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Original Research

The real-life impact of vaccination on COVID-19 mortality in Europe and Israel

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ABSTRACT

Objectives: This study aimed at estimating the real-life impact of vaccination on COVID-19 mortality, with adjustment for SARS-CoV-2 variants spread and other factors across Europe and Israel.

Study design: Time series analysis.

Methods: Time series analysis of the daily number of COVID-19 deaths was performed using non-linear Poisson mixed regression models. Variables such as variants' frequency, demographics, climate, health, and mobility characteristics of thirty-two countries between January 2020 and April 2021 were considered as potentially relevant adjustment factors.

Results: The analysis revealed that vaccination efficacy in terms of protection against deaths was 72%, with a lower reduction of the number of deaths for B.1.1.7 vs non-B.1.1.7 variants (70% and 78%, respectively). Other factors significantly related to mortality were arrivals at airports, mobility change from the prepandemic level, and temperature.

Conclusions: Our study confirms a strong effectiveness of COVID-19 vaccination based on real-life public data, although lower than expected from clinical trials. This suggests the absence of indirect protection for non-vaccinated individuals. Results also show that vaccination effectiveness against mortality associated with the B.1.1.7 variant is slightly lower than that with other variants. Lastly, this analysis confirms the role of mobility reduction, within and between countries, as an effective way to reduce COVID-19 mortality and suggests the possibility of seasonal variations in COVID-19 incidence.

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Introduction

The pandemic of the coronavirus infectious disease 2019 (COVID-19) is continuously evolving, driven by the spread of new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During the second half of 2020 and early 2021, a variety of new SARS-CoV-2 variants emerged. EU2 variant (mutation S:447N), first observed in July 2020 in Western Europe, was found to be capable of increasing virus infectivity.^{1,2} Then, several variants of concern (VOCs) have been identified, including B.1.1.7 developed first in the UK in September 2020,³ B.1.351 in South Africa in December 2020,⁴ P.1 in Brazil in January 2021,⁵ and the 'Indian' variant B.1.617 reported first in Maharashtra in January 2021.⁶ The

disease mortality has been increased in these countries after new variants were developed.^{7–10} An increased risk of transmissibility, hospitalization, and death associated with the B.1.1.7 variant was reported by a number of authors.^{8,11–16} The B.1.351 variant was found to have an increased transmissibility and immune escape¹⁷ and was estimated to be 50% more transmissible than pre-existing variants.¹⁸ Higher incidence of COVID-19 cases in younger age groups was observed in the Amazonas state, suggesting changes in pathogenicity of the P.1 variant.¹⁹ Preliminary findings suggest also a significant increase in case fatality rate in young and middle-aged population for the P.1 mutant.²⁰ The region of Maharashtra, where the B.1.617 variant emerged, experienced a significant rise in daily infection rate after the new variant appeared.¹⁰

To control the SARS-CoV-2 spread, a number of different vaccines have been developed and analyzed in clinical trials, including eight vaccines having emergency use or conditional marketing authorizations worldwide or across regions, as of May 2021.²¹ The worldwide vaccination campaign started in December 2020 aiming

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to provide herd immunity across societies. The threshold for COVID-19 ‘herd immunity’ was placed between 60 and 70% of the population gaining immunity through vaccinations or past disease exposure; however, scientists warn that herd immunity is unlikely to be achieved owing to factors such as vaccine hesitancy and the spread of new variants.^{22,23} Israel was far ahead of other countries in terms of the proportion of vaccinated inhabitants, exceeding 62% at the end of April 2021, with the UK reaching 50% and the USA 42% at the same time.²⁴

Results of clinical trials on vaccine efficacy revealed that Pfizer-BioNTech had 95% efficacy at preventing symptomatic COVID-19 infection in people without prior infection.²⁵ Efficacy of 94.1% was reported for Moderna,²⁶ 70.4% for Oxford-AstraZeneca,²⁷ 66.5% for Johnson & Johnson,²⁸ and 96.4% for Novavax,²⁹ with the latter being still under the investigation before authorization. For the prevention against a severe disease course, Pfizer, Moderna, AstraZeneca, and Novavax reported a 100% efficacy, whereas 84% was observed for Johnson & Johnson; however, the latter was tested on a broader range of countries, including the USA, South Africa, and Brazil, after the new VOCs spread.

Clinical evidence suggests that newly developed virus variants may affect the protective efficacy of both naturally acquired immunity and vaccinations. Studies on neutralization of convalescent sera against distinct strains showed that VOCs were harder to neutralize than the original strain, an early Wuhan-related strain of SARS-CoV-2. Neutralization titers against the B.1.1.7 variant showed a threefold reduction,³⁰ a 3.4-fold reduction was observed for the P.1 variant,³¹ and a 13.3-fold reduction for the B.1.531 variant.³² Johnson & Johnson vaccine was found to have 64% efficacy against infection in South Africa and 68% in Brazil after the spread of B.1.135 and P.1 variants, whereas the efficacy against severe-disease was 82% and 88% in both countries.²⁸ Late March 2021, AstraZeneca was observed as having 70.4% efficacy against the B.1.1.7 variant;³³ however, the vaccine did not protect as well against the B.1.351 variant.³⁴ For Novavax, the initial evidence suggests 86.3% efficacy against the B.1.1.7 variant³⁵ and 49.4% against the B.1.351 variant.³⁶ Early May 2021, Pfizer vaccine was found to be 87% effective against infection with the B.1.1.7 variant and 72% against B.1.351 variant, whereas 97.4% efficacy against severe disease course was observed for any of these mutations.³⁷ On the other hand, Wang et al.³⁸ observed a reduced neutralization of Moderna and Pfizer vaccine-immune sera against the B.1.351 variant (12.4-fold for Moderna; 10.3-fold for Pfizer), but no significant impact was observed for the B.1.1.7 variant. Next, a 3.8- to 4.8-fold reduced neutralization of Moderna vaccine was observed against the P.1 variant.³¹ Preliminary evidence suggests a significant drop in neutralization of B.1.617 compared with other variants, including B.1.1.7 and P.1, with sera of Indian’s vaccine, Covaxine.¹⁰

The other concern is the probability of reinfection after recovery or vaccination. Hansen et al.³⁹ observed an 80.5% protection against reinfection in a population-level observational study on Danish patients previously tested positive for SARS-CoV-2; however, the study was performed before VOCs spread. The probability of reinfection after vaccination is also a big concern. As reported by the US Centers for Disease Control and Prevention (CDC), there were around 9200 infections among vaccinated inhabitants among 95 million of those who have already been vaccinated in the USA (0.01%) as of 26 April 2021.⁴⁰ Despite these optimistic preliminary data, experts alarm that additional data are needed to assess the potential impact of VOCs on future vaccine efficacy.⁴¹ Considering all the concerns associated with new VOC spread, the real vaccination effectiveness becomes hard to assess and judge but can be expected to decrease over time. Also, it is likely that vaccination may favor the emergence of new variants by selection of new, better fitted mutants. Some scientists suggest that, similarly as for

seasonal flu vaccines, COVID-19 vaccines will need to be redesigned or even updated periodically to protect against new variants.^{42,43}

Vaccination efficacy and distinct variants spread are the only two factors among numerous other variables affecting COVID-19 infection and death rates across the world. A variety of potential predictors were assessed in the literature, including demographic characteristics, mobility and social-distancing measures, environmental and climate variables, as well as health characteristics.^{44–53}

This study aims at estimating the real-life impact of vaccination on COVID-19 mortality based on publicly available data from Europe and Israel, using time series analysis with non-linear mixed regression models. Variants frequency, including B.1.1.7 and other variants, as well as country-specific demographic and meteorological characteristics, health indicators, and mobility factors were considered as potentially relevant adjustment factors. Results of the current study should inform policy decision-makers, scientists, and the general public about the role of vaccination and social-distancing strategies in controlling the COVID-19 pandemic in the face of new VOCs spread.

Methods

Data collection

A total of 32 countries were considered in the analysis, including European countries and Israel. The daily number of COVID-19 deaths was the primary outcome of interest. Values were smoothed using 7-day moving average, divided by the number of inhabitants of a given country and reported as daily numbers of deaths per 1 million inhabitants.

The main explanatory variables of interest were proportion of vaccinated inhabitants (vaccination coverage), as well as average proportions of SARS-CoV-2 variants calculated across strains forming 12 Nextstrain clades. The focus was on 20A (EU2), 20E (EU1), and 20I (B.1.1.7) variants, with the two formers being dominant in Europe during the summer 2020 and the latter VOC being most frequent early 2021. Other time-varying covariates were maximum daily temperature, mean daily wind speed, the number of arrivals at two biggest airports of a country, and change in mobility from the prepandemic level (considering the average across retail/recreation, transit stations, and groceries/pharmacies). Additional fixed covariates were proportion of population aged 65 years or older, prevalence of diabetes, and rate of cardiovascular deaths.

Data on COVID-19 deaths and vaccination were obtained from Our World in Data on 15 April 2021.²⁴ Metadata on SARS-CoV-2 virus variants (clades) identified up to mid-April 2021 were downloaded from the Nextstrain platform.^{54–56} We assumed that if a strain was observed on a given date, it could be observed in a range of ± 14 days from the observation date. Because the data were not reported daily, linear interpolation was used to impute missing observations, assuming zeros a month before the first and after the last (if up to 1 March 2021) reported occurrence of a variant. Finally, data were smoothed with the use of 14-day moving average.

Countries’ characteristics were obtained from Our World in Data, Eurostat, the National Centers for Environmental Information, Aviation Intelligence Portal, and Google COVID-19 Community Mobility Reports.^{24,57–60} Data on arrival flights and mobility were smoothed using 7-day moving average.

Statistical analysis

Regression analysis was used to investigate the association between COVID-19 mortality and daily reported time-varying variables and fixed covariates.

The primary analysis of the daily number of COVID-19 deaths was performed with the use of non-linear Poisson mixed model with random country-level intercept and mobility effect. The considered period was from the date of the first reported death in Europe, 29 January 2020, up to 15 April 2021.

Owing to the presence of autocorrelations, and to consider the fact that the number of infections on a given day is dependent on the number of infectious cases in the population over previous days which translates into the respective number of deaths, the model was adjusted for the logarithm of the daily number of COVID-19 deaths reported 7 days earlier. To capture the fact that increasing or decreasing trends in COVID-19 mortality over time are generally stable over several weeks or months, the logarithm of quotient of COVID-19 deaths 7 days before divided by deaths 14 days before the actual date was added as a covariate. All other time-varying variables were considered with a 21-day lag, to account for the virus incubation period, assuming 7 days from contact to symptoms onset, and a delay between symptoms onset and death due to the disease, assuming another 14 days. In addition, heterogeneity between countries was considered with random intercepts and mobility effects varying between countries.

Assuming M indicates mortality with vaccination coverage ' c ', M_0 is the mortality without vaccination, and ' VE ' represents the vaccine efficacy, we have:

$$M = M_0 \cdot (1 - c \cdot VE).$$

After applying the logarithmic transformation and considering a set of covariates x_1, \dots, x_k and random effects u_0, u_1, \dots, u_n on intercept and selected x_1, \dots, x_n , this equation was extended as shown in the following to specify the non-linear model:

$$\begin{aligned} \text{Log}(E(M)) &= \beta_0 + \text{Log}((1 - c \cdot VE)) + \\ &\beta_1 x_1 + \dots + \beta_k x_k + u_0 + u_1 x_1 + \dots + u_n x_n. \end{aligned}$$

For the exploratory analysis, vaccine efficacy against B.1.1.7 and non-B.1.1.7 variants was analyzed using a similar approach. Assuming that there are two classes of virus variants with known proportions equaled p_1 and p_2 , the vaccine efficacy could be considered as the average efficacy weighted by variants proportions:

$$VE = p_1 \cdot VE_1 + p_2 \cdot VE_2.$$

The formula for the non-linear model is then as follows:

$$\begin{aligned} \text{Log}(E(M)) &= \beta_0 + \text{Log}((1 - c \cdot (p_1 \cdot VE_1 + p_2 \cdot VE_2))) + \\ &\beta_1 x_1 + \dots + \beta_k x_k + u_0 + u_1 x_1 + \dots + u_n x_n. \end{aligned}$$

Additionally, three scenarios were tested as sensitivity analyses, varying either the time to symptoms onset or the time between symptoms onset and death. A detailed methodology is presented in [Supplementary Materials](#).

A P -value lower than 0.05 was considered as statistically significant. Akaike's information criterion (AIC) was provided to inform about models' fit statistic. Analyses were performed using SAS, version 9.4, software.

Results

Descriptive statistics

Descriptive statistics of outcomes and covariates across 32 countries included in the analysis, for the period between January 2020 and April 2021, are presented in [Table 1](#). Mean proportions of SARS-CoV-2 variants, EU2, EU1, and B.1.1.7, for each country are

presented in [Fig. 1](#). Until mid-April 2021, the variant EU2 was the most frequently spread for vast majority of countries, except Israel and the UK for which B.1.1.7 was more frequent, as well as Spain and Lithuania with EU1 being more commonly observed.

Primary analysis

Analysis of the non-linear Poisson mixed model of the number of COVID-19 deaths revealed that the effect of vaccination effectiveness against mortality was assessed as significant and equaled to 0.720 ($P < 0.001$; [Table 2](#)). Other covariates that were found significant in the model were temperature (-0.005 , $P < 0.001$), arrivals at airports (0.709, $P < 0.001$), and mobility change from the prepandemic level (0.753, $P < 0.001$). Variables used to account for autocorrelation and minimize the effect of trend were assessed as significant (Log of the number of daily COVID-19 deaths 7 days before: 0.926, $P < 0.001$; Log of the number of COVID-19 deaths 7 days before/14 days before: 0.158, $P < 0.010$). The random intercept variance was statistically significant, which indicated significant unexplained variability between countries (0.014, $P = 0.023$).

Exploratory analysis

Results of the analysis of the exploratory model revealed numerically lower vaccine effectiveness against B.1.1.7 than against non-B.1.1.7 variants, although the difference was not statistically significant (0.697, $P = 0.002$ and 0.778, $P = 0.049$, respectively; [Table 3](#)). The same set of covariates was found significant in the exploratory model as in the primary analysis: temperature (-0.005 , $P < 0.001$), arrivals at airports (0.703, $P < 0.001$), and mobility change from the prepandemic level (0.753, $P < 0.001$). Variables used to account for autocorrelation and minimize the effect of trend were assessed as significant (Log of the number of daily COVID-19 deaths 7 days before: 0.926, $P < 0.001$; Log of the number of COVID-19 deaths 7 days before/14 days before: 0.158, $P < 0.010$), as was the variance for random intercept (0.013, $P = 0.025$).

Sensitivity analysis

Sensitivity analyses yielded overall vaccination effectiveness estimates against mortality between 0.60 and 0.72 ([Fig. 2](#)). Regarding vaccination effectiveness associated with variants, two out of three scenarios provided consistent results with the main analysis, i.e., a trend towards lower effectiveness against the B.1.1.7 variant, and the opposite trend was observed in the remaining scenario ([Fig. 2](#)). Detailed results are provided in [Supplementary Materials](#).

Discussion

In this study, we investigated the association between daily mortality due to COVID-19 and vaccination coverage, proportions of SARS-CoV-2 variants, and additional factors, such as demographics, health, mobility, and meteorological variables, analyzing country-level data across Europe and Israel. Results of the analysis suggest that vaccination effectiveness against deaths is equal to 72% and that it is slightly lower against the B.1.1.7 variant than against non-B.1.1.7 variants (difference not statistically significant). These findings suggest lower effectiveness against death than reported efficacy against severe or critical disease course in clinical trials of vaccines (84–100%).^{25–29}

This lower-than-expected effectiveness might be explained by the difference in considered populations: clinical trials included restrictive populations, and our study covers general populations, irrespective of age, concomitant therapies, medical condition, and

Table 1
Descriptive statistics of outcomes and covariates across 32 countries (January 2020–April 2021).

Variable	N	Mean	Standard deviation	Median	Lower quartile	Upper quartile	Minimum	Maximum
Number of daily COVID-19 deaths	13,229	3.355	4.618	1.159	0.206	4.933	0	28.770
Proportion of vaccinated inhabitants	13,181	0.018	0.058	0	0	0	0	0.616
Proportion of 20A (EU2) variant	13,106	0.349	0.250	0.313	0.154	0.509	0	1.000
Proportion of 20E (EU1) variant	12,754	0.090	0.159	0	0	0.114	0	0.741
Proportion of 20I (B.1.1.7) variant	13,099	0.124	0.256	0	0	0.065	0	1.000
Max daily temperature	13,008	15.597	9.347	15.833	8.750	22.389	-17.111	43.111
Mean daily wind speed	13,010	6.227	3.353	5.600	3.700	8.100	0.100	25.800
Arrivals at two biggest airports	12,748	140.609	195.648	66.429	27.714	177.929	1.857	1780.143
Mobility change from prepandemic ^a	12,918	-0.217	0.170	-0.201	-0.322	-0.091	-0.792	0.199
Proportion of inhabitants aged ≥65 years	13,229	0.184	0.025	0.190	0.168	0.198	0.117	0.230
Diabetes prevalence	13,229	0.062	0.019	0.058	0.048	0.072	0.033	0.101
Cardiovascular death rate	13,229	2.037	1.124	1.535	1.148	2.783	0.861	5.398

^a Average mobility change from prepandemic level calculated across retail/recreation, transit stations, and groceries/pharmacies [0.01]. Descriptive statistics were calculated for 32 countries based on daily data between 29 January 2020 and 15 April 2021.

general condition. In particular, vaccinated people in real life are older on average than subjects enrolled in clinical trials (12.2% aged ≥55 years in the AstraZeneca trial; 24.7% aged ≥65 years in the Moderna trial; 33.5% aged ≥60 years in the Johnson & Johnson trial; 42.3% aged ≥55 years in the Pfizer trial). However, our results suggesting lower protection against the B.1.1.7 variant are consistent with reported data so far from in vivo experiments and patient-level studies, providing an external validation of these findings. Laboratory evidence revealed a slight reduction in neutralization against the B.1.1.7 variant compared with the original strain. Neutralization titers against this VOC were threefold lower when analyzing convalescent sera and 3.3-fold and 2.5-fold lower for Pfizer and AstraZeneca vaccinees, respectively.³⁰ Real-world studies on the B.1.1.7 VOC suggested that it caused increased

mortality compared with non-B.1.1.7 variants,^{15,61} which, therefore, might not have been contained with similar effectiveness by vaccination. Our results evoke the question of variants evading vaccine antibodies in the future and the need to adapt such vaccine for each new season, which was earlier suggested by experts.^{42,43}

While the utilization of individual-level data, collected in real-world setting, could provide more precise estimates of vaccine effectiveness, the use of aggregate data at country level also has a major advantage: the vaccination impact estimated in this analysis should capture the indirect protection provided by vaccination. If the vaccine protects against infection, the number of infectious cases would decrease as more people are vaccinated. The lower number of infectious cases in the population would lead to a reduced probability for susceptible individuals to get in contact

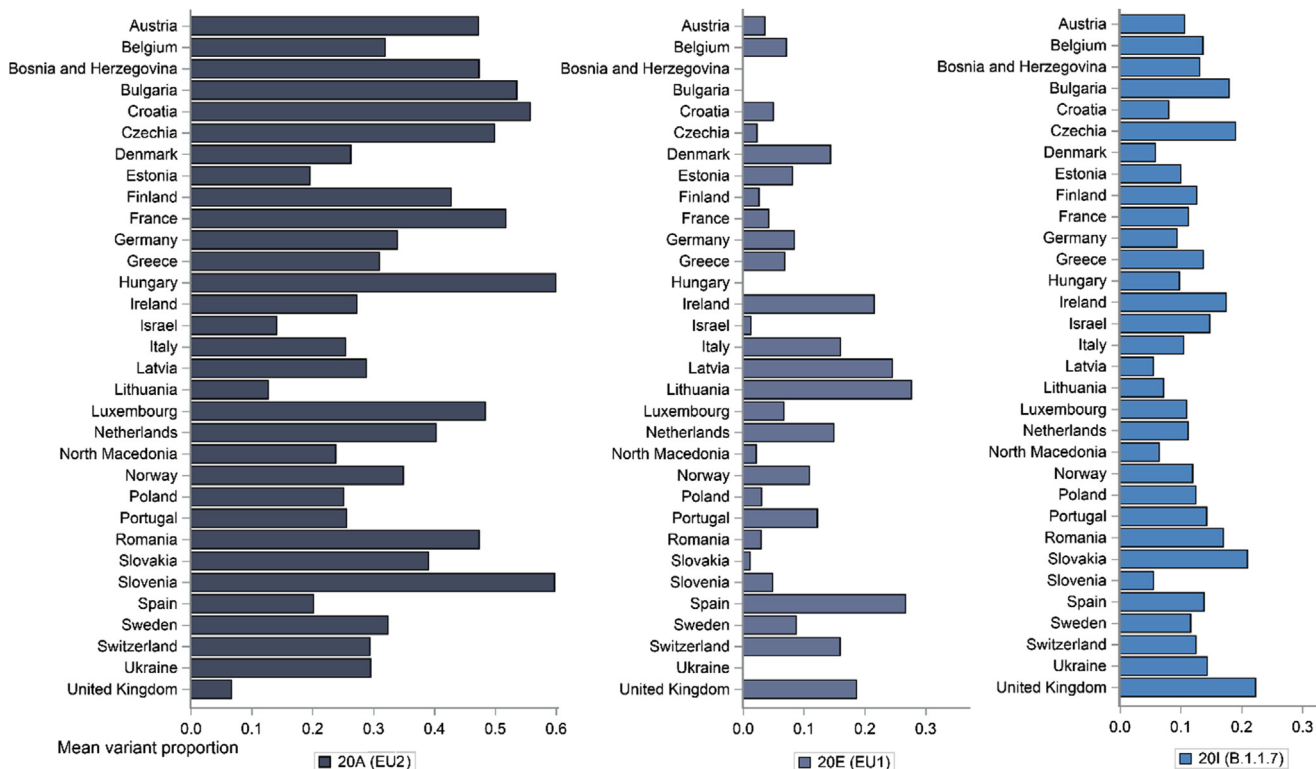


Fig. 1. Mean SARS-CoV-2 variants proportions across countries, between January 2020 and April 2021. Mean proportions of variants were calculated based on daily data on variants proportions across observed strains used to form Nextstrain clades (variants), between 29 January 2020 and 15 April 2021.

Table 2
Results of the non-linear Poisson mixed model of the number of daily COVID-19 deaths.

Variable	Estimate	Standard error	P value
Intercept	0.467	0.202	0.028
Logarithm of the number of daily COVID-19 deaths 7 days before ^a	0.926	0.007	<0.001
Logarithm of the number of COVID-19 deaths 7 days before/14 days before	0.158	0.015	<0.001
Proportion of 20A (EU2) variant ^b	0.012	0.036	0.746
Proportion of 20E (EU1) variant ^b	−0.032	0.046	0.501
Proportion of 20I (B.1.1.7) variant ^b	0.059	0.033	0.084
Max daily temperature ^b	−0.005	0.001	<0.001
Mean daily wind speed ^b	−0.002	0.002	0.351
Arrivals at two biggest airports [in thousands] ^b	0.709	0.085	<0.001
Mobility change from prepandemic ^{b,d}	0.753	0.064	<0.001
Proportion of inhabitants aged ≥65 years ^c	−1.238	0.930	0.193
Diabetes prevalence ^c	0.544	1.293	0.677
Cardiovascular death rate ^c	0.023	0.023	0.322
Vaccination effectiveness ^b	0.720	0.132	<0.001
Variance for RE on intercept	0.014	0.006	0.023
Variance for RE on mobility	0.036	0.023	0.126

AIC = 30,184.

Abbreviations: AIC = Akaike’s information criterion; mln = million; RE = random effects.

Non-linear Poisson mixed model of the daily number of COVID-19 deaths per 1 mln inhabitants, with country-specific random effects on intercept and mobility. Daily data for 32 countries were included, from 29 January 2020 to 15 April 2021. Assumed time to symptoms onset is 7 days; assumed time between symptoms onset and death is 14 days.

- ^a Time-varying variable with a 7-days lag.
- ^b Time-varying variable with a 21-days lag.
- ^c Fixed variable.
- ^d Average mobility change from prepandemic level calculated across retail/recreation, transit stations, and groceries/pharmacies [0.01].

with infectious cases, thus leading to a reduction in incidence among all people, including non-vaccinated people. This indirect protection can be captured when comparing different populations with different rates of vaccination coverage, but could not be captured when comparing vaccinated and non-vaccinated individuals from the same population. Interestingly, the fact that our estimated vaccine effectiveness is relatively low compared with vaccine efficacy reported in clinical trials suggests that there is no or little indirect protection provided by vaccination. This could indicate that the vaccine protects against disease but not against infection or that vaccinated groups of population are not those that contribute to the propagation of the virus.

A positive relationship between the number of arrivals at airports and mortality has been observed in this analysis, similarly as between mobility change and mortality. It suggests that both increased long-distance travel and increased mobility are strong predictors of growth in the daily number of COVID-19 deaths. These findings highlight the role of mobility reduction, both within and between countries, as an effective way to reduce COVID-19 mortality, especially when new virus variants spread across the world. Our results are in line with previous study by Jabłońska et al.⁵⁰ suggesting that countries with lower reduction in mobility at the beginning of the pandemic experienced a higher COVID-19 daily deaths peak. The role of social distancing was also underlined by

Table 3
Results of the non-linear Poisson mixed model of the number of daily COVID-19 deaths with interactions between variants proportions and vaccination effectiveness.

Variable	Estimate	Standard error	P value
Intercept	0.409	0.204	0.054
Logarithm of the number of daily COVID-19 deaths 7 days before ^a	0.926	0.007	<0.001
Logarithm of the number of COVID-19 deaths 7 days before/14 days before	0.158	0.015	<0.001
Proportion of 20A (EU2) variant ^b	0.012	0.036	0.747
Proportion of 20E (EU1) variant ^b	−0.034	0.047	0.467
Proportion of 20I (B.1.1.7) variant ^b	0.059	0.033	0.085
Max daily temperature ^b	−0.005	0.001	<0.001
Mean daily wind speed ^b	−0.002	0.002	0.346
Arrivals at two biggest airports [in thousands] ^b	0.703	0.085	<0.001
Mobility change from prepandemic ^{b,d}	0.753	0.064	<0.001
Proportion of inhabitants aged ≥65 years ^c	−0.805	0.925	0.391
Diabetes prevalence ^c	0.124	1.285	0.924
Cardiovascular death rate ^c	0.025	0.023	0.278
Vaccination effectiveness against 20I (B.1.1.7) ^b	0.697	0.201	0.002
Vaccination effectiveness against variants other than 20I (B.1.1.7) ^b	0.778	0.379	0.049
Variance for RE on intercept	0.013	0.006	0.025
Variance for RE on mobility	0.035	0.023	0.132

AIC = 30,186.

Abbreviations: AIC = Akaike’s information criterion; mln = million; RE = random effects.

Non-linear Poisson mixed model of the daily number of COVID-19 deaths per 1 mln inhabitants, with country-specific random effects on intercept and mobility, including interactions between variants proportions and vaccination effectiveness. Daily data for 32 countries were included, from 29 January 2020 to 15 April 2021. Assumed time to symptoms onset is 7 days; assumed time between symptoms onset and death is 14 days.

- ^a Time-varying variable with a 7-days lag.
- ^b Time-varying variable with a 21-days lag.
- ^c Fixed variable.
- ^d Average mobility change from prepandemic level calculated across retail/recreation, transit stations, and groceries/pharmacies [0.01].

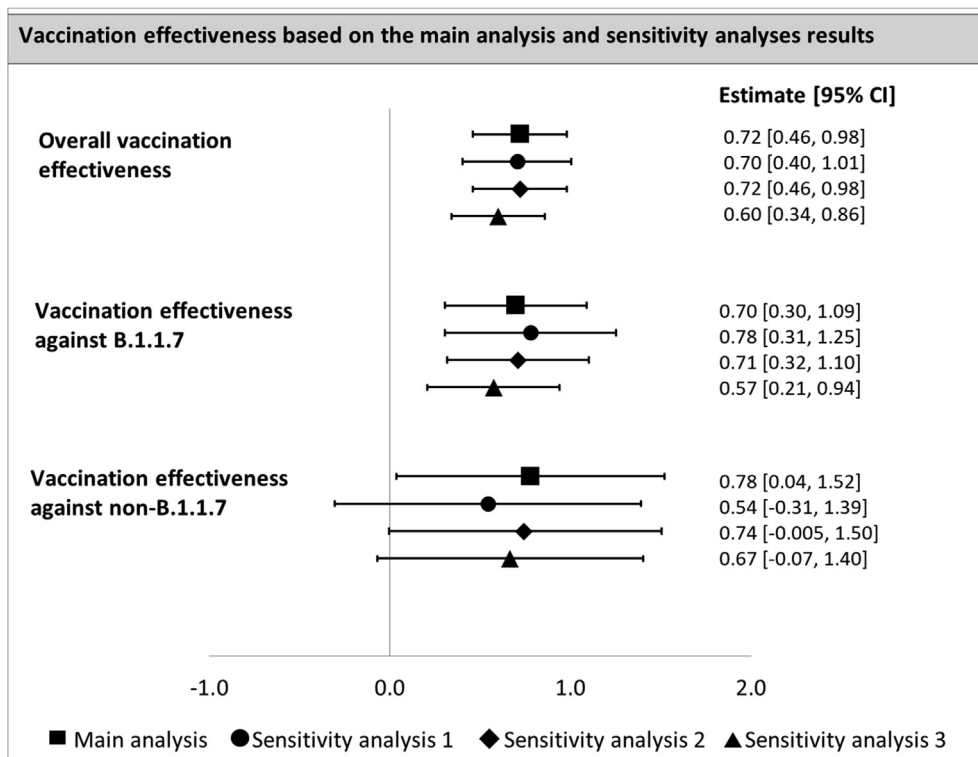


Fig. 2. Estimates of the vaccination effectiveness against mortality – main analysis and sensitivity analyses results. Abbreviations: 95% CI = 95% Confidence Interval. Assumptions of the analyses: Main analysis: time to onset = 7 days, time between symptoms onset and death = 14 days. Sensitivity analysis 1: time to onset = 14 days, time between symptoms onset and death = 14 days. Sensitivity analysis 2: time to onset = 14 days, time between symptoms onset and death = 7 days. Sensitivity analysis 3: time to onset = 7 days, time between symptoms onset and death = 7 days.

Badr et al.⁶² who observed a significant impact of mobility on COVID-19 transmission in the USA.

The daily temperature was found as a significant predictor of COVID-19 mortality in this study, with increasing temperature associated with the reduction in the number of deaths. Kerr et al.⁶³ found no consensus on the impact of meteorological factors on COVID-19 spread in their literature review; however, they suggested existence of environmental sensitivity of COVID-19, but not as significant as non-pharmaceutical interventions and human behavior. Several authors underlined that disease seasonality may exist,^{64–67} including Liu et al.⁶⁶ who found that COVID-19 infection and mortality rates were higher in colder climates and that the cold season caused an increase in total infections, while the warm season contributed to the opposite effect. Because our analysis covered a full annual cycle of COVID-19, our result suggests the possibility of seasonal variations in COVID-19 incidence. Such seasonality has been well established in temperate climate for other respiratory viruses.^{68,69}

Limitations

Our study has several limitations. First, our analysis was conducted on a country-level basis to estimate the vaccination efficacy, which should be seen as a less precise method than analysis of individual-level data, as previously noted. However, given the range of included countries, our results shed light on the problem of vaccination effectiveness from a broader perspective and investigate the effect of vaccination across societies, considering variability of vaccination coverage through time and between countries. Second, the quality of data on variants distribution varied between countries and was low for some of them; therefore, results

of the exploratory analysis should be treated with cautious. To limit bias and avoid fluctuations, we used methods of interpolation and smoothing. Countries with limited data were excluded. Third, the set of covariates used in the multivariate analysis can be assessed as non-exhaustive. We decided to consider factors that were previously assessed as significantly impacting the risk of severe illness or mortality from COVID-19 in the literature.^{44–53} Also, the significant random intercept observed in our models reflects unexplained between-countries variability resulting from the omission of influential variables. It was previously shown, for example, that COVID-19 mortality may be influenced by economic factors, which were not considered in this analysis.⁴⁶ Finally, we were not able to consider other new SARS-CoV-2 VOCs, except B.1.1.7, in the current analysis, which was due to their limited spread in Europe as of April 2021. It rises a need for further research on this topic in the future.

Conclusions

This study confirms a strong effectiveness of COVID-19 vaccination based on real-life public data, in terms of protection against deaths being around 72%, although it appears to be slightly lower than could be expected from clinical trial results. This suggests the absence of indirect protection for non-vaccinated individuals. Results also suggest that vaccination effectiveness against mortality associated with the B.1.1.7 variant is high but slightly lower than other variants (70% and 78%, respectively). Finally, this analysis confirms the role of mobility reduction, both within and between countries, as an effective way to reduce COVID-19 mortality and supports the possibility of seasonal variations in COVID-19 incidence.

Author statements

Ethical approval

Not required. This study does not require ethical approval as it was conducted on country-level data and involved information freely available in the public domain.

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Competing interests

None declared.

Contributors

MT conceptualized the study. KJ and SA validated the study concept. KJ and SA collected and analyzed the data. KJ, SA, and MT interpreted the results. KJ wrote the first draft of the manuscript. KJ, SA, and MT revised the manuscript and approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.puhe.2021.07.037>.

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