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Age-Specific Excess Mortality Patterns During the 1918–1920 Influenza Pandemic in Madrid, Spain

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Although much progress has been made to uncover age-specific mortality patterns of the 1918 influenza pandemic in populations around the world, more studies in different populations are needed to make sense of the heterogeneous death impact of this pandemic. We assessed the absolute and relative magnitudes of 3 pandemic waves in the city of Madrid, Spain, between 1918 and 1920, on the basis of age-specific all-cause and respiratory excess death rates. Excess death rates were estimated using a Serfling model with a parametric bootstrapping approach to calibrate baseline death levels with quantified uncertainty. Excess all-cause and pneumonia and influenza mortality rates were estimated for different pandemic waves and age groups. The youngest and oldest persons experienced the highest excess mortality rates, and young adults faced the highest standardized mortality risk. Waves differed in strength; the peak standardized mortality risk occurred during the herald wave in spring 1918, but the highest excess rates occurred during the fall and winter of 1918/1919. Little evidence was found to support a "W"-shaped, age-specific excess mortality curve. Acquired immunity may have tempered a protracted fall wave, but recrudescent waves following the initial 2 outbreaks heightened the total pandemic mortality impact.

1918 pandemic; age-specific mortality patterns; excess mortality; herald wave; influenza; mortality baseline; Spain

Abbreviation: SMR, standardized mortality ratio.

The 1918–1920 influenza pandemic, or the so-called Spanish flu, was responsible for more than 50 million deaths worldwide (1, 2). In Europe, the excess mortality rate associated with the 1918–1919 influenza pandemic has been estimated at 1.1%, or approximately an 86% increase in all-cause mortality (3). This pandemic rapidly spread in a series of pandemic waves that gripped the world beginning in early 1918 (4). However, according to results of various phylogenetic and molecular-clock analyses, the initial circulation of the virus from avian or swine and other mammal species to humans may have occurred a few years earlier (5–7). Moreover, the symptoms and age-specific mortality patterns associated with this particular pandemic are unique. For example, the most severely affected patients were often young adults who had heliotrope cyanosis and acute respiratory distress. In fact, according to several detailed historical investigations, the highest excess mortality rates consistently were among young adults. This finding is in contrast to those indicating seasonal influenza epidemics primarily affect the very young and elderly (8, 9).

The name Spanish flu comes from the first news reports of influenza-like-illness in Madrid in the late spring of 1918. However, this pandemic gained its nickname because the first mentions of the virus were published in Spain, where the press faced no censorship during World War I, owing to the country's neutrality (10). Many people fell ill with respiratory symptoms in May 1918, including King Alfonso XIII, which was well documented in the press (10). Because respiratory disease outbreaks occurred in neighboring France as early as April 1918, it is likely that the virus was introduced into Spain via Spanish and Portuguese labor migrants in southern France (11). Research has provided abundant information regarding the timing, severity, and excess mortality of the 1918 influenza pandemic in Spain (10–12), as well as some estimates of transmission potential of the virus within the city of Madrid (12–14). Nevertheless, these analyses provide a primarily descriptive picture of the pandemic in Spain through the lens of period press reports and midcentury publications, including a sense of the evolution of sanitation and health in Spain (10, 11, 15, 16), though

newly digitized data sources provide increased opportunities to quantify the impact of the pandemic on the Spanish population (12). For instance, estimates of pandemic excess respiratory death rates have ranged from 6.1 per 10,000 for the Canary Islands to 169.7 per 10,000 for Burgos (12). Moreover, approximately 40% of between-province variation in cumulative excess death rates in Spain during 1918–1919 are explained by spatial factors, such as latitude, population density, and the proportion of children, have explained (12). However, in few of these analyses did researchers take into account a recrudescent wave in Spain, which peaked in Madrid in late December 1919 and in later months in the rest of Spain (3, 15, 16).

Although much progress has been made in uncovering the age-specific mortality patterns of this pandemic in several populations in Latin America (17–20), the United States, and Europe (21–24), more studies are needed to make sense of the heterogeneous death impact of this pandemic across different populations around the world. For instance, by characterizing and comparing the age-specific excess death rates across pandemic waves during 1918–1920 in different populations, researchers could suggest alternative hypotheses on the drivers of pandemic mortality risk at the time and place more emphasis on less-studied phenomena associated with the pandemic.

Despite previous efforts to characterize the impact of the 1918 influenza pandemic in Spain, prior studies have not systematically investigated differences in death impact between age groups and pandemic waves. In this study, we analyzed detailed series of deaths after retrieving more than 70,000 individual death certificates representing all-cause deaths during 1917–1920. We assessed the timing of pandemic waves and their magnitude in absolute and relative terms on the basis of all-cause and respiratory excess death rates across age groups and 3 pandemic waves in the city of Madrid during 1918–1920, including a recrudescent wave in winter 1919–1920.

METHODS

Spanish death data

We retrieved all death certificates from the Madrid Civil Registry to construct time series of deaths during the 1918–1920 influenza pandemic (Figure 1). Each record provides specific details of the deceased, including the date of death, age, and causes of death. For years 1917–1920, the registry holds a total of 70,061 death records (an average, 17,650 deaths per year). Cause-of-death information for each death record allowed us to extract data on deaths attributed to influenza and respiratory causes.

It is now well recognized that a significant fraction of the pandemic deaths resulted from secondary respiratory ailments (e.g., most commonly bacterial pneumonia) following influenza infection, rather from influenza infection alone (25, 26). Additional influenza-related deaths have been attributed to other types of bacterial infections and severe acute respiratory distress, often evidenced by the appearance of bluish-gray skin shortly before death (25). As such, estimates of death attributed to respiratory causes also provide key information regarding the impact of influenza-specific deaths. As was done in prior studies (e.g., Chowell et al. (17)), we have estimated in this study excess death rates for all-cause deaths and for pneumonia- and influenza-related deaths, a category that comprises all death records indicating influenza, pneumonia, bronchopneumonia, or bronchitis as a cause of death after removing death certificates reporting tuberculosis as a cause of death.

Furthermore, to estimate death rates, information regarding the population composition of Madrid was obtained from the city's yearly population books (27). With this information, we were able to standardize our results according to the age structure of the population of Madrid at the time. We describe methods to

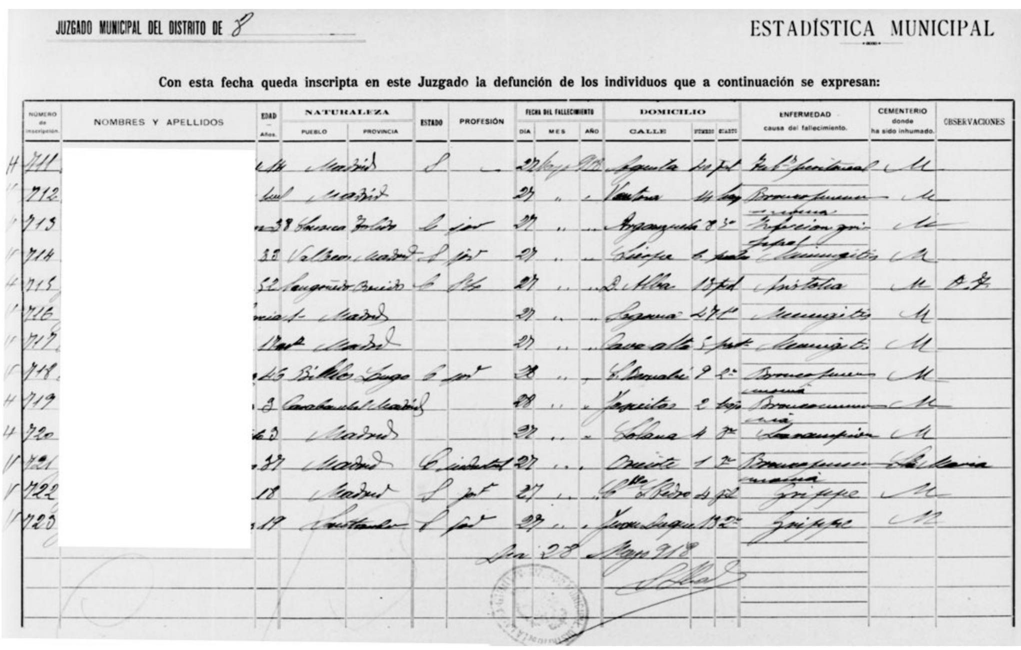


Figure 1. Sample of death records from May 27, 1918, from the Civil Register of Madrid (49).

estimate baseline and excess mortality rates as well as excess mortality ratios across age groups and pandemic waves.

Spain experienced one of the highest excess mortality rates during the 1918 influenza pandemic in Europe (3), although this country did not take part in World War I. Perhaps this pandemic outcome is associated with the fact that Spain was going through a demographic transition and experiencing elevated death rates that were only comparable to those of eastern Europe. Of note, the life expectancy in Spain was 41 years in 1910 and 40 years in 1920 (28).

Estimating mortality baselines with quantified uncertainty

Using mortality data for 1917, we characterized baseline death levels using weekly death rates and a simple, cyclical, Serfling linear regression model (29). However, this initial attempt to characterize the baseline did not capture a small but noticeable summer mortality peak. To account for this variation, we modified the initial Serfling model with additional parameters, as was done in another study of the 1957 influenza pandemic in Maricopa County, Arizona (30). The added coefficients in the model account for time (α) and seasonal (β and γ) variations in normal influenza activity, such that the oscillations (at time t) may be written as:

$$\frac{Deaths_{xt}}{Population_{xt}} = \upsilon + \alpha_1 * (t) + a_2 * \left(\frac{100}{t}\right)^2 + \beta_1 * \sin\left(2 * \frac{\pi}{52.17} * t\right) + \beta_2 * \sin\left(4 * \frac{\pi}{52.17} * t\right) + \beta_3 * \sin\left(8 * \frac{\pi}{52.17} * t\right) + \gamma_1 * \cos\left(2 * \frac{\pi}{52.17} * t\right) + \gamma_2 * \cos\left(4 * \frac{\pi}{52.17} * t\right) + \gamma_3 * \cos\left(8 * \frac{\pi}{52.17} * t\right)$$

To account for uncertainty in our 1917 baseline death level, we used a parametric bootstrap approach (31). With this method, we first simulated data before fitting the regression model displayed in the previous paragraph, accounting for fluctuations in the annual timing of winter and summer death peaks. For each of the weekly sets of death counts, we simulated a Poisson-distributed number of expected deaths, because the number of deaths each week is a "count" variable that must be 0 or greater. Our Poisson estimations assumed the mean and variance of a week were equal to the observed total number of deaths in a given week of 1917.

From each of 500 simulated data sets, α and β parameters were estimated according to the aforementioned modified seasonal regression model. We calculated the 5-year baseline from the mean values of the coefficients from 500 models and computed the upper baseline from the upper quartile value of the 95% confidence interval of coefficients. As in other reports in which Serfling regression was used to estimate baseline death rates, we defined weeks with death counts above the upper baseline as "pandemic weeks" (18, 30, 32). We defined 3 distinct wave periods: May to July 1918, August 1918 to April 1919, and November 1919 to February 1920. Although there is evidence to suggest the city of Madrid experienced a 1918 fall wave and a 1918/1919 winter wave, these become unclear when disaggregating the data into smaller categories such as age groups. For this reason and to facilitate comparisons with prior studies (12, 33, 34), we analyzed the successive fall and winter increases in excess mortality as 1 pandemic wave.

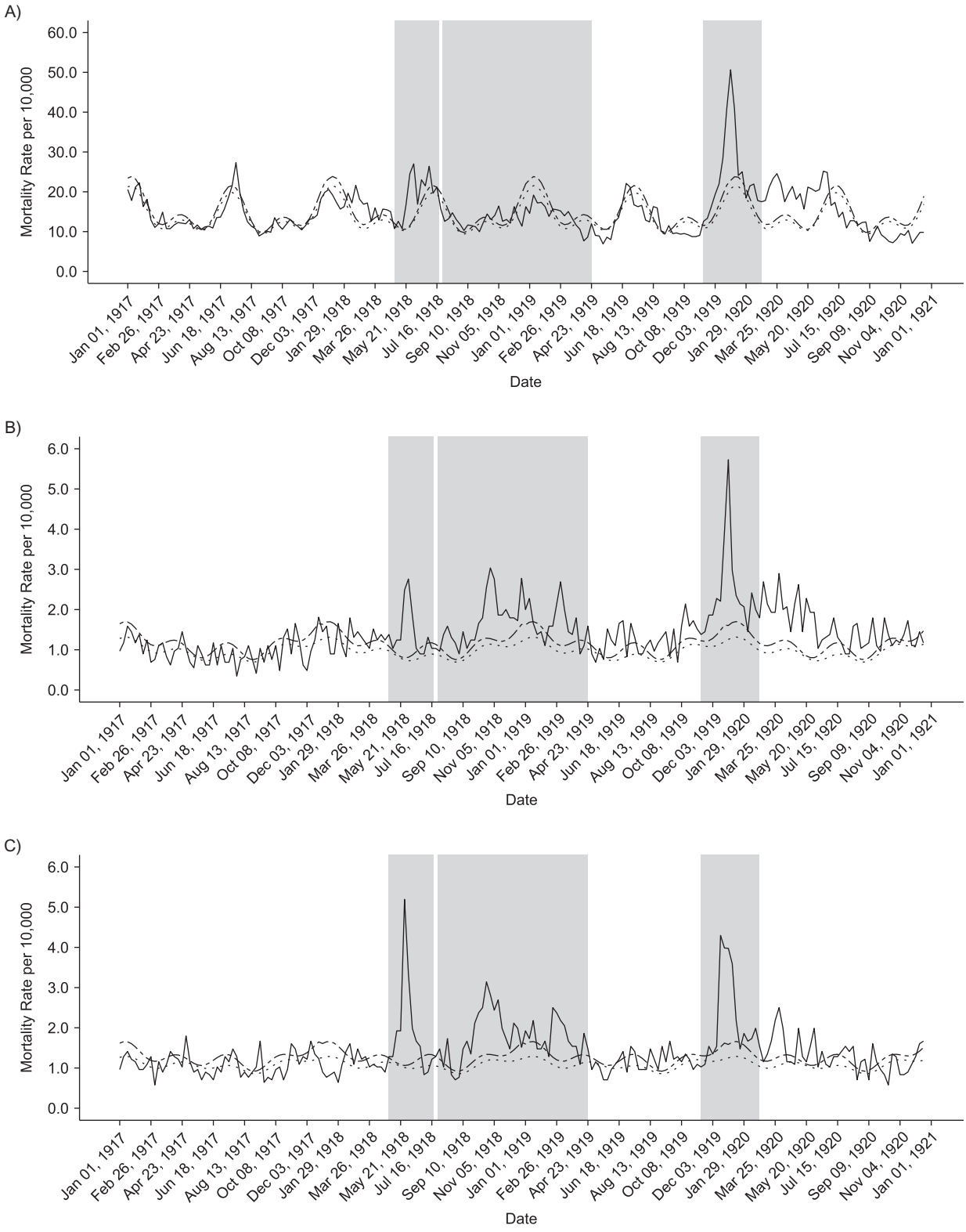
We characterized excess mortality for each wave by summing the total death rate above the baseline rate during the epidemic periods. To aid in the comparison of our results with other research, we also provide relative estimates for each wave and age group to allow relative comparisons across age groups (12, 35). For each wave, we defined relative risk as the ratio of total excess mortality observed to expected baseline number of deaths during pandemic weeks, when total mortality exceeded the 95% confidence interval of the baseline. This aids in the direct comparison of the total influenza pandemic between study groups, because baseline death counts varied substantially by age group (18).

RESULTS

Our analyses of weekly death rates from January 1917 to December 1921 revealed 3 distinct periods of pandemic-related mortality: a brief but well-defined spring wave (May to July 1918), an intense fall-winter wave during August 1918 to April 1919, and a recrudescent winter wave during November 1919 to February 1920 (Figures 2 and 3). Overall, peaks in respiratory and all-cause death rates were well synchronized. All-cause and respiratory-related excess deaths for all age groups generally followed the same pattern of excess mortality by wave: The fall-/winter wave had the highest excess rates, followed by the third recrudescent wave, then the herald wave in spring 1918 (Tables 1 and 2). In addition, the pattern of the age-specific standardized mortality risk (SMR) remains the same, but the total elevated risk in all waves is much more pronounced when considering only respiratory mortality. Our cumulative estimates of excess mortality for these 3 pandemic waves were 86.8 per 10,000 from all-cause death and 44.6 per 10,000 from respiratory-related deaths, or approximately 6,500 total excess deaths, of which 3,300 were respiratory related.

Total excess mortality for epidemic weeks during the observed period was highest during the second fall-winter wave in 1918/1919. We found a total excess rate of approximately 33.5 deaths per 10,000 persons, based on all-cause deaths and 22.3 per 10,000 based on respiratory-related deaths. In contrast, the spring-summer wave was associated with an excess death rate at 8.2 per 10,000 persons, based on respiratory-related deaths and 19 per 10,000 for all-cause deaths. It is interesting that the third wave in winter of 1919–1920 generated a substantial death rate at 34 deaths per 10,000 persons, based on all-cause deaths, which is comparable to that of the intense fall-winter 1918/1919 wave. However, it is worth noting that the first and third waves were relatively brief and had a pointed shape, whereas some age groups had 2 well-defined death peaks during the protracted second wave in fall-winter 1918/1919 (Figure 3).

In general, age-specific excess mortality rates were lowest during the spring wave and highest during the protracted



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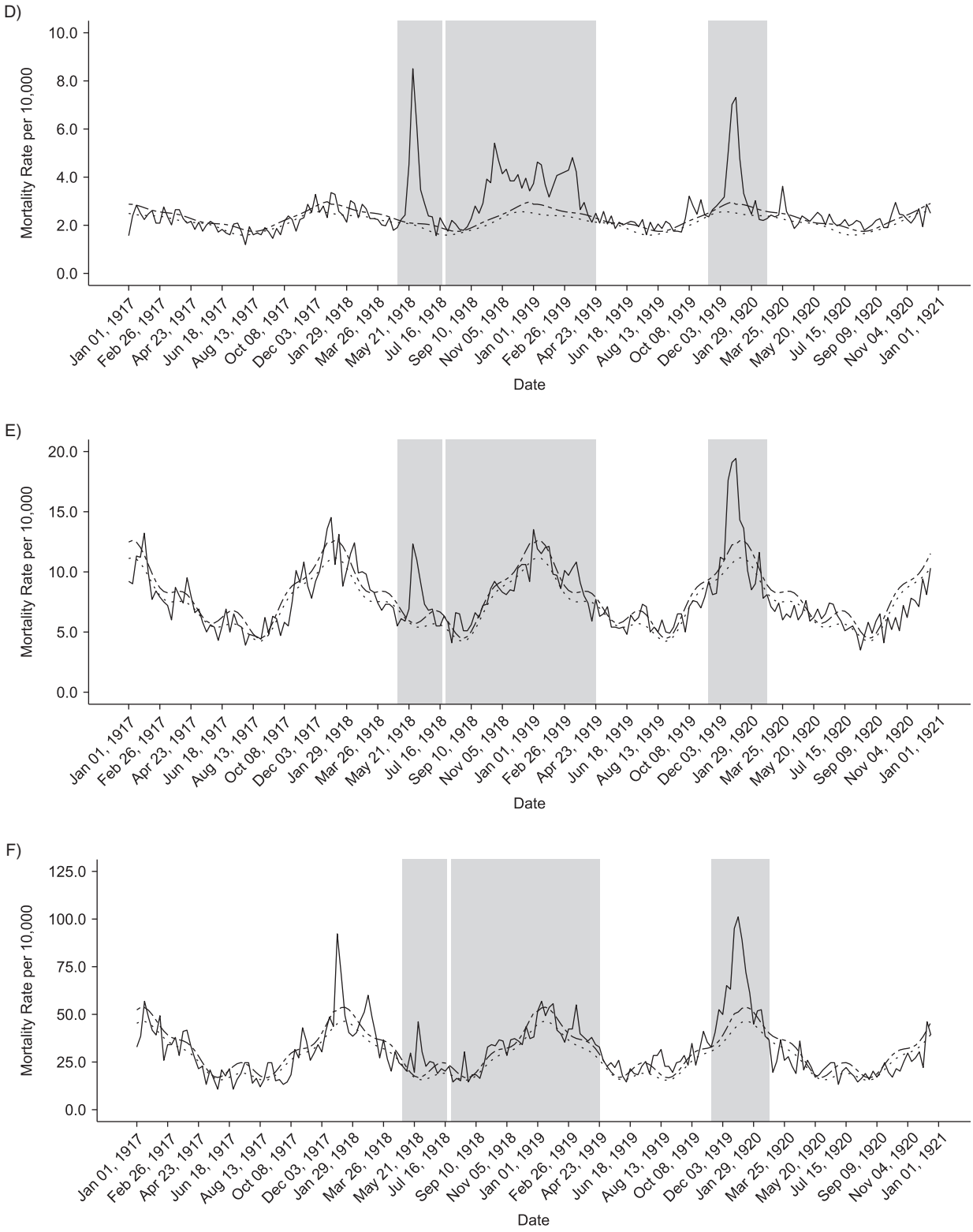

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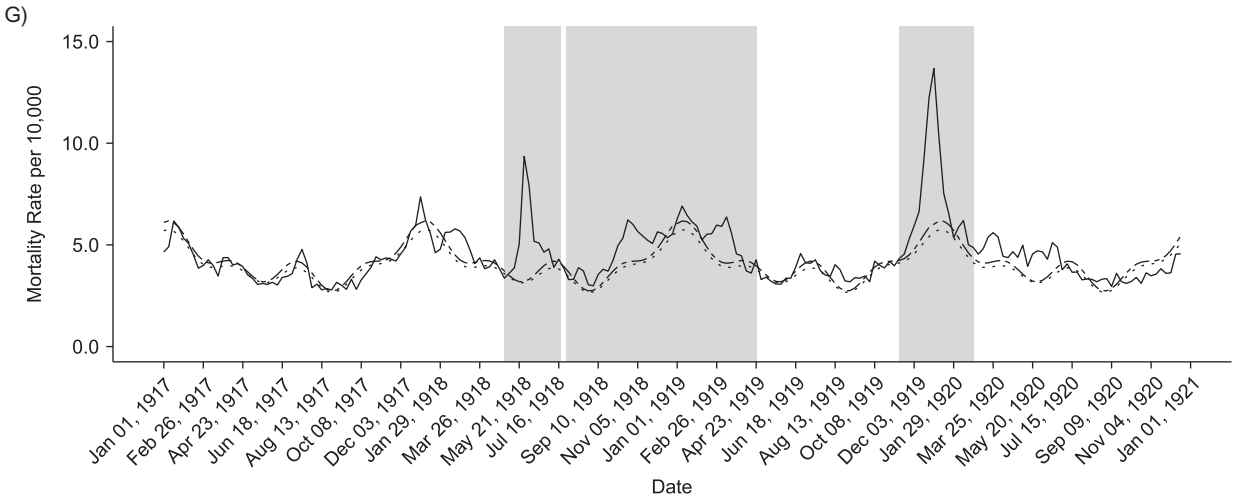


Figure 2. Weekly time series of all-cause death rates, 1917–1920. Solid lines show the real weekly mortality rates from 1917 to 1922, and dotted and dashed lines show the mean and upper 95% bound baseline rates from simulated 1917 death data. Shaded gray blocks indicate the 3 epidemic wave periods. A–F) The figure panels correspond to the following age groups: <5, 5–14, 15–24, 25–49, 50–69, and ≥70 years. G) Graph shows data for all ages combined.

second wave, as shown in Figure 4. Compared with the first 2 pandemic waves, the youngest and oldest groups were particularly affected during the recrudescent wave in the winter of 1919–1920. In fact, during the third wave, those older than 70 years faced excess all-cause and respiratory-related death rates that were more than 3 times higher than in the first wave. Furthermore, during the last wave, infants and children aged up to 15 years experienced more than double the all-cause and respiratory-related excess mortality rates estimated for the first 2 waves. The age groups 5–14 years and 15–24 years maintained similar patterns in each of the waves, facing the lowest excess rates in the spring herald wave and highest in the combined fall and winter waves of 1918/1919. The highest excess mortality rate in the age group 25–49 years occurred in the second wave in fall-winter 1918/1919.

Although the herald spring wave accounted for slightly more than 20% of all total excess deaths, we note that the SMR during this period was higher than in the succeeding waves, due to lower baseline numbers of deaths during spring and summer (see Figure 5). Remarkably, although individuals 15–24 years of age had low excess mortality rates relative to other age groups, this age group had the highest SMR across all pandemic waves. Generally, the age-specific pattern of the SMR is that of an inverted "v," with the exception of the oldest age group. During the first and third waves, those older than 70 years experienced a higher SMR than individuals aged 50–69 years. Most generally, the highest SMRs occur in the first and last waves, though the highest calculated SMRs for respiratory-related deaths (4.4 and 4.2, respectively,) occurred in those 15–24 years of age in the first and second waves.

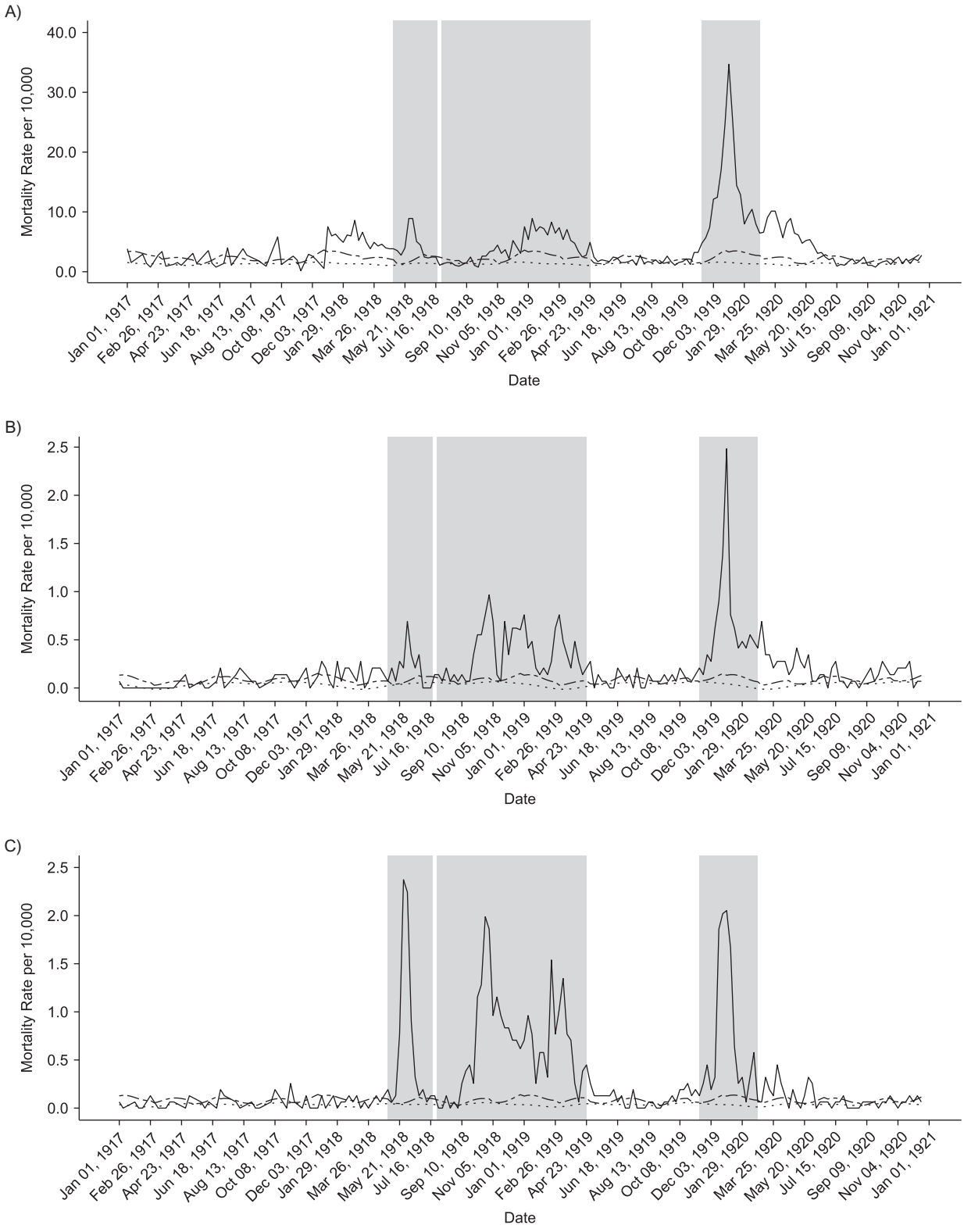
DISCUSSION

Although estimates of excess mortality reveal variability in age-specific patterns throughout the world, our results are unique in that the highest absolute excess rates occurred among older populations (≥70 years) compared with findings in previous reports from Europe and the United States (9, 21, 22). Specifically, the Madrid age-specific excess dominant pattern resembles that of seasonal influenza epidemics in which the highest excess rates occurred in the youngest and oldest groups (17, 18, 36). However, much of the elderly population of Madrid would have been exposed to other viruses; for example, in the decades preceding the Spanish flu, the "Russian" influenza pandemic that struck Madrid in the winter of 1889–1990 produced overall all-cause excess mortality rates of 58.3 per 10,000 persons and produced an age-specific excess mortality pattern similar to each of the 3 pandemic waves in Madrid (34).

Our results also confirm those of earlier analyses of a particularly lethal spring wave in Madrid relative to smaller peaks in numbers of deaths, but high incidence rates in some locations, such as Norway and Denmark (4, 21, 22). In Madrid, weekly excess death rates during the spring wave nearly rivaled that of the protracted fall-winter 1918/1919 wave.

We can contextualize the timing of this first wave in Madrid relative to herald pandemic waves in North America and outbreaks among civilian populations in Europe. Many of the first purported spring outbreaks occurred in US military camps; these outbreaks spread to larger cities in April and May, before the herald wave in Madrid (4). However, the mid-late May outbreak was the first reported in civilian populations in Europe. In the following months, reported influenza outbreaks in Europe occurred eastward and northward to other parts of Spain and Italy, then England, Sweden, and Norway, and Switzerland and Poland (4, 12, 22–25, 37, 38). However, it remains difficult to distinguish to what extent the virus spread through military rather than civilian population movement (4).

According to analyses of hospitalization, deaths, and other surveillance sources in military and civilian settings, there is evidence of cross-protection between spring and fall influenza outbreaks during waves of the 1918–1919 epidemic (39–42). The high pandemic death rate we found, together with evidence of high incidence rates during spring-summer waves (10, 15, 43),



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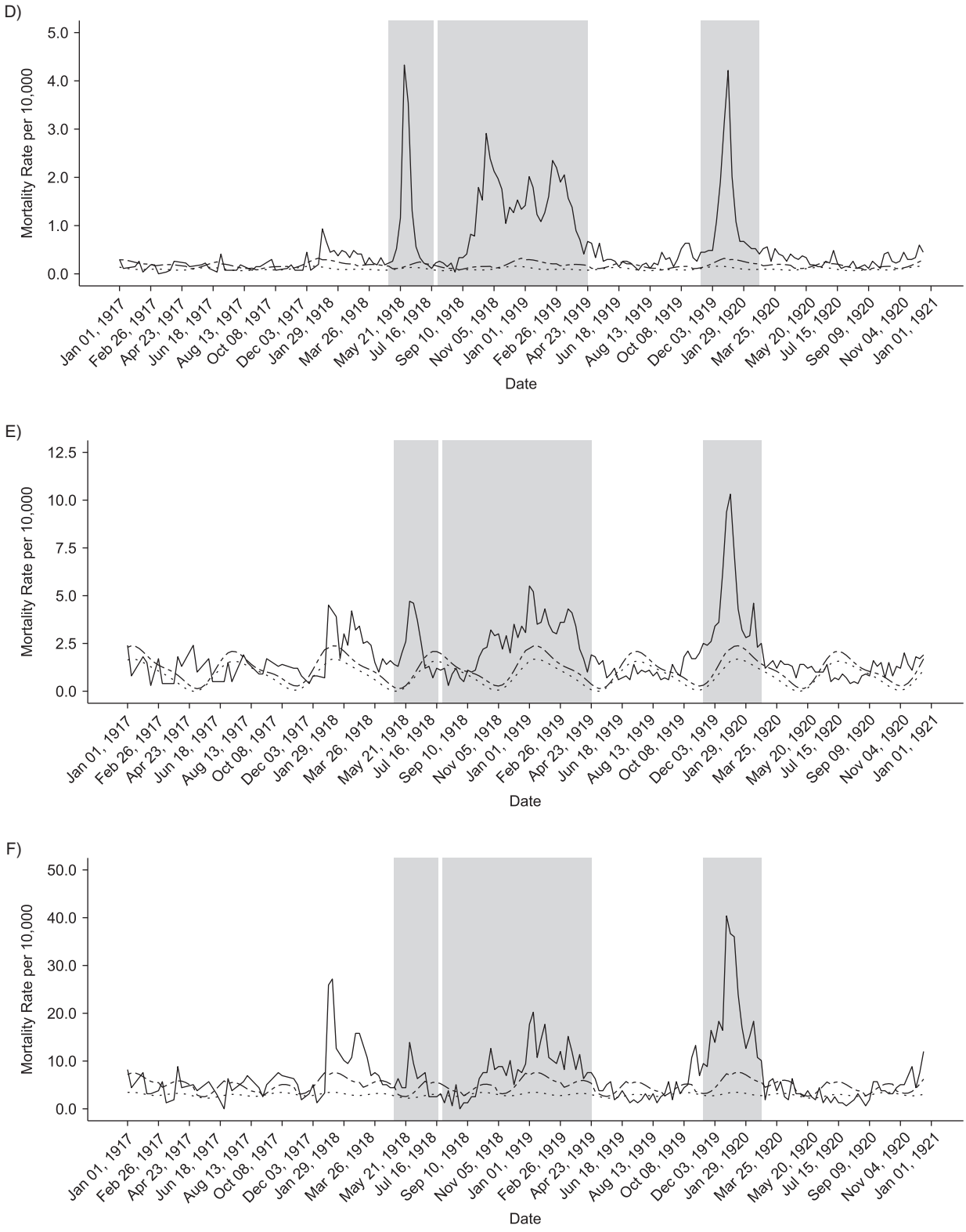

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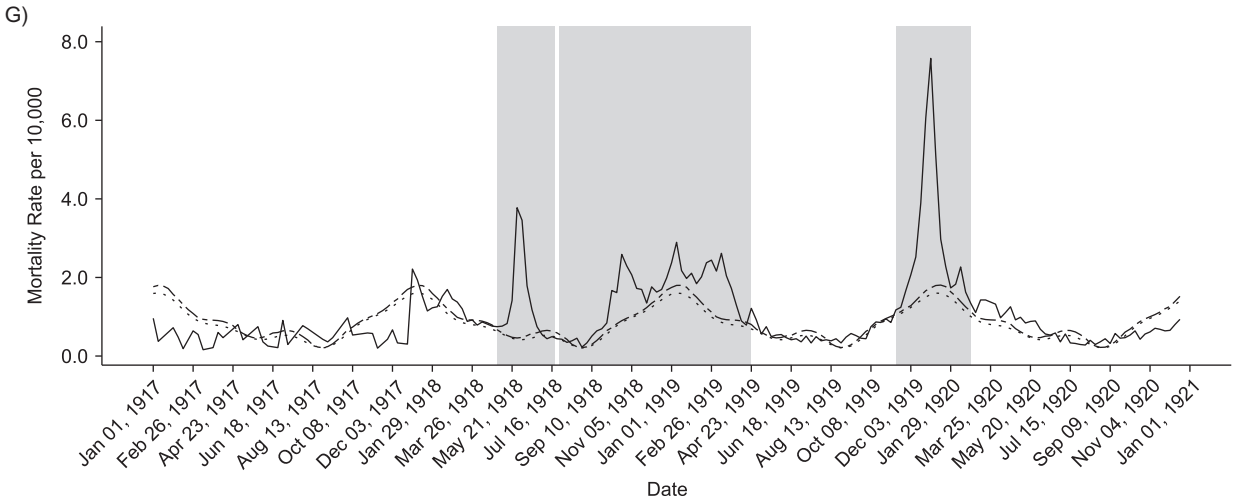

Figure 3. Weekly time series of respiratory-related death rates, 1917–1920. Solid lines show the real weekly mortality rates from 1917 to 1922, and dotted and dashed lines show mean and upper 95% bound baseline rates from simulated 1917 death data. Shaded gray blocks indicate the 3 epidemic wave periods. A–F) Figure panels correspond to the following age groups: <5, 5–14, 15–24, 25–49, 50–69, and ≥70 years. G) Graph shows data for all ages combined.

could have provided some immunity and cross-protection to the strain of virus in the succeeding fall wave. Conversely, in New York City, a noticeable age shift in influenza death patterns occurred in early 1918, perhaps suggesting the presence of the new virus strain. Yet, there was little total excess mortality until the strong fall wave, which killed more than 9 times

Table 1. Age-Specific Excess All-Cause Deaths by Wave in Madrid During 3 Epidemic Periods From 1918 to 1920

Age Group, years	Total No. of Excess Deaths	Total Excess Mortality Rate per 10,000	Standardized Mortality Risk
		Spring Wave, 1918	
Overall	1,456	19.42	1.57
<5	375	57.57	1.40
5–14	95	6.58	2.03
15–24	165	10.59	2.28
25–49	486	18.13	1.95
50–69	213	21.32	1.55
≥70	127	80.39	1.68
		Fall and Winter Wave, 1918/1919	
Overall	2,511	33.50	1.27
<5	293	44.90	1.22
5–14	364	25.11	1.82
15–24	401	25.73	1.83
25–49	1,250	46.63	1.58
50–69	262	26.22	1.24
≥70	275	173.58	1.24
		Winter Wave 1919/1920	
Overall	2,538	33.86	1.52
<5	823	126.34	1.59
5–14	261	17.98	2.18
15–24	235	15.08	2.14
25–49	467	17.41	1.63
50–69	344	34.45	1.41
≥70	485	306.51	1.63

Table 2. Age-Specific Excess Respiratory-Related Deaths by Wave in Madrid During 3 Epidemic Periods From 1918 to 1920

Age Group, years	Total No. of Excess Deaths	Total Excess Mortality Rate per 10,000	Standardized Mortality Risk
Spring Wave, 1918			
Overall	613	8.17	2.59
<5	253	38.81	2.62
5–14	19	1.31	3.11
15–24	49	3.12	4.43
25–49	114	4.25	2.89
50–69	100	9.98	2.27
≥70	77	48.72	3.15
Fall and Winter Wave, 1918/1919			
Overall	1,670	22.28	1.82
<5	308	47.25	1.69
5–14	82	5.64	2.27
15–24	185	11.87	4.20
25–49	524	19.56	2.77
50–69	346	34.66	1.65
≥70	250	157.79	1.88
Winter Wave 1919/1920			
Overall	1,061	14.15	1.86
<5	397	61.01	2.04
5–14	58	3.97	2.35
15–24	83	5.33	3.56
25–49	180	6.71	2.18
50–69	168	16.85	1.67
≥70	193	121.84	1.89

as many people (21). This pattern may partially explain the slower growth and protracted wave in Madrid that began in September 1918 and continued through the winter and early spring of 1919.

We also found evidence of a powerful recrudescent wave after the enduring second wave; the recrudescent wave peaked at the very end of 1919 and appeared throughout the world in the spring of 1920 (1, 3, 9, 17, 19–21, 24, 37, 44). In Madrid, all-cause excess rates were on par with those of the elongated second wave, and all-cause and respiratory-related excess mortality rates were higher than in the spring 1918 wave. In other countries and cities where this wave has been documented, a slight shift in the age-specific mortality often occurred, with a return to high excess mortality among people older than 65 years (9, 17, 19, 21, 24). As in our study, the death rate of young adults reported in these locations often dropped slightly but remained persistently high and well above the prepandemic level. In line with previous studies in Spain, during this fourth wave, death rates of infants and young children were particularly high (10, 15, 16). Because high rates of excess mortality existed in all age groups, lack of acquired immunity from earlier waves may only explain the excess mortality among infants and young children. Antigenic shift or mutation in the virus also could have contributed to the elevated mortality remaining elevated across all ages, but it remains difficult to ascertain the exact mechanisms that shaped the strong wave.

Another all-cause and respiratory-related peak in deaths occurred in late December 1921; although we did not specifically analyze this peak, it was present in all age groups and predominately in those age 50 years and those younger than 5 years (45). Recrudescent waves can still occur years after the initial and main pandemic waves, echoing the initial impact of an outbreak, such as in the 2011 A/H1N1 influenza epidemic recurrence in Mexico following the 2009 A/H1N1 influenza pandemic (46). The presence and impact of recrudescent waves of the pandemic should continue to be studied and quantified because they may substantially change the overall death impact of the influenza pandemic.

Our estimates of the influenza pandemic death impact in Madrid can be compared with those derived from a previous study in which excess monthly all-cause and respiratory-related deaths were analyzed in all provinces of Spain during the herald spring wave and second fall-winter wave (12). We found higher overall excess rates in the spring wave (19.4 vs. 11.7 per 10,000 persons) but lower excess rates in the second wave (33.5 vs. 55.0 per 10,000 persons). We also found lower excess respiratory-related mortality rates in both the herald and protracted second waves. These differences may stem from various factors, including differences in death data sources and the fact that the earlier study (12) analyzed pandemic impact in the entire province of Madrid, whereas our study focused on the capital city alone. Moreover, the spring wave may have largely affected the city

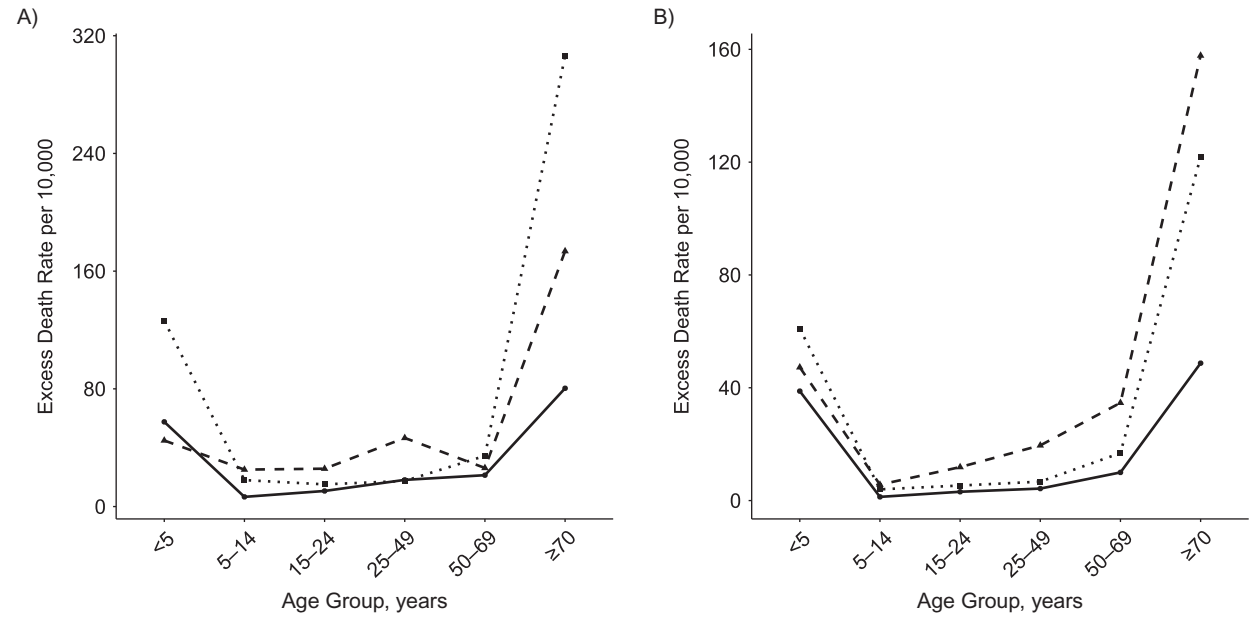

Figure 4. Total excess mortality rates per 10,000 persons for all-cause (A) and respiratory-related (B) deaths according to age groups for each wave. The solid line represents the first spring wave, the fall and winter waves are represented by the dashed line, and the final winter wave is represented by the dotted line.

itself (which we analyzed) and the surrounding province (the subject of the prior study (12)) to a lesser degree, resulting in different excess mortality estimates. The total impact of the spring wave could also extend to the second wave; perhaps those living in the city gained some immunity from exposure to the first wave, whereas those without this exposure did not benefit from cross-protection. Disentangling additional factors that drove these differences could be the focus of future study.

Considering the pandemic events collectively known as the Spanish influenza, the case of Madrid provides additional insights into how, in a large urban environment, individual waves and their progression contributed to the overall death impact on

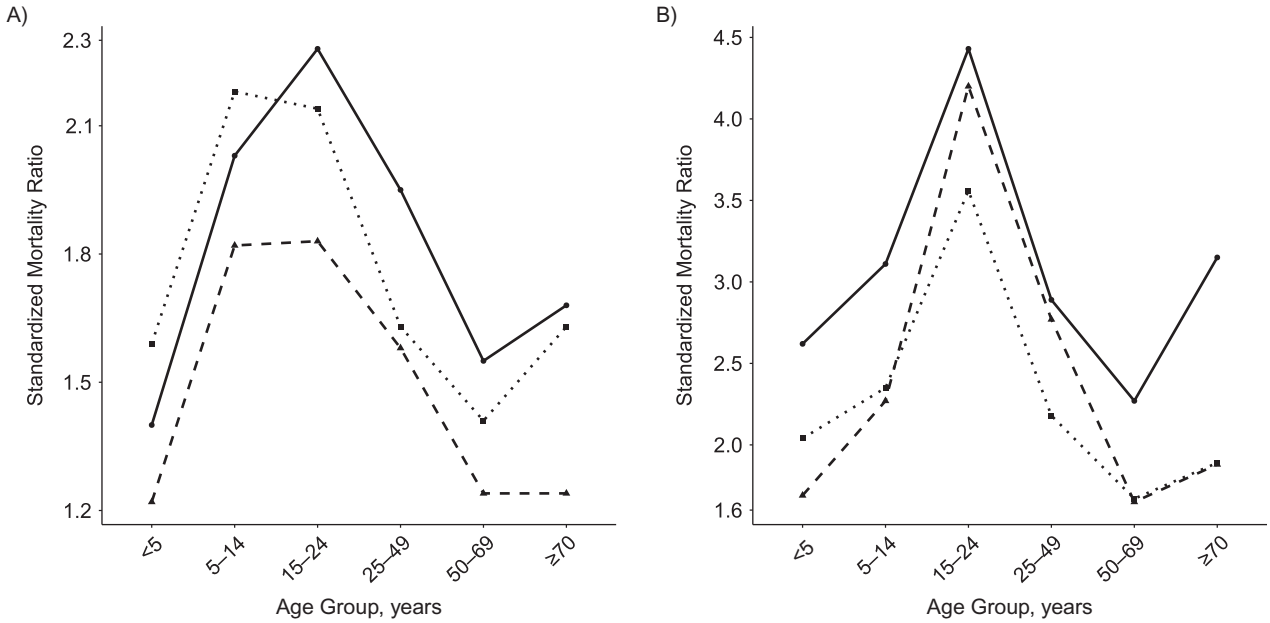

Figure 5. Standardized mortality ratio for all-cause (A) and respiratory-related (B) deaths according to age groups for each wave. The solid line represents the first spring wave, the fall and winter waves are represented by the dashed line, and the final winter wave is represented by the dotted line.

the city. Although other analyses looked at herald waves and questioned the impacts of acquired immunity from spring to fall (21, 22), the force of the spring wave in Madrid, relative to the successive fall and winter outbreaks, does appear to indicate some type of protective influence of the initial outbreak on succeeding waves, possibly due to a small amount of antigenic shift in the virus between the 2 periods. Only strains from the spring and fall waves of 1918 have been studied, to our knowledge, meaning that the extent to which earlier and later strains differed cannot be confirmed (5, 47, 48). Yet, continued analyses of successive waves using new data sources and innovative approaches should be undertaken to better understand acquired immunity and the protection it may provide against successive outbreaks. Using contemporary and historic demographic death and surveillance data of recent and historic epidemics, additional insights into the ways early outbreaks affected immunity and disease transmission can influence the way public health officials respond to contain outbreaks.

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