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Unmet need for COVID-19 therapies in community settings



There was widespread coverage in the media of Merck and Ridgeback's interim results of their phase 3 trial of the antiviral molnupiravir. According to a press release from Merck on Oct 1, molnupiravir reduced the risk of hospitalisation or death by roughly 50% compared with placebo in non-hospitalised patients with mild-to-moderate COVID-19 and at least one risk factor for disease progression. Despite not yet being peer-reviewed, these data incited excitement, in part because of the oral route of administration of molnupiravir, which means the drug could be easily taken at home and used widely in settings with inadequate health-care infrastructure. Of note, Merck has announced that it plans to implement a tiered pricing approach based on World Bank income criteria—although what this means in practice, we do not yet know—and there are reports that the company has agreements with established generic drug manufacturers in more than 100 countries to allow rapid and local production of molnupiravir upon the drug's approval by licensing authorities.

Owing to the urgent need for treatments for hospitalised, critically ill COVID-19 patients, research on drugs for use in the outpatient setting has understandably lagged behind. Additionally, the existence of SARS-CoV-2 vaccines that are highly effective against hospital admission and death might be impacting the sense of urgency for these drugs. Yet, global inequity in access to vaccines means that there is a serious unmet need for pharmaceutical interventions to limit SARS-CoV-2 infection or progression of COVID-19.

There are also cases where individuals do not mount adequate and lasting immune responses to the vaccines. Speaking at the *COVID-19: Advances and Remaining Challenges* conference in Paris, France, on Sept 30, Florence Ader (Inserm) described how the outcome of SARS-CoV-2 infection and severity of disease appear to be related to the viral load and how long it remains elevated. Generally, the viral load peaks in the first week, soon after symptom onset, and declines thereafter; antibodies are typically detectable after 2 weeks. In certain risk groups (including the immunocompromised), viral load remains high for longer owing to delayed or inadequate development of antibodies, resulting in greater risk of progression to serious illness or death. According to Ader, these people would benefit from a drug that accelerates antiviral clearance.

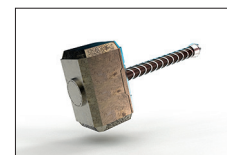
As well as molnupiravir, another drug that might benefit people with prolonged high viral load is remdesivir; after disappointing results in hospitalised patients—potentially due to the drug being administered too late in the disease to make a difference—remdesivir has shown promise for use in the outpatient setting. In the PINETREE study, whose results were presented in a late-breaker session at IDWeek 2021, remdesivir reduced the risk of hospitalisation by 87%, and of COVID-19-related medically attended visits or all-cause death by day 28 by 81%, compared with placebo in outpatients at high risk of severe disease.

Despite the promising preliminary results for these two antivirals, there are caveats. Remdesivir is administered intravenously, which might preclude its widespread use in community settings. Since the press release on Oct 1, two pharma companies in India have sought permission to end late-stage trials of molnupiravir in patients with moderate COVID-19 owing to lack of efficacy. There can be many explanations for different results arising from similar trials—in the case of molnupiravir, it might be due to differences in study design—but we will not know for sure until publication of the peer-reviewed trial results. The findings from India could suggest that molnupiravir has efficacy only in the very early stages of disease, which limits its usefulness due to delays in testing and health-care seeking.

Monoclonal antibodies (mAbs) are also being tested in the outpatient setting, with some promising results. For example, AstraZeneca has sought emergency use authorisation from US regulators for AZD7442—a cocktail of two long-acting mAbs—after it was shown to reduce the risk of any COVID-19 symptoms by 77% in a phase 3 trial. AZD7442 is administered intramuscularly, which might make it more attractive than other mAbs under investigation, which typically require intravenous administration. However, the high cost of mAbs will be a barrier to their widespread use.

Given it seems likely that SARS-CoV-2 will become endemic, research should focus on identifying safe, affordable, and globally accessible drugs for treatment and prevention of COVID-19 in the community.

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For the **press release on molnupiravir** see <https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/>

For more on **remdesivir in hospitalised COVID-19 patients** see **Articles** *Lancet Infect Dis* 2021; published online Sept 14. [https://doi.org/10.1016/S1473-3099\(21\)00485-0](https://doi.org/10.1016/S1473-3099(21)00485-0)