BRIEF REPORT

Efficacy of COVID-19 vaccination in individuals designated as clinically extremely vulnerable in Scotland [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: Although COVID-19 vaccines have been shown to have high efficacy in the general population, it has not been established whether this applies to vulnerable groups. The objective of this study was to estimate the efficacy of vaccination in reducing the risk of severe COVID-19 among those designated as clinically extremely vulnerable in Scotland.

Methods: In a matched case-control design (REACT-SCOT), all 111295 cases of COVID-19 in Scotland diagnosed from 1 December 2020 to 16 March 2021 were matched for age, sex and primary care practice to 1093449 controls from the general population. This was linked to national data on vaccinations and those designated as clinically extremely vulnerable and thus eligible for shielding support. Severe COVID-19 was defined as cases with entry to critical care or fatal outcome. Rate ratios associated with vaccination within risk groups were estimated by conditional logistic regression.

Results: The rate ratio for severe COVID-19 associated with vaccination at least 14 days before was 0.29 (95% CI 0.22 to 0.37) in those eligible for shielding, compared with 0.29 (95% CI 0.25 to 0.34) in those ineligible for shielding. The rate ratio for hospitalized or fatal COVID-19 was 0.39 (95% CI 0.33 to 0.46) in those eligible and 0.37 (95% CI 0.33 to 0.41) in those not eligible for shielding. Examined by specific shielding conditions, the rate ratio for hospitalized or fatal COVID-19 ranged from 0.33 (95% CI 0.21 to 0.51) in those with specific cancers to 0.74 (95% CI 0.36 to 1.51) in solid organ transplant

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Any reports and responses or comments on the article can be found at the end of the article.

recipients, and 0.53 (95% CI 0.33 to 0.84) in others on immunosuppressants (excluding solid organ transplant recipients).

Conclusions: These results are reassuring with respect to efficacy in clinically vulnerable individuals including immunocompromised individuals, but studies in larger populations are needed to estimate efficacy in solid organ transplant recipients.

Keywords

COVID-19, record linkage, case-control studies, vaccination, efficacy, solid organ transplant, immunosuppression, severe respiratory disease, cancer

This article is included in the **Coronavirus** collection.

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Introduction

A primary-care based observational study that included cases diagnosed up to 15 Feb 2021 in Scotland estimated maximal efficacy of a single vaccine dose to be 70% for ChAdOx1 nCoV-19 and 85% for BNT162b2 mRNA at 28 days post-vaccination.¹ However policy on managing the epidemic depends critically upon the extent to which vaccination protects clinically vulnerable individuals, who account for most hospitalizations and deaths,² against severe COVID-19. What levels of vaccine efficacy pertain among those designated as clinically extremely vulnerable to COVID-19 is unclear. In Scotland early in the epidemic Public Health Scotland established a register of all those with certain conditions or on certain drugs that were likely to lead to extreme vulnerability to COVID-19 was established based on electronic health care records and primary care physician reporting.^{3,4} This register was used to determine eligibility for the national shielding support programme. We previously reported on the risk of severe COVID-19 in this shielding eligibility cohort compared to the rest of the population.⁵ If vaccine efficacy were estimated to be lower in clinically extremely vulnerable individuals than in the rest of the population, additional measures to shield these individuals would be needed until overall transmission rates in the population are low. Lower vaccine efficacy is possible since many such persons are immunocompromised or on immunosuppressants. Therefore, the aim of this study was to examine the efficacy of COVID-19 vaccination in reducing the risk of severe COVID-19 among those designated as clinically extremely vulnerable in Scotland.

Methods

This analysis is based on the REACT-SCOT matched case-control study, established at the beginning of the epidemic to investigate risk factors for severe COVID-19 in the population of Scotland.² We used this study to take advantage of data linkages already established. The design has been described in detail previously.² In brief, for every incident case of COVID-19 in the population ten controls matched for one-year age, sex and primary care practice and alive on the day of presentation of the case that they were matched to were selected using the Community Health Index database. COVID-19 cases are those with a positive nucleic acid test, or a hospital admission or death with COVID-19 ICD-10 codes. The REACT-SCOT case-control dataset is refreshed regularly and is linked to the vaccination database and to the regularly updated dataset of all individuals deemed eligible for the shielding programme.

As previously,² to minimise ascertainment bias we pre-specified the primary outcome measure as severe COVID-19, defined as cases with entry to critical care within 28 days of presentation or fatal outcome (any death within 28 days of a positive test or any death for which COVID-19 was coded as underlying cause). As previously, cases and controls were classified as eligible or ineligible for shielding.⁵ For further analyses, the shielding category was subdivided as described previously into six categories: solid organ transplant, specific cancers, severe respiratory conditions, other rare conditions, on immunosuppressants, and additional conditions.⁵ Those ineligible for shielding were classified according to the presence of conditions designated by public health agencies as “moderate risk conditions” as described previously.² This analysis is based on cases presenting from 1 December 2020 to 16 March 2021 (the latest linkage dataset available at the time of preparing this report).

Vaccination status in cases was coded as having had at least one dose of any vaccine at least 14 days before presentation date. This assigns cases (and their matched controls) who were vaccinated less than 14 days prior to the case date to the unexposed category. The numbers of cases and controls were too few to allow further subdivision of time since vaccination.

The effect of vaccination in each of the clinical vulnerability categories was estimated in a conditional logistic regression model (R function `survival::clogit`, package version_3.2-7, R version 3.6.3) fitted to the full dataset, specifying effects $\beta_{R2}, \dots, \beta_{RJ}$ for the log rate ratio associated with risk categories 2 to J ($\beta_{R1} = 0$ for the reference category $J = 1$), and nested effects $\beta_{V1}, \dots, \beta_{VJ}$ for the log rate ratio associated with vaccination in each of the J risk categories. With this incidence density sampling design, the conditional odds ratio is the rate ratio. The efficacy of vaccination is 1 minus the rate ratio. The strata in the conditional logistic regression model are matched sets: typically one case and up to 10 controls, but where two cases with the same age, sex and GP practice present on the same day the matched set comprises two cases and up to 20 controls. When estimating the rate ratio within a risk group such as a shielding category, only cases and controls in that risk group are retained in the matched sets. Matched sets in which all are vaccinated or none are vaccinated do not contribute to the rate ratio. We emphasize that the unconditional odds ratios calculated from summary tables of the vaccination status of cases and controls in each risk group cannot be used to estimate rate ratios.^{6,7} The design controls not only for the matching factors of age, sex and general practice but also for calendar time. Because severe COVID-19 is strongly associated with care home residence and care home residents were a priority group for vaccination, the model includes care home residence as a covariate.

Severe COVID-19 is strongly associated with recent hospital admission. This might confound the association of severe COVID-19 with vaccination if hospital admission causes vaccination appointments to be missed or alternatively if hospital admission increases the probability of being vaccinated by a given date. Therefore the analysis was repeated with adjustment for any hospital discharge from 2 to 8 weeks before presentation date, and for being an inpatient for at least 8 days before presentation date (the criterion for probable/definite hospital-acquired infection⁸). We also reported the vaccine efficacy for severe COVID-19 separating out those with conditions designated previously by Public Health Scotland as moderate risk from the remainder not eligible for shielding.

To allow inference on vaccine efficacy in smaller groups, the vaccine efficacy analysis was repeated with the case definition extended to include all cases that were hospitalized or fatal.

Ethical considerations

This study was performed within Public Health Scotland as part of its statutory duty to monitor and investigate public health problems. Under the [UK Policy Framework for Health and Social Care Research](#) set out by the NHS Health Research Authority, this does not fall within the definition of research and ethical review is not required. Individual

Figure 1. (a) Daily severe cases by risk category; (b) Controls eligible for shielding: proportion vaccinated at least 14 days before, by 7-day window of date on which they were sampled as controls.

consent is not required for Public Health Scotland staff to process personal data to perform specific tasks in the public interest that fall within its statutory role. The statutory basis for this is set out in Public Health Scotland's [privacy notice](#).

A Data Protection Impact Assessment (DPIA) allows Public Health Scotland staff to link existing datasets. This study was approved under COVID-19 Rapid DPIA 20210023. Datasets were de-identified before analysis.

Results

Over the study period there were 863 severe cases among those eligible for shielding of which 731 were fatal and 3482 severe cases among those not eligible for shielding of which 2641 were fatal. 97% of severe cases had a positive nucleic acid test for SARS-CoV-2 and this proportion did not differ between those eligible and ineligible for shielding. [Figure 1](#) shows the time course of daily severe cases in Scotland and vaccination among those eligible for shielding. The proportion vaccinated at least 14 days before is estimated from those sampled as controls who were eligible for shielding. From January to February 2020 the daily number of severe cases declined rapidly and the proportion vaccinated among those eligible for shielding rose from 2% to 87%. The association between vaccination and severe disease is thus confounded by calendar time. This confounding is controlled by the matching of cases and controls on calendar date but we reiterate that because of this the unconditional odds ratios calculated from [Tables 1 and 2](#) cannot be used to estimate rate ratios.⁷ Information about vaccine efficacy in those eligible for shielding is contributed by matched sets of cases and controls in the narrow time window during which incidence of severe COVID-19 was high and at least some of those eligible for shielding had been vaccinated at least 14 days before. Up to 16 March 2021 the proportion who had received a second dose at least 14 days before the date of sampling was very low: 1069 (0.06%) of the 1831776 controls ineligible for shielding and 33 (0.05%) of the 65573 controls eligible for shielding.

[Table 1](#) shows the vaccination status of severe cases and their controls by risk stratum. [Table 2](#) shows the same breakdown for hospitalised cases and controls. These tables illustrate that the data are very sparse for certain shielding groups especially solid organ transplant recipients.

Table 1. Numbers of controls and cases of severe COVID-19 by risk group and vaccination status.

	Controls		Cases	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Ineligible for shielding	30666 (85%)	5494 (15%)	2944 (85%)	538 (15%)
Solid organ transplant	38 (86%)	6 (14%)	25 (83%)	5 (17%)
Specific cancers	290 (83%)	60 (17%)	102 (87%)	15 (13%)
Severe respiratory	1287 (84%)	244 (16%)	328 (85%)	57 (15%)
Rare diseases	125 (83%)	25 (17%)	35 (81%)	8 (19%)
On immunosuppressants	284 (85%)	52 (15%)	52 (83%)	11 (17%)
Additional conditions	610 (81%)	145 (19%)	203 (90%)	22 (10%)

Presentation dates from 1 December 2020 to 16 March 2021.

Vaccine status coded as 1 if at least one dose at least 14 days before, 0 otherwise.

Table 2. Numbers of controls and cases of hospitalized or fatal COVID-19 by risk group and vaccination status.

	Controls		Cases	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Ineligible for shielding	78222 (86%)	13088 (14%)	7538 (87%)	1109 (13%)
Solid organ transplant	94 (78%)	27 (22%)	54 (77%)	16 (23%)
Specific cancers	588 (79%)	154 (21%)	183 (85%)	32 (15%)
Severe respiratory	2614 (81%)	624 (19%)	678 (84%)	125 (16%)
Rare diseases	254 (76%)	80 (24%)	59 (77%)	18 (23%)
On immunosuppressants	624 (80%)	159 (20%)	114 (80%)	29 (20%)
Additional conditions	1271 (79%)	348 (21%)	374 (83%)	78 (17%)

Presentation dates from 1 December 2020 to 16 March 2021.

Vaccine status coded as 1 if at least one dose at least 14 days before, 0 otherwise.

The rate ratio for severe COVID-19 associated with vaccination at least 14 days before was 0.29 (95% CI 0.22 to 0.37) in those eligible for shielding, compared with 0.29 (95% CI 0.25 to 0.34) in those ineligible for shielding. When inpatient stay for at least 8 days before presentation and any hospital discharge from 15 to 56 days before presentation were included as covariates, the corresponding rate ratios were 0.40 (95% CI 0.30 to 0.53) in those eligible and 0.39 (95% CI 0.33 to 0.46) in those ineligible for shielding. Table 3 gives a breakdown of the rate ratios for severe COVID-19 associated with vaccination by shielding condition. Point estimates for the rate ratio associated with vaccination in risk groups were similar to the estimated rate ratio in those not eligible for shielding, with the exception of solid organ transplant recipients and others on immunosuppressants in whom the numbers of cases were small (Table 1) and confidence intervals were wide.

When those ineligible for shielding were separated into those with moderate risk conditions and those with no risk condition the rate ratios for severe COVID-19 associated with vaccination were 0.26 (95% CI 0.22 to 0.30) and 0.37 (95% CI 0.29 to 0.47) respectively. Among people with diabetes who were ineligible for shielding (and thus in the “moderate risk conditions” category), the rate ratios for severe COVID-19 associated with vaccination were 0.09 (95% CI 0.01 to 0.70) and 0.16 (95% CI 0.11 to 0.22) in those with Type 1 and Type 2 diabetes respectively.

For a secondary analysis with larger numbers of cases, the case definition was broadened to include all hospitalized or fatal cases. The rate ratio for hospitalised or fatal COVID-19 was 0.39 (95% CI 0.33 to 0.46) in those eligible and 0.37 (95% CI 0.33 to 0.41) in those not eligible for shielding. Table 4 shows that there was evidence for efficacy in all groups except solid organ transplant recipients in whom even with this broader case definition the numbers of cases and controls were too small for efficacy to be estimated reliably.

Table 3. Rate ratios for severe COVID-19 associated with vaccination, within each risk group.

Effect	Rate ratio (95% CI)	p-value
Ineligible for shielding	0.29 (0.25, 0.34)	3×10^{-56}
Solid organ transplant	0.97 (0.26, 3.60)	1
Specific cancers	0.25 (0.13, 0.48)	3×10^{-5}
Severe respiratory	0.32 (0.22, 0.46)	4×10^{-10}
Rare diseases	0.33 (0.12, 0.88)	0.03
On immunosuppressants	0.48 (0.22, 1.06)	0.07
Additional conditions	0.16 (0.10, 0.28)	2×10^{-11}

Conditional logistic regression model matched on age, sex, general practice and presentation date.

Vaccine effects nested within each level of risk group.

Care home residence included as covariate.

Presentation dates from 1 December 2020 to 16 March 2021.

Vaccine status coded as 1 if at least one dose at least 14 days before, 0 otherwise.

Table 4. Rate ratios for hospitalized or fatal COVID-19 associated with vaccination within each risk group.

Effect	Rate ratio (95% CI)	p-value
Ineligible for shielding	0.37 (0.33, 0.41)	6×10^{-83}
Solid organ transplant	0.74 (0.36, 1.51)	0.4
Specific cancers	0.33 (0.21, 0.51)	5×10^{-7}
Severe respiratory	0.35 (0.28, 0.44)	6×10^{-19}
Rare diseases	0.43 (0.23, 0.80)	0.007
On immunosuppressants	0.53 (0.33, 0.84)	0.007
Additional conditions	0.39 (0.29, 0.53)	6×10^{-10}

Conditional logistic regression model matched on age, sex, general practice and presentation date.

Care home residence included as covariate.

Presentation dates from 1 December 2020 to 16 March 2021.

Vaccine status coded as 1 if at least one dose at least 14 days before, 0 otherwise.

Conclusions

Statement of principal findings

Efficacy of a single vaccination dose in protecting against severe COVID-19 was as high or higher in those eligible for shielding as in those without risk conditions. This is reassuring in the light of reports that vaccine-induced antibody conversion is impaired in clinically vulnerable groups such as those with haematologic malignancies⁹ and those on immunosuppressants for chronic inflammatory disease.¹⁰ However for solid organ transplant recipients – the group at highest risk among those eligible for shielding – the number of cases in the Scottish population is too small for the efficacy of vaccination to be estimated.

Strengths and limitations

Strengths of this analysis are the linkage to a pre-existing register of individuals designated as clinically extremely vulnerable, the ability to adjust for recent hospital exposure for which there was evidence of some confounding effect and the focus on severe COVID-19 rather than all test-positive cases. To ensure complete ascertainment of severe cases the case definition was pre-specified to include clinically diagnosed cases without a positive nucleic acid test; as only 3% of severe cases during the study period did not have a positive test, any diagnostic misclassification of these cases is unlikely to change the results appreciably. Limitations of our analysis are the small numbers with specific risk conditions, especially solid organ transplant recipients, and that the estimates of efficacy are effectively for first dose only as very few of those eligible for shielding had received a second dose of vaccine during the study period. Although data published by Public Health Scotland show that by 29 May 2021 90% of those eligible for shielding had received two vaccine doses, there have been too few cases of severe disease after February 2020 for an updated estimate of the efficacy of two doses in those eligible for shielding to be reliable. The estimates of vaccine efficacy that we report for the general population are similar to results reported from other countries but we cannot comment on generalizability with respect to the clinically extremely vulnerable, as studies of this in other countries have not been reported.

Comparison with other studies

These estimates of efficacy of a first dose of vaccine over all time periods from 14 days post-vaccination were similar to those estimated at 14-20 days post-vaccination for the total population of Scotland.¹ As we have previously shown that the shielding group overall have approximately six-fold higher risk of severe COVID-19 than those of the same age and sex without risk conditions,⁵ efficacy of at least 82% (a rate ratio no more than 0.18) with a single dose would be required to lower risk to the level of unvaccinated persons of the same age and sex without risk conditions.

Policy implications

Whilst these results give reassurance that the vaccine is showing efficacy overall in people with extreme clinical vulnerability to COVID-19, such persons should also be advised that they remain at increased risk after a single dose (about twofold compared to those of the same age and sex without risk conditions, given the vaccine-associated rate ratio of about 0.3), and should remain vigilant until they have received their second dose and background transmission rates in their locale are low. A study in a larger population is needed to estimate efficacy in solid organ transplant recipients. This would lay the basis for advising people in this group about their ongoing risk level, for whether to recommend a third dose of vaccine to improve immunogenicity,¹¹ and for assessing the need for development of alternatives to vaccines such as synthetic antibodies.

Declarations

Data availability

The component datasets used in this study are available via the [COVID-19 Research Database](#) hosted by Public Health Scotland's electronic Data Research and Innovation Service (eDRIS). A [guidance document](#) for applicants is available on the eDRIS website. There are no restrictions on eligibility to apply.

Analysis code available from: https://github.com/pmckeigue/covid-scotland_public/releases/tag/beta

Archived analysis code as at time of publication: <https://doi.org/10.5281/zenodo.5082340>

License: OSI

Acknowledgements

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Thank you for the invitation. In this study, McKeigue and colleagues evaluated the efficacy of vaccines in an extremely vulnerable population. This study is conducted with a good design, the research question is quite reasonable and hypothesis testing is also up to the mark. However, I have a few additions, if the authors could incorporate them in the revised version:

- The authors have to define a few terms in the methodology section under the heading of "operational definitions", these include a definition of a vulnerable population, definitions of vaccine efficacy (prime outcomes of the study), and definition of vaccine status.
- To my knowledge about statistics, the authors used appropriate and relevant tests to make an inferential comparison. However, I suggest putting the information on how variables opted for logistic regression.
- Please mention the total number of participants in the abstract section too.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious Diseases, Pharmaceutical Care, Nephrology, Vaccines

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 22 September 2021

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Andreas Martin Lisewski

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McKeigue and colleagues report from a controlled observational study on COVID-19 (mRNA and adenoviral vector) vaccine efficacy (VE) among the clinically vulnerable population in Scotland. These individuals were identified at increased risk for severe COVID-19 and thus were specifically eligible for shielding support through vaccination. The study was conducted between 1 December 2020 and 16 March 2021 and severe COVID-19 was defined "as cases with critical care or fatal outcome." It can thus be viewed as a continuation of earlier reports in a similar context (Vasileiou *et al.*, 2021¹)

While the authors' reasoning that has lead to the present study seems quite clear, the underlying COVID-19 epidemiology data from "Public Health Scotland" (PHS) for the above time period appears to be problematic.

Specifically, the "PHS COVID-19 Statistical Report, as of 21 June 2021" [2, p 28], reports mortality data that is directly relevant to the study by McKeigue *et al.*: the number of "overall deaths that have occurred within 28 days of a COVID-19 vaccination" between 8 December 2020 and 11 June 2021, where a total of 5522 people died within 28 days of receiving a COVID-19 vaccine in Scotland (number of days between vaccine and death is 0-27, where 0 is the day of vaccination, all age groups). In contrast, by comparing the 2015-19 death rate, 8718 deaths would have been

expected among the vaccinated population within 28 days of receiving their COVID-19 vaccination leading to mortality rate ratio of 0.59 (after 1 dose) and 0.66 (after 2 doses). When taking the 2020-21 death rate as reference [3], the overall reduction in mortality following COVID-19 vaccinations is even more striking because between Dec 2020 and June 2021 the number of deaths in Scotland was on average ~6% higher than in the corresponding 2015-19 months. Thus, following COVID-19 vaccination, we are facing an almost ~50% reduction in mortality across all causes of death during the study's relevant time period (Note 1: The remarks on page 29 of the PHS report do not explain this reduction. Note 2: During the same period, deaths involving COVID-19 [4] amounted to only about ~10% of the total deaths in Scotland.)

From these PHS data, it would be therefore possible to infer a considerable efficacy of COVID-19 vaccines against all causes of death, including COVID-19. Clearly, such a conclusion would be epidemiologically unacceptable.

Because the observational study of McKeigue *et al.* is apparently based on these PHS data (e.g., compare Fig. 1a in McKeigue *et al.* with Fig. 7 in [2]), I ask the authors to clarify the above anomaly in mortality associated with COVID-19 vaccinations as well as its relationship to their own results. Without such clarification their reported COVID-19 VE among vulnerable groups cannot be fully trusted. I even predict that a complete explanation of the above anomaly would be of considerable public interest.

In my opinion, this important point first needs to be comprehensively addressed before reviewing any further details of their manuscript.

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[4] <https://www.nrscotland.gov.uk/files//statistics/covid19/covid-deaths-21-data-week-36.xlsx>

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1. Vasileiou E, Simpson C, Shi T, Kerr S, et al.: Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *The Lancet*. 2021; **397** (10285): 1646-1657 [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: computational life sciences; infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 06 Oct 2021

Paul McKeigue, University of Edinburgh, Edinburgh, UK

The reviewer does not comment directly on our paper but rather queries whether the underlying dataset is correct. His concerns are based on a routine surveillance report from Public Health Scotland, not written by us, which reported a rate ratio of 0.59 for all-cause mortality in the first 28 days after first vaccination dose. As the reviewer notes, this is unlikely to be a causal effect of vaccination. The report from Public Health Scotland noted that this could be explained by a number of factors but did not elaborate further.

A plausible explanation for lower total mortality shortly after vaccination in vaccine recipients is allocation bias. Specifically, people who are terminally ill and likely to die in the next few weeks are less likely to attend when they are sent an appointment for vaccination. Thus mortality in the first few weeks after vaccination will be lower than the average for people of the same age and sex. On this basis we would predict that mortality from cancer and other conditions that cause death after prolonged illness would be especially low in the first few weeks after vaccination, but mortality from causes where deaths are often sudden (circulatory disease, external causes) would be reduced less.

Further comments can be found [here](#).

Competing Interests: Already disclosed in manuscript

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