Positive association between COVID-19 deaths and influenza vaccination rates in elderly people worldwide

Christian Wehenkel [Corresp. 1]

[1] Instituto de Silvicultura e Industria de la Madera, Universidad Juárez del Estado de Durango, Durango, Mexico

Corresponding Author: Christian Wehenkel
Email address: wehenkel@ujed.mx

Background. The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis, directly and indirectly impacting all spheres of human life. Some pharmacological measures have been proposed to prevent COVID-19 or reduce its severity, such as vaccinations. Previous reports indicate that influenza vaccination appears to be negatively correlated with COVID-19-associated mortality, perhaps as a result of heterologous immunity or changes in innate immunity. The understanding of such trends in correlations could prevent deaths from COVID-19 in the future. The aim of this study was therefore to analyze the association between COVID-19 related deaths and influenza vaccination rate (IVR) in elderly people worldwide, and a negative association was expected. **Methods.** To determine the association between COVID-19 deaths and influenza vaccination, available data sets from countries with more than 0.5 million inhabitants were analyzed (in total 39 countries).To accurately estimate the influence of IVR on COVID-19 deaths and mitigate effects of confounding variables, a sophisticated ranking of the importance of different variables was performed, including as predictor variables IVR and some potentially important geographical and socioeconomic variables as well as variables related to non-pharmaceutical intervention. **Results.** The results showed a positive association between COVID-19 deaths and IVR of people ≥ 65 years-old. Further exploration is needed to explain these findings, and additional work on this line of research may lead to prevention of deaths associated with COVID-19.

1 **Positive association between COVID-19 deaths and influenza vaccination**
2 **rates in elderly people worldwide**
3

4 Christian Wehenkel[1]*
5

6 [1]Instituto de Silvicultura e Industria de la Madera, Universidad Juárez del Estado de Durango,
7 Durango, Mexico
8

9 Corresponding Author:
10 Christian Wehenkel, Boulevard 501, Ciudad Universitaria, 34120 Durango, Dgo., Mexico
11 Email address: wehenkel@ujed.mx
12

13 ## Abstract

14

15 **Background.** The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute

16 respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis, directly

17 and indirectly impacting all spheres of human life. Some pharmacological measures have been

18 proposed to prevent COVID-19 or reduce its severity, such as vaccinations. Previous reports

19 indicate that influenza vaccination appears to be negatively correlated with COVID-19-

20 associated mortality, perhaps as a result of heterologous immunity or changes in innate

21 immunity. The understanding of such trends in correlations could prevent deaths from COVID-

22 19 in the future. The aim of this study was therefore to analyze the association between COVID-

23 19 related deaths and influenza vaccination rate (IVR) in elderly people worldwide, and a

24 negative association was expected.

25 **Methods.** To determine the association between COVID-19 deaths and influenza vaccination,

26 available data sets from countries with more than 0.5 million inhabitants were analyzed (in total

27 39 countries).To accurately estimate the influence of IVR on COVID-19 deaths and mitigate

28 effects of confounding variables, a sophisticated ranking of the importance of different variables

29 was performed, including as predictor variables IVR and some potentially important

30 geographical and socioeconomic variables as well as variables related to non-pharmaceutical

31 intervention.

32 **Results.** The results showed a positive association between COVID-19 deaths and IVR of people

33 ≥ 65 years-old. Further exploration is needed to explain these findings, and additional work on

34 this line of research may lead to prevention of deaths associated with COVID-19.

Introduction

35

36

37 The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory

38 syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis (Yuen et al. 2020),

39 directly and indirectly impacting all spheres of human life (Ozili & Arun 2020). More than

40 15,300,000 confirmed cases including more than 630,000 deaths have been documented

41 worldwide, affecting 213 countries and territories around the world (https://covid19.who.int/).

42 Determining the factors influencing the severity of COVID-19 is important (Armengaud et al.

43 2020). Although COVID-19 disease does not only affect elderly people, the severity of

44 symptoms increases with age (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-

45 precautions/older-adults.html). In the United States, people 65 years and older account for 45%

46 of hospitalizations, 53% of admissions to intensive care units and 80% of deaths (Le Couteur,

47 Anderson & Newman 2020).

48 Several other risk factors have been found for severe COVID-19, such as comorbidities,

49 dyspnea, chest pain, cough, expectoration, decreased lymphocytes, and increased inflammation

50 indicators (Li et al. 2020). Hypertension, diabetes, coronary heart disease, cerebrovascular

51 illness, chronic obstructive pulmonary disease and kidney dysfunction worsen clinical outcomes

52 (Ji et al. 2020). Low socioeconomic status is an additional risk factor, given the common

53 association between poverty and health issues, low access to healthy food, overcrowding, and

54 lack of labor privileges to practice social distancing (Yancy 2020).

55 In response to the increasing numbers of cases of infection and deaths, numerous non-

56 pharmaceutical interventions have been implemented, including social distancing, border

57 closures, school closures, measures to isolate symptomatic individuals and their contacts, and

58 large-scale lockdowns of populations (Courtemanche et al. 2020; Flaxman et al. 2020). Some

59 pharmacological measures have also (often controversially) been proposed in order to prevent

60 COVID-19 disease or reduce its severity, such as the use of remdesivir (e.g., Beigel et al. 2020),

61 dexamethasone (RECOVERY Collaborative Group 2020), adjunctive therapies

62 (https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_85.pdf), Vitamin D

63 (e.g., Grant et al. 2020), drugs (e.g., Jakhar and Kaur 2020; Wright et al. 2020) and COVID-19

64 vaccines (e.g., Graham 2020, https://www.who.int/publications/m/item/draft-landscape-of-covid-
65 19-candidate-vaccines.

66 The term "heterologous immunity" is applied when an infection by one pathogen can induce
67 and/or alter the immune response against another unrelated pathogen. Heterologous immunity
68 can improve or decrease protective immunity against a given pathogen, and/or cause severe
69 immunopathology or tolerance to self-antigens (Goodridge et al. 2016, Agrawal 2019). Arokiaraj
70 (2020) reported a negative correlation between influenza vaccination rates and COVID-19
71 related mortality and morbidity. Marín-Hernández et al. (2020) also showed epidemiological
72 evidence of an association between higher influenza vaccine uptake by elderly people and lower
73 percentage of COVID-19 deaths in Italy ($R^2 = 0.35$, $p = 0.0051$). In a study analyzing 92,664
74 clinically and molecularly confirmed COVID-19 cases in Brazil, Fink et al. (2020) reported that
75 patients who received a recent flu vaccine experienced on average 8% lower odds of needing
76 intensive care treatment (95% CIs [0.86, 0.99]), 18% lower odds of requiring invasive
77 respiratory support (0.74, 0.88), and 17% lower odds of death (0.75, 0.89).

78 Moreover, Pawlowski et al. (2020) analyzed the immunization records of 137,037 individuals
79 who tested positive in a SARS-CoV-2 PCR. They found that polio, Hemophilus influenzae type-
80 B (HIB), measles-mumps-rubella (MMR), varicella, pneumococcal conjugate (PCV13), geriatric
81 flu, and hepatitis A / hepatitis B (HepA-HepB) vaccines, which had been administered in the past
82 one, two, and five years, were associated with decreased SARS-CoV-2 infection rates, even after
83 taking into account the geographic SARS-CoV-2 incidence and testing rates, demographics,
84 comorbidities, and a number of other vaccinations. In addition, age, race/ethnicity, and blood
85 group stratified analyses showed a significantly lower rate of SARS-CoV-2 infection among
86 black individuals who had been given the PCV13 vaccine, with a relative risk of 0.45 at the 5-
87 year time horizon analyzed (n = 653, 95% CI = (0.32, 0.64), p = 0.000069).

88 By contrast, in a study with 6,120 subjects, Wolff (2020) reported that influenza vaccination was
89 significantly associated with a higher risk of some other respiratory diseases, due to virus
90 interference. In a specific examination of non-influenza viruses, the odds of coronavirus
91 infection (but not the COVID-19 virus) in vaccinated individuals were significantly higher, when
92 compared to unvaccinated individuals (odds ratio = 1.36).

93   Given that heterologous immunity could improve protective immunity against COVID-19 and,

94   thus, prevent COVID-19 deaths in the future, the aim in this study was to analyze the possible

95   association between COVID-19 deaths and the influenza vaccination rate in elderly people

96   worldwide, with a negative association expected.

Materials & Methods

97

98

99   To look for an association between COVID-19 deaths and influenza vaccination, available data

100   sets from 39 countries, each with ≥ 0.5 million inhabitants, were analyzed. In smaller states (i.e.,

101   < 0.5 million inhabitants), the rate of erroneous identification of COVID-19 deaths may be

102   particularly high due to the lack of expertise, measuring devices and experience. Moreover, in

103   such microstates small absolute changes in COVID-19 deaths may result in extreme values of

104   relative indices, such as COVID-19 deaths per million inhabitants (DP) and COVID-19 Case

105   Fatality Ratio (CFR). The variables DP and CFR, based on confirmed infected people per million

106   inhabitants (CIP) in 2020, COVID-19 tests per million inhabitants, and influenza vaccination rate

107   (IVR) (%) in people ≥ 65 years old in 2019 or latest available data were analyzed (Table 1). The

108   DP, CIP and CFR data were recorded from the public web site

109   https://www.worldometers.info/coronavirus/. CFR was calculated as the rate of DP per CIP. IVR

110   data were also taken from https://data.oecd.org/healthcare/influenza-vaccination-rates.htm,

111   https://oecdcode.org/disclaimers/israel.html and https://www.statista.com/chart/16575/global-flu-

112   immunization-rates-vary/ (retrieved on July 25, 2020). Vietnam's 2017 IVR was recorded from

113   Nguyen et al. (2020), and Singapore's 2016/2017 IVR from

114   https://www.todayonline.com/commentary/why-singapores-adult-vaccination-rate-so-low.

115   As the relationship between DP and the number of people tested for COVID-19 was not

116   statistically significant, the DP data set was not modified (corrected). To analyze the data, the

117   non-parametric Spearman's correlation coefficient (r_s) and its R_S^2 and respective p-value (2-

118   tailed) were first applied to determine any association between DP and CFR with IVR, using R

119   (R Core Team 2017). Regression curves were then created by Generalized additive model

120   (GAM) using the "ggplot2" package and function (method = 'gam') (Wickham et al. 2013), also

121   in R.

122   As the analysis included countries with different socioeconomic status, demographic structure,

123   urban/rural settings, time of arrival of the pandemic and national control strategies, there may be

124   complex interactions between IVR and other correlated predictor variables. With the aim of

125   accurately estimating the influence of IVR on DP and CFR and mitigating the effects of

126   confounding variables, variable importance ranking was performed, including as predictor

127   variables IVR and some potentially important geographical, socioeconomic and non-

128   pharmaceutical-intervention variables (Escobar et al. 2020). The centroid longitudes (º) and

129   latitudes (º) of each country were used as geographical variables calculated by the "rgeos" and

130   "rworldmap" packages, along with the "getMap" and "gCentroid" functions, implemented in *R*

131   (version 3.3.4; R Development Core Team, 2017). For each country considered, the study

132   recorded socioeconomic variables as the degree of urbanization (DUR) in 2020

133   (https://www.cia.gov/library/publications/the-world-factbook/fields/349.html), the population

134   density (PD) in 2018 (https://data.worldbank.org/indicator/EN.POP.DNST), the Human

135   Development Index (HDI) in 2018 (http://hdr.undp.org/en/composite/HDI) and the percentage of

136   elderly people (PEP) in 2019

137   (https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS?name_desc=false), which were all

138   retrieved on July 13, 2020 (Table 2). Finally, two aspects were recorded as Covid-19 prevention

139   measures, i.e. the degree of requirement to use masks (mask) in public (with three degrees: none,

140   parts of country, full country) (https://masks4all.co/what-countries-require-masks-in-public/) and

141   the lockdown degree (lockdown) (with three levels: no lockdown, partial lockdown, nationwide

142   lockdown); all of these sources and the noted in Table 3 were consulted on Aug 13, 2020.

143

144   Variable importance ranking was carried out using the "party" package and the non-parametric

145   random forest function "cforest", along with Out of bag (OOB) score (with the default option

146   "controls = cforest_unbiased" and the conditional permutation importance "varimp(obj,

147   conditional = TRUE)"). Following the permutation principle of the "mean decrease in accuracy"

148   importance, this machine learning algorithm guarantees unbiased variable importance for

149   predictor variables of different types (Strobl et al. 2008).

150

151   With the aim of mitigating the effects of confounding factors, IVR, DP and CFR evaluations

152   were also conducted for countries with similar social conditions (> 50% of DUR, HDI of > 0.80,

153   > 15% of PEP, and PD between 25 and 350 inhabitants per km^2) (Escobar et al. 2020) and for

154   countries with similar longitudes (10 - 20º, parts of Europe and 100 - 140º, East and Southeast

155   Asia along with Australia and New Zealand).

156   As IVR and the other eight predictor variables were not strongly correlated ($|r_s| \leq 0.57$; r_s (IVR x

157   DUR) = +0.52; r_s (IVR x Long) = -0.46; r_s (IVR x HDI) = 0.36), these variables were therefore

158   included in non-parametric Random Forest (RF) models of DP and CFR, including a 5-fold cross

159   validation approach, repeated 30 times using the package "caret" together with the function

160   "train" (Venables and Ripley, 1999; Williams et al., 2018,

161   http://topepo.github.io/caret/index.html) in R software. The goodness-of-fit of the regression

162   model was evaluated using the (pseudo) coefficient of determination (R^2) and the root mean

163   square error (RMSE).

164

165   **Results**

166   For the 26 European countries considered , the results indicated that COVID-19 deaths per

167   million inhabitants (DP) and the COVID-19 Case Fatality Ratio (CFR) were positively and

168   statistically significantly associated with influenza vaccination rate (IVR) in people ≥ 65 years-

169   old in 2019 or latest data available (r_s (IVR x DP) = +0.62 with $p = 0.0008$, R_s^2(IVR x DP) =

170   0.38; r_s (IVR x CFR) = +0.50 with $p = 0.01$, R_S^2(IVR x CFR) = 0.25) (Figs. 1 and 2, Table 4). In

171   evaluations including only countries with similar social conditions, r_s (IVR x DP) was equal to

172   +0.65 ($p = 0.002$, N = 20) and r_s (IVR x CFR) +0.48 ($p = 0.03$, N = 20). In analyses including

173   only countries with similar longitude of the country centroid (Long), r_s (IVR x DP) was equal to

174   +0.83 ($p = 0.003$, N = 10) (Long from 10 to 20º) and r_s (IVR x DP) +0.76 ($p = 0.046$, N = 7)

175   (Long from 100 to 140º).

176   At worldwide level (39 countries studied), the positive associations between DP and IVR were

177   also statistically significant (r_s (IVR x DP) = +0.49 with $p = 0.0016$, R_s^2 (IVR x DP) = 0.24) (Fig.

178   3, Table 5). However, the relationships between IVR and CFR were not statistically significant.

179   In the IVR interval from 7 to 50 %, the association was not significant, although a trend for DP

180   and CFR to be positively associated with IVR was observed. DP and CFR varied strongly when

181   IVR was 50% or higher (Figs. 1-3).

182   Worldwide, the unbiased ranking showed the degree of importance of each variable analyzed.

183   The variables Long (with 55.9 and 52.3 %) and IVR (with 36.3 and 24.5 %) were by far the most

184   important of the nine variables used to predict DP and CFR, respectively. The degree of

185 urbanization (DUR) in 2020 was the third most important variable, with an importance of 5.7%

186 for predicting DP. The percentage of elderly people (PEP) in 2019 was the third most important

187 variable (11.5%) in the CFR model (Figs. 4 and 5). The nine predictor variables considered in

188 this study explained 63% of the variation in DP (RMSE =161.9) and 43 % of the variation in

189 CFR (RMSE = 0.039).

190

191 **Discussion**

192

193 Contrary to expectations, the present worldwide analysis and European sub-analysis do not

194 support the previously reported negative association between COVID-19 deaths (DP) and

195 influenza vaccination rate (IVR) in elderly people, observed in studies in Brazil and Italy (Fink et

196 al. 2020; Marín-Hernández et al. 2020). Previous studies attributed the beneficial effect of

197 influenza vaccination in reducing severity of COVID-19 disease to better prevention of potential

198 influenza-SARS-CoV-2 coinfections (Arokiaraj 2020) and, more likely, to changes in innate

199 immunity (Netea et al. 2020). The innate immune response induced by recent vaccination could

200 result in more rapid and efficient SARS-CoV-2 clearance, preventing progressive dissemination

201 into lower areas of lung tissues (Fink et al. 2020).

202 The negative association between the proportion of DP and IVR found in Italy was explained as

203 probably caused by i) a higher influenza vaccine rate occurring in higher economic groups with

204 overall better health, ii) chance, iii) a relationship with seasonal respiratory virus infections, or

205 iv) an unrelated mechanistic association (Marín-Hernández et al. 2020). However, the induction

206 of cross-neutralizing antibodies and T-cells that directly target other RNA viruses like SARS-

207 CoV-2 and cross-protection seem unlikely, given the extraordinary diversity of influenza viruses

208 (Fink et al. 2020).

209 Therefore, the above-mentioned arguments cannot explain the positive, direct or indirect

210 relationship between IVR and both DP and CFR found in this study, which was confirmed by an

211 unbiased ranking variable importance (Figs. 4 and 5) using RF models. The influenza vaccine

212 may increase influenza immunity at the expense of reduced immunity to SARS-CoV-2 by some

213 unknown biological mechanism, as suggested by Cowling et al. (2012) for non-influenza

214 respiratory virus. Alternatively, weaker temporary, non-specific immunity after influenza virus

215 infection could cause this positive association due to stimulation of the innate immune response

216 during and for a short time after infection (McGill et al. 2009; Khaitov et al. 2009). People who

217 had received the influenza vaccination would have been protected against influenza but not

218 against other virus infections, due to reduced non-specific immunity in the following weeks

219 (Cowling et al. 2012), probably caused by virus interference (Isaacs & Lindenmann 1957;

220 Seppälä et al. 2011; Wolff 2020). Although existing human vaccine adjuvants have a high level

221 of safety, specific adjuvants in influenza vaccines should also be tested for adverse reactions

222 (Petrovsky 2015).

223 The strong variation in DP and CFR from an IVR of about 50% or larger may be the result of

224 interactions among the different measures applied in the analyzed countries (Figs. 1-3), e.g.

225 initiation of interventions, emergency plans and health systems against COVID-19. For example,

226 Australia and South Korea had a very low DP and CFR compared with Belgium and United

227 Kingdom (Table 1).

228 The high correlation between the longitude of the country centroid and DP and CFR emphasize a

229 significant increase in CP and CFR from eastern to western regions in the world (Table 5, Figs. 4

230 and 5), as confirmed by Leung et al. (2020) and Skórka et al. (2020). Longitude could act as a

231 proxy for variables such as lifestyle, social behavior, genetics, geographically isolated and

232 remote populations, which may also be associated with CP and CFR. In the severe 1918–1919

233 influenza pandemic, remote or isolated populations were also most affected, at least partly

234 because of a lack of prior immunity in locations that had not been recently affected by any form

235 of influenza (Mathews et al. 2009). Therefore, crossing geographical and ecological barriers is

236 also is a key factor in spreading diseases (Hallatschek & Fisher 2014; Murray et al. 2015).

237 Both DP and CFR were weakly and positively correlated ($p < 0.05$) with the absolute value of

238 geographical latitude (abs(Lat)), degree of urbanization (DUR), percentage of elderly people

239 (PEP) and population density (Tables 4 and 5). In a global analysis, Escobar et al. (2020) also

240 found positive associations between COVID-19 mortality and the percentage of population aged

241 ≥ 65 years and urbanization, but still more strongly with the Human Development Index. Leung

242 et al. (2020) also reported positive associations between latitude, temperature by week and by

243 month prior to the first reported COVID-19 case. Lower temperature at northern latitudes was a

244 strong independent predictor of national COVID-19 mortality.

245 Although countywide lockdowns and use of face masks by the general public should reduce
246 COVID-19 transmission (Conyon, He & Thomsen 2020; Eikenberry et al. 2020), the variables
247 lockdown degree and the degree of requirement for mask use in public were not associated with
248 DP and CFR in the present study (Tables 4 and 5, Figs 4 and 5). Leffler et al. (2020) reported in
249 a global study that internal lockdown requirements were not associated with mortality, but that in
250 countries that recommended use of face masks early on at the national level, the COVID-19
251 death rate was lower than expected.

252 As is often the case, the success of these two interventions could be a matter of the details.
253 Although countywide lockdowns were proclaimed in many countries, the restrictive measures
254 and their implementations differed in degree, strictness and implementation date in relation to the
255 advance of the disease (see references in Table 3). Also, although the use of face masks may be
256 similar in many countries, the mask quality and correct use may differ from country to country.
257 Fischer et al. (2020) found that speaking through some types of face mask seemed to disperse the
258 largest droplets into a multitude of smaller droplets which remain in the air longer than large
259 droplets. This explains the apparent rise in droplet count relative to no mask. Thus, the use of
260 ineffective masks could be counterproductive.

261 **Conclusions**
262
263 Given the positive relationship between influenza vaccination rate and the number of deaths per
264 million found in this study, further exploration would be valuable to explain these findings and to
265 make conclusions. Additional work on this line of research may yield results to improve
266 prevention of COVID-19 deaths.

267 **Acknowledgements**
268
269 I am grateful to María del Socorro González-Elizondo and Jose Ciro Hernández-Díaz for their
270 comments on the manuscript, and to Dr. Daniela Marín-Hernández and an anonymous reviewer
271 for their careful review and insightful comments.
272
273 **References**
274

275 Agrawal B. 2019. Heterologous immunity: Role in natural and vaccine-induced resistance to

276 infections. *Frontiers in immunology* 10.

277 Armengaud J, Delaunay-Moisan A, Thuret JY, Van Anken E, Acosta-Alvear D, Aragón T, ... ,

278 Courcol R. 2020. The importance of naturally attenuated SARS-Cov-2 in the fight against

279 Covid-19. *Environmental Microbiology* 22(6): 1997-2000.

280 Arokiaraj MC. 2020. Correlation of Influenza Vaccination and the COVID-19 Severity.

281 *Available at SSRN* https://ssrn.com/abstract=3572814 or http://dx.doi.org/10.2139/ssrn.3572814

282 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY,

283 Luetkemeyer A, Kline S, Lopez de Castilla D. 2020. Remdesivir for the treatment of Covid-19 -

284 preliminary report. New England Journal of Medicine.

285 Conyon MJ, He L, Thomsen S. 2020. Lockdowns and COVID-19 deaths in Scandinavia.

286 Available at SSRN 3616969.

287 Courtemanche C, Garuccio J, Le A, Pinkston J, Yelowitz A. 2020. Strong Social Distancing

288 Measures in the United States Reduced The COVID-19 Growth Rate: Study evaluates the impact

289 of social distancing measures on the growth rate of confirmed COVID-19 cases across the

290 United States. *Health Affairs* 10: 1377.

291 Cowling BJ, Fang VJ, Nishiura H, Chan KH, Ng S, Ip DK, ... , Peiris JM. 2012. Increased risk of

292 noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine.

293 *Clinical Infectious Diseases* 54(12): 1778-1783.

294 Eikenberry SE, Mancuso M, Iboi E, Phan T, Eikenberry K, Kuang Y, ... Gumel AB. 2020. To

295 mask or not to mask: Modeling the potential for face mask use by the general public to curtail the

296 COVID-19 pandemic. Infectious Disease Modelling.

297 Escobar LE, Molina-Cruz A, Barillas-Mury C. 2020. BCG vaccine protection from severe

298 coronavirus disease 2019 (COVID-19). *Proc Natl Acad Sci USA* 117(30):17720-17726.

299 doi:10.1073/pnas.2008410117

300 Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer AP, Daubenberger C, Brentani A. 2020.

301 Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19

302 patients in Brazil. *medRxi*.

303 Fischer EP, Fischer MC, Grass D, Henrion I, Warren WS, Westman E. 2020. Low-cost

304 measurement of facemask efficacy for filtering expelled droplets during speech. Science

305 Advances, eabd3083.

306 Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, ... Monod M. 2020.

307 Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature*:1-5.

308 Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, ... Wilson CB. 2016.

309 Harnessing the beneficial heterologous effects of vaccination. *Nature Reviews Immunology*

310 16(6): 392-400.

311 Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, ... Monod M. 2020.

312 Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature*:1-5.

313 Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, ... Wilson CB. 2016.

314 Harnessing the beneficial heterologous effects of vaccination. *Nature Reviews Immunology*

315 16(6): 392-400.

316 Graham BS 2020. Rapid COVID-19 vaccine development. *Science* 368(6494): 945-946.

317 Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. 2020.

318 Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19

319 infections and deaths. *Nutrients* 12(4): 988.

320 Hallatschek O, Fisher DS. 2014. Acceleration of evolutionary spread by long-range dispersal.

321 PNAS 111: E4911–E4919.

322 Isaacs A., Lindenmann J. 1957. Virus interference. I. The interferon. Proceedings of the Royal

323 Society of London. *Series B-Biological Sciences* 147(927): 258-267.

324 Jakhar D, Kaur I. 2020. Potential of chloroquine and hydroxychloroquine to treat COVID-19

325 causes fears of shortages among people with systemic lupus erythematosus. *Nature medicine*

326 26(5): 632-632.

327 Ji HL, Zhao R, Matalon S, Matthay MA. 2020. Elevated plasmin (ogen) as a common risk factor

328 for COVID-19 susceptibility. *Physiological reviews*.

329 Khaitov M, Laza-Stanca V, Edwards MR, Walton RP, Rohde G, Contoli M., ... , Johnston SL.

330 2009. Respiratory virus induction of alpha-, beta-and lambda-interferons in bronchial epithelial

331 cells and peripheral blood mononuclear cells. *Allergy* 64(3): 375-386.

332 Le Couteur DG, Anderson RM, Newman AB. 2020. COVID-19 is a disease of older people. *J

333 Gerontol A Biol Sci Med Sci* 10.

334 Leffler CT, Ing EB, Lykins JD, Hogan MC, McKeown CA, Grzybowski A. 2020. Association of

335 country-wide coronavirus mortality with demographics, testing, lockdowns, and public wearing

336 of masks. Update June 2, 2020. *medRxiv*.

337 Leung NY, Bulterys MA, Bulterys PL. 2020. Predictors of COVID-19 incidence, mortality, and

338 epidemic growth rate at the country level. *medRxiv*.

339 Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. 2020. The clinical and chest CT features

340 associated with severe and critical COVID-19 pneumonia. *Investigative Radiology*.

341 Marín-Hernández D, Schwartz RE, Nixon DF. 2020. Epidemiological Evidence for Association

342 between Higher Influenza Vaccine Uptake in the Elderly and Lower COVID-19 Deaths in Italy.

343 *Journal of Medical Virology*.

344 McGill J, Heusel JW, Legge KL. 2009. Innate immune control and regulation of influenza virus

345 infections. *Journal of Leukocyte Biology* 86(4): 803-812.

346 Murray KA, Preston N, Allen T, Zambrana-Torrelio C, Hosseini PR, Daszak P. 2015. Global

347 biogeography of human infectious diseases. Proceedings of the National Academy of Sciences

348 112(41): 12746-12751.

349 Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E., ... , Riksen

350 NP. 2020. Defining trained immunity and its role in health and disease. *Nature Reviews*

351 *Immunology* 1-1

352 Nguyen TTM., Lafond KE, Nguyen TX, Tran PD, Nguyen HM, Do TT, ... , McFarland JW.

353 2020. Acceptability of seasonal influenza vaccines among health care workers in Vietnam in

354 2017. *Vaccine* 38(8): 2045-2050.

355 Petrovsky N. 2015. Comparative safety of vaccine adjuvants: a summary of current evidence and

356 future needs. *Drug safety* 38(11): 1059-1074.

357 Ozili PK, Arun T. 2020. Spillover of COVID-19: impact on the Global Economy. *Available at*

358 *SSRN 3562570*.

359 Pawlowski C, Puranik A, Bandi H, Venkatakrishnan AJ, Agarwal V, Kennedy R, ... Badley AD.

360 2020. Exploratory analysis of immunization records highlights decreased SARS-CoV-2 rates in

361 individuals with recent non-COVID-19 vaccinations. *medRxiv*.

362 R Core Team. 2017. R: A language and environment for statistical computing. R Foundation for

363 Statistical Computing, Vienna, Austria. URL http://www.R-project.org.

364 RECOVERY Collaborative Group, 2020. Dexamethasone in hospitalized patients with Covid-

365 19—preliminary report. *New England Journal of Medicine*.

366 Seppälä E, Viskari H, Hoppu S, Honkanen H, Huhtala H, Simell O, ..., Hyöty H. (2011). Viral

367 interference induced by live attenuated virus vaccine (OPV) can prevent otitis media. *Vaccine*

368 29(47): 8615-8618.

369 Skórka P, Grzywacz B, Moroń D, Lenda M. 2020. The macroecology of the COVID-19

370 pandemic in the Anthropocene. *Plos one* 15(7): e0236856.

371 Strobl C, Boulesteix AL, Kneib T, Augustin T, Achim Zeileis A. 2008. Conditional Variable

372 Importance for Random Forests. *BMC Bioinformatics* 9: 307.

373 http://www.biomedcentral.com/1471-2105/9/307

374 Mathews JD, Chesson JM, McCaw JM, McVernon J. 2009. Understanding influenza

375 transmission, immunity and pandemic threats. *Influenza and other respiratory viruses* 3(4): 143-

376 149.

377 Venables WN, Ripley BD. 1999. Chapter 10: Tree-based methods. *In Modern Applied Statistics*

378 *with S-PLUS*. 3rd ed. *Eds*. J. Chambers, W. Eddy, W. Härdle, S. Sheather, L. Tierney. Statistics

379 and Computing (Springer-Verlag, Press), New York, NY, 303-327. doi: 10.1007/978-1-4757-

380 3121-7_10

381 Wickham H, Chang W, Wickham MH. 2013. Package 'ggplot2'. Computer software manual.

382 Retrieved from http://cran.r-project.org/web/packages/ggplot2/ggplot2.pdf (R package version

383 0.9. 3.1) Google Scholar.

384 Williams CK, Engelhardt A, Cooper T, Mayer Z, Ziem A, Scrucca L, Kuhn MM. 2018. Package

385 'caret'.

386 Wolff GG. 2020. Influenza vaccination and respiratory virus interference among Department of

387 Defense personnel during the 2017–2018 influenza season. *Vaccine* 38(2): 350-354.

388 Wright C, Ross C, McGoldrick N. 2020. Are hydroxychloroquine and chloroquine effective in

389 the treatment of SARS-COV-2 (COVID-19)? *Evidence-based dentistry* 21(2): 64-65.

390 Yancy CW. 2020. COVID-19 and African Americans. *Jama*.

391 Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. 2020. SARS-CoV-2 and COVID-19: The most

392 important research questions. *Cell & bioscience* 10(1): 1-5.

393 Venables WN, Ripley BD. 1999. Chapter 10: Tree-based methods. *In Modern Applied Statistics*

394 *with S-PLUS*. 3rd ed. *Eds*. J. Chambers, W. Eddy, W. Härdle, S. Sheather, L. Tierney. Statistics

395 and Computing (Springer-Verlag, Press), New York, NY, 303-327. doi: 10.1007/978-1-4757-

396 3121-7_10

Figure 1

Association of COVID-19 deaths per million inhabitants (DP) up to July 25, 2020 with influenza vaccination rate (IVR) of people aged 65 and older in 2019 or latest data available in Europe.

Association of COVID-19 deaths per million inhabitants (DP) up to July 25, 2020 with influenza vaccination rate (IVR) of people aged 65 and older in 2019 or latest data available in Europe (26 countries with more than 0.5 million inhabitants). The mean (blue line) and standard deviation (grey area) are based on generalized additive models (GAM); r_s (IVR x DP) = +0.687 with p = 0.00015.

Figure 2

Association of COVID-19 Case Fatality Ratio (CFR) up to July 25, 2020 with influenza vaccination rate (IVR) of people aged 65 and older in 2019 or latest data available in Europe.
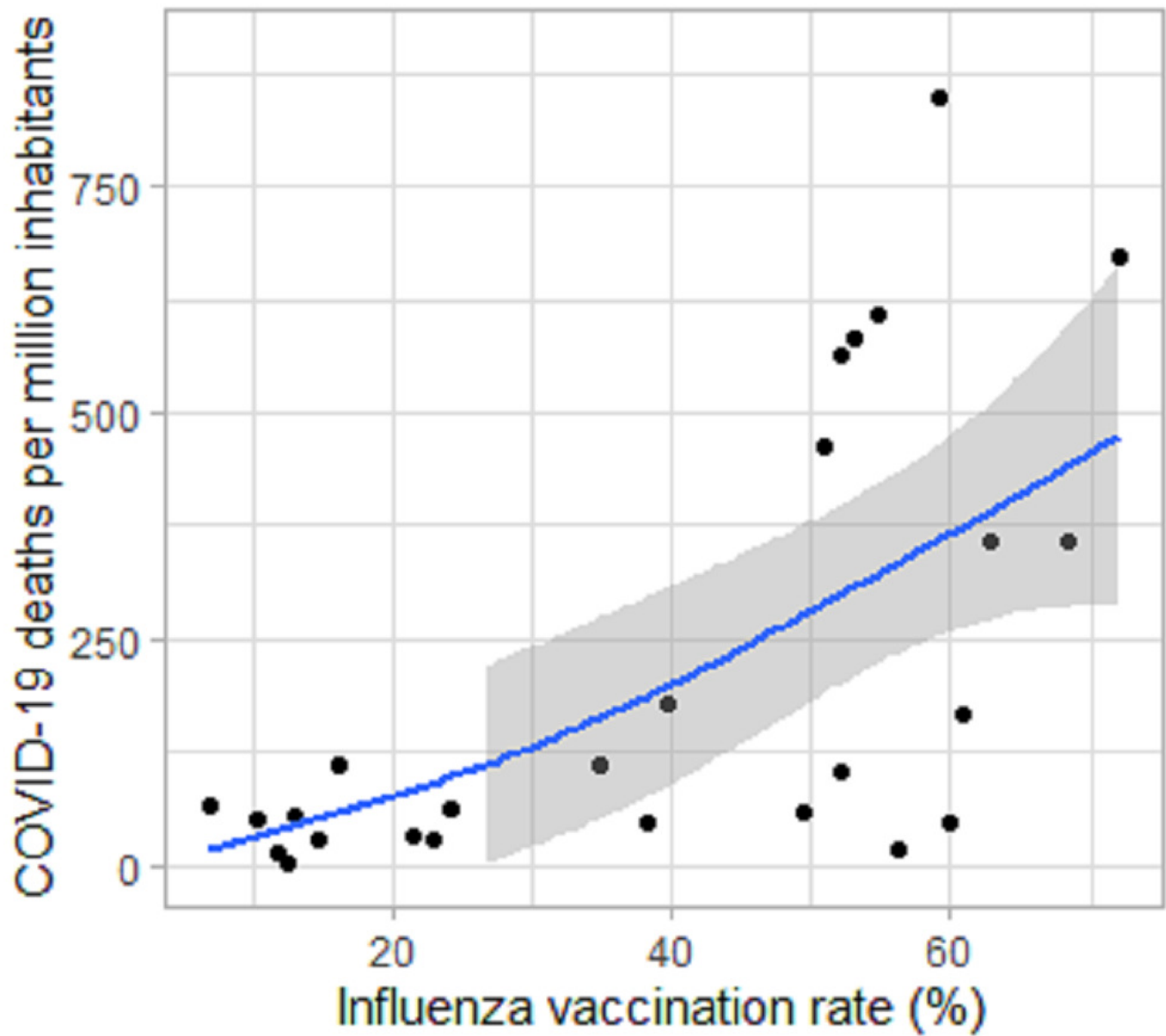
Association of COVID-19 Case Fatality Ratio (CFR) up to July 25, 2020 with influenza vaccination rate (IVR) of people aged 65 and older in 2019 or latest data available in Europe (26 countries with more than 0.5 million inhabitants). The mean (blue line) and standard deviation (grey area) are based on generalized additive models (GAM); r_s(IVR x CFR) = +0.629 with p = 0.00075.

Figure 3

Association of COVID-19 deaths per million inhabitants (DP) up to July 25, 2020 with influenza vaccination rate of people aged 65 and older in 2019 or latest data available worldwide.
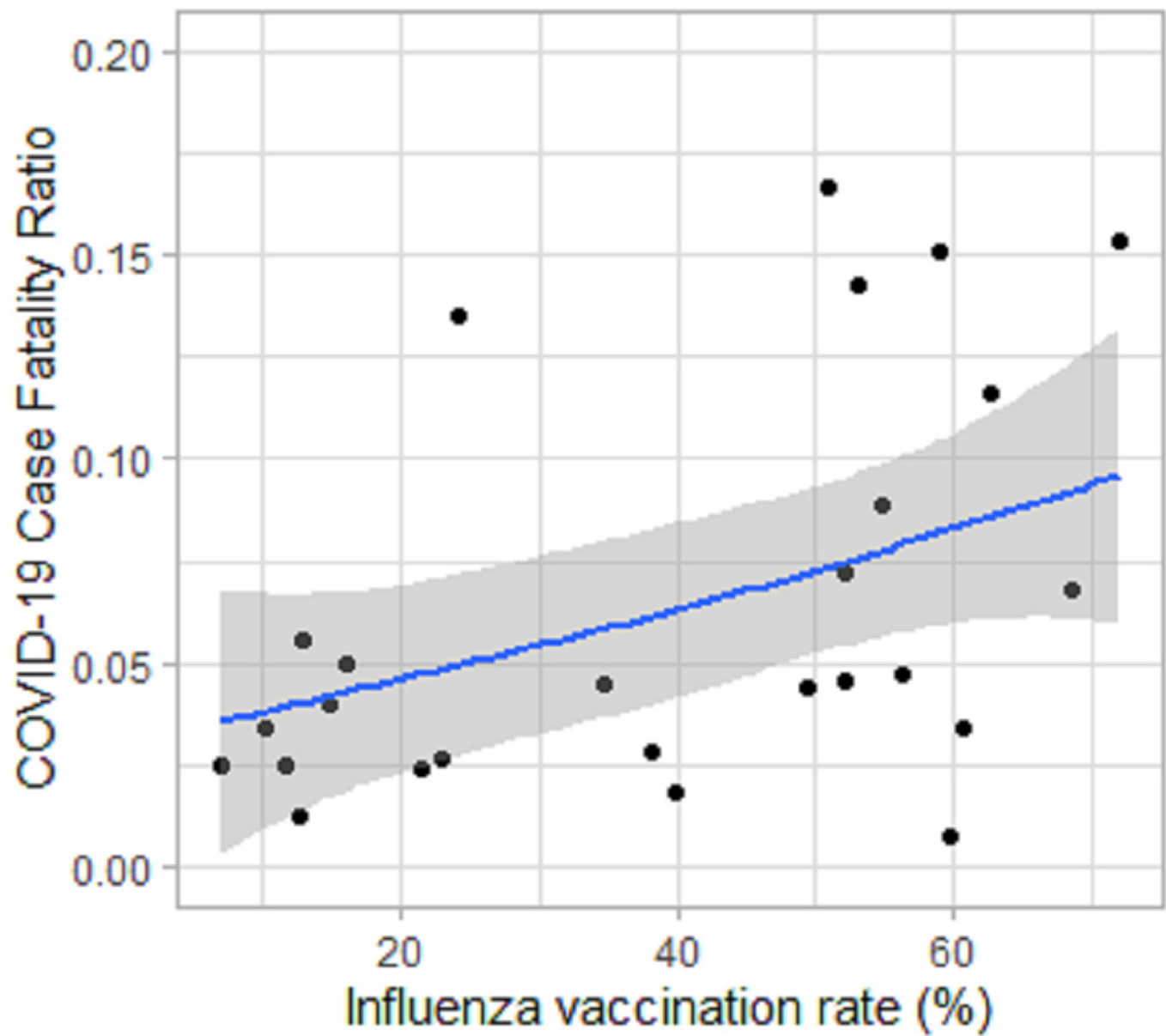
Association of COVID-19 deaths per million inhabitants (DP) up to July 25, 2020 with influenza vaccination rate of people aged 65 and older in 2019 or latest data available worldwide (39 countries with more than 0.5 million inhabitants). The mean (blue line) and standard deviation (grey area) are based on generalized additive models (GAM); r_s (IVR x DP) = +0.487 with p = 0.0017.

Figure 4

Unbiased Conditional variables importance ranking to predict COVID-19 deaths per million inhabitant.

Unbiased conditional variables importance ranking (%) to predict COVID-19 deaths per million inhabitants using the package "party" and the non-parametric random forest function "cforest" in the software *R*; IVR = influenza vaccination rate, Long = centroid longitude (°), Lat = centroid latitude (°), DUR = degree of urbanization in 2020, HDI = Human Development Index in 2018, PEP = percent of elder people in 2019, PD = population density in 2018, mask = the requirement degree of using masks in public (with three degrees: none, parts of country, full country), lockdown = lockdown degree (with three levels: no lockdown, partial lockdown, nationwide lockdown) of each country, at worldwide level (39 countries studied).
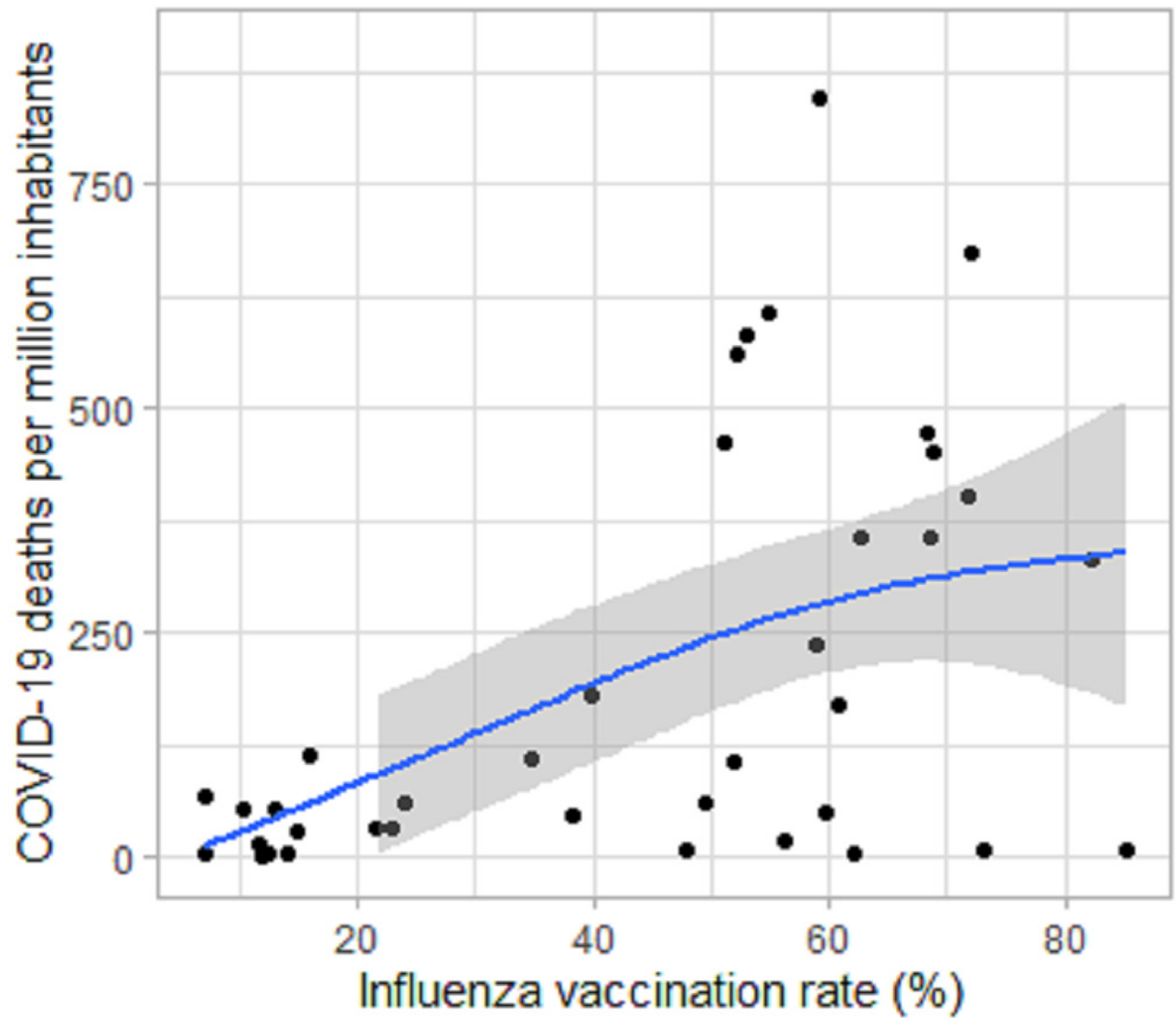
Figure 5

Conditional variables importance ranking to predict COVID-19 Case Fatality Ratio.

Unbiased conditional variables importance ranking (%) to predict COVID-19 Case Fatality Ratio using the package "party" and the non-parametric random forest function "cforest" in the software *R*; IVR = influenza vaccination rate, Long = centroid longitude (°), Lat = centroid latitude (°), DUR = degree of urbanization in 2020, HDI = Human Development Index in 2018, PEP = percent of elder people in 2019, PD = population density in 2018, mask = the requirement degree of using masks in public (with three degrees: none, parts of country, full country), lockdown = lockdown degree (with three levels: no lockdown, partial lockdown, nationwide lockdown) of each country, at worldwide level (39 countries studied).

Table 1(on next page)

Raw data (part 1).

Countries with their influenza vaccination rate (IVR) (%) of people aged 65 and older in 2019 or latest available, COVID-19 deaths per million inhabitants (DP), COVID-19 Case Fatality Ratio (CFR) based on confirmed infected people (CIP) in 2020, COVID-19 tests per million inhabitants.

1

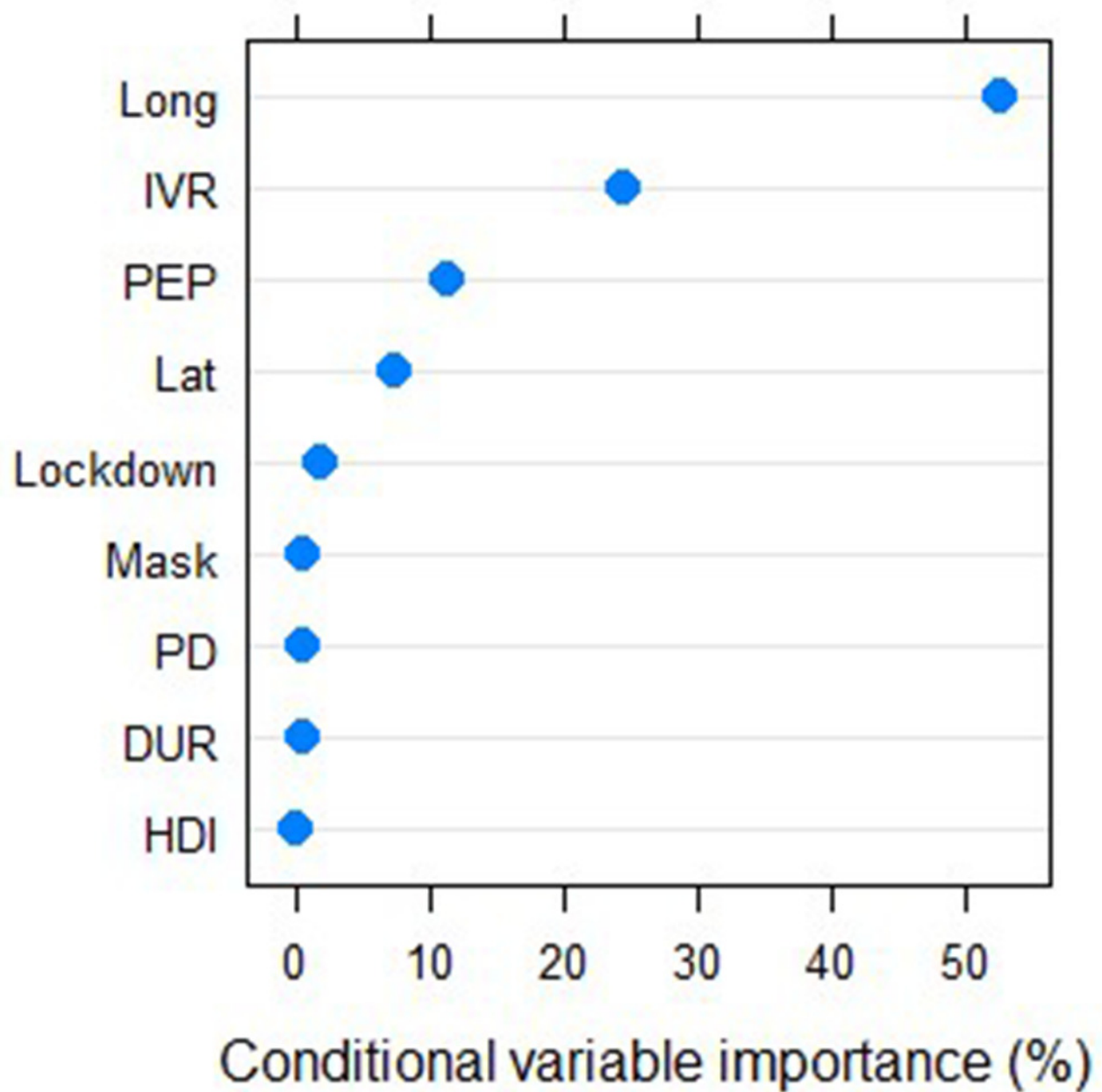| Country	IVR* (%)	Year of IVR	DP+ (N per M)	CIP+ (N per M)	CFR+	COVID-19 tests +	Continent
Australia	73.0	2018/2019	6	547	0.011	151,037	Australia and Ozeanien
Belgium	59.1	2019	847	5,624	0.151	130,601	Europe
Brazil	71.8	2018/2019	402	11,078	0.036	23,094	America
Canada	59.0	2019	235	3,006	0.078	98,442	America
Chile	68.3	2019	472	17,964	0.026	78,678	America
China	7.0	2018/2019	3	58	0.052	62,814	Asia
Croatia	23.0	2017	31	1,168	0.027	26,932	Europe
Czech Republic	21.5	2019	34	1,413	0.024	61,332	Europe
Denmark	52.0	2019	106	2,319	0.046	243,677	Europe
Estonia	10.2	2019	52	1,532	0.034	87,692	Europe
Finland	49.5	2019	59	1,333	0.044	59,654	Europe
France	51.0	2019	462	2,765	0.167	45,683	Europe
Germany	34.8	2019	110	2,460	0.045	88,528	Europe
Greece	56.2	2019	19	400	0.048	42,244	Europe
Hungary	24.1	2019	62	458	0.135	33,116	Europe
Ireland	68.5	2019	357	5,235	0.068	121,496	Europe
Israel	59.8	2019	49	6,577	0.007	173,662	Europe
Italy	53.1	2019	581	4,067	0.143	107,848	Europe
Japan	48.0	2019	8	221	0.036	5,516	Asia
Latvia	11.7	2019	16	640	0.025	100,009	Europe
Lithuania	14.8	2019	29	736	0.039	182,847	Europe
Luxembourg	39.8	2019	179	9,665	0.019	618,326	Europe
Mexico	82.3	2018/2019	331	2,932	0.113	6,946	America
Netherlands	62.7	2019	358	3,077	0.116	49,709	Europe
New Zealand	62.0	2019	4	311	0.013	90,746	Australia and Ozeanien
Norway	38.2	2019	47	1,677	0.028	77,531	Europe
Portugal	60.8	2019	168	4,900	0.034	149,941	Europe
Romania	16.1	2017	112	2,272	0.049	56,571	Europe
Singapore**	14.0	2016/2017	5	8,523	0.001	199,896	Asia
Slovak Republic	12.5	2019	5	392	0.013	46,285	Europe
Slovenia	12.9	2019	55	994	0.055	61,108	Europa
South Korea	85.1	2019	6	275	0.022	29,619	Asia
Spain	54.9	2019	608	6,833	0.089	135,188	Europe
Sweden	52.2	2019	562	7,819	0.072	74,353	Europe
Thailand	12.0	2018/2019	0.8	47	0.017	9,817	Asia
Turkey	7.0	2019	66	2,668	0.025	53,707	Europe

United Kingdom	72.0	2019	673	4,398	0.153	214,532	Europe
United States	68.7	2019	450	12,929	0.035	159,672	America
Vietnam***	12.0	2017	0	4	0.000	2,824	Asia

2   Note: *Taken from https://data.oecd.org/healthcare/influenza-vaccination-rates.htm,

3   https://oecdcode.org/disclaimers/israel.html and https://www.statista.com/chart/16575/global-flu-immunization-

4   rates-vary/ on July 25, 2020, **from https://www.todayonline.com/commentary/why-singapores-adult-

5   vaccination-rate-so-low. ***from Nguyen et al. (2020), + from https://www.worldometers.info/coronavirus/

6   on July 25, 2020.

7

Table 2(on next page)

Raw data (part 2).

Countries with their centroid coordinates (longitude (Long) and latitude (Lat)), Degree of urbanization in 2020, Human Development Index (HDI) in 2018, Percent elder people in 2019 and Population density in 2018.

1

Country	Long (°)	Lat (°)	Degree of urbanization (2020)*	HDI (2018)**	Percent elder people (%) (2019)***	Population density (people per km² of land area) (2018)****
Australia	134.5	-25.7	86.2	0.938	15.92	3.2
Belgium	4.6	50.6	98.1	0.919	19.01	377.4
Brazil	-53.1	-10.8	87.1	0.761	9.25	25.1
Canada	-98.3	61.4	81.6	0.922	17.65	4.1
Chile	-71.4	-37.7	87.7	0.847	11.88	25.2
China	103.8	36.6	61.4	0.758	11.47	148.3
Croatia	16.4	45.1	57.6	0.837	20.86	73.0
Czech Republic	15.3	49.7	74.1	0.891	19.80	137.7
Denmark	10.0	56.0	88.1	0.930	19.97	138.0
Estonia	25.5	58.7	69.2	0.882	19.99	30.4
Finland	26.3	64.5	85.5	0.925	22.14	18.1
France	2.5	46.2	81.0	0.891	20.39	122.3
Germany	15.3	49.7	77.5	0.939	21.56	237.3
Greece	23.0	39.1	79.7	0.872	21.94	83.3
Hungary	19.4	47.2	71.9	0.845	19.69	108.0
Ireland	-8.1	53.2	63.7	0.942	14.22	70.7
Israel	35.0	31.5	92.6	0.906	12.21	410.5
Italy	12.1	42.8	71.0	0.883	23.01	205.4
Japan	138.0	37.6	91.8	0.915	28.00	347.1
Latvia	24.9	56.9	68.3	0.854	20.34	31.0
Lithuania	23.9	55.3	68.0	0.869	20.16	44.7
Luxembourg	6.1	49.8	91.5	0.909	14.27	250.2
Mexico	-102.5	23.9	80.7	0.767	7.42	64.9
Netherlands	5.3	52.1	92.2	0.933	19.61	511.5
New Zealand	171.5	-41.8	86.7	0.921	15.99	18.4
Norway	15.3	68.8	83.0	0.954	17.27	14.5
Portugal	-8.5	39.6	66.3	0.850	22.36	112.3
Romania	25.0	45.9	56.4	0.816	18.79	84.6
Singapore	103.8	1.4	100.0	0.935	12.39	7953.0
Slovak Republic	19.5	48.7	53.8	0.857	16.17	113.3
Slovenia	14.8	46.1	55.1	0.902	20.19	103.0
South Korea	127.8	36.4	81.4	0.906	15.06	529.4
Spain	-3.6	40.2	80.8	0.893	19.65	93.7
Sweden	16.7	62.8	88.0	0.937	20.20	25.0
Thailand	101.0	15.1	51.4	0.765	12.41	135.9
Turkey	35.2	39.1	76.1	0.806	8.73	107.0
United Kingdom	-2.9	54.1	83.9	0.920	18.51	274.7

United States	-112.5	45.7	82.7	0.920	16.21	35.7
Vietnam	106.3	16.6	37.3	0.693	7.55	308.1

2 Note: * https://www.cia.gov/library/publications/the-world-factbook/fields/349.html, **

3 http://hdr.undp.org/en/composite/HDI, *** https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS?name_desc=false, ****

4 https://data.worldbank.org/indicator/EN.POP.DNST, all retrieved on July 13, 2020.

Table 3(on next page)

Raw data (part 3).

Countries with some Covid-19 measures (degree of mask requirements in public, lockdown degree and lockdown beginning).

1

Country	Degree of mask requirement *	Lockdown degree	Lockdown beginning	Sources about lockdown (retrieved on Aug 13, 2020)
Australia	Parts of Country	Lockdown	3/23/20	https://www.straitstimes.com/asia/australianz/australia-starts-lockdown-measures-as-coronavirus-cases-jump
Belgium	Full Country	Lockdown	3/17/20	https://www.euractiv.com/section/coronavirus/news/belgium-enters-lockdown-over-coronavirus-crisis-until-5-april/
Brazil	Parts of Country	Lockdown	5/5/20	https://www.reuters.com/article/us-health-coronavirus-brazil-lockdown/major-brazilian-cities-set-lockdowns-as-virus-spreads-idUSKBN22H2V3
Canada	Parts of Country	Partial lockdown	3/17/20	https://www.manitoulin.ca/updated-canada-goes-on-covid-19-lockdown/
Chile	Full Country	Partial lockdown	3/25/20	https://www.gob.cl/noticias/ministerio-de-salud-anuncia-cuarentena-total-para-siete-comunas-de-la-region-metropolitana/
China	None, but voluntary Universal Mask Usage	Lockdown	1/23/20	https://www.who.int/bulletin/volumes/98/7/20-254045/en/
Croatia	Full Country	Lockdown	3/18/20	https://www.telegram.hr/zivot/koronavirus-krizni-stozer-danas-ce-objaviti-sto-se-sve-zatvara-u-hrvatskoj/; https://m.vecernji.hr/vijesti/oxford-hrvatska-ima-najstroze-mjere-u-europi-iza-su-samo-srbija-i-sirija-1389281
Czech Republic	Full Country	Lockdown	3/16/20	https://archiv.radio.cz/en/section/breaking/czech-republic-severely-limits-freedom-of-movement-in-order-to-slow-down-coronavirus-spread
Denmark	None	Lockdown	3/13/20	https://nyheder.tv2.dk/samfund/2020-03-11-danmark-lukker-ned-her-er-regeringens-nye-tiltag
Estonia	None, but Recommends Masks	No lockdown		https://www.euronews.com/2020/05/13/coronavirus-lockdown-latvia-lithuania-and-estonia-re-open-borders-to-each-other
Finland	None, but Recommends Masks	Partial lockdown	3/28/20	https://newseu.cgtn.com/news/2020-04-16/Finland-to-lift-coronavirus-lockdown-in-region-around-capital--PIiAE4MM36/index.html
France	Full Country	Lockdown	3/17/20	https://www.leparisien.fr/societe/coronavirus-etat-d-urgence-aux-etats-unis-800-nouveaux-cas-en-france-79-morts-au-total-suivez-notre-direct-14-03-2020-8279826.php
Germany	Full Country	Lockdown	3/23/20	https://www.welt.de/politik/deutschland/article206725829/Coronavirus-Deutschland-Kontaktverbote-zu-mehr-als-zwei-Personen-Friseure-zu.html
Greece	Full Country	Lockdown	3/23/20	https://www.in.gr/2020/04/23/politics/se-ekseliksi-enimerosi-tou-kyvernitikou-ekprosopou-steliou-petsa-2/
Hungary	Parts of Country	Lockdown	3/28/20	https://www.theguardian.com/world/2020/mar/30/hungary-jail-for-coronavirus-misinformation-viktor-orban
Ireland	No, but Recommends Masks	Lockdown	3/12/20	https://www.irishtimes.com/news/health/coronavirus-schools-colleges-and-childcare-facilities-in-ireland-to-shut-1.4200977
Israel	Full Country	Lockdown	4/1/20	https://www.haaretz.com/israel-news/coronavirus-israeli-health-minister-netanyahu-mossad-chief-quarantine-1.8720108; https://www.timesofisrael.com/israelis-will-be-required-to-wear-face-masks-outdoors-under-new-order/
Italy	Full Country	Lockdown	2/25/20	https://metro.co.uk/2020/02/25/towns-italy-lockdown-coronavirus-12298246/
Japan	No, but Universal Mask Usage	No lockdown		https://asia.nikkei.com/Spotlight/Coronavirus/Japan-quietly-reopens-as-much-of-world-locks-down
Latvia	Full Country	No lockdown		https://www.euronews.com/2020/05/13/coronavirus-lockdown-latvia-lithuania-and-estonia-re-open-borders-to-each-other
Lithuania	Full Country	No		https://www.euronews.com/2020/05/13/coronavirus-lockdown-latvia-lithuania-and-estonia-re-open-borders-to-each-other

		lockdown		
Luxembourg	Full Country	Lockdown	4/15/20	https://www.tageblatt.lu/headlines/pressekonferenz-nach-dem-regierungsrat-kommt-das-ende-des-lockdowns/
Mexico	Full Country	Lockdown	3/23/20	https://www.eluniversal.com.mx/english/mexico-city-closes-museums-bars-nightclubs-and-movie-theaters-bid-halt-coronavirus-spread
Netherlands	Full Country	Lockdown	3/12/20	Maarten Keulemans (12 March 2020). "Are we doing enough? RIVM boss Van Dissel: 'As soon as something indicates infection in the family: isolation'". de Volkskrant (in Dutch). Retrieved 13 March 2020.
New Zealand	None	Lockdown	3/26/20	https://www.newstalkzb.co.nz/news/national/coronavirus-covid-19-state-of-emergency-declared-in-new-zealand-50-new-cases-confirmed/
Norway	None	Lockdown	3/12/20	https://www.nrk.no/norge/alle-utdanningsinstitusjoner-stenges-_-flere-arrangementer-og-virksomheter-far-forbud-1.14940952
Portugal	Full Country	Lockdown	3/19/20	http://www.presidencia.pt/?idc=22&idi=176060
Romania	Full Country	Lockdown	3/25/20	http://www.ms.ro/2020/03/25/buletin-informativ-25-03-2020/
Singapore	Full Country	Lockdown	4/7/20	https://www.channelnewsasia.com/news/business/suntec-city-waives-april-rent-for-tenants-covid-19-12614802
Slovak Republic	Full Country	Lockdown	3/12/20	*https://spectator.sme.sk/c/22356193/emergency-situation-applies-from-thursday-morning.html?ref=njctse*
Slovenia	Full Country	Lockdown	3/13/20	https://www.rtvslo.si/zdravje/novi-koronavirus/katalonija-zeli-razglasiti-karanteno-za-celotno-pokrajino/517068
South Korea	None, but voluntary Universal Mask Usage	No lockdown		https://www.sciencemag.org/news/2020/03/coronavirus-cases-have-dropped-sharply-south-korea-whats-secret-its-success
Spain	Full Country	Lockdown	3/14/20	https://administracion.gob.es/pag_Home/atencionCiudadana/Estado-de-alarma-crisis-sanitaria.html#.Xn3xj0dKjIU
Sweden	None	No lockdown		Sayers, Freddy (17 April 2020). Swedish expert: why lockdowns are the wrong policy – The Post. UnHerd.
Thailand	Full Country	Lockdown	4/3/20	https://www.bangkokpost.com/thailand/general/1891910/curfew-starts-today
Turkey	Full Country	Partial lockdown	3/21/20	ttps://www.bbc.com/news/world-europe-52831017; https://www.aa.com.tr/tr/koronavirus/cumhurbaskanligi-sozcusu-kalin-ilk-orta-ve-liseler-1-hafta-universiteler-3-hafta-tatil-edilecek/1763918
United Kingdom	Full Country	Lockdown	3/23/20	https://www.thesun.co.uk/news/11304061/uk-coronavirus-lockdown-month-lasted-start-end/
United States	Parts of Country	Lockdown	3/19/20	https://www.wsj.com/articles/china-reports-no-new-domestic-coronavirus-infections-for-the-first-time-since-outbreak-started-11584611233
Vietnam	Full Country	Lockdown	4/1/20	https://e.vnexpress.net/news/news/covid-19-lockdown-hanoi-hospital-lacks-food-necessities-for-3-500-inmates-4077071.html

2   Note: * https://masks4all.co/what-countries-require-masks-in-public/(retrieved on Aug 13, 2020)

Table 4(on next page)

Spearman correlations (r_s) of COVID-19 deaths per million inhabitants (DP) with nine predictor variables.

Spearman correlations (r_s) of COVID-19 deaths per million inhabitants (DP) with the variables (var): IVR = influenza vaccination rate (IVR, %) of people aged 65 and older in 2019 or latest data available, Long and Lat = Longitude and Latitude of the country centroid (°), DUR = Degree of urbanization in 2020, HDI = Human Development Index in 2018, PEP = Percent elder people in 2019, PD = Population density in 2018, Mask = the requirement degree of using masks in public (with three degrees: none, parts of country, full country), Lockdown = lockdown degree (with three levels: no lockdown, partial lockdown, nationwide lockdown) and their *p* values based on 26 countries in Europe (Tables 1 – 3).

1

var	r_s (DP x var)	p value
Long	**-0.65**	**0.0003**
IVR	**0.62**	**0.0008**
DUR	0.43	0.0273
PD	0.41	0.0375
HDI	0.38	0.0533
Lockdown	0.25	0.2146
PEP	-0.07	0.7387
Lat (abs)	-0.02	0.9313
Mask	0	0.9949

2   Note: bold = statistically significant after Bonferroni correction (α = 0.0019).

3

Table 5(on next page)

Spearman correlations (r_s) of COVID-19 deaths per million inhabitants (DP) and COVID-19 Case Fatality Ratio (CFR) with nine predictor variables.

Spearman correlations (r_s) of COVID-19 deaths per million inhabitants (DP) and COVID-19 Case Fatality Ratio (CFR) with the variables: IVR = influenza vaccination rate (%) of people aged 65 and older in 2019 or latest available, Long = Longitude of the centroid of the country (°), Latitude of the centroid of the country (°), DUR = Degree of urbanization in 2020, HDI = Human Development Index in 2018, PEP = Percent elder persons in 2019, PD = Population density in 2018, Mask = the requirement degree of using masks in public (with three degrees: none, parts of country, full country), Lockdown = lockdown degree (with three levels: no lockdown, partial lockdown, nationwide lockdown), based on 39 countries worldwide (Tables 1 – 3).

r_s	DP	CFR
Long	**-0.81**	**-0.56**
IVR	**0.49**	0.25
DUR	0.32	0.39
Lat (abs)	0.32	0.03
HDI	0.20	0.10
PEP	0.15	0.38
Mask	0.14	-0.01
Lockdown	0.08	0.09
PD	-0.07	-0.01
***p* values**		
Long	**0**	**0.0002**
IVR	**0.0016**	0.1275
DUR	0.0436	0.8698
Lat (abs)	0.0451	0.0155
HDI	0.2167	0.5529
PEP	0.3523	0.0174
Mask	0.3819	0.9436
Lockdown	0.6448	0.5980
PD	0.6713	0.9347

Note: bold = statistically significant after Bonferroni correction (α = 0.0019).