

Mortality Patterns Associated with the 1918 Influenza Pandemic in Mexico: Evidence for a Spring Herald Wave and Lack of Preexisting Immunity in Older Populations

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Background. Although the mortality burden of the devastating 1918 influenza pandemic has been carefully quantified in the United States, Japan, and European countries, little is known about the pandemic experience elsewhere. Here, we compiled extensive archival records to quantify the pandemic mortality patterns in 2 Mexican cities, Mexico City and Toluca.

Methods. We applied seasonal excess mortality models to age-specific respiratory mortality rates for 1915–1920 and quantified the reproduction number from daily data.

Results. We identified 3 pandemic waves in Mexico City in spring 1918, autumn 1918, and winter 1920, which were characterized by unusual excess mortality among people 25–44 years old. Toluca experienced 2-fold higher excess mortality rates than Mexico City but did not experience a substantial third wave. All age groups, including that of people ≥ 65 years old, experienced excess mortality during 1918–1920. Reproduction number estimates were < 2.5 , assuming a 3-d generation interval.

Conclusion. Mexico experienced a herald pandemic wave with elevated young adult mortality in spring 1918, similar to the United States and Europe. In contrast to the United States and Europe, there was no mortality sparing among Mexican seniors ≥ 65 years old, highlighting potential geographical differences in preexisting immunity to the 1918 virus. We discuss the relevance of our findings to the 2009 pandemic mortality patterns.

The 1918 influenza pandemic is considered by some to have been the “mother of all pandemics” and may have caused upward of 20–50 million deaths worldwide during 1918–1920 [1]. Historical influenza pandemics, in particular the 1918 influenza A(H1N1) pandemic, have received increasing attention in the past few years in

an effort to better understand the factors driving the emergence of novel influenza viruses and their impact on human populations. Archeoepidemiological studies have shed light on the age, temporal, and transmissibility patterns of historical pandemics in several regions of the world [2–11]. Influenza pandemics are characterized by an age shift in the proportion of influenza-related mortality toward younger age groups, relative to seasonal epidemics; the occurrence of multiple waves over short time periods, sometimes outside of typical winter seasons; and increased transmission resulting from lack of population immunity [10]. In addition, substantial geographical variations in pandemic mortality impact can occur within and between countries [5], perhaps due to differences in prior immunity, economy, background mortality levels, and population density. In particular, studies of the 1918 pandemic in England and Wales [12] and New Zealand [8] have sug-

Received 27 October 2009; accepted 2 March 2010; electronically published 1 July 2010.

Potential conflicts of interest: none reported.

Financial support: RAPIDD program of the Science and Technology Directorate, Department of Homeland Security (grant to L.S.); Fogarty International Center, National Institutes of Health (grant to L.S.); Office of Global Health Affairs' International Influenza Unit, Office of the Secretary of the Department of Health and Human Services.

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The Journal of Infectious Diseases 2010;202(4):000–000

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0022-1899/2010/20204-00XX\$15.00

DOI: 10.1093/infdis/jiq347

gested that influenza-related mortality rates were higher in cities than in rural areas.

Quantitative studies of the 1918 pandemic are hampered by the amount of time and effort required to access archival paper records and digitize data. Reports from the Americas are scarce, with only a few studies from the United States [3, 4], Canada [13, 14], and Brazil [15]. Because of the recent emergence of the swine-origin influenza A(H1N1)-pdm virus in Mexico [16, 17], followed by the global pandemic activity during 2009, it is pertinent to gain more knowledge about past pandemic experiences in the Americas. To start filling this gap, we collected archival data on age-specific respiratory mortality to characterize the epidemiology and transmissibility of the 1918 pandemic in 2 Mexican cities, Mexico City and Toluca.

MATERIALS AND METHODS

Data sources. For both cities, Mexico City and Toluca, we examined mortality archives for the 2–3 years before the pandemic to estimate the baseline mortality in prepandemic years and assess the impact of the pandemic in subsequent years (1918–1920).

Mexico City. Mexico City is located in a valley in the central part of Mexico at an elevation of 2240 m. The census of 1910 registered 720,753 inhabitants in the city, whereas the population size in 1921 was 906,063, representing a mean annual increase of 2.3% [18]. We used age-specific population estimates from the 1910 decennial census to derive age-specific mortality rates.

We obtained monthly numbers of pneumonia and influenza deaths from the epidemiological bulletins published by Mexico City's Superior Council of Hygiene during the period 1916–1920 [19] and stratified the deaths by age group (<5, 5–19, 20–29, 30–49, 50–69, and ≥ 70 years of age) (Figure 1). Monthly time series stratified into 8 smaller administrative regions that compose Mexico City were also available.

To obtain more detailed information about the temporal dynamics of the pandemic waves during the year 1918 in Mexico City and to allow estimation of the transmission characteristics from the daily time series, we explored Mexico City's Civil Registry. We recorded all respiratory deaths during April–May and September–December 1918, which were periods of large increases in mortality, based on the monthly statistics. For each death record from the registry, we manually retrieved the age, cause of death, and exact date of death. On the basis of this information, we compiled daily and weekly respiratory mortality (due to influenza, pneumonia, and bronchitis) time series. A total of 4749 respiratory deaths were identified during the spring and autumn waves of 1918 through this system.

Toluca, Mexico State. The city of Toluca is located in one of the valleys of central Mexico at an elevation of 2667 m. We selected this city because it experienced stable and slow pop-

ulation growth for at least 8 years prior to the influenza pandemic of 1918. The census of 1910 registered 31,023 inhabitants in the city, whereas the population size in 1921 was 34,265, representing a mean annual increase of 0.9% [20]. We estimated the age-specific population size of Toluca from the 1910 decennial census data for the state of Mexico, where the city is located [21] (no city-specific census data were available).

We manually retrieved a total of 2998 mortality records for the period 1915–1920 from the Office of the General Cemetery in Toluca and recorded the age, cause of death, and exact date of death. Death certificates were completed by physicians, and all burials were performed in a single cemetery (Panteon General Cemetery); the complete set of records remains at the cemetery office. We compiled daily and weekly respiratory mortality (due to influenza, pneumonia, and bronchitis) time series stratified into 6 age groups (0–4, 5–14, 15–24, 25–44, 45–64, and ≥ 65 years of age) (Figure 2). These age groups were chosen for comparison with a detailed quantitative study of the 1918 pandemic in New York City [4].

Estimation of excess mortality attributable to influenza. To estimate the mortality attributable to the influenza pandemic, we calculated the excess mortality for each wave during 1918–1920 over a traditional Serfling model baseline [7, 22, 23]. We established the baseline by applying a cyclical Serfling linear regression model to weekly or monthly respiratory mortality time series, after excluding data from the year 1918 and the winter months (December–March) in other years. Influenza periods were defined as months or weeks when mortality exceeded the upper limit of the 95% confidence interval on this baseline. Weekly or monthly excess mortality was defined as mortality in excess of the baseline during influenza periods. We summed the excess deaths above the model baseline during each influenza period identified during 1918–1920 to estimate the mortality burden of each pandemic wave. Separate models were fitted to each age group and city; all model fits were good ($0.65 \leq R^2 \leq 0.73$).

As a sensitivity analysis, we also estimated the excess mortality associated with each pandemic wave using a model-free approach, in which reference months in prepandemic years are used to estimate baseline mortality (adapted from Murray et al [5]). Finally, we also calculated the relative risk of pandemic death, defined as the ratio of excess mortality during pandemic periods to the expected mortality in the absence of influenza virus activity from the model baseline. The relative risk facilitates comparison between age groups and locations, which have different baseline risks of death [4, 23].

Estimation of transmission characteristics (reproduction number). We also characterized the intrinsic transmission parameter for each pandemic wave. The basic reproduction number (R_0) is defined as the mean number of secondary cases generated by a primary case during the initial epidemic period

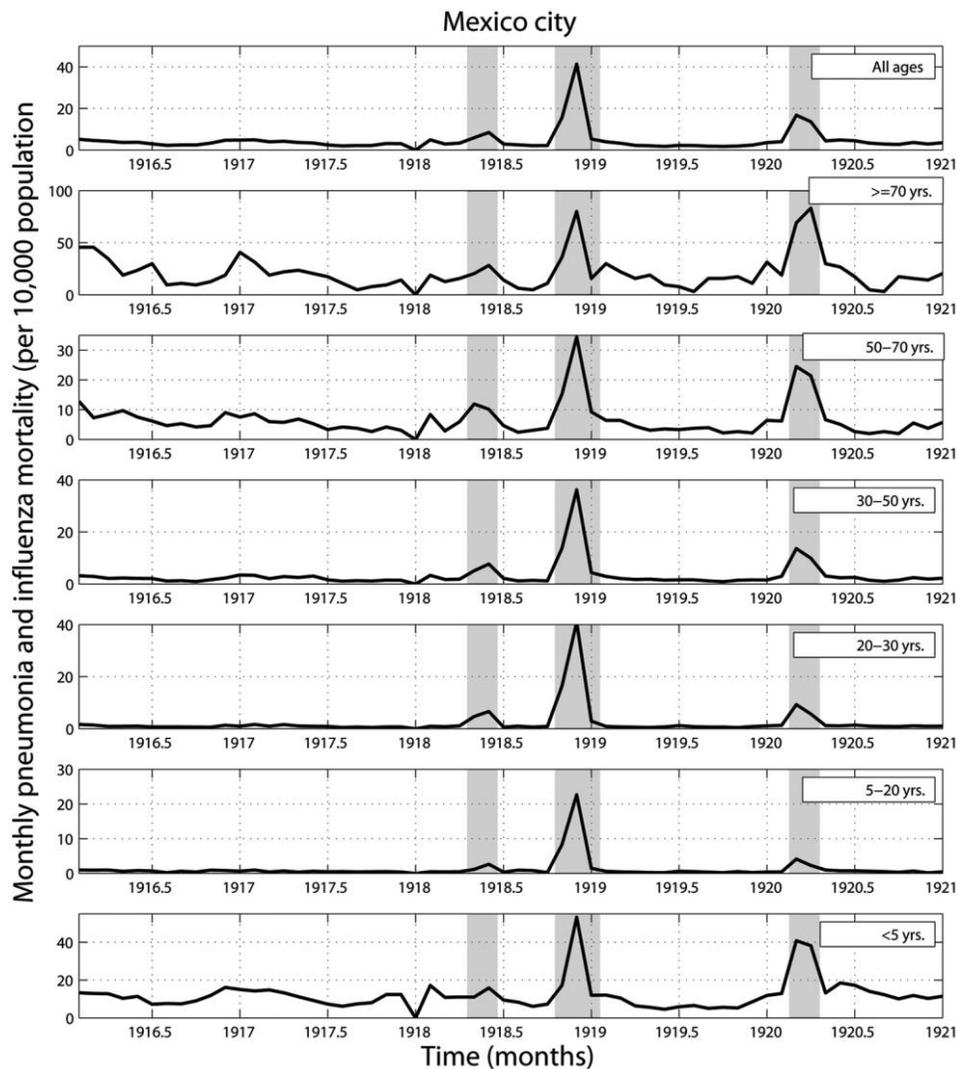


Figure 1. Age-specific monthly time series of pneumonia and influenza mortality rates for Mexico City, 1916–1920. Shaded areas highlight 3 time periods of high mortality associated with 3 waves of the 1918–1920 pandemic occurring in spring (April–May 1918), autumn (October–December 1918), and winter (February–March 1920).

in an entirely susceptible population [24, 25], whereas the reproduction number (R) measures the transmission potential at the beginning of an epidemic in a partially immune population [12]. During the initial wave of a pandemic, there is little or no background population immunity, and hence we can expect R to approximate R_0 . Nevertheless, the reproduction number could vary spatially and temporally depending on the season in which the novel influenza virus is introduced into local populations.

We estimated the reproduction number, R , using the intrinsic growth rate method, as in Chowell et al [12] and Wallinga et al [26]. The growth rate was estimated by fitting an exponential function to the initial increase in the daily number of respiratory deaths [27], assuming exponentially distributed latent and infectious periods [26, 28] or a fixed generation interval

[26]. We also tested the robustness of R to the choice of mortality outcomes and compared estimates derived from crude respiratory deaths and excess respiratory deaths.

To account for the uncertainty associated with the generation interval for influenza, we considered 2 extreme values that have been used in past research: a short interval of 3 d [26, 29, 30] and a longer interval of 6 d [3, 31]. The same approach was used by Andreasen et al [7] to quantify R for the summer and autumn 1918 pandemic waves in Copenhagen, Denmark, so the Copenhagen and Mexico estimates are directly comparable.

RESULTS

Timing of pandemic waves and age mortality patterns. The age-stratified time series of pneumonia and influenza mortality

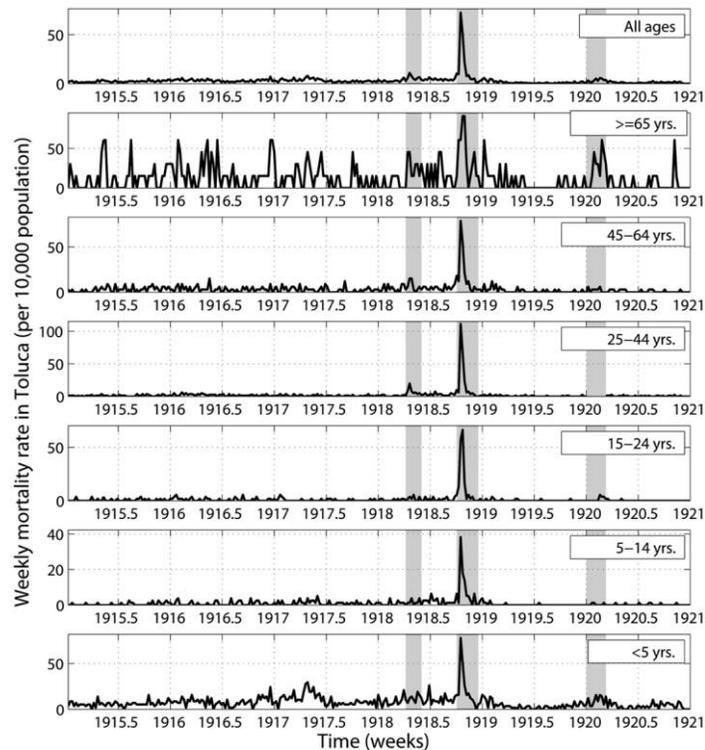


Figure 2. Age-specific weekly time series of respiratory mortality per 10,000 people in the city of Toluca, Mexico State, 1915–1920. Shaded areas highlight 3 time periods of high mortality associated with 3 waves of the 1918–1920 pandemic occurring in spring (2 April–3 June 1918), autumn (1 October–23 December 1918), and winter (1 January–11 March 1920).

in Mexico City (Figure 1) reveals a pattern of 3 successive waves of increased mortality occurring in spring (April–May 1918), autumn (September–December 1918), and winter (January–April 1920). These mortality waves were synchronized across the 8 administrative regions of Mexico City (not shown). In the spring wave (April–May 1918), pneumonia and influenza mortality rates increased by 10%–150% above baseline levels, depending on the administrative region. In the main autumn pandemic wave, pneumonia and influenza mortality rates increased by 400%–1100% over baseline. In contrast, in the third wave, which occurred during winter 1919–1920, the increase in pneumonia and influenza mortality rates was more moderate, ranging from 23% to 76% across all administrative regions of Mexico City.

In contrast to Mexico City, the smaller city of Toluca (Figure 2) experienced a small increase in respiratory mortality rates during spring (2 April–3 June 1918), a large increase during autumn (1 October–23 December 1918), and little excess mortality in the winter 1919–1920. Of note in Toluca, the respiratory mortality remained elevated throughout summer 1918, persisting at levels 2–3-fold above that of baseline pre-pandemic summers.

Figure 3 illustrates the comparison between seasonal regression and model-free approaches to estimate age-specific excess

respiratory mortality rates. Age-specific estimates were consistent with the 2 approaches, with correlation coefficients of >0.90 ($P < .01$), although the Serfling approach tended to produce somewhat higher estimates (by ~8% on average for Mexico City and 14% for Toluca). Overall, the age-specific excess mortality rates were consistent across cities and were reminiscent of a W-shaped pattern, with the lowest excess mortality rates in children and teenagers 5–19 years old and adults 45–64 years old and high excess mortality in all other age groups, including seniors ≥ 65 years old (Tables 1 and 2). Although few deaths occurred during the spring 1918 wave, young adults aged 20–50 years experienced unusually high excess death rates. The unusual elevation in the mortality among young adults persisted in autumn 1918 and almost disappeared by the following winter in 1920.

Estimates of the relative risk of death associated with each pandemic wave, age group, and city are provided in Tables 1 and 2 to facilitate comparison between population groups that experienced different baseline risks of death. In both cities, a substantial increase in the mortality rate was observed among seniors ≥ 65 years of age during the autumn 1918 and winter 1920 waves, with a 2–6-fold elevation over baseline. Despite the high absolute excess mortality rates among seniors, however, the highest relative pandemic risk increase was experienced

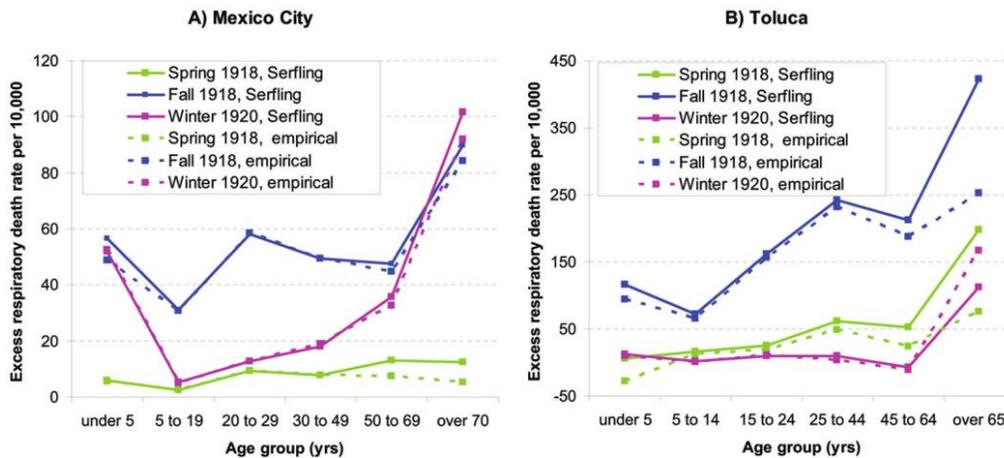


Figure 3. Age-specific estimates of excess respiratory mortality rates during the spring 1918, autumn 1918, and winter 1919–1920 influenza pandemic waves in Mexico City and Toluca. Estimates are based on 2 independent methods: (1) a Serfling approach using seasonal linear regression to estimate the baseline noninfluenza mortality [7, 22, 23] and (2) an empirical method using mortality during the prepandemic years 1915–1917 as a baseline [5].

by young adults, with a 25–50-fold increase above baseline during autumn 1918. In Mexico City, where a more detailed age breakdown is available, the peak relative risk of death was observed among 20–29-year-olds during the autumn wave. During the same period in Toluca, the peak relative risk of death was found in the broader age group of 25–44 years.

Transmissibility estimates. Estimates of the reproduction numbers and 95% confidence intervals for the spring and autumn waves of the 1918 influenza pandemic in Toluca and Mexico City are provided in Tables 3 and 4. For Mexico City, the mean reproduction number was 1.3–1.8 for the spring wave and 1.3–1.7 for the autumn wave, assuming a serial interval of either 3 or 6 d. Estimates of the reproduction number were higher for the city of Toluca, being 1.6–3.1 for the spring wave

and 2.1–6.1 for the autumn wave. These estimates did not change substantially when the estimation was based on the excess respiratory deaths instead of all respiratory deaths.

DISCUSSION

To the best of our knowledge, this is the first study to quantify the age-specific excess mortality impact of the devastating 1918 influenza pandemic in Mexico, a country that remained neutral during World War I. This work involved intense primary data collection efforts to compile archival age-stratified respiratory mortality rates for years before and during the pandemic in 2 cities, Mexico City and Toluca. We document a pattern of 3 successive pandemic waves in Mexico City and Toluca in spring

Table 1. Age-Specific Mortality Impact Associated with the Spring, Autumn, and Winter Waves of the 1918–1920 Influenza Pandemic in Mexico City, Mexico

Age group	Spring 1918 wave, April–May 1918		Autumn 1918 wave, October–December 1918		Winter 1920 wave, February–March 1920	
	No. of excess deaths per 10,000 people	Relative risk over baseline mortality	No. of excess deaths per 10,000 people	Relative risk over baseline mortality	No. of excess deaths per 10,000 people	Relative risk over baseline mortality
All ages	6.6	1.2	47.0	7.0	19.3	2.6
0–4 years	5.9	0.3	56.6	2.2	52.0	1.8
5–19 years	2.6	2.3	31.2	24.5	5.4	4.5
20–29 years	9.2	4.7	58.3	26.3	12.7	5.0
30–49 years	7.9	7.7	49.5	9.9	18.0	18.9
50–69 years	13.0	1.4	47.5	4.2	35.8	3.3
≥70 years	12.5	0.3	89.8	2.1	101.8	2.0

NOTE. Excess mortality estimates are based on a seasonal regression approach applied to monthly respiratory mortality rates and presented as the number of deaths per 10,000 people. A relative risk of death is also presented, based on the ratio of excess mortality to baseline mortality, facilitating comparisons across age groups, which have different background risks of death.

Table 2. Age-Specific Mortality Impact Associated with the Spring, Autumn, and Winter Waves of the 1918–1920 Influenza Pandemic in the City of Toluca, Mexico

Age group	Spring 1918 wave, 5 April–7 June 1918		Autumn 1918 wave, 27 September–20 December 1918		Winter 1920 wave, 27 February–26 March 1920	
	No. of excess deaths per 10,000 people	Relative risk over baseline mortality ^a	No. of excess deaths per 10,000 people	Relative risk over baseline mortality ^a	No. of excess deaths per 10,000 people	Relative risk over baseline mortality ^a
All ages	18.6	1.0	162.3	14.4	9.9	1.3
0–4 years	1.3	0.1	118.2	3.8	15.0	0.7
5–14 years	4.6	0.8	72.6	27.1	0.6	1.0
15–24 years	12.5	2.1	161.6	39.6	10.8	5.0
25–44 years	47.5	4.8	245.1	53.1	12.1	4.2
45–64 years	25.8	1.1	208.6	13.1	0.0	0.0
≥65 years	0.0	0.0	381.3	6.5	106.8	1.4

NOTE. Excess mortality estimates are based on a seasonal regression approach applied to weekly respiratory mortality rates and presented as the number of deaths per 10,000 people. A relative risk of death is also presented, based on the ratio of excess mortality to baseline mortality, facilitating comparisons across age groups, which have different background risks of death.

^a Calculated as the excess mortality divided by the baseline mortality during influenza epidemic months

1918, autumn 1918, and winter 1920, although the third pandemic wave was very minor in Toluca. In line with reports from the United States and Europe [4, 7, 32], young Mexican adults aged 25–44 years experienced an unusually elevated risk of respiratory mortality, especially during the first 2 pandemic waves. However, in contrast to previous studies, the mortality data available from 2 Mexican cities suggest that individuals aged ≥65 years were not spared by this pandemic and experienced substantial influenza-related excess mortality.

The early wave of respiratory mortality reported in Mexico City and Toluca in spring 1918 was associated with increased death rates among young adults compared with the baseline mortality in previous years, which is consistent with the signature age mortality patterns of the 1918 influenza A(H1N1) pandemic virus [4, 7]. Similar herald waves of excess respiratory mortality among young adults in spring and summer 1918 have been reported for other regions of the world, including New York City [4], Geneva [2, 33], Copenhagen [7], the US military [7], the United Kingdom [12], and Singapore [34]. Hence, our study and others are suggestive of the early emergence and circulation of a mild form of the pandemic influenza A(H1N1) virus in February–May 1918 in North America. We note that although the pattern of increased mortality among young adults was particularly marked in the autumn 1918 wave in Mexico City, it had almost disappeared by winter 1920, which suggests that high immunity levels were achieved in the young adult population because of infection during prior waves, possibly also because of decreasing severity of the influenza A(H1N1) virus infection.

The exact mortality patterns associated with the 1918 pandemic virus have long been debated [4, 7, 35, 36]. Visual inspection of age-specific respiratory mortality rates for the year 1918 suggests a W-shaped pattern of death in many locations,

which is characterized by high mortality among infants, young adults, and seniors aged >65 years [35]. However, annual respiratory mortality is a crude and biased indicator of the actual burden of pandemic influenza, because it includes background death rates from other pathogens, which are particularly high among infants and seniors. Careful studies that have quantified the monthly mortality that occurred in excess of the background have shown that seniors >65 years of age in New York City and Copenhagen experienced little to no excess mortality that was attributable to influenza during the pandemic [4, 7]. A recent study that explored influenza-specific mortality in Madrid and Paris reported that the proportion of deaths in seniors >65 years old was only 5%–6% in autumn 1918, much lower than in previous interpandemic seasons (36%–42%), which suggests that seniors were at least partially spared during the 1918 pandemic in these European cities [11]. In contrast to these studies, our Mexican data suggest that seniors ≥65 years of age experienced 1.5–2.4-fold higher excess mortality rates than young adults during autumn 1918, a >2-fold elevation over their baseline mortality rate. To our knowledge, this is the first quantitative study to document high excess mortality among seniors during the 1918 pandemic and to produce a true W-shaped pattern of excess mortality risk by age, even after carefully accounting for the high background

Table 3. Mean Estimates of Transmissibility for the Summer 1918 and Autumn 1918 Waves of the Pandemic in Mexico City, Assuming a Serial Interval of 3 or 6 d That Is Either Exponentially Distributed or Fixed (δ Distribution)

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Table 4. Mean Estimates of Transmissibility for the Spring 1918 and Autumn 1918 Waves of the Pandemic in the City of Toluca, Mexico, Assuming a Serial Interval of 3 or 6 d That Is Either Exponentially Distributed or Fixed (δ Distribution)

This table is available in its entirety in the online version of the *Journal of Infectious Diseases*

risk of death among seniors. This finding of elevated mortality among seniors is in agreement with anecdotal evidence from aboriginal populations in Alaska in 1918 [37], although with such remote populations it is difficult to integrate data on the background risk of death and to obtain reliable estimates of population size. Overall, the Mexican experience suggests that the pronounced mortality sparing of seniors that has been documented in the historical US and European studies may not have been a global phenomenon.

The biological and immunological reasons for the complicated age pattern of mortality associated with the 1918 pandemic are still being debated. Previous studies have put forward the hypothesis that childhood exposure to antigenically related influenza A(H1N1) viruses before 1870 might account for mortality sparing among seniors, which is consistent with the pandemic age mortality profiles described in the United States and Europe [4, 7]. Our Mexican data provide evidence that some urban North American senior populations lacked protection against pandemic mortality, which suggests there were differences between countries in prior immunity to the 1918 influenza A(H1N1) virus. Such differences may result from heterogeneous circulation of influenza viruses in the 19th century, at a time when long-distance travel among populations was much less developed than it is today.

A theoretical scenario has been proposed for populations that lacked prior immunity to the 1918 pandemic virus, in which the age-specific mortality curve follows a V-shape that bottoms in the early teenage years and increases rapidly and monotonously in older age groups [38]. Our Mexican mortality data do not support this pessimistic scenario but suggest that 2 factors may have driven the age distribution of pandemic-related mortality in 1918: (1) an unidentified factor that increased the risk of death among young adults and was likely present globally and (2) a partially protective factor in people ~65 years of age and older that was present in Europe [7], the United States [4], and Japan [32] but absent in Mexico and remote populations [37]. It has been hypothesized that the mortality risk factor among young adults may have been mediated by an increased probability of cytokine storm upon influenza virus infection, although this remains a subject of debate [39].

Overall, we estimated that 0.7% of the population of Mexico City died of influenza during 1918–1920. This estimate falls in

the low range of reported excess pandemic death rates in countries in Europe [40] and elsewhere [5], but it is about twice as high as that experienced in New York City [4] and Copenhagen [7]. By contrast, the pandemic-related excess death rate in Toluca was in the midrange of the available global estimates at 1.9% [5]. Substantial variability in the pandemic excess mortality rate within and between countries has been linked with variation in socioeconomic conditions [5] and latitude [40], but it remains poorly understood. It is possible that poorer socioeconomic conditions, issues with access to health care, or environmental conditions may explain the higher death rate in Toluca than in Mexico City.

In past research, transmissibility estimates derived from 1918–1920 pandemic morbidity and mortality data were in the range of 1.5–5.4 for community-based settings in several regions of the world [3, 7, 41–43] and 2.1–7.5 for some confined settings [41]. In the present study, the reproduction number was significantly higher for Toluca than that for Mexico City. Of note, Toluca is located at a higher elevation than Mexico City (2667 m vs 2240 m), and hence the absolute humidity is generally lower in Toluca than in Mexico City. Therefore, it is possible that aerosol spread is more efficient in Toluca than in Mexico City, perhaps due to increased survival of the virus within aerosolized droplets (as recently suggested by experimental and epidemiological studies [44, 45]), which could potentially explain the higher influenza virus transmissibility.

It is interesting to compare reproduction number estimates across successive pandemic waves to gauge potential changes in the virus characteristics and population immunity. Although the reproduction number estimate was lower in spring 1918 than in autumn 1918 in Toluca, it was similar for both waves in Mexico City. Low estimates for the spring wave in both cities are in line with the results of a previous study in Geneva ($R \sim 1.5$) [33] and in the lower range of previous estimates for Copenhagen [7]. The apparent increase in reproduction number from spring to autumn in Toluca is in agreement with the results of the Geneva study [33] and is perhaps partially explained by increased fitness of the influenza virus during more propitious weather conditions in the autumn, even after accounting for decreased population susceptibility after the spring and summer outbreaks. In contrast, reproduction number estimates substantially decreased from spring to autumn in Copenhagen [7]. Differences in reproduction number estimates across locations and pandemic waves may reflect true differences that are attributable to spatiotemporal variation in attack rates of successive waves or local factors that affect transmission, or these differences may simply illustrate the difficulties in measuring this important parameter with precision [27].

Although mortality data for the 2009 influenza A(H1N1) pandemic are still preliminary, seniors appear to have been partially spared, with only ~12% of influenza-related deaths

occurring among people >60 years old, compared with >90% of influenza-related deaths in typical interpandemic seasons [17, 46–49]. This pattern is reminiscent of the 1918 pandemic in Europe and the United States, where only ≤6% of excess deaths occurred among people >65 years old, compared with 33%–42% of excess deaths in prepandemic influenza seasons [4, 7]. The pattern of multiple pandemic waves of the influenza A(H1N1)-pdm virus in most of the Northern Hemisphere is also reminiscent of the 1918 pandemic, with a first wave in spring 2009 followed by an autumn wave that was associated with high attack rates in most places. Although the impact of the novel influenza A(H1N1)-pdm virus has been significantly lower than that of the 1918 pandemic, and the fear of a returning lethal autumn wave has not materialized so far, planning for the worst and monitoring the pandemic mortality burden across age groups and countries is a prudent course of action until this virus has circulated in the population for several years. In parallel, our study highlights the importance of collecting historical mortality data from multiple locations around the world to quantify the impact of past influenza pandemics on populations, especially in lesser studied areas of the Americas, Asia, and Africa.

Acknowledgment

This research was conducted in the context of the Multinational Influenza Seasonal Mortality Study, an ongoing international collaborative effort to understand influenza epidemiological and evolutionary patterns, led by the Fogarty International Center, National Institutes of Health (<http://www.origem.info/misms/index.php>).

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