2022 Health Advisory #28:
Prescribe COVID-19 Therapeutics to Prevent Severe Disease, Hospitalization and Death This Winter

- **Transmission of COVID-19 and other respiratory viruses is increasing:** New York is experiencing an early increase in severe respiratory infections, particularly in pediatric populations. Vaccination is still the best protection against severe COVID-19 and influenza.
- **COVID-19 antivirals are available and effective:** The oral antivirals (OAVs) Paxlovid and molnupiravir and IV remdesivir are effective at preventing COVID-19-associated hospitalizations and deaths. OAVs are widely available in NYC pharmacies but are underutilized.
- **COVID-19 rebound after Paxlovid treatment is typically mild and is not a reason to avoid prescribing:** Rebound of COVID-19 symptoms and/or antigen test positivity can occur between 2 and 8 days after initial recovery. COVID-19 rebound usually consists of mild symptoms that do not require additional treatment.
- **Paxlovid is the preferred outpatient treatment for COVID-19 or IV remdesivir:** The NIH COVID-19 treatment Guidelines recommend Paxlovid as the preferred treatment or IV remdesivir. Molnupiravir and the monoclonal antibody (mAb) bebtelovimab are authorized as alternatives if the preferred treatments are not appropriate or accessible.
- **The monoclonal antibody (mAb) bebtelovimab is commercially available, though the prevalence of resistant variants is increasing:** mAb treatment sites are encouraged to offer outpatient remdesivir, especially for immunocompromised patients for whom Paxlovid may not be clinically appropriate and for high-risk pediatric patients.
- **Vaccination, testing and treatment for influenza are essential, especially for higher-risk patients:** COVID-19 virus variants are co-circulating with influenza and other respiratory viruses this season. Providers can refer to our recent letter on seasonal influenza vaccination.
- **Racial inequities persist in COVID treatment and in COVID morbidity and mortality:** Longstanding systemic health and social inequities contribute to an increased risk of severe COVID-19 for people of color. Recent national data show that Black and Hispanic people are less likely to get treated for COVID-19. Non-white race and Hispanic ethnicity should be considered social risk factors for worse outcomes.

November 4, 2022

Dear Colleagues,

COVID-19 variants are co-circulating with influenza and other respiratory viruses (e.g., respiratory syncytial virus, enteroviruses) and severe respiratory infections are increasing throughout New York State, particularly in the pediatric population. Providers should be aware that the potential for more severe manifestations of RSV, influenza and other respiratory viruses exists due to lower
levels of exposure since 2020. Although up to date vaccination offers the best protection against severe COVID-19, therapeutics offer additional protection against COVID-19-related hospitalization and death. Please counsel patients with risk factors for severe disease on how to promptly get treatment if they develop COVID-19 or influenza. This advisory provides updates on outpatient treatments for COVID-19.

**COVID-19 antivirals are available and effective**

Outpatient antiviral treatments for COVID-19, including oral antivirals (OAVs) and IV remdesivir (Veklury), are effective in reducing the risk for hospitalization and death. Nirmatrelvir with ritonavir (Paxlovid) is the preferred treatment for most outpatients or IV remdesivir if Paxlovid is contraindicated. The oral antiviral molnupiravir (Lagevrio) and the monoclonal antibody bebtelovimab are authorized as alternatives when Paxlovid and remdesivir are not accessible or clinically appropriate. ([NIH COVID-19 Treatment Guidelines for Non-Hospitalized Adults](#))

**Efficacy of outpatient oral antivirals against COVID-19 Including Omicron subvariants**

In clinical trials conducted with unvaccinated patients before Omicron variants were circulating, nirmatrelvir with ritonavir (Paxlovid) reduced the risk of hospitalization and death by 88% compared to placebo in non-hospitalized, high-risk adult patients with COVID-19 treated within five days of symptom onset ([Hammond, 2022](#)). Molnupiravir (Lagevrio) reduced the risk of these outcomes by 30% ([Jay Bernal, 2022](#)). Despite the demonstrated benefits, Paxlovid continues to be vastly underutilized, with only 25% or less of eligible patients receiving prescriptions ([COVID States Project; EPIC Research](#)).

Recent studies on the benefits of Paxlovid in highly COVID-19 immune populations during omicron circulation have also demonstrated significant reductions in hospitalizations among patients aged 18 years or older who had risk factors for more severe disease (46% overall relative risk reduction, 67% in people 65 years or older)\(^1,2\) and studies have shown 60-66% reduction in deaths with up to an 81% mortality reduction among patients 65 years or older.\(^1-6\) The largest benefits were seen in those 65 years or older or immunocompromised (vaccinated or not) and in unvaccinated patients.\(^1-3\) Molnupiravir also demonstrated benefits with up to a 52% reduced risk for death among high-risk patients with mild to moderate illness hospitalized within 3 days before or after COVID-19 diagnosis, a 24% risk reduction of all-cause mortality for non-hospitalized patients and a 44% risk reduction of hospitalization and death among solid organ transplant recipients.\(^5-7\) (see appendix)

Paxlovid, given within 5 days of symptom onset, is the preferred treatment for eligible patients aged 12 years and older with a positive SARS-CoV-2 test result who have risk factors for progression to severe COVID-19, including:

- **Age over 50 years**, with risk increasing substantially at age ≥ 65 years
- **Being unvaccinated** or not being up to date on COVID-19 vaccinations
- **Specific medical conditions, social factors, and behaviors**

Paxlovid can alter the concentrations of other drugs, so it is important to assess for potential drug-drug interactions. The Infectious Disease Society of America offers guidance on simple steps that can be taken to avoid significant interactions with commonly prescribed medications, such as brief suspension or dose reduction. Do not prescribe Paxlovid for patients who are taking rivaroxaban or salmeterol; avoid it in patients with severe renal impairment (eGFR <30).
Remdesivir by IV infusion for outpatients

In clinical trials, remdesivir (Veklury) reduced the risk of hospitalization or death by 87% among high-risk unvaccinated patients with COVID-19 treated within 7 days of symptom onset (Gottlieb, 2021). It must be administered daily by IV infusion for 3 days. It is the only treatment approved for children under 12 years of age.

Given the emergence of variants resistant to mAbs, providing remdesivir in the outpatient setting may be of particular importance for facilities and providers that see large numbers of immunosuppressed patients such as transplant and oncology centers, or high-risk pediatric populations. Providers are encouraged to order remdesivir to have on hand for patients unable to take Paxlovid. To order, Nonhospitals can contact AmerisourceBergen Specialty Distribution by calling 1-800-746-6273 or emailing C19therapies@AmerisourceBergen.com for more information. Visit for velkuryhcp.com coding and reimbursement information.

COVID-19 rebound is typically mild

COVID-19 rebound is the term used describe a recurrence of symptoms and/or SARS CoV-2 antigen positivity which can occur between 2 and 8 days after initial recovery. It has been observed among patients treated with Paxlovid and molnupiravir, as well as patients with COVID-19 who were not treated (Pre-print Deo, 2022, Pre-print Wang 2022). Recent studies suggest that patients who experience rebound have an extremely low probability of developing severe COVID-19. Retreatment is not currently recommended.

People with rebound can transmit to others (Boucau, 2022), and patients should re-isolate for at least 5 days from the recurrence of symptoms as per CDC guidance. It is essential to advise your patients that COVID-19 rebound does not represent a failure of treatment or resistance.

Bebtelovimab is now available commercially and through Federal Replacement Program for uninsured patients

Bebtelovimab is the only mAb authorized for the treatment of COVID-19. It is has become commercially available and is no longer distributed for free by the U.S. Government (USG). Remaining doses provided by the USG should be used to fill in gaps for underinsured or uninsured individuals. In addition, the USG announced a product replacement program which will allow health care providers who use a commercially procured doses of bebtelovimab to treat uninsured or underinsured patients to have the doses replaced for free. Participating providers are asked to waive or discount administration fees. For more information go to the HHS Bebtelovimab information page or contact COVID19Therapeutics@hhs.gov.

COVID-19 variants and resistance to monoclonal antibodies

Some emerging omicron subvariants (e.g., BQ.1 and BQ.1.1) are likely resistant to the mAbs bebtelovimab and Evusheld (authorized for pre-exposure prophylaxis) (Bebtelovimab Fact Sheet, section 12). The proportions of these resistant subvariants are increasing and their prevalence is currently moderate in NYC. The NYC Health Department and Centers for Disease Control are closely monitoring the situation and the National Institute of Health (NIH) COVID-19 Treatment Guidelines will be updated as the prevalence of resistant subvariants increases. The antivirals Paxlovid, remdesivir, and molnupiravir are expected to be active against these subvariants.

Due to the increasing risk of resistance, bebtelovimab should only be considered when Paxlovid or IV remdesivir are not an option. Facilities that offer monoclonal antibodies are strongly encouraged to offer outpatient remdesivir infusions into their treatment programs. If treating with bebtelovimab, consider molnupiravir in eligible patients, particularly for those at highest risk for...
severe outcomes (65 years and older, immunocompromised, unvaccinated <65 years of age with medical comorbidities). Continue to check The COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants and Anti-SARS-CoV-2 Monoclonal Antibodies for updates.

Given the risk of infection by Evusheld resistant variants, ensure patients with moderate to severe immune compromise are up to date on COVID-19 vaccinations, counseled on general prevention measures, and have a treatment plan in place to seek timely medical care if they develop symptoms.

**Vaccination, testing and treatment for influenza is essential**
This fall and winter, influenza, RSV and COVID-19 are co-circulating. Providers should use every opportunity to administer flu vaccines and COVID-19 primary and booster vaccines to patients to reduce the burden of respiratory illnesses and protect populations at increased risk for severe illness. In addition, initiation of influenza antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalized or has severe, complicated, or progressive illness or is at higher risk for influenza complications.

Testing can help distinguish between the two infections. Clinical algorithms for the testing and treatment of influenza when SARS-CoV-2 and influenza viruses are circulating are available (CDC). Providers can access the NIH COVID-19 Treatment Guidelines: Influenza and COVID-19 for more information.

**Structural racism drives inequities in COVID morbidity and mortality**
Providers play an essential role in addressing social, racial, and economic inequities in our city. We reported during the initial omicron wave a COVID-19 hospitalization rate more than two times greater among Black New Yorkers compared to White New Yorkers. And nationwide, despite higher population-level risks, Black and Hispanic patients have been less likely to receive Paxlovid (36% and 30% fewer treat Black and Hispanic patients compared to White and non-Hispanic patients, respectively) or mAbs (Boehmer, 2022; Wiltz, 2022).

Treatments are effective in reducing disease severity and deaths, particularly among those that are unvaccinated, over 50 years of age, or immunocompromised. In addition, race and ethnicity and other social risk factors should be considered when assessing risk of adverse outcomes from COVID-19.

Together we can eliminate barriers in access to vaccination, testing and treatment. If you see opportunities for our health department to reduce access to care barriers and participate more deeply in the response to racism as a public health crisis, please email us at chiefmedicalofficer@health.nyc.gov.

Sincerely,
Michelle Morse, MD, MPH
Chief Medical Officer, NYC Health Department
Deputy Commissioner, Center for Health Equity and Community Wellness

Mary Foote, MD, MPH
Medical Director, Office of Emergency Preparedness and Response
Resources

Accessing COVID-19 Oral Antivirals
- Paxlovid and molnupiravir are widely available in NYC pharmacies listed on the [COVID-19 Therapeutics Locator and the Test to Treat Locator](https://www.nyc.gov/html/doh/index.html).  
- Alto Pharmacy can deliver anywhere in the 5 boroughs on the same or next day at no cost. Visit the NYC Health Department's [COVID-19 Therapeutics webpage](https://www1.nyc.gov/site/health/covid-19/therapeutics.page) for instructions.  
- [NYC Health + Hospitals mobile Test to Treat](https://www1.nyc.gov/site/health/covid-19/therapeutics.page) units offer free testing, evaluation, and antivirals at locations throughout NYC.

Resources for COVID-19 Treatment and Managing Drug-Drug Interactions
- NYC Health Department: [nyc.gov/health/covidprovidertreatments](https://www1.nyc.gov/site/health/covid-19/therapeutics.page)  
- NIH: [COVID-19 Treatment Guidelines](https://www.nih.gov)  
- HHS: [Clinical Decision Aid for COVID-19 Outpatient Therapeutics](https://www.hhs.gov)  
- CDC: [Interim Clinical Considerations for COVID-19 Treatment in Outpatients](https://www.cdc.gov)  
- FDA: [PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers](https://www.fda.gov)  
- HHS: [Paxlovid Information Sheet – Eligibility and Effectiveness](https://www.hhs.gov)  
-Liverpool Drug Interactions Checker
- IDSA: Management of Drug Interactions with Nirmatrelvir/Ritonavir: Resource for Clinicians

Resources for vaccination
- COVID-19 vaccination: CDC’s [Interim Clinical Considerations for Use of COVID-19 Vaccines](https://www.cdc.gov)  
- Influenza vaccination: CDC’s [Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season](https://www.cdc.gov)

Resources on Undoing Racism in Healthcare
- Association of American of Medical Colleges: [Anti-racism Resources](https://www.aamc.org)  
- Commonwealth Fund: [Confronting Racism in Health Care](https://www.commonwealthfund.org)

Resources on Access to Health Care
- Patients can get free enrollment assistance to sign up for low- or no-cost health insurance, by calling 311, texting CoveredNYC (SeguroNYC for Spanish) to 877877, or visiting the GetCoveredNYC webpage at [nyc.gov/getcoverednyc](https://www.nyc.gov). To connect with a Health Department Certified Application Counselor, visit [nyc.gov/health/healthcoverage](https://www.nyc.gov).  
- Patients who do not have a health provider or are uninsured can visit [ExpressCare](https://www1.nyc.gov/health/healthcoverage) or call 212-COVID19 (212-268-4319) to speak with a doctor about treatment options or go to a NYC Health + Hospitals [Mobile Test to Treat Site](https://www1.nyc.gov/site/health/covid-19/therapeutics.page).

Table: Summary of studies analyzing the effectiveness of OAVs during omicron

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Drug</th>
<th>Time analyzed</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Najjar-Debbiny et al. 2022 | 180,351 patients 18 years or older at high risk for severe COVID-19  
85.1% COVID-19 vaccinated                  | Paxlovid | January - February 2022 | • 46% risk reduction of hospitalizations or death  
• Most benefit in older patients, patients with cardiovascular disease, patients with |
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size/Characteristics</th>
<th>Treatment</th>
<th>Time Period</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbel et al., 2022</td>
<td>109,213 patients 40 years or older at high risk for severe disease (42,819 65 years or older) 78% of patients had prior immunity (vaccination, prior infection, or hybrid immunity)</td>
<td>Paxlovid</td>
<td>January - March 2022</td>
<td>In 65 years or older patients: 67% risk reduction of hospitalizations 81% risk reduction of death. No significant benefit in younger adults</td>
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<tr>
<td>Dryden-Peterson et al., 2022 (pre-print)</td>
<td>30,322 patients 50 years old or older 87.2% vaccinated</td>
<td>Paxlovid</td>
<td>January - May 2022</td>
<td>45% risk reduction of hospitalization In unvaccinated individuals 84% risk reduction of hospitalization and death</td>
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<tr>
<td>Ganatra et al., 2022</td>
<td>1130 patients receiving nirmatrelvir/ritonavir and 1:1 propensity score matched controls 18 yrs or older, fully vaccinated outpatients</td>
<td>Paxlovid</td>
<td>December – April 2022</td>
<td>45% relative risk reduction in all-cause ED visits, hospitalizations, or death 60% relative risk reduction in hospitalizations and 100% reduction in deaths</td>
</tr>
<tr>
<td>Wong et al., 2022</td>
<td>1,856 molnupiravir-receiving patients, 890 nirmatrelvir/ritonavir and 2,746 control patients Hospitalized within 3 days before or after COVID diagnosis</td>
<td>Paxlovid and molnupiravir</td>
<td>February - April 2022</td>
<td>52% risk reduction of all-cause mortality with molnupiravir 66% risk reduction of all-cause mortality with nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td>Wong et al., 2022</td>
<td>5,383 molnupiravir receiving patients and 6,464 nirmatrelvir/ritonavir 1:10 propensity score matched controls &lt;50% vaccinated Molnupiravir group older and higher % vaccinated vs. nirmatrelvir/ritonavir group</td>
<td>Paxlovid and molnupiravir</td>
<td>February – June 2022</td>
<td>24% risk reduction of all-cause mortality with molnupiravir 66% risk reduction of all-cause mortality with nirmatrelvir/ritonavir 24% reduced risk of hospitalization with nirmatrelvir/ritonavir Similar effects of nirmatrelvir/ritonavir across vaccination status and age</td>
</tr>
<tr>
<td>Radcliffe et al., 2022</td>
<td>122 solid organ transplant recipients 49 (40%) received molnupiravir 24 (20%) received sotrovimab 48 (39%) untreated 48% ≥3 doses of an mRNA vaccine series or two doses of Ad26.COV2.S</td>
<td>Molnupiravir</td>
<td>January – February 2022</td>
<td>44% risk reduction of hospitalization or death</td>
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