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GW Covid-19 Intelligence Unit-Brief Report Omicron Variant of SARS-CoV2

George Washington University

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GW COVID-19 Intelligence Unit – Brief Report
Omicron Variant of SARS-CoV2

Authors' Summary: *The national capital region and much of the U.S. is currently experiencing a surge in COVID-19 diagnoses and critical health care workforce shortages due to the rise of a new SARS-CoV2 variant. Critically, the Omicron variant seems to generate higher viral loads faster in the upper airways, and has substantial difference in epitopes leading to enhanced ability to cause infection in previously immune/vaccinated persons, compared even to the Delta variant. While early data suggests that disease caused by the Omicron variant is milder on average, and severe cases in immunocompetent people who have received third or "booster" doses of vaccine remain rare, a significant proportion of the population remains at risk, especially medically vulnerable and unvaccinated persons. Coupled with increased transmission due to holiday gatherings, discontinuation of public precautions, social divisions, and lack of clarity in public messaging, key healthcare resources including emergency, critical, pediatric, and nursing care is affecting the availability and quality of medical care for other conditions as well. While previous strategies for exiting the pandemic leaned heavily on primary vaccination, with the dominance of the more highly transmissible Omicron variant it is necessary to use all available modalities of prevention – vaccination with boosters, higher-quality masking/PPE, attention to ventilation and avoiding of crowding, to "flatten the curve" and reduce overload of the health care system.*

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This edition of the COVID-19 Intelligence Report was produced by Drs. Tara Palmore, Tenagne Haile-Mariam, Farnaz Farhi, Jose Lucar, and Himmelfarb Librarian Stacy Brody, for the GW Intelligence Unit led by Dr. Lawrence Deyton and Dr. Hana Akselrod.

Feedback and any special requests should go to: ldeyton@gwu.edu or hakselrod@gwu.edu.
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Regional situation

- The US CDC reports over 53.8 million cumulative COVID-19 cases and over 820,000 deaths.
- The CDC Nowcast estimates that approximately 95% of COVID-19 cases nationally and in the Mid-Atlantic Region (including Washington, DC) are currently due to the Omicron variant.
- As per DC district government data, community transmission skyrocketed in December 2021, with daily cases reaching unprecedented rates in excess of 200 per 100,000 population.
- The relatively high vaccination rate in DC (~67% of residents having completed primary vaccination series) along with other regional variables including public health policy are believed to have been protective up to this point in the pandemic. However, with substantial disparities in vaccine coverage by ward, neighborhood, and age group, along with a highly mobile population and discontinuation of key pandemic precautions on the public level, DC is experiencing a surge.
- DC Mayor's Office in late December has re-issued guidance for masks in indoor settings and issued new requirements for proof of vaccination to enter certain indoor facilities.
- At this time many Emergency Departments in our region are experiencing long wait times and may be diverting ambulances due to surging numbers of patients coupled with shortages in staffing. The University of Maryland system is currently operating under crisis standards of care.
- The CDC and DC Health have issued updated and evolving guidance on isolation and quarantine.

What is currently known about the Omicron variant

- Omicron (B.1.1.529) was detected in samples from South Africa, Botswana, and Hong Kong in late November due to its S gene target failure (i.e. missing one of three common targets identified by PCR testing). When it was detected, it had already spread widely in Gauteng province and, as sequencing later revealed, was already spreading in multiple countries around the world.
- Omicron has elevated transmissibility, which modeling suggests is due in part to immune evasion and due in part to more rapid replication in the airways. A study demonstrated 70 times faster replication in bronchial tissue than Delta or the original wild type SARS-CoV-2. However, its replication in the lungs and therefore severe disease may be lower based on animal model studies.
- A cohort study among households in the UK found significantly higher household transmission from Omicron index cases compared to Delta (adjusted odds ratio 3.2, 95% CI 2.0-5.0, p <0.001).
- In a Danish household infection study, during a one-week follow-up period, secondary attack rate was 21% with Delta and 31% with Omicron, with evidence of significant immune evasion.
- Epidemiological data demonstrate that the incubation period of omicron is shorter than that of previous variants. Whereas median incubation for the original SARS-CoV-2 was ~5-6 days, and that for previous variants was 4-5, the Omicron incubation period appears to be 3 days.
- Disease severity in the U.S. remains uncertain, as the age range, prevalence of relevant chronic comorbidities, and vaccine status of the U.S. population differ from those in early-hit countries.
- In South Africa, hospitalizations were lower than those seen during the Delta surge and Omicron-infected patients had a reduced severity of disease compared with Delta-infected patients.
- Preliminary data from Ontario suggest disease severity may be about 50% lower than that seen during the wave of Delta variant. A study from the UK showed the risk of hospitalization or ED visit with Omicron to be 2/5 that of Delta. A separate study from Imperial College London showed that patients with Omicron infection had 15-25% (Hazard ratio 0.8; 95% CI 0.75-85) reduced risk of ED visit and 40-49% (HR 0.55, 95% CI 0.51-59) reduced risk of hospitalization.
- Important caveats in the discussion of disease severity are 1) that a large surge with reduced severity of disease will still result in a large absolute number of hospitalizations and deaths, and 2) that the mortality of hospitalized patients with COVID increases when hospital case-loads surge.
- While most PCR tests in commercial use do not distinguish between variants, more specialized and public health labs can test for S-gene target failure or use genomic sequencing to identify Omicron variants. Most antigen tests currently in use are believed to remain accurate, however scientific studies are ongoing and the FDA keeps track of tests whose performance is affected.

Efficacy of currently available vaccines against the Omicron variant

A. Efficacy of COVID-19 vaccination re: Omicron and severe disease

- Evidence at this point consistently indicates that vaccine immunogenicity, efficacy in trials, and effectiveness in practice after primary vaccination series with either mRNA and J&J vaccines, all:
  1. Decline substantially with time against all variants in the general population.
  2. Decline more in persons who are older, immunocompromised, or have multiple comorbidities
  3. Are significantly lower against the Omicron variant compared to all prior variants
  4. Increase in persons who receive a booster dose of vaccine after completing the primary series
  - While severe disease is less likely to occur in people who were previously vaccinated, those at high risk (especially frail elderly or immunocompromised patients) are still at substantial risks of poor outcomes. Additionally the untrammeled spread of SARS-CoV2 in the community increases the odds of transmission to a vulnerable person as well as the emergence of further immune-evading variants.
  - This has led to expert consensus that all persons eligible for a booster dose should get one. Although the CDC has not changed its prior definition of "fully vaccinated" it has recommended that all persons "should get" a booster. This would effectively render the primary series, or the definition of "fully vaccinated" to a 3-dose series for mRNA vaccines and a 2-dose series for the J&J vaccine.
  - The recommendation and use of additional vaccine doses (as part of an "accelerated" primary series or for booster) in certain countries and communities when vaccines have not been made available to persons in under-resourced areas globally has raised both the issues of vaccine equity and the concomitant increased risk of evolving additional variants of concern (VOC).

B. Current CDC recommendations

- These are the **current vaccine recommendations**, U.S. dosing schedules, including guidance for additional doses for immunocompromised patients and booster doses for the general population.
- The CDC has shortened the time interval to receive Pfizer boosters to 5 months after completion of the primary series. The interval for Moderna vaccine remains 6 months and for J&J 2 months.

C. Vaccinations and prevention of Omicron infection in special populations

- CDC definitions for persons at increased risk of severe COVID-19 can be found here; note the inclusion of people who are pregnant or have recently given birth in this group.
- Severely immunocompromised (i.e. those recommended to receive additional doses of vaccines before the general recommendation for population-wide boosters, and those prioritized for treatment with monoclonal antibody products as discussed below) groups are found here.
- Pregnant and recently pregnant patients with COVID-19 are at increased risk of more severe illness compared with nonpregnant peers, with adjusted risk ration increased 3-fold for ICU admission, 2.9-fold for invasive ventilation, 2.4-fold for ECMO, and 1.7-fold for death. Pregnant and recently pregnant patients with comorbidities such as obesity and diabetes may be at an even higher risk of severe illness compared with the general population with similar comorbidities.
- A large multinational study showed significantly higher risk of pregnancy complications, preterm birth, severe neonatal morbidity and mortality, among patients with COVID-19.
- All leading national clinical and public health authorities (e.g. CDC, ACOG, AAP) **strongly recommend** that all (including those with prior COVID-19 infection) pregnant and lactating persons receive COVID-19 vaccination.
- It is safe to initiate and continue breastfeeding by patients who receive a COVID-19 vaccine.
- COVID-19 vaccine can be administered simultaneously with other vaccines that are routinely given during pregnancy (such as influenza and Tdap).

- The CDC/FDA/ACIP continue to monitor vaccine safety in pregnancy through tools such as such VAERS, V-safe, and VSD. Findings are regularly updated by the CDC.
- National and international efforts to document the impact of COVID-19 infections on pregnant people and their babies continue both nationally and internationally.

D. Update on Johnson & Johnson / Janssen (J&J) vaccine

- After further review of safety and efficacy data, the CDC now considers mRNA vaccines preferred over J&J/Janssen for both primary and booster vaccinations. Exceptions can be made for patients who would otherwise remain unvaccinated due to a severe allergy, vaccine availability or personal preference.
- After initially receiving FDA EUA status in 2/2021 as a one-dose primary series for persons over 18, in 4/2021 use of the J&J vaccine was paused by joint CDC-FDA statement citing 6 cases of cerebral venous sinus thrombosis among the 6.8+ million persons who had been received the J&J vaccine nationally, prompting further review. Later that month its use was reinstated on the opinion that the benefit of administration outweighed risk.
- In 10/2021 the FDA EUA was expanded to allow use of the J&J vaccine as booster both after J&J primary dose (encouraged due to evidence of greater decline in immunity) and as "mix and match" for mRNA vaccines.
- In 12/2021 citing both ongoing concerns for side effects profile and adequate nationwide supply of mRNA vaccine, CDC has stated a preference for mRNA vaccines over J&J given in almost all instances including as a booster dose. Ongoing data collection regarding efficacy against Delta and Omicron VOC is likely to show higher efficacy of mRNA vaccines as well.
- As of mid-December 2021, 57 cases of thrombosis with thrombocytopenia syndrome (TTS) have been confirmed among 17.2 million doses of J&J vaccine doses administered. Although TTS has been reported with mRNA COVID-19 vaccines (3 cases/470 million doses), an increased risk has not been determined. See American Society of Hematology diagnostic criteria/recommendations for TTS.
- Rate of Guillain-Barré Syndrome (GBS) was found to be 21x and 11x higher, within 21 and 42 days of administration of J&J vaccine respectively compared to mRNA vaccine.

E. Update on myocarditis and pericarditis associated with COVID-19 vaccination

- Per VAERS data as of 10/2021, 3,336 cases of myocarditis were reported in >400 million vaccine doses; myocarditis was ~17 times more likely to occur with mRNA vaccines than with J&J, with most cases occurring in adolescent and young adult males, and more likely to occur after the 2nd dose. Most cases were self-resolved or treated successfully to hospital discharge.
- No significant concerns over myocarditis risk have been raised with boosters up to this point and the FDA has now authorized use of the Pfizer mRNA vaccine as booster for 12-to-15-year olds.

F. "Mix and match" (heterologous booster doses) vaccination strategies and schedules

- Vaccination protocols that deviate from EUA or approved vaccinations or schedules have the potential to alter vaccine immunogenicity, efficacy, or effectiveness. Reasons for such alterations can include**:**
  1. Delivery and equity, i.e. when decreased availability or high cost of vaccine makes it difficult to maintain vaccine schedules and/or vaccinate the maximum number of eligible persons.
  2. Evidence that efficacy improves from changing dosing intervals and/or administering mixed vaccine series. For example, in some studies increasing the interval by several weeks led up to a tenfold increases antibody levels and was associated with vaccine effectiveness.

3. Evidence that efficacy is not harmed, and may improve from heterologous vaccine series.
4. To improve the benefit: risk profile of vaccine administration on an individual (e.g. due to known allergy) or population (e.g. TTS with J&J) based on current evidence.

Currently CDC recommends:

1. Completing primary 2-dose mRNA series with same vaccine (Pfizer or Moderna preferred)
2. Boosting all eligible persons
   - Can use either Pfizer or Moderna to boost for ≥18 years
   - Pfizer booster approved for those aged 12-17 years
   - Additional doses of Pfizer approved for certain immunocompromised 5-11 year old children
3. J&J is not preferred but may be used as either a primary or booster vaccine in cases where the patient would otherwise remain unvaccinated or unboosted

Efficacy of currently available therapeutic products against Omicron

A. Monoclonal antibodies (SUMMARY)

- Laboratory-produced monoclonal antibodies (mAbs) against the spike protein of SARS-CoV-2 work by blocking viral entry into host cells.
- Currently, casirivimab-imdevimab (REGEN-COV), bamlanivimab-etesevimab, and sotrovimab are authorized for the **treatment** of outpatients with mild to moderate COVID-19 disease who are at high risk for progressing to severe COVID-19 and/or hospitalization. These may be given to inpatients with mild COVID-19 who are hospitalized for another reason. Following *in-vitro* studies showing loss of neutralization activity against the Omicron variant by the first two products, their distribution was paused. *At present, all three products are being distributed, however, only sotrovimab has shown neutralization activity against the Omicron variant.*
- Additionally, casirivimab-imdevimab and bamlanivimab-etesevimab are authorized for **post-exposure prophylaxis** in patients who have a recent confirmed SARS-CoV-2 exposure, and are at high risk for progression to severe COVID-19, and are immunocompromised or not fully vaccinated. Distribution of both products is on hold due to loss of efficacy against Omicron.
- A fourth mAb product, tixagevimab-cilgavimab (Evusheld), is authorized for **pre-exposure prophylaxis** in patients who are not infected with SARS-CoV-2 and have not had a recent exposure, who are moderately to severely immunocompromised or are unable to receive any COVID-19 vaccine (i.e., severe adverse reaction). It is expected to retain activity against Omicron at least partially. Its distribution via the US DHHS to infusion sites is now beginning.
- **For a more detailed profile of each mAb product please see SUPPLEMENT below.**

B. Antiviral drugs (SUMMARY)

- Antiviral drugs work best if given during the period of high viral replication in earlier infection. In later stages of severe COVID-19 illness, the disease process is driven more by inflammatory mechanisms and secondary damage, and the benefit from antiviral therapy is relatively lessened while anti-inflammatory (steroids) and immunomodulating therapies (e.g. tocilizumab, baricitinib) play a greater role. This approach is summarized in current NIH guidelines.
- Two new oral drugs received FDA EUA in 12/2021. The first, nirmatrelvir/ritonavir (Paxlovid), combines a novel protease inhibitor specific to SARS-CoV2 with ritonavir, a phamracologc booster used for over 20 years in HIV treatment. Trial results showed a significant reduction in COVID-19-related hospitalization or death from any cause, as well as faster clearance of virus. The study was done during the Delta wave but *in vitro* data suggests that activity is maintained against Omicron. When prescribing, close attention must be paid to renal function and drug-drug interactions. US DHHS is expected to start distributing this product soon to select pharmacies.

- The second, molnupiravir (Lagevrio), is a novel drug that interferes with SARS-CoV-2 viral genome replication. Trial data showed a more modest but statistically significant reduction in hospitalization or death, and there are more concerns about drug safety based on the potential for teratogenicity and mutagenicity. The EUA for molnupravir states it should only be prescribed when "alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate." US DHHS is expected to start distributing this product soon.
- The intravenous drug remdesivir (Veklury) has been in broad use since fall 2020 in hospitalized patients, under FDA EUA. Based on its mechanism of action, remdesivir is expected to remain active against the Omicron variant. More recent RCT data suggests it may be beneficial to ambulatory patients with risk factors for severe disease if given as an infusion for three days earlier in the illness. Operational and supply-chain issues may limit the utility of this approach.
- **For a more detailed profile of each mAb product please see SUPPLEMENT below.**

Public Perception in the Washington, DC Region

- Recent news articles reflect increasing worries, particularly among vaccinated adults, but reluctance to return to more conservative behaviors (KFF COVID-19 Vaccine Monitor: Early Omicron Update | KFF; In the face of another winter COVID surge, will Marylanders be willing to compromise? - Baltimore Sun; D.C. Reinstates Mask Mandate And Expands Access To Rapid Testing Amid COVID-19 Surge – DCist). There is a level of pandemic fatigue and a recognition of the emotional toll of restricting movement and social gatherings. Though there may be reluctance to reinstating restrictions, vaccinated adults feel motivated to get a booster shot in response to the new variant, omicron (KFF COVID-19 Vaccine Monitor: Early Omicron Update | KFF)
- Throughout the fall (September 2021 - November 2021), D.C. trended more cautious in norms and behaviors than the country as a whole, particularly with regards to mask wearing, and a low proportion of the population expressed no concern about catching COVID-19 (COVID Behaviors Dashboard - Johns Hopkins Center for Communication Programs; COVID STATES PROJECT (shinyapps.io)).
- Data dating to December 2, 2021 shows that, compared to last November, D.C. residents were generally more likely to engage in activities outside the home and less likely to adhere to health recommendations (COVID STATES PROJECT (shinyapps.io)).
- In response to the current surge in cases, schools, religious institutions, and businesses have closed or returned to virtual programming and services (COVID Cases Are At All-Time High In D.C. – And Among The Worst In The Country – DCist, D.C. Reinstates Mask Mandate And Expands Access To Rapid Testing Amid COVID-19 Surge – DCist). Prior to the holiday break, D.C. educators expressed strong concerns about their risk of contracting COVID-19 and launched an online petition to move to virtual learning ('A Train Wreck In Slow Motion:' COVID Cases Rise In Some D.C. Schools, Straining Teachers And Families – DCist, Petition · DCPS needs to pivot to virtual learning for all schools Dec 20-22 · Change.org).
- Interest in COVID-19, as illustrated by Google Search Trends in the D.C. Metro Area, has increased, beginning in early December and reaching levels not seen since May 2020, though not as high as the peak in March 2020. (Interest over time on Google Trends for Coronavirus disease 2019 - Washington DC (Hagerstown MD), 12/3/19 - 1/3/22)

SUPPLEMENT: Detailed Monoclonal Antibody Product Information

A. Monoclonal antibodies

a. **Casirivimab-imdevimab** (AKA REGEN-COV or Ronapreve®) was granted emergency use authorization (EUA) by the FDA to treat mild to moderate COVID-19 in those at high risk for progression to severe COVID-19 based on a phase 3, randomized, placebo-controlled, outpatient clinical trial that demonstrated a significant reduction in COVID-19–related hospitalization or any cause mortality, with faster resolution of symptoms and viral load reduction compared to placebo. Casirivimab-imdevimab was also granted EUA as post-exposure prophylaxis (PEP) based on a separate clinical trial in asymptomatic household contacts of individuals with SARS-CoV-2 infection that demonstrated a significant reduction of asymptomatic infection and symptomatic COVID-19 compared to placebo. Both clinical trials were conducted prior to the emergence of the Delta and Omicron variants. *In vitro* viral neutralization assays [Wilhelm et al, Planas et al, Planas et al (preprint)] have shown that casirivimab-imdevimab is expected to retain activity against the Delta variant. A retrospective study suggested that at-risk outpatients that presented during a Delta surge and were treated with casirivimab-imdevimab had lower rates of hospitalization compared to untreated patients. Also, another retrospective study that is not yet peer-reviewed reported that casirivimab-imdevimab administration in patients with mild-to-moderate COVID-19 during the Delta variant surge, and who were eventually hospitalized, was independently associated with a lower likelihood of subsequent clinical deterioration. On the other hand, several recent not-yet-peer-reviewed studies (Aggarwal et al, Syed et al, Wilhelm et al, Ikemura et al, Sheward et al, Liu et al, Cameroni et al, VanBlargan et al, Planas et al, Hoffmann et al, Dejnirattisai et al) have reported that casirivimab-imdevimab has no significant *in vitro* neutralization activity against the Omicron variant and as such is highly unlikely to play any significant role in the treatment or post-exposure prophylaxis against this variant. Based on these results, as well as with the rising prevalence of the Omicron variant in the US, on December 23, 2021 the ASPR temporarily paused allocation of casirivimab-imdevimab. This has now restarted.

b. **Bamlanivimab-etesevimab** was granted EUA to treat mild to moderate COVID-19 in those at high risk for progression to severe COVID-19 based on a phase 3, randomized, placebo-controlled, outpatient clinical trial that showed a significant reduction in COVID-19–related hospitalization or death of any cause, as well as more rapid resolution of symptoms and viral load decline compared to placebo. A follow up portion of the same clinical trial using lower doses of bamlanivimab and etesevimab confirmed the previous findings with a comparable efficacy profile. Bamlanivimab-etesevimab was also granted EUA as post-exposure prophylaxis after extrapolating data from a separate clinical trial of residents and staff at US skilled nursing and assisted living facilities that had at least 1 confirmed SARS-CoV-2 index case in the previous 7 days. In that study, a single infusion of bamlamivimab alone reduced the incidence of mild or worse COVID-19 compared with placebo. Both clinical trials were conducted prior to the emergence of the Delta and Omicron variants. *In vitro* viral neutralization assays [(Planas et al, Gruell et al (preprint), Ikemura et al (preprint), Planas et al (preprint)] have shown that bamlanivimab-etesevimab combination, but not bamlanivimab alone, is expected to retain activity against the Delta variant, although it may have reduced activity against certain Delta sublineages (AY.1/AY.2). On the other hand, recent not-yet-peer-reviewed studies have reported that bamlanivimab-etesevimab (Gruell et al, Sheward et al, Liu et al, Cameroni et al, VanBlargan et al, Planas et al, Hoffmann et al, Dejnirattisai et al) or bamlanivimab alone (Aggarwal et al) have no significant *in vitro* neutralization activity against the Omicron variant and as such are highly unlikely to play any significant role in the treatment or post-exposure prophylaxis against this variant. Based on these results, as well as with the rising prevalence of the Omicron variant in the US, on December 23, 2021 the ASPR temporarily paused allocation of casirivimab-imdevimab. This has now restarted.

c. **Sotrovimab** (AKA VIR-7831) was granted EUA by the FDA to treat mild to moderate COVID-19 in those at high risk for progression to severe COVID-19 based on the prespecified interim

analysis of a phase 3, randomized, placebo-controlled, outpatient clinical trial that demonstrated a significant reduction in progression of COVID-19 versus placebo. The clinical trial was conducted prior to the emergence of the Delta variant. Sotrovimab is not authorized for PEP at this time. Additional sotrovimab studies evaluating the role of intramuscular (IM) administration for both treatment and prophylaxis are ongoing. A recent press release by the manufacturer preliminarily reported non-inferiority of IM compared to IV administration for the treatment mild to moderate COVID-19 in those at high risk for disease progression; complete data set and publication are not yet available. Recent not-yet-peer-reviewed studies that performed *in vitro* viral neutralization assays have shown that sotrovimab (or its parental form S309) appears to retain activity against both Delta and Omicron variants (Cathcart et al, Sheward et al, Liu et al, Mannar et al, Cameroni et al, VanBlargan et al, Planas et al, Hoffmann et al, Dejnirattisai et al). The federal government's current supply of sotrovimab remains extremely limited at this time.

d. Tixagevimab-cilgavimab (AKA AZD7442 or EVUSHELD®) was granted EUA by the FDA for pre-exposure prophylaxis (PrEP) of symptomatic COVID-19 (prior to exposure to SARS-COV-2) for individuals with moderate to severe immunocompromise (who may not mount an adequate immune response to COVID-19 vaccination) and in those for whom COVID-19 vaccination is not recommended. The full results of the randomized, placebo-controlled, outpatient phase 3 clinical trial that served as the basis of the EUA have not yet been published in a peer-reviewed journal. Primary results revealed that, at a median follow up time of 83 days (range 3 to 166 days), tixagevimab-cilgavimab significantly reduced the risk of developing PCR positive symptomatic COVID-19 compared to placebo. The duration of protection predicted by pharmacokinetic modelling is 6 months, but more follow up is needed. Only 3 subjects in that trial had confirmed infection with the Delta variant. Tixagevimab-cilgavimab is not currently authorized for treatment or PEP. Preliminary data using *in vitro* viral neutralization assays and reported by the FDA showed that tixagevimab-cilgavimab appears to retain activity against the Delta variant. However, they also reported reduced activity of tixagevimab alone, cilgavimab alone, and their combination against the Omicron variant. The manufacturer reported via a press release preclinical data findings that suggests tixagevimab-cilgavimab to still retain neutralization efficacy against the Omicron variant. Two additional not-yet-peer-reviewed studies that performed *in vitro* viral neutralization assays (VanBlargan et al, Dejnirattisai et al) have shown that although reduced, the tixagevimab-cilgavimab combination appears to maintain neutralizing activity against the Omicron variant. ASPR is expected to start distributing this product soon.

B. New oral antiviral drugs

a. Nirmatrelvir/ritonavir (AKA Paxlovid®), a novel protease inhibitor combination, was granted EUA by the FDA to treat mild-to-moderate COVID-19. Nirmatrelvir appears to inhibit viral replication by blocking the SARS-COV-2 3CL protease, which cleaves the large polyproteins produced from viral RNA to form proteins essential for viral function. Ritonavir, a drug that has been used against HIV as part of combination regimens for over 20 years, was added for a pharmacologic boosting effect. The full results of the randomized, placebo-controlled, outpatient phase 3 clinical trial that served as the basis of the EUA have not yet been published in a peer-reviewed journal. Primary results revealed that a 5-day course of oral nirmatrelvir/ritonavir significantly reduced the risk of COVID-19 related hospitalization or death from any cause compared to placebo in unvaccinated outpatients at high-risk of progression to severe COVID-19 who had symptom onset of ≤5 days. Of note, this trial excluded those individuals with history of prior COVID-19 or vaccination. The investigators also found a faster decline in viral RNA levels in nasopharyngeal samples compared to placebo. The primary SARS-CoV-2 variant in this study was Delta (98%). A separate ongoing clinical trial is evaluating nirmatrelvir/ritonavir in standard risk subjects, with interim analysis showing mixed results. The manufacturer as well as FDA report that *in vitro* biochemical assays suggest that nirmatrelvir maintains activity against the Omicron variant. A careful evaluation of drug-drug interactions must be done prior to prescribing

nirmatrelvir/ritonavir. Also, dose adjustment is needed for renal impairment (and is not recommended when eGFR is <30 mL/min or in those with severe hepatic impairment). ASPR is expected to start distributing this product soon.

b. **Molnupiravir** (AKA MK-4482 or Lagevrio®), a prodrug of a ribonucleoside analogue (NHC) that interferes with SARS-CoV-2 viral genome replication, was granted EUA by the FDA to treat mild-to-moderate COVID-19 based on the results of a randomized, placebo-controlled, outpatient phase 3 clinical trial that showed that in unvaccinated outpatients at high-risk of progression to severe COVID-19 who had symptom onset of ≤5 days, a 5-day course of molnupiravir had a modest (31%) but statistically significant relative risk reduction of hospitalization or death compared to placebo. Recently, two Indian generic manufacturers decided to halt enrollment in an outpatient moderate COVID-19 molnupravir study (which included some hospitalized subjects and individuals with oxygen saturation levels of 90%-93%) citing lack of efficacy. Data for their mild COVID-19 study is not yet available. Based on these results, the FDA EUA included language in which molnupravir should only be prescribed for "whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate". Molnupiravir is not recommended for use in pregnancy because it may cause fetal harm based on findings from animal reproduction studies. There are also theoretical safety concerns about molnupiravir potential to induce mutagenesis in human cells, however, if that were to be the case, whether it can cause any significant harm with very short courses of treatment remains uncertain. Finally, although unlikely, there are also concerns about the potential for non-lethal viral mutagenesis and selecting for new variants. Further research is ongoing. ASPR is expected to start distributing this product soon.

C. Other antiviral drugs

- **Remdesivir** (AKA Veklury®) is an IV nucleotide prodrug of an adenosine analog that interferes with the viral RNA polymerase and leads to termination of SARS-CoV-2 viral genome replication. It is FDA approved for the treatment of COVID-19 in hospitalized patients since October 2020. More recently, a randomized, placebo-controlled, clinical trial evaluated the impact of IV remdesivir in non-hospitalized patients with mild/moderate COVID-19 (symptom onset of ≤ 7 days) at high risk for disease progression. Participants assigned to the intervention arm received daily IV remdesivir infusions for 3 days, and it was associated with a significant (87%) relative risk reduction of hospitalization or death compared to placebo. It is expected that, based on its mechanism of action, remdesivir should remain active against the Omicron variant. Of note, unless the FDA approval is expanded, outpatient remdesivir administration would be an off-label use. This adds to significant logistical challenges in designing a strategy for outpatient remdesivir infusion over three consecutive days for individuals with a transmissible disease.