Epidemiology and transmission dynamics of the 1918–19 pandemic influenza in Florence, Italy

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ABSTRACT

To investigate the 1918/19 influenza pandemic daily number of new hospitalizations in the only hospital in Florence (Central Italy) were analyzed. In order to describe the transmission dynamics of the 1918/1919 pandemic influenza a compartmental epidemic model was used. Model simulations show a high level of agreement with the observed epidemic data. By assuming both latent and infectious period equal to 1.5 days, the estimated basic reproduction number was \( R_0 = 1.03 \) (95% CI: 1.00–1.08) during the summer wave and \( R_0 = 1.38 \) (95% CI: 1.32–1.48) during the fall wave. Varying the length of the generation time or the estimation method, \( R_0 \) ranges from 1.32 to 1.71. The hospitalization rate was found significantly different between summer and fall waves. Notably, the estimated basic reproductive numbers are lower compared to those observed in other countries, while the age distribution of deaths resulted to be consistent with the patterns generally observed during the 1918–1919 pandemic. Our knowledge on past pandemics, as for the 1918–19 Spanish influenza, would help improving mathematical modeling accuracy and understanding the mechanisms underlying the dynamics of future pandemics.

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1. Introduction

Knowledge of past pandemics is of substantial help when planning for a future one [1] and, indeed, the epidemiological aspects of the three 20th century influenza pandemics (1918–1920, 1957–1958, 1968–1969) have been extensively investigated [2]. The 1918–1919 A/H1N1 influenza pandemic killed approximately 50 million people worldwide [3], with age distributions of deaths and symptomatic cases that are different from those observed during seasonal influenza epidemics, with higher attack rates in younger individuals [4]. Historical records suggest that an early pandemic wave occurred in Europe during the summer of 1918 [5,6]. However, during the early wave in spring 1918, no significant increase in mortality was recorded in Italy, whereas during fall 1918 Italy showed the highest mortality rate in Europe (10.6 per 1000 inhabitants) [5].

The analysis of the epidemiological patterns of past influenza pandemics has become crucial to inform on the best practices to be adopted for preventing, containing and mitigating a new A/H1N1 season, as occurred in 2009 [7]. In Italy very few data are currently available on Spanish influenza, mainly due to the military censorship, aimed to avoid negative effects on the moral of both the troops and the civil population. The extent of the censorship was such that even the main national news-paper (“Corriere della Sera”) hardly reported news on the disease.

In order to gain more knowledge about Spanish influenza in Italy, where the highest mortality rate in Europe was reported [5,8], data from the registries of a civil hospital were analyzed. A recent search in the archives of a civil hospitals in Tuscany allowed us to find the registry of the main Tuscany hospital at that time (Ospedale di Santa Maria Nuova, Florence). The registry provided daily numbers of new hospitalizations with their causes (pneumonia, influenza and fever), and of deaths.

2. Methods

2.1. Demographic and epidemic data

Daily hospitalization data were derived from the registries (4 for males and 5 for females) of the civil hospital “Santa Maria Nuova”, the only one available in the Florence municipality during 1910s, from January 1918 to December 1919. In Florence, there
was also a military hospital, but no register was available. The information collected included name and surname, age, address, name of parents, occupation, diagnosis, date of hospitalization, date of discharge, and date of death. We collected data on hospitalized individuals affected by influenza, fever and pneumonia (two types: haemorrhagic pneumonia and pneumonia). Moreover, we used population data derived from the 1921 census: at that time Florence had 280,133 inhabitants, which is about 76% of today's Florence population (National Bureau of Statistics, Italy).

2.2. Model description

In order to describe the transmission dynamics of the Spanish Influenza in Florence, Italy, a compartmental homogeneous mixing model was used. The population was divided into the following classes: susceptible individuals (S), latent individuals (E), infectious individuals (I), hospitalized individuals (H) and recovered individuals (R) [9,10]. The dataset on the number of hospitalized individuals was split in two temporal windows: the first refers to the period from week 18 to week 34 of 1918 (“summer wave”), the second refers to the period from week 35-1918 to week 6-1919 (“fall wave”). For weeks 1-17, 1918 we assume to have observed hospitalization due to seasonal influenza, while, substantially, no hospitalization associated to influenza were observed from the end of the fall/winter wave until the end of 1919. An initial fully susceptible population is assumed at the start of the summer wave; moreover, recovered individuals from the first wave were assumed to be protected against the second wave [10].

The system of ordinary differential equations describing the disease transmission process is the following:

\[
\begin{align*}
\dot{S} &= -\beta_I(I + H)\frac{S}{N} - \omega E \\
\dot{E} &= -\beta_I(I + H)\frac{E}{N} - \omega E \\
\dot{I} &= \omega E - (\gamma + \alpha_I)I \\
\dot{H} &= \alpha_I I - \rho_I H \\
\dot{R} &= \gamma I + \rho_I H \\
\end{align*}
\]

where \(N\) is the total population size (assumed constant i.e. we disregard the impact of influenza mortality on transmission); \(\beta_I\) is the transmission rate; \(1/\beta_I\) is the average duration of the period of hospitalization during which individuals are able to transmit the disease; \(\alpha_I\) is the hospitalization rate for infective individuals; \(1/\omega\) is the average length of the latent period; \(1/\gamma\) is the average length of the infectivity period; and the index \(j = 1\) or \(2\) refers to the temporal window considered (summer and fall waves, respectively).

2.3. The reproduction number

The basic reproduction number is defined as the number of secondary cases generated by a primary infectious case during her/his infectiousness period in a completely susceptible population [9]. The basic reproduction number of the proposed model, as computed by using the next generation matrix approach [11,12], is \(R_0 = (\beta_I(\gamma + \alpha_I)) + (\beta_I(1 + \rho_I)/(\gamma + \alpha_I)(\alpha_I/\rho_I))\). The first term of the equation refers to the infections generated by infective (non-hospitalized) individuals, while the second term refers to the infections generated by infective hospitalized individuals.

The reproduction number for the summer \((R_0)\) and for the fall \((R_0)\) waves was computed independently by using the best parameter estimates as obtained for the summer and for the fall influenza waves, respectively.

2.4. Model calibration and parameters estimation

Briefly, model parameters were estimated through least-squares model fit to the weekly number of hospitalized individuals due to influenza, pneumonia and fever during the first and second waves of the 1918/1919 pandemic in Florence, Italy. The two periods were fitted separately and the status of the population (e.g. the number of susceptible individuals) at the end of the first wave was used as initial condition for the second fit. A similar procedure was used also in [10,13]. Let \(Z_T\) be the observed weekly number of new hospitalized individuals. The weekly number of new hospitalized individuals \(U_T(j)\) predicted by model simulations during either of the two waves \(j\) can be computed as \(U_T(j) = \int_{T-1}^{T} \alpha_I(\tau) d\tau\) and we assume \(Z_T = U_T + N(0, \sigma^2)\), where \(N\) is a normal distribution of mean 0 and variance \(\sigma^2\). The square error \(e\) between predicted and observed incidence is defined as \(e = \sum_{T=1}^{16}(Z_T - U_T(1))^2 + \sum_{T=17}^{28}(Z_T - U_T(2))^2\), where week \(T = 0\) corresponds to week 17, 1918 and week \(T = 17\) corresponds to week 35, 1918. From influenza natural history, we assumed that the average length of the latent period is 1.5 days [14,15], while different assumptions on the average length of the infectivity period were made in order to have the sum of the latent and of the infectious period in the range 2.1-3.9 days, according to recent and past estimate on influenza serial interval [16-20]. All other parameters (namely, \(N(0), \beta_I, \alpha_I\) and \(\rho_I\), for \(j = 1, 2\) were estimated through model fit, i.e. by minimizing \(e\). The variance \(\sigma^2\) was computed as the average of the estimated residuals of the model (i.e. the average of the quadratic differences \((Z_T - U_T)^2\) between the hospitalization data and the best model fit \(U_T\)).

The uncertainty of the parameters was estimated by using a technique similar to that used in [21]. Specifically, for any given choice of the infectivity period length, we simulated 500 different realizations of the epidemic trajectory, obtained by perturbing the best-fit curve of number of new hospitalized individuals. Specifically, we added a simulated error to the best-fit curve which was sampled from a normal distributed \(N(0, \sigma^2)\) and we repeated the optimization procedure described above.

To test for differences in parameters between the two waves, we also considered model variants where a single hospitalization rate or length was assumed for the two waves: a usual \(F\)-test between nested models was used to assess the significance of the models with different parameters in summer and fall.

2.5. The exponential growth rate

The basic reproduction number can be estimated also from the intrinsic growth rate of the epidemic in the early exponential phase (when the depletion of susceptible individuals is negligible) [22]. Specifically, for SEIR models \(R_0\) can be computed as \(R_0 = (1 + rT_f)/(1 + rT_i)\), where \(r\) is the intrinsic growth rate of the epidemic, \(T_f = 1/\omega\) is the average length of the latent period and \(T_i\) is the average length of the infective period. By ignoring the latent class, i.e. by considering SIR models, \(R_0\) can be computed as \(R_0 = 1 + rT_i\) [22]. The intrinsic growth rate was computed only for the fall wave, by considering all growth rate observed from week 34-1918 to week 41-1918 in periods 2, 3 and 4 weeks long.

3. Results

3.1. Epidemiological Data

As experienced by other European countries, the Spanish influenza affected Italy in several waves: the first one occurred in July 1918, the second and most severe one in October–November 1918 and then the epidemic declined. Mortality rates were higher during the October–November wave (Fig. 1).
### Table 1
Number and proportion of hospitalized cases by diagnosis and period, Florence, 1918/1919 season, Italy.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pre-pandemic activity (1–17/1918)</th>
<th>Summer wave (18–34/1918)</th>
<th>Fall wave (35/1918–6/1919)</th>
<th>Other (7–53/1919)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N.</td>
<td>%</td>
<td>N.</td>
<td>%</td>
<td>N.</td>
</tr>
<tr>
<td>Fever</td>
<td>117</td>
<td>40.1</td>
<td>314</td>
<td>84.6</td>
<td>573</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
<td>1.1</td>
<td>1809</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>175</td>
<td>59.9</td>
<td>53</td>
<td>14.3</td>
<td>373</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>292</td>
<td>100.0</td>
<td>371</td>
<td>100.0</td>
<td>2755</td>
</tr>
</tbody>
</table>

The total number of hospitalized cases was 3674, with 939 deaths. The proportion of hospitalized cases and case fatality rates (CFR) by age group, during the pre-pandemic period (weeks 1–17 of 1918), and the summer (18–34 of 1918) and fall waves (35 of 1918–6 of 1919), are reported in Fig. 2. Data clearly show that during the pre-pandemic and the summer wave periods the proportion of hospitalized cases and the CFR increased with age, with elderly (individuals aged more than 45 years old) suffering the highest CFR. The age distribution of hospitalized patients during the summer wave shows a higher hospitalization among young adults. During the fall wave the highest proportion of hospitalized cases was reported in the 25–44 age class, with an average age of 33 and a median of 32 years and the CFR was higher in all ages compare to the two other periods (Fig. 2). The overall average age at death was 43 years (range 1–99), with a median of 40 years.

![Fig. 1. Number of observed weekly hospitalized cases and deaths from week 1-1918 to week 53-1919, in Florence, Italy.](image1)

![Fig. 2. Percentage distribution of hospitalized cases, and case fatality rate (CFR) by age group associated with pre-pandemic (weeks 1–17/1918), summer (weeks 18–34/1918) and fall (weeks 35/1918–6/1919) waves in Florence, Italy.](image2)
The 50% of hospitalized cases were discharged with an Influenza diagnosis, 28% with fever and 22% with pneumonia. The distribution of different diagnosis by pre-pandemic period, fall and summer waves are reported in Table 1.

3.2. Reproduction number and parameters estimate

The intrinsic growth rate of the fall wave was estimated to be $r = 1.089$ week$^{-1}$ (standard deviation, SD = 0.49). By assuming that the growth rate of the hospitalized individuals would be the same as the infective individuals we are able to obtain a rough estimate of the transmissibility potential for different choices of the length of the infectivity period. In particular, when a SIR model is considered, our estimates of the reproduction number ranged from 1.33 (SD = 0.147) to 1.61 (SD = 0.273), for infectivity period equal to 0.6 and 2.4, respectively. When a SEIR model is considered the figures become 1.35 (SD = 0.165) to 1.71 (SD = 0.347), for infectivity period equal to 0.6 and 2.4, respectively (latent period fixed to 1.5 days). Estimates of the reproduction number are reported in Table 2.

By considering the full model as described in Section 2, we are able to estimate from hospital records data of 1918/19 pandemic in Florence, not only the reproduction number, but also other epidemiologically relevant parameters. Such estimates, together with the corresponding confidence intervals for the first and the second wave, are reported in Table 3, when the infectivity period is assumed 1.5 days (i.e. a central estimates in good agreement with the value of the serial interval observed in empirical studies [16,17]). Model simulations showed a very good agreement with the observed epidemic curve (Fig. 3A). By using the estimated epidemiological parameters, the resulting basic reproduction numbers for the fall wave $R_0$ ranged from 1.32 (SD = 0.055) to 1.49 (SD = 0.063), for infectivity period equal to 0.6 and 2.4, respectively. Values obtained by assuming intermediate values of the length of the infective period are reported in Table 2 and in Fig. 3B. The estimates of the basic reproduction number for the summer wave are very close to 1 (see Fig. 3B). These results highlight that the reproduction numbers were significantly different in the two waves.

Testing for differences in hospitalization rates, we found, that the length of the infectivity period is assumed equal to 1.5 days, that the full model (different rates for summer and fall) gives a statistically better fit ($F(1,34) = 20.9$, p-value < 0.001) than the reduced model (same rate in the two waves). By applying the same procedure to a model with a single $\rho$ for the two waves, we found $F(1,34) = 6.4$, p-value = 0.016; this implies a slightly significant better fit of the full model. However, other statistical indicators suggest that the difference between the two models is minimal: for instance, the coefficient of determination $R^2$ increases only from 0.957 to 0.964, by adding one free parameter. In conclusion, our results suggest that the hospitalization rates were significantly different in the two waves, while data do not clearly support the hypothesis of different lengths of the hospitalization period during which individuals are able to transmit the disease.

4. Discussion

Our analysis revealed that two different pandemic waves occurred in Florence (Central Italy), similarly to what observed in Bologna (Northern Italy) [8]. As experienced by other European Countries, the Spanish influenza affected Italy in several waves: the first one during the summer 1918, the second and most severe one in October–November 1918. Mortality rates were higher during the fall wave.

In Italy, the prevention measures introduced (or non-pharmaceutical interventions) during the Spanish influenza were largely the same as those considered today: restrictions on public gatherings, isolation and quarantine, health education, and personal hygiene (especially hand washing and mask wearing) and in some cases also non-systematic school closure [23].

The timing of the 1918 A/H1N1 pandemic was similar to that observed in the 2009 A/H1N1 pandemic: Italy experienced one major wave during the fall (epidemic peak on week 46, 2009) and only a moderate activity was detected during the summer [24]. In both pandemics such timing could have been influenced by the scholastic calendar [24,25], by climatic factors [26] or by the population behavior [27].

A compartmental homogeneous mixing model was used to describe the transmission dynamics of the Spanish influenza in Florence and to calculate the basic reproduction number for both summer and fall waves, using hospitalization data. Our estimate of the reproduction number for the second wave was much larger than that of the first one. This is consistent with what was estimated for other countries, such as United States, for which an $R_0$ value ranging between 2 and 3 was estimated by using mortality data [14], and in Geneva, for which the reproduction number was estimated to be 1.49 and 3.75 for the first and second wave, respectively [10,13]. Quite the contrary, in UK reproduction number was estimated to be larger in the first wave ($R_0 = 2$) than in the second one ($R_0 = 1.55$) [28].

The estimated hospitalization rate was higher during the summer wave with respect to the fall one. The decrease of the hospitalization rate during the second wave might be due to several factors such as different public health policies, and the possibility that, due to the higher impact of the second pandemic wave in terms of morbidity and mortality the hospitals become overcrowded and therefore the threshold for admissions increased. The latter point is well documented by the correspondence available in the archive of the second major civil hospital in Tuscany at the time, Ospedali Riuniti di Santa Chiara in Pisa, where the responsible of the Hospital inquires other local institutions in order to acquire further spaces for treating seek people, as a consequence of the hospital overcrowding.

The CFR was higher during the fall wave compared to the summer, probably because during the fall wave more severe cases were hospitalized, while during the summer wave the hospitalization rate was higher but cases were less likely to die. During the early wave in spring 1918, no significant increase in mortality was recorded in Italy, and the illness appeared to be mild with a relative small mortality, whereas during the 1918 fall wave Italy showed the highest mortality rate in Europe (10.6 per 1000 inhabitants) [5].

This pattern could be attributable to defects of nutrition, and poor living conditions, due to the ongoing First World War. We recall that the armistice between Italy and the Central Empires was signed only on November 3, 1918, when much of the fall influenza wave was already over, and that 1918 was the most difficult phase of the war economy. During 1918 the availability of wheat and
Table 3
Average value of the epidemiological model parameters (and 95% CI, in parenthesis) for the two waves as estimated through model fit to the hospitalization time series. Both latent and infectious periods are assumed 1.5 days.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter interpretation</th>
<th>Summer wave</th>
<th>Fall wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I(0)$</td>
<td>Initial number of infective individuals</td>
<td>48.1 (13.8, 76.4)</td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission rate (days$^{-1}$)</td>
<td>0.64 (0.51, 0.74)</td>
<td>0.86 (0.8, 0.92)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Hospitalization rate for symptomatic individuals (days$^{-1}$)</td>
<td>0.21 (0.01, 0.42)</td>
<td>0.08 (0.05, 0.12)</td>
</tr>
<tr>
<td>$1/\rho$</td>
<td>Average length of the hospitalization during which individuals are able to transmit the disease (days)</td>
<td>2.23 (1.06, 4.51)</td>
<td>2.7 (1.22, 5.32)</td>
</tr>
</tbody>
</table>

Fig. 3. (A) Observed weekly number of new hospitalized individuals (red) and average of model fit as obtained by assuming the length of both latent and infectious periods equal to 1.5 days (black). Dark gray region refers to 95% CI of model simulations, while light gray region refers to minimum and maximum of model simulations. (B) Distribution of $R_0$ (2.5%, 25%, 50%, 75% and 97.5% percentiles) for the summer (green) and fall (red) waves by assuming different lengths of the infectious period (the latent period is kept fixed to 1.5 days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

meat fell dramatically down (and food rationing was extended to essentially all main foods and to the whole population), due to a variety of factors: the invasion of a large part of Northern Italy by the Austro-Hungarians with direct loss of fertile agricultural lands and livestock, a disastrous epidemics of foot-and-mouth disease occurred since September 1918, the large inefficiency of the State in its monopolist role in the trading and distribution of food resources, so that it happened that even when food was available in the Country’s stores it did not actually reach the population for long time, and also the massive attacks by German sub-marines to the Italian merchant navy. Moreover, compared to the country side where some degree of food self-sufficiency was preserved, big city areas, like Florence, suffered the most from this situation [29–34]. Parallel to this, the major indicator of the dramatic decline in the general living conditions is the well documented dramatic resurgence of various infectious diseases, also favored by the fast population and troops displacements, and the related mortality, including cholera, tuberculosis (as also reported for the UK [35]), malaria, pesteccial typhus and smallpox [36]. Shortage of food, and poor living conditions, could have therefore played a role in both increasing the general flu-induced mortality, and in biasing age-specific flu-induced mortality toward less immunocompetent people, e.g. the elderly.

The performed investigation has several limitations. First of all the present data tell us only a part of the story of the Spanish influenza in Italy. Italian Spanish influenza is indeed known to have impacted dramatically on Italian soldiers, killing about 113,000 men, i.e. about 18% of all deaths suffered by the Italian Army, and 70% of all disease-induced deaths among Italian troops during the First World War [37]. The influenza-specific death rate among sold-iers is estimated to be around 2.3%.

Moreover, we acknowledge that the assumption, used in the derivation of confidence intervals, of constant variance of errors during the course of the epidemics is a crude one; given the type of data we felt it represented the most reasonable compromise between accuracy and simplicity; however, this implies that the confidence intervals are mainly meant to reflect the existing uncer-tainty. Finally, note that while confidence intervals on the values of some parameters are quite large, the estimation of the basic reproduction number results to be more reliable.

As regards the present hospitalization data about the civil popula-tion only, we do not know how representative they are of the actual number of cases in Florence, due to the disruption of the population age structure caused by the war. It is to be kept in mind first that not only soldiers but also all those depending in some way from the military authority had to compulsorily attend, in the event of sickness, the military hospitals (there was a big one in Florence at the time). The number of Italian birth cohorts mobilized in the army was huge: 27 male cohorts (those born 1874–1900), with an average “mobilization” rate of 40.3% [37], but close to 65% for younger cohorts (and it must be taken into account that figures relative to older cohorts were seriously under-estimated). In particular Tuscany has been, among Italian regions, the one with the fourth highest mobilization rate. In addition most of the remaining male population in fighting age remained under the military author-ity [37]. There was also a shortage of young and adult women, either because supporting the troops (e.g. as infirmaries in mili-tary hospitals) or because replacing male manpower in factories, which were located outside the city areas. For Italy, but essen-tially everywhere, World War I is documented as the major women empowerment phenomenon in terms of labor participation. These phenomena explain, to some extent, the bias toward older indi-viduals in the age data, for example the very high average age of influenza-related deaths (43 years), recorded in the Florence civil hospital.

The objective of our work was mainly to give estimates of key epidemiological parameters, such as the basic reproduction num-ber, from the analysis of 1918–19 pandemic hospitalizations data from a country where overall mortality was, for many reasons, particularly high. Our knowledge on past pandemics would help understanding the mechanisms underlying pandemic dynamics and thus improving mathematical modeling accuracy to be prepared to face future pandemic threats.
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Conflict of Interest Statement: None declared.

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