

Evolving role of novel COVID-19 Medicine Delivery Units

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COVID-19 rapidly evolved into a global pandemic, initially without available preventative or therapeutic interventions. The licensing and provision of outpatient treatments in the UK since December 2021 has caused a paradigm shift in our approach to treatment of COVID-19 infection.¹ This involves a three-pronged approach to target COVID-19 at multiple stages of the pandemic lifecycle: preventative vaccines, early pre-emptive treatments following COVID-19 diagnosis and inpatient therapeutics in severe disease.

Early outpatient treatments have been enabled in the UK through novel nationwide COVID-19 Medicine Delivery Units (CMDUs). The prior identification of high-risk individuals by general practitioner (GP) surgeries has enabled direct provision of medication to vulnerable outpatients. In England, CMDUs benefit from integrated information from primary care with NHS Digital. There are similar processes in the devolved nations. At the time of writing, National Health Service (NHS) England has written to all those recognised as at 'highest risk' of severe COVID-19. On receipt of a positive COVID-19 PCR or reporting of a positive lateral flow test (LFT), they are automatically referred to their nearest CMDU ([figure 1](#)). This novel system avoids burdening already pressured GP surgeries with the role of screening patients and prescribing eligible treatment.

However, this system may miss many individuals: those who struggle to report results online, of no fixed abode or those without NHS healthcare records. Instead, such patients may interact with medical services through primary care, emergency departments or NHS 111. Clinician awareness of CMDU referral pathways is important to ensure high-risk patients are offered suitable pre-emptive COVID-19 treatment. This is particularly important for newly diagnosed patients as there is lag in updating the NHS

digital list of clinical extremely vulnerable patients. During this period, primary care physicians need to refer directly to CMDUs. Eligibility criteria and access to pre-emptive treatments are regulated according to the Clinical Commissioning Guidelines, with a nationwide list of CMDUs and their referral details found online at NHS Directory.¹ To date, the UK antivirals taskforce has currently enabled four therapeutics licensed for pre-emptive outpatient intervention in COVID-19 infection: sotrovimab, nirmatrelvir/ritonavir, remdesivir and molnupiravir ([table 1](#)).

Sotrovimab, a neutralising monoclonal antibody (nMAB) administered as a single infusion, is one of two first-line interventions. Many monoclonal antibodies in existing use, such as tocilizumab, act on the host and cause immunosuppression.² Sotrovimab acts exclusively against the virus. This is one of a new class of nMABs which do not cause host immune suppression. The COMET-ICE trial showed a relative risk reduction of 85% ($p=0.0002$) in rates and hospitalisation and death compared with placebo.³ Overall, sotrovimab has an excellent tolerability and safety profile with minimal drug interactions, making it suitable for most patients. A drawback is potential for infusion reactions, and it therefore must be given with adequate clinical supervision.⁴

An alternative first-line option for pre-emptive treatment in COVID-19 is the oral therapeutic nirmatrelvir/ritonavir (Paxlovid), which can be delivered to patients' homes as a 5-day course. The doorstep delivery ensures broad access for people who would otherwise be unable to collect the medication. Nirmatrelvir/ritonavir demonstrated an 89% reduction in hospitalisation in the EPIC-HR trial.⁵ It requires careful prescribing due to the possible complications of CYP3A4 inhibition by ritonavir; indiscriminate drug retention results in contraindications with many drugs metabolised by the liver. Severe liver and kidney disease are further contraindications.



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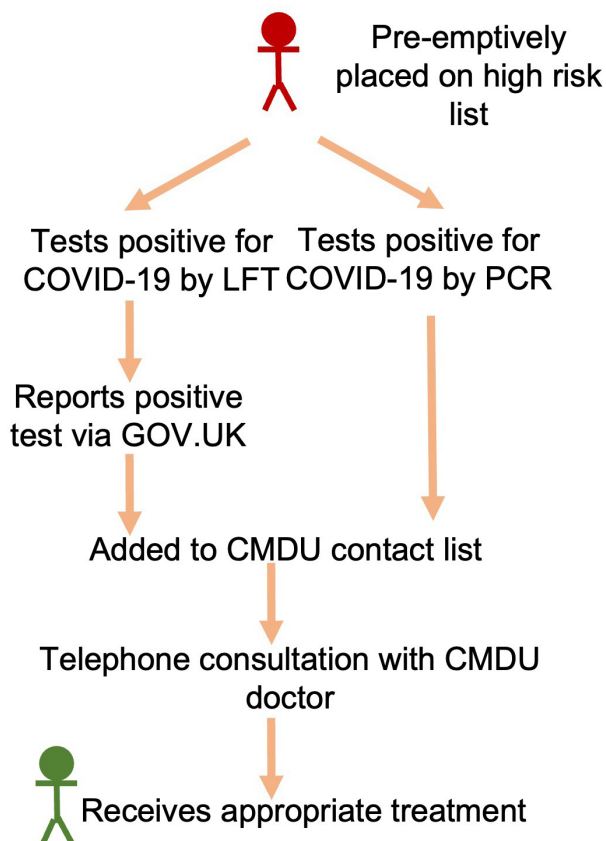


Figure 1 Referral pathway for COVID 19 Medicine Delivery Unit (CMDU) .

CMDUs provide critical advice to ensure these medications are taken correctly as they are prescribed as separate capsules which must be taken at the same time. Nirmatrelvir is a protease inhibitor, while ritonavir acts to boost the effect of the nirmatrelvir, meaning neither agent is effective alone. CMDU clinicians consider a patient's

medical history to select the most appropriate treatment. Those not suitable for nirmatrelvir/ritonavir may be offered sotrovimab as an alternative.¹

Remdesivir is an alternative second-line infusion given as a 3-day course. Many clinicians will be aware of remdesivir as an inpatient intervention in the early COVID-19 surges. Initial promising trials led to its emergency use authorisation in May 2020.⁶ Later, larger scale trials (including DiSCoVeRy, published in September 2021) identified less clear benefit of inpatient remdesivir: a slightly quicker recovery in those already recovering.⁷ In the PINETREE trial, unvaccinated outpatients recruited between September 2020 and April 2021 received a 3-day course of intravenous remdesivir. Overall, it demonstrated a significant reduction in hospitalisation or death at 28 days of 87% ($p=0.008$).⁸ In conjunction with the growing body of evidence for the safety of remdesivir in both an inpatient and outpatient setting, CMDUs provide a new avenue for the outpatient use of remdesivir in high-risk individuals.

The current third-line UK treatment option is molnupiravir, licensed in November 2021. The MOVE-OUT Study, trialled in unvaccinated patients only, identified a 31% reduction in hospitalisation and death.⁹ This was quickly overshadowed by the 89% reduction produced by the oral alternative, nirmatrelvir/ritonavir (also trialled solely in the unvaccinated).⁵ Nevertheless, molnupiravir has almost no interactions or contraindications and few mild side effects. It therefore has a niche in the outpatient COVID-19 treatment arsenal. It is currently under further investigation in the national PANORAMIC trial to establish its ongoing value in the vaccinated, Omicron era.

Some may ask, in a post-vaccine era, why are COVID-19 treatments needed? A total of 85.8% of over 12s in the UK are double vaccinated, and 67.2% are triple vaccinated.¹⁰ The Omicron variant also provided hope that COVID-19 is becoming less lethal. Omicron's daily case rate had nowhere near the initial feared impact on hospitalisation rates.¹¹ However, we should not be overly reassured by this. Omicron demonstrated the ability of variants to escape vaccine-induced immunity and to make targeted therapeutics redundant.¹² This was highlighted through casirivimab/imdevimab's brief inpatient use in November 2021, when Omicron rapidly outcompeted the dominant Delta strain. The reduced *in vitro* activity of casirivimab/imdevimab against Omicron,¹³ combined with the widespread dominance of the Omicron variant, has led to its withdrawal in the UK as an inpatient COVID-19 treatment since 24 February 2022.¹⁴ Furthermore, while Omicron produced a milder disease,¹¹ future variants may not be so forgiving. Of course, Omicron still can and does cause hospitalisation and death, particularly in the unvaccinated and immunocompromised. This is easily overlooked in a world fatigued and desensitised to COVID-19 mortality rates.

Many pre-emptive treatments were tested in a pre-vaccine era. The four trials investigating our current

Table 1 Currently available treatment options from CMDUs, administration methods, and suitability in pregnancy.

1st line	Sotrovimab
	<ul style="list-style-type: none"> ▶ Intravenous ▶ 1 clinic attendance ▶ Pregnancy ✓
	Nirmatrelvir/ritonavir
	<ul style="list-style-type: none"> ▶ Oral ▶ Delivered to home ▶ Pregnancy ✗
2nd line	Remdesivir
	<ul style="list-style-type: none"> ▶ Intravenous ▶ 3 clinic attendances ▶ Pregnancy ?
3rd line	Molnupiravir
	<ul style="list-style-type: none"> ▶ Oral ▶ Delivered to home ▶ Pregnancy ✗

pre-emptive therapeutics, COMET-ICE (sotrovimab), EPIC-HR (nirmatrelvir/ritonavir), PINETREE (remdesivir) and MOVE-OUT (molnupiravir), all had any previous COVID-19 vaccination as an exclusion criterion.^{3 5 8 9} The PINETREE trial stopped early due to the potential impact of vaccines and new inpatient monoclonal treatments on their results.⁸ This limits the conclusions we can draw about their efficacy in vaccinated individuals.

Certain immunocompromised groups were excluded from COVID-19 treatment trials, such as MOVE-OUT and COMET-ICE. Severely immunocompromised patients are unlikely to have a robust immune response either to COVID-19 infection or previous COVID-19 vaccination.¹⁵ Variation between immunocompromised subgroups has been noted, with the lowest levels of vaccine efficacy in organ or stem cell transplant recipients.¹⁶ Immunocompromised patients potentially have much to gain from sotrovimab and other antivirals. The variation in response to vaccines among the immunocompromised emphasises the importance of their inclusion in antiviral trials and wider clinical research. The integration of ongoing research with clinical guidelines will help CMDUs target treatment to those who are most likely to benefit.

The above trials were conducted during surges of previous variants. The playing field is markedly different now. The potential for rapid dominance of new strains impacts on the utility and longevity of therapeutics. Early in vitro assays suggest the same may occur to sotrovimab, with far lower impact on the increasingly dominant Omicron variant BA.2.¹⁷ The United States Food and Drug Administration (FDA) no longer recommends sotrovimab in any US region due to the increased proportion of cases caused by BA.2.¹⁸ It remains in use in the UK at present. This demonstrates the importance of ongoing research to assess the continuing benefit of drugs which are already licensed.

As is usual in clinical trials of novel therapeutics, these trials were widely limited to adult, non-pregnant and non-breastfeeding populations. According to the clinical commissioning guidelines, sotrovimab can be used in pregnancy, and remdesivir requires a risk–benefit clinical assessment. Both tablets, molnupiravir and nirmatrelvir/ritonavir, are contraindicated in pregnancy.¹ This leaves only intravenous options for pregnant individuals who may struggle to attend CMDUs in person to receive these treatments. In view of the significant maternal morbidity and mortality from COVID-19 infection,¹⁹ further research is required to widen the scope of early outpatient treatments towards pregnancy, the puerperium and in breast feeding.

Free routine testing has been phased out across the UK from April 2022. While government policy outlines allow patients labelled as high risk to receive free testing, it may still affect the systems of CMDU referral. These are automated and based on a positive test result uploaded to a government website. As discussed previously, there are many who may not easily access such systems, such

as those with no fixed abode. MOVE-OUT and EPIC-HR results were based on treatment given within 5 days of symptom onset—results were improved if medications were received within 3 days.^{5 9} The increased benefit of earlier treatment highlights the need for a system which enables rapid and equitable access.

The negative impacts of limited testing access are recognised in inpatient COVID-19 care in low/middle-income countries.²⁰ When testing is a prerequisite of use, pre-emptive therapeutics are again likely to be more accessible to those in high-income countries. As with access to vaccines, outpatient therapeutics may further exacerbate global inequity. Sequencing may continue to be used to guide prescribing choices. Prior to the withdrawal of sotrovimab in the USA, sequencing determined whether patients received sotrovimab for BA.1 or bebtelovimab for BA.2. This is particularly difficult in areas with limited resources.

So, where do we go from here? CMDUs integrate into the wider healthcare system to enable rapid delivery of pre-emptive therapeutics and prevention of severe outcomes. As we have outlined, this has limitations when applying study data which quickly become outdated. Desire for new treatments should not result in a lack of scrutiny. Ongoing clinical guidelines must be built on evidence we can confidently apply. Health services must ensure they allocate resources wisely. The changing nature of the pandemic highlights the importance of continuing research into the application of both novel and long-standing treatments, which can later be tailored to patients most likely to benefit from them. Trials such as PANORAMIC, which is conducted in a vaccinated era, help achieve this goal. PANORAMIC is designed to analyse a series of pre-emptive antivirals as they become available. It should help appropriately direct limited NHS resources and prevent the risk of oversupply, as occurred in stockpiling of oseltamivir during the swine influenza pandemic.

The ongoing, rapid development of therapeutics demonstrates the immense capacity of global research to adapt to moving goal posts. Ongoing clinical trials combined with a critical assessment of the impact of licensed medications will ensure that we are providing appropriate treatment to vulnerable groups. The Omicron variant will not be the last strain of SARS-CoV-2. The establishment of the CMDU national infrastructure helps ensure we are adequately prepared, and continually preparing, for the next.

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