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Original Article

Incidence of influenza-associated mortality and hospitalizations in Argentina during 2002–2009

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Background We estimated rates of influenza-associated deaths and hospitalizations in Argentina, a country that recommends annual influenza vaccination for persons at high risk of complications from influenza illness.

Methods We identified hospitalized persons and deaths in persons diagnosed with pneumonia and influenza (P&I, ICD-10 codes J10-J18) and respiratory and circulatory illness (R&C, codes I00-I99 and J00-J99). We defined the influenza season as the months when the proportion of samples that tested positive for influenza exceeded the annual median. We used hospitalizations and deaths during the influenza off-season to estimate, using linear regression, the number of excess deaths that occurred during the influenza season. To explore whether excess mortality varied by sex and whether people were age <65 or ≥65 years, we used Poisson regression of the influenza-associated rates.

Results During 2002–2009, 2411 P&I and 8527 R&C mean excess deaths occurred annually from May to October. If all of these excess deaths were associated with influenza, the influenza-associated mortality rate was 6/100 000 person-years (95% CI 4–8/100 000 person-years for P&I and 21/100 000 person-years (95% CI 12–31/100 000 person-years) for R&C. During 2005–2008, we identified an average of 7868 P&I excess hospitalizations and 22 994 R&C hospitalizations per year, resulting in an influenza-associated hospitalization rate of 2/10 000 person-years (95% CI 1–3/10 000 person-years) for P&I and 6/10 000 person-years (95% CI 3–8/10 000 person-years) for R&C.

Conclusion Our findings suggest that annual rates of influenza-associated hospitalizations and death in Argentina were substantial and similar to neighboring Brazil.

Keywords Argentina, hospitalizations, incidence, influenza, mortality, respiratory.

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Introduction

Influenza is documented as an important cause of deaths and hospitalizations in countries where data are available.[1–3] Most severe disease occurs in subpopulations at high risk for complications from influenza illness, such as persons aged ≥65 years, persons with preexisting respiratory and circulatory conditions, pregnant women, and very young children. For example, during 1976–2007, persons in the United States aged ≥65 years had substantially higher average influenza-associated mortality rate (66·1/100 000 person-years) than those aged 19–64 years (1·5/100 000 person-years) or <19 years (0·2/100 000 person-years).[1] Such data have helped health authorities target influenza prevention and control campaigns to subpopulations at greatest risk of death and hospitalization.[4]

Estimating influenza-associated rates of deaths and hospitalizations often is difficult because physicians do not typically test, diagnose, or report influenza illness. To compensate for these challenges, countries often use multiplier[3] or time-series regression models[5] to estimate the proportion of persons with respiratory illnesses that might be associated with influenza infections. Argentina, for example, has used autoregressive integrated moving average models and pneumonia and influenza (P&I) mortality data to estimate the excess number of P&I deaths during the influenza season. Kusznierz *et al.*[6] identified excess P&I mortality during Argentina's 1992–1999 influenza A

(H3N2) seasons. Imaz *et al.*[7] found that 80–95% of the excess mortality occurred among persons >65 years during 1992–2002. Estimates of annual mortality associated with influenza ranged from zero to 69/100 000 person-years among persons aged >65 years.

Using these decade-old estimates, Argentina and the Pan American Health Organization have worked to provide seasonal and pandemic influenza vaccines to populations at risk of hospitalization and death. Starting in 2003, the Argentina Ministry of Health vaccine program started purchasing seasonal influenza vaccines from the PAHO Revolving Fund to administer free to persons aged 65 years or older. Seasonal vaccine campaigns have gained public acceptability and the Ministry of Health has steadily fostered an increase in influenza vaccine use. For example, during the 2010 influenza campaign the Ministry of Health was able to vaccinate approximately 82–99·8% of healthcare workers, pregnant and postpartum women, children aged 6 months to 5 years, and persons aged 5–64 years with pre-existing medical conditions who were targeted for the then available influenza A 2009 (H1N1)pdm monovalent vaccine.[8]

To support such investments in the influenza vaccine program and other investments in non-pharmaceutical interventions aimed at preventing respiratory infections, it is useful to better understand the current influenza-associated mortality and hospitalization rates in Argentina. In this study, we used P&I and R&C mortality and hospital discharge data, viral surveillance data, and census data to estimate the excess influenza-associated P&I and R&C deaths during 2002–2009 and excess hospitalizations during 2005–2008.

Methods

Population denominator, age, sex, and region

Argentina is a temperate climate, upper middle-income country.[9] During 2002–2009, the average population of Argentina was 39 861 274 (Table 1) of which 4 956 836 (12%) were aged ≥65 years.[10] Overall, 51% of all the population was female although there were more women 3 070 579 (62%) than men (1 886 257) aged >65 years.

Determining the timing of the influenza season through surveillance

We used Argentina's influenza surveillance system to identify the timing of the influenza season. In 1997, physicians in Argentina started testing patients with respiratory symptoms for influenza and other respiratory viruses. In 2007, Argentina adopted the PAHO-CDC generic protocol for influenza surveillance.[11] The national influenza and other respiratory virus laboratory surveillance network and three national influenza centers geographically distributed throughout the country tested respiratory samples for influenza virus using immunofluorescence, real-time reverse transcription-polymerase chain reaction,[12] and viral culture.[13,14] The National Influenza Centers also conducted antigenic characterization from isolated viruses.

We defined the influenza season as the first week when the proportion of respiratory samples that tested positive for influenza was above the median proportion positivity for at least three consecutive weeks that year. To be conservative, we defined the influenza season as the first week when the proportion of respiratory samples being tested for influenza was above the median for at least three consecutive weeks that year through the last week when the proportion of respiratory samples being tested for influenza was above the median. We determined the average start and end of the influenza season during the 2002–2009 to determine when excess respiratory and circulatory deaths and hospitalizations might be attributed to influenza infections. We defined a subtype or type as predominant if it represented >50% of typed or subtyped strains. If two or more subtypes or types were identified during the same season, we considered each a predominant virus if it represented >25% of identified strains.

Observed P&I and R&C deaths and hospitalizations

We identified pneumonia P&I *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes J10-J18 and R&C codes I00-I99 and J00-J99 from PAHO's mortality databases and Argentina's hospitalization databases because we believed a proportion of these deaths and hospitalizations could be associated with influenza illness if they occurred during the influenza season. In Argentina, death certificates are routinely completed on persons who were under medical care before their death. Death certificates were compiled into a mortality database later submitted to PAHO for code verification using PAHO standardized database cleaning protocols. The statistics unit of the Ministerio de Salud de la Nación also records the ICD-10 code of the primary discharge diagnosis of all persons who seek care government-operated hospitals, the hospital system that serve persons with and without private insurance in Argentina.

Excess influenza-associated P&I and R&C deaths and hospitalizations

We used a linear regression model[5,15] and fitted a regression line to ICD-10 coded respiratory and circulatory hospitalizations and deaths that occurred during the influenza off-season to estimate the expected number of events during the season and its 95% confidence interval.

Table 1. Excess numbers and rates of deaths previously diagnosed by clinicians with pneumonia, influenza, respiratory, and circulatory illnesses during influenza seasons, Argentina, 2002–2009

Year	Census population	Excess pneumonia and influenza mortality (95% confidence interval) during the influenza season	Excess respiratory and circulatory mortality during the influenza season (95% confidence interval)	Influenza-associated pneumonia and influenza mortality per 100 000 person-years	Influenza-associated respiratory and circulatory mortality* per 100 000 persons-years	Predominant strain**
2002	38 482 498	870 (457–1283)	7371 (4146–10 596)	2·3 (1·2–3·3)	19·2 (10·8–27·5)	B/Hong Kong/330/2001 (A/New Caledonia/20/99 (H1N1))***
2003	38 859 604	2307 (1526–3089)	9807 (5666–13 948)	5·9 (3·9–7·9)	25·2 (14·6–35·9)	A/Panama/2007/99 (H3N2) (A/New Caledonia/20/99 (H1N1))***
2004	39 239 226	2230 (1454–3006)	8888 (4775–13 001)	5·7 (3·7–7·7)	22·7 (12·2–33·1)	A/Fujian/411/02 (H3N2)
2005	39 630 559	2252 (1463–3040)	6402 (3241–9564)	5·7 (3·7–7·7)	16·2 (8·2–24·1)	A/California/07/04 (H3N2)
2006	40 036 781	1855 (892–2818)	5661 (1572–9751)	4·6 (2·2–7·0)	14·1 (3·9–24·4)	A/New Caledonia/20/99 (H1N1)
2007†	40 454 942	4303 (3340–5267)	14 819 (10 726–18 913)	10·6 (8·3–13·0)	36·6 (26·5–46·7)	A/Wisconsin/67/05 (H3N2) (A/Brisbane/10/07 (H3N2))
2008	40 880 468	2010 (1220–2799)	6213 (3045–9381)	4·9 (3·0–6·8)	15·2 (7·4–22·9)	A/ Brisbane/59/07 (H1N1) (B/Shanghai/361/02)***
2009	41 306 115	3463 (2684–4242)	9053 (4922–13 185)	8·4 (6·5–10·3)	21·9 (11·9–31·9)	A/California/7/09 (H1N1) pdm09
2002–2009††	39 861 274	2411 (1629–3193)	8527 (4762–12 292	6·0 (4·1–8·0)	21·4 (11·9–30·8)	

*We assumed the excess respiratory and circulatory events during the influenza season approximate the totality of the annually influenza-associated mortality.
**We defined a strain as predominant if it represented >50% of isolates.
***If a second strain was also identified during the season, we also considered it predominant if it represented >25% of isolates.
†Predominant H3N2 year.
††Average values for study period.

P&I hospitalization Serfling model

$$\text{P I hospitalizations} = A_0 + A_1 * T + B_1 * \sin(2 * \text{Time}_i * \pi/12) + B_2 * \cos(2 * \text{Time}_i * \pi/12) + e_i$$

Where: A_0 = intercept; A_1 = coefficient associated with month T, and; B_1 and B_2 = coefficients associated with seasonal fluctuations in deaths; e_i is the error.

We subtracted the predicted events during the influenza season from the number of events documented by Ministerio de Salud de la Nación to quantify the excess events we associated with influenza infection. We assumed the excess R&C events would approximate the totality of influenza-associated hospitalizations and deaths.

We divided excess events during the influenza season by the census population to quantify the annual incidence of influenza-associated P&I and R&C hospitalization and deaths. We used the estimates from the Serfling model, which are stratified by age and sex, in a Poisson regression to explore whether excess in mortality and hospitalizations varied significantly by year, sex, and age <65 or ≥65 years.

Results

Laboratory-confirmed influenza season

During 2002–2009, Argentina tested 258 040 respiratory specimens of which 19 672 were positive for influenza (annual median 1%) (Figure 1). Typically, the influenza season started each year during May, peaked during July and ended in October. We assumed this May through October epidemic period as the time when excess P&I and R&C case-patients could be potentially associated with influenza illness.

Anticipated, observed, and excess P&I and R&C deaths

During 2002–2009, 123 863 deaths were coded as P&I (annual average 15 483) and 860 883 deaths were coded as of R&C (annual average 107 610) (Table 1) (Annex 1). In this period, our model identified an excess of 2411 P&I (95% confidence interval [95% CI] 1629–3193) and 8527 (95% CI 4762–12 292) R&C deaths (Figures 2 and 3A). We estimated that the average influenza-associated mortality rate was 6·0/100 000 person-years (95% CI 4·1–8·0/100 000 person-years) using P&I diagnostic codes and 21·4/100 000 person-years (95% CI 11·9–30·8/100 000 person-years) using R&C codes (Table 1).

Anticipated, observed, and excess P&I and R&C hospitalizations

During 2005–2008, physicians diagnosed 325 568 P&I (annual average 81 392) and 1 492 124 R&C (annual average 373 031) illnesses among hospitalized patients (Table 2) (Annex 2). Our model identified an excess of 7868 (95% CI 2 932–12 804) P&I and 22 994 (95% CI 11 647–34 342) R&C hospitalizations during the 2005–2008 influenza seasons (Figures 3B and 4). We estimated that the average influenza-associated hospitalization rate was 2·0/10 000 person-years (95% CI 0·7–3·2/10 000 person-years) using P&I diagnostic codes and 5·7/10 000 person-years (95% CI 2·9–8·5/10 000 person-years) using R&C codes (Table 2).

Influenza-associated mortality and hospitalization rates by age, sex, and year

Influenza-associated P&I and R&C mortality and hospitalization rates were associated with the year of the influenza epidemic, and the age and sex of the patients ($P < 0{\cdot}001$ for each comparison). Influenza-associated mortality rates

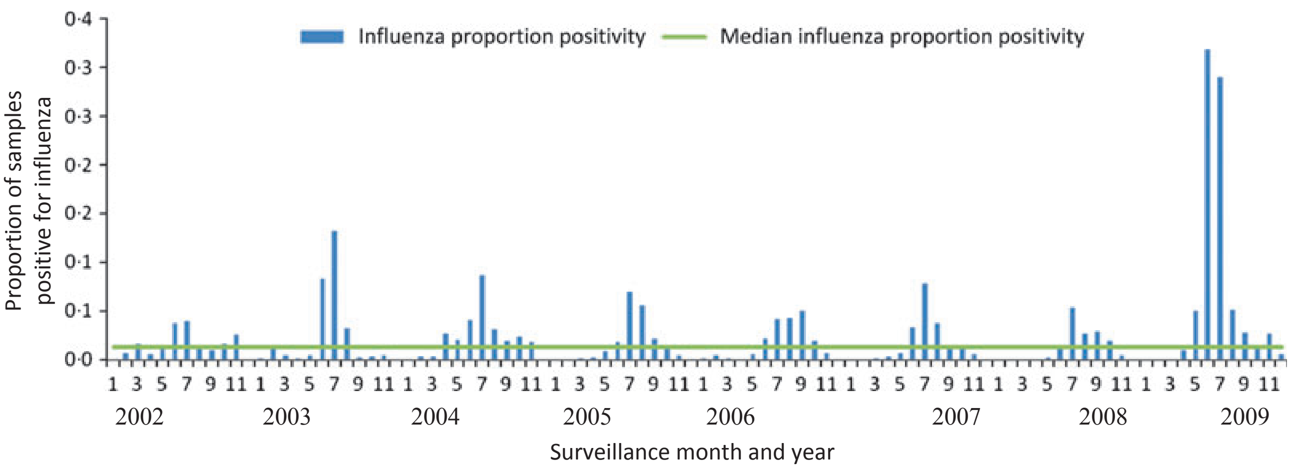

Figure 1. Proportion of clinical respiratory samples tested in Argentina during 2002–2009 which were positive for influenza virus, by month.

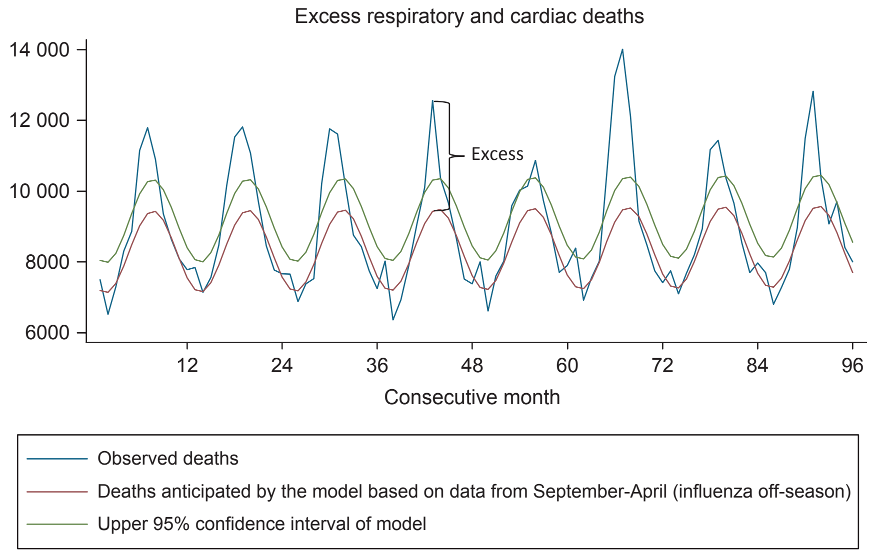

Figure 2. Observed, predicted, and excess deaths diagnosed by clinicians with respiratory and circulatory[a] causes of death during influenza season, Argentina, 2002–2009. [a]We assumed the excess respiratory and circulatory events during the influenza season approximate the totality of the annually influenza-associated mortality. We considered excess deaths (difference between observed and predicted) to be significant only if observed deaths exceeded the upper 95% confidence interval of the predicted deaths.

were higher among men aged ≥65 years (average P&I rate = 37/100 000 person-years, R&C rate = 171/100 000 person-years) than among women aged ≥65 years (average P&I rate = 36/100 000 person-years, R&C rate = 136/100 000 person-years); and higher among men aged <65 years (average 2/100 000 person-years P&I rate and R&C rate = 4/100 000 person-years) than women aged <65 years (1/100 000 person-years P&I rate and R&C rate = 2/100 000 person-years). Influenza-associated mortality and hospitalization P&I and R&C rates were also higher among all age groups during 2007 when influenza A (H3N2) was the predominant virus in circulation (e.g., 34·2/100 000 person-years influenza-associated R&C deaths and 8·4/10 000 person-years R&C hospitalizations) compared with years in which with influenza A H1N1 or B influenza viruses were predominant (e.g., 11·4–23·4/100 000 person-years influenza-associated R&C deaths and 3·9–6·3/10 000 person-years R&C hospitalizations) ($P < 0{\cdot}001$). In 2009, when influenza A H1N1pdm was first introduced into Argentina, persons aged <65 years had higher influenza-associated R&C rates of death (8/100 000 person-years) than they did during periods of seasonal influenza (3/100 000 person-years) ($P < 0{\cdot}001$).

Discussion

During 2002–2009, we estimated that influenza contributed to an average of approximately 2000–9000 deaths and 8000–23 000 hospitalizations in Argentina (lower figures based on P&I, higher on R&C). R&C mortality rates among adults ≥65 ranged from 136 to 171/100 000 person-years versus 2–4/100 000 person-years among persons aged <65 years. This disparity justifies Argentina's policy to target persons aged 65 years or older for annual influenza vaccination. The only year during which persons aged <65 years were disproportionately affected by influenza was 2009, during the pandemic.[16] Of note, when influenza A (H3N2) was the predominant circulating influenza virus subtype, higher mortality rates were observed among all age groups.[6,7,17,18]

Our findings are similar to those of other studies in Argentina and the Americas and may underscore the value of collecting standardized virology and epidemiology surveillance data.[1,12] For example, our mortality rates are similar to those estimated in Argentina during 1992–1999,[6,7] in neighboring Brazil,[19] and in the United States.[1] Our influenza-associated hospitalization rates during the pandemic are similar to those estimated using a multiplier model from three sentinel cities in Argentina (2.4 (95% CI 2.0–2.8) per 10 000 person-year).[20] In addition, our hospitalization rates are similar to seasonal influenza rates estimated in the United States (e.g., 1979–2001) and in other countries.[2,3,17] These influenza-associated hospitalizations and deaths may be associated with a costly economic burden. Such findings, based on virology and epidemiology data, are an important step in assessing the influenza disease and economic burden and determining the potential value of influenza vaccine.

It is known that other viruses, including respiratory syncytial virus, co-circulate with influenza viruses and cause substantial morbidity and mortality. Viral surveillance in Argentina, which is overrepresented by pediatric samples, demonstrated co-circulation of respiratory syncytial virus during each of the May through October influenza seasons. Therefore, a proportion of outcomes that we attributed to influenza infections were likely associated with respiratory syncytial virus infections, particularly among the 21% of hospitalized patients and 0·1% of deaths aged <2 years of age. In addition, our estimates do not account for likely

Table 2. Excess numbers and rates of hospitalizations of patients diagnosed by clinicians with pneumonia, influenza, respiratory, and circulatory illnesses during influenza seasons, Argentina, 2005–2008

Year	Census population	Excess hospitalizations (95% confidence interval) during the influenza season		Influenza-associated pneumonia and influenza hospitalizations per 10 000 person-years	Influenza-associated respiratory and circulatory* hospitalizations per 10 000 persons-years	Predominant strain**
		Pneumonia and influenza	Respiratory and circulatory			
2005	39 630 559	3245 (905–5584)	16 662 (7143–26 181)	0·8 (0·2–1·4)	4·2 (1·8–6·6)	A/California/07/04 (H3N2)
2006	40 036 781	12 135 (3600–20 671)	25 312 (11 729–38 897)	3·0 (0·9–5·2)	6·3 (2·9–9·7)	A/New Caledonia/20/99 (H1N1)
2007	40 454 942	13 234 (6630–19 838)	34 026 (20 609–47 442)	3·3 (1·6–4·9)	8·4 (5·1–11·7)	A/Wisconsin/67/05 (H3N2) A/Brisbane/10/07 (H3N2)
2008	40 880 468	2860 (595–5125)	15 978 (7108–24 848)	0·7 (0·1–1·3)	3·9 (1·7–6·1)	A/ Brisbane/59/07 (H1N1) (B/Shanghai/361/02)***
2005–2008[†]	40 250 688	7868 (2932–12 804)	22 994 (11 647–34 342)	2·0 (0·7–3·2)	5·7 (2·9–8·5)	

*We assumed the excess respiratory and circulatory events during the influenza season approximate the totality of the annually influenza-associated mortality.
**We defined a strain as predominant if it represented >50% of isolates.
***If a second strain (in parenthesis) was also identified during the season, we also considered it predominant if it represented >25% of isolates.
[†]Average values for study period.

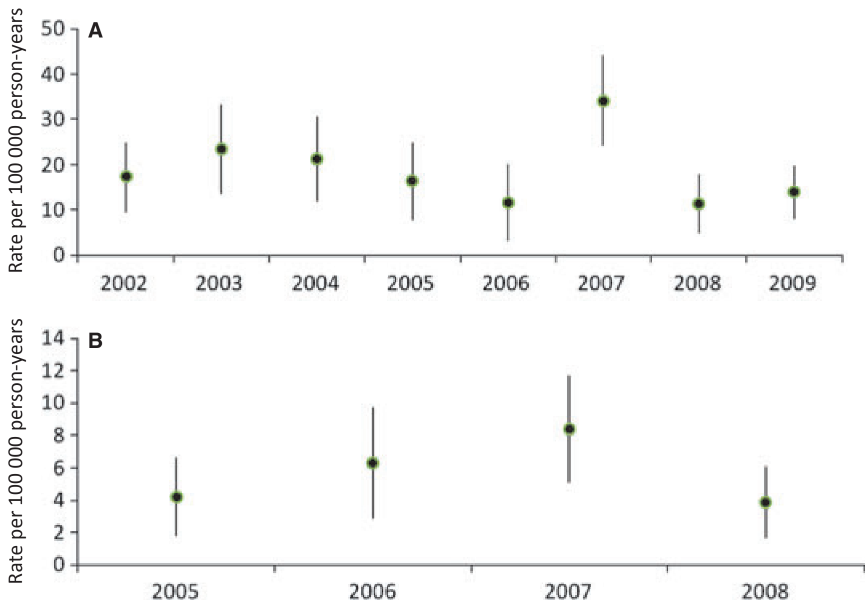

Figure 3. (A) Rates of influenza-associated deaths due to respiratory and circulatory[a] disease and their 95% confidence interval, Argentina, 2002–2009. (B) Rate of influenza-associated hospitalizations for respiratory and circulatory[a] causes and their 95% confidence interval, Argentina, 2002–2009. [a] We assumed the excess respiratory and circulatory events during the influenza season approximate the totality of the annually influenza-associated mortality.

associations between temperature and wintertime increases in mortality. Our hospitalization data included only government-operated hospitals. While this includes the majority of Argentina's hospitalizations, it nevertheless is an underestimate of the total number of national hospitalizations. Therefore, the rates estimated in this study should be validated in future investigations using different methodologies, such as Poisson regression or multiplier models that

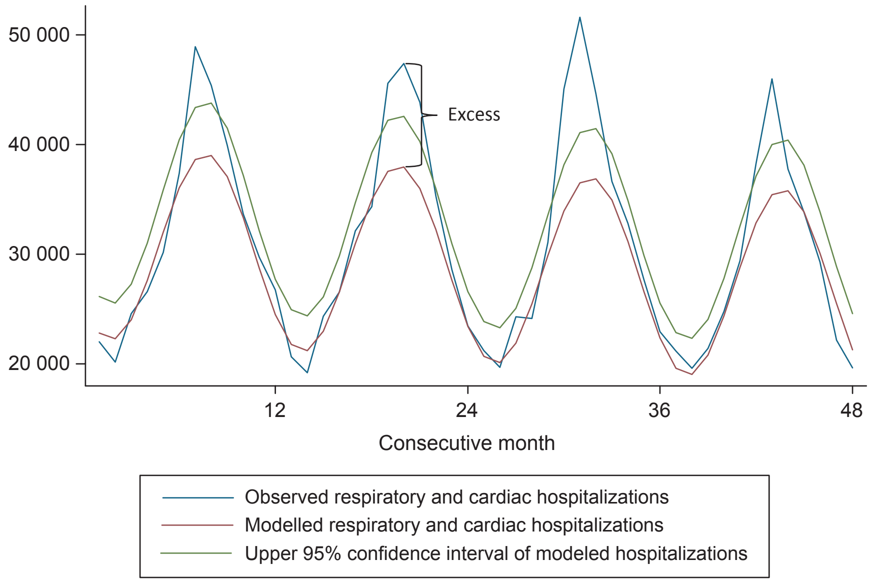

Figure 4. Number of observed, predicted, and excess respiratory and circulatory[a] hospitalizations during the influenza season in Argentina, 2005–2008. [a]We assumed the excess respiratory and circulatory events during the influenza season approximate the totality of the annually influenza-associated mortality. We only considered difference between observed and predicted deaths (the excess deaths) to be significant if observed deaths exceeded the upper 95% confidence interval of the model.

may better differentiate the contribution of individual viral pathogens to respiratory and circulatory disease.[3,20]

Conclusion

Our findings suggest that similar to neighboring Brazil, Argentina annually had thousands of influenza-associated deaths and hospitalizations, particularly among the elderly. Our findings also suggests the value of standardized, reliable and integrated epidemiologic and viral surveillance needed to quantify influenza disease burden and useful in exploring the effectiveness of pharmaceutical (e.g., influenza vaccine and antiviral drugs, such as oseltamivir) and non-pharmaceutical interventions (e.g., hand washing and respiratory hygiene campaigns) aimed at preventing mortality and morbidity as a result of influenza illness. For example, Argentina and regional influenza vaccine policy may benefit from influenza-associated economic burden studies to determine how much is being spent as a result of influenza illness and to explore the potential value of expanding targeted influenza vaccine use and coverage.

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CDC disclaimer

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Annex 1

Observed pneumonia, influenza, respiratory and cardiac mortality in Argentina, 2002–2009 .

Annex 2

Observed pneumonia, influenza, respiratory and cardiac hospitalizationsin Argentina, 2002–2009 .