Trends, regional variation and clinical characteristics of recipients of antivirals and neutralising monoclonal antibodies for non-hospitalised COVID-19: a descriptive cohort study of 23.4 million people in OpenSAFELY

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ABSTRACT

Background

From December 16th 2021, antivirals and neutralising monoclonal antibodies (nMABs) were available to treat high-risk non-hospitalised patients with COVID-19 in England.

Aims

To develop a framework for detailed near real-time monitoring of treatment deployment, to ascertain eligibility status for patients and to describe trends and variation in coverage of treatment between geographic, clinical and demographic groups.

Methods

With the approval of NHS England we conducted a retrospective cohort study using routine clinical data from 23.4m people in the OpenSAFELY-TPP database, approximately 40% of England's population. We implemented national eligibility criteria and generated descriptive statistics with detailed clinical, demographic and geographic breakdowns for patients receiving an antiviral or nMAB.

Results

We identified 50,730 non-hospitalised patients with COVID-19 between 11th December 2021 and 23rd February 2022 who were potentially eligible for antiviral and/or nMAB treatment. 6420 (15%) received treatment (sotrovimab 3600 (56%); molnupiravir 2680 (42%); nirmatrelvir/ritonavir (Paxlovid) 80 (1%); casirivimab 50 (1%); and remdesivir <5). The proportion treated varied by risk group, with the lowest proportion treated in those with liver disease (10%; 95% CI 9-11). Treatment type also varied, with molnupiravir favoured over sotrovimab in only two high risk cohorts: Down syndrome (67%; 95% CI 59-74) and HIV/AIDS (63%; 95% CI 56-70). The proportion treated varied by ethnicity, from White (14%; 95% CI 13-14) or Asian (13%; 95% CI 12-14) to Black (9%; 95% CI 8-11); by NHS Regions (from 6% (95% CI 5-6) in Yorkshire and the Humber to 17% (95% CI 16-18) in the East of England); and by rurality from 16% (95% CI 14-17) in "Rural - village and dispersed" to 10% (95% CI 10-11) in "Urban - conurbation". There was also lower coverage among care home residents (4%; 95% CI 3-4), those with dementia (4%; 95% CI 3-5), those with sickle cell disease (7%; 95% CI 5-8), and in the most socioeconomically deprived areas (9%; 95% CI 8-9, vs least deprived: 15%; 95% CI 15-16). Patients who were housebound, or who had a severe mental illness had a slightly reduced chance of being treated (10%; 95% CI 8-11 and 10%; 95% CI 8-12, respectively). Unvaccinated patients were substantially less likely to receive treatment (5%; 95% CI 4-6).

Conclusions

Using the OpenSAFELY platform we have developed and delivered a rapid, near real-time data-monitoring framework for the roll-out of antivirals and nMABs in England that can deliver detailed coverage reports in fine-grained clinical and demographic risk groups, using publicly auditable methods, using linked but pseudonymised patient-level NHS data in a highly secure Trusted Research Environment. Targeted activity may be needed to address apparent lower treatment coverage observed among certain groups, in particular (at present): different NHS regions, socioeconomically deprived areas, and care homes.

Abbreviations COVID-19 Medicines Units (CMDUs); neutralising monoclonal antibodies (nMABs)

Keywords Antivirals, neutralising monoclonal antibodies, non-hospitalised COVID-19, OpenSAFELY

BACKGROUND

Since the emergence of COVID-19, a number of approaches to treatment have been tried and evaluated[1]. In UK hospitals, treatments such as dexamethasone were used from early in the pandemic to prevent progression to severe disease[2]. However, no treatments have been widely used in the community, where care has been supportive and focussed on detection of need for hospital admission[3]. In April 2021, the UK government established a Therapeutics and Antivirals Taskforce with the aim of identifying and deploying new medicines to treat COVID-19 in community settings to reduce the risk of hospital admission[4].

On 16th December 2021, new COVID-19 Medicine Delivery Units (CMDUs) were launched across England, offering antiviral medicines and neutralising monoclonal antibodies (nMABs) as treatment to patients with COVID-19 at high risk of severe outcomes in outpatient clinics or their own home[5]. Initially sotrovimab, casirivimab/imdevimab, and molnupiravir were available at these units with nirmatrelvir/ritonavir (Paxlovid) and remdesivir becoming available in February 2022. The UK government established an expert clinical group to develop criteria to support identification of high risk groups eligible for these treatments using NHS data[6]. The NHS in England issued detailed clinical commissioning policies[7] and people identified as high risk were sent letters notifying them that in the event that they test positive for SARS-CoV-2 they would be eligible for these treatments.

OpenSAFELY is a secure analytics platform for electronic patient records built by our group on behalf of NHS England to deliver urgent academic and operational research during the pandemic[8,9]. Analyses can currently run across all patients' full pseudonymised primary care records, with patient-level linkage to various sources of secondary care data. Data on patients receiving antivirals and nMABs from CMDUs was similarly linked and is now updated weekly with approximately one week's lag time. Code and analysis is shared openly for inspection and re-use.

We therefore set out to identify patients registered with OpenSAFELY-TPP practices who were potentially eligible to receive antivirals or nMABs or in a community setting and assess the coverage of these new treatments amongst these patients, in as close to real-time as the available data flows can support. We also describe how coverage varied between key clinical, regional, and demographic subgroups, and describe whether any treatments given may have been potentially inconsistent with guidance.

METHODS

Study design

We conducted a retrospective cohort study beginning on the 11th December 2021. Data in this report is current to 23rd February 2022. We are producing weekly treatment coverage reports and will update this analysis regularly with extended follow-up time using near real-time data as the treatment programme progresses. Current data will be shared at https://reports.opensafely.org/reports/antivirals-and-nmabs-for-non-hospitalised-covid-19-patients-coverage-report/.

Data sources

This analysis was conducted using the OpenSAFELY-TPP platform which executes code across records for all patients currently registered with general practices using TPP SystmOne electronic health records (EHR) software: this is approximately 23.4 million people, or 40% of the English population. It includes pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. This primary care data is linked, via hashed NHS numbers, to: accident and emergency (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 the "COVID-19 therapeutics dataset", a patient-level dataset on antiviral and nMAB treatments, newly sourced from NHS England, derived from Blueteq software that CMDUs use to notify NHS England of COVID-19 treatments. Vaccination status is available in the GP records directly via the National Immunisation Management System (NIMS).

Study population

We included all patients with either a positive SARS-CoV-2 test on or after 11th December 2021 (this is the earliest date that a patient could have tested positive and still been eligible for receiving treatment when they became available from CMDUs from 16th December 2021) or with a treatment record on or after 16th December 2021, who were also registered at the time of their test/treatment. Patients aged under 12 or with an unknown date of birth were excluded.

Eligibility for treatment

We identified the population who were potentially eligible for treatment as those meeting the eligibility criteria for COVID-19 antiviral or nMAB treatment in the community: being a member of a high risk cohort (described below under *High Risk Cohorts*) and with SARS-CoV-2 infection confirmed by a PCR or lateral flow test (Table 1). There were two main differences to the official criteria in our implementation. Firstly, prior to 10th February 2022, infection should have been confirmed by a PCR test, however this was then relaxed to include lateral flow tests. We were not able to always distinguish between lateral flow and PCR tests in all test records, and therefore included all positive SARS-CoV-2 test results. Secondly, having symptomatic COVID-19 was also an eligibility criteria: however due to difficulties in determining symptom status (i.e. it was only possible to determine whether a patient's positive test had a "symptomatic" flag at the time of the test, but not whether symptoms developed later) we did not implement this requirement in our analysis; however we do address this in a separate sensitivity analysis, where we restricted the potentially eligible population to only those with a "symptomatic" flag associated with their positive SARS-CoV-2 test to determine its use as an indicator of being potentially asymptomatic.

As we were unable to implement all of the eligibility criteria, patients who received treatment (see below) were also included in the population even if they were not identified as meeting eligibility criteria (e.g. having no positive SARS-CoV-2 test). All patients with records of more than one treatment in the community within two weeks of one another (potentially due to a data quality issue early in the rollout), or with an implausible treatment date (such as dates far into the future) were excluded due to not being able to accurately determine which

treatment they received and when. The number of patients included/excluded for these reasons are reported.

Table 1: Eligibility and exclusion criteria, as per the Interim Clinical Commissioning Policy (published on 28 January 2022, effective from 10 February 2022)[7] for non-hospitalised COVID-19 patients, and how these were applied in the present study. *Earlier versions of the policy had some minor differences but this version was applied to the whole study period.*

Eligibility/Exclusion Criteria		Criteria applied in present study*
Eligibility Criteria	SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) testing OR Lateral flow test (registered via gov.uk or NHS 119)	Positive PCR OR lateral flow SARS-CoV-2 test in SGSS. (As per NHS Digital's tests rule set logic[6], patients with a prior positive SARS-CoV-2 within the last 30 days were excluded.)
	Symptomatic with COVID-19 and showing no signs of clinical recovery	Not possible[†1]
	Patient was a member of a 'high risk' cohort.	See Table 2 and Table S1
Exclusion criteria	Requirement for hospitalisation for COVID-19	Discharged from hospital within 30 days prior to positive test or treatment, where COVID-19 was the primary diagnosis.
	New supplemental oxygen requirement specifically for the management of COVID-19 symptoms	Not possible
	Known hypersensitivity reaction to the active substances or to any of the excipients of the medications below as listed in their respective Summary of Product Characteristics	Not possible

** Note: patients who received treatment (described below) were also included in the population even if they were not identified as meeting these criteria.*

[†1] *It was only possible to identify whether or not the patient's positive test had a "symptomatic" flag, but not whether symptoms developed later; therefore the symptomatic flag was used in a sensitivity analysis for our assessment of consistency with guidance (see below) rather than within inclusion criteria.*

High risk cohorts

The detailed recommendations on the ten high risk cohorts derived by an expert clinical group (Box 1) have been transformed by NHS Digital into detailed logic and analytic code that could be used on datasets held by NHS Digital to identify all patients eligible for treatment by CMDUs. NHS Digital created a range of codelists to identify patients meeting various criteria in electronic health records data, and made information available on its website[6]. However, NHS Digital recognised potential limitations in identifying all eligible patients using centrally held data, and freedom was permitted for CMDUs to use "non-digital" solutions to identify additional eligible patients locally based on the criteria outlined by the expert group. For example, patients with stage 4 chronic kidney disease would be eligible for treatment, but if the stage of disease is not coded in their primary care record[10] they would not be automatically identified by NHS Digital; however, renal units may contact people

under their care with stage 4 chronic kidney disease and alert them that they are eligible for treatment if they test positive. In addition, with respect to GP EHR data, NHS Digital holds only the GPES dataset, a substantially smaller rules-based derived subset of the full GP dataset accessible through OpenSAFELY.

Where possible, we implemented the NHS Digital logic and associated codelists in the OpenSAFELY platform to identify patients in high risk groups. Codelists were used as published with the exception of minor adaptations made to i) code type where codes did not exist or were erroneous in the published codelist, and ii) code formatting for implementation in OpenSAFELY. Further details, including all limitations in implementing any of the logic or with the codelists are detailed in Supplementary Table S1. If patients had records indicating that they fell into multiple high risk cohorts, all cohorts to which they belonged were used. While we predominantly assigned high risk cohorts to a patient by implementing the digital cohorting rule logic created by NHS Digital, the COVID-19 therapeutics dataset also included the high risk cohort(s) recorded by the clinician on the submitted form. If different or additional high risk cohorts were recorded on this dataset, patients were also assigned to these cohorts.

Box 1: Patient cohorts considered at higher risk from COVID-19 and to be prioritised for treatment with antivirals and nMABs, as determined by an independent advisory group commissioned by the UK Department of Health and Social Care (DHSC)[7]. For further details on these criteria and how they were applied in the present study see Supplementary Table S1.

- Patients with **down's syndrome**;
- Patients with a **solid cancer,** such as active metastatic cancer, or active solid cancers at any stage;
- Patients with a **haematological disease and stem cell transplant recipients**, such as those with sickle cell disease;
- Patients with **renal disease**, such as those with chronic kidney stage 4 or 5;
- Patients with **liver disease**, such as those on immune suppressive therapy;
- Patients with **immune-mediated inflammatory disorders,** such as those treated with rituximab or other B cell depleting therapy in the past 12 months;
- Patients with **primary immune deficiencies**, such as severe combined immunodeficiency;
- Patients with **HIV/AIDS** with high levels of immune suppression;
- **Solid organ transplant recipients**;
- Patients with **rare neurological conditions** (multiple sclerosis motor neurone disease, myasthenia gravis or huntington's disease)

Treated patients

We identified the subset of patients who received treatment in the COVID-19 therapeutics dataset, along with the treatment and the date they were given, restricted to those labelled "non_hospitalised". We included first-line treatments Paxlovid and sotrovimab as per the most recent national policy[11], as well as second- and third-line options remdesivir and molnupiravir respectively; sotrovimab and molnupiravir were available from the start of the study while Paxlovid and remdesivir were only available from 10th February 2022. As

previous versions of the policy also included casirivimab/imdevimab, patients who received this treatment were also included[12].

Key demographic and clinical characteristics of treated patients

We classified patients by age group, sex, NHS region of their general practice and other key demographics including ethnicity and the level of deprivation. Deprivation was measured by Index of Multiple Deprivation (IMD), in quintiles, derived from the patient's postcode at lower super output area level for a high degree of precision. Ethnicity was ascertained using 270 clinical codes grouped into broad categories White, Black or Black British, Asian or Asian British, Mixed, Other, and Unknown; all codelists are shared under open licenses for review and re-use as below. Individuals with missing sex, ethnicity, IMD or region were included as "Unknown". Treated patients were also described according to whether they were in other groups of interest who are sometimes subject to variation in care[13], including autism, dementia, learning disability, serious mental illness, care home residents, and housebound. Patients were also classified by their COVID-19 vaccination status (unvaccinated, unvaccinated with a record of declining vaccination, one vaccination, two vaccinations, or three or more).

Consistency with guidance

For patients who received treatment but who were not otherwise identified as potentially being eligible for treatment, we report which eligibility or exclusion criteria were not met according to the data available (i.e. no positive SARS-CoV-2 test result, or not identified as part of a high risk group). Where possible within available data, we also report other potential inconsistencies with guidance for patients who received treatment, such as where the high risk cohort identified within their records did not match the high risk cohort associated with their treatment.

We also assess consistency with treatment-specific criteria (as detailed in Table S2), such as patients having a recorded contraindication to the specific treatment given (e.g. adolescents treated with sotrovimab/remdesivir with weight under 40kg, Table S2), or patients treated outside the prescribed timescale, 5-7 days from symptom onset, depending on the treatment (Table S2). As symptom onset date was not available, here we used positive SARS-CoV-2 test as a proxy to estimate the extent to which patients may or may not have been treated outside the guidance time window.

Descriptive statistics

We generated charts showing the cumulative number of potentially eligible and treated patients per week, stratified by high risk group, and also stratified by treatment type for treated patients. We used simple descriptive statistics to summarise the counts and proportions of potentially eligible patients treated, stratified by treatment type and either high risk cohort or clinical and demographic groups, and to describe potential inconsistencies with guidelines.

Charts and results not presented in this manuscript are available online for inspection in the associated GitHub repository[14]. Patient counts of 0-5 are shown as "<5" with remaining counts rounded to the nearest 10 to protect against small number differences in our routinely updating data. All percentages (%) are calculated with 95% confidence intervals (CI).

Codelists and implementation

Information on all covariates were obtained from primary care, secondary care and other records by searching TPP SystmOne records and linked datasets for specific coded data. Detailed information on compilation and sources for every individual codelist is available at https://www.opencodelists.org/ and all codelists are available under open licenses for review and re-use by the broader research community.

Software and Reproducibility

All data were linked, stored and analysed securely through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). All activity on the platform is publicly logged and all analytic code and supporting clinical codelists are automatically published at the time of results publication or sooner. In addition, the framework provides assurance that the analysis is reproducible and reusable. Further details on our information governance can be found on page 20, under information governance and ethics.

Data management and analysis was performed using the OpenSAFELY software libraries, Python 3 and R version 4.0.2. All code for the OpenSAFELY platform is freely available under open licenses for review and re-use on GitHub (https://github.com/opensafely). All code for data management and analysis for this paper is freely available under open licenses for review and re-use on GitHub (https://github.com/opensafely/antibody-and-antiviral-deployment).

Patient and Public Involvement

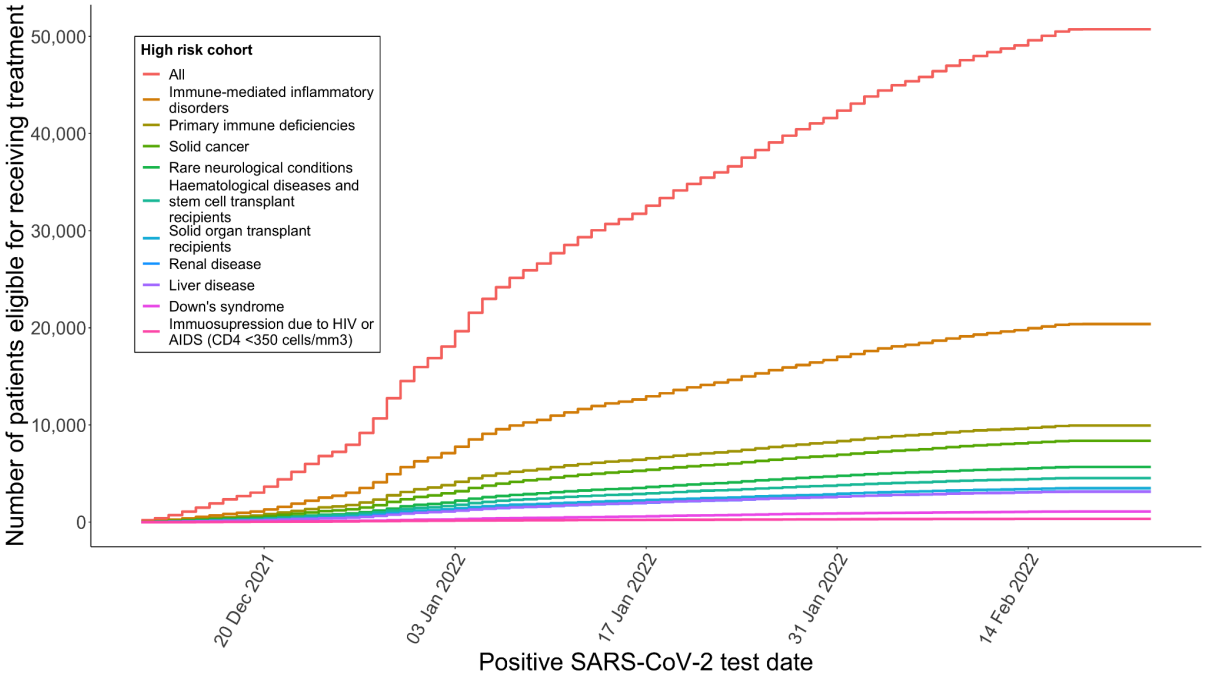
Patients were not formally involved in developing this specific study design, as it was developed in the context of the rapid rollout of a new treatment service during a global health emergency. We have developed a publicly available website https://opensafely.org/ through which we invite any patient or member of the public to contact us regarding this study or the broader OpenSAFELY project.

RESULTS

Eligibility for treatment

Between 11th December 2021 and 23rd February 2022, a total of 50,730 patients registered at a TPP practice in England were identified as potentially being eligible for receiving an antiviral or nMAB for treating COVID-19 (1,255/50,730 patients were included due to receiving treatment but who were not otherwise considered eligible). The number of patients potentially eligible in each high risk cohort is described in Figure 1 and Table 2, with the greatest number of potentially eligible patients classified as those having an Immune mediated inflammatory disorder (n=20,390).

Figure 1 Cumulative total of potentially eligible patients for receiving an antiviral or nMABs for treating COVID-19 since 11th December 2021, stratified by high risk cohort. *Patients are considered eligible on the date of their positive SARS-CoV-2 test. Note, patients can appear in more than one high risk group, and the overall number in each group is likely to be an overestimation due to including SARS-CoV-2 infection confirmed by either lateral flow or PCR test (where only PCR-confirmed infections should have been treated according to guidance in effect prior to 10th February 2022), and potentially including non-symptomatic patients.*



Coverage of COVID-19 treatment

Of the 50,730 potentially eligible patients, 6420 (13%) received treatment from a CMDU (Table 2, Figure 2; 53 patients were excluded due to having records of multiple treatments within a two week period, or an implausible treatment date). Sotrovimab was the most widely used treatment over the study period (n=3600, 56% of those treated) followed by molnupiravir (n=2680, 42% of those treated) although use varied over time (Figure 2a). Use of Paxlovid (n=80), casirivimab (n=50) and remdesivir (n<5) was low (Figure 2b, Table 2).

A sensitivity analysis restricting the population to only those with a “symptomatic” flag associated with their positive SARS-CoV-2 test reduced the potentially eligible population from 50,730 to 15,500 and the treated population from 6,460 to 2,380; a 69% and 63% reduction, respectively, and equivalent to 15% of patients receiving treatment from a CMDU.

Table 2 Count and proportion of potentially eligible patients in OpenSAFELY-TPP who have received treatment for COVID-19 between 16th December 2021 23rd February 2022, broken down by high risk cohort and treatment type. *Patient counts >5 are rounded to the nearest 10; as a result percentages may not add up to 100%.*

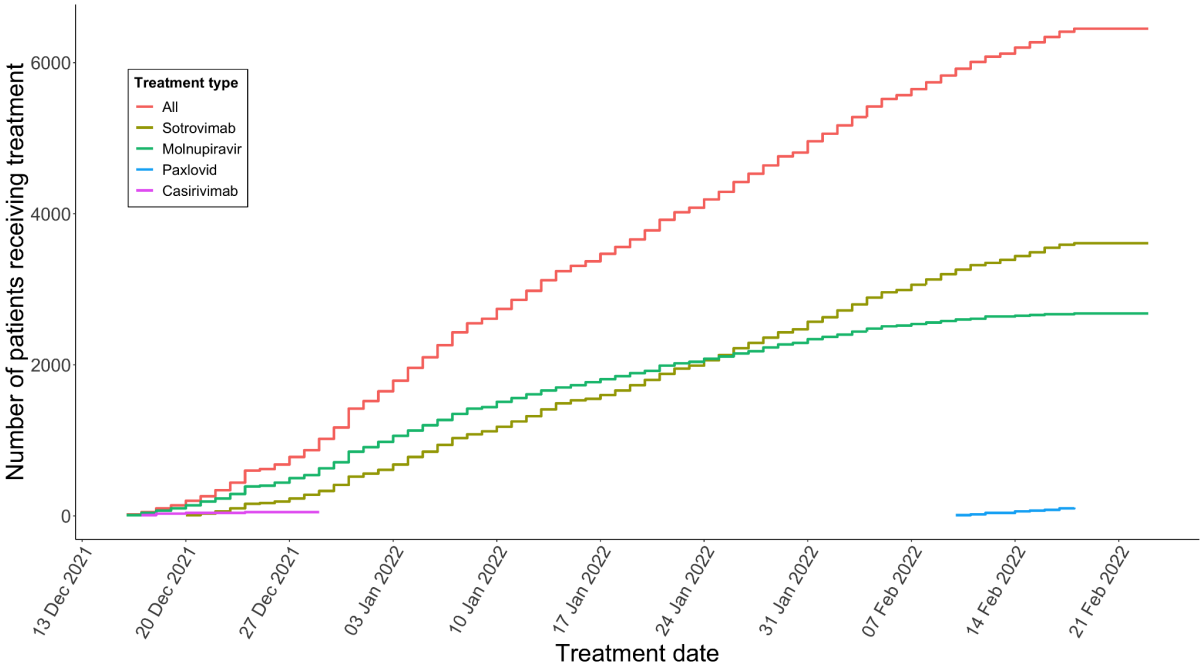
High risk cohort*		Treated											
	Potentially eligible	All		Paxlovid		Sotrovimab		Remdesivir		Molnupiravir		Casirivimab	
	Count	Count	%†	Count	%†	Count	%†	Count	%†	Count	%†	Count	%†
All	50730	6420	13 (12-13)	80	1 (1-2)	3600	56 (55-57)	<5	–	2680	42 (41-43)	50	1 (1-1)
Immune-mediated inflammatory disorders	20390	3030	15 (14-15)	30	1 (1-1)	1720	57 (55-59)	<5	–	1250	41 (40-43)	20	1 (0-1)
Primary immune deficiencies	9940	1190	12 (11-13)	20	2 (1-2)	620	52 (49-55)	<5	–	540	45 (43-48)	10	1 (0-1)
Solid cancer	8370	950	11 (11-12)	10	1 (0-2)	550	58 (55-61)	<5	–	380	40 (37-43)	10	1 (0-2)
Rare neurological conditions	5680	920	16 (15-17)	20	2 (1-3)	480	52 (49-55)	<5	–	420	46 (42-49)	10	1 (0-2)
Haematological diseases and stem cell transplant recipients	4530	930	21 (19-22)	10	1 (0-2)	520	56 (53-59)	<5	–	390	42 (39-45)	10	1 (0-2)
Solid organ transplant recipients	3490	860	25 (23-26)	<5	–	560	65 (62-68)	<5	–	290	34 (31-37)	10	1 (0-2)
Renal disease	3160	800	25 (24-27)	<5	–	540	68 (64-71)	<5	–	260	32 (29-36)	10	1 (0-2)
Liver disease	3130	320	10 (9-11)	<5	–	170	53 (48-59)	<5	–	140	44 (38-49)	<5	–
Down's syndrome	1090	150	14 (12-16)	<5	–	50	33 (26-41)	<5	–	100	67 (59-74)	<5	–
Immunosuppression due to HIV or AIDS	330	190	58 (52-63)	<5	–	70	37 (30-44)	<5	–	120	63 (56-70)	<5	–

** High risk cohorts are arranged in descending order, according to number of potentially eligible patients*

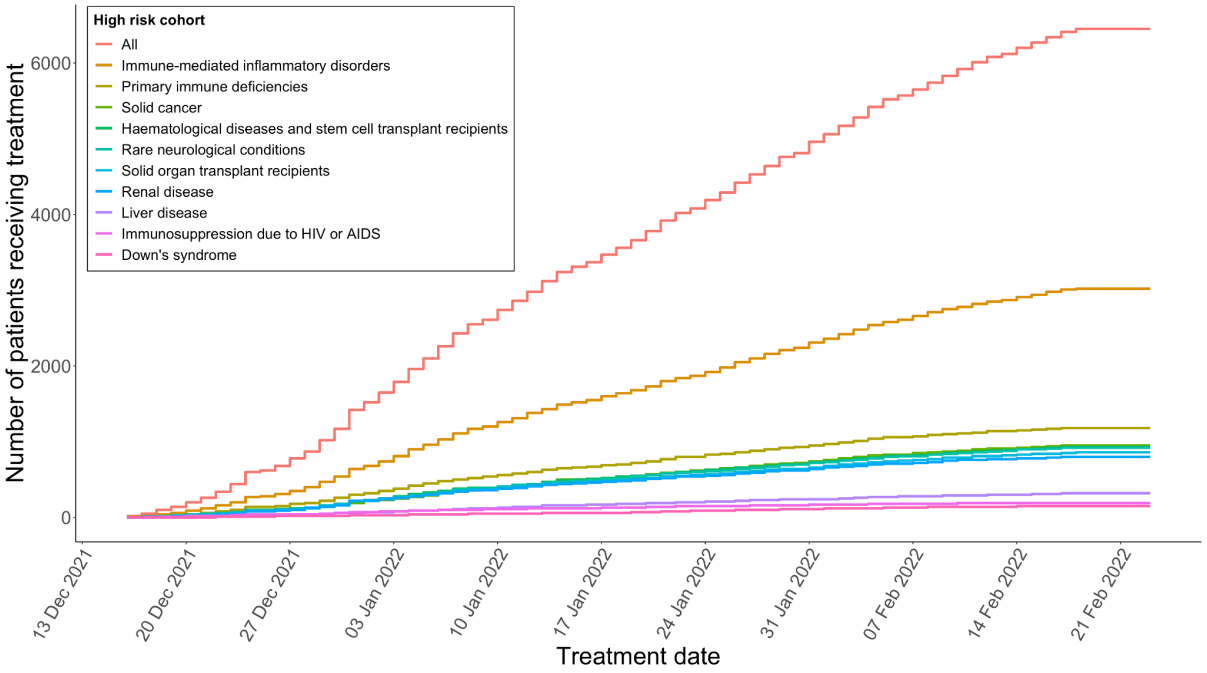
† All percentages (%) are calculated with 95% confidence intervals

Figure 2 Cumulative total of patients who received an antiviral or nMAB for treating COVID-19 since 16th December 2021, stratified by (a) treatment type and (b) high risk cohorts. *Shorter lines for Paxlovid and casirivimab reflect availability and guidance. Note, treated patients can appear in more than one high risk group.*

(a)



(b)



High risk patient cohorts

Of all potentially eligible patients, 15% (n=7,690) were classified into more than one high risk cohort (range 1 - 6). Of the 6,420 patients who received treatment, the high risk cohort(s)

identified using patient GP records 72% (n=4,640) matched the high risk cohort(s) recorded in the COVID-19 therapeutics dataset, while 12% (n=755) did not match. The remaining 16% (n=1,065), did not have a high risk cohort identified in their electronic health records, the majority of which (73%) were recorded as having either an Immune-mediated inflammatory disorder or Solid cancer in their COVID-19 therapeutics dataset record.

The proportion of potentially eligible patients receiving treatment varied by high risk cohort. For example: 15% (n=3030) of patients in the largest eligible group, Immune-mediated inflammatory disorders, received treatment; values ranged from 10% (n=320) in Liver disease, to 25% in both Renal disease (n=800) and Solid organ transplant recipients (n=860). Treatment type also varied by high risk cohort with sotrovimab used more commonly in all high risk cohorts except two: Down's syndrome (67% molnupiravir) and Immunosuppression due to HIV/AIDS (63% molnupiravir).

Key demographic and clinical characteristics of treated patients

Table 3 shows the count and proportion of potentially eligible patients who received treatment for COVID-19 by the 23rd February 2022, broken down by demographic and clinical categories and by treatment type. Patients most likely to be treated were those aged 40-49 (16%). Among eligible patients, patients who were White (14%) or Asian or Asian British (13%) were most likely to receive treatment, with Black or Black British patients least likely (9%). The percentage treated correlated with deprivation quintile (least deprived 15%, most deprived 9%) and similarly with rurality (from "Rural - village and dispersed": 16% to "Urban - conurbation": 10%). The region with the highest rate of treatment was the East of England (17%) followed by the South West (16%); the lowest was Yorkshire and the Humber (6%). Some clinical groups were much less likely to be treated (dementia 4%, care home residents 4%, and sickle cell disease 7%) and others had a slightly reduced chance (housebound 10%, severe mental illness 10%). Those in the clinically extremely vulnerable group were slightly more likely to be treated (17%).

Table 3: Count and proportion of potentially eligible patients in OpenSAFELY-TPP who have received treatment for COVID-19 between 11th December 2021 and 23rd February 2022, broken down by demographic and clinical categories and by treatment type. *Patient counts >5 are rounded to the nearest 10; as a result percentages may not add up to 100%.*

Group	Variable		Treated											
		Potentially eligible	All		Paxlovid		Sotrovimab		Remdesivir		Molnupiravir		Casirivimab	
		Count	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
All		50730	6420	13 (12-13)	80	1 (1-2)	3600	56 (55-57)	<5	-	2680	42 (41-43)	50	1 (1-1)
Age band	**12-29**	5050	550	11 (10-12)	10	2 (1-3)	300	55 (50-59)	<5	--	230	42 (38-46)	10	2 (1-3)
	30-39	6470	990	15 (14-16)	10	1 (0-2)	570	58 (54-61)	<5	--	390	39 (36-42)	10	1 (0-2)
	40-49	8390	1320	16 (15-17)	20	2 (1-2)	750	57 (54-59)	<5	--	530	40 (38-43)	10	1 (0-1)
	50-59	10050	1450	14 (14-15)	40	3 (2-4)	820	57 (54-59)	<5	--	580	40 (37-43)	10	1 (0-1)
	60-69	8740	1130	13 (12-14)	20	2 (1-3)	640	57 (54-60)	<5	--	460	41 (38-44)	10	1 (0-1)
	70-79	7330	760	10 (10-11)	10	1 (1-2)	410	54 (50-57)	<5	--	340	45 (41-48)	<5	--
	80+	4700	270	6 (5-6)	<5	--	110	41 (35-47)	<5	--	150	56 (50-61)	<5	--
Sex	**Female**	28640	3810	13 (13-14)	70	2 (1-2)	2170	57 (55-59)	<5	--	1550	41 (39-42)	20	1 (0-1)
	Male	22090	2650	12 (12-12)	40	2 (1-2)	1440	54 (52-56)	<5	--	1130	43 (41-45)	30	1 (1-2)
	Unknown	<5	<5	--	<5	--	<5	--	<5	--	<5	--	<5	--
Ethnicity	**White**	40570	5480	14 (13-14)	100	2 (1-2)	3090	56 (55-58)	<5	--	2240	41 (40-42)	40	1 (1-1)
	Asian or Asian British	2540	330	13 (12-14)	<5	--	210	64 (58-69)	<5	--	120	36 (31-42)	<5	--
	Black or Black British	2030	190	9 (8-11)	<5	--	100	53 (46-60)	<5	--	80	42 (35-49)	<5	--
	Mixed	670	80	12 (9-14)	<5	--	40	50 (39-61)	<5	--	40	50 (39-61)	<5	--
	Other ethnic groups	830	90	11 (9-13)	<5	--	40	44 (34-55)	<5	--	50	56 (45-66)	<5	--
	Unknown	4090	290	7 (6-8)	10	3 (1-6)	130	45 (39-51)	<5	--	150	52 (46-57)	<5	--

Group	Variable		Treated											
		Potentially eligible	All		Paxlovid		Sotrovimab		Remdesivir		Molnupiravir		Casirivimab	
		Count	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
IMD	1 most deprived	10310	920	9 (8-9)	20	2 (1-3)	530	58 (54-61)	<5	--	370	40 (37-43)	10	1 (0-2)
	2	10000	1180	12 (11-12)	20	2 (1-2)	650	55 (52-58)	<5	--	500	42 (40-45)	10	1 (0-1)
	3	10340	1450	14 (13-15)	20	1 (1-2)	800	55 (53-58)	<5	--	610	42 (40-45)	10	1 (0-1)
	4	9720	1350	14 (13-15)	20	1 (1-2)	770	57 (54-60)	<5	--	550	41 (38-43)	10	1 (0-1)
	5 least deprived	8970	1380	15 (15-16)	30	2 (1-3)	760	55 (52-58)	<5	--	580	42 (39-45)	10	1 (0-1)
	Unknown	1400	180	13 (11-15)	<5	--	100	56 (48-63)	<5	--	80	44 (37-52)	<5	--
Rurality	Urban - conurbation	13660	1370	10 (10-11)	20	1 (1-2)	770	56 (54-59)	<5	--	580	42 (40-45)	<5	--
	Urban - city and town	26040	3470	13 (13-14)	70	2 (2-2)	1840	53 (51-55)	<5	--	1520	44 (42-45)	30	1 (1-1)
	Rural - town and fringe	5900	850	14 (14-15)	10	1 (0-2)	520	61 (58-64)	<5	--	310	36 (33-40)	10	1 (0-2)
	Rural - village and dispersed	3790	590	16 (14-17)	10	2 (1-3)	380	64 (61-68)	<5	--	200	34 (30-38)	0	0 (0-0)
	Unknown	1350	180	13 (12-15)	<5	--	100	56 (48-63)	<5	--	80	44 (37-52)	<5	--
Region	East Midlands	9050	1060	12 (11-12)	20	2 (1-3)	740	70 (67-73)	<5	--	280	26 (24-29)	20	2 (1-3)
	East of England	12000	2040	17 (16-18)	10	0 (0-1)	1110	54 (52-57)	<5	--	890	44 (41-46)	20	1 (1-1)
	London	3210	420	13 (12-14)	10	2 (1-4)	160	38 (33-43)	<5	--	250	60 (55-64)	<5	--
	North East	2730	320	12 (11-13)	<5	--	240	75 (70-80)	<5	--	80	25 (20-30)	<5	--

Group	Variable		Treated											
		Potentially eligible	All		Paxlovid		Sotrovimab		Remdesivir		Molnupiravir		Casirivimab	
		Count	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
	North West	5340	610	11 (11-12)	20	3 (2-5)	300	49 (45-53)	<5	--	290	48 (44-52)	<5	--
	South East	3240	430	13 (12-14)	10	2 (1-4)	240	56 (51-61)	<5	--	180	42 (37-47)	<5	--
	South West	5880	940	16 (15-17)	30	3 (2-4)	440	47 (44-50)	<5	--	460	49 (46-52)	<5	--
	West Midlands	2080	250	12 (11-13)	<5	--	200	80 (75-85)	<5	--	50	20 (15-25)	<5	--
	Yorkshire and the Humber	7140	400	6 (5-6)	10	2 (1-4)	180	45 (40-50)	<5	--	210	52 (48-57)	<5	--
	Unknown	70	10	14 (6-22)	<5	--	0	0 (0-0)	<5	--	<5	--	<5	--
Additional clinical risk groups	Autism	300	40	13 (9-17)	<5	--	20	50 (35-65)	<5	--	30	75 (62-88)	<5	--
	Care home	1700	60	4 (3-4)	<5	--	10	17 (7-26)	<5	--	50	83 (74-93)	<5	--
	Dementia	1230	50	4 (3-5)	<5	--	10	20 (9-31)	<5	--	30	60 (46-74)	<5	--
	Learning disability	1310	170	13 (11-15)	0	0 (0-0)	60	35 (28-42)	<5	--	100	59 (51-66)	<5	--
	Serious mental illness	700	70	10 (8-12)	<5	--	30	43 (31-54)	<5	--	30	43 (31-54)	<5	--
	Housebound	1830	180	10 (8-11)	<5	--	90	50 (43-57)	<5	--	80	44 (37-52)	<5	--
	CEV	26850	4570	17 (17-17)	70	2 (1-2)	2600	57 (55-58)	<5	--	1860	41 (39-42)	40	1 (1-1)
	Sickle cell disease	750	50	7 (5-8)	<5	--	20	40 (26-54)	<5	--	20	40 (26-54)	<5	--

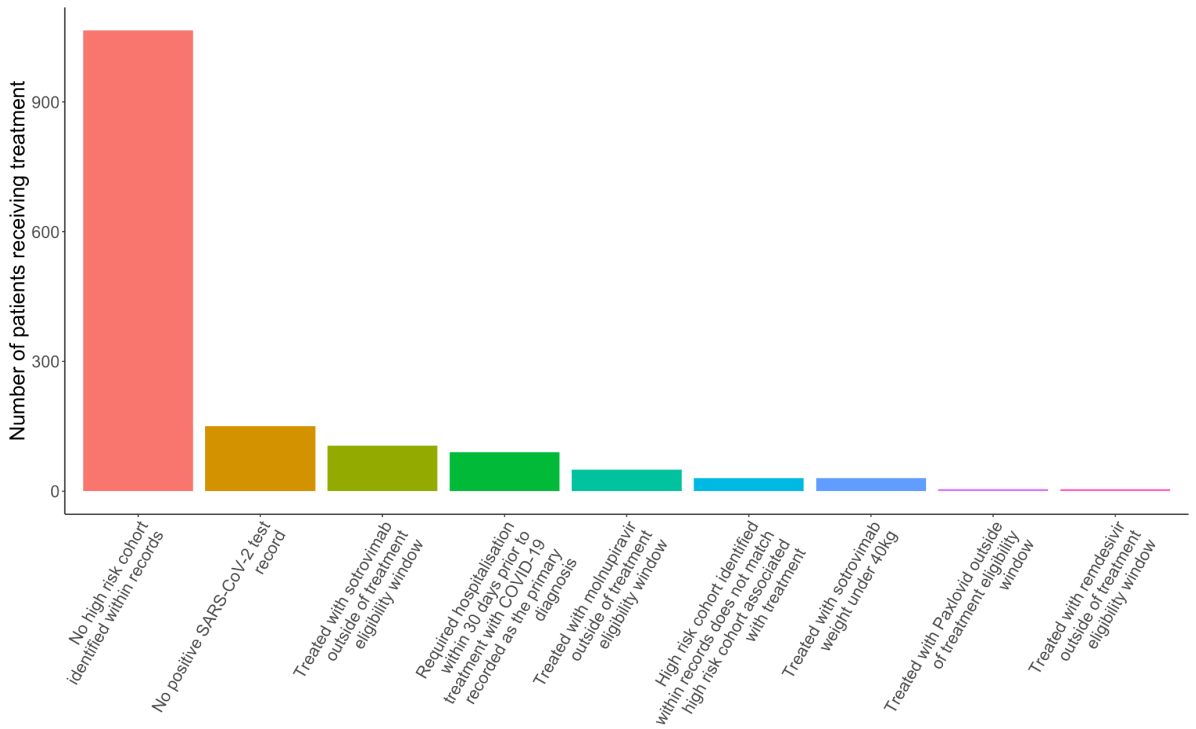
Group	Variable		Treated											
		Potentially eligible	All		Paxlovid		Sotrovimab		Remdesivir		Molnupiravir		Casirivimab	
		Count	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Vaccination status	Unvaccinated (declined)	790	30	4 (2-5)	<5	--	20	67 (50-84)	<5	--	10	33 (16-50)	<5	--
	Unvaccinated	2310	120	5 (4-6)	<5	--	60	50 (41-59)	<5	--	60	50 (41-59)	<5	--
	One vaccination	1580	130	8 (7-10)	<5	--	70	54 (45-62)	<5	--	50	38 (30-47)	<5	--
	Two vaccinations	7330	520	7 (7-8)	10	2 (1-3)	280	54 (50-58)	<5	--	220	42 (38-47)	10	2 (1-3)
	Three or more vaccinations	38720	5660	15 (14-15)	100	2 (1-2)	3190	56 (55-58)	<5	--	2340	41 (40-43)	40	1 (0-1)

Consistency with guidance

Of the 6460 patients who received treatment for COVID-19 between 16th December 2021 and 23rd February 2022, 2% (n=150) did not have evidence of a positive SARS-CoV-2 test, 16% (n=1,065) did not have a high risk cohort identified from their GP records alone, and 1% (n=90) were discharged from hospital within 30 days prior to positive test or treatment, where COVID-19 was the primary diagnosis (Figure 3).

There were a small number of other potential inconsistencies with guidance for patients who received treatment (Figure 3), such as having a potential contraindication to the treatment given: of the contraindications included, the only one identified in results was recorded adolescent weight ≤40kg for sotrovimab (<1%) (however see Discussion). Overall, of patients who received treatment, 95% did so within the respective treatment-specific eligibility window as estimated from test date (as symptom date is not consistently available) (Supplementary figures S1 and S2). Treatment occurred most commonly two days (38%), or three days (29%) after a patient's positive SARS-CoV-2 test. There was minor variation between the two most common treatments: molnupiravir treatment occurred slightly earlier compared to sotrovimab, with 56% vs 51% of patients being treated within two days of their positive test, respectively.

Figure 3 Breakdown of possible inconsistencies with guidance on eligibility/exclusion criteria in treated COVID-19 patients. *Treatment eligibility window for Paxlovid, sotrovimab and molnupiravir was 5 days from positive SARS-CoV-2 test (used as a proxy for symptom onset date) and 7 days for remdesivir.*



Discussion

Summary

The NHS in England rapidly established CMDUs to support delivery of COVID-19 therapeutics to people in the community from December 2021. In our study, out of 50,730 patients likely to be eligible based on national clinical criteria, 13% (n=6,420, 95% CI 12-13) received an antiviral or nMAB between 16th December 2021 and February 23rd 2022. The proportion of these potentially eligible patients receiving treatment varied by high risk cohort, e.g. 25% in those with Renal disease, 10% in Liver disease. We also observed differences in treatment rates between different demographic and clinical sub-groups. Those living in more socioeconomically deprived areas generally had lower treatment coverage (9% in the most deprived quintile, vs: 15% in the least deprived quintile) and similarly those living in care homes or housebound had lower than average treatment coverage (4% and 10%, respectively). Patients who were White or Asian or Asian British were most likely to receive treatment, with Black or Black British patients the least likely (14% and 13% vs 9%, respectively). We also observed substantial geographic variation in treatment rates between NHS Regions, from 6% in Yorkshire and the Humber to 17% in the East of England. Over the study period sotrovimab was the most widely used treatment, followed by molnupiravir (56% and 42%, respectively), although use varied over time. Treatment choice also varied by high risk cohort, with molnupiravir used more commonly in two high risk cohorts: Down's syndrome (67%) and Immunosuppression due to HIV or AIDS (63%). There was limited use of other treatments, reflective of availability and guidance.

Strengths and weaknesses

The key strengths of this study are the scale, detail and completeness of the underlying raw electronic health record data. The OpenSAFELY-TPP platform runs analyses across the full dataset of all raw, pseudonymised, single-event-level clinical events for all 23.4 million current patients at all 2,545 general practices in England using TPP software; whereas the GPES dataset available in NHS Digital is a subset of this raw data created through a series of processing rules for specific aspects of GP records applied at source before extraction. OpenSAFELY-TPP also provides data in near-real time, providing unprecedented opportunities for audit and feedback to rapidly identify and resolve concerns around health service activity and clinical outcomes related to the COVID-19 pandemic. The delay from entry of a clinical event into the EHR to its appearing in the OpenSAFELY-TPP platform varies from two to nine days. This is substantially faster than any other source of comprehensive GP data. Additionally OpenSAFELY now contains linked COVID-19 therapeutics data which is collected from CMDUs with typically only 2-3 days delay between form submission and data being available for analysis. This can support timely monitoring of treatments administered through CMDUs as well as safety and efficacy studies of these treatments and other COVID-19 analyses.

We recognise some limitations to our analysis. Our population, although extremely large, may not be fully representative: there is some geographic clustering in the EHR system used by general practices, and only 17% of general practices in London use TPP software. However other GP data sources such as the CPRD data download service similarly contain a convenience sample (practices that have elected to participate in data extraction) rather than a random sample of the general population; and there are no a priori reasons to expect

that this issue will substantially affect the relationships observed between patient factors and outcomes.

As with other analyses of the same data, the newly sourced COVID-19 therapeutics data represent treatment notifications, not prescriptions, and as such there may be some missingness caused by delays in paperwork being completed. In addition, this data does not allow us to determine the reasons why some patients who were considered eligible may not have received treatment; many patients would not have been treated because they were asymptomatic or clinically improving which can not be elucidated from the data. Because the presence of symptoms could not be reliably determined for the purposes of inclusion criteria (as highlighted by our sensitivity analysis which showed that restricting to only those with a "symptomatic" flag associated with their positive SARS-CoV-2 test reduced the population by ~70%) and as it was not possible distinguish between PCR and lateral flow tests, we are likely to somewhat overestimate the total number of potentially eligible people.

Electronic health records data may not always fully capture some eligibility criteria and as such, may underestimate the true number of eligible people in some groups or misclassify some people, particularly those identified through "non-digital" routes, e.g. patients with kidney disease. Related to this, as previously described, we may not have ascertained all people in the Immunosuppression due to HIV/AIDS group due to specific arrangements around HIV data[15]. In addition, our ascertainment of eligibility status may sometimes deviate from NHS Digital ascertained eligibility status on specific patients for two reasons: OpenSAFELY has different and more detailed primary care records available; and when translating information from the NHS Digital website into analytic code, we had to make pragmatic decisions to resolve some discrepancies (as described). We have notified NHS Digital of discrepancies identified by our team with their codelists - which we regard as normal and expected with complex cohorting work - and additionally made all our analytic code and codelists openly available for inspection as with all OpenSAFELY analyses. It is additionally reasonable to expect marginal differences in the proportion of the potentially eligible in each risk group who were treated between different data sources from different analytic teams due to minor differences in the speeds of data flow, specific data available, and the ascertainment of denominators. Finally, our findings on apparent inconsistencies with treatment guidance should be taken as indicative only, as there were several limitations such as: the date of treatment may occasionally be entered incorrectly on the submitted form; some SARS-CoV-2 test records may not pass into EHRs; hospitalisation due to COVID-19 is difficult to determine accurately in SUS data (as it is not possible to fully determine whether the patient was treated for COVID-19 during hospitalisation or if it was an incidental finding); and the latest weight recorded in EHR (required to be over 40kg for adolescents treated with sotrovimab or remdesivir) may not be current at the time of treatment.

Policy Implications and future research

To our knowledge this paper is the first study to describe in detail the demographic and clinical features of those who have received treatments from CMDUs across England; and the first to report variation in treatment by detailed demographic and clinical characteristics. Our finding that only 13% of potentially eligible patients (those who tested positive for SARS-CoV-2 in a group eligible for treatment) received treatment could be of concern,

however, this may just reflect the number of patients who were asymptomatic or improving by the time they were assessed by the CMDU. While these clinical data are not captured in the primary care record or the CMDU data, we understand that CMDU data recording is being iterated to capture some reasons for non-treatment among those who were assessed; we will update our analyses as this data becomes available. Although sotrovimab was the first-line treatment available during the majority of the study period, >40% of patients received oral molnupiravir; this may be explained by sotrovimab requiring an infusion in a clinic setting, presenting greater logistical challenges. Our findings of discrepancies in treatment between different groups is notable and consistent with our analysis of sociodemographic and ethnic variation in the receipt of COVID-19 vaccinations[8]: further research and investigation is required to understand and address the causes of any inequity. Additionally, understanding variation in the choice of individual treatment option beyond clinical indications and cautions will be of utmost importance as more information on the relative efficacy emerges from ongoing trials.

The reasons underpinning variation in treatments delivered by CMDUs are not yet understood, and information presented here should not be misinterpreted as a criticism of the rapidly established CMDUs in the context of high levels of infection[16], but rather as an example of the value of rapid turnaround data monitoring to help optimise the successful delivery of an ambitious national treatment programme. We will produce routine data updates at https://reports.opensafely.org/ to assist with ongoing monitoring and targeted initiatives to address gaps in coverage as well as informing development of study designs on the efficacy and safety of these new treatments. It should lastly be noted that all findings in this paper are from the first few preliminary weeks of these treatments being made nationally available: substantial changes in coverage among different groups are to be expected over the coming months.

Summary

The NHS in England has rapidly deployed facilities to offer novel therapeutics for the rapid treatment of COVID-19 in the community. Targeted activity may be needed to address lower treatment rates observed among certain regions and key groups including ethnic minorities, people living in areas of higher deprivation, and in care homes. Near real-time data monitoring can help support those on the front line making complex operational decisions around treatment delivery.

Administrative

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Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK, the Health Foundation, the World Health Organisation, UKRI, Asthma UK, the British Lung Foundation, and the Longitudinal Health and Wellbeing strand of the National Core Studies programme; he also receives personal income from speaking and writing for lay audiences on the misuse of science. IJD has received unrestricted research grants and holds shares in GlaxoSmithKline (GSK).

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The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care. Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Information governance and ethical approval

NHS England is the data controller; TPP is the data processor; and the researchers on OpenSAFELY are acting with the approval of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant;[17,18] patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell

counts.[19] The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[20] Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.
This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (reference 21863).

Data access and verification

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY is drawn from General Practice data across England where TPP is the Data Processor. TPP developers (CB, JC, and SH) initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. DataLab developers and PIs (BG,) holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY Data Access Agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline—from raw data to completed results for this analysis—and for the OpenSAFELY platform as a whole is available for review at github.com/OpenSAFELY.

Authors' contributions

Contributions are as follows:
Conceptualisation: AG, HC, SE, LT, BMK, BG
Funding acquisition: BG
Methodology: AG, HC, SE, LT, BMK, BG
Formal analysis: AG, HC
Codelists: RH, PI, AG, BMK
Software: RS, SB, SD, ID, CM, TW, CB, JC, JP, FH, SH
Visualisation: AG, HC
Writing - original draft: AG, HC, BMK
Writing- review & editing: ALL
Information governance: CB BG AM

Guarantor

BG is the guarantor.

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