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RESEARCH ARTICLE



Characteristics and outcomes of patients with COVID-19 at high risk of disease progression receiving sotrovimab, oral antivirals or no treatment in England: a retrospective cohort study

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ABSTRACT

Objective: To describe characteristics and acute clinical outcomes for patients with COVID-19 treated with sotrovimab, nirmatrelvir/ritonavir or molnupiravir, or untreated patients at highest risk per National Health Service (NHS) criteria.

Methods: Retrospective study of non-hospitalized patients between 1 December 2021 and 31 May 2022, using data from the Discover-NOW dataset (North-West London). Included patients were aged ≥ 12 years and treated with sotrovimab, nirmatrelvir/ritonavir or molnupiravir, or untreated but expected to be eligible for early treatment per NHS highest-risk criteria. COVID-19-related and all-cause hospitalizations were reported for 28 days from COVID-19 diagnosis (index). Subgroup analyses were conducted in patients with advanced renal disease, those aged 18–64 and ≥ 65 years, and by period of Omicron BA.1, BA.2 and BA.5 (*post-hoc* exploratory) predominance.

Results: Overall, 1503 treated and 4044 eligible high-risk untreated patients were included. A high proportion of patients on sotrovimab had advanced renal disease (29.3%), ≥ 3 high-risk comorbidities (47.6%) and were aged ≥ 65 years (36.9%). Five of 696 (0.7%) patients on sotrovimab, $< 5/337$ (0.3–1.2%) on nirmatrelvir/ritonavir, 10/470 (2.1%) on molnupiravir and 114/4044 (2.8%) untreated patients were hospitalized with COVID-19. Similar results were observed across all subgroups. The proportion of patients dying within 28 days of the index period was similarly low across all cohorts ($< 2\%$).

Conclusion: Patients receiving sotrovimab appeared to show evidence of multiple high-risk comorbidities. Low hospitalization rates were observed for all treated cohorts across subgroups and periods of predominant variants of concern. These results require confirmation with comparative effectiveness analyses adjusting for differences in underlying patient characteristics.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was initially identified in December 2019¹. The rapid global spread of SARS-CoV-2 resulted in the declaration of a pandemic by the World Health Organization in March 2020². Some patients, such as the elderly or those with advanced renal disease, diabetes, cancer, chronic obstructive pulmonary disease or cardiovascular disease, are at higher risk of developing severe COVID-19, which may result in hospitalization or death^{3,4}. Moreover, data have suggested that immunocompromised individuals, those undergoing dialysis, or transplant recipients (who are also considered at high risk of severe COVID-19) have blunted serological responses to vaccines^{5–8}.

In England, early treatment of mild-to-moderate COVID-19 with either antiviral agents or monoclonal antibodies (mAbs) is recommended for those with “highest-risk” conditions, as defined by national clinical guidance⁹. During the study period these included cancer, advanced renal and liver disease, human immunodeficiency virus or acquired immune deficiency syndrome (HIV or AIDS), solid organ and stem cell transplant recipients and rare neurological conditions¹⁰. Of particular note, it has been recently reported that people with advanced renal disease are at particularly high risk of severe COVID-19 outcomes⁴.

Sotrovimab is a recombinant human IgG1κ mAb derived from the parental mAb S309, a potent neutralizing mAb directed against the spike protein of SARS-CoV-2^{11–14}. In a

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randomized clinical trial, sotrovimab significantly reduced the risk of all-cause >24-h hospitalization or death compared with placebo in high-risk COVID-19 patients¹⁵. The oral antiviral nirmatrelvir/ritonavir inhibits the main protease of SARS-CoV-2 and has been shown to reduce the risk of progression to severe COVID-19 compared with placebo among symptomatic patients^{16,17}. Another oral antiviral, molnupiravir, a ribonucleoside prodrug with antiviral activity against SARS-CoV-2, has proven effective in reducing the risk of hospitalization or death among at-risk, unvaccinated adults with COVID-19¹⁸. Molnupiravir was first approved in November 2021 by the UK Medicines and Healthcare products Regulatory Agency for use in patients with mild-to-moderate COVID-19 deemed at risk of developing severe illness¹⁹. Sotrovimab and nirmatrelvir/ritonavir received conditional marketing authorization in December 2021 for use in patients with COVID-19 who do not require supplemental oxygen and are deemed to be at increased risk of progression to severe COVID-19^{20,21}. During the study period, the National Health Service (NHS) England clinical guidelines recommended sotrovimab and nirmatrelvir/ritonavir as first-line treatment options, and molnupiravir as a third-line option¹⁰.

In March 2022, Omicron BA.2 became the dominant subvariant globally²². A moderate reduction in activity for sotrovimab against Omicron BA.2 (16-fold change in IC₅₀ relative to Wuhan-Hu-1 wild-type) has been observed in *in vitro* neutralization assays²³. Similar fold-shifts have also been reported for other Omicron subvariants, including BA.5, which predominated in the UK from July to October 2022^{23,24}. It is unclear if or how *in vitro* antibody neutralization activity translates to clinical effectiveness, especially for antibodies (such as sotrovimab) that have potent effector functions such as antibody-dependent cellular cytotoxicity and phagocytosis^{14,25,26}. It is challenging to assess the effectiveness of interventions against rapidly emerging variants of concern, especially in light of population-wide immunity due to vaccination or natural infection, which may reduce the titers of therapeutic mAbs required for neutralization²⁷. As a result, evidence obtained from real-world clinical practice is important to assess effectiveness of treatments outside of preclinical studies or clinical trials.

Here, we describe the real-world use of, and outcomes from, early, mild-to-moderate COVID-19 treatments for the management of highest-risk patients in North-West London (NWL) following the emergence of Omicron subvariants. Gaining insight on these early treatment options will help to inform future comparative analyses.

Methods

Study design and data source

This retrospective cohort study used data from the Discover dataset, one of Europe's largest linked longitudinal datasets²⁸. It holds depersonalized coded primary and secondary care data (starting from 1990 and 2015, respectively) for over 2.5 million patients who live and are registered with a general practitioner (GP) in NWL, a region

inhabited by a population of high ethnic diversity. The data also contain information on acute health, mental health, community health and social care for these patients. The dataset is fed by data from over 400 provider organizations, including over 350 GP practices, two mental health and two community trusts, and all acute providers attended by NWL patients.

The age profile of the population in NWL is comparable to the age profile of patients across the whole of London. Furthermore, the Discover population has broadly comparable age-sex distribution and prevalence of comorbidities to the overall UK population but is more ethnically diverse²⁸. The dataset is accessible *via* Discover-NOW Health Data Research Hub for Real World Evidence through their data scientist specialists and Information Governance (IG) committee-approved analysts, hosted by Imperial College Health Partners.

The index date was defined as the earliest date of COVID-19 diagnosis or a positive polymerase chain reaction (PCR) or lateral flow test for SARS-CoV-2, where that event occurred between 1 December 2021 and 31 May 2022; if the date of the diagnosis was not available, date of treatment was used as a proxy. During the course of this study, the Omicron BA.5 variant began circulating. Given the importance of generating evidence on emerging COVID-19 strains, a *post-hoc* analysis was undertaken among patients diagnosed or treated between 1 June 2022 and 31 July 2022, a period during which Omicron BA.5 was the predominant strain in England²⁹. This cut-off date is reflective of when the study was conceived and initiated, and was intended to ensure collection of contemporary data for circulating variants of interest. A key strength of the Discover database is the short lag time (approximately one month) from an activity occurring in clinical practice to being assessable in the database). The baseline period was defined as the 365 days prior to index. Patient outcomes were reported during the acute period, defined as the 28-day period starting on the index date. This time scale was used as it allowed for inclusion of patients who received treatment beyond the guideline-recommended period (at a time when real-world treatment patterns were unclear), while also minimizing the risk that the received treatment was linked to a second event and not the index diagnosis.

This study was approved by the Discover Data Access Group which has derogated powers to approve studies under its overarching approval as a Health Research Database. This study complies with all applicable laws regarding subject privacy. Data were aggregated and counts less than five were suppressed in line with IG suppression rules. No direct subject contact or primary collection of individual human subject data occurred. Study results were in tabular form and aggregate analyses that omit subject identification, therefore informed consent, ethics committee or institutional review board approval were not required. Any publications and reports do not include subject identifiers.

Study population

Non-hospitalized patients were eligible for inclusion if they were aged ≥ 12 years on the index date; had a COVID-19

Table 1. High- and highest-risk conditions criteria.

Highest-risk conditions	High-risk conditions
Down's syndrome	Age ≥ 70 years
Solid cancer	Long-term respiratory conditions
Hematological disease and stem cell transplant recipients	Chronic heart disease
Advanced renal disease ^a	Chronic kidney disease (stage 1–3)
Liver disease ^b	Chronic liver disease (e.g. hepatitis)
IMiD	Chronic neurological condition
Immune deficiencies	Diabetes
HIV or AIDS	Weakened immune system caused by medical condition or medication
Solid organ transplant	Obesity (class III)
Rare neurological conditions ^c	Pregnancy
	Severe respiratory conditions
	Rare disease and inborn errors of metabolism ^d

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; IMiD, immune-mediated inflammatory diseases.

^aRenal transplant recipients (including those with failed transplants within the past 12 months), particularly those who received B cell depleting therapy within the past 12 months, have an additional substantial risk factor which would in isolation make them eligible for mAbs or oral antivirals, or not been vaccinated prior to transplantation.

^bPatients with a liver transplant; patients with liver disease on immune suppressive therapy (including patients with and without liver cirrhosis).

^cMultiple sclerosis, motor neurone disease, myasthenia gravis, Huntington's disease.

^dSevere combined immunodeficiency, homozygous sickle cell.

diagnosis/positive SARS-CoV-2 PCR or lateral flow test; and received outpatient treatment with sotrovimab, nirmatrelvir/ritonavir or molnupiravir, or received no treatment and met at least one of the NHS highest-risk criteria for receiving early treatment with sotrovimab, nirmatrelvir/ritonavir, or molnupiravir. At the time of study, these criteria included Down's syndrome, solid cancer, hematologic diseases (including cancers), advanced renal disease, advanced liver disease, immune-mediated inflammatory disorders, immune deficiencies, HIV or AIDS, solid organ and stem cell transplant recipients and rare neurological conditions⁹. Patients meeting the highest-risk criteria were identified *via* the presence of International Classification of Disease version 10 (ICD-10) and Systematized Nomenclature of Medicine (SNOMED) codes appearing at any time in the patient's records since first registration in NWL (source datasets included in [Supplemental Table S1](#); conditions included in [Table 1](#)).

Patients were excluded if they received more than one treatment (sotrovimab, nirmatrelvir/ritonavir, molnupiravir or remdesivir) in an outpatient setting during the acute period; they received remdesivir as an early treatment; or they received sotrovimab, nirmatrelvir/ritonavir or molnupiravir while in an inpatient setting (involving an overnight or longer stay in a hospital), or more than 28 days following first diagnosis of COVID-19. At the time of protocol development, remdesivir was mainly used in hospitalized patients and we did not anticipate that it would be used as a community-based treatment in a modest number of patients; hence, it was considered appropriate to exclude patients treated with remdesivir.

Study outcomes

The primary outcomes of this study were acute period clinical outcomes, namely COVID-19-related and all-cause hospitalizations. COVID-19-related hospitalizations were defined

as any non-elective hospital visit for which COVID-19 (ICD-10 U07.1) was listed in the primary diagnosis field. All-cause hospitalizations were defined as non-elective hospital visits for any diagnosis. The secondary outcome reported in this study was the number of deaths due to any cause.

Patient characteristics were also recorded, including age, sex, ethnicity, vaccination status and comorbidity history. Cohorts were described in relation to "highest-risk" conditions which made patients eligible for early treatment with mAbs and antiviral therapies, as mentioned above. Additionally, the cohorts were described in relation to other "high-risk" conditions which may predispose patients to severe COVID-19 outcomes ([Table 1](#)).

Outcomes were reported for the following cohorts: Cohort 1, patients receiving early treatment with sotrovimab; Cohort 2, patients receiving early treatment with nirmatrelvir/ritonavir; Cohort 3, patients receiving early treatment with molnupiravir; and Cohort 4, patients at highest risk who received no early treatment.

Subgroup analyses were also undertaken. We examined highest-risk patients with advanced renal disease (defined as patients with chronic kidney disease stage 4 or 5 [including codes for peritoneal and hemodialysis] and kidney transplant recipients, or non-transplant recipients receiving a comparable level of immunosuppression; chronic kidney disease stage 1–3 reported separately as a high-risk condition). A subgroup analysis was also undertaken by age group for patients aged 18–64 and ≥ 65 years. We also investigated outcomes among patients diagnosed or treated during periods of Omicron BA.1 (1 December 2021–28 February 2022) and Omicron BA.2 (1 March–31 May 2022) subvariant predominance. During our Omicron BA.1 period, 71.2% of sequenced cases across England were BA.1, while during our Omicron BA.2 period, 90.1% of sequenced cases across England were BA.2³⁰. In addition, a *post-hoc* exploratory analysis was conducted to examine patients diagnosed and treated during early BA.5 variant predominance (1 June–31

July 2022) once more recent data had become available. During this time, 70.6% of sequenced cases were attributable to the Omicron BA.5 variant²⁹.

Data analysis

Continuous variables (e.g. age) were summarized using mean, standard deviation, median, interquartile range and range. Categorical variables (e.g. sex) were described using frequencies and percentages. For clinical outcomes, 95% confidence intervals (CIs) were calculated. No inferential statistics were performed as part of the analysis. Due to information governance and data suppression rules used in the study, counts of between one and four were suppressed and are reported as $n < 5$ throughout.

Patient and public involvement

Patients were not directly involved in the study design due to its retrospective nature, however the results will be widely available through open access.

Results

Patient demographics and baseline characteristics

The analysis included 696 patients treated with sotrovimab, 337 patients treated with nirmatrelvir/ritonavir, 470 patients treated with molnupiravir and 4044 eligible highest-risk untreated patients (Table 2). Across all cohorts, 232 patients were excluded for receiving remdesivir as an early treatment.

A high percentage of patients treated with sotrovimab had advanced renal disease (29.3%, $n = 204/696$), while lower percentages were reported for other highest-risk comorbidities (solid organ transplant recipients: 7.2% [$n = 50/696$]; rare neurological conditions: 8.0% [$n = 56/696$]; hematologic disease or stem cell transplant recipient: 6.9% [$n = 48/696$]). Of the patients identified to receive nirmatrelvir/ritonavir, 28.5% ($n = 96/337$) had immune deficiencies, 30.3% ($n = 102/337$) had HIV or AIDS and 15.4% ($n = 52/337$) had rare neurological disorders. Advanced renal disease was the most frequently reported highest-risk condition for patients treated with molnupiravir (12.8%, $n = 60/470$).

Two or more highest-risk conditions were recorded for 15.7% ($n = 109/696$) of patients treated with sotrovimab, 26.7% ($n = 90/337$) of patients treated with nirmatrelvir/ritonavir, 17.0% ($n = 80/470$) of those treated with molnupiravir and 27.4% ($n = 1109/4044$) of untreated patients. No highest-risk conditions were recorded in 39.2% ($n = 273/696$) of patients treated with sotrovimab, 41.8% ($n = 141/337$) of patients treated with nirmatrelvir/ritonavir and 45.7% ($n = 215/470$) of patients treated with molnupiravir. No untreated patients had zero highest-risk conditions since inclusion within this cohort was based on the presence of an identifiable highest-risk condition.

A high percentage of sotrovimab-treated patients had high-risk comorbidities such as chronic heart disease (51.0%, $n = 355/696$), chronic kidney disease (20.4%, $n = 142/696$),

chronic neurological conditions (51.9%, $n = 361/696$), diabetes (25.3%, $n = 176/696$) and severe respiratory conditions (21.3%, $n = 148/696$). For patients treated with nirmatrelvir/ritonavir, 17.8% ($n = 60/337$) had chronic heart disease, 5.3% ($n = 18/337$) had chronic kidney disease, 34.4% ($n = 116/337$) had chronic neurological conditions, 8.6% ($n = 29/337$) had diabetes and 13.9% ($n = 47/337$) had severe respiratory conditions. Patients treated with molnupiravir also presented with high-risk comorbidities: 40.4% ($n = 190/470$) had chronic heart disease, 11.5% ($n = 54/470$) had chronic kidney disease, 42.8% ($n = 201/470$) had chronic neurological conditions, 17.2% ($n = 81/470$) presented with diabetes and 17.9% ($n = 84/470$) had severe respiratory conditions. Similarly, 35.1% ($n = 1419/4044$) of untreated patients had chronic heart disease, 15.0% ($n = 605/4044$) had chronic kidney disease, 41.0% ($n = 1659/4044$) had chronic neurological conditions, 20.4% ($n = 824/4044$) had diabetes and 15.5% ($n = 625/4044$) presented with severe respiratory conditions.

The proportion of patients with at least three high-risk comorbidities was 47.6% ($n = 331/696$) among those treated with sotrovimab, 17.2% ($n = 58/337$) among those treated with nirmatrelvir/ritonavir, 35.1% ($n = 165/470$) for those treated with molnupiravir and 35.2% ($n = 1422/4044$) for patients who were untreated. Percentages for patients with no or unidentifiable high-risk conditions were 11.8% for sotrovimab ($n = 82/696$), 14.7% for molnupiravir ($n = 69/470$), 31.2% for nirmatrelvir/ritonavir ($n = 105/337$) and 21.2% for untreated patients ($n = 856/4044$).

In addition, patients aged ≥ 70 years accounted for 27.3% ($n = 190/696$) of the sotrovimab-treated group, 13.6% ($n = 46/337$) of those treated with nirmatrelvir/ritonavir, 20.6% ($n = 97/470$) of those treated with molnupiravir and 17.8% ($n = 720/4044$) of untreated patients. A high proportion of untreated patients were of Black/Black British ethnicity (16.1%, $n = 651/4044$); this was 8.6% ($n = 60/696$) for sotrovimab-, 11.3% ($n = 38/337$) for nirmatrelvir/ritonavir- and 6.4% ($n = 30/470$) for molnupiravir-treated patients. A low proportion of untreated patients had received more than one booster vaccination (13.7%, $n = 553/4044$). The proportions of patients treated with sotrovimab, nirmatrelvir/ritonavir and molnupiravir who received more than one booster were 34.2% ($n = 238/696$), 30.3% ($n = 102/337$) and 16.6% ($n = 78/470$), respectively.

Patients with advanced renal disease, untreated or treated with sotrovimab

Due to the low numbers of patients with advanced renal disease being treated with nirmatrelvir/ritonavir ($n < 5$) or molnupiravir ($n = 60$), characteristics have only been reported for the sotrovimab-treated and untreated patient cohorts (Table 3). In total, 204 patients treated with sotrovimab and 880 untreated patients were included in this subgroup analysis.

Amongst patients with advanced renal disease, the characteristics of those treated with sotrovimab were generally similar to untreated patients. The proportion of patients who received more than one booster vaccine was 29.4% ($n = 60/204$) for sotrovimab-treated patients and 16.9% ($n = 149/880$) for untreated patients. The percentage of patients who had a

Table 2. Patient characteristics (all patients).

	Sotrovimab (n = 696)	Nirmatrelvir/ritonavir (n = 337)	Molnupiravir (n = 470)	Untreated (n = 4044)
Age, years ^a				
Mean (SD)	58.0 (16.4)	52.6 (15.5)	53.7 (17.4)	52.4 (17.5)
Median (IQR)	58 (25)	54 (22)	54 (27)	52 (24)
Female sex, n (%)	356 (51.1)	159 (47.2)	217 (46.2)	1834 (45.4)
Ethnicity, n (%)				
White	391 (56.2)	227 (67.4)	261 (55.5)	1986 (49.1)
Asian/Asian British	166 (23.9)	45 (13.4)	130 (27.7)	940 (23.2)
Black/Black British	60 (8.5)	38 (11.3)	30 (6.4)	651 (16.1)
Mixed	21 (3.0)	8 (2.4)	14 (3.0)	150 (3.7)
Other	45 (6.5)	15 (4.5)	26 (5.5)	232 (5.7)
Unknown	13 (1.9)	<5 (0.3–1.2) ^b	9 (1.9)	85 (2.1)
Vaccination, n (%)				
No doses	34 (4.9)	31 (9.2)	16 (3.4)	460 (11.4)
1 dose	11 (1.6)	5 (1.5)	6 (1.3)	96 (2.4)
2 doses	53 (7.6)	22 (6.5)	42 (8.9)	698 (17.3)
3 doses	360 (51.7)	177 (52.5)	328 (69.8)	2237 (55.3)
>3 doses	238 (34.2)	102 (30.3)	78 (16.6)	553 (13.7)
Time since last vaccination (days) ^a				
Mean (SD)	115.5 (73.0)	121.3 (72.7)	88.1 (61.5)	116.7 (78.1)
Median (IQR)	106 (87)	122 (92)	79 (52)	99 (98)
Time to treatment (days) ^{a,c}				
Mean (SD)	1.7 (1.6)	0.7 (1.6)	1.1 (1.4)	–
Median (IQR)	1 (1)	0 (1)	1 (1)	–
Highest-risk conditions, n (%)				
Down's syndrome	<5 (0.1–0.6) ^b	5 (1.5)	6 (1.3)	61 (1.5)
Solid cancer	35 (5.0)	9 (2.7)	9 (1.9)	380 (9.4)
Hematological disease and stem cell transplant recipients	48 (6.9)	11 (3.3)	21 (4.5)	330 (8.2)
Advanced renal disease	204 (29.3)	<5 (0.3–1.2) ^b	60 (12.8)	880 (21.8)
Liver disease	29 (4.2)	5 (1.5)	22 (4.7)	413 (10.2)
IMiD	30 (4.3)	9 (2.7)	45 (9.6)	415 (10.3)
Immune deficiencies	50 (7.2)	96 (28.5)	47 (10.0)	1080 (26.7)
HIV or AIDS	44 (6.3)	102 (30.3)	46 (9.8)	1000 (24.7)
Solid organ transplant	50 (7.2)	0 (0.0)	32 (6.8)	203 (5.0)
Rare neurological conditions	56 (8.0)	52 (15.4)	48 (10.2)	438 (10.8)
Number of highest-risk conditions, n (%)				
0	273 (39.2)	141 (41.8)	215 (45.7)	0 (0.0)
1	314 (45.1)	106 (31.5)	175 (37.2)	2935 (72.6)
2	109 (15.7)	90 (26.7)	80 (17.0)	1109 (27.4)
High-risk conditions, n (%)				
Age ≥70 years	190 (27.3)	46 (13.6)	97 (20.6)	720 (17.8)
Long-term respiratory conditions	178 (25.6)	72 (21.4)	108 (23.0)	884 (21.9)
Chronic heart disease	355 (51.0)	60 (17.8)	190 (40.4)	1419 (35.1)
Chronic kidney disease	142 (20.4)	18 (5.3)	54 (11.5)	605 (15.0)
Chronic liver disease	49 (7.0)	10 (3.0)	30 (6.4)	490 (12.1)
Chronic neurological condition	361 (51.9)	116 (34.4)	201 (42.8)	1659 (41.0)
Diabetes	176 (25.3)	29 (8.6)	81 (17.2)	824 (20.4)
Weakened immune system caused by medical condition or medication	122 (17.5)	25 (7.4)	91 (19.4)	600 (14.8)
Obesity (class III)	16 (2.3)	5 (1.5)	14 (3.0)	72 (1.8)
Pregnancy	<5 (0.1–0.6) ^b	9 (2.7)	9 (1.9)	224 (5.5)
Severe respiratory conditions	148 (21.3)	47 (13.9)	84 (17.9)	625 (15.5)
Rare disease and inborn errors of metabolism	<5 (0.1–0.6) ^b	9 (2.7)	9 (1.9)	224 (5.5)
Number of high-risk conditions, n (%)				
0	82 (11.8)	105 (31.2)	69 (14.7)	856 (21.2)
1	144 (20.7)	112 (33.2)	139 (29.6)	968 (23.9)
2	139 (20.0)	62 (18.4)	97 (20.6)	798 (19.7)
3	140 (20.1)	36 (10.7)	78 (16.6)	585 (14.5)
4	99 (14.2)	13 (3.9)	46 (9.8)	407 (10.1)
5+	92 (13.2)	9 (2.7)	41 (8.7)	430 (10.6)

Abbreviations: AIDS, acquired immune deficiency syndrome; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IMiD, immune-mediated inflammatory disease; IQR, interquartile range; SD, standard deviation.

^aData are not normally distributed based on Shapiro–Wilk test.

^bDue to a total sample size of <5, this number was suppressed; a range of 1–4 events has been used to calculate the range given.

^cNo COVID-19 diagnosis date was available for 52 patients on sotrovimab, 121 patients on nirmatrelvir/ritonavir and 16 patients on molnupiravir. A time to treatment of zero days was assumed for these patients.

solid organ transplant was 16.2% ($n = 33/204$) for patients who were treated with sotrovimab and 8.1% ($n = 71/880$) for untreated patients. In total, 29.9% ($n = 61/204$) of sotrovimab-treated patients and 38.0% ($n = 334/880$) of untreated patients with advanced renal disease were aged ≥70 years.

Patients aged 18–64 and ≥65 years

Characteristics among patients aged 18–64 years were similar to those of patients aged ≥65 years (Supplemental Tables S2 and S3). It should be noted that due to overall small patient numbers, those aged 12–17 years were not included in the age subgroup analysis.

Table 3. Characteristics of patients with advanced renal disease, untreated or treated with sotrovimab.

	Sotrovimab (n = 204)	Untreated (n = 880)
Age, years ^a		
Mean (SD)	59.0 (16.3)	62.6 (17.2)
Median (IQR)	59.5 (27.8)	64.0 (26.0)
Female sex, n (%)	89 (43.6)	383 (43.5)
Ethnicity, n (%)		
White	67 (32.8)	262 (29.8)
Asian/Asian British	81 (39.7)	354 (40.2)
Black/Black British	33 (16.2)	170 (19.3)
Mixed	9 (4.4)	26 (3.0)
Other	12 (5.9)	53 (6.0)
Vaccination, n (%)		
No doses	9 (4.4)	76 (8.6)
1 dose	6 (2.9)	19 (2.2)
2 doses	25 (12.3)	132 (15.0)
3 doses	104 (51.0)	504 (57.3)
>3 doses	60 (29.4)	149 (16.9)
Time since last vaccination (days) ^a		
Mean (SD)	126.1 (84.9)	122.3 (82.7)
Median (IQR)	107 (87)	104 (102)
Time to treatment (days) ^a		
Mean (SD)	2.5 (2.2)	–
Median (IQR)	2 (2)	–
Highest-risk conditions, n (%)		
Down's syndrome	<5 (0.5–2.0) ^b	0 (0.0)
Solid cancer	<5 (0.5–2.0) ^b	<5 (0.1–0.5) ^b
Hematological disease and stem cell transplant recipients	5 (2.5)	8 (0.9)
Advanced renal disease	204 (100)	880 (100)
Liver disease	<5 (0.5–2.0) ^b	21 (2.4)
IMID	<5 (0.5–2.0) ^b	15 (1.7)
Immune deficiencies	6 (2.9)	14 (1.6)
HIV or AIDS	<5 (0.5–2.0) ^b	11 (1.3)
Solid organ transplant	33 (16.2)	71 (8.1)
Rare neurological conditions	<5 (0.5–2.0) ^b	<5 (0.1–0.5) ^b
Number of highest-risk conditions, n (%)		
0	0 (0.0)	0 (0.0)
1	156 (76.5)	761 (86.5)
2	48 (23.5)	119 (13.5)
High-risk conditions, n (%)		
Age ≥70 years	61 (29.9)	334 (38.0)
Long-term respiratory conditions	40 (19.6)	215 (24.4)
Chronic heart disease	155 (76.0)	627 (71.3)
Chronic kidney disease	100 (49.0)	435 (49.4)
Chronic liver disease	9 (4.4)	33 (3.8)
Chronic neurological condition	126 (61.8)	466 (53.0)
Diabetes	98 (48.0)	442 (50.2)
Weakened immune system caused by medical condition or medication	37 (18.1)	130 (14.8)
Obesity (class III)	7 (3.4)	14 (1.6)
Pregnancy	<5 (0.5–2.0) ^b	<5 (0.1–0.5) ^b
Severe respiratory conditions	32 (15.7)	170 (19.3)
Rare disease and inborn errors of metabolism	<5 (0.5–2.0) ^b	<5 (0.1–0.5) ^b
Number of high-risk conditions, n (%)		
0	10 (4.9)	54 (6.1)
1	20 (9.8)	96 (10.9)
2	32 (15.7)	163 (18.5)
3	55 (27.0)	167 (19.0)
4	43 (21.1)	184 (20.9)
5+	44 (21.6)	216 (24.5)

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; IMID, immune-mediated inflammatory disease; IQR, interquartile range; SD, standard deviation.

^aData are not normally distributed based on Shapiro–Wilk test.

^bDue to a total sample size of <5, this number was suppressed; a range of 1–4 events has been used to calculate the range given.

Acute period clinical outcomes

A low proportion of patients treated with sotrovimab ($n = 5/696$, 0.7% [95% CI 0.1% to 1.3%]), nirmatrelvir/ritonavir ($n < 5/337$, 0.3–1.2%) or molnupiravir ($n = 10/470$, 2.1% [95% CI 0.8% to 3.4%]) experienced COVID-19-related hospitalizations. For untreated patients, the percentage of COVID-19-related hospitalizations was 2.8% (95% CI 2.3% to 3.3%; $n = 114/4044$)

(Table 4A). The percentage of patients who experienced an all-cause hospitalization was 5.0% (95% CI 3.4% to 6.6%; $n = 35/696$) for sotrovimab-treated patients, 1.5% (95% CI 0.2% to 2.8%; $n = 5/337$) for nirmatrelvir/ritonavir, 4.0% (95% CI 2.2% to 5.8%; $n = 19/470$) for molnupiravir and 6.2% (95% CI 5.5% to 6.9%; $n = 251/4044$) for untreated patients. The proportion of patients dying within 28 days of the index period was similarly low across all cohorts (<2% in each).

Table 4. Acute period clinical outcomes.

	Sotrovimab (n = 696)	Nirmatrelvir/ritonavir (n = 337)	Molnupiravir (n = 470)	Untreated (n = 4044)
A. All patients				
N	696	337	470	4044
COVID-19-related hospitalization, n (%)	5 (0.7)	<5 (0.3–1.2) ^a	10 (2.1)	114 (2.8)
95% CI	0.1 to 1.3	–	0.8 to 3.4	2.3 to 3.3
All-cause hospitalization, n (%)	35 (5.0)	5 (1.5)	19 (4.0)	251 (6.2)
95% CI	3.4 to 6.6	0.2 to 2.8	2.2 to 5.8	5.5 to 6.9
Patient death within one month of index, n (%)	8 (1.1)	<5 (0.3–1.2) ^a	7 (1.5)	75 (1.9)
95% CI	0.3 to 1.9	–	0.4 to 2.6	1.5 to 2.3
B. Patients with renal disease				
N	204	–	–	880
COVID-19-related hospitalization, n (%)	<5 (0.5–2.0) ^a	–	–	39 (4.4)
95% CI	–	–	–	3.0 to 5.8
All-cause hospitalization, n (%)	17 (8.3)	–	–	94 (10.7)
95% CI	4.5 to 12.1	–	–	8.7 to 12.7
Patient death within one month of index, n (%)	<5 (0.5–2.0) ^a	–	–	36 (4.1)
95% CI	–	–	–	2.8 to 5.4
C. Patients aged 18–64 years				
N	439	263	339	2977
COVID-19-related hospitalization, n (%)	<5 (0.2–0.9) ^a	0 (0.0)	8 (2.4)	64 (2.1)
95% CI	–	–	0.8 to 4.0	1.6 to 2.6
All-cause hospitalization, n (%)	19 (4.3)	<5 (0.4–1.5) ^a	15 (4.4)	131 (4.4)
95% CI	2.4 to 6.2	–	2.2 to 6.6	3.7 to 5.1
Patient death within one month of index, n (%)	<5 (0.2–0.9) ^a	0 (0.0)	<5 (0.3–1.2) ^a	17 (0.6)
95% CI	–	–	–	0.3 to 0.9
D. Patients aged ≥65 years				
N	257	73	131	999
COVID-19-related hospitalization, n (%)	<5 (0.4–1.6) ^a	<5 (1.4–5.5) ^a	<5 (0.8–3.1) ^a	50 (5.0)
95% CI	–	–	–	3.6 to 6.4
All-cause hospitalization, n (%)	16 (6.2)	<5 (1.4–5.5) ^a	<5 (0.8–3.1) ^a	117 (11.7)
95% CI	3.2 to 9.2	–	–	9.7 to 13.7
Patient death within one month of index, n (%)	<5 (0.4–1.6) ^a	<5 (1.4–5.5) ^a	5 (3.8)	58 (5.8)
95% CI	–	–	0.5 to 7.1	4.3 to 7.3

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

^aDue to a total sample size of <5, this number was suppressed; a range of 1–4 events has been used to calculate the range given.**Patients with advanced renal disease, untreated or treated with sotrovimab**

Fewer than five of 204 (0.5–2.0%) patients treated with sotrovimab and 39 of 880 (4.4% [95% CI 3.0% to 5.8%]) untreated patients experienced a COVID-19-related hospitalization during the acute period (Table 4B). Similarly, fewer than five (0.5–2.0%) patients treated with sotrovimab and 36 (4.1% [95% CI 2.8% to 5.4%]) untreated patients died within one month of index. All-cause hospitalization was experienced by 8.3% (95% CI 4.5% to 12.1%; $n = 17/204$) of sotrovimab-treated patients and 10.7% (95% CI 8.7% to 12.7%; $n = 94/880$) of untreated patients.

Patients aged 18–64 and ≥65 years

Table 4C details acute period clinical outcomes for those aged 18–64 years. As for the overall population, a low proportion of patients aged 18–64 years who were treated with sotrovimab (0.2–0.9%, $n < 5/439$), nirmatrelvir/ritonavir (0.0%, $n = 0/263$) or molnupiravir ($n = 8/339$, 2.4% [95% CI 0.8 to 4.0]) had COVID-19-related hospitalizations during the acute clinical period. This was 2.1% ($n = 64/2977$) for untreated patients. Similarly, the proportion of patients treated with nirmatrelvir/ritonavir who had an all-cause hospitalization during this period was low (0.4–1.5%, $n < 5/263$). For those treated with sotrovimab or molnupiravir or who were untreated, the proportions of patients with all-cause hospitalizations were 4.3% (95% CI 2.4% to 6.2%; $n = 19/439$), 4.4% (95% CI 2.2% to 6.6%; $n = 15/339$) and 4.4% (95% CI 3.7% to

5.1%; $n = 131/2977$), respectively. No patient deaths were recorded for nirmatrelvir/ritonavir within one month of index, while fewer than five deaths were reported for patients treated with sotrovimab (0.2–0.9%) and patients treated with molnupiravir (0.3–1.2%). A total of 17 deaths (0.6% [95% CI 0.3% to 0.9%]) were reported within one month of index amongst the 2977 patients who received no treatment.

Table 4D details acute period clinical outcomes for patients aged ≥65 years. The proportion of patients treated with sotrovimab who experienced a COVID-19-related hospitalization was 0.4–1.6% ($n < 5/257$) and was 5.0% (95% CI 3.6% to 6.4%; $n = 50/999$) for untreated patients. In addition, a low proportion of patients treated with sotrovimab (6.2% [95% CI 3.2% to 9.2%], $n = 16/257$) experienced an all-cause hospitalization during the acute clinical period. Similarly, a low proportion of patients treated with sotrovimab (0.4–1.6%, $n < 5/257$) died within one month of their index date. This percentage was 5.8% (95% CI 4.3% to 7.3%; $n = 58/999$) for untreated patients. Due to the small sample size in the subgroup aged 65 years and above, acute period clinical outcome results for patients treated with nirmatrelvir/ritonavir and molnupiravir should be treated with caution.

COVID-19-related hospitalizations during periods of BA.1, BA.2 and BA.5 predominance

During the BA.1 period, 281 patients were treated with sotrovimab, 68 with nirmatrelvir/ritonavir, 409 with molnupiravir and 2742 patients received no treatment (Table 5). Similar to

Table 5. COVID-19-related hospitalizations during periods of BA.1, BA.2 and BA.5 predominance.

	Sotrovimab (n = 696)	Nirmatrelvir/ritonavir (n = 337)	Molnupiravir (n = 470)	Untreated (n = 4044)
Omicron BA.1 period				
N	281	68	409	2742
COVID-19-related hospitalization, n (%)	<5 (0.4–1.4) ^a	–	9 (2.2)	87 (3.2)
95% CI	–	–	0.8 to 3.6	2.5 to 3.9
Omicron BA.2 period				
N	415	269	59	1302
COVID-19-related hospitalization, n (%)	<5 (0.2–1.0) ^a	–	<5 (1.7–6.8) ^a	27 (2.1)
95% CI	–	–	–	1.3 to 2.9
Omicron BA.5 period				
N	197	228	13	657
COVID-19-related hospitalization, n (%)	<5 (0.5–2.0) ^a	0 (0.0)	<5 (7.7–30.8) ^a	12 (1.8)
95% CI	–	–	–	0.8 to 2.8

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019.

^aDue to a total sample size of <5, this number was suppressed; a range of 1–4 events has been used to calculate the range given. Due to the overall number of COVID-19-related hospitalizations being <5, stratification by BA.1 and BA.2 period could not be reported.

the overall analysis, a low proportion of patients treated with sotrovimab (0.4–1.4%, $n < 5/281$) experienced a COVID-19-related hospitalization. Percentages for molnupiravir and untreated patients were 2.2% (95% CI 0.8% to 3.6%; $n = 9/409$) and 3.2% (95% CI 2.5% to 3.9%; $n = 87/2742$), respectively. During the BA.2 period, there were 415 patients treated with sotrovimab, 269 treated with nirmatrelvir/ritonavir, 59 treated with molnupiravir and 1302 who did not receive any treatment (Table 5). As for the BA.1 period, a low proportion of patients treated with sotrovimab (0.2–1.0%, $n < 5/415$) experienced a COVID-19-related hospitalization during the BA.2 period of prevalence. Molnupiravir-treated (1.7–6.8%, $n < 5/59$) and untreated patients (2.1% [95% CI 1.3% to 2.9%], $n = 27/1302$) proportions were similarly low. It should be noted that as the total number of COVID-19-related hospitalizations in the nirmatrelvir/ritonavir cohort was fewer than five, stratification in the BA.1 and BA.2 periods was not possible due to suppression rules.

In a *post-hoc* exploratory analysis of BA.5 variant predominance during June and July 2022, Omicron BA.5 represented 70.6% of sequenced cases, with BA.2 and BA.4 representing 11.4% and 16.9% of sequenced cases, respectively²⁶. We found that 197 patients were treated with sotrovimab during this period, of whom fewer than five (0.5–2.0%) had a COVID-19-related hospitalization (Table 5). Of 228 patients treated with nirmatrelvir/ritonavir, no patients (0.0%) experienced a COVID-19-related hospitalization. In addition, fewer than five patients treated with molnupiravir experienced a COVID-19-related hospitalization (7.7–30.8%; $n < 5/13$). Lastly, of 657 patients who received no treatment, 1.8% (95% CI 0.8% to 2.8%; $n = 12$) experienced a COVID-19-related hospitalization.

Discussion

The aim of this study was to provide a detailed description of patients with evidence of a COVID-19 diagnosis in the UK Discover-Now database during the study period, including their clinical and demographic characteristics and any therapies they received. This is reflected in the selected design and subsequent study implementation. Our results indicate that the characteristics of patients treated with the various

early treatments are different, with evidence that sotrovimab is utilized amongst older and more at-risk patients.

Highest- and high-risk conditions were identified using SNOMED and ICD-10 codes from all available patient history. An unexpectedly large proportion of the treated cohorts had no evidence of the highest-risk conditions that make patients eligible for early COVID-19 treatment (sotrovimab: 39.2%; nirmatrelvir/ritonavir: 41.8%; molnupiravir: 45.7%). When these patient records were further evaluated, we found that a large proportion had an active outpatient appointment for oncology, renal, hematology, gastroenterology or rheumatology services (sotrovimab: 54.2%; nirmatrelvir/ritonavir: 35.5%; molnupiravir: 47.9%). The majority of these patients also had the presence of a SNOMED code primarily used to identify patients who required shielding (a generic high-risk code shown *via* the Discovery dataset analysis to be predominantly used in the period during which shielding was introduced), thus indicating they were felt to be at high risk of developing COVID-19-related complications at some time during the pandemic (sotrovimab: 70.0%; nirmatrelvir/ritonavir: 62.4%; molnupiravir: 72.1%). This indicates that while these patients did not meet the case definition of highest-risk used in this study *per se*, they likely did have one or more underlying conditions that increased their risk of developing COVID-19-related complications and, therefore, would have been eligible for early treatments at an earlier time (aligned to national guidelines¹⁰). Further studies to fully understand why these patients did not receive treatment would be informative. At the time of the study, patients eligible for treatment were referred to a local COVID-19 Medicine Delivery Unit (CDMU)³¹; it is possible that some patients may not have been able to attend these units for geographical or logistical reasons. Also, guidance issued in December 2021 indicated that treatment should be reserved for those with symptomatic COVID-19 who were showing no signs of clinical recovery³²; while we have no data on how long this policy change took to embed in practice, this may have contributed to the number of patients who did not receive treatment. In addition, as the majority of untreated patients required shielding, some may have chosen to stay at home rather than travel to a CDMU to receive treatment.

Amongst the treated cohorts, the proportion of COVID-19-related hospitalizations was particularly low for sotrovimab-

treated patients (0.7%) and nirmatrelvir/ritonavir-treated patients (0.3–1.2%). In total, 2.1% of molnupiravir-treated patients experienced a COVID-19-related hospitalization, although it should be noted that the vast majority of patients receiving molnupiravir treatment ($n=409/470$) received treatment during the earlier Omicron BA.1 period. In addition, 2.8% of untreated patients experienced a COVID-19-related hospitalization across the entire study period. Higher percentages of all-cause hospitalizations were reported across all cohorts compared with COVID-19-related hospitalizations. A similarly low proportion of patients with advanced renal disease treated with sotrovimab experienced severe outcomes due to COVID-19 (COVID-19-related hospitalization and death within one month of index), although there was some evidence of worse outcomes for untreated patients. The relatively low numbers of patients with advanced renal disease receiving nirmatrelvir/ritonavir reflects the fact that this treatment is contraindicated in patients with severe renal impairment; sotrovimab is recommended as a first-line alternative to nirmatrelvir/ritonavir in patients with stage 3–5 CKD³³. COVID-19-attributable hospitalizations appeared numerically consistent across age groups (18–64 and ≥ 65 years), as well as across the Omicron BA.1, BA.2 and BA.5 periods for the treated cohorts. However, formal statistical comparison adjusting for underlying patient characteristics is needed to confirm these results. The proportion of untreated patients with a COVID-19-related hospitalization appeared to reduce across the variant time periods (3.2% during Omicron BA.1, 2.1% during BA.2 and 1.8% during BA.5). This could be explained by a reduction in the severity of circulating variants³⁴ or in immune naivety/susceptibility due to increasing rates of vaccination or previous infection. It is also possible that, with increased uptake of treatments, patients at greatest risk were receiving treatment (and thus would have been included in the treated cohorts), such that those still untreated were at lower risk of developing severe COVID-19. For example, on 24 December 2021, NHS guidance was updated to advise that only eligible patients whose symptoms had not shown signs of resolving should be offered treatment³⁵. Due to the differences in the underlying populations across each of the cohorts, no inferences can be made regarding the relative treatment benefits as part of this descriptive study. This will be the subject of a comparative effectiveness analysis adjusting for patient characteristics and potential other cofounders, which will be published subsequently.

There were also differences in participant characteristics between the treated cohorts included in this study and the populations of patients recruited for pivotal trials for each of the treatments. For example, the **COVID-19 Monoclonal Antibody Efficacy Trial-Intent to Care Early** (COMET-ICE) randomized clinical trial, which compared sotrovimab with placebo¹⁵, required patients have ≥ 1 risk factor for progression to severe COVID-19, including obesity, diabetes, congestive heart failure, chronic kidney disease and age ≥ 55 years. Of note, our sotrovimab-treated cohort had substantially more Asian/Asian British patients (23.9% vs 4.5% in COMET-ICE), while the COMET-ICE population included more

White patients (and did not recruit patients from the UK). In addition, our cohort included more patients with chronic kidney disease (20.4% vs 0.9% in COMET-ICE) and the COMET-ICE population included more patients with obesity (62.5% vs 2.3% in our sotrovimab-treated cohort), although it should be noted that obesity is often underreported in administrative data.

Although this study has not been designed to compare cohorts, there is evidence that a higher proportion of Black/Black British patients were untreated compared with those who received one of the early treatments investigated. These data highlight the ongoing need to support access for all patients eligible for such treatments, particularly when considering the association between social inequalities and COVID-19 morbidity, which is aggravated even further in the context of underlying comorbidities³⁶.

The results of this study complement other recent real-world studies on early treatments for COVID-19 in the UK^{37–39}. For example, the findings of a recent publication on the comparative effectiveness of sotrovimab versus molnupiravir in England, conducted using the OpenSAFELY platform, showed that sotrovimab treatment was associated with a significant reduction in risk of severe COVID-19 outcomes in comparison to treatment with molnupiravir during BA.1 (primary analysis) and BA.2 (exploratory analysis) predominance³⁷. Moreover, sotrovimab was found to offer a similar level of protection against disease progression in patients with COVID-19 infected with the Omicron BA.1 and BA.2 subvariants³⁸. Similarly, in an observational study in the US, treatment with sotrovimab was associated with a reduced risk of all-cause hospitalization and mortality during the predominance of early Omicron variants³⁹.

This study has several limitations that should be considered. Firstly, the study presents descriptive analyses with no adjustments for differences in patient characteristics between cohorts, meaning that any potential associations may be subject to bias and confounding. This will be addressed as part of a future comparative effectiveness analysis. The exclusion of patients who received remdesivir as an early treatment is another potential source of bias. This exclusion criterion was implemented in order to reduce the risk of hospitalized patients being included in the study (at the time the study protocol was developed, remdesivir was mainly used in hospitalized patients). However, since this was a descriptive study and the number of patients involved was relatively small ($n=232$), we would expect the impact to be minimal. Nevertheless, future studies should consider inclusion of remdesivir-treated patients. Also, the severity of symptoms at baseline has not been captured as part of this study. This may affect treatment decisions as patients who have reducing symptoms are unlikely to be treated. We were also unable to distinguish the subset of patients with AIDS from the HIV or AIDS subgroup. CD4 cell counts of $<350/\mu\text{L}$ have been identified as a risk factor for poorer COVID-19 outcomes among patients with HIV/AIDS⁴⁰; however, the impact of this subset on the overall study observations is expected to be minimal, since a low number of patients would fall into this subset (from an already small proportion of patients

with HIV or AIDS in each treatment group). In addition, the Discover dataset includes patients from a geographically restricted region (NWL), and, therefore, sub-national variation in treatment practices or patient demographics cannot be described. It should also be noted that, as for any real-world database study, ascertainment of positive COVID-19 cases and patient characteristics, including high-risk comorbidities, is reliant upon healthcare encounters and reliable administrative data recording, and missing data cannot, therefore, be ruled out. Also, as there were no sequencing data available for patients included in the study, we used dominance period for Omicron subvariant as a surrogate²⁹. Finally, as with many analyses of electronic health records, the absence of a recorded diagnosis code is assumed to be synonymous with the absence of the disease itself.

Conclusions

There is evidence of differences in the characteristics and risk profiles of patients with COVID-19 who are treated with sotrovimab, nirmatrelvir/ritonavir and molnupiravir, as well as eligible untreated patients. Sotrovimab was observed to be utilized frequently amongst patients with high-risk comorbidities, such as advanced renal disease, which may place patients at increased risk of severe COVID-19. The proportion of patients with COVID-19-related hospitalizations was particularly low for sotrovimab- and nirmatrelvir/ritonavir-treated patients, with findings for sotrovimab being maintained amongst patients with advanced renal disease, as well as patients aged both 18–64 and ≥ 65 years. Across the Omicron BA.1, BA.2 and BA.5 periods (through July 2022), COVID-19 hospitalizations for all treated cohorts were consistently low.

Transparency

Declaration of funding

This study was funded by GSK (study number 214907). GSK employees were involved in analysis and interpretation of the data, writing of the report, and the decision to submit for publication.

Declaration of financial/other relationships

VP, DCG, MD, WK, EJP and HJB are employees of, and/or shareholders in, GSK. MJY, JDW, SY, BFP and TK are employees of Imperial College Health Partners, which received funding from GSK to conduct the study. BL is an employee of OPEN Health, which received funding from GSK to conduct the study. SJB is an employee of Imperial College Healthcare NHS Trust, London; a consultancy fee was paid to SJB's institutional account.

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Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. Study design/conception: VP, MJY, BL, DCG, MD, JDW, SY, BFP, HJB, TK, SJB. Study execution: VP, MJY, BL, DCG, MD, JDW, SY, BFP, TK, SJB. Data acquisition: MJY, JDW, SY, BFP, TK. Data

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Data availability statement

The Discover-NOW data that support the findings of this study are available from Imperial College Health Partners via approval from the Discover Data Access Group (DRAG) under certain restrictions.

Ethics statement

This study was approved by the Discover Data Access Group (DRAG) which has derogated powers to approve studies under its overarching approval as a Health Research Database. This study complies with all applicable laws regarding subject privacy. Data were aggregated and counts less than five were suppressed in line with information governance suppression rules. No direct subject contact or primary collection of individual human subject data occurred. Study results were in tabular form and aggregate analyses that omit subject identification, therefore informed consent, ethics committee or institutional review board approval were not required. Any publications and reports do not include subject identifiers.

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