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Original Article

Mortality attributable to pandemic influenza A (H1N1) 2009 in San Luis Potosí, Mexico

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Background Acute respiratory infections are a leading cause of morbidity and mortality worldwide. Starting in 2009, pandemic influenza A(H1N1) 2009 virus has become one of the leading respiratory pathogens worldwide. However, the overall impact of this virus as a cause of mortality has not been clearly defined.

Objectives To determine the impact of pandemic influenza A(H1N1) 2009 on mortality in a Mexican population.

Methods We assessed the impact of pandemic influenza virus on mortality during the first and second outbreaks in San Luis Potosí, Mexico, and compared it to mortality associated with seasonal influenza and respiratory syncytial virus (RSV) during the previous winter seasons.

Results We estimated that, on average, 8·1% of all deaths that occurred during the 2003–2009 seasons were attributable to influenza and RSV. During the first pandemic influenza A(H1N1) 2009 outbreak, there was an increase in mortality in persons 5–59 years of age, but not during the second outbreak (Fall of 2009). Overall, pandemic influenza A (H1N1) 2009 outbreaks had similar effects on mortality to those associated with seasonal influenza virus epidemics.

Conclusions The impact of influenza A(H1N1) 2009 virus on mortality during the first year of the pandemic was similar to that observed for seasonal influenza. The establishment of real-time surveillance systems capable of integrating virological, morbidity, and mortality data may result in the timely identification of outbreaks so as to allow for the institution of appropriate control measures to reduce the impact of emerging pathogens on the population.

Keywords Acute respiratory infections, influenza virus, mortality, pandemic influenza A (H1N1) 2009, pneumonia, respiratory syncytial virus.

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Background

Acute respiratory tract infections (ARIs) are among the most common causes of morbidity and mortality worldwide.[1,2] Influenza and respiratory syncytial virus (RSV) are leading causes of respiratory infections, as well as of hospitalizations among children and older adults.[3–8] It is estimated that 20% of children and 5% of adults suffer influenza infections each year.[9] In 2009, a novel influenza virus emerged as the predominant influenza strain in the human population causing the first pandemic of the 21st century.[10,11] Although the clinical and pathological features of infections caused by the pandemic influenza A(H1N1) 2009 virus have been well described, the impact of this virus on mortality has not been completely defined.[12,13]

Although deaths confirmed to be caused by influenza infections have continued to be reported throughout the world since the onset of the pandemic, it is now evident that many cases of influenza cannot/are not readily confirmed by laboratories. In addition, morbidity and mortality associated with influenza infections may manifest as a decompensation of underlying chronic cardio-pulmonary conditions leading to increased mortality.[2] It has previously been demonstrated that both influenza and other viral respiratory infections may cause an inflammatory state capable of destabilizing atherosclerotic plaques which in turn lead to fatal cardiovascular events.[14–18] Therefore, in this paper we have included medical diagnosis other than '*deaths attributable to respiratory infections*' to evaluate the impact on mortality of influenza and RSV. The Centers for

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Disease Control and Prevention estimate that seasonal influenza viruses cause an average of 51 203 deaths per year in the United States, whereas RSV is thought to cause an average of 17 358 deaths per year.[2] However, other researchers have estimated that the impact of respiratory viruses on mortality may be much higher than currently thought; for instance, Madjid *et al.*[19] estimated that influenza virus ARIs were responsible for as many as 92 000 deaths per year in United States when cardiovascular events triggered by influenza were taken into account[19].

Mexico was the first country where widespread dissemination of pandemic influenza A(H1N1) 2009 virus was recorded.[20,21] However, the impact of this virus as a cause of mortality in contrast to seasonal influenza has been difficult to assess because of several factors: (i) the unavailability of an adequate diagnostic assay early on during the initial phases of the outbreak, (ii) the technical difficulties of detecting the presence of the virus in hospitalized patients with late complications of the influenza infection, (iii) the restriction of virological testing to patients fulfilling the case definitions initially recommended, and (iv) the paucity of epidemiological data regarding the number of deaths associated with seasonal influenza that is available in Mexico.[22] As of October 2002, we established a program to detect the presence of respiratory viruses associated with acute respiratory infections in the State of San Luis Potosí, Mexico. We have reviewed results from our surveillance program as well as local mortality data to assess the impact of pandemic influenza A(H1N1) 2009 virus in our region. In addition, this data was compared to that obtained by analyzing the impact of seasonal influenza and RSV epidemics over previous years. Although several methods have been used to define influenza epidemic periods, as well as to estimate excess mortality associated with this virus, no consensus exists regarding the best approach to define these variables.[23,24] However, excess mortality estimates obtained with the use of simple rate difference methods have shown high correlation with those obtained with more complex statistical modeling methods.[23] In addition, rate difference methods are more suitable to be used in areas of the world where virological data is limited. In this study, we have used an adaptation of the summer-baseline rate difference method that has been used by other authors to estimate excess morbidity and mortality associated with influenza epidemics.[23,25,26]

Materials and methods

Study population

The State of San Luis Potosí is located in central Mexico and, according to the 2005 census, has a population of 2 410 414. There are four geographic regions in the state and a major city in each region. San Luis Potosí City is the largest city and capital of the state; the population for this metropolitan area was 957 753 in 2005.[27]

Mortality data

To determine the number of deaths attributable to influenza and RSV, we used publicly available epidemiological data derived from death certificate databases;[28] provisional data for 2009 was provided by the local Health Department (Servicios de Salud en el Estado de San Luis Potosí). These databases register the cause of death according to the International Classification of Diseases, 10th revision (ICD-10) codes. All registered deaths that occurred in the State of San Luis Potosí for which the date of death was reported were included in the analysis. We included all deaths caused by respiratory (ICD-10 codes J00-J99) and cardiovascular (ICD-10 codes I00-I99) causes as reported by Thompson *et al.*[2] In addition, the contribution of influenza and RSV to all-cause mortality (all ICD-10 codes) was also estimated.

Seasonal fluctuations of respiratory virus infections

Local records maintained by the Virology Laboratory (Facultad de Medicina, UASLP, San Luis Potosí, Mexico) were reviewed to determine the weekly number of influenza and RSV detections in our region. Viral surveillance data is obtained with the use of immunofluorescence and molecular detection assays for influenza and RSV in samples obtained from ambulatory and hospitalized subjects with ARI. The weekly number of RSV- and influenza-positive cases was used to generate graphs depicting the seasonal fluctuations for these two viruses.

Mortality attributable to each virus

Based on the previously mentioned graphs of seasonal RSV and influenza infection fluctuations, we analyzed data for each respiratory season to define weeks with influenza and RSV activity; all weeks not included in these activity periods were considered as baseline and used to determine the number of excess cases attributable to each respiratory virus. A respiratory season included all weeks starting on epidemiological week 27 of a given year through epidemiological week 26 of the following year. The periods (weeks) of activity for each virus (and each season) were determined using the following algorithm: initially, we included all weeks in which the viruses were detected at least once, these weeks had to be flanked by at least three consecutive weeks in which no detection of that virus was recorded. Those weeks in which both viral agents were detected were assigned to the predominantly circulating (based on the percentage of the yearly detections of each virus). Finally, distinct RSV and influenza periods were defined based on the number of consecutive weeks in which each virus was prevalent so as to include only one epidemic period for each virus per year. We analyzed the weekly number of cardiovascular and respiratory deaths, and deaths because of all causes during the epidemic periods of each virus; the average weekly number of cases during the corresponding baseline period was subtracted to determine the number of excess deaths that occurred during each influenza and RSV season (from here on referred to as influenza and RSV-attributable deaths). To assess overall and age-specific rates, we used the estimated population of the State of San Luis Potosí in 2005 as mentioned previously.[27]

Seasonal and pandemic influenza periods

We analyzed data for the period spanning between 2003–2008 to determine the impact of seasonal influenza on morbidity and mortality. To assess the impact of pandemic A(H1N1) 2009 influenza virus, we analyzed data for two periods: the 2008–2009 influenza epidemic, which included the initial outbreak of the virus[29] as well as the second outbreak of pandemic A(H1N1) 2009 registered in our city during the Fall of 2009. The impact of RSV epidemics was estimated for six winter seasons encompassed between 2003 and 2009.

Statistical analysis

The proportion of RSV and influenza-attributable deaths throughout the study years were compared using the chi-square for trend test. The effect of pandemic influenza on mortality was assessed by comparing attributable mortality rates during the first and second pandemic outbreaks with the average influenza attributable mortality rate observed during the five previous winter seasons using the chi-square test. A P value <0·05 was considered as significant. Statistical analysis was performed with the use of Epi Info 3.4.3 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Results

During the six winter seasons for which complete data was available (2003–2009), there were 68 583 deaths (mean 11 430·5 deaths/year; rate 474·2/100 000 persons) recorded in the State of San Luis Potosí. Of the total number of deaths, 16 310 (23·78%) were caused by cardiovascular and 6364 (9·28%) by respiratory disorders. RSV was detected in 708 and influenza virus in 192 samples tested at our Virology Laboratory during the same study period. The weekly numbers of influenza and RSV detections, as well as the seasonal mortality fluctuations, are shown in Figure 1.

The numbers of cardiovascular and respiratory deaths attributable to each virus during the 2003–2009 winter seasons are shown in Table 1. There was a trend toward decreasing numbers of cardiovascular and respiratory deaths attributable to influenza throughout the study period. Whereas cardiovascular and respiratory deaths attributable to influenza during the 2003–2004 season were

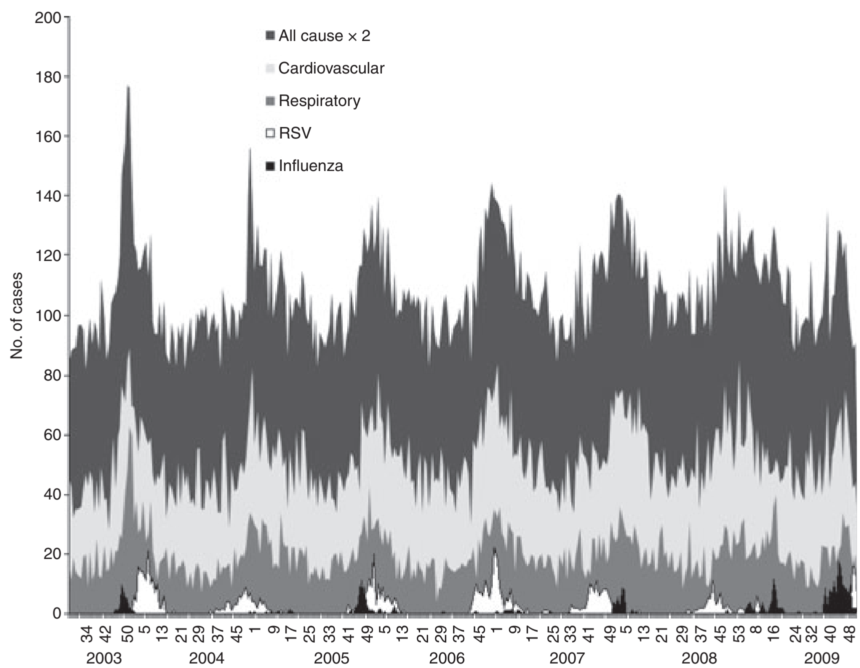

Figure 1. Seasonal fluctuations in the weekly number of all-cause deaths (no. of cases × 2), cardiovascular deaths, respiratory deaths, influenza detections, and RSV detections in San Luis Potosí, Mexico (2003–2009).

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Table 1. Number of cardiovascular, respiratory, and all-cause deaths associated with influenza and RSV epidemics in San Luis Potosi, Mexico (2003–2009)

Virus	Study year	Duration (weeks) of epidemic period	Attributable cardiovascular deaths	Attributable respiratory deaths	Attributable cardiovascular and respiratory deaths	Attributable all-cause deaths
Influenza	2003–2004	8	226	180	406	801
	2004–2005	12	60	73	133	153
	2005–2006	7	72	56	128	205
	2006–2007	8	107	72	179	343
	2007–2008	11	209	103	312	591
	2008–2009*	17	89	126	215	475
RSV	2003–2004	14	197	135	332	497
	2004–2005	24	103	108	211	345
	2005–2006	17	277	150	427	667
	2006–2007	14	252	149	401	673
	2007–2008	18	27	37	64	282
	2008–2009	20	193	121	314	528

*The 2008–2009 season includes the initial pandemic influenza A(H1N1) 2009 outbreak.

Table 2. Proportion of cardiovascular, respiratory, and all-cause associated deaths attributable to influenza and RSV in San Luis Potosi, Mexico (2003–2009)

Year	Total cardiovascular and respiratory deaths	Influenza-attributable cardiovascular and respiratory deaths (%)	RSV-attributable cardiovascular and respiratory deaths (%)
2003–2004	3815	406 (10·64)	332 (8·70)
2004–2005	3567	133 (3·73)	211 (5·91)
2005–2006	3639	128 (3·52)	427 (11·73)
2006–2007	3826	179 (4·68)	401 (10·48)
2007–2008	3912	312 (7·97)	64 (1·63)
2008–2009*	3915	215 (5·49)	314 (8·02)
Total 2003–2009	22 674	1373 (6·05)	1749 (7·71)

Year	Total all-cause deaths	Influenza attributable all-cause deaths (%)	RSV-attributable all-cause deaths (%)
2003–2004	11 342	801 (7·06)	497 (4·38)
2004–2005	10 898	153 (1·40)	345 (3·16)
2005–2006	11 036	205 (1·86)	667 (6·04)
2006–2007	11 619	343 (2·95)	673 (5·79)
2007–2008	11 671	591 (5·06)	282 (2·42)
2008–2009*	12 017	475 (3·95)	528 (4·39)
Total 2003–2009	68 583	2568 (3·74)	2992 (4·36)

*The 2008–2009 season includes the initial pandemic influenza A(H1N1) 2009 outbreak.

around 10·64% of all deaths, during the 2008–2009 season this percentage decreased to only 5·49% (Table 2; $P<0·001$; chi-square for trend). On the other hand, there was no change in the proportion of deaths attributable to RSV (8·7% for the 2003–2004 season, compared to 8% for the 2008–2009 season; $P = 0·48$; chi-square for trend). Mortality associated with RSV tended to be higher in most years, except the 2003–2004 and the 2007–2008 seasons.

The average estimated mortality rates for influenza and RSV infections according to age during the 2003–2008 seasons are shown in Table 3. As expected, the age group with highest mortality rates was that of adults ≥60 years.

When we analyzed the impact of pandemic influenza A(H1N1) 2009 virus epidemics (including the first outbreak and the Fall of 2009 outbreak), there was no increase in overall mortality compared to previous winter seasons. However, significant differences were observed in different age groups, as shown in Table 4: while no significant increases in mortality was registered for children <5 years or adults ≥60 years of age, there was a significant increase in cardiovascular- and respiratory-associated deaths for adults 20–59 years of age during both pandemic influenza A(H1N1) 2009 outbreaks ($P < 0·001$); a significant increase in all-cause mortality was registered during the first outbreak in this age group, but no increase in all-cause mortality was evident during the second outbreak of pandemic influenza A(H1N1) 2009 virus. For the 5–19 years age group, there was a significant increase in all-cause mortality during the initial pandemic influenza A(H1N1) 2009 outbreak, whereas no significant differences in mortality rates compared to previous seasons was registered during the Fall of 2009 outbreak.

Table 3. Estimated average annual influenza and RSV-associated mortality rates per 100 000 person-years in San Luis Potosí, Mexico (2003–2008)

Virus	Age group (years)	Cardiovascular and respiratory death rate	All-cause death rate
Influenza	0–4	5·3	14·22
	5–19	0·6	0·6
	20–59	1·21	3·81
	≥60	92·51	154·71
	Total	9·88	17·59
RSV	0–4	6·81	15·9
	5–19	0	0
	20–59	2·37	3·97
	≥60	108·26	183·55
	Total	11·66	20·46

The total number of all-cause deaths attributed to pandemic influenza (H1N1) 2009 virus during the first outbreak and the Fall of 2009 outbreak in San Luis Potosí was 865. Although 31·6% of influenza attributable deaths occurred in young adults (20–59 years of age) during the first pandemic influenza A (H1N1) 2009 outbreak, during the Fall of 2009 epidemic only 4·9% of attributed deaths occurred in this age group. Overall, 6·2% of influenza attributable deaths occurred in persons 0–19 years of age, while 74·1% of all deaths occurred in adults ≥60 years of age.

Discussion

Respiratory viruses are responsible for a large proportion of medical consultations and deaths throughout the world. The impact of these pathogens is observed not only as ARIs, but also as exacerbations and decompensations of chronic underlying disorders, particularly cardiovascular and respiratory diseases.[2,15,19] It is important to estimate the burden of disease for these infectious agents to assess the impact of emerging viruses, such as pandemic influenza A(H1N1) 2009 virus, as well as of the utility of preventive programs, such as vaccination campaigns.

In this study, we have estimated the impact of influenza and RSV in a Mexican population prior to and after the emergence of the pandemic influenza A(H1N1) 2009 virus. Overall, pandemic influenza A (H1N1) 2009 virus was not associated with an increase in all-cause mortality compared to previous influenza seasons. Results of an integral assessment of the first pandemic influenza wave in Réunion Island also did not find a significant increase in all-cause mortality.[30] However, we found a significant increase in mortality during the initial pandemic outbreak for persons 5–59 years of age; this was also accompanied by a significant increase in hospital admissions and intensive care unit admissions in young adults.[29] Similar results have been reported recently from an analysis of the impact of pandemic influenza (H1N1) 2009 virus in the United States:[12] while the overall number of deaths attributed to this virus was within the range registered for seasonal influenza viruses over previous years, there was a significant impact on estimated years of life lost because of the younger age group of deceased patients. An important observation in our study is that during the second pandemic influenza A (H1N1) 2009 outbreak in our region (which occurred during the Fall of 2009), we did not observe an increase in all-cause deaths for any age group compared to previous seasonal influenza epidemics.

Although young adults were affected more seriously by pandemic influenza A (H1N1) 2009 virus than by seasonal influenza viruses, the greatest impact in attributable mortality was observed in older adults. These results contrast

Table 4. Estimated influenza-associated deaths during the 2003–2008 influenza seasons, 2008–2009 season (first pandemic outbreak), and the Fall of 2009 pandemic influenza outbreak

Age group (years)	Cardiovascular and respiratory death rate*			All-cause death rate*		
	2003–2008 seasons	2008–2009 season	Fall 2009	2003–2008 season	2008–2009 season	Fall 2009
0–4	5·3	NA	2·37	14·22	12·19	NA
5–19	0·6	0·86	NA	0·6	2·9	NA
20–59	1·21	3·76	5·09	3·81	13·58	1·7
≥60	92·51	75·91	90·51	154·71	122·24	164·72
Total	9·88	8·91	10·84	17·59	19·71	16·05

*Rates per 100 000 population.
NA, no increase over baseline mortality recorded.

with the age distribution reported for confirmed pandemic influenza-associated deaths in our country in which most deaths have been recorded in adults 20–59 years of age.[31] This difference could be explained by the fact that we included all-cause mortality, in addition to pneumonia-associated deaths, in our analysis; of note, testing for pandemic influenza virus infection has been restricted to subjects fulfilling a clinical case definition of suspected influenza infection and with short duration since the onset of symptoms (usually <5 days). Therefore, patients who may have presented with non-immediate complications of influenza infections, such as exacerbations of chronic underlying illnesses or cardiovascular events, were not eligible for testing. Castilla *et al.*[13] have also reported that limiting the analysis of the impact of pandemic influenza to confirmed cases probably underestimates the effect of this virus in the elderly. In addition, studies carried out in diverse populations have shown that the highest case-fatality rates associated with confirmed pandemic influenza infections occurred in older adults.[30,32–34]

Overall, the estimated mortality rates attributable to seasonal influenza that we describe for our population are similar to those reported from the United States, except for children <5 years of age; in this age group, the estimated mortality rate for Mexican children was significantly higher. This finding is consistent with the overall higher mortality rate for children under 5 years of age estimated by the Pan American Health Organization[35] for Mexico (22/1000 live births) compared to that of the United States (8/1000 live births).

An additional finding in our study is the estimated effect of RSV on mortality for the Mexican population. No prior studies have addressed the impact of this virus in our country. Although the estimated cardiovascular and respiratory mortality rates attributable to influenza that we found are comparable to those reported for the United States population during the period of 1991–1999, RSV-attributable deaths were higher than those estimated in the United States.[2] However, studies performed in other geographic areas have also found that the impact of RSV and influenza on mortality to be comparable; for instance, Fleming *et al.*[36] estimated that the number of deaths attributable to RSV in England was almost the same as the one attributable to influenza. Our results show that, in addition to influenza virus, RSV is a major cause of mortality in Mexico in practically all age groups.

In summary, the emergence of pandemic influenza A (H1N1) 2009 was not associated with an increase in all-cause mortality compared to previous influenza seasons in San Luis Potosí, Mexico. During the initial epidemic outbreak, there was a significant increase in all-cause mortality for young persons (5–59 years of age), but no increase in mortality was evident during the second pandemic influenza A (H1N1) 2009 wave. Strengthening of regional respiratory virus surveillance, as well as continuous monitoring of morbidity and mortality data is required for timely identification of emerging viruses and institution of appropriate control measures geared toward limiting the social, economical, and sanitary impact of such pathogens.

Conflict of interest

Daniel E. Noyola is a member of the speakers' bureau for Abbott Laboratories de México.

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