

COVID-19 UPDATE: OMICRON UPDATE

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UNC
SCHOOL OF MEDICINE

Disclosures: Consultancy; Pfizer, Merck, Sanofi, PDI, Germitec, Wellair
All drugs/vaccines issues discussed consistent with FDA approvals or authorizations

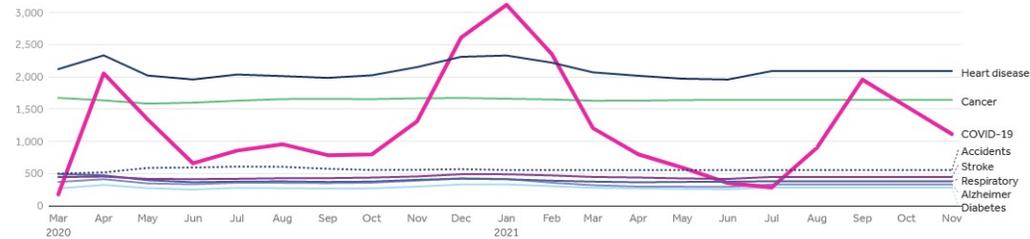
COVID-19: RECENT SUMMARY

- Increasing cases and hospitalizations due to Omicron
 - Hospitalizations largely limited to unvaccinated and immunocompromised
- Omicron
 - Dominant variant; highly transmissible; escape from most mABs; escape for “natural immunity” and vaccine (“fully vaccinated”)
- Advances in therapy – active against Omicron (therapy for mild-moderate illness) - limited supply for all but remdesivir
 - Paxlovid: FDA authorized, substantial drug interactions, CYP3A4 inhibitor; ~88% effective to prevent hospitalizations, oral
 - Sotrovimab: FDA authorized, IV infusion
 - Remdesivir: FDA approved but “off label”, IV infusion each day for 3 days
 - Molnupiravir: FDA authorized, limited effectiveness (~30% to prevent hospitalization), oral
- Advances in preventive therapy (IM)
 - Evusheld (tixagevimab co-packaged with cilgavimab and administered together)

IMPACT OF COVID-19 ON DEATHS BY AGE GROUP, US

COVID-19 rank fell to number 7 among leading causes of death in July but is back up to number 3 in November 2021

Average daily deaths in the United States, by cause (March 2020 - November 2021)



Notes: For accidents in 2021, the 2020 daily average is plotted. For all other leading causes, July through November data is the average from January - June 2021. Respiratory disease represents chronic lower respiratory disease.

Source: KFF analysis of CDC mortality and KFF COVID-19 tracker • [Get the data](#) • PNG

Peterson-KFF
Health System Tracker

COVID-19 was the number 1 leading cause of death for people ages 45-54 years in October 2021

Age-specific rank of COVID-19 deaths among leading causes of death in the U.S., 2021

Ages	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+	All Ages
January	7	6	4	2	2	1	1	1	1	1	1
February	13	7	5	4	4	2	2	2	1	2	1
March	15	8	6	6	5	4	3	3	3	5	3
April	7	7	6	6	5	4	3	3	3	5	3
May	11	8	5	6	5	4	3	3	5	6	3
June	13	11	7	6	5	4	4	6	7	8	6
July	13	8	5	6	5	4	3	4	6	7	7
August	7	6	4	2	1	1	1	2	3	3	3
September	7	5	4	2	1	1	1	1	3	2	2
October	7	6	4	2	2	1	2	3	3	3	3

Note: Monthly deaths due to COVID-19 for each month in 2021 (as of December 8, 2021 data) were compared to age-specific death counts due to other rankable leading causes.

Source: KFF analysis of CDC Provisional data, CDC Wonder data, and KFF COVID-19 Tracker data • [Get the data](#) • PNG

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Health System Tracker

<https://www.healthsystemtracker.org/brief/covid19-and-other-leading-causes-of-death-in-the-us/>

FREQUENCY AND SYMPTOMS OF LONG-COVID-19

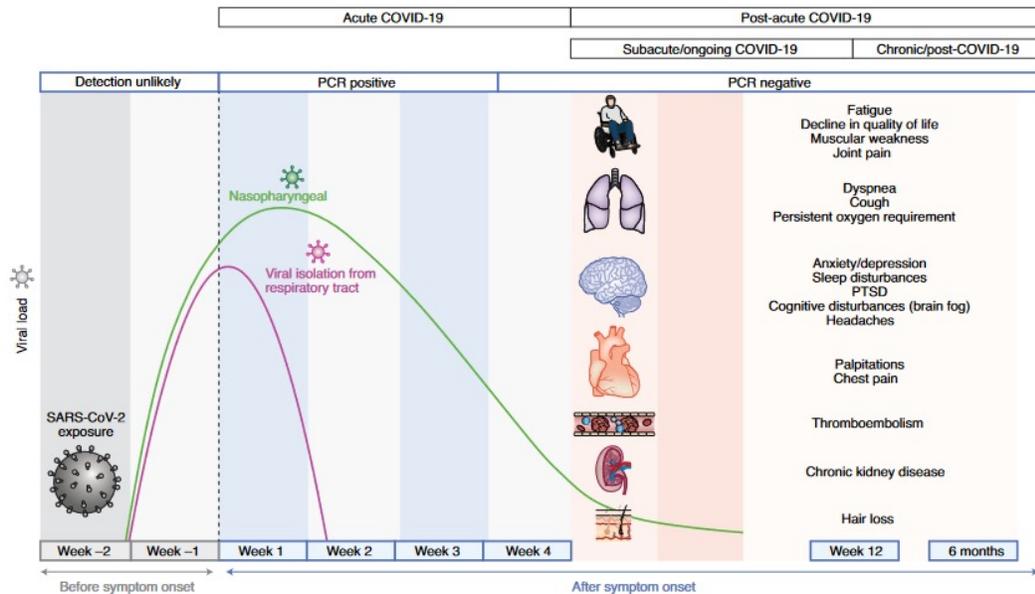
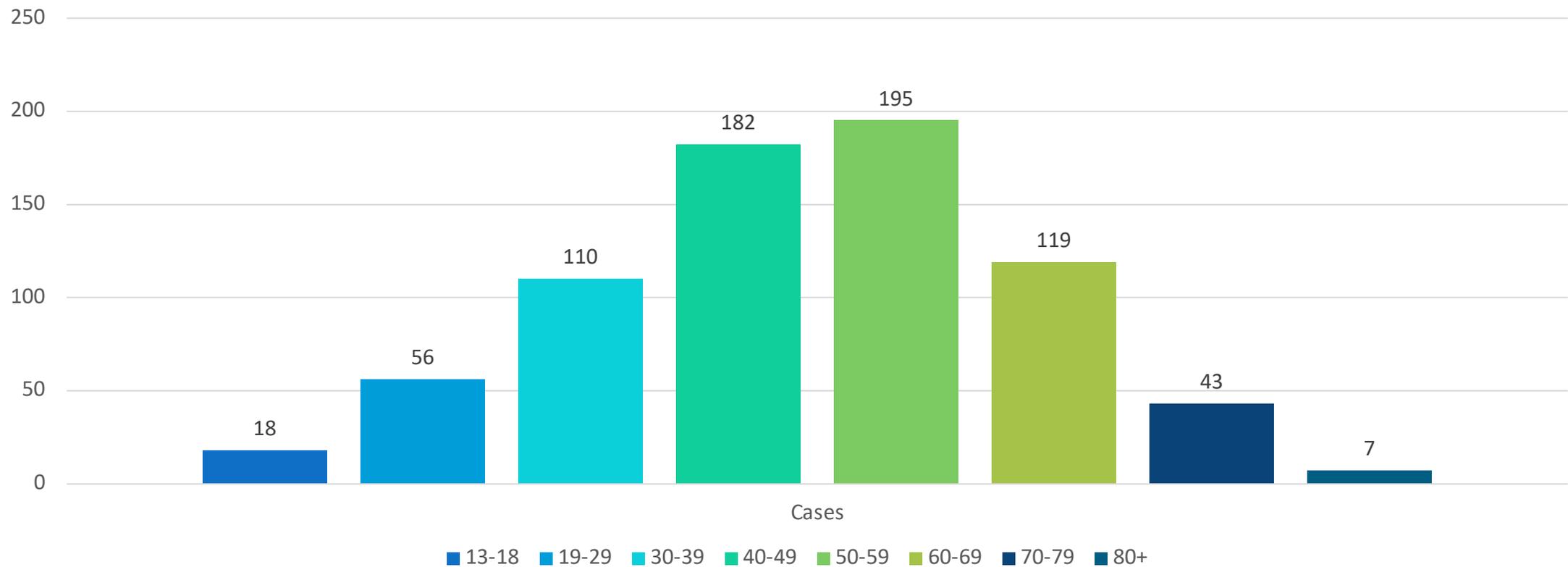


Fig. 1 | Timeline of long-COVID. Nalbandian et al. define long-COVID as persistent symptoms and/or delayed or long-term complications beyond four weeks from the onset of symptoms. Credit: Adapted with permission from A. Nalbandian et al. *Nat. Med.* 27, 601-615 (2021), Springer Nature

- Goal: Assess long-COVID-19 in large EMR database
- Methods: Retrospective cohort study using EMR data from 81 million patients, 273,618 COVID-19 survivors; incidence within 6 months and 3-6 months after diagnosis
- Results: Among COVID-19 survivors (mean [SD] age: 46.3 [19.8], 55.6% female), 57.00% had one or more long-COVID feature recorded during the whole 6-month period (i.e., including the acute phase), and 36.55% between 3 and 6 months.
 - 1 in 3 patients had one or more features of long-COVID recorded between 3 and 6 months after a diagnosis of COVID-19. This was significantly higher than after influenza.
 - 2 in 5 of the patients who had long-COVID features in the 3- to 6-month period, had no record of any such feature in the previous 3 months.
 - The risk of long-COVID features was higher in patients who had more severe COVID-19 illness, and slightly higher among females and young adults. White and non-white patients were equally affected.

UNC-CH LONG COVID-19 CLINIC

Frequency COVID-19 Cases Seen in Long COVID-19 Clinics, UNC-MC, by Age

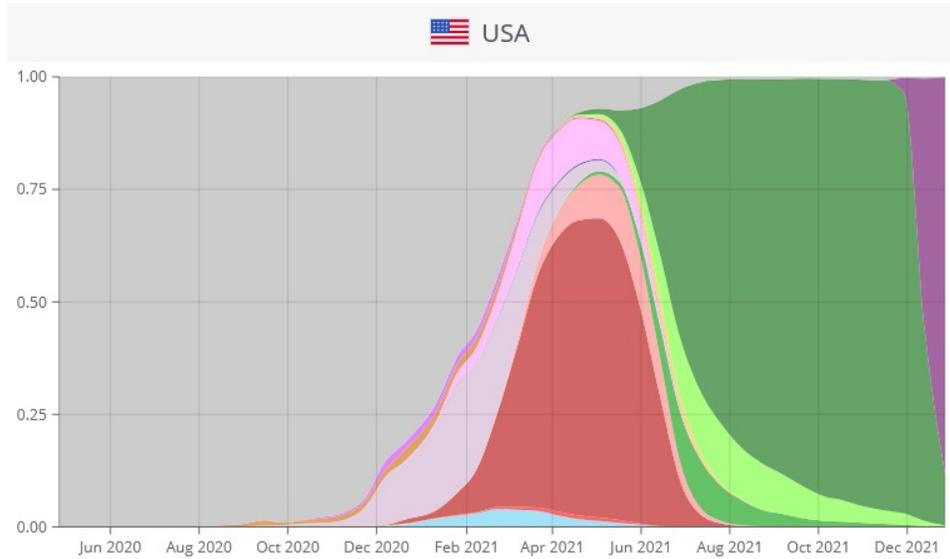


Data supplied by Dr. Jonh Baratta

COVID-19 VARIANTS

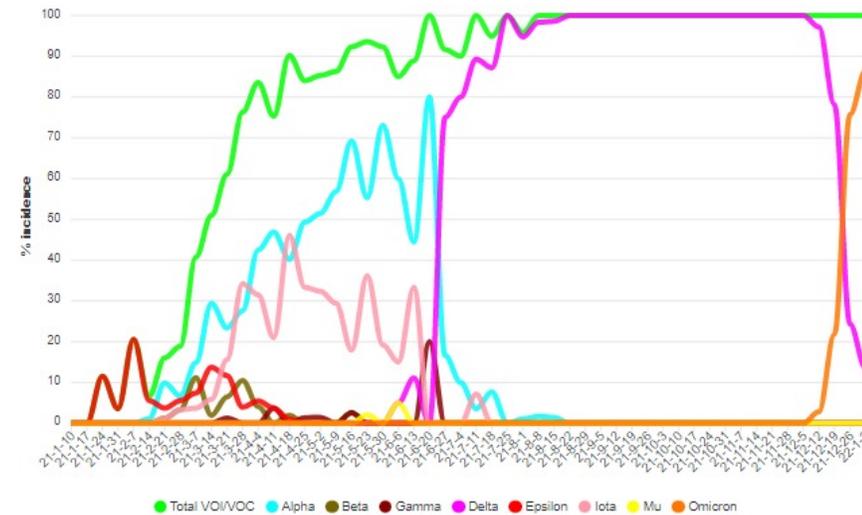
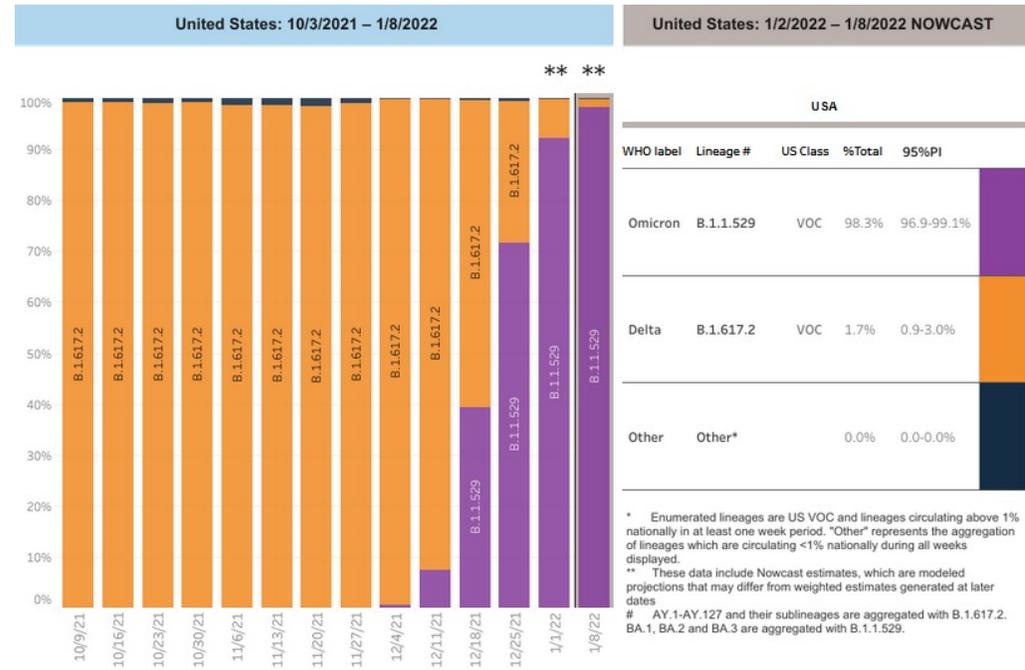
- Variants are of concerns if they impact:
 - Transmissibility (intrinsic)
 - Performance of diagnostics
 - Immunity (immune evasion): Vaccination, prior infection, monoclonal antibodies/convalescent plasma
 - Effectiveness of treatments
 - Severity of illness
- Omicron (~30 mutations in spike protein; variant derived from early variants)
 - Detected in South Africa in late November (but isolates from early November have been detected)
 - Dominant variant worldwide and US
 - Increased infectivity: Inherent, escape from “natural immunity”, escape from vaccines (including fully vaccinated)
 - Detected by most current diagnostic tests
 - Escape by *in vitro* testing from most mABs
 - Lower virulence
- Prevention: 1) Encourage or require vaccine be “up to date”, 2) Universal pandemic precautions (masks, eye protection, N95s for COVID care/AGPs), 3) Avoid presenteeism

OMICRON, US & UNC-MC



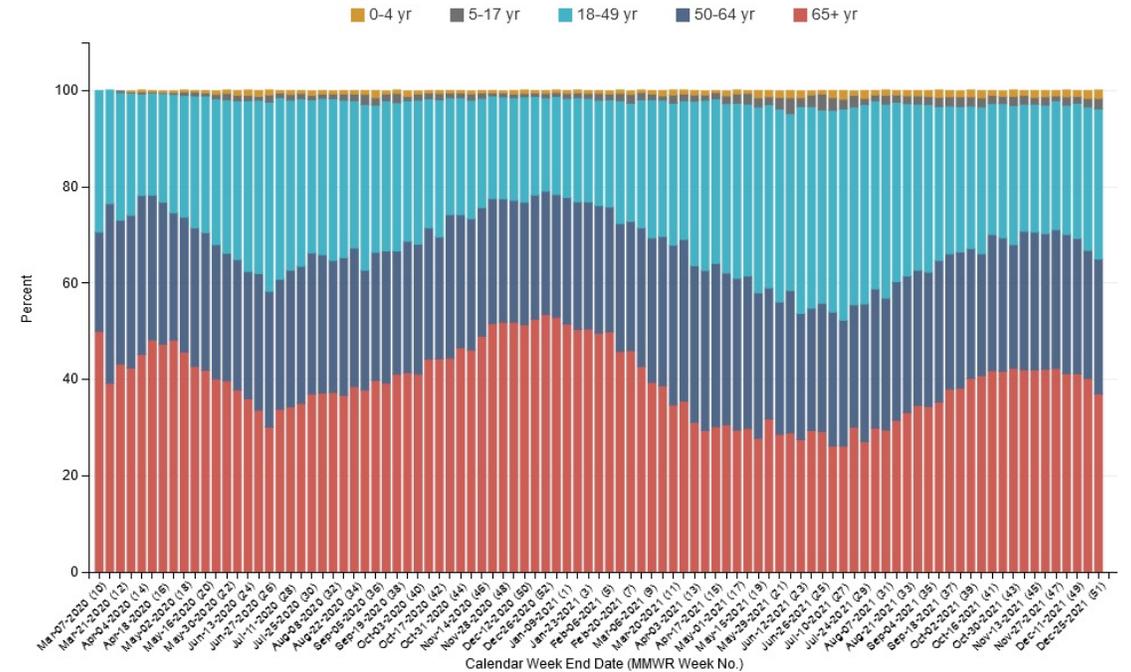
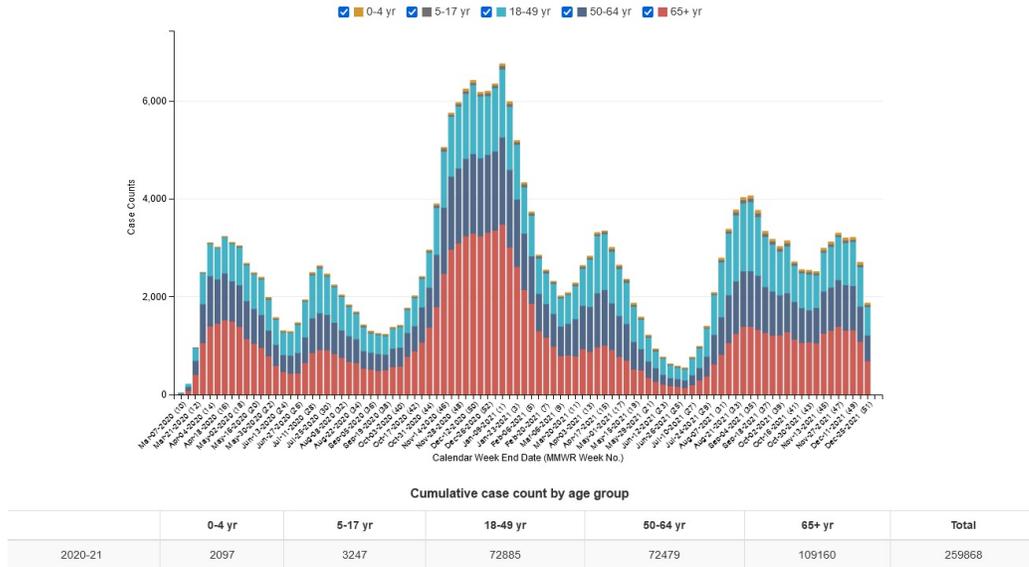
- ✓ 20I (Alpha, V1)
- ✓ 20H (Beta, V2)
- ✓ 20J (Gamma, V3)
- ✓ 21A (Delta)
- ✓ 21I (Delta)
- ✓ 21J (Delta)
- ✓ 21K (Omicron)

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



3,477 genomes, samples through 2 Jan 2022

HOSPITALIZATIONS BY AGE (numbers & percent), CDC



United States | 0 - 17 Years

80,271

Total Admissions

Aug 01, 2020 - Jan 02, 2022

672

Current 7-Day Average

Dec 27, 2021 - Jan 02, 2022

313

Prior 7-Day Average

Dec 20, 2021 - Dec 26, 2021

672

Peak 7-Day Average

Dec 27, 2021 - Jan 02, 2022

+114.4%

Percent change from prior 7-day

avg. of Dec 20, 2021 - Dec 26, 2021

0.0%

Percent change from peak 7-day

avg. of Dec 27, 2021 - Jan 02, 2022

Based on reporting from all hospitals (N=2,861). Due to potential reporting delays, data reported in the most recent 7 days (as represented by the shaded bar) should be interpreted with caution.

Small shifts in historic data may occur due to changes in the CMS Provider of Services file, which is used to identify the cohort of included hospitals. Data prior to this date may have anomalies that are still being resolved. Note that the above graphs are often shown on different states. Data prior to August 1, 2020 are unavailable.

Last Update: Jan 05, 2022

Unifed Hospital Dataset, White House COVID-19 Team, Data Strategy and Execution Workgroup

New Admissions of Patients with Confirmed COVID-19 per 100,000 Population by Age Group, United States
Aug 01, 2020 - Jan 02, 2022

By Jurisdiction and Age Group

By Jurisdiction

Select a Jurisdiction

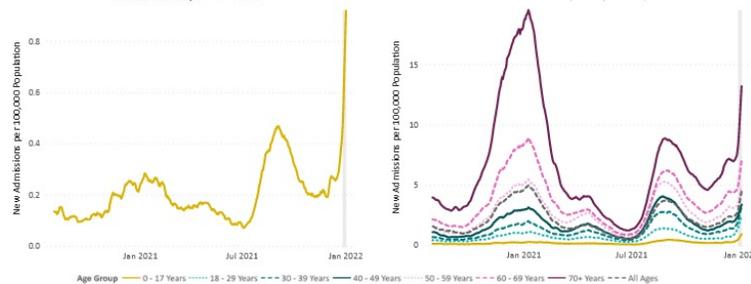
Select an Age Group

United States

0 - 17 Years

United States | 0 - 17 Years

United States | All Age Groups

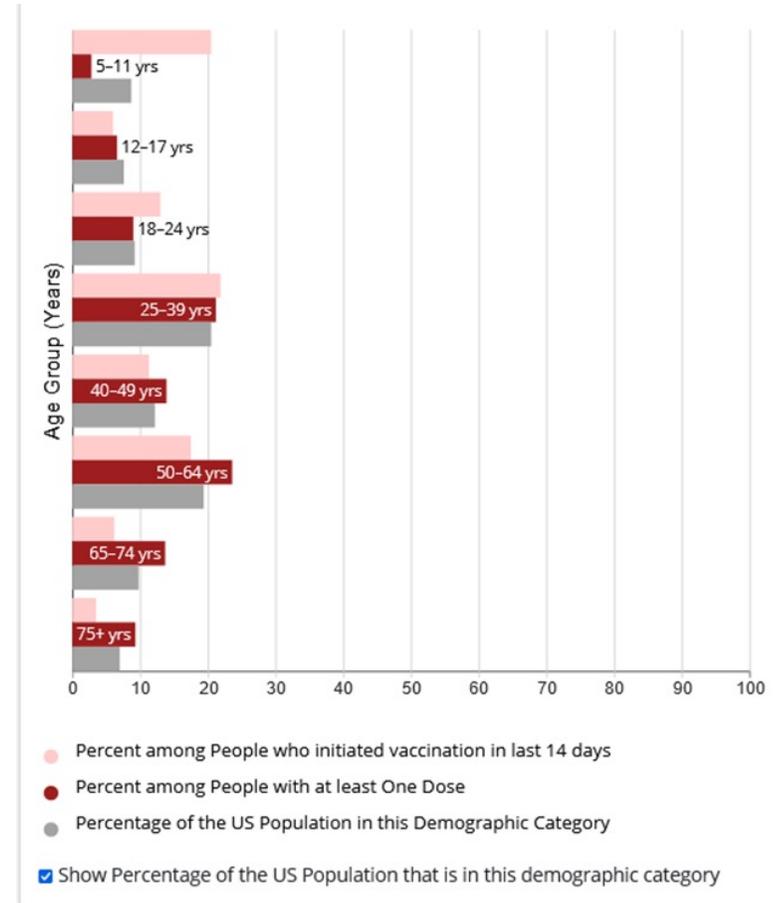


https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

COVID-19 VACCINE COVERAGE BY “UP TO DATE” AND AGE, US, CDC

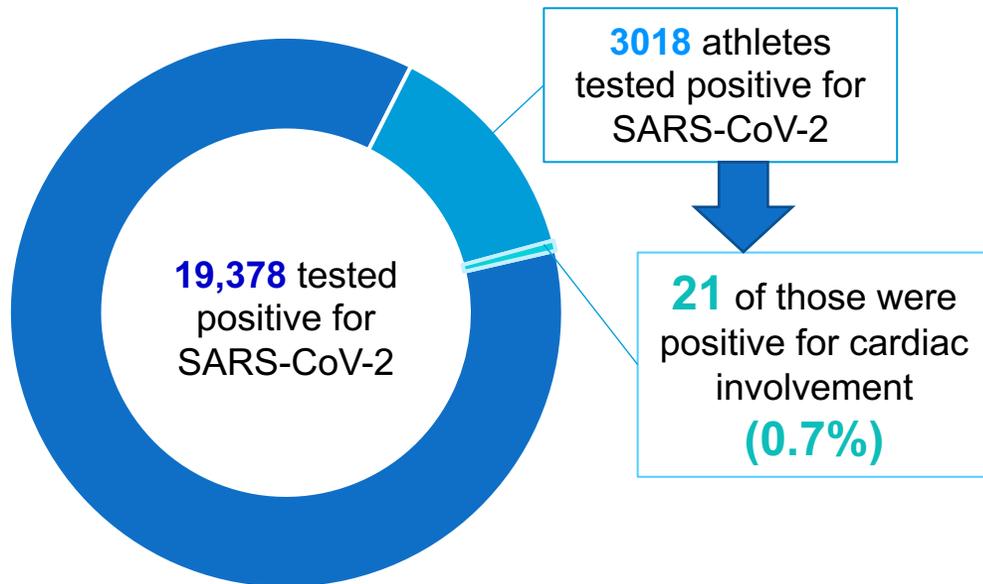
Total Vaccine Doses Delivered 632,575,655 Administered 515,162,867 Learn more about the distribution of vaccines.	At Least One Dose	Fully Vaccinated	Booster Doses***
	Fully Vaccinated* People	Count	Percent of US Population
207.0M People fully vaccinated 73.0M People received a booster dose**	Total	207,016,514	62.4%
	Population ≥ 5 Years of Age	207,006,442	66.3%
	Population ≥ 12 Years of Age	202,375,514	71.4%
	Population ≥ 18 Years of Age	188,777,814	73.1%
	Population ≥ 65 Years of Age	48,079,504	87.7%

Total Vaccine Doses Delivered 632,575,655 Administered 515,162,867 Learn more about the distribution of vaccines.	At Least One Dose	Fully Vaccinated	Booster Doses***
	Fully Vaccinated* People with a Booster Dose**	Count	Percent of Fully Vaccinated*
207.0M People fully vaccinated 73.0M People received a booster dose**	Total	72,991,028	35.3%
	Population ≥ 18 Years of Age	72,344,151	38.3%
	Population ≥ 50 Years of Age	49,191,993	50.1%
	Population ≥ 65 Years of Age	28,668,993	59.6%



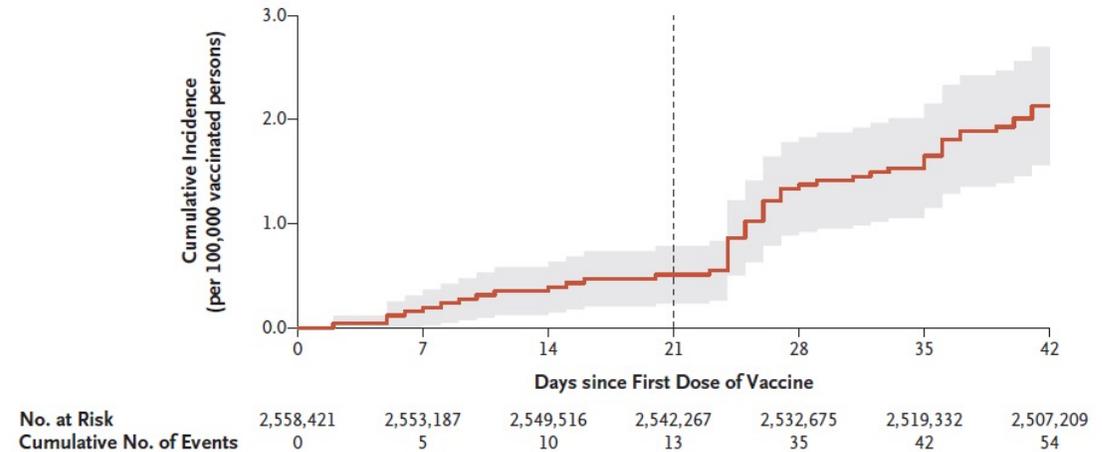
Risk of Myocarditis Post-COVID-19 Infection or mRNA Vaccination

Young (20 years of age) competitive athletes across 42 colleges and universities in the US were prospectively followed and tested over a 4-month time period¹



Retrospective analysis of healthcare records of 2.5 million vaccinated individuals (>16 years) in Israel²

Kaplan–Meier Estimates of Myocarditis at 42 Days²



Overall estimated IR: 2.13 cases per 100,000 (95% CI: 1.56–2.70)²
Highest incidence rate: 10.69 cases per 100,000 (95% CI: 6.93–14.46) among males aged 16–29 yrs²

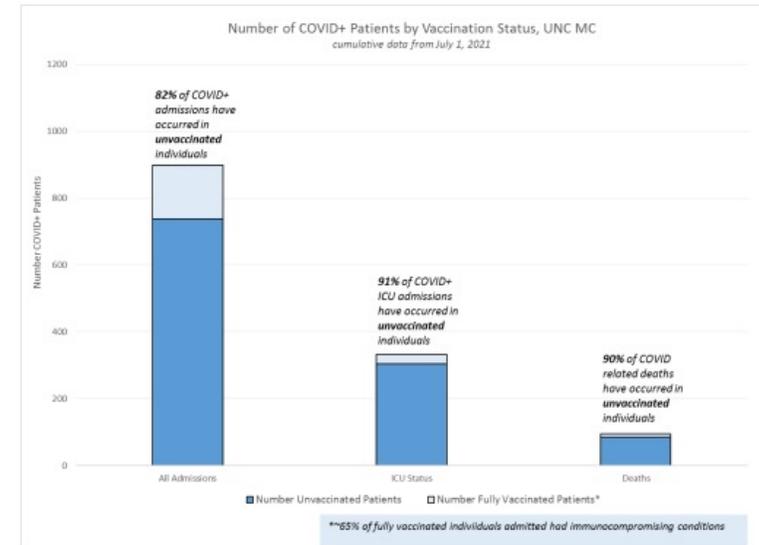
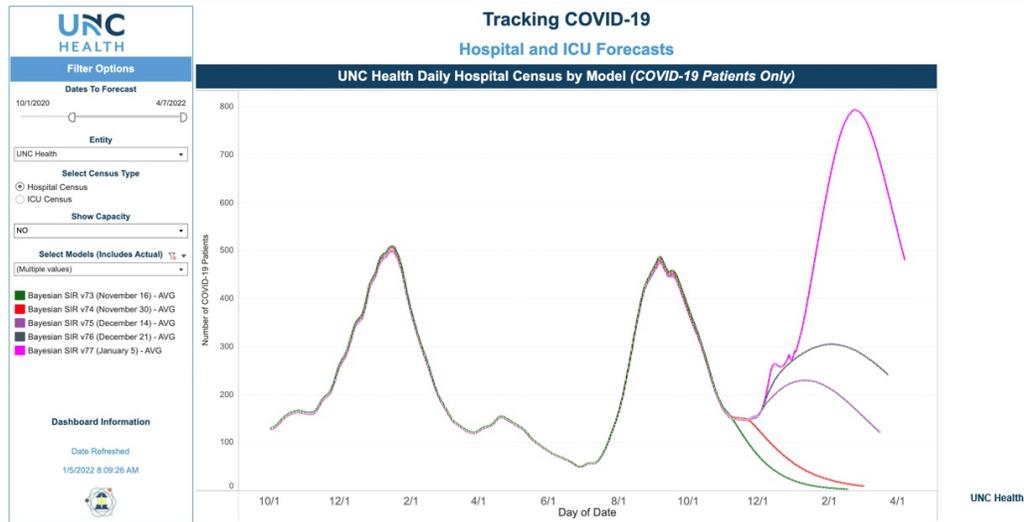
Cases of myocarditis after COVID-19 or vaccine both were relatively rare and tended to be mild or moderate in severity^{1,2}

CI, confidence interval.

1. Moulson N, et al. *Circulation*. 2021;144:256-266. 2. Witberg G, et al. *N Engl J Med*. 2021. Oct 6. DOI: 10.1056/NEJMoa2110737

FORCASTING OMICRON IMPACT ON UNC-MC

The UNC Health forecast is up significantly based on State-wide experience
 The model forecast assumes a continuation of the current rate of person to person transmission



COVID-19 positive admissions to UNC Hospitals and deaths broken down by vaccination status. Vaccination status is captured in Epic and may be an underrepresentation of the true number of vaccinated patients. Patients are considered fully vaccinated 14 days after their second dose or 14 days after receipt of J&J vaccine.

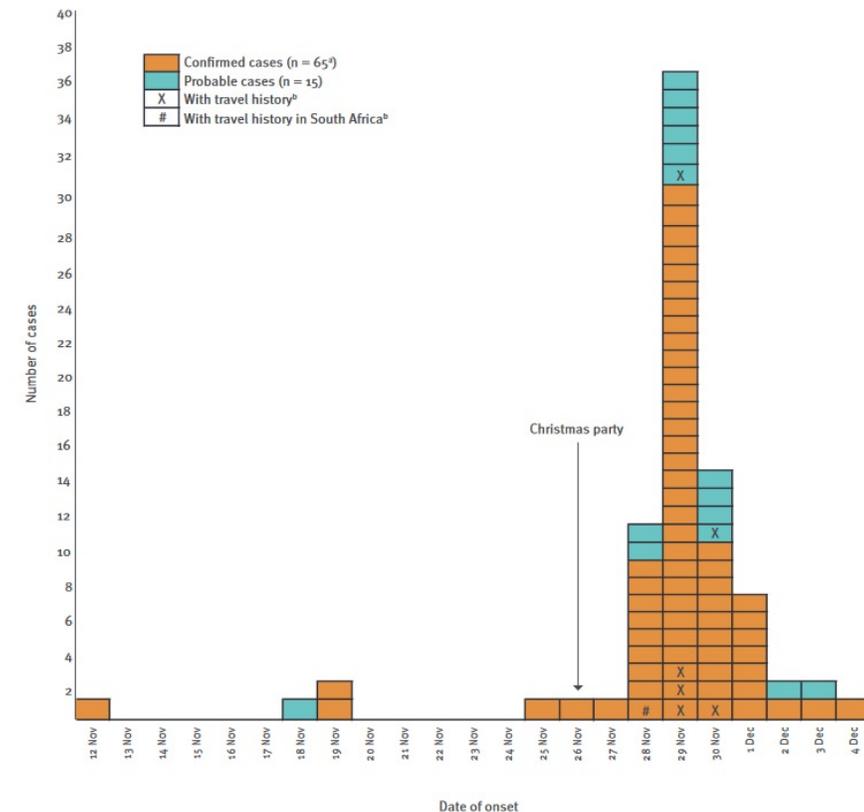
Investigation of a SARS-CoV-2 B.1.1.529 (Omicron) Variant Cluster, Nebraska, Nov.–Dec. 2021

- Goal: Outbreak evaluation
- Index case had symptomatic COVID-19 in 11/20, unmasked contact with coughing person during conference in Nigeria. Pre-travel test 11/21/21 negative. On 11/23/21 while still asymptomatic, had unmasked contact with 5 household members (1, fully vaccinated plus COVID-19 in 8/21; 3, unvaccinated plus previous COVID-19; 1, unvaccinated with mild URI but negative COVID-19 test. No household members immunocompromised.
- On 11/24/21 index case developed symptoms; positive COVID-19 test on 11/26/21. All 6 household members developed symptoms 11/24-11/26 (**incubation period, median = 73hr (range, 33-75hr)**). None hospitalized.
- Median incubation period SARS-CoV-2, ≥ 5 d; Delta, 4d; Omicron, 3d
- **Conclusions: 1) Omicron highly infectious; 2) Shortened incubation period; 3) Reinfection common; 4) Reduced effectiveness of vaccines; 5) Less virulent**

Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021

- In late November 2021, an outbreak of Omicron SARS-CoV-2 following a Christmas party with 117 attendees was detected in Oslo, Norway. The observed Omicron **attack rate was 74%** and **most cases developed symptoms**.
- As of 13 December, none have been hospitalized. Most participants were 30–50 years old. **96% were fully vaccinated (none boosted)**. All were to be test negative prior to event.
- **Assuming exposure at the event, the incubation period for symptomatic cases had a median of 3 days (IQ range, 3-4).**
- Party was a closed event held in a separate room of a restaurant.
- These findings corroborate reports that the Omicron variant may be more transmissible, and that vaccination may be less effective in preventing infection compared with Delta.

Distribution of COVID-19 cases infected with the SARS-CoV-2 Omicron variant by date of symptom onset and case classification, after attending Christmas party, Oslo, Norway, November–December 2021 (n = 81)



High Rate of Asymptomatic Carriage Associated with Variant Strain Omicron

- In early December 2021, the Ubuntu clinical trial, designed to evaluate efficacy of the mRNA-1273 vaccine (Moderna) among persons living with HIV (PLWH), began enrolling participants.
- Nasal swabs are routinely obtained at the initial vaccination visit, which requires participants to be clinically well to receive their initial jab. **Of the initial 230 participants enrolled between 12/2-12/17/21, 71 (31%) were PCR+ for SARS-CoV-2: all of whom were subsequently confirmed by S gene dropout to be Omicron; 48% of the tested samples had cycle threshold (CT) values <25 and 18% less than 20, indicative of high titers of asymptomatic shedding.** Asymptomatic carriage rates were similar in SARS-CoV-2 seropositive and seronegative persons (27% respectively).
- We also evaluated asymptomatic carriage in a sub study of the Sisonke vaccine trial conducted in South African HCP, which indicated 2.6% asymptomatic carriage during the Beta and Delta outbreaks and subsequently rose to 16% in both PLWH and PHLWH during the Omicron period.

Table 1b . Prevalence of asymptomatic SARS-CoV-2 infection upon entry in vaccine studies.

Trial	Vaccine (developer)	Location	Dates	Predominant variant	Total participants	SARS-CoV-2 PCR+ [†]	Prevalence
COVE (CoVPN 3001; NCT04470427)	mRNA-1273 (Moderna)	US	Aug-Oct 2020	Ancestral	30,022	182	0.6%
Teen COVE (NCT04649151)	mRNA-1273 (Moderna)	US	Dec 2020-Feb 2021	Ancestral	3,469	22	0.6%
Ensemble (CoVPN 3003; NCT04505722.)	Ad26.COVS.2 (Janssen)	US South Africa S. America	Sept 2021-Jan 2020	USA: ancestral South Africa: Beta S. America: Gamma, ancestral, P.2	Overall: 41,273 PLWH [§] : 1,227	Overall: 227 PLWH [§] : 7	Overall: 0.55% PLWH [§] : 0.58%
Sisonke sub study (NCT04838795)	Ad26.COVS.2 (Janssen)	South Africa	June-Aug 2021	Delta	1,604	39	2.4%
Ubuntu (PACTR202105817814362)	mRNA-1273 (Moderna)	South Africa	Dec 2021-ongoing	Omicron	230*	71*	31%

Garrett N, et al.
<https://doi.org/10.1101/2021.12.20.21268130>

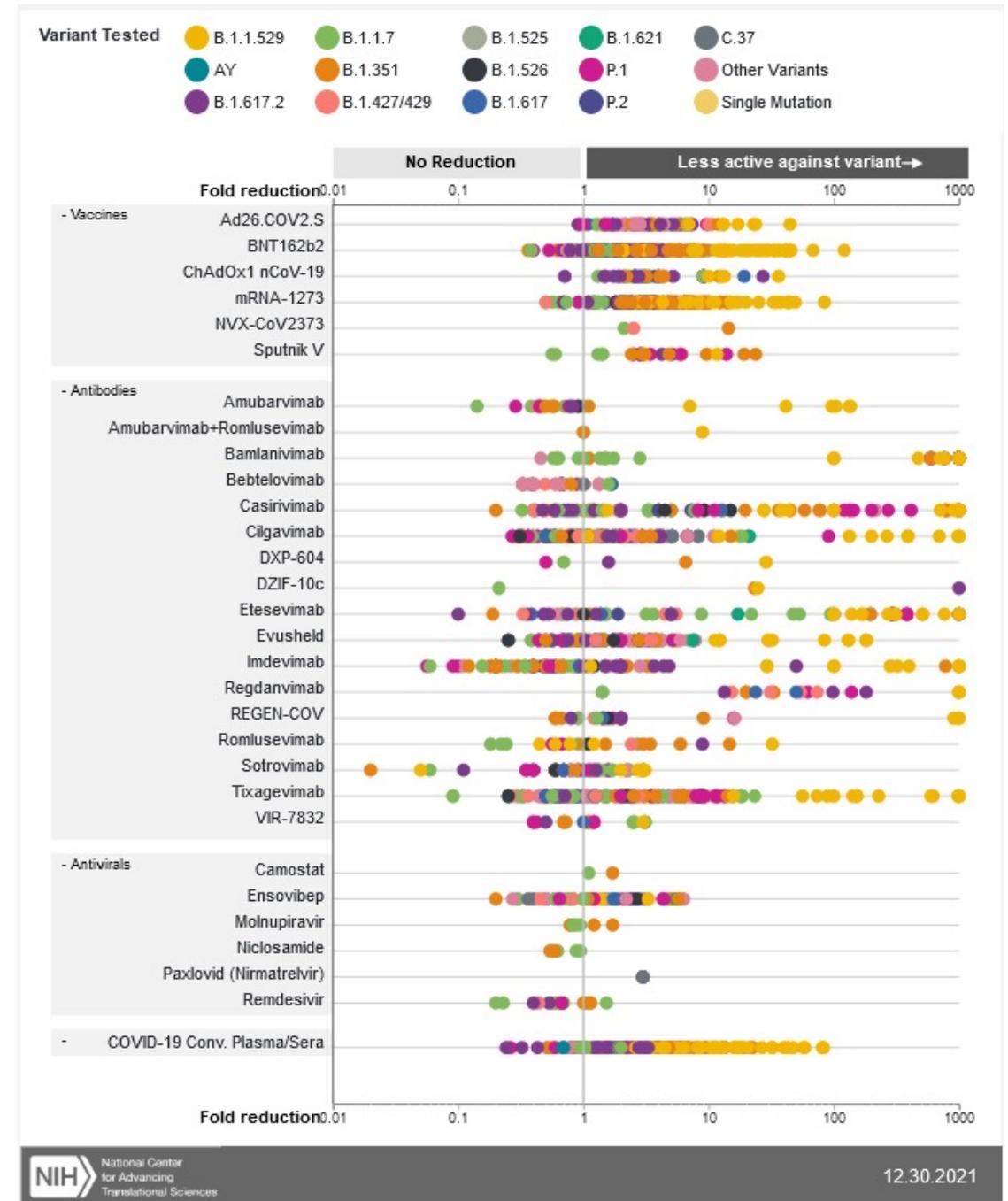
[†]At time of vaccination visit

[§]Most enrollment of people living with HIV (PLWH) occurred in South Africa

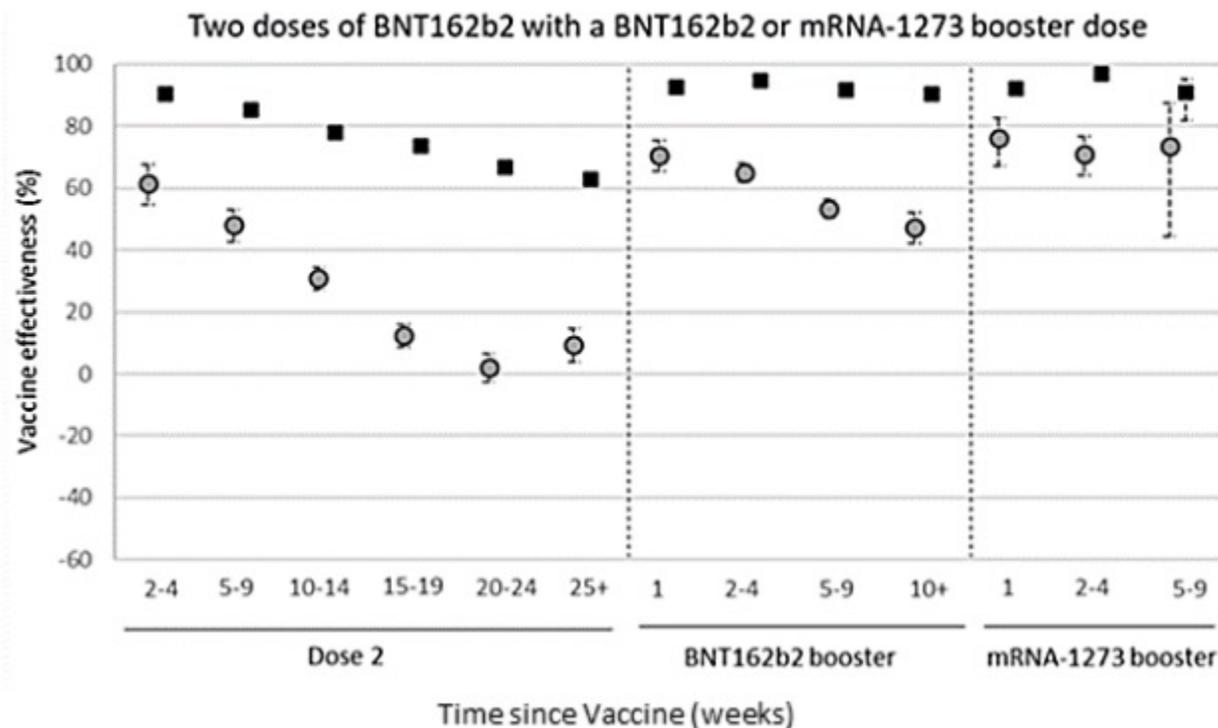
*Participants with baseline data as of Dec. 17, 2021

SARS-CoV-2 Variants: Reported in vitro Therapeutic Activity

- Omicron = B.1.1.529
- Available monoclonal antibodies with Omicron activity
 - Sotrovimab
 - Evusheld
- Available COVID-19 vaccines have reduced effectiveness against Omicron
 - mRNA boosted persons have good effectiveness to prevent and/or ameliorate COVID-19



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



■ Delta
● Omicron

- **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

[SARS-CoV-2 variants of concern and variants under investigation:](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf)

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf

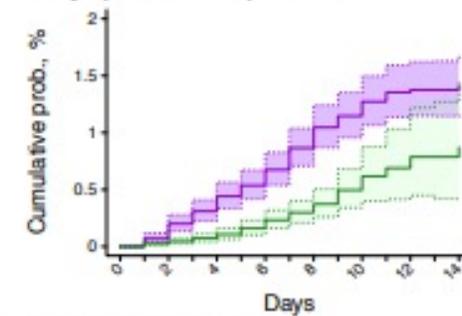
DISCOVERY HEALTH: OMICRON REPORT

- Real-world analysis of Omicron outbreak based on 211,000 COVID-19-positive test results in South Africa, 14 Dec.
- **Pfizer vaccine effectiveness:** Two-dose Pfizer-BioNTech vaccination provides 70% protection against severe complications of COVID-19 requiring hospitalization, and 33% protection against COVID-19 infection, during the current Omicron wave (test-negative design) - represents a significant drop from the 80% protection against infection afforded during the earlier period, probably on the basis of lower antibody susceptibility, following the extensive spike protein mutations in the Omicron variant.
- **Reinfection risk:** For individuals who have had COVID-19 previously, the risk of reinfection with Omicron is significantly higher, relative to prior variants. People who were infected with COVID-19 in South Africa's third (Delta) wave face a 40% relative risk of reinfection with Omicron; people who were infected with COVID-19 in South Africa's second (Beta) wave face a 60% relative risk of reinfection with Omicron.
- **Severity:** The risk of hospital admission among adults diagnosed with COVID-19 is 29% lower for the Omicron variant infection compared to infections involving the D614G mutation in South Africa's first wave in mid-2020, after adjusting for vaccination status
- **Children:** Despite very low absolute incidence, preliminary data suggests that children have a 20% higher risk of hospital admission in Omicron-led fourth wave in South Africa, relative to the D614G-led first wave.
- **Limitations on data:** 1) limited to first 3 weeks of Omicron-driven wave in SA; 2) data confounded by various factors, including high seroprevalence of COVID-19 antibodies in the South African population as a whole

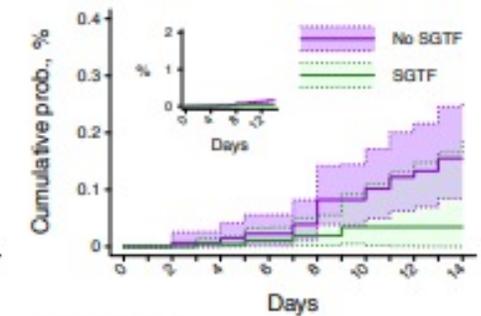
Clinical outcomes in patients infected with Omicron in CA

- Methods: Assessed ~53,000 with S gene target failure (SGTF, surrogate for Omicron) and ~17,000 with non-SGTG (surrogate for Delta)
- Results: Hospital admissions occurred among 235 (0.5%) and 222 (1.3%) of cases with Omicron and Delta variant infections, respectively. Among cases first tested in outpatient settings, the aHR for any subsequent hospital admission and symptomatic hospital admission associated with Omicron variant infection were 0.48 (0.36-0.64) and 0.47 (0.35-0.62), respectively. Rates of ICU admission and mortality after an outpatient positive test were 0.26 (0.10-0.73) and 0.09 (0.01-0.75) fold as high among cases with Omicron compared to cases with Delta. Median duration of hospital stay was 3.4 (2.8-4.1) days shorter for hospitalized cases with Omicron.

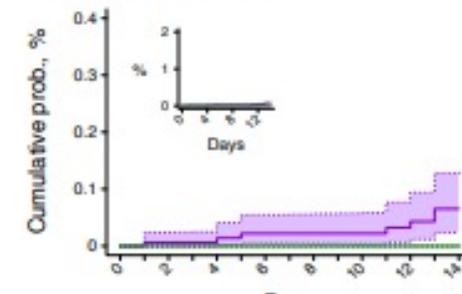
A: Symptomatic hospitalization



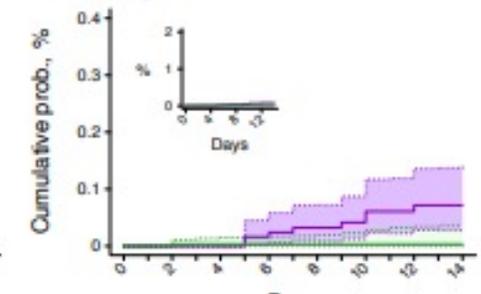
B: ICU admission



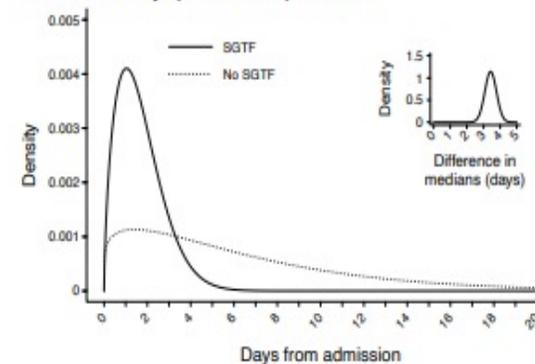
C: Mechanical ventilation



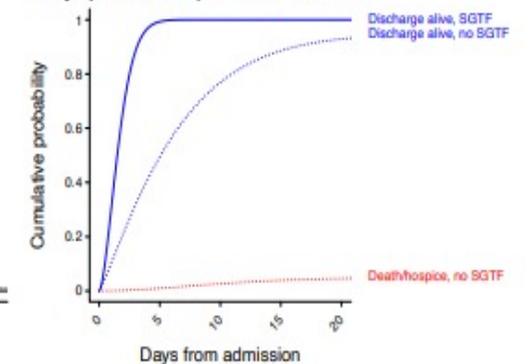
D: Mortality



A: Duration of symptomatic hospitalization

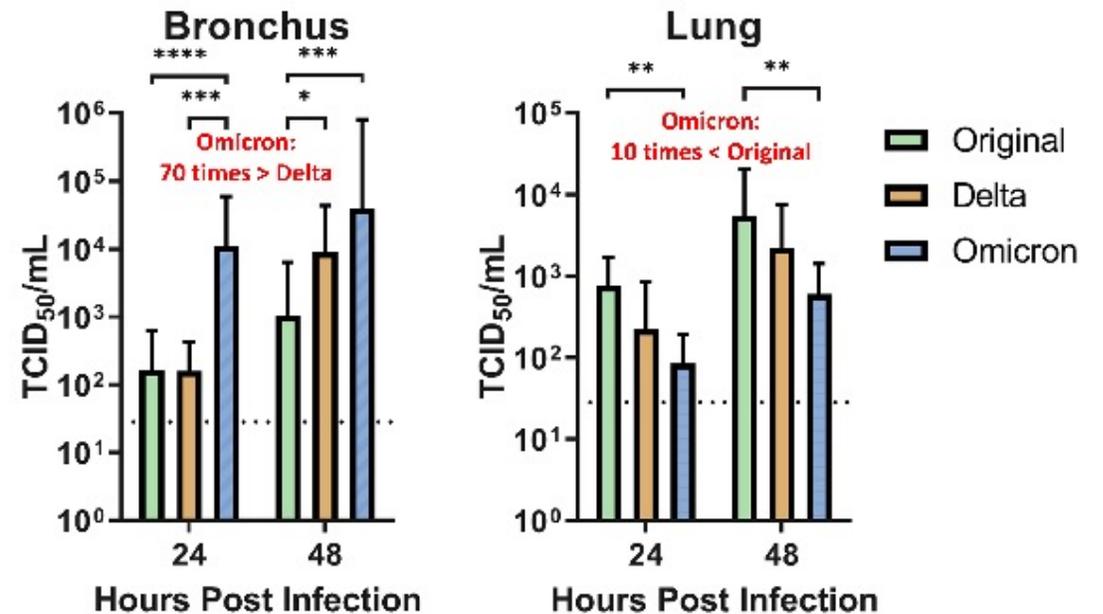


B: Symptomatic hospitalization outcomes



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 infects 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.

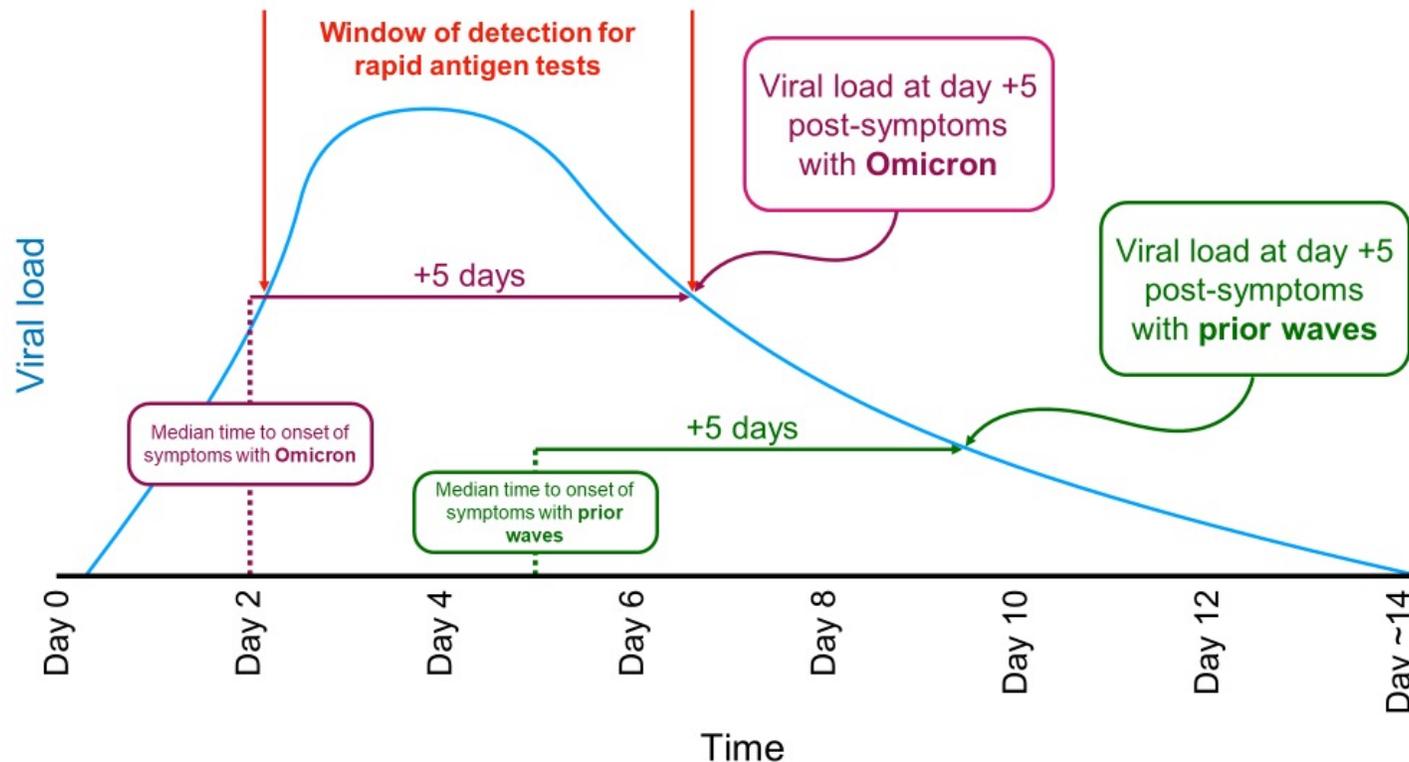


ISOLATION AND QUARANTINE, CDC, 4 JAN. 2022

- Who does not need to quarantine: If you came into close contact with someone with COVID-19 and you are in one of the following groups, you do not need to quarantine.
 - You are ages 18 or older and have received all recommended vaccine doses, including boosters and additional primary shots for some immunocompromised people.
 - You are ages 5-17 years and completed the primary series of COVID-19 vaccines.
 - You had confirmed COVID-19 within the last 90 days (you tested positive using a viral test).
- Who should quarantine? If you come into close contact with someone with COVID-19, you should quarantine if you are in one of the following groups:
 - You are ages 18 or older and completed the primary series of recommended vaccine, but have not received a recommended booster shot when eligible.
 - You received the single-dose Johnson & Johnson vaccine (completing the primary series) over 2 months ago and have not received a recommended booster shot.
 - You are not vaccinated or have not completed a primary vaccine series.
- Ending isolation for people who had COVID-19 and had symptoms
 - You can end isolation after 5 full days if you are fever-free for 24 hours without the use of fever-reducing medication and your other symptoms have improved (Loss of taste and smell may persist for weeks or months after recovery and need not delay the end of isolation).
 - You should continue to wear a well-fitting mask around others at home and in public for 5 additional days (day 6 through day 10) after the end of your 5-day isolation period.

Is my rapid antigen test a false negative?

Hypothesis for why rapid tests can be falsely negative with omicron



Hypothesis

- Symptoms arise earlier in infection by Omicron due to pre-existing immunity

Consequences

- Higher risk that antigen tests could be falsely negative with Omicron because viral loads are lower at median time to onset of symptoms (day 2)
- Viral loads at day +5 from symptoms may be higher in Omicron

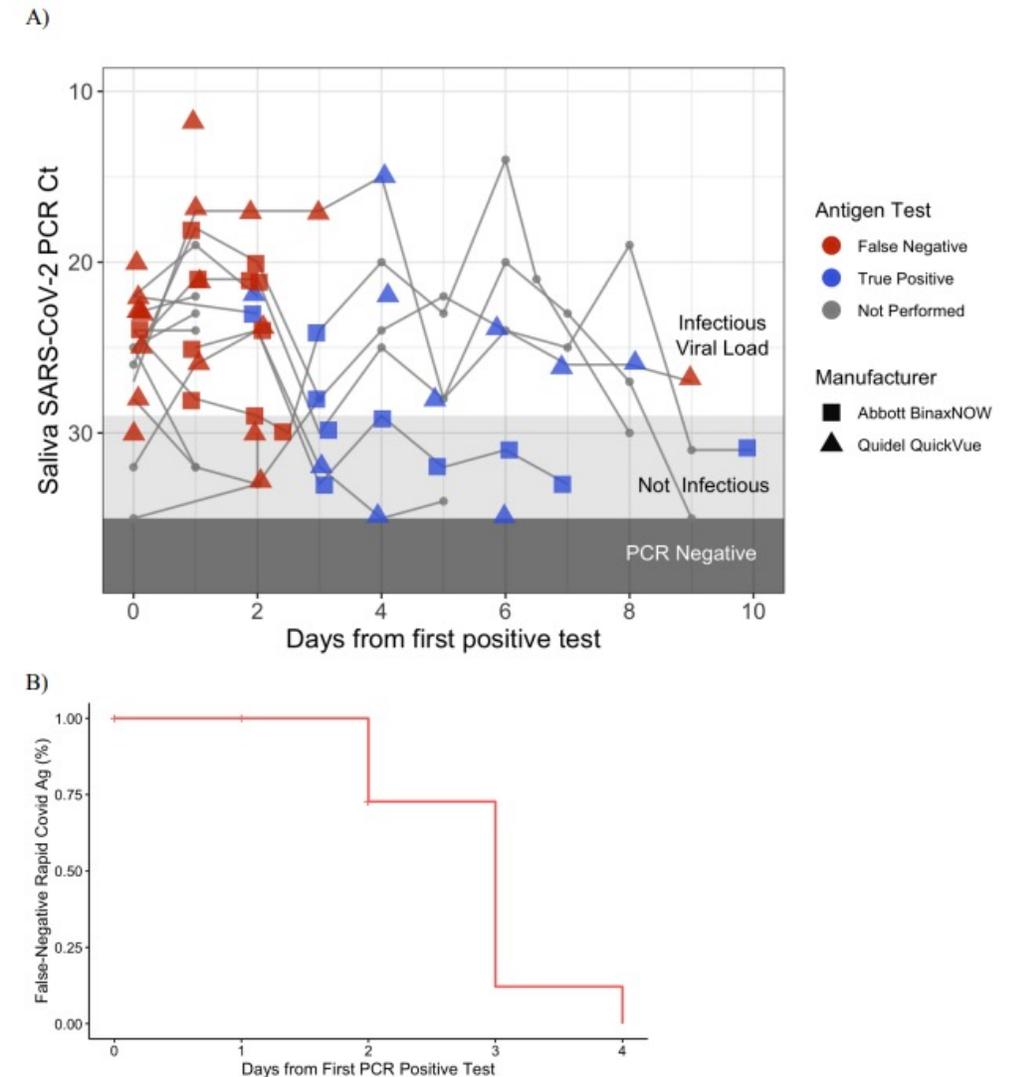
Assumptions

- Viral load kinetics with omicron unchanged from prior waves
- No differences in viral loads between symptomatic and asymptomatic people

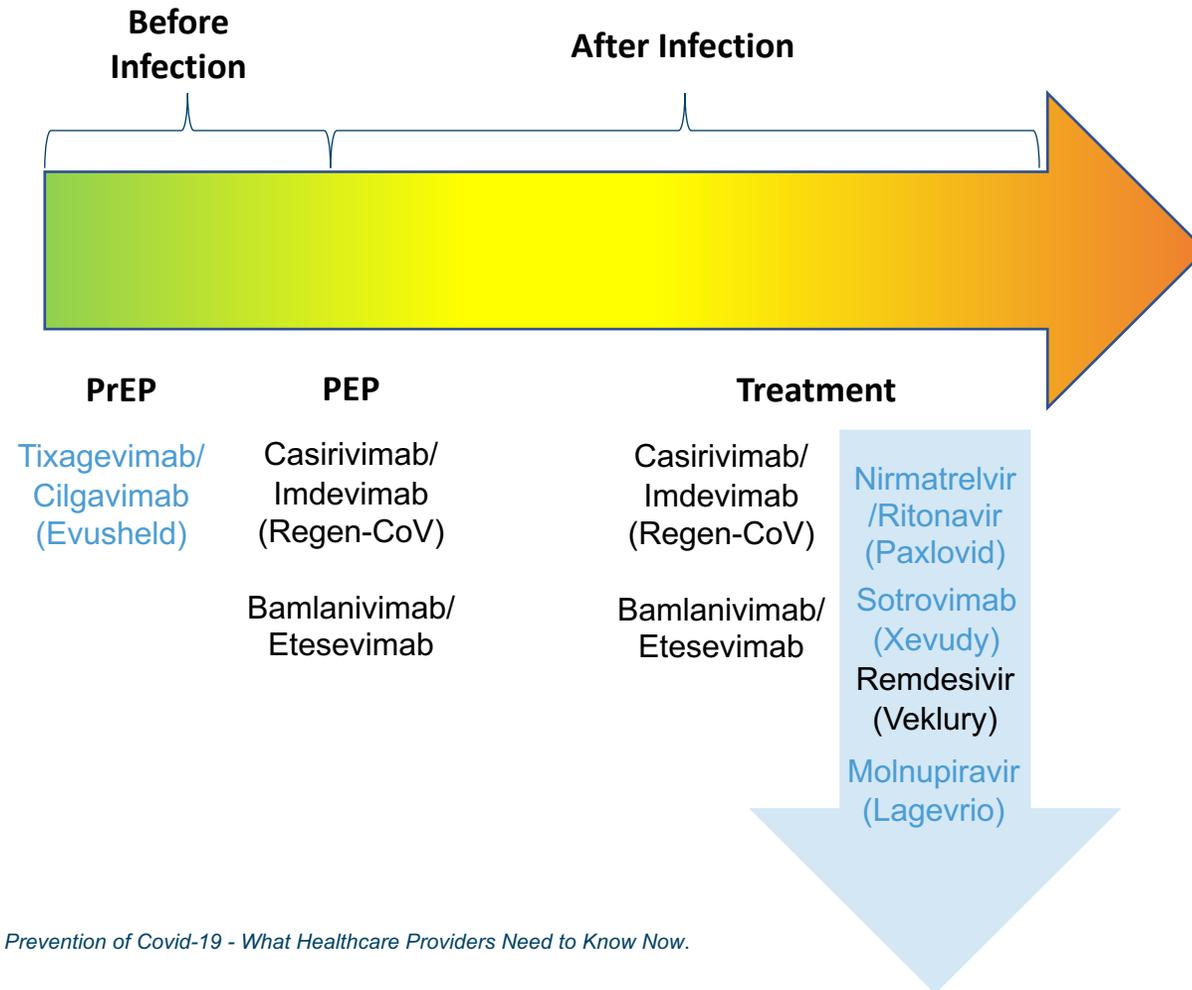
Discordant SARS-CoV-2 PCR and Rapid Antigen Test Results When Infectious: A December 2021 Occupational Case Series

- Retrospective cohort study, 1-31 Dec 2021, NYC, LA, SF
- We identified 30 individuals with 62 matched pairs of rapid antigen and positive PCR results from specimens collected at the same time. The S-gene dropout associated with Omicron was observed in 29 of 30 cases. Viral dynamics and discordance in test results are shown in Figure 1. Four cases were confirmed to have transmitted the virus between false-negative antigen tests, with saliva PCR cycle threshold (Ct) values between 23-28 for the N gene. **On Days 0 and 1, all rapid antigen tests produced false-negative results, despite 28 of 30 pairs having infectious viral load within the range of confirmed Omicron transmissions in the cohort (Ct <29). The median time from first positive PCR to first detectable antigen positive was 3 days (95% CI: 2-NA).** After infection was detected, a subgroup (n=5) who received daily saliva PCR, nasal swab PCR, and nasal swab rapid Ag testing showed viral load peaked in saliva 1-2 days before nasal tests. All individuals in the cohort developed symptoms within two days of the first PCR positive test

Shown are Cycle Threshold (Ct) counts and rapid antigen test results from paired samples of infected patients (Panel A). Also shown is the Kaplan Meier analysis of time from positive PCR to positive rapid antigen test (Panel B).



COVID Therapeutics Overview



Wohl, D. (2021, December). *Treatment and Prevention of Covid-19 - What Healthcare Providers Need to Know Now.*

