communications medicine

Article

https://doi.org/10.1038/s43856-024-00720-7

Uptake and safety of Sotrovimab for prevention of severe COVID-19 in a cohort and self-controlled case series study

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Abstract

Background Sotrovimab is a neutralising monoclonal antibody (nMAB) currently available to treat extremely clinically vulnerable COVID-19 patients in England. Trials have shown it to have mild to moderate side effects, however, evidence regarding its safety in real-world settings remains insufficient.

Methods Descriptive and multivariable logistic regression analyses were conducted to evaluate uptake, and a self-controlled case series analysis performed to measure the risk of hospital admission (hospitalisation) associated with 49 pre-specified suspected adverse outcomes in the period 2–28 days post-Sotrovimab treatment among eligible patients treated between December 11, 2021 and May 24, 2022.

Results Here we show that among treated and untreated eligible individuals, the mean ages (54.6 years, SD: 16.1 vs 54.1, SD: 18.3) and sex distribution (women: 60.9% vs 58.1%; men: 38.9% vs 41.1%) are similar. There are marked variations in uptake between ethnic groups, which is higher amongst individuals categorised ethnically as Indian (15.0%; 95%CI 13.8, 16.3), Other Asian (13.7%; 95%CI 11.9, 15.8), white (13.4%; 95%CI 13.3, 13.6), and Bangladeshi (11.4%; 95%CI 8.8, 14.6); and lower amongst Black Caribbean individuals (6.4%; 95%CI 5.4, 7.5) and Black Africans (4.7%; 95%CI 4.1, 5.4). We find no increased risk of any of the suspected adverse outcomes in the period 2–28 days post-treatment.

Conclusions We find no safety signals of concern for possible adverse outcomes in the period 2-28 days post treatment with Sotrovimab. However, there is evidence of unequal uptake of Sotrovimab treatment across ethnic groups.

Plain language summary

Sotrovimab is a medical treatment which may improve the chance of recovery and survival of patients with weak immune systems who have COVID-19. However, the safety of Sotrovimab treatment and the characteristics of the people who receive it are not well understood. We analysed the risk of serious side-effects which resulted in those who were treated with Sotrovimab needing to be hospitalised, along with the characteristics of the treated patients. No evidence of serious side-effects from Sotrovimab treatment requiring hospitalisation was found, but some ethnic groups were more likely to be treated than others. Therefore, there is evidence that Sotrovimab may be a safe treatment for people with weak immune systems who have COVID-19, but some work may be needed to make sure the treatment is used more equitably among different ethnic groups.

On December 2, 2021, the United Kingdom's (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) approved the use of the neutralising monoclonal antibody (nMAB) Sotrovimab (Xevudy) as a COVID-19 treatment for extremely clinically vulnerable patients in the community[1]. nMABs are synthetic monoclonal antibodies that bind to the spike protein of the SARS-CoV-2 virus and prevent entry into the host cell and its subsequent replication. Sotrovimab is recommended for use as a treatment option in the UK for eligible, non-hospitalised adults and children (aged 12 years and above) with COVID-19[2]. Non-hospitalised patients are eligible for treatment if: SARS-CoV-2 infection is confirmed by either reverse transcription-polymerase chain reaction (RT-PCR) testing or a lateral flow test. They should also exhibit symptoms of COVID-19, show no signs of clinical recovery; and be on the registry of extremely clinically vulnerable patients. These are patients with one or more of a set of clinical conditions, determined and compiled by a group of experts, which are considered to put patients at an increased risk of developing severe COVID-19 outcomes (i.e., hospitalisation or death)[3]. Sotrovimab is administered in a single intravenous infusion by a healthcare professional, to be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset.

Recent evidence[4,5] suggests that Sotrovimab treatment significantly improves clinical outcomes in non-hospitalised patients with COVID-19 who are at high risk of developing severe COVID-19 disease. A clinical trial reported that a single infusion of Sotrovimab reduced the risk of

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hospitalisation and death by an average of 79% in extremely clinically vulnerable adults with symptomatic COVID-19 infection[4]. In terms of safety, a randomised controlled trial of 546 patients, of which 184 were treated with Sotrovimab, found that the side effects of Sotrovimab treatment were only mild to moderate[6]. However, clinical trials recruiting several hundred people are likely to lack the necessary statistical power to be able to detect very rare adverse events (for example, where the incidence is less than one in a thousand). Identification of any adverse effects is of considerable importance for assessing the risk-benefit balance of therapeutics and informing clinical research and policymakers. It is also important to evaluate the uptake of new therapeutic agents since there is evidence that the introduction of novel interventions may exacerbate pre-existing health inequalities (inverse equity hypothesis)[7]. This is a crucial point given the well-documented disparity in severity of COVID-19 outcomes by ethnic group, resulting in a higher risk of hospitalisation and mortality among some non-white groups[8]. As large volumes of population data become increasingly available, it is important to evaluate the uptake and safety of Sotrovimab in real-world settings. In this study, we have used linked national datasets for England to report on the uptake of Sotrovimab treatment to assess whether it has been administered in line with guidance, ensuring equitable access and use of the therapeutic treatment. We also investigated the safety of Sotrovimab treatment administered to patients in the community. This study shows no increased risk of any of the suspected adverse outcomes in the period 2–28 days post-treatment with Sotrovimab. Uptake of Sotrovimab is similar between male and female patients but differs by patient age group, vaccination status, ethnic group, and medical history.

Methods

Data sources

We used the national specialised commissioning database for England, also known as Blueteq, which includes information submitted by NHS hospitals and COVID Medicine Delivery Units (CMDUs) treating patients who have been determined to be clinically eligible for (and have consented to) treatment to prevent severe COVID-19. This included the type of treatment, e.g., antivirals or nMAB including Sotrovimab, date of treatment, date of the latest SARS-CoV-2 positive test and where the treatment was administrated, i.e. community or hospital-based patient.

We linked the Blueteq database at individual level to the list of extremely clinically vulnerable patients eligible for COVID-19 treatments[3], the SARS-CoV-2 infection data (Pillar2 data), the hospital admissions data (Hospital Episode Statistics—Secondary Uses Service), ONS (Office for National Statistics) mortality data, and COVID-19 vaccination data from the National Immunisation Management System (NIMS) database. All the data were linked and analysed within the QResearch Trusted Research Environment.

Study design

A descriptive cohort study followed by multivariable logistic regression analyses was used to investigate the uptake of Sotrovimab treatment. The self-controlled case series (SCCS) design was used to study the safety of Sotrovimab treatment. This design was originally developed to examine vaccine safety[9,10] and has been frequently used for pharmacological vigilance[11]. The analyses are conditional on each case (person with an outcome of interest). Therefore, any fixed patient characteristics such as sex, ethnicity, or chronic conditions, are inherently controlled for. Further reading and resources on the SCCS method and analyses may be found in Supplementary Note 1.

Study period and population

The study period was from December 11, 2021 (the date Sotrovimab became available for use in the NHS) to May 24, 2022, the date of the most recent primary care patient data available. The study population for the cohort study included all patients recorded in the extremely clinically vulnerable patients eligible for the COVID-19 treatments cohort and any other patients treated with Sotrovimab in the community in England during the study period. Patients were excluded if they were less than 12 years of age; had a missing NHS number; were treated with antivirals; received treatment which was unapproved or not completed by the commissioning team; were not on the eligible list; received a nMAB treatment other than Sotrovimab; or their nearest SARS-CoV-2 positive test result to the treatment date was performed in a hospital setting.

The study population was derived from a larger, base population ($n = 10{,}185{,}073$), which included all patients in England who fell into the following three categories: all patients listed as extremely clinically vulnerable by the NHS ($n = 1{,}265{,}047$), patients with a record of a positive SARS-CoV-2 test ($n = 9{,}087{,}649$), and all patients recorded in the Blueteq database as having been treated with Sotrovimab ($n = 62{,}583$). A detailed data flow diagram is included in Fig. 1.

We identified SARS-CoV-2 positive patients in the community in this period using Pillar 2 testing data, which included non-hospital administered test results from the wider population. In the UK, mass SARS-CoV-2 testing was coordinated and carried out through commercial and government partnerships and processed either in a laboratory (PCR) or more rapidly with antigen tests (lateral flow test)[12].

For the safety analyses, we identified a list of possible adverse outcomes of interest (listed in Supplementary Table 1). For each outcome of interest, we identified the cohort of patients from the study population who were admitted to the hospital or died from the outcome during the study period. Patients were followed up from the start (December 11, 2021) to the end of the study period or until death, whichever occurred first. Patients who were admitted to hospital for an outcome in the 2 years prior to the study start were excluded.

Exposures

For the descriptive cohort, we reported uptake of Sotrovimab by age, sex, ethnic group, vaccine status, and a history of blood, neurological, or cardiovascular-related hospital admission in the 2 years prior to the study start date. Sex, age, ethnic group, vaccine status, and medical history were likewise, included in the multivariable analyses for uptake. Self-assigned ethnicity data (white, Bangladeshi, Pakistani, Indian, Black African, Caribbean, Other Asian, Chinese, Other, Not Recorded) were derived from hospital admissions data and mapped to the self-assigned ethnic categories used in primary care.

For the self-controlled case series safety analysis, the exposure variable was Sotrovimab treatment administered in a community setting during the study period in England and recorded in the Blueteq dataset. We defined the exposure risk intervals as the 2–28 days after the Sotrovimab treatment. Since there might be a recording delay of 1 day between Blueteq and SUS-HES data (i.e. between the time of hospital admission and the time of the Sotrovimab treatment), results for the day following a Sotrovimab exposure could be misleading. Therefore, day 0 (the day of treatment) and day 1 (the day after the treatment) were kept as separate risk intervals.

A pre-risk interval of 1–28 days before the Sotrovimab exposure date was included to account for potential bias that might arise if the occurrence of the outcome temporarily influenced the likelihood of exposure. The baseline period comprised the remaining observation time from December 11, 2021 until 29 days before the date of Sotrovimab exposure and from 29 days after the exposure date until May 24, 2022 or the censored date (death), if earlier. All UK deaths (hospital or community) are captured in the ONS Mortality dataset.

Outcomes

The outcome in the multivariable analyses for uptake was treatment with Sotrovimab during the observation period. The outcomes of the safety analysis were pre-specified complications, including those monitored in drug safety studies by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the MHRA, or those with prior indications of an association with SARS-CoV-2 infection (see Supplementary table 1). These outcomes were identified using diagnostic (International

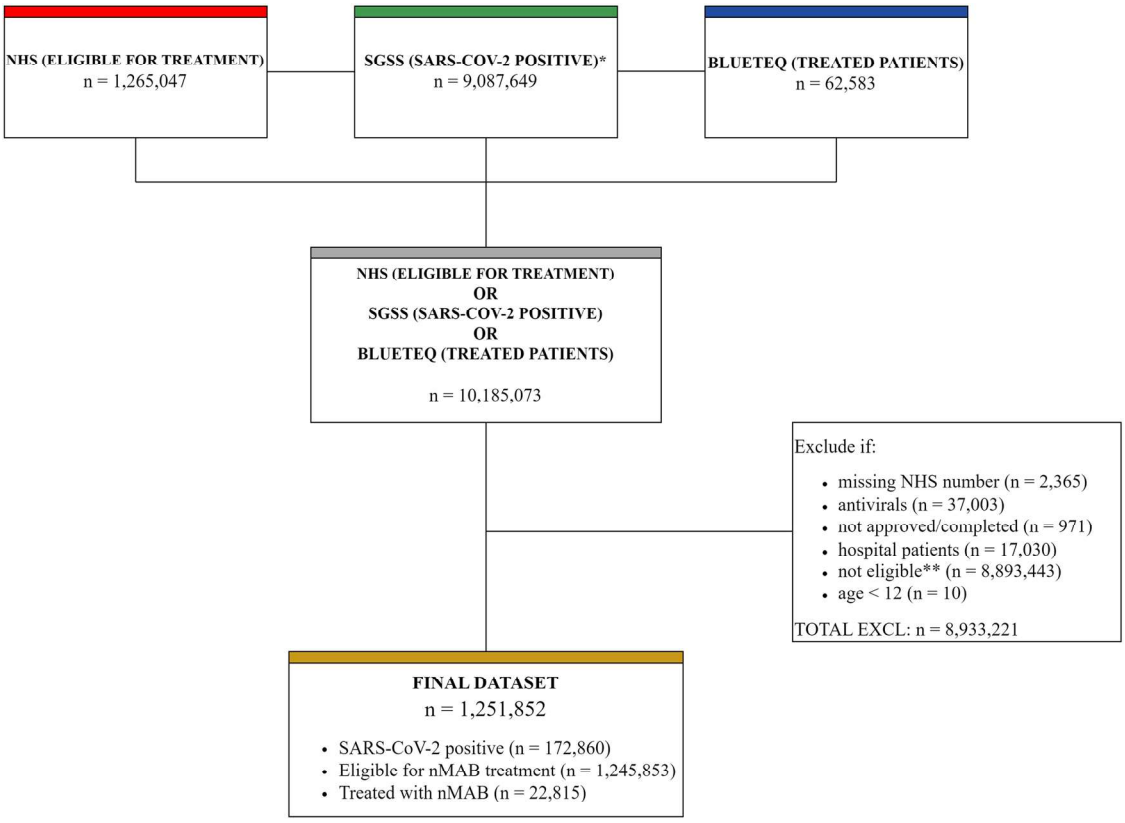

Fig. 1 | Data flow diagram. The composition of the base population used to define the study population. *Between December 1, 2021 and May 24, 2022; **Excludes patients not eligible for nMAB if they were not treated.

Classification of Diseases, ICD-10) codes recorded at hospital admission (13 in the SUS database and 21 in the HES database). ICD-10 codes used to identify the outcomes of interest are available at https://www.qresearch.org/data/qcode-group-library/. The outcomes were defined as the first hospital admission due to the outcome of interest (as the primary reason for admission) or a death, with an ICD-10 code related to the outcome recorded on the death certificate, within the study period.

Some patients with community prescribed Sotrovimab treatment may have had it administered in a hospital setting. In this event, it is possible that some outcomes which are associated with a hospital admission occurring on the same day as Sotrovimab treatment, may be pre-existing conditions. This overlap makes it difficult to determine the time sequence of exposure and outcome, and for this reason, outcomes associated with hospital admissions occurring on the same day as Sotrovimab treatment were placed in a separate 'day 0' group for the safety analysis.

Confounders

In each model in the self-controlled case series analysis, we treated a first, second, third or fourth dose of the three main COVID-19 vaccines in use in the UK (i.e. ChAdOx1, BNT162b2 or mRNA-1273) as time-varying factors. Due to the small number of events, we did not stratify by vaccine type. We also included SARS-CoV-2 positive tests as a time-varying confounder. COVID-19 vaccinations and SARS-CoV-2 positive tests were treated as time-varying factors to account for the temporarily heightened immune response brought on by both[13]. This was achieved through the creation of groups (29 days or earlier (baseline); 28 to 1 day prior; 0 days (exposure date); 1 day post-exposure; 2 to 28 days post-exposure; 29 days or later (baseline)), exposure categories. These grouped variables were adjusted for in the final models for each outcome. A link to a sample of the code can be found in the "Code Availability" section. Age was not included in the model (I.e. was treated as a fixed variable) because the study period was short.

Hospital admissions during the pandemic were likely influenced by the pressure on the health systems due to COVID-19, which was not uniform during this period. To account for these underlying *seasonal effects*, we split the study observation period into weeks and adjusted for weeks as a factor variable in the statistical models.

Statistics and reproducibility

We described the characteristics of age, sex, ethnicity, vaccine status, and prior medical history for the cohort who were eligible for or treated with Sotrovimab, and who had received a positive SARS-CoV-2 test result in the study period. Odds Ratios and 95% CIs for uptake of Sotrovimab treatment during the study period were calculated through the fitting of multivariable logistic regression models for SARS-CoV-2 positive/symptomatic patients, adjusting for ethnicity, sex, age group, vaccine status, and medical history (haematologic, neurological, or cardiovascular conditions). Likelihood ratio tests (LRT) were used to assess the goodness-of-fit of all independent variables included in the final models.

For the safety analysis, we described the characteristics of age, sex, and prior medical history by Sotrovimab treatment for each set of cases (patients with the outcomes of interest). The SCCS models were fitted with cases with each outcome using a conditional Poisson regression model with an offset term for the length of the exposure risk period. The incidence rate ratios (IRR), the relative rate of hospital admission (or death) for each outcome in the exposure risk periods relative to the baseline periods, and their 95% confidence intervals (CI) were estimated adjusting for week, SARS-CoV-2 test status, and COVID-19 vaccine dose as time-varying covariates. Sotrovimab treatment, SARS-CoV-2 test status, vaccine dose and calendar week were included in the same model. Sensitivity analyses were conducted by restricting analyses to SARS-CoV-2 positive patients and COVID-19 symptomatic patients only. Out of 49 conditions studied (Supplementary Table 1), 26 had 5 or more events in the 2–28 days post-treatment. We have conducted analysis only for these 26 outcomes. The 5-event cut-off was

determined in line with disclosure control policies which are designed to protect patient confidentiality. Stata version 17 was used for these analyses. All reported *p*-values are two-sided.

Patient and public involvement

This project was part of a large COVID-19 study supported by a patient and public involvement advisory panel who we thank for their continued support and guidance. PPIE (patient and public involvement and engagement) advisers were supportive of the study and the importance of identifying the differences in and barriers to COVID-19 therapeutics uptake and understanding any risks which may be associated with treatment. The panel's input helped us identify and prioritise questions for further investigation.

Ethical approval

National Health Service Research Ethics Committee (NHS REC) approval for the use of the data in the QResearch Trusted Research Environment was obtained from the East Midlands-Derby Research Ethics Committee [reference 04/03/2021]. This study was reviewed and approved by the QResearch Scientific Committee, which constitutes Research Ethics Approval under REC 23/EM/0166. All participant GP data is provided by EMIS through the upload of anonymised data from participating GP practices using EMIS Web throughout the UK. Practices may withdraw their participation at any time without providing a reason. As the patient data is anonymised, informed consent is obtained and required from the guardian (GP practice) of the records. Participating GP practices are required to inform their patients accordingly of the practice's participation and patients at these practices may withdraw their participation through the National Data opt-out website at any time. Further information may be found on the QResearch website: https://www.qresearch.org/about/ethics-and-confidentiality/.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Characteristics of patients eligible for or treated with Sotrovimab

In England, between December 11, 2021 and May 24, 2022, there were 1,245,853 patients recorded as potentially eligible for Sotrovimab, should they become infected with the SARS-CoV-2 virus on the national database which includes test results from patients tested in a community setting (Pillar 2). An additional 5999 patients were identified who were treated with Sotrovimab while not being on the eligible list. The characteristics for the combined 1,251,852 people who were eligible and/or treated with Sotrovimab are shown in Supplementary Data 1. The demographic and medical characteristics of patients eligible for Sotrovimab treatment and who received a SARS-CoV-2 positive test, are also shown in Supplementary Data 1. Hospital admissions associated with medical conditions used to identify patients at high risk were prevalent in the cohort of eligible patients during the study period. Examples of these are multiple sclerosis ($n = 45{,}371$, 3.6%), acute renal failure ($n = 75{,}733$, 6.0 %) and rheumatoid arthritis ($n = 42{,}621$, 3.4 %).

Uptake of Sotrovimab

Of the 1,251,852 patients eligible for or treated with Sotrovimab, there were 172,860 (13.8%) patients with one or more SARS-CoV-2 positive tests between December 1, 2021 and May 24, 2022 based on Pillar 2 testing data. There were 22,815 (1.8%) patients who received Sotrovimab treatment, and of these, 21,487 (94.1%) had a SARS-CoV-2 positive test recorded in either the Pillar 2 or the Blueteq database. Of those receiving the treatment, there were 8089 (37.6%) patients who were recorded as having symptomatic COVID-19. The number of treated community patients per day is shown in Fig. 2.

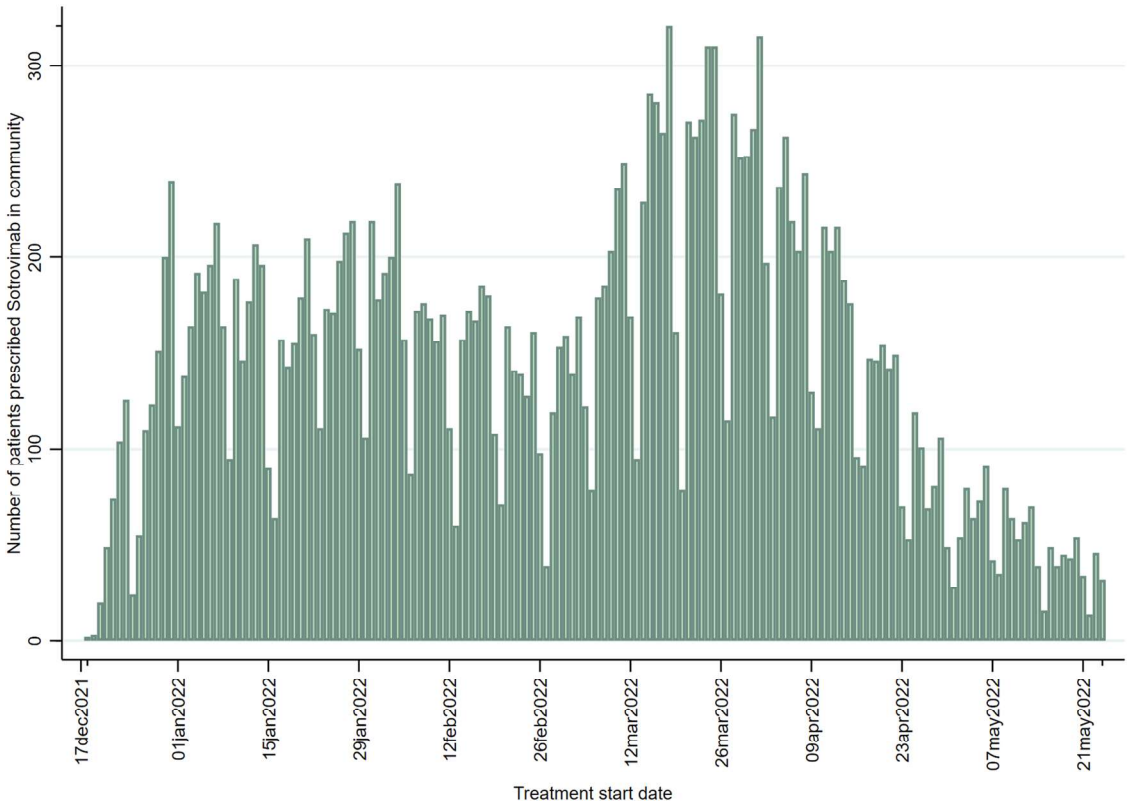

Fig. 2 | Daily number of patients prescribed Sotrovimab in the community in England. Histogram showing patients treated with Sotrovimab ($n = 22{,}815$) during the study period (December 11, 2021 to May 24, 2022) of 1,251,852 patients eligible for or treated with Sotrovimab.

We compared the demographic and medical characteristics of those treated with Sotrovimab (21,487; 12.4%) versus those who were untreated (151,373; 87.5%) amongst the 172,860 SARS-CoV-2 positive patients who were eligible for treatment or who had been treated (Supplementary Data 1). Gender and age distribution were similar between the two groups. Amongst those treated, 13,090 (60.9%) were female, and 8369 (38.9%) were male with a mean age of 54.6 (SD 16.1); in those untreated, there were 87,885 (58.1%) female patients and 62,247 (41.1%) male patients with a mean age of 54.1 (SD 18.3).

Of those who were treated and had a SARS-CoV-2 positive test recorded, 96.3% (20,694/21,487) received the treatment in the 7-day period following the test. The SARS-CoV-2 variant type had been sequenced for half (50.0%) of those who received Sotrovimab in the community. Of those sequenced, there were 6882 (32.0%) individuals infected with the Omicron BA.1 and 3613 (16.8%) infected with the Omicron BA.2 variant (Supplementary Table 2).

Counts and proportions of SARS-CoV-2 positive patients eligible for or treated with Sotrovimab between December 11, 2021 and May 24, 2022, broken down by demographics and medical history, are shown in Supplementary Data 2. Uptake was similar between female (12.96%; 95% CI 12.76, 13.17) and male patients (11.85%; 95% CI 11.62, 12.09) and higher in those aged 60–69 years (14.56%; 95%CI 14.17, 14.97) while lower amongst the youngest (6.36%; 95% CI 5.62, 7.19) and the oldest (4.34%; 95% CI 3.57, 5.27). Uptake differed across ethnic groups. Higher uptake of Sotrovimab treatment was observed for patients of Indian (15.0%; 95% CI 13.8, 16.3), Other Asian (13.7%; 95% CI 11.9, 15.8), white (13.4%; 95% CI 13.3, 13.6), and Bangladeshi ethnicity (11.4%; 95% CI 8.8, 14.6); whereas uptake was lower amongst individuals of Black Caribbean (6.4%; 95% CI 5.4, 7.5) and Black African ethnicity (4.7%; 95% CI 4.1, 5.4).

Results from the multivariable analyses are reported in Table 1. Patients of Pakistani (OR 0.76; 95% CI 0.64, 0.91), Black Caribbean (OR 0.61; 95% CI 0.51, 0.72), Black African (OR 0.41; 95% CI 0.36, 0.48), Other (OR 0.77; 95% CI 0.69, 0.86), and those with no recorded ethnicity (OR 0.59; 95% CI 0.56, 0.63) had lower odds of uptake compared to those of white ethnicity, while those of Indian ethnicity (OR 1.18; 95% CI 1.07, 1.30) showed higher odds of uptake. Those of male sex (OR 0.88; 95% CI 0.85, 0.90) or no recorded sex (OR 0.28; 95% CI 0.19, 0.42) were less likely to be treated than females. Patients between the ages of 30–39 (OR 1.16; 95% CI 1.08, 1.25), 40–49 (OR 1.30; 95% CI 1.22, 1.40), 50–59 (OR 1.23; 95% CI 1.15, 1.31), 60–69 (OR 1.17; 95% CI 1.09, 1.26) were more likely to be treated than the baseline group (18–29), while those between 80 and 89 (OR 0.54; 95% CI 0.50, 0.60) and above 90 years (OR 0.28; 95% O.23, 0.35) of age were significantly less likely to be treated. Patients with at least one vaccination dose were significantly more likely to be treated than patients with no history of vaccination, with the greatest difference observed amongst those receiving four doses prior to treatment (OR 6.29; 95% CI 5.42, 7.30). Patients with a record of hospital admission relating to pre-specified blood (OR 1.77; 95% CI 1.55, 2.02), neurological (OR 1.42; 95% CI 1.33, 1.50), or cardiovascular (OR 1.59; 95% CI 1.52, 1.66) conditions in the preceding 2 years, were more likely to be treated than those with no record.

Cumulative proportions of SARS-CoV-2 positive eligible patients who received Sotrovimab between December 11, 2021 and May 24, 2022, stratified by demographics and medical history, are shown in Fig. 3.

Safety of Sotrovimab

Of the 49 adverse conditions selected (Supplementary Table 1) to assess the safety of the Sotrovimab treatment, 26 had at least 5 hospitalisations each during the period 2–28 days post-treatment. Characteristics of patients with those conditions are shown in Supplementary Data 3. We found no overall association between Sotrovimab and any of the 26 adverse outcomes in the 2–28 days following the treatment. However, for some outcomes, the numbers were small, and the confidence intervals were wide (Supplementary Data 4 and Fig. 4).

Sensitivity analyses and robustness of the results

Supplementary Data 2 and Table 1 show the uptake of Sotrovimab treatment restricted to eligible patients recorded as having symptomatic COVID-19 disease and the differences in uptake between different ethnic groups were still apparent in this subset of the cohort. In addition, uptake was lower when compared to the main analysis for the Black Caribbean (4.2%, 95% CI: 3.0, 5.8 vs 6.4%, 95% CI: 5.4, 7.5) and Chinese (9.0%, 95% CI: 5.1, 15.5 vs 14.9%, 95% CI: 11.2, 19.5) ethnic groups in the descriptive results. The multivariable analyses produced comparable results with low or lower odds of uptake observed in patients of Black Caribbean (OR 0.42; 95% CI 0.30, 0.59 vs OR 0.61; 95% CI 0.51, 0.72) and Black African (OR 0.44; 95% CI 0.35, 0.55 vs OR 0.41; 95% CI 0.36, 0.48) ethnicity. No significant association was observed for patients of Chinese ethnicity (OR 0.61; 95% CI 0.33, 1.14 vs OR 1.13; 95% CI 0.81, 1.57) in either model.

Supplementary Data 5 and Fig. 4 compare the results of the sensitivity analyses with the main safety analysis. In both cases, when including only SARS-CoV-2 positive patients or COVID-19 symptomatic cases exclusively, the IRR estimates for the subset generally agreed with the main results.

Discussion

In this population-based national study of more than 1 million people eligible for treatment or treated with Sotrovimab in England, we identified several key findings of policy and clinical importance. We found that about a quarter of patients treated with Sotrovimab (5999/22,815) were not on the extremely clinically vulnerable patients list, but that the medical histories of the remaining treated patients did include a large number with co-morbidities used to determine extremely clinically vulnerable status, such as multiple sclerosis, acute renal failure, or rheumatoid arthritis[3]. This suggests that while not every patient treated was on the eligible list, overall, the government guidelines were followed. It is also possible that these non-eligible patients were considered high-risk at an earlier time but were removed from the high-risk category as they no longer met all criteria in accordance with national methodology, or were removed by their hospital consultant/GP practice[14]. Patel et al.[15] found that most patients treated with a COVID-19 therapeutic without clear evidence of a high-risk condition had an SNOMED code (1300561000000107) used to identify high-risk patients requiring shielding present in their GP records. This indicates that they were considered at high risk of developing COVID-19-related complications at some point during the pandemic. Many such patients also had active out-patient appointments for renal, oncology, haematology, rheumatology, or gastroenterology services.

Importantly, we found that the proportion of patients treated and odds of patient treatment differed across ethnic groups, with higher uptake in patients of white, Indian, Bangladeshi and Other Asian ethnicity, with patients of Indian ethnicity showing higher odds of uptake compared to those of white ethnicity in the multivariable analyses. Lower uptake was observed in patients of Black Caribbean and Black African ethnicity in both the descriptive and multivariable analyses. This suggests that inequalities in the uptake of treatment, is at least in part, associated with ethnicity. In terms of safety, we did not find any overall increased risk of hospitalisation for any of the 26 suspected adverse outcomes in the period 2–28 days following treatment.

The results of a large, descriptive cohort study in the UK of 23.4 million patients[16] showed that 10.3% ($n = 9660$) of 93,870 eligible SARS-CoV-2 patients received treatment with Sotrovimab between 11 December 2021 and 28 April 2022. This is comparable in size to the proportion (12.4%) of the eligible population who received Sotrovimab treatment in this study. In comparison to the study above, this study utilised the national cohort of patients who received Sotrovimab treatment in England and was not restricted to patients who registered with GP practices using a particular clinical software system, such as TPP. Limiting the analyses to one system may increase the risk of underrepresenting sections of the population as practices using TPP software are not equally represented across all regions in England. However, the reported uptake of Sotrovimab treatment among different ethnic groups was similar, although slightly lower, in the study in

Table 1 | Adjusted odds ratios (OR 95% CI) and *p*-values for uptake of Sotrovimab among SARS-CoV-2 positive/symptomatic patients by ethnicity, sex, age, vaccination status, and medical history

	Treatment with Sotrovimab (SARS-CoV-2 positive patients*)		Treatment with Sotrovimab (SARS-CoV-2 symptomatic patients**)	
	Adjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Ethnicity				
White	1.00	–	1.00	
Indian	1.18 (1.07; 1.30)	0.001	1.15 (0.99; 1.33)	0.064
Pakistani	0.76 (0.64; 0.91)	0.002	0.75 (0.59; 0.96)	0.021
Bangladeshi	1.04 (0.78; 1.39)	0.783	0.91 (0.60; 1.38)	0.649
Other Asian	1.12 (0.95; 1.32)	0.194	1.06 (0.82; 1.37)	0.674
Black Caribbean	0.60 (0.51; 0.72)	3.922×10^{-8}	0.42 (0.30; 0.59)	6.252×10^{-7}
Black African	0.41 (0.36; 0.48)	5.674×10^{-33}	0.44 (0.35; 0.55)	1.411×10^{-12}
Chinese	1.13 (0.81; 1.57)	0.47	0.61 (0.33; 1.14)	0.125
Other	0.77 (0.69; 0.86)	4.556×10^{-6}	0.79 (0.67; 0.94)	0.007
not recorded	0.59 (0.56; 0.63)	2.482×10^{-69}	0.57 (0.52; 0.63)	4.722×10^{-29}
Sex				
Female	1.00	–	1.00	
Male	0.88 (0.85; 0.90)	1.424×10^{-17}	0.82 (0.78; 0.86)	1.666×10^{-15}
Not recorded	0.28 (0.19; 0.42)	8.849×10^{-11}	0.41 (0.24; 0.70)	0.001
Age				
17–29	1.00	–	1.00	
12–16	0.98 (0.83; 1.16)	0.834	1.09 (0.83; 1.45)	0.527
30–39	1.16 (1.08; 1.24)	7.535×10^{-5}	1.23 (1.10; 1.38)	2.336×10^{-4}
40–49	1.29 (1.21; 1.38)	1.074×10^{-13}	1.38 (1.24; 1.54)	3.348×10^{-9}
50–59	1.22 (1.14; 1.30)	4.763×10^{-9}	1.26 (1.13; 1.40)	1.653×10^{-5}
60–69	1.16 (1.09; 1.24)	1.157×10^{-5}	1.18 (1.06; 1.32)	0.002
70–79	0.93 (0.87; 1.00)	0.047	0.97 (0.87; 1.09)	0.642
80–89	0.54 (0.49; 0.59)	8.985×10^{-40}	0.59 (0.50; 0.69)	4.893×10^{-11}
90+	0.28 (0.22; 0.34)	4.926×10^{-32}	0.47 (0.31; 0.70)	2.108×10^{-4}
Not recorded	1.73 (1.35; 2.21)	1.205×10^{-5}	1.21 (0.78; 1.89)	0.399
Vaccine status (prior to treatment/end of the study if not treated)				
No vaccine	1.00	–	1.00	
1 dose before MABS	1.88 (1.54; 2.31)	9.194×10^{-10}	2.21 (1.62; 3.01)	5.489×10^{-7}
2 doses before MABS	1.81 (1.55; 2.12)	1.018×10^{-13}	2.09 (1.64; 2.67)	2.127×10^{-9}
3 doses before MABS	3.70 (3.19; 4.28)	2.889×10^{-68}	4.85 (3.86; 6.09)	6.791×10^{-42}
4 doses before MABS	6.25 (5.38; 7.26)	7.31×10^{-128}	6.43 (5.09; 8.12)	5.703×10^{-55}
Hospital admissions in the previous 2 years for				
Haematologic condition	1.77 (1.55; 2.02)	8.675×10^{-18}	2.02 (1.65; 2.48)	1.714×10^{-11}
Neurological condition	1.41 (1.33; 1.50)	1.803×10^{-30}	1.57 (1.43; 1.73)	1.089×10^{-21}
Cardiovascular condition	1.59 (1.52; 1.66)	1.202×10^{-97}	1.42 (1.32; 1.53)	4.908×10^{-21}

*Population: $n = 172{,}860$.
**Population: $n = 66{,}425$.

question compared to the uptake reported in this study. The highest level of uptake of Sotrovimab was recorded among patients of white (10.7% vs 13.4%) and Asian or Asian British (9.6% vs 8.5% to 15%) ethnicity, and the lowest among patients of Black or Black British (4.8% vs 4.7 to 6.3%) ethnicity.

Data on the uptake of Sotrovimab in other populations internationally remains very limited. A cross-sectional analysis of nMAB (bamlanivimab; casirivimab/ imdevimab; bamlanivimab/etesevimab) uptake in the United States[17] reported that following emergency use authorisation of outpatient nMAB treatments by the U.S. Food and Drug Administration (FDA) from November 9, 2020 to April 11, 2021, 69,377 patients received an infusion, nationwide. This study did not determine the size of the population which may have been eligible for treatment. However, the demographic characteristics of the treated population in the US were similar to those reported in this study. The treated population were more likely to be under 65 years old (57.5%), female (53.8%), and white (54.8%). The causes behind the relatively low levels of uptake reported in this study and others are unknown and should be the subject of future research. However, it's possible but not substantiated that stockpiling of available treatments; unequal distribution; hesitancy to adopt treatments by patients or provides; or barriers to patient access to treatments requiring intravenous infusion may have been contributing factors[17].

While the results of the safety analysis in this study are supported by the literature, safety analyses performed on much smaller cohorts have been far

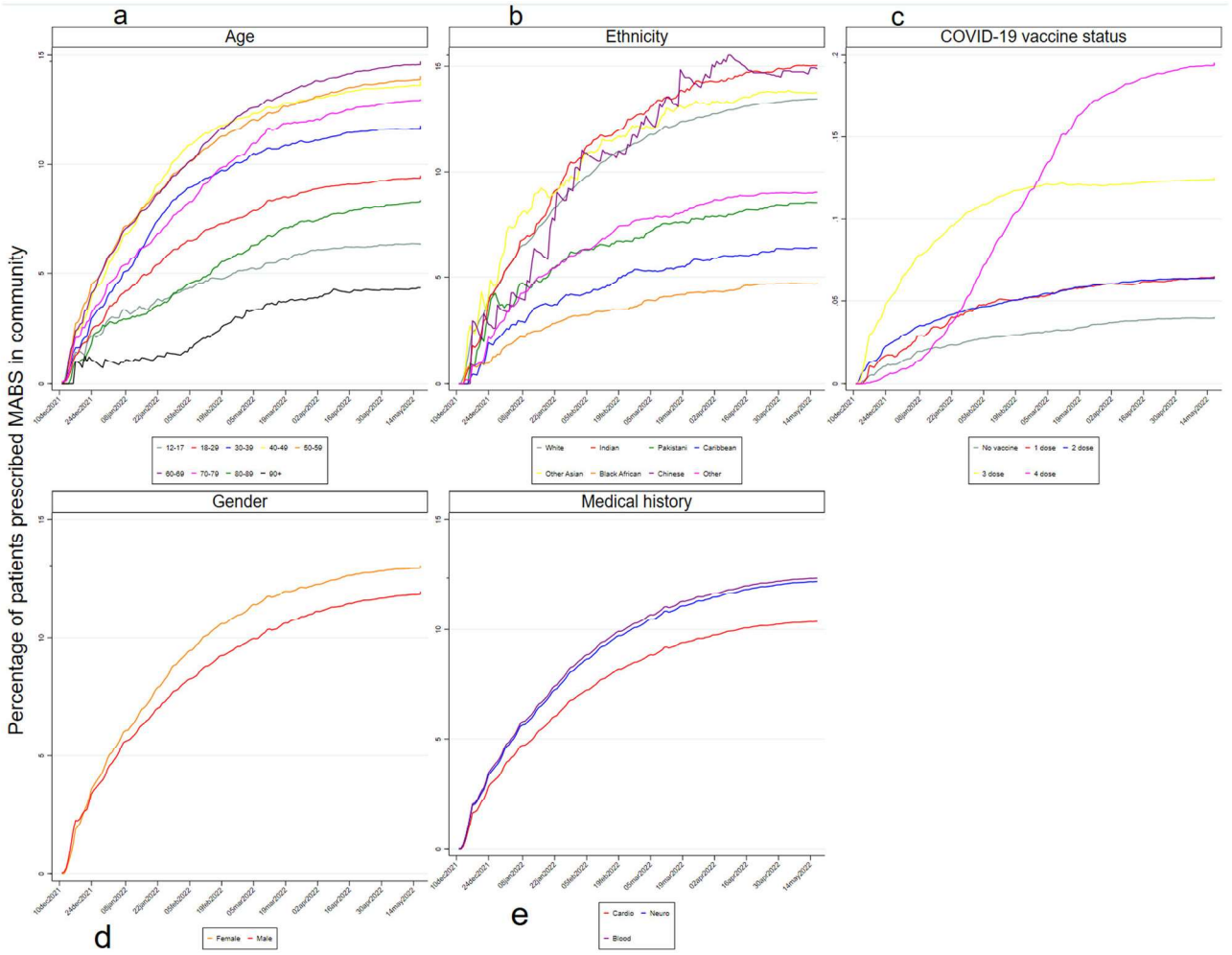

Fig. 3 | Cumulative total (%) of SARS-CoV-2 positive patients who received Sotrovimab stratified by demographics, vaccine status and medical history. Line charts showing uptake of Sotrovimab. **a** Age: Sotrovimab uptake by age group. Grey line = 12–17 years old, Red line = 18–29 years old, Dark blue line = 30–39 years old, Yellow line = 40–49 years old, Orange line = 50–59 years old, Purple line = 60–69 years old, Pink line = 70–79 years old, Green line = 80–89 years old, Black line = 90+ years old. **b** Ethnicity: Sotrovimab uptake by self-assigned ethnicity. Grey line = White ethnicity, Red line = Indian ethnicity, Green line = Pakistani ethnicity, Dark blue line = Caribbean ethnicity, Yellow line = Other Asian ethnicity, Orange line = Black African ethnicity, Purple line = Chinese ethnicity, Pink line = Other ethnicity. **c** COVID-19 vaccine status: number of SARS-COV-2 vaccinations received, if any. Grey line = no doses, Red line = one dose, Dark blue line = two doses, Yellow line = three doses, Pink line = four doses. **d** Gender: Sotrovimab uptake by gender. Orange line = Female, Red line = Male. **e** Medical History: Diagnosed with a haematologic, neurological, or cardiovascular condition. Red line = cardiovascular condition, Dark blue line = neurological condition, Purple line = haematologic condition. Population includes 1,251,852 patients eligible for or treated with Sotrovimab of which 22,815 were treated with Sotrovimab in the study period (December 11, 2021 to May 24, 2022).

more common and likely lack the requisite statistical power to detect rare adverse events. A rapid review and meta-analysis of the safety and efficacy of Sotrovimab treatment in patients with COVID-19, involving 17 studies and 27,429 patients, 9790 of which were treated with Sotrovimab, showed no difference in the incidence of adverse events between the treatment and control groups in the pooled estimate (OR = 0.98; 95% CI: 0.78–1.23, $p = 0.88$)[18]. However, only 5 of the 17 studies ($n = 5211$ patients) contained analyses on adverse outcomes. As first mentioned in the introduction, a randomised controlled trial of 546 patients, of which 184 were treated with Sotrovimab, found only mild to moderate side effects associated with treatment[6]. Similarly, a retrospective study conducted by Venturini et al.[19], analysed the safety of off and on-label Sotrovimab treatment in a cohort of 33 high-risk children with COVID-19 seen in five Italian paediatric referral centres between December 2021 and April 2022. All children were treated with Sotrovimab, and the study collected data on all possible side effects. Though no serious side effects were reported, mild to moderate side effects (vomiting and skin irritation) were experienced by two children receiving on-label treatment ($p = 0.17$)[19]. At present, the evidence suggests that the safety of Sotrovimab in COVID-19 patients does not seem to differ depending on the SARS-CoV-2 variant detected. The review by Amani and Amani[18] found no significant difference in the risk of adverse events from treatment with Sotrovimab based on the SARS-CoV-2 variant type (Omicron and Delta).

Assessing drug-drug interactions (DDI) was beyond the scope of this study. However, as Sotrovimab is neither renally excreted nor metabolised by cytochrome P450 enzymes, interactions with medications which are renally excreted or are substrates, inducers, or inhibitors of CYP enzymes, are unlikely[20]. A recently published Expert Opinion by Davoutis et al.[21] examining the evidence for the risk of DDI between COVID-19 drug therapies and antidepressants, reported a low risk of potential DDI between Sotrovimab and antidepressants. However, the body of literature analysing the risk of DDI's with Sotrovimab and COVID-19 therapeutics, generally, is very small.

This study had several strengths. Firstly, we used prospectively recorded national medical data obtained from high-quality, national electronic health record databases. These data were all used for operational purposes

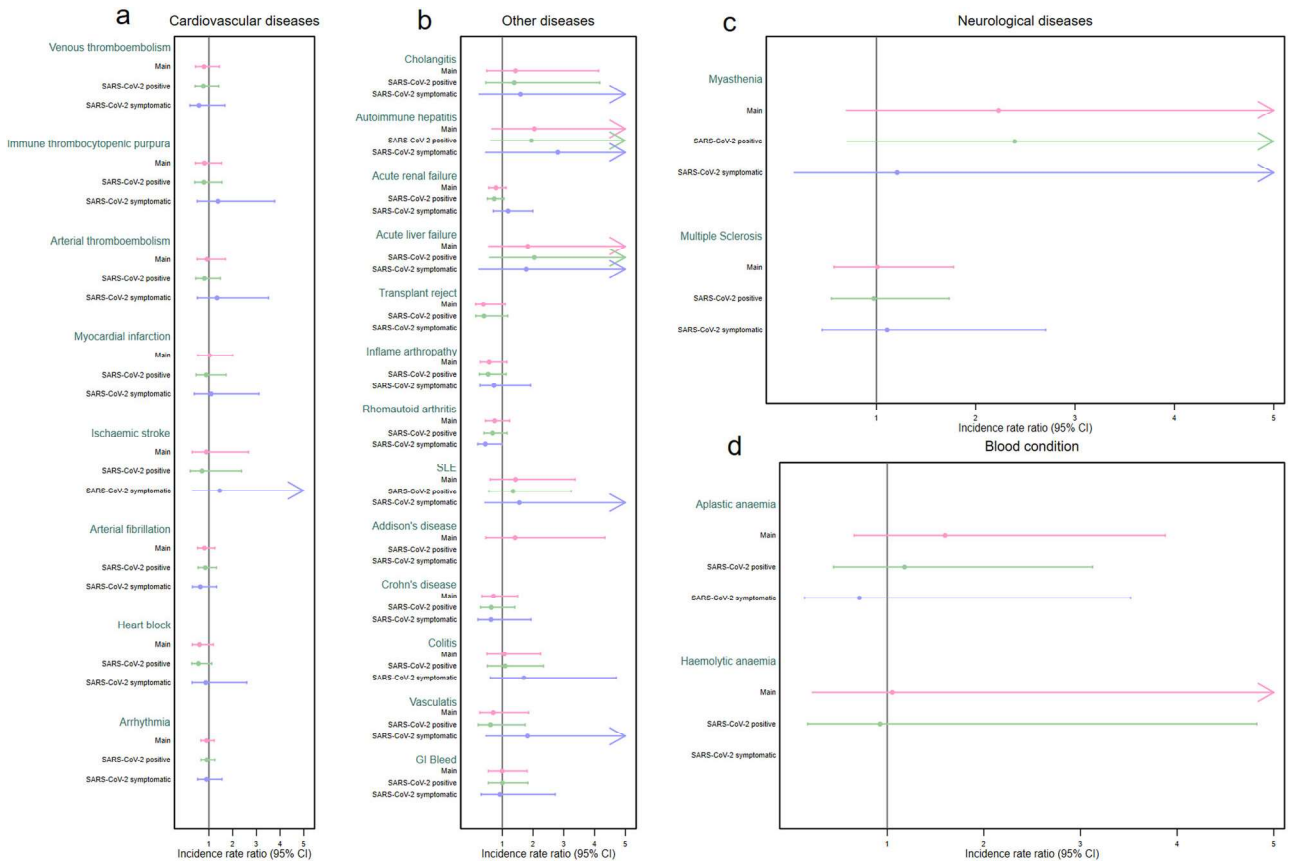

Fig. 4 | Incidence rate ratios (IRR 95% CI) for individual outcomes in the 2–28 days after Sotrovimab treatment, adjusted for calendar time, SARS-CoV-2 positive test and vaccine status. Box plots showing IRR and 95% confidence intervals for safety outcomes grouped by disease/condition type (**a** Cardiovascular, **b** Other, **c** Neurological, and **d** Haematologic (blood condition) during the study period (December 11, 2021 to May 24, 2022)). Pink line = Main (eligible population or patients treated with Sotrovimab, n = 1,251,852; Treated with Sotrovimab, n = 22,815). Green line = SARS-CoV-2 positive (population with a positive SARS-CoV-2 test result, n = 172,860; Treated with Sotrovimab, n = 21,487). Blue line = SARS-CoV-2 symptomatic (patients recorded as showing symptoms of COVID-19 disease, n = 66,425; Treated with Sotrovimab, n = 8,089). Small circles found on each coloured line represent sample estimates. A vertical light grey line in each box represents an IRR of 1. Small circles located to the right side of the light grey line = IRR > 1 and to the left of the line = IRR < 1.

and collected during the course of NHS clinical care giving the maximum possible power to investigate rare adverse events. The use of routinely collected electronic data means our study is not subject to recall or selection biases. Secondly, the breakdown of the study period into weekly blocks for the safety analyses accounted for temporal confounding, which is important as the pandemic's different waves and variants might have had different effects on health and healthcare systems. Thirdly, to assess the safety of the treatment we used the self-controlled case series study design, which uses a within-person comparison and, hence, removes potential confounding for all fixed characteristics. The UK was also among the first countries to roll out the COVID-19 vaccination and therapeutics treatments against COVID-19 and has some of the world's best data for evaluating the uptake and safety of new drugs[22–25]. Other strengths of our study include representativeness, data completeness, and timeliness.

There were several limitations to this study. Our study evaluated clinical adverse outcomes resulting in hospitalisation or death and, therefore, analysed the risk associated with severe outcomes over less severe outcomes, which may occur after treatment but typically do not result in hospital admission. We used electronic health record data collected during the process of clinical care rather than detailed clinical assessments or questionnaire data. As a result, our focus has been on medically diagnosed conditions rather than the symptoms used to inform those diagnoses. Although we did have data available on symptomatic SARS-CoV-2 infection, this was only recorded at a single point in time, and COVID-19 symptoms may have developed over time including after the date of the test. Unfortunately, no data were available related to other socio-demographic factors, such as deprivation, which could act as potential confounders for associations between other factors, such as specifically, ethnicity and uptake. Moreover, although we had information on all the patients treated with Sotrovimab in the community in England, out of the 49 conditions studied to determine the safety of the treatment, only 26 conditions had 5 or more events in the 2- to 28-day period post-treatment. Confidence intervals were also wide for a number of these outcomes, and as a result, we cannot rule out a potential increase in risk.

The inequality of uptake of novel COVID-19 treatment across ethnic groups has major implications for healthcare policy. Early studies[8,26] showed marked disparities by ethnic group in COVID-19 mortality for non-white ethnic groups compared with white, which persisted during the Omicron wave[27]. Ethnic differences in treatment uptake could further exacerbate these disparities and worsen health inequalities. This information can provide evidence to enable policymakers to identify strategies to improve and strengthen the use of Sotrovimab by supporting the construction and use of targeted interventions to address these inequalities. Moreover, we found that Sotrovimab treatment is, overall, safe in terms of the outcomes studied, which can help to inform clinical decision-making. However, these findings would benefit from corroboration by research from other countries using similarly robust analytical approaches and large datasets.

In summary, in this study of the safety of Sotrovimab, we found no safety signals of concern in the 2–28 day period post-treatment. We found, however, evidence for inequalities in the uptake of the treatment across ethnic groups, with uptake being higher in patients of white, Indian, Bangladeshi and Other Asian ethnicity and lower in patients of Black Caribbean

and Black African ethnicity. This is particularly important given existing evidence of ethnic disparities in severe COVID-19 outcomes, indicating that those who may have the greatest clinical need are not receiving treatments from which they could benefit, thereby potentially exacerbating existing health inequalities[7].

Data availability

The data that support the findings of this study—Blueteq, National Immunisation (NIMS) Database of COVID-19, mortality (ONS), hospital admissions (HES) and SARS-CoV-2 infection data (NHS England)—are not publicly available because they are based on de-identified national clinical records. Due to national and organisational data privacy regulations, individual-level data such as those used for this study cannot be shared openly. Supplementary Data 1 contains the tabulated demographic characteristics of patients who did and did not receive Sotrovimab treatment in the community in England. Supplementary Data 2 contains a tabulation of SARS-CoV-2 positive community patients who received Sotrovimab, stratified by demographic characteristics and medical history. Supplementary Data 3 contains the tabulated demographic characteristics of patients who experienced outcomes in the baseline period and in the 2–28 days following the Sotrovimab treatment. Supplementary Data 4 contains a tabulation of the incidence rate ratios (IRR 95% CI) for hospitalisation for outcomes in pre-defined risk periods immediately before and after Sotrovimab treatment, adjusted for calendar time, SARS-CoV-2 positive test, and vaccine status. Supplementary Data 5 contains a tabulation of the incidence rate ratios (IRR 95% CI) for individual outcomes in pre-defined risk periods immediately before and after nMAB treatment, adjusted for calendar time, vaccine status and SARS-CoV-2 positive test. Supplementary Data 6 contains the source data for Fig. 2, which is the daily number of patients prescribed Sotrovimab in the community in England during the study period. Supplementary Data 7 contains the source data for Fig. 3, which includes the cumulative proportions per day for patients treated with Sotrovimab by demographics (age group, sex, and ethnic group), vaccine status, and medical history (cardiovascular, neurological, and haematologic conditions) during the study period. Supplementary Data 8 contains the source data for Fig. 4. This includes the IRRs (irr_95), event counts (n_events), *p*-values (p), 95% CIs (min; max), and standard errors (stderr) for each safety outcome in the period 2–28 days after Sotrovimab treatment, adjusted for calendar time, SARS-CoV-2 positive test and vaccine status for each population (model), where applicable. Upper CIs (max) for all IRRs were truncated to 5 if >5. The unrounded IRRs may be found in the "irr" column and the untruncated upper/lower CIs in the "irr_95" column. Counts below five have been censored (<5) to prevent deductive disclosure. All other source data may be made available by the corresponding author upon reasonable request.

Code availability

Sample STATA code is available online at https://doi.org/10.5281/zenodo.13913591[28]. This code may be used to conduct SCCS analyses similar to that performed for this study.

Received: 27 October 2023; Accepted: 17 December 2024;
Published online: 16 January 2025

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Acknowledgements

This project involves data derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The SARS-Cov-2 test data are collated, maintained and quality assured by the United Kingdom Health Security Agency (UKHSA). Access to the data was facilitated by the UKHSA Office for Data Release. The Hospital Episode Statistics, Secondary Users Service (SUS-PLUS) datasets and civil registration data are used with permission from NHS England, who retain the copyright in that data. We acknowledge the contribution of EMIS practices who contribute to QResearch® and EMIS Health and the Universities of Nottingham and Oxford for expertise in establishing, developing or supporting the QResearch database. NHS England and the UKHSA bear no responsibility for the analysis or interpretation of the data. This project was funded by the National Institute of Health Research (Grant reference 135561). The funders of this study had no role in the design and conduct of the study and did not review or approve the manuscript. The views expressed are those of the authors and not necessarily the funders. M.P., J.H.C. and A. Snelling had full access to all the study data and J.H.C. had final responsibility for submission.

Authors contribution

M.P., J.H.C. and C.C. led the study conceptualisation and development of the research question. J.H.C. obtained funding, designed the analysis, obtained data approvals, contributed to the interpretation of the analysis, and reviewed the first and final drafts of the paper. M.P. undertook the data specification, curation, and analysis and wrote the first draft of the paper. A. Snelling contributed towards the data analysis, interpretation of the results, and the writing/reviewing of the first and final drafts of the paper. C.C. contributed to the analysis and interpretation of the results and reviewed the paper drafts. H.T. and A. Sheikh contributed to the discussion on protocol development and provided critical feedback on drafts of the paper. All authors approved the protocol, contributed to the critical revision of the paper and approved the final version of the paper.

Competing interests

The authors declare the following competing interests: AS was a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group, the Scottish Government's Standing Committee on Pandemics, and AstraZeneca's Thrombotic Thrombocytopenic Advisory Group. All roles were unremunerated. J.H.C. reports grants from the National Institute for Health Research (NIHR) Biomedical Research Centre, Oxford, grants from John Fell Oxford University Press Research Fund, grants from Cancer Research UK (CR-UK) grant number C5255/A18085, through the Cancer Research UK Oxford Centre, grants from the Oxford Wellcome Institutional Strategic Support Fund (204826/Z/16/Z) and other research councils, during the conduct of the study. J.H.C. is an unpaid director of QResearch, a not-for-profit organisation which is a partnership between the University of Oxford and EMIS Health who supply the QResearch database used for this work. J.H.C. is a founder and previously a shareholder of ClinRisk Ltd. and was its medical director until 31st May 2019 and shareholder until Aug 2023 when 100% of the company was donated to Endeavour Health Care Charitable Trust. ClinRisk Ltd. produces open and closed-source software to implement clinical risk algorithms (outside this work) into clinical computer systems. J.H.C. was chair of the NERVTAG risk stratification subgroup and a member of SAGE COVID-19 groups and the NHS group advising on prioritisation of the use of monoclonal antibodies in SARS-CoV-2 infection. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-024-00720-7.

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Peer review information *Communications Medicine* thanks Angel Wong, Stephen Brett and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer review reports are available.