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

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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. **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. The associations were measured by non-parametric Spearman rank correlation coefficients and random forest functions. **Results.** The results showed a positive association between COVID-19 deaths and IVR of people $\geq$ 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.

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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

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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.

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

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

26 39 countries).To accurately estimate the influence of IVR on COVID-19 deaths and mitigate

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

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

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

30 intervention. The associations were measured by non-parametric Spearman rank correlation

31 coefficients and random forest functions.

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

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis (Yuen et al. 2020), directly and indirectly impacting all spheres of human life (Ozili & Arun 2020). More than 15,300,000 confirmed cases including more than 630,000 deaths have been documented worldwide, affecting 213 countries and territories around the world (https://covid19.who.int/).

Determining the factors influencing the severity of COVID-19 is important (Armengaud et al. 2020). Although COVID-19 disease does not only affect elderly people, the severity of symptoms increases with age (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html; Le Couteur, Anderson & Newman 2020). Several other risk factors have been found for severe COVID-19, such as comorbidities, dyspnea, chest pain, cough, expectoration, decreased lymphocytes, and increased inflammation indicators (Li et al. 2020). Low socioeconomic status is an additional risk factor (Yancy 2020).

In response to the increasing numbers of COVID-19 cases and deaths, numerous non-pharmaceutical interventions have been implemented, including social distancing, border closures, school closures, measures to isolate symptomatic individuals and their contacts, and large-scale lockdowns of populations (Courtemanche et al. 2020; Flaxman et al. 2020). Some pharmacological measures have also (often controversially) been proposed in order to prevent COVID-19 disease or reduce its severity, such as the use of remdesivir (e.g., Beigel et al. 2020), dexamethasone (RECOVERY Collaborative Group 2020), adjunctive therapies (https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_85.pdf) and COVID-19 candidate vaccines (e.g., Graham 2020, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

The term "heterologous immunity" is applied when an infection by one pathogen can induce and/or alter the immune response against another unrelated pathogen. Heterologous immunity can improve or decrease protective immunity against a given pathogen, and/or cause severe immunopathology or tolerance to self-antigens. Heterologous immunity can also result in non-specific effects (also called "heterologous effects") of vaccines which affect unrelated infections and diseases, such as extending the protective outcomes of vaccinations (Goodridge et al. 2016,

65   Agrawal 2019). Arokiaraj (2020) reported a negative correlation between influenza vaccination

66   rates and COVID-19 related mortality and morbidity. Marín-Hernández et al. (2020) also showed

67   epidemiological evidence of an association between higher influenza vaccine uptake by elderly

68   people and lower percentage of COVID-19 deaths in Italy. In a study analyzing 92,664 clinically

69   and molecularly confirmed COVID-19 cases in Brazil, Fink et al. (2020) reported that patients

70   who received a recent flu vaccine experienced on average 17% lower odds of death. Moreover,

71   Pawlowski et al. (2020) analyzed the immunization records of 137,037 individuals who tested

72   positive in a SARS-CoV-2 PCR. They found that polio, Hemophilus influenzae type-B (HIB),

73   measles-mumps-rubella (MMR), varicella, pneumococcal conjugate (PCV13), geriatric flu, and

74   hepatitis A / hepatitis B (HepA-HepB) vaccines, which had been administered in the past one,

75   two, and five years, were associated with decreased SARS-CoV-2 infection rates.

76   By contrast, in a study with 6,120 subjects, Wolff (2020) reported that influenza vaccination was

77   significantly associated with a higher risk of some other respiratory diseases, due to virus

78   interference. In a specific examination of non-influenza viruses, the odds of coronavirus

79   infection (but not the COVID-19 virus) in vaccinated individuals were significantly higher, when

80   compared to unvaccinated individuals (odds ratio = 1.36).

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

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

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

84   worldwide, with a negative association expected.

85   **Materials & Methods**

86

87   To look for an association between COVID-19 deaths and influenza vaccination, I analyzed

88   available data sets from 39 countries, each with ≥ 0.5 million inhabitants. In smaller states (i.e., <

89   0.5 million inhabitants), the rate of erroneous identification of COVID-19 deaths may be

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

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

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

93   Fatality Ratio (CFR). I analyzed the variables DPMI and CFR, based on documented COVID-19

94   cases per million inhabitants (CPMI) in 2020, COVID-19 tests per million inhabitants, and

95 influenza vaccination rate (IVR) (%) in people $\geq$ 65 years old in 2019 or latest available data

96 (Table 1). I recorded the DPMI, CPMI and CFR data from the public web site

97 https://www.worldometers.info/coronavirus/. Then, I calculated CFR as the rate of DPMI per

98 CPMI. IVR data were also taken from https://data.oecd.org/healthcare/influenza-vaccination-

99 rates.htm, https://oecdcode.org/disclaimers/israel.html and

100 https://www.statista.com/chart/16575/global-flu-immunization-rates-vary/ (retrieved on July 25,

101 2020). Vietnam's 2017 IVR was recorded from Nguyen et al. (2020), and Singapore's 2016/2017

102 IVR from https://www.todayonline.com/commentary/why-singapores-adult-vaccination-rate-so-

103 low.

104 To analyze the data, I first calculated the non-parametric Spearman rank correlation coefficient

105 (r_s) and its R_S^2 and respective p-value (2-tailed) to determine any association between DPMI and

106 CFR with IVR, using R (R Core Team 2017). As the relationship between DPMI and the number

107 of people tested for COVID-19 was not statistically significant based on r_s and its p-value, I did

108 not modified (corrected) the DPMI data set. Then, I created regression curves by Generalized

109 additive model (GAM) using the "ggplot2" package and function (method = 'gam') (Wickham et

110 al. 2013), also in R.

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

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

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

114 accurately estimating the influence of IVR on DPMI and CFR and mitigating the effects of

115 confounding variables, I performed variable importance ranking, including as predictor variables

116 IVR and some potentially important geographical, socioeconomic and non-pharmaceutical-

117 intervention variables (Escobar et al. 2020). I used the centroid longitudes (º) and latitudes (º) of

118 each country as geographical variables calculated by the "rgeos" and "rworldmap" packages,

119 along with the "getMap" and "gCentroid" functions, implemented in R (version 3.3.4; R

120 Development Core Team, 2017). For each country considered, the study recorded socioeconomic

121 variables as the degree of urbanization (DUR) in 2020

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

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

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

125 elderly people (PEP) in 2019

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

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

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

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

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

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

132

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

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

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

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

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

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

139

140   To mitigate the effects of confounding factors, IVR, DPMI and CFR evaluations were also

141   conducted for countries with similar social conditions (> 50% of DUR, HDI of > 0.80, > 15% of

142   PEP, and PD between 25 and 350 inhabitants per km^2) (Escobar et al. 2020) and for countries

143   with similar longitudes (10 - 20º in parts of Europe and 100 - 140º, East and Southeast Asia

144   along with Australia and New Zealand).

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

146   DUR) = +0.52; r_s (IVR x Long) = -0.46; r_s (IVR x HDI) = 0.36), therefore, I included these

147   variables in non-parametric Random Forest (RF) models of DPMI and CFR, including a 5-fold

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

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

150   http://topepo.github.io/caret/index.html) in *R* software. Finally, I evaluated the goodness-of-fit of

151   the regression model using the (pseudo) coefficient of determination (R^2) and the root mean

152   square error (RMSE).

153

154   **Results**

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

156   million inhabitants (DPMI) and the COVID-19 Case Fatality Ratio (CFR) were positively and

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

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

159 = 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).

160 In evaluations including only countries with similar social conditions, r_s (IVR x DPMI) was

161 equal to +0.65 (p = 0.002, N = 20) and r_s (IVR x CFR) +0.48 (p = 0.03, N = 20). In analyses

162 including only countries with similar longitude of the country centroid (Long), r_s (IVR x DPMI)

163 was equal to +0.83 (p = 0.003, N = 10) (Long from 10 to 20º) and r_s (IVR x DPMI) +0.76 (p =

164 0.046, N = 7) (Long from 100 to 140º).

165 At worldwide level (39 countries studied), the positive associations between DPMI and IVR

166 were also statistically significant (r_s (IVR x DPMI) = +0.49 with p = 0.0016, R_s^2 (IVR x DPMI) =

167 0.24) (Fig. 3, Table 5). However, the relationships between IVR and CFR were not statistically

168 significant.

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

170 DPMI and CFR to be positively associated with IVR was observed. DPMI and CFR varied

171 strongly when IVR was 50% or higher (Figs. 1-3).

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

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

174 important of the nine variables used to predict DPMI and CFR, respectively. The degree of

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

176 for predicting DPMI. The percentage of elderly people (PEP) in 2019 was the third most

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

178 considered in this study explained 63% of the variation in DPMI (RMSE =161.9) and 43 % of

179 the variation in CFR (RMSE = 0.039).

180

181 **Discussion**

182

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

184 support the previously reported negative association between COVID-19 deaths (DPMI) and

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

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

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

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

189   immunity (Netea et al. 2020). The innate immune response induced by recent vaccination could
190   result in more rapid and efficient SARS-CoV-2 clearance, preventing progressive dissemination
191   into lower areas of lung tissues (Fink et al. 2020).

192   The negative association between the proportion of DPMI and IVR found in Italy was explained
193   as probably caused by i) a higher influenza vaccine rate occurring in higher economic groups
194   with overall better health, ii) chance, iii) a relationship with seasonal respiratory virus infections,
195   or iv) an unrelated mechanistic association (Marín-Hernández et al. 2020). However, the
196   induction of cross-neutralizing antibodies and T-cells that directly target other RNA viruses like
197   SARS-CoV-2 and cross-protection seem unlikely, given the extraordinary diversity of influenza
198   viruses (Fink et al. 2020).

199   Therefore, the above-mentioned arguments cannot explain the positive, direct or indirect
200   relationship between IVR and both DPMI and CFR found in this study, which was confirmed by
201   an unbiased ranking variable importance (Figs. 4 and 5) using RF models. The influenza vaccine
202   may increase influenza immunity at the expense of reduced immunity to SARS-CoV-2 by some
203   unknown biological mechanism, as suggested by Cowling et al. (2012) for non-influenza
204   respiratory virus. Alternatively, weaker temporary, non-specific immunity after influenza viral
205   infection could cause this positive association due to stimulation of the innate immune response
206   during and for a short time after infection (McGill et al. 2009; Khaitov et al. 2009). People who
207   had received the influenza vaccination would have been protected against influenza but not
208   against other viral infections, due to reduced non-specific immunity in the following weeks
209   (Cowling et al. 2012), probably caused by virus interference (Isaacs & Lindenmann 1957;
210   Seppälä et al. 2011; Wolff 2020). Although existing human vaccine adjuvants have a high level
211   of safety, specific adjuvants in influenza vaccines should also be tested for adverse reactions,
212   such as additionally increased inflammation indicators (Petrovsky 2015) in Covid-19 patients
213   with already strongly increased inflammation (Qin et al. 2020).

214   The strong variation in DPMI and CFR from an IVR of about 50% or larger may be the result of
215   interactions among the different measures applied in the analyzed countries (Figs. 1-3), e.g.
216   initiation of interventions, emergency plans and health systems against COVID-19. For example,
217   Australia and South Korea had a very low DPMI and CFR compared with Belgium and United
218   Kingdom (Table 1).

219   The high correlation between the longitude of the country centroid and DPMI and CFR

220   emphasize a significant increase in CP and CFR from eastern to western regions in the world

221   (Table 5, Figs. 4 and 5), as confirmed by Leung et al. (2020) and Skórka et al. (2020). Longitude

222   could act as a proxy for variables such as lifestyle, social behavior, genetics, geographically

223   isolated and remote populations, which may also be associated with CP and CFR. In the severe

224   1918–1919 influenza pandemic, remote or isolated populations were also affected, at least partly

225   because of the lack of prior immunity in locations that had not been recently affected by any

226   form of influenza (Mathews et al. 2009). Therefore, crossing geographical and ecological

227   barriers also is a key factor in spreading diseases (Hallatschek & Fisher 2014; Murray et al.

228   2015).

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

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

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

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

233   ≥ 65 years and urbanization, but still more strongly with the Human Development Index. Leung

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

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

236   strong independent predictor of national COVID-19 mortality.

237   Although countywide lockdowns and use of face masks by the general public should reduce

238   COVID-19 transmission (Conyon, He & Thomsen 2020; Eikenberry et al. 2020), the variables

239   lockdown degree and the degree of requirement for mask use in public were not associated with

240   DPMI and CFR in the present study (Tables 4 and 5, Figs 4 and 5). Leffler et al. (2020) reported

241   in a global study that internal lockdown requirements were not associated with mortality, but that

242   in countries that recommended use of face masks early on at the national level, the COVID-19

243   death rate was lower than expected.

244   Although countywide lockdowns were proclaimed in many countries, the restrictive measures

245   and their implementations differed in degree, strictness and implementation date in relation to the

246   advance of the disease (see references in Table 3). Also, although many countries have required

247   masks in public, the mask quality and correct use may differ from country to country. In this

248   regard, Fischer et al. (2020) found that the use of ineffective masks could be counterproductive.

249 This could explain the non-significant differences between the means of DPMI among countries

250 with and without one or both requirements, lockdown and masks.

251 Finally, the study is limited by the fact that I didn't normalize the time of arrival of the

252 pandemic. Moreover, the associations found may change in the future because the COVID-19

253 pandemic was not over at the end of the study.

254 **Conclusions**

255

256 Given the positive relationship between influenza vaccination rate and the number of deaths per

257 million found in this study, further exploration would be valuable to explain these findings and to

258 make conclusions. Additional work on this line of research may also yield results to improve

259 prevention of COVID-19 deaths.

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261

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265

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Figure 1

Association of COVID-19 deaths per million inhabitants (DPMI) 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 (DPMI) 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.
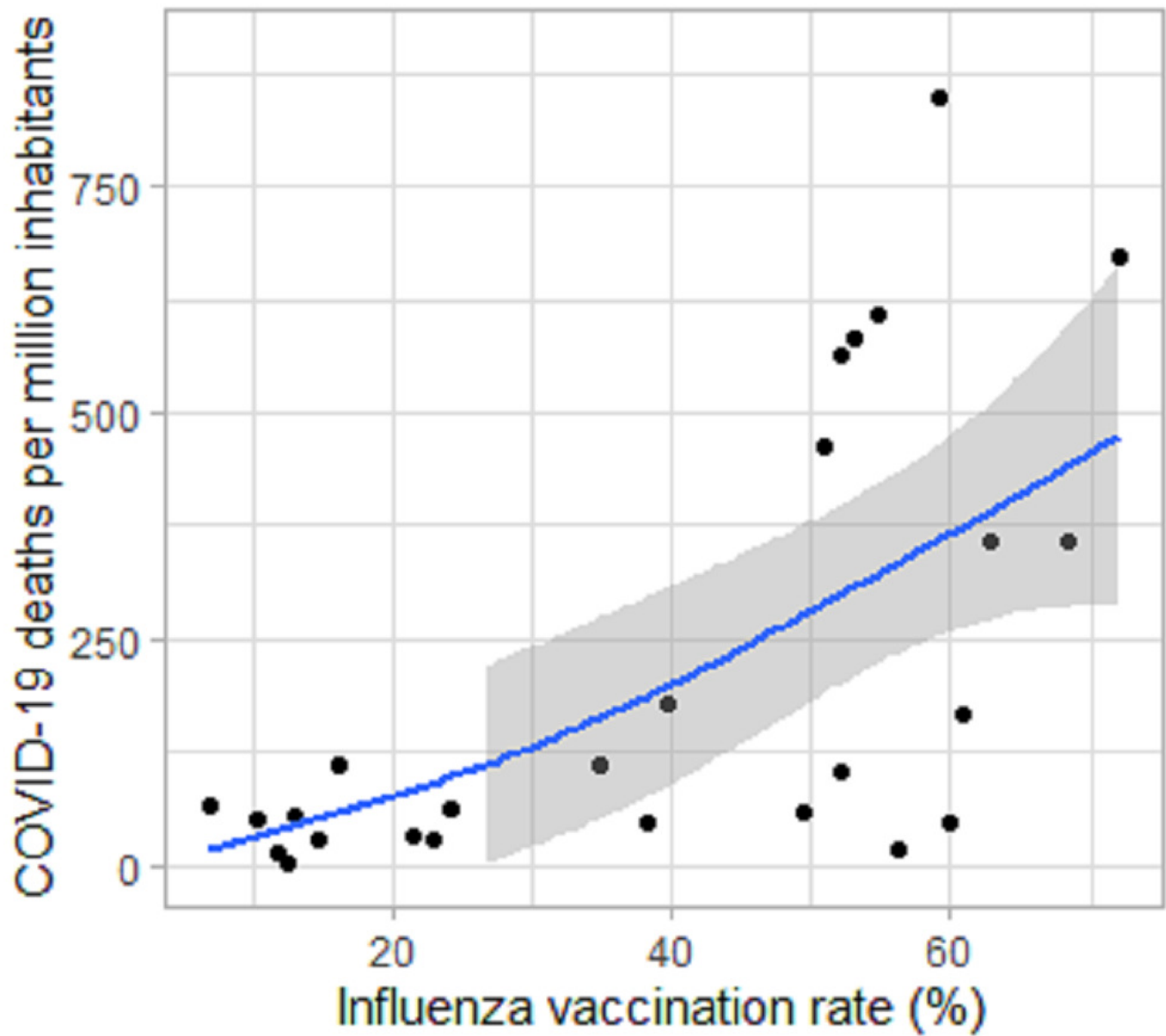
Association of COVID-19 Case Fatality Ratio (CFR) up to July 25, 2020 with influenza vaccination rate (IVR) of people aged 65 and older in 2019 or latest data available in Europe (26 countries with more than 0.5 million inhabitants). The mean (blue line) and standard deviation (grey area) are based on 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 (DPMI) up to July 25, 2020 with influenza vaccination rate of people aged 65 and older in 2019 or latest data available worldwide.
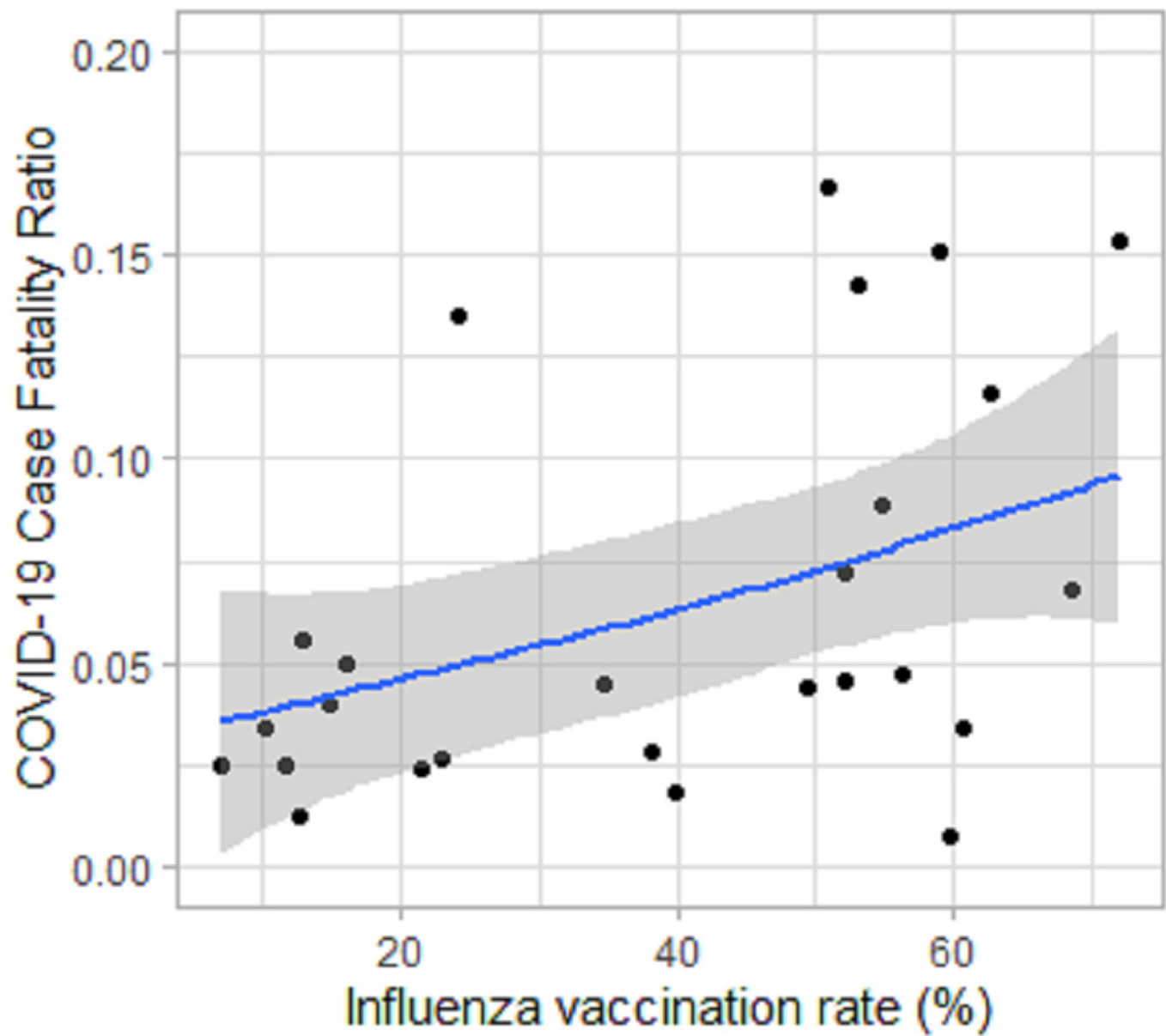
Association of COVID-19 deaths per million inhabitants (DPMI) up to July 25, 2020 with influenza vaccination rate of people aged 65 and older in 2019 or latest data available worldwide (39 countries with more than 0.5 million inhabitants). The mean (blue line) and standard deviation (grey area) are based on generalized additive models (GAM); r_s (IVR x DP) = +0.487 with p = 0.0017.
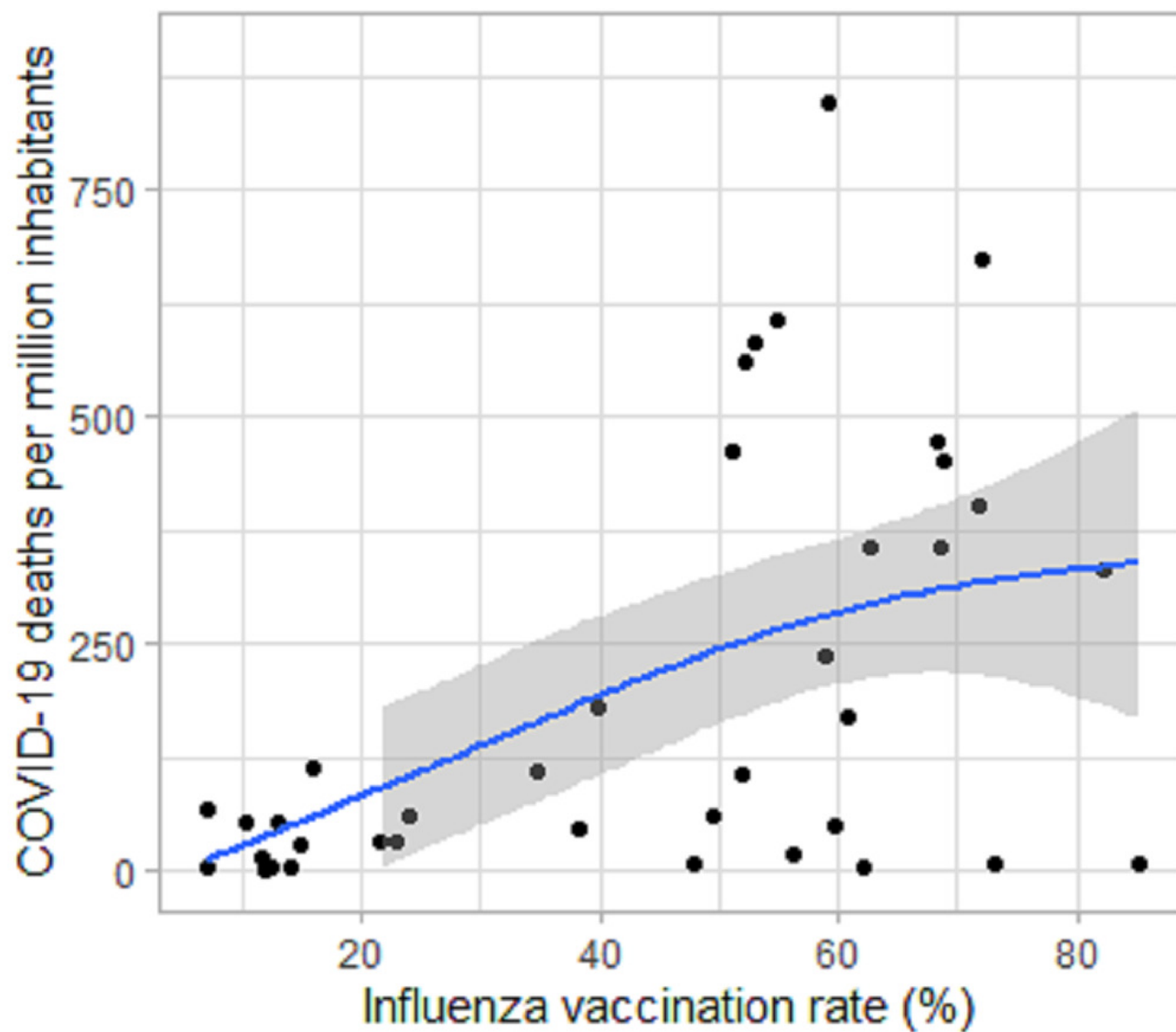
Figure 4

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).
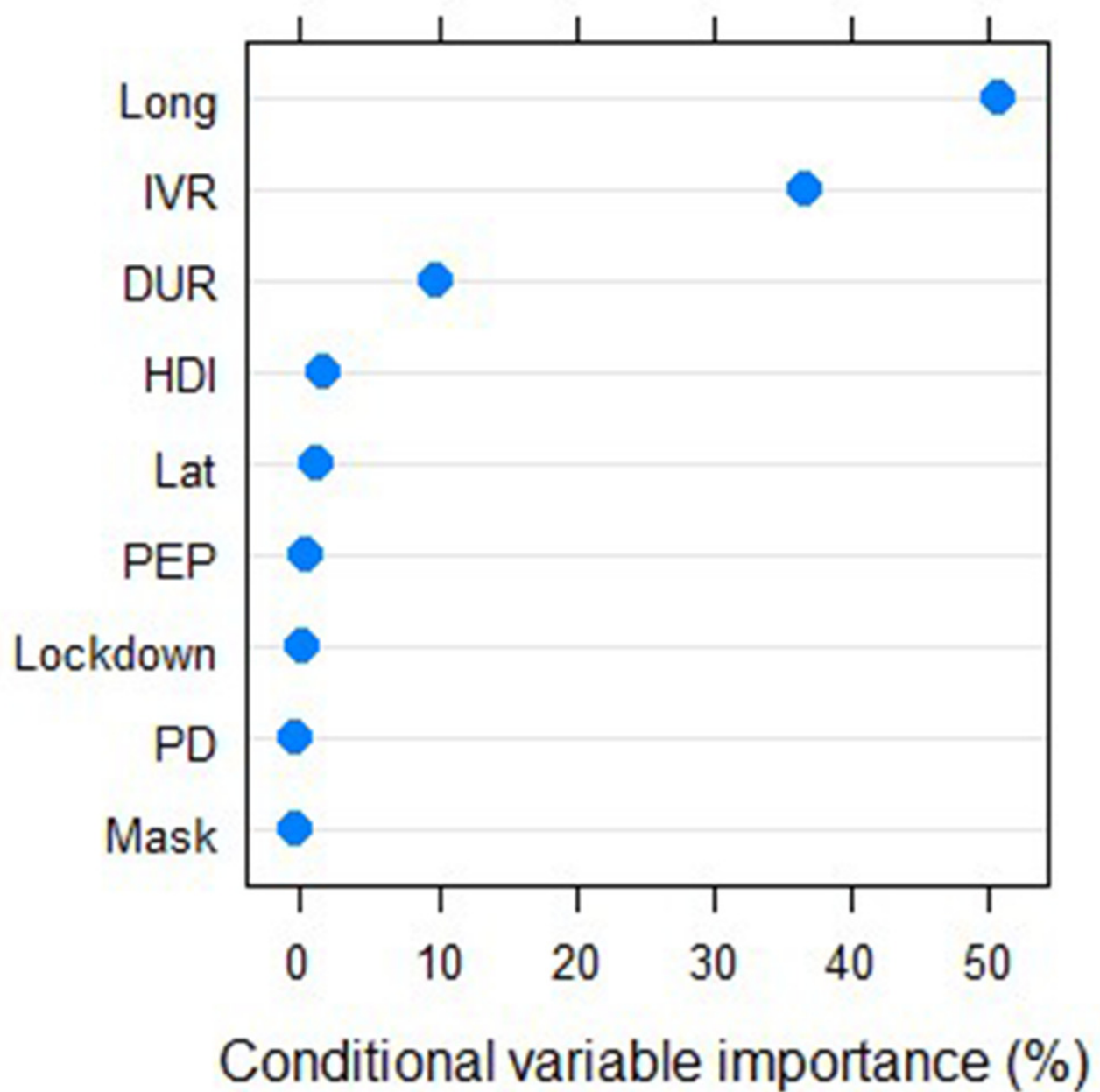
Figure 5

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).
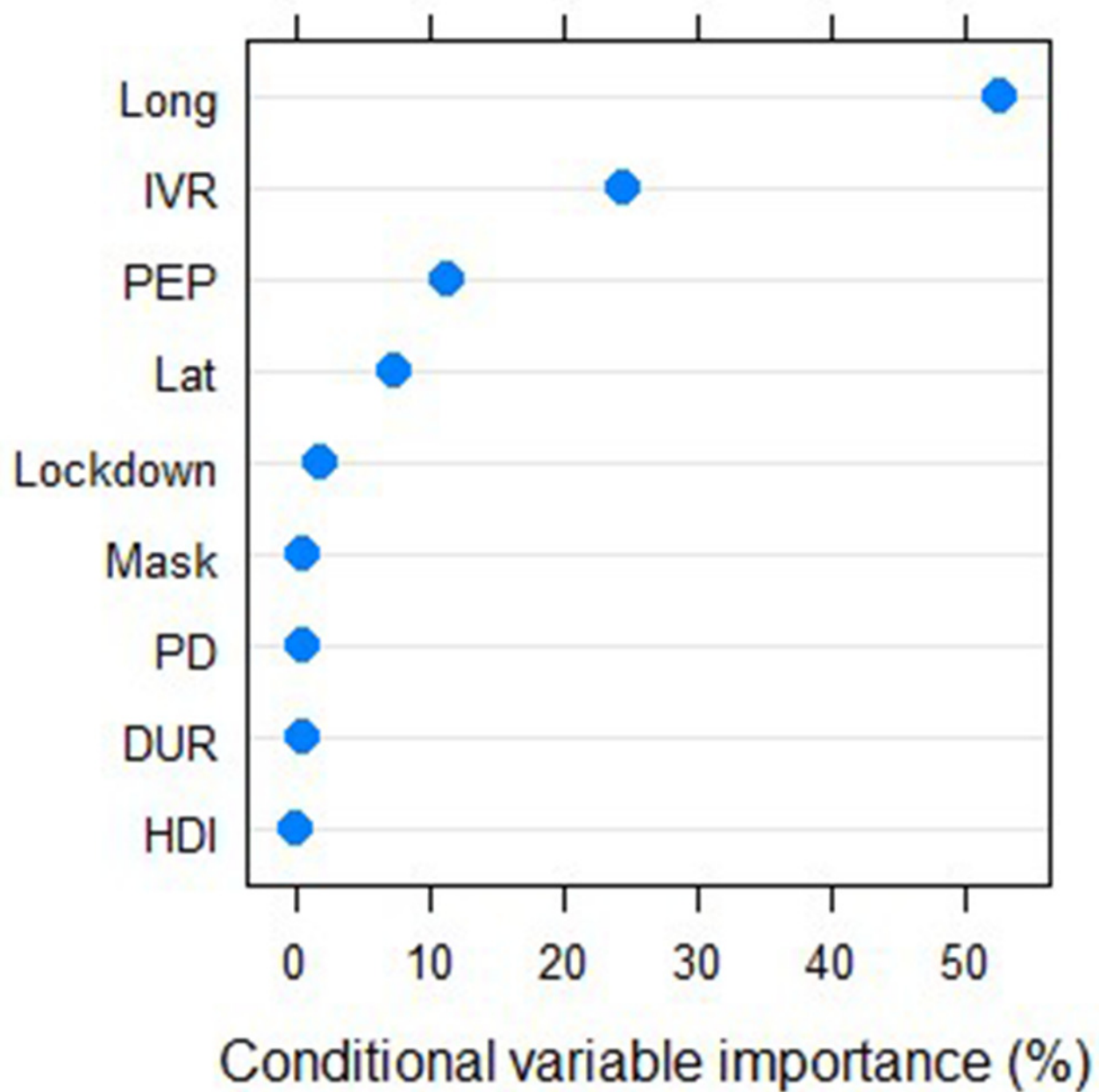
Table 1(on next page)

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 (DPMI), COVID-19 Case Fatality Ratio (CFR) based on documented COVID-19 cases per million inhabitants (CPMI) in 2020, COVID-19 tests per million inhabitants.

1

Country	IVR* (%)	Year of IVR	DPMI+ (N per M)	CPMI+ (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).

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 lockdown		https://www.euronews.com/2020/05/13/coronavirus-lockdown-latvia-lithuania-and-estonia-re-open-borders-to-each-other
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

1

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 (DPMI) 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 (DPMI 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 (DPMI) 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	DPMI	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).