Update from the Field:
Paxlovid for Prevention of Long COVID

A Series on Long COVID

Introduction

This update will focus on available literature on the role of Paxlovid in the prevention of long COVID. This update **will not** address the use of Paxlovid to treat manifestations of long COVID due to lack of studies, nor will it address Paxlovid for treating acute COVID-19. Research trials RECOVER (https://recovercovid.org/) and STOP-PASC (https://stanfordhealthcare.org/trials/p/NCT05576662.html) to evaluate treatments (including Paxlovid) for long COVID are ongoing.

Literature Limitations

We found eight published observational studies on the use of Paxlovid (nirmatrelvir/ritonavir) to prevent long COVID. The initial search was completed in November 2023 and updated search was done in June 2024 (see end of document for description of literature search).

The following are some limitations of the available studies:

- The studies are heterogeneous in terms of populations, timelines, and symptom definitions; therefore, it is challenging to make overall conclusions on the effectiveness of Paxlovid in preventing long COVID.
- Studies are observational and typically retrospective, so they are subject to potential bias and confounding.
- Studies mimicking randomized controlled trials need more rigorous study designs to validate the findings.
- These studies were primarily done in 2022, which limits generalizability to strains not prevalent during this time.
- All studies were done on non-hospitalized patients; one study looked at high-risk patients discharged from the hospital after acute COVID-19.
- Not all studies had been published at the time of review, some were in pre-print or available as an abstract or a Letter to the Editor.
- Not all studies accounted for potential differences in baseline health between untreated and treated persons.

Notable Findings

- Paxlovid treatment during acute COVID-19 **may** be associated with a reduction in the risk of long COVID. However, available studies do not show a consistent benefit.
    - Questions remain about the magnitude of a potential effect and the subgroups of patients/symptoms who may benefit.
- One study found that Paxlovid was associated with a significant decrease in the risk of development of neuropsychiatric sequelae within 90 days to 1 year following a diagnosis of COVID-19.
- Additional studies of the potential effects of antiviral therapy for the prevention or treatment of long COVID and the populations most likely to benefit are urgently needed.

Summary of Literature

Study	Population	Outcomes
Chuang 2023 Retrospective cohort study	Adult patients with COVID-19 Total population: 24,490 12,245 in each group Treatment group given Paxlovid within five days of COVID-19 diagnosis	Post-acute symptoms, hospitalization, ED visits, and death 90 -180 days after COVID-19 • Paxlovid associated with lower risk of all-cause hospitalization and ER visits. • Overall risk of post-acute COVID-19 symptoms did not significantly differ between treated and untreated. • Risk of all-cause death did not differ significantly between treated and untreated.
Dalton 2023 **ID Week abstract** Retrospective cohort study based on claims data.	Patients aged ≥ 12 years with COVID-19 (outpatient, ED, telehealth) at increased risk for severe COVID-19 due to age, underlying conditions, or immune-suppressing medications. Total population: 874,299 Treated: 291,433 Untreated: 582,866 Treatment group given Paxlovid within five days of COVID-19 diagnosis	New conditions >60 days after COVID-19 diagnosis • Adults aged ≥ 50 years: risks of overall and individual post-covid conditions (PCCs) were generally lower among patients treated with Paxlovid. • Adults 18-49 years: no overall difference in risk of PCCs. • Adolescents 12-17 years: risks of overall and individual PCCs were higher among patients treated with Paxlovid.
Durstenfeld 2023 Cross-sectional survey	Vaccinated individuals with positive SARS-CoV-2 test. Self-reported treatment with Paxlovid: 988 Self-reported not treated with Paxlovid: 3696 Treatment group given Paxlovid within 30 days of COVID-19 diagnosis	Presence of any self-reported long COVID symptoms more than 90 days after positive SARS-CoV-2 test: • No association between treatment and long COVID symptoms. • Among treated, rebound symptoms or test positivity were not associated with Long COVID symptoms.
Ioannou 2023 Retrospective target trial emulation study	Veterans (vaccinated and non-vaccinated) who were at high risk for severe COVID-19 and tested positive for SARS-CoV-2 Total population: 19,214 Treated: 9593 Untreated: 9593 Treatment group given Paxlovid within five days of positive test	Cumulative incidence of 31 potential post covid conditions (PCCs) 31-180 days after treatment. • Incidence of individual and organ system PCCs similar between treatment and non-treatment groups, apart from combined thromboembolic events: ○ Treatment group had lower combined risk for VTE and PE. • Risk for PCCs similar between vaccinated and unvaccinated persons.

Study	Population	Outcomes
Liu 2023 Retrospective cohort study	Adult patients with COVID -19 at high risk of severe COVID-19 Total population: 54,388 27,194 in each group No information on vaccination status.	Incidence of neuropsychiatric sequela within a 90-day to 1-year period following a diagnosis of COVID-19: • Decreased risk of any neuropsychiatric sequelae in the treatment group. • Decreased risk of neurocognitive sequelae and psychiatric sequelae in the treatment group. • Decreased risk of developing dementia, depression, insomnia and anxiety disorder in treatment group. • No difference between groups in risk of delirium or psychotic disorder. Specific neuropsychiatric sequelae included: dementia, delirium, anxiety disorder, depression, insomnia, or psychotic disorder.
Patel 2023 **Pre-print** Retrospective cohort study.	Vaccinated patients ≥18 years old with COVID-19 Total population: 2,008 1,004 in each group Treatment group given Paxlovid within five days of diagnosis	Symptoms associated with post-acute sequelae of SARS-CoV-2 (PASC) up to 180 days after index Covid-19 infection: • Paxlovid associated with reduced odds of PASC symptoms. • Lower rates of healthcare utilization (including radiology and cardiovascular diagnostic tests and ambulatory/virtual visits) in treatment group.
Priess 2024 **Pre-print** Retrospective observational study (EHR-based data target trial emulation)	Electronic health records from the National Covid Cohort Collaborative (N3C) of a cohort of 426,352 patients who had COVID-19 since April 1, 2022, and were eligible for Paxlovid treatment due to risk for progression to severe COVID-19.	Long COVID incidence was estimated in overlapping 100-day periods that progress through time, and probability was issued for each 100-day period. • Paxlovid treatment did not have a significant effect on overall Long COVID incidence. • Paxlovid did not reduce the long COVID cognitive or fatigue symptoms. • Modest improvement in respiratory symptoms.
Wang 2023 **Letter to the Editor** Prospective cohort study	High-risk patients hospitalized with COVID-19 who were treated with Paxlovid and subsequently discharged. Total population: 647 Treated: 456 Untreated: 178	One or more symptoms of long Covid, CAT scores (COPD assessment test), and all-cause mortality 6 months after discharge: • Paxlovid associated with lower CAT scores after adjustment for age, vaccination, comorbidities, and other therapies during hospitalization. • Paxlovid associated with decreased all- cause mortality. • Paxlovid associated with reduced risk of long Covid 6 months after discharge.

Study	Population	Outcomes
Xie 2023 Retrospective cohort study	Patients in the VA health care database with a positive SARS-CoV-2 test and at least one risk factor for progression to severe COVID-19 Total population: 281,793 Treated: 35,717 Untreated: 246,076 Treatment group given Paxlovid within five days of diagnosis	Risk of post-Covid conditions (PCCs), hospitalization, or death at 180 days. • Paxlovid associated with reduced risk of PCCs, including reduced risk of 10 of 13 post-acute sequelae (dysrhythmia, ischemic heart disease, PE, DVT, fatigue and malaise, AKI, muscle pain, neurocognitive impairment, dysautonomia, and shortness of breath) regardless of vaccination status and prior infection. • Paxlovid associated with reduced risk of post-acute death and hospitalization.
Xu 2024 Non-randomized controlled clinical trial	Adult patients 18-50 years old infected with the COVID-19 Omicron variant who were admitted to the designated hospital for treating COVID-19 in China Total population: 320 Treated: 200 Untreated: 120 Treatment group given Paxlovid twice a day for five consecutive days	Compared to patients in the standard treatment group, those in Paxlovid group had: • Significantly shorter nucleic acid shedding time, • Shorter days until negative swab test, • Shorter days of first symptoms resolution, • Higher in nucleic acid test negative rate within 3 days, • Nucleic acid higher negative rate within 5 days, • Nucleic acid negative rate within 7 days, • Less likely to have post-COVID-19 condition, • No significant difference in duration of post-COVID-19 condition*. *Post-COVID condition defined as usually 3 months from the onset, with symptoms that lasted for at least 2 months and could not be explained by an alternative diagnosis. Common symptoms included, but were not limited to, fatigue, shortness of breath, and cognitive dysfunction, and generally had an impact on daily functioning.

Literature Search Description:

The initial search was run in November 2023 with a broader search engine (EBSCO Discovery Health), including randomized controlled trials, systematic reviews/meta-analyses, cohort studies, case studies, and general summary reports. The following search terms were used and included both MeSH terms and subject terms: ("post-COVID conditions" OR "long COVID" OR "post-acute COVID-19 syndrome" OR "PASC" OR "post-acute sequelae of SARS-CoV-2") **AND** (Paxlovid OR ritonavir OR nirmatrelvir)". The initial search produced 62 articles of which eight were relevant to the question of "relationship of Paxlovid treatment for prevention and treatment of Long COVID". An updated search was done in June 2024 for any new article published between December 2023 – June 2024. Seven new articles came up in the updated search of which two were relevant to include. The two new articles did not change the initial findings.

Acknowledgments

Thank you to our work group members for their expertise, feedback, and review to review available evidence and develop this update. The work group members included *(in alphabetical order by organization)*:

- Jane Rudd, Essentia Health
- Sandra Turbes, Genevieve
- Charlene McEvoy, Health Partners
- Ravindra Ganesh, Mayo Clinic
- Stephanie Grach, Mayo Clinic
- Tanya Melnik, M Health Fairview
- Farha Ikramuddin, M Health Fairview
- Sarah Lim, Minnesota Department of Health

Document last updated: July 2024. Updates to this document will be made as new evidence becomes available.

This project is funded through the State of Minnesota and by a grant to the Minnesota Department of Health by the Centers for Disease Control and Prevention (CDC).