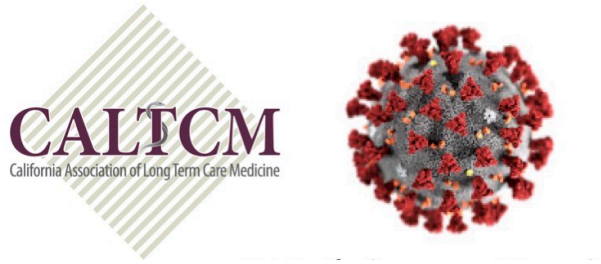

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COVID-19 Webinar Series

January 10, 2022

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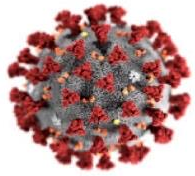

Next Webinar

February 14

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Infection Prevention & Control Resources

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Webinar Faculty

Jay Luxenberg, MD
Chief Medical Officer, On Lok
CALTCM, Wave Editor-in-Chief
San Francisco, CA

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Omicron Open Mic

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Topics for Discussion

- Provide an update on the COVID-19 surge due to the Omicron variant
- Discuss the vaccination status and its impact on the Omicron variant
- Review testing for COVID-19 infection: when to suspect Omicron
- Outline the available prophylactic and therapeutic agents for COVID-19 in the era of the Omicron variant

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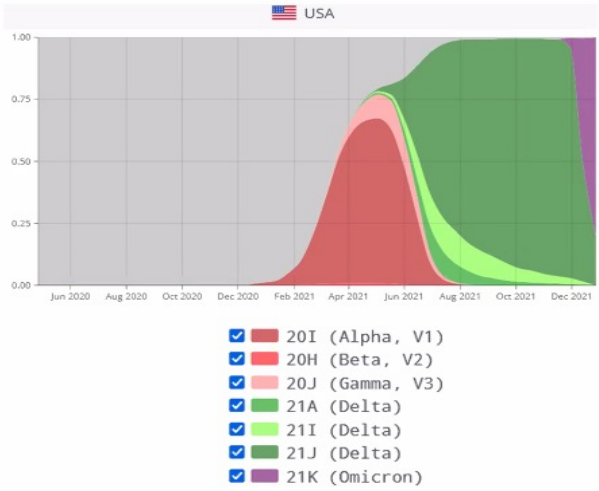
The COVID-19 Variants, Delta and Omicron United States

OMICRON, US



https://covid.cdc.gov/covid-data-tracker/#variant-proportions; https://covariants.org/per-country

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COVID-19 cases rapidly increased since the first U.S. Omicron case was reported on December 1, 2021.

January 22, 2020* - January 05, 2022

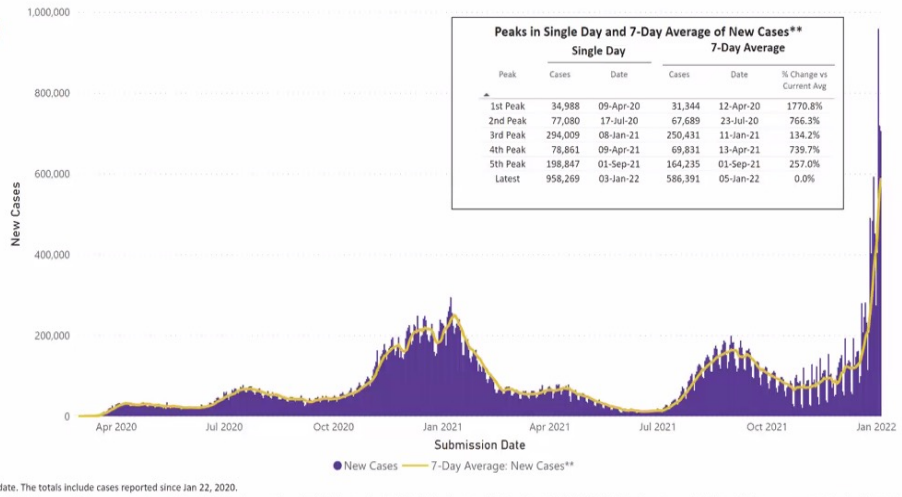
57,898,239
Total Cases Reported

705,264
New Cases Reported**

586,391
Current 7-Day Average**
Dec 30, 2021 - Jan 05, 2022

315,851
Prior 7-Day Average**
Dec 23, 2021 - Dec 29, 2021

85.7%
Change in 7-Day Average



Peaks in Single Day and 7-Day Average of New Cases**

	Single Day		7-Day Average		
Peak	Cases	Date	Cases	Date	% Change vs Current Avg
1st Peak	34,988	09-Apr-20	31,344	12-Apr-20	1770.8%
2nd Peak	77,080	17-Jul-20	67,689	23-Jul-20	766.3%
3rd Peak	294,009	08-Jan-21	250,431	11-Jan-21	134.2%
4th Peak	78,861	09-Apr-21	69,831	13-Apr-21	739.7%
5th Peak	198,847	01-Sep-21	164,235	01-Sep-21	257.0%
Latest	958,269	03-Jan-22	586,391	05-Jan-22	0.0%

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*Graph displays data for Mar 01, 2020, to date. The totals include cases reported since Jan 22, 2020.

** The histogram, total of new cases in the last 24 hours, and 7-day averages do not include historical cases retroactively that are not yet attributed to the correct date of report. Of 352,811 historical cases reported retroactively, none were reported on the most recent submission date; 134 in the current week; and 621 in the prior week.

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U.S. hospitalizations with confirmed COVID-19 are surpassing peaks from last winter.

3,773,704
Total New Admissions
Aug 01, 2020 – Jan 04, 2022

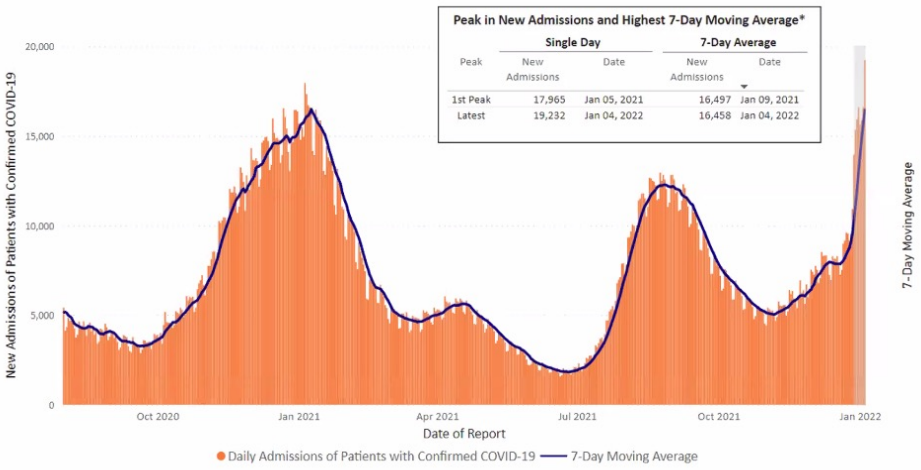
19,232
New Admissions
Jan 04, 2022

16,458
Current 7-Day Average
Dec 29, 2021 – Jan 04, 2022

10,271
Prior 7-Day Average
Dec 22, 2021 – Dec 28, 2021

+60.2%
Change in 7-Day Average

-0.2%
Change Since Peak 7-Day Average



https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions

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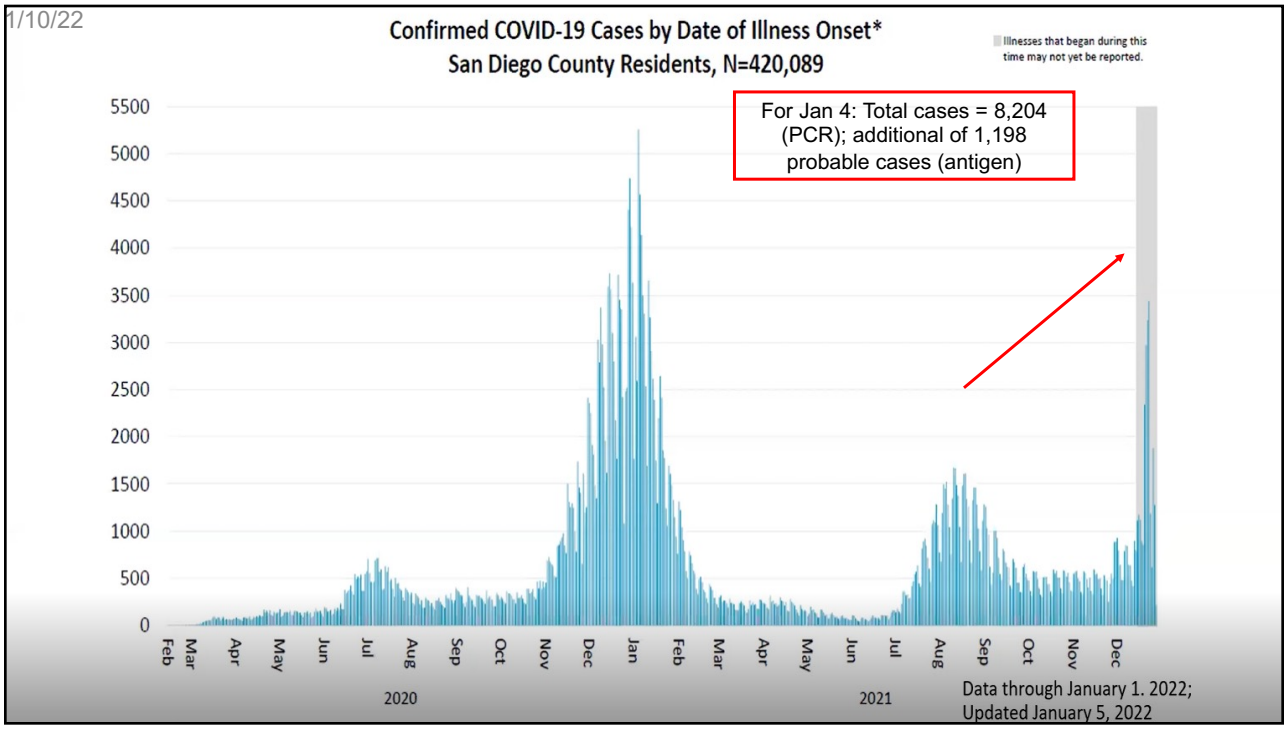

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December 30, 2021

Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves

Caroline Maslo, MD, PhD[1]; Richard Friedland, MD, BVSc[1]; Mande Toubkin, RN, RM, Rpaeds[1]; et al

> Author Affiliations | Article Information

JAMA. Published online December 30, 2021. doi:10.1001/jama.2021.24868

Table 1. Characteristics of Patients Admitted With a Positive COVID-19 Result in the 4 Waves[a]

	No. (%) of patients				
	Wave 1[a]	Wave 2	Wave 3	Wave 4	*P* value
COVID-19 patients treated	3875	4632	6342	2351	
COVID-19 patients admitted	2628 (67.8)	3198 (69.0)	4400 (69.3)	971 (41.3)	<.001
Age, median (IQR), y	53 (21.75)	54 (21)	59 (24)	36 (32)	<.001
Sex, female/male	1337/1291	1657/1541	2035/2365	590/381	<.001
Patients with comorbidities[b]	1472 (56.0)	1868 (58.4)	2311 (52.5)	227 (23.3)	<.001
Acute respiratory condition on admission	1909 (72.6)	2783 (87.0)	4013 (91.2)	307 (31.6)	<.001
Vaccination status[c]					
Vaccinated	No vaccine available	No vaccine available	No register available	235 (24.2)	
Not vaccinated				645 (66.4)	
Vaccination status unknown				91 (9.4)	

Table 2. Outcomes of Patients Admitted With a Positive COVID-19 Result in the 4 Waves[a]

	No. (%) of patients				
	Wave 1 (n = 2628)	Wave 2 (n = 3198)	Wave 3 (n = 4400)	Wave 4[b] (n = 971)	*P* value
Receiving oxygen therapy	2119 (80.3)	2624 (82.0)	3260 (74.0)	171 (17.6)	<.001
Receiving mechanical ventilation	431 (16.4)	259 (8.0)	548 (12.4)	16 (1.6)	<.001
Admission to intensive care	1104 (42)	1172 (36.6)	1318 (29.9)	180 (18.5)	<.001
Length of stay, median (IQR), d	8.0 (9)	7.8 (8)	7 (9)	3 (3)	<.001
Deaths	520 (19.7)	790 (25.5)	1284 (29.1)	27 (2.7)	<.001

[a] Wave 1: June 14-July 6, 2020; wave 2: December 1-23, 2020; wave 3: June 1-23, 2021; wave 4: November 15-December 7, 2021.

[b] Seventy-two patients (7%) still admitted.

Hospitalization rates have been relatively lower during the Omicron wave in multiple countries.

- Hospitalization rates for persons infected with Omicron: 0.4% in United Kingdom, and 0.6% in Denmark
- Risk of hospitalization due to Omicron infections estimated to be 38% (England) and 54% (Canada) lower than hospitalization for Delta infections

Omicron daily overview: 30 December 2021 (publishing.service.gov.uk)
report-omicronupdate-dec2021.pdf (ukhsa.gov.uk)
Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada | medRxiv

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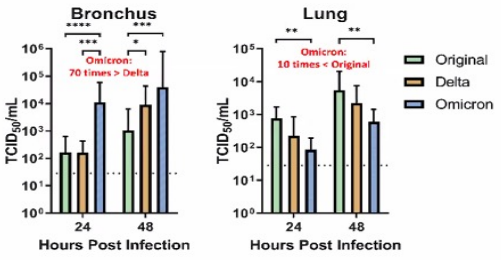
OMICRON INFECTIVITY FOR BRONCHIAL AND LUNG TISSUES

A study led by researchers from the LKS Faculty of Medicine at The University of Hong Kong (HKUMed) provides the first information on how the novel Variant of Concern (VOC) of SARS-CoV-2, the Omicron SARS-CoV-2 infect human respiratory tract. The researchers found that Omicron SARS-CoV-2 infects and multiplies 70 times faster than the Delta variant and original SARS-CoV-2 in human bronchus, which may explain why Omicron may transmit faster between humans than previous variants. Their study also showed that the Omicron infection in the lung is significantly lower than the original SARS-CoV-2, which may be an indicator of lower disease severity. This research is currently under peer review for publication.



https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection?utm_medium=social&utm_source=twitter&utm_campaign=press_release

Slide courtesy of David Weber, MD

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Neutralization of the Omicron variant is reduced compared with ancestral and Delta strains.

Sera from persons with different vaccination and infection scenarios	Time of collection after last vaccine dose	Neutralization of Omicron and range reduction compared with ancestral and Delta strains	References
Infection-naïve, primary mRNA vaccine series	0.5–6 months	Undetectable to 11–127x lower for Omicron	Wilhelm et al https://www.medrxiv.org/content/10.1101/2021.12.07.21267432v1.full.pdfCele et al https://www.ahri.org/wp-content/uploads/2021/12/MEDRXIV-2021-267417v1-Sigal.pdf Denjnirattisai et al https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1 Aggarwal et al https://www.medrxiv.org/content/10.1101/2021.12.14.21267772v1.full.pdf Zeng et al https://www.biorxiv.org/content/10.1101/2021.12.16.472934v1 Lu et al https://pubmed.ncbi.nlm.nih.gov/34915551/ Edara et al https://www.biorxiv.org/content/10.1101/2021.12.20.473557v1.full.pdf Schmidt et al https://www.nejm.org/doi/full/10.1056/NEJMc2119641?query=RP Basile et al https://www.biorxiv.org/content/10.1101/2021.12.12.472252v1.full.pdf Planas et al https://www.biorxiv.org/content/10.1101/2021.12.14.472630v1.full.pdf Rossler et al https://www.medrxiv.org/content/10.1101/2021.12.08.21267491v1.full
Infection-naïve, primary mRNA vaccine series + booster (homologous or heterologous)	0.5–3 months	Increased compared with primary series alone but 3–37x lower for Omicron	
Previous infection and vaccination (1 or 2 doses of mRNA vaccine)	1–6 months	Increased compared with infection or vaccination alone but 18–44x lower for Omicron	

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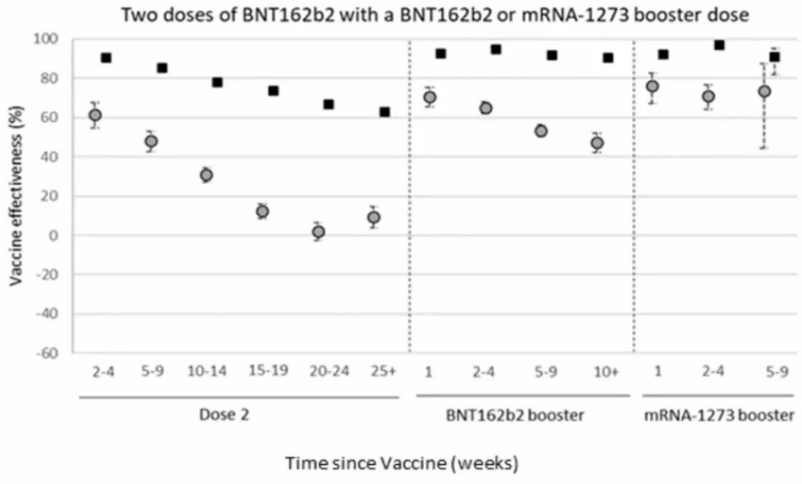
Pfizer mRNA vaccine effectiveness (VE) is lower for symptomatic infection due to Omicron compared to Delta.



- **Post 2-dose**: increased waning immunity for Omicron (~15%) vs. Delta (~60%) at 25+ weeks post 2nd dose
- **Booster**: ~65% VE against Omicron 2 weeks; decreases to 45% at 10+ weeks

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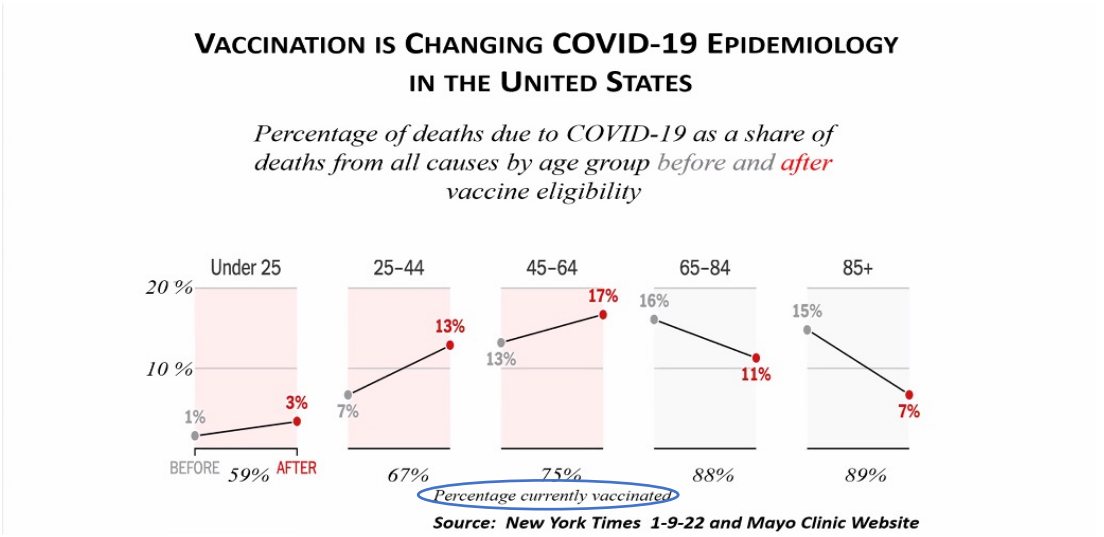

Hospitalizations in San Diego: 30-40% of those breakthrough "fully vaccinated"; < 4% boosted

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Diagnosis of the Omicron Variant

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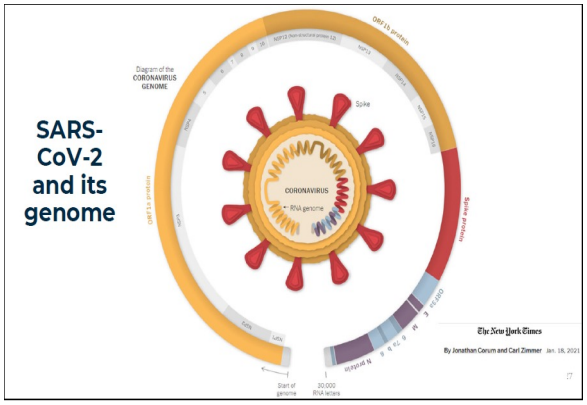
Envelope, Nucleocapsid, Spike Genes; ORF1a/1b proteins, and RdRp (RNA-dependent RNA polymerase)



Results

COVID-19 : Positive SARS-CoV-2

C_T values for viral gene targets : Orf1ab (31.9), N (32.93), S ()

Results

COVID-19 : Positive SARS-CoV-2

C_T values for viral gene targets : Orf1ab (32.23), N (34.01), S (34.67)

https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests#omicron

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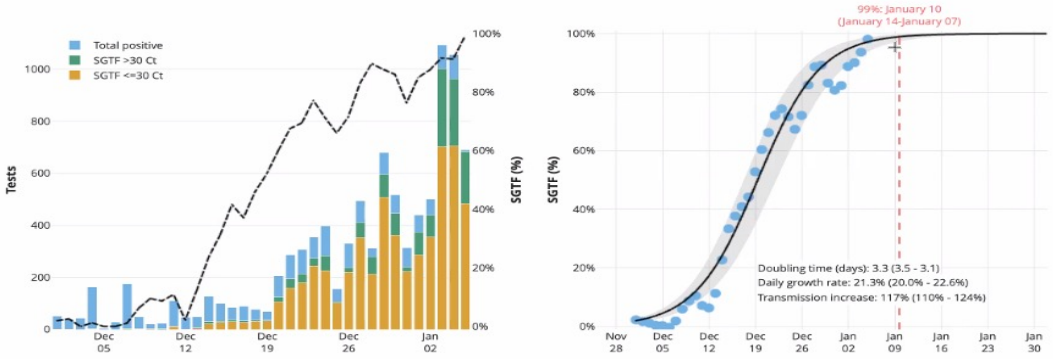
To gain insight into the spread of the Omicron variant in our community, we are working with a large number of partners to track S-gene target failures (SGTFs). SGTFs are a feature of the TaqPath PCR assay that fails to detect the spike gene of certain variants of interest due to a deletion in these viruses' spike gene. Most Omicron sequences have this deletion while most Delta sequences do not. As a result, the proportion of SGTF in positive tests can be used to estimate the prevalence of Omicron. The data shown here is collected by our collaborating partners in San Diego and can be found on our GitHub repository. More information on Omicron and other estimates of its prevalence in San Diego and elsewhere can be found at Outbreak.info.



Updated on January 06 @ 04:04 PM PST

Wastewater surveillance in San Diego: 80% Omicron – 20% Delta; projection this week: 90% Omicron

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Treatment and Prophylaxis

Treatment studies conducted in unvaccinated subjects

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Guidelines for the Treatment of COVID-19 for Residents of Skilled Nursing Facilities

- Mild to moderate illness: O2 saturation ≥ 94%
- Not for residents who require O_2 for treatment of COVID-19, **OR**
- Residents who require an increase in baseline O_2 flow rate due to COVID-19
- SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation
- **DO NOT** use steroids (dexamethasone) in this early phase of illness!

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High Risk Individuals Who Would Progress to Severe COVID-19 (Adults, Pediatrics, Age 12-17 ≥ 40 Kg

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m2 , or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

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Prioritization of Patients for Treatment

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.

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https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

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Advanced Therapeutics for Omicron

Rx	Risk Reduction	When Requires Positive Test	Route	Duration	Availability
Sotrovimab	79%	Within 10 days of symptom onset	IV	Single Infusion	Hospitals - Limited
Paxlovid (nirmatrelvir/ritonavir)	89%	Within 5 days of symptom onset	PO	5 days	Retail/LTC Rx – Limited
Remdesivir	87%	Within 7 days of symptom onset	IV	3 days	Hospitals
Molnupiravir	30%	Within 5 days of symptom onset	PO	5 days	Expected in Retail Rx/LTC
Pre-exposure Prophylaxis	**Risk Reduction**	**When**	**Route**	**Duration**	**Availability**
Evusheld (tixagevimab/cilgavimab)	77%	Q 6 mos. for immunocompromised hosts	IM	Two Consecutive Injections	Hospitals - Limited

Slide adapted from Albert Lam, MD

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	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication; Inflammation				
Potential Treatment	Antiviral therapy; Antibody therapy; Antiinflammatory therapy				
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

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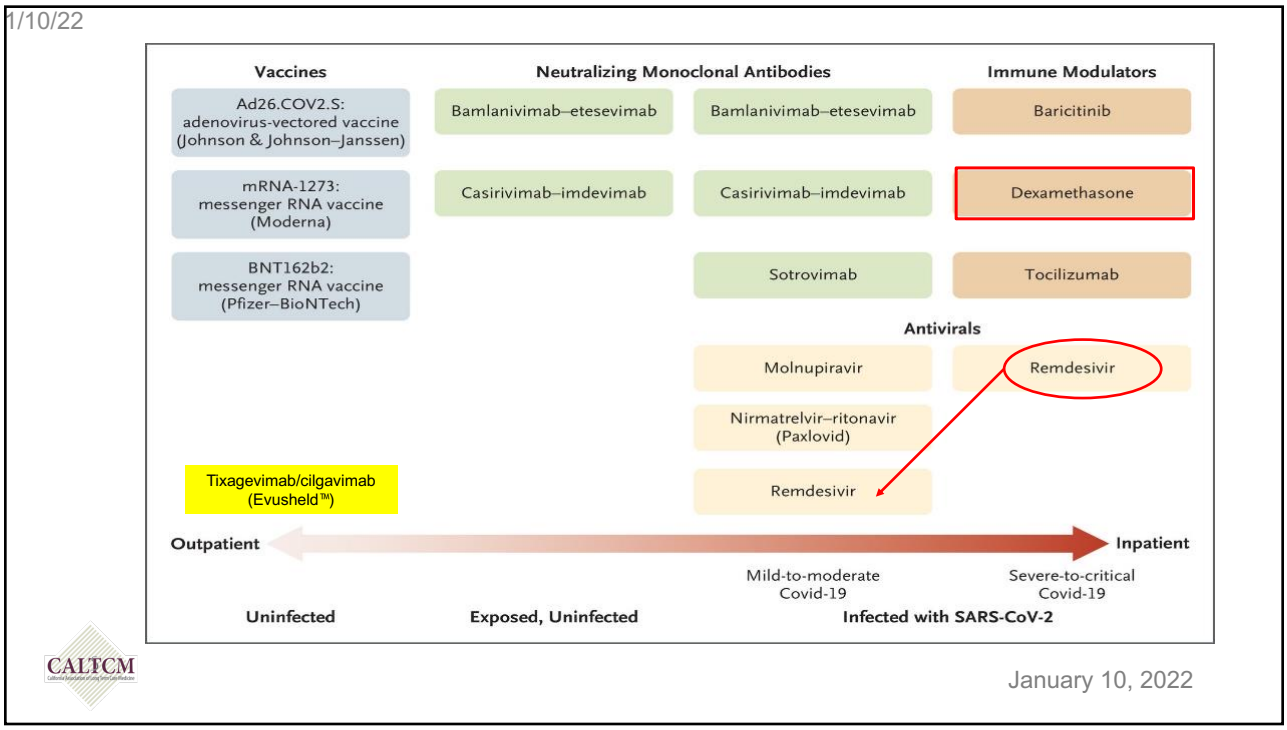
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Vaccines
Neutralizing Monoclonal Antibodies
Immune Modulators
Ad26.COV2.S: adenovirus-vectored vaccine (Johnson & Johnson–Janssen)
Bamlanivimab–etesevimab
Bamlanivimab–etesevimab
Baricitinib
mRNA-1273: messenger RNA vaccine (Moderna)
Casirivimab–imdevimab
Casirivimab–imdevimab
Dexamethasone
BNT162b2: messenger RNA vaccine (Pfizer–BioNTech)
Sotrovimab
Tocilizumab
Antivirals
Molnupiravir
Remdesivir
Nirmatrelvir–ritonavir (Paxlovid)
Tixagevimab/cilgavimab (Evusheld™)
Remdesivir
Outpatient
Inpatient
Mild-to-moderate Covid-19
Severe-to-critical Covid-19
Uninfected
Exposed, Uninfected
Infected with SARS-CoV-2
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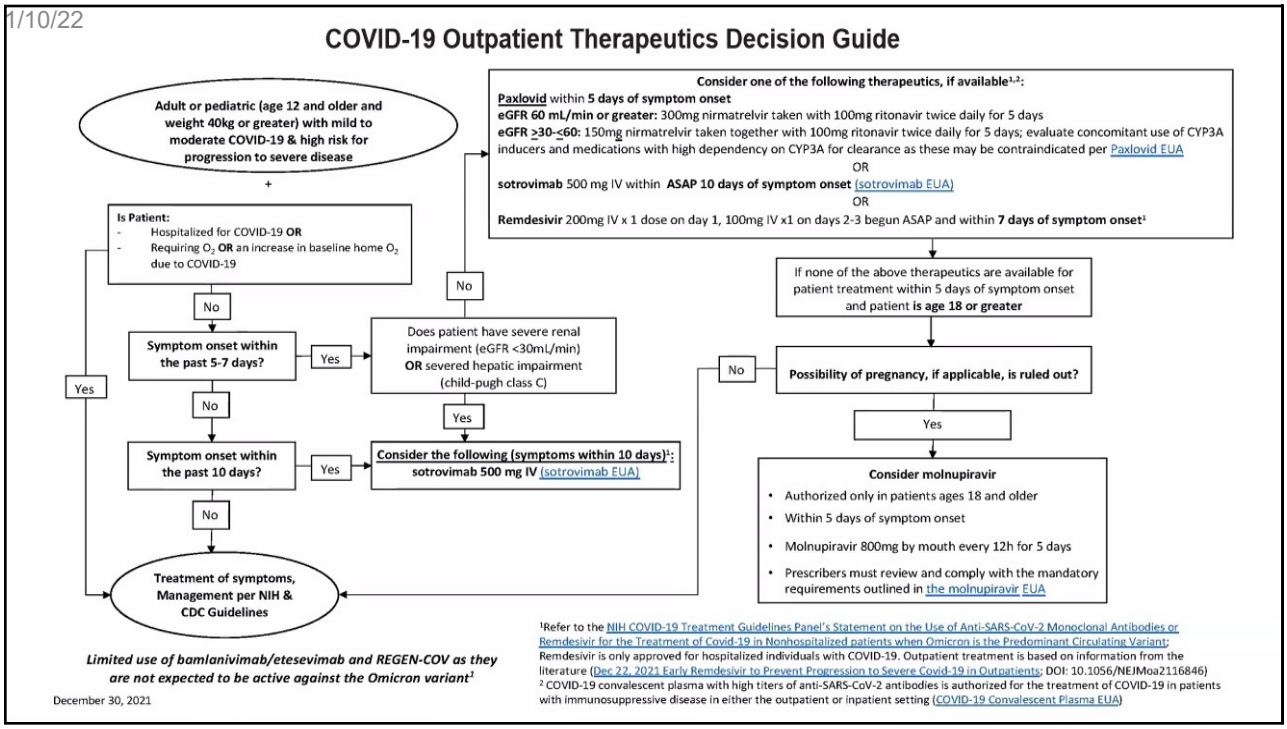
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COVID-19 Outpatient Therapeutics Decision Guide
Adult or pediatric (age 12 and older and weight 40kg or greater) with mild to moderate COVID-19 & high risk for progression to severe disease
+
Is Patient:
- Hospitalized for COVID-19 OR
- Requiring O2 OR an increase in baseline home O2 due to COVID-19
No
Symptom onset within the past 5-7 days?
Yes
No
Symptom onset within the past 10 days?
Yes
No
Treatment of symptoms, Management per NIH & CDC Guidelines
Yes
Does patient have severe renal impairment (eGFR <30mL/min) OR severed hepatic impairment (child-pugh class C)
Yes
Consider the following (symptoms within 10 days)[1]: sotrovimab 500 mg IV (sotrovimab EUA)
No
Consider one of the following therapeutics, if available[1,2]:
Paxlovid within 5 days of symptom onset
eGFR 60 mL/min or greater: 300mg nirmatrelvir taken with 100mg ritonavir twice daily for 5 days
eGFR ≥30-≤60: 150mg nirmatrelvir taken together with 100mg ritonavir twice daily for 5 days; evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated per Paxlovid EUA
OR
sotrovimab 500 mg IV within ASAP 10 days of symptom onset (sotrovimab EUA)
OR
Remdesivir 200mg IV x 1 dose on day 1, 100mg IV x1 on days 2-3 begun ASAP and within 7 days of symptom onset[1]
No
If none of the above therapeutics are available for patient treatment within 5 days of symptom onset and patient is age 18 or greater
No
Possibility of pregnancy, if applicable, is ruled out?
Yes
Consider molnupiravir
• Authorized only in patients ages 18 and older
• Within 5 days of symptom onset
• Molnupiravir 800mg by mouth every 12h for 5 days
• Prescribers must review and comply with the mandatory requirements outlined in the molnupiravir EUA
Limited use of bamlanivimab/etesevimab and REGEN-COV as they are not expected to be active against the Omicron variant[1]
December 30, 2021
[1]Refer to the NIH COVID-19 Treatment Guidelines Panel's Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of Covid-19 in Nonhospitalized patients when Omicron is the Predominant Circulating Variant; Remdesivir is only approved for hospitalized individuals with COVID-19. Outpatient treatment is based on information from the literature (Dec 22, 2021 Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients; DOI: 10.1056/NEJMoa2116846)
[2] COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease in either the outpatient or inpatient setting (COVID-19 Convalescent Plasma EUA)

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1/10/22

Therapeutics in the Era of the Omicron Variant

Agent	Paxlovid Nirmatrilvir/retonavir	Sotrovimab	Remdesivir	Molnuprinivir
Pros	• Highly efficacious • PO administration • Ritonavir safe in pregnancy	• Highly effacacious • Monoclonal antibodies typically safe in pregnancy • Few/no drug-drug interactions	• High efficacious • Studied in pregnancy • Few/no drug-drug interactions	• PO administration • Not anticipated to have drug-drug interactions
Cons	• Significant drug-drug interactions CYA45 cytochrome inducer and • Dosage modification in chronic kidney disease	• Requires IV infusion followed by an hour of observation • No EUA for postexposure prophylaxis	Requires IV infusion 30-120 minutes daily for 3 days	• Low efficacy • Mutagenic in mice • Not recommended in pregnancy • Not recommend in children: issues with bone growth
Use in skilled nursing facilities	Transplant recipients and patients with leukemia due to supply issues	• High risk, unvaccinated or not expected to mount antibody response to vaccination • If available, identify those residents with an "S" drop (S gene target failure – SGTF) • Requires nursing that can administer IV infuse and observe for adverse reactions • With other mAbs, some residents developed congestive heart failure during and up to 14 days after infusion	Requires nursing that can administer infusion and monitor during infusion	• If no other therapies available; but administration should be discussed with resident (next of kin etc.) regarding efficacy

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Monoclonal Antibody Fact Sheets Updated with Virology Information for Omicron

FDA

Casirivimab and Imdevimab Together (REGEN-COV)			
B.1.1.529/BA.1 Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	Pseudotyped Virus-Like Particle Neutralization Data	>1,013 - fold reduction in susceptibility

Bamlanivimab and Etesevimab Together			
B.1.1.529/BA.1 Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G493S+ Q498R+N501Y+Y505H	Pseudotyped Virus-Like Particle Neutralization Data	>2,938 - fold reduction in susceptibility

EVUSHELD™ Fact Sheet Updated with Virology Information for Omicron

FDA

Tixagevimab and cilgavimab together			
B.1.1.529/BA.1 Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	Authentic Virus	12* to 30 - fold reduction in susceptibility

* Assay used parenteral antibodies

- Discussions ongoing regarding implications
- The terms of the authorization have not been changed at this time.

Monoclonal Antibody Fact Sheets Updated with Virology Information for Omicron

FDA

Sotrovimab			
B.1.1.529/BA.1 Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	Pseudotyped Virus-Like Particle Neutralization Data	No change (<5 - fold reduction in susceptibility)

- Casirivimab and imdevimab together are unlikely to be active against variants from this lineage.
- Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.
- Healthcare providers should choose an authorized therapeutic option with activity against the circulating variants in their state, territory, or US jurisdiction. Current variant frequency data are available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions

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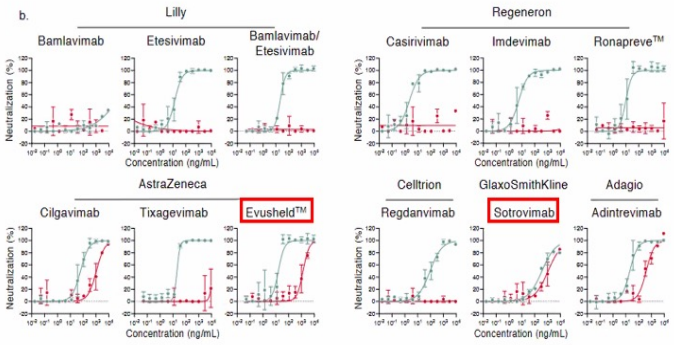
Considerable Escape of SARS-CoV-2 Variant Omicron to Antibody Neutralization



BRII (Chinese drug) combination maintains activity with reduced IC_{50}

Planas D et al MEDRxIV: https://doi.org/10.1101/2021.12.14.472630

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EVUSHELD™ Authorization for PrEP

FDA

- Tixagevimab co-packaged with cilgavimab, SARS-CoV-2 spike protein-directed attachment inhibitor.

Authorization: for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):
- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination **or**
- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID19 vaccine component(s)

EVUSHELD™ – Clinical Considerations

FDA

- Not authorized for treatment of COVID-19, nor for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.
- Examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination are provided in the Health Care Provider Fact Sheet.

Health Care Provider Fact Sheet: https://www.fda.gov/media/154701/download

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SOTROVIMAB

- Comparable reduction in progression to severe disease, hospitalization as with other monoclonals (Gupta A et al, NEJM 2021):

Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)
Data missing — no. (%)		
All patients with missing data	4 (1)	1 (<1)
Patients with missing data because of withdrawal of consent before receipt of sotrovimab or placebo	3 (1)	1 (<1)
Relative risk reduction (97.24% CI)	85 (44–96)	—
P value	0.002	—

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PAXLOVID™ Authorization for Treatment

FDA

- Nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use
- Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor.

Authorization: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

PAXLOVID™ – Clinical Considerations

FDA

- Drug-drug interactions with CONTRAINDICATIONS for co-administration with some drugs highly dependent on CYP3A for clearance and some potent CYP3A inducers
- Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)
- Not recommended for patients with severe renal impairment (eGFR < 30mL/min)
- Not recommended for patients with severe hepatic impairment (Child-Pugh Class C)
- Consider risk of development of HIV-1 resistance to protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Health Care Provider Fact Sheet: https://www.fda.gov/media/155050/download

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Paxlovid™
Medication Contraindications and Resources

Drugs highly dependent on CYP3A for clearance and subject to increased concentrations

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Drugs that can speed up the metabolism of nirmatelvir

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (hypericum perforatum)

Resources to assess drug-drug interactions:

- https://www.covid19-druginteractions.org
- Htttp://www.hiv-druginteractions.org
- The EUA fact sheet for ritonavir-boosted nirmatrelvir (Paxlovid)
- Liverpool COVID-19 Drug Interactions website

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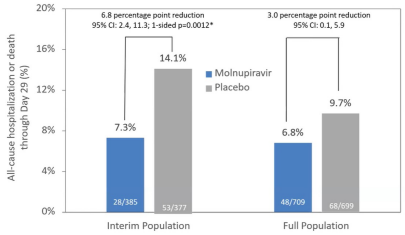
Molnupiravir Authorization for Treatment

- Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis.

Authorization: for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

P002 Primary Efficacy Analysis



www.fda.gov

* Met the pre-specified interim assessment stopping boundary (1-sided p-value <0.0092)
Formal statistical testing was not performed for the full population assessment, because statistical significance was demonstrated at the interim population assessment. The nominal 1-sided p-value was 0.0218.

Molnupiravir (Lagevrio™)

- **Recommendation (NEW): In ambulatory patients (>/= 18 years) with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir.**
  - **(Conditional recommendation, Low certainty of evidence)**

- **Remarks:**
  - Patients who put a higher value on the putative mutagenesis, adverse events or reproductive concerns, and a lower value on the uncertain benefits, would reasonably decline molnupiravir.
  - Molnupiravir 800 mg for 5 days.
  - 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 molnupiravir.
  - Molnupiravir is not authorized under the FDA EUA for use in patients < 18 years, because it may affect bone and cartilage growth.
  - Molnupiravir is not authorized under the FDA EUA for pre-exposure or post- exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19, because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

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IDSA Updated 30Dec2021

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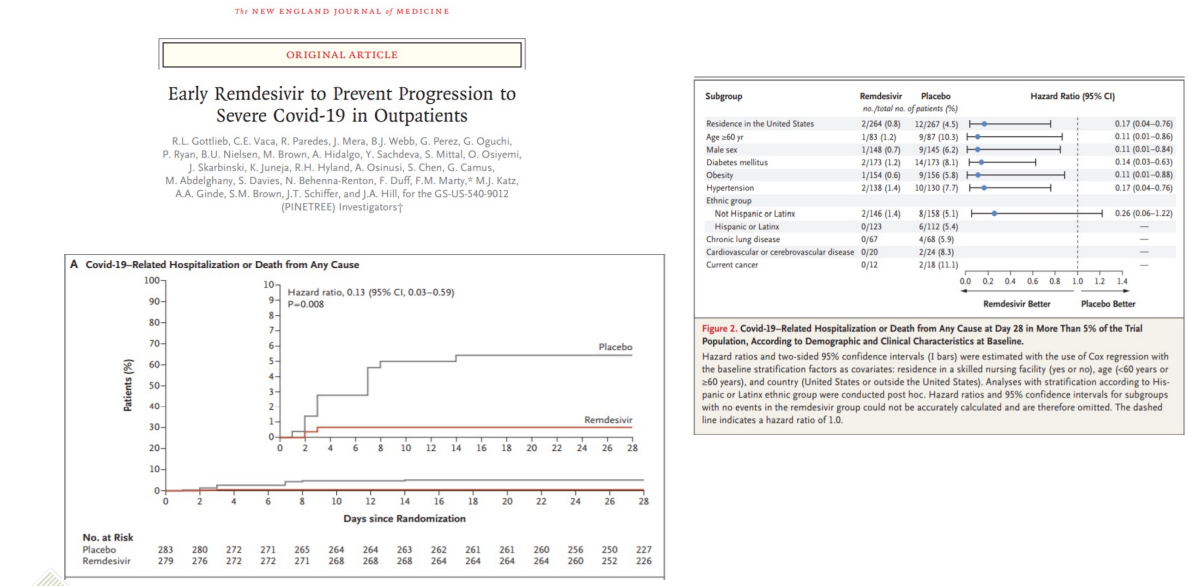

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

A Covid-19–Related Hospitalization or Death from Any Cause

Hazard ratio, 0.13 (95% CI, 0.03–0.59)
P=0.008

Placebo

Remdesivir

Patients (%)

Days since Randomization

No. at Risk

Placebo	283	280	272	271	265	264	264	263	262	261	261	260	256	250	227
Remdesivir	279	276	272	272	271	268	268	268	264	264	264	264	260	252	226

Subgroup	Remdesivir no./total no. of patients (%)	Placebo	Hazard Ratio (95% CI)
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4

Remdesivir Better Placebo Better

Figure 2. Covid-19–Related Hospitalization or Death from Any Cause at Day 28 in More Than 5% of the Trial Population, According to Demographic and Clinical Characteristics at Baseline.

Hazard ratios and two-sided 95% confidence intervals (I bars) were estimated with the use of Cox regression with the baseline stratification factors as covariates: residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States). Analyses with stratification according to Hispanic or Latinx ethnic group were conducted post hoc. Hazard ratios and 95% confidence intervals for subgroups with no events in the remdesivir group could not be accurately calculated and are therefore omitted. The dashed line indicates a hazard ratio of 1.0.

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Prevention Strategies

- Continue layered approaches to prevention, e.g., non-pharmacologic strategies with greater emphasis on masking, improved ventilation
- Vaccinate with greater urgency, recommended for everyone ≥ 5 years; booster ≥ 12 years, additional dose for immunocompromised children ages 5-11 so “up to date on vaccines”
- Expand test availability, both for diagnosis and prevention – including self testing
- Increase genomic surveillance capacity
- Adhere to guidance on quarantine and isolation
- If immune escape substantial:
  - Reformulate vaccine
  - Alter formulation of monoclonal antibodies
  - Greater focus on early use of new/existing oral treatment for individuals at risk for disease progression

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Summary

- The Omicron variant is more transmissible than the Delta variant; however, the risk of hospitalization and death are decreased
- “Up to date” vaccination status provides the best protection, along with practicing the non-pharmacologic strategies
- Even after natural infection, it is important to vaccinate
- Therapeutic studies are conducted on unvaccinated persons
- Limitation of the supply of therapeutics requires prioritization

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