SARS-CoV-2 infection is rebound COVID-19, which follows the second wave of COVID-19 pandemic is now over [8]. However, SARS-CoV-2 is now endemic worldwide, and the pathogenesis and mechanisms of spread and persistence continue to provide new challenges for patient management [9].

One of the most recently described clinical associations with SARS-CoV-2 infection is rebound COVID-19, which occurs between five and eight days following the cessation of antiviral treatment. Most case reports of rebound COVID-19 have been associated with cessation of treatment with the combined oral antiviral agent nirmatrelvir/ritonavir (Paxlovid). On 24 May 2022, the US Centers for Disease Control and Prevention (CDC) issued a Health Alert Network (HAN) Health Advisory update for patients, healthcare providers, and public health departments on COVID-19 rebound or recurrence of COVID-19. However, population data from the US showed no significant differences in the risk of developing rebound COVID-19 between patients treated with Paxlovid and Molnupiravir. The mechanisms of rebound COVID-19 remain unclear but may involve the development of resistance to the antiviral drug, impaired immunity to the virus, or insufficient drug dosing. A further explanation may be the persistence of a high viral load of SARS-CoV-2 in individuals who are no longer symptomatic. This Editorial aims to provide an update on what is known about rebound COVID-19 and the current public health implications.

Keywords: Rebound Infection • Paxlovid • Molnupiravir • SARS-CoV-2 • COVID-19 • Editorial

It has been almost three years since the first cases of COVID-19 due to infection with SARS-CoV-2 were identified in China [1]. The spread of the SARS-CoV-2 virus rapidly resulted in a pandemic with patient mortality and acute and chronic consequences of COVID-19 [2]. As of 26 September 2022, 615 million cases of COVID-19 have been reported, and global mortality from COVID-19 currently stands at 6.54 million [3]. The development of vaccines to prevent SARS-CoV-2 has occurred with astonishing rapidity and now aims to match the rapid development of variants and subvariants of SARS-CoV-2, including the Omicron variant [4,5].

Developed countries have benefitted from the availability of vaccines. For example, as of 26 September 2022, 80% of the population of the US had received both primary and booster SARS-CoV-2 vaccines [6]. Because vaccines provide limited duration and degree of immune protection, antiviral agents are now available, particularly in developed countries [7]. Social restrictions and infection control measures have been reduced in many countries, where there may be a false belief that the COVID-19 pandemic is now over [8]. However, SARS-CoV-2 is now endemic worldwide, and the pathogenesis and mechanisms of spread and persistence continue to provide new challenges for patient management [9].

One of the most recently described clinical associations with SARS-CoV-2 infection is rebound COVID-19, which follows the cessation of antiviral treatment with symptoms recurring at five and eight days [10]. Most case reports of rebound COVID-19 are associated with cessation of treatment with the combined oral antiviral agent nirmatrelvir/ritonavir (Paxlovid) (Pfizer, New York, NY, USA) [10]. Because antiviral agents are available mainly in developed countries, cases of rebound COVID-19 have been reported primarily in the US and Europe [10]. Rebound COVID-19 was brought to world attention following the recent diagnosis and treatment of COVID-19 in the current US President, who experienced rebound COVID-19 following completion of a course of Paxlovid [11], but who also recently expressed the opinion that the COVID-19 pandemic is over [12]. Currently, the US Centers for Disease Control and Prevention (CDC) reports that an average of 4,000 patients are hospitalized each day, and 400 deaths per day from COVID-19 [12,13]. Global data and data from the US do not currently support that the COVID-19 pandemic is over [3,13].

Paxlovid tablets contain the dual antiviral agents nirmatrelvir and ritonavir [14]. On 22 December 2021, Paxlovid received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for the treatment of adults and pediatric patients >12 years of age with a diagnosis of SARS-CoV-2 infection, mild to moderate COVID-19 not requiring hospitalization, and one or more risk factors for progression to severe disease [15]. The EUA for Paxlovid recommends that treatment...
Rebound COVID-19 is not unique to patients treated with Paxlovid but also follows treatment with Molnupiravir [18]. Molnupiravir was associated with Paxlovid usually have a mild form of the disease [10,17]. The US CDC does not recommend the additional use of Paxlovid or other treatments for SARS-CoV-2 when rebound COVID-19 is suspected or diagnosed [10,17]. The risk of transmission during rebound COVID-19 can be managed by isolation, wearing a mask, and repeat SARS-CoV-2 testing [10,17]. Currently, the (HAN) Health Advisory update relates to rebound COVID-19 following cessation of Paxlovid [17].

However, rebound COVID-19 is not unique to patients treated with Paxlovid but also follows treatment with Molnupiravir [18]. Molnupiravir was associated with Paxlovid within five days of the onset of symptoms [15]. Regulatory approval of Molnupiravir was based on an interim analysis of the Phase 2/3 Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) randomized, double-blind trial (NCT04960202) [16]. The EPIC-HR trial included nonhospitalized adult patients with COVID-19 at high risk of progressing to severe illness [16]. Interim data analysis showed an 89% reduction in the risk of COVID-19-related hospitalization or death from any cause compared with placebo in patients treated within three days of the onset of symptoms [16].

On 24 May 2022, the CDC issued a Health Alert Network (HAN) Health Advisory update for patients, healthcare providers, and public health departments on COVID-19 rebound or recurrence of COVID-19 following cessation of Paxlovid [17]. COVID-19 rebound has been reported to occur between 2 and 8 days after initial clinical recovery [10,17,18]. COVID-19 rebound is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having a negative test [10,17,18]. In some patients, brief symptoms may return as part of the natural history of SARS-CoV-2 infection, independent of treatment or vaccination status [10,17]. Also, patients with rebound COVID-19 associated with Paxlovid usually have a mild form of the disease [10,17]. The US CDC does not recommend the additional use of Paxlovid or other treatments for SARS-CoV-2 when rebound COVID-19 is suspected or diagnosed [10,17]. The risk of transmission during rebound COVID-19 can be managed by isolation, wearing a mask, and repeat SARS-CoV-2 testing [10,17]. Currently, the (HAN) Health Advisory update relates to rebound COVID-19 following cessation of Paxlovid [17].

The mechanisms of rebound COVID-19 remain unclear but may involve the development of resistance to the antiviral drug, impaired immunity to the virus, or insufficient drug dosing. A further explanation may be the persistence of a high viral load of SARS-CoV-2 in individuals who are no longer symptomatic, irrespective of antiviral treatment. This latter explanation is supported by studies showing the presence of culturable SARS-CoV-2 virus in nasal swabs for up to 2 weeks after symptomatic COVID-19 [21]. This finding has future implications for viral surveillance and isolation of treated patients, with revision of current public health guidelines.

Conclusions

Rebound COVID-19 can occur following cessation of antiviral treatment with Paxlovid and Molnupiravir. These findings support that continuous patient surveillance should be undertaken not only during antiviral treatment but also up to 30 days after treatment. Further studies on COVID-19 rebound are required, and the association between drug dosing and treatment duration may lead to treatment regimens that prevent rebound infection. Further analysis of risk factors, including patient comorbidities and other treatments, might identify vulnerable patients who require changes in treatment regimens combined with regular post-treatment testing of their SARS-CoV-2 status.
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