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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 $R_0^1 = 1.03$ (95% CI: 1.00–1.08) during the summer wave and $R_0^2 = 1.38$ (95% CI: 1.32–1.48) during the fall wave. Varying the length of the generation time or the estimation method, R_0^2 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 of 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.

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

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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: haemorragic 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:

$$\begin{cases} \dot{S} = -\beta_j (I+H)\dfrac{S}{N} \\ \dot{E} = -\beta_j (I+H)\dfrac{S}{N} - \omega E \\ \dot{I} = \omega E - (\gamma + \alpha_j) I \\ \dot{H} = \alpha_j I - \rho_j H \\ \dot{R} = \gamma I + \rho_j H \end{cases}$$

where N is the total population size (assumed constant i.e. we disregard the impact of influenza mortality on transmission); β_j is the transmission rate; $1/\rho_j$ is the average duration of the period of hospitalization during which individuals are able to transmit the disease; α_j 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 $R_0^j = (\beta_j/(\gamma_j + \alpha_j)) + (\beta_j/(\gamma_j + \alpha_j))(\alpha_j/\rho_j)$. 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_0^1) and for the fall (R_0^2) 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 $U_T(j) = \int_{T-1}^{T} \alpha_j I(\tau) d\tau$ and we assume $Z_T = U_T + N(0,\sigma^2)$,where N is a normal distribution of mean 0 and variance σ^2. The square error ε between predicted and observed incidence is defined as $\varepsilon = \sum_{T=1}^{16} [Z_T - U_T(1)]^2 + \sum_{T=17}^{41} [Z_T - U_T(2)]^2$, 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, $I(0)$, β_j, α_j and ρ_j, for $j = 1, 2$) were estimated through model fit, i.e. by minimizing ε. The variance $\tilde{\sigma}^2$ was computed as the average of the estimated residuals of the model (i.e. the average of the quadratic differences $(Z_T - \tilde{U}_T)^2$ between the hospitalization data and the best model fit $\tilde{U}_T$).

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 $N(0, \tilde{\sigma}^2)$ 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 $R_0 = (1 + rT_\text{I})(1 + rT_\text{L})$, where r is the intrinsic growth rate of the epidemic, $T_\text{L} = 1/\omega$ 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 $R_0 = 1 + rT_\text{I}$ [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).