Spanish Influenza in Spain:

Re-examining strength and timing differences across space

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1 Background

Considerable research has examined how spatial differences and temporal patterns affect flu mortality. While climatic differences between tropical and northern countries play a role in seasonal influenza activity, the extreme world-wide mortality of the 1918 Spanish flu pandemic indicates these climactic patterns did not play a major role in regional death outcome [1, 2]. Yet even within countries, the presence and severity of each successive epidemic wave, beginning in spring 1918, differed by location, creating a debate regarding transmission mechanisms and the role acquired immunity in consecutive breakouts may have played in the tempering of each successive wave [3, 4, 5].

For example, a virus will spread more slowly in a population with some immunity (i.e. the reproduction number $R_{effective}$ in a partially-immune population will be lower than R_0),[1] assuming the virus has not yet mutated and evolved to be significantly different from the initial strain [7]. Additionally, the total length of pandemic wave is important, as it describes the heightened risk of others to contract the virus, allowing it to continue to spread.

A comprehensive background on the Spanish Influenza virus in Spain qualitatively describes the four unique, but not universally experienced waves of influenza in Spain beginning with a herald wave in May 1918 and ending with a large echo wave in the winter of 1919-1920 [8, 9]. Attempts to quantify the spatial-temporal influenza patterns throughout Spain found significant variations in excess mortality among 49 provinces of Spain, finding cumulative (across all waves) excess rates as high as 212.2 (per 10,000) in Zamora and 6.2 in the Canary Islands [10]. Slightly over half of the provinces experienced fall and or winter waves, but with the exception of Madrid, this mortality paled in comparison to the dramatic fall wave of 1918. In older and more qualitative research the echo wave in 1919-1920 is well documented, but the impact of this outbreak in contemporary literature is muted [11, 8, 12].

Moreover, the data used in this prior work has several issues limiting the overall interpretation of the results. Not only does the "Boletín mensual de estadística demográfica sanitaria" data end in 1919, making the study of the aforementioned echo wave impossible, the death counts are presented as monthly statistics, which make it difficult to pinpoint the onset timing of each wave. The quality of the data in these monthly bulletins also varies by each Spanish province, as the data was aggregated based on reported statistics from each town in the province and do not have universal coverage based on various response rates [13].[2]

Prior research focusing on entire cities examines transmission mechanisms and the role acquired immunity in consecutive breakouts may have played in the tempering of each successive wave of Spanish Influenza [3, 4, 5]. Other recent research explores the correlation between district level demographic and

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[1] The Reproduction Number (R_0), can be interpreted as the number of additional cases a single case will cause [6]. In an epidemic period, the Reproduction number will be greater than one, meaning that the number of infected individuals increases as time progresses.

[2] For example, in the province of Cuenca, the median percentage of reported statistics (based on a weighted average of the total population in the province) is only 38 percent (low of 21% in July/September and a high of 53% in August), but in the province of Toledo, generally, there is 89% coverage of statistics.

social levels and flu mortality during the 1918 pandemic, yet the papers focus on single waves; for example, a census tract analysis found that during the strong fall wave in Chicago (the end of September to November 1918), influenza and related mortality was higher in places with greater illiteracy [14]. Madrid, in the middle of a large period of growth and urbanization, also had a large degree of social and economic district variation, which may have played a role in the spread of influenza and spatial mortality differences [15, 16, 17].

A large debate also revolves around the role of social status and mortality risk. At the individual and community level, those with lower social status, especially among youth and elderly, tend to experience a higher mortality risk from seasonal influenza [18, 19], but questions remain about this pattern during epidemic outbreaks. Some analyses point to the similar gradients [16, 20, 21, 14], while others find no relationship or conflicting results between class and mortality, perhaps a result of extreme virulence of the strain [22, 20, 23, 17]. In the context of Spain during the Spanish Influenza outbreaks, provinces and their capitals can be examined as individual entities with varying population structures, main occupational sectors, median incomes, population density, etc.

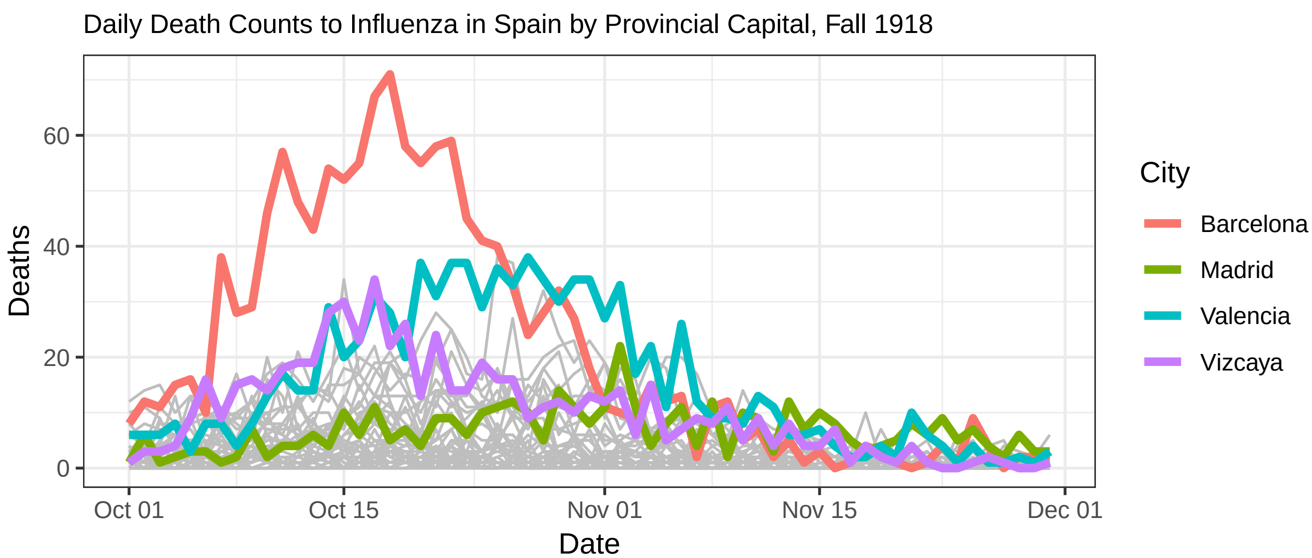
Disentangling the role immunity and environment (and thereby transmission processes) played in total and wave-specific mortality risk has been and remains a complex process. This paper first attempts to quantify the progression and strength of each epidemic Spanish influenza wave in Spain, using newly uncovered daily mortality logs for each province and provincial capital of Spain in 1918. Using linearizion techniques to estimate breakpoints and linear slopes of the start, peak, and end dates of each wave, we can estimate to the day when each wave began and map its progression through Spain, as well as the wave strength (via the R). After these initial estimations, we analyze the relationship between wave strength and province-specific measures to examine to what extent preceding waves (immunity) and other socio-demographic variables may have played a role in overall excess mortality due to these waves.

2 Data

As noted, the spring outbreak did not universally affect Spain; in fact, the brunt of this outbreak was found in the city of Madrid [10, 24]. Thus, we are unable to provide exact estimates of the spring herald wave. However, beginning in 1918, the Spanish Institute of Geography and Statistics began to collect daily mortality death counts for each provincial capital and entire province in Spain, thus capturing with detail the entirety of the immense fall wave [25]. Called the "Resumen (Mensual) del Movimiento Natural de la Población de España y de las Capitales de provincia," or Monthly Spanish Statistics Bulletin, these reports include daily death counts by five causes of death related to influenza. This means we will also be able to calculate the difference between all cause mortality and that of influenza and related causes such as bronchitis, pneumonia, and broncopneumonia. In total, these bulletins have been processed into 1200 images which are nrealy finished being digitized for analysis.

In the provincial capitals of Spain in October and November 1918, 21,048 deaths were recorded attributed to "Gripe" (influenza). This does not take into account deaths according to other diseases (but all other causes will be included in analysis outlined here). Figure 1 displays the daily death counts for influenza in the provincial capitals of Spain in October and November 1918, highlighting selected cities. The figure shows clear differences in the rate of growth in the initial phase of the fall wave, as well as differences in timing.

Figure 1: Daily death counts for each of the 49 provincial capitals in Spain are plotted for the period October 1st through November 30th in gray. Notable cities are plotted in distinct colors.



With respect to the rest of Spain, the experience of Spanish flu in Madrid was extremely different, and so we also examine the differences in strength and timing by wave within the city [24]. To do this, we aggregate death records from the Civil Register records on deaths between 1917-1922 by day and district [26]. This source contains more than 103,500 mortality records, which allows us to look at differences in the progression of the Spanish flu and each wave's (Spring 1918, Fall 1918,Winter 1919, and Winter 1918-19) strength within the city, to see to what extent differences exist within a singular urban environment.

3 Methods

Mathematically estimating the starting, peak, and ending dates of the wave allows for a precise understanding of the timing of each attribute of an outbreak; simply using secondary sources and visual analysis of the timeline of deaths can lead to an observation bias and subsequently estimate incorrect values for the reproduction number. These dates are calculated according to a segmented method that estimates the break points of each wave based on a traditional model of an epidemic outbreak of influenza [27, 28, 29]. The typical outbreak may be generalized into four roughly linear parts: initial seasonal baseline mortality (pre-epidemic), period of increasing deaths as the epidemic breaks out and spreads, the decline of new daily cases following the peak outbreak period, and finally a return to baseline mortality. Due to the expected exponential increase in the number of deaths during the ascending phase, we use the log number of deaths as the response variable. We then assume each phase can be considered a log-linear component of a piecewise regression.

Muggeos linearization technique allows us to estimate break points in the data, thereby identifying likely dates and associated standard errors of the beginning, peak, and end of each wave [27]. First, we fit a Poisson regression examining the log number deaths each day during a period of time that fully encompasses the potential dates of the wave of study. We then estimate breakpoints and fit the piecewise regression model based on the Poisson parameters using the R `Segmented` package [28]. The outcome provides estimates and standard errors for the breakpoints that delineate the change in phase according to the general epidemic model. We use the first and second breakpoint to find the Reproduction Number using the equation:

$$R_0 = e^{r*t}$$

which is equal to the slope of the increase in deaths during the ascending period of the epidemic.

Given the importance of excess (vs. total) mortality as a measure of total epidemic impact, we will also provide estimates of baseline and excess mortality per geographic unit. Excess mortality is calculated as the deaths above the baseline during weeks when overall mortality is higher than the 95% upper bound of the baseline.

4 Examples of results and expected outcomes

Below, we present initial results from the city of Madrid calculated from death records. Figure 2 shows results of the segmented regression for each wave, and results are presented in Table 1. Similar results for each district in the city during the spring wave are presented in Table 2.

Figure 2: Estimated piecewise segmented model based on fitted poisson regression for each wave using all deaths in Madrid.

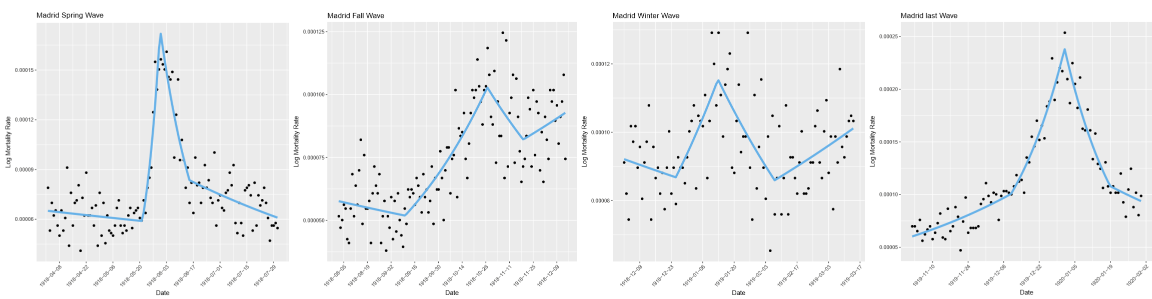


Table 1: Variations in Wave Timing and Strength in Madrid, 1918-1920

Start Date	**Peak Date**	**End Date**	**Length *(days)***	R_0
Spring 1918				
21 May	31 May	15 June	25	2.97
Fall 1918				
24 Sept	26 Oct	19 Nov	56	1.81
Winter 1918-19				
25 Dec	11 Jan	26 Feb	44	1.33
Winter 1919-20				
25 Dec	11 Jan	18 Jan	39	2.38

Between May 1918 and April 1919, the city of Madrid experienced three epidemic waves of influenza, each with lower intensity than the preceding one. The spring herald wave occurs throughout the month of May and early June, beginning in the districts of Inclusa, Latina, and Hospital, then moving towards other parts of the city. The reproduction number is highest in the district of Hospicio. Considering the entire city, the winter wave is much shorter and lower in intensity (R_0) than both the Spring and Summer.

Even at the district level within Madrid, we see considerable variation between the start of the ascension phase and peak of the epidemic. In fact, the calculated date of some districts peak influenza occurrence

Table 2: Spring Wave in Madrid, 1918

District	**Start Date**	**Peak Date**	**End Date**	**Length *(days)***	R_0
Inclusa	04 May	23 May	28 May	24	1.20
Latina	09 May	29 May	21 June	42	3.03
Hospital	11 May	03 June	16 June	36	2.49
Hospicio	20 May	29 May	15 June	25	4.83
Centro	21 May	27 May	09 June	19	3.46
Buenavista	22 May	27 May	25 June	33	2.79
Congreso	23 May	27 May	02 Jul	40	2.08
Palacio	23 May	02 June	23 June	30	2.22
Universidad	23 May	01 June	12 June	20	3.71
Chamberi	25 May	01 June	12 June	18	3.70

arrives before others are estimated to have entered the epidemic period. Within a single wave, districts experience varying lengths of epidemic-level activity.

Thus far, our analysis shows wide differences in epidemic outbreaks within a single city, but based on previous research, we expect the differences in strength and timing are even wider ranging throughout the entire country of Spain. Continuing work on this paper will first identify wave timing and excess mortality (as above for the city of Madrid) for all provinces. Continued analysis will use the results and additional socio-economic and geographic variables to try and better understand if any relationship between the role of herald waves, each province's composition, and the strength of each wave exists. Especially in regards to wave strength and total excess mortality, we assume that socio-demographic and geographic indicators at the provincial level, such as population density, will play a role in the strength and length of each wave.

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