Intense Seasonal A/H1N1 Influenza in Mexico, Winter 2013–2014

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Abstract

Background and Aims—A recrudescence wave of pandemic influenza A/H1N1 affected Mexico during the winter of 2013–2014 following a mild 2012–2013 A/H3N2 influenza season.

Methods—We compared the demographic and geographic characteristics of hospitalizations and inpatient deaths for severe acute respiratory infection (SARI) and laboratory-confirmed influenza during the 2013–2014 influenza season compared to previous influenza seasons, based on a large prospective surveillance system maintained by the Mexican Social Security health care system.

Results—A total of 14,236 SARI hospitalizations and 1,163 inpatient deaths (8.2%) were reported between October 1, 2013 and March 31, 2014. Rates of laboratory-confirmed A/H1N1 hospitalizations and deaths were significantly higher among individuals aged 30–59 years and lower among younger age groups for the 2013–2014 A/H1N1 season compared to the previous A/H1N1 season in 2011–2012 (χ^2 test, $p < 0.001$). The reproduction number for the winter 2013–2014 influenza season in central Mexico was estimated at 1.3–1.4, in line with that reported for the 2011–2012 A/H1N1 season but lower than during the initial waves of pandemic A/H1N1 activity in 2009.

Conclusions—We documented a substantial increase in the number of A/H1N1-related hospitalizations and deaths during the period from October 2013–March 2014 in Mexico and a proportionate shift of severe disease to middle-aged adults, relative to the preceding A/H1N1

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Competing interests

The authors declare no relevant competing interests.

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2011–2012 season. In the absence of clear antigenic drift in globally circulating A/H1N1 viruses in the post-2009 pandemic period, the gradual change in the age distribution of A/H1N1 infections observed in Mexico suggests a slow build-up of immunity among younger populations, reminiscent of the age profile of past pandemics.

Keywords

A/H1N1 influenza pandemic; Influenza vaccine; Age distribution; Transmissibility; Drift; Immunity

Introduction

The resurgence of swine-origin pandemic A/H1N1 influenza virus in winter 2013–2014 generated substantial morbidity and mortality in Mexico, following a mild 2012–2013 A/H3N2 influenza season. Mexico has experienced a series of three A/H1N1 pandemic waves in the spring, summer, and fall of 2009 (1,2) and a recrudescence pandemic fourth wave in the winter of 2011–2012 (3). The excess mortality impact of the 2009 pandemic was particularly severe in Mexico, relative to that of other countries (4,5).

Because past influenza pandemics have had substantial morbidity and mortality burden for several seasons after the initial pandemic waves (6–10), continued vigilance is prudent in the post-pandemic period. The 2013–2014 influenza season was dominated by A/H1N1 in North America and prompted alarm due to its unusual severity in young and middle-aged adults (11,12). We previously reported on the early phase of the 2013–2014 A/H1N1 outbreak in Mexico based on data until January 2014 (accounting for only 55.4% of total SARI patients) (13). We elaborate on these findings to provide an epidemiological description of the full influenza season from October 2013–March 2014 and document the changing epidemiology of this virus since its emergence in 2009. We compare the demographic and clinical characteristics of laboratory-confirmed A/H1N1 hospitalizations and deaths in winter 2013–2014 with those reported for previous A/H1N1 seasons. Our data highlight a change in the age distribution of patients compared to the 2011–2012 A/H1N1 outbreak, whereas the reproduction number remained similar.

Materials and Methods

Epidemiological Data

Individual level hospitalization data were available from a prospective epidemiological surveillance system that was initiated especially for the 2009 influenza pandemic by the Mexican Institute for Social Security (IMSS) (1,14). IMSS is a tripartite Mexican health system covering ~40% of the Mexican population comprising workers in the private sector and their families, relying on a network of 1,099 primary health-care units and 259 hospitals nationwide. Age and gender distributions of persons affiliated with the IMSS medical system are representative of the general Mexican population (1).

We analyzed all patients admitted to the hospital for >24 h with a diagnosis of severe acute respiratory infection (SARI) during October 2013–March 2014. SARI was defined as the presence of respiratory difficulty with fever >38°C and cough, together with one or more of

the following clinical symptoms: confinement to bed, thoracic pain, polypnea, or acute respiratory distress syndrome. Children <5 years of age with pneumonia or severe pneumonia that required hospitalization were also considered as SARI cases. Respiratory swabs were obtained for ~56% of SARI hospitalizations in winter 2013–2014 and were tested for the influenza virus by RT-PCR (15). For reference, the average influenza testing rate was 26% in the IMSS system for the 2011–2012 A/H1N1 season (3) and 33% during the 2009 pandemic period (1).

For all SARI hospitalizations, we retrieved age, gender, influenza laboratory test results (for patients tested), discharge status (alive or deceased), reporting state (including 31 states plus the Federal District), and self-reported symptom onset dates. We also obtained population size information by state and age group in 2009 and 2013 for all persons affiliated with IMSS to calculate incidence rates.

Age Distribution and Severity of A/H1N1 Influenza in Winter 2013–2014

We examined the age distribution of all SARI hospitalizations, laboratory-confirmed influenza A/H1N1 hospitalizations and deaths from October 2013–March 2014 with those associated with the 2011–2012 A/H1N1 influenza season (October 1, 2011–March 15, 2012) using the same IMSS reporting system. We also calculated estimates of in-hospital case fatality rate for SARI and laboratory-confirmed A/H1N1 influenza.

Spatial Distribution of A/H1N1 Influenza in Winter 2013–2014 and Reproduction Number Estimate

We analyzed the geographic dissemination of the 2013–2014 A/H1N1 outbreak in Mexico based on state- and age-specific time series of laboratory-confirmed hospitalizations according to day of symptom onset.

Further, we estimated the reproduction number, R , in central Mexico where the great majority of cases have been reported, based on a simple method previously used in the context of the 2009 A/H1N1 pandemic (1) and the 2011–2012 A/H1N1 influenza season (3). Specifically, we estimate the initial epidemic growth rate by fitting an exponential function to the early ascending phase of daily A/H1N1 case series or A/H1N1 daily hospitalizations according to date of symptom onset (16). We assumed a mean generation interval of 3 and 4 days, which are within the range of mean estimates for the 2009 influenza pandemic (17–20). As a sensitivity analysis we also assessed small variations in the length of the ascending epidemic phase used to estimate the exponential growth rate. This study did not need approval from a scientific committee; all individual data were kept de-identified. Analyses were performed using SPSS 20.0 and Matlab (The Mathworks, Inc.).

Results

Overall Epidemiological Patterns

Characteristics of all SARI and A/H1N1-positive hospitalizations reported to the IMSS medical system between October 1, 2013 and March 31, 2014 are shown in Table 1. The time series of daily SARI hospitalizations and deaths and laboratory-confirmed influenza

hospitalizations are shown in Figures 1 and 2, respectively. The total number of SARI hospitalizations and deaths in winter 2013–2014 increased by 88% relative to the preceding 2011–2012 A/H1N1 influenza pandemic (Figure 1). The largest increase in hospitalizations and deaths relative to the 2011–2012 season was reported by the central states of Mexico.

Severity of Disease

A total of 14,236 SARI hospitalizations and 1,163 inpatient SARI deaths (fatality rate, 8.2% [95% CI: 7.7, 8.6]) were reported to the IMSS system between October 1, 2013 and March 31, 2014. The case fatality rate estimate for laboratory-confirmed A/H1N1 inpatients was 17.9% (95% CI: 16.4, 19.6) during the same period (2241 inpatients and 402 deaths). Overall case fatality rate for hospitalized A/H1N1 SARI patients in 2013–2014 is significantly higher than the preceding 2011–2012 A/H1N1 season (13.8% [95% CI: 11.7, 15.9]), but it overlaps with that of the 2009 A/H1N1 pandemic (16.1% [95% CI: 15.0, 17.2]).

Age

Overall, the majority of laboratory-confirmed influenza inpatients from October 1, 2013–March 31, 2014 were among persons aged 30–59 years (54.7%) followed by persons 60 years of age (18.7%) (Table 1). Severity increased with older age, with an inpatient fatality rate of 25.1% (95% CI: 20.9, 29.4) for persons 60 years of age.

Comparison of the age-specific A/H1N1 hospitalization and death rates between the 2013–2014 season and the previous A/H1N1 season in 2011–2012 reveals an increasing burden among adults (30 years), particularly among middle-aged individuals (Figure 3). The shift is seen both in absolute and relative terms. Specifically, we note a significantly higher proportion of individuals aged 30–59 years hospitalized with laboratory-confirmed A/H1N1 during 2013–2014, relative to the 2011–2012 A/H1N1 season, as well as a significant decrease in the proportion of hospitalizations among younger persons (I^2 test, $df = 5$, $p < 0.001$). We found a similar change in the age distribution of A/H1N1 inpatient deaths in 2013–2014 compared to the 2011–2012 A/H1N1 influenza season (I^2 test, $df = 5$, $p < 0.001$).

Geography

The majority of A/H1N1 hospitalizations during the 2013–2014 A/H1N1 season have been reported in the central Mexican states (56.7%) followed by the southeastern states (8.1%) (Table 1) with a synchronized temporal pattern of SARI hospitalizations in the central and northern regions but slightly delayed in the southern regions (Figure 4). The case fatality rate was not significantly different across geographic regions (I^2 test, $p = 0.33$).

Estimates of the Reproduction Number

Assuming a mean generation interval of 3 (4) days, the mean R was estimated to be 1.2 (1.3) during the monotonically ascending period December 4, 2013–January 17, 2014 based on daily laboratory-confirmed A/H1N1 case series in central Mexican states. As a sensitivity analysis, we also estimated R using a slightly shorter ascending phase and obtained a similar estimate at 1.2 (1.3) (Figure 5). Our R estimate was similar to that estimated for the 2011–12 A/H1N1 season, with R at 1.2 (1.3).

Discussion

We characterized the epidemiology of a recrudescent A/H1N1 influenza transmission in Mexico spanning October 1, 2013–March 31, 2014 based on hospitalizations for severe acute respiratory infections and laboratory-confirmed A/H1N1 infections. We compared the impact, severity, age patterns, and reproduction number of this intense influenza season with those of the preceding 2011–2012 A/H1N1 season and the 2009 A/H1N1 pandemic period in Mexico (1,3). We used individual-level patient information collected through a prospective influenza surveillance system established especially for the 2009 A/H1N1 pandemic by the largest Mexican Social Security medical system (14). Our data show that daily SARI hospitalizations in 2013–2014 exceeded those reported during the preceding 2011–2012 A/H1N1 influenza season. We also documented a significant increase in the proportion of A/H1N1 hospitalizations and deaths among persons 30–59 years of age, relative to the preceding 2011–2012 A/H1N1 season and a significant reduction in the proportion of A/H1N1 hospitalizations and deaths among younger age groups. We note that our conclusions based on preliminary data (13) did not change except that our most recent data of the 2013–2014 outbreak indicates that the reproduction number remained similar to the prior 2011–2012 A/H1N1 outbreak.

The observed gradual change in age distribution of hospitalization and deaths in the post 2009 pandemic period is reminiscent of the influenza seasons following the 1918 influenza pandemic (6,21,22) and the 1968 pandemic (23). A quantitative analysis of excess mortality prior to and after the 1918 influenza pandemic found that the age distribution of influenza-related mortality returned to pre-pandemic mortality levels a few years after the initial pandemic waves as a result of emerging drift variants (6,24). Hence the age shift seen in the 2011–2012 and 2013–2014 A/H1N1 seasons could signal a build-up of immunity among younger populations, which has implications for influenza prevention and mitigation strategies.

It is now well recognized that during the first year of circulation of the 2009 A/H1N1 influenza pandemic virus, persons ≥ 60 years of age enjoyed protection from influenza-related morbidity and mortality. This phenomenon of “senior sparing” in age cohorts born prior to the 1957 pandemic is consistent with first exposure to antigenically related A/H1N1 viruses in childhood, a pattern consistent with the antigen recycling and original antigenic sin hypotheses (11,25–28). A high fraction of the Mexican population is now presumably protected against the 2009 A/H1N1 influenza virus through natural exposure since 2009 (children and young adults) or prior immunity (persons ≥ 60 years of age) (29) and by pandemic vaccines. In parallel, waning of immunity is also expected in individuals who are not periodically revaccinated. To the best of our knowledge, no serological studies were conducted prior to this influenza season or are currently being carried out in Mexico.

For the first time since the emergence of the 2009 pandemic virus, the absolute risk of hospitalization is greater among individuals ≥ 30 years of age compared to that of individuals <30 years of age in Mexico (Figure 3). The declining rates of severe cases in younger age groups are most consistent with the build-up of immunity in these age groups. In contrast, persons ≥ 60 years of age still experience relative protection against A/H1N1 hospitalization

and death compared to persons aged 30–59 years in the A/H1N1 2013–14 season, indicating residual immunity in this population. Residual protection among persons ≥60 years of age is consistent with a lack antigenic drift in A/H1N1 viruses circulating in Mexico or elsewhere during the winter 2013–2014. Overall, the age distribution of A/H1N1 is gradually progressing to an older adult age risk profile that characterizes seasonal influenza but is not yet that of a typical inter-pandemic season, with 90% of deaths occurring in persons ≥60 years of age. In the longer term, we expect the pandemic A/H1N1 virus to drift genetically to escape mounting population immunity—perhaps with the result that persons ≥60 years of age are less protected (11). It was not within the scope of our study to conduct an analysis of risk factors for A/H1N1 death. However, findings from a recent study based on epidemiological data for 102 adults with suspected influenza pneumonia and admitted to a hospital in Mexico indicate that unvaccinated status against A/H1N1 influenza and presence of comorbidities were frequently reported among the study cohort (30).

We estimated a reproduction number for the A/H1N1 2013–2014 season ($R \sim 1.2$ – 1.3) to be similar to that estimated for the preceding A/H1N1 2011–12 season ($R \sim 1.2$ – 1.3) based on the case series of laboratory-confirmed A/H1N1 influenza. This finding suggests that the increased burden of SARI hospitalizations and deaths for the A/H1N1 2013–2014 season relative to the preceding A/H1N1 2011–2012 season is likely due to increased susceptibility levels among middle-age adults and adults ≥60 years of age or older rather than an increase in the transmission potential of the A/H1N1 2013–2014 season. This is despite the early timing of onset of the on-going 2013–2014 season (early October 2013, Figure 2), which could have prevented the population from having immunizations and reaching protective antibody levels by the time transmission started. Of note, influenza vaccination coverage among the IMSS population has increased in the last three seasons and mid-December estimates were 8.7% in 2011, 11% in 2012 and 14% in 2013. Influenza vaccination through the IMSS is focused primarily on high-risk groups including infants, pregnant women, health care workers and persons ≥60 years of age. In particular, among persons ≥60 years, the influenza vaccination coverage was ~16% in 2011–2012 and 2012–2013 and 29% in 2013–2014.

In summary, our findings indicate a changing age distribution of laboratory-confirmed A/H1N1 influenza hospitalizations and deaths during winter 2013–2014, relative to the preceding 2011–2012 A/H1N1 influenza season and the 2009–2010 A/H1N1 pandemic patterns. The proportion of hospitalizations and deaths is increasing, particularly among those 30–59 years of age. In contrast, rates of A/H1N1 hospitalizations and deaths are declining significantly among children, consistent with a gradual build-up of immunity. This gradual change in the age distribution of A/H1N1 influenza during 2013–2014 in Mexico is reminiscent of post-pandemic patterns in past influenza pandemics. A systematic multinational comparison of the epidemiology of pandemic and post-pandemic waves would be useful to shed light on the long-term transmission dynamics and build-up of immunity to pandemic viruses and to report control strategies.

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Figure 1.
Daily curves of all severe acute respiratory infections (SARI) hospitalizations and deaths by dates of symptoms onset in Mexico, April 1, 2009–March 31, 2014.

Figure 2.

Daily number of influenza tests among SARI hospitalizations and laboratory-confirmed influenza hospitalizations by dates of symptoms onset spanning April 1, 2009–March 31, 2014 in the 32 Mexican states according to influenza subtype.

Figure 3.

Age-specific A/H1N1 influenza hospitalization rates (left) and A/H1N1 inpatient death rates (right) for the A/H1N1 2013–14 influenza season (October 1, 2013–March 31, 2014) compared to the preceding 2011–12 A/H1N1 season and those of the entire 2009 A/H1N1 pandemic period (April 1, 2009–March 31, 2010).

Figure 4.

Daily epidemic curves of all SARI hospitalizations according to dates of symptom onset in northern, central, and southeastern states of Mexico (December 1, 2011–March 30, 2014).

Figure 5. Model fits (solid line) obtained after fitting an exponential curve to the growth phase of the initial epidemic phase of the 2013–14 A/H1N1 influenza season to estimate the initial growth rate based on the case series of laboratory-confirmed A/H1N1 SARI A/H1N1 hospitalizations (left) and using a slightly shorter ascending phase as a sensitivity analysis (right).

Characteristics of all SARI hospitalizations and laboratory-confirmed A/H1N1 influenza hospitalizations, Mexico, October 2013–March 2014

Table 1

Variable	SARI hospitalizations (% of total ILI)	SARI Deaths (% of total deaths)	Samples (% of total samples)	A/H1N1 confirmed hospitalizations (% of total H1N1 inpatients)	A/H1N1 confirmed deaths (% of total H1N1 deaths)
Geographic location					
Central	5875 (41.3)	499 (42.9)	4183 (42.9)	1271 (56.7)	214 (53.2)
Southern	2056 (14.4)	147 (12.6)	1099 (12.7)	182 (8.1)	31 (7.7)
Other states	6305 (44.3)	517 (44.5)	2811 (44.5)	788 (35.2)	157 (39.1)
Age (years)					
0–4	2668 (18.7)	47 (4)	1433 (17.7)	201 (9)	11 (2.7)
5–14	884 (6.2)	18 (1.6)	525 (6.5)	127 (5.6)	9 (2.3)
15–29	1626 (11.4)	59 (5.1)	954 (11.8)	268 (12)	17 (4.2)
30–44	2655 (18.7)	220 (18.9)	1579 (19.5)	619 (27.6)	99 (24.6)
45–59	2738 (19.2)	355 (30.5)	1624 (20.1)	608 (27.1)	161 (40.1)
60	3665 (25.8)	464 (39.9)	1978 (24.4)	418 (18.7)	105 (26.1)
Total	14236 (100)	1163 (100)	8093 (100)	2241 (100)	402 (100)

SARI, severe acute respiratory infections.