The 1918-19 Influenza Pandemic in Portugal: A Regional Analysis of Mortality Impact.

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List of abbreviations

MMR: Mortality Rate Ratio

aMRR: adjusted Mortality Rate Ratio

Abstract

Although many archeo-epidemiological studies have assessed the mortality impact of the 1918-19 influenza pandemic, detailed estimates are not available for Portugal.

We applied negative binomial models to monthly mortality data from respiratory and all-causes at the national and district-level from Portugal, 1916-1922. Influenza-related excess mortality was computed as the difference between observed and expected deaths. Poisson regression was used to estimate the association between geographic, socio-demographic factors and excess mortality.

Two waves of pandemic influenza were identified between July 1918-January 1919 and April-May 1919, representing an excess all-cause death rate of 195.7 per 10,000. All districts of Portugal were affected. The pandemic hit earlier in southeastern districts and the main cities, while excess mortality was highest in the Northeast, in line with the high mortality burden experienced by northern Spanish provinces. During the period of intense excess mortality (fall winter 1918-19), population density was negatively associated with pandemic impact. This pattern changed in the March 1919-June 1920 wave, where excess mortality increased with population density, and north and west directions. Portuguese islands were less and later affected.

Given the geographic heterogeneity evidenced in our study, subnational socio-demographic characteristics and connectivity should be integrated in pandemic preparedness plans.

Keywords:
Influenza

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Excess mortality
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Socio-demographic

The 1918/19 *influenza* pandemic has been described as the infectious disease with the greatest impact on mortality in recent human history, with an estimated 20 to 50 million of deaths (1).

The highest mortality, disproportionally affecting young adults (20-40 years), was observed during fall/winter 1918. The mortality impact on elderly populations varied across the world, probably due to different immune background (2). Regions where a more intense spring-summer wave was felt were less affected in the fall (3), thus suggesting cross-protection and supporting the circulation of related viruses in both waves (2).

Other periods of excess mortality were described in following winters (4,5), but after 1919 specific mortality rate in young adults declined and the mortality age profile aligned with that observed in years before 1918 (4).

The mortality rate attributed to the 1918/19 pandemic was estimated at 11 per 1,000 in Europe, which corresponds to a relative excess risk of death of 86 % and translates into 2.6 million excess of deaths (about 1.1 % of the European population) (6). Southern countries were hardest hit: Italy (relative excess risk, 172 %), Portugal (102 %), Bulgaria (102 %) and Spain (87 %)(6).

In 1918, Portugal was a predominantly rural country, and participation in World War I 1914-1918 aggravated hunger, food shortage, poverty and social conflicts. It was a period of particular vulnerability marked by recurrent epidemic outbreaks such as exanthematous typhus (February to May 1918 and March to June 1919) (7,8) and smallpox (1918) (8), in addition to the high burden of endemic diseases, such as tuberculosis. Further, the most intense influenza pandemic wave coincided with a troubled political period, during October - December 1918 with a military uprising, a siege, and a general strike, which culminated in the assassination of the President of the Republic Sidónio Pais in December 1918. These problems did not prevent the collection of epidemiological information and coordination of interventions by public health authorities to minimize the impact of the pandemic.

The first pandemic influenza cases were identified in May 1918 in the south of Portugal (Vila Viçosa, Évora district) among farmers returning from the Spanish province of Badajoz; the infection rapidly spread across the country (9,10). The pandemic reached Porto (the second most populated town) and Lisboa (the capital) in June and the Açores and Madeira archipelagos in September. The occurrence of the first severe cases of pneumonia in early September in the north of the country (Vila Nova de Gaia) marks the beginning of the second and lethal pandemic wave that rapidly spreads throughout the mainland (11).

Although there are no official statistics of the mortality attributed to 1918/19 pandemic in Portugal, between 1917 and 1918 the overall mortality rate almost doubled from 220 to 420 per 10,000, returning to pre-pandemic levels only after 1921 (12). This represents a crude excess death rate of 2%. In the same period influenza mortality rate increased 53 folds from 1.8 per 10,000 to 96.2 per 10,000 (12). Two international studies have reported mortality estimates for Portugal, nevertheless both present limitations. In 2006, Murray et al (3) estimated an all-cause excess rate of 264 deaths per 10,000 for the period of 1918 to 1920, but this was based on annual deaths which lack specificity. The second study estimated an all-cause excess death of 223 per 10,000 for the period March 1918 to June 1919 , based on monthly data (6). However these data should be taken with caution, as the authors reported that the 1918 pandemic first hit Finland in January 1918, followed by Portugal, Germany and Bulgaria in March 1918, which contrast with contemporaneous newspapers and recent reviews (2). The impact of the 1918-19 influenza pandemic in Portugal needs to be revised with a more consistent approach.

A detailed description of the spatial-temporal distribution of pandemic mortality is lacking, and the heterogeneity between Portuguese cities remains unexplained. Accordingly to Arnaldo

Sampaio´s studies (5), influenza incidence was highest in cities in 1918, while highest mortality was reported in rural areas. Differences in medical care and access to health care may have played a role in these pandemic burden differences, as well as nutrition, hygiene and other social-economics factors. Sociodemographic factors were not correlated with the annual 1918 influenza mortality at the district and municipal levels (12). However, this observation could be biased by the very high proportion of deaths of 'unknown cause' that were not considered in this study.

Given the lack of resolved mortality estimates of the 1918-19 influenza pandemic in Portugal at national and regional levels, and the putative role of sociodemographic factors on pandemic impact, we analyzed a detailed spatio-temporal mortality dataset to explore these questions.

We estimated the excess mortality impact of the 1918/19 influenza pandemic on all-cause and respiratory causes in Portugal´s mainland districts, and the Açores and Madeira archipelagos. We identified the beginning, peak and duration of the different pandemic waves across Portugal. Finally, we identified the association between excess mortality and social, demographic and geographic factors across Portugal.

METHODS

All datasets were compiled from the Demographic Statistics reports available from the Digital Library of Statistics Portugal Portal (13). These digitized documents were copied, printed and the data was manually entered.

To estimate the impact of 1918-19 influenza pandemic in Portugal we used monthly mortality time series from all causes and respiratory causes (including influenza, pulmonary tuberculosis, acute bronchitis, chronic bronchitis and pneumonia) for the 17 mainland districts, and the Açores and Madeira archipelagos, from 1916 to 1922. We refer to these administrative areas as "districts" thereafter (n=19). Monthly district-level mortality rates were estimated based on annual population estimates, obtained by linearly interpolation of census data from 1911, 1920 and 1930.

District-level socio-demographic information was obtained for 1918 by linear interpolation of the 1911 and 1920 censuses, including population density (per Km^2), proportion of the population aged 5-14 years, illiteracy rate (population aged over 7 years who cannot read or write). (13) Pre-pandemic infant mortality rate, calculated from 1917 data, was also used.(13) Infant mortality and literacy rates were considered as indicators of the level of development of the regions. The percentage of the population aged 5-14 years was chosen as proxy for influenza transmission within the community given that children are high-transmitters. Population density is likely to be an indicator of exposure and economic development. Further, we included capital district longitude and latitude to measure spatial distribution and to account for spatial dependency (Web table 1).

To estimate national and district-level baseline mortality rates (all-cause or respiratory) expected in the absence of the 1918-19 influenza pandemic, we used an interrupted time series approach. We standardized the monthly number of deaths to a fixed number of days each month (30.4 days), and excluded the extended pandemic period between June 1918 and May 1920 for model fitting. A negative binomial regression model was fitted to each time series, adjusting for seasonality (periods of 12 and 6 months) and time trends (third degree polynomial), including population estimates as offset (Web Appendix). Separate models were fitted to each geographic area and cause of death. The expected mortality in the absence of pandemic influenza was obtained based on model predictions. The prediction intervals were estimated using a parametric bootstrap method (14) using 1000 samples with replacement.

We evaluated the presence of overdispersion in the Poisson regression model (15). The prediction accuracy of negative binomial models was evaluated by a leave-one-out cross-validation procedure (14) and compared with Poisson models. Excess mortality periods were defined as those during which the observed mortality was greater or equal than the upper limit of the 95% prediction interval.

The mortality burden of the 1918-1919 influenza pandemic was estimated as the difference between the observed and the expected number of deaths during periods of excess mortality.

Since periods of excess mortality may vary by geographic area, we defined four pandemic phases to compare influenza dynamics at the district level. Phase one ran from June to August 1918 (summer), phase two from September 1918 to February 1919 (autumn/winter 1918-19), phase three from March to September 1919 (spring/summer 1919) and phase four from October 1919 to June 1920. Excess mortality estimates were generated for each phase, geographic areas, and mortality outcome.

To measure the consistency between excess mortality estimates from all causes and respiratory diseases, we used Spearman ρ correlation coefficient.

Sociodemographic variables were categorized for analysis as follows: population density and infant mortality rates by tertiles; literacy rate and percentage of population aged between 5-14 years were stratified according to the median.

To explore the relationship between mortality and socio-demographic factors, we estimated crude and adjusted (Poisson regression) excess mortality rate ratios by category of sociodemographic variable. Excess mortality rate ratios confidence intervals were obtained using the robust sandwich covariance matrix estimator.

Spatial correlation in the Poisson regression residuals was evaluated using the global Moran I statistics.

All statistical analysis was performed in R version 3.4.3 (16).

RESULTS

Negative Binomial models presented better fits to the interrupted mortality time series than Poisson regression models for the majority of the districts and all-cause deaths. All time series were overdispersed. (Web table 2-3)

Two periods of all-cause excess mortality were observed at national level during the first year of circulation of the pandemic virus, June 1918 - June 1920. A first extended pandemic period ran from July 1918 to January 1919, with a peak in October 1918. A second, shorter, pandemic period was identified during April- May 1919, with a peak in April (Figure 1).

Overall, the 1918-19 pandemic was associated with an estimated 117,764 excess all-cause deaths, representing a rate of 195.7 deaths per 10,000 inhabitants. The highest impact was observed in the first pandemic period that extends from summer 1918 to winter 1918-19, accounting for 95% of excess deaths (186.88 per 10,000 inhabitants). The second period in spring 1919 accounted for 8.86 deaths per 10,000 inhabitants.

The distribution of these periods of excess deaths was not homogenous at the district level, and reveals 4 pandemics waves (summer 1918, fall-winter 1918-19, spring 1919, winter 1-19-1920, Table 1, Web figures 1-2). The southeast of Portugal and the districts encompassing the main cities districts, Lisboa and Porto, were first hit. In the first wave (June-August 1918), excess mortality was identified in 11 districts, six of them on the east border with Spain. The average all-cause mortality rate was 6.25, ranging from 0 to 20.36 per 10,000 inhabitants in Porto.

The second pandemic phase (September 1918 - February 1919) reached all districts with much higher impact. The average all-cause mortality rate was 173.12, ranging between 130.64 in Porto and 239.55 per 10,000 in Bragança, in the mainland. The archipelagos had the lowest excess mortality rates, respectively 106.35 and 58.46 deaths per 10,000 inhabitants.

In Vila Real, Porto, Viseu, Aveiro and Lisboa the first and second pandemic phases were indistinguishable, as excess mortality started in summer and extended to fall or winter (Web figure 2).

The third (March-September 1919) and fourth pandemic phases (October 19-June 20) had much smaller impact that the second. The highest impact of the third phase was observed in the north and west coast. The fourth phase had also high impact in the islands, more specifically in Madeira where all-cause excess mortality rate was higher than that seen in the second phase (62.15 per 10,000 inhabitants).

Overall, for the period 1918-20, the district with highest excess all-cause mortality was Vila Real, in the north of Portugal, with an excess rate of 299.00 deaths per 10,000 inhabitants; the lowest rate was observed in Madeira, with 121.14 deaths per 10,000.

Considering respiratory excess mortality, we attribute 63,869 excess deaths to the full pandemic period (106.15 per 10,000, Web table 4, Web figure 3-5). There was no clear correspondence between periods of excess mortality in respiratory and all-cause data at the district level. The district with highest excess respiratory mortality rate was Castelo Branco (it ranked seventh in all-cause mortality), while Madeira had lowest rate. The correlation between all-cause and respiratory excess mortality was moderate at the district level (Spearman rho=0.56, 95% CI: 0.15, 0.81). When restricting to the second phase of the pandemic (September 1918 to February 1919), the correlation increased somewhat (Spearman rho=0.62, 95% CI: 0.23, 0.84).

Socio-demographic factors associated with excess deaths

There was no spatial dependency in the residuals of the Poisson regression models (Table 2)

In the first pandemic phase (June-August 1918), longitude and latitude were the only significant predictors associated with excess mortality (Table 2). Excess mortality rates were higher in the east (adjusted MRR (aMRR): 4.47, 95% confidence interval (CI): 1.13, 19.66) and south (aMMR: 0.56, 95% CI 0.37-0.85) directions.

In the second pandemic phase, population density was associated with all-cause excess mortality. More specifically, the third tertile of population density (aMRR: 0.73, 95% CI: 0.56, 0.95) was protective, as well as longitude (aMRR: 1.05, 95%CI 1.03,1.06)

Considering the third and fourth pandemic phases together, the positive predictors of excess mortality were latitude (aMRR: 1.30, 95% CI: 1.08, 1.58), with increased excess mortality rate in the north direction, and second and third tertiles of population density. Longitude was this time negatively associated (aMRR: 0.93 95% CI: 0.85, 0.97), suggesting an increased excess mortality rate in the western direction.

DISCUSSION

As far as we know our study generates the first estimates of excess mortality associated with the 1918-19 pandemic in Portugal using detailed primary data sources and up-to-date statistical methods. The 1918-19 influenza pandemic was associated with an estimated 117,764 excess all-cause deaths, representing an excess mortality rate of 195.7 deaths per 10,000 (95% CI 185.8 to 206.0). On a national scale, two main periods of excess mortality were identified from July 1918 to January 1919 and April to May 1919; however the timing of excess mortality differed by district, with up to four waves identified during 1918-1920.

Our mortality estimate for Portugal is significantly lower than those reported in previous studies; Murray et al estimated an excess death rate of 264 per 10,000 and Ansart et al 223 per 10,000 (3,6). It is plausible that these other studies have overestimated the pandemic impact in Portugal. Murray *et al* (3) analysed annual time series, which is a less precise approach than modeling of monthly data. Ansart *et al* (6), although using monthly data, reported that Portugal was first affected in March 1918, which is inconsistent with official data published by Portuguese authorities (17). The first influenza pandemic cases were reported in the Évora district (southeast of Portugal) in May 1918, imported from Spain (17). These official reports, as well as 1918 Spanish and Portuguese press (18,19), are more consistent with our findings of a rise in pandemic mortality in June 1918. We note that the excess mortality identified in March 1918 by Ansart et al (6) coincided with an outbreak of exanthematous typhus outbreak (8).

The spatial-temporal pattern of all-cause excess mortality observed in our study are in accordance with data from Spain reported by Chowell et al (20). During summer 1918, the most affected districts were located in the southeast border of Spain, except for the districts encompassing the main cities of Porto and Lisboa.

The early onset of the pandemic in the south of Portugal and the cities of Lisboa and Porto could reflect the main entry routes of the pandemic virus into Portugal in 1918(21). At the time, international travel was primarily by boat and by land from Spain, mainly by railway or other terrestrial transportation.

Considering the total pandemic period, 1918-20, the most affected districts were located in northeast of the country (Bragança, Vila Real and Guarda) and in the south (Beja and Faro). The most affected districts in the north of Portugal border with Zamora, Orense and Salamanca, aligning with the northwest of Spain and forming an Iberian cluster of a high excess mortality (20).

There was considerable variability in pandemic timing between districts, with four phases of excess mortality. The first milder on ran from June and ending in August 1918, although in some districts, like Lisboa and Porto, this first period was indistinct from the later pandemic wave. The second pandemic wave had a 20-fold higher impact than the summer period at the national level, affected all districts, and ran from September 1918 to February 1919. The third and fourth phases in spring 1919 and fall/winter 1919-20 were milder. These patterns are concordant with the periods with excess mortality identified in Spain, with a 1-2 months delay (20). Similar mortality patterns, with the brunt of mortality occurring in fall-winter 1918-19, have observed in Europe (6) and other parts of the globe (3).

We found associations between all-cause excess mortality and geographic and socio-demographic factors, which differed by pandemic phase. During the summer phase, longitude and latitude, reflecting the higher impact in the south east of Portugal. In the fall and winter 1918-19 wave, excess mortality was negatively associated with population density, consistent with a Spanish study (20). This indicates that the second pandemic phase had higher impact in rural districts. On the other hand, during the drawn-out third and fourth phases, population density was positively associated with excess deaths rate. These results are somehow consistent with Portuguese health authority's reports that describe these later mortality waves to be more prevalent in urban areas (5). During the third-four phases, the geography of excess mortality was the opposite of the first phase, with higher impact in the northern and western districts (including Azores and Madeira) .

Previous studies in Portugal did not identified any association between socio-demographic factors and influenza mortality rates in 1918 (12). This lack of association could be partly explained by the high rate of deaths of 'unknown cause' reported in 1918 (44%), with considerable variation between districts, from 1.1% in Madeira to 82.4% in Bragança. This limits the validity of any excess death estimate based on cause-specific mortality in Portugal, and may explain the moderate correlation between all-cause and respiratory excess mortality in our data (Spearman rho=0.56, compared to 0.82 in Spain (20)).

The present study has some limitations. First, we used data published in demographic statistics, scanned and typewritten. Nevertheless, the times series data were overall very consistent except for cause-specific deaths in Bragança district (Web figure 3). We used a nonspecific outcome, all-cause mortality, which could overestimate the excess deaths given that includes deaths that could not be attributed to influenza infection such as those related to injuries. However, with a very high and variable proportion of unspecified deaths, using respiratory excess deaths was not appropriate for the main analysis.

On the other hand, the use of all-cause mortality time series has been shown to be a consistent approach to identify excess deaths attributable to influenza epidemics, especially in the case of the lethal 1915-19 influenza pandemic. Additionally, the all-cause excess mortality periods identified in the present study are consistent with the national (12,17,22) and international literature (20,21).

We cannot fully exclude that our all-cause mortality estimates could be overestimated in some districts and periods. During the years 1918-1919 there were other concurrent epidemics with considerable impact on mortality. Namely exanthematous typhus, during the months of March to June 1919 and a national smallpox epidemic from May 1918 to December 1918. These epidemics overlapped the identified periods of pandemic activity. However, smallpox and exanthematous typhus deaths corresponds to only 2% of the total of deaths in those periods.

Another limitation of our study was the lack of monthly data by age group that was not available at national or district levels, and precluded any description of the heterogeneity of the pandemic impact by wave and age group, as described in other European countries (4).

In conclusion, our results clarify the impact of the 1918-19 influenza pandemic in Portugal, providing updated and more accurate estimates at national and subnational levels. We note remarkable consistencies with the pandemic dynamics in Spain, which shed light on the pandemic experience in the Iberian Peninsula. It is clear from this study that the influenza pandemic arrived in the south of Portugal in summer, originating from Spain, turning Portugal, probably, one of the only countries that could name the 1918-19 influenza pandemic the

“Spanish flu” (10). Additionally by combining our results with those of Chowell *et al* (20), we identify a cluster of high excess mortality in the northwest of the Iberian peninsula.

Overall, we found a very high impact of the 1918-19 influenza pandemic in Portugal that extended from June 1918 to June 1920. Mortality varied considerable between districts, mainly associated with several socio-demographic characteristics, like population density and a north-south and west-east gradient.

Archeo-epidemiologic studies, of the kind presented here, are useful for pandemic preparedness, as they may contribute to prioritization of preventive and prophylactic measures, not only accordingly to known health risk factor, but also to vulnerable socio-demographic groups. Additionally, knowledge of domestic and international population mobility would be essential to establish active surveillance systems and build scenarios of pandemic spread.

Figure 1 – Observed, baseline (in the absence of influenza pandemic impact) and upper 95% baseline prediction limit monthly all-cause mortality rates per 10,000 inhabitants (in logarithm base 10 scale) from 1916 to 1922. Vertical box represents the periods with excess mortality, where observed all-cause mortality was above the 95% prediction limit of the baseline. Panels: A) Portugal, B) Bragança, C) Viana do Castelo, D) Braga, E) Vila Real, F) Porto, G) Viseu, H) Aveiro, I) Guarda, J) Coimbra, K) Castelo Branco, L) Leiria, M) Portalegre, N) Santarém, O=) Lisboa, P) Évora, Q) Beja, R) Faro, S) Açores, T) Madeira

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Table 1: All-cause excess mortality rates (per 10,000) and 95% confidence limits, according to the defined 1918-19 pandemic phase, mainland districts and archipelagos of Madeira and Azores.

District [a]	Phase 1 Jun-Aug 18		Phase 2 Sep 18 – Feb 19		Phase 3 Mar-Sep 19		Phase 4 Oct 19 – Jun 20		Total	
	Rate	95%CI	Rate	95%CI	Rate	95%CI	Rate	95%CI	Rate	95%CI
Portugal	8.82	4.54, 12.67	178.05	171.18, 185.54	8.86	5.65, 12.1	0.00		195.73	185.84, 206.00
Bragança	11.09	4.28, 16.68	239.55	226.58, 251.09	0.00		0.00		250.20	234.38, 264.23
Viana do Castelo	0.00		133.66	124.12, 142.93	14.77	6.45, 22.2	0.00		148.01	134.94, 160.49
Braga	0.00		141.28	129.69, 151.68	41.42	28.65, 52.9	0.00		182.41	165.33, 200.02
Vila Real	8.82	4.54, 12.67	178.05	171.18, 185.54	8.86	5.65, 12.1	0.00		299.00	277.40, 320.60
Porto	20.36	9.92, 29.83	130.64	117.06, 142.07	22.41	14.06, 29.4	0.00		173.10	152.22, 193.03
Viseu	8.82	4.54, 12.67	178.05	171.18, 185.54	8.86	5.65, 12.1	0.00		207.18	190.20, 221.57
Aveiro	7.06	3.99, 9.80	143.06	132.63, 152.75	30.22	22.29, 37.5	3.69	0.13, 6.65	183.89	167.42, 198.45
Guarda	0.00		212.12	197.07, 226.33	0.00		9.40	3.54, 14.41	221.07	204.63, 236.36
Coimbra	0.00		202.01	193.59, 209.08	5.08	2.17, 7.8	0.00		206.95	198.16, 214.99
Castelo Branco	4.94	0.73, 8.90	211.57	203.14, 219.05	0.00		0.00		216.43	207.56, 224.68
Leiria	0.00		218.04	208.16, 228.02	7.26	2.85, 11.6	0.00		225.20	213.80, 237.03
Portalegre	5.30	0.07, 9.63	143.04	132.24, 153.37	0.00		11.26	5.26, 16.57	159.47	144.76, 172.75
Santarém	0.00		197.58	189.00, 205.02	4.94	0.95, 8.1	4.95	1.02, 8.54	207.36	196.63, 216.67
Lisboa	12.48	7.45, 17.33	184.18	175.94, 192.17	4.22	1.21, 6.9	14.85	8.77, 20.23	215.43	202.78, 229.48
Évora	11.43	5.29, 17.10	176.53	168.94, 183.26	0.00		0.00		187.90	177.42, 197.54
Beja	15.01	6.45, 22.00	212.82	202.01, 223.33	0.00		0.00		227.49	213.32, 241.43
Faro	13.38	6.45, 19.36	222.29	214.48, 229.51	0.00		4.16	0.25, 7.10	239.55	228.24, 250.59
Açores	0.00		106.35	99.06, 113.92	0.00		16.51	12.69, 19.63	122.48	113.31, 130.94
Madeira	0.00		58.46	52.20, 64.22	0.00		62.15	52.86, 71.69	121.14	109.00, 134.03

CI: confidence interval.

[a] Districts are ordered from North to South, except the archipelagos of Açores and Madeira.

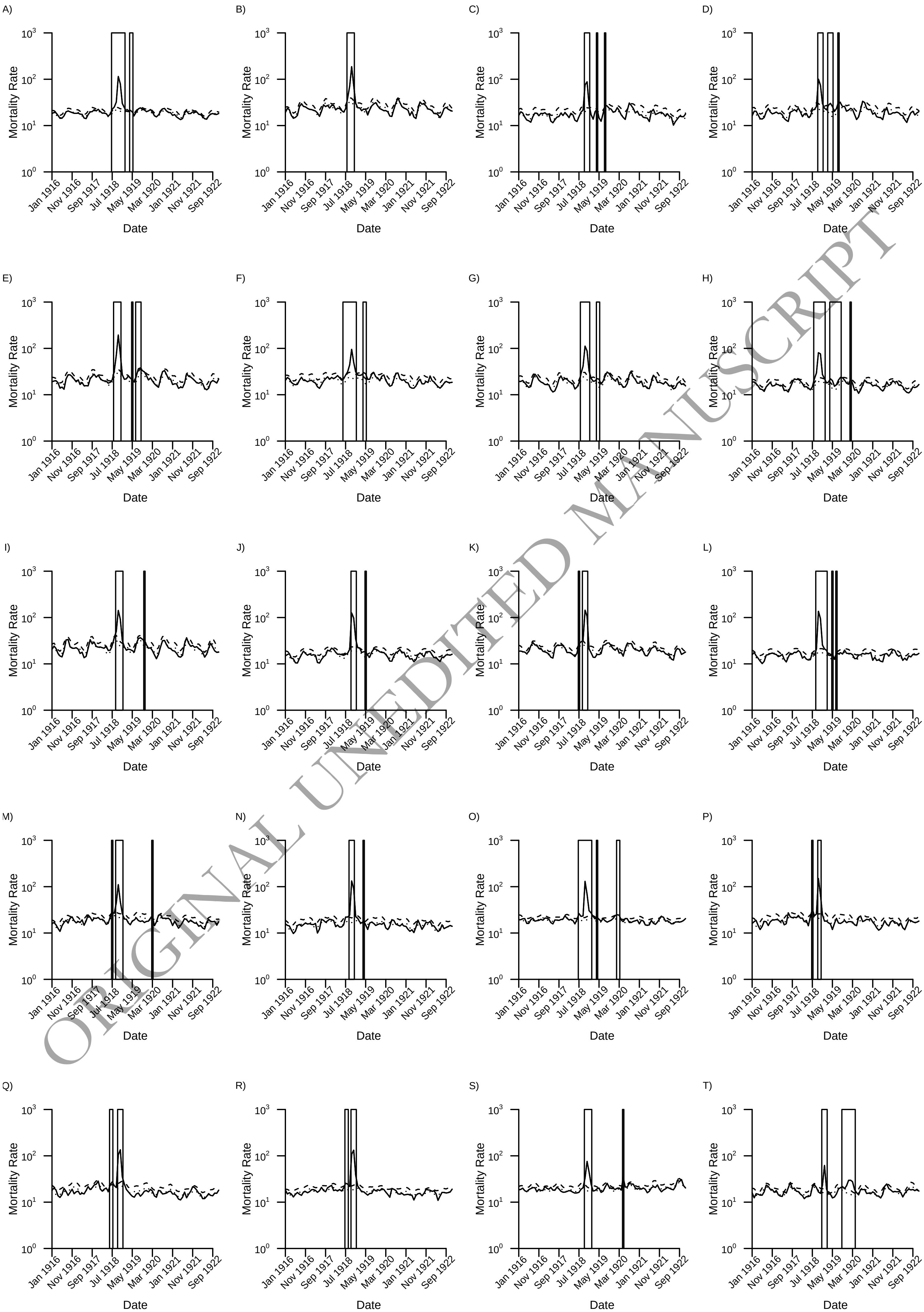
Table 2 – All-cause excess mortality rate distribution, crude and adjusted (Poisson regression) excess mortality rate ratios (MRR) according to the district level socio-demographic characteristics, for the different pandemic phases (1, 2 and 3-4). Portugal during the 1918-19 influenza pandemic.

Predictor		**Rate (/10,000 hab)**	**MRR[a] (crude)**	**CI95%**	**aMRR[b] (adjusted)**	**CI95%**
Phase 1 (Jun-Aug 1918)[c]						
Poulation density						
	< 49/km2	7.35	1	Referent	1	Referent
	49-101/km2	4.73	0.64	0.23,1.84	1.42	0.48,4.18
	>= 101/km2	9.43	1.28	0.52,3.17	9.41	0.97,91.21
Iliteracy rate						
	< 73%	8.86	1	Referent	1	Referent
	>= 73%	5.90	0.67	0.28,1.59	0.58	0.06,5.57
Infant mortality rate						
	<142‰	4.17	1	Referent	1	Referent
	142-159‰	9.77	2.34	0.70,7.81	1.58	0.49,5.06
	>=159‰	8.44	2.02	0.80,5.11	0.76	0.23,2.59
Pop aged 5-14 years						
	< 23%	7.87	1	Referent	1	Referent
	>= 23%	7.44	0.95	0.35,2.57	0.98	0.36,2.68
Longitude		-	1.67	0.99,1.38	4.71	1.13,19.66
Latitude		-	1.04	0.81,1.34	0.56	0.37,0.85
Phase 2 (Sep 1918 – Feb 1919)§						
Poulation density						
	< 49/km2	202.99	1	Referent	1	Referent
	49-101/km2	210.44	1.04	0.91,1.18	1.11	0.93,1.33
	>= 101/km2	143.93	0.71	0.57,0.88	0.73	0.56,0.95
Iliteracy rate						
	< 73%	162.65	1	Referent		Referent
	>= 73%	193.55	1.19	0.98,1.44	0.88	0.73,1.05
Infant mortality rate						
	<142	189.08	1	Referent		Referent
	142-159	155.59	0.82	0.63,1.08	1.02	0.90,1.15
	>=159	183.87	0.97	0.80,1.18	1.14	0.96,1.35
Pop aged 5-14 years						
	< 23%	176.18	1	Referent		Referent
	>= 23%	176.15	1.00	0.84,1.19	0.99	0.87,1.11
Longitude			1.69	1.06,1.08	1.05	1.03,1.06
Latitude		-	1.02	0.95,1.09	0.99	0.96,1.03
Phase 3-4 (Mar 1919 – Jun 1920)§						
Poulation density						
	< 49/km2	3.47	1	Referent	1	Referent
	49-101/km2	11.12	3.20	0.92,11.08	3.72	1.14,12.16
	>= 101/km2	26.60	7.66	2.40,24.42	6.12	1.33,28.16
Iliteracy rate						
	< 73%	22.75	1	Referent	1	Referent
	>= 73%	10.22	0.45	0.20,1.01	0.76	0.30,1.96
Infant mortality rate						
	<142‰	17.06	1	Referent	1	Referent
	142-159‰	23.36	1.37	0.65,2.90	0.93	0.54,1.60
	>=159‰	12.08	0.71	0.32,1.56	1.85	0.75,4.55
Pop aged 5-14 years						
	< 23%	14.71	1	Referent	1	Referent
	>= 23%	18.34	1.25	0.7,2.21	1.56	0.78,3.13
Longitude (°)			0.93	0.91,0.95	0.91	0.85,0.97
Latitude (°)			1.10	0.91,1.32	1.30	1.08,1.58

[a] Mortality Rate Ratio;

[b] adjusted mortality rate ratio by Poisson regression;

[c]Moran I statistics for Phase 1 model residuals P=0.637, Phase 2 model residuals P=0.867 and Phase 3-4 model residuals P= 0.820.


A)
B)
C)
D)
E)
F)
G)
H)
I)
J)
K)
L)
M)
N)
O)
P)
Q)
R)
S)
T)
Mortality Rate
Date
10^0
10^1
10^2
10^3
Jan 1916
Nov 1916
Sep 1917
Jul 1918
May 1919
Mar 1920
Jan 1921
Nov 1921
Sep 1922