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THE AGE OF PANDEMICS: FIRST COVID NOW MONKEYPOX

- JOSEPH B. MCCORMICK, MD
- SUSAN P. FISHER-HOCH, MD
- **Professors of Epidemiology**
- **UTHealth School of Public Health, Brownsville Campus**
- **Adjunct Professors of Medicine, McGovern School of Medicine**

Pandemics (plagues) have been recorded over at least 5 millenniae

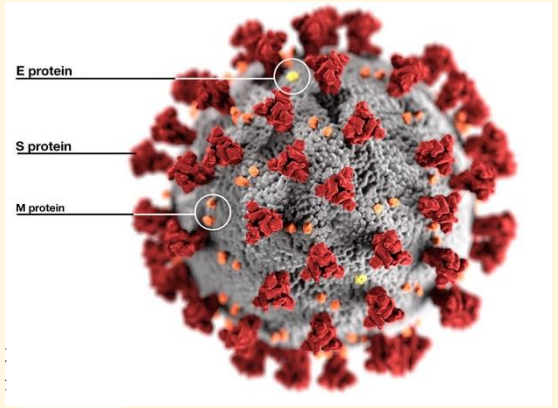
Mass grave: China, 3000 BC

Just in case you thought COVID was somethings new.....
Common underlying features are crowding and increased transport

	Dates	Deaths	Cause
Prehistoric epidemics	c3000 BC	?	?
Plague of Athens	430 BC	100,000	?
Antonine Plague	165-180	>5 million	?smallpox
Plague of Cyprian	250-271	?	?
Plague of Justinian	541-542	10% of global population	Bubonic plague
The Black Death	1346-1353	Half of Europe's population	Pneumonic plague
Cocoliztli epidemic	1545-1548	15 million	Salmonella paratyphi C
American plagues	16th century	Decimated Inca and Aztecs	Several including smallpox
Great Plague of London	1665-1666	>100,000	Pneumonic plague
Great Plague of Marseille	1720-1723	30% of population	Plague
Russian Plague	1770-1772	>100,000	Plague
Philadelphia Yellow Fever	1793	>5,000	Yellow fever
Flu Pandemic	1889-1890	> 1 million	Influenza
American Polio Epidemic	1916	6000	Polio
Spanish Flu	1918-1920	500 million	Influenza
AIDS	1980s on	35 million	HIV
COVID-19	2019-??	>6 million & counting	Coronavirus

COVID IS A CoORONOAVIRUS

The virus is named
Severe Acute Respiratory Syndrome
Coronavirus-2
SARS-CoV-2



The disease is named
Coronavirus Infectious Disease 2019
COVID-19

There are millions, billions or more likely trillions of viruses everywhere in nature including many unknown coronaviruses

BASIC CORONAVIRUS FACTS

- **There are at least 36 known animal coronaviruses**

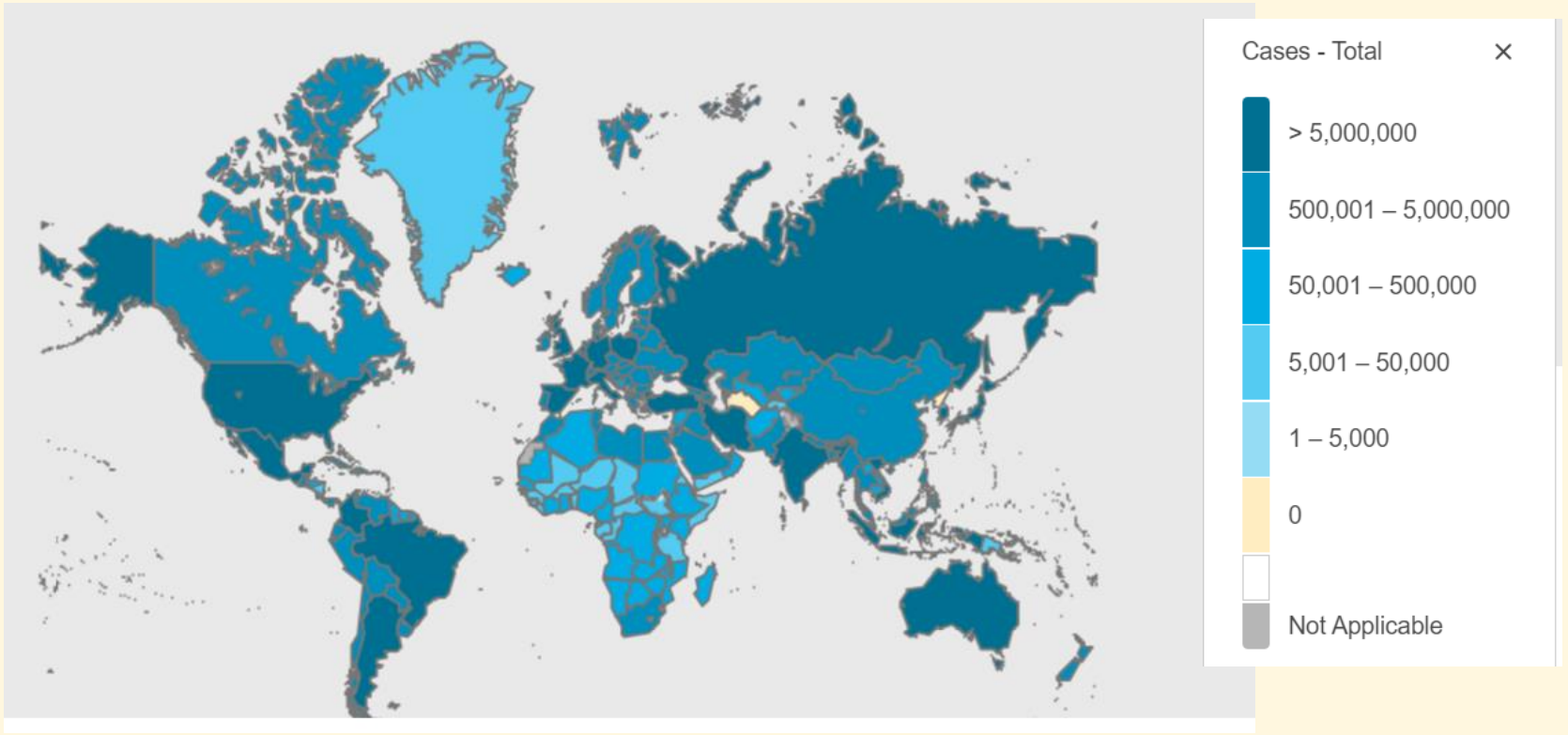
- **There are 4 human coronaviruses**
  - **They cause 1/3 of all common colds,**
  - **They are winter viruses**
  - **IMMUNITY LASTS LESS THAN A YEAR**

WHO data. Worldwide reports as of August 2022

391,177
new cases in last 24hrs

587,396,589
cumulative cases

6,428,661
cumulative deaths



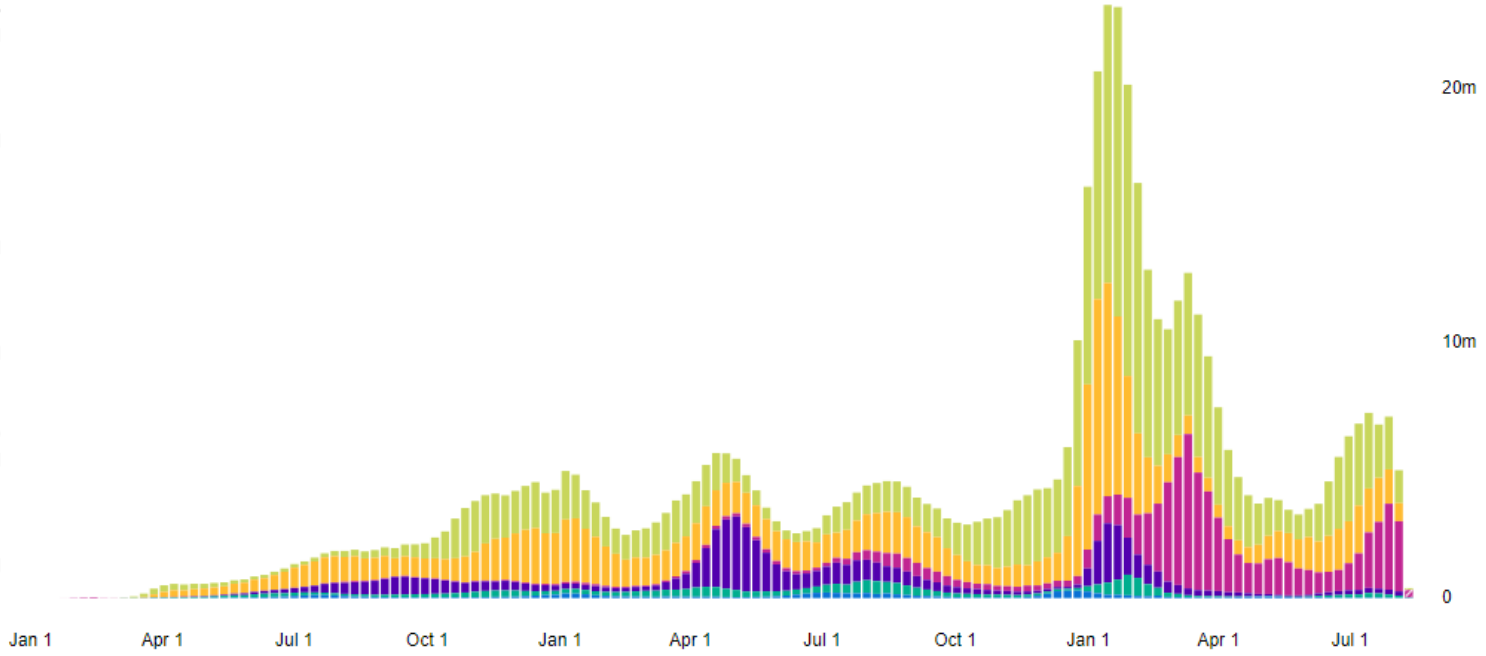
https://covid19.who.int/

These are underestimates of the true situation

Situation by WHO Region

Daily | Weekly | Cases | Deaths | Count

Europe	244,590,524 confirmed
Americas	172,847,252 confirmed
Western Pacific	78,124,789 confirmed
South-East Asia	59,726,002 confirmed
Eastern Mediterranean	22,854,766 confirmed
Africa	9,252,492 confirmed

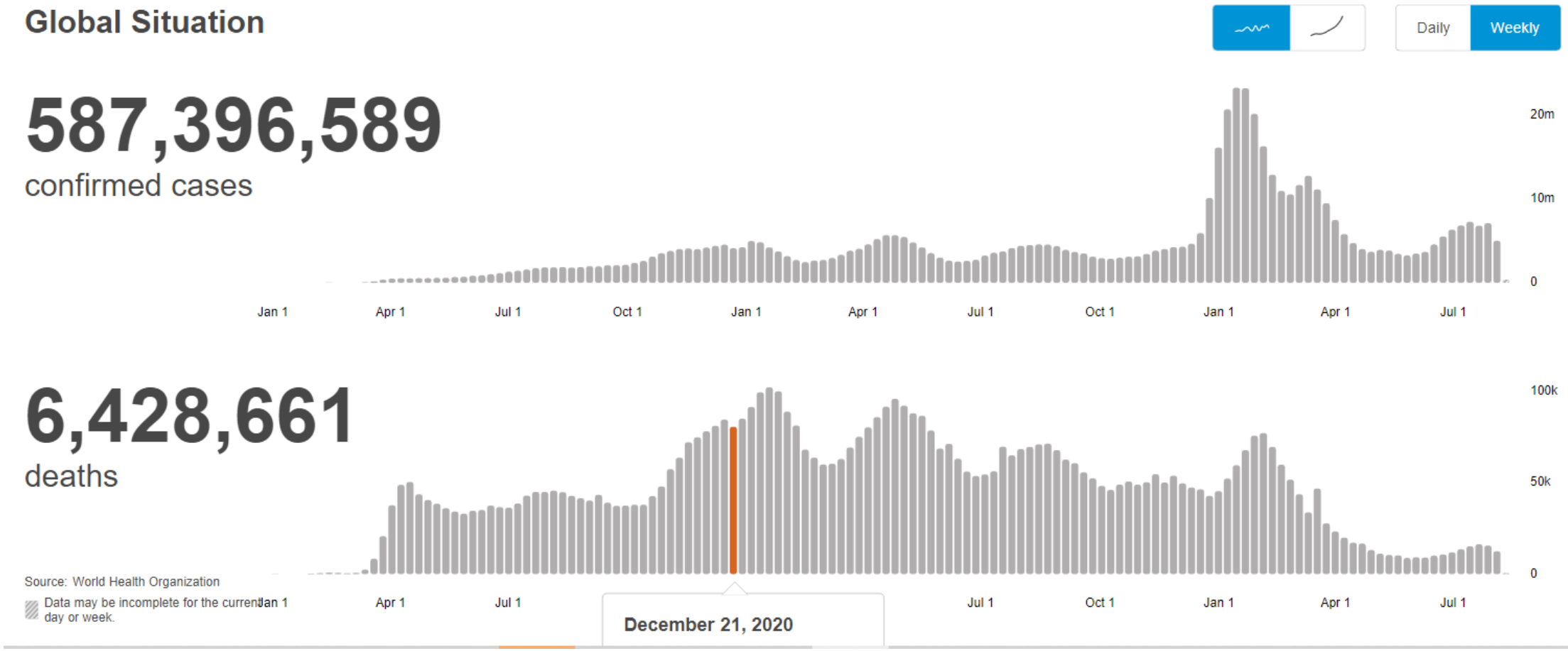


Source: World Health Organization

Data may be incomplete for the current day or week.

The differences may result from underreporting artefacts.

WHO Coronavirus (COVID-19) Dashboard



These are underestimates of the true situation

VARIANT EPIDEMIOLOGY

What viral factors lead to new variants?

- **Very high rate of infection which means billions and trillions of new virus replication events**
- **On person has 10^9 to 10^{11} RNA copies and 10^5-10^7 virus particles at peak infection***
- **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**

***10^9=10 billion to 10^{11} =100 billion RNA copies. 10^5 to10^7 infectious virus particles**
PNAS June 3, 2021 118 (25) e2024815118 https://doi.org/10.1073/pnas.2024815118

THIS IS EVOLUTION FAST FORWARD

VARIANT EPIDEMIOLOGY

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

VARIANTS AND MOLECULAR VIROLOGY

The variants!!!

We are over halfway down the Greek alphabet

Variants of concern (VOC)

Variants of interest (VOI)

OMICRON IS A NEW LINEAGE

The new omicron subvariants such as the BA.5 series have not been given Greek Alphabet names.

It is now clear that omicron variants are less virulent and that long COVID symptoms are less frequent.

However, the omicron series are increasingly more transmissible.

VARIANTS AND MOLECULAR VIROLOGY

A look at the spike

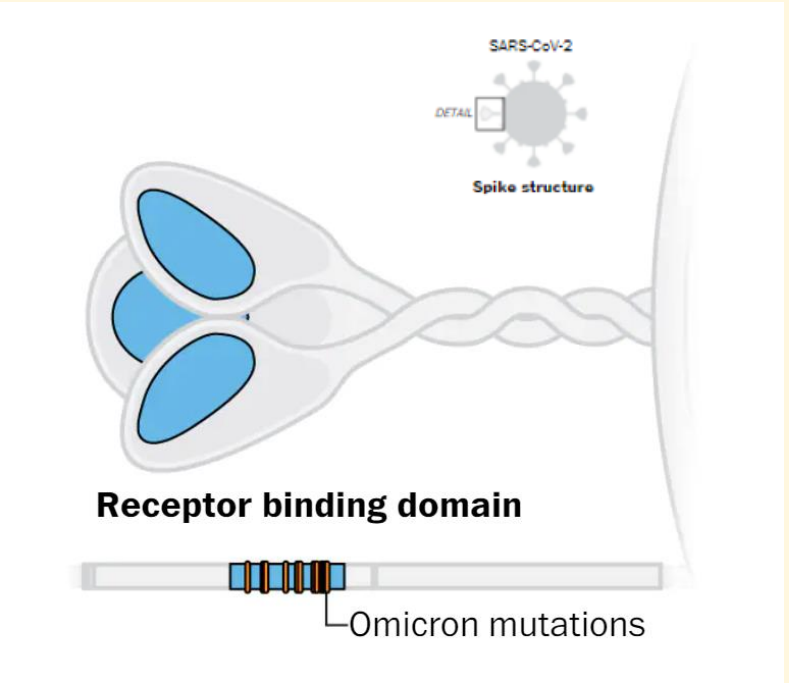
Every spike on a coronavirus's surface is made of three identical proteins twisted together, making it look a little like a head of broccoli with three stalks.

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/

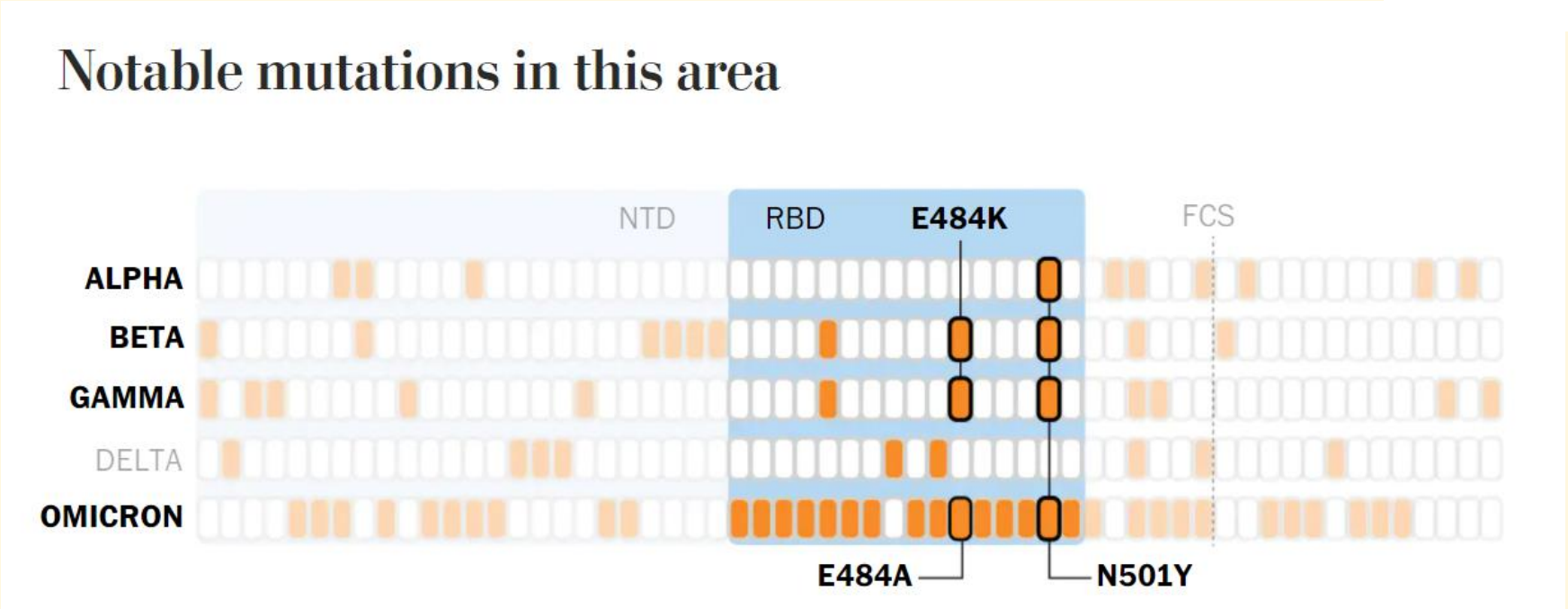
VARIANTS AND MOLECULAR VIROLOGY

Time to take a closer look at the famous spike



TRANSMISSIBILITY

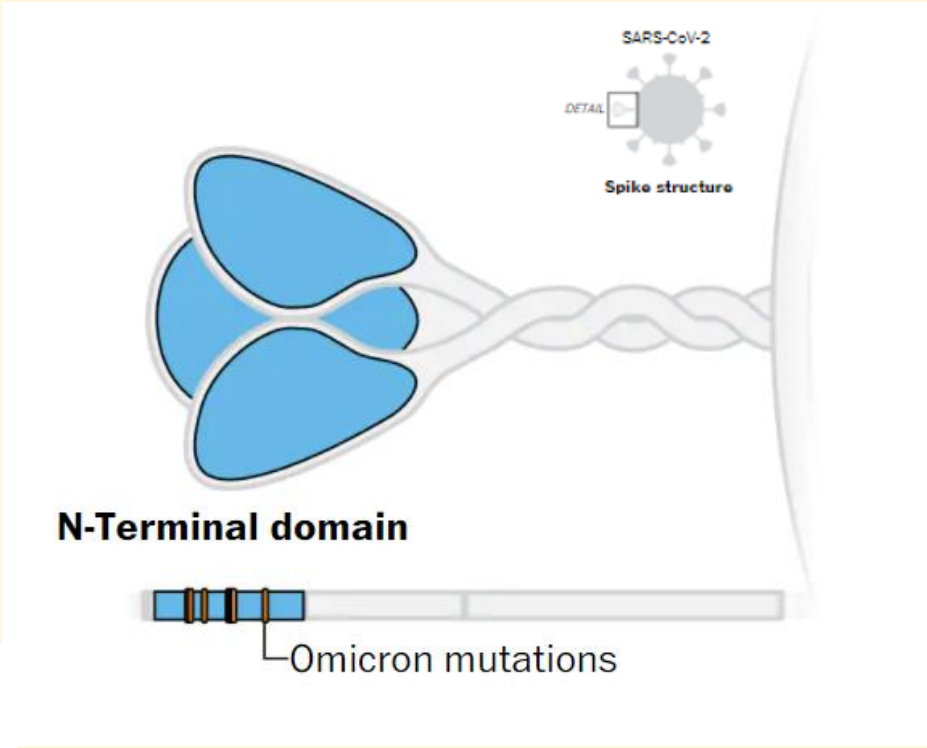
The receptor binding site acts like a key to open the cell to the virus

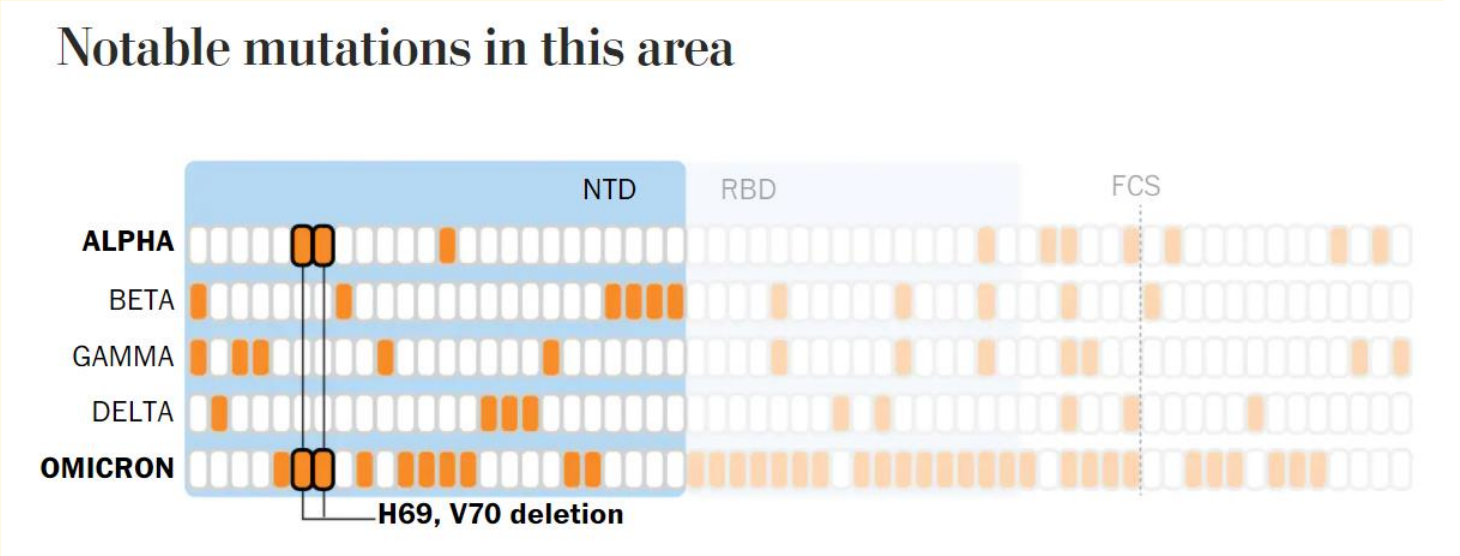


IMMUNITY

The N-terminal domain which is recognized by the immune system.\, Changes in this region are responsible for evasion of the monoclonal antibodies.

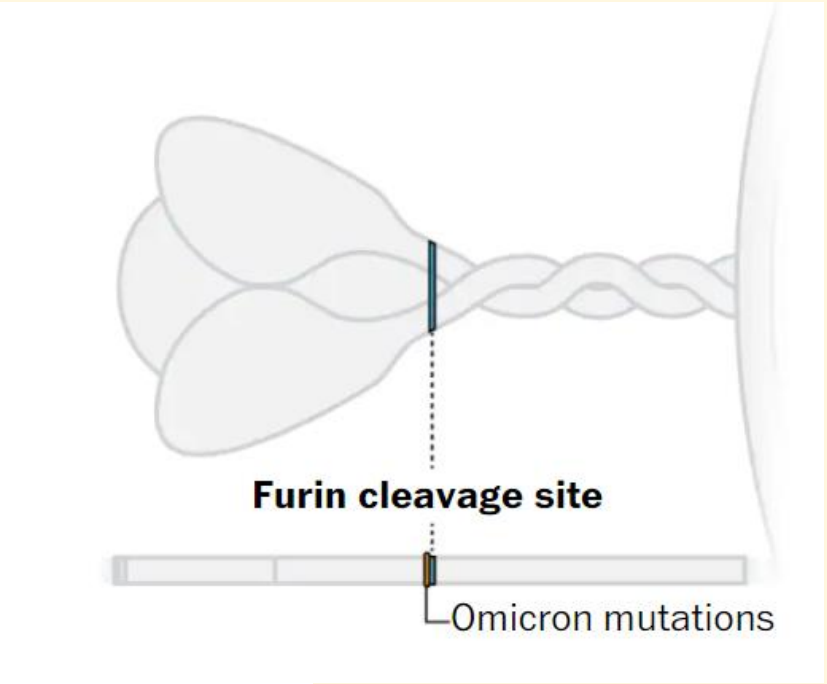
This is the site where the BA.5 series subvariants areevading neutralizing antibody resulting in reinfections





SEVERE ILLNESS

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



SURVEILLANCE

CAVEAT

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

Poor and remote communities are not tested

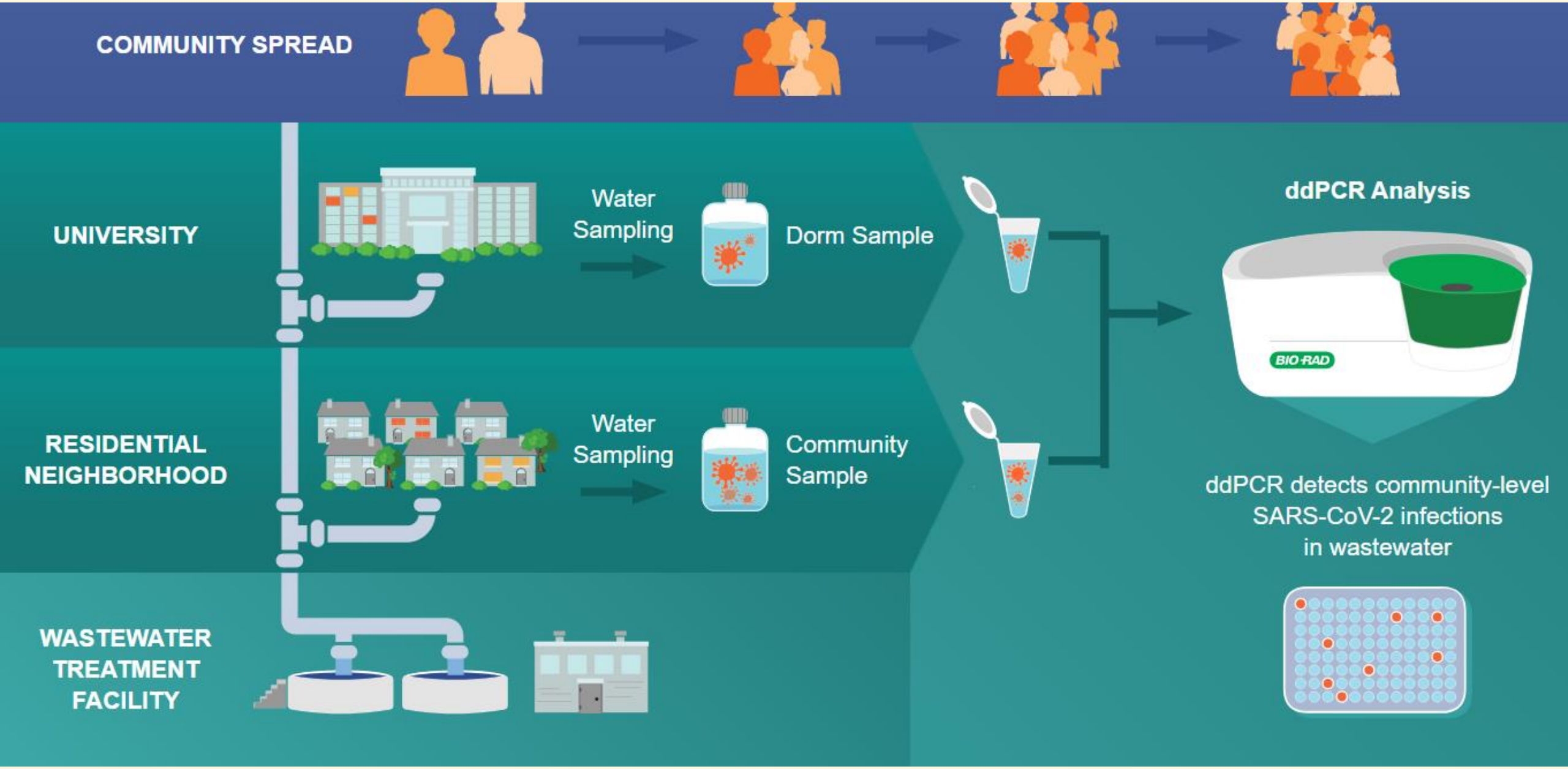
People do not come forward for testing

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 most powerful tool for surveillance is now wastewater testing



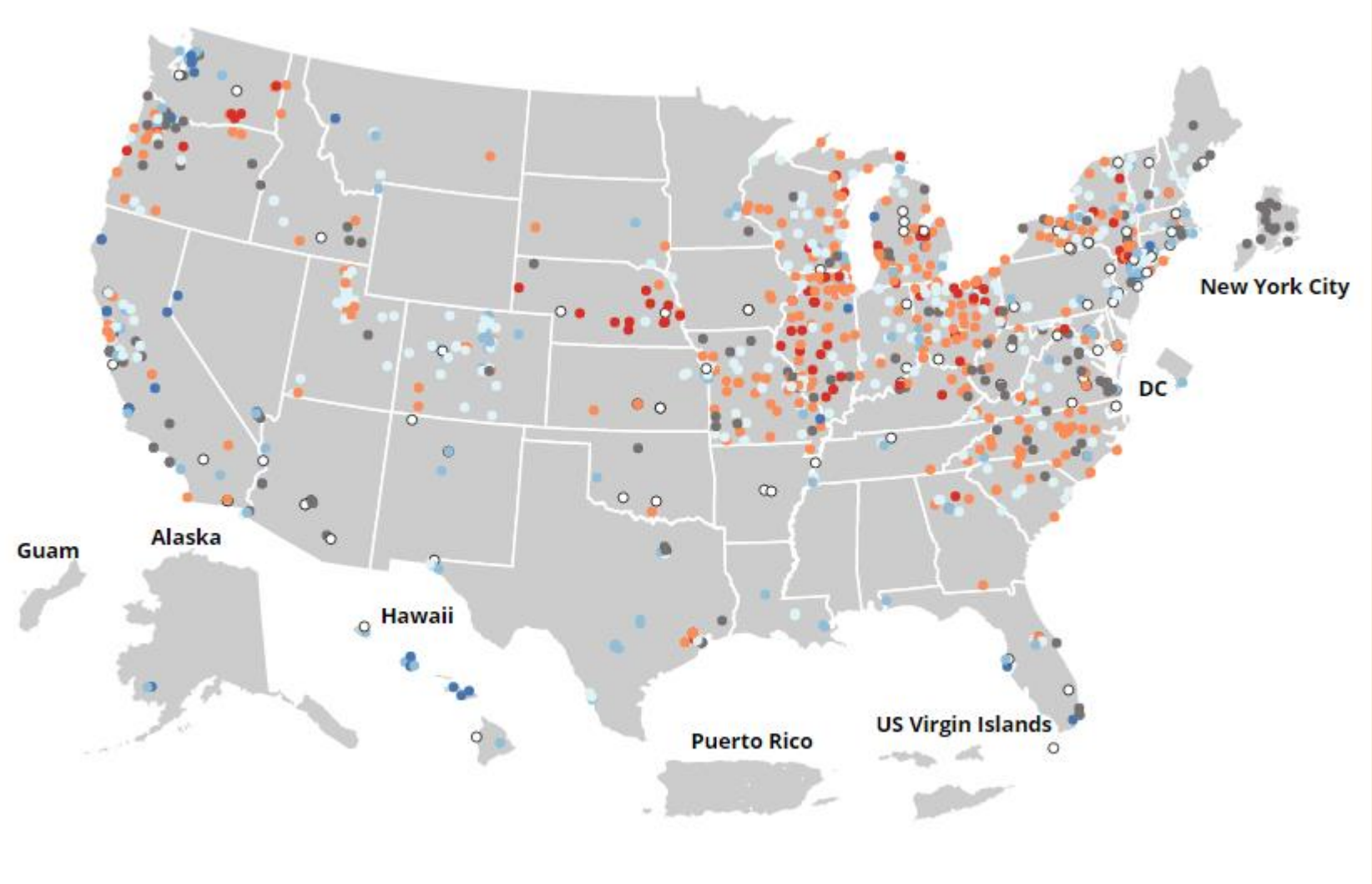
SURVEILLANCE

WASTEWATER SURVEILLANCE PROGRAMS

- **Wastewater contains the genetic material from viruses and bacteria which can be captured by PCR.**
- **A recent study from New York has shown the utility of this system**
- **September 2020: CDC launched the National Wastewater Surveillance System (NWSS) in response to the COVID-19 pandemic.**
- **People infected with SARS-CoV-2 shed virus in feces even without symptoms.**
- **Wastewater enables capture of early warning of spread in the community.**
- **NWSS works with health department to track SARS-CoV-2 levels in wastewater so communities can proactively mitigate the spread of COVID-19**
- **This will transform independent local efforts into a robust, sustainable national surveillance system.**

SURVEILLANCE

The CDC Wastewater Surveillance System collaborating sites



Study: New Wastewater Surveillance Method Detected SARS-CoV-2 Variants of Concern Up to 2 Weeks Before Clinical Tests

JAMA. Published online August 24, 2022. doi:10.1001/jama.2022.12563

UCSD campus and larger San Diego, from November 2020

The new approach detected:

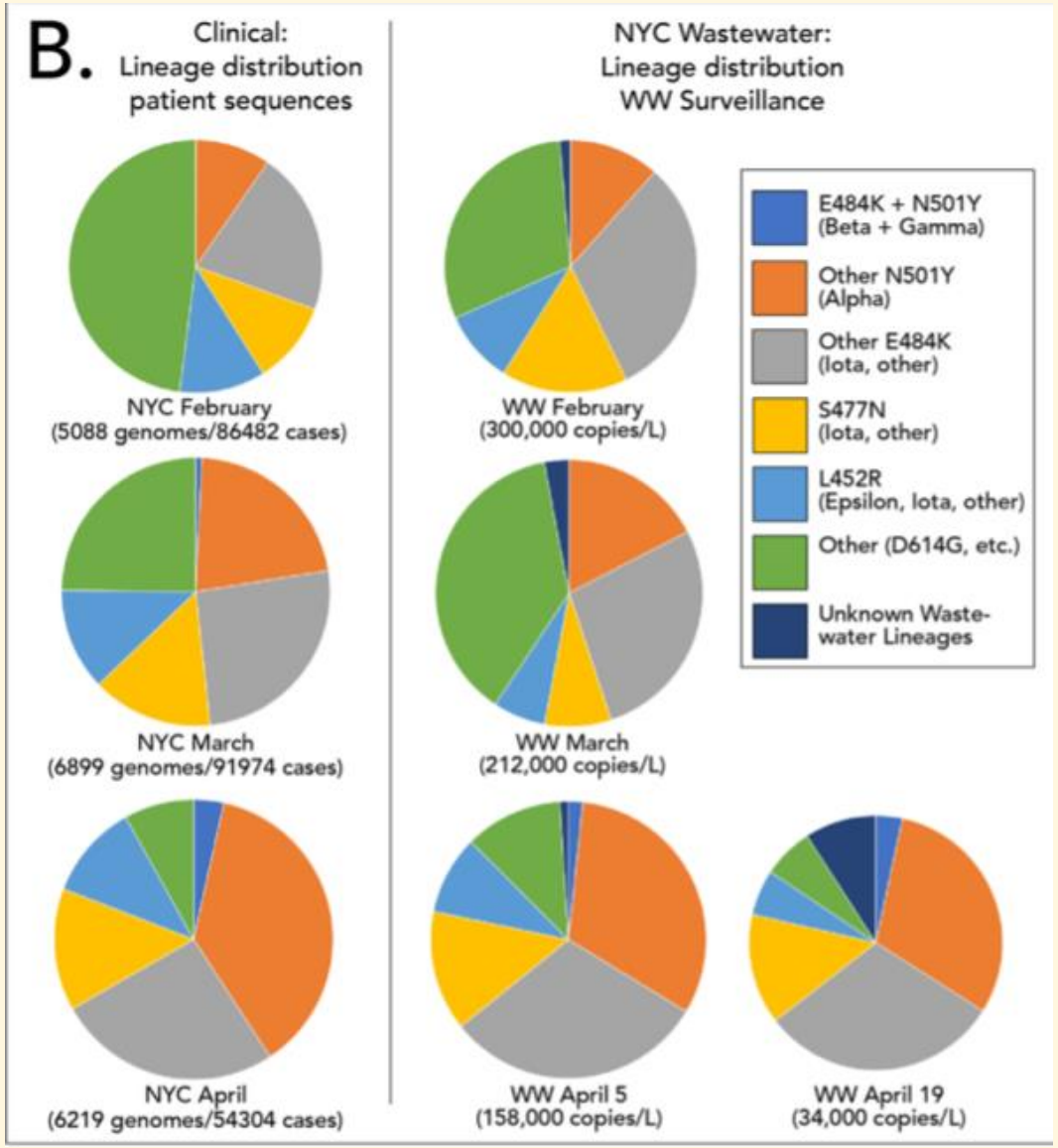
- The Alpha and Delta variants 2 weeks before nasal swab tests confirmed their presence in San Diego
- The Omicron variant 10 days before the county's first positive clinical test
- When BA.1 Omicron variant infections overtook Delta infections in late 2021
- SARS-CoV-2 transmission that was missed by clinical genomic surveillance

WASTEWATER SURVEILLANCE

Coronavirus variants detected in clinical and wastewater samples in New York. Some variants are not found in clinical samples, suggesting animal reservoir. Shown in figure.

The New York WW program also detected a polio virus sequence identical to the active polio case which was thought to be a type 2 vaccine derived reversion mutation to wild type polio causing a paralytic case, probably in an imported OPV recipient.

The WW system can now detect monkeypox virus.



COVID-19 LONG HAUL SYNDROME

- **A wide range of symptoms and signs seen after infections with SARS-Co-V-2 infection**
- **Poorly understood**
- **As a result, treatment is symptomatic and supportive.**
- **We need a lot more data**

Common signs and symptoms

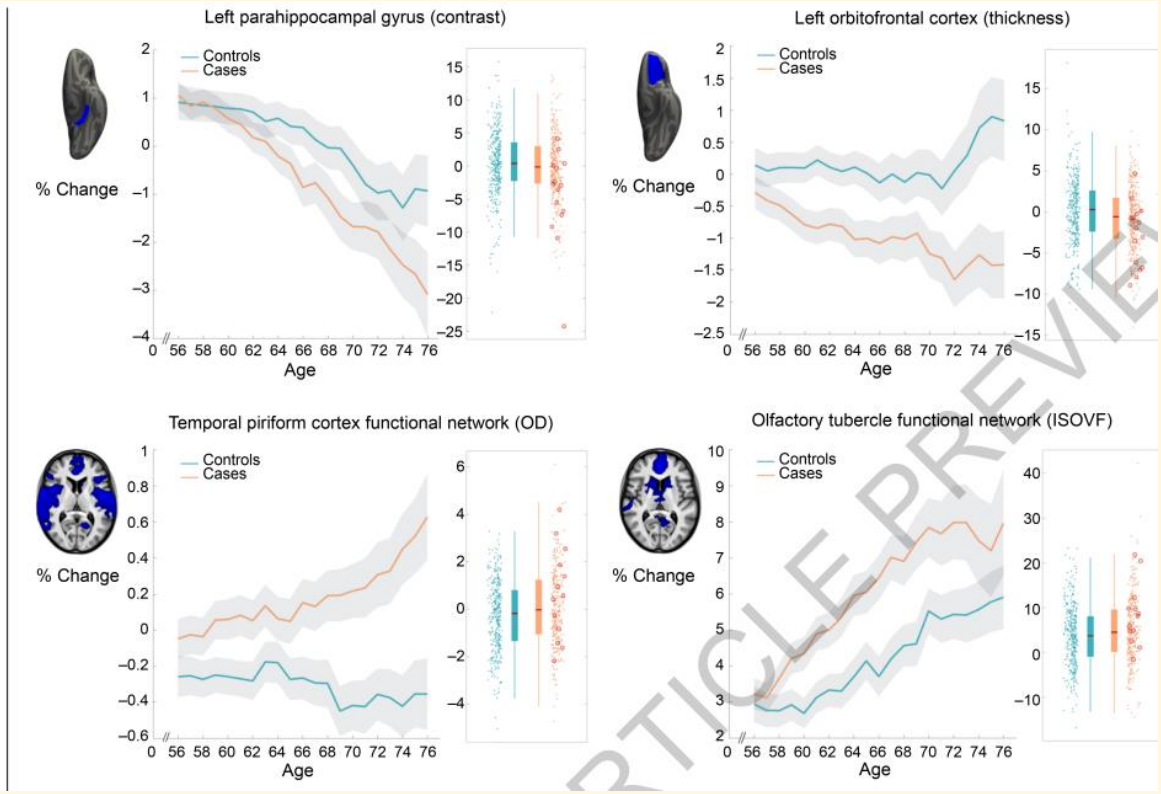
- **Fatigue**
- **Shortness of breath/cough/chest pain**
- **Joint/muscle pain**
- **Memory, concentration/sleeping problems**
- **Headache**
- **Loss of smell/taste**
- **Depression/anxiety**
- **Fever**
- **Dizziness**
- **Racing heartbeat**
- **Worsening after physical of mental effort**

Systems that can be involved

- **Heart**
  - **Heart failure**
  - **Other complications**
- **Lungs**
  - **Damage to alveoli**
  - **Scar tissue**
- **Brain**
  - **Strokes**
  - **Seizures**
  - **Guillain-Barre syndrome**
  - **Parkinson's & Alzheimer's**
- **Multi-inflammatory condition in children**
  - **Heart attacks**
  - **Strokes**
  - **Damage to liver and kidneys**
- **Blood clots**
- **Gastrointestinal**
- **Fatigue**
- **?Other effects**

COVID-19 LONG HAUL SYNDROME

SARS-CoV-2 is associated with changes in brain structure in UK Biobank



METHODS

- **401 cases infected with SARS-CoV2 between March 2020 and April 2021.**
- **Only 4% hospitalized.**
- **384 matched controls who had not been infected with SARS-CoV-2**

FINDINGS

- **Loss of gray matter thickness and tissue damaged in areas associated with the sense of smell**
- **Whole-brain vol. decrease**
- **Decline in ability to perform complex tasks**

TAKE AWAY

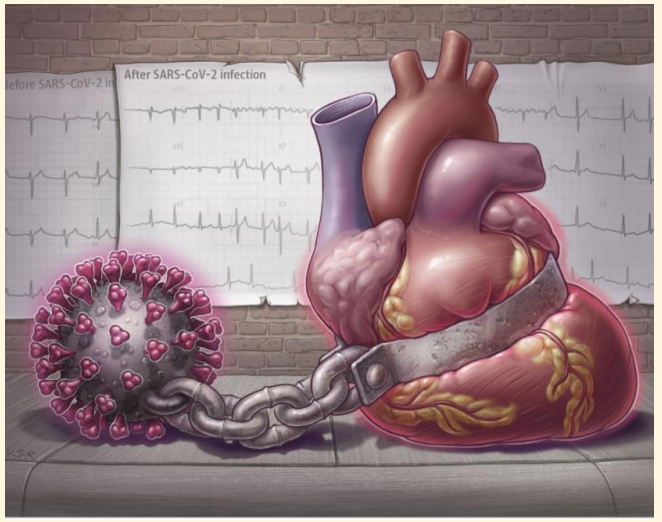
- **Marked changes associated with olfactory pathway**
- **Changes increase with age**
- **Not known if reversible**
- **Cognition is also affected**
- **Study needs to be replicated**

nature
https://doi.org/10.1038/s41586-022-04569-5

COVID-19 Long Haul Syndrome

The COVID Heart—One Year After SARS-CoV-2 Infection, Patients Have an Array of Increased Cardiovascular Risks

JAMA. Published online March 2, 2022. doi:10.1001/jama.2022.2411



• All CVD outcomes	45.3/1000
• Major adverse events (MI, stroke, mortality)	23.5/1000
• Abnormal heart rhythms (dysrhythmias)	19.9/1000
• atrial fibrillation	10.7/1000
• Inflammation (non-ischemic cardiomyopathy)	3.6/1000
• Thrombotic disorders	9.9/1000
• Strokes	4.1/1000
• Deep vein thrombosis/pulmonary embolism	10.0/1000
• Heart failure	9.9/1000

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 USA and EU for 18 and above, Indonesia and Philippines. Stored 6 months at 4^{o}C. These and similar low-cost, temperature stable vaccines need to be widely available in developing countries.

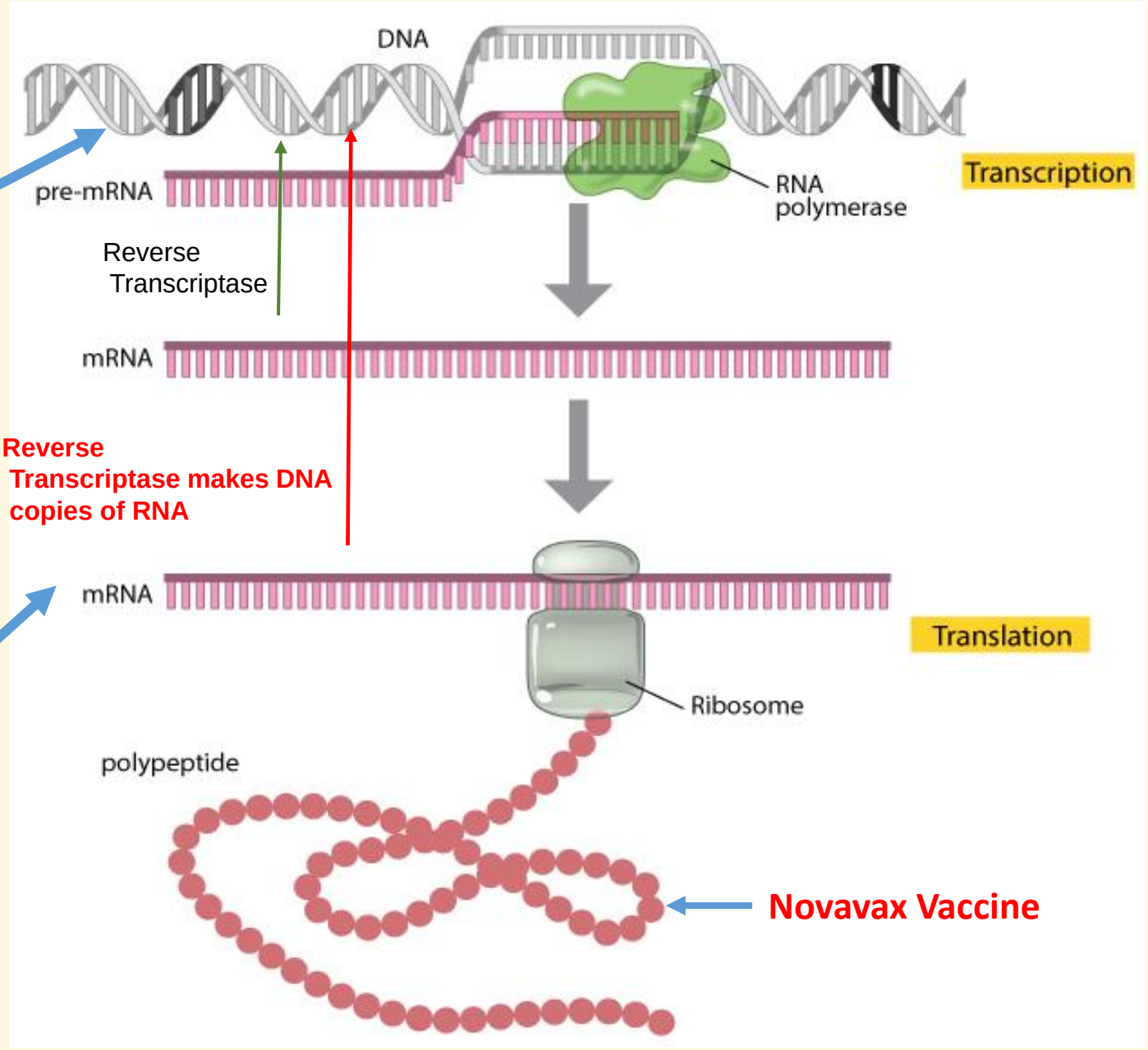
VACCINES

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

J&J Vaccine DNA in adenovirus

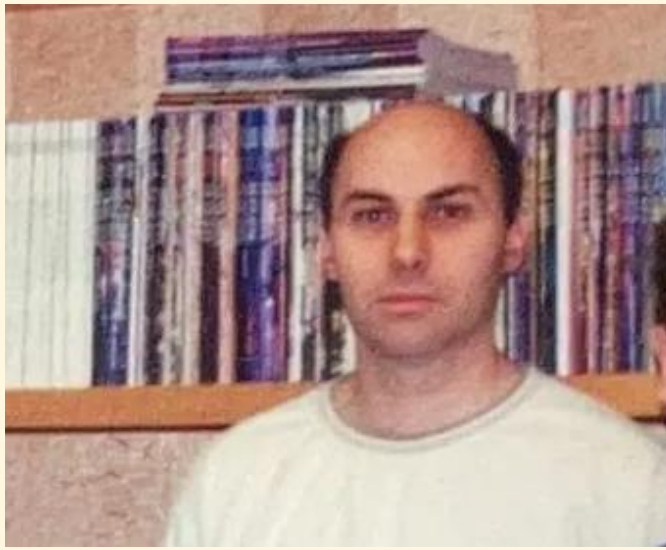
Positive Strand RNA viruses: SARS-CoV-2, Dengue, west Nile, Zika, rhinoviruses, rubella

Moderna and Pfizer vaccines

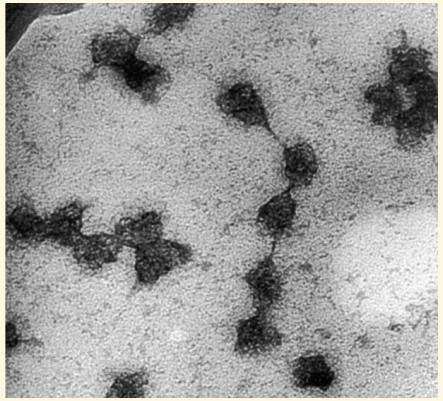


VACCINES

mRNA history



Dr. Katalin Karikó
and Dr. Drew Weissmann



Electron microscopy image of mRNA in a cell

1998 Penn State department of Medicine

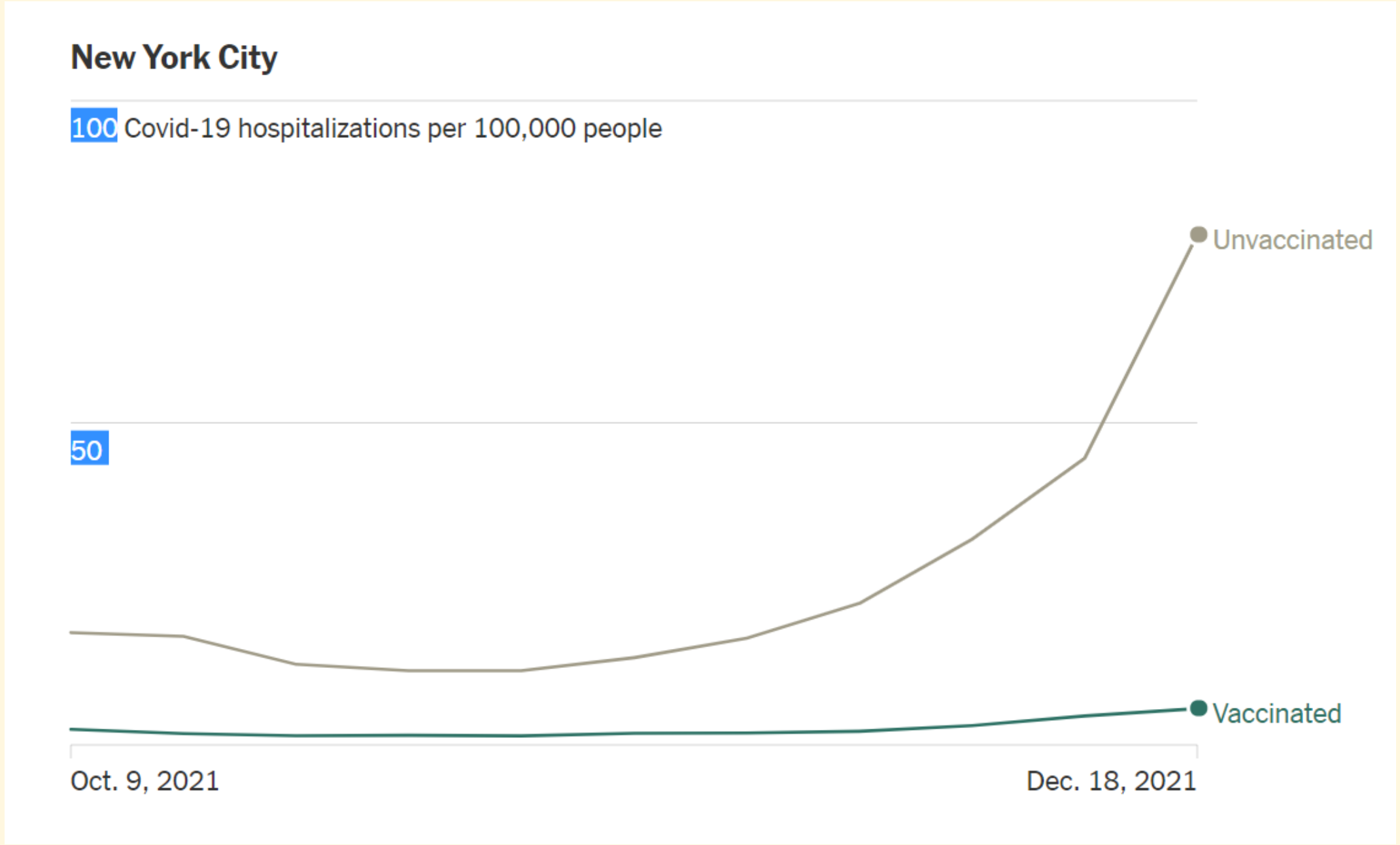
Dr. Karikó was focused on and MRNA believed that it could coerce a cell into producing any kind of protein but unfunded and marginalized.

Dr Weissmann was physician and virologist collaborator.

Together they worked out that natural mRNA, normally toxic and destroyed by cells, was protected with a particular molecule.

THIS WAS THE BREAKTHROUGH THAT PRODUCED INJECTABLE mRNA

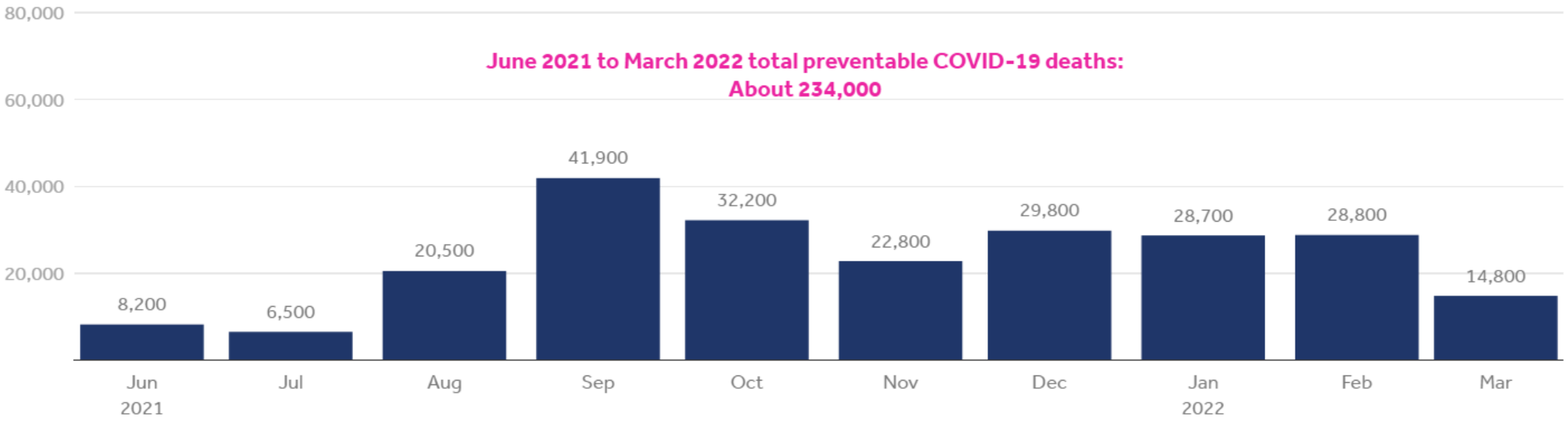
VACCINES


New York City
100 Covid-19 hospitalizations per 100,000 people
Unvaccinated
50
Vaccinated
Oct. 9, 2021
Dec. 18, 2021

VACCINES

About 234,000 COVID-19 deaths since June 2021 could have been prevented with vaccinations

COVID-19 deaths among unvaccinated adults that likely could have been prevented with primary series vaccinations, June 2021-March 2022



Note: See brief for detailed assumptions and methods.

Source: KFF analysis of CDC and KFF COVID-19 tracker data • Get the data • PNG

Peterson-KFF Health System Tracker

INSIDER

Rebecca Cohen Aug 11, 2022, 9:40 AM

- **Moderna's CEO compared a future COVID-19 vaccine to the iPhone, saying we will need a new one every year.**
- **Stéphane Bancel predicted a single-shot vaccine that protects against COVID-19 and flu strains.**
- **Pharmaceutical companies are attempting to keep up with emerging COVID-19 variants by updating their vaccines.**

VACCINES

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**
- **Complete evasion of antibody by Delta nor Omicron has not been demonstrated. However, the Omicron BA.5 series of subvariants partially evade protective neutralizing antibody.**

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

We need redesigned vaccines but keeping ahead of the virus will be a challenge.

TREATMENT

Selected treatments including antivirals and anti-inflammatory drugs

FDA approved

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

EUA approved or widely used

Evusheld (AZD7442) injectable 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

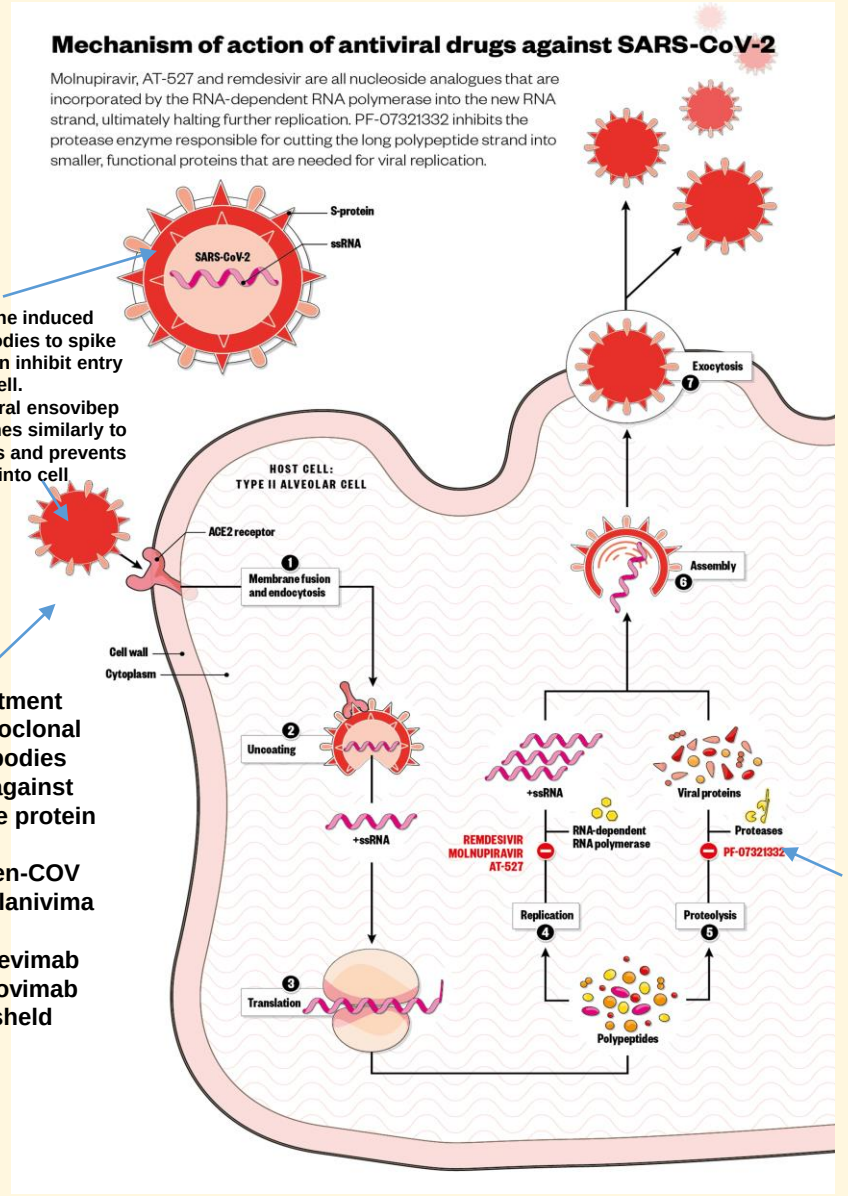
Ivermectin
Oleandrin
Lopinavir
Ritonavir
Hydroxychloroquine
Chloroquine
Azithromycin
Blood filtration

Fraudulent

Bleach injections or ingestion
Sliver
UV light

TREATMENT

Monoclonal antibodies



Vaccine induced antibodies to spike protein inhibit entry into cell.
Antiviral ensovibep attaches similarly to 3 sites and prevents entry into cell

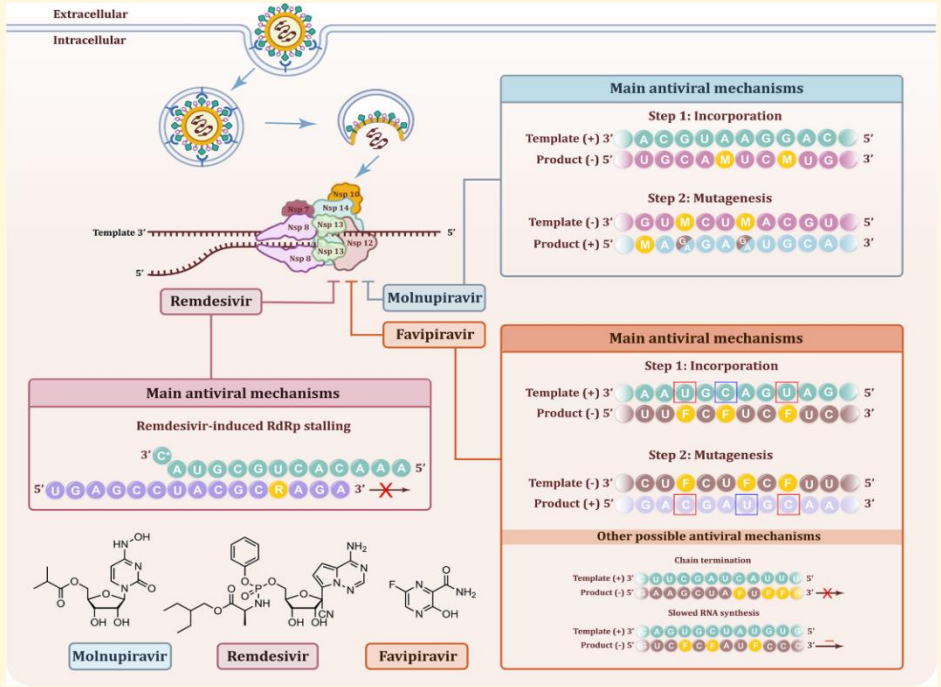
Treatment monoclonal antibodies are against spike protein

Regen-COV
Bamlanivimab &
Etesevimab
Sotrovimab
Evusheld

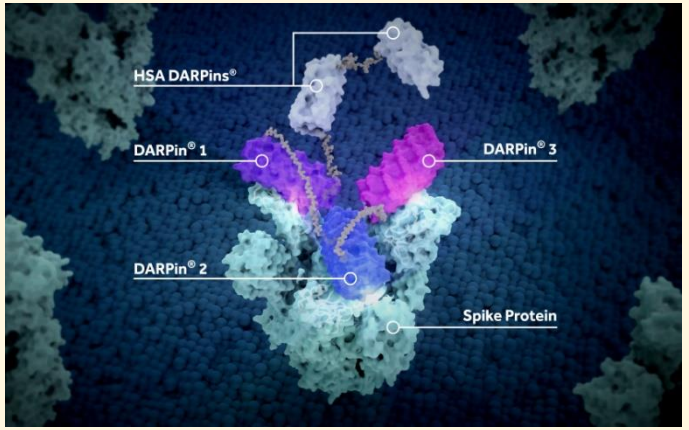
Paxlovid (PF-07321332) binds to 3C-like protease

Drugs

Nucleoside analogues interfere with polymerase function or induce fatal mutations



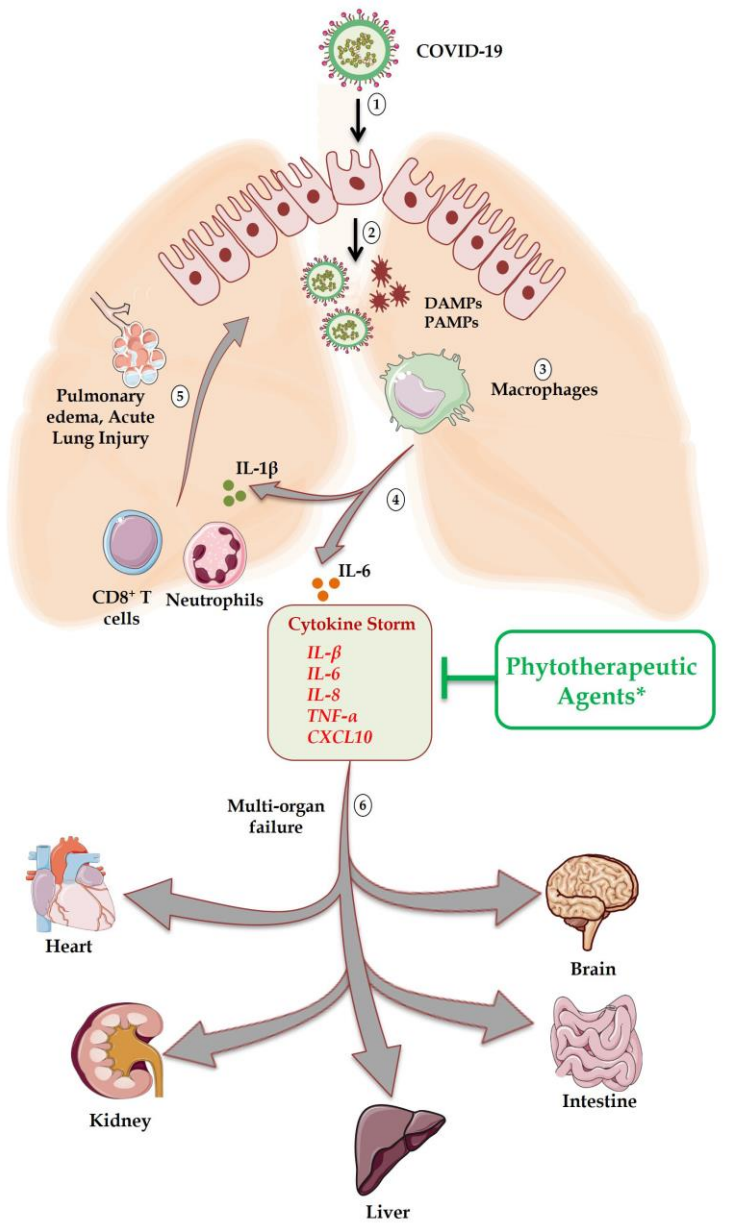
Ensovibep binds spike protein at 3 sites



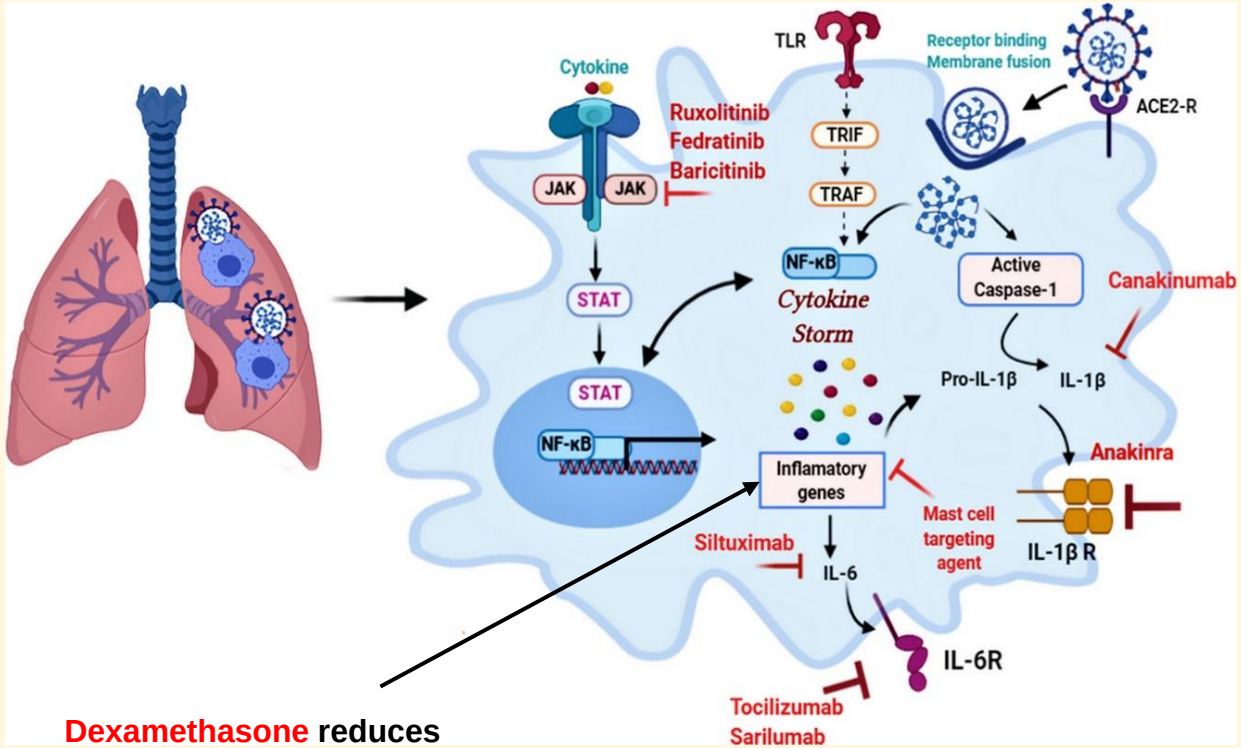
The Pharmaceutical Journal, PJ, October 2021, Vol 307, No 7954;307(7954)::DOI:10.1211/PJ.2021.1.111364

TREATMENT

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.

MITIGATION

Update on masks

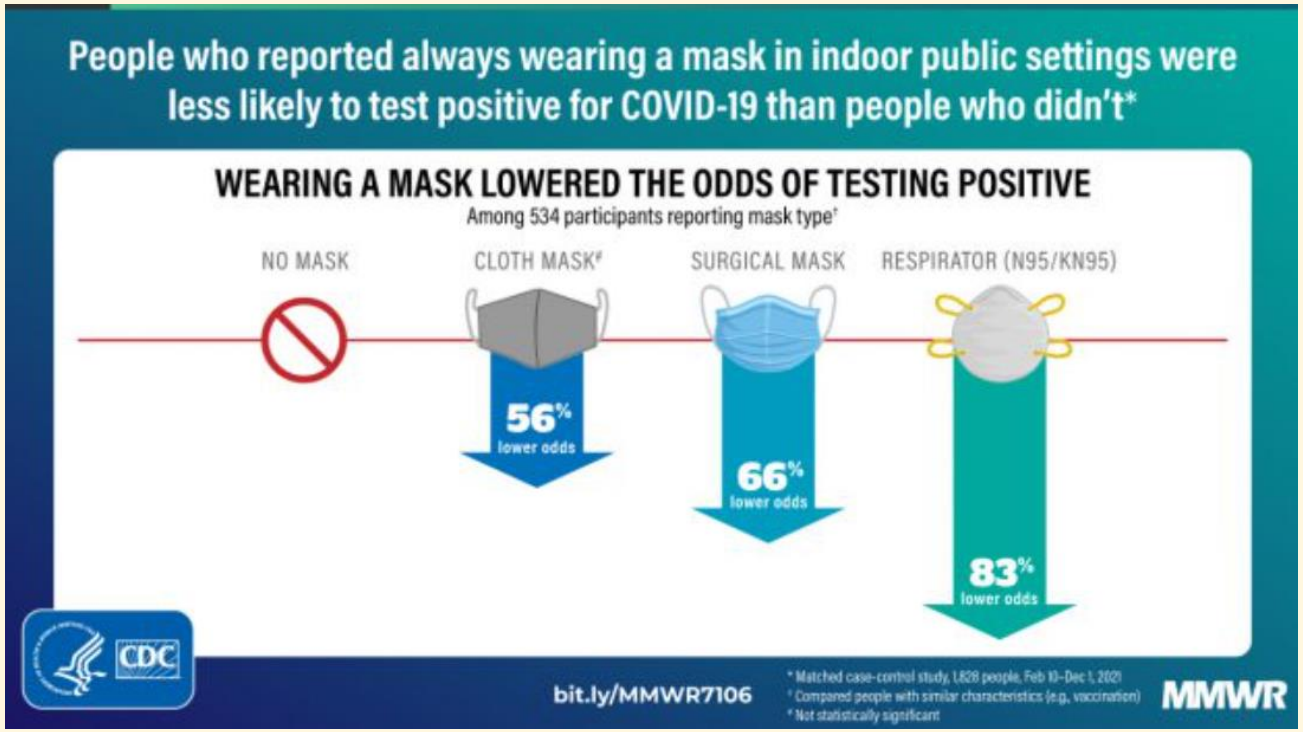
Because Omicron spreads so much more easily cloth masks are not effective

The recommended masks are N95 or KN95

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 71
February 4, 2022

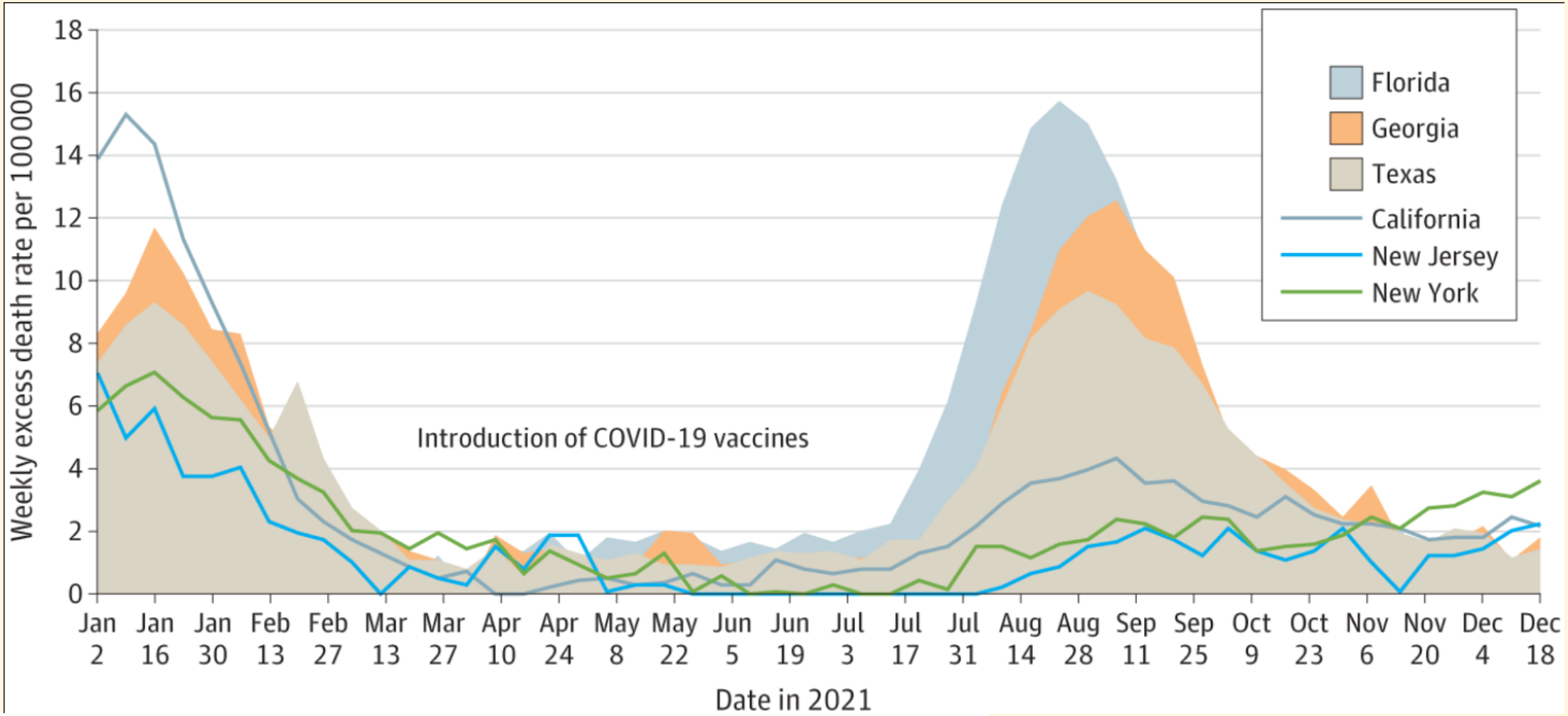
Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection — California, February–December 2021

Kristin L. Andrejko[1,2,*]; Jake M. Pry, PhD[2,*]; Jennifer F. Myers, MPH[2]; Nozomi Fukui[2]; Jennifer L. DeGuzman, MPH[2]; John Openshaw, MD[2]; James P. Watt, MD[2]; Joseph A. Lewnard, PhD[1,3,4]; Seema Jain, MD[2]; California COVID-19 Case-Control Study Team



MITIGATION

Weekly Excess Death Rate (per 100 000) in Selected States, 2021

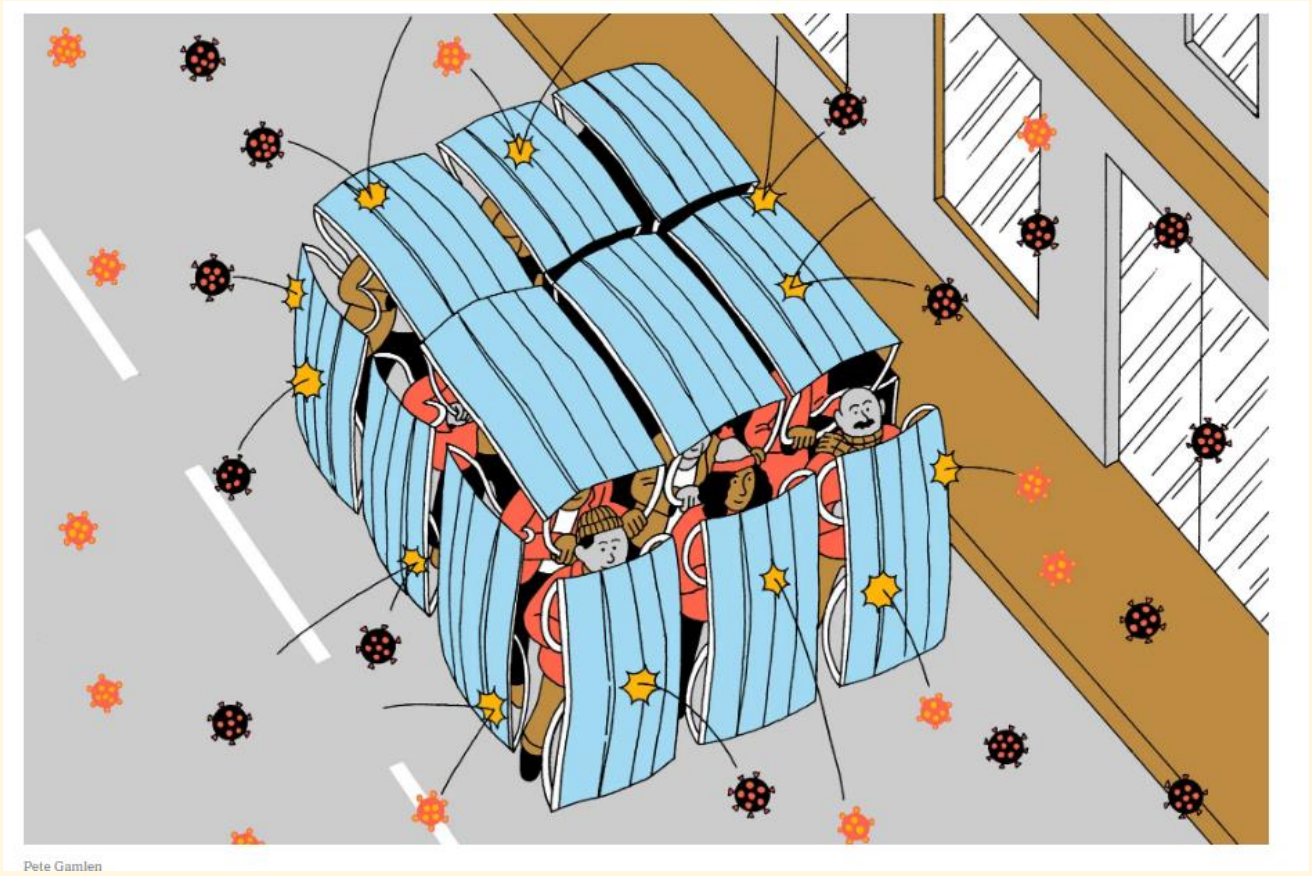


From: **The Growing Influence of State Governments on Population Health in the United States**

JAMA. Published online March 11, 2022. doi:10.1001/jama.2022.3785

MITIGATION

The key to spread is crowded, poorly ventilated spaces



- **Always wear a mask in a poorly ventilated crowded space**
- **Wear a mask among people you do not know in crowded spaces**
- **Avoid these spaces if you can**
- **Open windows to improve ventilation**
- **Use floor-standing HEPA filters**
- **Check HVAC systems and filters**

MITIGATION

REASONS FOR GETTING THE VACCINE AND WEARING A MASK IN CROWDED PLACES

Getting vaccinated is both common sense and a civic responsibility

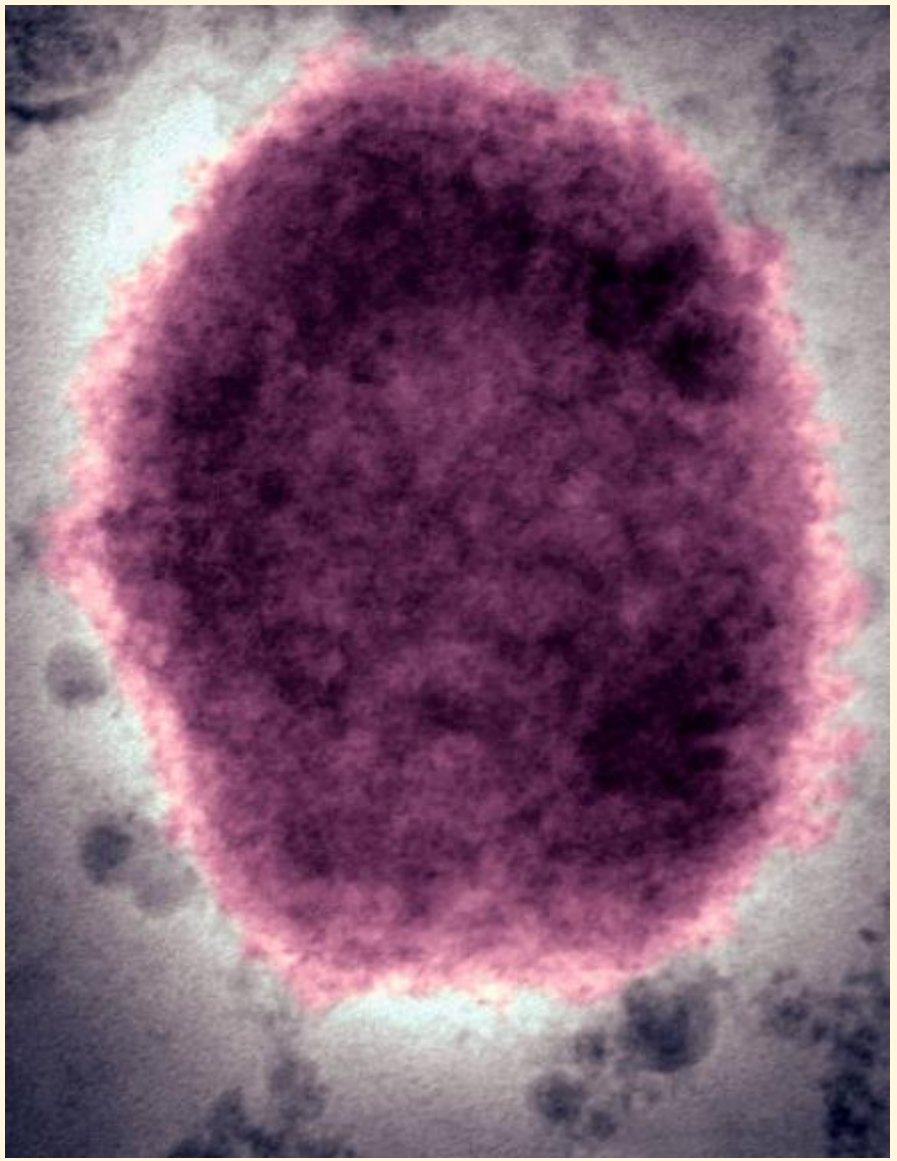
PERSONAL

- **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.**

MONKEYPOX



- **A member of the family Poxviridae, genus Orthopoxvirus to which Smallpox (variola virus), and Cowpox virus also belong. (IT IS NOT RELATED TO CHICKENPOX)**
- **A DNA virus. There is a central African and a west African strain**
- **First identified in 1958 in monkey colony, but thought to be a virus endemic in African rodents.**
- **2003 there was a small outbreak of the West African virus in the US in imported pet animals.**

Phylogenetic tree of different orthopoxvirus species, strains or isolates based on nucleic acid sequence alignment

SMALLPOX

COWPOX

MOUSEPOX

CAMELPOX

VACCINIA

MONKEYPOX SRAINS

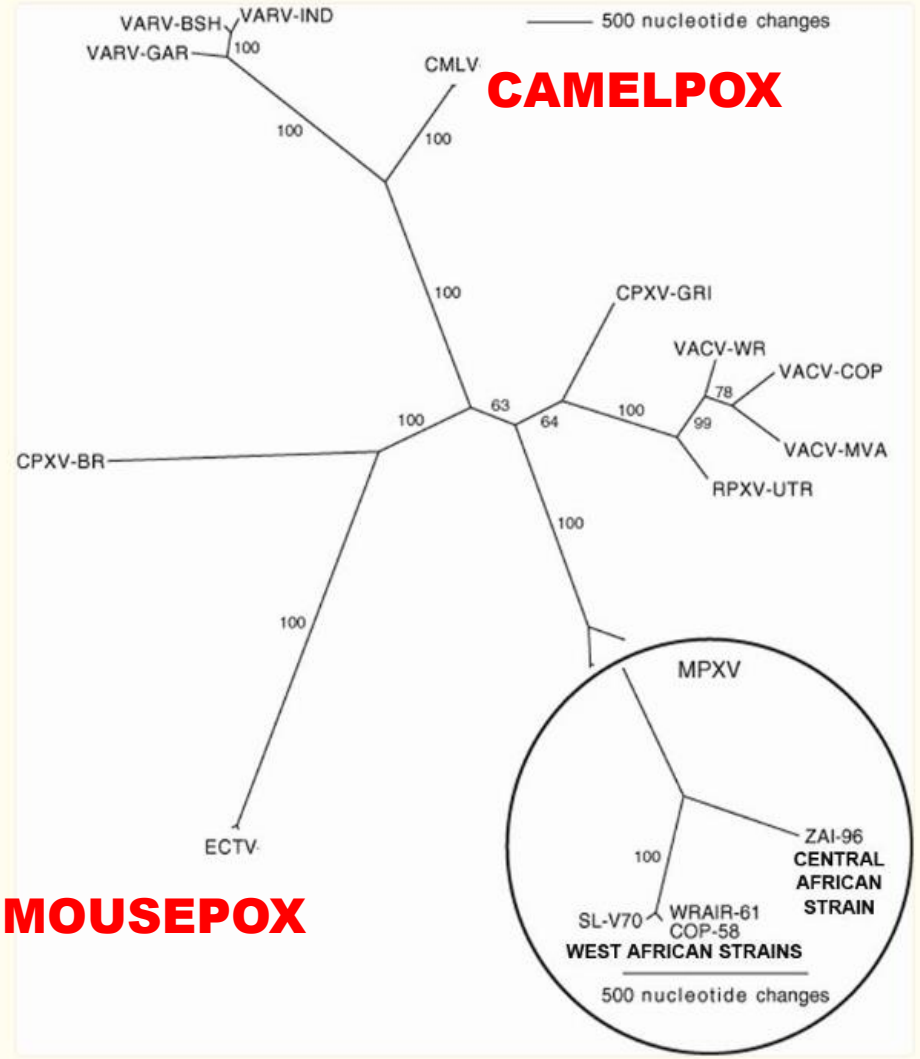


Fig. 2

Phylogenetic tree of different orthopoxvirus species, strain, or isolate based on nucleic acid sequence alignment

Monkeypox in Humans and Animals

What we know about monkeypox in humans

- **Monkeypox is a zoonotic disease, it can spread between animals and people**
- **People can get infected with the virus through direct contact with infected animals, often while hunting, trapping, and processing infected animals or the infected body parts and fluids.**
- **In 2003, an outbreak of monkeypox in domesticated prairie dogs occurred after they shared bedding and caging with a shipment of infected small mammals from West Africa. This led to 47 human cases in 6 states in the United States.**
- ***Monkeypox virus* can be found in the rash caused by monkeypox (scabs, crusts, fluids) and infected bodily fluids, including respiratory secretions, and potentially in urine and feces.**

What we know about monkeypox in animals

- **While the animal reservoir is uncertain, small mammals (e.g. rope and sun squirrels, giant-pouched rats, African dormice) appear to maintain the virus in the environments of West and Central Africa**
- **Small mammals can carry the virus, sometimes without apparent symptoms, while non-human primates can get sick with monkeypox and have signs of disease like humans.**
- ***Monkeypox virus* can infect a wide range of mammal species including dogs.**
- **Infected animals can spread *Monkeypox virus* to people, and it is possible that people who are infected can spread Monkeypox virus to animals through close contact, including petting, cuddling, hugging, kissing, licking, sharing sleeping areas, and sharing food.**

WHO Monkeypox field team Democratic Republic of the Congo circa 1980

Epidemiology 2022

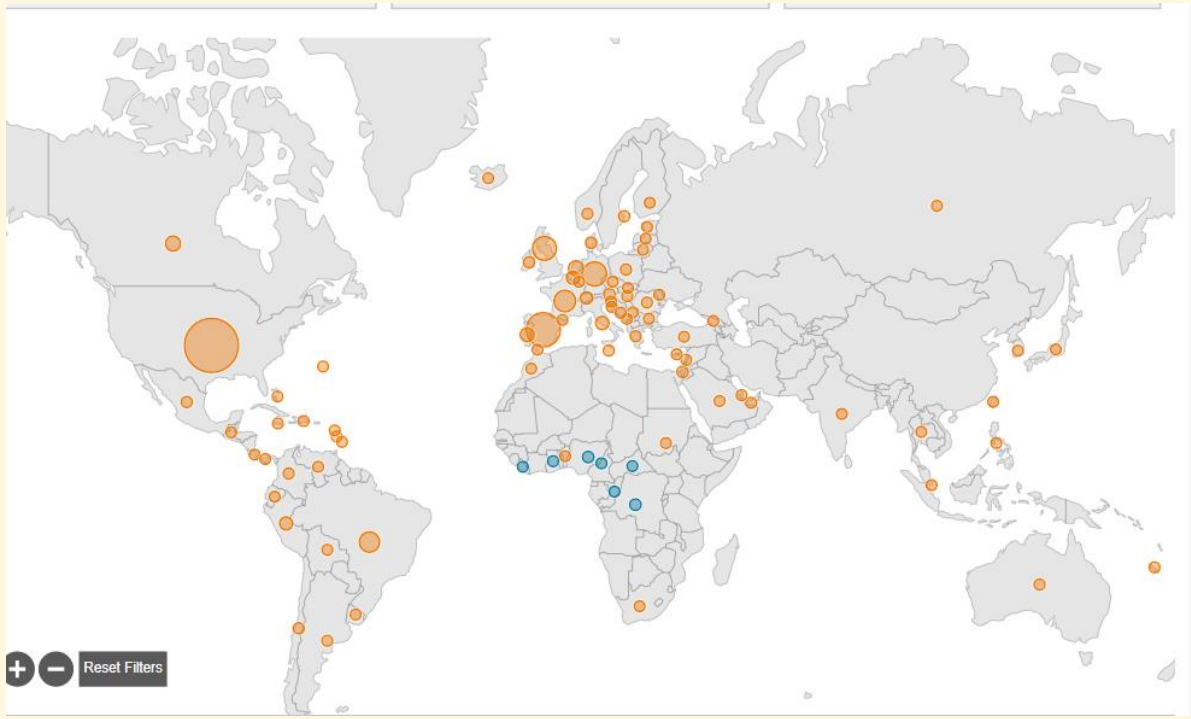
- **Declared a public health emergency July 23, 2022**
- **First US case May 7, 2022**
- **August 4th, 2022, public health emergency declared in US.**
- **As of August 9, 2022 nearly 32,000 confirmed cases across 82 nonendemic countries including 9,500 in the US.**

Transmission

- **Spread by direct skin-to-skin contact with infectious lesions**
- **In this outbreak mainly among men with intimate sexual contact**
- **Also spread through fomites (sex toys, clothing, bedding).**
- **Mean incubation period estimated at 7 days**

2022 Monkeypox Outbreak Global Map

Data as of 12 Aug 2022 5:00 PM EDT

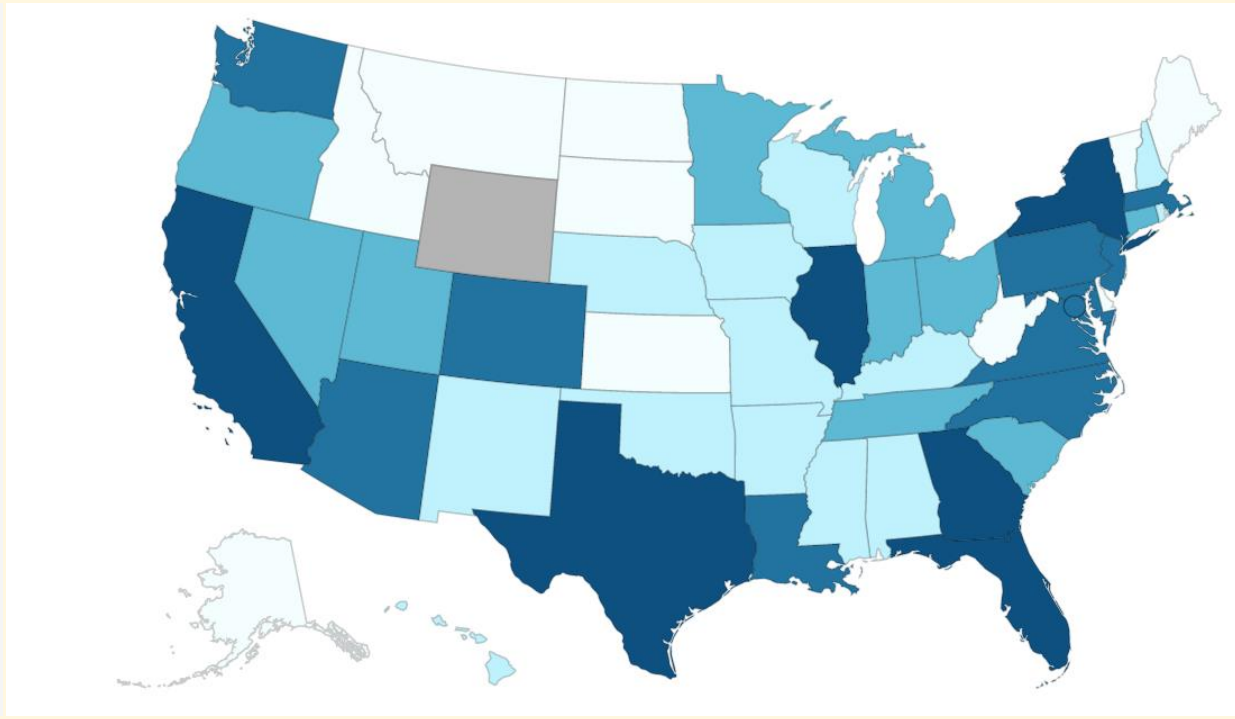


Has not historically reported monkeypox

Has historically reported monkeypox

2022 U.S. Map & Case Count

Data as of 12 Aug 2022 2:00 PM EDT



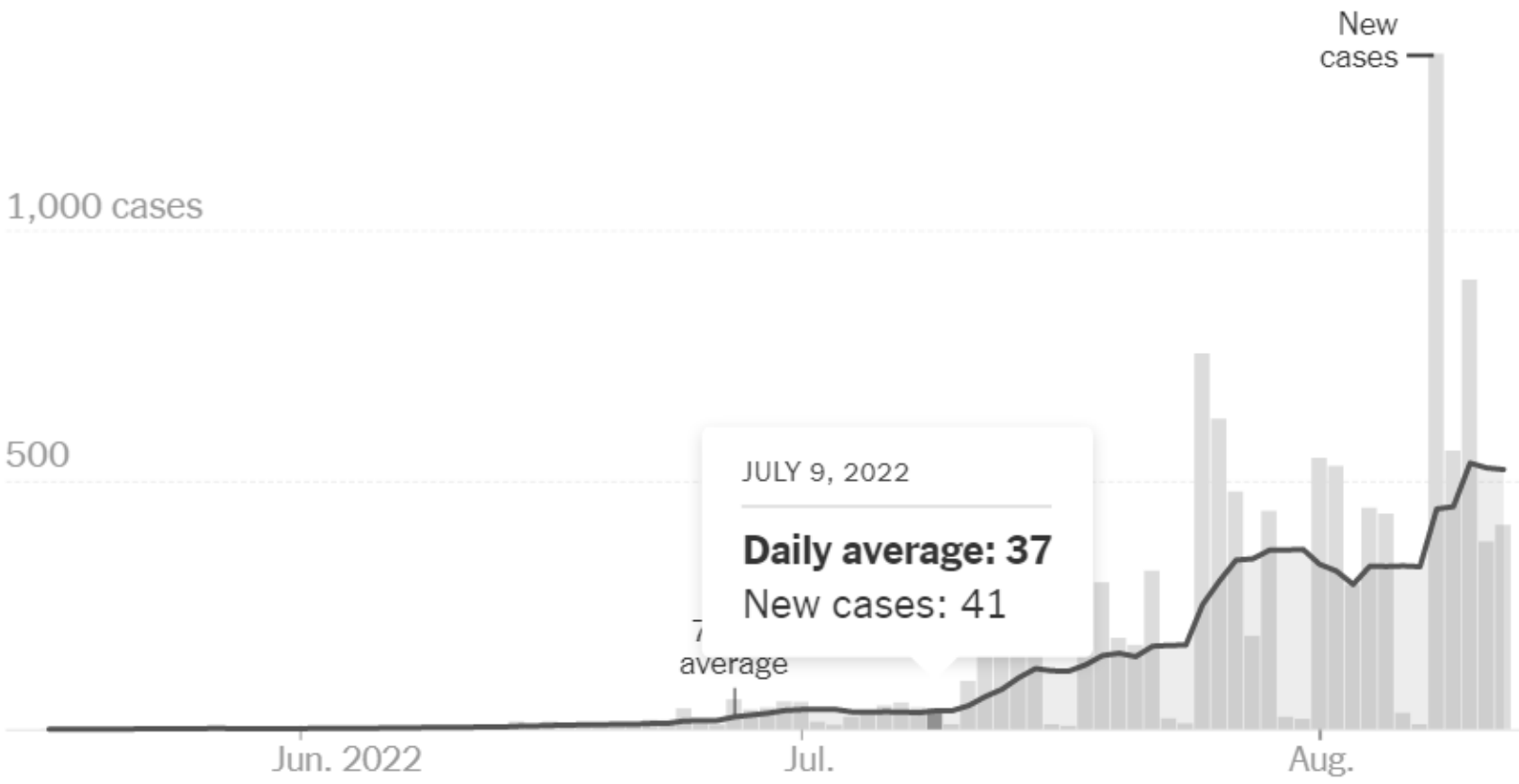
Case Range

- 0
- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- >500

Confirmed Monkeypox Cases in the U.S.

TOTAL	IN PAST TWO WEEKS	DAILY AVERAGE	14-DAY CHANGE
11,177	5,918	520	+45%

Cases by day



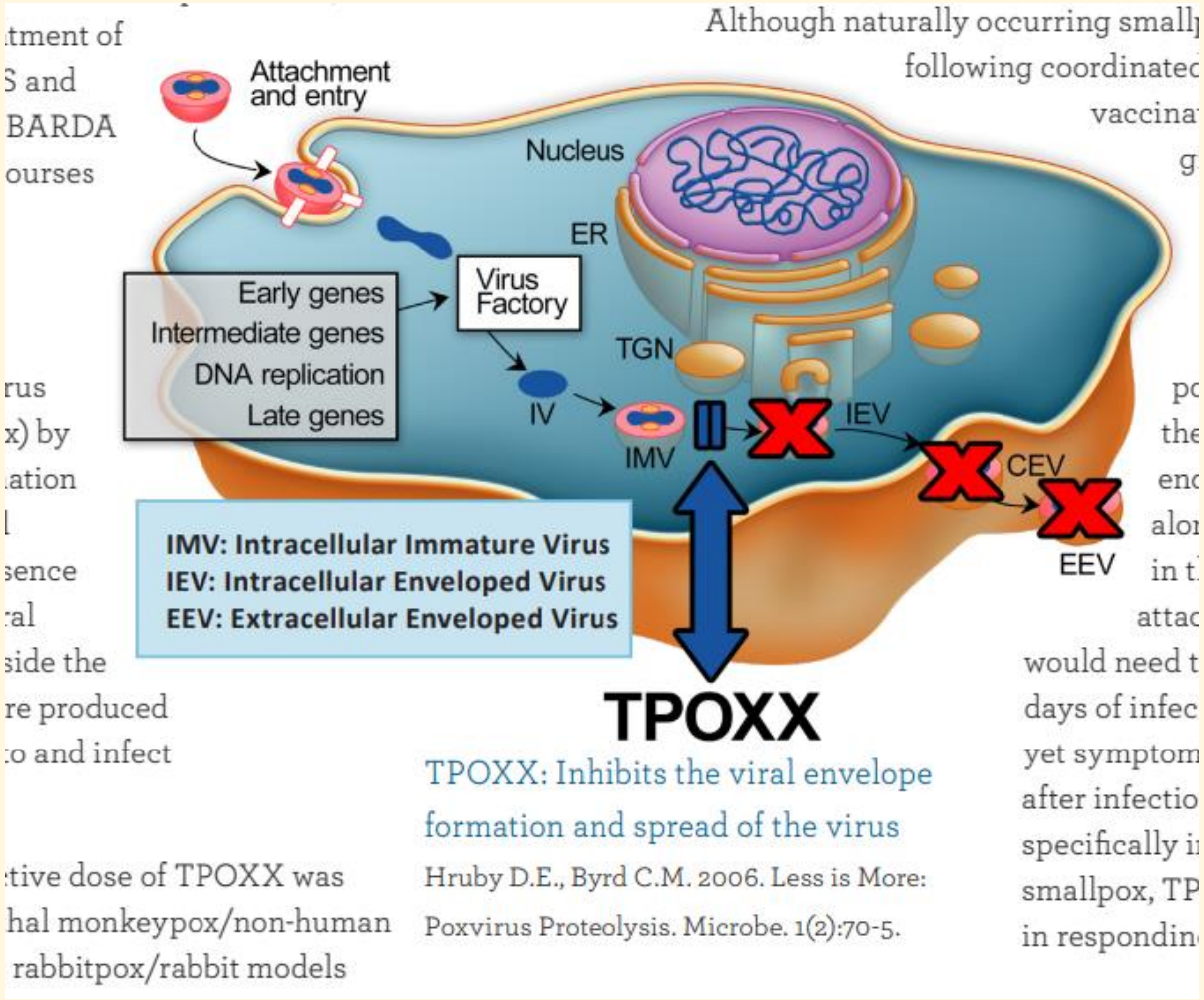
Symptoms

- Analagous to smallpox but much milder; rarely fatal.
- Initially flu like symptoms, headache, fatigue, malaise.
- Rash appears with macule progressing to papules, vesicle, and pustules.
- Pain, sore throat, epiglottitis and tonsillitis have been reported
- Rarely pneumonia, encephalitis and eye infections usually in young children
- Impact on immunocompromised unknown

Treatment

- Mainly symptomatic
- Tecovirimat not FDA approved for Monkepox, only covered by IND and in short supply and only available for high-risk patients.
- Several clinical trials are underway

TREATMENT: Tecovirimat (TPOXX)



- **Developed for smallpox and approved by the FDA for smallpox only**
- **Inhibits secondary viral envelope formation and thus viral maturation**
- **Inhibits systemic spread of smallpox virus**
- **TPOXX is the only treatment for monkeypox available**
- **Not approved by FDA for monkeypox, so CDC holds an IND protocol for its use in people likely to become severely ill with monkeypox due to weakened immune system**
- **Side effects and adverse drug interactions may occur.**

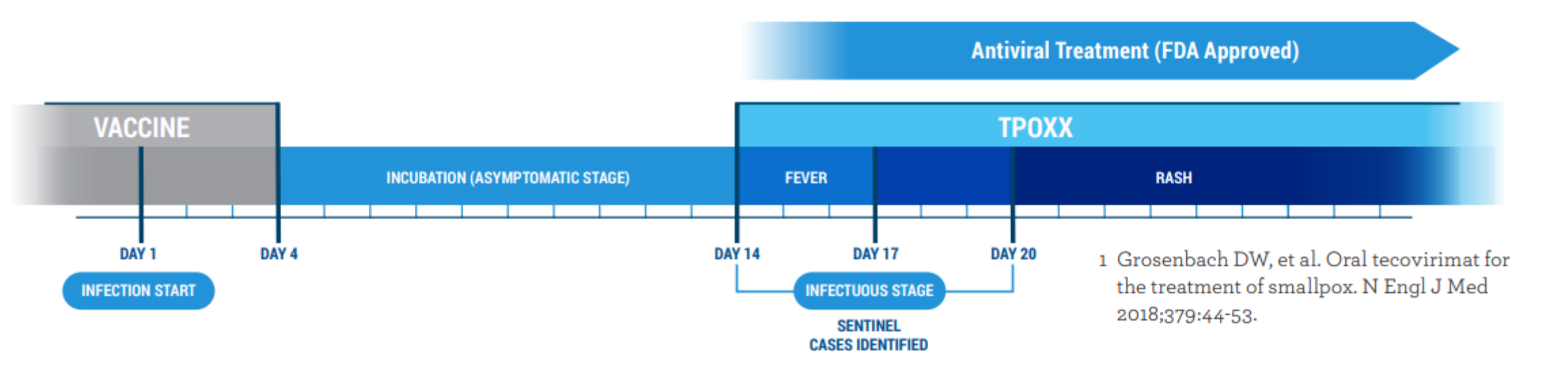
PREVENTION

1. **PROTECT YOURSELF:**
   a. **Limit numbers of sexual partners, including kissing**
   b. **Avoid saunas, sex clubs, or any event where intimate anonymous contact may occur**
   c. **Condoms may protect, but may not prevent all exposures**
   d. **Wash hands, gear, fomites, etc.**

2. **VACCINES**
   a. **Vaccinia virus is a naturally modified orthopoxvirus used as an effective vaccine for smallpox which was eradicated in 1977 with the use of this virus**
   b. **This is marked as JYNNEOS. Immunity is only 14 days after the second dose.**
   c. **CAM200 is an alternative and is single dose but has more potential for side effects. It is not recommended for people with weakened immune systems and several other conditions.**

TIMING OF VACCINE AND TREATMENT IS CRITICAL

- **Vaccine course must be completed at least 14 days before exposure**
- **Treatment must be at onset of symptoms (fever)**



1 Grosenbach DW, et al. Oral tecovirimat for the treatment of smallpox. N Engl J Med 2018;379:44-53.