COVID-19 severity in Europe and the USA: Could the seasonal influenza vaccination play a role?

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Abstract

The factors affecting COVID-19 infection risk and disease severity have been widely discussed. The role that seasonal influenza vaccinations may play is generally not included in the debate. We performed an analysis investigating a possible link between the vaccination coverage rate (VCR) in the elderly (≥ 65 years of age) and COVID-19 infection risk or disease severity. Data from Europe (country-wise) and the USA (state-wise) were investigated separately. We found statistically significant positive correlations between the VCR and reported COVID-19 incidence, as well as mortality for Europe and the USA. A statistically significant positive correlation was also found between the VCR and the COVID-19 case fatality rate (CFR) for Europe. For the USA, the VCR/CFR correlation was not statistically significant. Our analysis indicates that receiving seasonal influenza vaccination(s) in the past might be an additional risk factor for the elderly in terms of enhanced susceptibility to infection with SARS-CoV-2 and higher likelihood of a lethal outcome in case of infection. More research about this possible risk factor is urgently needed.

Keywords:

COVID-19, SARS-CoV-2, seasonal influenza vaccination, vaccination-associated virus interference

1. Introduction

Since the outbreak in China of a novel coronavirus disease (COVID-19) in December 2019, associated with infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2], COVID-19 has caused a global pandemic with more than 6.7 million confirmed cases (as of 7 June 2020, WHO).

Risk factors for infection with SARS-CoV-2 and for a more severe clinical course of COVID-19 have been identified as age, sex, ethnicity, smoking, obesity, and comorbidities like hypertension, diabetes, cardiovascular diseases, respiratory disease and malignancy [3-17].

Limited information has been available as to whether seasonal influenza vaccinations have an effect on COVID-19 infection risk or disease severity. Two (not peer-reviewed) studies have been published so far with regard to this aspect. While one study found that countries with a higher seasonal influenza vaccination coverage rate (VCR) have lower COVID-19 infections and deaths rates [18], the other study found the opposite [19].

The aim of the present study was to further explore the possible link between the VCR in the elderly (≥ 65 years of age) and COVID-19 infection risk or disease severity. We therefore separately gathered and investigated data from Europe (country-wise) and the USA (state-wise).

2. Data and methods

2.1 Data

The number of total confirmed COVID-19 deaths and cases per million people for Europe[1] as of 22 May 2020 were obtained from the Global Change Data Lab project website Our World in Data (ourworldindata.org). For the USA, data from the Johns Hopkins University Center for Systems Science and Engineering were used (https://cnn.it/2znU7bS). The case fatality rate (CFR) in percent was then calculated based on case and death count data as CFR = 100 × (cases/deaths)). The VCR in percent for the seasonal influenza vaccination and for people older than 65 years of age was obtained for countries in Europa using the data provided by EUROSTAT (https://bit.ly/3cbiPtn) and the European Centre for Disease Prevention and Control (ECDC) (https://bit.ly/2AcpS7u). These sources were screened for the latest available data. If data for the same date were available, an average of the VCR from both sources was then used. VCR data for Switzerland were found to be outdated in the data sets provided by EUROSTAT and ECDC. Therefore the VCR as an average for the year 2017–2019 was calculated taking the latest data provided by the Swiss Federal Office of Public Health (FOPH; https://bit.ly/2XuQTuV) and the study of Brunner et al. [20]. VCR data for the USA were obtained from the Centers for Disease Control and Prevention (CDC; https://bit.ly/2ZFeBr2). The age group 65 and older has been selected as this is the age slot most sensitive with the highest CFRs observed and therefore enables best visibility of the observed correlations. The data of the percent of population aged 65 and older for countries in Europe were taken from the Population Reference Bureau (PRB; https://bit.ly/2TFNeJw).

Tables with the data can be found in the appendix (**Tab. 1–3**).

2.2 Data analysis

A linear correlation analysis was performed for VCR vs. log-transformed COVID-19 case rate, death rate and CFR for Europe and the USA, and the percent of population aged 65 and older for countries in Europe vs. the log-transformed COVID-19 case rate, death rate and CFR for Europe. Data analysis and visualization was performed with R (RStudio, version 1.1.447).

3. Results

3.1 Correlations between VCR and incidence, mortality and case fatality rates among the population aged 65 and older as a result of COVID-19 for both Europe and the USA

A statistically significant ($p < 0.05$) positive correlation is evident between the VCR and incidence, as well as mortality for Europe and the USA of the population aged 65 and older. The correlation between the VCR and the CFR for Europe is also statistically significant whereas the VCR-CFR relationship for the USA is not ($p = 0.1995$) (**Fig. 1**).

The two strongest correlations are those between the VCR in Europe and the incidence and mortality of COVID-19 in Europe ($r = 0.66 \pm 0.13$, $p = 0.000017$ and $r = 0.68 \pm 0.13$, $p = 0.000006$, respectively).

[1] The term "Europe" in this publication refers not to the European Union but to the geographical definition of Europe.

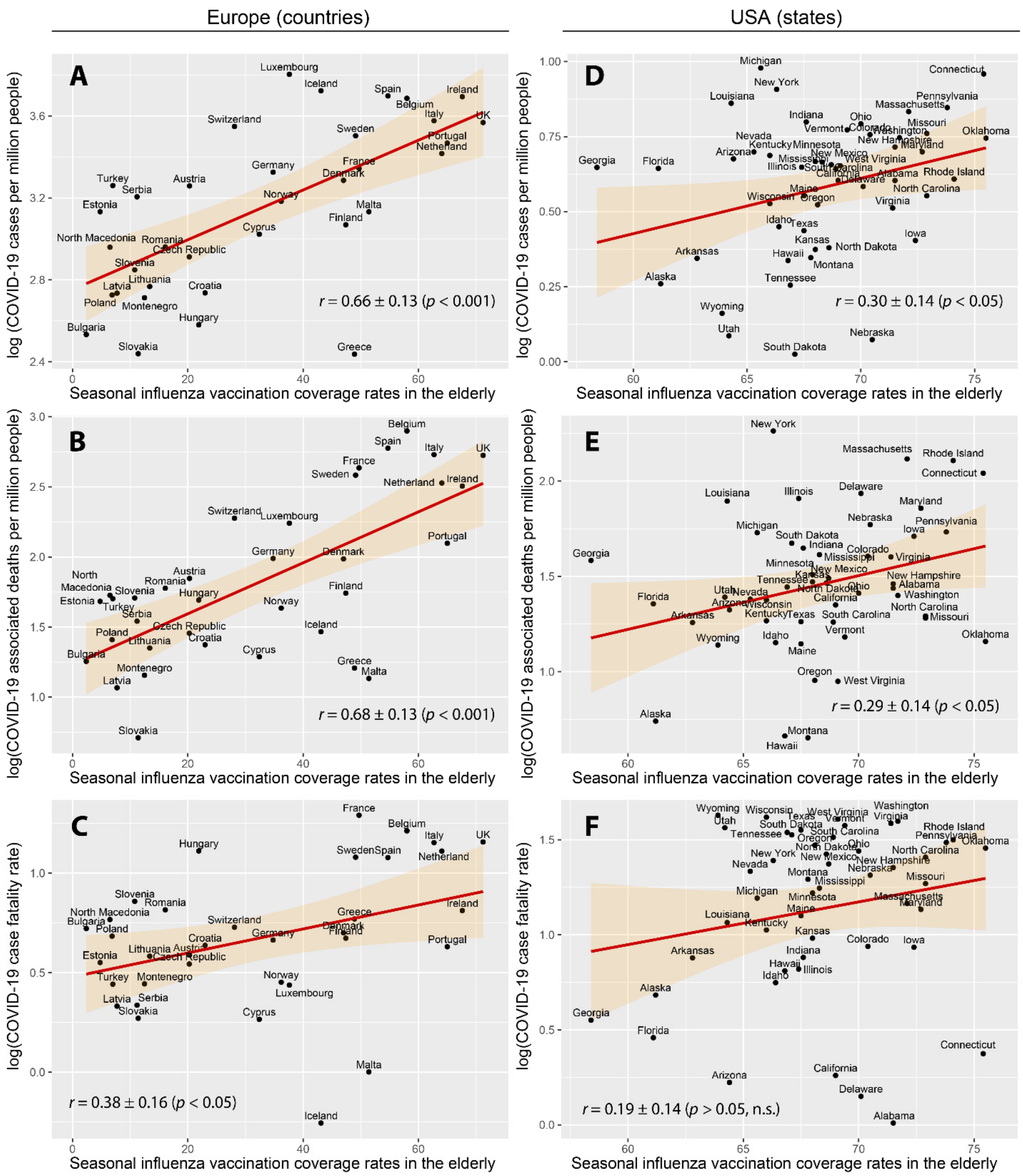

Fig. 1: Correlations between the seasonal influenza vaccination coverage rates (VCR) in the elderly for Europe (country-wise) as well as the USA (state-wise) and epidemiological parameters for COVID-19 (**A, D**: cases, **B, E**: deaths, **C, F**: CFR).

3.2 Correlations between percent of population aged 65 and older and incidence, mortality and CFR of COVID-19 for Europe

The correlations between the incidence, mortality and CFR of COVID-19 in Europe with the percentage of population aged 65 and older was not statistically significant ($p > 0.05$). There is also no statistically significant correlation between the VCR and the percent of population ages 65 and older for Europe (**Fig. 2**).

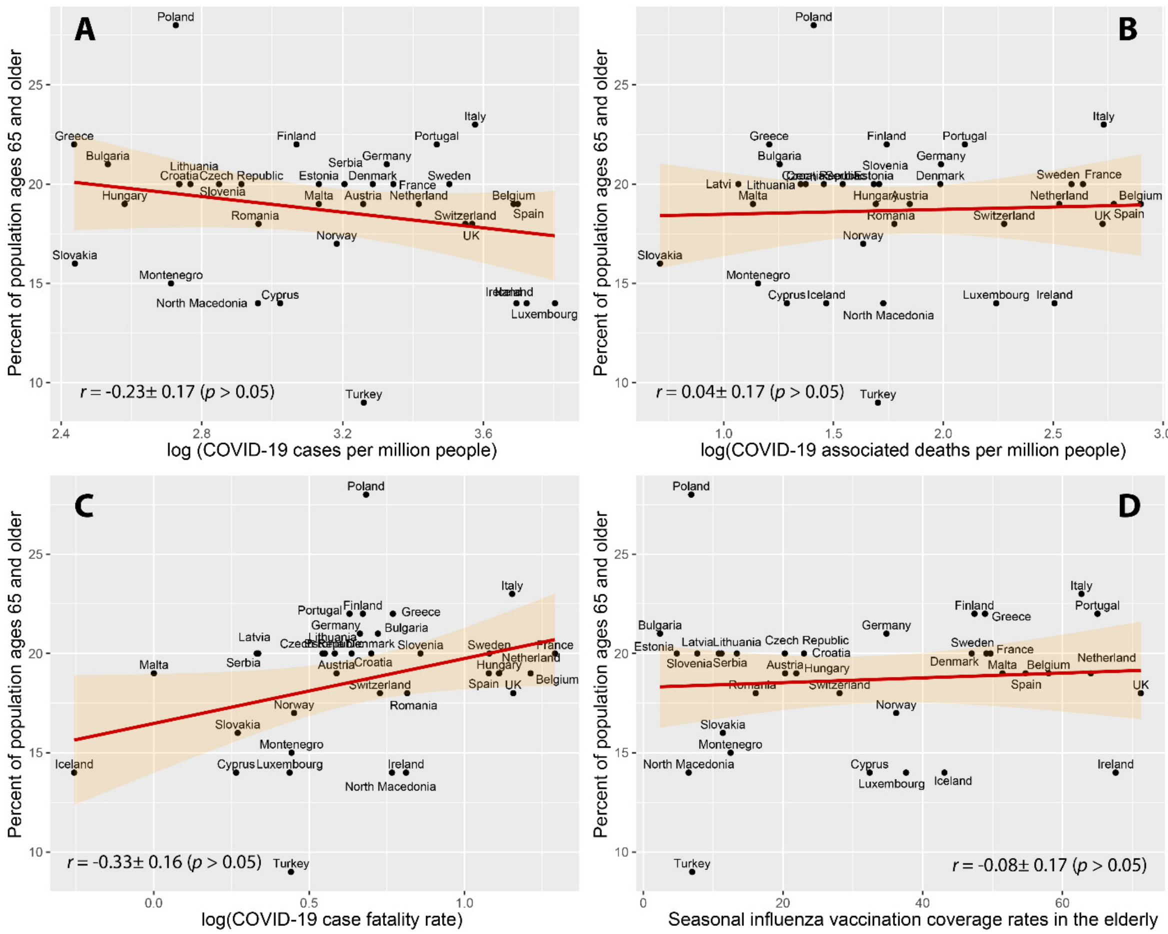

Fig. 2: Correlations between the percent of population aged 65 years and older in Europe (country-wise) and epidemiological parameters for COVID-19 (cases, deaths, CFR) (**A–C**), as well as the correlation between the VCR and the percent of population aged 65 years and older (**D**).

4. Discussion

4.1 Seasonal influenza vaccination coverage rate: A relevant parameter to help explain differences in worldwide COVID-19 epidemiological parameters?

Our analysis of the epidemiological data for COVID-19 (incidence, mortality and case fatality rate) for Europe and the USA with respect to the VCR showed (i) for Europe (at country level) a statistically significant positive correlation between the VCR and the case rate, death rate and CFR, (ii) for the USA (at state level) also a statistically significant positive correlation between the VCR and the case rate and death rate, and (iii) for the USA, no significantly significant correlation between the VCR and the CFR. Furthermore, no statistically significant correlation was evident for Europe between the epidemiological parameters for COVID-19 and the percent of population aged 65 and older.

The results show that the seasonal influenza VCR is positively associated with the severity of the COVID-19 outbreak in Europe as well as in the USA. The fact that there is a statistically significant positive correlation between the VCR and the epidemiological data for both Europe and the USA underlines the association, which applies not only at country level (Europe) but also at state level (USA).

The percent of population aged 65 and older seems less important in explaining the epidemiological data for COVID-19 in Europe than the seasonal influenza VCR in this age group.

These results raise the important question of how the positive correlation between the VCR and the COVID-19 epidemiological parameters should be interpreted. Several explanations are possible. First, the correlations could simply be down to chance and have no direct significant meaning. Since the correlations are statistically robust and follow the same trend in the Europe and in the USA, this seems rather unlikely. Second, the correlations found could indicate that VCR is not the causal factor per se but rather itself correlated with another factor or factors that are responsible for the causal link (e.g., air pollution, nutritional status, lifestyle factors). The exact nature of these factors is not directly evident but the possibility of this explanation cannot be ruled out. Third, the correlations found in our analysis could indeed indicate that the VCR is causally linked to the severity of the COVID-19 outbreak in Europe and the USA. In this case, seasonal influenza vaccination of the elderly must have affected the elderly population in such a way that they were more susceptible to infection with SARS-CoV-2, development of COVID-19 and a fatal outcome of COVID-19.

It is a topic of ongoing debate whether those vaccinated against seasonal influenza are more susceptible to developing a non-influenza-caused respiratory disease. One mechanism mediating this effect is vaccination-associated virus interference, i.e. a change of an organism (with respect to susceptibility or disease severity) to an infection by viruses other than the virus used in the vaccine administered to the organism. These mechanisms have been observed, e.g. an enhanced pathogenicity of the H9N2 avian influenza virus (AIV) after vaccination with live infectious bronchitis coronavirus (IBV) vaccine (a study in broiler chickens) [21].

To the best of our knowledge, there are six studies to date investigating a possible influenza vaccination-associated virus interference in human populations.

Kelly et al. [22] published a study investigating the influenza vaccine effectiveness in children aged 6 to 59 months ($n = 289$). They noted a "significantly higher vaccination coverage among those who tested positive for other respiratory viruses than among those who tested negative for all viruses", i.e. an increased risk of a non-influenza virus infection due to the influenza vaccination. However, the authors, regarded this as "biologically implausible" and the presence of false negatives for influenza detection in the control group as more plausible.

Cowling et al. [23] showed that children ($n = 115$) receiving a trivalent inactivated influenza vaccine (TIV) or a placebo had an increased risk of virologically-confirmed non-influenza infections (relative risk: 4.40, 95%, CI: 1.31–14.8) over the following 9 months. When stratified according to the specific type of non-influenza virus, infections with rhinoviruses and coxsackie/echoviruses were increased in the recipient of the TIV; infections with coronaviruses, however, were not statistically significantly increased in this population.

Sundaram et al. [24] reported a study not finding an association of influenza vaccination status and the detection of non-influenza respiratory viruses in children ($n = 1616$) and adults ($n = 1568$) over a period of six influenza seasons, disputing the hypothesis that influenza vaccination may likewise increase the risk of non-influenza viral infections.

An increase in detection of non-influenza viruses in recipients of influenza vaccines was not found in a study of Feng et al. [25] either. Feng et al. investigated a large population (n = 10.650) and detected influenza in 35%.

This year, Wolff [26] published a study showing "little to no evidence supporting the association of virus interference and influenza vaccination" by comparing the vaccination status of people with detected non-influenza respiratory viruses ($n = 2880$) to people with pan-negative results ($n = 3240$). For those who had received an influenza vaccination, the odds for non-influenza virus detection was significantly higher compared to unvaccinated subjects (OR = 1.15 (95% CI: 1.05–1.27)). In particular, the odds for the detection of coronavirus (OR = 1.36 (95% CI: 1.14, 163)) or human metapneumovirus (OR = 1.51 (95% CI: 1.20, 1.90)) were increased in vaccinated individuals, and the odds for parainfluencavirus (OR = 0.67 (95% CI: 0.51, 0.87)) and respiratory syncytial virus (OR = 0.81 (95% CI: 0.68, 0.96)) decreased. Despite Wolff's assertion that there is little to no evidence of association of virus interference and influenza vaccination, the figures can be interpreted as showing an influenza vaccination-associated virus interference with an increased probability of a coronavirus infection.

The study of Wolff was criticized in a recently published paper by Skowronski et al. [27], which pointed out that the evidences provided by Wolff about a vaccination-associated virus interference were due to a methodological error, i.e. improperly including influenza test-positive specimens in the analysis. In addition, Skowronski et al. performed a new analysis based on own data from specimens collected during the 2010–11 to 2017–17 influenza seasons. No statistically significant indications for a vaccination-associated virus interference with regard to non-influenza viruses were found. The authors concluded that their findings "provide reassurance against the speculation that influenza vaccine may negatively affect COVID-19 risk" [27]. However, the authors also conceded that although they "did not find evidence for vaccine interference, population surveillance signals elsewhere suggesting cross-pathogen immunological interactions still warrant immune-epidemiological investigations" [27]. At the time of writing, Wolff had not yet publicly responded to alleged shortcomings in his statistical analysis.

From these studies discussed, it can thus be concluded that the discussion is ongoing as to whether there is a possible vaccination-associated virus interference with regard to vaccinations against seasonal influenza and a subsequent increase in the probability of infections with non-influenza viruses, in particular with coronaviruses. The present epidemiological evidences are currently more in favor for the absence of such an association. However, as pointed out by Laurie et al [28], the inconsistent study results may also be, at least, partially explained by the time interval between the initial infection (in this case vaccination) and the subsequent natural exposure with viruses. The authors came to this conclusion based on their own experimental work in animals showing that the time interval between primary infection and subsequent challenge is a determining factor for viral interference.

All the studies discussed so far about a vaccination-associated virus interference with regard to seasonal influenza vaccination and coronavirus infections [22-27] were based on data obtained before the COVID-19 pandemic and thus do not offer concrete insights into whether seasonal influenza vaccination was associated with an increased incidence or pathogeny of SARS-CoV-2 infection.

With regard to the COVID-19 pandemic, two studies have been published (as online articles on ssrn.com, not peer-reviewed) until now investigating the role of influenza vaccinations in the ongoing pandemic. Arokiaraj [18] published an analysis about associations of the VCR for seasonal influenza and epidemiological parameters for COVID-19 for the OECD member states. Overall, negative correlations were found between the VCR and the COVID-19 epidemiological parameters. However, no statistical analysis was performed (only scatter plots were shown with linear fits) and the epidemiological data were normalized in an unusual way, including the VCR and thus rendering it difficult to assess any potential association between VCR and the epidemiological parameters. In another study, Lisewski [19] found a statistically significant positive correlation between the VCR for OECD countries and the COVID-19 outbreak severity, quantified as the attack rate ($AR(\mathrm{t}) = (R_0\text{-}1)/R_0((CN_2\text{-}CN_1)\ POP)^{1/2}$, with R_0 the basic reproduction number during the outbreak, CN_1 and CN_2 confirmed COVID-19 cases for t_1 and t_2, POP the population size in millions, and t_1 = 27 February 2020, t_2 = 12 March 2020 and $t = t_2$). The findings of Lisewski agreed with ours concerning a positive association between the VCR and the severity of COVID-19 when analyzing the epidemiological data from Europe.

Concerning a general virus-virus interaction in organisms, it is known that “natural” virus inference occurs with respect to influenza and common cold viruses in humans. The prevalence of specific viruses causing respiratory disease in humans represents a complex interplay between the viruses with “negative interactions between influenza and non-influenza viruses and positive interactions among non-influenza viruses” [29]. With respect to the human coronaviruses (229E, NL63, HKU1), a positive interaction was found with respiratory syncytial virus, human adenoviruses, human parainfluenza 1 and 3 viruses [29]. It would be worthwhile to update this study with the SARS-CoV-2 prevalence data.

Regardless of vaccination-associated virus interference, the findings of our study might be also interpreted as showing that the influenza vaccination causes physiological (or pathophysiological) reactions different to virus interference that lead to higher susceptibility to SARS-CoV-2 infection or a more severe disease progression. Such mechanisms have already been observed due to influenza vaccinations and include autoimmune reactions [30], vasculitides [31-33] and lung injuries [34, 35].

4.2 Strengths and limitations of the study

Our analysis is the first to investigate a possible connection between influenza VCR and epidemiological parameters of COVID-19 for Europe (country-wise) and the USA (state-wise).

Although carefully conducted, our study has the following limitations.

First, the epidemiological data for COVID-19 used in the present study are approximations of the final ones that will available after the end of the pandemic. The analysis is thus based on an epidemiological data set that will differ in the future to a specific (and as yet unknown) extent. The analysis is based on epidemiological data as of 22 May 2020.

Second, the quality of the available epidemiological data for COVID-19 is insufficient for several reasons, including the dependence of the case rate on the number of tests performed [36, 37], differences in counting COVID-19 deaths within states in Europe (for example, Italy counts every death accompanied by a positive SARS-CoV-2 test result as a death due to COVID-19 [38]), different accuracies of the PCR test kits used [39-44], dependence on the sampled material (salvia vs. nasopharyngeal swabs) [45, 46], and the impact of the testing time on the testing outcome [47-49].

Third, for Europe, the influenza VCR was in general not available for 2019 and the VCR for the last available year or years has been used instead. The VCR used is therefore not necessarily reflecting the actual VCR for 2019. However, since the seasonal influenza VCR was quite stable over the last couple of years for countries in Europe, we can expect that the margin of error introduced is small. For the USA, the VCR for 2018/19 was available and thus should reflect the VCR for the influenza season 2019/20 quite well.

Fourth, different influenza vaccination sera are used worldwide. Since the vaccines from different companies have differences with respect to efficacy and side effects, this aspect should be also considered in the correlation analysis.

5. Conclusions and outlook

Out study showed that the seasonal influenza VCR for Europe and for the USA is positively correlated with key epidemiological parameters of the current COVID-19 pandemic. This positive correlation can be interpreted as a possible negative effect from seasonal influenza vaccination on individual susceptibility to a SARS-CoV-2 infection and lethal outcome of infection.

To further investigate a possible link between seasonal influenza vaccination and COVID-19, future studies should (i) analyze the individual vaccination history of COVID-19 patients (with special focus on seasonal influenza vaccination) compared to health controls, (ii) extend our study by including also data from other countries, analyzing if correlations exist between the VCR and other epidemiological COVID-19 data, including possible confounding variables in the regression analysis, and to (iii) explore in detail possible physiological mechanisms underlying the associations between influenza vaccination and COVID-19 pathophysiology. In addition, (iv) further studies should investigate if vaccinations other than those against seasonal influenza are associated with COVID-19 epidemiological parameters. A detailed analysis of the vaccination status of COVID-19 infected patients compared to healthy controls is urgently warranted. Finally, we would urge caution among medical professionals in advising people to get vaccinated against seasonal influenza as part of preventative health strategies during the COVID-19 crisis as well as in preparation of upcoming flu-seasons. While the intention to avoid simultaneous viral infection with SARS-CoV-2 and influenza is laudable, a more restrictive approach might be more appropriate until more conclusive evidence is available.

References

1. Wu, F., et al., *A new coronavirus associated with human respiratory disease in China.* Nature, 2020. **579**(7798): p. 265-269.
2. Zhou, P., et al., *A pneumonia outbreak associated with a new coronavirus of probable bat origin.* Nature, 2020. **579**(7798): p. 270-273.
3. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* The Lancet, 2020. **395**(10229): p. 1054-1062.
4. Jordan, R.E., P. Adab, and K.K. Cheng, *Covid-19: risk factors for severe disease and death.* Bmj, 2020: p. m1198.
5. Li, X., et al., *Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan.* Journal of Allergy and Clinical Immunology, 2020.
6. Stachel, A., et al., *Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission.* Clinical Infectious Diseases, 2020.
7. Vardavas, C. and K. Nikitara, *COVID-19 and smoking: A systematic review of the evidence.* Tobacco Induced Diseases, 2020. **18**(March).
8. Shi, Y., et al., *Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan.* Critical Care, 2020. **24**(1).
9. Zheng, Z., et al., *Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis.* Journal of Infection, 2020.
10. Wang, B., et al., *Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis.* Aging, 2020.
11. Yang, J., et al., *Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis.* International Journal of Infectious Diseases, 2020. **94**: p. 91-95.
12. Pareek, M., et al., *Ethnicity and COVID-19: an urgent public health research priority.* The Lancet, 2020. **395**(10234): p. 1421-1422.
13. Guan, W.-j., et al., *Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis.* European Respiratory Journal, 2020. **55**(5): p. 2000547.
14. Yancy, C.W., *COVID-19 and African Americans.* Jama, 2020. **323**(19): p. 1891.
15. Webb Hooper, M., A.M. Nápoles, and E.J. Pérez-Stable, *COVID-19 and Racial/Ethnic Disparities.* Jama, 2020.
16. Li, B., et al., *Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China.* Clinical Research in Cardiology, 2020. **109**(5): p. 531-538.
17. Li, A.Y., et al., *Multivariate Analysis of Factors Affecting COVID-19 Case and Death Rate in U.S. Counties: The Significant Effects of Black Race and Temperature.* medRxiv, 2020.
18. Arokiaraj, M.C., *Correlation of Influenza Vaccination and the COVID-19 Severity.* SSRN Electronic Journal, 2020.
19. Lisewski, A.M., *Association between Influenza Vaccination Rates and SARS-CoV-2 Outbreak Infection Rates in OECD Countries.* SSRN Electronic Journal, 2020.
20. Brunner, I., et al., *The economic and public health impact of influenza vaccinations: contributions of Swiss pharmacies in the 2016/17 and 2017/18 influenza seasons and implications for vaccination policy.* Swiss Med Wkly, 2019. **149**(51-52).
21. Ismail, Z.M., et al., *Enhanced pathogenicity of low-pathogenic H9N2 avian influenza virus after vaccination with infectious bronchitis live attenuated vaccine.* Veterinary World, 2018. **11**(7): p. 977-985.
22. Kelly, H., et al., *Vaccine Effectiveness Against Laboratory-confirmed Influenza in Healthy Young Children: A Case-Control Study.* Pediatr Infect Dis J, 2011. **30**(2): p. 107-11.
23. Cowling, B.J., et al., *Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine.* Clin Infect Dis, 2012. **54**(12): p. 1778-83.
24. Sundaram, M.E., et al., *Influenza vaccination is not associated with detection of noninfluenza respiratory viruses in seasonal studies of influenza vaccine effectiveness.* Clin Infect Dis, 2013. **57**(6): p. 789-93.
25. Feng, S., et al., *Assessment of Virus Interference in a Test-negative Study of Influenza Vaccine Effectiveness.* Epidemiology, 2017. **28**(4): p. 514-524.
26. Wolff, G.G., *Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017-2018 influenza season.* Vaccine, 2020. **38**(2): p. 350-354.
27. Skowronski, D.M., et al., *Influenza vaccine does not increase the risk of coronavirus or other non-influenza*

respiratory viruses: retrospective analysis from Canada, 2010-11 to 2016-17. Clin Infect Dis, 2020.

28. Laurie, K.L., et al., *Interval Between Infections and Viral Hierarchy Are Determinants of Viral Interference Following Influenza Virus Infection in a Ferret Model.* J Infect Dis, 2015. **212**(11): p. 1701-10.
29. Nickbakhsh, S., et al., *Virus–virus interactions impact the population dynamics of influenza and the common cold.* Proceedings of the National Academy of Sciences, 2019. **116**(52): p. 27142-27150.
30. Toplak, N., et al., *Autoimmune response following annual influenza vaccination in 92 apparently healthy adults.* Autoimmunity Reviews, 2008. **8**(2): p. 134-138.
31. Zafrir, Y., N. Agmon-Levin, and Y. Shoenfeld, *Post-Influenza Vaccination Vasculitides.* JCR: Journal of Clinical Rheumatology, 2009. **15**(6): p. 269-270.
32. Watanabe, T., *Henoch-Schönlein purpura following influenza vaccinations during the pandemic of influenza A (H1N1).* Pediatric Nephrology, 2010. **26**(5): p. 795-798.
33. Shimada, S., T. Watanabe, and S. Sato, *A Patient with Kawasaki Disease Following Influenza Vaccinations.* The Pediatric Infectious Disease Journal, 2015. **34**(8).
34. Satoh, E., et al., *Acute Lung Injury Accompanying Alveolar Hemorrhage Associated with Flu Vaccination in the Elderly.* Internal Medicine, 2015. **54**(24): p. 3193-3196.
35. Yamamoto, Y., et al., *Influenza Vaccination-associated Acute Thrombocytopenia and Diffuse Alveolar Hemorrhage: A Case Report.* Internal Medicine, 2020.
36. Cohen, F., et al., *The Challenge of Using Epidemiological Case Count Data: The Example of Confirmed COVID-19 Cases and the Weather.* medRxiv, 2020.
37. Kaashoek, J. and M. Santillaa, *COVID-19 Positive Cases, Evidence on the Time Evolution of the Epidemic or An Indicator of Local Testing Capabilities? A Case Study in the United States.* SSRN Electronic Journal, 2020.
38. Onder, G., G. Rezza, and S. Brusaferro, *Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy.* Jama, 2020.
39. Wikramaratna, P., et al., *Estimating false-negative detection rate of SARS-CoV-2 by RT-PCR.* medRxiv, 2020.
40. Xiao, A.T., Y.X. Tong, and S. Zhang, *False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence.* Journal of Medical Virology, 2020.
41. Wang, H., et al., *Limits of Detection of 6 Approved RT–PCR Kits for the Novel SARS-Coronavirus-2 (SARS-CoV-2).* Clinical Chemistry, 2020.
42. Vogels, C.B.F., et al., *Analytical sensitivity and efficiency comparisons of SARS-COV-2 qRT-PCR primer-probe sets.* medRxiv, , 2020.
43. Kim, S., D.-M. Kim, and B. Lee, *Insufficient Sensitivity of RNA Dependent RNA Polymerase Gene of SARS-CoV-2 Viral Genome as Confirmatory Test using Korean COVID-19 Cases.* preprints, 2020.
44. Etievant, S., et al., *Sensitivity assessment of SARS-CoV-2 PCR assays developed by WHO referral laboratories.* medRxiv, 2020.
45. Wyllie, A.L., et al., *Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs.* medRxiv, 2020.
46. Han, H., et al., *SARS-CoV-2 RNA more readily detected in induced sputum than in throat swabs of convalescent COVID-19 patients.* The Lancet Infectious Diseases, 2020. **20**(6): p. 655-656.
47. Sethuraman, N., S.S. Jeremiah, and A. Ryo, *Interpreting Diagnostic Tests for SARS-CoV-2.* Jama, 2020.
48. Ren, S., et al., *Potential false-negative nucleic acid testing results for Severe Acute Respiratory Syndrome Coronavirus 2 from thermal inactivation of samples with low viral loads.* Clinical Chemistry, 2020.
49. Li, Y., et al., *Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19.* Journal of Medical Virology, 2020.

Appendix

Country	VCR [%]	Year	Age [y]	Source	Deaths [p. Mill]	Cases [p. Mill]	CFR [%]
Austria	20.3	2014	≥ 65	EUROSTAT	70.283	1813.377	3.88
Belgium	58	2014	≥ 65	EUROSTAT	792.606	4852.188	16.34
Bulgaria	2.4	2014	≥ 65	EUROSTAT	17.99	341.371	5.27
Croatia	23	2017	≥ 65	EUROSTAT	23.628	544.91	4.34
Cyprus	32.4	2014	≥ 65	EUROSTAT	19.409	1053.774	1.84
Czech Rep.	20.26	2017	≥ 65	EUROSTAT	28.574	817.445	3.50
Denmark	47	2016/17	≥ 65	ECDC	96.854	1930.526	5.02
Estonia	4.8	2017	≥ 65	EUROSTAT	48.246	1356.914	3.56
Finland	47.4	2016/17	≥ 65	ECDC, EUROSTAT	55.227	1171.87	4.71
France	49.7	2017	≥ 65	EUROSTAT	432.258	2208.599	19.57
Germany	34.8	2016/17	≥ 60, ≥ 65	ECDC, EUROSTAT	97.56	2115.107	4.61
Greece	48.91	2014	≥ 65	EUROSTAT	16.118	273.72	5.89
Hungary	21.9	2017/18	≥ 60	ECDC	49.274	380.732	12.94
Iceland	43.1	2017/18	≥ 60	ECDC	29.304	5283.516	0.55
Ireland	67.6	2017/18	≥ 65	ECDC	320.588	4939.653	6.49
Italy	62.7	2018	≥ 65	EUROSTAT	537.298	3771.074	14.25
Latvia	7.73	2018	≥ 65	EUROSTAT	11.664	543.42	2.15
Lithuania	13.4	2017	≥ 65	EUROSTAT	22.408	585.536	3.83
Luxembourg	37.61	2017	≥ 65	EUROSTAT	174.128	6358.071	2.74
Malta	51.4	2018	≥ 65	EUROSTAT	13.589	1356.619	1.00
Montenegro	12.5	2017	≥ 65	EUROSTAT	14.33	515.873	2.78
Netherland	64.05	2016/17	≥ 65	ECDC, EUROSTAT	337.032	2608.715	12.92
N. Macedonia	6.5	2017	≥ 65	EUROSTAT	53.279	911.02	5.85
Norway	36.2	2016/17	≥ 65	ECDC, EUROSTAT	43.164	1525.112	2.83
Poland	6.87	2016/17	≥ 65	ECDC	25.683	532.227	4.83
Portugal	65	2017/18	≥ 65	ECDC	125.237	2933.496	4.27
Romania	16.1	2017	≥ 65	EUROSTAT	59.83	914.09	6.55
Serbia	11.2	2017	≥ 65	EUROSTAT	34.829	1604.651	2.17
Slovakia	11.4	2016/17	≥ 65	ECDC, EUROSTAT	5.129	275.11	1.86
Slovenia	10.8	2016/17	≥ 65	ECDC, EUROSTAT	50.988	706.132	7.22
Spain	54.7	2017/18	≥ 65	ECDC, EUROSTAT	597.586	4984.239	11.99
Sweden	49.1	2016/17	≥ 65	ECDC	383.295	3185.577	12.03
Switzerland	28.1	2017/19	≥ 64, ≥ 65	BAG, Brunner et al.	189.148	3536.956	5.35
Turkey	7	2016	≥ 65	EUROSTAT	50.38	1820.603	2.77
UK	71.2	2016/18	≥ 65	ECDC	530.919	3696.02	14.36

Table 1: Data for vaccination coverage rate (VCR), incidence, mortality and case fatality rate (CFR) for Europe.

Country	VCR [%]	Year	Age [y]	Source	Deaths [p. Mill]	Cases [p. Mill]	CFR [%]
Alaska	61.2	2018/19	≥ 65	CDC	5.5	1.818	4.82
Alabama	71.5	2018/19	≥ 65	CDC	27.4	4.015	1.02
Arizona	64.4	2018/19	≥ 65	CDC	21.1	4.739	1.67
Arkansas	62.8	2018/19	≥ 65	CDC	18.1	2.210	7.57
California	69	2018/19	≥ 65	CDC	22.4	4.018	1.82
Colorado	70.4	2018/19	≥ 65	CDC	40.3	5.707	8.70
Connecticut	75.4	2018/19	≥ 65	CDC	110	9.091	2.37
Delaware	70.1	2018/19	≥ 65	CDC	86.1	3.833	1.41
Florida	61.1	2018/19	≥ 65	CDC	22.7	4.405	2.88
Georgia	58.4	2018/19	≥ 65	CDC	38.3	4.439	3.56
Hawaii	66.8	2018/19	≥ 65	CDC	4.6	2.174	6.46
Idaho	66.4	2018/19	≥ 65	CDC	14.2	2.817	5.60
Illinois	67.4	2018/19	≥ 60	CDC	81	4.444	6.60
Indiana	67.6	2018/19	≥ 60	CDC	44.5	6.292	7.60
Iowa	72.4	2018/19	≥ 65	CDC	51.3	2.534	8.60
Kansas	68	2018/19	≥ 65	CDC	29.6	2.365	9.60
Kentucky	66	2018/19	≥ 65	CDC	18.5	4.865	10.60
Louisiana	64.3	2018/19	≥ 65	CDC	78.5	7.261	11.60
Maine	67.5	2018/19	≥ 65	CDC	14	3.571	12.60
Maryland	72.7	2018/19	≥ 65	CDC	72	5.000	13.60
Massachusetts	72.1	2018/19	≥ 65	CDC	130.7	6.809	14.60
Michigan	65.6	2018/19	≥ 65	CDC	53.6	9.515	15.60
Minnesota	68	2018/19	≥ 65	CDC	32.3	4.644	16.60
Mississippi	68.3	2018/19	≥ 65	CDC	41.1	4.623	17.60
Missouri	72.9	2018/19	≥ 65	CDC	19.1	5.759	18.60
Montana	67.8	2018/19	≥ 65	CDC	4.5	2.222	19.60
Nebraska	70.5	2018/19	≥ 65	CDC	59.1	1.184	20.60
Nevada	65.3	2018/19	≥ 65	CDC	24	5.000	21.60
New Hampshire	71.5	2018/19	≥ 65	CDC	28.9	5.190	22.60
New Mexico	68.7	2018/19	≥ 65	CDC	30.9	4.531	23.60
New York	66.3	2018/19	≥ 65	CDC	183.2	8.079	24.60
North Carolina	72.9	2018/19	≥ 65	CDC	19.6	3.571	25.60
North Dakota	68.6	2018/19	≥ 65	CDC	29.2	2.397	26.60
Ohio	70	2018/19	≥ 65	CDC	25.8	6.202	27.60
Oklahoma	75.5	2018/19	≥ 65	CDC	14.4	5.556	28.60
Oregon	68.1	2018/19	≥ 65	CDC	9	3.333	29.60
Pennsylvania	73.8	2018/19	≥ 65	CDC	54.1	7.024	30.60
Rhode Island	74.1	2018/19	≥ 65	CDC	128.1	4.059	31.60
South Carolina	68.9	2018/19	≥ 65	CDC	18.2	4.396	32.60
South Dakota	67.1	2018/19	≥ 65	CDC	47.2	1.059	33.60
Tennessee	66.9	2018/19	≥ 65	CDC	27.8	1.799	34.60
Texas	67.5	2018/19	≥ 65	CDC	18.3	2.732	35.60
Utah	64.2	2018/19	≥ 65	CDC	24.6	1.220	36.60
Vermont	69.4	2018/19	≥ 65	CDC	15.2	5.921	37.60
Virginia	71.4	2018/19	≥ 65	CDC	40	3.250	38.60
Washington	71.7	2018/19	≥ 65	CDC	25.1	5.578	39.60
West Virginia	69.1	2018/19	≥ 65	CDC	8.9	4.494	40.60
Wisconsin	66	2018/19	≥ 65	CDC	23.8	3.361	41.60
Wyoming	63.9	2018/19	≥ 65	CDC	13.8	1.449	42.60

Table 2: Data for vaccination coverage rate (VCR), incidence, mortality and case fatality rate (CFR) for the USA.

Country	PPA65y [%]
Austria	19
Belgium	19
Bulgaria	21
Croatia	20
Cyprus	14
Czech Rep.	20
Denmark	20
Estonia	20
Finland	22
France	20
Germany	21
Greece	22
Hungary	19
Iceland	14
Ireland	14
Italy	23
Latvia	20
Lithuania	20
Luxembourg	14
Malta	19
Montenegro	15
Netherland	19
N. Macedonia	14
Norway	17
Poland	28
Portugal	22
Romania	18
Serbia	20
Slovakia	16
Slovenia	20
Spain	19
Sweden	20
Switzerland	18
Turkey	9
UK	18

Table 3: Data for the percent of population ages 65 and older (PPA65y) for Europe. Italy has the highest PPA65y, Turkey the lowest.