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Proceeding Paper

Surveillance and Stewardship Approaches for COVID-19 Novel Therapeutics in England from 2021 to 2022 (ESPAUR Report) †

Alessandra Løchen [1,*], Hanna Squire [1], Diane Ashiru-Oredope [1], Kieran S. Hand [2], Hassan Hartman [1], Carry Triggs-Hodge [1], Holly Fountain [1], Sabine Bou-Antoun [1], Alicia Demirjian [1,3,4] and Sarah M. Gerver [1,*]

1 United Kingdom Health Security Agency (UKHSA), London NW9 5EQ, UK
2 Medical Directorate, NHS England, London SE1 8UG, UK
3 Department of Paediatric Infectious Diseases and Immunology, Evelina London Children's Hospital, London SE1 7EH, UK
4 Faculty of Life Sciences and Medicine, King's College London, London WC2R 2LS, UK
* Correspondence: alessandra.lochen@ukhsa.gov.uk (A.L.); sarah.gerver@ukhsa.gov.uk (S.M.G.)
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Abstract: The UK Health Security Agency's (UKHSA) COVID-19 therapeutics programme was commissioned by the Department of Health and Social Care with the remit to evaluate the use and role of COVID-19 treatments. COVID-19 therapeutics data were assessed from two main data sources: novel therapy requests via Blueteq and medicines supply data via Rx-info. The five COVID-19 therapies in use in England between 1 October 2021 and 31 March 2022 included nirmatrelvir plus ritonavir, remdesivir, molnupiravir, sotrovimab, and casirivimab with imdevimab. During this time period, treatment requests for novel therapies against COVID-19 were submitted for nearly 52,000 patients in England. The UKHSAs COVID-19 therapeutics programme has been key to supporting the deployment of novel COVID-19 therapies in England by undertaking genomic, virological, and epidemiologic surveillance, through both national surveillance systems and academic collaboration. Effective therapies are particularly important for protecting the health of patients at greater risk of developing severe COVID-19. This national surveillance and stewardship programme was successfully rolled out at pace at the start of the pandemic and leads on work nationally to reduce the development of resistance. These findings were presented at the ESPAUR Report webinar on 23 November 2022.

Keywords: COVID-19 novel therapeutics; neutralising monoclonal antibodies; antivirals; COVID-19; antimicrobial stewardship

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1. Introduction

In March 2020, the World Health Organisation (WHO) declared coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a Public Health Emergency of International Concern. Coordinated international efforts identified therapeutic candidates to treat severe illness from COVID-19, and since late 2020, England has had five direct-acting antiviral agents added to the clinical commissioning policy. These were three antivirals: nirmatrelvir plus ritonavir (Paxlovid), remdesivir (Veklury), and molnupiravir (Lagevrio), and two neutralising monoclonal antibody therapies (nMAbs): sotrovimab (Xevudy) and casirivimab with imdevimab (Ronapreve). The annual English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report, Chapter 7, commentates on the UK Health Security Agency's (UKHSA) COVID-19 therapeutics programme [1,2].

2. Methods

The UKHSA COVID-19 therapeutics programme was commissioned by the Department of Health and Social Care with the remit and objective to evaluate the use and role of COVID-19 treatments. COVID-19 therapeutics data were assessed from two main data sources: Blueteq and Rx-info. The Blueteq system supports the management of high-cost drugs for NHS England and, as such, contains clinical requests made for neutralising monoclonal antibodies (nMAB) and antiviral therapies used for the treatment of patients with COVID-19 who fall in the remit of the clinical commissioning policy. Not all treatment requests may have resulted in patients receiving treatment with these drugs; this is the most informative data source in the absence of patient-level prescribing data. The Rx-info data contain medicines supply data from all NHS acute hospital Trusts, including standardised transactional data on the procurement, stock-holding, and issuing of medicines by NHS Trusts, and therefore provides a picture of the total usage of COVID-19 therapeutics in England. COVID-19 therapeutics treatment requests were extracted from the Blueteq system on 22 August 2022 and medicines supply data in England via Rx-info on 12 June 2022, for the period 1 October 2021 to 31 March 2022, was inclusive and covered the five direct-acting antiviral agents in use in England during this period. The date of treatment recorded in the Blueteq data was used for treatment requests. Not all of these therapeutic agents were available throughout the whole period (Figure 1).

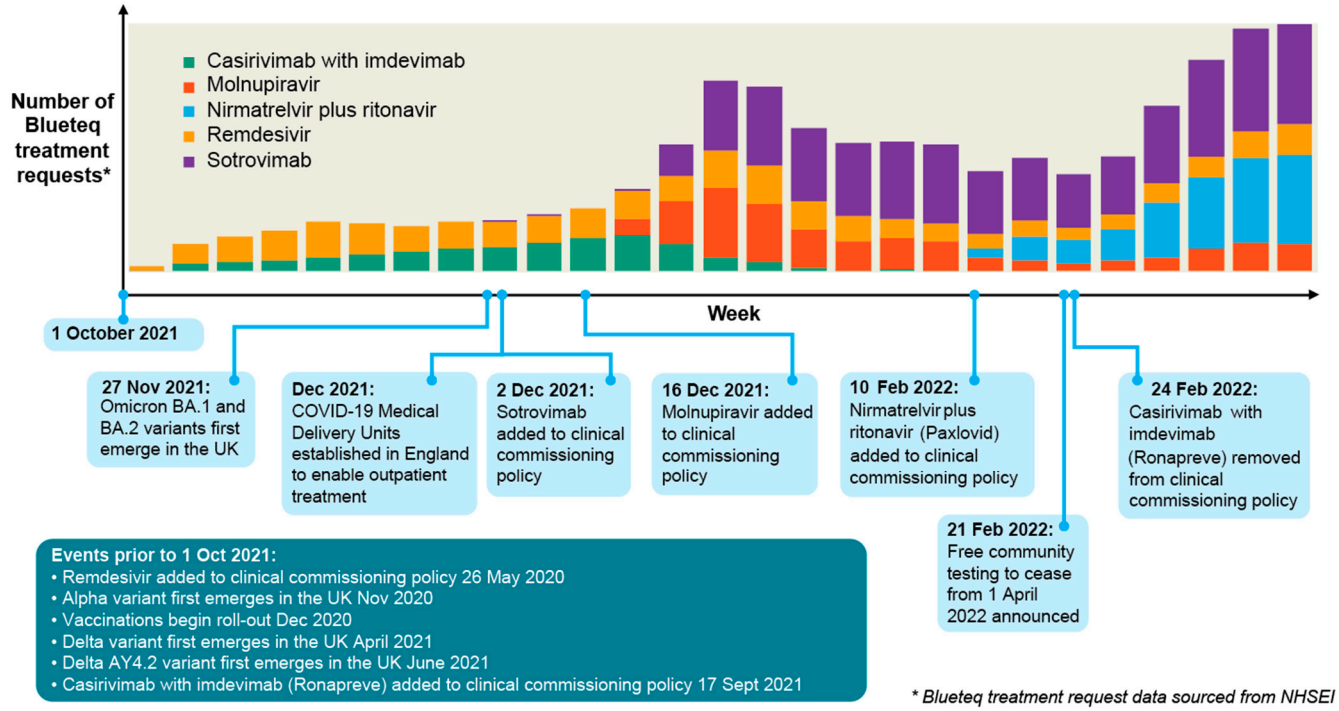

Figure 1. COVID-19 therapeutic Blueteq treatment requests by week (1 October 2021 to 31 March 2022) and a timeline of events.

Data from Blueteq patient treatment requests were cleaned (for non-approved entries, invalid NHS numbers, or duplicate entries) and linked to demographic, vaccination (National Immunisation Management Service [NIMS] dataset), hospital stay (Emergency Care Dataset and Secondary Uses Service (SUS) hospital data, the spell during which the patient received therapy), mortality data (as described in [3]), and viral genomic and mutations data, to provide patient-level epidemiological data on the use of these new therapeutic agents and the patients treated in England. Data were deterministically linked using NHS number. Treatment requests data were at the patient level.

Rx-info data captured the number of medicines dispensed daily (Virtual Medicinal Product [VMP] quantity in daily dispensed grams), and the use of these key therapies by NHS acute Trusts and regionally is described in [2]).

At the time of compiling this report, data on the number of patients eligible to receive COVID-19 therapeutics were unavailable to UKHSA, and so population data taken from the Office of National Statistics annual mid-year population estimates and number of persons with COVID-19 in that group over the specified period were used as denominators for rate calculations.

Comparisons of treated patients (Blueteq treatment requests) and medicines supplied (Rx-info medicine supply data) were completed by calculating the total grams of nMABs and antivirals that have an approved Blueteq request form (estimated from expected duration and dose) against the grams dispensed from Rx-info. Standardised doses for each therapy were used to calculate Rx-info usage [2]. The differences in grams between the two sources was calculated to highlight discrepancies in the total medicines supply and treatment requests. This analysis was completed for England, and also by NHS region, taking into account the stock provided to centres.

STATA 15 was used in all medicines supply data analysis. R was used in all other analyses.

3. Results

3.1. Treatment Requests (BlueTeq data)

Between 1 October and 31 March 2022, 51,962 treatment requests for neutralising monoclonal antibodies and antivirals against COVID-19 were made in England. Of these, sotrovimab had the highest number of treatment requests and made up almost 38% (n = 19,749 requests) of all English treatment requests.

The usage of COVID-19 therapies varies by age, sex, ethnicity, NHS region, and index of multiple deprivation (IMD). Overall request rates have shown a large range between NHS England regions (Table 1). The east of England had the highest rate of treatment requests per 100,000 population and per 100,000 COVID-19 cases; these accounted for approximately twice those observed in the northwest. In addition, the southeast, while having a higher treatment request rate per 100,000 population than the northeast and Yorkshire, had a lower rate per 100,000 COVID-19 cases. Regional differences in the establishment of COVID-19 Medical Delivery Units, responsible for outpatient treatment, and in the COVID-19 case rates, may have impacted the treatment rates per 100,000 COVID-19 cases. These findings highlight regional variations in COVID-19 reported cases that may impact treatment request rates.

Table 1. Number, percentage, and rate (per 100,000 population and per 100,000 COVID-19 cases) of treatment requests in Blueteq by NHS Region between 1 October 2021 and 31 March 2022.

NHS Region	No. Requests	Percent	Rates per 100,000 Population	Rates per 100,000 COVID-19 Cases
East of England	7967	15%	121.4	589.1
London	9910	19%	110.1	587.5
Southwest	6018	12%	106.2	522.8
Southeast	8161	16%	91.3	436.2
Northeast and Yorkshire	7115	14%	82.4	447.3
Midlands	8552	16%	80.2	433.7
Northwest	4178	8%	58.9	311.7

While differences exist in the number of treatment requests between males and females in corresponding age groups, males and females did not differ significantly in the rate of treatment requests per 100,000 COVID-19 cases in age–sex categories.

The breakdown in therapeutic agent requests by ethnicity, despite small numbers in some ethnic groups, indicates a divergence in treatment choice between the White, Indian, and Mixed ethnic groups compared to the Black, Pakistani, and Other Asian groups. While

the distribution of treatment requests is comparable between the White, Indian, and Mixed ethnic groups, a larger percentage of treatment requests for the Black, Pakistani, and other Asian groups are for remdesivir (over 30% compared to 18–20% for these other ethnic groups). Sotrovimab makes up less than 30% of requests in the Black group compared to White, Indian, and mixed ethnic groups, where it makes up 40–47% of requests.

When assessed by IMD decile, treatments commonly used in the community, such as nirmatrelvir plus ritonavir and sotrovimab, have a higher percentage of requests for patients from the most deprived areas compared to those from the least deprived areas, whereas treatments commonly administered in hospitals, such as remdesivir and casirivimab with imdevimab, show the reverse pattern.

3.2. Comparison of Treatment Requests with Rx-Info Medicines Supply Data

For all COVID-19 therapeutics, there was an apparent excess of grams dispensed according to Rx-info data compared to the grams expected from Blueteq requests for all months where the therapy was in use. Remdesivir generally had the highest percentage of excess Rx-info use (ranging 45–59% across the months it was in use), whereas sotrovimab (16–26%) and nirmatrelvir plus ritonavir (21–23%) had the lowest range of excess Rx-info usage across the months they were in use.

3.3. Genomic Surveillance

Treatment-emergent SARS-CoV-2 mutations were screened for by comparing the sequenced samples from patients before (>5000) and after treatment (>1400) and identifying significant changes in mutation frequencies between the pre- and post-treatment samples. The analysis was stratified by treatment and variant and yielded eleven mutations from Delta samples treated with casirivimab with imdevimab, BA.1 and BA.2 samples treated with sotrovimab, and Alpha samples treated with remdesivir [1].

4. Discussion

The UKHSAs COVID-19 therapeutics programme has supported the deployment of novel COVID-19 therapies in England by undertaking genomic, virological, and epidemiological surveillance and stewardship approaches, through both national surveillance systems and academic collaboration. Effective therapies are particularly important for protecting the health of patients at greater risk of developing severe COVID-19. Genomic surveillance has allowed for the rapid identification of mutations and variants associated with a resistance to certain therapeutics. This national surveillance and stewardship programme was successfully rolled out at pace at the start of the pandemic and contributes to work nationally to reduce the development of resistance. The programme has provided an evidence base to guide clinical commissioning policies for COVID-19 therapeutics. For example, epidemiological surveillance directly informed national discussions on the use of sotrovimab for the treatment of Omicron BA.1 versus BA.2 after the US Food and Drug Administration removed the therapy for use against Omicron BA.2 based on laboratory analyses. This helped ensure that patients were receiving the most effective treatments available.

Absolute numbers of treatment requests from Blueteq showed variation by NHS region, age, sex, ethnicity, and IMD by therapeutic agent, although denominator data were not available for each subgroup. Therapeutic treatment requests largely followed the trends that would be expected within the context of the setting they were administered in. For instance, remdesivir, which is commonly used in the hospital setting, had more treatment requests during the Delta wave than the Delta sublineagee AY4.2 wave, as the Delta variant had higher hospitalisation rates. Furthermore, a divergence in the crude number of treatment requests by intervention and by setting between certain ethnic groups and between the least versus most deprived groups highlights the need to explore differential access by way of comparison using a denominator dataset with the total eligible population. Overall, the interpretation of the work presented here is limited as it uses the overall population; therefore, differences between sub-populations merit further exploration to

understand whether they are significant based on treatment eligibility. This highlights the need for the work that NHSE conducts, through its NHS Foundry platform and beyond, to rapidly deploy antiviral agents and manage operational delivery and performance, complemented by UKHSAs therapeutic surveillance.

One key finding on the usage of COVID-19 therapies is that there is a discrepancy between the treatment requests (Blueteq) and the medicines supply data (Rx-info). Whereas Blueteq captures patient-level applications for the renumeration of high-cost medicines, Rx-info captures stock movements within hospital pharmacies and potentially provides a more comprehensive picture of usage. The use of standardised doses for Rx-info data may account for some of the discrepancies between BlueTeq and Rx-info usage where varying doses or treatment durations are used in practice. Despite these limitations, the addition of the Blueteq system to the toolkit of antimicrobial resistance is a helpful and welcome one and can be used as a blueprint for the roll out of new antimicrobial agents in the future.

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