SARS-CoV-2 vaccine uptake and risks of severe COVID-19 disease among people prescribed opioid agonist therapy in Scotland

Yeung, Alan; Wilkinson, Max; Bishop, Jen; Taylor, Bob; Palmateer, Norah; Barnsdale, Lee; Lang, Jaroslaw; Cameron, Claire; McCormick, Duncan; Clusker, Tracey; McAuley, Andrew; Hutchinson, Sharon

Published in:
Journal of Epidemiology and Community Health

DOI:
10.1136/jech-2023-221602

Publication date:
2024

Document Version
Author accepted manuscript

SARS-CoV-2 vaccine uptake and risks of severe COVID-19 disease among people prescribed opioid agonist therapy in Scotland

Authors: Alan Yeung[1,2], Max Wilkinson[1,2], Jen Bishop[2], Bob Taylor[2], Norah Palmateer[1,2], Lee Barnsdale[2], Jaroslaw Lang[2], Claire Cameron[2], Duncan McCormick[2], Tracey Clusker[2], Andrew McAuley[1,2], Sharon Hutchinson[1,2]

[1]Glasgow Caledonian University
[2]Public Health Scotland

Corresponding Author: Alan Yeung, alan.yeung@phs.scot

Running title: COVID-19 among OAT patients in Scotland

Word count: 3,213

Number of figures and tables: 1 figure and 4 tables; supplementary: 3 figures and 1 table

Declaration of interest: None to declare

Funding: This research was supported by funding from Public Health Scotland

Acknowledgements: We thank all staff at NHS boards involved with service delivery of vaccinations in Scotland as well as staff at Public Health Scotland and partner organisations involved in the collation of national healthcare data, establishment of information governance arrangements and the design of the case-control datasets for COVID-19.

Author Contribution: SH conceived and designed the study. AY did the statistical analyses and wrote the first draft of the manuscript. JB, BT, LB and JL contributed to data curation. MW, BT, NP, CC, DM, TC AM and SH reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability: Data may be obtained from a third party and are not publicly available. Access to the individual level data can be sought through approval of the Public Benefit and

Privacy Panel for Health and Social Care
(www.informationgovernance.scot.nhs.uk/pbpphsc/home/for-applicants/).

Keywords: COVID-19, vaccine, opioid agonist therapy, drugs, case-control, data linkage

ABSTRACT

Background

There is limited evidence quantifying the risk of severe COVID-19 disease among people with opioid-dependence. We examined vaccine uptake and severe disease (admission to critical-care or death with COVID-19) among individuals prescribed opioid agonist therapy (OAT).

Method

A case-control design was used to examine vaccine uptake in those prescribed OAT compared to the general population, and association between severe disease and OAT. In both analyses, ten controls from the general population were matched (to each OAT recipient and COVID-19 case, respectively) according to socio-demographic factors. Conditional logistic regression was used to estimate rate ratios (RR) for severe disease.

Results

Vaccine uptake was markedly lower in the OAT cohort (dose 1: 67%, dose 2: 53%, and dose 3: 31%) compared to matched-controls (76%, 72% and 57%, respectively). Those prescribed OAT within the last 5 years, compared to those not prescribed, had increased risk of severe COVID-19 (RR 3.38, 95% CI 2.75-4.15), particularly in the 4th wave (RR 6.58, 95% CI 4.20-10.32); adjustment for comorbidity and vaccine status attenuated this risk (aRR 2.43, 95% CI 1.95-3.02; wave 4 aRR 3.78, 95% CI 2.30-6.20). Increased risk was also observed for those prescribed OAT previously (>3 months ago) compared with recently (aRR 1.74, 95% CI 1.11-2.71).

Conclusions

The widening gap in vaccine coverage for those prescribed OAT, compared to the general population, is likely to have exacerbated the risk of severe COVID-19 in this population over the pandemic. However, continued OAT use may have provided protection from severe COVID-19 among those with opioid-dependence.

What is already known on this topic

People with an opioid dependence have more comorbidities than the general population and lower vaccine uptake for COVID-19. However, there is limited evidence on the risk of COVID-19 disease and how disparities in vaccine uptake may have affected risks in this vulnerable group. Scotland has comprehensive surveillance systems that allow for risks to be measured based on a nationally-representative cohort of patients with opioid dependence.

What this study adds

There was a substantial gap in vaccine uptake among patients prescribed opioid agonist therapy (OAT) compared to a group of similar individuals from the general population. The vaccine uptake gap widened as the pandemic progressed which exacerbated the risk of severe COVID-19 disease over time. Patients that had continuing engagement with OAT had a reduced risk of severe COVID-19 compared with patients last prescribed OAT more than three months ago.

How this study might affect research, practice or policy

Our findings highlight that continued engagement with OAT was important in reducing risks of COVID-19 disease. Efforts aimed at addressing vaccine hesitancy and improving access to vaccination are required to improve vaccine coverage among those prescribed OAT.

INTRODUCTION

Compared with the general population, people with an opioid dependence have a higher burden of comorbidities and are therefore potentially more vulnerable to SARS-CoV-2 infection and associated severe outcomes [1–3]. Relatively few studies have however examined the risk of COVID-19 disease in this population group [4–8]. Vaccination for COVID-19 helps to mitigate the risks associated with SARS-CoV-2 infection [9–11]. There are concerns however that COVID-19 vaccine uptake could be lower in this population group, given their sub-optimal uptake of other harm reduction measures [12] and reduced contact with healthcare providers during the pandemic [13].

Through linkage of national data on patients prescribed OAT for their opioid dependence to other healthcare data, we aimed to (i) estimate COVID-19 vaccine uptake among those prescribed OAT compared to the general population, (ii) investigate the factors associated with vaccine uptake, and (iii) examine the risks of COVID-19 disease among OAT patients compared to the general population, before and after accounting for differences in comorbidity and vaccination.

METHODS

Study Cohort and Linked Data

The cohort followed up includes individuals who were prescribed OAT – either methadone, buprenorphine or buprenorphine-naloxone – for opioid dependence at least once during 2015-2020, based on data extracted from the Public Health Scotland (PHS) Prescribing Information System (PIS); a national system relating to all medicines prescribed and dispensed in the community in Scotland [14]. The patient's NHS board of residence, OAT prescription type and prescribed date of items were extracted from PIS. The Community Health Index (CHI) number (a unique patient identifier used in Scotland) was available for approximately 75-80% of OAT prescription records during 2015-2020 [15]. Members of the overall 'OAT cohort' (N=40,650) were linked to a range of other national datasets held at PHS using the CHI number (Figure S1). Approval for the record linkage was provided by the NHS Public Benefit and Privacy Panel for Health and Social Care (PBPP 2021-0203).

Date and type of vaccination were ascertained through linkage of the cohort to the SARS-CoV-2 vaccination database held at PHS. Those who died (identified by linkage to the national death register) before the date of the first vaccination in the OAT cohort (8th December 2020; referred to hereafter as the 'vaccination start date') were excluded (n=5,358). Additionally, those aged <18 or >99 years (n=37) and those resident outside Scotland (n=15) were also excluded. After exclusions, 35,240 individuals were included in the OAT cohort for analysis on vaccine uptake (Figure S2).

Data Sources for Covariates

Comorbidities were derived by linking to hospital admissions data (SMR01) going back five years and PIS data going back 9 months based on listed conditions designated as 'risk conditions' for COVID-19 by public health agencies, and according to the REACT-SCOT study [16]. In addition, the cohort was linked to a database of patients considered 'clinically extremely vulnerable' (CEV) [17]. We then defined the 'comorbidity status' of patients hierarchically as (i) CEV, (ii) other comorbidities derived from SMR01/PIS data, and (iii) no comorbidities. We also linked to other PHS national datasets to obtain the Scottish Index of Multiple Deprivation (SIMD) quintile related to a patient's latest known residence and SARS-CoV-2 PCR testing history (Figure S2). Data on OAT prescriptions, SARS-CoV-2 PCR tests, SARS-CoV-2 vaccination and mortality were available to March 2022.

Vaccine Uptake

In Scotland, delivery of vaccinations was prioritised to those considered to be at greatest risk of COVID-19 disease such as those with underlying health conditions (particularly those considered CEV) and older age groups. Vaccine supply was expected to be sufficient to meet targets set out by the Scottish Government [18]. Vaccine uptake for each dose 1-3 was measured daily from 8th December 2020 up to 31st March 2022, with those who had died excluded from the OAT cohort following their date of death. Uptake was compared to the Scottish general population by selecting ten controls from the CHI database for each patient in the OAT cohort according to the same 1-year age band, sex and SIMD quintile and time period of first testing PCR positive for SARS-CoV-2 (where time periods were set according to 'waves' of infection [19]; wave 1: March to August 2020, wave 2: August 2020 to April 2021, wave 3: May 2021 to November 2021, wave 4: December 2021 to March

2022, and never tested positive). Note that those missing SIMD data in the OAT cohort (n=152) were assigned the most-deprived quintile (the most frequent quintile among the cohort) for matching purposes and resampling of controls was allowed (thus 352,400 sampled controls relates to 287,280 unique individuals).

Logistic regression was used to identify factors associated with receiving at least one vaccine dose. The determinants considered included time period of last OAT prescription, last OAT prescription type, age, sex, NHS board of residence, SIMD quintile, comorbidity status and time period of first testing PCR positive for SARS-CoV-2.

Risk of Hospitalisation, Critical Care and Death

A case-control approach was used to assess the risk of COVID-19 disease (during the period from 1st March 2020 to 31st March 2022) associated with prescribed OAT use. Aligned to previous studies [10,16,17,20], two case definitions were considered: (i) hospitalisation or death with COVID-19, with cases defined as an admission with a specific cause of COVID-19 (ICD-10 diagnostic codes U07.1, U07.2 or U07.5) or any admission/death occurring within 28 days of a first positive test or having first tested positive for SARS-CoV-2 while in hospital; and (ii) critical care or death with COVID-19 (defined hereafter as 'severe COVID-19 disease'), with cases defined as in (i) but excluded those hospitalised and not admitted to critical care (i.e. intensive care or high dependency units). For each case, up to ten controls were selected as described in the REACT-SCOT study [16] with matching age, sex and by SIMD quintile (with the latter used instead of primary care practice due to the extent of missing information for our population group of interest).

Conditional logistic regression models were used to assess the risk of both outcomes. Models were used firstly to obtain risk ratios (RR) for each outcome, associated with OAT prescribing (with adjustment by age, sex and SIMD quintile achieved through matching). Then a second model was fitted to adjust for comorbidity status and finally, a third model further adjusted for vaccination status, defined as the number of doses received at least 14 days before presentation date. Analyses were conducted across all COVID-19 waves combined and also stratified by each of the waves 1-4.

RESULTS

Cohort Characteristics

Of 35,240 in the cohort (not known to have died by the start of the COVID-19 vaccination programme), over half were last prescribed OAT in March/February 2022 (the latest two months of the study period) (51.6%, n=18,181) and 21.6% (n=7,619) were last prescribed OAT between January 2021 to January 2022 (Table 1). The majority (79.2%) were prescribed methadone in their most recent prescription. Over 70% of the cohort were aged 30-49 years when vaccination started (December 2020), 67.2% were male and over 75% resided in areas belonging to the two most deprived quintiles. Almost 40% of patients had at least one comorbidity (see Table S1 for a breakdown of comorbidities), with 6.1% listed as CEV. Around 12.5% had ever tested PCR positive for SARS-CoV-2 in any of the first four waves up to 31st March 2022.

Vaccine Uptake

Stratified by either age group or comorbidity status, the scale-up in vaccine uptake in the OAT cohort initially aligned with that of matched general population controls but thereafter plateaued at a lower level of coverage (Figure 1). The gap in vaccine coverage between the OAT cohort and matched controls also widened with each successive dose: 67.2% vs 75.9% received dose 1 by the end of follow-up, respectively; 53.0% vs 72.0% received dose 2, respectively; and 30.8% vs 56.6% received dose 3, respectively. Among those with a first dose, 60.5% of the OAT cohort had received their second dose within 12 weeks compared to 86.7% in controls (Figure S3). By 31st March 2022, those surviving in the OAT cohort were less likely than their matched controls to have received a first dose (aOR 0.74, 95% CI 0.73-0.75; adjusting for comorbidity status), second dose (aOR 0.56, 95% CI 0.55-0.57) and third dose (aOR 0.39, 95% CI 0.38-0.40).

Factors associated with vaccine uptake

Patients last prescribed OAT between January 2021 to March 2022 had higher odds of receiving a first dose compared to those last prescribed between 2015-2018 (aOR 1.43, 95% CI 1.33-1.53) (Table 2). In addition, those last prescribed buprenorphine (aOR 1.19, 95% CI 1.11-1.28) or suboxone (aOR 1.19, 95% CI 1.07-1.32) also had higher odds of receiving a first dose compared to those last prescribed methadone. Other factors associated with vaccine uptake included older age (aOR 1.96, 95% CI 1.63-2.34 in those

aged 60+ compared to those aged 40-49), comorbidity status (aOR 2.67, 95% CI 2.34-3.05 in those CEV compared to those with no comorbidities), male gender (aOR 1.16, 95% CI 1.11-1.22), lower deprivation status (aOR 1.71, 95% CI 1.47-1.98 among those in SIMD quintile 5 (least deprived) compared to those living in SIMD quintile 1 (most deprived)), and having tested PCR positive for SARS-CoV-2 (aOR 2.53, 95% CI 1.12-5.73 in those that tested positive in the first wave compared to those that have never tested positive).

Risk of Hospitalisation, Critical Care and Death

Across all four waves of the pandemic, those prescribed OAT within the last 5 years were at increased risk of severe COVID-19 disease compared to those not prescribed OAT in the last 5 years (wave 1-4 RR 3.38, 95% CI 2.75-4.15; wave 1 RR 2.92, 95% CI 1.73-4.94; wave 2 RR 2.64, 95% CI 1.82-3.81; wave 3 RR 3.10, 95% CI 2.12-4.51; wave 4 RR 6.58, 95% CI 4.20-10.32) (Table 3). Adjustment for comorbidity status and vaccination attenuated this risk (wave 1-4 aRR 2.43, 95% CI 1.95-3.02; wave 2 aRR 1.82, 95% CI 1.24-2.68; wave 3 aRR 2.57, 95% CI 1.69-3.90; wave 4 aRR 3.78, 95% CI 2.30-6.20). The relative risks were similar but lower when considering hospitalisation/death with COVID-19 (e.g. wave 1-4 aRR 1.78, 95% CI 1.64-1.93; wave 2 aRR 1.30, 95% CI 1.10-1.53; wave 3 aRR 1.77, 95% CI 1.52-2.05; wave 4 aRR 2.32, 95% CI 2.01-2.68, adjusting for comorbidity status and vaccination). In additional analysis, relative risks were also higher for those prescribed OAT in the period 3 months to 5 years ago compared to those prescribed OAT recently within the last 3 months (for waves 1-4, critical care/death aRR 1.74, 95% CI 1.11-2.71; hospitalisation/death aRR 1.37, 95% CI 1.16-1.63) (Table 4).

DISCUSSION

COVID-19 vaccine uptake was markedly lower among over 35,000 individuals prescribed OAT between 2015-2020 in Scotland compared with matched general population controls. Moreover, the gap in vaccine uptake between the OAT cohort and general population widened with the roll-out of each additional recommended dose. Across all four epidemic waves, those prescribed OAT in the last 5 years had a three-fold increased risk of severe COVID-19 disease compared to those in the general population not prescribed; the highest risk was observed in the fourth wave (RR 6.6, 95% CI 4.2-10.3) which was attenuated with

adjustment for comorbidity and vaccination status (aRR 3.8, 95% CI 2.3-6.2). This is the first study to highlight that the growing disparity in vaccine coverage over time for people with a history of opioid dependence may have exacerbated their risk of severe COVID-19 disease, relative to the wider general population, as the pandemic evolved. Further, we found that those last prescribed OAT more than 3 months ago had a 1.7-fold increased risk of severe COVID-19 disease compared with those prescribed OAT within the last 3 months. A finding that suggests that the continued engagement with and receipt of OAT may have provided protection from severe COVID-19 disease in this population with a history of opioid dependence.

Although around two-fifths of those prescribed OAT had a recorded comorbidity regarded a risk condition for COVID-19, we found lower uptake of vaccination in this cohort compared with the general population, across all comorbidity status and age groups. These findings are comparable to earlier smaller studies that investigated vaccine uptake among those with OUD [3] and PWID [21,22]. For those deemed clinically extremely vulnerable, vaccine coverage was lower in the Scottish OAT cohort (85% with dose 1, 77% dose 2 and 54% dose 3 by March 2022) than in the matched control cohort (94%, 91%, 80%, respectively). Several studies have found concerning levels of COVID-19 vaccine hesitancy among PWID [23,24]. Factors that may have contributed to vaccine hesitancy include exposure to misinformation and disinformation resulting in medical mistrust, vaccine safety concerns, and fear of side-effects after vaccination [25].

Structural barriers may also have contributed to lower vaccine uptake among those prescribed OAT. In Scotland, the primary method of arranging vaccination appointments was through letters to residences but these are less likely to have reached individuals prescribed OAT as some may have unstable housing arrangements or live in congregate settings [26–28]. Although walk-in centres became available and facilitated individuals to be vaccinated without an appointment, convenience and complacency have also been found to be significant barriers for achieving better vaccine coverage in those with OUD [3]. This may be caused by logistical issues such as transportation challenges in reaching vaccination sites, which may disproportionately affect vulnerable populations and those with lower socioeconomic status.

During the pandemic, our monitoring of COVID-19 disease and vaccine coverage among people prescribed OAT informed Scottish Government guidance to enhance vaccine uptake [29]. This included promoting community-based approaches to vaccinate those in contact with drug and alcohol services. Improved vaccine coverage can be achieved through concerted efforts such as targeted outreach and utilising existing harm reduction staff, who may have more trusting relationships relationships and can impart brief medical advice to patients [3,25,30]. While this may help to address vaccine hesitancy, structural supports may still be needed to facilitate vaccination. This could include offering transportation assistance to reach vaccination clinics and offering vaccination in sites frequented by this group such as needle and syringe programmes, drug treatment centres, community pharmacies and prisons [31]. We found that those prescribed OAT recently (since the onset of vaccination programme) were more likely to have received vaccination, which is similar to an Australian study [21] suggesting that engagement with harm reduction services can influence vaccine uptake.

Despite efforts to enhance vaccine coverage among people attending drug services in Scotland, the gap in vaccine coverage between those prescribed OAT and the general population widened from approximately 10% for dose one to 25% for dose three, thus placing an already vulnerable population at increased risk of COVID-19 disease. During the first three waves of SARS-CoV-2 in the UK, those prescribed OAT had around 2-fold increased risk of severe COVID disease (adjusting for age, sex, deprivation and comorbidity status). By the fourth epidemic wave, this risk increased to 4.6-fold; adjusting for vaccination attenuated this risk. This highlights the importance of vaccination on reducing risks of severe outcomes. In addition to lower vaccine coverage increasing risks, vaccine effectiveness may also have been reduced in vulnerable individuals such as those with compromised immune systems [32,33].

Although risks were greater among the overall OAT cohort, those last prescribed OAT more than 3 months ago had a 1.7-fold increased risk of severe COVID-19 disease compared with those prescribed OAT within the last 3 months. This suggests that within the group with current or past exposure to OAT, being on OAT was nevertheless protective. By drawing comparison to those with a history of OAT (more than 3 months ago but within the last 5

years), we have attempted to ensure comparison with a population group most similar to those on OAT, but some level of residual confounding cannot be ruled out. Previous studies have advocated for further clinical investigation on the effect that OAT may have against COVID-19 infection [5]. In particular, some studies have suggested the possibility of protective effects against COVID-19 infection, with potential reasons being the OAT treatment itself [6,7] or higher levels of cross-immunity among OAT patients [8].

Our results are in agreement with earlier studies that looked at risks of COVID-19 disease among patients with opioid, substance and alcohol use disorder from a variety of countries [4,34–37]. One of the key strengths of this study is the use of the case-control design to investigate outcomes. This matched controls to cases by the same age, sex, and SIMD quintile which helps to ensure cases and controls have similar populations at risk [16], while being able to adjust for other key variables such as comorbidities and vaccination in models. We also sampled general population controls to investigate vaccine uptake which allows for a fairer comparison to those prescribed OAT, based on factors that have an important influence on vaccine uptake such as socioeconomic status.

There are also limitations to this study. In the analysis on factors associated with a first dose of vaccination, all individuals had been prescribed OAT at least once before being vaccinated but it was possible for patients to have been vaccinated before testing PCR positive for COVID-19. Almost everybody that tested positive in the first or second waves were positive before vaccination. However, most patients who tested positive in the third and fourth waves were vaccinated before testing positive and therefore, those results should be interpreted with caution. Sub-optimal vaccine uptake has been noted in other groups such as ethnic minorities [38], among whom disparities compared to the general population also increased with successive doses, but this data was not available for the cohort. However, this is unlikely to have affected results as nearly all drug users presenting at drug and treatment services in Scotland are white [39].

Those prescribed OAT recently are likely to have different health-seeking behaviour compared to those last prescribed OAT longer ago. This is a confounding factor that affects OAT uptake, vaccine uptake and consequently risks of COVID-19 but is unlikely to have

been fully accounted for with the available data. Only records with a CHI number available in the OAT prescribing data were included for analysis (approximately 75-80% of methadone and buprenorphine prescriptions between 2015-2020 [15]) and PIS only captures community prescribing. While this includes most patients on OAT, it will not cover the entirety of patients on OAT as some patients may have no OAT records with a CHI number included and some may be prescribed in non-community settings such as prisons. We categorised patients into groups based on the timing of their most recent OAT prescription and used this as an indicator of currently being on OAT. However, this data does not directly record who is currently or no longer on OAT, and we were not able to identify those currently on OAT if their OAT prescribing was disrupted due to, for instance, incarceration.

Conclusion

Those prescribed OAT in Scotland had lower uptake of COVID-19 vaccination compared with the general population. The divergence in vaccine uptake increased with each recommended dose which had adverse consequences on the risk of severe COVID-19 disease among those prescribed OAT over time. However, among those with a history of prescribed OAT, those continuing to receive OAT had a reduced risk of severe COVID-19 disease. Our data highlight the need for additional efforts to improve vaccine coverage among those prescribed OAT, particularly initiatives that help to address vaccine hesitancy and improve access to vaccination.

References

1 Santo Jr T., Campbell G., Gisev N., Tran L. T., Colledge S., Di Tanna G. L., *et al.* Prevalence of childhood maltreatment among people with opioid use disorder: A systematic review and meta-analysis. *Drug Alcohol Depen* 2021;**219**:108459.

2 Benzano D., Ornell F., Schuch J. B., Pechansky F., Sordi A. O., Diemen L. von, *et al.* Clinical vulnerability for severity and mortality by COVID-19 among users of alcohol and other substances. *Psychiat Res* 2021;**300**:113915.

3 Vallecillo G., Durán X., Canosa I., Roquer A., Martinez M. C., Perelló R. COVID-19 vaccination coverage and vaccine hesitancy among people with opioid use disorder in Barcelona, Spain. *Drug Alcohol Rev* 2022;

4 Wang Q. Q., Kaelber D. C., Xu R., Volkow N. D. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. *Mol Psychiatr* 2021;**26**:30–9.

5 Ataei M., Shirazi F. M., Lamarine R. J., Nakhaee S., Mehrpour O. A double-edged sword of using opioids and COVID-19: a toxicological view. *Subst Abuse Treat Pr* 2020;**15**:1–4.

6 Fenton F., Stokes S., Eagleton M. A cross-section observational study on the seroprevalence of antibodies to COVID-19 in patients receiving opiate agonist treatment. *Irish J Med Sci* 2021;1–6.

7 Eagleton M., Stokes S., Fenton F., Keenan E. Does opioid substitution treatment have a protective effect on the clinical manifestations of COVID-19? Comment on Br J Anaesth 2020; 125: e382–3. *Brit J Anaesth* 2021;**126**:e114–6.

8 Bruggmann P., Senn O., Frei A., Puhan M. A., Fehr J., Falcato L. High SARS-CoV-2 seroprevalence but no severe course of COVID-19 disease among people on opioid agonist treatment in Zurich: a cross-sectional study. *Swiss Med Wkly* 2022;

9 Bernal J. L., Andrews N., Gower C., Robertson C., Stowe J., Tessier E., *et al.* 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* 2021;**373**.

10 McKeigue P. M., McAllister D. A., Hutchinson S. J., Robertson C., Stockton D., Colhoun H. M. Vaccine efficacy against severe COVID-19 in relation to delta variant (B. 1.617. 2) and

time since second dose in patients in Scotland (REACT-SCOT): a case-control study. *Lancet Respir Med* 2022;**10**:566–72.

11 Shah S. A., Robertson C., Rudan I., Murray J. L., McCowan C., Grange Z., *et al.* BNT162b2 and ChAdOx1 nCoV-19 vaccinations, incidence of SARS-CoV-2 infections and COVID-19 hospitalisations in Scotland in the Delta era. *J Glob Health* 2022;**12**.

12 Colledge-Frisby S., Ottaviano S., Webb P., Grebely J., Wheeler A., Cunningham E. B., *et al.* Global coverage of interventions to prevent and manage drug-related harms among people who inject drugs: A systematic review. *Lancet Glob Health* 2023;

13 Schofield J., Dumbrell J., Matheson C., Parkes T., Bancroft A. The impact of COVID-19 on access to harm reduction, substance use treatment and recovery services in Scotland: a qualitative study. *Bmc Public Health* 2022;**22**:1–10.

14 Alvarez-Madrazo S., McTaggart S., Nangle C., Nicholson E., Bennie M. Data resource profile: the Scottish national prescribing information system (PIS). *Int J Epidemiol* 2016;**45**:714.

15 Public Health Scotland. Opioid Substitution Therapy (OST) Drug Prescribing - Community, 2021. https://www.scotpho.org.uk/media/2107/2020221-opioid-substitution-therapy-in-scotland.xlsx (accessed December 24, 2022).

16 McKeigue P. M., Weir A., Bishop J., McGurnaghan S. J., Kennedy S., McAllister D., *et al.* Rapid epidemiological analysis of comorbidities and treatments as risk factors for COVID-19 in Scotland (REACT-SCOT): a population-based case-control study. *Plos Med* 2020;**17**:e1003374.

17 McKeigue P. M., McAllister D. A., Caldwell D., Gribben C., Bishop J., McGurnaghan S., *et al.* Relation of severe COVID-19 in Scotland to transmission-related factors and risk conditions eligible for shielding support: REACT-SCOT case-control study. *Bmc Med* 2021;**19**:1–13.

18 Scottish Government. COVID-19 vaccine deployment plan, 2021. https://www.gov.scot/publications/coronavirus-covid-19-vaccine-deployment-plan-2021 (accessed February 23, 2024).

19 Leslie K., Findlay B., Ryan T., Green L. I., Harvey C., Whettlock A. E., *et al.* Epidemiology of SARS-CoV-2 during the first three waves in Scotland: a national record linkage study. *J Epidemiology Community Health* 2023;**77**:1–8.

20 Shah A. S., Wood R., Gribben C., Caldwell D., Bishop J., Weir A., *et al.* Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: Nationwide linkage cohort study. *BMJ* 2020;**371**.

21 Iversen J., Wand H., Kemp R., Bevan J., Briggs M., Patten K., *et al.* Uptake of COVID-19 vaccination among people who inject drugs. *Harm Reduct J* 2022;**19**:1–9.

22 Cioffi C. C., Kosty D., Nachbar S., Capron C. G., Mauricio A. M., Tavalire H. F. COVID-19 Vaccine Deliberation Among People Who Inject Drugs. *Drug Alcohol Depend Rep* 2022;100046.

23 Strathdee S. A., Abramovitz D., Harvey-Vera A. Y., Vera C., Rangel G., Artamonova I., *et al.* Correlates of COVID-19 Vaccine Hesitancy among People who Inject Drugs in the San Diego-Tijuana Border Region. *Clin Infect Dis* 2021;

24 Dietze P. M., Hall C., Price O., Stewart A. C., Crawford S., Peacock A., *et al.* COVID-19 vaccine acceptability among people in Australia who inject drugs: implications for vaccine rollout. *Drug Alcohol Rev* 2022;**41**:484–7.

25 Aronson I. D., Bennett A. S., Ardouin-Guerrier M.-A., Rivera-Castellar G., Gibson B., Santoscoy S., *et al.* How vaccine ambivalence can lead people who inject drugs to decline COVID-19 vaccination, and ways this can be addressed: a Qualitative Study. *JMIR Form Res* 2022;

26 Degenhardt L., Peacock A., Colledge S., Leung J., Grebely J., Vickerman P., *et al.* Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health* 2017;**5**:e1192–207.

27 Topp L., Iversen J., Baldry E., Maher L., Australian NSPs C. of. Housing instability among people who inject drugs: results from the Australian needle and syringe program survey. *J Urban Health* 2013;**90**:699–716.

28 Vasylyeva T. I., Smyrnov P., Strathdee S., Friedman S. R. Challenges posed by COVID-19 to people who inject drugs and lessons from other outbreaks. *J Int AIDS* 2020;**23**:e25583.

29 Scottish Government. Inclusive vaccinations: Phase one of the COVID-19 vaccination programme, 2022. https://www.gov.scot/publications/vaccine-inclusion-phase-one-covid-19-vaccination-programme (accessed February 23, 2024).

30 Treloar C., Rance J., Yates K., Mao L. Trust and people who inject drugs: The perspectives of clients and staff of needle syringe programs. *Int J Drug Policy* 2016;**27**:138–45.
31 Palmateer N. E., Goldberg D. J., Munro A., Taylor A., Yeung A., Wallace L. A., *et al.* Association between universal hepatitis B prison vaccination, vaccine uptake and hepatitis B infection among people who inject drugs. *Addiction* 2018;**113**:80–90.
32 Wang L., Wang Q., Davis P. B., Volkow N. D., Xu R. Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021. *World Psychiatry* 2022;**21**:124–32.
33 Hassold N., Brichler S., Ouedraogo E., Leclerc D., Carroue S., Gater Y., *et al.* Impaired antibody response to COVID-19 vaccination in advanced HIV infection. *AIDS* 2022;
34 Hasin D. S., Fink D. S., Olfson M., Saxon A. J., Malte C., Keyes K. M., *et al.* Substance Use Disorders and COVID-19: an analysis of nation-wide Veterans Health Administration electronic health records. *Drug Alcohol Depen* 2022;109383.
35 Pavarin R. M., Fabbri C., De Ronchi D. COVID-19 hospitalization rates in individuals with substance or alcohol use disorders. *Psychiat Res* 2022;114521.
36 Board A. R., Kim S., Park J., Schieber L., Miller G. F., Pike J., *et al.* Risk Factors for COVID-19 among Persons with Substance Use Disorder (PWSUD) with Hospital Visits–United States, April 2020–December 2020. *Drug Alcohol Depen* 2022;109297.
37 Wallin A. S., Ohlis A., Dalman C., Ahlen J. Risk of severe COVID-19 infection in individuals with severe mental disorders, substance use disorders, and common mental disorders. *Gen Hosp Psychiat* 2022;
38 Morrison K., Cullen L., James A. B., Chua V., Sullivan C., Robertson C., *et al.* Predictors of incomplete COVID-19 vaccine schedule among adults in Scotland: Two retrospective cohort analyses of the primary schedule and third dose. *Vaccine* 2023;
39 Public Health Scotland. Drug and Alcohol Information System: Overview of Initial Assessments for Specialist Drug and Alcohol Treatment 2021/22 and 2022/23, 2023. https://www.publichealthscotland.scot/media/20486/2023-06-27-daisy-treatment-report.pdf (accessed September 08, 2023).

Table 1 Characteristics of the cohort prescribed OAT in Scotland during 2015-2020, and not known to have died by the start of the COVID-19 vaccination programme in December 2020 (N=35,240).

	n	Col %
Last Prescribed OAT		
2015 to 2018	4,622	13.1%
2019 to 2020	4,818	13.7%
Jan 2021 to Jan 2022	7,619	21.6%
Feb/Mar 2022	18,181	51.6%
Last OAT Prescription Type		
Methadone	27,922	79.2%
Buprenorphine	5,219	14.8%
Suboxone	2,099	6.0%
Age (Years)		
18-29	1,942	5.5%
30-39	9,972	28.3%
40-49	15,505	44.0%
50-59	6,824	19.4%
60+	997	2.8%
Sex		
Female	11,563	32.8%
Male	23,677	67.2%
SIMD Quintile		
1 (most deprived)	18,355	52.1%
2	9,011	25.6%
3	4,344	12.3%
4	2,316	6.6%
5 (least deprived)	1,062	3.0%
Missing	152	0.4%
Comorbidities		
0	21,286	60.4%
1	9,821	27.9%
2+	4,133	11.7%
Clinically Extremely Vulnerable		
No	33,094	93.9%
Yes	2,146	6.1%
First Positive SARS-CoV-2 PCR Test		
Never Tested Positive by March 2022	30,826	87.5%
1st wave: Mar 2020 to Jul 2020	51	0.1%
2nd wave: Aug 2020 to Apr 2021	722	2.0%
3rd wave: May 2021 to Nov 2021	1,659	4.7%
4th wave: Dec 2021 to Mar 2022	1,982	5.6%

Table 2 Odds ratio for at least one dose of vaccination by 31st March 2022 in the surviving OAT cohort (N=33,697).

	n	Vaccinated (%)	OR (95% CI)	aOR (95% CI)*
Last Prescribed OAT				
2015 to 2018	4,478	2793 (62.4%)	1.00	1.00
2019 to 2020	4,488	2922 (65.1%)	1.13 (1.03-1.23)	1.17 (1.07-1.28)
Jan 2021 to Mar 2022	24,731	16930 (68.5%)	1.31 (1.23-1.40)	1.43 (1.33-1.53)
Last OAT Prescription Type				
Methadone	26,594	17788 (66.9%)	1.00	1.00
Buprenorphine	5,064	3482 (68.8%)	1.09 (1.02-1.16)	1.19 (1.11-1.28)
Suboxone	2,039	1375 (67.4%)	1.03 (0.93-1.13)	1.19 (1.07-1.32)
Age (Years)				
18-29	1,900	941 (49.5%)	0.44 (0.40-0.49)	0.45 (0.41-0.50)
30-39	9,669	5712 (59.1%)	0.65 (0.61-0.68)	0.67 (0.63-0.71)
40-49	14,853	10250 (69.0%)	1.00	1.00
50-59	6,379	4999 (78.4%)	1.63 (1.52-1.74)	1.54 (1.44-1.66)
60+	896	743 (82.9%)	2.18 (1.83-2.60)	1.96 (1.63-2.34)
Sex				
Female	11,102	7155 (64.4%)	1.00	1.00
Male	22,595	15490 (68.6%)	1.20 (1.15-1.26)	1.16 (1.11-1.22)
SIMD Quintile				
1 (most deprived)	17,498	11570 (66.1%)	1.00	1.00
2	8,622	5866 (68.0%)	1.09 (1.03-1.15)	1.17 (1.11-1.24)
3	4,178	2819 (67.5%)	1.06 (0.99-1.14)	1.16 (1.07-1.25)
4	2,230	1549 (69.5%)	1.17 (1.06-1.28)	1.33 (1.20-1.47)
5 (least deprived)	1,022	760 (74.4%)	1.49 (1.29-1.72)	1.71 (1.47-1.98)
Missing	147	81 (55.1%)	0.63 (0.45-0.87)	0.73 (0.52-1.03)
Comorbidity Status				
Neither	20,584	12996 (63.1%)	1.00	1.00
Other Comorbidities	11,223	8037 (71.6%)	1.47 (1.40-1.55)	1.38 (1.31-1.45)
Clinically Extremely Vulnerable	1,890	1612 (85.3%)	3.39 (2.97-3.86)	2.67 (2.34-3.05)
First Positive SARS-CoV-2 PCR Test				
Never Tested Positive by March 2022	29,404	19553 (66.5%)	1.00	1.00
1st wave: Mar 2020 to Jul 2020	48	41 (85.4%)	2.95 (1.32-6.58)	2.53 (1.12-5.73)
2nd wave: Aug 2020 to Apr 2021	668	506 (75.7%)	1.57 (1.32-1.88)	1.69 (1.41-2.03)
3rd wave: May 2021 to Nov 2021	1,615	1120 (69.3%)	1.14 (1.02-1.27)	1.27 (1.14-1.42)
4th wave: Dec 2021 to Mar 2022	1,962	1425 (72.6%)	1.34 (1.21-1.48)	1.49 (1.35-1.66)

*Also adjusts for NHS board of residence.

Table 3 Risk ratio of (a) hospitalisation or death with COVID-19 and (b) critical care or death with COVID-19, associated with prescribed OAT in the last 5 years.

	Controls*	Cases*	RR (95% CI)**	aRR (95% CI)***	aRR (95% CI)****
(a) Hospitalisation/Death					
Wave 1-4: Mar 2020 to Mar 2022					
Not prescribed OAT in last 5 years	687,094 (99.5%)	68,307 (98.8%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	3,432 (0.5%)	849 (1.2%)	2.61 (2.42-2.83)	1.79 (1.65-1.95)	1.78 (1.64-1.93)
Wave 1: Mar 2020 to Jul 2020					
Not prescribed OAT in last 5 years	91,069 (99.7%)	9,082 (99.2%)	1.00	1.00	
Prescribed OAT in last 5 years	291 (0.3%)	73 (0.8%)	2.67 (2.04-3.49)	1.82 (1.38-2.40)	
Wave 2: Aug 2020 to Apr 2021					
Not prescribed OAT in last 5 years	214,707 (99.5%)	21,405 (99.1%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	1,038 (0.5%)	198 (0.9%)	1.97 (1.69-2.31)	1.29 (1.10-1.52)	1.30 (1.10-1.53)
Wave 3: May 2021 to Nov 2021					
Not prescribed OAT in last 5 years	179,666 (99.4%)	17,856 (98.6%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	1,174 (0.6%)	253 (1.4%)	2.25 (1.96-2.59)	1.65 (1.43-1.92)	1.77 (1.52-2.05)
Wave 4: Dec 2021 to Mar 2022					
Not prescribed OAT in last 5 years	201,652 (99.5%)	19,964 (98.4%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	929 (0.5%)	325 (1.6%)	3.83 (3.35-4.38)	2.59 (2.25-2.99)	2.32 (2.01-2.68)
(b) Critical Care/Death					
Wave 1-4: Mar 2020 to Mar 2022					
Not prescribed OAT in last 5 years	155,793 (99.7%)	15,523 (99.2%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	434 (0.3%)	133 (0.8%)	3.38 (2.75-4.15)	2.43 (1.95-3.01)	2.43 (1.95-3.02)
Wave 1: Mar 2020 to Jul 2020					
Not prescribed OAT in last 5 years	42,997 (99.8%)	4,301 (99.6%)	1.00	1.00	
Prescribed OAT in last 5 years	69 (0.2%)	19 (0.4%)	2.92 (1.73-4.94)	2.34 (1.36-4.00)	
Wave 2: Aug 2020 to Apr 2021					
Not prescribed OAT in last 5 years	61,536 (99.7%)	6,142 (99.4%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	158 (0.3%)	39 (0.6%)	2.64 (1.82-3.81)	1.79 (1.22-2.63)	1.82 (1.24-2.68)
Wave 3: May 2021 to Nov 2021					
Not prescribed OAT in last 5 years	27,120 (99.5%)	2,690 (98.6%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	138 (0.5%)	39 (1.4%)	3.10 (2.12-4.51)	2.27 (1.51-3.42)	2.57 (1.69-3.90)
Wave 4: Dec 2021 to Mar 2022					
Not prescribed OAT in last 5 years	24,140 (99.7%)	2,390 (98.5%)	1.00	1.00	1.00
Prescribed OAT in last 5 years	69 (0.3%)	36 (1.5%)	6.58 (4.20-10.32)	4.58 (2.81-7.47)	3.78 (2.30-6.20)

*Cases are individuals having (a) hospitalisation/death with COVID-19 and (b) critical care/death with COVID-19; up to 10 controls were selected for each case according to the same age/sex/SIMD.

**Matching adjusts for age/sex/SIMD.

***Additionally adjusts for comorbidity status.

****Additionally adjusts for comorbidity status and vaccination status; the aRR is missing for wave 1 as this took place prior to the first vaccinations.

Table 4 Risk ratio of (a) hospitalisation or death with COVID-19 and (b) critical care or death with COVID-19, associated with prescribed OAT less than three months ago and between 3 months and 5 years ago.

	Controls*	Cases*	RR (95% CI)**	aRR (95% CI)***	aRR (95% CI)****
a) Hospitalisation/Death Wave 1-4: Mar 2020 to Mar 2022					
Prescribed OAT <3 months ago	2,412 (0.3%)	551 (0.8%)	1.00	1.00	1.00
Prescribed OAT 3 months to 5 years ago	1,020 (0.1%)	298 (0.4%)	1.28 (1.09-1.51)	1.36 (1.15-1.61)	1.37 (1.16-1.63)
Not prescribed OAT in last 5 years	687,094 (99.5%)	68,307 (98.8%)	0.41 (0.38-0.46)	0.61 (0.56-0.68)	0.62 (0.56-0.69)
b) Critical Care/Death Wave 1-4: Mar 2020 to Mar 2022					
Prescribed OAT <3 months ago	313 (0.2%)	84 (0.5%)	1.00	1.00	1.00
Prescribed OAT 3 months to 5 years ago	121 (0.1%)	49 (0.3%)	1.58 (1.03-2.41)	1.69 (1.08-2.63)	1.74 (1.11-2.71)
Not prescribed OAT in last 5 years	155,793 (99.7%)	15,523 (99.2%)	0.34 (0.27-0.44)	0.49 (0.37-0.63)	0.49 (0.38-0.64)

*Cases are individuals having (a) hospitalisation/death with COVID-19 and (b) critical care/death with COVID-19; up to 10 controls were selected for each case according to the same age/sex/SIMD.

**Matching adjusts for age/sex/SIMD.

***Additionally adjusts for comorbidity status.

****Additionally adjusts for comorbidity status and vaccination status.

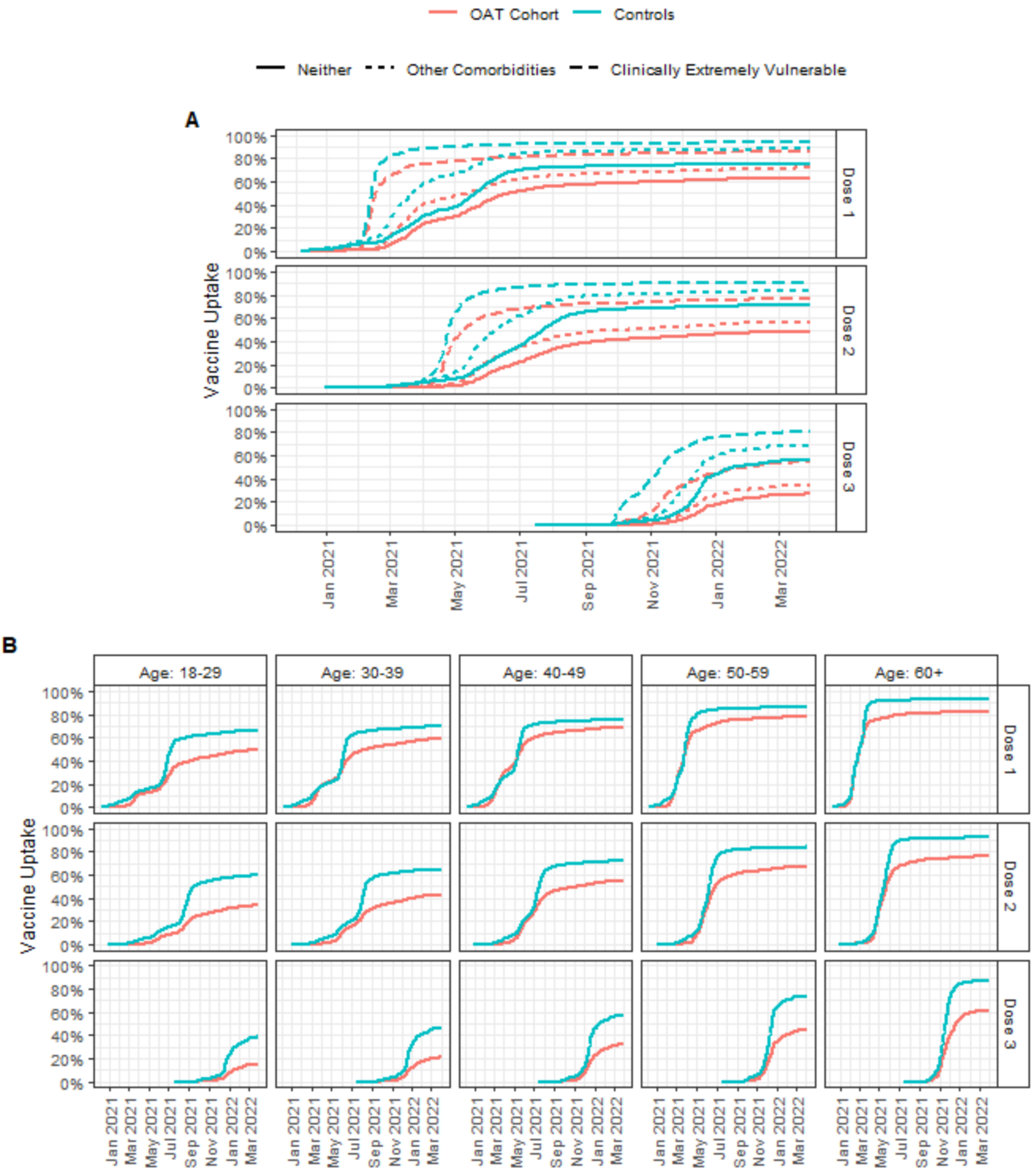

Figure 1 Vaccine uptake by those in the OAT cohort compared to matched controls selected from the general population, split by (A) comorbidity status and (B) age group.

Table S1 Breakdown of comorbidities among the OAT cohort.

Condition	n	% of Cohort
Type 1 diabetes	240	0.7%
Type 2 diabetes	427	1.2%
Ischaemic heart disease	727	2.1%
Other heart disease	1,698	4.8%
Other circulatory system diseases	3,402	9.7%
Asthma or chronic airway disease	9,574	27.2%
Chronic kidney disease or transplant recipient	46	0.1%
Neurological (except epilepsy) or dementia	867	2.5%
Liver disease	528	1.5%
Immune deficiency or suppression	265	0.8%
Malignant neoplasms	762	2.2%
Disorders of oesophagus, stomach, and duodenum	1,545	4.4%
Any comorbidity	13,954	39.6%

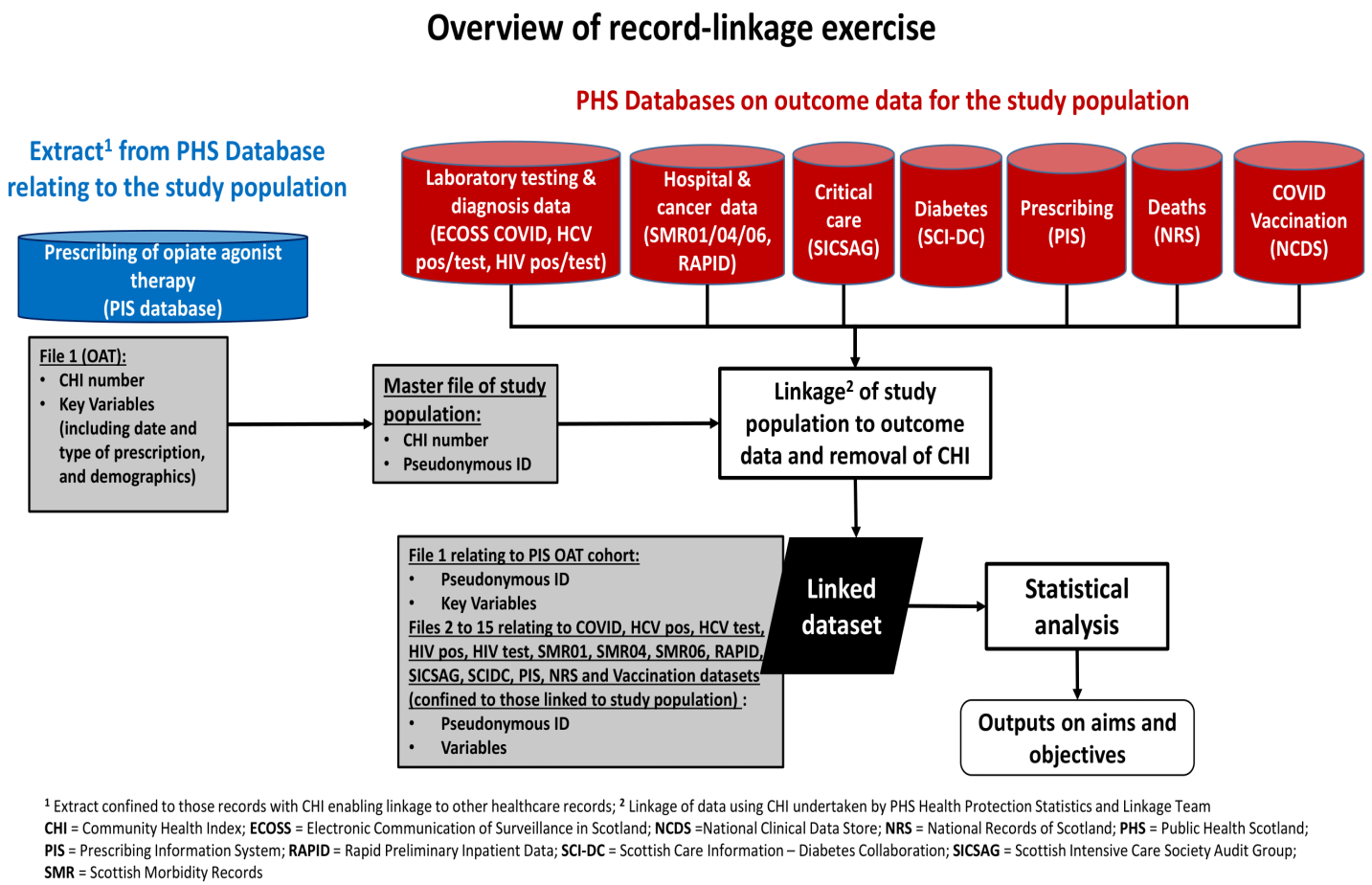

Figure S1 Overview of the record linkage process used for creating the OAT cohort and extracting data for analysis.

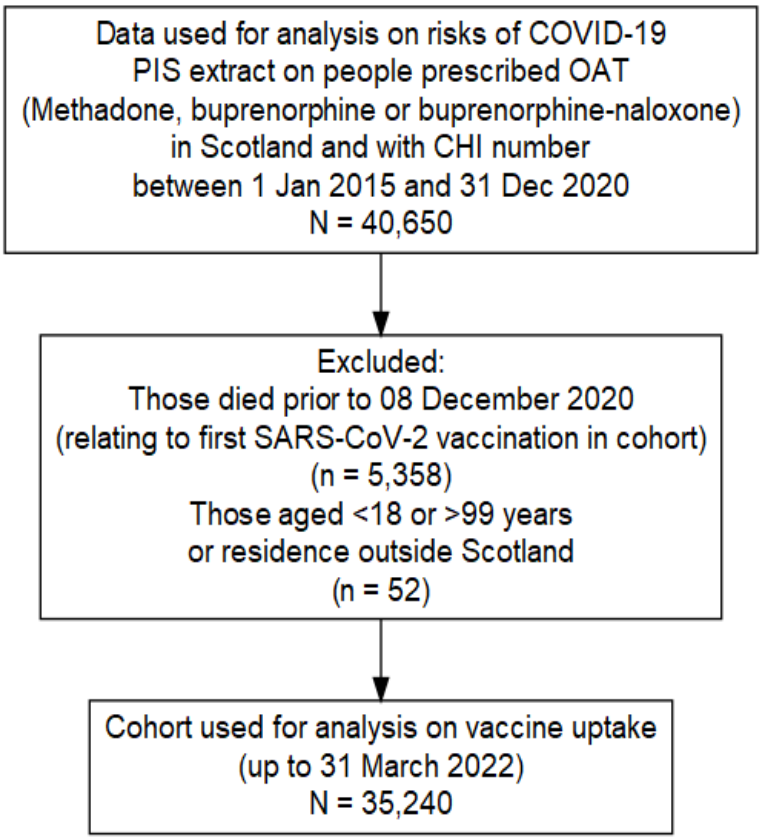

Figure S2 Flowchart showing how patients were selected for inclusion in the OAT cohort.

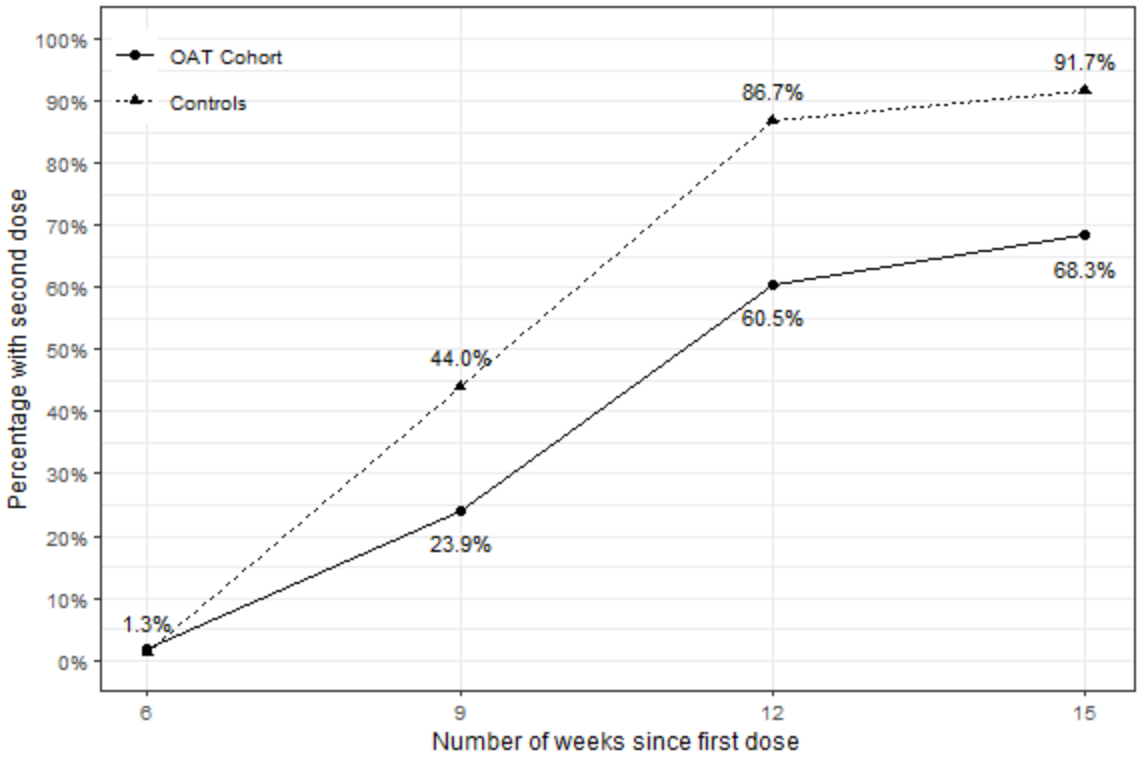

Figure S3 Extent of vaccination with second dose among individuals in receipt of first dose, according to those with at least 6, 9, 12 and 15 weeks of follow-up available for the second dose; comparison of OAT cohort with matched general population controls.