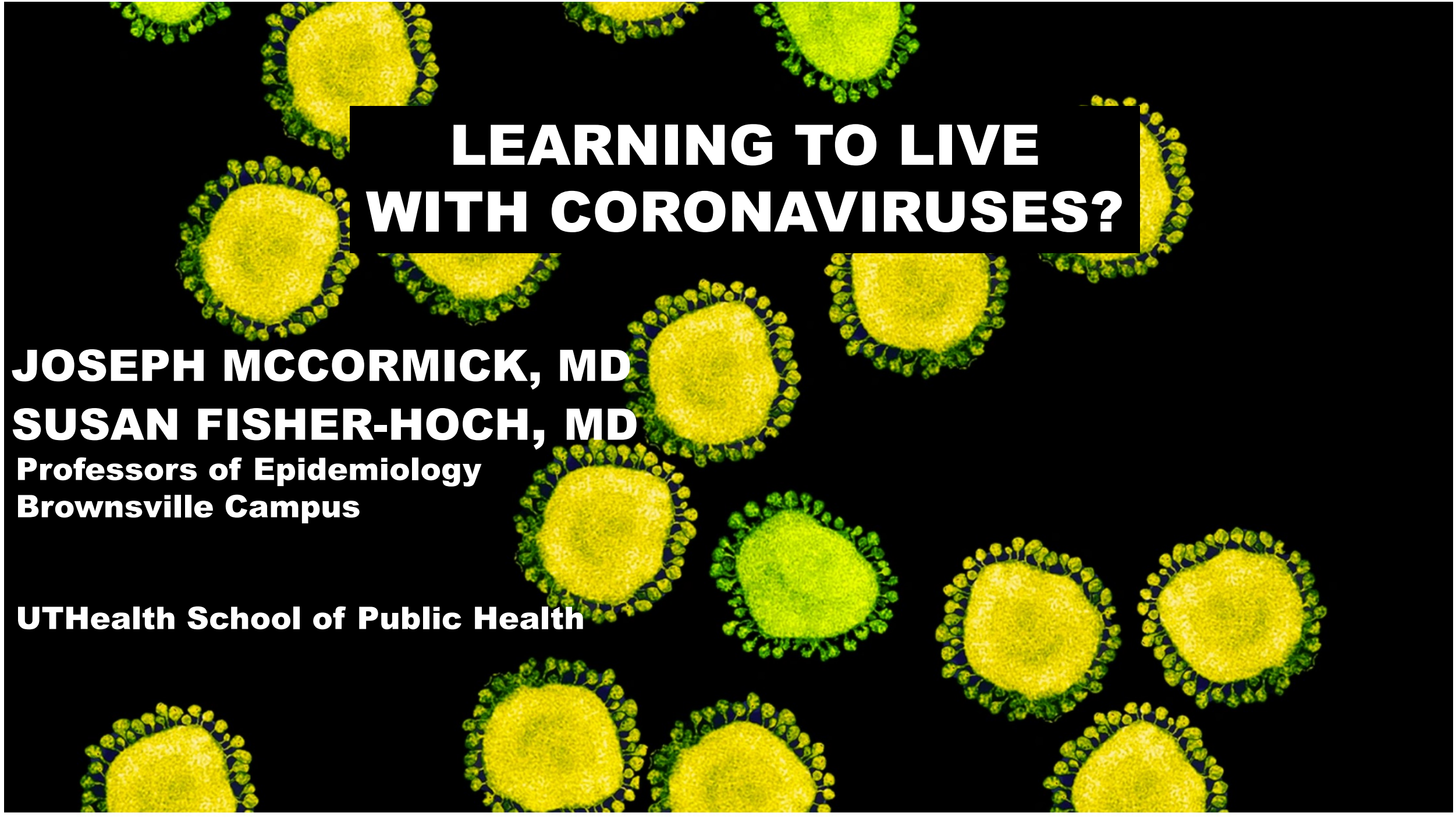


LEARNING TO LIVE WITH CORONAVIRUSES?

JOSEPH MCCORMICK, MD

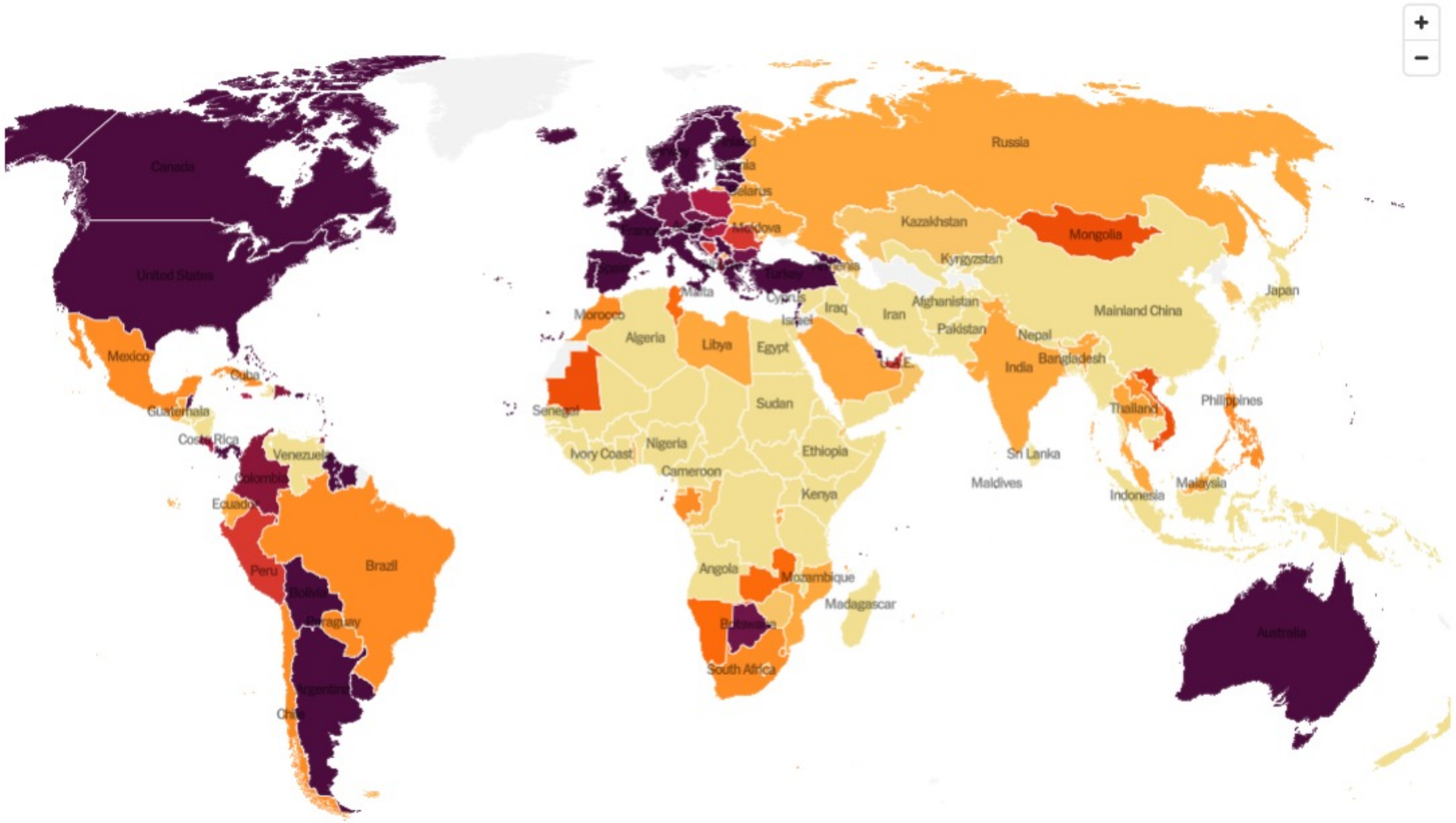
SUSAN FISHER-HOCH, MD

Professors of Epidemiology
Brownsville Campus

UTHealth School of Public Health

Hot spots

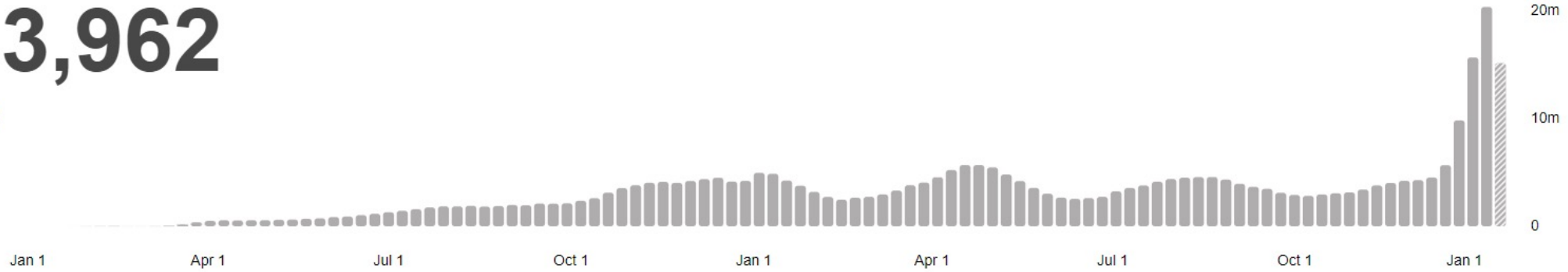
January 2022



WHO data. Worldwide reports as of January 2022

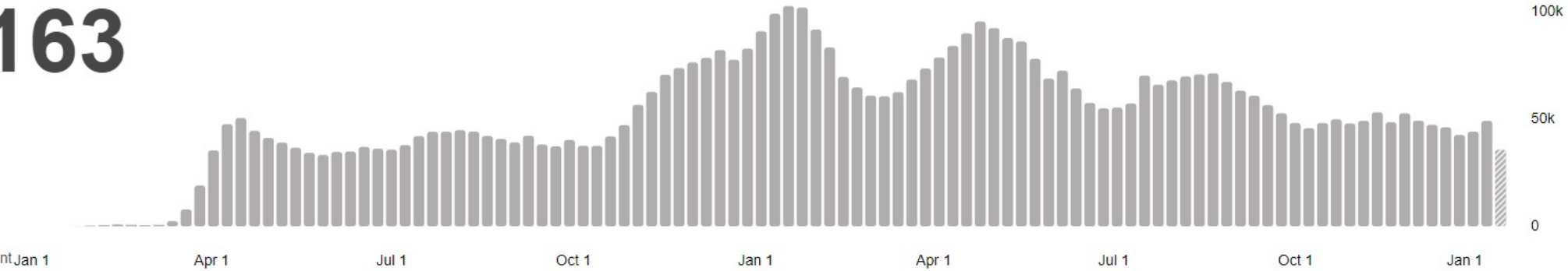
340,543,962

confirmed cases



5,570,163

deaths



Source: World Health Organization

Data may be incomplete for the current day or week.

WARNING

Local, national and global data are subject to major reporting artefacts.

Poor and remote communities are not tested

People do not come forward for testing

Home testing and other kits and sites do not report

Testing will miss most of the asymptomatic cases

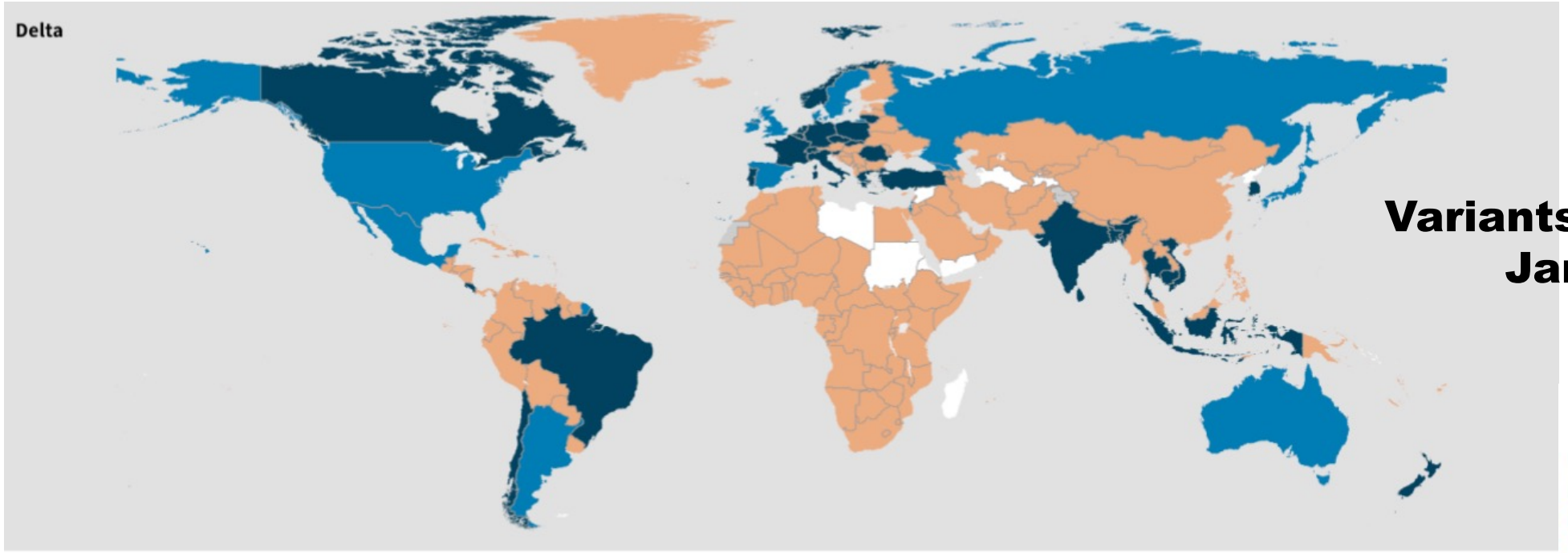
Testing misses people who die at home or elsewhere

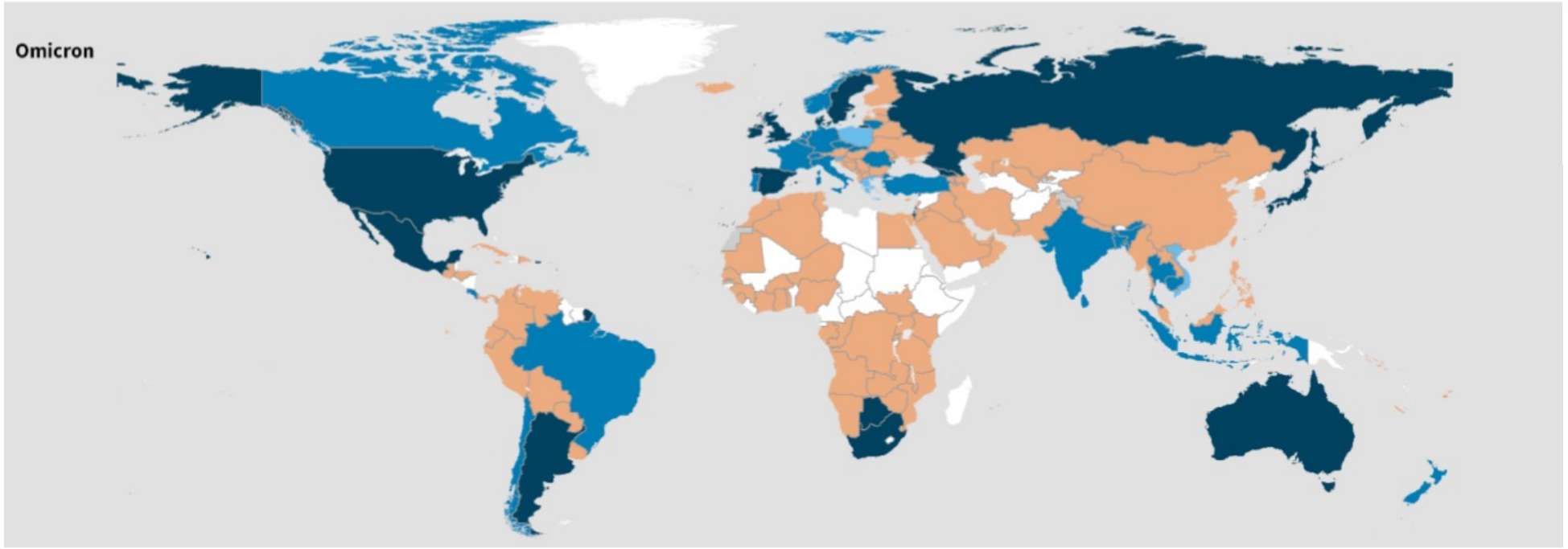
The variants!!!

Time to learn your Greek alphabet

Variants of concern (VOC)

Variants of interest (VOI)



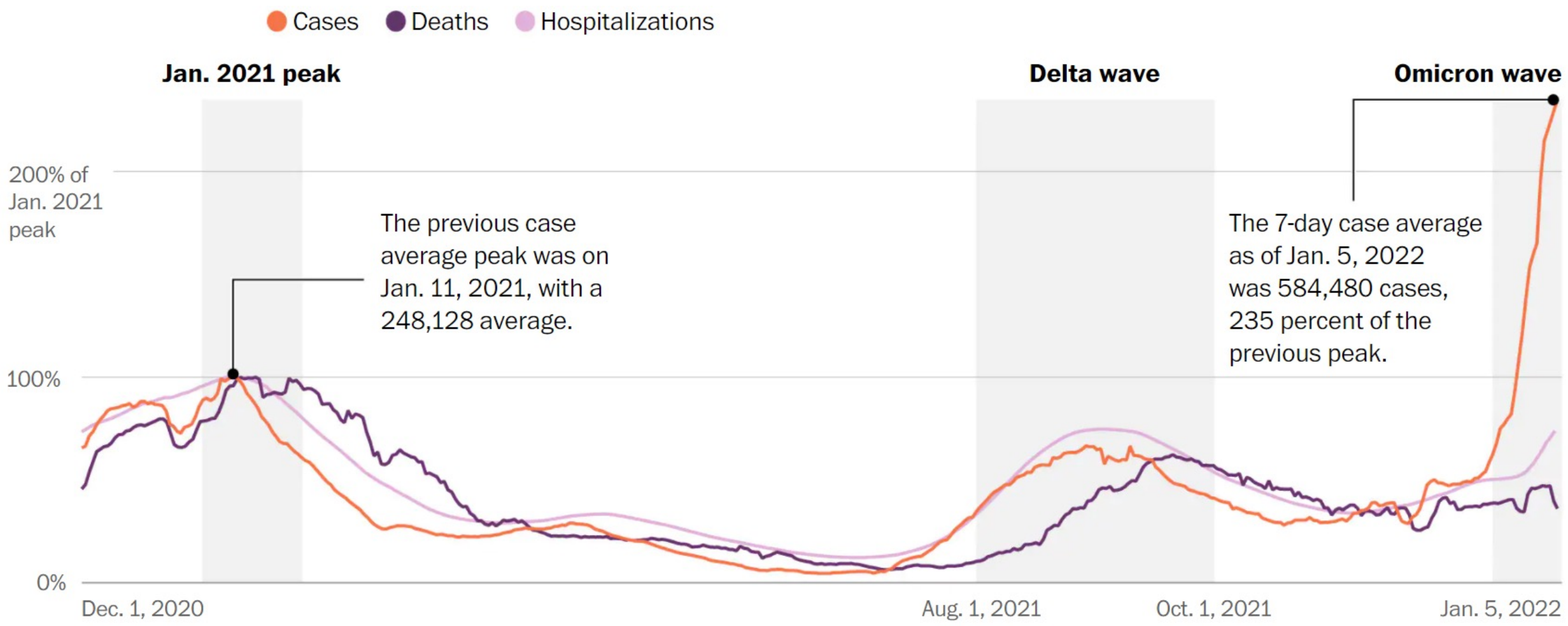


Variants of Concern (VOC)
January11 2022

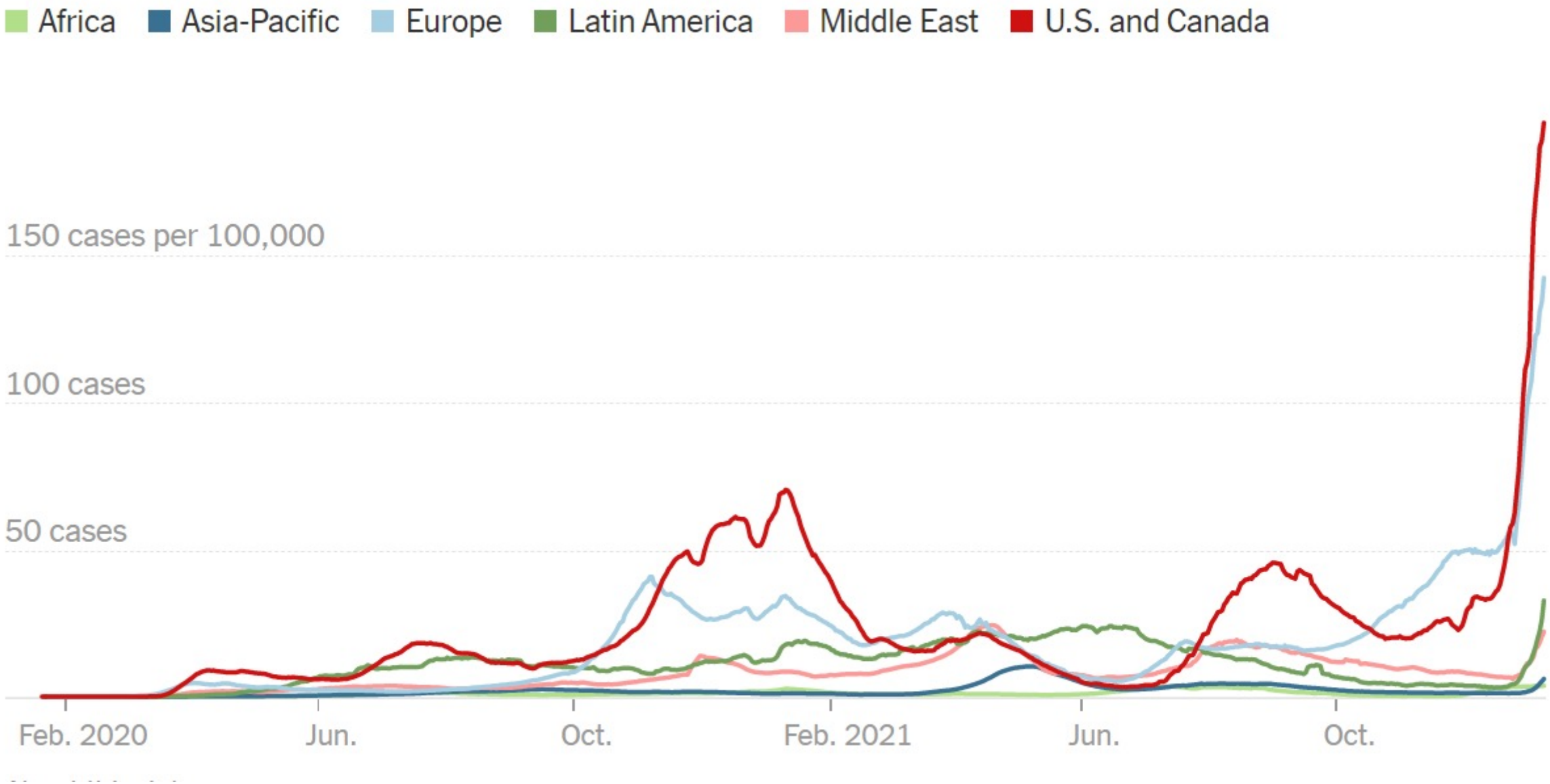
Proportion of VOC among total sequences
(countries with ≥100 sequences in last 30 days)*

- 0.501 - 1.000
- 0.101 - 0.500
- 0.011 - 0.100
- >0.000 - 0.010
- VOC detected, proportion not estimated**
- No presence of VOC reported

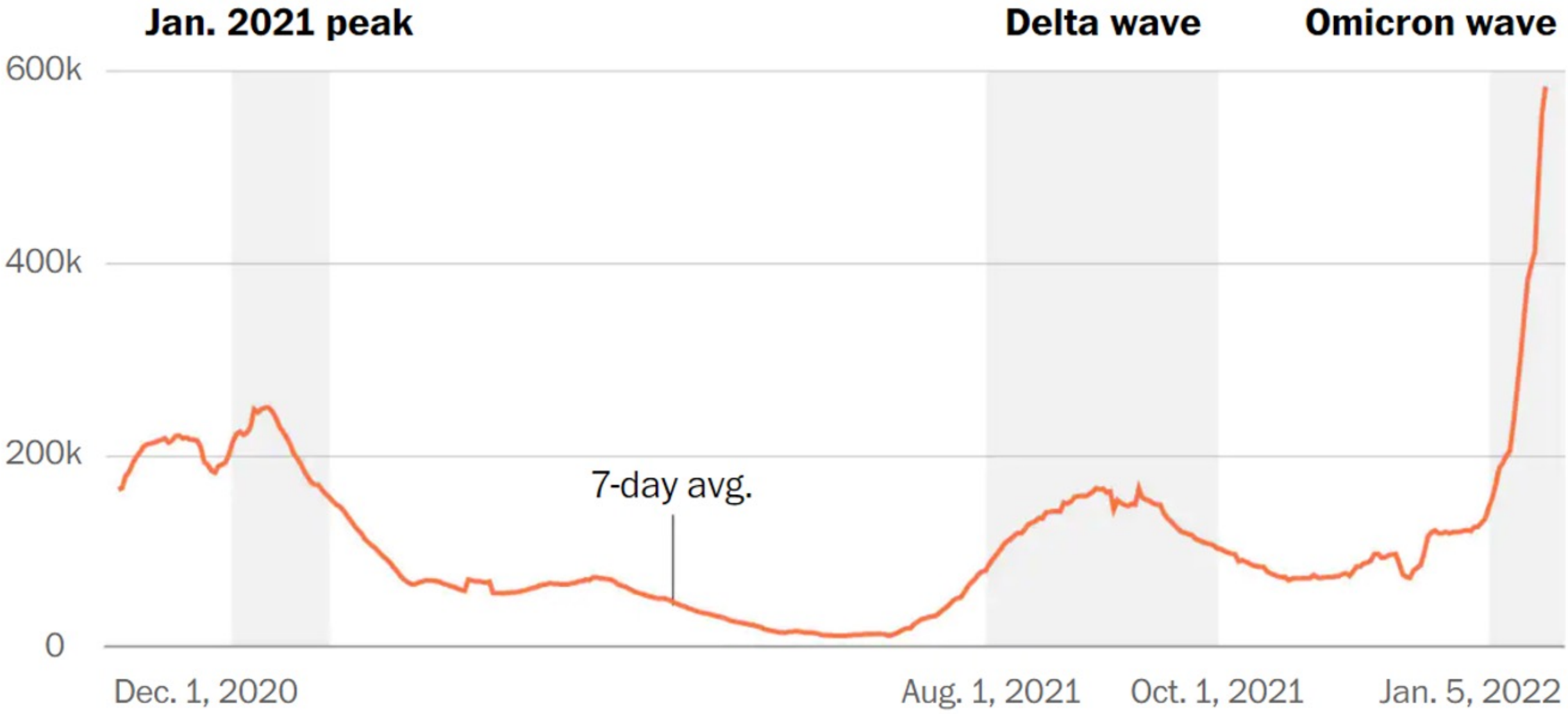
Cases, hospitalizations and deaths in US comparing Delta and Omicron waves



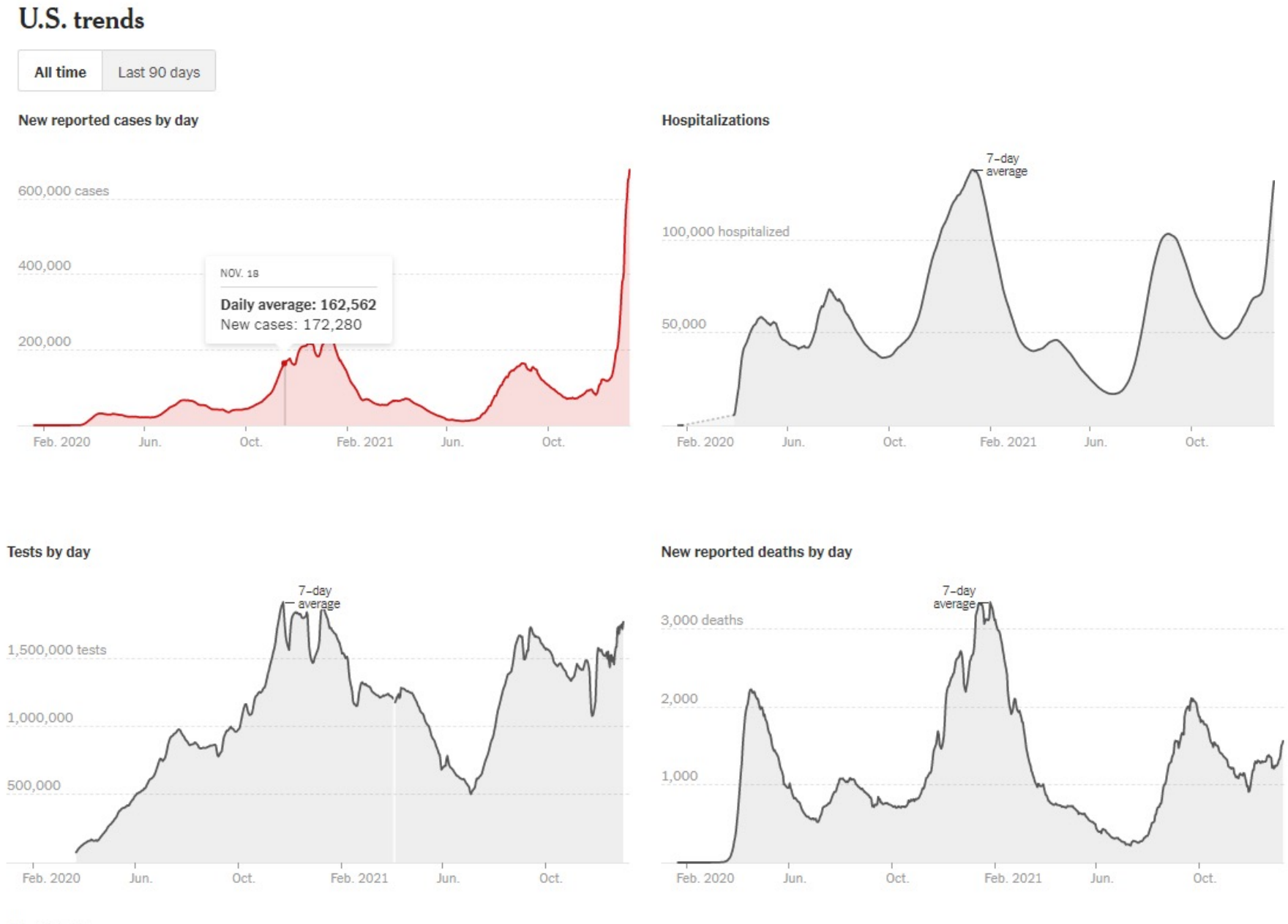
Despite differences in testing and surveillance marked case increases occurred in each area with Omicron



Reported cases per day from Omicron in the US are more than double that of Jan. 2021 peak



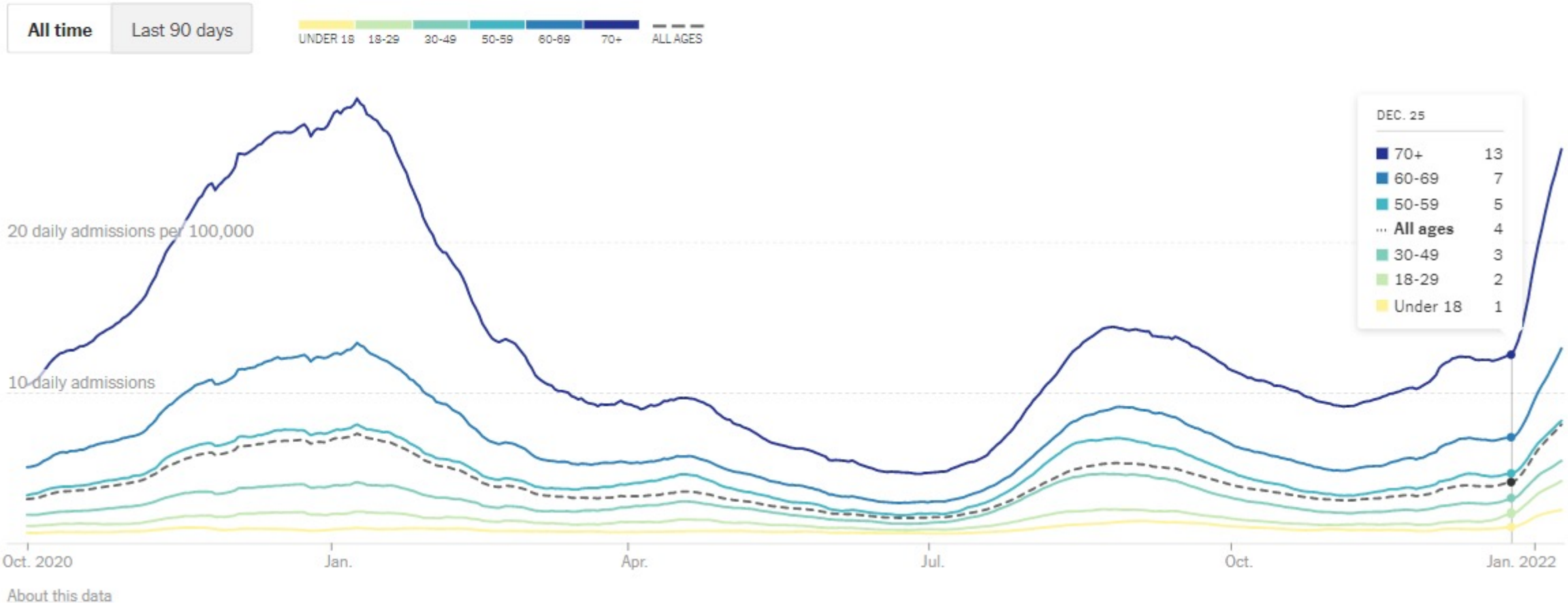
Omicron is associated with marked increase in testing, cases reported, hospitalizations and deaths in the US



All age groups experienced sharp increases in hospitalizations from Omicron including children

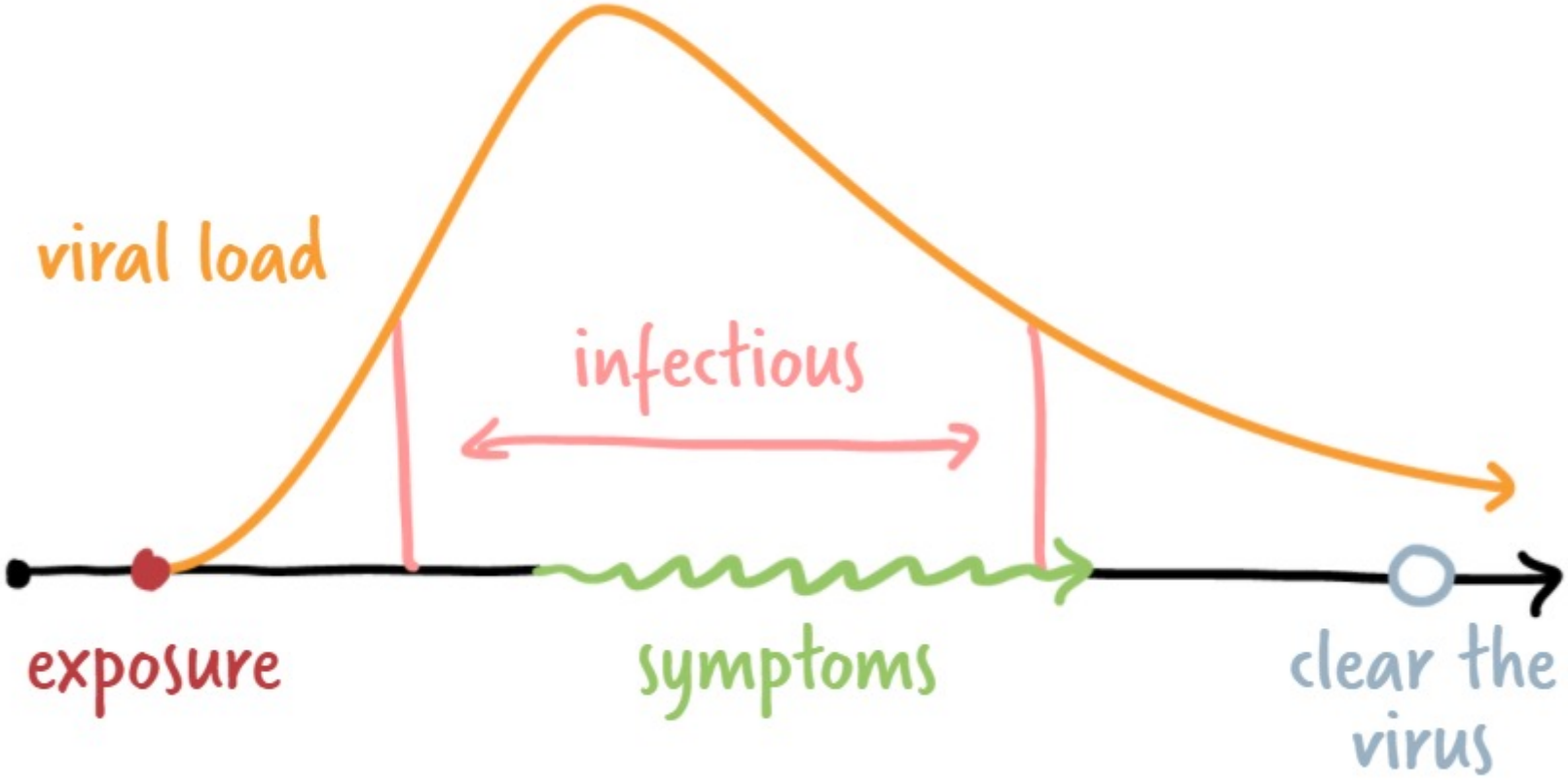
Daily new hospital admissions by age

This chart shows for each age group the number of people per 100,000 that were newly admitted to a hospital with Covid-19 each day, according to data reported by hospitals to the U.S. Department of Health and Human Services.

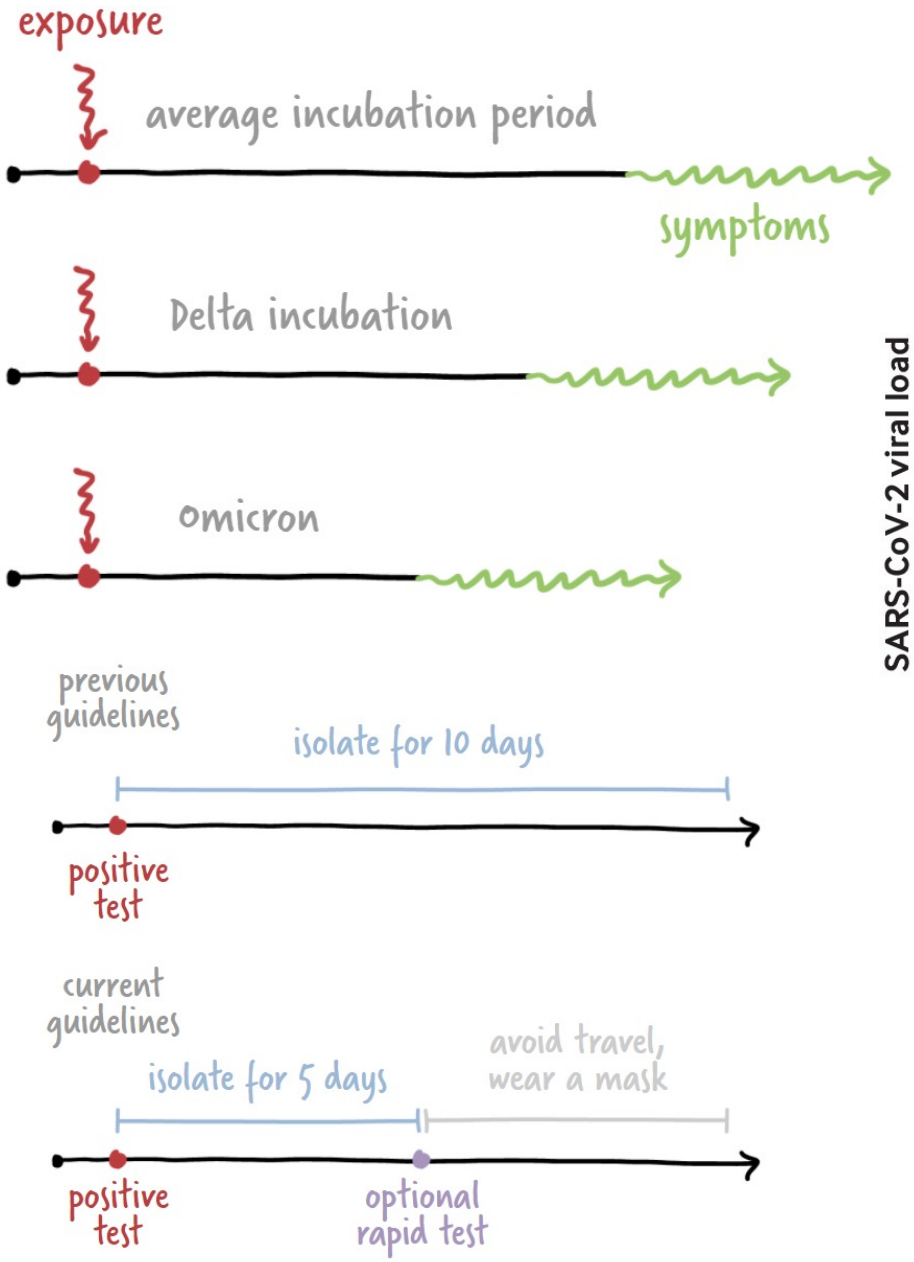


About this data

Sequence of events in SARS-COV2 infection and virus clearance



Comparison of incubation and infectious periods for delta and omicron variants



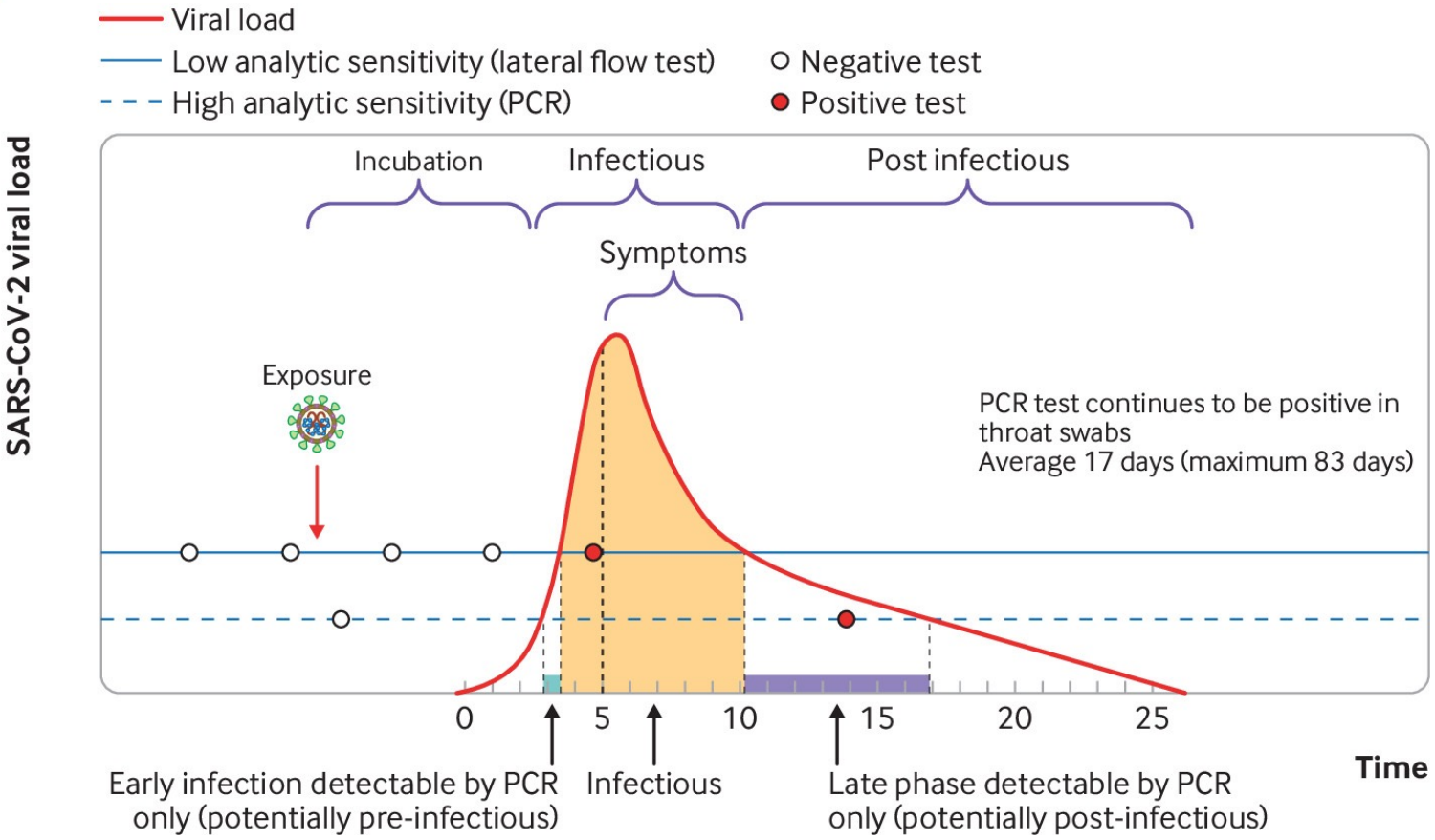


Table 2: Summary of phenotypic impacts* of variants of concern

WHO label	Alpha	Beta	Gamma	Delta	Omicron
Transmissibility	Increased transmissibility[12]	Increased transmissibility[13,14]	Increased transmissibility[14,15]	Increased transmissibility [14,16,17]	Increased transmissibility.[1–4]
Disease severity	Possible increased risk of hospitalization[18,19], possible increased risk of severe disease and death[20,21]	Possible increased risk of hospitalization[19], possible increased in-hospital mortality[22]	Possible increased risk of hospitalization[19], possible increased risk of severe disease[23]	Possible increased risk of hospitalization[24,25]	Possible reduced risk of hospitalization and severe disease [5–8]
Risk of reinfection	Neutralizing activity retained[26], risk of reinfection remains similar[27]	Reduction in neutralizing activity reported; T cell response elicited by D614G virus remains effective[28]	Moderate reduction in neutralizing activity reported[29]	Reduction in neutralizing activity reported[30–32]	Increased risk of reinfection [11,33]
Impacts on diagnostics	Limited impact – S gene target failure (SGTF), no impact on overall result from multiple target RT-PCR; No impact on Ag RDTs observed[34]	No impact on RT-PCR or Ag RDTs observed[32]	None reported to date	No impact on RT-PCR or Ag RDTs observed[35]	PCR continues to detect Omicron. Impact on Ag-RDTs is under investigation: Results are mixed as to whether or not there may be decreased sensitivity to detect Omicron. [1,8,36–38]

**Generalized findings as compared to previously/co-circulating variants. Based on emerging* evidence, including non-peer-reviewed preprint articles and reports, all subject to ongoing investigation and revision.

Number of mutations identified in each variant's spike, date of earliest documented sample

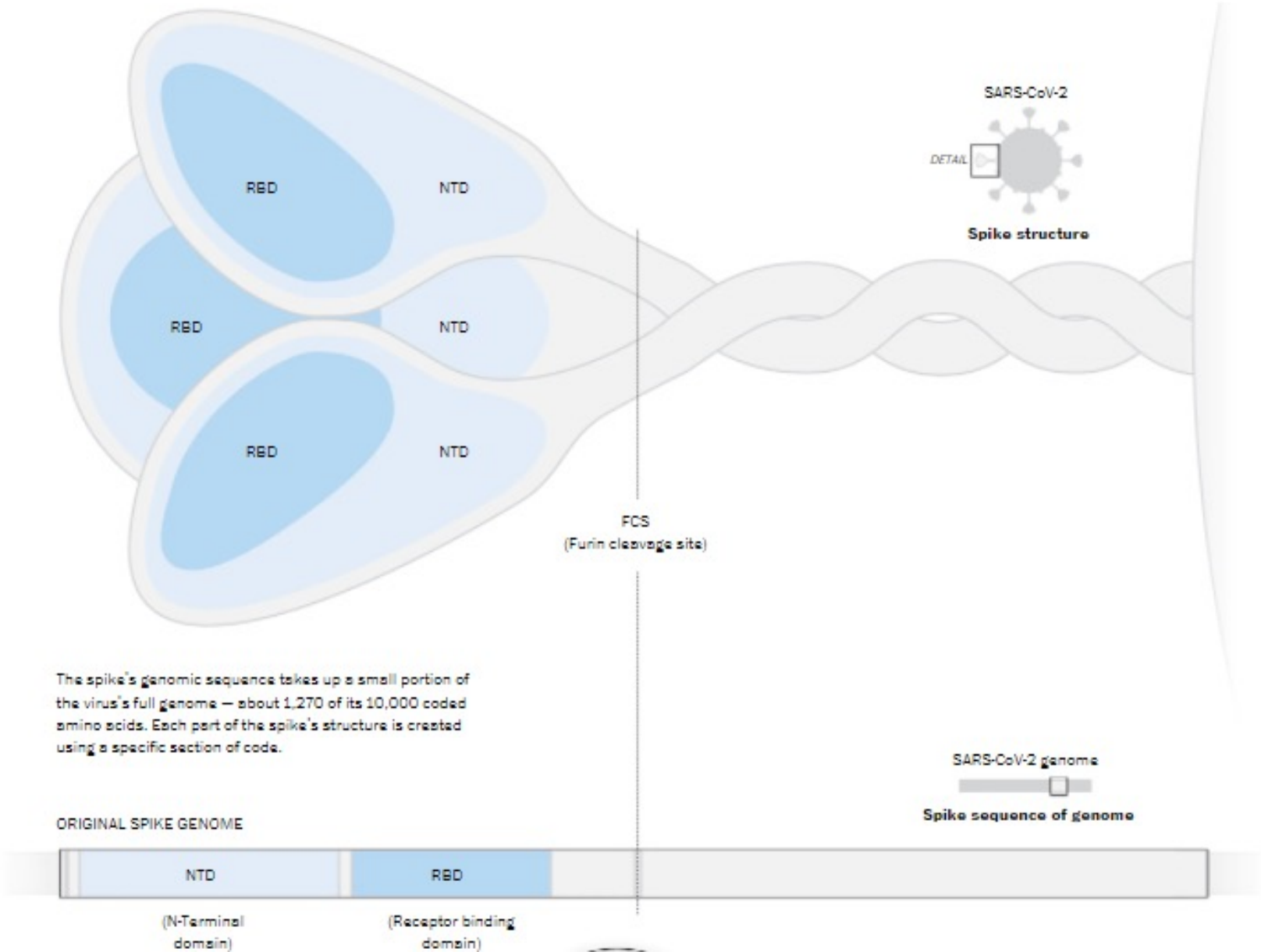
A look at the spike

Every spike on a coronavirus's surface is made of three identical proteins twisted together, making it look a little like a head of broccoli with three stalks.

Each stalk has three vital regions — the receptor binding domain (RBD), the N-terminal domain (NTD) and the furin cleavage site (FCS) — and most of omicron's mutations are in these three areas.

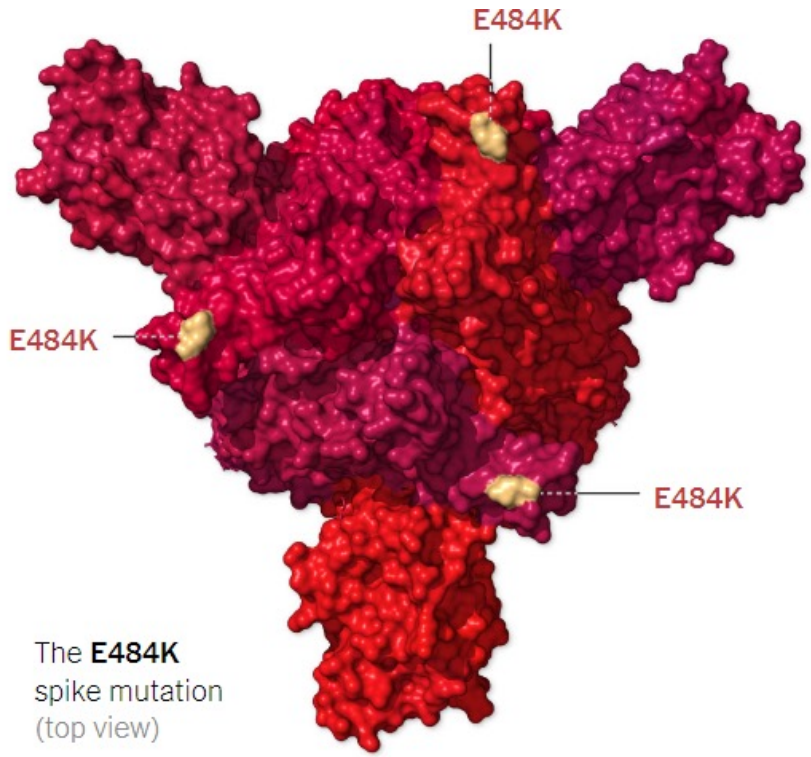
https://www.washingtonpost.com/health/2021/12/16/omicron-variant-mutations-covid/

Time to take a closer look at the famous spike



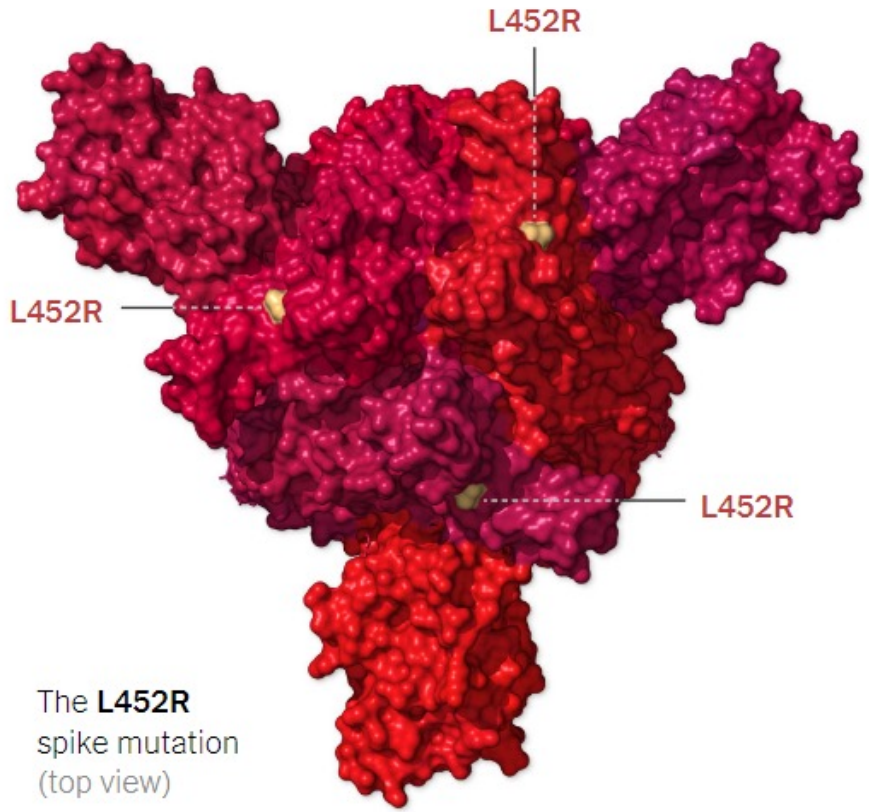
Delta, Kappa: The B.1.617 Lineage

B.1.617 carries more than a dozen mutations, but is sometimes called a "double mutant" because of two prominent mutations: **E484Q** and **L452R**.



The **E484K** spike mutation (top view)

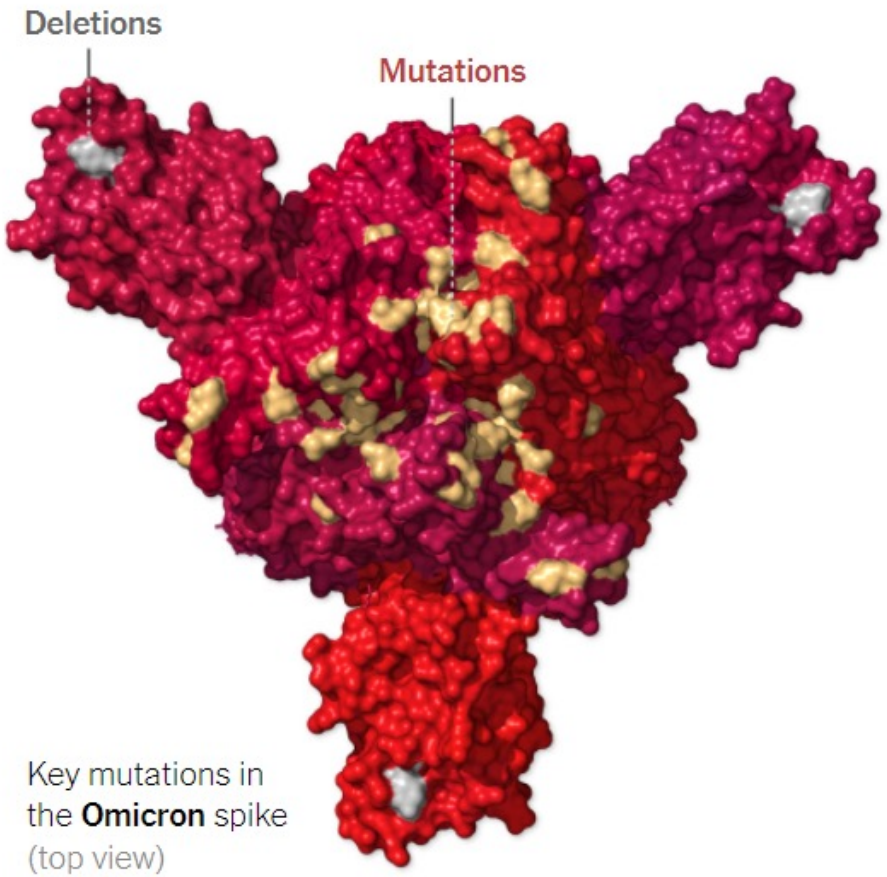
The B.1.617 lineage has continued to evolve, splitting into new lineages including **B.1.617.1**, known as **Kappa**, and **B.1.617.2**, known as **Delta**. It has emerged as a fast-growing virus, outpacing other variants of concern.



The **L452R** spike mutation (top view)

E484Q lies at the same location as **E484K**, the "Eek" mutation that might help the virus evade some types of antibodies.

The Omicron variant is a new lineage



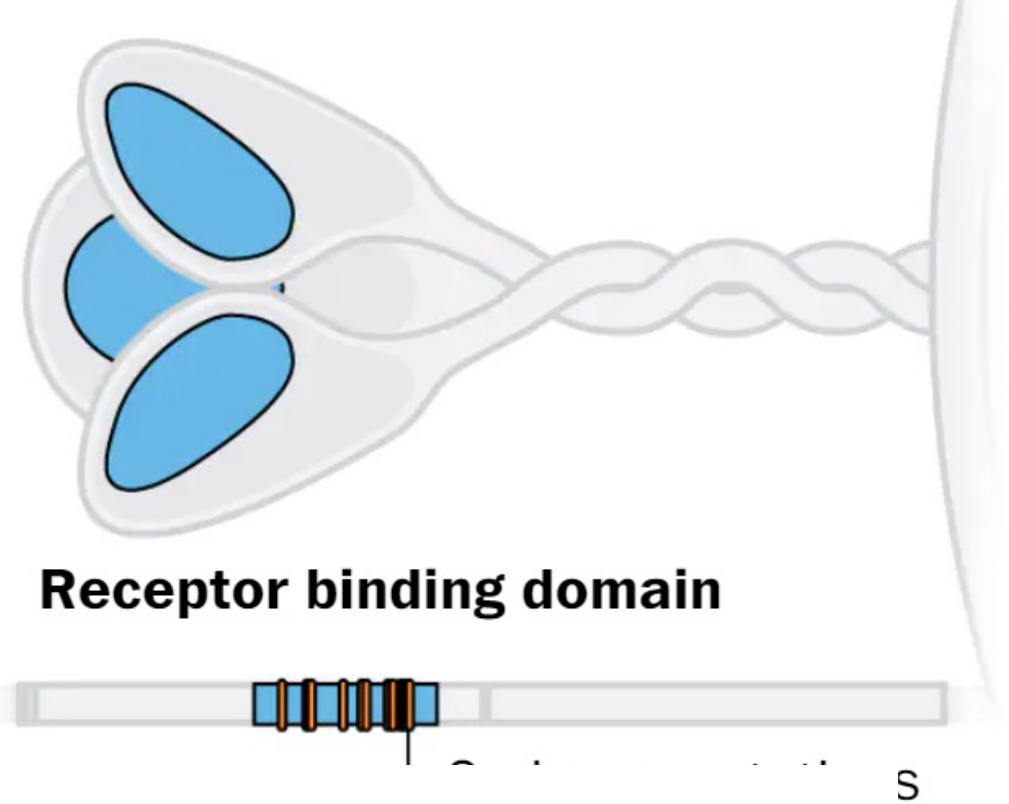
Key mutations in the **Omicron** spike (top view)

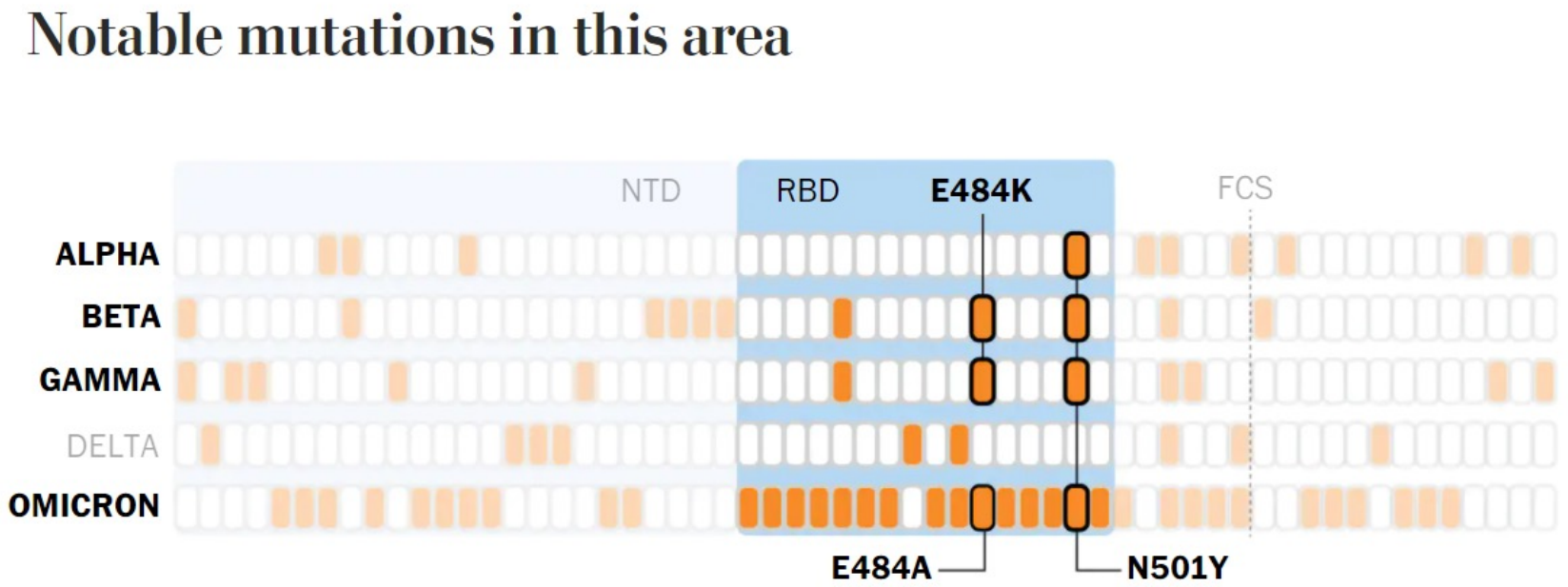
Key mutations in the **Omicron** spike

Omicron's spike protein has several mutations that are found other variants of concern and that are thought to make the virus more infectious, including **D614G**, **N501Y** and **K417N**.

TRANSMISSIBILITY

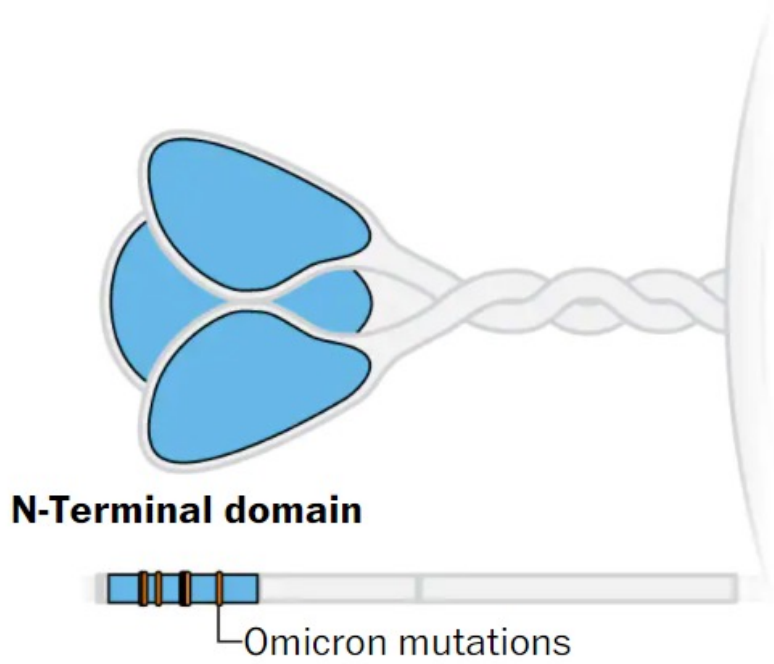
The receptor binding site which acts like a key to open the cell to the virus

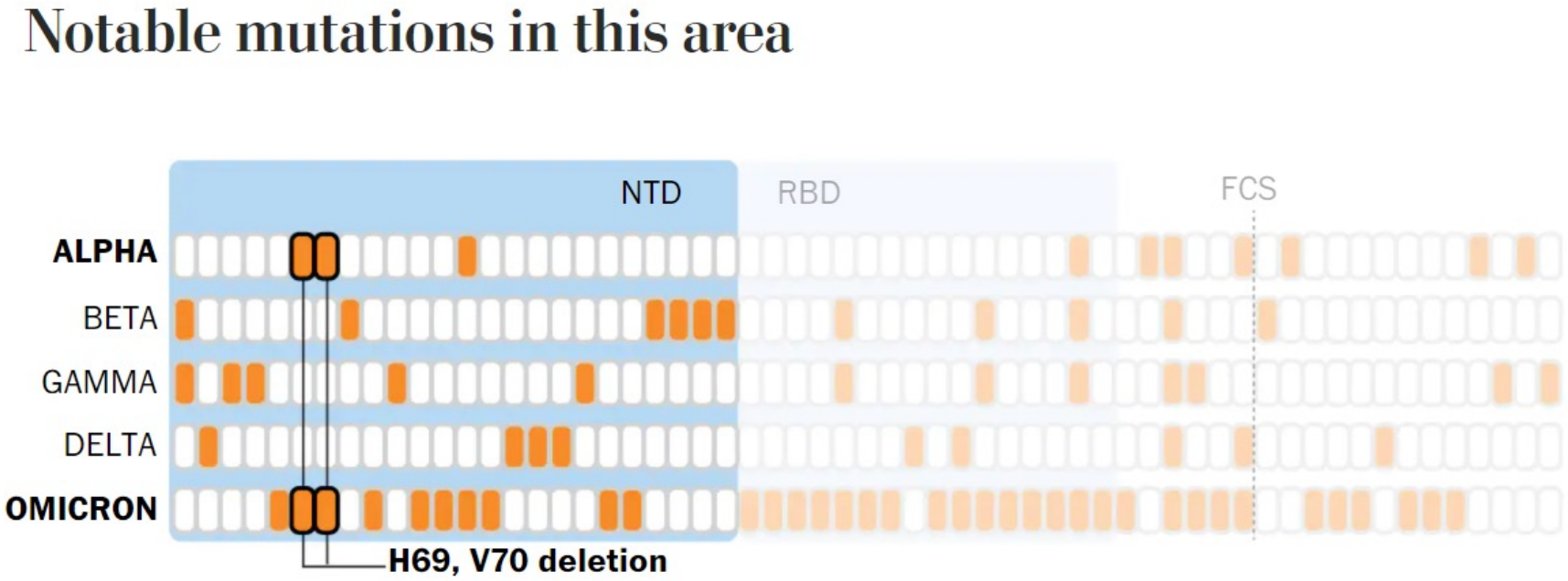




IMMUNITY

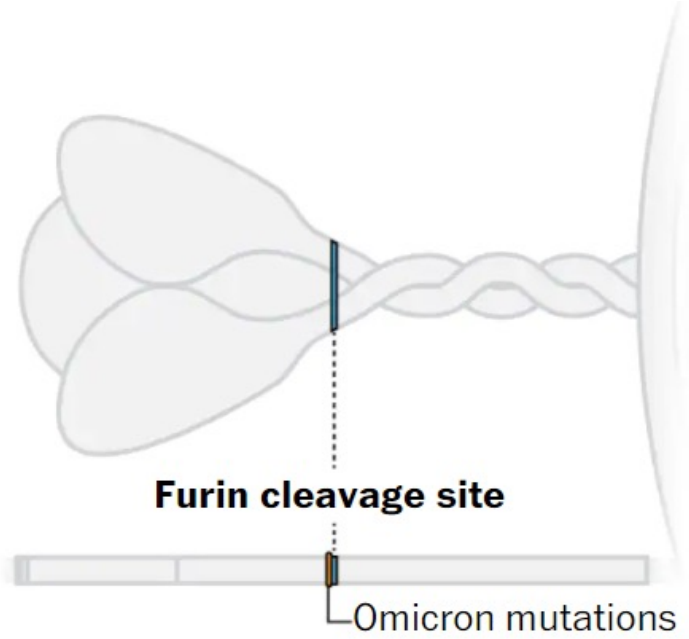
The N-terminal domain which is recognized by the immune system





SEVERE ILLNESS

The furin cleavage site which allows the virus to spread from cell to cell



What viral factors lead to new variants?

- Very high rate of infection which means billions and trillions of new virus replication events
- A virus may make multiple errors each time it replicates
- Most of these either make no difference or are fatal to the virus
- But multiply that by billions and trillions and variants with new or different properties emerge
- A very few give the virus an advantage. These are the ones that then overtake the others

THIS IS EVOLUTION FAST FORWARD

WHAT ARE THE HUMAN FACTORS DRIVING MUTATIONS AND THEIR SPREAD?

- **High rates of infection in unvaccinated individuals**
- **Vaccine refusal**
- **High rates of infection in crowded and disadvantaged places**
- **Uncontrolled large gatherings**
- **Failure to wear masks (correct masks worn correctly) in crowded and poorly ventilated settings**
- **Persistence of virus in the immunosuppressed (e.g. HIV)**

The Ganges Festival
January 2022

VACCINES

Leading vaccines

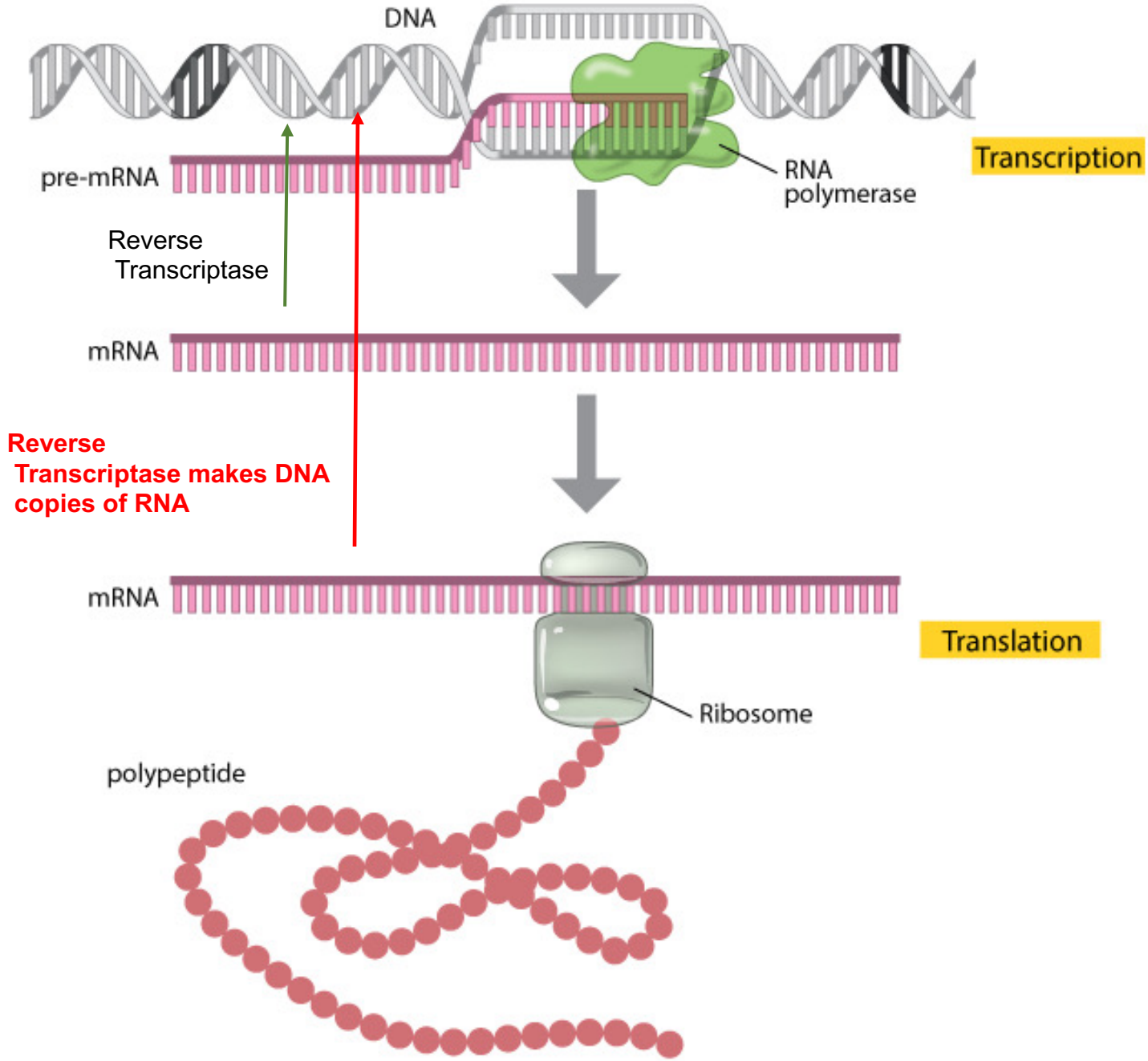
Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., E.U., other countries.
Gamaleya	Ad26, Ad5	3	Emergency use in Russia, other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Approved in Brazil. Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Approved in China. Emergency use in other countries.
Johnson & Johnson	Ad26	3	Emergency use in U.S., E.U., other countries.
Vector Institute	Protein	3	Early use in Russia. Approved in Turkmenistan.
Novavax	Protein	3	*
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in other countries.
Sinovac	Inactivated	3	Approved in China. Emergency use in other countries.
Sinopharm-Wuhan	Inactivated	3	Approved in China. Limited use in U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India, other countries.

*Novavax protein nanoparticle vaccine is approved in the EU for 18 and above, Indonesia and Philippines, and EUA requested in the US. Stored 6 months at 4^{o}C. These and similar low-cost, temperature stable vaccines need to be widely available in developing countries.

DNA viruses: Herpes, CMV, smallpox, adenoviruses, chickenpox

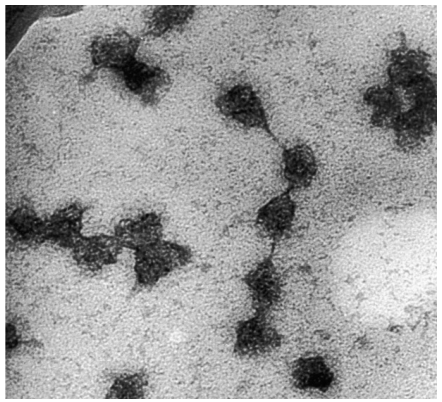
Negative Strand RNA viruses: HIV, Polio, Influenza, Ebola, measles, mumps,

Positive Strand RNA viruses: SARS-CoV-2, Dengue, west Nile, Zika, rhinoviruses, rubella



mRNA history

Dr. Katalin Karikó
and Dr. Drew Weissmann



Electron microscopy image of mRNA in a cell

1998 Penn State department of Medicine

Dr. Karikó was obsessed with MRNA but unfunded and marginalized but believed that it could coerce a cell into producing any kind of protein as long as you had the genetic code.

Dr Weissmann was physician and virologist.

However, injected mRNA was highly toxic and destroyed by cells

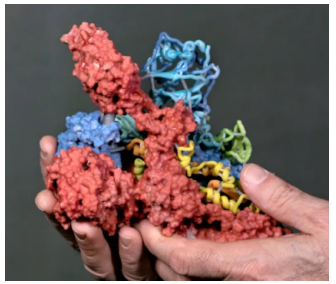
Together they worked out that natural mRNA was protected with a particular molecule.

THIS WAS THE BREAKTHROUGH THAT PRODUCED INJECTABLE mRNA

2013-2019

Working with the MERS virus Dr. Ian McLellan along with Dr. Barney Graham worked out where to put stabilizing mutations on the coronavirus spike.

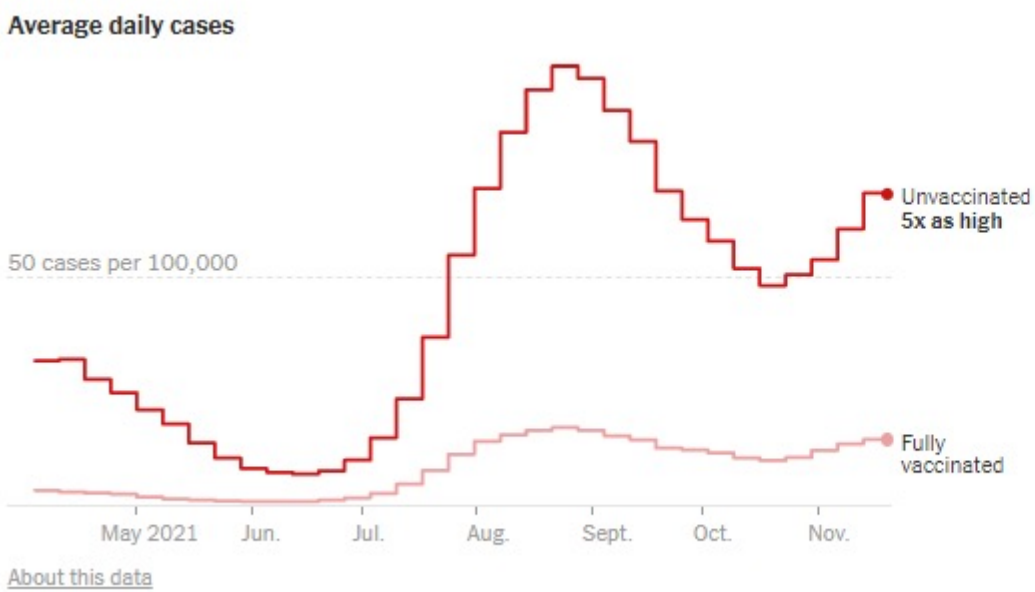
This was a crucial step in elucidating the structure of the spike allowing the mRNA molecules to synthesize stable spikes.

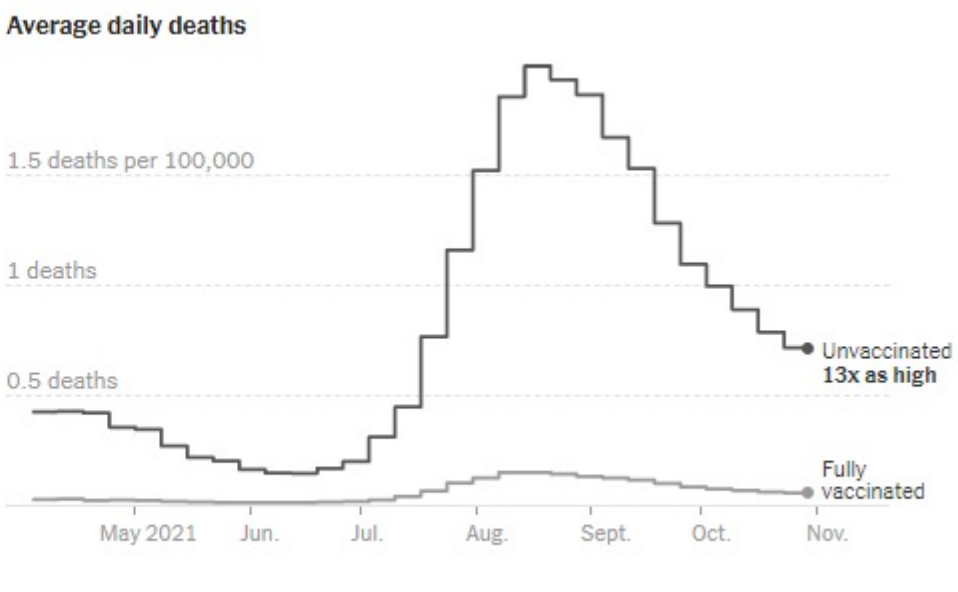


2014

To protect the mRNA for injection a Canadian team, led by Dr. Collis, developed the lipid wrapping to preserve the structure as it entered the body

Daily Case and Death rates in vaccinated and unvaccinated in the US





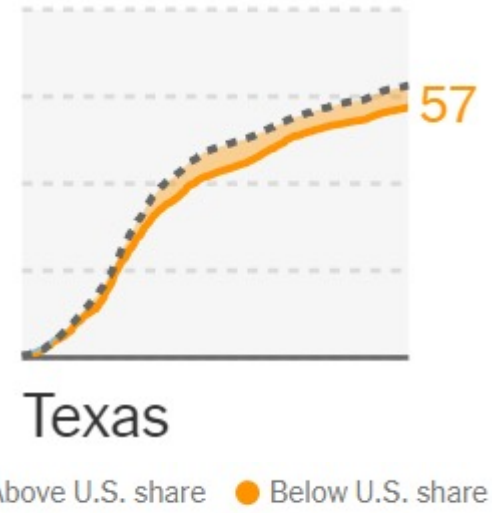
Vaccination rates by age group and geographic areas US

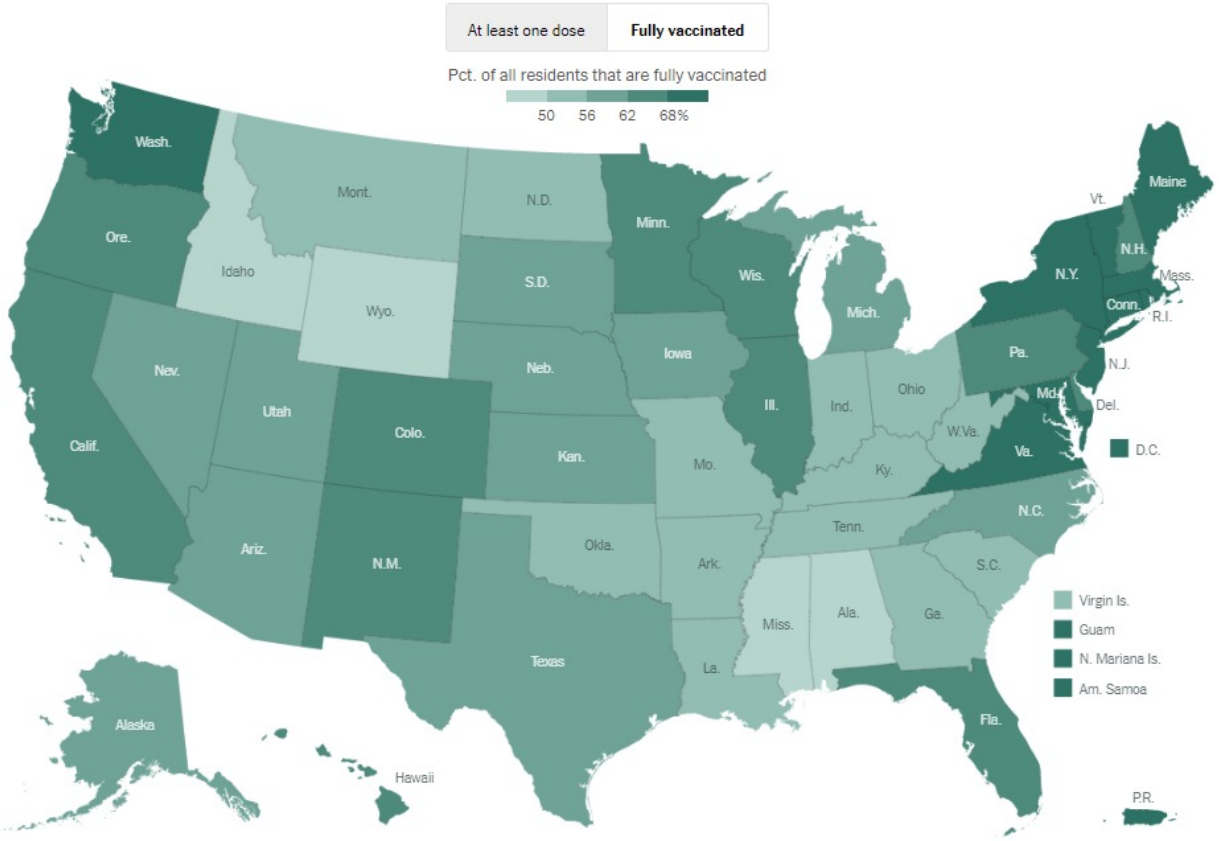
United States vaccinations

	At least one dose*	Fully vaccinated
All ages	74%	63%
5 and up	79%	67%
12 and up	85%	72%
18 and up	86%	73%
65 and up	95%	88%

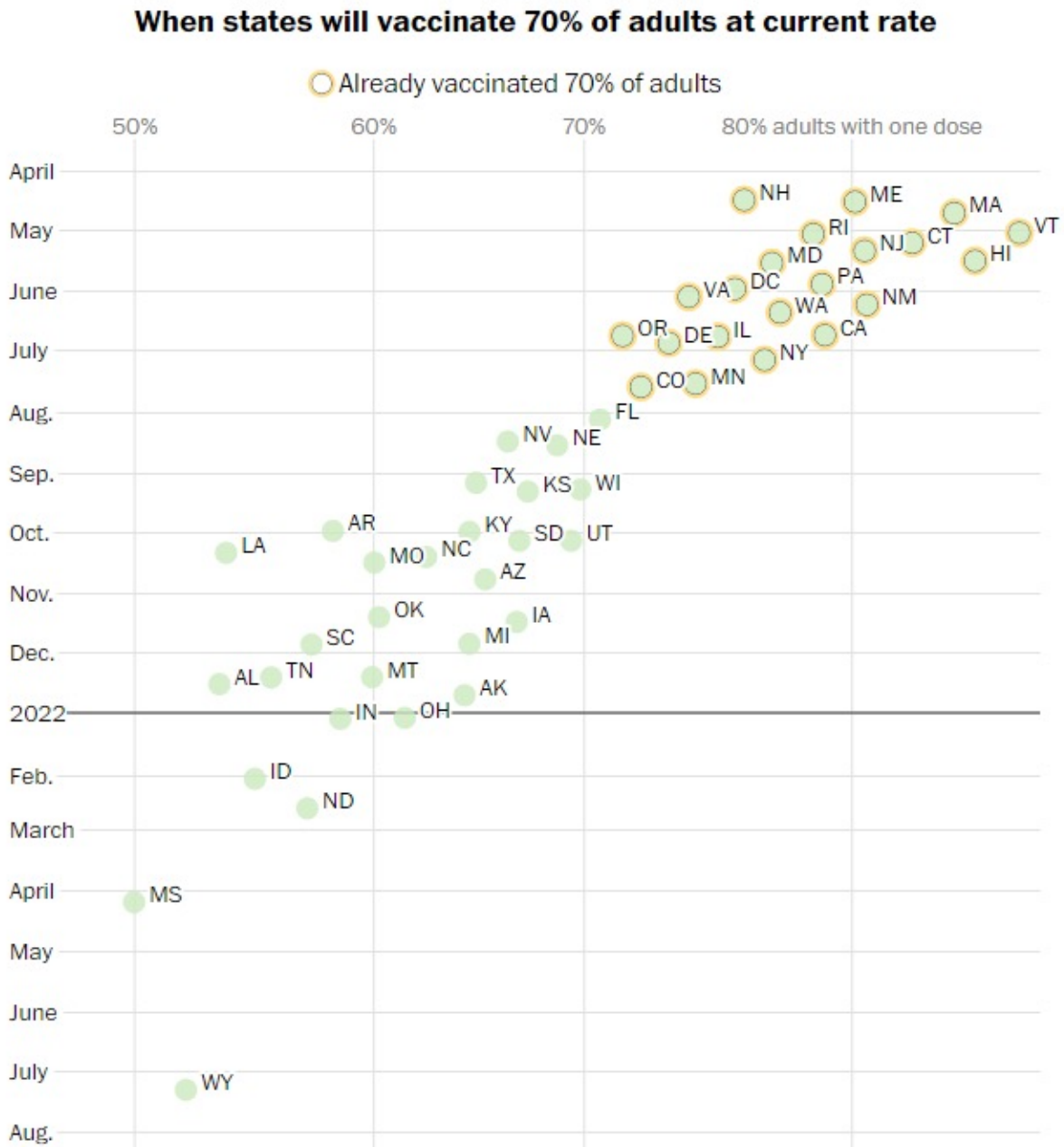
*The C.D.C. reported on Nov. 30, 2021 that booster doses are sometimes misclassified as first doses, which may overestimate first dose coverage among adults.

Sources: Centers for Disease Control and Prevention, U.S. Census Bureau | Note: Figures include the U.S. territories and three countries with special agreements.





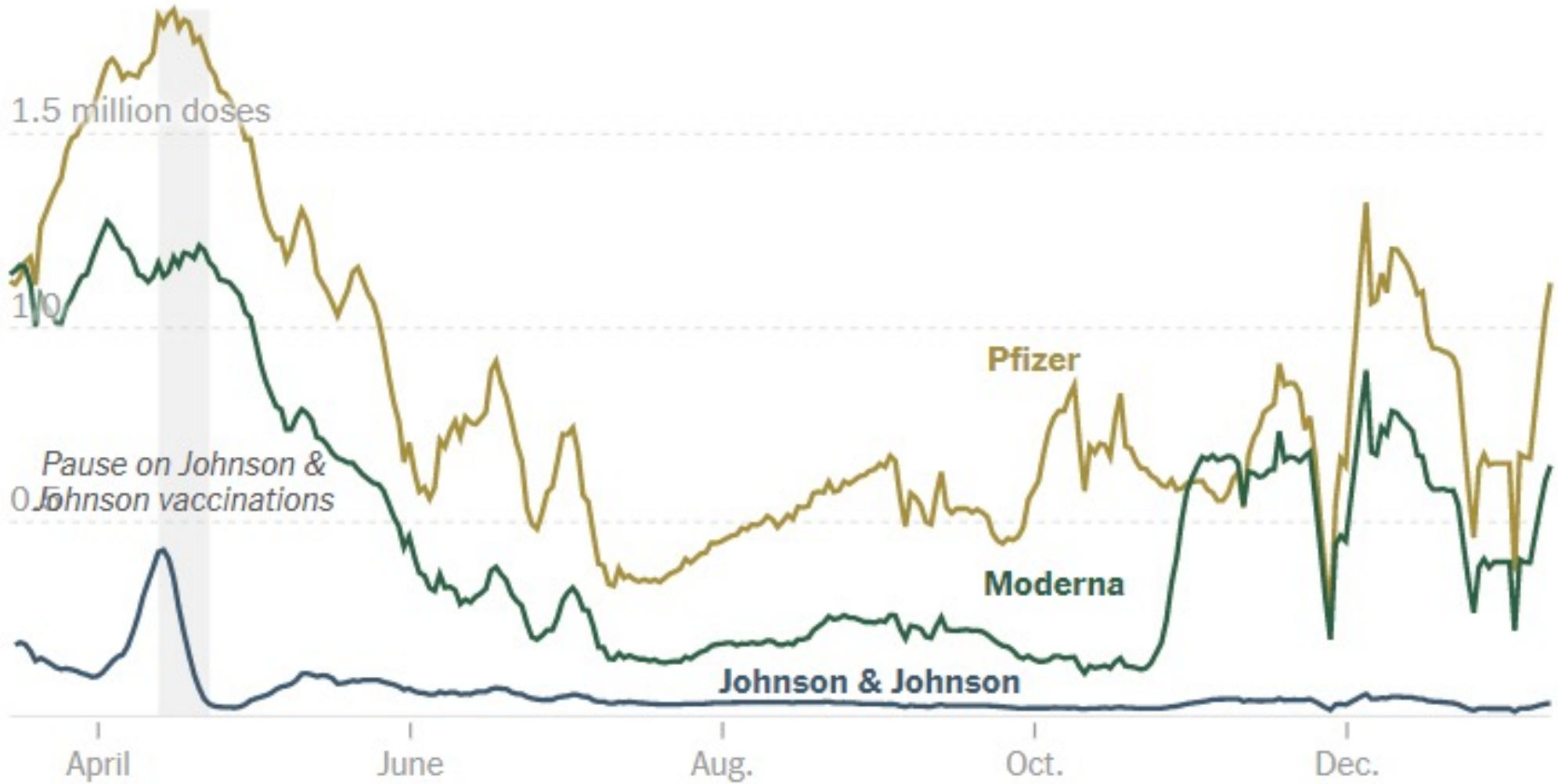
Sources: Centers for Disease Control and Prevention, U.S. Census Bureau



West Virginia is off he map only achieving 70% in late October 2022

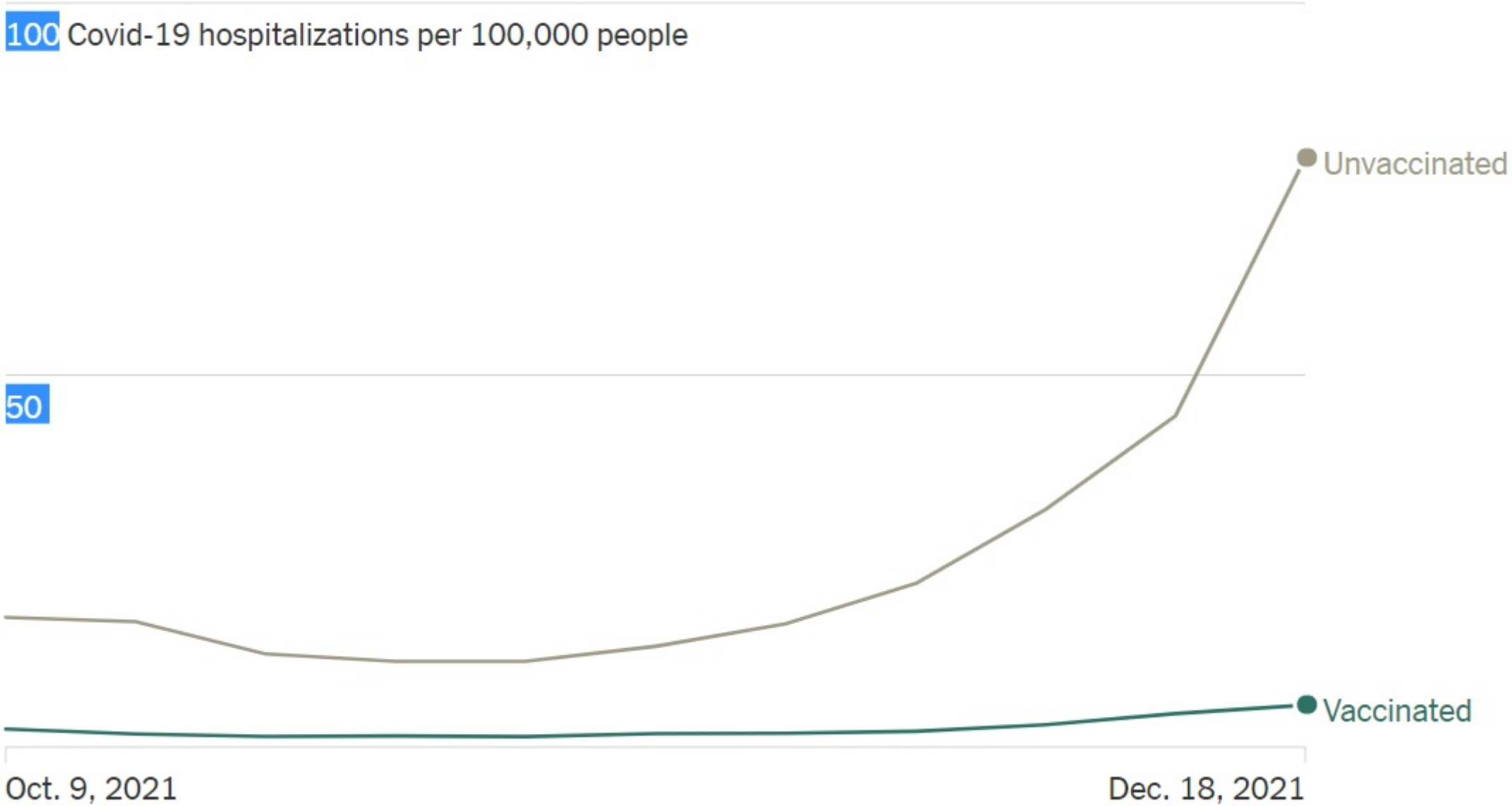
Daily reported doses given by manufacturer

Each line shows the seven-day average.



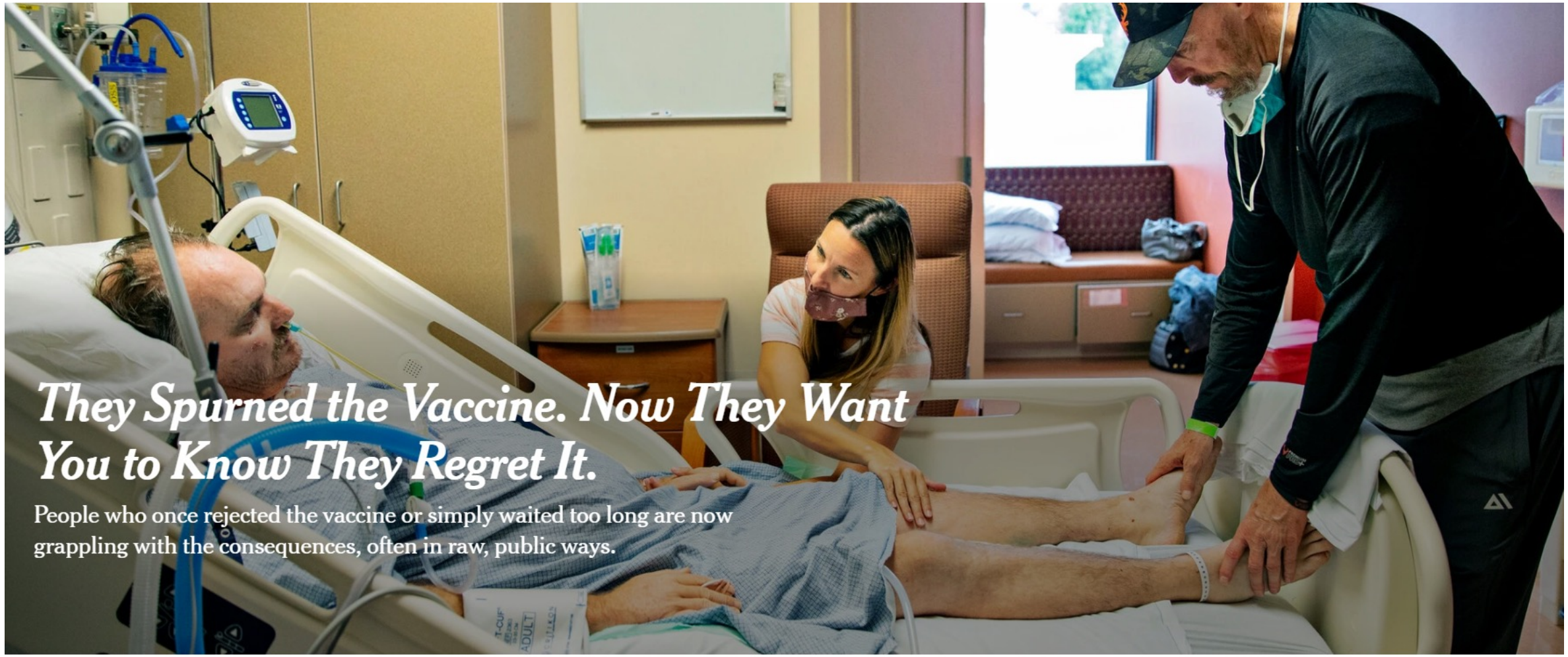
Source: Centers for Disease Control and Prevention

New York City



They both caught Covid, but one was vaccinated

She got the shot. Her vaccine hesitant husband didn't. Now he's in a Mississippi ICU bed battling coronavirus.



They Spurned the Vaccine. Now They Want You to Know They Regret It.

People who once rejected the vaccine or simply waited too long are now grappling with the consequences, often in raw, public ways.

Glen Arnell, right, and Mindy Greene visited her husband, Russ Greene, at Utah Valley Specialty Hospital. Mr. Greene was hospitalized with complications from Covid-19 after choosing not to receive a vaccination for the virus. Kim Raff for The New York Times

VIGNETTES

New 32 year old unvaccinated mother dies from Covid-19 before she can hold her newborn

Quote from a father “My 16 month old son was lucky to get a pediatric ICU bed when he needed one for a non-COVID condition. He shouldn't have needed luck”

Effectiveness of Pfizer and Moderna vaccines against all COVID-19 over time

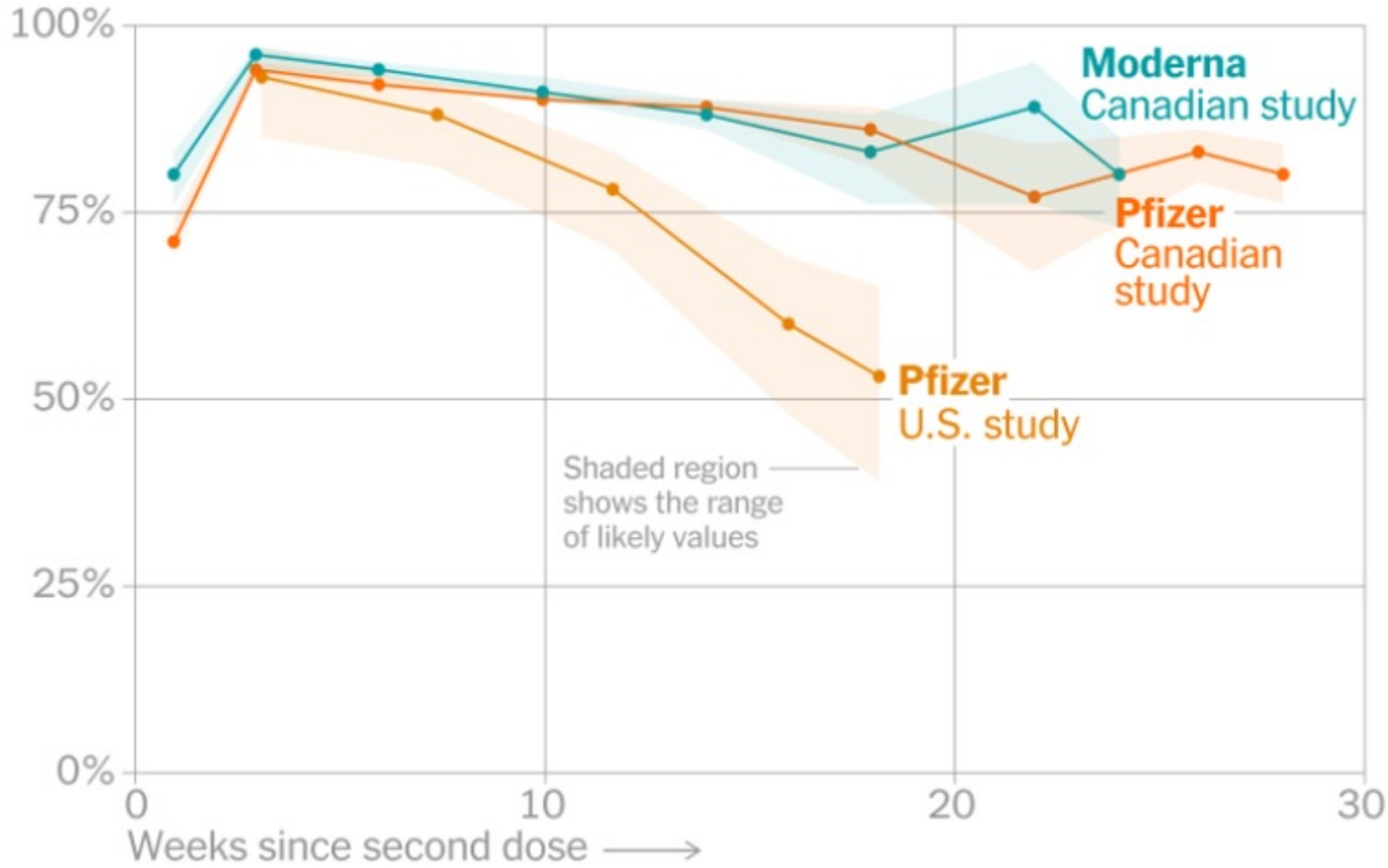
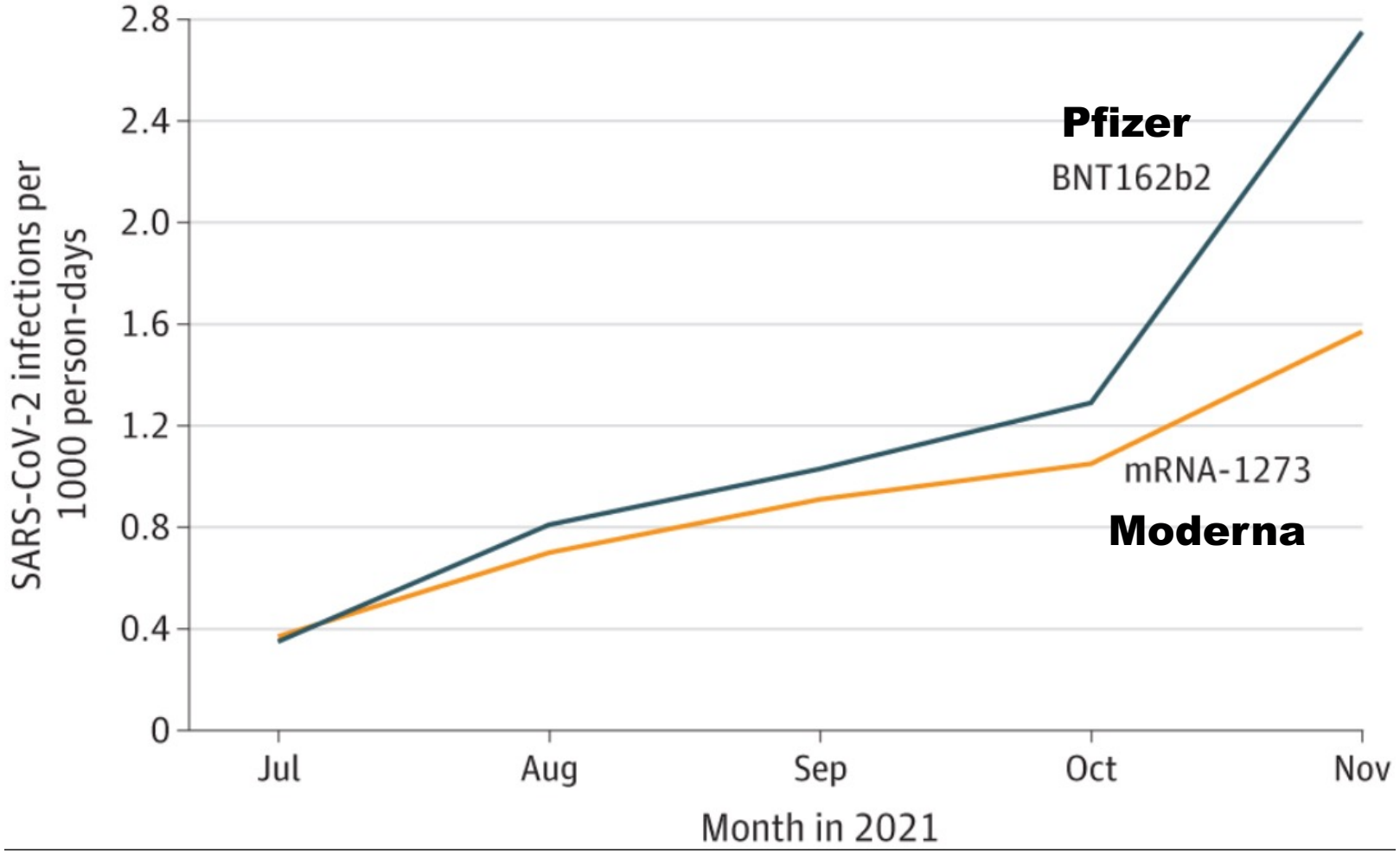
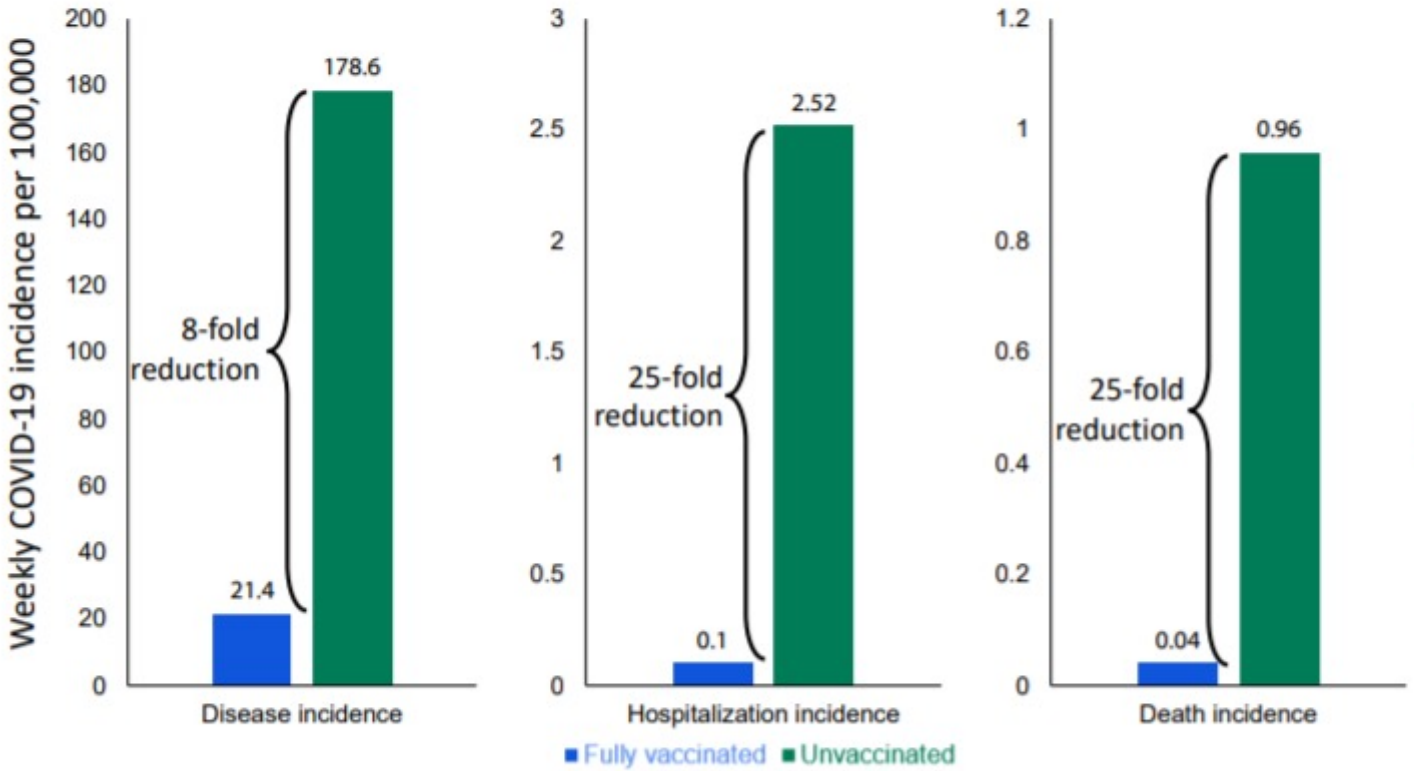


Figure. Monthly Incidence Rates of Breakthrough SARS-CoV-2 Infections From July to November 2021 in 2 Cohorts



Fully vaccinated cohorts with two shots during the delta period

Greater risk of disease, hospitalization and death among unvaccinated vs. vaccinated people: National estimates



At current incidence, 35,000 symptomatic infections per week among 162 million vaccinated Americans

Data from COVID Tracker as of July 24, 2021. Average incidence 100 cases per 100,000 persons per week. Vaccine effectiveness against symptomatic illness = 88% (Lopez Bernal et al. NEJM 2021), where risk is [1 – VE] or 12%. Vaccine effectiveness hospitalization (or death) = 96% (Stowe et al. PHE preprint), where risk is [1 – VE] or 4%. Rate in unvaccinated = Community rate/[(1-fully vaccinated coverage) + (1-VE)*fully vaccinated coverage). Rate in fully vaccinated=(1-VE)*Rate in unvaccinated. Fully vaccinated coverage proportions were from COVID Data Tracker as of July 24, 2021 (50% for US,).

EVIDENCE FOR EFFICACY OF BOOSTER SHOTS

- **Improved protection in immunocompromised people.**
- **Vaccine breakthrough hospitalization more common with the Pfizer vaccine**
- **Protections from the Pfizer vaccine declined after 4 months from 2nd vaccine**
- **Higher antibody responses are seen from Moderna vaccine than Pfizer**
- **Differences in memory cell responses have not been assessed**
- **Complete evasion of antibody by Delta nor Omicron has not been demonstrated.**

Overall conclusion is that vaccination with either vaccine reduced hospitalization, disease progression and likelihood of death

CAN WE CREATE A UNIVERSAL VACCINE FOR ALL COVID-10 VARIANTS

- **Research is in progress**
- **Current vaccines based on the original spike sequences may need further boosters**
- **Knowing which regions of the spike proteins are highly conserved but susceptible to antibodies might allow design of a universal SARS-CoV-2 vaccine for all variants**
- **The spike protein receptor binding domain also flips between up and down positions. Significance uncertain, but demonstration of plasticity of the virus**
- **Researchers who have used cryogenic electron microscope to visualize the two most potent antibodies, say that these skirt around locations lower on the tip where the mutation spots are found and avoid them. This seems to allow them to identify other sites which are highly conserved, not appreciably affected by variations in sequence.**

Selected treatments including antivirals and anti inflammatory drugs

FDA approved

Paxlovid oral treatment reduces hospitalizatio n and death by 88% if given within 5 days of onset.

EUA approved or widely used

Evusheld (AZD7442) injectible antibodies 77% effective EUA

Molnupiravir antiviral about 30%

Ensovibep antiviral protein reduce 78%

Remdesivir

Baricitinib* anti IL-6 arthritis EUA

Tocilizumab* anti IL-6 arthritis EUA
*** With dexamethasone**

Not Promising

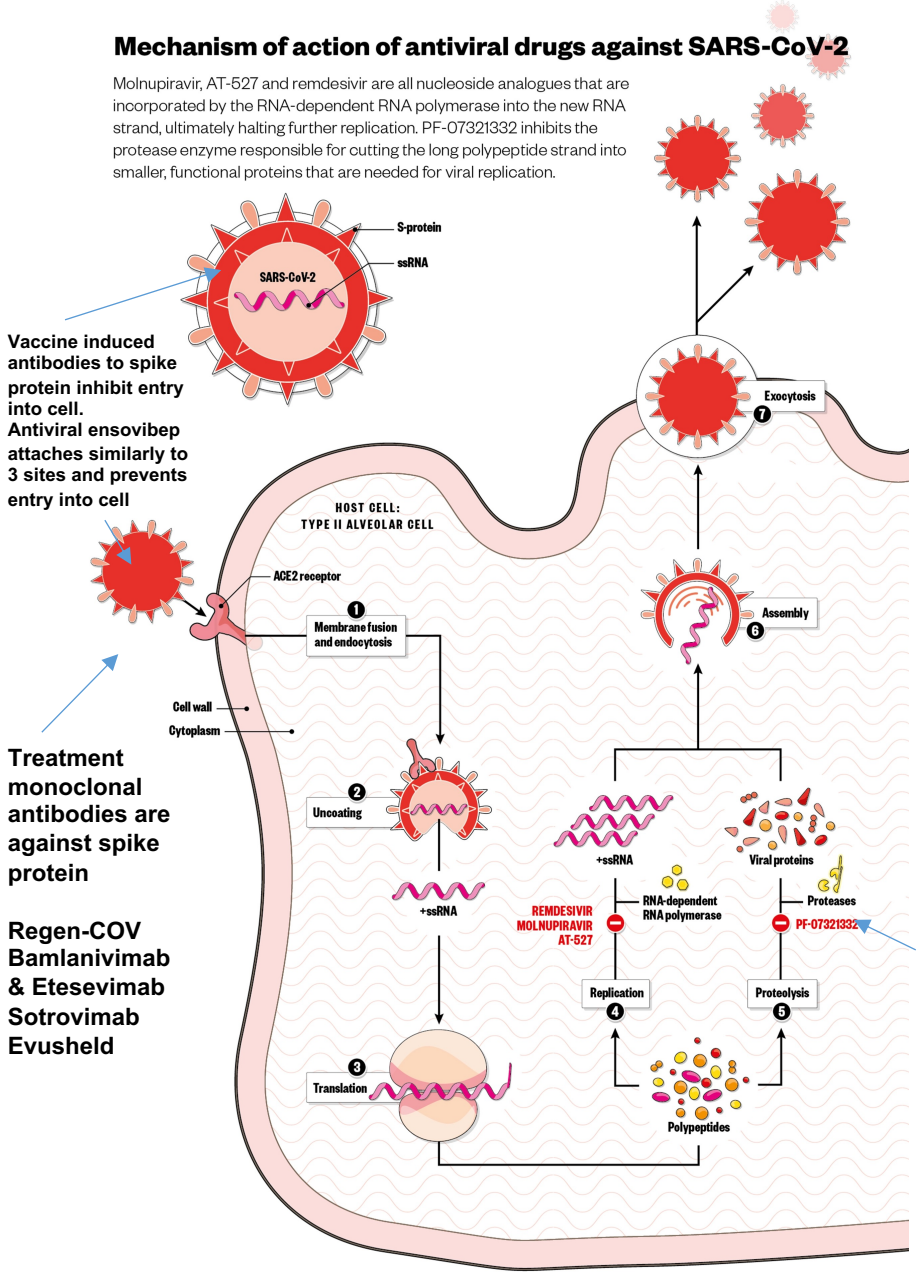
Ivermectin
Oleandrin
Lopinavir
Ritonavir
Hydroxycholorquine
Chlorquine
Azithromycin
Blood filtration

Fradulent

Bleach injections or ingestion
Sliver
UV light

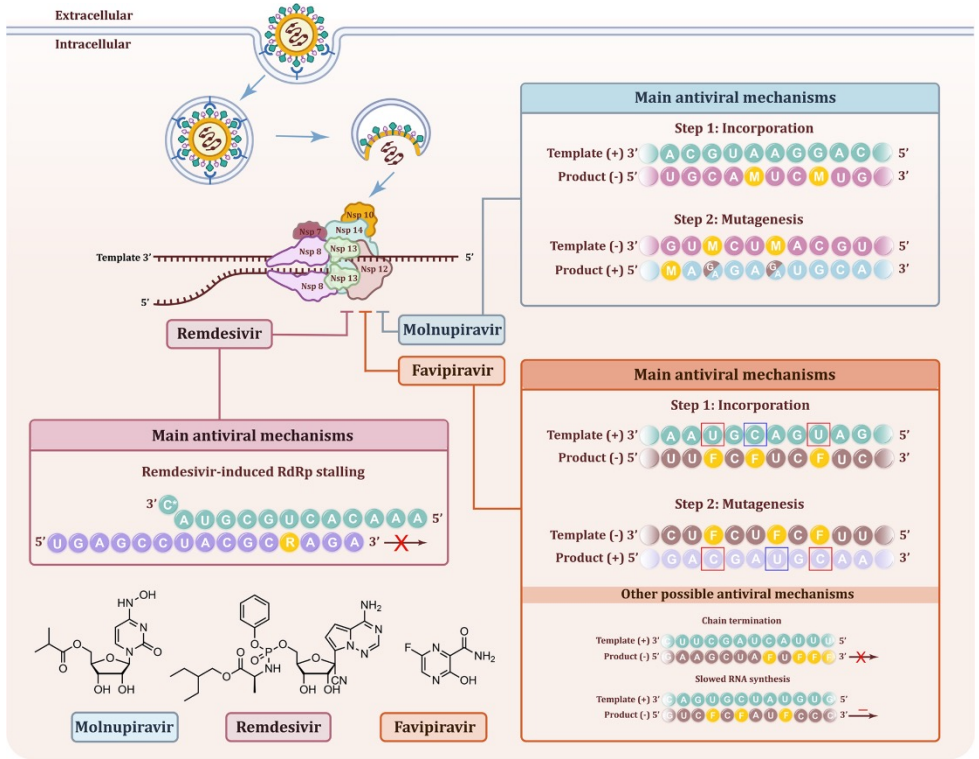
Mechanism of action of antiviral drugs against SARS-CoV-2

Molnupiravir, AT-527 and remdesivir are all nucleoside analogues that are incorporated by the RNA-dependent RNA polymerase into the new RNA strand, ultimately halting further replication. PF-07321332 inhibits the protease enzyme responsible for cutting the long polypeptide strand into smaller, functional proteins that are needed for viral replication.

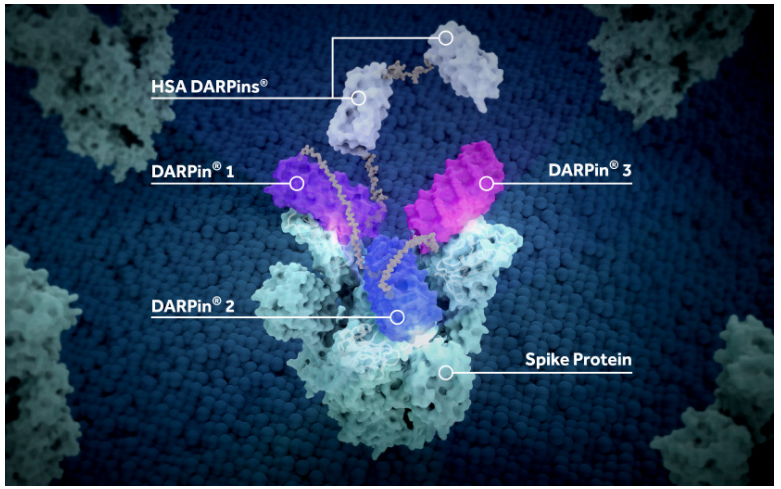


Paxlovid (PF-07321332) binds to 3C-like protease

Nucleoside analogues interfere with polymerase function or induce fatal mutations

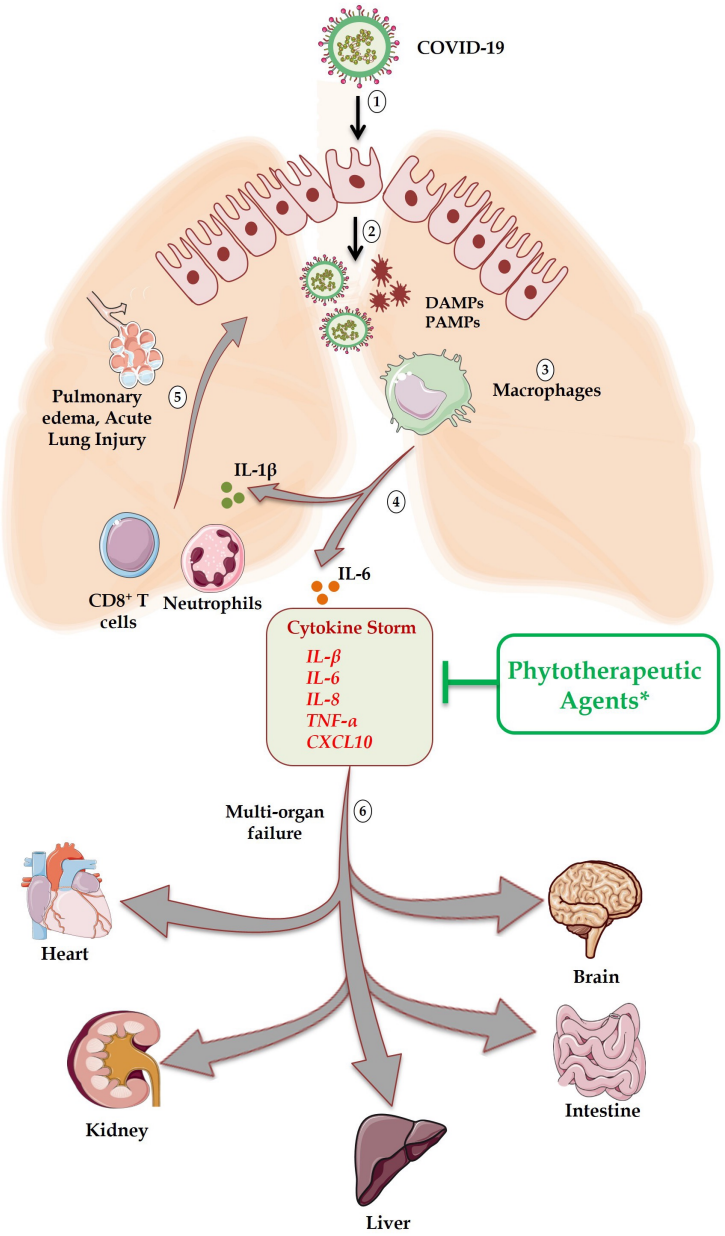


Ensovibep binds spike protein at 3 sites

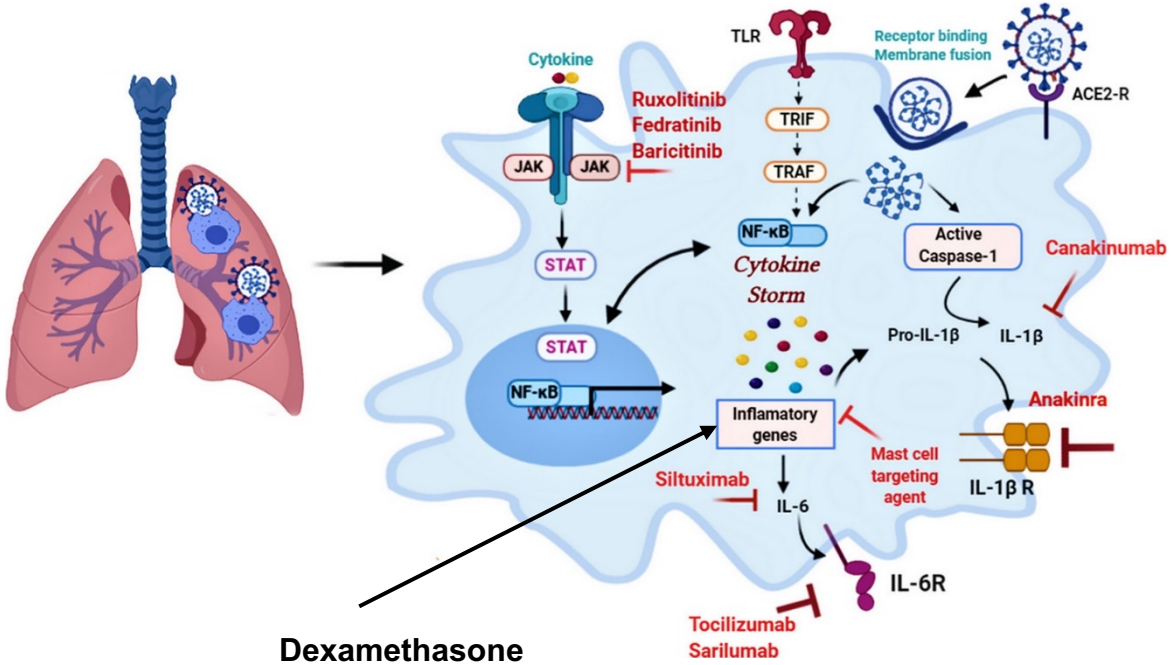


The Pharmaceutical Journal, PJ, October 2021, Vol 307, No 7954;307(7954)::DOI:10.1211/PJ.2021.1.111364

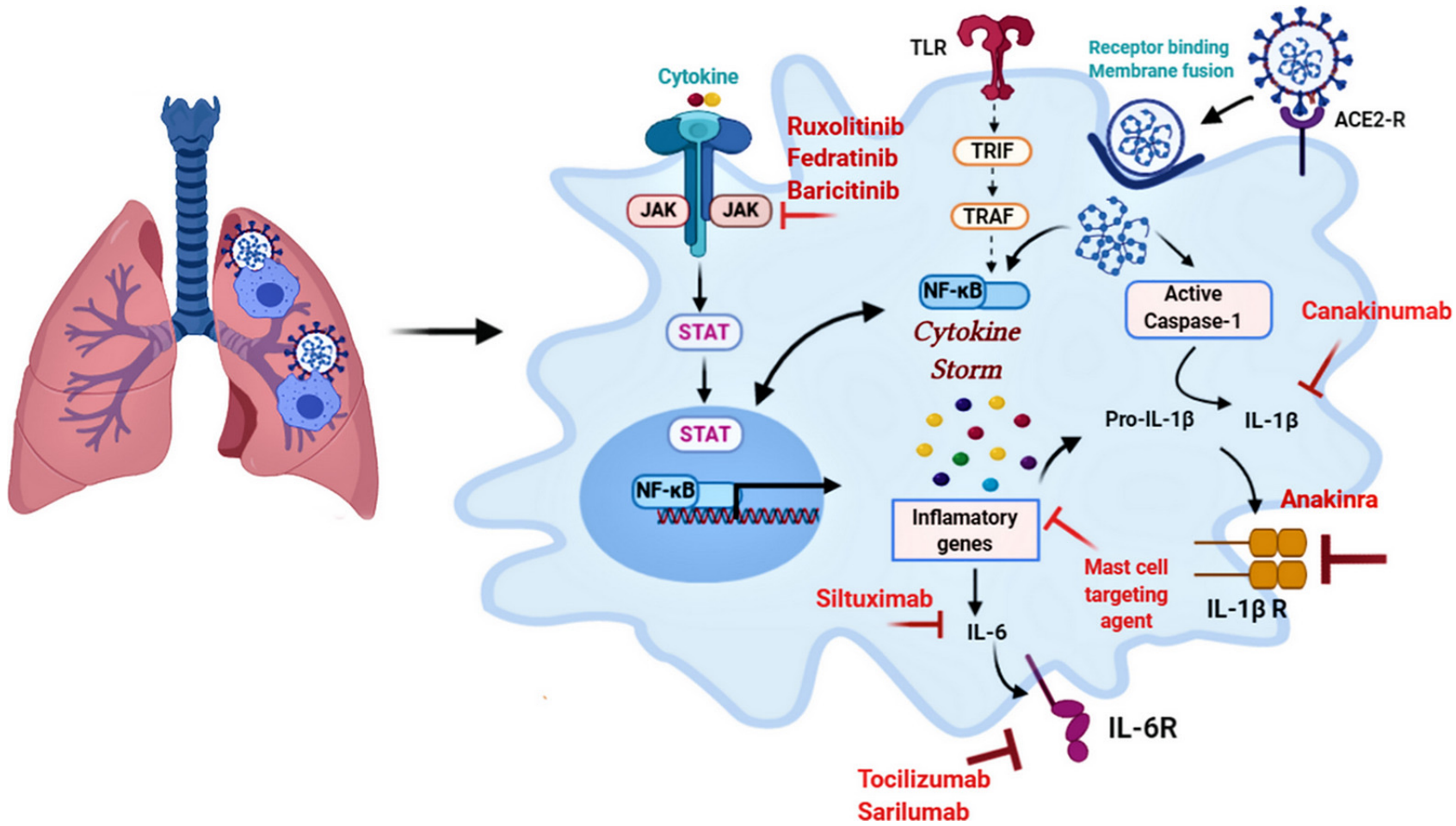
Much of damage by COVID is the body reaction in the form of cytokine storm



Drug approaches to controlling cytokine storm



Dexamethasone reduces transcription of inflammatory genes that can also have a detrimental effect on viral clearance by T-cells.


Cytokine
TLR
Receptor binding
Membrane fusion
ACE2-R
Ruxolitinib
Fedratinib
Baricitinib
JAK
JAK
TRIF
TRAF
NF-κB
Active
Caspase-1
Canakinumab
STAT
Cytokine
Storm
STAT
NF-κB
Pro-IL-1β
IL-1β
Anakinra
Inflamatory
genes
Mast cell
targeting
agent
IL-1β R
Siltuximab
IL-6
IL-6R
Tocilizumab
Sarilumab

Update on masks

Because Omicron spreads so much more easily cloth masks are not effective

The recommended masks are N95 or KN95

REASONS FOR GETTING A VACCINE

Getting vaccinated is both common sense and a civic responsibility

PERSONAL

- To avoid getting sick,
- To avoid being hospitalized
- To avoid ending up in Intensive Care, intubated.
- To avoid dying
- To avoid the disabling, long-COVID syndrome
- If you are pregnant, to protect the mother from severe, possibly fatal disease and to protect the baby, which could be lost

COMMUNITY

- To spare overworked and stressed nurses and medical staff the burden of your care
- To limit your ability to spread a deadly infection to vulnerable people
- To protect your community
- To protect your family
- To protect your workplace
- To help control and limit this deadly pandemic.

WHAT A VACCINE DOES NOT DO

Some myths debunked, and some solid science.

- **No, there is no chip. (Why would anyone want to do this since you already have a cellphone???)**
- **No, it cannot magnetize you. You are not made of metal.**
- **No, it has no effect on fertility for men or women. Infection may.**
- **No, It does not lead to so called 'enhancement'. This is a rare phenomenon only so far associated with dengue virus, and not with any respiratory virus.es, and only occurring in children.**
- **No, it cannot possibly cause COVID disease itself because it only contains a part of the virus, and not the internal mechanisms the virus uses to replicate itself.**
- **SARS type coronavirus pandemics depend on human behavior, not seasons.**
- **It does not induce 'enhancement' of other infectious diseases.**

SO DO WE HAVE TO LEARN TO LIVE WITH CORONAVIRUSES?

Probably Yes

WHAT DOES THIS MEAN?

- We **ALL** need to be vaccinated.
- Boosters or updated vaccines may become routine
- mRNA or protein vaccines with modified structures may be optimal
- For now, masks need to be universal in crowded and poorly ventilated places.
- Constant monitoring for new variants with flexible rapid responses.
- This is a global condition so:

WE NEED LOW COST, STABLE VACCINES FOR THE ENTIRE WORLD AND WORK TO PREVENT THE CONDITIONS THAT FACILITATE THE EMERGENCE OF NEW VARIANTS.