COVID-19 autumn booster vaccine regression discontinuity analysis: protocol

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Background

The UK COVID-19 vaccination programme started offering the 2022 autumn booster to help mitigate the spread of COVID-19. People over 65 years, care home residents and their staff, housebound people, immunosuppressed people and people in other clinical high risk groups became eligible to receive the autumn booster vaccine from 12 September.(1,2) People aged 50-64 years became eligible starting from October 15.(3) This coincided with the rollout of the 2022/23 influenza vaccine, which became eligible to people who would turn 50 by March 2023 on 15 October.(3)

We used the OpenSAFELY-TPP database, covering 40% of English primary care practices in England and linked to national coronavirus surveillance, hospital episodes, and death registry data, to estimate the effect of the 2022 autumn booster campaign on COVID-19-related and all cause outcomes using a quasi-experimental study design, regression discontinuity.(4) This approach has previously been used to estimate the effectiveness of vaccines and vaccination programmes, including the first COVID-19 vaccine dose on COVID-19 mortality in England(5) and influenza vaccination in England and Wales.(6)

Objectives

Using a regression discontinuity analysis, our primary objective is to estimate the effectiveness of receipt of the COVID-19 autumn booster on COVID-19-related outcomes among people aged 50 years. Our secondary objective is to estimate the overall effectiveness of the combined autumn booster/influenza vaccination campaign.

Methods

Data source

This study will use the OpenSAFELY platform, providing secure access to the OpenSAFELY-TPP database containing primary care records managed by the GP software provider TPP, roughly 40% of English primary care practices in England. These recorded are linked, using NHS numbers, to A&E attendance and in-patient hospital spell records via NHS Digital's Hospital Episode Statistics (HES), national coronavirus testing records via the Second Generation Surveillance System (SGSS), and national death registry records from the Office for National Statistics (ONS). COVID-19 vaccination history is available in the GP record directly via the National Immunisation Management System (NIMS).

Study population

We will include all adults aged 45-54 years who were alive and registered at a GP practice using TPP's SystmOne clinical information system for at least 12 weeks prior to their index date, and have complete information on age and sex.

As certain groups of people within the age range of our study population became eligible for the autumn booster vaccine earlier in the season(1) and were not the target of the campaign of interest, we will exclude the following people:

- health or social care workers;
- residents in a care or nursing home and housebound people;
- part of any other clinically high-risk group, specifically:
  - anyone with one of the following conditions: chronic respiratory disease, chronic heart/vascular disease, chronic kidney disease, chronic liver disease,

chronic neurological disease, diabetes, immunosuppression, asplenia, morbid obesity, and/or severe mental illness;

– anyone with evidence of having received a third primary dose of the COVID-19 vaccine which may be a marker of immunosuppression.

We will also exclude people who are otherwise ineligible or unlikely to be vaccinated, including people who:

- Received a COVID-19 vaccine within 3 months prior to October 15;
- Have not received the first two doses of the COVID-19 vaccine;
- Reside in a care home;
- Are housebound;
- Are at the end of life.

Appendix Table 1 lists the exclusion criteria and their definitions. Clinically high-risk individuals will be identified using primary care data using the same approach as has been done previously (7,8).

Exposure

The exposure is eligibility for the autumn booster. Vaccine eligibility will be defined as being 50 years or older on the index date. Age will be measured in months on the index date. If there are few outcomes by age in months, we will consider combining months into 2-month or 3-month periods to increase power. As only the month of birth is recorded in OpenSAFELY, the date of birth will be set to the 15th of the month.

Primary outcomes

Our primary outcomes will be a composite outcome of COVID-19-related unplanned hospitalisation, A&E attendance, or death. Only unplanned admissions will be included as these are more likely to be due to incident COVID-19 disease. We have not included a positive COVID-19 test as an outcome due to under testing and bias associated with who gets tested.

Secondary outcomes

Due to potential mis-diagnosis of COVID-19 related outcomes, we will also include a composite outcome of respiratory unplanned admission or death.

To determine if the effect is COVID-19 specific or broader, we will look at all-cause unplanned hospital admission and all-cause deaths.

The definition and codes used to identify outcomes are in **Appendix Table 2**.

Other variables of interest

We will quantify uptake of the 2022/23 autumn booster by age over time. We will define receipt of the autumn booster as the presence of a third or fourth COVID-19 vaccination record on or after 5 September 2022 (the date autumn boosters first became available). We will construct a cumulative incidence curve of autumn booster uptake over the study period to visualise separation above/below the cutoff and how it changed over the study period.

We will also identify the following other characteristics:

- Receipt of influenza vaccine in 2022/23 season (defined as any influenza vaccine from July 2022 onwards);

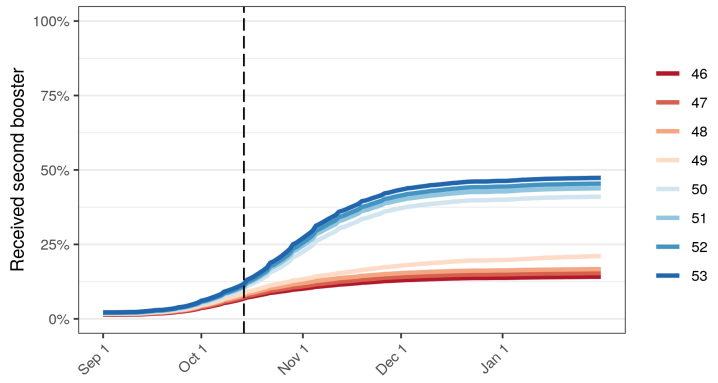
- Ethnicity (White, Mixed, Asian/Asian British, Black/Black British, Other, Unknown);
- Deprivation, measured by the English Index of Multiple Deprivation (IMD), grouped by quintile of national rank;
- Practice region (East, East Midlands, London, North East, North West, South East, South West, Yorkshire and The Humber);
- Sex (male, female).

We will plot the frequency distribution of these characteristics by age to identify any potential discontinuities at the cutoff.

Study design

We will have three index dates: 3 September 2022 (prior to start of vaccination campaign); 15 October 2022 (start of vaccination campaign); and 26 November 2022 (42 days after start of vaccination campaign). Follow-up will be split into 28-day periods after the index date, and will end at the end of available hospitalisation and mortality data in OpenSAFELY. The follow-up starting on 3 September will represent the pre-vaccination campaign period and act as a negative control. The 15 October period starts on the first date of the vaccination campaign; it is expected that during this time period, many people who were vaccinated would not have had enough time to develop full immunity. We expect to observe no difference in outcomes above/below age 50 in the first period; potentially a small difference in the second period; and the greatest difference in the third period. If a difference is observed in the first period, this suggests that other factors are contributing to any observed effect, rather than the vaccination campaign. If there are too few outcomes when using 28-day follow-up, we will consider extending this to 42 weeks or 56 weeks.

Figure. Percentage who received second COVID booster by age in years (preliminary data)



We will use both sharp and fuzzy regression discontinuity designs with age as the “forcing variable”, as they answer different research questions. The sharp design determines the intent-to-treat effect of the vaccination programme (rather than vaccination itself). As both the second booster and the influenza vaccine became available on the same date, this will represent the effect of both vaccination campaigns.

Using a fuzzy design, we will then estimate the effectiveness of receiving the vaccine. For this question, the fuzzy design is more appropriate as being 50 years or older increases the probability of receiving the vaccine, but does not predict it perfectly.

For the main analysis our bandwidth will be 5 years (60 months) either side of the cutoff.

Statistical Analysis

Outcomes will be expressed as the rate per 100,000 population. For a given index date and follow-up period, only the first event of a given type will be counted.

First, to estimate the impact of the vaccination program (sharp design), we will estimate the discontinuity in the probability of the outcome at the cut-off by fitting a regression model with an interaction between age (continuous) and a binary variable representing the vaccine age cutoff (50+ years). We will also include a variable for month of birth for additional precision. Age will be centred, so that "0" represents the cutoff. We will allow the slope of the change in the probability of the outcome by age to vary above and below the cutoff. Here, the estimated discontinuity will represent the intent-to-treat effect of being eligible for the COVID-19 second booster/influenza vaccine among people aged 50 years..

Second, we will use the instrumental variable approach to estimate the local average treatment effect (LATE); that is, the treatment effect among the compliers (i.e., people who only get vaccinated if they are above the cutoff). The instrumental variable is being 50 years or older. Here, we will use the two stage least squares regression analysis. We will first estimate the association between program eligibility and receipt of vaccination, and next use the predicted values from the first stage to predict the outcomes defined above. To estimate the effect of vaccination on outcomes, we will divide the association between turning 50 and each outcome, by the association of turning 50 on vaccination status. To account for receipt of flu vaccination, we will include this variable in the model as well.

Sensitivity analyses

We will perform the following sensitivity analyses and robustness checks:

- We will use different bandwidths, at 12 month intervals above/below the cutoff.
- Given that only month of birth is available in OpenSAFELY, we will exclude people within 3 months of the cutoff.

Software, code, and reproducibility

Data management and analyses will be conducted in Python version 3.8.10 and R version 4.0.2. All code will be shared openly for review and re-use under MIT open license at https://github.com/opensafely/vax-fourth-dose-RD.

This study will follow the STROBE-RECORD reporting guidelines.

Disclosure control

Any reported figures based on counts below 7 will be redacted and all counts will be rounded to nearest 5. Redaction and rounding combined will reduce the risk of both primary and secondary disclosure.

Appendix

Appendix Table 1. List of exclusion criteria and their definition. Unless otherwise stated, all criteria were identified using primary care date.

Exclusion criteria		**Definition**
JCVI high risk groups prioritised for vaccination(9)	Chronic respiratory disease (including poorly controlled asthma)	- Chronic respiratory disease diagnosis anytime prior to index date; - Asthma admission recorded in primary care anytime prior to index date; OR - Asthma diagnosis anytime prior to index date with a prescription for systemic steroids in each of the 3 months prior to the index date.
	Chronic heart disease and vascular disease	Diagnosis anytime prior to index date
	Chronic kidney disease	Diagnosis anytime prior to index date
	Chronic liver disease	Diagnosis anytime prior to index date
	Chronic neurological disease	Diagnosis anytime prior to index date
	Learning disability	Diagnosis anytime prior to index date
	Diabetes mellitus and other endocrine disorders	Diagnosis anytime prior to index date, either in the absence, or occurring after, a resolved diabetes code
	Immunosuppressed (including HIV/AIDS)	- Diagnosis of condition causing immunosuppression (including HIV infection/AIDS or solid organ transplant) anytime prior to index date; OR - Cancer diagnosis anytime in 3 years prior to index date; OR - Prescription for a chemotherapeutic, immunosuppressant, or immunomodulating medicine in 6 months prior to the index date
	Morbid obesity	- Diagnosis of severe obesity (BMI >=40) following date of BMI being recorded; OR - Most recent recorded BMI value >=40
	Asplenia	Diagnosis anytime prior to index date
	Severe mental illness	Diagnosis anytime prior to index date, either in the absence, or occurring after, a severe mental illness in remission code

Receipt of third or fourth booster dose prior to first availability to non-immunosuppressed population		Evidence of a third COVID-19 vaccination prior to 16 September 2021(10), or a fourth COVID-19 vaccination prior to 5 September 2022(3)
Health or social care worker		Stated that they were a health or social care worker when receiving at least one of their COVID-19 vaccinations
End of life		- Code indicating end of life recorded in primary care; OR - Prescription for midazolam injection indicated for treatment of pain at end of life anytime prior to index date.
Residents in a care or nursing home and housebound people		- Care home residence code anytime prior to index date; OR - Current address maps to list of care homes(11)
Housebound people		- Code indicating person is housebound, in absence of: a code indicating that the person is no longer housebound; a code indicating the person is in a care home

Appendix Table 2. List of codes used to define outcomes.

	Codelist
COVID-19 hospital admission	Unplanned hospital admission with any of the following ICD-10 codes in any position (primary or secondary): U071, U072, U099, U109
COVID-19 A&E attendance	A&E attendances with any of the following SNOMED codes: 1240751000000100, 1325161000000102, 1325171000000109, 132581000000106 (https://www.opencodelists.org/codelist/opensafely/covid-19-ae-diagnosis-codes/1df1c0b2)
COVID-19 death	Deaths with any of the following ICD-10 codes on the death certificate in any position (underlying or contributing): U071, U072, U099, U109
Respiratory admission	Unplanned hospital admission with any of the following ICD-10 codes in the primary position (J00-J99)
Respiratory death	Deaths with any of the following ICD-10 codes on the death certificate (underlying only): (J00-J99)

References

1. NHS England. NHS COVID-19 vaccine bookings to open to millions of people as autumn booster campaign kicks off [Internet]. 2022 [cited 2023 Mar 10]. Available from: https://www.england.nhs.uk/2022/09/vaccine-bookings-to-open-to-millions-of-people-as-autumn-booster-campaign-kicks-off/
2. NHS England. Over 65s can now book autumn COVID booster [Internet]. 2022 [cited 2023 Mar 10]. Available from: https://www.england.nhs.uk/2022/09/over-65s-can-now-book-autumn-covid-booster/
3. NHS England. NHS invites people 50 and over for autumn boosters and flu jab [Internet]. 2022 [cited 2023 Mar 10]. Available from: https://www.england.nhs.uk/2022/10/nhs-invites-people-50-and-over-for-autumn-boosters-and-flu-jab/
4. Oldenburg CE, Moscoe E, Bärnighausen T. Regression Discontinuity for Causal Effect Estimation in Epidemiology. Curr Epidemiol Rep. 2016;3:233.
5. Bermingham C, Morgan J, Ayoubkhani D, Glickman M, Islam N, Sheikh A, et al. Estimating the Effectiveness of First Dose of COVID-19 Vaccine Against Mortality in England: A Quasi-Experimental Study. Am J Epidemiol. 2023 Feb 1;192(2):267–75.
6. Anderson ML, Dobkin C, Gorry D. The Effect of Influenza Vaccination for the Elderly on Hospitalization and Mortality. Ann Intern Med. 2020 Apr 7;172(7):445–52.
7. Horne EMF, Hulme WJ, Keogh RH, Palmer TM, Williamson EJ, Parker EPK, et al. Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose: OpenSAFELY cohort study using linked electronic health records. BMJ. 2022 Jul 20;378:e071249.
8. Hulme WJ, Horne EMF, Parker EPK, Keogh RH, Williamson EJ, Walker V, et al. Comparative effectiveness of BNT162b2 versus mRNA-1273 covid-19 vaccine boosting in England: matched cohort study in OpenSAFELY-TPP. BMJ. 2023 Mar 15;380:e072808.
9. UK Health Security Agency. COVID-19: the green book, chapter 14a [Internet]. GOV.UK. 2023 [cited 2023 Mar 10]. Available from: https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a
10. NHS England. NHS begins COVID-19 booster vaccination campaign [Internet]. [cited 2023 Mar 17]. Available from: https://www.england.nhs.uk/2021/09/nhs-begins-covid-19-booster-vaccination-campaign/
11. Schultze A, Bates C, Cockburn J, MacKenna B, Nightingale E, Curtis HJ, et al. Identifying Care Home Residents in Electronic Health Records - An OpenSAFELY Short Data Report. Wellcome Open Res. 2021;(6):90.