The Econometrics Journal

Econometrics Journal (2024), volume **00**, pp. 1–24.
https://doi.org/10.1093/ectj/utae005

Vaccination policy and mortality from COVID-19 in the European Union

ELEONORA AGOSTINI, FRANCESCO BLOISE AND MASSIMILIANO TANCIONI

Department of Economics and Law, Sapienza University of Rome, Rome, Italy.
Email: eleonora.agostini@uniroma1.it, francesco.bloise@uniroma1.it, massimiliano.tancioni@uniroma1.it

First version received: 26 September 2022; final version accepted: 29 August 2023.

Summary: This paper estimates the dynamic effect of vaccination on mortality from COVID-19 using weekly data from 26 European Union countries during 2021. Our analysis relies on the double machine learning method to control for multiple confounders, including nonpharmaceutical interventions, climate variables, mobility factors, variants of concern, country- and week-specific shocks. In our baseline specification, we show that a 10 percentage point increase in cumulative doses per hundred inhabitants averts 5.08 COVID-19 deaths per million inhabitants at the eight-week horizon and 26.41 deaths in the eight-week time window considered. The average reduction in mortality in this window is close to 50%. Further estimates reveal that the effect of doses administered to adults aged 18–59 does not statistically differ from that of doses received by people aged 60 and over. Finally, vaccine-specific estimates document that mRNA-1273 (Moderna) and Vaxzevria (AstraZeneca) are more cost-effective in saving lives than Comirnaty (Pfizer), while we are unable to demonstrate any effect of Ad26.COV2.S (Johnson & Johnson).

Keywords: *COVID-19*, *double machine learning*, *policy evaluation*, *vaccination*.

JEL codes: *C01*, *C23*, *I18*.

1. INTRODUCTION

As of 31 December 2021, the share of the European Union (EU) population fully vaccinated against the SARS-CoV2 was more than 69%, indicating the vaccine campaign implemented at the beginning of 2021 as one of the most critical public health policies implemented to date.[1] As the first round of the mass vaccination campaign has been completed, an analysis of its (cost) effectiveness in terms of mortality is key to both *ex post* evaluation of policies, and the calibration of perspective campaigns to which the balancing of nonpharmaceutical interventions (NPIs) is necessarily related.

From this perspective, this paper develops an observational analysis to determine the dynamic effect of total and type-specific (i.e., by manufacturer) vaccinations on COVID-19 deaths in EU countries, providing specific evidence regarding cost-effectiveness.

[1] This share indicates that 309.4 million European Union residents are fully vaccinated, with 193 vaccine doses administered per 100 people (Mathieu et al., 2020).

The primary motivation for our study is to complement the results of previous analyses on vaccines' efficacy from at least three perspectives. First, in contrast to the vast majority of studies in the literature targeting the causal effects of vaccines on transmission and symptomatic disease (Hodgson et al., 2021; Imai et al., 2021), we evaluate vaccines' effect on recorded deaths from COVID-19 and conduct a vaccine-specific cost-effectiveness analysis. Second, using publicly available real-world data, we focus our analysis on vaccines' effectiveness in the population rather than estimating efficacy in a controlled environment.[2] Third, we improve estimates of the dynamic effect of vaccination on deaths by using the recently developed double/debiased machine learning (DML) estimator (Chernozhukov et al., 2018), which is specifically designed to perform causal inference in the high-dimension case (i.e., when the number of potential confounders is higher than the number of observations).

We evaluate vaccines' effectiveness over a time window of 8 weeks (horizons). To this end, we first consider total doses administered to adults aged 18 and over, then distinguish between doses administered to adults below and above 60. We then repeat the estimates by considering the vaccine types approved by the European Medicine Agency (EMA) to evaluate possible heterogeneity in the effectiveness of the two viral vector vaccines, i.e., Vaxzevria (AstraZeneca, henceforth) and Ad26.COV2.S (Johnson & Johnson, or J&J), and the two gene vaccines, i.e., Comirnaty-BNT162b2 (Pfizer) and mRNA-1273 (Moderna).

To the best of our knowledge, this is the first study to estimate the effectiveness of specific vaccines against mortality from COVID-19 in a real-world data environment. Using the estimated vaccine-specific effectiveness and information regarding price by dose, we indicate the relative cost-effectiveness associated with specific compositions of the vaccination policy. The empirical assessment of the effectiveness of vaccination policy is obtained using aggregate EU country-level data and a set of statistical learning estimators encompassing a wide variety of epidemiological models.

It is noteworthy that the DML methodology satisfies the main requirements raised by our empirical setting. The policy intervention considered in our analysis (vaccines) is likely affected by high-dimensional endogeneity, as many variables dynamically influence the outcome variable (COVID-19-related deaths), possibly through unknown nonlinear relations. The willingness to be inoculated necessarily depends on idiosyncratic factors and responds to changes in pandemic conditions (Fernández-Villaverde and Jones, 2022), on the regulatory framework describing the strength and width of multiple and simultaneous NPIs (Mills and Rüttenauer, 2022), on informational campaigns (Loomba et al., 2021), and to complex and unclear relationships between human behaviour and policy in general (Chernozhukov et al., 2021; Laliotis and Minos, 2022). These factors unavoidably also affect the spread of contagion and resulting deaths.

We acknowledge that randomised-controlled trials (RCTs) are conceived as the 'gold standard' in evaluating specific causal associations; however, their implementation is not always promptly feasible and free of sample selection issues. For this reason, vaccine efficacy estimated in RCTs is not usually observed in real-world studies (Hodgson et al., 2021; Imai et al., 2021). Furthermore, assessing causality from highly selective real-world individual data can be methodologically challenging in environments where the outcome variable depends on the interplay of unobserved changes in human behaviour, social interaction, and vaccination policy.

[2] Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances. In contrast, effectiveness refers to its performance under real-world conditions (see Revicki and Frank, 1999, for a general pharmacological approach to the evaluative distinction, and Hodgson et al., 2021, for a study specifically related to COVID-19 vaccines).

An alternative strategy adopted in the literature is fitting mathematical epidemiological models to assess the effect of NPIs and vaccination on the spread of COVID-19 (Schneider et al., 2021; Cuñat and Zymek, 2022; Watson et al., 2022). This strategy allows to derive a counterfactual scenario without a vaccination campaign by eliminating the estimated vaccine efficacy parameters. However, the results of such approaches are model-specific (i.e., they are unavoidably affected by structural model misspecification and model uncertainty issues). In such circumstances, rational decision-making regarding the calibration of mass vaccine policies becomes demanding or unfeasible.

Considering the potential shortcomings of alternative approaches, we contend that our econometric strategy can provide a novel and robust contribution to the expanding literature on vaccines' effectiveness for three reasons: (i) the study avoids sample selection issues by targeting policy effectiveness in the population; (ii) it overcomes most of the complex endogeneity issues by controlling for a large set of potential confounders; (iii) it is not model-specific, as it can incorporate high-dimensional information sets to encompass and select from several structural models with unspecified, and possibly nonlinear, functional forms.

To feed our data-demanding empirical method, we construct a rich country-level dataset for the EU, gathering weekly data regarding COVID-19 deaths and vaccines for all of 2021, along with information referencing a large set of potential confounders. We can summarise our control set into four primary conceptual aggregates: (i) information on the pandemic's evolution, including data on testing and variants of concern (VOCs); (ii) data on NPIs, incorporating a collection of variables indicating the activation of social distancing measures; (iii) behaviour, approximated by location-specific human mobility; (iv) climatic variables.

DML-based results reveal that a 10 percentage point increase in administered COVID-19 vaccine doses per 100 inhabitants reduces fatal outcomes 8 weeks ahead by 5.08 per one million. The estimated effect of vaccines on death avoidance increases up to horizon 6, remaining approximately constant until the end of the estimation horizon. This dynamic pattern is consistent with previous research results demonstrating an increasing build-up of antibodies in the near term (Bradley et al., 2021; Naaber et al., 2021) and the reinforcing effects of multiple vaccine doses (Dagan et al., 2021). Considering the entire 8-week time window, the estimated reduction in deaths from a 10 percentage point increase in cumulative doses administered per 100 inhabitants is 26.41 per one million. Back-of-the-envelope calculations show that, on average, the reduction in mortality due to the EU vaccination campaign is about 48% in the 8-week time window. This result is at the lower end of the distribution of results reported in the literature (Meslé et al., 2021; Schneider et al., 2021; Nordström et al., 2022; Watson et al., 2022).

Disaggregating estimates by age group show that the effectiveness of doses administered to those aged 60 and over on COVID-19 deaths is higher than that of doses administered to people aged 18–59. Notably, this estimated difference is not statistically significant, possibly due to the limited sample size and indirect immunisation effects (reduced disease circulation) from the widespread vaccination of the population.

Type-specific estimates for the four EMA-approved vaccines show that all vaccines but J&J are effective in reducing COVID-19 deaths. The size of the estimated coefficients at the different time horizons is quite similar for AstraZeneca and Pfizer, while those for Moderna are higher at any horizon. Point estimates indicate that a 10 percentage point increase in administered doses of Moderna per 100 inhabitants saves 22.43 lives in one million at horizon 8. The same 10 percentage point increase in cumulative doses per 100 people of Pfizer (AstraZeneca) only saves 7.35 (5.65) lives in one million. Combining the vaccine-specific estimates and information and vaccine price by dose in EU contractual agreements, we determine that Moderna and AstraZeneca

are more cost-effective than Pfizer. One averted death at horizon 8 is equated with about $62,000 and $114,000 for AstraZeneca and Moderna, respectively. The cost for one averted death from the Pfizer vaccine is significantly higher, at nearly $315,000.

The paper is organised as follows. Section 2 summarises the literature to which our work is related. Section 3 describes the data employed in the analysis, providing some (aggregate) descriptive information regarding the outcome, treatment variables, and main confounders. Section 4 provides the details of the modelling and estimation strategy adopted to learn about the parameters of interest. Section 5 presents and discusses the results of the analysis, and Section 6 concludes.

2. LITERATURE REVIEW

The literature on vaccine efficacy is abundant but characterised by substantially heterogeneous findings. The studies to which our work is generally related have been conducted in specific periods and countries, targeting specific population segments, and using different methodologies. These consider both RCTs (Polack et al., 2020; Baden et al., 2021; Voysey et al., 2021) and real-world observational analyses, primarily based on contact-case and test-negative case-control individual data (Dagan et al., 2021; Lopez Bernal et al., 2021; Eyre et al., 2022), and on model-based evaluations and counterfactual simulations (Meslé et al., 2021; Schneider et al., 2021; Watson et al., 2022).

Although previous results suggest that vaccines against SARS-CoV-2 effectively prevent infection transmission and symptomatic disease, point estimates are quite sparse, possibly reflecting the (heterogeneous) specificity of various evaluation approaches and the time-specific characteristics of the pandemic. Imai et al. (2021) provide an early systematic review of the most significant results in the literature examining vaccine efficacy.

With the emergence of VOCs, the overall picture of vaccines' expected efficacy against transmission becomes even more uncertain (Pouwels et al., 2021; Eyre et al., 2022). In an observational study on transmission based on indexed patient contacts, Eyre et al. (2022) find that the point estimates of the adjusted risk rate ratios for vaccinated contacts are 0.48 and 0.32 with the Alpha variant, increasing to 0.76 and 0.50 with the Delta variant (for AstraZeneca and Pfizer, respectively).[3]

Evidence regarding vaccines' efficacy on fatal disease outcomes remains relatively scarce (Meslé et al., 2021; Nordström et al., 2022), primarily because of limitations in patient follow-up in RCT studies and observational analyses based on indexed patient contacts (Hodgson et al., 2021; Imai et al., 2021; Nordström et al., 2022). Among the limited number of studies addressing vaccines' efficacy against severe disease and death, Lopez Bernal et al. (2021) presents a test-negative case-control study on older patients in England, determining that the point estimate of the hazard ratio for being hospitalised after 14 days from vaccination is 0.57 for Pfizer and 0.63 for AstraZeneca. Due to follow-up issues, the hazard ratio for deaths is only estimated for patients aged 90+ and vaccinated with Pfizer, with a value of 0.49.

In a scenario study, based on expected COVID-19 deaths and hypothetical (fixed) coefficients for vaccine efficacy, Meslé et al. (2021) estimate that the vaccination campaign averted at least 51%

[3] The adjusted risk ratio is an intuitive measure comparing the risks for two groups (vaccinated and unvaccinated). A risk ratio greater than 1.0 indicates an increased risk for the exposed group in the numerator (vaccinated). A risk ratio of less than 1.0 indicates a decreased risk for the exposed group (i.e., the vaccination protects against disease transmission). The adjustment is made to render the two groups comparable.

of the expected deaths across World Health Organization (WHO) European regions. Schneider et al. (2021) conduct a study based on an age-stratified agent-based model to evaluate deaths averted by vaccination in the United States. The model is calibrated to match aggregate daily data for the period 1 October 2020–1 November 2021, considering estimates of vaccine efficacy in the literature. Vaccines' effectiveness is evaluated by considering model simulations against the pandemic evolution that would have prevailed under the counterfactual scenario of no vaccination programme. The results show an average 69% reduction of potential deaths in the United States during the observed period.

In a retrospective Swedish population study based on two-dose vaccinated (randomly matched) individuals observed from 28 December 2020 to 4 October 2021, Nordström et al. (2022) reveal progressively waning vaccine effectiveness against infection from any severe disease, leading to statistical ineffectiveness after seven months, with differences among vaccine types.[4] Waning effectiveness is less pronounced when considering severe disease and deaths (from 89% to 64% after four months), with this waning being stronger for older adults.

Watson et al. (2022) propose a mathematical modelling study based on a susceptible-exposed-infectious-recovered-susceptible (SEIRS) model (Walker et al., 2020; Hogan et al., 2021) extended to the consideration of vaccines to quantify the effectiveness of COVID-19 vaccination policies at the global level. The authors' model-based analysis, fitted to data from 185 countries from 8 December 2020 to 8 December 2021, shows that the vaccination campaign prevented 46% of official COVID-19 registered deaths and 63% of excess deaths at the global level, with nearly 30% of averted excess deaths in European countries.

Our paper also relates to the empirical literature in which quantitative policy evaluation relies on observational analyses using publicly available information at the aggregate level. Within the abundant COVID-19 literature, Cho (2020) and Flaxman et al. (2020) address the effectiveness of NPIs in eleven EU countries and Sweden, respectively. Chernozhukov et al. (2021) estimate the causal effect of the face mask mandates and other social distancing measures in the United States on new contagions and deaths by considering the relationship between human behaviour and government interventions. Bonacini et al. (2021) and Cerqueti et al. (2022) provide evidence of the effectiveness of the lockdown measures in Italy. Famiglietti and Leibovici (2022) estimate a structural panel vector autoregression for the United States to evaluate the effects of containment measures and economic aids on economic activity before the implementation of the vaccination policy.

Finally, the empirical methodology employed in our paper references previous and ongoing approaches to causal inference in which statistical learning is applied to manage high-dimensional control variable sets. In this vein, Belloni et al. (2014) provide the foundations of the methodologies belonging to this group, developed primarily using the least absolute shrinkage and selection operator (LASSO). Javanmard and Montanari (2014), Van de Geer et al. (2014), and Zhang and Zhang (2014) describe the asymptotic properties of the approach and provide insights for confidence intervals and hypothesis testing. Belloni et al. (2014) and Farrell (2015) develop the approach to cases in which confounders can interact with treatments. Dube et al. (2020) apply the DML estimator to depict the degree of monopsony in online labour markets.

[4] Pfizer: from 92% point estimated efficacy after 15–30 days to 47% after four months, and to 23% after six months; Moderna: from 96% efficacy after 15–30 days to 59% after four months; AstraZeneca shows a 68% efficacy after 15–30 days and becomes statistically not significant after four months; Heterologous AstraZeneca + mRNA vaccine: from 89% effectiveness after 15–30 days to 64% after four months.

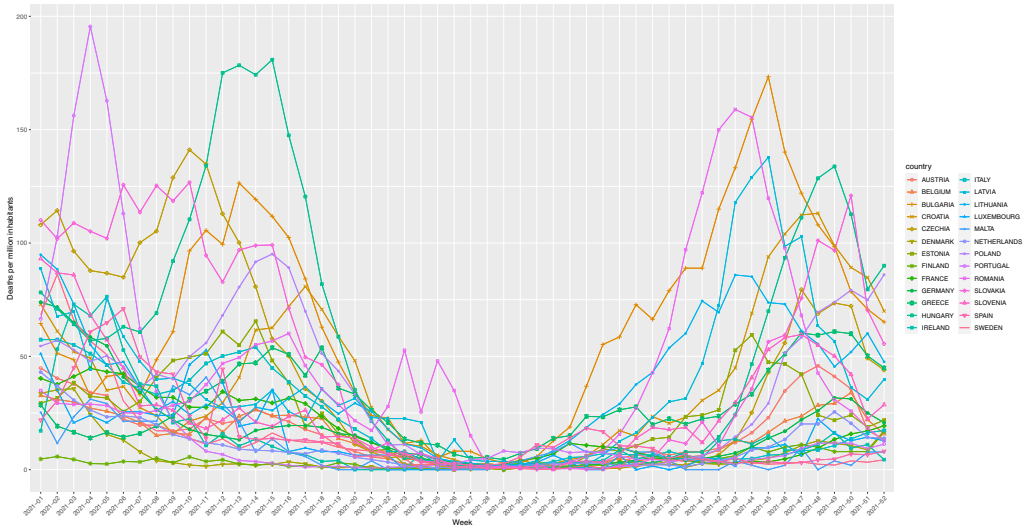

Figure 1. Weekly registered mortality from COVID-19 in European countries.
Notes: Authors' elaboration on the Our World in Data COVID-19 dataset.

3. DATA

We estimate the effect of vaccines on registered mortality from COVID-19 by constructing a rich dataset, including information on the evolution of the pandemic and many other potentially confounding factors obtained from different data sources. To focus on the core period of the European mass vaccination campaign, we consider in our sample weekly observations for 26 EU countries observed from the first to the last week of 2021. Among countries in the EU27 group, we exclude Cyprus from the analysis due to missing population mobility information. Our final sample amounts to 1,352 panel data observations. It is noteworthy that information on vaccine doses administered to the two age groups (below and above 60 years) is available for all the above countries except for the Netherlands. For this reason, we perform analyses by age group on a restricted sample of 25 countries observed over the entire 52 weeks period (1,300 country–week observations).

The variables considered in the analysis can be classified into four conceptual aggregates: (i) pandemic evolution and mass vaccination campaign; (ii) NPIs, consisting of a collection of 74 dichotomous variables indicating the activation of coded social distancing measures and a stringency index; (iii) location-specific human mobility; and (iv) climatic variables.

Pandemic and mass vaccination campaign data include observations of the number of swab tests per million inhabitants, the number of new confirmed cases of COVID-19 per million inhabitants, deaths attributed to COVID-19 per million inhabitants, and information regarding coded viral VOC and administered doses of vaccines. Data on tests, confirmed cases, and deaths are provided by the Our World in Data COVID-19 dataset, which collects information from the COVID-19 Data Repository of the Centre for Systems Science and Engineering at Johns Hopkins University (Mathieu et al., 2020). To eliminate the (likely noisily) daily variability, we convert daily observations on deaths, tests, and confirmed cases into weekly observations by aggregating

Table 1. Variants of concern considered in the analysis.

Code	Definition	Detection date	Severity
AY.4.2	N.A.	09/20, UK	Increase
B.1.1.529	N.A.	11/20, Mexico	Unknown
B.1.1.7	Alpha	09/20, UK	Increase
B.1.1.7+ E484K	N.A.	12/20, UK	Increase
B.1.351	N.A.	12/20, South Africa	Unclear
B.1.525	Eta	12/20, Nigeria	Unclear
B.1.617	N.A.	12/20, India	Unknown
B.1.617.1	Kappa	12/20, India	Unknown
B.1.617.2	Delta	12/20, India	Increase
B.1.617.3	N.A.	02/21, India	Unknown
B.1.621	Mu	01/21, Colombia	Unknown
C.37	Lambda	12/20, Peru	Unknown
P.1	Gamma	12/20, Brazil	Increase
Other	N.A.	N.A.	N.A.
Unknown	N.A.	N.A.	N.A.

Notes: Information regarding the date of detection and severity of each VOC is provided by the European Centre for Disease Prevention and Control (ECDC). The inclusion in the ECDC's VOC list follows the 31 May 2021 World Health Organization proposed labels.

the data over a defined day of each week (Sunday). Figure 1 presents the evolution of total deaths in the countries included in the analysis over time.

Information regarding the SARS-CoV-2 coded variants, released on a weekly basis, is obtained from the European Centre for Disease Prevention and Control (ECDC, 2022), which collects data submitted to the GISAID Initiative EpiCoV database and the European Surveillance System by laboratories operating in sequencing activities. For each VOC, we consider its incidence with respect to the volume of COVID-19 sequencing and the sequencing-to-cases ratio. The fraction of cases sequenced per week is based on the number of weekly cases provided by ECDC Epidemic Intelligence. A detailed description of the full set VOCs considered in our analysis is given in Table 1.

Data for the mass vaccination campaign provide information on the SARS-CoV-2 vaccine types administered in the EU, including AstraZeneca, Pfizer, Moderna, and J&J. We adopt the ECDC's convention, for which the total number of doses administered involves only the adult population (18+). Accordingly, our vaccination data refers to the weekly number of doses administered to adults (18+) and the population in two separate age groups (18–59 and 60+) as apportioned by the ECDC. We include all doses prescribed by the specific vaccination protocol and those administered as boosters (e.g., a third dose after a two-dose primary vaccination protocol for AstraZeneca, Pfizer, Moderna, or a second dose after one dose primary vaccination course for J&J). Table 2 presents descriptive information regarding total doses administered per 100 inhabitants and by vaccine type. Figure 2 presents the evolution over time of the mass vaccination campaign in the 26 European countries included in the analysis.[5]

Information regarding country-level NPIs is obtained from the ECDC. NPIs likely denote the most critical confounders in our analysis, given their influence on contagions, deaths, individuals'

[5] Figure 1 to Figure 6 in Section S2 of the Online Appendix present the evolution of the mass vaccination campaign by vaccine type (e.g., AstraZeneca, J&J, Moderna, and Pfizer) and age group (e.g., 18–59 and 60+).

Table 2. Administered vaccine doses in the EU during 2021 per 100 inhabitants, by type.

Vaccine type	Technology	Total doses per 100 inhabitants
All vaccines	Viral or gene	159.86
AstraZeneca	Viral vector	15.33
J&J	Viral vector	4.18
Pfizer	Gene-mRNA	116.77
Moderna	Gene-mRNA	23.58

Note: Data is obtained from the European Centre for Disease Prevention and Control's Vaccine Tracker.

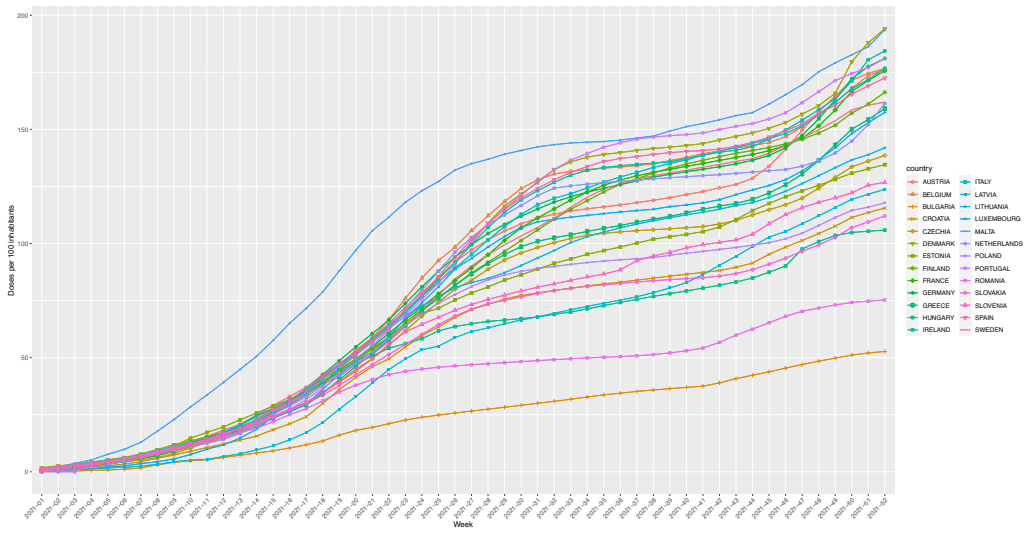

Figure 2. Cumulative administered vaccine doses in European countries.
Notes: Authors' elaboration on ECDC data.

behaviour, and participation in the vaccination campaign. To keep track of the social distancing measures adopted by national authorities to curb SARS-CoV-2 transmission, the ECDC catalogues 74 NPIs, based on information available from official country-level public sources. Information on NPIs indicates the date when a specific measure is issued or cancelled, and the strength of implementation when a measure is in place. The recorded NPI categories include cancellation of mass gatherings, closure of public spaces, closure of educational institutions, 'stay-at-home' recommendations, lockdowns, closure of economic activities, use of protective masks, teleworking, and closure of workplaces. Interventions can assume different levels of implementation (full strength or partial adoption). They can be mandatory or just recommendations, and refer to specific spaces (close/open) and the size of events. To create the weekly dataset of NPIs, the 74 ECDC NPIs are converted into 37 binary variables, set to 1 if the intervention is in place for more than three days per week, whether at partial or full strength, and 0 if it is implemented for three days or less.

Moreover, to provide insights on government policy response indicators, we also control for the stringency index sourced from the Oxford Coronavirus Government Response Tracker (Hale

et al., 2021). The stringency index is a composite measure based on nine metrics, including workplace closures, cancellation of public events, restrictions on public gatherings, closures of public transport, stay-at-home requirements, public information campaigns, restrictions on internal movements, and international travel controls. The index takes a value between 0 and 100, wherein a higher score indicates a stricter government response.

Mobility data are taken from the Google COVID-19 community mobility reports (Google LLC, 2022) to capture insights into population movement during the pandemic or independent behavioural adaptations in response to NPIs (Chernozhukov et al., 2021; Ilin et al., 2021). Mobility data refers to six locational categories of grocery and pharmacy, parks, transit stations, retail and recreation, residential, and workplaces. Since the data are provided at a daily frequency, we calculate seven-day averages to obtain weekly observations. For each 2021 week considered, all mobility variables are expressed as percentage deviations from the observed mobility in the corresponding week of a non-pandemic period.

Finally, we include weather condition variables to consider the role of seasonality in the spread of the SARS-CoV-2 pandemic (Bashir et al., 2020; Xie and Zhu, 2020). Weather condition data is provided by the professional platform Ogimet (2022), considering three meteorological variables, the average country-level temperature (expressed in Celsius), the concentration of vapor present in the air (denoting the likelihood of precipitation, fog, or saturation, expressed as percentage relative humidity), and the sunny hours per day. As in the case of mobility data, we calculate seven-day averages to obtain all weather condition variables on a weekly basis. Detailed information regarding the complete set of variables used in the analysis is presented in Section S1 of the Online Appendix.

4. METHODOLOGY

We develop our empirical analysis in two steps. First, we estimate the effectiveness of the 2021 vaccination policy against COVID-19 deaths on a panel of 26 European countries using the two-way Mundlak regression (TWM) described by Wooldridge (2021). Given that vaccination (our policy variable of interest) is highly endogenous due to multiple confounding factors with potential simultaneous correlations to both administered vaccine doses and COVID-related deaths, we include many control variables in our specifications together with week and country fixed effects.

In the second step of the analysis, we address potential bias due to possible nonlinearities among confounders and poor inference issues due to the high-dimensional control setting by exploiting the DML method developed by Chernozhukov et al. (2018). We apply the DML method as a natural extension of the TWM regression adopted in the first stage of the analysis.

4.1. Two-way mundlak estimates

We begin our empirical analysis by estimating the dynamic effect of administered vaccine doses on reported COVID-19 deaths through local projections (LP):[6]

$$d_{i,t+h} = \alpha + \theta v_{i,t} + \sum_{l=0}^{4} \rho_l x_{i,t-l} + \vartheta \bar{x}_i + \gamma \bar{x}_t + \varepsilon_{i,t+h}, \tag{4.1}$$

[6] For applications of the local (linear) projection method within different identification strategies, useful references include Jordà (2005), Jordà et al. (2013), Ramey (2016), Nakamura and Steinsson (2018), and Stock and Watson (2018).

where $d_{i,\,t+h}$ measures COVID-19 deaths per million inhabitants (i.e., mortality from COVID-19) in country i and week $t+h$, with $h = 1, 2, \ldots 8$; $v_{i,t}$ is our policy variable, which measures vaccine doses administered per 100 inhabitants; $x_{i,\,t}$ is a vector of controls including reported COVID-19 deaths, cases, and tests per million, NPIs (37 variables), the stringency index, Google mobility measures (six variables), climate variables (three variables); VOCs (sixteen variables); cumulative reported cases, deaths, and tests per million observed from the beginning of the pandemic to include the potential incidence of infection-induced immunity; and $\bar{x}_i$ and $\bar{x}_t$ respectively capture the country- and week-specific averages of all previously mentioned controls included in vector $x_{i,\,t}$ to consider any country- and week-specific shocks that are not captured by all other control variables. We further control for additional endogeneity deriving from a possible lag between the decision to get a dose of a specific vaccine and the actual vaccination by adding four lags of controls in the vector $x_{i,\,t}$. The inclusion of dynamic controls is based on the perspective that individuals' adaptive behaviour in response to an unexpected increase in either COVID-19 reported cases or deaths, or a change in policies, is likely slowed down due to incomplete information and psychological rigidities. By considering lagged controls, our dynamic specification described in (4.1) controls for 483 confounders and assumes a linear data-generating process for the outcome variable.[7]

By including the vectors $\bar{x}_i$ and $\bar{x}_t$ in (4.1), we are adopting the TWM approach recently described by Wooldridge (2021). Similar to what is demonstrated by Mundlak (1978) on the equivalence between the fixed effects estimator and the Mundlak regression, Wooldridge (2021), demonstrates that the TWM is fully equivalent to the two-way fixed effects (TWFE) method and can be adopted in any empirical context for which unit- and time-specific shocks should be controlled.[8]

We then estimate two additional specifications to capture possible differences in the effectiveness of vaccination against COVID-19 deaths by considering administered doses to two different population groups by age. The first considers people aged 18–59 years old. The second considers administered doses to inhabitants aged 60 years old and over. In this case, our age-specific specification is:

$$d_{i,t+h} = \alpha + \theta v_{i,t} + \varphi_a v^a_{i,t} + \sum_{l=0}^{4} \rho_l x_{i,t-l} + \vartheta \bar{x}_i + \gamma \bar{x}_t + \varepsilon_{i,t+h}, \tag{4.2}$$

where the policy variable $v_{i,t}$, in this case, measures the number of administered doses per million inhabitants of a specific age group (i.e., 18–59 and 60+ years) and $v^a_{i,t}$ controls for the concurrent administration of doses to the other age group to avoid possible endogeneity issues.

Finally, we estimate four additional specifications to determine the type-specific effectiveness of different COVID-19 EMA-approved vaccines on COVID-19-related deaths. To avoid endogeneity issues arising from the simultaneous administration of different vaccines, for each vaccine type iteratively chosen as the policy variable of interest, we further control for all other vaccine doses administered up to the same week. Accordingly, our vaccine-specific model becomes:

$$d_{i,t+h} = \alpha + \theta v_{i,t} + \sum_{k=1}^{3} \varphi_k v^k_{i,t} + \sum_{l=0}^{4} \rho_l x_{i,t-l} + \vartheta \bar{x}_i + \gamma \bar{x}_t + \varepsilon_{i,t+h}, \tag{4.3}$$

[7] Note that our final (operational) sample size is 1,040, given that we are considering up to the eighth horizon and up to the fourth lag of controls included in the vector $x_{i,\,t}$.

[8] The Mundlak regression replicates FE estimator results by including $\bar{x}_i$ on the right-hand side without employing the within transformation. To obtain the TWM, both $\bar{x}_i$ and $\bar{x}_t$ should be included on the right-hand side as controls.

where our policy variable $v_{i,t}$ measures the number of administered doses of a specific vaccine per million inhabitants (Pfizer, Moderna, AstraZeneca, or J&J), and $\sum_{k=1}^{3} \varphi_k v_{i,t}^k$ controls for the number of administered doses per 100 people of each of the other EMA-approved COVID-19 vaccines.

4.2. DML estimates

Notably, a favourable feature of aggregate-level analyses is that available information on potential controls is ample. However, the number of 'nuisance' parameters to be estimated in (4.1)–(4.3) are too large with respect to the sample size. In these cases, the TWM method (equivalent to the TWFE) produces biased estimates and poor inference with large standard errors, as the number of parameters to be estimated is vast and the time dimension is limited (Chernozhukov et al., 2018; 2021).

Further dimensionality issues may also arise in estimates since the way in which nuisance parameters map the outcome and treatment variable is unknown. In these cases, the conditional exogeneity-given-controls condition might be met only for a model's dimensionality making the analysis unfeasible or subject to overfitting. Specifically, the confounders' mapping might be non-additively linear, given the complex and unstable relationships linking human behaviour (thus contagious and fatal outcomes) and policy actions (NPIs and vaccinations).

Our final identification strategy relies on the DML method applied to the previously described TWM specification. The complete set of controls, including cross-sectional and time averages, can be easily included, without any further transformation, in the set of variables to be selected by the machine learning (ML) algorithms. DML combines ML algorithms, cross-fitting, and 'partialling out' regressions to minimise endogeneity issues while simultaneously overcoming both regularisation and overfitting biases. We hypothesise that endogeneity derives from highly complex data-generating processes for both the outcome and the treatment variables in our empirical framework. Accordingly, we let four different ML algorithms, LASSO, Elastic Net (EN), Random Forest, and XGBoost, learn the control variables to be considered and the specific functional form of the 'true' data-generating process of the outcome and the treatment variables. Among all possible ML algorithms, we consider LASSO and EN for sparsity and Random Forest and XGBoost to handle dimensionality reduction and high-order nonlinearities among controls.

The main advantage of DML is that it allows the inclusion of an extensive set of potential confounding factors (in the high-dimension case, the number of controls can be higher than the number of observations in the sample) while considering high-order interacting controls.[9] By considering possible nonlinearities among controls, we mitigate further endogeneity issues deriving from *country*week*-specific factors not captured by all other control variables. DML can be implemented by using the following partially linear model set-up:[10]

$$d_{i,t+h} = \theta v_{i,t} + g_d\left(x_{i,t}^{+}\right) + \epsilon_{i,t+h}, \qquad E\left(\epsilon_{i,t+h} | v_{i,t}, x_{i,t}^{+}\right) = 0 \tag{4.4}$$

$$v_{i,t} = g_v\left(x_{i,t}^{+}\right) + u_{i,t}^{v}, \qquad E\left(u_{i,t} | x_{i,t}^{+}\right) = 0, \tag{4.5}$$

where $d_{i,\,t+h}$ is COVID-19 deaths per million observed in country i at time $t+h$, $v_{i,t}$ is vaccine doses administered per 100 people, θ denotes the structural parameter of interest (the treatment

[9] LASSO searches for sparsity by using a regularisation parameter to select among the 483 controls included in our main specification. Random Forest automatically incorporates potential nonlinearities among regressors. It is easy to demonstrate that in the simplest case of two-order interaction terms among 483 controls, the number of potential controls is 116,886.

[10] A partially linear model allows for high-order nonlinearities among confounders while assuming a linear relationship between the outcome and the policy variables of interest.

effect), $x_{i,t}^{+}$ is a vector that includes the complete set of (contemporaneous and lagged) controls considered in (4.1), g_d and g_v are unknown and possibly non-additively linear functions, and $\epsilon_{i,t}$ and $u_{i,t}$ are conditionally zero-mean structural and reduced-form errors, respectively.

The basic approach of the DML estimator is to estimate the parameter θ by eliminating both regularisation bias and overfitting bias. The former derives from using some regularisation procedures (penalties) in ML to manage the variance-bias trade-off and minimise the prediction error. The latter emerges from the excessive adaptation of the model to specific data, which arises when the same observations are exploited to estimate parameters and make predictions with bad out-of-sample performance. As Chernozhukov et al. (2018) demonstrate, the two biases vanish by applying the Neyman orthogonality condition[11] and cross-fitting.[12]

DML relies on two reduced-form (thus, prediction) relations, $d_{i,t+h} = g_d^r\left(x_{i,t}^{+}\right) + u_{i,t+h}^{d}$ and $v_{i,t} = g_v\left(x_{i,t}^{+}\right) + u_{i,t}^{v}$, where $g_d^r \neq g_d$ denotes the reduced-form generic mapping function of the outcome variable, estimated by excluding the treatment variable from (4.4). Then, for each equation, the corresponding residuals are calculated, and the following partialling out regression is estimated:[13]

$$\hat{u}_{i,t+h}^{d} = \theta \hat{u}_{i,t}^{v} + \epsilon_{i,t+h}, \qquad h = 1, 2 \ldots 8, \tag{4.6}$$

To avoid overfitting, estimates can be obtained using cross-sample splits, in which subsamples (folds) are randomly drawn. In the simplest case of two-fold cross-fitting, with subsamples S_1 and S_2, the mapping functions g_d^r and g_v are estimated over the first subsample (S_1), and out-of-sample residuals are calculated on the second subsample (S_2), including observations that are not used to train the model. This procedure is repeated using S_2 to train the model and S_1 to obtain the out-of-sample residuals. The final parameter of interest θ is then estimated using a partialling out regression on the whole sample.

In this study, we implement the DML method in eight steps. (i) We randomly divide our original sample into a training sample (80% of observations) and a test sample (the remaining 20%). (ii) We run a ten-fold cross-validation procedure on the training sample to tune the ML algorithms for the outcome variable, specifically selecting the parameter in the case of LASSO, or the combination of parameters in the case of EN, Random Forest, and XGBoost, associated with the lowest prediction error.[14] (iii) We repeat the procedure described in point (ii) for the treatment variable (i.e., vaccine doses per 100 people). (iv) We select the two ML algorithms that best predict the outcome and treatment variables by calculating the corresponding out-of-sample R-squared on the test sample. (v) Once the best ML algorithms for the outcome and treatment variables are selected, we split the entire sample into five equally sized folds. (vi) We apply the cross-fitting procedure to each fold, specifically training a model for the outcome variable (i.e.,

[11] In practice, orthogonalisation is obtained from a residual-on-residual regression resembling Robinson's (1988) partialling out procedure, in which the confounder's mapping functions for the outcome and the treatment variables are obtained from (nonlinear) kernel regressions. The DML estimator replaces the kernel regressions with statistical learning methods that can manage multiple nuisance parameters even greater than the sample size.

[12] Cross-fitting extends the idea of the split-sample method to overcome the bias and slow convergence problems due to overfitting. Overfitting implies that g_d and g_v might capture some of the noisy component, leading to a spurious statistical association between the reduced-form residuals $\hat{u}_{i,t}^{d}$ and $\hat{u}_{i,t}^{v}$. Cross-fitting adds a second-round fit/estimation stage to the sample-split method, increasing the efficiency and statistical power of the estimator.

[13] Chernozhukov et al. (2021) adopt a similar strategy when applying the DML methodology to estimate the effect of NPIs for COVID-19 case and death counts three weeks ahead (21 days). In this case, the LP approach is adapted to the residual-on-residual partialling out strategy.

[14] A more detailed description of k-fold cross-validation and ML algorithms tuning is provided in Section S3 of the Online Appendix.

deaths per million) using 5–1 folds and computing the out-of-sample residual of the outcome variable on the remaining observations, which are not used to train the model. (vii) We repeat the cross-fitting procedure described in point (vi) for the treatment variable. (viii) Finally, we estimate the policy effect by applying the partialling out regression. In practice, we regress the out-of-sample residual of the outcome variable on the out-of-sample residual of the treatment variable using the corresponding ML algorithm for each of the equations that attains the highest out-of-sample R-squared.[15] This estimator can be defined as DML (best) since it uses the best performing algorithm for each of the two predicting Eqs. (4.4) and (4.5).

4.3. Limitations and caveats

Our observational analysis has some limitations and should be interpreted with caution. First, our estimated parameters can be interpreted as the (dynamic) causal impact of vaccination on mortality from COVID-19 only if the conditional exogeneity assumption holds. Our specification considers a broad set of controls to mitigate endogeneity deriving from unobservables that are simultaneously correlated to vaccination and mortality. However, we acknowledge that this strong assumption is unlikely to hold wholly in our case since vaccination can be endogenous to individual behaviour and precautionary measures adopted as a reaction to new information.

For instance, while we are indirectly controlling for endogeneity deriving from unobservables by considering country- and week-specific factors, and country-specific nonlinear trends (i.e., potential interaction terms between country- and week-specific factors), we cannot directly control for individual choices that influence the evolution of the pandemic such as the number of people wearing a mask, the number of those accurately washing their hands, or the number of individuals who enforce social distancing rules. For these reasons, generally characterizing nonexperimental analyses, causal identification may be problematic in our setting.[16]

Second, mobility and weather patterns measured at an aggregate level (i.e., EU countries) could not be representative of the conditions of most inhabitants. Given the potential variability of mobility and weather at the micro-level, the relationship between mortality, vaccination, mobility, and weather factors could be better assessed by considering a more disaggregated unit of analysis. Unfortunately, this limitation cannot be solved given that, to the best of our knowledge, reliable information on COVID-19 deaths and administered vaccine doses at a subnational level are unavailable for EU members.[17]

5. RESULTS AND DISCUSSION

In this section, we examine the results of the dynamic effect of the vaccination policy on mortality from COVID-19 in EU countries. First, we present our baseline results by focusing on total vaccine doses administered to the population aged 18+ years. Subsequently, we evaluate the potential differences in vaccination effectiveness by considering: (i) doses administered to individuals aged 18–59 years; (ii) doses administered to adults aged 60 years and over. Second, we examine the potential differences in the effectiveness of type-specific vaccines against COVID-19 deaths by

[15] As suggested by Chernozhukov et al. (2018), we repeat steps (v) to (vii) many times (i.e., 50 times) to minimise the dependence of our results on a unique five-fold sample splitting.

[16] See Cho (2020) and Chernozhukov et al. (2021) for a detailed discussion on endogeneity issues emerging from the interaction between containment policies, information on the pandemic, and human behaviour.

[17] Note that, by considering many possible data sources, we find data on vaccination and COVID-19 deaths by country subdivision for Poland only.

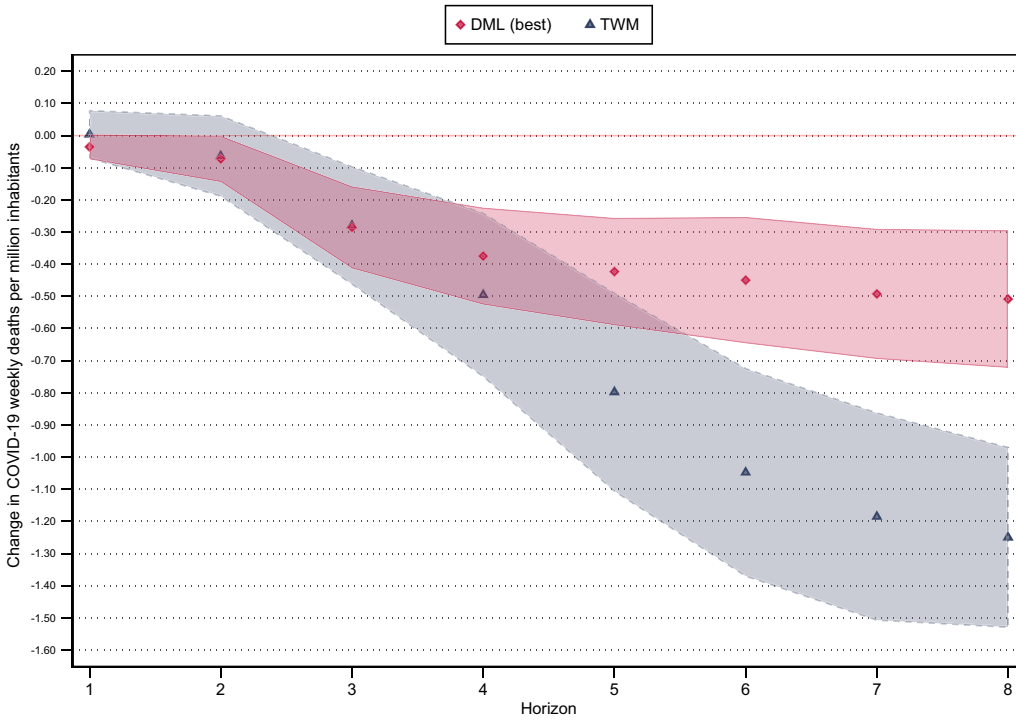

Figure 3. DML (best) and TWM estimates of the effectiveness of vaccination against mortality from COVID-19.

Notes: 90% confidence intervals are computed using clustered standard errors (at the country level). Control variables include deaths per million, cases per million, tests per million people, NPIs, mobility variables, climate factors, cumulative deaths per million, cumulative cases per million, cumulative tests per million, variants of concern, country- and week-level control variables, and their lagged values observed from $t-1$ to $t-4$.

Source: Authors' elaboration.

repeating the analysis for the two viral vector vaccines (i.e., AstraZeneca and J&J) and the two gene vaccines (i.e., Pfizer and Moderna) approved by the EMA. Finally, using vaccine-specific estimates, we present a cost-effectiveness analysis for the four EMA-approved vaccines. More precisely, we assess the cost of each vaccine type for preventing one COVID-19-related death according to the vaccine-specific price defined in the contractual agreements between producers and the European Commission.

5.1. Effectiveness of the vaccination policy against registered mortality from COVID-19

Figure 3 presents the estimated dynamic effect of vaccine doses administered to inhabitants aged 18+ over an eight-week horizon, with 90% confidence intervals.[18] Comparing TWM

[18] Standard errors are clustered at the country level by adopting the procedure recently developed by Chiang et al. (2022).

point estimates and DML (best) point estimates, reveals that the vaccination policy is effective in reducing COVID-19 death counts starting from horizon 3. This result is consistent with the reference literature, showing that most of the immunity is acquired in the first two weeks after vaccination, while death generally occurs one week after contagion. Lags in the efficacy of a single or double vaccine dose (i.e., most of immunity is acquired in the first two weeks after vaccination and death generally occurs one week after contagion) have been documented in early vaccine RCTs on transmission (Polack et al., 2020; Baden et al., 2021; Voysey et al., 2021) and subsequent clinical trials addressing the dynamics of the antibody response (Bradley et al., 2021; Naaber et al., 2021).

Interestingly, while the size of TWM estimated coefficients consistently increases from horizon 1 to horizon 8, DML (best) estimates become relatively stable from horizon 7, with estimated coefficients close to −0.50. This result likely occurs because TWM coefficients are dynamically biased, as they do not consider any possible nonlinearity among control variables, which can capture country-specific trends in the weekly death counts that are simultaneously associated with vaccinations.[19] Focusing on horizon 8, the DML (best) point estimate is −0.508, indicating that a 10 percentage point increase in cumulative doses administered per 100 inhabitants (about 1,720,000 more vaccine doses at the population average in our sample) reduces the weekly COVID-19 death count by 5.08 per million inhabitants at horizon 8 (about 87 averted weekly deaths if we consider the sample average for the population of 17.2 million people). Considering the whole 8-week time window, the estimated reduction in deaths from a 10 percentage point increase in cumulative doses administered per 100 inhabitants is 26.41 per million.

Back-of-the-envelope calculations can help provide approximate evidence on the proportion of COVID-19 averted deaths due to vaccination in the 8-week timespan considered. By using the sample average values of the population (17.2 million), COVID-19 deaths (22.5 weekly deaths per million inhabitants), and cumulative vaccine doses administered (63.1 per 100 inhabitants), the estimated reduction in COVID-19 deaths is 48.1% over the 8-week time window considered. Our result is at the lower end of the distribution of estimates in previous literature addressing the effectiveness of vaccination policies in reducing fatal outcomes. For instance, Meslé et al. (2021) propose a scenario analysis based on expected (no-policy) deaths and fixed vaccines' efficacy coefficients, showing that the vaccination campaign averted at least 51% of expected deaths in a no-policy scenario in EU-WHO countries. Schneider et al. (2021) simulate an estimated/calibrated age-stratified agent-based model, determining a point estimate of averted deaths due to the vaccination campaign in the United States close to 69%. In a retrospective-matched individual study on second-dose vaccination in the Swedish population, Nordström et al. (2022) estimate a reduction of severe and fatal outcomes ranging from 89% between two and three weeks to 64% after four months. In a simulation study based on a SEIRS global model, Watson et al. (2022) estimate averted expected deaths from the vaccination campaign close to 46% when considering COVID-19 registered fatalities, and 63% when considering excess mortality.

As stressed in Section 4.3, our results should be interpreted with caution due to additional uncontrolled endogeneity deriving from the interplay of human behaviour, vaccination, and contagion. Suppose vaccination is correlated to preventative measures that people take regardless of NPIs and the past dynamics of the pandemic. In that case, our estimated parameters are biased and should be interpreted as a mere association between vaccination and mortality. From an agnostic point of view, vaccination can be either positively or negatively correlated to individual

[19] At almost all horizons, XGBoost is the best performing algorithm. This algorithm considers high-order nonlinearities among confounders.

choices. Specifically, some individuals could get a vaccine dose in response to new information about COVID-19 risk of death and, at the same time, increase precautionary measures. Some others could instead substitute protective actions with vaccination. In the former case, the bias in our estimates would be positive; in the latter, our estimates would be downward biased.

Although we cannot directly control for the share of people taking preventative actions (e.g., wearing a face mask or washing their hands), we try to tackle this issue by testing the sensitivity of results to the inclusion of two additional 'behavioural' controls. Specifically, in the sensitivity analysis (Model 2) the vector $x_{i,t}^{+}$ of (4.4) includes two additional controls possibly capturing the propensity to get some information on the evolution of the pandemic and the attitude towards personal protective equipment (PPE). Compared to our baseline specification (Model 1), Model 2 considers also two Google Trends variables measuring the amount of search interest in two topics: *surgical face mask* and *coronavirus disease 2019*.[20]

Figure 9 in Section S4 of the Online Appendix compares the estimated parameters obtained from Model 1 to those from Model 2. Reassuringly, results are unchanged up to horizon 4. Starting from horizon 5, point estimates obtained from Model 2 are slightly higher, albeit not statistically different, than the corresponding parameters obtained from Model 1. This result suggests that individuals may weakly substitute precautionary measures with vaccination.

According to coefficients obtained from Model 2, the estimated reduction in deaths from a 10 percentage point increase in cumulative doses administered per 100 inhabitants is 30.44 per million over the 8-week horizon considered. Using back-of-the-envelope calculations, we can conclude that the estimated reduction in mortality from Model 2 (51.6%) is comparable to that obtained from Model 1 (48.1%). However, we acknowledge that even this sensitivity analysis cannot directly take into account voluntary actions that individuals may adopt to prevent contagion, which can be correlated to both vaccination and mortality from COVID-19.

5.2. Additional results by age group and vaccine type

The usefulness of a fourth dose of mRNA vaccines for fragile and elderly individuals (Bar-On et al., 2022; Regev-Yochay et al., 2022) and the possibility of targeting prospective vaccination campaigns to specific sections of the population (Kissling et al., 2022) is currently debated. To contribute to this debate, we use the same strategy to separately estimate the effect of vaccine doses administered to people aged 18–59 years and the effect of doses administered to those aged 60+. We find that the magnitude of the effect of vaccination on COVID-19 deaths is higher (in absolute value) for the elderly than for the younger population, starting from horizon 3 and up to horizon 8 (Figure 4). Specifically, at horizon 8, the estimated effectiveness of vaccination against COVID-19 deaths is −1.029 (−0.661) for the 60+ age group (18–59 age group). However, the latter difference is not statistically significant, possibly due to the limited sample size of our observational study and the emergence of the indirect effects of reduced disease circulation.[21]

To analyse possible differences in the effectiveness of specific vaccines against COVID-19 deaths, we perform disaggregated analyses by distinguishing administered doses for each of the four EMA-approved vaccines. The results are presented in Figure 5, indicating that all

[20] Search words are obtained from Google Trends (2022) and can be defined as terms or topics. A term is a specific word in a chosen language. In contrast, a topic is a group of terms that share the same concept in any language.

[21] Age-group estimates obtained by further controlling for the two Google Trends topics described in Section 5.1 are presented in Section S4 (Figure 10) of the Online Appendix. Disaggregated results by age group obtained using the TWM estimator are presented in Section S4 (Figure 7) of the Online Appendix. Note that when the DML method is not adopted, the results for the 60+ age group are counterintuitive and likely biased, as long as nonlinearities among confounders are not controlled for.

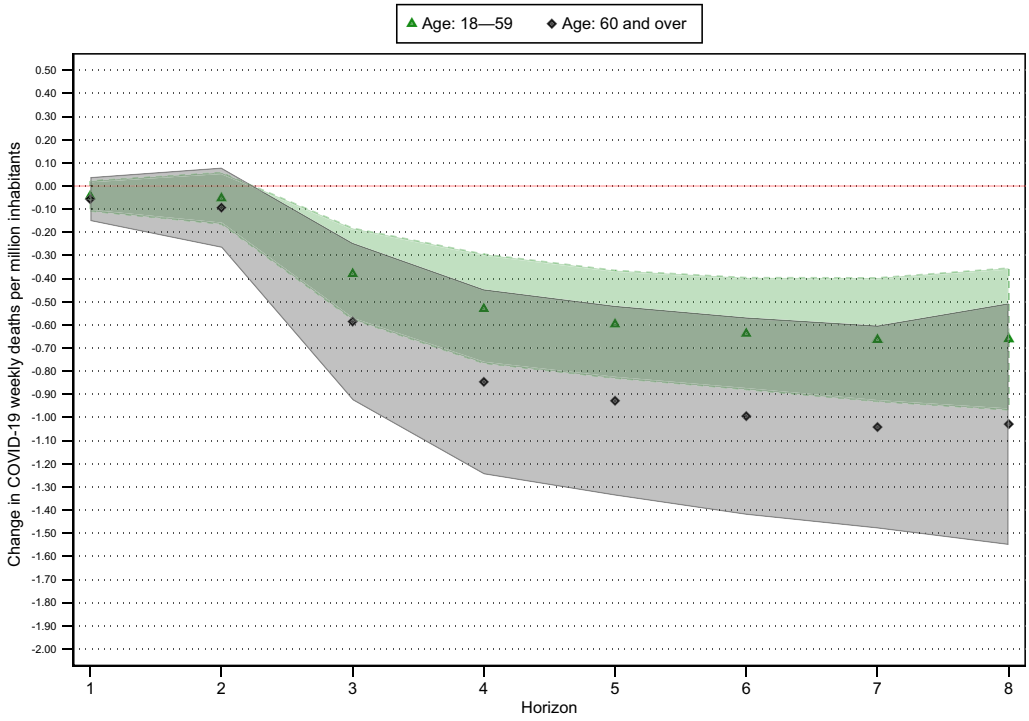

Figure 4. Effectiveness of doses administered to different age groups against overall mortality from COVID-19: DML (best) estimates.

Notes: 90% confidence intervals are computed using clustered standard errors (at the country level). Control variables include deaths per million, cases per million, tests per million, nonpharmaceutical interventions (NPIs), mobility variables, climate factors, cumulative deaths per million, cumulative cases per million, cumulative tests per million, variants of concern, country- and week-level control variables, and their lagged values observed from $t-1$ to $t-4$. For each age group chosen as a treatment variable, we also control for the other group.

Source: Authors' elaboration.

EMA-approved vaccines except J&J are effective in reducing COVID-19 deaths. Point estimates for Moderna are higher, albeit not statistically different, than those for AstraZeneca and Pfizer.[22]

5.3. Cost-effectiveness analysis

Although the estimated difference in the effectiveness of different vaccines against COVID-19 deaths is statistically significant for Moderna only, performing a cost-effectiveness analysis by investigating the differences in the price paid per single dose of a specific vaccine could

[22] Vaccine-specific estimates obtained by further controlling for the two Google Trends topics described in Section 5.1 are presented in Section S4 (Figure 11) of the Online Appendix. Disaggregated results by vaccine type obtained using the TWM estimator are presented in Section S4 (Figure 8) of the Online Appendix.

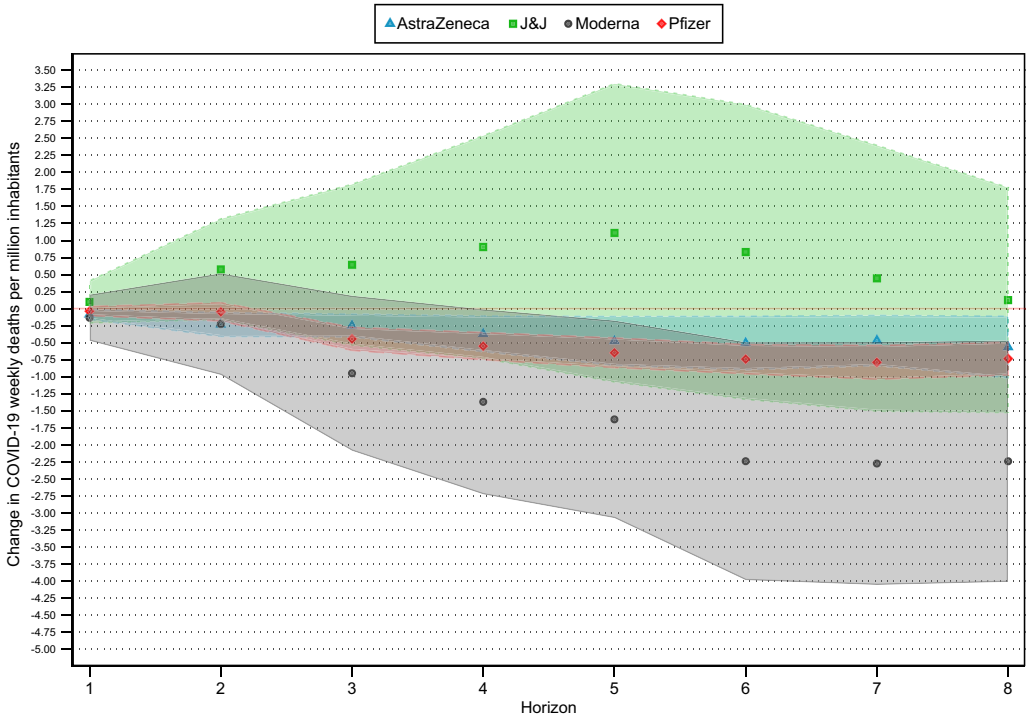

Figure 5. Effectiveness of different vaccines against mortality from COVID-19: DML (best) estimates.
Notes: 90% confidence intervals are computed using clustered standard errors (at the country level). Control variables include deaths per million, cases per million, tests per million, nonpharmaceutical interventions (NPIs), mobility variables, climate factors, cumulative deaths per million, cumulative cases per million, cumulative tests per million, variants of concern, country- and week-level control variables, and their lagged values observed from $t-1$ to $t-4$. For each vaccine chosen as a treatment variable, we also control for the other vaccines.
Source: Authors' elaboration.

still provide valid evidence for rational decision-making in public health policy implementation (Claxton, 2008).

The vaccination campaign implemented in EU countries was a fundamental public policy tool for mitigating the adverse effects of COVID-19; thus, the relaxation of NPIs and overcoming related economic costs (Famiglietti and Leibovici, 2022). Although all vaccines except J&J reduce the COVID-19 death count in the 8-week time window, Moderna seems to be the most effective COVID-19 vaccine against COVID-19 deaths.[23] Nevertheless, from a public policy perspective, it is not only essential to analyse the effectiveness of specific vaccines against COVID-19 deaths. It is also relevant to estimate their cost-effectiveness (i.e., a vaccine-specific cost for one death reduction). In principle, a cost-effectiveness analysis can inform policymakers on how to minimise the cost of vaccination campaigns while maintaining a constant number of

[23] The lack of cross-sectional variability and the low levels of cumulative administered doses (see Figure 2 in Section S3 of the Online Appendix) possibly explain the estimated noneffectiveness of the J&J vaccine.

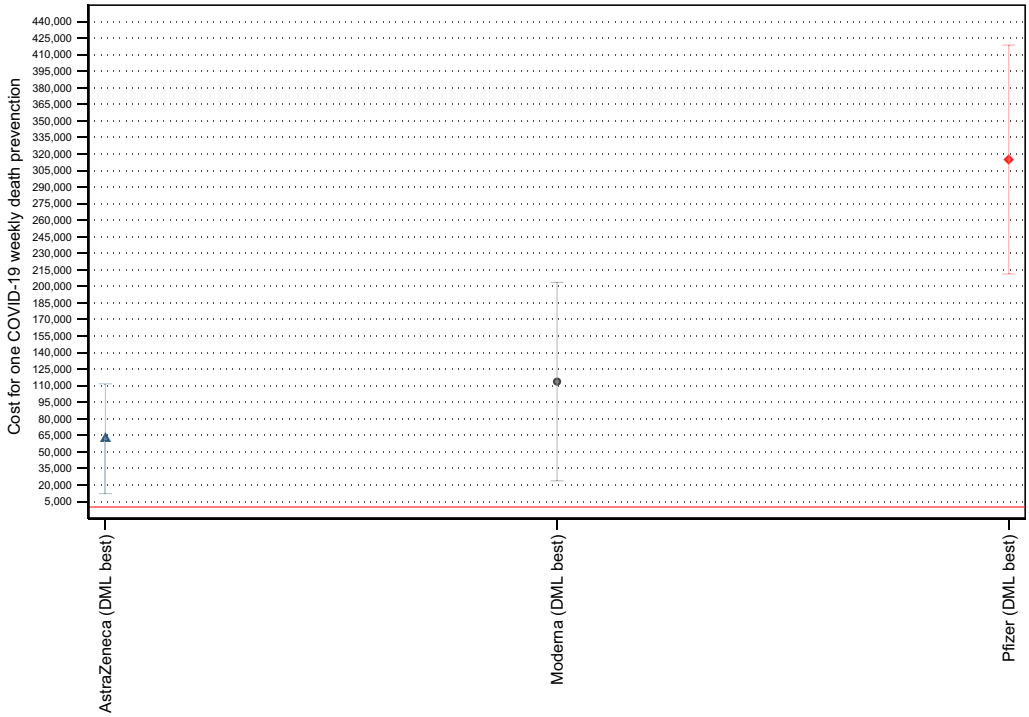

Figure 6. Cost-effectiveness of different vaccines at week $t + 8$: DML (best) estimates.
Notes: 90% confidence intervals are computed using clustered standard errors (at the country level). Control variables include deaths per million, cases per million, tests per million, nonpharmaceutical interventions (NPIs), mobility variables, climate factors, cumulative deaths per million, cumulative cases per million, cumulative tests per million, variants of concern, country- and week-level control variables, and their lagged values observed from $t - 1$ to $t - 4$. For each vaccine chosen as a treatment variable, we also control for the other vaccines.
Source: Authors' elaboration.

lives saved. Such analyses could be helpful for the implementation of future campaigns based on the purchase of specific vaccines against new variants.

Our cost-effectiveness analysis relies on the fact that the price for one dose varies significantly across different vaccines. According to official contractual agreements between vaccine producers and the European Commission provided by the UNICEF COVID-19 Vaccine Market Dashboard (29 April 2022), the price for one dose paid by European countries is $3.5 for AstraZeneca, $23.15 for Pfizer, and $25.50 for Moderna. We can thus provide evidence regarding the vaccine-specific cost for preventing one COVID-19 death using our vaccine-specific effectiveness estimates (Figure 5) evaluated at the eighth horizon and information on the vaccine-specific price paid for one dose by European countries.

Figure 6 shows that, considering the population of European countries at its sample average, the cost paid by public authorities for one COVID-19 death reduction is significantly lower when comparing AstraZeneca and Moderna vaccines with the Pfizer vaccine. Specifically, one

(weekly) averted death at horizon 8 costs about $62,000 and $114,000 for AstraZeneca and Moderna, respectively, with an insignificant statistical difference. In contrast, the cost for one COVID-19 averted death at the eighth week following treatment is significantly higher for the Pfizer vaccine, for which one (weekly) averted death costs around $315,000.

6. CONCLUSIONS

In this paper, we conducted an observational analysis to evaluate the effect of the 2021 EU vaccination policy and its cost-effectiveness, considering registered mortality from COVID-19 as the outcome variable. We contribute to the literature in two ways. First, due to the high degree of endogeneity of our policy variables and the goal of abstracting from a definite epidemiological model, we estimated the effectiveness of the vaccination policy against mortality from COVID-19 using the DML methodology. With this strategy, we consider a high-dimensional set of confounders, possibly affecting the outcome and treatment equations through unknown nonlinear relations. Second, we contribute to the research on vaccine effectiveness by estimating the effect of different vaccine types on mortality from COVID-19 to evaluate vaccine-specific cost-effectiveness.

Our findings demonstrate the general effectiveness of the vaccination policy adopted by EU countries in 2021 in averting COVID-19-related deaths. While we find that, except J&J, all other vaccines approved by the EMA have effectively reduced mortality at the horizons considered in the analysis (about two months), our estimates also indicate that their effectiveness is heterogeneous, with the Moderna vaccine outperforming the others.

By considering differences in the price of a single dose of vaccine, we determine that Moderna and AstraZeneca vaccines are more cost-effective than Pfizer's. In addition, we find that, although vaccines administered to inhabitants aged 60 years and above have a larger effect on deaths than those administered to adults below 60 years of age, the difference is not statistically significant, possibly because of the indirect effects of the widespread vaccination of the EU population and reductions in overall disease exposure.

Our analysis complements previous literature results on the effectiveness of vaccines against COVID-19 transmission, severe disease, and death; however, such studies remain quite scarce in addressing the disease's fatal outcome endpoint, and the few exceptions are primarily based on scenario analyses and mathematical simulation models. We argue that the outcomes from these approaches are necessarily affected by model and parameter uncertainty issues or by the specificity of the scenario assumptions behind counterfactual simulations. Consequently, our analysis might inform and contribute to the design of prospective vaccination policies in a later stage of a pandemic, when past evidence tends to rule out mass vaccination as a tool to build herd immunity. A substantial amount of information on vaccination policy has now been accumulated. It can provide insights into the expected effects and the related costs of specific vaccines for specific population targets.

Finally, we emphasise that our study is observational and should be interpreted with caution. Since the decision to get a vaccine dose is not exogenous to individual choices, it can be correlated to unobservables influencing the probability of contagion and death from COVID-19. Although we controlled for a high-dimensional set of potential confounders and we conducted sensitivity analysis with respect to our baseline regression specification, we carefully recognise that our results should not be interpreted as the causal impact of vaccination on mortality if the exogeneity-given-controls assumption does not hold.

ACKNOWLEDGEMENTS

We thank the editor and the two anonymous referees for their insightful suggestions that have substantially improved this article. We also thank Milos Ciganovic, Federico D'Amario, Francesco Simone Lucidi, and Michele Raitano for their helpful comments. All the remaining errors are ours.

REFERENCES

Baden, L. R. et al. (2021). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine 384*(5), 403–16.

Bar-On, Y. M., Y. Goldberg, M. Mandel, O. Bodenheimer, O. Amir, L. Freedman, S. Alroy-Preis, N. Ash, A. Huppert and R. Milo (2022). Protection by a fourth dose of BNT162b2 against Omicron in Israel. *New England Journal of Medicine 386*(18), 1712–20.

Bashir, M. F., B. Ma, Bilal, B. Komal, M. A. Bashir, D. Tan and M. Bashir (2020). Correlation between climate indicators and COVID-19 pandemic in New York, USA. *Science of the Total Environment 728*, 138835.

Belloni, A., V. Chernozhukov and C. Hansen (2014). Inference on treatment effects after selection among high-dimensional controls. *Review of Economic Studies 81*(2), 608–50.

Bonacini, L., G. Gallo and F. Patriarca (2021). Identifying policy challenges of COVID-19 in hardly reliable data and judging the success of lockdown measures. *Journal of Population Economics 34*(1), 275–301.

Bradley, T. et al. (2021). Antibody responses after a single dose of SARS-CoV-2 mRNA vaccine. *New England Journal of Medicine 384*(20), 1959–61.

Cerqueti, R., R. Coppier, A. Girardi and M. Ventura (2022). The sooner the better: Lives saved by the lockdown during the COVID-19 outbreak. The case of Italy. *Econometrics Journal 25*(1), 46–70.

Chernozhukov, V., D. Chetverikov, M. Demirer, E. Duflo, C. Hansen, W. Newey and J. Robins (2018). Double/debiased machine learning for treatment and structural parameters. *Econometrics Journal 21*(1), C1–C68.

Chernozhukov, V., H. Kasahara and P. Schrimpf (2021). Causal impact of masks, policies, behavior on early COVID-19 pandemic in the US. *Journal of Econometrics 220*(1), 23–62.

Chiang, H. D., K. Kato, Y. Ma and Y. Sasaki (2022). Multiway cluster robust double/debiased machine learning. *Journal of Business and Economic Statistics 40*(3), 1046–56.

Cho, S.-W. (2020). Quantifying the impact of nonpharmaceutical interventions during the COVID-19 outbreak: The case of Sweden. *Econometrics Journal 23*(3), 323–44.

Claxton, K. (2008). Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics 26*(9), 781–98.

Cuñat, A. and R. Zymek (2022). The (structural) gravity of epidemics. *European Economic Review 144*, 104082.

Dagan, N., N. Barda, E. Kepten, O. Miron, S. Perchik, M. A. Katz, M. A. Hernán, M. Lipsitch, B. Reis and R. D. Balicer (2021). BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine 384*(15), 1412–23.

Dube, A., J. Jacobs, S. Naidu and S. Suri (2020). Monopsony in online labor markets. *American Economic Review: Insights 2*(1), 33–46.

ECDC (2022). COVID-19 data sets. European Centre for Disease Prevention and Control. Available at: https://www.ecdc.europa.eu/en/covid-19/data.

Eyre, D. W., D. Taylor, M. Purver, D. Chapman, T. Fowler, K. B. Pouwels, A. S. Walker and T. E. Peto (2022). Effect of COVID-19 vaccination on transmission of alpha and delta variants. *New England Journal of Medicine 386*(8), 744–56.

Famiglietti, M. and F. Leibovici (2022). The impact of health and economic policies on the spread of COVID-19 and economic activity. *European Economic Review 144*, 104087.

Farrell, M. H. (2015). Robust inference on average treatment effects with possibly more covariates than observations. *Journal of Econometrics 189*(1), 1–23.

Fernández-Villaverde, J. and C. I. Jones (2022). Estimating and simulating a SIRD model of COVID-19 for many countries, states, and cities. *Journal of Economic Dynamics and Control 140*, 104318.

Flaxman, S. et al. (2020). Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature 584*(7820), 257–61.

Google LLC (2022). Google COVID-19 community mobility reports. Available at: https://www.google.com/covid19/mobility/.

Google Trends (2022). Google Trends. Available at: https://trends.google.com/trends/explore.

Hale, T. et al. (2021). A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nature Human Behaviour 5*(4), 529–38.

Hodgson, S. H., K. Mansatta, G. Mallett, V. Harris, K. R. Emary and A. J. Pollard (2021). What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infectious Diseases 21*(2), e26–e35.

Hogan, A. B. et al. (2021). Within-country age-based prioritisation, global allocation, and public health impact of a vaccine against SARS-CoV-2: A mathematical modelling analysis. *Vaccine 39*(22), 2995–3006.

Ilin, C., S. Annan-Phan, X. H. Tai, S. Mehra, S. Hsiang and J. E. Blumenstock (2021). Public mobility data enables COVID-19 forecasting and management at local and global scales. *Scientific Reports 11*(1), 1–11.

Imai, N. et al. (2021). Interpreting estimates of coronavirus disease 2019 (COVID-19) vaccine efficacy and effectiveness to inform simulation studies of vaccine impact: A systematic review. *Wellcome Open Research 6*, 185.

Javanmard, A. and A. Montanari (2014). Confidence intervals and hypothesis testing for high-dimensional regression. *Journal of Machine Learning Research 15*(1), 2869–909.

Jordà, Ò. (2005). Estimation and inference of impulse responses by local projections. *American Economic Review 95*(1), 161–82.

Jordà, Ò., M. Schularick and A. M. Taylor (2013). When credit bites back. *Journal of Money, Credit and Banking 45*(s2), 3–28.

Kissling, E. et al. (2022). Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: Multicentre analysis, I-MOVE-COVID-19 and ECDC networks, July to August 2021. *Eurosurveillance 27*(21), 2101104.

Laliotis, I. and D. Minos (2022). Religion, social interactions, and COVID-19 incidence in Western Germany. *European Economic Review 141*, 103992.

Loomba, S., A. de Figueiredo, S. J. Piatek, K. de Graaf and H. J. Larson (2021). Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. *Nature Human Behaviour 5*(3), 337–48.

Lopez Bernal, J. et al. (2021). Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. *BMJ 373*, n1088.

Mathieu, E. et al. (2020). Coronavirus pandemic (COVID-19). *Our World in Data*. Available at: https://ourworldindata.org/coronavirus.

Meslé, M. M. et al (2021). Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021. *Eurosurveillance 26*(47), 2101021.

Mills, M. C. and T. Rüttenauer (2022). The effect of mandatory COVID-19 certificates on vaccine uptake: Synthetic-control modelling of six countries. *The Lancet Public Health 7*(1), e15–e22.

Mundlak, Y. (1978). On the pooling of time series and cross section data. *Econometrica 46*(1), 69–85.

Naaber, P. et al. (2021). Dynamics of antibody response to BNT162b2 vaccine after six months: A longitudinal prospective study. *Lancet Regional Health-Europe 10*, 100208.

Nakamura, E. and J. Steinsson (2018). Identification in macroeconomics. *Journal of Economic Perspectives 32*(3), 59–86.

Nordström, P., M. Ballin and A. Nordström (2022). Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: A retrospective, total population cohort study in Sweden. *Lancet 399*(10327), 814–23.

Ogimet (2022). Meteorological country summaries, Ogimet. Available at: https://www.ogimet.com/resynops.phtml.en.

Polack, F. P. et al. (2020). Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *New England Journal of Medicine 383*(27), 2603–15.

Pouwels, K. B. et al. (2021). Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nature Medicine 27*(12), 2127–35.

Ramey, V. A. (2016). Macroeconomic shocks and their propagation. In J. B. Taylor and H. Uhlig (Eds.), *Handbook of Macroeconomics*, 2nd edn, vol. 2, 71–162. Amsterdam: North-Holland.

Regev-Yochay, G. et al. (2022). Efficacy of a fourth dose of COVID-19 mRNA vaccine against Omicron. *New England Journal of Medicine 386*(14), 1377–80.

Revicki, D. A. and L. Frank (1999). Pharmacoeconomic evaluation in the real world. *Pharmacoeconomics 15*(5), 423–34.

Robinson, P. M. (1988). Root-N-consistent semiparametric regression. *Econometrica 56*(4), 931–54.

Schneider, E. C., A. Shah, P. Sah, S. M. Moghadas, T. Vilches and A. Galvani (2021). The US COVID-19 vaccination program at one year: How many deaths and hospitalizations were averted. *Commonwealth Fund*, 14 December.

Stock, J. H. and M. W. Watson (2018). Identification and estimation of dynamic causal effects in macroeconomics using external instruments. *Economic Journal 128*(610), 917–48.

Van de Geer, S., P. Bühlmann, Y. Ritov and R. Dezeure (2014). On asymptotically optimal confidence regions and tests for high-dimensional models. *Annals of Statistics 42*(3), 1166–202.

Voysey, M. et al. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet 397*(10269), 99–111.

Walker, P. G., et al. (2020). The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. *Science 369*(6502), 413–22.

Watson, O. J., G. Barnsley, J. Toor, A. B. Hogan, P. Winskill and A. C. Ghani (2022). Global impact of the first year of COVID-19 vaccination: A mathematical modelling study. *Lancet Infectious Diseases 22*(9), 1293–302.

Wooldridge, J. M. (2021). Two-way fixed effects, the two-way Mundlak regression, and difference-in-differences estimators. Working Paper 3906345, SSRN.

Xie, J. and Y. Zhu (2020). Association between ambient temperature and COVID-19 infection in 122 cities from China. *Science of the Total Environment 724*, 138201.

Zhang, C.-H. and S. S. Zhang (2014). Confidence intervals for low dimensional parameters in high dimensional linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology) 76*(1), 217–42.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Online Appendix
Replication Package

Co-editor Victor Chernozhukov handled this manuscript.