–0	0·0	0·0	300 707	6345	1526–11 163	5·2	2·1

CI, Confidence interval.

* The 95% confidence intervals of modelled influenza excess deaths exceeded the observed number of deaths.

Table 2. *Total and excess deaths, and influenza-associated excess mortality (pneumonia/influenza and respiratory/circulatory) for persons aged ⩾60 years, 1980–2008 in southern Brazil*

	Pneumonia and influenza					Respiratory and circulatory				
Year	Total number of deaths	Excess number of deaths	95 % CI	Excess death rate/100 000	Excess deaths/total deaths (%)	Total number of deaths	Excess number of deaths	95 % CI	Excess death rate/100 000	Excess deaths/total deaths (%)
1980	6868	621	309–934	13·0	9·0	127 510	5457	3363–7551	114·3	4·3
1981	6794	0*	0–0	0·0	0·0	128 768	5957	2744–9170	120·1	4·6
1982	6946	0*	0–0	0·0	0·0	128 440	0*	0–0	0·0	0·0
1983	8165	0*	0–0	0·0	0·0	137 776	5384	1908–8860	99·5	3·9
1984	9049	0*	0–0	0·0	0·0	143 473	4392	1989–6794	77·9	3·1
1985	9943	0*	0–0	0·0	0·0	149 310	7202	3439–10 964	122·8	4·8
1986	10 897	334	139–529	5·5	3·1	151 774	5756	1848–9663	94·6	3·8
1987	10 860	0*	0–0	0·0	0·0	154 104	3598	901–6295	57·0	2·3
1988	13 160	1308	684–1932	20·1	9·9	169 221	12 346	8158–16 534	189·3	7·3
1989	12 045	287	72–502	4·3	2·4	164 171	7995	3673–12 316	118·8	4·9
1990	14 257	1666	1003–2329	24·0	11·7	171 485	12 658	6719–18 596	182·5	7·4
1991	12 420	0*	0–0	0·0	0·0	163 539	2247	711–3784	31·3	1·4
1992	13 689	490	14–966	6·5	3·6	171 752	3759	564–6954	50·1	2·2
1993	16 098	2267	1098–3437	30·8	14·1	185 464	16370	8521–24 219	222·4	8·8
1994	16 605	2213	1501–2924	29·7	13·3	186 128	13 203	8426–17 979	177·1	7·1
1995	16 605	2168	971–3364	28·7	13·1	187 154	12 602	6150–19 054	167·0	6·7
1996	16 699	2210	1413–3007	26·5	13·2	198 077	14 978	9629–20 326	179·5	7·6
1997	15 098	946	405–1488	11·2	6·3	194 815	8013	4379–11 647	94·7	4·1
1998	16 530	1642	1094–2190	19·2	9·9	202 001	13 802	8291–19 312	161·3	6·8
1999	15 408	588	33–1142	6·8	3·8	200 816	11 608	4199–19 016	134·2	5·8
2000	15 462	0*	0–0	0·0	0·0	202 566	2353	249–4457	24·0	1·2
2001	16 533	0*	0–0	0·0	0·0	203 040	0*	0–0	0·0	0·0
2002	18 702	0*	0–0	0·0	0·0	209 615	0*	0–0	0·0	0·0
2003	20 061	498	174–823	4·9	2·5	215 111	3076	897–5254	30·3	1·4
2004	22 287	1495	512–2477	14·5	6·7	224 557	12 699	3904–21 494	123·6	5·7
2005	21 202	506	170–843	4·8	2·4	215 505	3260	1001–5519	31·0	1·5
2006	25 665	2761	1396–4125	25·9	10·8	226 513	14 172	5014–23 330	133·0	6·3
2007	27 211	1216	401–2031	9·7	4·5	229 454	0*	0–0	0·0	0·0
2008	27 790	0*	0–0	0·0	0·0	233 376	0*	0–0	0·0	0·0

CI, Confidence interval.

* The 95 % confidence intervals of modelled influenza excess deaths exceeded the observed number of deaths.

Table 3. *Influenza-associated excess mortality rates per 100 000 person-years in southern Brazil, Singapore, Hong Kong, USA and South Africa*

Country	Period of study	Statistical method	Underlying pneumonia and influenza deaths (/100 000 person-years)	Underlying respiratory and circulatory deaths (/100 000 person-years)
Southern Brazil	1980–2008	Serfling regression model using monthly number of deaths	All ages: 1·4 ⩾60 yr: 10·0	All ages: 9·2 ⩾60 yr: 86·6
Singapore [13]	1996–2003	Negative binominal regression model using monthly number of deaths and monthly proportion of positive influenza test results	All ages: 2·9 ⩾65 yr: 46·9	All ages: 11·9 ⩾65 yr: 155·4
Hong Kong [14]	1996–1999	Poisson regression model using weekly number of deaths and weekly proportion of positive influenza test results	All ages: 4·1 ⩾65 yr: 39·3	All ages: 12·4 ⩾65 yr: 102·0
USA [15]	1976–2007	Poisson regression model using weekly number of deaths and weekly proportion of positive influenza test results	All ages: 2·4 ⩾65 yr: 17·0	All ages: 9·0 ⩾65 yr: 66·1
South Africa [28]	1998–2005	Serfling regression model using monthly number of deaths	⩾65 yr: 42·0	

We conducted additional sensitivity analysis for our models, considering May–August as the epidemic period and using a 99% CI to define the 'epidemic months' and found similar results with no significant statistical difference from the results presented (data not shown).

DISCUSSION

We present estimates of influenza-associated excess mortality for two categories of underlying cause of death codes for southern Brazil. The estimates of respiratory/circulatory deaths are more likely to provide an estimate of the full range of influenza-associated deaths than estimates made with pneumonia/influenza data because the former category includes deaths caused by exacerbations of chronic cardiac and respiratory diseases which can be secondary to influenza infection [15]. Our estimates of influenza-associated excess mortality for all ages and the elderly in southern Brazil are similar to rates in tropical Singapore, subtropical Hong Kong and even to temperate countries like the USA [13–15] (Table 3). South Africa, however, a country at a similar latitude (22° S to 35° S) and income level [27] to southern Brazil had a higher influenza-associated excess pneumonia/influenza mortality during 1998–2005 (i.e. 42/100 000 in persons aged ⩾65 years) [28] than southern Brazil (i.e. 10·0 deaths/100 000 in persons aged ⩾60 years) and other countries as well. Difference in age group composition, lower influenza vaccine coverage, limited access to healthcare, high prevalence of underlying illnesses and malnutrition, and crowded living conditions in parts of South Africa may be attributed to their higher influenza mortality rate [28, 29]. One study performed in the city of São Paulo, the main urban centre located in southern Brazil, from 1993–2002 using a Serfling regression model and assuming influenza seasonal periods where observed deaths rates exceeded the epidemic threshold for at least two consecutive weeks, found similar rates of influenza-associated excess pneumonia/influenza mortality for those aged ⩾65 years, with yearly variation from 0·0 to 24·1/100 000 inhabitants [30].

There was year-to-year variability in influenza-associated mortality estimates in southern Brazil. Seasons with highest estimates of excess deaths are characterized by a dominance of influenza A(H3N2) influenza viral subtype [13–15]. We worked with IFA data from the states' public health laboratories, thus we do not have viral data on influenza dominant strains for each season. Nevertheless, according to data published from two Brazilian NICs that studied 29 isolates from Belém, northern Brazil and 38 isolates from São Paulo, southern Brazil, from 1999 to 2007, the years with highest influenza-associated mortality in southern Brazil correspond to the years with the detection of new strains of influenza A(H3N2) in São Paulo (A/Fujian/411/2002 in 2004, A/California/7/2004 and A/Wisconsin/67/2005 in 2006) [31].

We used Serfling regression models which are useful when there is no robust viral data available. This model is simpler when compared to other regression models because it assumes that influenza mortality is seasonal and the impact of respiratory syncytial virus (another respiratory virus capable of causing severe disease in infants and the elderly) is accounted for in the baseline. Nevertheless, studies from the Northern and Southern Hemispheres have demonstrated that estimates of influenza-associated mortality are similar between the Serfling regression models and other methods [32, 33]. This method is often applied in temperate countries with distinct influenza seasons. However, such models may not be the best for tropical and subtropical areas where influenza may circulate throughout much of the year [16, 17]. Indeed, we found that influenza viruses circulate throughout the year in southern Brazil, and thus our baseline periods probably included periods when influenza-associated deaths occurred. This bias would lead to underestimates of influenza-associated mortality rates. Nevertheless, viral surveillance data paralleled mortality data. For example, during 2000–2008, pneumonia/influenza and respiratory/circulatory mortality peaked once during June–July in southern Brazil. Moreover, Alonso *et al.* in a study that addressed influenza seasonality in Brazil using mortality data from 1979 to 2001, observed a peak in pneumonia/influenza mortality in the same period in southern Brazil [19]. Distinct influenza seasonality was more difficult to discern in northern Brazil given the available viral data, which may be due in part a more complex, year-round influenza activity near the equator. Alonso *et al.* did not find evidence of variations in the amplitude of the seasonal cycles in the northern equatorial zones, but found only a peak of pneumonia/influenza deaths during April–May in the northern states of Brazil [19]. For these reasons, we did not apply our models, which rely on defined influenza seasonality, to the northern region of Brazil.

The Brazilian Mortality System has limitations. Although the coverage of the system has steadily improved, the proportion of deaths reported to the Brazilian Mortality System reached about 100% of the mortality estimated by the Brazilian Institute of Geography and Statistics in southern Brazil by the early 1990s. Before that period, there was underreporting of deaths to the system and a higher proportion of ill-defined coded diseases, especially in the elderly [34, 35]. This may explain the poorer adjustment of the model's baseline in the earliest years and the underestimation of influenza-associated mortality in the 1980s and early 1990s.

In conclusion, the mortality burden of influenza in southern Brazil appears comparable with that found in other countries with different climates and incomes. These data need to be confirmed in the future as more robust viral data become available in Brazil. Future investments in influenza surveillance are needed, especially in northern tropical Brazil, to better understand the seasonality and associated burden of influenza in this region. Vaccine effectiveness studies are necessary as Brazil will face an even greater influenza-associated burden as its population grows older. Increasing vaccination coverage may be a strategy to further decrease the burden of influenza-associated mortality, especially in those at highest risk of death as a result of infection.

ACKNOWLEDGEMENTS

The authors thank Nancy Cox, Ann Moen, Joseph Bresee, Otavio Olivia, Tomas Rodriguez and Marcia Lopes de Carvalho for their support and cooperation which made this manuscript possible, and Patricia Marques Ferreira for providing assistance with the figures.

The opinions expressed by authors contributing to this work do not necessarily reflect the opinions of the Centers for Disease Control and Prevention or the institutions with which the authors are affiliated.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Simonsen L, *et al.*** The impact of influenza epidemics on mortality: introducing a severity index. *American Journal of Public Health* 1997; **87**: 1944–1950.
2. **Simonsen L, *et al.*** Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *Journal of Infectious Diseases* 1998; **178**: 53–60.
3. **World Health Organization.** Adoption of global agenda on influenza. *Weekly Epidemiological Record* 2002; **77**: 191–195.

4. **Bisno AL, *et al.*** Pneumonia and Hong Kong influenza: a prospective study of the 1968–69 epidemic. *American Journal of the Medical Sciences* 1971; **116**: 51–53.
5. **Gupta RK, George R, Nguyen-Van-Tam JS.** Bacterial pneumonia and pandemic influenza planning. *Emerging Infectious Diseases* 2008; **14**: 1187–1192.
6. **Nichol KL, Baken L, Nelson A.** Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Annals of Internal Medicine* 1999; **130**: 397–403.
7. **Upshur REG, Knight K, Goel V.** Time-series analysis of the relation between influenza virus and hospital admissions of the elderly in Ontario, Canada, for pneumonia, chronic lung disease, and congestive heart failure. *American Journal of Epidemiology* 1999; **149**: 85–92.
8. **Griffin MR, *et al.*** Winter viruses: influenza and respiratory syncytial virus related morbidity in chronic lung disease. *Archives of Internal Medicine* 2002; **162**: 1229–1236.
9. **Alling DW, Blackwelder WC, Stuart-Harris CH.** A study of excess mortality during influenza epidemics in the United States, 1968–1976. *American Journal of Epidemiology* 1981; **113**: 30–43.
10. **Lui KJ, Kendal AP.** Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *American Journal of Public Health* 1987; **77**: 712–716.
11. **Reichert T, *et al.*** Influenza and the winter increase in mortality in the United States, 1959–1999. *American Journal of Epidemiology* 2004; **160**: 492–502.
12. **Thompson WW, *et al.*** Mortality associated with influenza and respiratory syncytial virus in the United States. *Journal of the American Medical Association* 2003; **289**: 179–86.
13. **Chow A, *et al.*** Influenza-associated deaths in tropical Singapore. *Emerging Infectious Diseases* 2006; **12**: 114–121.
14. **Wong CM, *et al.*** Influenza-associated mortality in Hong Kong. *Clinical Infectious Diseases* 2004; **39**: 1611–1617.
15. **Centers for Disease Control and Prevention.** Estimates of deaths associated with seasonal influenza – United States, 1976–2007. *Morbidity and Mortality Weekly Report* 2010; **59**: 1057–1062.
16. **Viboud C, Alonso WJ, Simonsen L.** Influenza in tropical regions. *PLoS Medicine* 2006; **3**: e89.
17. **Moura FEA.** Influenza in the tropics. *Current Opinion in Infectious Diseases* 2010; **23**: 415–420.
18. **Carvalho MTB, *et al.*** The National Immunization Program in the 20 years of Unified Health System in Brazil. In: *Health Brazil 2008: 20 years of Unified Health System* (*SUS*) *in Brazil*. Brasilia: Ministry of Health, 2009, pp. 63–83.
19. **Alonso WJ, *et al.*** Seasonality of influenza in Brazil: a traveling wave from the Amazon to the subtropics. *American Journal of Epidemiology* 2007; **165**: 1434–1442.
20. **Brazilian Institute of Geography and Statistics.** Censo demografico 1980, 1990, 2000. (http://www.ibge.gov.br). Accessed 25 November 2010.
21. **National Institute of Meteorology.** (http://www.inmet.gov.br). Accessed 21 May 2011.
22. **Brazilian Ministry of Health.** Vital Statistics Brazil, DATASUS (http://www.datasus.gov.br). Accessed 1 December 2010.
23. **World Health Organization.** Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on Recommendations of the Ninth Revision Conference, 1975. Geneva: World Health Organization; 1977.
24. **World Health Organization.** Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on Recommendations of the Tenth Revision Conference, 1992. Geneva: World Health Organization; 1992.
25. **Serfling RE.** Methods for current statistical analysis of excess pneumonia-influenza deaths. *Public Health Reports* 1963; **78**: 494–506.
26. **Serfling RE, Sherman IL, Houseworth WJ.** Excess pneumonia-influenza mortality by age and sex in three major influenza A2 epidemics, United States, 1957–58, 1960 and 1963. *American Journal of Epidemiology* 1967; **86**: 433–441.
27. **The World Bank.** (http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Upper_middle_income). Accessed 19 January 2011.
28. **Cohen C, *et al.*** Elevated influenza-related excess mortality in South African elderly individuals, 1998–2005. *Clinical Infectious Diseases* 2010; **51**: 1362–1369.
29. **The Macroepidemiology of Influenza Vaccination (MIV) Study Group.** The macroepidemiology of influenza vaccination in 56 countries, 1997–2003. *Vaccine* 2005; **23**: 5133–5143.
30. **Antunes JL, *et al.*** Effectiveness of influenza vaccination and its impact on health inequalities. *International Journal of Epidemiology* 2007; **36**: 1319–1326.
31. **de Mello WA, *et al.*** The dilemma of influenza vaccine recommendations when applied to the tropics: the Brazilian case examined under alternative scenarios. *PLoS One* 2009; **4**: e5095.
32. **Thompson WW, *et al.*** Estimates of US influenza-associated deaths made using four different methods. *Influenza and Other Respiratory Viruses* 2009; **3**: 37–49.
33. **Newall AT, Viboud C, Wood JG.** Influenza-attributable mortality in Australians aged more than 50 years: a comparison of different modelling approaches. *Epidemiology and Infection* 2010; **138**: 836–842.
34. **Inter-Agency Health Information Network (RIPSA).** *Basic Indicators for Health in Brazil: Concepts and Applications*, 2nd edn. Brasilia: Pan-American Health Organization, 2008, pp. 292–293.
35. **Mello-Jorge MHP, Gotlieb SLD, Laurenti R.** The national mortality information system: problems and proposals for solving them. I – Deaths by natural causes. *Revista Brasileira de Epidemiologia* 2002; **5**: 197–211.