Coverage of neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19: Study Protocol

Version: v1.2

Date: 24 January 2021

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Background

While vaccines remain the best strategy to prevent COVID-19, recent evidence suggests monoclonal antibodies (nMABs) or antivirals could potentially benefit certain vulnerable populations before or after exposure to SARS-CoV-2, such as the unvaccinated or recently vaccinated high-risk patients.

On 16th December 2021, new COVID Medicine Delivery Units (CMDUs) were launched across England, offering antiviral medicines and neutralising monoclonal antibodies (nMABs) as treatment to patients with COVID-19 at high risk of severe outcomes in outpatient clinics or their own home[1]. Initially sotrovimab, casirivimab/imdevimab, and molnupiravir were available at these units with nirmatrelvir/ritonavir (Paxlovid) and remdesivir becoming available in February 2022. The UK government established an expert clinical group to develop criteria to support identification of high risk groups eligible for these treatments using NHS data[2]. The NHS in England issued detailed clinical commissioning policies[3] and people identified as high risk were informed by letter that in the event that they test positive for SARS-CoV-2 they would be eligible for these treatments.

With the rollout of these new treatment opetions, there is an urgent need for knowledge and understanding around the use of nMABs and antivirals in the treatment of patients with COVID-19, such as factors of relevance in determining who receives an nMAB or antiviral.

Objectives

Primary Objective

The main aim of this study is to assess the coverage of nMABs and antivirals in all patients registered with a TPP practice in England, with COVID-19, in near real time; and to describe how coverage varied between geographical areas, and between key clinical and demographic subgroups.

Secondary Objectives

This study also aims to:

1. Determine the uptake of treatments to ensure that they are being used in line with guidance (including describing any breaches in guidance on who is getting treatments and patients co-administered mabs/antivirals with a medication that potentially interacts)
2. Describe how the different interventions vary between clinical and demographic subgroups.

Methods

Data

We will use data from general practice (GP) records, obtained from the GP software provider TPP, linked to:

- Second Generation Surveillance System (SGSS) data on SARS-CoV-2 test results;
- Secondary Uses Service (SUS) data on hospital admissions (Admitted Patient Care Statistics (APCS) dataset);
- Death registration data held by the Office for National Statistics (ONS), including date and ICD-10 coded cause of death for all deaths occurring in England and Wales;
- A Patient-level dataset on nMABs and antiviral treatments, sourced from NHS England.

The data will be accessed, linked and analysed through openSAFELY.org - a data analytics platform created by our team on behalf of NHS England to address urgent questions relating to the epidemiology and treatment of COVID-19.

Study Population

The base population will consist of all patients registered with a general practice using TPP in England on 16th December 2021 (the start of the roll out of nMABS and antiviral for COVID patients in England). Patients with unknown date of birth (that is default age >121 years) or unknown sex will be excluded. Follow-up will start on the 16th December 2021 and continue until [the most recent date with adequate data coverage], death or deregistration.

Eligibility criteria for nMABS and antivirals

We will identify the population who are potentially eligible for treatment as those meeting the eligibility criteria for COVID-19 antiviral or nMAB treatment in the community, as per the Interim Clinical Commissioning Policy (published on 24th February 2022) [3] pre hospitalised adults and children (aged 12 years and above). Details on how we will implement these eligibility and exclusion criteria can be seen in Table 1.

Table 1: Eligibility and exclusion criteria, as per the Interim Clinical Commissioning Policy (published on 24th February 2022)[3] **for non-hospitalised COVID-19 patients, and how these were applied in the present study.** Earlier versions of the policy had some minor differences but this version was applied to the whole study period.

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Eligibility/Exclusion Criteria		**Criteria applied in present study***
Eligibility Criteria	SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) testing OR Lateral flow test (registered via gov.uk or NHS 119)	Positive PCR OR lateral flow SARS-CoV-2 test in SGSS. (As per NHS Digital's tests rule set logic[2], patients with a prior positive SARS-CoV-2 within the last 30 days will be excluded.)

	Symptomatic with COVID-19 and showing no signs of clinical recovery	Not possible[†1]
	Patient was a member of a 'high risk' group.	See Table 2
Exclusion criteria	Requirement for hospitalisation for COVID-19	Discharged from hospital within 30 days prior to positive test or treatment, where COVID-19 was the primary diagnosis.
	New supplemental oxygen requirement specifically for the management of COVID-19 symptoms	Not possible
	Known hypersensitivity reaction to the active substances or to any of the excipients of the medications below as listed in their respective Summary of Product Characteristics	Not possible

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

[†1] It was only possible to identify whether or not the patient's positive test had a "symptomatic" flag, but not whether symptoms developed later; therefore the symptomatic flag was used in a sensitivity analysis rather than within inclusion criteria.

High risk groups

Box 1 shows the high risk patient cohorts which were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC). It also gives details on the codelists used by NHS Digital when creating the digital rule logic used to identify people within England who are at most risk of developing severe complications of COVID-19 infection [2]. In order to replicate and identify any possible discrepancies in the eligibility criteria derived for those people most at risk of developing the severe effects of COVID-19 infection, where possible, these codelists have been uploaded to OpenCodelists [4].

Box 2: Patient groups considered at higher risk from COVID-19 and to be prioritised for treatment with antivirals and nMABs, as determined by an independent advisory group commissioned by the UK Department of Health and Social Care (DHSC)[3]**.**

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

nMABS and antivirals

As of 24th January 2022, two possible treatment types are in circulation for those people most at risk of developing the severe effects of COVID-19 infection; sotrovimab (nMAB) and molnupiravir (oral antiviral). Eligible patients, as outlined above, should initially have been considered for treatment with an nMAB. Where an nMAB was contraindicated or the administration of an nMAB was not possible, patients are likely to have been treated with a five-day course of an antiviral.

Descriptive statistics

Coverage of COVID-19 treatment

Simple descriptive statistics (frequencies and percentages; means and quantiles) will be used to describe eligible patients and those going on to receive treatment. This will include calculating cumulative totals of COVID-19 treatment recorded in OpenSAFELY-TPP, starting on the 16th December, up until [the most recent date with adequate data coverage] and generating step charts of treatment coverage, stratified by the high risk groups.

Key demographic and clinical characteristics of treated patients

To highlight any inequalities in patients receiving treatment, the proportion of eligible people receiving treatment (as of [the most recent date with adequate data coverage]) in each of the following categories will be calculated:

- **Demographic**; age, sex, ethnicity, IMD, region, CMDUs/ICS
- **Clinical**; asplenia, asthma, blood pressure, cancer (non-haematological), chronic kidney disease, diabetes, obesity (most recent adult body mass index (BMI) ≥30), dialysis, heart disease, haematological malignancy, immunocompromised, learning disability, liver disease, neurological diseases, respiratory disease, severe mental illness, transplant
- **Other**; previous CEV lists, vaccine status, vaccine eligibility, SARS-CoV-2 test type, prior SARS-CoV-2 infection, recent prescription of a medication that potentially interacts with an antiviral

Delivery of nMAB and antiviral treatment

To determine which modality seems preferred and to describe any potential preferences in treatment type given/received, we will calculate the proportion of eligible people receiving each treatment, stratified by the high risk cohort and region. To help understand any possible trends, weekly usage incidence by high risk group will be calculated and plotted.

Consistency with guidance

Simple descriptive statistics (frequencies and percentages; means and quantiles) will be used to describe any breaches in guidance in terms of:

- Non-eligible patients receive treatment and potential explanations as to why, such as time between eligibility date and treatment date and SARS-CoV-2 test type
- Patients receiving treatment who have a contraindication, such as renal patients and paxlovid
- Children receiving molnupiravir as a treatment (molnupiravir is only licensed for adults aged 18 years and above)

In the near future, it is possible that additional data will become available on patients who are offered treatment, but do not go on to receive it, and the reason why. If and when this data becomes available, simple descriptive statistics will be used to describe the most likely reasons for non-treatment uptake. Where numbers allow, these will be stratified by demographic and clinical characteristics.

Time to treatment

While descriptive summaries involving time to treatment will be made difficult due to the possible inaccuracies in the recording of SARS-CoV-2 test and treatment initiation dates (along with the speed of data flow and testing time), we will calculate the mean and IQR of time to treatment for treated patients, stratified by high risk cohort.

References

1 Department of Health and Social Care. UK's most vulnerable people to receive life-saving COVID-19 treatments in the community. GOV.UK. 2021.https://www.gov.uk/government/news/uks-most-vulnerable-people-to-receive-life-saving-covid-19-treatments-in-the-community (accessed 23 Feb 2022).

2 Population health: COVID-19 treatment methodology. NHS Digital. https://digital.nhs.uk/coronavirus/treatments/methodology (accessed 22 Jan 2022).

3 England NHS. Interim clinical commissioning policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. NHS England. 2022.https://www.england.nhs.uk/coronavirus/documents/c1603-interim-clinical-commissioning-policy-antivirals-or-neutralising-monoclonal-antibodies-for-non-hospitalised-patients-with-covid-19-version-5/ (accessed 1 May 2022).

4 OpenCodelists. https://www.opencodelists.org/ (accessed 13 Dec 2021).