Preventive Medicine 143 (2021) 106351

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Short Communication

Vaccination against seasonal influenza and socio-economic and environmental factors as determinants of the geographic variation of COVID-19 incidence and mortality in the Italian elderly

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ARTICLE INFO

Keywords:
COVID-19
Influenza
Vaccine
Epidemiology

ABSTRACT

Background: A possible protective effect of seasonal influenza vaccination against the spread of the COVID-19 epidemic has been suggested.
Methods: We used publicly available data bases to explore the hypothesis as well as the effect of multiple social and environmental factors in the 20 Italian regions.
Results: Our results suggest that vaccination against seasonal influenza might beneficially impact on incidence and severity of the novel corona virus epidemic. Population density and vehicular traffic were also moderately associated with cumulative incidence of COVID-19. None of the other variables we considered showed an effect on cumulative incidence, case fatality rate or mortality from COVID-19.
Conclusions: Extending influenza vaccination coverage particularly among the elderly, vulnerable individuals with specific chronic medical conditions, health care workers, and workers in other essential services, early in the upcoming 2020 influenza season, might help reduce the health impact of a second epidemic wave of COVID-19.

1. Introduction

The 2019–2020 novel corona virus SARS-CoV-2 pandemic hit at different times, with variable force worldwide. Reasons for such geographical variation in virulence are not clearly understood; various factors have been suggested, including environmental pollution (Bashir et al., 2020), temperature, humidity, UV index (Ma et al., 2020; Gunthe et al., 2020), and smoking (Vardavas and Nikitara, 2020). In the first quarter of year 2020, Italy has been the first and one of the worst hit western countries, with COVID-19 showing a peculiar, southward decreasing trend in cumulative incidence and mortality (Italian National Institute of Health, 2020). Also, consistently with what reported in other countries, almost 60% deaths occurred among the elderly living in retirement homes (Italian National Institute of Health, 2020), where social contact is considered a benefit; therefore, vulnerable subjects were not appropriately isolated from the rising epidemic, and the staff taking care of them often acted as carrier.

One hundred fifteen cases of co-occurrence of influenza A and COVID-19 have been described in Wuhan, China (Ding et al., 2020), and several clinical reports have described the same co-occurrence worldwide (Konala et al., 2020). A survey conducted in Italy between April and June 2020 reported a significant reduction in risk of SARS-CoV-2 naso-pharyngeal swab test positivity associated with previous influenza and pneumococcal vaccination among younger subjects. The statistical power was not sufficient to exclude chance as the determinant of the same size reduction in risk observed among subjects aged ≥65 years (Noale et al., 2020). On the other hand, a direct correlation between influenza (H1N1) vaccination status and the attack rate of COVID-19 as a measure of outbreak severity was observed in 34 world countries, limited to the 15 days between 27 February and 12 March 2020 (Lisewski, 2020) which the author interpreted as suggestive of influenza vaccine possibly favouring COVID-19 respiratory tract infections, due to vaccine interference. However, another cross-sectional survey, conducted among the U.S.A. military in 2019, observed that influenza vaccination conferred a reduction in risk for several other influenza and parainfluenza infections, while vaccine interference showed its effects in increasing risk of coronavirus and human metapneumovirus infection (Wolff, 2020).

We explored the relationship between vaccination against seasonal influenza in subjects aged ≥65 years and the concurrent effect of

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https://doi.org/10.1016/j.ypmed.2020.106351
Received 13 June 2020; Received in revised form 1 October 2020; Accepted 26 November 2020
Available online 2 December 2020

multiple socio-economic and environmental factors and COVID-19 cumulative incidence, cumulative death rate, and case fatality rate in the 20 Italian regions.

2. Methods

We used publicly available online resources to extract data on the following socio-economic and environmental variables for each of the 20 Italian regions: average number of household residents (100 x residents/m^2), average *per capita* income (€/1000), deprivation index (modified from http://istat.it), circulating vehicles per 100 residents (www.comuni-italiani.it/statistiche/), average temperature in March in the main urban area of the region in the Celsius scale (https://www.ilmeteo.it/portale/archivio-meteo/), and population density (https://www.tuttitalia.it/regioni/densita/). The Italian National Institute of Statistics (ISTAT) deprivation index combines several characteristics, such as educational level, percent of unemployed, housing and familiar conditions, to express the level of social disadvantage of a given population (National Observatory on Health in the Italian Regions. Rapporto Osservasalute, 2009). As the ISTAT deprivation index varies around zero, for the purposes of our analysis, we modified it by eliminating the negative values through adding an equal quantity to each regional value, corresponding to 1+ the lowest negative value, so to have the lowest representing the wealthiest region. We extracted the 2019–2020 seasonal influenza vaccination rates among the resident population aged ≥65 by region from the Italian National Institute of Health (ISS) web site (https://www.epicentro.iss.it/influenza/coperture-vaccinali). ISS was also the source for the number of total COVID-19 incident cases (all ages, both genders), number of COVID-19 deaths in March 2020 by region, age, and gender, and for the COVID-19 case fatality rate (deaths/100 diagnoses, all ages, both genders) by region (https://www.epicentro.iss.it/ en/coronavirus/sars-cov-2-integrated-surveillance-data). The resident population of each region aged 65 years or older was extracted from the ISTAT web site (https://www.istat.it/). Seasonal influenza vaccination rates among the Italian population in the winter 2019–2020 were available by region for the total population aged ≥65, but not gender stratified. Also, COVID-19 incidence and case fatality rate were available for the total population at the regional level; however, as 91% of incident cases, and 94% of deaths from COVID-19 occurred among subjects aged ≥65, we used the overall cumulative incidence and case fatality rate as *proxies* for mortality among the elderly. Also, based on the nationwide proportion of COVID-19 cases aged ≥65 years, we estimated the number of incident cases among elderly by region, and the cumulative incidence rate in the corresponding age group. Of note, we could not find data on the number of residents in retirement homes for the elderly and disabled, nor on the prevalence of occupational groups at higher risk, such as healthcare workers by region.

We first conducted univariate linear regression analyses to assess the relationship between seasonal influenza vaccination rate, and COVID-19 cumulative incidence, cumulative deaths, and case-fatality rate from the date of registration of the first case through 31 March 2020. This period was selected because it included the phase of logarithmic growth of the epidemic curve in Italy. We used the Pearson's correlation statistic to test the chance probability associated with the observed regression line.

Based on the available data, we calculated the cumulative COVID-19 incidence (1000 x number of cases diagnosed with COVID-19 among subjects aged ≥65 years/ total residents aged ≥65 years as of 1 January 2020), and the cumulative COVID-19 death rate among the population aged ≥65 years (10,000 x number of deaths among subjects aged ≥65 years /total residents aged ≥65 years as of 1 January 2020) by Italian region. We used multiple regression analysis to predict COVID-19 cumulative incidence, cumulative death rate, and case fatality rate, as a function of average number of household residents, average *per capita* income, deprivation index, circulating vehicles, average temperature in March, population density, and seasonal influenza vaccination rate among subjects aged ≥65. We followed a stepwise backward procedure, and retained the variables included in the best fitting model, as indicated by the adjusted R^2 value.

We used SPSS® 20.0 to conduct the analysis.

3. Results

Fig. 1 shows significant negative association between COVID-19 cumulative incidence (a), cumulative death rate (b), and case fatality rate (c) and the respective seasonal influenza vaccination rates among the population aged ≥65 years in the 20 Italian regions. The inverse trend by vaccination rate did not change after replacing the estimated cumulative incidence in the elderly with that over the total resident population (r = 0.546, p = 0.006).

We explored a few potentially contributing factors from environmental and socio-economic origin with multiple regression analysis. Table 1 shows the correlation matrix of the selected predictive variables.

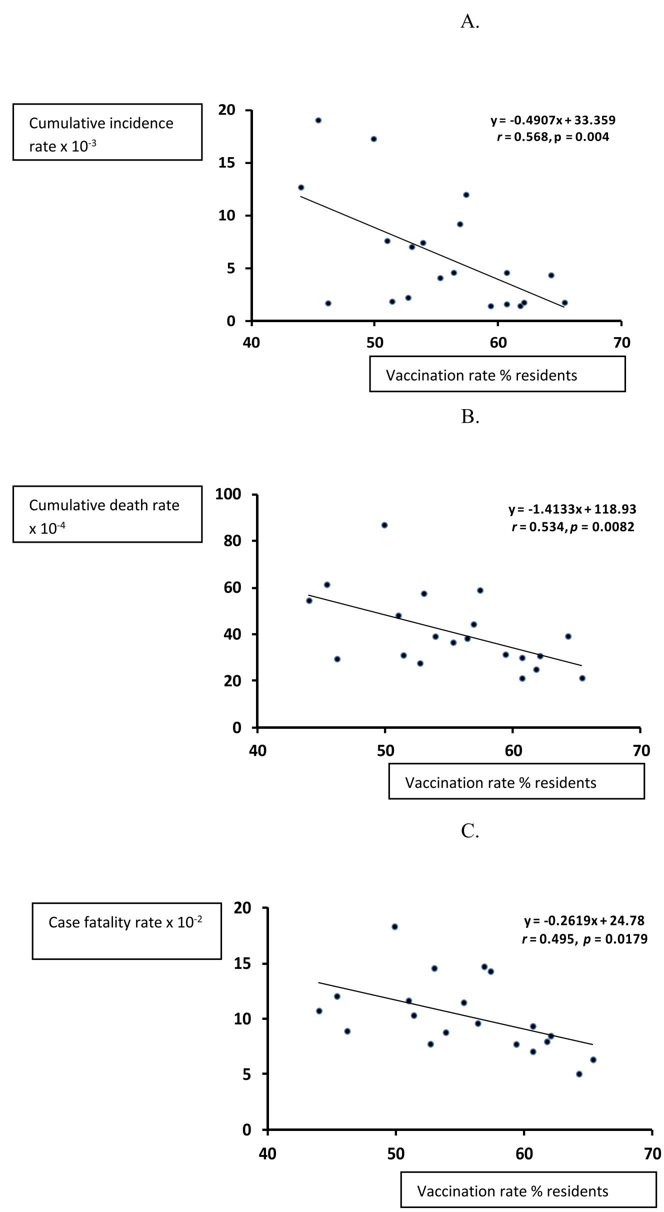

Fig. 1. Effects of seasonal flu vaccination rate on COVID-19 cumulative incidence (A), cumulative death rate (B), and case-fatality rate (C) in March 2020 among the Italian population aged ≥65 resident in the 20 Italian regions. The equation of the regression line and the related statistics are included in the graphs.

Table 1
COVID-19 cumulative incidence up to 31 March 2020, influenza vaccination rate in the elderly, and environmental and socio-economic variables in the 20 regions of Italy. Correlation matrix.

	COVID-19 cumulative incidence rate x 10^{-3}	Crowding (residents/ 100 m^2)	Deprivation index (modified)	Income (euro/ 1000)	Circulating vehicles/ 100 inhabitants	Average temperature in march 2020	Population density	Influenza vaccination rate (age > 65)
COVID-19 cumulative incidence rate x 10^{-3}	1000	−0,239	0,468	0,654	0,600	−0,430	0,060	−0,568
Crowding (residents/100 m^2)	−0,239	1000	0,786	−0,453	−0,180	0,286	0,419	0,141
Deprivation index (modified)	0,468	0,786	1000	−0,784	−0,203	0,606	0,270	0,102
Income (euro/ 1000)	0,654	−0,453	−0,784	1000	0,183	−0,418	0,144	−0,361
Circulating vehicles/100 inhabitants	0,600	−0,180	−0,203	0,183	1000	−0,374	−0,501	−0,426
Average March 2020 temperature	−0,430	0,286	0,606	−0,418	−0,374	1000	0,324	−0,078
Population density	0,060	0,419	0,270	0,144	−0,501	0,324	1000	0,011
Influenza vaccination rate (age > 65)	-0,568	0,141	0,102	-0,361	−0,426	-0,078	0,011	1000

As expected, average income, crowding index, and deprivation index showed a strong reciprocal correlation. Average income and crowding index were not significant predictors of COVID-19 cumulative incidence in the multiple regression analysis, and therefore these variables are not included, and only deprivation index is retained in the best fitting regression models, which results are shown in Table 2. After the reciprocal adjustments, vaccination rate against seasonal influenza still showed an inverse association of borderline significance, which was weakened, but still visible, when using the crude cumulative incidence calculated over the whole resident population. The association was stronger with cumulative death rate, and severity of the disease, as represented by the case fatality rate. Population density and vehicular traffic increased cumulative incidence of COVID-19 among the elderly, perhaps by reducing social distance and increasing the susceptibility of the respiratory system already affected by the particulate emissions in the atmosphere. Deprivation index was instead inversely associated with cumulative incidence of COVID-19, which might be suggestive of an increased risk among the wealthier, possibly because of a more intense social activity. Contrasting previously reported effect of a higher average temperature in reducing the impact of the COVID-19 epidemic (Ma et al., 2020; Gunthe et al., 2020), average temperature did not affect any of the outcomes, and circulating vehicles did not affect either cumulative mortality or case fatality rate.

Table 2
Parameters (β = regression coefficient; *se* = standard error, *t* = *t*-test; *p* = *p*-value) of the multiple regression analyses predicting COVID-19 cumulative incidence, case fatality rate and cumulative deaths in March 2020 among the Italian population aged ≥65 by region.

Variables	Outcomes		
	Cumulative incidence	*Cumulative death rate*	*Case fatality rate*
	β se t p	*β se t p*	*β se t p*
Constant	10.94 13.67 0.80 0.437	114.0 26.36 4.33 0.0005	23.44 5.317 4.41 0.0004
Deprivation index	−0.919 0.434–2.12 0.052	−3.151 1.535–2.05 0.057	−0.601 0.310–1.94 0.070
Circulating vehicles (N/1000 residents)	0.227 0.068 3.35 0.005	–	–
Average march temperature	−0.641 0.561–1.14 0.272	–	–
Population density	0.024 0.007 3.45 0.004	0.057 0.026 2.16 0.046	0.013 0.006 1.89 0.075
Vaccination rate	−0.265 0.128–2.06 0.058	−1.322 0.469–2.82 0.012	−0.245 0.094–2.59 0.020
Adjusted R^2	0.723	0.410	0.401

4. Discussion

Our results suggest that vaccination against seasonal influenza might beneficially impact on incidence and severity of the novel corona virus epidemic in subjects aged 65 years or older.

Our findings are in agreement with a recent ecological study that evaluated this hypothesis in Italy, but it did not have access to the most recent 2019–2020 regional influenza vaccination coverage rate (Amato et al., 2020); therefore, our work confirms and extends these results.

Long lasting cross-protection has been described in the elderly from pre-existing antibodies against different H1N1 viral strains or previous contacts with the same strain (Chuah et al., 2018; Hancock et al., 2009; Rizzo et al., 2010). SARS-CoV-2 genomic sequence has been recently characterized as closely related to two SARS-like coronaviruses, with a similar receptor-binding domain structure, and some amino acid variation at key residues (Lu et al., 2020), allowing its identification as a new human-infecting *b* coronavirus. However, the pathogenesis of influenza and SARS-CoV-2 viruses requires similar hemagglutinin-esterase proteins (Menachery et al., 2014); both share spike protein features with class 1 viral membrane fusion proteins (Zeng et al., 2008; Li, 2016); and, alike SARS-CoV-2, influenza A viruses also link to the ACE-2 receptors in the lung (Chung et al., 2020).

Although suggestive, the circumstantial evidence and the results of our ecological analysis do not prove that seasonal influenza vaccination would prevent COVID-19 occurrence by inducing antibodies against common specific antigens. First, we conducted an exploratory analysis of public data on influenza vaccination coverage, which were available for subjects aged ≥65 years only; therefore, we could not explore the suggested age-related varying response to viral infections. Second, the so-called ecological fallacy is a main problem limiting the interpretation of the ecological studies, as the geographic area and not the individual is the unit of measurement, and all subjects within the same area are considered equally exposed to the same factors, while we could not assess whether the within region variance in exposure to each factor would be smaller, similar, or even greater than the between regions variance. Therefore, it is never justified interpreting such results in terms of the individuals composing the population of the area (Piantadosi et al., 1988). Third, the outcomes we explored refer to the ≥65 year old population segment, and not to the whole population, while the socio-economic and environmental indicators we used refer to the total population of each region. This is a further reason for suggesting caution in interpreting our findings. Finally, we cannot exclude that possible confounding, due to factors associated with influenza vaccination other than those selected, might have affected our results. For instance, as influenza vaccination is a personal choice, it is quite plausible that the resulting benefits against other infections would result from a generic healthier lifestyle of the persons who choose to be vaccinated in respect to those who did not, and not from the vaccine itself. Still, the U.S. Centers for Disease Control recommends vaccination against seasonal influenza for poultry workers to prevent avian flu (US Centers for Disease Control and Prevention, 2020), and a few reports suggested (Ding et al., 2020; Konala et al., 2020), that preventing seasonal influenza *via* vaccination would also avoid superimposing its effects on COVID-19, thus worsening the prognosis. On the other hand, mathematical models suggest that efforts in extending public health measures against seasonal influenza would prevent overburdening the healthcare system from co-occurrence of respiratory outbreaks, and shortage of laboratory equipment and treatment devices (Li et al., 2020). For instance, beneficial effects might result from excluding influenza in the differential diagnosis of COVID-19-like symptomatic cases, which would restrict the number of cases requiring a deeper diagnostic work up, so lightening the burden on the healthcare system capacity.

Further formal observational epidemiological analyses are warranted to test this hypothesis. Nonetheless, 1) a specific vaccine against SARS-CoV-2 would not be expected to become available to the general population worldwide in a short time; and 2) benefits and no harm would result from a more extensive influenza vaccination coverage in the general population worldwide. Besides social distancing and use of face masks, enforcing the WHO recommendation on the use of seasonal influenza vaccination (World Health Organization, 2020), and extending the coverage particularly among the elderly, vulnerable individuals with specific chronic medical conditions, health care workers, and workers in other essential services, early in the upcoming 2020 influenza season, might help reduce the health impact of a second epidemic wave of COVID-19.

Contributors

PC and SDM conceived the study; PC conducted the analysis and wrote the manuscript; FM, AC, and DS contributed to the analysis and the revision of the manuscript; MC and SDM revised the manuscript. All authors participated in the interpretation of the results, provided critical feedback, and approved the final version.

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