COVID-19 Update March 2022

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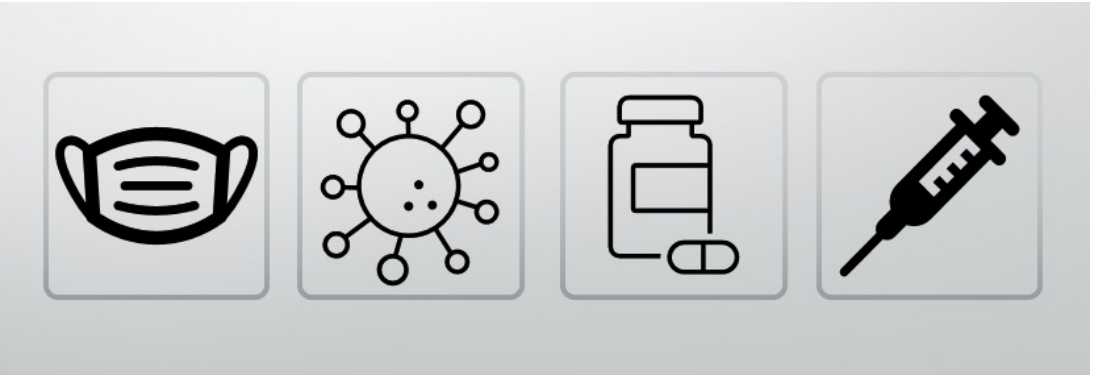
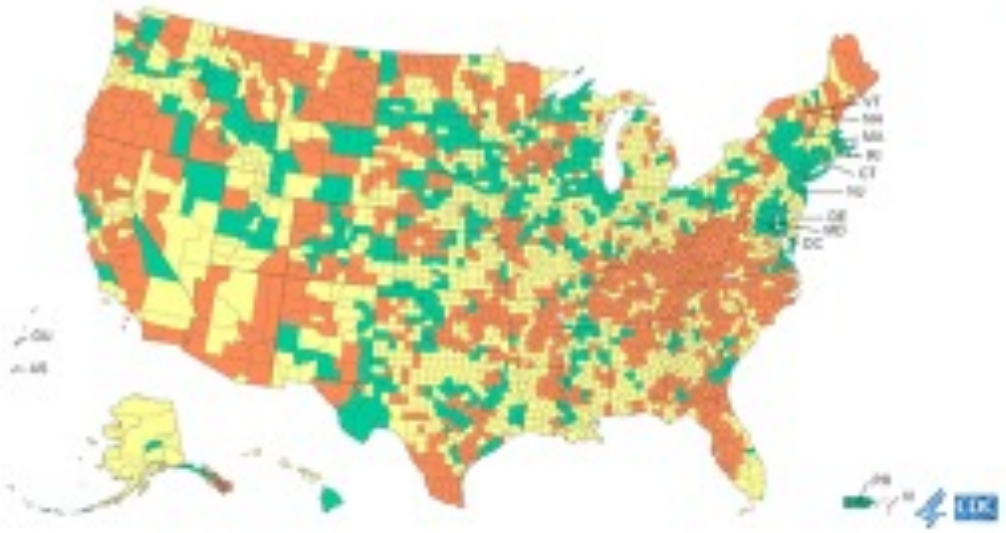
Outline

- Mask Updates
- Variant Updates
- Treatment Updates
- Vaccine Efficacy Updates



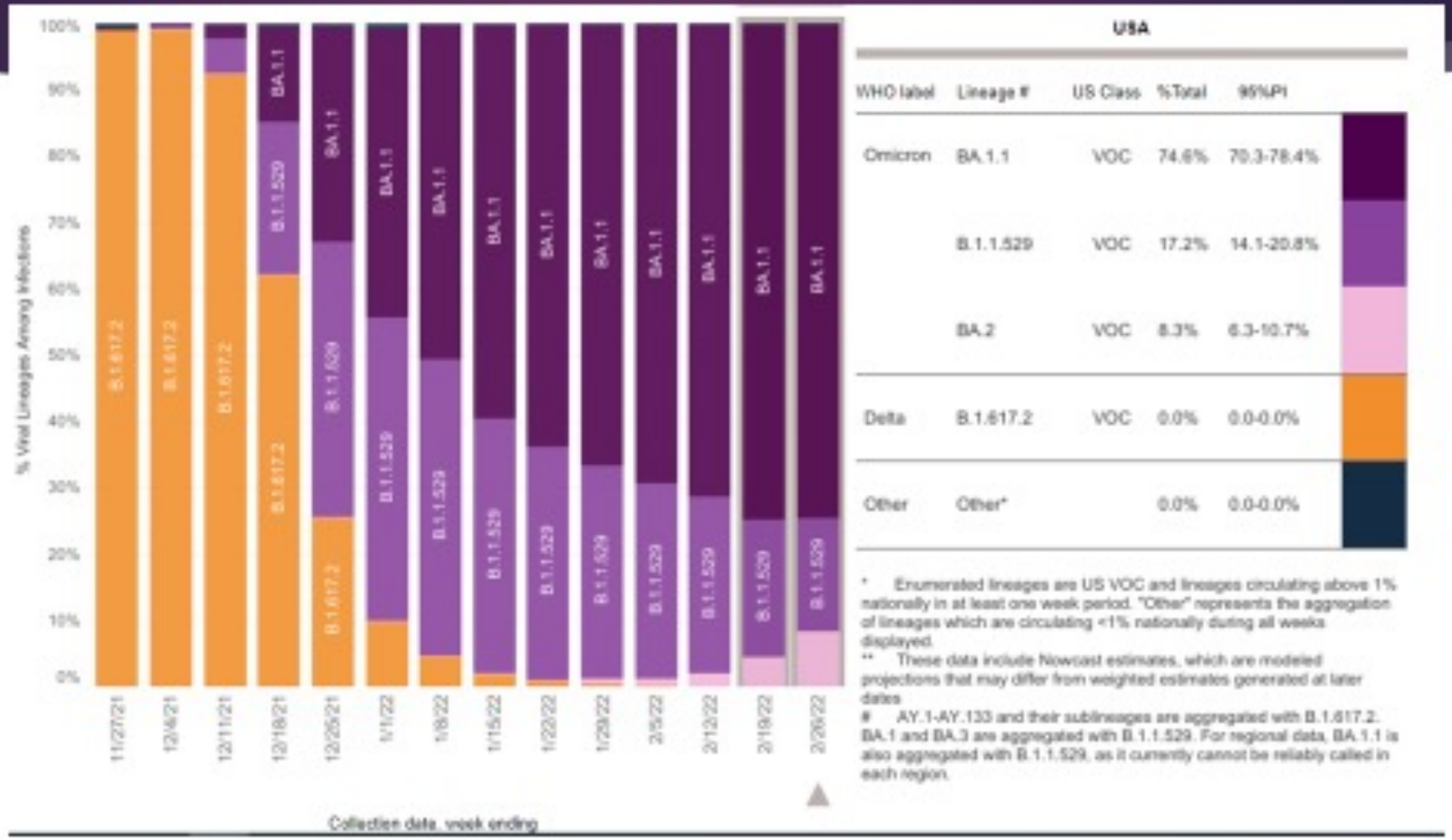
Prevention Based on COVID-19 Community Level



Low	Medium	High
•Stay up to date with COVID-19 vaccines •Get tested if you have symptoms **•Wear a mask based on your personal preference, informed by your personal level of risk**	•If you are at high risk for severe illness, **talk to your healthcare provider about whether you need to wear a mask and take other precautions** •If you live with or have social contact with someone at high risk for severe illness, **consider testing yourself for infection before you get together and wearing a mask when indoors with them** •Stay up to date with COVID-19 vaccines •Get tested if you have symptoms	**•Wear a mask indoors in public, regardless of vaccination status or individual risk** •Stay up to date with COVID-19 vaccines •Get tested if you have symptoms •Additional precautions may be needed for people at high risk for severe illness

https://www.cdc.gov/coronavirus/2019-ncov/your-health/covid-by-county.html

Variant Report as of 2/26/22



USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.1.1	VOC	74.6%	70.3-78.4%
	B.1.1.529	VOC	17.2%	14.1-20.8%
	BA.2	VOC	8.3%	6.3-10.7%
Delta	B.1.617.2	VOC	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1 and BA.3 are aggregated with B.1.1.529. For regional data, BA.1.1 is also aggregated with B.1.1.529, as it currently cannot be reliably called in each region.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Omicron

- **Spread**
  - The Omicron variant spreads more easily than the original virus that causes COVID-19 and the Delta variant. It can be transmitted to others regardless of vaccination status
- **Symptoms**
  - The presence and severity of symptoms can be affected by COVID-19 vaccination status, the presence of other health conditions, age, and history of prior infection.
- **Severe Illness**
  - Generally causes less severe disease than infection with prior variants although some people may still have severe disease, need hospitalization, and could die
- **Vaccines remain the best public health measure to protect people from COVID-19 and reduce the likelihood of new variants**
  - People who are up to date with their COVID-19 vaccines and get COVID-19 are less likely to develop serious illness than those who are unvaccinated and get COVID-19.

Prophylactic and Therapeutic Options against Omicron SARSCoV2

Preexposure Prophylaxis (Mod to Severe Immunosuppression):

- Evusheld (tixagevimab/cilgavimab)

Post-exposure Prophylaxis

Mild to Moderate Ambulatory COVID19 (with Risk Factors for severe disease):

- Sotrovimab 500mg IV once
- Bebtelovimab (recently authorized monoclonal ab)
- Paxlovid
- IV Remdesivir
- Oral Molnupiravir (when other options are not available)

https://www.covid19treatmentguidelines.nih.gov

Summary of COVID-19 Preventative Agents & Therapeutics

Remdesivir

Vaccines

Pre-Exposure Prophylaxis (Tixagevimab ,Cilgavimab)

Masks

Paxlovid
Sotrovimab
Bebtelovimab
Remdesivir
Molnupiravir

Dexamethasone
Tocilizumab
Baricitinib

Summary of COVID-19 Preventative Agents & Therapeutics

Pre-exposure Prophylaxis:
Evusheld
(Tixagevimab+Cilgavimab)

Pre-exposure Prophylaxis: *Evusheld®*

Two monoclonal antibodies

- **Tixagevimab+Cilgavimab**

Authorized by FDA EUA:

- **Not infected with SARS-CoV-2** and who have **not had a known recent exposure** to an individual infected with SARS-CoV-2 **and**
- **Moderate to Severe immune compromise** due to a medical condition or receipt of immunosuppressive medications or treatments
- Do **not mount an adequate immune** response to COVID-19 vaccination **or**
- **Severe reaction that contraindicates vaccination** schedule, is not recommended due to a history of severe adverse reaction

https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing

Examples of Moderate to Severe Immunosuppression:

Active Treatment for Solid Tumors
Hematopoietic stem cell Transplant (<2yr) or CAR-T-cell Therapy
Reception of Solid Organ Transplant and taking immunosuppressing medications
Advanced/uncontrolled HIV
High dose corticosteroids (>20mg Pred for >2weeks) or immune-modulators (TNF, B-cell depleting) alkylating agents, antimetabolites

Supporting Clinical Trials for Evusheld ®

- Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). Both trials are evaluating the safety and efficacy of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) for the prophylaxis SARSCoV-2 symptomatic illness (COVID-19)

Table 6 Incidence of Symptomatic COVID-19 in Adults (PROVENT)

	N*	Number of events, n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD†	3,441	8 (0.2%)	77% (46, 90)
Placebo	1,731	17 (1.0%)	

https://www.fda.gov/media/154701/download

EVUSHELD

Hypersensitivity Including Anaphylaxis

- Clinically monitor individuals after injections and observe for at least 1 hour.

Clinically Significant Bleeding Disorders:

- As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

Cardiovascular Events:

- A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events.
- All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern.
- A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. (5.3

EVUSHELD

- May be less active against certain Omicron subvariants (BA.1, BA.1.1)
- The dosing regimen was revised, a higher dose may be more likely to prevent infection by the COVID-19 Omicron subvariants than the originally authorized dose.
- Dose increased to 300mg of tixagevimab and 300 mg cilgavimab
- Contact patients who received the previously authorized Evusheld dose to return for an additional 150 mg tixagevimab and 150 mg cilgavimab dose as soon as possible.
- The volume of each injection for the higher dose will be larger, 3 mL instead of 1.5 mL. Limit injections to large muscles on the body (e.g., the gluteal muscles).
- Is expected to have greater neutralizing activity against BA.2 which will become dominant

https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing

Summary of COVID-19 Preventative Agents & Therapeutics

Post-Exposure Prophylaxis: No currently authorized Monoclonal has activity against Omicron Variant

Summary of COVID-19 Preventative Agents & Therapeutics

Nirmatrelvir+Ritonavir (Paxlovid®)
Sotrivimab
Remdesivir (Velklury®)
Molnulpiravir (Lagrevio®)
Bebtelovimab

Important to Check Drug-Drug Interactions with Paxlovid®

Nirmatrelvir/Ritonavir

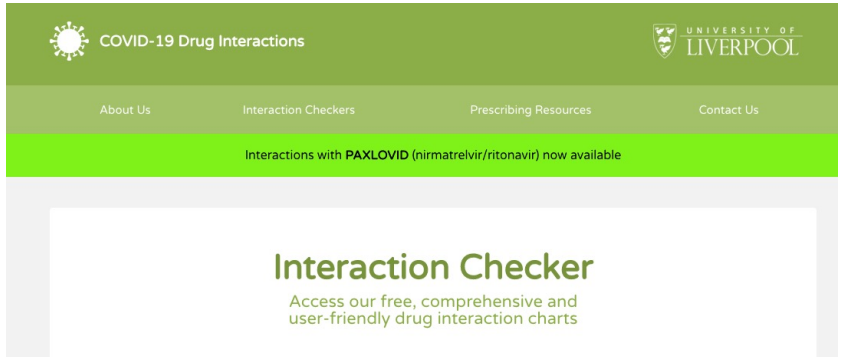
Figure 2. Nirmatrelvir/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions [1]

- 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

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) for Paxlovid™ Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.

IDSA Guidelines



https://covid19-druginteractions.org/

Remdesivir (Veklury®)

REMDESIVIR administered in Hospitalized patients

REMDESIVIR used early (<7 days of symptom onset)

New extension of the Remdesivir FDA Approval and Authorization:

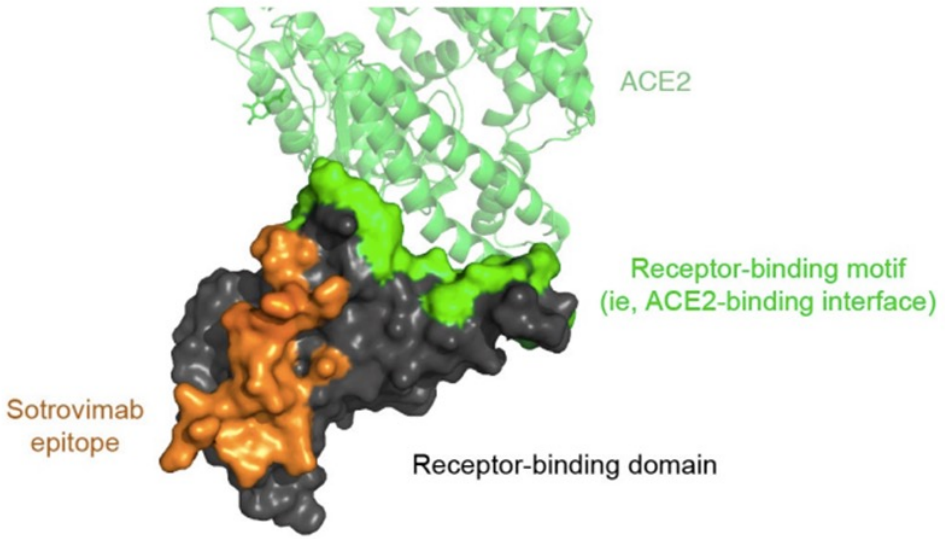
Expanded **approval** for ≥12 years and older with **Mild-to-Moderate** COVID-19, and are at high risk for progression to severe COVID-19

Revised EUA to include Pediatric patients weighing 3.5-40 kg with positive results of direct SARS-CoV-2 viral testing who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19

IDSA Guidelines recommends its use within **7 days** of Symptoms onset

Sotrovimab (Xevudy®)

Figure S1. The conserved, pan-sarbecovirus binding site of sotrovimab on the spike protein of SARS-CoV-2.



https://www.fda.gov/media/149534/download

- Authorized (EUA)
  - Mild-to-moderate (COVID-19) in **adults and pediatric patients (12 years of age and older weighing at least 40 kg)**, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Sotrovimab

- Less in vitro activity against Omicron BA.2.
- Clinical relevance of the 16-fold reduction in susceptibility is unknown
- Updated authorization for those likely to have been infected with or have been exposed to a susceptible SARS-CoV-2 variant

Molnupiravir (Lagevrio®)

- **≥18yr** Mild to Moderate COVID19 and risk of progression to severe disease, < 5 days from symptom onset, when other treatment options are not available
- Contraindicated in Pregnancy
- **Molnupiravir 200mg caps** dosing:
  4 tabs (800mg) po bid
- No renal adjustment needed

https://www.fda.gov/media/155054/download

Medication	Reduction in Hospitalization & Death	Route	Treatment Duration	Indication by Time from Symptom Onset
Paxlovid	88%	Oral	5 days	≤5 days
Remdesivir	87%	Intravenous	3 days (three separate 1-2 hour infusions)	≤7 days
Sotrovimab	85%	Intravenous	30 minutes	≤10 days
Molnupiravir	30%	Oral	5 days	≤5 days

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant

Bebtelovimab may only be used for the treatment of mild-to-moderate 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, including hospitalization or death, and
- **For whom alternative COVID-19 treatment options** approved or authorized by FDA are **not accessible or clinically appropriate**.

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains

Bebtelovimab

- **Bebtelovimab works by binding to the spike protein of the virus that causes COVID-19**
- **Laboratory testing showed activity against both omicron variants (BA.1 and BA.2)**
- **BLAZE-4 is a Phase 1/2, randomized, single-dose clinical trial evaluating treatment of subjects with mild-to-moderate COVID-19 who are not hospitalized. Efficacy of bebtelovimab, alone and together with bamlanivimab and etesevimab, was evaluated in**
  - Low risk adults in a randomized part of the trial which included a placebo control arm
  - High-risk adults and pediatric subjects received open-label active treatments.
  - Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination.
- **No subject in BLAZE-4 was infected with virus of the Omicron lineage or sub-lineages, the majority were infected with Delta (49.8%) and Alpha (28.6%)**

https://www.fda.gov/media/156152/download

Bebtelovimab

- **The placebo-controlled portion of the trial enrolled 380 low-risk patients**
  - They were randomized to receive a single infusion of bebtelovimab alone, bebtelovimab with other monoclonal antibodies or a placebo.
  - Treatment with bebtelovimab resulted in a reduction in time to sustained symptom resolution compared to placebo. Reduction in viral load relative to placebo was also seen on Day 5 after treatment.
- **The portion of the trial that enrolled high-risk individuals had a**
  - Randomized arm: 150 patients randomized to receive a single infusion of bebtelovimab alone or a single infusion of bebtelovimab with other monoclonal antibodies.
  - Open label arm: An additional 176 high-risk patients received bebtelovimab with other monoclonal antibodies .
  - The rates of COVID-19 related hospitalization and death through Day 29 seen in those who received bebtelovimab alone or with other monoclonal antibodies were generally lower than the placebo rate reported in prior trials of other monoclonal antibodies in high risk patients.
- **Conclusions are limited as these data are from different trials that were conducted when different viral variants were circulating and baseline risk factors varied.**
- **Clinical data were similar for bebtelovimab alone as compared to the combination of bebtelovimab with other monoclonal antibodies**.

Protection against the Omicron Variant from Previous SARS-CoV-2 Infection

Table 1. Effectiveness of Previous Infection with SARS-CoV-2 against Symptomatic Reinfection, According to Variant.*

Type of Analysis and Variant	Cases (PCR-Positive)		Controls (PCR-Negative)		Effectiveness (95% CI)†
	Previous Infection	No Previous Infection	Previous Infection	No Previous Infection	
	number of patients				*percent*
Effectiveness against symptomatic infection					
Primary analysis‡					
Alpha	2	334	94	1548	90.2 (60.2 to 97.6)
Beta	14	1322	450	6084	85.7 (75.8 to 91.7)
Delta	23	2153	1154	8782	92.0 (87.9 to 94.7)
Omicron	412	5284	1620	9053	56.0 (50.6 to 60.9)

In this national database study from Qatar, previous infection (defined as a +PCR >90 day before) conferred high protection (90%) against reinfection for all variants except Omicron (60%)

ORIGINAL ARTICLE

Effectiveness of the BNT162b2 Vaccine after Recovery from Covid-19

Ariel Hammerman, Ph.D., Ruslan Sergienko, M.A., Michael Friger, Ph.D., Tanya Beckenstein, B.Sc., Alon Peretz, M.D., Doron Netzer, M.D., Shlomit Yaron, M.D., and Ronen Arbel, Ph.D.

- **Methods**: Retrospective cohort study compared reinfection rates among patients who had subsequently received Pfizer–BioNTech and those who had not been vaccinated between March 1 and November 26, 2021.
- Recurrent infection was defined as a +PCR 100days after primary infection
- A total of 149,032 patients, 56% received subsequent vaccination during the 270-day study period (March 1 and November 26, 2021)

February 16, 2022
DOI: 10.1056/NEJMoa2119497

Results

- Reinfection rate in vaccinated: 2.46 cases/100,000 persons/day
- Reinfection rate in unvaccinated: 10.21 cases/100,000 persons/day
- Vaccine Effectiveness:
  - More effective in younger population
    - 82% (95% confidence interval [CI], 80 to 84) among 16 to 64 years
    - 60% (95% CI, 36 to 76) among 65 years of age or older
  - No differences in effectiveness when one or two doses were compared
    - Adjusted hazard ratio for reinfection among patients who had received one dose as compared with those who had received two doses was **0.98 (95% CI, 0.64 to 1.50).**

February 16, 2022
DOI: 10.1056/NEJMoa2119497

Conclusions

- Vaccination (with at least one dose) decreases 5x risk of reinfection
- No difference in the protection between one or two doses if you have been infected with SARSCoV2 before vaccination

February 16, 2022
DOI: 10.1056/NEJMoa2119497

Teaching Points

- Infection confers good protection from reinfection with most variants but Omicron (Qatar Study)

- Vaccination of those previously infected
  -Decreased the incidence of reinfection 5x (Israel Study)
  -One dose may be enough

- Vaccination of those previously infected increases protection to around 90% and prevents the **waning** of the protection >1year

ORIGINAL ARTICLE

Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection

Victoria Hall, F.F.P.H., Sarah Foulkes, M.Sc., Ferdinando Insalata, M.Sc., Peter Kirwan, B.Sc., Ayoub Saei, Ph.D., Ana Atti, M.Sc., Edgar Wellington, M.Sc., Jameel Khawam, M.Sc., Katie Munro, M.Sc., Michelle Cole, D.B.M.S., Caio Tranquillini, M.D., Andrew Taylor-Kerr, M.P.P., et al., for the SIREN Study Group*