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**Health Update on Recurrence of COVID-19 Symptoms After
Treatment with Paxlovid (nirmatrelvir/ritonavir)**

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Background

The California Department of Public Health is issuing this Health Alert to update public health departments, healthcare providers, and the public about the potential for “rebound” symptoms of COVID-19 after completion of a 5-day course of Paxlovid.

This recurrence of symptoms has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. [Reports](#) suggest that the viral load with the relapse of symptoms is similar to the initial infection and transmission can occur from individuals with recurrent symptoms to susceptible individuals.

Currently there is no recommendation from the Food and Drug Agency (FDA) or Centers for Disease Control and Prevention (CDC) to extend treatment with Paxlovid beyond the recommended 5 days.

Persons with relapsing symptoms are advised to re-isolate for at least 5 days and follow the recommended actions for the general public in [Table 1 of the CDPH Guidance on Isolation and Quarantine](#), which includes masking for 10 days, to prevent further transmission. Hospital inpatients and residents of long-term healthcare facilities should be re-isolated following [CDC healthcare infection control guidance](#).

Rebound of Symptoms After Paxlovid Treatment

There have been increasing media and case reports of recurring or “rebound” symptoms after a full treatment course of Paxlovid, including in patients who are up to date on COVID-19 vaccinations. All reported cases appear to be mild to moderate in nature. In one [case series](#), patients were determined to have a viral load consistent with their initial infection and likely transmission was reported during the recurrent symptoms.

In the [Paxlovid clinical trial](#), around 1-2% of patients who had completed a course of Paxlovid had one or more positive SARS-CoV-2 RT-PCR test results after testing negative, however this finding was also observed in persons receiving placebo. There was no increased occurrence of hospitalization or death in persons experiencing recurrent symptoms in the trial, and no evidence that the rebound in detectable viral RNA was the result of SARS-CoV-2 resistance to Paxlovid. There are several theories as to why this is occurring:

1. The SARS-CoV-2 virus has had a bimodal or recrudescence tendency in certain individuals.^{1,2} SARS-CoV-2 does appear to have the capacity to replicate for longer periods of time. A brief return of symptoms is a well-described phenomenon over the last two years, independent of treatment and vaccination status. As this is the natural history of SARS-CoV-2 infection, recurrence of symptoms may not have anything to do with Paxlovid treatment.
2. Paxlovid suppresses the virus so quickly early on in the disease course that the immune system may not have a chance to fully respond. Once Paxlovid is stopped the virus is able to replicate while the immune response lags behind.

Paxlovid as a Treatment for COVID-19

In clinical trials, Paxlovid was [88% effective](#) in preventing severe COVID-19 and death among high-risk, unvaccinated patients primarily treated during the Delta variant wave. Although population-level data is still lacking, by all accounts Paxlovid continues to be effective at preventing severe disease progression and mortality.

Paxlovid continues to be recommended for early-stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease, and, because the goal of treatment is to avoid hospitalization and/or death, mild to moderate recurrent COVID-19 symptoms do not indicate treatment failure.

If recurrent symptoms do occur, there is currently no evidence that additional or longer treatment is needed with Paxlovid or that patients should receive other anti-SARS-CoV-2 therapies.

Reporting Recurrent Symptoms after Paxlovid Treatment

Healthcare providers are encouraged to report cases of COVID-19 rebound to Pfizer after Paxlovid treatment using the following online tool: [Pfizer Safety Reporting](#) and to [FDA MedWatch](#). Complete and submit a MedWatch form, or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1-800-FDA-1088 for questions.

Guidance on Isolation and Quarantine

People with COVID-19 rebound should follow CDC and CDPH recommendations regarding isolation of infected persons regardless of treatment with an antiviral agent and/or previous isolation after the initial infection.

People with recurrence of COVID-19 symptoms or a new positive viral test after having tested negative should restart isolation and isolate again for at least 5 days. Per CDC and CDPH guidance, they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The individual should wear a mask for a total of 10 days after rebound symptoms started. Some people continue to test positive after day 10 but are considerably less likely to shed infectious virus. Hospital inpatients and residents of long-term healthcare facilities should be re-isolated following [CDC healthcare infection control guidance](#).

¹ [Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series | The BMJ](#)

² [Acute-care hospital reencounters in COVID-19 patients - PubMed \(nih.gov\)](#)