PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends, variation and clinical characteristics of recipients of antivirals and neutralising monoclonal antibodies for non-hospitalised COVID-19: a descriptive cohort study of 23.4 million people in OpenSAFELY
AUTHORS	Goldacre, Ben; Green, Amelia; Curtis, Helen; Higgins, Rose; Nab, Linda; Mahalingasivam, Viyaasan; Smith, Rebecca; Mehrkar, Amir; Inglesby, Peter; Drysdale, Henry; DeVito, Nicholas; Croker, Richard; Rentsch, Christopher; Bhaskaran, Krishnan; Tazare, John; Zheng, Bang; Andrews, Colm; Bacon, Sebastian; Davy, Simon; Dillingham, Iain; Evans, David; Fisher, Louis; Hickman, George; Hopcroft, Lisa; Hulme, William; Massey, Jon; MacDonald, Orla; Morley, Jessica; Morton, Caroline; Park, Robin; Walker, Alex; Ward, Tom; Wiedemann, Milan; Bates, Christopher; Cockburn, Jonathan; Parry, John; Hester, Frank; Harper, Sam; Douglas, Ian; Evans, Stephen; Tomlinson, Laurie; MacKenna, Brian

VERSION 1 - REVIEW

REVIEWER 1	Fiscella, Kevin. Competing Interest: None
REVIEW RETURNED	12-Jun-2022

GENERAL COMMENTS	This is an important and timely study. The results are plausible and will inform policy. My comments are mostly minor. - Abstract: The conclusion neglects to mention the need to target ethnic inequities and older people. - It is not clear why the authors have not conducted multivariable analyses to tease out independent factors associated with receipt of antivirals. This could help determine whether area deprivation or ethnicity is the driver of inequities in treatment. It might help explain the lower rates among the unvaccinated. It would also allow the analyses to control for age. These analyses could better inform policy. This is an important limitation of the study. - Limitations pg 19: The authors mention geographic clustering within the EHR system. Can they quantify its potential impact on the findings? In which direction would the authors expect the results related to geography, area deprivation, and ethnicity to be biased? Sorting this out will make the policy implications clearer. - I don't understand the authors' comment (pg 19) that "there are no apriori reasons to expect that this issue will substantially affect the relationships between observed patient factors and outcomes." What do the authors mean by outcomes? They did not measure outcomes, only presumptive antiviral treatment.

	- Why is age not discussed (pg 21)? Table 2 suggests no relationship between age and treatment. This warrants some comment since even though age is not considered an NHS risk factor, it is robust risk factor for hospitalization and mortality, capturing function, frailty, and unmeasured comorbidity. The trend towards older people being less likely to receive treatment in crude analyses suggests a risk/treatment paradox. In particular, only 9% of people 80+ years of age received treatment compared to an overall rate of nearly double this. Some of this could represent healthy survivor effects but this is why multivariable analyses are needed. - Policy implications (pg 23). The authors may wish to comment on Nirmatrel/ritonavir rates and changing rates given its advantages over agents related to efficacy and oral administration. - Conclusion: The authors may want to expand slightly (perhaps in the preceding paragraphs) regarding what targeted activities might mean including lessons learned from equity-promoting vaccine-related activities.

REVIEWER 2	Hill, Andrew; University of Liverpool Department of Pharmacology and Therapeutics. Competing Interest: Academic Research Grant from UNITAID in 2021, to evaluate repurposed treatments for SARS-CoV-2 Academic Research Grant from the Rainwater Charitable Foundation in 2021 to evaluate re-purposed treatments for SARS-CoV-2
REVIEW RETURNED	14-Jun-2022

GENERAL COMMENTS	In 2021, patients in the UK considered at high risk of hospitalisation from COVID-19 infection were contacted by letter to inform them that they would be eligible to receive novel antiviral treatments as outpatients, if they tested positive for SARS-CoV-2. The main treatments offered were sotrovimab, molnupiravir and nirmatrelvir/ritonavir. In this analysis of 23.3 million patients using the OpenSAFELY platform, the percentage of these high risk patients who received these treatments is estimated. The time interval selected was between late November 2021 and the end of April 2022. In the OpenSAFELY database, 102,000 of the 23.2 million patients were both in a high-risk group and tested SARS-CoV-2 positive. Of these 102,000 patients potentially eligible for treatment, 18,000 (18%) received an antiviral treatment. Of the unvaccinated patients in high risk groups, only 5% received treatment. By December 2021, the UK government had ordered 2.25 million courses of molnupiravir, 2.75 million courses of nirmatrelvir/ritonavir and 100,000 doses of sotrovimab (UK press release 21 December 2021). The details of these orders should be included in the Introduction. In the Discussion, the future use of these treatments could be assessed, given clinical evidence gathered so far. The World Health Organisation COVID-19 Guidelines recommend the use of either molnupiravir or nirmatrelvir only for patients at the “highest risk” of hospitalisation – above 10%. It would help to show from the database how many of the 102,000 patients identified in the database were hospitalised in the 28 days after a first positive

test result. If rates of hospitalisation are lower than the 10% threshold, the potential for benefit may be more limited. In this case, the potential harms from these treatments need to be discussed. For example molnupiravir treatment can lead to birth defects in two animal studies so should not be used by adults of reproductive age without adequate contraception. Nirmatrelvir/ritonavir can lead to serious drug-drug interactions if used with certain co-medications metabolised by the CYP3A4 pathway.

It would help with the interpretation of these results to include more categories in the analysis, in a flowchart. In particular, how many of the 23.2 million patients were in a high risk category, whether tested or not? Of this total number, how many had test results available in the database? This will divide the patients into three groups. Those with no test results available, those always testing negative and those with at least one positive result. The current analysis seems to include only the high risk patients who tested SARS-CoV-2 positive. The total number of high risk patients might be larger.

It would also help to know how frequently the patients were tested. Given that SARS-CoV-2 viraemia can be detectable only for 10-14 days in most patients, infrequent testing could result in missed diagnoses.

Another important measure of success would be the percentage of high risk patients who were tested frequently (at least twice per month during the time interval) and found to be either positive or negative. Those tested less frequently, or not at all, may have missed the chance to receive the treatments available.

After the 29th March 2022, free lateral flow testing was stopped in the UK. It would be important to state whether this had an impact on patients in these high risk groups. Were fewer patients testing positive after this time? With free testing no longer available, it is not clear whether this system could allow the high risk patients to continue to be identified as needing treatment. The paper could be updated to evaluate the effects of stopping free testing on the uptake of these treatments in the UK.

When this UK project was started in November 2021, the treatments in question – sotrovimab, molnupiravir and nirmatrelvir – only had results available from randomised trials of unvaccinated patients. Very few of the unvaccinated patients in the OpenSAFELY database received antiviral treatment – only 5%. It is not clear whether vaccinated patients show a clinical benefit from these treatments. This question is being studied in the UK PANORAMIC trial for molnupiravir, including over 23,000 patients, but results are not yet available. When results are announced, this paper could be updated to estimate the clinical benefit which might be seen. Similarly, the clinical benefits of nirmatrelvir are being evaluated for mainly vaccinated patients in a new phase of UK PANORAMIC, but recruitment is very limited at the moment.

The MOVE-OUT, EPIC-HR and sotrovimab trials had recruited patients with earlier variants of SARS-CoV-2 which were more severe, leading to higher rates of hospitalisation. Rates of hospitalisation are likely to be lower now, in the era of Omicron. This could limit the potential of these treatments to benefit patients.

During the interval of this analysis, from November 2021 to April

	2022, the predominant variants in the UK were Omicron, initially BA2. The BA4 and BA5 variants are now growing in prevalence. Sotrovimab was the most widely used drug in this study, given to 51% of the high risk patients. However sotrovimab has been withdrawn from use by the US Food and Drug Administration because of low or no predicted activity against the BA2 variant. Therefore it is not clear whether the 9340 UK patients who received sotrovimab between late November and April 2022 derived any clinical benefit from treatment, since BA2 was the predominant variant in the UK at the time. Overall, there is an assumption in this paper that the high-risk patients would be receiving effective antivirals, so the efforts to contact them and initiate treatment rapidly would lead to clinical benefits. In October 2022, this would have been justified from the first clinical trials to report. Merck's MOVE-OUT trial initially showed a 50% reduction in hospitalisation. The Pfizer EPIC-HR trial showed an 89% reduction in hospitalisation for those given nirmatrelvir within 3 days of symptoms. The GSK trial of sotrovimab showed an 80% lower risk of hospitalisation. However, these initial trial results have been undermined by more recent evidence. The later analysis of Merck's MOVE-OUT trial showed trends for more hospitalisations among molnupivavir treated patients, in the second half of the study. Ten large molnupiravir randomised trials were registered in India, but no results were formally published. It appears that some of these trials may have been fraudulent. Media reports suggested that two of the Indian molnupiravir trials had failed and then been discontinued. For nirmatrelvir, the second "EPIC-SR" trial failed to show benefits in the primary analysis, and has not been published. As mentioned above, sotrovimab has been withdrawn from use in the US because of predicted loss of efficacy against BA2. So it is not clear whether these treatments are causing overall benefits to the high-risk patients in the UK who are receiving them. If the OpenSAFELY database also has access to hospitalisation data, it may be possible to analyse this question in more detail, comparing outcomes for those treated versus not treated. Similar analyses have been conducted to analyse the "real-life" efficacy of vaccination in the UK. This type of analysis would not be within a randomised setting, but may be worth more analysis for the antiviral drugs.

REVIEWER 3	Lowe, David; UCL, Institute of Immunity and Transplantation. Competing Interest: Personal fees from Gilead for an educational video on COVID-19 in immunodeficiency and from Merck for a roundtable discussion on risk of COVID-19 in immunosuppressed patients. Speaker fees from Biotest for lecture on diarrhoea in primary immunodeficiency. Research grants from LifeArc, MRC, Blood Cancer UK, Bristol Myers Squibb and the British Society for Antimicrobial Chemotherapy.
REVIEW RETURNED	23-Jun-2022

GENERAL COMMENTS	Green et al present a description of patients treated in the community for COVID-19 via COVID Medicine Delivery Units. There are some important findings around equity of access, with treatment being influenced by eg deprivation, ethnicity, region and vaccination status. However, I think there are some points which need to be addressed: 1. The biggest issue is the size of the denominator groups (i.e. the 'potentially eligible' patients). This is clearly far too large for some groups. For example, there were apparently 18,910 potentially eligible patients in the 'Primary immune deficiencies' group: this far exceeds the total number of patients in the entire country with these diagnoses. CVID, the most common condition listed, is estimated to affect 2000-3000 people nationally, while there are only around 5000 people in the UK Primary Immunodeficiency Network registry across all immunodeficiency diagnoses – not all of whom would be eligible for treatment. However, the figures in the manuscript would imply around 150,000 people per year nationally with a primary immune deficiency AND COVID-19. It is not clear who has been captured in this group. The population prevalence of eg IgA deficiency and MBL deficiency (neither of which confer eligibility for treatment via CMDUs) are higher, but many of these diagnoses will not be known and recorded as the conditions are usually clinically silent. Beyond this, it is difficult to discern which diagnoses have been coded into this group but it cannot be patients with eligibility under this category. Many other groups also seem very large – for example, the numbers with IMID would equate to over 300,000 people across the UK having one of these conditions and COVID-19 over a year. The authors acknowledge that the denominators may be over-estimates, but I think it is difficult to conclude that the percentage of potentially eligible patients treated via CMDUs is only 18% (or even close to this). If the issue cannot be rectified, it at least needs to be acknowledged as a significant limitation. 2. Inaccurate classification of primary immune deficiencies may also help to explain the counter-intuitive finding that this group was less likely to be treated with sotrovimab. Nearly all of the patients in this group have antibody deficiency syndromes and therefore many CMDUs would favour nMabs over oral antivirals in this group (notwithstanding potentially reduced efficacy of sotrovimab versus omicron – see below). Again, this needs to be either rectified with further investigation into the diagnoses captured within this grouping, or at least discussed as a significant limitation. 3. It is not entirely clear to me how the authors excluded patients who were currently hospitalised at the time they might be eligible for treatment – the exclusion criterion applied is for people who have already been discharged (in the 30 days prior to the test or treatment). How did the authors exclude patients who were still inpatients at the time of the test or – though it would be more difficult – those who were hospitalised soon after having the test and therefore became ineligible for community-based treatment? I am sure this was done but please make it clearer. 4. Treatment via CMDUs is very tightly controlled and is

	monitored/audited via the Blueteq system. It seems highly unlikely that there were significant inconsistencies with the guidance (eg treating people without a qualifying diagnosis or without a positive test). The authors acknowledge this in the Discussion, but I think the point should be made more clearly that most inconsistencies are likely to reflect issues with the data rather than issues with the correct implementation of guidance by CMDUs. 5. Further reasons affecting choice of treatment to be considered in the Discussion include the logistical challenges of administering remdesivir in the community (IV infusion over several days) and more recent concerns regarding the efficacy of sotrovimab against omicron variants of SARS-CoV-2. Minor points: 1. The 'Primary immune deficiencies' group was changed to 'Immune deficiencies' and includes patients with secondary antibody deficiency receiving, or eligible for, immunoglobulin replacement therapy. This should be updated. Even with this change, the numbers would not come close to those suggested for this group (see point 1 above). 2. The authors frequently refer to casirivimab + imdevimab as just 'casirivimab'. This is misleading and should be corrected. 3. On Page 7, the authors use 'sotrovimab/remdesivir' – the slash is confusing here and might imply that the two treatments are given together: suggest replace with 'or'. 4. Personally, I am not sure that the 'clinically extremely vulnerable' grouping is useful here. This is a problematic term in itself, developed pragmatically at the start of the pandemic but without a clear scientific basis. The eligible population for community treatment via CMDUs was defined on the basis of accumulated evidence in terms of risk from COVID-19 and capacity to benefit from treatment, and in some ways supersedes the CEV group. However, this is a minor point.

REVIEWER 4	de Silva, Thushan. Competing Interest: I am a member of the Independent Advisory Group that helped to define the highest priority groups described in this manuscript. I do not think this is a competing interest.
REVIEW RETURNED	24-Jun-2022

GENERAL COMMENTS	The authors present data from the first large analysis of non-hospitalised patients eligible for COVID-19 treatment in England using the OpenSAFELY-TPP database, covering 23.4 million people (~40% of the English population), identifying the numbers of potentially eligible patients receiving treatment and demographic/clinical factors which may be associated with a lower proportion of patients being treated. These are very important data for considering how to improve delivery of CMDU services moving forwards, in particular to address some of the potential health inequalities relating to geography, deprivation and ethnicity, that are highlighted by the manuscript. The manuscript deserves to be in the public domain asap. I have some minor comments and questions: 1. The precise definitions in 'Appendix 1' of the interim clinical commissioning guidance went through several iterations. It looks like the authors took one static list from towards the end of the study period. It may not make a large impact on the number of 'potentially

	eligible' patients, but it would be good to address this in case this impact the % of those treated. 2. The authors state that some patients who were not deemed eligible were included in the study as they received treatment, the assumption being that miscoding led to them being erroneously considered not eligible (4690 of the 102170). Could this have inflated the % treated metrics? Presumably it is hard then to know what the true denominator of eligible patients are if coding were 100%? It would be worth acknowledging this unless the authors can estimate what the rate of misclassification is. 3. It is hard to get a sense of how granular the NHS digital and associated code lists are. Specifically, whether they capture the precise definitions in the highest risk categories or broader groups. This is important for several reasons. Firstly, it may give an indication of what proportion of non-treatment is due to patients not actually being eligible when assessed by a clinician, based on their disease state. See the preprint of a service evaluation in 4 CMDUs (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4123333), where only 17% of those referred were deemed to be eligible. This is similar to the % treated in the OPENSAFELY data. The authors should discuss and reference this. Secondly, are there differences in how accurately NHS digital can define eligibility across different diseases? For example is it easier with coded data to precise identify all the renal disease patients compared to the haematological disease patients? If so, this may have some impact on the differences in % treated across disease groups. This latter point may just be one for discussion, but the authors should provide some idea of how precise the coding is across different disease categories. 4. Is there any way to look at the number of CMDUs serving different areas to see if geographical distribution/per capita population had an impact on the % treated? 5. Where there are data on symptom onset and PCR time, is it possible to see whether time between these two variables were associated with the % not treated? I realise that the design of this study does not allow teasing apart of why patients were not treated, but this could given an indication of how much was related to time to presentation and being out of window. 6. Box 2: While the overall cohort names are correct, the authors have selectively chosen 1 or 2 criteria within these to further expand the descriptive terminology. In some cases this is appropriate but in others, it is a bit odd to say 'such as those with sickle cell disease' in the haematological disease and SCT, given the whole group is very diverse. I would have just the main category names in 'Appendix 1' of the clinical commissioning guidance and full details in Supplementary. Make it clear that the highest risk subgroups within these cohorts were those identified as eligible. Using the same descriptors as in Table 1 would be appropriate. 7. Authors state that they assessed consistency with treatment-specific criteria such as contraindications. I assume that the granularity of data available did not allow assessment of contraindications to Paxlovid due to drug-drug interactions?

REVIEWER 5	Riley, Richard; Keele University, School of Medicine. Competing Interest: None
REVIEW RETURNED	06-Jul-2022

GENERAL COMMENTS	I've screened this from a statistical point of view, and do not have any comments or suggestions. This is an important, largely descriptive study (without substantive analyses or models), and is well presented and with a clear message.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author
This is an important and timely study.
The results are plausible and will inform policy.
My comments are mostly minor.
We thank the author for the positive comments.
1.1) Abstract: The conclusion neglects to mention the need to target ethnic inequities and older people.
Authors' reply: In the abstract of the revised manuscript, these groups are now mentioned in the conclusion on page 5 lines 3-5:
*"Targeted activity may be needed to address apparent lower treatment coverage observed among certain groups, in particular (at present): different NHS regions, **ethnic minorities**, **people aged 80 years or over**, socioeconomically deprived areas, and care homes."*
1.2) It is not clear why the authors have not conducted multivariable analyses to tease out independent
factors associated with receipt of antivirals. This could help determine whether area deprivation or ethnicity is the driver of inequities in treatment. It might help explain the lower rates among the unvaccinated. It would also allow the analyses to control for age. These analyses could better inform policy. This is an important limitation of the study.
Authors' reply: The aim of this study was to describe coverage of nMABs and antivirals as treatment for COVID-19 in community settings. Our results show variations in coverage between key clinical and
demographic groups. While we acknowledge the importance of determining drivers of these inequities in
treatment, this is outside the scope of current resource and we believe our study design is not suited to
identify these drivers using multivariable models. An appropriate study design for answering these causal questions is needed for the identification of these drivers. We comment on this as potential area
of investigation in future work in the discussion on page 22 lines 47-49:
*"Further research and investigation is required to understand and **address the causes of any inequity***
such as those that have been undertaken to identify barriers of uptake of COVID-19 vaccines [1]."
1.3) Limitations pg 19: The authors mention geographic clustering within the EHR system. Can they quantify its potential impact on the findings? In which direction would the authors expect the results related to geography, area deprivation, and ethnicity to be biased? Sorting this out will make the policy
implications clearer.
Authors' reply: Since we submitted our original manuscript we have completed and published a paper
in Wellcome Open Research studying the representativeness of OpenSAFELY-TPP which addresses this
comment. Briefly, we concluded that OpenSAFELY-TPP was broadly representative of the English population. We therefore have no reason to believe that our results are biased due to the geographical
clustering in our data. Effects of clustering on the standard errors of estimates will be small and largely

irrelevant in a descriptive paper. To clarify, we added a citation to this recent paper on page 21 lines 3-11:
"Our population, although extremely large, is geographically clustered as a result of the geographic clustering in the EHR system used by general practices, and only 17% of general practices in London using TPP software. ***However, OpenSAFELY-TPP has been shown to be broadly representative of the English population*** *[2]. There are no a priori reasons to expect that the geographical clustering in our data will substantially affect estimates of the coverage of nMABs and antivirals in England and variations thereof in key clinical and demographic groups."*

1.4) I don't understand the authors' comment (pg 19) that "there are no apriori reasons to expect that this issue will substantially affect the relationships between observed patient factors and outcomes." What do the authors mean by outcomes? They did not measure outcomes, only presumptive antiviral treatment.

Authors' reply: We agree with the reviewer that the meaning of this sentence is not clear and changed the sentence accordingly on page 21 lines 8-10:
"Our population, although extremely large, is geographically clustered as a result of the geographic clustering in the EHR system used by general practices, and only 17% of general practices in London using TPP software. However, OpenSAFELY-TPP has been shown to be broadly representative of the English population [2]. There are no a priori reasons to expect that the geographical clustering in our data will substantially ***affect estimates of the coverage of nMABs and antivirals in England and variations thereof in key clinical and demographic groups.****"*

1.5) Why is age not discussed (pg 21)? Table 2 suggests no relationship between age and treatment. This warrants some comment since even though age is not considered an NHS risk factor, it is robust risk factor for hospitalization and mortality, capturing function, frailty, and unmeasured comorbidity. The trend towards older people being less likely to receive treatment in crude analyses suggests a risk/treatment paradox. In particular, only 9% of people 80+ years of age received treatment compared to an overall rate of nearly double this. Some of this could represent healthy survivor effects but this is why multivariable analyses are needed.

Authors' reply: Thank you for the comments. We have added the following to the revised manuscript on page 20 lines 30-32:
*"****People aged 80 and over had lower treatment coverage (13% vs 23% in people aged 50-59 years old).****"*
We have also added the following on page 22 42-45:
"Additionally the finding of ***lower coverage amongst the 80+ requires investigation*** *particularly as age is associated with COVID-19 death and hospitalisation [3]."*
In addition, people aged 80 and over are now mentioned in the abstract (see comment 1.1) and the conclusion of the revised manuscript on page 23 lines 25-29:
"Targeted activity may be needed to address lower treatment rates observed among certain geographic areas and key groups including ethnic minorities, ***people aged 80 years or over****, people living in areas of higher deprivation, and in care homes."*

1.6) Policy implications (pg 23). The authors may wish to comment on Nirmatrel/ritonavir rates and changing rates given its advantages over agents related to efficacy and oral administration.

Authors' reply: We commented on Paxlovid and changing rates on page 22 lines 33-35:
"Paxlovid was implemented as a first-line treatment next to sotrovimab on 10th February 2022 [4], reflected by a slowing in the uptake of molnupiravir from that date [5]. Both the antivirals molnupiravir and Paxlovid are administered orally [6]."
We were unable to identify why Paxlovid was implemented as a first-line treatment in the clinical commissioning policy [5] and we think it is outside the scope of the paper to speculate on the changing place in therapy due to efficacy.

1.7) Conclusion: The authors may want to expand slightly (perhaps in the preceding paragraphs) regarding what targeted activities might mean including lessons learned from equity-promoting vaccine-related activities.

Authors' reply: We expanded slightly on further research needed to identify what targeted activities might be needed to address the inequity in uptake of treatments (see our reply to comment 1.1) on page 22 lines 47-49:
"Further research and investigation is required to understand and address the causes of any inequity such as those that have been undertaken to identify barriers of uptake of COVID-19 vaccines [1]."

Reviewer: 2
Comments to the Author
2.1) In 2021, patients in the UK considered at high risk of hospitalisation from COVID-19 infection were
contacted by letter to inform them that they would be eligible to receive novel antiviral treatments as outpatients, if they tested positive for SARS-CoV-2. The main treatments offered were sotrovimab, molnupiravir and nirmatrelvir/ritonavir.
In this analysis of 23.3 million patients using the OpenSAFELY platform, the percentage of these high risk patients who received these treatments is estimated. The time interval selected was between late November 2021 and the end of April 2022.
In the OpenSAFELY database, 102,000 of the 23.2 million patients were both in a high-risk group and tested SARS-CoV-2 positive. Of these 102,000 patients potentially eligible for treatment, 18,000 (18%)
received an antiviral treatment. Of the unvaccinated patients in high risk groups, only 5% received treatment.
By December 2021, the UK government had ordered 2.25 million courses of molnupiravir, 2.75 million courses of nirmatrelvir/ritonavir and 100,000 doses of sotrovimab (UK press release 21 December 2021).
2.1.1) The details of these orders should be included in the Introduction.
Authors' reply: Your suggestion has been added to the introduction on page 7 lines 22-25:
"By December 2021, the UK government had ordered 2.25 million courses of molnupiravir, 2.75 million
courses of nirmatrelvir/ritonavir [7] and 100,000 doses of sotrovimab [8]."
2.1.2) In the Discussion, the future use of these treatments could be assessed, given clinical evidence gathered so far.
Author's reply: We comment on the effectiveness of these drugs in the section 'Policy implications and
future research':
"Finally all our analytic code is openly available for re-use and can be used to underpin observational work on clinical effectiveness and safety of treatments. To our knowledge no head to head comparative
interventional research has been reported to date for these treatments. The effectiveness of these COVID-19 treatments is supported by the original randomised controlled trials [9–11]. A few observational studies have been published studying the effectiveness of these treatments in the clinical
setting [12–17]."
2.2) The World Health Organisation COVID-19 Guidelines recommend the use of either molnupiravir or
nirmatrelvir only for patients at the "highest risk" of hospitalisation – above 10%.
2.1.1) It would help to show from the database how many of the 102,000 patients identified in the database were hospitalised in the 28 days after a first positive test result. If rates of hospitalisation are lower than the 10% threshold, the potential for benefit may be more limited.
Authors' reply: The purpose of our study is to investigate coverage of nMABS and antivirals related to
the NHSE guidelines, which are not necessarily the same as WHO guidelines. Assessment against WHO
guidelines or assessing effectiveness with regards to hospitalisation is outside the scope of this current
study although we agree it is worthwhile and needed.
2.1.2) In this case, the potential harms from these treatments need to be discussed. For example molnupiravir treatment can lead to birth defects in two animal studies so should not be used by adults of
reproductive age without adequate contraception. Nirmatrelvir/ritonavir can lead to serious drug-drug

interactions if used with certain co-medications metabolised by the CYP3A4 pathway.
Authors' reply: We agree with the reviewer that safety analyses of these drugs are needed however it
is outside the scope of this study. We are currently preparing another analysis on the safety of these COVID-19 treatments where we will use the granular data in OpenSAFELY to assess the safety of these
treatments (see also our reply to comment 4.7 below).
2.3) It would help with the interpretation of these results to include more categories in the analysis, in a
flowchart. In particular, how many of the 23.2 million patients were in a high risk category, whether tested or not? Of this total number, how many had test results available in the database? This will divide
the patients into three groups. Those with no test results available, those always testing negative and those with at least one positive result. The current analysis seems to include only the high risk patients
who tested SARS-CoV-2 positive. The total number of high risk patients might be larger.
Authors' reply: We added the total number of people in a high risk category at the start of the study period, regardless of whether they were tested positive or not, to the manuscript, on page 16 line 28:
"The total number of people in a high risk group registered at a TPP practice was 661,609."
In our paper, we intend to describe the percentage of people prescribed nMABs or antivirals who were
deemed eligible by NHS Digital. By definition, people were only deemed eligible if they had a positive test. Consequently, people without a positive test are not part of our study population.
We acknowledge that people could not be testing positive for various reasons. People could be not infected; infected but not being tested; infected but having a false-negative test result. While we agree it is important to know how many people with an infection do not have a positive test and whether these
people might benefit from treatment, it is practically impossible to offer treatment to infected people without a positive test in a real world setting. What is more, infected people without a positive test may be more likely to be asymptomatic, another criteria needed to be eligible for these COVID-19 treatments. For these reasons, a positive test is a strict inclusion criteria in our study.
2.4) It would also help to know how frequently the patients were tested. Given that SARS-CoV-2 viraemia can be detectable only for 10-14 days in most patients, infrequent testing could result in missed diagnoses.
Authors' reply: Our study relies on testing data available from the Second Generation Surveillance System, which captures routine laboratory surveillance data on infectious diseases across England. These data include pillar 1 and pillar 2 test results. We agree that infrequent testing might make a missed diagnosis more likely but infrequent testing is inevitably part of the real world setting in which this study is conducted. Treatment cannot be offered to people who have a missed diagnosis. Missed diagnoses do not affect the findings on coverage which is the objective of our study.
2.5) Another important measure of success would be the percentage of high risk patients who were tested frequently (at least twice per month during the time interval) and found to be either positive or negative. Those tested less frequently, or not at all, may have missed the chance to receive the treatments available.
Authors' reply: We agree with the reviewer that it is important to study who might have missed the chance to receive treatment as a consequence of infrequent testing but we are unable to study this in the real world setting this study is conducted in. We refer to comment 2.4 for a discussion of why missed
diagnosis do not affect the findings on coverage which is the objective of our study.
2.6) After the 29th March 2022, free lateral flow testing was stopped in the UK. It would be important to
state whether this had an impact on patients in these high risk groups. Were fewer patients testing positive after this time? With free testing no longer available, it is not clear whether this system could allow the high risk patients to continue to be identified as needing treatment. The paper could be updated to evaluate the effects of stopping free testing on the uptake of these treatments in the UK.
Authors' reply: Although free lateral flow testing was stopped on March 30 2022, those eligible for COVID-19 antiviral and other treatments were sent a pack of tests and could request replacements if they needed them [18]. The stopping of free lateral flow testing might therefore have less impact in this
high risk population. We refer to comment 2.4 for a discussion of the reason why missed diagnoses

(here as a consequence of a change in testing policy) is not relevant for our study.

2.7) When this UK project was started in November 2021, the treatments in question – sotrovimab, molnupiravir and nirmatrelvir – only had results available from randomised trials of unvaccinated patients. Very few of the unvaccinated patients in the OpenSAFELY database received antiviral treatment – only 5%. It is not clear whether vaccinated patients show a clinical benefit from these treatments. This question is being studied in the UK PANORAMIC trial for molnupiravir, including over 23,000 patients, but results are not yet available. When results are announced, this paper could be updated to estimate the clinical benefit which might be seen. Similarly, the clinical benefits of nirmatrelvir are being evaluated for mainly vaccinated patients in a new phase of UK PANORAMIC, but recruitment is very limited at the moment.

Author's reply: We agree with the reviewer that careful assessment of the effectiveness of these treatments in clinical settings is of utmost importance however it is outside the scope of this study. A preprint from our group can be found on MedRXiv estimating the comparative effectiveness of sotrovimab versus molnupiravir in a clinical setting [17]. As another example, we are currently conducting an observational study estimating the effectiveness of the use of sotrovimab or molnupiravir vs its non-use. When the PANORAMIC trial results become available it would not affect the findings on coverage which is the objective of our study. A comment in the discussion could be added if results become available, though it should be noted that the inclusion criteria for the trial are much wider than the NHSE guidelines.

2.8) The MOVE-OUT, EPIC-HR and sotrovimab trials had recruited patients with earlier variants of SARS-CoV-2 which were more severe, leading to higher rates of hospitalisation. Rates of hospitalisation are likely to be lower now, in the era of Omicron. This could limit the potential of these treatments to benefit patients.

During the interval of this analysis, from November 2021 to April 2022, the predominant variants in the UK were Omicron, initially BA2. The BA4 and BA5 variants are now growing in prevalence. Sotrovimab was the most widely used drug in this study, given to 51% of the high risk patients. However sotrovimab has been withdrawn from use by the US Food and Drug Administration because of low or no predicted activity against the BA2 variant. Therefore it is not clear whether the 9340 UK patients who received sotrovimab between late November and April 2022 derived any clinical benefit from treatment, since BA2 was the predominant variant in the UK at the time.

Author's reply: The study period of this study covers 11 December 2021 - 28 April 2022. Omicron B.1.1.529 and BA.1.1 were dominant from 15 December 2021 - 11 February 2022; Omicron BA.2 was the dominant variant from approximately 12 February onwards, covering slightly more than half of the study period.[19]

The MHRA has not followed the FDA's withdrawal of sotrovimab. We commented on the concerns regarding the low efficacy of sotrovimab against Omicron BA.2 in the discussion on page 22 lines 38-40 (see also comment 3.5):

"In addition, concerns were raised about the low efficacy of Sotrovimab against the Omicron BA.2 sublineage [20], the dominant circulating variant from mid-February [21]."

To study whether sotrovimab has lower effectiveness against the BA.2 variant, we are planning to extend our observational study into the comparative effectiveness of molnupiravir vs sotrovimab to the BA.2 period as well as our study into the use vs non-use of these drugs (see also comment 2.7).

2.9) Overall, there is an assumption in this paper that the high-risk patients would be receiving effective antivirals, so the efforts to contact them and initiate treatment rapidly would lead to clinical benefits. In October 2022, this would have been justified from the first clinical trials to report. Merck's MOVE-OUT trial initially showed a 50% reduction in hospitalisation. The Pfizer EPIC-HR trial showed an 89% reduction in hospitalisation for those given nirmatrelvir within 3 days of symptoms. The GSK trial of

sotrovimab showed an 80% lower risk of hospitalisation.
However, these initial trial results have been undermined by more recent evidence. The later analysis of
Merck's MOVE-OUT trial showed trends for more hospitalisations among molnupivavir treated patients, in
the second half of the study. Ten large molnupiravir randomised trials were registered in India, but no results were formally published. It appears that some of these trials may have been fraudulent. Media reports suggested that two of the Indian molnupiravir trials had failed and then been discontinued. For nirmatrelvir, the second "EPIC-SR" trial failed to show benefits in the primary analysis, and has not been
published. As mentioned above, sotrovimab has been withdrawn from use in the US because of predicted loss of efficacy against BA2.
So it is not clear whether these treatments are causing overall benefits to the high-risk patients in the UK who are receiving them. If the OpenSAFELY database also has access to hospitalisation data, it may
be possible to analyse this question in more detail, comparing outcomes for those treated versus not treated. Similar analyses have been conducted to analyse the "real-life" efficacy of vaccination in the UK.
This type of analysis would not be within a randomised setting, but may be worth more analysis for the
antiviral drugs.
Authors' reply: The purpose of our study is to assess coverage of treatments in an eligible population
defined by the NHS. It is reasonable to ask if the antivirals do offer genuine benefits overall, but this is outside the scope of the current study. We refer to our reply to comment 2.7.

Reviewer: 3
Comments to the Author
Green et al present a description of patients treated in the community for COVID-19 via COVID Medicine
Delivery Units. There are some important findings around equity of access, with treatment being influenced by eg deprivation, ethnicity, region and vaccination status.
We thank the author for the positive comments.
However, I think there are some points which need to be addressed:
3.1) The biggest issue is the size of the denominator groups (i.e. the 'potentially eligible' patients). This
is clearly far too large for some groups. For example, there were apparently 18,910 potentially eligible patients in the 'Primary immune deficiencies' group: this far exceeds the total number of patients in the
entire country with these diagnoses. CVID, the most common condition listed, is estimated to affect 2000-3000 people nationally, while there are only around 5000 people in the UK Primary Immunodeficiency Network registry across all immunodeficiency diagnoses – not all of whom would be
eligible for treatment. However, the figures in the manuscript would imply around 150,000 people per year nationally with a primary immune deficiency AND COVID-19.
It is not clear who has been captured in this group. The population prevalence of eg IgA deficiency and
MBL deficiency (neither of which confer eligibility for treatment via CMDUs) are higher, but many of these diagnoses will not be known and recorded as the conditions are usually clinically silent. Beyond this, it is difficult to discern which diagnoses have been coded into this group but it cannot be patients with eligibility under this category.
Many other groups also seem very large – for example, the numbers with IMID would equate to over 300,000 people across the UK having one of these conditions and COVID-19 over a year.
The authors acknowledge that the denominators may be over-estimates, but I think it is difficult to conclude that the percentage of potentially eligible patients treated via CMDUs is only 18% (or even close to this). If the issue cannot be rectified, it at least needs to be acknowledged as a significant limitation.
Authors' reply:

A key methodological decision in our study was to replicate, as closely as possible, the eligibility criteria
for COVID therapeutics published by NHS Digital within OpenSAFELY-TPP. The published NHS Digital
codelist can be viewed at
https://www.opencodelists.org/codelist/nhsd/immunosupression-pcdcluster-snomed-ct/0993606d/)
which contains, for example, secondary immune deficiency disorder.
We have changed the label of the 'Primary Immune Deficiencies' group to 'Immune Deficiencies'. The labels of our groups were based on the interim clinical commissioning policy published on 16 December
2021. NHS Digital relabeled the group to 'Immune Deficiencies' in the version of the interim clinical commissioning policy published on 27th January.
The codelists used are inclusive but not specific, and as a consequence these groups do not represent
strict clinical groupings. We commented on this in the discussion on page 21 lines 46-52:
The codelists used are inclusive but not specific, and as a consequence these groups do not represent
strict clinical groupings. This is in accordance with a service evaluation of CMDUs in four regions across
England [22], showing that the most common reason for being ineligible was not being in an at-risk clinical group. The service evaluation found that 17% of the patients referred to CMDUs were judged eligible for treatment, which is in line with the coverage found in our study (20%).

3.2) Inaccurate classification of primary immune deficiencies may also help to explain the counter-intuitive finding that this group was less likely to be treated with sotrovimab. Nearly all of the patients in this group have antibody deficiency syndromes and therefore many CMDUs would favour nMabs over oral antivirals in this group (notwithstanding potentially reduced efficacy of sotrovimab versus omicron – see below). Again, this needs to be either rectified with further investigation into the diagnoses captured within this grouping, or at least discussed as a significant limitation.

Authors' reply: We agree with the reviewer that this is a counterintuitive finding and comment on it in our discussion on page 22 lines 29-33:
"Focusing on the three groups (Down syndrome, Rare neurological conditions, and Immune deficiencies)
where sotorvimab was not first choice may be a pragmatic first step for investigations on the reasons for
these choices."
We refer to comment 3.1 for a more detailed discussion of our methodological decision to replicate the
eligibility criteria for COVID therapeutics published by NHS Digital, and that these do not represent strict
clinical groupings.

3.3) It is not entirely clear to me how the authors excluded patients who were currently hospitalised at the time they might be eligible for treatment – the exclusion criterion applied is for people who have already been discharged (in the 30 days prior to the test or treatment). How did the authors exclude patients who were still inpatients at the time of the test or – though it would be more difficult – those who were hospitalised soon after having the test and therefore became ineligible for community-based
treatment? I am sure this was done but please make it clearer.

Authors' reply: Thank you for pointing us to this important limitation of our study.
In the first version of the manuscript analysis, we did not exclude patients who were hospitalised at their date of positive test for the purposes of eligibility.
We have updated our analysis and excluded all patients hospitalised before or on the date of their positive test who were not discharged before or on that date. The revised manuscript includes the updated results. The eligible population changed from 102,170 to 93,870 people.
We additionally reported the number of people hospitalised soon after having a positive test on page 16
lines 16-18:
"Of the 74,830 patients who were eligible but did not receive treatment, 2% (n=1,500) were hospitalised within 5 days after their positive test, which may have been the reason for not being treated."

3.4) Treatment via CMDUs is very tightly controlled and is monitored/audited via the Blueteq system. It
seems highly unlikely that there were significant inconsistencies with the guidance (eg treating people without a qualifying diagnosis or without a positive test). The authors acknowledge this in the Discussion, but I think the point should be made more clearly that most inconsistencies are likely to reflect issues with the data rather than issues with the correct implementation of guidance by CMDUs.
Authors' reply: We added a sentence to our discussion to clarify this on page 21 lines 39-42:
"As an example, 5,010/19,040 people treated were not identified as eligible for treatment in our data. This is possibly due to false-negatives due to missing data rather than significant deviation from the guidance by CMDUs."
When we updated the study our results suggest that there have been a substantial number of treatment
notification forms submitted via the Blueteq system some time after administration. Would it be possible
for the reviewer to provide more information on the tight control and audit described please?
3.5) Further reasons affecting choice of treatment to be considered in the Discussion include the logistical challenges of administering remdesivir in the community (IV infusion over several days) and more recent concerns regarding the efficacy of sotrovimab against omicron variants of SARS-CoV-2.
Authors' reply: We commented on the low uptake of remdesivir in the discussion on page 22 lines 35-37:
"The low uptake of remdesivir may be explained by logistical challenges, as remdesivir is administered
intravenously in a three day course [5]."
We additionally commented on the concerns regarding the low efficacy of sotrovimab against Omicron
BA.2 in the discussion on page 22 lines 38-40 (see also comment 2.8):
"In addition, concerns were raised about the low efficacy of Sotrovimab against the Omicron BA.2 sublineage [20], the dominant circulating variant from mid-February [21]."
Minor points:
3.6) The 'Primary immune deficiencies' group was changed to 'Immune deficiencies' and includes patients with secondary antibody deficiency receiving, or eligible for, immunoglobulin replacement therapy. This should be updated. Even with this change, the numbers would not come close to those suggested for this group (see point 1 above).
Authors' reply: Also see our reply to comment 3.1. We changed the label of the 'Primary Immune Deficiency' group to 'Immune Deficiency' to better align the label with the group included and align with
the current group labels published by NHS Digital [6]. We additionally discussed that the groups in our study do not necessarily represent clinical groupings as a consequence of the methodological decision to
replicate, as closely as possible, the eligibility criteria for COVID therapeutics published by NHS Digital
within OpenSAFELY-TPP (see also comment 3.1).
3.7) The authors frequently refer to casirivimab + imdevimab as just 'casirivimab'. This is misleading and should be corrected.
Authors' reply: We changed all occurrences of 'casirivimab' to 'casirivimab/imdevimab' in the revised manuscript.
3.8) On Page 7, the authors use 'sotrovimab/remdesivir' – the slash is confusing here and might imply that the two treatments are given together: suggest replace with 'or'.
Authors' reply: We changed 'sotrovimab/remdesivir' to 'sotrovimab or remdesivir' in the revised manuscript.
3.9) Personally, I am not sure that the 'clinically extremely vulnerable' grouping is useful here. This is a
problematic term in itself, developed pragmatically at the start of the pandemic but without a clear scientific basis. The eligible population for community treatment via CMDUs was defined on the basis of
accumulated evidence in terms of risk from COVID-19 and capacity to benefit from treatment, and in some ways supersedes the CEV group. However, this is a minor point.
Authors' reply: We pragmatically selected groups to include in our key demographic and clinical characteristics section. These groups were selected if we have previously seen variations in care

throughout the pandemic for example during the COVID-19 vaccination campaign. We have added the
following to the methods to make it clear this is pragmatic selection on page 11 lines 50-53:
"Treated patients were also described according to whether they were in other pragmatically selected groups of interest who are sometimes subject to variation in care [...]"

Reviewer: 4
Comments to the Author
The authors present data from the first large analysis of non-hospitalised patients eligible for COVID-19
treatment in England using the OpenSAFELY-TPP database, covering 23.4 million people (~40% of the
English population), identifying the numbers of potentially eligible patients receiving treatment and demographic/clinical factors which may be associated with a lower proportion of patients being treated.
These are very important data for considering how to improve delivery of CMDU services moving forwards, in particular to address some of the potential health inequalities relating to geography, deprivation and ethnicity, that are highlighted by the manuscript. The manuscript deserves to be in the public domain asap. I have some minor comments and questions:
We thank the author for the positive comments.
4.1) The precise definitions in 'Appendix 1' of the interim clinical commissioning guidance went through
several iterations. It looks like the authors took one static list from towards the end of the study period. It may not make a large impact on the number of 'potentially eligible' patients, but it would be good to address this in case this impact the % of those treated.
Authors' reply: The reviewer makes a very reasonable point and for the purposes of this study we had
to pragmatically select a version to describe those patients at highest risk [23]. Updating the list in near
real time is technically feasible in OpenSAFELY however the guidance and criteria is not published in a
machine readable version so every change has to be manually converted from the information released
by the NHS to analytic code. Additionally EHR data available to us would not be able to necessarily capture all the subtleties of the definitions used in the guidance. We acknowledge this is a limitation. See
also our response at 3.1 above.
4.2) The authors state that some patients who were not deemed eligible were included in the study as they received treatment, the assumption being that miscoding led to them being erroneously considered
not eligible (4690 of the 102170). Could this have inflated the % treated metrics? Presumably it is hard
then to know what the true denominator of eligible patients are if coding were 100%? It would be worth
acknowledging this unless the authors can estimate what the rate of misclassification is.
Authors' reply: The untreated but misclassified as non-eligible are missed in the denominator, while the numerator includes the treated but misclassified as non-eligible. Depending on the number of people
not in our denominator, this may lead to inflated percentages treated. Our analysis investigating the clinician-assigned high risk group of the treated without EHR-derived high risk group, showed there was
differential misclassification across the high risk groups (the majority had a clinician-assigned high risk group of Immune-mediated inflammatory disorder or Solid cancer). We additionally do not know whether the misclassification in the treated is comparable to the misclassification in the untreated. Strong assumptions are therefore needed to correct our estimates for these misclassification errors and
consequently, we do not regard these corrected estimates as informative. We therefore decided to add
this as a limitation to our manuscript on page 21 lines 42-46:

"Because of our decision to include the treated and erroneously classified as ineligible people in our numerators but the impossibility of including the untreated and erroneously classified as ineligible in our
denominator, the estimated coverages of nMABs and antivirals are likely to be be inflated."
4.3) It is hard to get a sense of how granular the NHS digital and associated code lists are. Specifically,
whether they capture the precise definitions in the highest risk categories or broader groups. This is important for several reasons. Firstly, it may give an indication of what proportion of non-treatment is due to patients not actually being eligible when assessed by a clinician, based on their disease state. See
the preprint of a service evaluation in 4 CMDUs (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4123333), where only 17% of those referred were deemed to be eligible. This is similar to the % treated in the OPENSAFELY data.
4.3.1) The authors should discuss and reference this.
Authors' reply: We refer to Supplementary material Table S1 for an overview of how the high risk groups were defined by NHS Digital and the codelists used in our study. We thank the reviewer to pointing us to this important service evaluation, which we discussed and referred to in our discussion on
page 21 lines 46-52:
"*The codelists used are inclusive but not specific, and as a consequence these groups do not represent*
strict clinical groupings. ***This is in accordance with a service evaluation of CMDUs in four regions***
across England *[22]****, showing that the most common reason for being ineligible was not being in an at-risk clinical group.*** *The service evaluation found that 17% of the patients referred to CMDUs*
were judged eligible for treatment, which is in line with the coverage found in our study (20%)."
4.3.2) Secondly, are there differences in how accurately NHS digital can define eligibility across different
diseases? For example is it easier with coded data to precise identify all the renal disease patients compared to the haematological disease patients? If so, this may have some impact on the differences in
% treated across disease groups.
This latter point may just be one for discussion, but the authors should provide some idea of how precise
the coding is across different disease categories.
Author's reply: We comment in our discussion on the suspected differences in the accuracy of identifying people in different at-risk groups in EHR data on page 21 lines 27-34:
"EHR data may not always fully capture some eligibility criteria and as such, may underestimate the true
number of eligible people in some groups or misclassify some people, particularly those identified through "non-digital" routes, e.g. patients with kidney disease. Related to this, as previously described,
we may not have ascertained all people in the Immunosuppression due to HIV/AIDS group due to specific arrangements around HIV data."
We are unfortunately unable to compare our method of identification with NHS Digitals.
4.4) Is there any way to look at the number of CMDUs serving different areas to see if geographical distribution/per capita population had an impact on the % treated?
Author's reply: In our view, the per capita population per CMDU should not matter but the number of people in the eligible population could matter. We pragmatically used STP membership to illustrate geographical variation. The full list of CMDUs in England is available (https://digital.nhs.uk/coronavirus/covid-medicine-delivery-unit-directory?key=h58vqkRUup40o27K04xOrtfh7ZXqwRQoOLhXTkGWlbOrVSkwzfTeetw39uGFlc28) and most regions have 1 or 2 CMDUs at the
time of the original manuscript.
We agree it is an interesting idea to study whether the size of the eligible population affected coverage
of nMABs or antivirals and indeed, the organisational factors associated with high/low coverage may inform further rollout of the programme. However this is outside the scope of this study and assembling

organisational information on new NHS CMDU units was not possible during a fast roll-out campaign.
4.5) Where there are data on symptom onset and PCR time, is it possible to see whether time between
these two variables were associated with the % not treated? I realise that the design of this study does
not allow teasing apart of why patients were not treated, but this could given an indication of how much
was related to time to presentation and being out of window.
Authors' reply: We unfortunately do not have data on time between symptom onset and PCR test. We
only know if a patient's positive test had a 'symptomatic' flag or not.
4.6) Box 2: While the overall cohort names are correct, the authors have selectively chosen 1 or 2 criteria within these to further expand the descriptive terminology. In some cases this is appropriate but
in others, it is a bit odd to say 'such as those with sickle cell disease' in the haematological disease and
SCT, given the whole group is very diverse. I would have just the main category names in 'Appendix 1'
of the clinical commissioning guidance and full details in Supplementary. Make it clear that the highest risk subgroups within these cohorts were those identified as eligible. Using the same descriptors as in Table 1 would be appropriate.
Authors' reply: References to 'sickle cell disease' in our manuscript point to the results from Table 2. In
this table, treated patients were described according to whether they were in other groups of interest who are sometimes subject to variation in care. Sickle cell disease and clinically extremely vulnerable were, however, erroneously omitted from the listed groups in our methods section, and are added in the
revised manuscript accordingly on page 11 lines 50-55:
"Treated patients were also described according to whether they were in other pragmatically selected groups of interest who are sometimes subject to variation in care, including autism, dementia, learning disability, serious mental illness, care home residents, and housebound, ***clinically extremely vulnerable and sickle cell disease****."*
4.7) Authors state that they assessed consistency with treatment-specific criteria such as contraindications. I assume that the granularity of data available did not allow assessment of contraindications to Paxlovid due to drug-drug interactions?
Authors' reply: A lot of the drugs for which Paxlovid is contraindicated may be prescribed in secondary
care (e.g. cancer immune therapies, transplant immunosuppression, hepatitis C antivirals) and translating Paxlovid's contraindications, interactions profile and side-effects is a substantial piece of work which is outside the scope of this coverage paper.
We are currently preparing another analysis on the safety of these COVID-19 treatments where we will
use the granular data in OpenSAFELY to assess the safety of these treatments.

Reviewer: 5
Comments to the Author
I've screened this from a statistical point of view, and do not have any comments or suggestions. This is
an important, largely descriptive study (without substantive analyses or models), and is well presented and with a clear message.
Authors' reply: Thank you for your positive appraisal.

VERSION 2 – REVIEW

REVIEWER 3	Lowe, David; UCL, Institute of Immunity and Transplantation. Competing Interest: Personal fees from Gilead for an educational video on COVID-19 in immunodeficiency, from Merck for a

	roundtable discussion on risk of COVID-19 in immunosuppressed patients and speaker fees from Biotest. Support to attend a conference (to deliver an educational talk) from Octapharma. Research grants from GSK, Bristol Myers Squibb, NIHR, MRC, Blood Cancer UK and the British Society for Antimicrobial Chemotherapy.
REVIEW RETURNED	08-Nov-2022

GENERAL COMMENTS	Many thanks to the authors for revising their manuscript – all but one of my points have been well addressed. However, I still have concerns about the denominators in some of the groups, eg immune deficiencies (and probably immune-mediated inflammatory disorders) as they remain extremely high. I have reviewed the NHS Digital codelist provided (many thanks). The 'Immunosuppression PCD Cluster' includes many types of haematological malignancy, complications of HIV, some types of solid malignancy etc. I assume that these diagnoses were not counted as part of the 'immune deficiencies' group, otherwise many patients will have been counted twice. The codelist also includes many people on immunosuppressive treatments who are likely to have been part of another group (eg IMID) – again, I assume they have not been counted twice. Yet if all malignancy, HIV and medication-related conditions are removed from this codelist you are left with a collection of rare disorders which cannot come anywhere close to the numbers suggested. However, I note that there is a category in the codelist simply labelled 'immunosuppressive therapy (procedure)' – I am not sure on the timescale of prior treatments captured by this or which medications are captured, but perhaps this helps to explain the size of the group. For example, if this coding includes patients treated historically or with weakly immunosuppressive medication, this could be a large number who should not have been eligible for CMDU treatment. I wonder if the authors can comment on this. The authors do now indicate in the Discussion that the main reason why people were 'untreated' is likely to be because they were incorrectly captured by the codelist and were in fact ineligible for treatment anyway. However, I think this message could be clearer. I also think it is important to state that some of the group sizes (eg Immune deficiencies) are likely to be very significant over-estimates due to the coding. Otherwise, I worry that one of the main interpretations of the manuscript will be that only 20% of people who 'should' be treated are actually receiving the medication – this will not inspire confidence among patient groups etc.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Comments to the Author

Many thanks to the authors for revising their manuscript – all but one of my points have been well addressed.

Authors' reply: We thank Dr David Lowe for their positive and detailed feedback and would be happy to discuss general issues raised by this manuscript directly upon completion of the peer review process.

1.1) However, I still have concerns about the denominators in some of the groups, eg immune deficiencies (and probably immune-mediated inflammatory disorders) as they remain extremely high.

I have reviewed the NHS Digital codelist provided (many thanks). The 'Immunosuppression PCD Cluster' includes many types of haematological malignancy, complications of HIV, some types of solid malignancy etc. I assume that these diagnoses were not counted as part of the 'immune deficiencies' group, otherwise many patients will have been counted twice. The codelist also includes many people on immunosuppressive treatments who are likely to have been part of another group (eg IMID) – again, I assume they have not been counted twice. Yet if all malignancy, HIV and medication-related conditions are removed from this codelist you are left with a collection of rare disorders which cannot come anywhere close to the numbers suggested.

However, I note that there is a category in the codelist simply labelled 'immunosuppressive therapy (procedure)' – I am not sure on the timescale of prior treatments captured by this or which medications are captured, but perhaps this helps to explain the size of the group. For example, if this coding includes patients treated historically or with weakly immunosuppressive medication, this could be a large number who should not have been eligible for CMDU treatment.

I wonder if the authors can comment on this.

Authors' reply: Patients have not been counted twice in the overall potentially eligible population if they were identified as members of more than one at-risk group. People can however appear in more than one at-risk group in Table 1, as stated in the caption. The aim of our paper was to replicate the eligible criteria as used by NHS Digital as closely as possible and we therefore did not strive to make the at-risk groups mutually exclusive. People were flagged as eligible if they have been treated with immunosuppressive therapy on or before the date that they were tested positive.

1.2) The authors do now indicate in the Discussion that the main reason why people were 'untreated' is likely to be because they were incorrectly captured by the codelist and were in fact ineligible for treatment anyway. However, I think this message could be clearer. I also think it is important to state that some of the group sizes (eg Immune deficiencies) are likely to be very significant over-estimates due to the coding. Otherwise, I worry that one of the main interpretations of the manuscript will be that only 20% of people who 'should' be treated are actually receiving the medication – this will not inspire confidence among patient groups etc.

Authors' reply: We agree with the reviewer that the coverage of 20% found in our paper needs to be interpreted with caution and have made amendments to the abstract and manuscript described below. However we think the reviewers concerns are best addressed to NHS England and NHS Digital who set the eligibility criteria and provided codelists that we used (as we have done and described in the manuscript).

We added a sentence to our abstract to make readers aware of this important nuance:

"In the context of a rapid deployment of a new service, the NHS analytic code used to determine eligibility may have been overinclusive and some of the eligibility criteria not fully captured in health care data."

To make the message more clear, we changed the order of our discussion and addressed the inclusivity of our used codelists as a self-contained issue.

"First, the codelists used are inclusive but not specific, and as a consequence these groups do not represent strict clinical groupings. People identified as potentially eligible in our study may not be in the identified at-risk group because of overinclusion within the NHSD codelists used (e.g. immune deficiencies). A service evaluation of CMDUs in four regions across England [25] showed that the most common reason for being ineligible on presentation to CMDUs was not being in an at-risk clinical group. The service evaluation found that 17% of the patients referred to CMDUs were judged eligible for treatment, which is in line with the coverage found in our study (20%)."