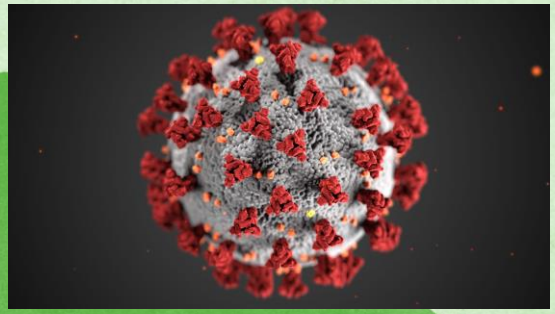
COVID-19 Variants, Vaccines, and you

Christopher Baliga MD

November 6, 2021



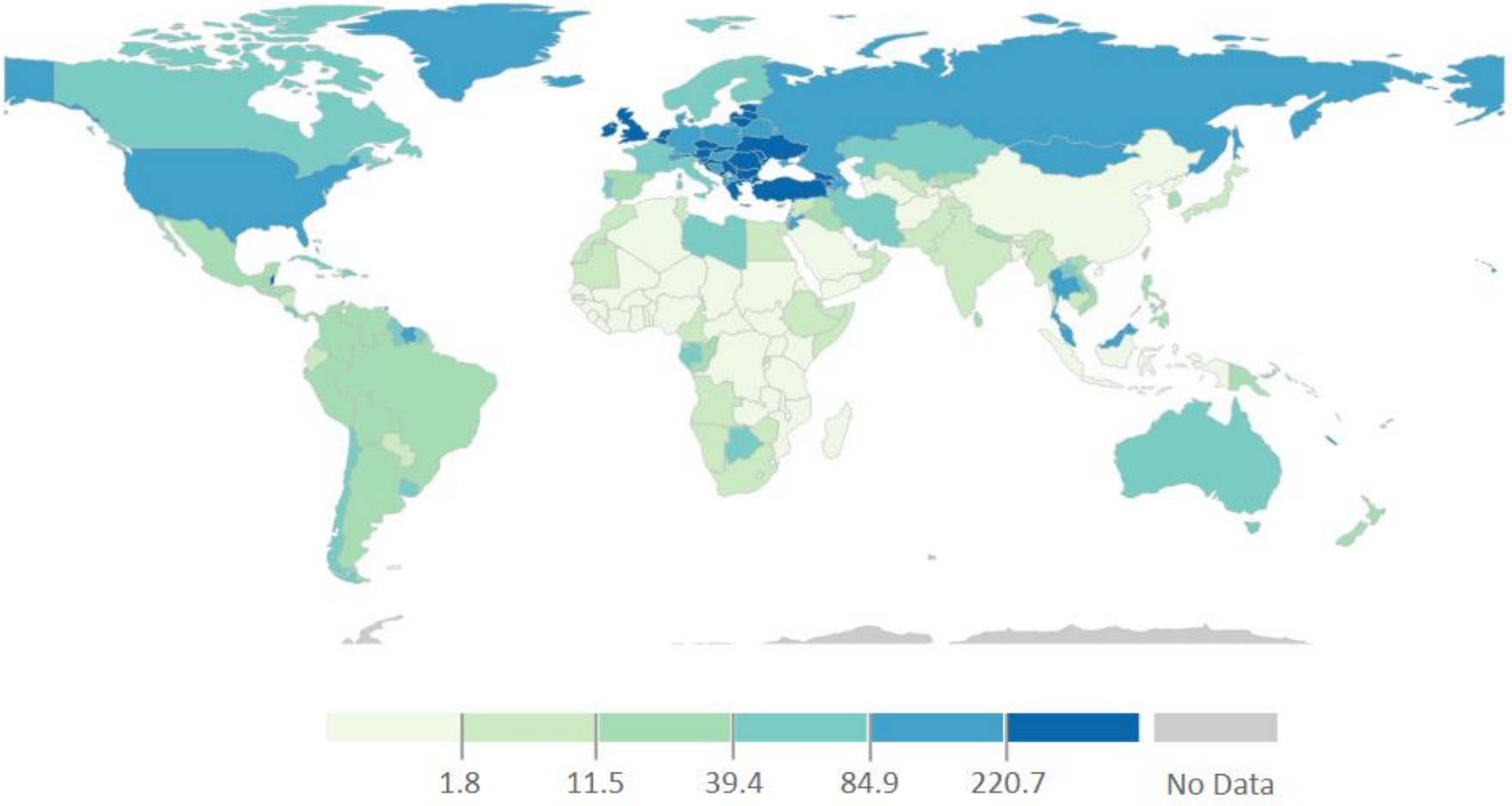
Virginia Mason Franciscan Health™

Objectives

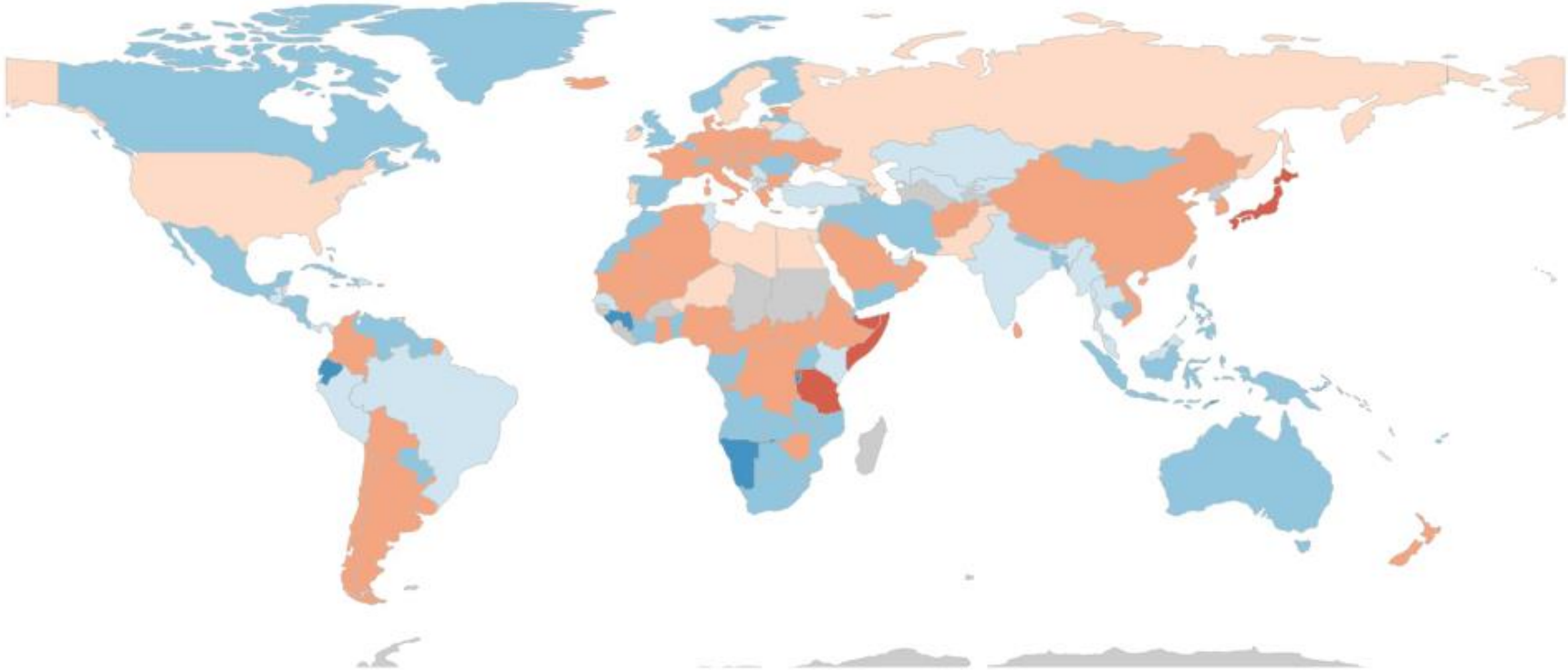
1. Understand the current international, national, and local epidemiology of COVID-19
2. Understand the current types of variants and their role in the pandemic
3. Understand the current vaccination options for COVID
4. Understand the current outpatient and inpatient treatment options for COVID-19

Virginia Mason Franciscan Health

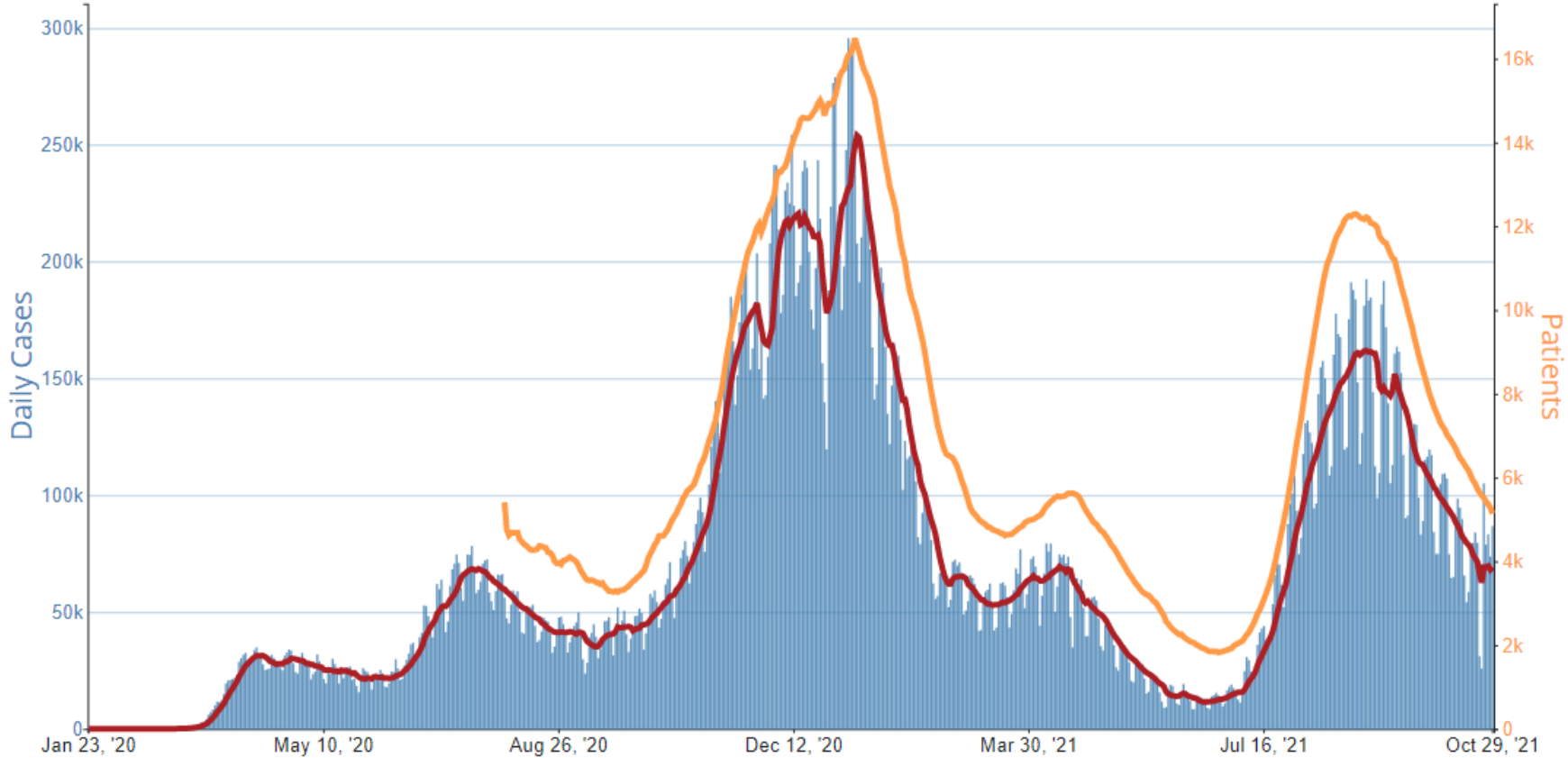
Global cases of COVID-19 reported per 100,000 population in the past 7 days



Percent Change in Cases Reported in the Past 7 days



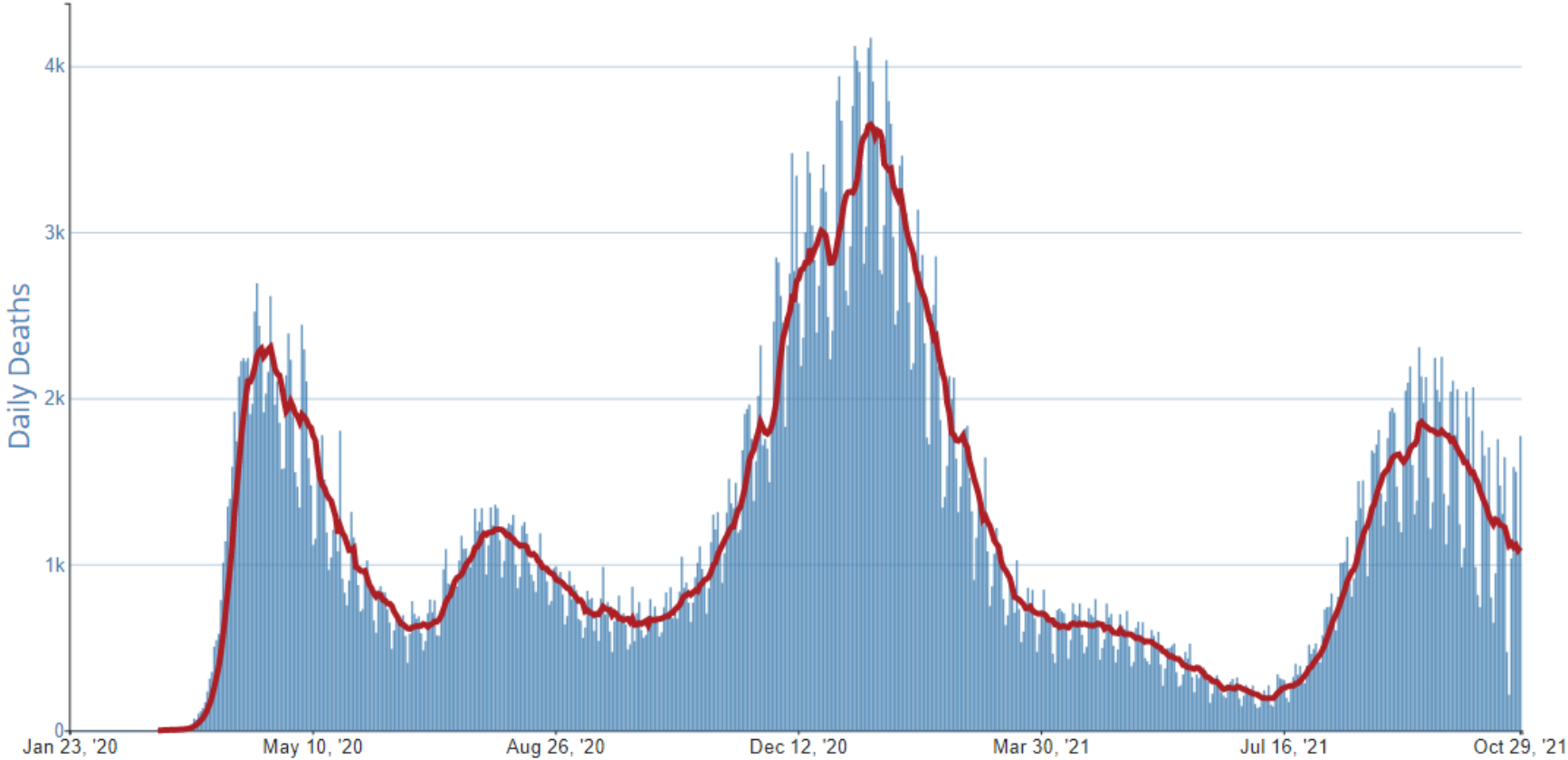
Daily Cases and Hospitalized population in the US



Franciscan Health

CDC Tracker

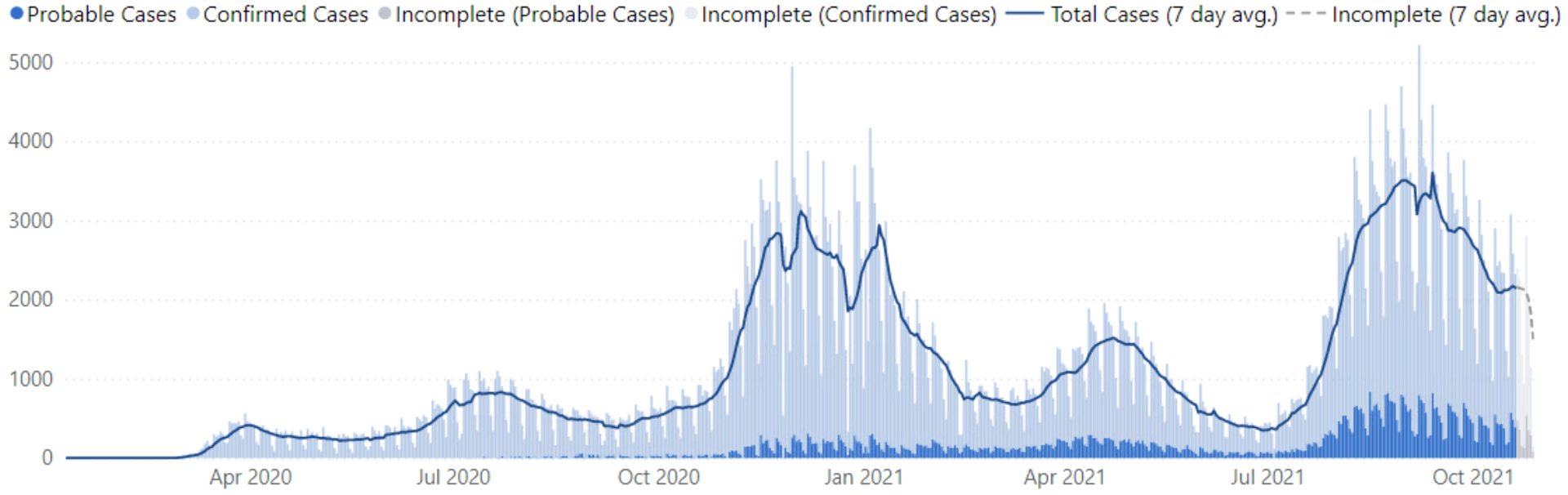
Daily Deaths in the US



Franciscan Health

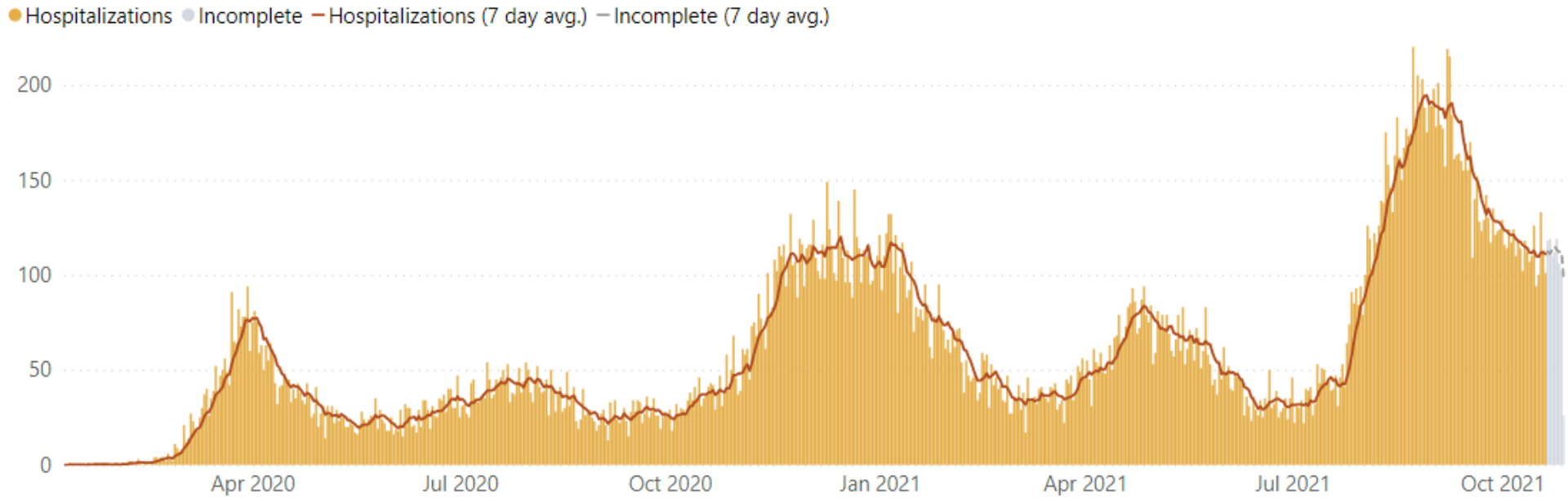
CDC Tracker

Daily Cases in WA



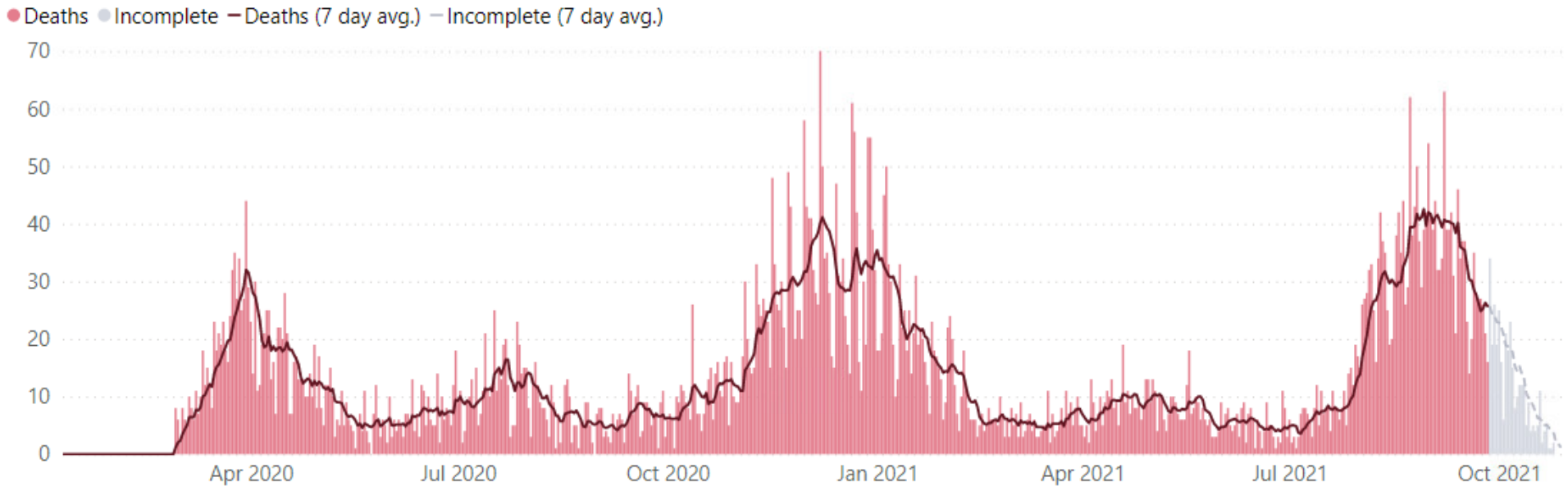
Virginia Mason Franciscan Health

Daily Hospitalizations in WA



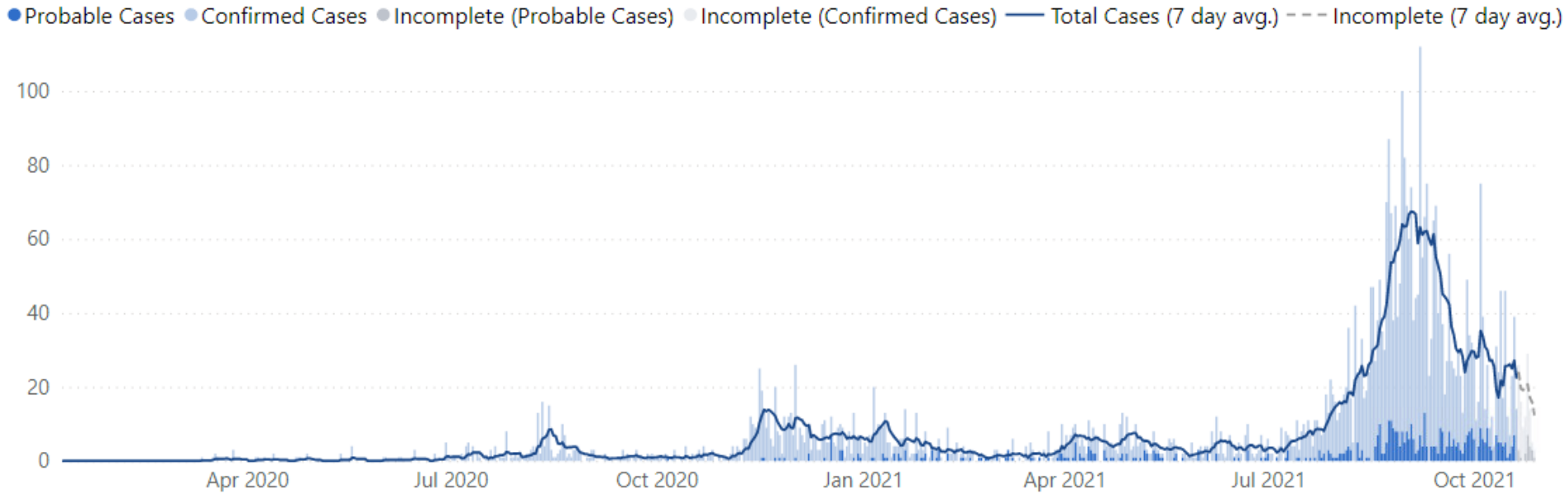
Virginia Mason Franciscan Health

Daily Deaths in WA



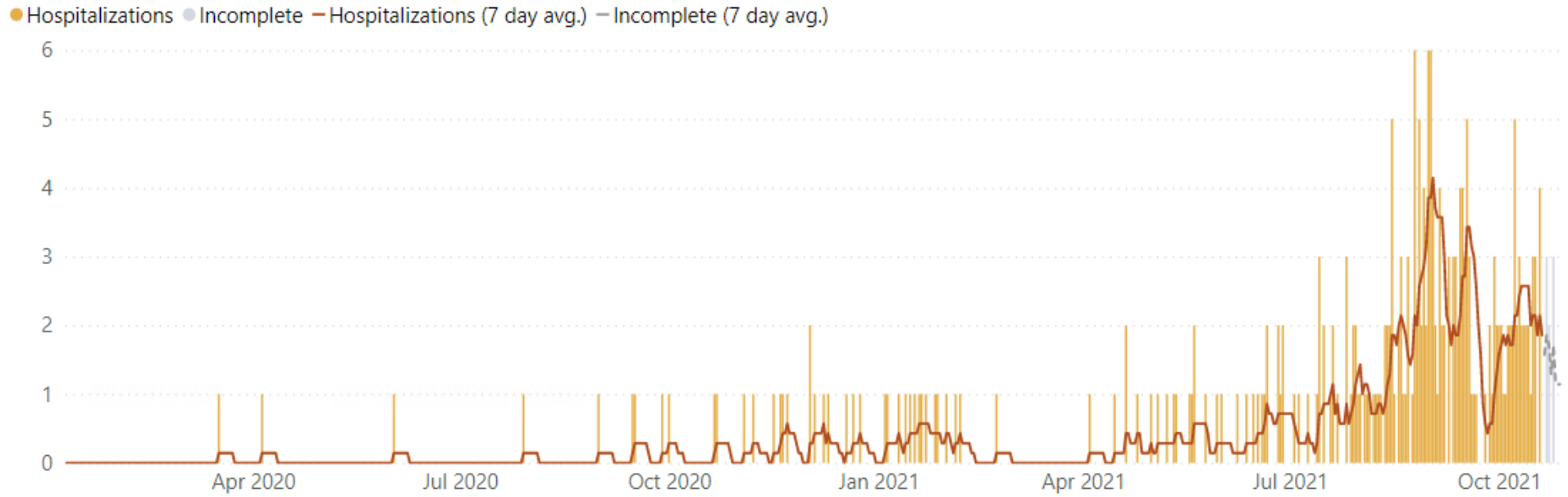
Virginia Mason Franciscan Health

Daily Cases in Clallam County



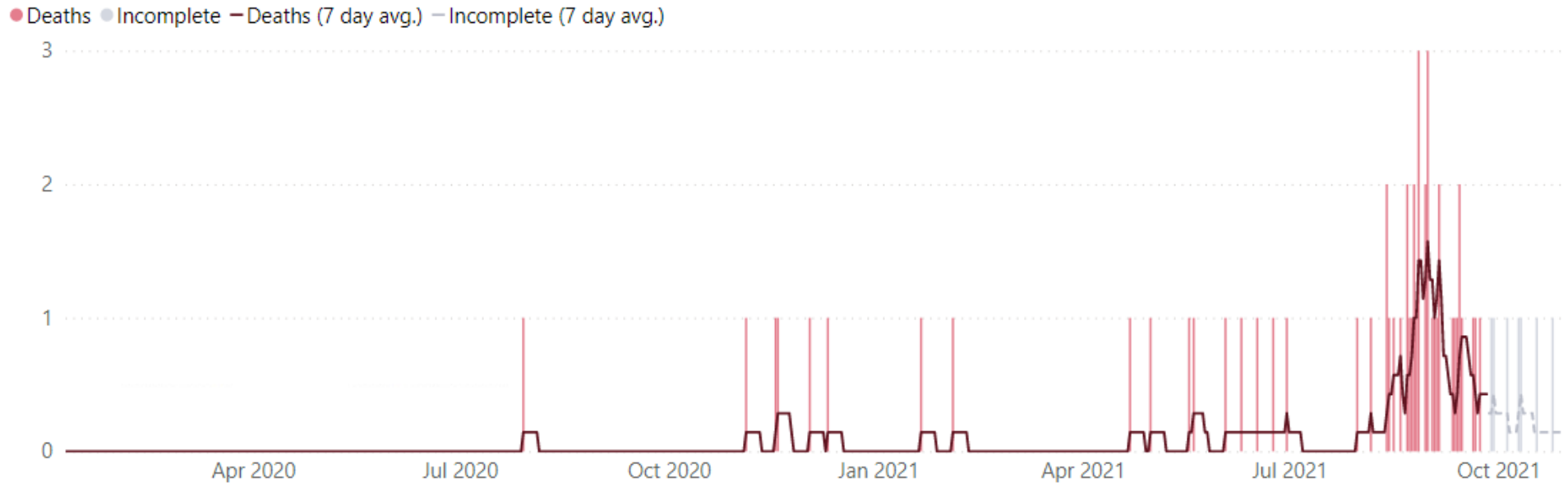
Virginia Mason Franciscan Health

Daily Hospitalizations in Clallam County



Virginia Mason Franciscan Health

Daily Deaths in Clallam County



Virginia Mason Franciscan Health

Variants

Virginia Mason Franciscan Health

Variants?

- **Variant being monitored**
  - Variants for which there are data indicating a potential or clear impact on approved or authorized medical countermeasures or that has been associated with more severe disease or increased transmission but are no longer detected or are circulating at very low levels in the United States, and as such, do not pose a significant and imminent risk to public health in the United States.
- **Variant of Interest**
  - A variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.
- **Variant of Concern**
  - A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.
- **Variant of High Consequence**
  - A variant of high consequence has clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants.

Variants Being Monitored

WHO Label	Pango Lineage	Date of Designation		
Alpha	B.1.1.7 and Q lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Beta	B.1.351 and descendent lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Gamma	P.1and descendent lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Epsilon	B.1.427 B.1.429	**VOC**: March 19, 2021	**VOI**: February 26, 2021 **VOI**: June 29, 2021	**VBM**: September 21, 2021
Eta	B.1.525		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Iota	B.1.526		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Kappa	B.1.617.1		**VOI**: May 7, 2021	**VBM**: September 21, 2021
N/A	B.1.617.3		**VOI**: May 7, 2021	**VBM**: September 21, 2021
Zeta	P.2		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Mu	B.1.621, B.1.621.1			**VBM**: September 21, 2021

Variant of Concern

Delta - B.1.617.2

First identified: India

Spread: Much faster than other variants

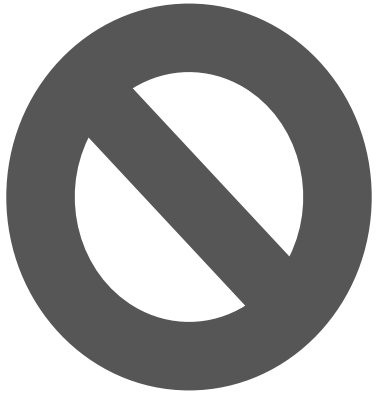
Severe illness and death: May cause more severe cases than the other variants

Vaccine: Infections happen in only a small proportion of people who are fully vaccinated, even with the Delta variant. Some breakthrough infections are expected but remain rare. However, preliminary evidence suggests that fully vaccinated people who do become infected with the Delta variant can spread the virus to others. All vaccines are particularly effective against severe illness, hospitalization and death.

Treatments: Certain monoclonal antibody treatments are less effective against this variant.

Virginia Mason Franciscan Health

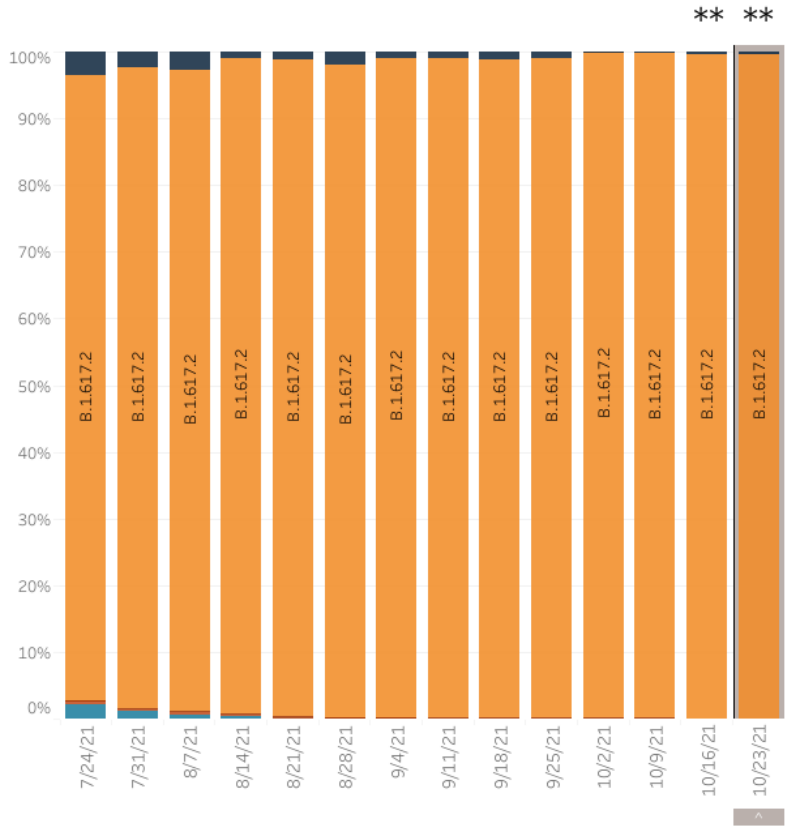
Variant of High Consequence



Virginia Mason Franciscan Health™

Variants in the US

United States: 7/18/2021 – 10/23/2021



United States: 10/17/2021 – 10/23/2021 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Alpha	B.1.1.7	VBM	0.0%	0.0-0.0%
Delta	B.1.617.2	VOC	99.5%	99.2-99.7%
	AY.1	VOC	0.1%	0.0-0.1%
	AY.2	VOC	0.0%	0.0-0.0%
Other	Other*		0.4%	0.3-0.8%

* 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

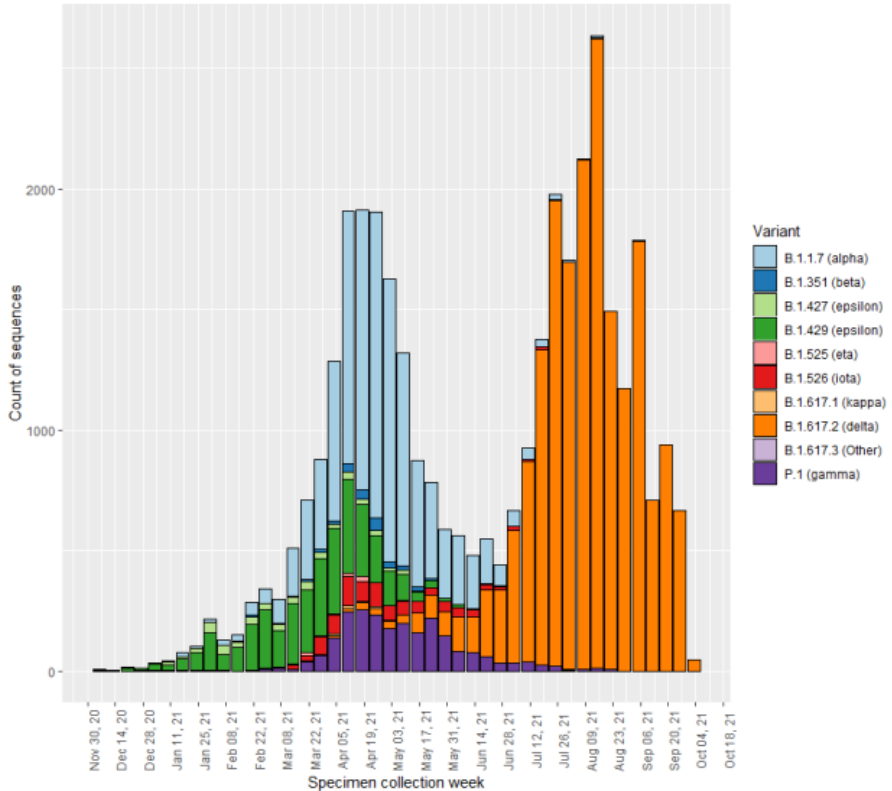
Q.1-Q.8 are aggregated with B.1.1.7. AY.3-AY.38 and their sublineages are aggregated with B.1.617.2.

Virginia M
Francisca

Variants in the Washington

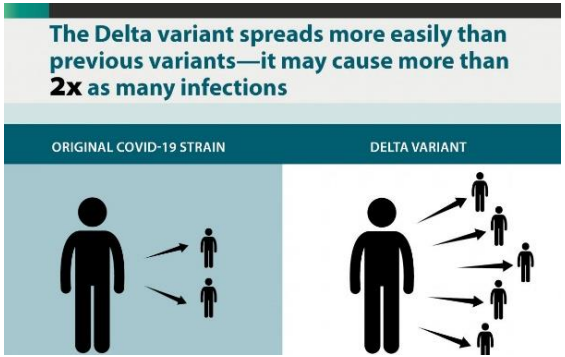
Sequencing Trends Over Time

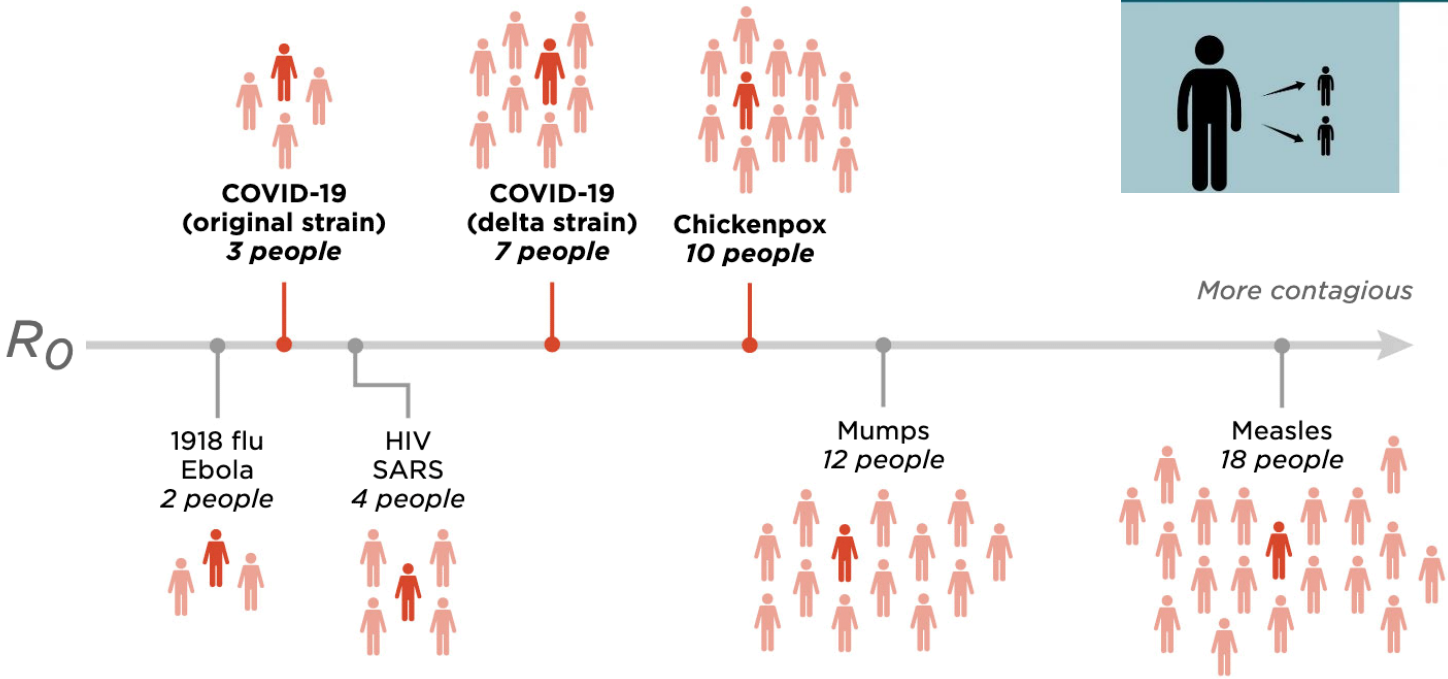
Epidemiologic curve of variants of interest and concern by week of specimen collection date as of Oct 19, 2021



Virginia Mason Franciscan Health

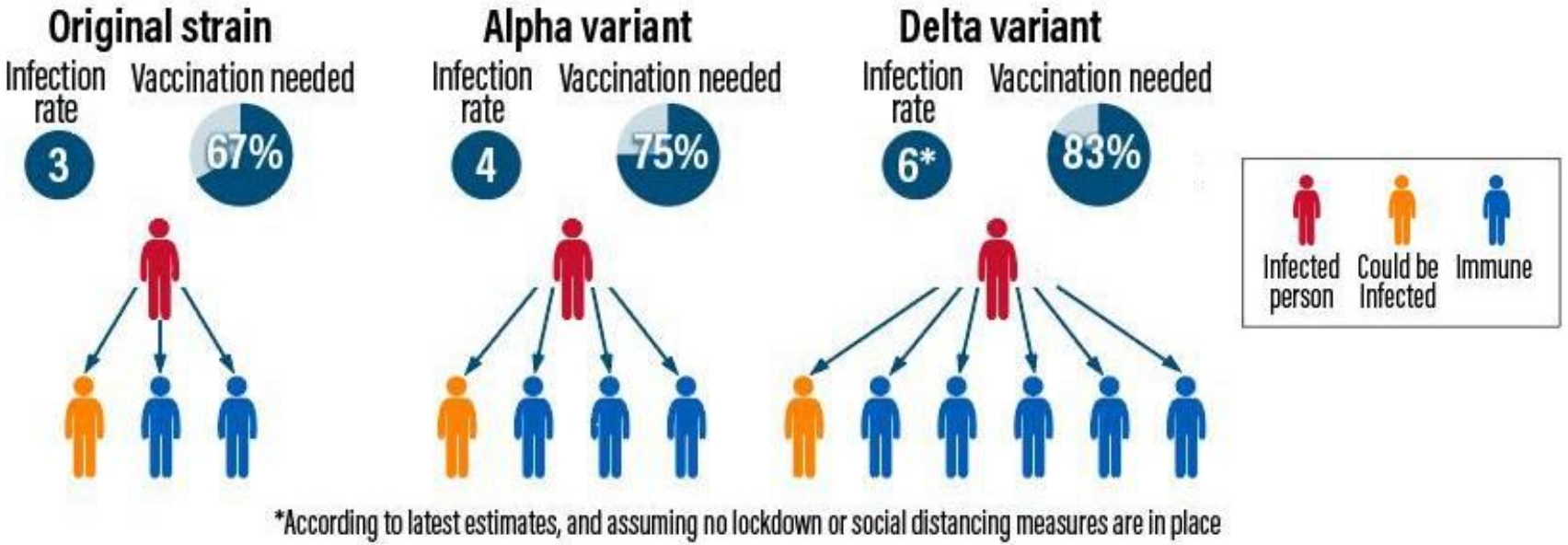
Delta variant is more contagious





NPR

Delta Variant: Impact on Herd Immunity



Virginia Mason Franciscan Health

Delta Variant: What we know

- Twice as contagious as previous variants
- Greatest risk of transmission remains among the unvaccinated
- Some evidence of increase disease severity among unvaccinated
- Fully vaccinated persons with delta breakthrough infections may transmit to others. However, they are infectious for shorter duration than the unvaccinated.

Virginia Mason Franciscan Health

KTVB

'I am scared for all of us:' Idaho hospitals move into crisis standards as COVID-19 cases surge

BOISE, Idaho — There is despair now, in Idaho's hospital hallways and ICU wards and waiting rooms and morgues.

15 hours ago

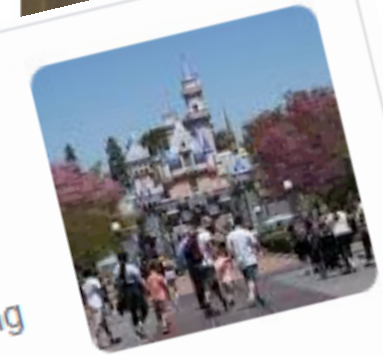
Virginia Mason Franciscan Health

KTVB

'I am scared for all of us:' Idaho hospitals move into cri… standards as COVID-19 cases surge

BOISE, Idaho — There is despair n… wards and waiting re…

15 h…



The Washington Post

Alaska's largest hospital implements 'crisis standards of care …

Alaska's largest hospital has implemented crisis standards of care, prioritizing limited resources as a surge in coronavirus cases driven by...

1 day ago

Virginia Mason Franciscan Health

The New York Times

Oregon and Idaho Run Short of I.C.U. Beds as Covid Resurges

Oregon and Idaho are running out of I.C.U. beds as Covid cases hit records. ... crisis standards of care," Mr. Little said in his statement.

2 days ago

Virginia Mason Franciscan Health

KIRO-TV

WA Hospitals stretch to care for Idaho COVID-19 patients

"We are keeping our heads above water — but barely," said Dr. Chris Baliga, an infectious disease doctor at Virginia Mason in Seattle.

2 days ago

Virginia Mason Franciscan Health

Vaccines

Virginia Mason Franciscan Health™

Current US Vaccines

Pfizer-BioNTech mRNA	Moderna mRNA	Johnson & Johnson/Jansen viral vector vaccine
• FDA approved 16 and up • EUA 12 -16 • 2 shots 21 days apart	• EUA approved 18 and up • 2 shots 28 days apart	• EUA approved 18 and up • Single dose

Virginia Mason Franciscan Health

Third Dose: moderately to severely immunocompromised patients, aged ≥12, 28 days after getting the second Pfizer or Moderna dose

Moderately to severely immunocompromised patients include those who have:

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

Third Dose: moderately to severely immunocompromised patients, aged ≥12, 28 days after getting the second Pfizer or Moderna dose

- If unable to get the same mRNA vaccine as the original series, it is ok to get the other type of mRNA vaccine (i.e. if the original series was with Moderna, ideally the third dose should also be with Moderna, but can be with Pfizer if Moderna is not available).

- Recipients of the Johnson and Johnson vaccine should receive a booster dose 2 months after their first, as outlined in the booster guidance above. There is no additional dose for J&J vaccine recipients

- While I expect the CDC to eventually authorize a booster dose for immunocompromised patients 6 months after receiving three doses of the mRNA vaccines, the current CDC guidance says only that it is being studied.

Virginia Mason Franciscan Health™

Booster: J&J

- Anyone aged 18 and up, 2 months after the last dose
- Officially a booster, but to paraphrase Fauci, this should have been a two dose vaccine

Virginia Mason Franciscan Health™

Booster mRNA

- 6 months after second mRNA vaccine dose if:

· Anyone age 65 and older
· Anyone age 18 and older with medical conditions placing them at higher risk for severe illness
· Anyone age 18 and older working or living in a higher risk setting
· Anyone age 18 and older residing in a long-term care setting

Virginia Mason Franciscan Health

Mixing and matching vaccines for boosters

· Anyone can choose any vaccine for the booster dose, regardless of the initial vaccine given

· Any vaccine booster is considered appropriate for protecting against COVID-19, and any booster produces better immunity than no booster

· The Pfizer booster dose is the same as the primary series, whereas the Moderna booster dose is half the strength of the primary series

Virginia Mason Franciscan Health™

Factors to consider for mixing and matching

· mRNA vaccines (Moderna > Pfizer) have the rare risk of myocarditis and pericarditis in male adolescents and young adults

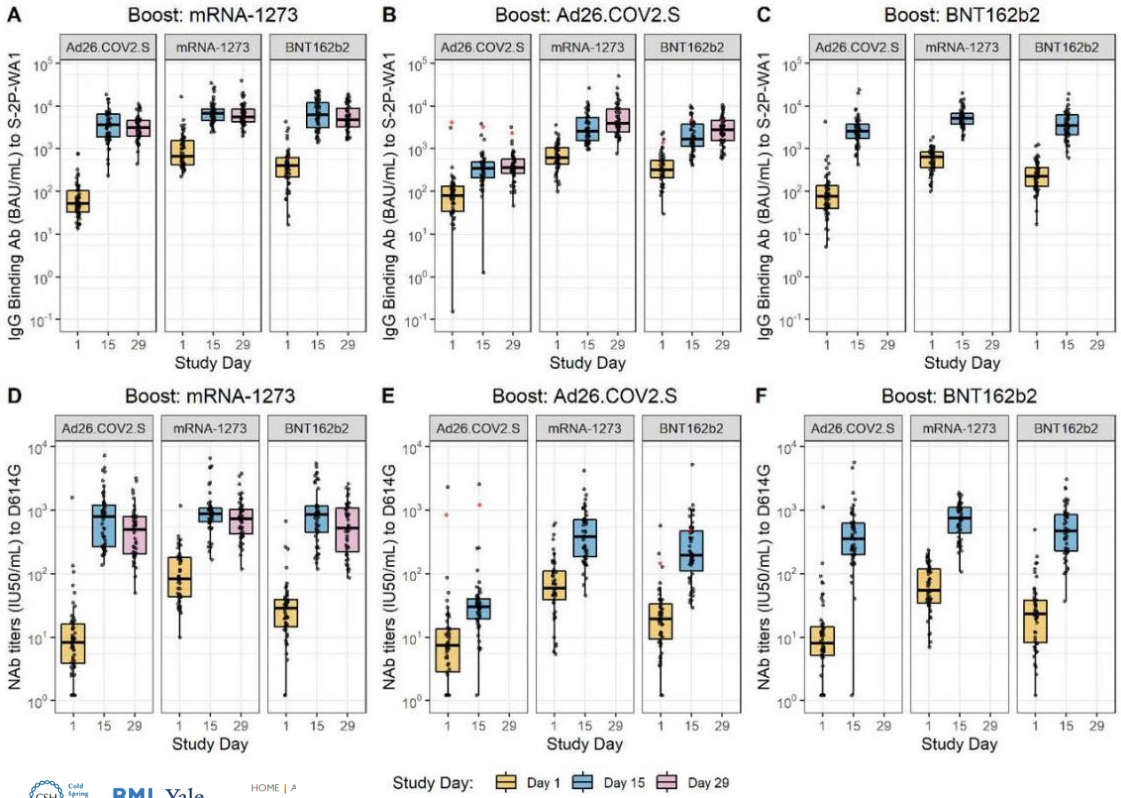
· Johnson and Johnson has rarely been associated with thrombosis and thrombocytopenia syndrome (TTS) in adult women below the age of 50

· People with a severe allergy to the mRNA vaccines or to the Johnson and Johnson vaccine may consider boosting with the other vaccine class.

Mixing & Matching Data

- J&J followed by mRNA better than J&J followed by J&J
- Slight advantage of any vaccine followed by Moderna

- Officially, all vaccines when boosted provide great protection



Comments (

Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report

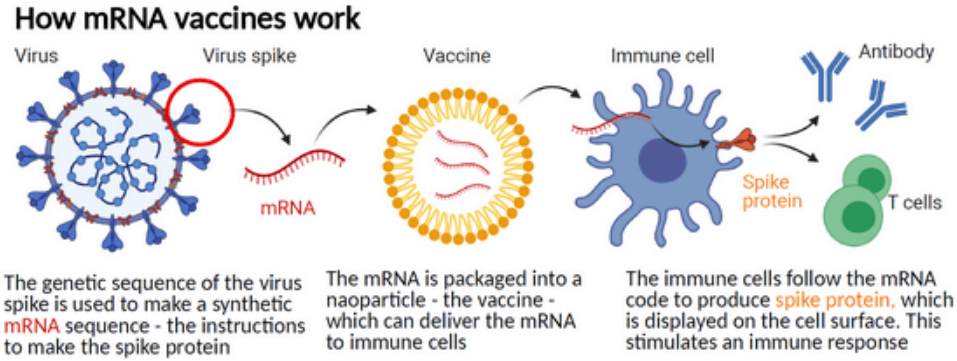
Robert L. Atmar, Kirsten E. Lyke, Meagan E. Deming, Lisa A. Jackson, Angela R. Branche, Hana M. El Sahly, Christina A. Rostad, Judith M. Martin, Christine Johnston, Richard E. Rupp, Mark J. Mulligan, Rebecca C. Brady, Robert W. Frenck Jr., Martin Bäcker, Angelica C. Kottkamp, Tara M. Babu, Kumaravel Rajakumar, Srilatha Edupuganti, David Dobryzynski, Christine M. Posavad, Janet I. Archer, Sonja Crandon, Seema U. Nayak, Daniel Szydlo, Jillian Zemanek, Clara P. Dominguez Islas, Elizabeth R. Brown, Mehul S. Suthar, M. Juliana McElrath, Adrian B. McDermott, Sarah E. O'Connell, David C. Montefiori, Amanda Eaton, Kathleen M. Neuzil, David S. Stephens, Paul C. Roberts, John H. Beigel, the DMID 21-0012 Study Group

doi: https://doi.org/10.1101/2021.10.10.21264827

Virginia Mason Franciscan Health™

mRNA Vaccines

- Piece of mRNA for virus spike protein is packaged into nanoparticle that is injected
- Enters human (muscle) cell that starts to produce spike protein on the cell surface
- Immune cells then recognize this and develop antibodies
- If exposed to SARS-CoV2 preexisting antibodies and immune memory recognize it and work to eliminate it

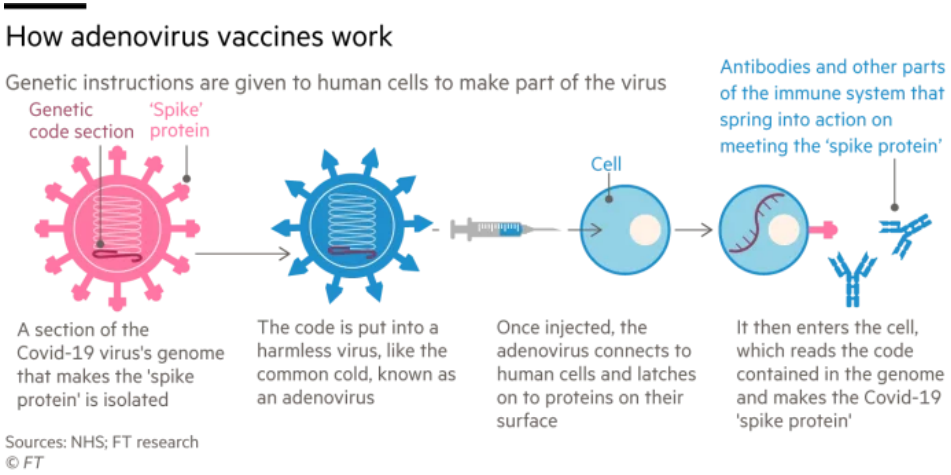


https://www.benaroyaresearch.org/blog/post/11-things-know-about-mrna-vaccines-covid-19

Virginia Mason Franciscan Health

J & J

- Replicative deficient adenovirus as vector
- Uptake by human cells that produce spike proteins on cell surface
- Immune cells then recognize this and develop antibodies
- If exposed to SARS-CoV2 preexisting antibodies and immune memory recognize it and work to eliminate it



Side Effect and Complications

- Common Side Effects
  - Pain, Redness, Swelling, Fatigue, Headaches, Fevers, Chills, Myalgia
- Serious Complications
  - Anaphylaxis 2-5/million
  - Myocarditis – 1,377 reported cases (<30 – male>female) - 4/million (of those 798 confirmed)
  - Thrombosis with thrombocytopenia syndrome
    - 46 cases reported (44 - J&J, 2 - Moderna) –3/million (J&J) – 7cases per million in women aged 18-49.
    - 294 (170 definite/50 probable) Cases associated with Oxford-AstraZeneca Vaccine – no sex predominance with 22% mortality – In UK – 8 cases per million
  - Guillain-Barré – men >50 – 176 cases with JJ (12/million)
  - Death – 7,218 deaths after vaccine (all reported to VAERS regardless of causality) – 20/million (dying of COVID? 650k deaths/ 328 million Americans approx. 1981/million – 1/500)

Side Effect and Complications

- Common Side Effects
  - Pain, Redness, Swelling, Fatigue, Headaches, Fevers, Chills, Myalgia
- Serious Complications
  - Anaphylaxis 2-5/million
  - Myocarditis – 1,377 repor[redacted]nfirmed)
  - Thrombosis with thrombo[redacted]
    - 46 cases reported (44[redacted]women aged 18-49.
    - 294 (170 definite/50 probable) Cases associated with Oxford-AstraZeneca Vaccine – no sex predominance with 22% mortality – In UK – 8 cases per million
  - Guillain-Barré – men >50 – 176 cases with JJ (12/million)
  - Death – 7,218 deaths after vaccine (all reported to VAERS regardless of causality) – 20/million (dying of COVID? 650k deaths/ 328 million Americans approx. 1981/million)

Risk of getting hit by lightning: 4/million

Virginia Mason Franciscan Health

Initial Studies - Efficacy

- RCT 1:1
- Over 40 thousand enrolled
- VE – 95% for symptomatic COVID infection
- Moderna – similar results- 36 K participants
- J&J – 67% efficacy but 85% efficacy against severe disease

Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

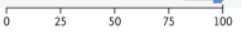
* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

FP Polack et al. N Engl J Med 2020;383:2603-2615.

The NEW ENGLAND JOURNAL of MEDICINE

Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)



LR Baden et al. N Engl J Med 2021;384:403-416.

The NEW ENGLAND JOURNAL of MEDICINE

Effect of vaccination in King County

Select a time period: ⦿ Since 1/17/2021 !

Cases

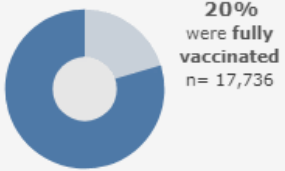
People who are **not fully vaccinated** are:

3x

more likely to test positive for COVID-19

Relative Risk trend

The vaccines effectively reduce a person's risk of catching COVID-19 and spreading it to others, although they are more effective at preventing serious infections leading to hospitalization and death. Vaccinated people who do get infected tend to have mild or non-severe illness.



Hospitalizations

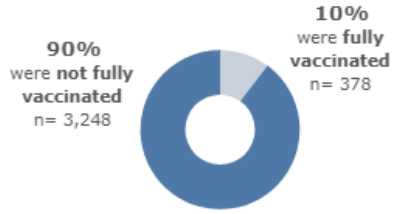
People who are **not fully vaccinated** are:

12x

more likely to be hospitalized for COVID-19

Relative Risk trend

The vaccines are highly effective at preventing severe illness from COVID-19 requiring hospitalization.



Deaths

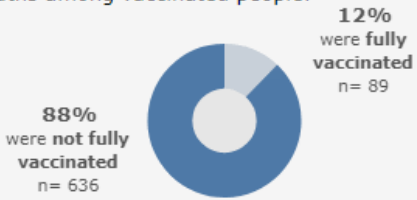
People who are **not fully vaccinated** are:

14x

more likely to die of COVID-19 related illness

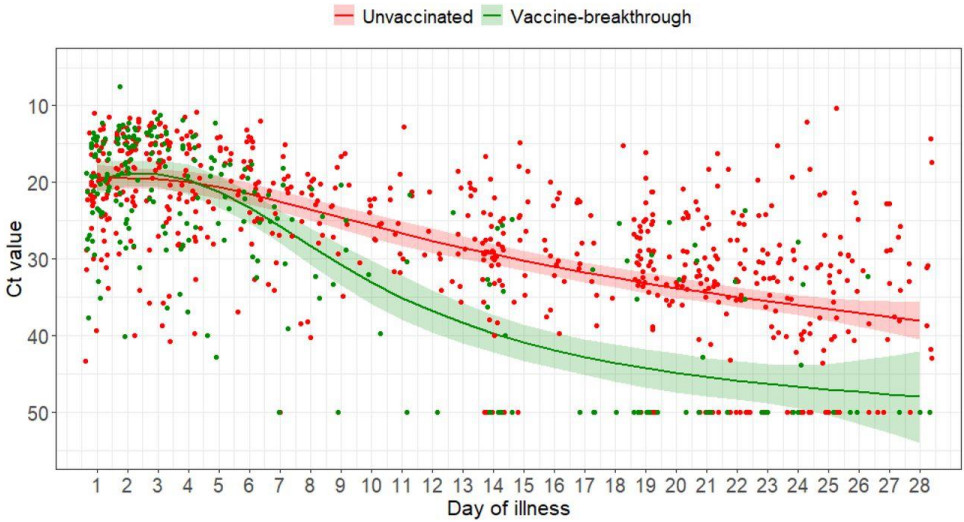
Relative Risk trend

Getting vaccinated dramatically reduces one's risk of dying from COVID-19. Deaths among the unvaccinated have tended to affect younger and healthier people than the comparatively rare deaths among vaccinated people.



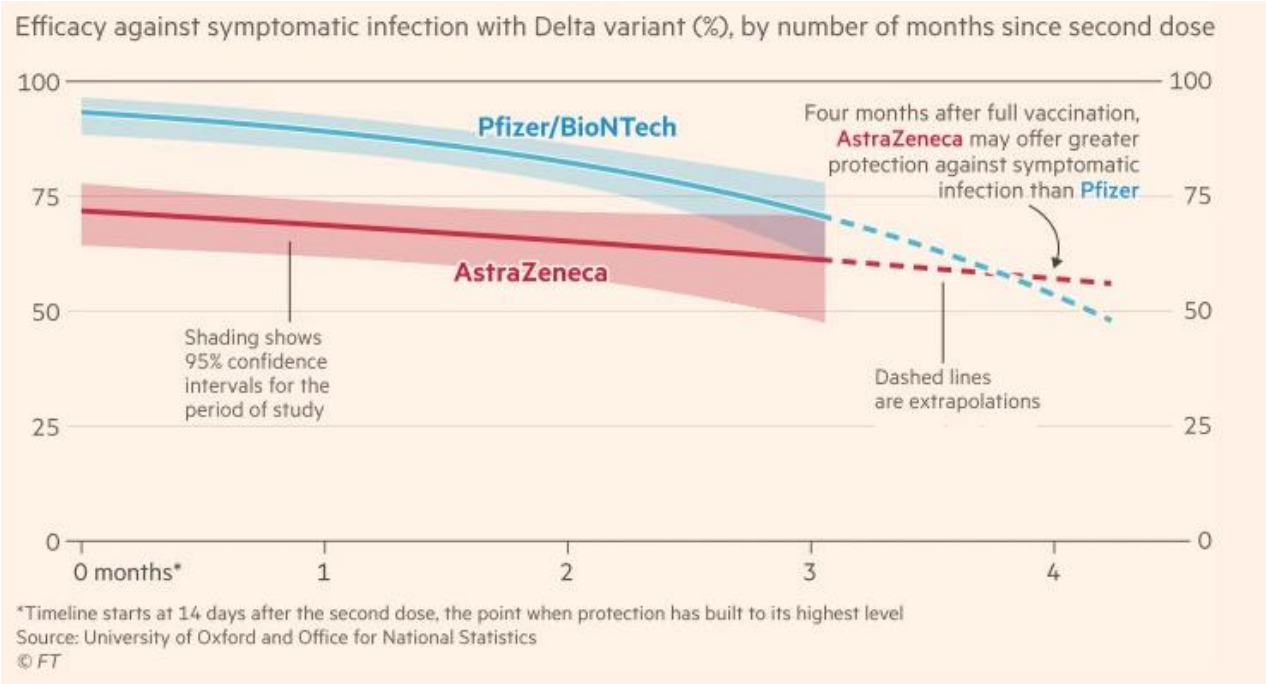
Singapore Study – viral shedding

- 218 patients with delta variant
- 84 vaccinated, 71 fully (33%)
- OR in fully vaccinated 0.07 of progressing to severe disease
- CT values – similar but with rapid decay in vaccinated – faster clearance



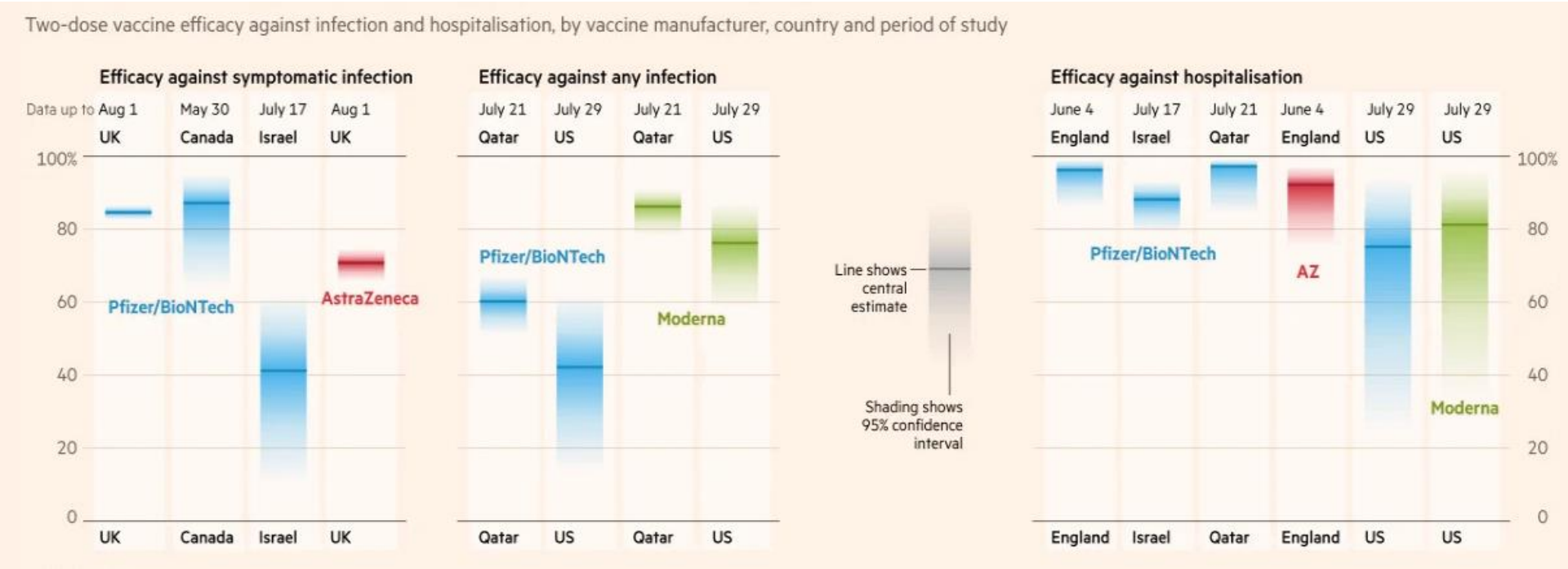
Virginia Mason Franciscan Health

Vaccine neutralizing antibody levels over time



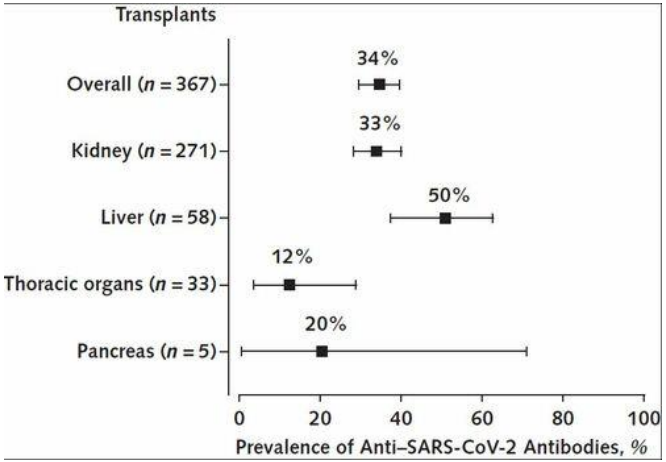
Virginia Mason Franciscan Health

Vaccine efficacy



Virginia Mason Franciscan Health

Third Dose (ie not a booster)

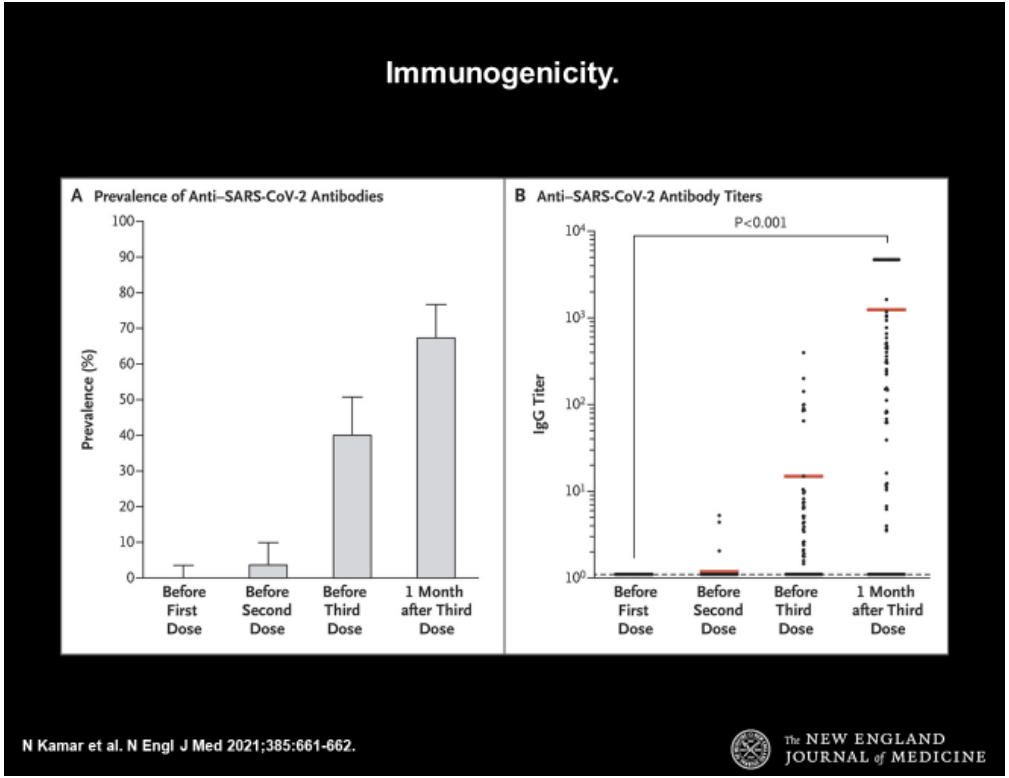


- Immune compromised patient
- mRNA vaccines – preferably same manufacturer
- 28 days or longer after 2nd dose
- No recommendations on checking abs
- Studies showed no ab response in SOT in 40 -85 % of patients (depending on suppressive medications and type of transplant).

Virginia Mason Franciscan Health

Data on 3rd Vaccine

- April 2021 – French National Authority for Health recommended 3rd dose in immunosuppressed patients
- Several small studies – NEJM
  - 101 consecutive SOT
  - Given 3rd dose of PBT – mean 61 days after 2nd dose
  - Variety of immunosuppression
  - Seropositivity (0, 4, 40,68)
  - Of 59 patients seronegative before 3rd dose – 44% had abs 4 weeks after
  - All 40 patients seropositive before 3rd dose remained so after third dose



Virginia Mason Franciscan Health

Updated vaccines?

Virginia Mason Franciscan Health™

The Coronavirus Pandemic › | Covid-19 Updates | Coronavirus Map and Cas

Health experts keep warning against using ivermectin as a Covid treatment. Some Americans refuse to listen.

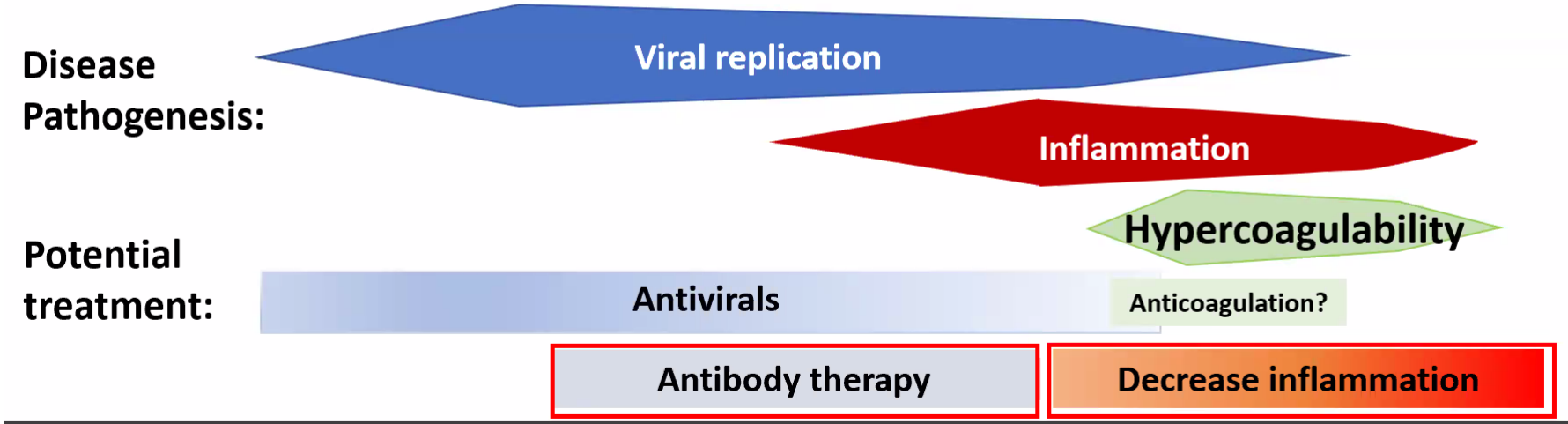
Highly concentrated veterinary ivermectin has been flying off the shelves of U.S. supply stores, despite its dangers to humans. Denis Farrell/Associated Press

Therapeutics

A doctor in rural Oklahoma says hospitals are backed up with patients who have overdosed on veterinary ivermectin, an anti-parasite medication. Mississippi's health department said that 70 percent of recent calls to the state poison control center in August came from

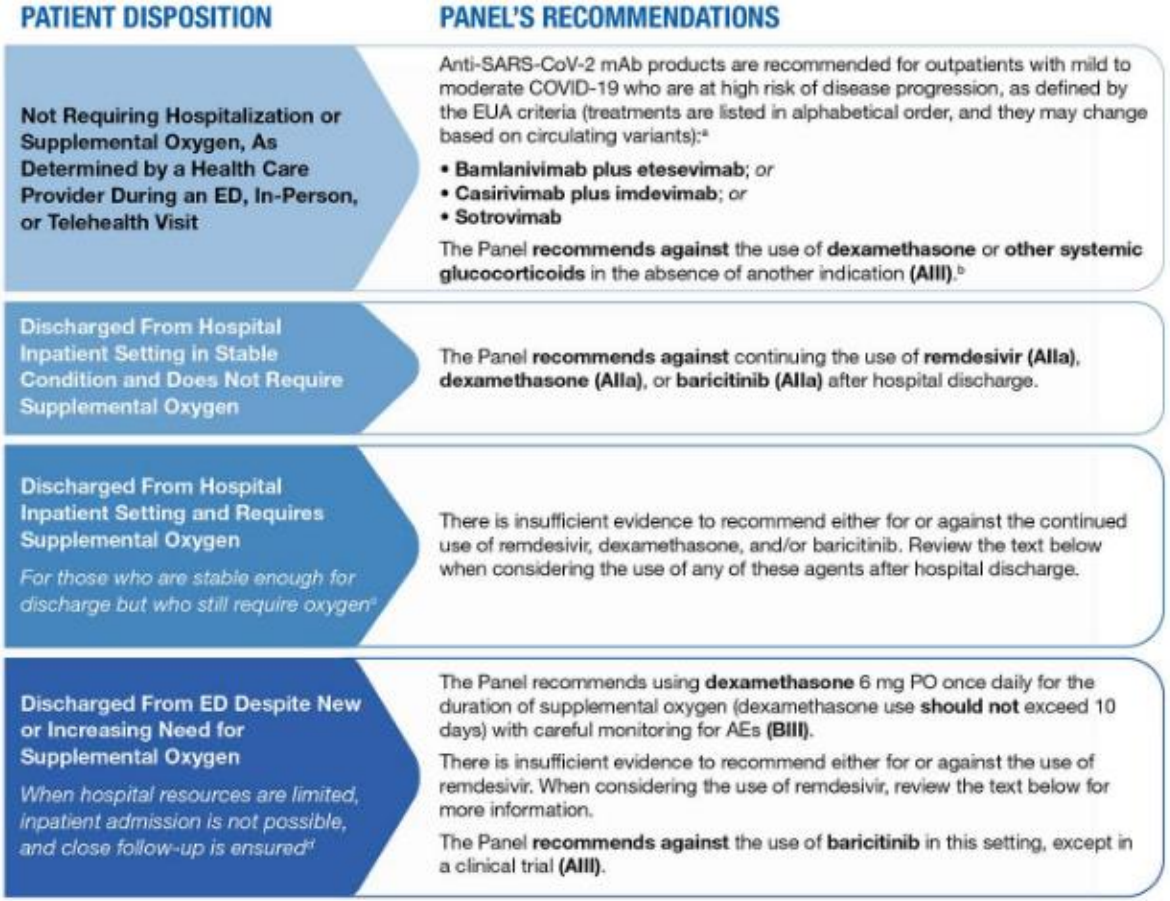
Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



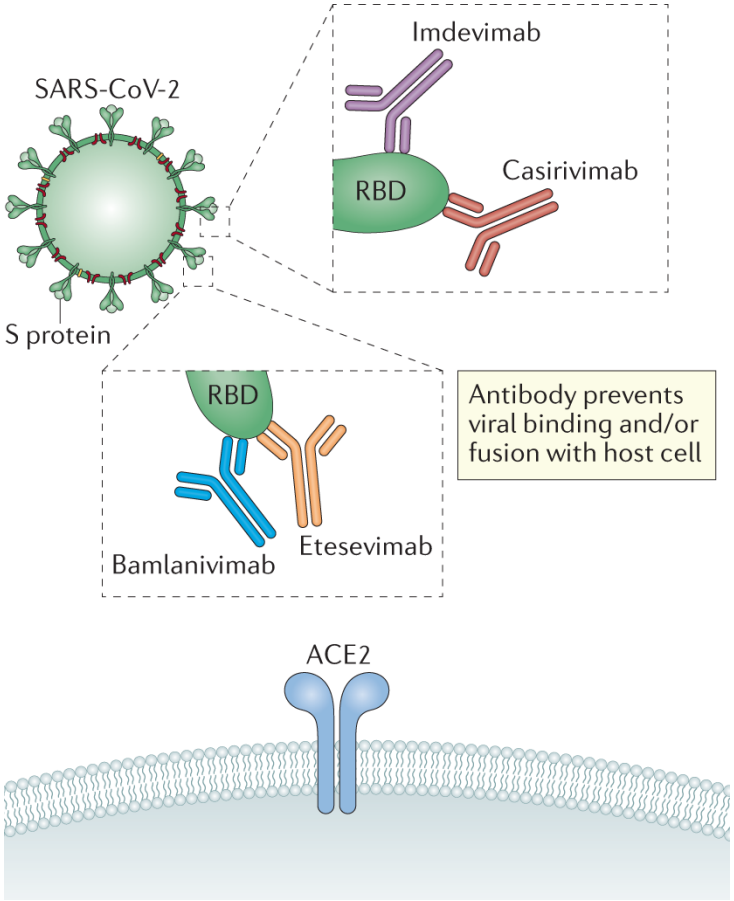
Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

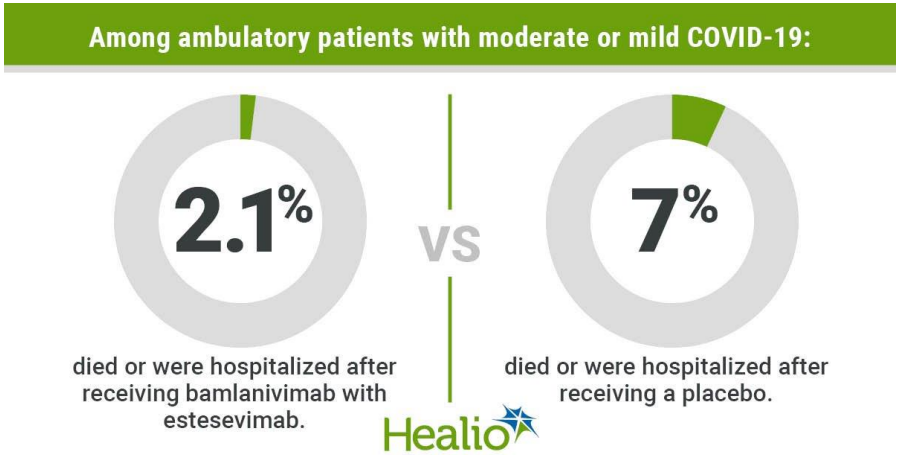
NIH Outpatient Recommendations



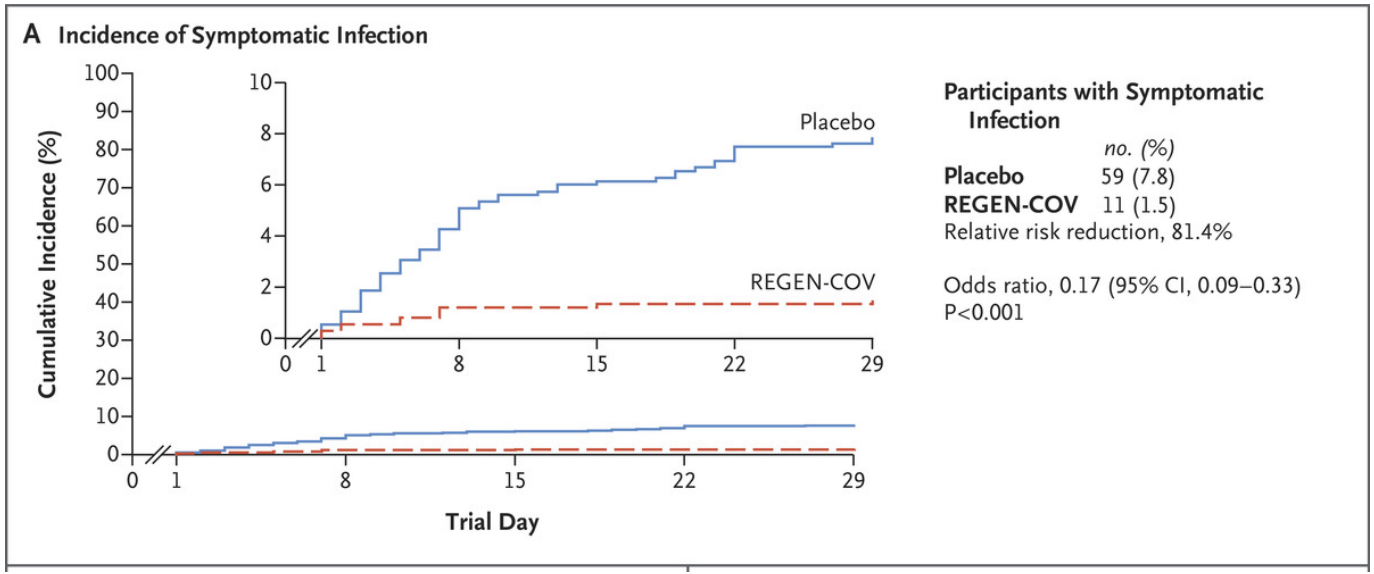
Virginia Mason Franciscan Health

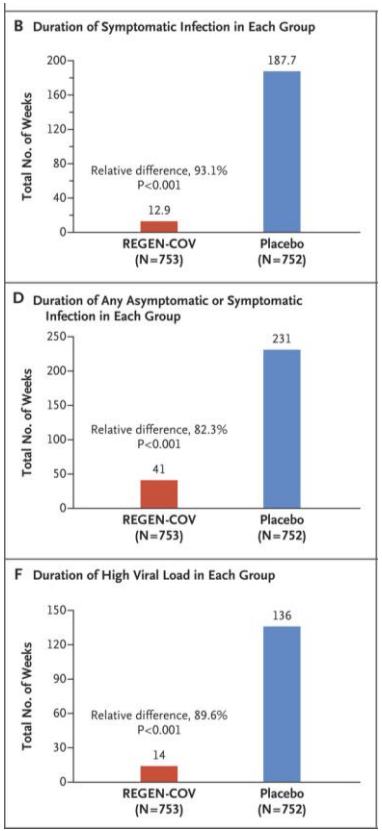
Neutralizing mAbs in Mild-Moderate Ambulatory COVID





Incidence of Symptomatic Infection in Casirivimab + Imdevimab (REGEN-COV) vs. Placebo Groups





70% relative reduction in hospitalizations or death in COVID-infected patients and an

81% risk reduction of developing symptomatic COVID in exposed patients

Virginia Mason Franciscan Health

MP O'Brien et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2109682

Bamlanivimab + Etesevimab: Loss of Activity against emerging strains

WHO Label	Bamlanivimab Plus Etesevimab		Casirivimab Plus Imdevimab	Sotrovimab
	In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]
Alpha	No change	Active	No change	Active
Beta	Marked change	Unlikely to be active	No change[c]	Active
Gamma	Marked change	Unlikely to be active	No change[c]	Active
Delta	Modest change[d]	Likely to be active	No change	Active
Epsilon	Modest change[d]	Likely to be active	No change	Active
Iota	Modest change[d]	Likely to be active	No change[c]	Active

Criteria for Using Anti-SARS-CoV-2 mAb, EUA

Medical Conditions Represented in Clinical Trials

- Aged ≥65 years (AIIa)
- Obesity (BMI >30) (AIIa)
- Diabetes (AIIa)
- Cardiovascular disease or hypertension (AIIa)
- Chronic lung diseases (e.g., COPD, moderate-to-severe asthma, interstitial lung disease) (AIIa)

Other Conditions

- Immunocompromising condition (AIII).
- Overweight (BMI 25–30) (BIII)
- Chronic kidney disease (BIII)
- Pregnancy (BIII)
- Sickle cell disease (BIII)
- Neurodevelopmental disorders (BIII)
- Medical-technological dependence (e.g., tracheostomy, gastrostomy, etc.) (BIII)

Casirivimab Plus Imdevimab (REGEN-COV as Post-Exposure Prophylaxis for SARS-CoV-2 Infection, EUA, Aug 17, 2021

SQ inj. **(AI)** or an IV infusion **(BIII)** for people at high risk for progression to severe COVID-19 **AND** who have the following vaccination status **AND** exposure history.

• *Vaccination Status:* • Not fully vaccinated *or* • Fully vaccinated, but not expected to mount an adequate immune response **AND** •

Exposure History: • Had a recent exposure consistent with the CDC criteria; *or* • At high risk of exposure because of recent occurrence of infection in other individuals in an institutional setting e.g., nursing homes

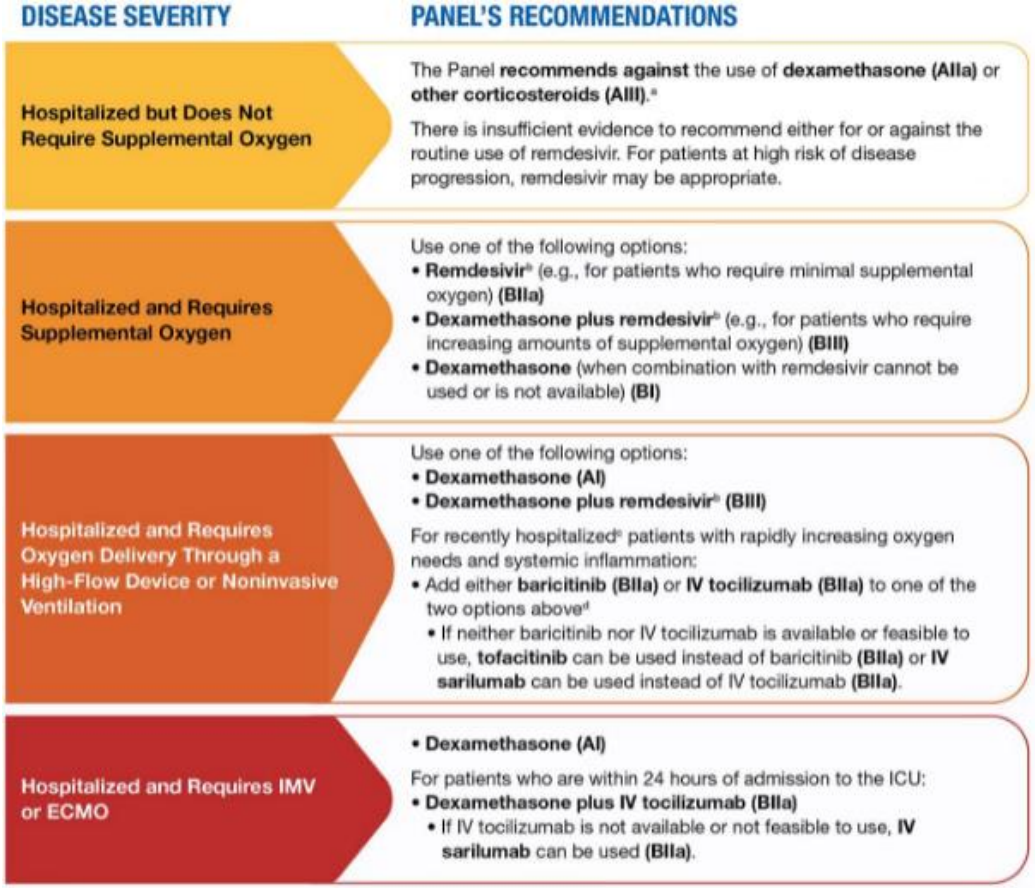
The doses should be administered as soon as possible, preferably within 7 d of high-risk exposure **(AIII)**.

Molnupiravir: Merck/Ridgeback oral antiviral

- Only press release data to go on from phase 3 MOVe-OUT trial
- Trial stopped early due to positive impact of the drug
- Reduced risk for hospitalization or death in half (14% of placebo group vs 7 in experimental group) by day 29
- Effective against gamma, delta, and mu variants
- No difference in side effect profiles between placebo and experimental groups

- Merck applied for an EUA

NIH Inpatient Guidelines



DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** • If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.

Virginia Mason Franciscan Health

Inpatient treatment for severe illness

- Support oxygenation
- Ensure no other diagnosis (coinfections documented)
- Dexamethasone 6 mg daily for 10 days

Meta-analysis of seven trials that included 1703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with standard care or placebo (32 versus 40 percent, odds ratio [OR] 0.66, 95% CI 0.53-0.82) and were not associated with an increased risk of severe adverse events

Systematic review and network meta-analysis of randomized trials that evaluated interventions for COVID-19 and were available through mid-August 2020, glucocorticoids were the only intervention for which there was at least moderate certainty in a mortality reduction (odds ratio [OR] 0.87, 95% CI 0.77-0.98) or risk of mechanical ventilation (OR 0.74, 95% CI 0.58-0.92) compared with standard care

if not on supplemental O2, no benefit and trend toward increased mortality (Recovery Trial)

Virginia Mason Franciscan Health™

Inpatient treatment: Remdesivir

- Remdesivir: only FDA-approved treatment for COVID-19 for those hospitalized with COVID-19 and age 12 or older
- 200 mg on day 1, and then 100 mg for 4 more days (can go up to 10 days in critically ill patients)
- SOLIDARITY WHO trial preliminary results showed no difference in 28 day mortality. Trend toward lower mortality in patients not mechanically ventilated at start of use
- ACTT-1 trial showed shorter time to recovery of 7 days with remdesivir vs 9 with placebo, lower percent progressing to high flow, mechanical ventilation, or ECMO (17 vs 24%) and shorter stays of 10 vs 15 days. Trend toward lower mortality, esp in the patients that progressed to needing more O2 with a HR for dying of 0.3; 95% CI 0.14-0.64). Limited data with no clear benefit in those without severe disease (not on supplemental O2)

Virginia Mason Franciscan Health

Inpatient treatment: Remdesivir

- Solidarity Trial showed no difference in deaths, progressing to mechanical ventilation, or in length of stay. But this was an open-label study
- ACTT-2 trial compared remdesivir alone to remdesivir plus a JAK-inhibitor, baricitinib, and showed 1 day shorter mean recovery time (7 vs 8 days), 23 vs 28% progressed to higher O2 requirement or death, and lower death rate 4.7 vs 7.1%

Virginia Mason Franciscan Health™

Inpatient treatment: IL-6 inhibitors/Janus-kinase inhibitors

Tocilizumab (anti-IL-6) and Baricitinib and Tofacitinib (JAKI)

- Implicated in the inflammatory cascade that causes lung injury and multi-organ dysfunction

- COV-Barrier study: Baricitinib vs standard of care, no change in progression to high-flow, NIVPPV, IVPPV, or death. But when death was looked at alone, all cause mortality at D28 was 38% less (HR 0.57; 95% CI 0.14-0.78). In subgroup on high-flow or NIVPPV, difference greatest.
- ACTT-2: Baricitinib with remdesivir improved time to recovery in hospitalized pt, effect greatest if on high-flow or NIVPPV, but people on steroids excluded

Virginia Mason Franciscan Health™

Inpatient treatment: IL-6 inhibitors

- REMAP-CAP and Recovery both showed mortality benefit for those with rapid resp deterioration who require O2 through high-flow or NIVPPV. Steroids were given to most in both studies. Recovery trial showed greatest benefit in those with CRP >75
- REMAP-CAP: ICU patients, tocilizumab reduced need for organ support (heart or lung) by 7 days compared to standard of care arm
- Recovery: only 14% on IMV, Day 28 mortality 31% vs 35%. ICU patients didn't see the same gain

- Should give with steroids. No clear benefit of one over the other.
- We restrict to ID, use tocilizumab, and should begin within 3 days of admission to ICU, CRP ≥ 75, in people with rapid deterioration

Virginia Mason Franciscan Health™

Thank you

Virginia Mason Franciscan Health