

Short Communication

Laboratory-confirmed deaths caused by influenza A (H1N1)pdm09 in the Santa Catarina State, Brazil, 2009-2014

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Abstract

Introduction: Little information is available on the evolution of influenza A (H1N1)pdm09-related mortality in Brazil. **Methods:** During the period 2009-2014, official epidemiological surveillance and mortality data were used to ascertain influenza-related deaths in the Santa Catarina State in Brazil. **Results:** The highest overall mortality rate (2.3 per 100,000) was observed in 2009. Pregnant women constituted the highest risk group (mortality rate 18.0 per 100,000). Following vaccination of high-risk groups, the rate reduced sharply but peaked again in 2012. It subsequently decreased, albeit more gradually. **Conclusions:** Influenza A (H1N1)pdm09 mortality demonstrated a cyclic pattern, with two peaks followed by a gradual decrease.

Keywords: Influenza A (H1N1). Mortality rate. Brazil.

Among new strains of influenza with an impact on mortality globally, A (H1N1)pdm09 is the most significant of this century. Despite the huge attention received since its emergence and the massive vaccination campaigns undertaken by many countries, the associated mortality has rarely been calculated with laboratory-proven case ascertainment. This is true of South America in general, and of Brazil, the largest South American country. In 2009, the year the new influenza strain emerged, Brazil registered the highest number of influenza-related deaths worldwide, although the mortality rate was relatively low at 0.39 per 100,000 inhabitants⁽¹⁾.

However, only 16.7% of these deaths were confirmed by real-time polymerase chain reaction (RT-PCR) laboratory testing, thus raising the question of the influence of the well-known regional variations in sensitivity of the Brazilian epidemiological surveillance systems on the above estimates. Another analysis, based only on RT-PCR-confirmed cases, estimated the A (H1N1)pdm09 mortality rate to be 1.15 per 100,000 in Brazil between May 2009 and May 2010, with the Southern States of Rio Grande do Sul and Santa Catarina exceeding the mortality rate of 3 per 100,000 for pneumonia and influenza⁽²⁾. Most other Brazilian studies on influenza A (H1N1)pdm09 mortality focused on the first pandemic year and clinical aspects of the disease (treatment, case-fatality, risk factors for hospital admission, and survival) in a particular state or health setting^{(3) (4) (5) (6) (7) (8)}. Thus, there is a paucity of published data on the evolution of the mortality related to this strain in Brazil.

This paper aimed to provide the first account of the evolution of influenza A (H1N1)pdm09 mortality using RT-PCR confirmed cases between 2009 and 2014 in the State of Santa Catarina – the state that registered the highest influenza – related mortality rate in Brazil.

The main data source for this analysis were the reports published by the Ministry of Health^{(9) (10) (11) (12) (13) (14)} and by the official epidemiological surveillance system [*Sistema Nacional de Agravos de Notificação (SINAN)*]⁽¹⁵⁾. A (H1N1)pdm09 identification was performed by RT-PCR in the Adolfo Lutz Institute laboratory (Rio de Janeiro, Brazil). The analysis focused on mortality as the main outcome measure since death is the most severe component of disease burden, and is also least likely to be missing from registers. Death caused by A (H1N1)pdm09 was identified by SINAN. In addition, for all suspected influenza cases reported to SINAN with no update on disease evolution, a death certificate search was conducted. From the death certificate search, any death where A (H1N1)pdm09 was mentioned, whether listed as the main cause or not, was included in order not to miss deaths resulting from complications of influenza. Annual mortality rates (MR) caused by A (H1N1)pdm09 were calculated by calendar year, region of residence, age group (<5, 5-19, 20-39, 40-59, and ≥60 years), and for pregnant women. The Brazilian Institute for Geography and Statistics census data and population projections for the aforementioned age groups were used as MR denominators. The pregnant population was derived from the Ministry of Health's database [acronym *Sistema de Informações sobre Nascidos Vivos (SINASC)*]. Influenza A (H1N1)pdm09 vaccination coverage and percentage of PCR-investigated cases by calendar year were also analyzed. Poisson distribution was used to estimate the 95% confidence intervals (CI) for the MR.

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In the first year of the influenza A (H1N1)pdm09 pandemic (2009), the percentage of PCR-investigated cases notified to the Santa Catarina State Epidemiological Surveillance reached almost 90%, ranging between 83% in the Southern region and 95% in the Northeastern region. The following year, the percentage remained high (94-100%) in all except the Mountain region. In 2011, the lowest percentage was observed in the Highland region (69%) while other regions varied from 87-97%. In 2012, when a second peak of influenza A (H1N1)pdm09 occurred, the percentage of cases notified ranged between 83% in the Far West to 99% in the Greater Florianopolis area, and remained at similar levels during next two years.

As mentioned, influenza A (H1N1)pdm09 in Santa Catarina showed two peaks: the first occurred in 2009, when the pandemic first reached Brazil, and the second in 2012. Of the total influenza deaths from 2009-2014, 86.3% (264/305) occurred in these two peak years (**Figure 1**). Both peaks occurred in roughly the same geographic areas and were followed by a 2-year respite. Overall, the influenza-related MR was largely determined by the A (H1N1)pdm09 component which caused almost 90% (144/162) and 94% (74/79) of all influenza-related deaths confirmed by PCR in the two peak years of 2009 and 2012, respectively. The MR for seasonal influenza A (H3N2) also peaked in these years, whereas only two influenza B-related deaths were confirmed during the period. Influenza A (H3N2) caused 18 PCR-confirmed deaths in 2009, one in 2011, five in 2012, six in 2011, and nine in 2014.

In 2009, the highest MR per 100,000 was observed among pregnant women (18.0), followed by 20-59-year-olds (3.2), and those aged ≥ 60 years (2.0) (**Table 1**). Although they initially had the highest MR, from 2010-2014 no influenza-related deaths were reported in pregnant women, not even during the second mortality peak in 2012. The age groups 40-59 and ≥ 60 years demonstrated a slower decline in MR after the second peak compared to other groups. In addition, no A (H1N1)pdm09 related deaths were registered among children aged < 2 years during the period analyzed.

Regional comparison of the MR peaks showed a significant reduction in 2012 compared to 2009 in five of the nine regions:

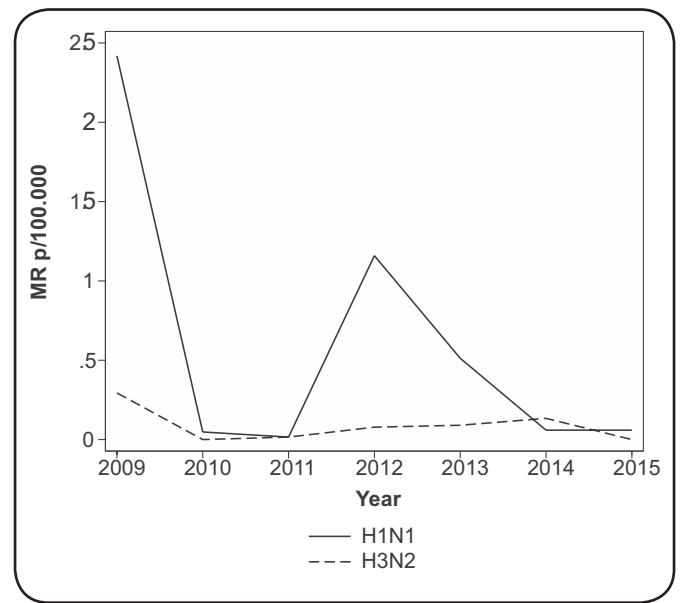


FIGURE 1. Mortality rates of influenza A(H1N1) and A(H3N2) in Santa Catarina, Brazil. **MR:** mortality rate.

the Far West, Midwest, Southern, Northeastern and Mountain regions (**Figure 2**). The Midwest had the highest MR per 100,000 in 2009 (4.5) but the Itajaí Valley took its place in 2012 with 2.3 per 100,000 inhabitants. The largest MR reduction (93%) was observed in the Northeastern region. The latter had one of the lowest MR in 2009 but bounced back to the 2009 level in 2013.

Official death certificates registered only 37 and 21 deaths related to influenza A versus the 148 and 74 A (H1N1)pdm09 related deaths registered by epidemiological surveillance in the peak years of 2009 and 2012, respectively. Hence, vital statistics data underestimated the number of deaths caused by the new pandemic strain by at least 75% in 2009 and 72% in 2012. The underestimation decreased to 59.5% in 2013 and 64.3% in 2014. In 2009, 57.6% of the total annual influenza-

TABLE 1
Annual influenza A (H1N1)pdm09 mortality rate per 100,000 by risk group in Santa Catarina, Brazil.

Risk group	Calendar year				
	2009 MR (95% CI)	2010 MR (95% CI)	2011 MR (95% CI)	2012 MR (95% CI)	2013 MR (95% CI)
0-4 years	0.45 (0.05, 1.60)	0.00 (0.00, 0.83)	0.00 (0.00, 0.83)	0.23 (0.01, 1.30)	0.00 (0.00, 0.84)
5-19 years	0.82 (0.44, 1.40)	0.00 (0.00, 0.23)	0.00 (0.00, 0.24)	0.26 (0.07, 0.66)	0.00 (0.00, 0.24)
20-39 years	3.26 (2.50, 4.10)	0.05 (0.00, 0.26)	0.00 (0.00, 0.17)	0.59 (0.32, 0.99)	0.13 (0.03, 0.39)
40-59 years	3.20 (2.40, 4.20)	0.06 (0.00, 0.35)	0.06 (0.00, 0.35)	2.70 (1.99, 3.70)	2.00 (1.40, 2.80)
≥ 60 years	1.97 (0.99, 3.40)	0.00 (0.00, 0.57)	0.00 (0.00, 0.55)	1.50 (0.77, 2.80)	1.10 (0.46, 2.10)
Pregnant women	18.00 (10.00, 30.00)	0.00 (0.00, 4.40)	0.00 (0.00, 4.20)	0.00 (0.00, 4.20)	0.00 (0.00, 4.20)

MR: mortality rate; **CI:** confidence interval.

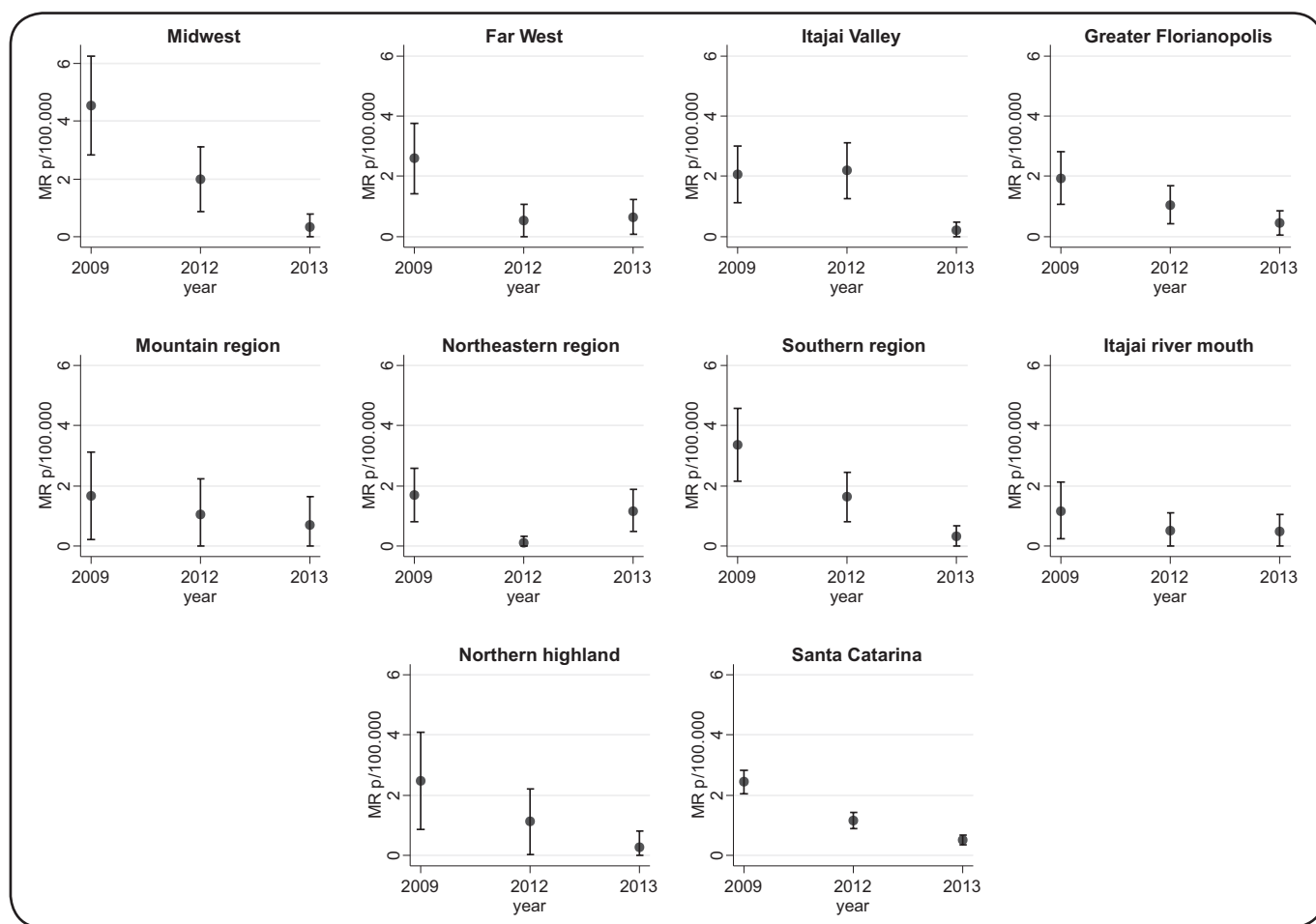


FIGURE 2. Influenza A (H1N1)pdm09 mortality rates per 100,000 inhabitants by regions of Santa Catarina in 2009, 2012, and 2013. **MR:** mortality rate.

related deaths occurred in August. July and September added 16.7% and 21.5%, respectively. In 2012, June was the month with the highest death toll (63.5%), followed by May (21.6%) and June (13.5%).

Influenza vaccination coverage of the target population in Santa Catarina was just more than 50% in 2010 but climbed to 85.6% in 2011 and remained at 95-98% over the following three years. Among pregnant women, the coverage was 90.3% in 2010, dropped to 64.1% in 2011, and increased to 88.7% and 85.9% in 2012 and 2013, respectively. The coverage of children <2 years of age was reported as 100% for all years analyzed except for 2011, when it was slightly lower (91%). In 2010, only older persons with chronic diseases such as diabetes; hypertension; or serious heart, lung, or kidney diseases, were targeted for vaccination, so the overall coverage for this group was low (42.5%). However, universal vaccination against influenza A (H1N1)pdm09 was offered to this group after 2010, which increased coverage to 84.7%, 89.8%, and 93.2% in the subsequent years.

Influenza A (H1N1)pdm09 in Santa Catarina showed two peaks: the first one in 2009, when the pandemic first reached Brazil, and the second in 2012. The second mortality peak

(MR 1.2 per 100,000) was about half the first, probably due to vaccination of high-risk groups (pregnant women, people with severe chronic diseases, children <2 years, and those aged ≥60 years). Further, after 2009, no subsequent influenza-related deaths were registered among pregnant women. A recent report also showed high vulnerability of pregnant women in the beginning of the pandemic in Brazil, when the case-fatality reached almost 7%⁽³⁾. Contrary to the widespread reports on low A (H1N1)pdm09 mortality among older- compared with younger- age groups in Brazil^{(1) (2) (4) (5) (6) (7)}, the present study found the opposite result in Santa Catarina, although the difference was not statistically significant. High mortality rates among older people were reported in Hong Kong and Japan, possibly due to influenza A(H3N2) which also circulated in those countries and which is known to cause significant mortality⁽¹⁴⁾. In line with these results, the present study found 18 PCR-confirmed deaths from A (H3N2) in 2009 and almost seven deaths per year in the period 2011-2014 in the general population.

In 2009, the A (H1N1)pdm09 mortality rate per 100,000 population based on laboratory-confirmed cases in Santa Catarina was twice the Brazilian average of 1.1⁽²⁾ and was even

greater compared with mortality rates in the Ceará State in the Northeast (0.9) and in the São Paulo State in the Southeast of Brazil (0.8) during winter (June–September)⁽⁶⁾. This result is in line with a comprehensive analysis of the A (H1N1)pdm09 spatial distribution in Brazil that found strong evidence for progressively milder disease at lower latitudes⁽²⁾, likely due to warmer winters. In 2012, the second highest influenza mortality year, winter began earlier and was much colder than usual. This may explain why in that year the highest proportion of A (H1N1)pdm09 deaths occurred in June, two months earlier than in 2009 when the month of August accrued the most deaths. Regional variations of A (H1N1)pdm09 mortality rate in Santa Catarina were more pronounced in 2009 compared to 2012. All regions except the Northeastern region registered a decrease in influenza mortality, although no significant differences in A (H1N1)pdm09 vaccination coverage were observed across the regions during the period analyzed. Some regions displayed a faster decline of the MR after the second peak whereas the others presented a more gradual decline (**Figure 2**). Influenza mitigation efforts should be analyzed and improved when necessary in order to further reduce the related mortality.

The present study showed that the vital statistics data based on death certificates underestimated influenza mortality in SC by >70% during the peak years of the A (H1N1)pdm09 epidemic, thereby missing a significant increase in excess mortality caused by influenza, independent of pneumonia-related deaths. Vital statistics in Brazil are based on the underlying cause of death which gives more weight to chronic diseases as opposed to secondary infections such as influenza, thus underestimating the latter as a cause of death. Statistical modeling of the worldwide A (H1N1)pdm09 data indicated up to a 20-fold higher mortality than officially reported in 2009. In Brazil, this study estimated a likely MR of about 3.5 (the ratio 3.5:1 means that 3.5/4.5 deaths were missed, i.e. 78%), consistent with the >70% underreporting found in the present study. Better communication between epidemiological surveillance and vital statistics would greatly improve the accuracy of data on causes of death.

Limitations of the present study include possible correlation between case severity and probability of being registered by epidemiological surveillance, e.g. patients requiring hospital care. Although the choice of mortality as the main outcome measure and stratification by region of residence partially accounted for these factors, their residual influence remains unknown. Further, the high percentage of laboratory-confirmed cases does not rule out selection bias as areas with lower sensitivity to detect influenza coincide with areas in which the capacity of the health care system to diagnose and treat influenza A (H1N1)pdm09 is low, therefore introducing bias in the MR estimates. Also, the high sensitivity of RT-PCR has likely been achieved at the expense of underestimation of the real MR in the population, and should be treated as its lower bound. Strengths of the study include high coverage of laboratory-based outcome confirmation, with excellent sensitivity and specificity of RT-PCR in diagnosing influenza A (H1N1)pdm09; active search for additional outcomes in the death certificate database; and comprehensive geographical coverage of the Santa Catarina State.

The A (H1N1)pdm09 pandemic interrupted more than a decade-long downward trend in respiratory disease mortality in Latin America⁽¹⁵⁾. The mitigation of the pandemic in the Southern Brazilian states with the largest disease burden in the country was largely successful but regionally heterogeneous, leaving some areas with great susceptibility to disease recrudescence. Continuous improvements in epidemiological surveillance, vaccination coverage, and treatment must be made to further reduce the disease burden in Brazil.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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