The Rapid Response Podcasts

COVID-19 Updates: What We Know Now
Releases monthly

Newest Episodes:
• SHEA Spring 2022 Recap
• CDC Guidance & Influence on COVID

COVID-19 Allies in Infection Prevention

LearningCE.shea-online.org

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SAFE HEALTHCARE FOR ALL
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With funding from the Centers for Disease Control and Prevention, IDSA has launched the COVID-19 Real Time Learning Network, an online community that brings together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

www.COVID19LearningNetwork.org
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SEE YOU NEXT YEAR!

We hope to see you in Seattle, Washington for SHEA Spring 2023 April 12-14.
Important Dates:

- Abstract & Travel Award Submission Deadline – May 4
- Case Submission Deadline – May 4
- Registration is scheduled to open for members May 3 & nonmembers on May 31.

Join Us LIVE in Washington, DC
Oct. 19-23, 2022
SHEA Webinar

COVID-19 Town Hall
Round 74

Music:
www.bensound.com
In Case of Technical Difficulties:

• Audio:
  • Select one form of audio only (computer speakers or telephone connection)
  • For full participation, you will need to join by computer

• If you are having trouble joining:
  • Use the emailed invitation to join via the URL, or call in with the provided phone numbers

• [https://support.zoom.us](https://support.zoom.us)
Webinar Recording Access:

This webinar will be recorded and uploaded to LearningCE’s Rapid Response Program.

Streaming Live on SHEA's Facebook page.

SAFE HEALTHCARE FOR ALL
Useful Features:

- **Chat**: Talk to each other or ask SHEA Staff questions if you are having technical difficulties.
- **Q&A**: Type in your question to be read aloud by SHEA Staff and answered by the Panelists.
Reported COVID-19 Cases in the United States

Cumulative Cases – 82,386,465

Increased by 58% from two weeks earlier

US COVID-19 HOTSPOTS

February 6, 2022

April 24, 2022

HOSPITALIZATIONS AND ICU ADMISSIONS FOR COVID-19 IN THE UNITED STATES

Hospitalizations Increased 21% from two weeks earlier

COVID-19 DEATHS IN THE UNITED STATES

Cumulative Deaths – 998,310

3% decrease from two weeks earlier

DAILY COVID-19 VACCINATIONS IN THE UNITED STATES

Source: Our World in Data 5-14-22
COVID-19 VACCINATIONS IN THE UNITED STATES

Source: Our World in Data 5-14-22

Percent Vaccinated

Percent Fully Vaccinated

257,710,000 (77.6%)

220,460,000 (66.4%)

Source: Our World in Data 5-14-22
COVID-19 BOOSTER DOSES IN THE UNITED STATES

CUMULATIVE DOSES ADMINISTERED 102.01 M

Source: Our World in Data 5-14-22
1. A New England Journal of Medicine study demonstrated the efficacy of a Chinese adjuvanted receptor-binding-domain dimer peptide in preventing SARS-CoV-2 infection.

2. A paper in the New England Journal of Medicine describing the second phase of the trial of the Moderna vaccine in children 6 to 11 found that two 50 microgram doses were safe, immunogenic and estimated as 88% effective in preventing SARS-CoV-2 infection.

3. An editorial accompanying this paper in the New England Journal of Medicine makes the case for continued and continuing vaccine development.

4. A Lancet paper found that two-years after COVID-19 infection survivors have significantly lower health status than the general population.

5. A paper in Science found that SARS-CoV-2 antigen challenge histories influence the speed and magnitude of antibody responses, functional cross-variant antibody repertoire composition, and longevity of protection.

6. A Journal of Infectious Diseases paper found that two-dose primary vaccination within the prior two months was effective in reducing severe sequelae of COVID.

7. A paper in Clinical Infectious Diseases noted that SARS-CoV-2 viremia is associated with COVID-19 severity and the level of viremia is predictive of clinical outcomes.

8. A preprint published in Nature Communications described the first SARS-CoV-2 challenge study conducted in humans and evaluated the early kinetics of infection.

References available in the chat
Panelists:

Dr. David Henderson  
NIH Consultant

Dr. Kristina Bryant  
University of Louisville

Dr. Sarah Haessler  
Baystate Health

Dr. David Weber  
UNC School of Medicine
Paxlovid: Beware the Drug Interactions

• 54 yo woman with RA on enbrel (and 20 other regular outpatient medications including atorvastatin, mirtazapine and quetiapine)

• prescribed Paxlovid after positive COVID PCR at PCP office

• 4 days later she was brought to ED by her family with lethargy and mental status changes

• Afebrile and hemodynamically stable but minimally responsive. Labs with no leukocytosis, Cr 1.3, CK 500. COVID/RSV/Flu PCR negative on admission

• CT of head was unremarkable

• Unable to have LP initially, treated with acyclovir, vancomycin, ceftriaxone, and ampicillin

• Hospital day 2-3, had 2nd head CT and LP which were normal, and was about to get MRI and EEG, when she had some gradual improvement

• an IV infiltrated into her hand which became swollen, so she underwent CT of her hand

• ID consult for mental status changes in immunocompromised patient: identified Paxlovid drug interaction as cause of patient’s symptoms

Case and slides courtesy of Jennifer Schimmel MD, 2022
Paxlovid Interaction: Downstream Consequences

- 4 day hospitalization
- 2 CT scans of the head
- Lumbar puncture
- Broad spectrum antibiotic exposure
- IV acyclovir
- IV infiltration
- CT scan of hand
## Liverpool Drug Interaction Checker

[https://www.covid19-druginteractions.org/checker](https://www.covid19-druginteractions.org/checker)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Aspirin (Anti-platelet)</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Do Not Coadminister</td>
<td></td>
</tr>
</tbody>
</table>

### Nirmatrelvir/Ritonavir (5 days)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>Potential Interaction</td>
<td></td>
</tr>
</tbody>
</table>

**Summary:**

Co-administration has not been studied but is not recommended. Quetiapine is primarily metabolised by CYP3A4 and co-administration with ketoconazole (a CYP3A4 inhibitor) increased quetiapine AUC by 5-6 fold. The European product label for quetiapine contraindictates quetiapine with CYP3A4 inhibitors (such as ritonavir). However, the US product label recommends that quetiapine should be reduced to one sixth of the original dose if coadministered with a potent CYP3A4 inhibitor. The decision to modify the dosage should be done in consultation with a specialist in mental health medicine as it could destabilize a patient. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, the adjusted dose of quetiapine would have to be maintained up to 3 days after the last dose of nirmatrelvir/ritonavir. Similarly, if it is decided to pause quetiapine during nirmatrelvir/ritonavir treatment, quetiapine would have to be resumed 3 days after the last dose of nirmatrelvir/ritonavir.

**Description:**

Co-administration is contraindicated. Increased plasma concentrations of quetiapine may lead to coma. Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase.

**Paxlovid Summary of Product Characteristics, Pfizer Ltd, February 2022.**

Co-administration may increase quetiapine concentrations. If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.

**Paxlovid FDA Emergency Use Authorisation, Pfizer Inc, April 2022.**

*slides courtesy of Jennifer Schimmel MD, 2022*
Executive Summary

- Nirmatrelvir/ritonavir (PAXLOVID) is the preferred treatment for most patients with mild-to-moderate COVID-19 at high risk of progression to severe disease and continues to be widely available and in adequate supply in Massachusetts.
- The dose pack presentation of nirmatrelvir/ritonavir (PAXLOVID) for individuals with moderate renal impairment has been updated.
Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Last Updated: May 6, 2022 - Version 1.2*

Nirmatrelvir/ritonavir has FDA Emergency Use Authorization to treat mild-to-moderate COVID-19 in patients at high risk of progression to severe disease who are ≥12 years of age and weigh ≥40 kg.

In such patients, IDSA guidelines suggest nirmatrelvir/ritonavir be initiated within 5 days of symptom onset. Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive nirmatrelvir/ritonavir. NRT guidelines also suggest nirmatrelvir/ritonavir for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk of disease progression.

Given conformation with ritonavir as a pharmacokinetic booster, there is potential for drug interactions. The following steps can be taken to minimize the risk of drug interactions for those who are eligible and would benefit from nirmatrelvir/ritonavir treatment:

1. Obtain a complete list of the patient's current medications, including over-the-counter agents and herbal supplements.
2. Confirm that the patient is taking each medication as prescribed. If the patient is not taking a medication, discontinue the medication from their medication profile.
3. Review the FDA Paxlovid Healthcare Provider Fact Sheet to identify any medications that the patient is currently taking that are contraindicated with nirmatrelvir/ritonavir. If the patient is taking a contraindicated medication, prescribe alternative treatment for mild to moderate COVID-19.
4. Review potential drug interactions between nirmatrelvir/ritonavir and the patient's current medications.

Resources:
• Liverpool COVID-19 Interactions (covid19-druginteractions.org)
• Paxlovid® Healthcare Providers Fact Sheet
• PAZLOVIR® Patient Eligibility Screening Checklist Tool for Prescribers (idsa.org)
• Nirmatrelvir/Ritonavir (Paxlovid®): What Prescribers and Pharmacists Need to Know - Ontario COVID-19 Science Advisory Table (covid19-scientifictable.ca)

5. Advise the patient on dose adjustments, temporary cessation of medication(s), or clinical monitoring that is needed during and after the 5 day nirmatrelvir/ritonavir treatment.
6. If relapse occurs after initial treatment and a second course of treatment is warranted, duration of treatment should be used to guide adjustments to concomitant medications.

*: Version 1.1 contains the following correction: “201” has been changed to “301” in the sentence that originally read: “Among the top 200 prescribed drugs, only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: rivaroxaban and salmeterol.

Among the top 100 prescribed drugs, only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: rivaroxaban and salmeterol.

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>Nirmatrelvir/ Ritonavir Effect on Drug Level</th>
<th>Possible Effect</th>
<th>Recommendation During Nirmatrelvir/Ritonavir Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td>Increased bleeding</td>
<td>Avoid nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td>Salmeterol</td>
<td></td>
<td>Increased cardiac effects</td>
<td>Avoid nirmatrelvir/ritonavir</td>
</tr>
</tbody>
</table>

The following table contains information on management of commonly prescribed medications that are known to interact with nirmatrelvir/ritonavir. This list was derived from Clinical's Top 200 Prescribed Medications in the United States in 2019. Please note:

• Inclusion on this list is not a contraindication to prescribe nirmatrelvir/ritonavir. Rather, additional management considerations may be necessary as shown below.
• If a drug is not on this list, it should still be checked for interactions, as it may be a less commonly prescribed medication that has interactions or is contraindicated.
• Routine lab testing for transaminases or creatinine is not needed, and clinical judgement should be used.

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>Nirmatrelvir/ Ritonavir Effect on Drug Level</th>
<th>Possible Effect</th>
<th>Recommendation During Nirmatrelvir/Ritonavir Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td></td>
<td>Excess sedation</td>
<td>Consider dose reduction, but do not stop if chronic use</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
<td>Increased Sedation</td>
<td>Consider dose reduction, but do not stop if chronic use</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td>Increased bleeding</td>
<td>Dose dependent: Apixaban 2.5 mg: Avoid nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apixaban 10 mg: Reduce dose by 50% until 3 days after nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td>Increased cardiac effects</td>
<td>Avoid nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td>BEZ235</td>
<td></td>
<td>Decreased effects</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Buspirone</td>
<td></td>
<td>Decreased effects</td>
<td>Reduce dose or monitor for side effects</td>
</tr>
<tr>
<td>Buspirone</td>
<td></td>
<td>Increased side effects</td>
<td>Reduce dose or monitor for side effects</td>
</tr>
<tr>
<td>Calcium-channel blockers (amilodipine, diltiazem)</td>
<td></td>
<td>Decreased blood pressure</td>
<td>Continue if tolerated based on symptoms.</td>
</tr>
<tr>
<td>Calcium-channel blockers (amlodipine, verapamil)</td>
<td></td>
<td>Decreased blood pressure</td>
<td>Reduce dose if patient has low blood pressure</td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td>Excess sedation</td>
<td>Consider dose reduction, but do not stop if chronic use</td>
</tr>
</tbody>
</table>

Example Provider Communication

Dear Providers

As we face rising numbers of COVID cases, we wanted to ensure that all providers are equipped with the tools to treat mild/moderate COVID in outpatients. Please see the summary below, as well as the attached information sheets.

1. Preferred therapy: Paxlovid (nirmatrelvir/ritonavir)
   - Within 5 days of symptom onset
   - 5-day course of oral therapy
   - Check drug-drug interactions (www.covid19-druginteractions.org)
   - Prescribe through any participating pharmacy. Free of charge, regardless of insurance status. See list of pharmacies at MA COVID-19 Therapeutics Locator

2. If Paxlovid not appropriate or available: Remdesivir
   - Within 7 days of symptom onset
   - 3-day course of intravenous therapy
   - Refer to Gothsam

3. If neither Paxlovid nor remdesivir appropriate or available: Beltevilinab (monoclonal Ab)

slides courtesy of Jennifer Schimmel MD, 2022
COVID-19 UPDATE:
FOCUS ON SARS-CoV-2 VARIANTS, INCLUDING BA.4 AND BA.5

David J. Weber, MD, MPH, FIDSA, FSHEA, FRSM (London)
Sanders Distinguished Professor of Medicine, Pediatrics and Epidemiology
Associate Chief Medical Officer
Medical Director, Hospital Epidemiology
Recently emerged Omicron sublineages: BA.2.12.1, BA.2.13, BA.4 and BA.5; all contain L452 mutations and show higher transmissibility over BA.2. It is currently unknown how differences in the mutation profiles of BA.4 and BA.5, relative to BA.2, will impact on the phenotype. Changes at spike amino acids 452, 486 and 493 are likely to influence human angiotensin-converting enzyme-2 (hACE2) and antibody binding. The 452 residue is in immediate proximity to the interaction interface of the hACE2 receptor. The L452R mutation has been associated with an increased affinity for receptor binding with a resultant increased infectivity. The L452R mutation is also present in the Delta, Kappa and Epsilon variants (and L452Q in Lambda), and mutations at this position have been associated with a reduction in neutralization by monoclonal antibodies (particularly class 2 antibodies) and polyclonal sera. Mutations at this position (L452R/M/Q) have also arisen independently in at least four BA.2 sublineages in different parts of the world, most notably BA.2.12.1.

https://www.who.int/activities/tracking-SARS-CoV-2-variants
COVID-19 VARIANTS: HISTORY

Waves of Variants in the United States

Current variants of concern

- **Omicron** B.1.1.529: Identified in southern Africa in Nov 2021 and spread around the world. Within a month it was dominant in the U.S.
- **Delta** B.1.617.2: Emerged in India in late 2020 and spread around the world. Delta carries the L452R spike mutation, among others.
- **Gamma** P1: Emerged in Brazil in late 2020.
- **Alpha** B.1.1.7: Emerged in Britain in late 2020.

Current variants of interest

- **Mu** B.1.621: Emerged in Colombia in early 2021.
- **Lambda** C.37: Emerged in Peru in late 2020.

Mutations that may help the coronavirus spread

- **D614G** B.1: Appeared in early 2020 and spread around the world.
- **N501Y** Several: A defining mutation in several lineages, including B.1.1.7 (Alpha), B.1.351 (Beta) and P1 (Gamma). Helps the virus bind more tightly to human cells.
- **E484K or "Eek"** Several: Appears in several lineages. May help the virus avoid some kinds of antibodies.
- **K417** Several: Appears in several lineages, including B.1.351 (Beta) and P.1 (Gamma). May help the virus bind more tightly to cells.
- **L452R** Several: Appears in several lineages, including B.1.617.2 (Delta).

SARS-CoV-2 VARIANTS PER COUNTRY

21.K = BA.1
21.L = BA.2
22A = BA.4
22B = BA.5
22C = BA.2.12.1

CoVariants, GISAID
https://covariants.org/
SARS-CoV-2 Variants: US (April 30) & UNC-MC (May 5)

Variants of concern (CDC) = Omicron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages)

Continued Emergence and Evolution of Omicron in SA: New BA.4 and BA.5 lineages

• Assessment new lineages BA.4 and BA.5, South Africa

• Results: The spike proteins of BA.4 and BA.5 are identical, and comparable to BA.2 except for the addition of 69-70del, L452R, F486V and the wild type amino acid at Q493. BA.4 and BA.5 have rapidly replaced BA.2, reaching more than 50% of sequenced cases in South Africa from the first week of April 2022 onwards. Using a multinomial logistic regression model, we estimate growth advantages for BA.4 and BA.5 of 0.08 (95% CI: 0.07-0.09) and 0.12 (95% CI: 0.09 - 0.15) per day respectively over BA.2 in South Africa. {this growth advantage is similar to that observed for BA.2 over BA.1.}

• Reasons for growth advantage: (i) an increase in its intrinsic transmissibility relative to other variants, (ii) an increase relative to other variants in its capacity to infect, and be transmitted from, previously infected and vaccinated individuals or (iii) both. Given that the transmission advantage becomes apparent approximately four months from the start of the Omicron wave, it is plausible that waning immunity (particularly that acquired from BA.1 infection) is an important contributory factor.

BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection

- Assessment of BA.2.12.1, BA.4, and BA.5; China
- Study showed that BA.2 sublineages, including A.2.12.1 and BA.2.13, exhibit increased ACE2-binding affinities compared to BA.1; while BA.4/BA.5 displays the weakest receptor-binding activity due to F486V and R493Q reversion. Importantly, compared to BA.2, BA.2.12.1 and BA.4/BA.5 exhibit stronger neutralization evasion against the plasma of 3-dose vaccinees and, most strikingly, of vaccinated BA.1 convalescents. As for therapeutic Nabs, LYCoV1404 (Bebtelovimab) and COV2-2130 (Cilgavimabcan) still effectively neutralize BA.2.12.1 and BA.4/BA.5, while the S371F, D405N and R408S mutations carried by BA.2/BA.4/BA.5 sublineages would undermine most broad sarbecovirus Nabs.
- Results indicate that Omicron can evolve mutations to specifically evade humoral immunity elicited by BA.1 infection. The continuous evolution of Omicron poses great challenges to SARS-CoV-2 herd immunity and suggests that BA.1-derived vaccine boosters may not be ideal for achieving broad-spectrum protection.

Omicron sub-lineages BA.4/BA.5 escape BA.1 infection elicited neutralizing immunity

Methods: We isolated live BA.4 and BA.5 viruses and tested them against neutralizing immunity elicited to BA.1 infection in participants who were Omicron/BA.1 infected but unvaccinated (n=24) and participants vaccinated with Pfizer or J&J vaccines with breakthrough Omicron/BA.1 infection (n=15).

Results: In unvaccinated individuals, FRNT50, the inverse of the dilution for 50% neutralization, declined from 275 for BA.1 to 36 for BA.4 and 37 for BA.5, a 7.6 and 7.5-fold drop, respectively. In vaccinated BA.1 breakthroughs, FRNT50 declined from 507 for BA.1 to 158 for BA.4 (3.2-fold) and 198 for BA.5 (2.6-fold). Absolute BA.4 and BA.5 neutralization levels were about 5-fold higher in this group versus unvaccinated BA.1 infected participants.

Conclusion: The observed escape of BA.4 and BA.5 from BA.1 elicited immunity is more moderate than of BA.1 against previous immunity. However, the low absolute neutralization levels for BA.4 and BA.5, particularly in the unvaccinated group, are unlikely to protect well against symptomatic infection. This may indicate that, based on neutralization escape, BA.4 and BA.5 have potential to result in a new infection wave.

Background: Omicron BA.2.11, BA.2.12.119 and BA.4/5 subvariants are becoming dominant in France, US and South Africa, respectively.

Study goal: Assess the sensitivity of these new Omicron subvariants (BA.2.11, BA.2.12.1 and BA.4/5) to eight therapeutic monoclonal antibodies (bamlanivimab, bebtelovimab, casirivimab, cilgavimab, etesevimab, imdevimab, sotrovimab and tixagevimab).

Results: Although cilgavimab is antiviral against BA.2, BA.4/5 exhibits higher resistance to this antibody compared to BA.2. Bamlanivimab, casirivimab, tesevimab, imdevimab and tixagevimab were not functional against BA.2. Bebtelovimab was ~2-fold more effective against BA.2 and all Omicron subvariants tested than the parental virus. Omicron subvariants bearing L452R substitution including BA.2.11 and BA.4/5 were more sensitive to sotrovimab than BA.2. Cilgavimab was also antiviral against BA.2, while the L452R; BA.4/5 exhibited ~30-fold more resistance to cilgavimab compared to BA.2

Yamasoba D, et al. https://doi.org/10.1101/2022.05.03.490409