Trends in mortality from respiratory disease in Latin America since 1998 and the impact of the 2009 influenza pandemic

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Abstracts in العربية, Français,  Русский  и Español at the end of each article.

Introduction

Respiratory diseases are important causes of morbidity and mortality worldwide. Each year, according to the World Health Organization (WHO), they are associated with more than 7.6 million deaths. Such diseases may be chronic conditions, such as asthma and chronic obstructive pulmonary disease, or acute infections, such as pneumonia and influenza.

The morbidity and mortality associated with influenza varies in each influenza season because of differences in attack rates and the types or subtypes of influenza virus that are in circulation. In the 1997–1998 and 1999–2000 seasons in the United States of America, for example, the main viral subtype in circulation – A(H3) – caused high morbidity and mortality.2,3

Influenza pandemics occur when a new influenza virus strain affects animals is transmitted to humans and causes disease worldwide. The first influenza pandemic of the 21st century is believed to have begun in April 2009, when the A(H1N1)pdm09 virus emerged in Mexico and the United States and then spread rapidly worldwide.4–6 By August 2010, the Pan American Health Organization (PAHO) had received reports – from 28 countries and four territories in the Americas – of more than 8500 deaths that had been confirmed, by laboratory tests, to be associated with the novel pandemic virus. The virus probably caused many deaths that were never confirmed in the laboratory as being attributable to it. According to estimates, the (H1N1) 2009 pandemic was associated with more than 12 000 deaths in the United States4 and 280 000 deaths worldwide.7

Assessment of the true impact of the (H1N1) 2009 pandemic on mortality is important if we are to plan and prepare well for future pandemics. As there seem to be few relevant data from Latin America, the aim of the present study was to determine trends in mortality from respiratory disease in seven areas of Latin America between 1998 and 2009 or 2010.

Methods

Data sources

We investigated mortality in seven areas of Latin America: Argentina, southern Brazil (i.e. the states of Paraná, Rio Grande do Sul, Santa Catarina and São Paulo), Chile, Costa Rica, Ecuador, Mexico and Paraguay. Data on mortality for the period 1998–2009 (for Argentina, Chile, Costa Rica, Ecuador and Paraguay) or 1998–2010 (for southern Brazil and Mexico) were extracted from PAHO’s regional mortality database.8 This database relies on registered deaths and on death certificates that show, among other variables, the underlying cause of death – coded using the International statistical classification of diseases and related health problems, 10th revision (ICD-10)


– and the date and place of death. Over the study period, registered deaths were estimated to represent more than 95% of all deaths in Argentina, Brazil, Chile, Costa Rica and Mexico, 85% of all deaths in Ecuador and about 70% of all deaths in Paraguay.\textsuperscript{11} The data on the registered deaths in Paraguay were considered to be of relatively poor quality because the cause of 12% of the deaths was “ill defined”.\textsuperscript{11} The cause of less than 10% of the deaths registered over the study period in each of the other six study areas was “ill defined”.\textsuperscript{11} 

Over the study period, the states of Paraná, Rio Grande do Sul, Santa Catarina and São Paulo accounted for about 50% of all deaths from respiratory disease in Brazil and for most of the Brazilian deaths attributed to the (H1N1) 2009 pandemic.\textsuperscript{12,13} 

Deaths given ICD-10 codes of J00–J99 were attributed to respiratory disease and some of these – those coded J09–J18 – were attributed to pneumonia and/or influenza.\textsuperscript{14} 

Mortality rates were expressed as deaths per 100 000 people of the age group of interest. To calculate these rates, we used the relevant estimates of the populations for each of the study areas, as provided by the United Nations,\textsuperscript{15} or – for southern Brazil – the Brazilian Institute of Geography and Statistics.\textsuperscript{16} 

\section*{Data analysis}
Like some previous investigators,\textsuperscript{17} we considered mortality among four age groups: 0–4, 5–49, 50–64 and ≥ 65 years. Although more age groups have been recommended for studies on influenza,\textsuperscript{18} we used only four to increase the power of our statistical analyses. Mortality rates were investigated by month (Argentina, Costa Rica and Ecuador) or “epidemiological week” (other study areas). 

A descriptive analysis was performed. In addition, to investigate trends and test for a possible increase in the baseline rate of mortality from respiratory disease in 2009, we fitted a robust linear model\textsuperscript{19} to the monthly or weekly rates of mortality from respiratory disease for 2003–2009. This model was used for all of the study areas except two – Costa Rica and Ecuador reported too few respiratory deaths, by month, to model – and was not used for data collected before 2003 because monthly rates of mortality from respiratory disease before that year could not be determined for another two study areas (Argentina and Ecuador). We included sine and cosine functions to model seasonality.\textsuperscript{21} The final model for the data analysed by epidemiological week was as follows:

\begin{equation}
\ln (\text{rate}_t) = \beta_1 + \beta_2 t + \beta_3 \sin(2\pi t / 52) + \beta_4 \cos(2\pi t / 52) + \beta_5 \text{year}_t + e_t,
\end{equation}

where \( t \) is the index corresponding to each epidemiological week, \( e \) is the error term, and \( \text{year}_t \) was given a value of 1 for 2009 and 0 for the other study years. For the data from southern Brazil, we also included an explanatory dummy variable – given a value of 0 for 2003 and a value of 1 for 2004–2009 – because a change in the procedure for death registration in the state of São Paulo led to a reduction in the proportion of deaths that were registered in that state after 2004.

The data were analysed and modelled using the R package of statistical software (R Foundation, Vienna, Austria), the rlm library\textsuperscript{22} and M-estimates.\textsuperscript{19} The aim was to produce robust estimates in the presence of outliers.

No ethics approval was needed for this investigation, which was a secondary analysis of data that had already been made anonymous.

\section*{Results}
The results of the descriptive analysis and data modelling are summarized in Table 1 and in Fig. 1, Fig. 2, Fig. 3 and Fig. 4. Between 1998 and 2009, respiratory diseases accounted for an annual mean of 142 521 reported deaths in the seven study areas combined – representing 10.7% and 11.0% of the all-cause mortality in these areas in 1998 and 2009, respectively. Over the same period, the annual mean numbers of deaths from respiratory disease and the corresponding age-adjusted rates of mortality from such disease – in deaths per 100 000 people – were, respectively, 39 395 and 80.5 in Argentina, 44 923 and 49.0 in Chile, 1428 and 40.6 in Costa Rica, 4967 and 62.5 in Ecuador, 41 797 and 51.7 in Mexico, and 1363 and 62.0 in Paraguay. Pneumonia and/or influenza accounted for 37.2% of the deaths from respiratory disease recorded in the study areas in 1998–2009 – 35.2%, 40.1%, 46.4%, 27.0%, 56.3%, 31.5% and 59.6% of those recorded in Argentina, southern Brazil, Chile, Costa Rica, Ecuador, Mexico and Paraguay, respectively.

\section*{Trends in mortality rates}

\subsection*{Descriptive analysis}
Over the study period, in the seven study areas combined, the percentage of deaths from respiratory disease represented by children younger than 5 years gradually fell, from 10% \((n = 13 635)\) in 1998 to 4% \((n = 6265)\) in 2008. Between 1998 and 2008, the corresponding mortality rates – in deaths per 100 000 children younger than 5 years – fell by 41% in Argentina, 63% in southern Brazil, 70% in Chile, 72% in Costa Rica, 42% in Ecuador, 46% in Mexico and 53% in Paraguay (Fig. 1). In Argentina, the otherwise steady decline in the respiratory-disease-attributable mortality of such young children was interrupted by two peaks: one in 2003 and the other in 2007 (Fig. 1). Among children younger than 5 years, Ecuador and Chile had the highest and lowest mortalities from respiratory disease, respectively (Table 1). In 2009, four of the seven study areas showed an increase in mortality from respiratory disease in this age group with respect to 2008. The increase ranged from just 1% in Costa Rica to 11% in Chile (Table 1). Southern Brazil showed no change, whereas Ecuador and Mexico showed decreases of 8% and 6%, respectively.

Between 1998 and 2008, rates of mortality from respiratory disease among those aged 5 to 49 years decreased in southern Brazil, Chile, Costa Rica and Paraguay but remained fairly stable in Argentina, Ecuador and Mexico (Fig. 2). In general, southern Brazil had the highest rates of mortality from respiratory disease among those aged 5 to 49 years and Costa Rica had the lowest rates (Fig. 2). Between 1998 and 2008, such mortality peaked twice in Argentina (in 2003 and 2007) and once in Paraguay (in 2007). In 2009, however, the rates of mortality from respiratory disease recorded among those aged 5 to 49 years were generally higher than those recorded in 2008 – only 13% higher in Chile but 84% higher in Paraguay (Table 1). In 2010, the corresponding rate in southern Brazil had fallen back to the level ob-
Table 1. Rates of mortality from respiratory disease, Latin America, 1998–2010

<table>
<thead>
<tr>
<th>Area</th>
<th>Age group (years)</th>
<th>Mortality rate*</th>
<th>Mean annual per cent change in 2003–2008 (SE)</th>
<th>P</th>
<th>Per cent change in 2009 (SE)</th>
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<td>351.8</td>
<td>291.2</td>
<td>244.0</td>
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</tbody>
</table>

ND, not determined; SE, standard error.

a Deaths per 100 000.

b As estimated by the robust linear model.

c Percentage change in mortality in 2009 relative to 2003–2008, as estimated by the robust linear model. This captures the change in mortality presumed to be related to the 2009 pandemic.

d Comprising the states of Paraná, Rio Grande do Sul, Santa Catarina and São Paulo.

Among the eldest subjects – those 65 years of age or older – the rate of mortality from respiratory disease decreased between 1998 and 2008 in all of the study areas except Argentina and Ecuador (Table 1 and Fig. 4). The decline over this period varied from 43.3% in Costa Rica to 15% in Mexico. Among those aged 65 years or older, rates of mortality from respiratory disease were highest in Argentina and southern Brazil and lowest in Paraguay. In 2009 they were similar or lower than the values recorded in 2008 except in Paraguay, where the rate in 2009 was 35% higher than that recorded in 2008 (Table 1).

Linear model estimates

The data modelling indicated that, between 2003 and 2008, mortality from respiratory disease decreased significantly among children younger than 5 years in all of the study areas except Chile. The mean annual decrease over this period varied from 3% in Mexico (95% confidence interval, CI: 2–4) to 12% in Paraguay (95% CI: 9–16) (Table 1). In terms of the mortality from respiratory disease among children younger than 5 years, the increases observed in 2009 – relative to 2008 – were not statistically significant except for the increase of 30% (95% CI: 0.4–59) recorded in Paraguay.

Between 2003 and 2008, rates of mortality from respiratory disease among people aged 5 to 49 years remained fairly stable in Argentina, southern Brazil and Paraguay but showed mean annual increases of 8% in...
Research

Trends in mortality from respiratory disease in Latin America

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Chile (95% CI: 4–11) and 4% in Mexico (95% CI: 3–5) (Table 1). Such mortality was significantly higher in 2009 than in 2008 only in Mexico (43%; 95% CI: 34–52), Paraguay (42%; 95% CI: 8–75) and southern Brazil (13%; 95% CI: 8–19) (Table 1).

Among those aged 50 to 64 years, rates of mortality from respiratory disease remained fairly stable between 2003 and 2008 in Argentina, southern Brazil, Chile and Mexico but decreased, by about 6% annually (95% CI: 2–10), in Paraguay (Table 1). They were significantly higher in 2009 than in 2008 in both Mexico (14% increase; 95% CI: 9–20) and Paraguay (60% increase; 95% CI: 20–100).

Seasonality of respiratory mortality

Each year between 1998 and 2008, the rate of mortality from respiratory disease among individuals aged 5 to 64 years increased during the winter months of June to August in Argentina, southern Brazil, Chile and Paraguay and during the winter months of December to February in Mexico. In tropical Costa Rica and Ecuador, no seasonal pattern in respiratory deaths was identified over the same period.

In 2009, the rate of mortality from respiratory disease among individuals aged 5 to 64 years peaked in southern Brazil over a few weeks in July and August (epidemiological weeks 28–35), in Paraguay in July (epidemiological weeks 27–31), in Argentina in June and July, and in Costa Rica in July and August. However, the corresponding rate in Mexico did not show the seasonal pattern seen over the previous decade. Instead, it showed three peaks in 2009, each representing an epidemic. The first Mexican epidemic of 2009 began in March, reached a peak in mid-April and decreased in mid-May. A second, smaller epidemic occurred between mid-June and mid-July. Finally, the number of deaths from respiratory disease rose rapidly over 5 weeks from the end of August – when deaths totalled 513 in epidemiological week 40 – before dropping back to levels that are more typical for the season.

Discussion

In our study of seven areas of Latin America, annual rates of mortality from respiratory disease generally either remained stable or fell between 1998 and 2008, as seen in several other regions. There were particularly marked reductions in such mortality among young children. In Latin America, decreases in respiratory mortality among children may have many causes but probably relate mostly to improvements in sanitation, perinatal care, health maintenance, nutrition, supportive care (e.g. oral rehydration therapy), accessibility to antibiotics and antivirals and/or vaccination programmes. Latin America
has achieved important gains in the use of vaccines to protect children against severe illness and death caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* type b or influenza virus. In the United States, the increased use of protein–polysaccharide conjugate vaccines has markedly reduced mortality caused by invasive pneumococcal disease among individuals aged 5 to 49 years were recorded in southern Brazil, Mexico and Paraguay. The timing of these increases and the return to more usual levels of mortality from respiratory disease in 2010 – at least in southern Brazil – indicate that these increases were largely – and perhaps entirely – attributable to the (H1N1) 2009 pandemic. Other studies have documented a disproportionate effect of this pandemic on individuals aged 5 to 49 years or similar age groups. The increases seen in 2009 in the rates of mortality from respiratory disease among individuals aged 50 to 64 years in Mexico and Paraguay may also represent the effects of the 2009 pandemic.

As for the national trends in mortality from respiratory disease observed since 2003, the (H1N1) 2009 pandemic appears to have had no significant effect in Chile, irrespective of the age group investigated. This finding might be related to Chile’s universal access to health care, the interventions the country conducts every winter to reduce severe respiratory outcomes, and the liberal distribution of oseltamivir during the pandemic. This drug was not restricted to severe cases but was also given to ambulatory patients who had known risk factors for severe infection.

Between 1998 and 2008, rates of mortality from respiratory disease among people aged 65 years or older that we investigated were found to be relatively high and to be stable in all of our study areas except Chile and Mexico. It remains unclear why the rates of reported mortality from respiratory disease among the elderly of Argentina and southern Brazil were, in general, more than 30% higher than those observed over the same period in Chile, but the differences may reflect variation in health-service performance. Data from PAHO indicate that the rates of all-cause mortality and mortality from communicable diseases recorded between 2007 and 2009 were lower in Chile than in Argentina and southern Brazil.

The present analyses have several limitations. First, the data available on mortality may have been badly affected by unregistered deaths, especially in Paraguay. Second, the linear model that we used was designed to provide stable trend estimates for entire years and may therefore mask short-lived peaks in mortality, such as the increases seen in Argentina over just two months in 2009.
When monthly – rather than weekly – summary data are the best available, such short-lived peaks are also likely to lose statistical significance. Third, the confidence intervals for the mortality rates for Chile and Paraguay were particularly wide – for all age groups – and therefore also made it difficult to detect significant patterns in the data. Fourth, some of the age groups that we used were very large. Although we considered splitting the data into 5-year age groups, this would have produced some age groups that were too sparsely populated to allow the robust analysis of the temporal trends in mortality.

In conclusion, we identified important post-1998 declines in mortality from respiratory disease in several areas of Latin America, particularly among children younger than 5 years. In Latin America, as in some other regions, vaccination appears to be helping to reduce mortality from respiratory disease, although other factors also probably contributed to the declines observed before the (H1N1) 2009 pandemic. Although this pandemic often led to increases in mortality from respiratory disease, these increases may well be short-lived. We encourage clinicians and scientists to explore the impact and potential value of interventions designed to prevent or mitigate respiratory disease. The results of such research may help support and guide the policy-makers who are involved in the funding of such interventions. Additional information on regional rates of mortality from respiratory disease will aid in the planning and preparation for future influenza pandemics and lead to a better understanding of the levels and trends in the key causes of pandemic-associated deaths.

Competing interests: None declared.

### ملخص

في عام 2008، وعلى مدار هذه الفترة، كانت معدلات الوفيات الناجمة عن الأمراض التنفسية عموماً هي الأعلى بين البالغين الذين تراوحت أعمارهم من 65 سنة وال أقل بين الأفراد الذين تراوحت أعمارهم من 5 إلى 49 سنة. وفي عام 2009، كان معدل الوفيات الناجمة عن الأمراض التنفسية إما مشابهاً لذلك الذي تم تسجيله في عام 2008 أو أظهر ارتفاعًا - لوحظت ارتفاعات كبيرة بين الأطفال الذين تراوحت أعمارهم من 5 إلى 49 سنة في جنوب البرازيل والمكسيك وباراغواي. وتم ملاءمة النماذج الخطية القوية بين معدلات الوفيات الناجمة عن الأمراض التنفسية المسجلة في الفترة من 2003 إلى 2009. في النتائج من الفترة من 1998 إلى 2008، انخفضت معدلات الوفيات الناجمة عن الأمراض التنفسية تدريجياً في جميع الفئات العمرية في معظم مناطق الدراسة. على سبيل المثال، انخفضت معدلات الوفيات السنوية لهذه الحالات بين الأطفال الذين تراوحت أعمارهم من 5 سنوات عبر جميع مناطق الدراسة السبعة - من 56.9 حالة وفاة لكل 100000 منlàl في عام 1998 إلى 26.6 حالة وفاة لكل 100000

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### 摘要

1998 年以来拉丁美洲呼吸系统疾病的死亡率趋势和 2009 年流感大流行的影响

目的 1998 年至 2009 年之间拉丁美洲数个地区呼吸系统疾病的死亡率趋势和。

方法 从阿根廷、巴西南部、智利、哥斯达黎加、厄瓜多尔、墨西哥和巴拉圭的死亡数据中提取方法。运用稳健回归模型对这些数据进行拟合。结果

结果

结束 2009 年，这些趋势停止，这可能是受（H1N1）2009 年大流行的影响。
Trends in mortality from respiratory disease in Latin America since 1998 and the impact of the 2009 pandemic

### Resumen

Las tendencias de la mortalidad por enfermedades respiratorias en América Latina desde 1998 y el impacto de la pandemia de gripe de 2009

**Objetivo** Determinar las tendencias de la mortalidad por enfermedades respiratorias en varias zonas de América Latina entre 1998 y 2009.

**Métodos** El número de muertes atribuidas a enfermedades respiratorias entre 1998 y 2009 se obtuvo de los datos sobre la mortalidad en Argentina, Brasil, Colombia, Costa Rica, Ecuador, México, y Paraguay, y se adaptaron modelos lineales sólidos a las tasas de mortalidad por enfermedades respiratorias registradas entre 2003 y 2009.

**Resultados** Entre 1998 y 2008, las tasas de mortalidad por enfermedades respiratorias disminuyeron gradualmente en todos los grupos de edad en la mayoría de las áreas de estudio. Entre los niños menores de 5 años, por ejemplo, las tasas anuales de dicha mortalidad (en las siete áreas de estudio) se redujeron de 56,9 decés por 100 000 en 1998 a 26,6 decés por 100 000 en 2008. Durante este periodo, las tasas de mortalidad por enfermedades respiratorias fueron en general más altas entre los adultos mayores de 65 años y más bajas entre las personas de 5 a 49 años. En 2009, la mortalidad por enfermedades respiratorias fue similar a la registrada en el 2008 o mostró un incremento, pues se observó un aumento significativo entre los niños menores de 5 años en Paraguay, entre individuos de edades de 5-49 años de edad en el sur de Brasil, México y Paraguay, así como entre los adultos con edades comprendidas entre 50 y 64 años en México y Paraguay.

**Conclusión** En gran parte de América Latina, la mortalidad por enfermedades respiratorias se redujo gradualmente entre 1998 y 2008. Sin embargo, esta tendencia a la baja se detuvo en 2009, probablemente como resultado de la pandemia (H1N1) de 2009.
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