

# KEEP CALM & OMICRON

UNDERSTANDING THE LATEST  
CORONAVIRUS VARIANT

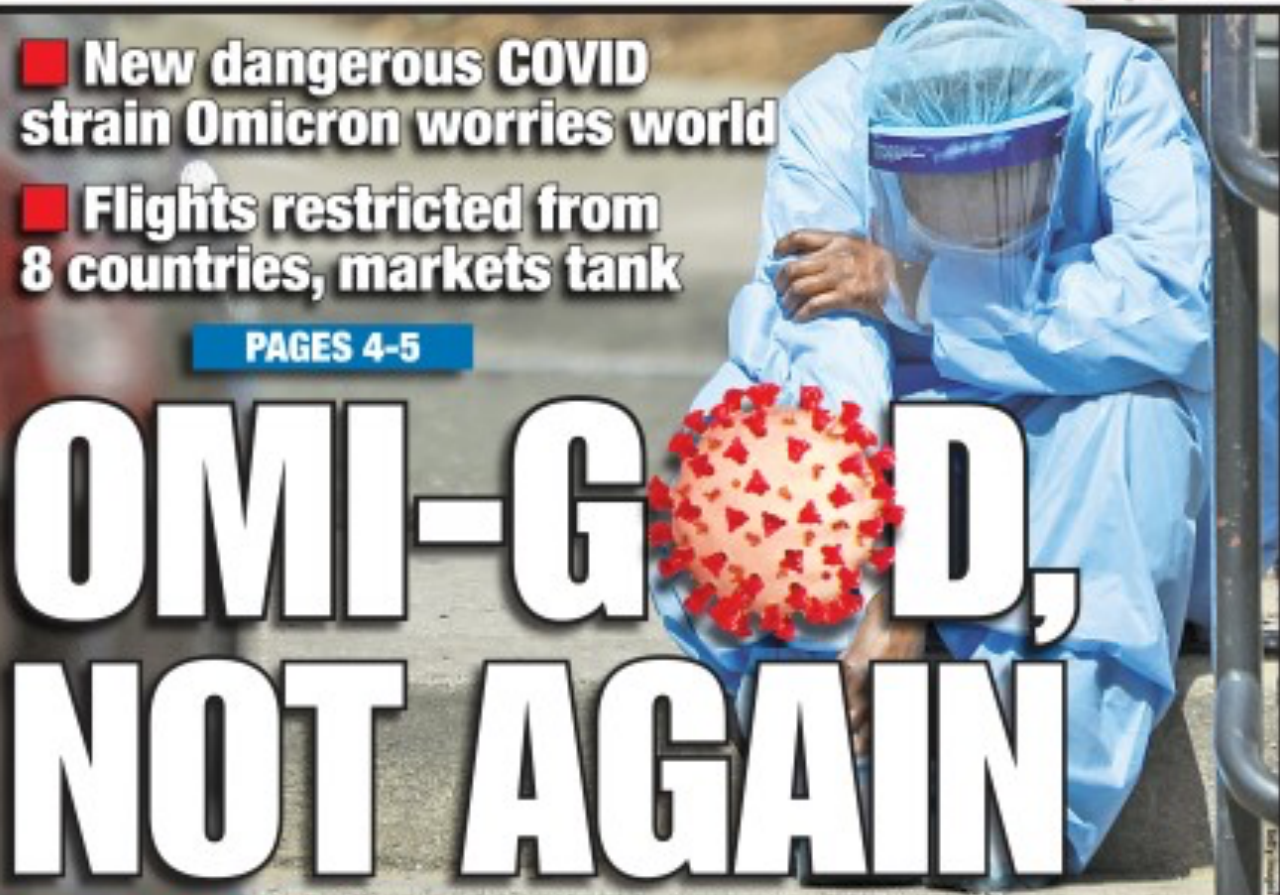
NICK MARK MD  
2020/12/17

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 [www.onepagericu.com](http://www.onepagericu.com)

**Broadway great exits stage left**  
**Stephen Sondheim**  
 1930-2021



**New dangerous COVID strain Omicron worries world**  
**Flights restricted from 8 countries, markets tank**  
 PAGES 4-5

**OMI-G, NOT AGAIN**

**THE POST SAYS: GET THIS ONE RIGHT, BIDEN**

**Merck: New data shows COVID pill is just 30% effective**  
**TREATMENT | An FDA panel is set to review the drug's safety and efficacy.**

Seattle Times news services  
 Drugmaker Merck and its partner, Ridgeback Biotherapeutics, released data Friday showing their experimental pill to treat COVID-19 is less effective than early clinical trials predicted, a finding that emerged as the Food and Drug Administration raised questions about the drug's safety.  
 Molnupiravir, a pill that could be taken at home, had shown promise in cutting the risk of hospitalization and death by half among high-risk patients in data released by the company in October. But according to the latest findings Merck presented to the FDA, the pill reduced the risk of hospitalization and death only by 30%.  
 The study by the drugmakers found that, among participants receiving the pill, just one participant died during the trial, compared with nine deaths in the placebo group, the companies said in a news release Friday.  
 "It's still a 30% effect, which is still good for a high-risk population," said David Boulware, an infectious-disease physician and professor of medicine at the  
 See > MERCK, A5

**Push to vote for more than one candidate gains traction in Seattle area**  
 By DANIEL BEERMAN  
 Seattle Times staff reporter

**NEW VARIANT STIRS FEARS OF SETBACK; TRAVEL BANS RISE**  
**Markets Tumble and Optimism Wanes After Cases Found in South Africa**  
 By RICHARD PÉREZ-PEÑA and JASON HOROWITZ

The world reacted with alarm on Friday to the highly mutated new coronavirus variant discovered in southern Africa, as the United States, the European Union and nations across the globe imposed new travel restrictions, financial markets swooned and visions of finally emerging from the pandemic started to dim.  
 Just two days after the world learned of the variant, the World Health Organization officially labeled it a "variant of concern," its most serious category — the first since the Delta variant, which emerged a year ago. The designation means that the variant has mutations that might make it more contagious or more virulent, or make vaccines and other preventive measures less effective — though none of those effects has yet been established.  
 After an emergency meeting, the W.H.O. warned in a statement that "preliminary evidence suggests an increased risk of reinfection with this variant" in people who have already had Covid-19. In keeping with the practice of naming variants for letters of the Greek alphabet, it dubbed the new one Omicron.  
 The W.H.O. and scientists on multiple continents cautioned that very little is known yet about the Omicron variant, or about whether the dangers it poses will justify the fears it is stoking. South African scientists announced its existence on Wednesday, and the number of cases definitively identified, all of them within the past three weeks, is still small, under 100.  
 But the swift global responses demonstrated that after nearly two years of facing accusations that they were too slow and timid in tackling the pandemic, many policymakers would rather risk overreacting to a new threat than underreacting.  
 "We are following the path of maximum caution," said Roberto Speranza, the health minister of Italy, which suffered terribly when Covid first hit Europe early last year.  
 On Friday, Israel, Singapore, several European nations individually, and then the European Union as a whole, the United States and Canada followed the lead set by Britain on Thursday night, temporarily barring foreign travelers.  
 Continued on Page A7

**Omicron Mutations May Allow A Quick Spread, W.H.O. Says**  
 By CARL ZIMMER  
 Scientific experts at the World Health Organization warned on Friday that a new coronavirus variant discovered in southern Africa was a "variant of concern," the most serious category the agency uses for such tracking.  
 The designation, announced after an emergency meeting of the health body, is reserved for dangerous variants that may spread quickly, cause severe disease or decrease the effectiveness of vaccines or treatments. The last coronavirus variant to receive this label was Delta, which took off this summer and now accounts for virtually all Covid cases in the United States.  
 The W.H.O. said the new version, named Omicron, carries a number of genetic mutations that may allow it to spread quickly, perhaps even among the vaccinated.  
 Independent scientists agreed that Omicron warranted urgent attention, but also pointed out that it would take more research to determine the extent of the threat. Although some variants of concern, like Delta, have lived up to initial worries, others have had a limited impact.  
 "Epidemiologists are trying to say, 'Easy, tiger,'" said William Hanage, an epidemiologist at the  
 Continued on Page A6

**Nations shaken as new variant of virus emerges**  
**TRAVEL FROM AFRICA CURBED; MARKETS FALL**  
**Race is on to tame possibly more infectious 'omicron'**

By PERRY STEIN, WILLIAM BOOTH AND FRANCIS STRAD SELLERS  
 abundance of caution," officials said, as scientists work to learn more about the new variant.  
 This latest variant arrived nearly two years after the first ominous warnings about a novel coronavirus that emerged from China. Now, even as the world grows increasingly weary of mandates to contain the virus, this new threat is casting a shadow across holiday celebrations.  
 On Friday, the World Health Organization declared the mutation-laden virus a "variant of concern" after a full-day review by the group's scientists and  
 Variant: Travel restriction is precautionary, Biden says. A5  
 Stock sell-off: Dow plummets on fears 2021 gains will unravel. A14

**Southern states dawdle in vaccinating children**  
 By KATHY SHEPHERD AND DAN KEATING  
 Many Southern states, especially Louisiana, Alabama and Mississippi, have fallen behind the rest of the nation in vaccinating children as the threat of a winner surge casts a pall over the holiday season.  
 These states also rank near the bottom for vaccinating adolescents and adults, and they have among the nation's highest overall covid-19 death rates, according to a review of state vaccination and death data by The Washington Post. Their slow uptake of children's — as well as adults' —  
 vaccines have heightened fears that another pandemic wave could hit hard as families gather for the holidays and spend more time indoors.  
 "I think it is a potentially dangerous situation," said Paul Offit, director of the Vaccine Education Center at Children's Hospital of Philadelphia. "You're going to have a large number of susceptible people all in one place, especially in communities where vaccine rates are generally low and the transmission is higher."  
 Those concerns increase as colder weather drives families inside for social gatherings and

**Times** Late Edition  
 Today, partly sunny, windy, cold, high 43. Tonight, cloudy, flurries late, low 31. Tomorrow, mostly cloudy, a rain and snow shower, high 40. Weather map is on Page B12.  
 \$3.00

**n Post** SATURDAY, NOVEMBER 27, 2021 - \$2



"YOU FEAR THE LEAST  
WHAT YOU KNOW  
THE MOST ABOUT"

-JOHN GLENN

(1921-2016)

# Objectives:

- What is ***the Omicron variant***?
- ***Molecular***: What mutations are present & what is potential for immune evasion?
- ***Epidemiologic***: How far has it spread & what is the evidence for increased transmissibility?
- ***Clinical***: is it really "mild"? What are the implications for vaccines & treatments?

# Disclosure:

- I have no conflict of interest in relation to this program/presentation

# PRONUNCIATION: ä-mə-krän vs ō-mə-kron ?

Omicron American pronunciation ▾

Sounds like American pronunciation ▾

aa · muh · kraan 🔊

Omicron British pronunciation ▾

Sounds like British pronunciation ▾

o · muh · kron 🔊

Ω

*big* ○

Ωμέγα

Omega

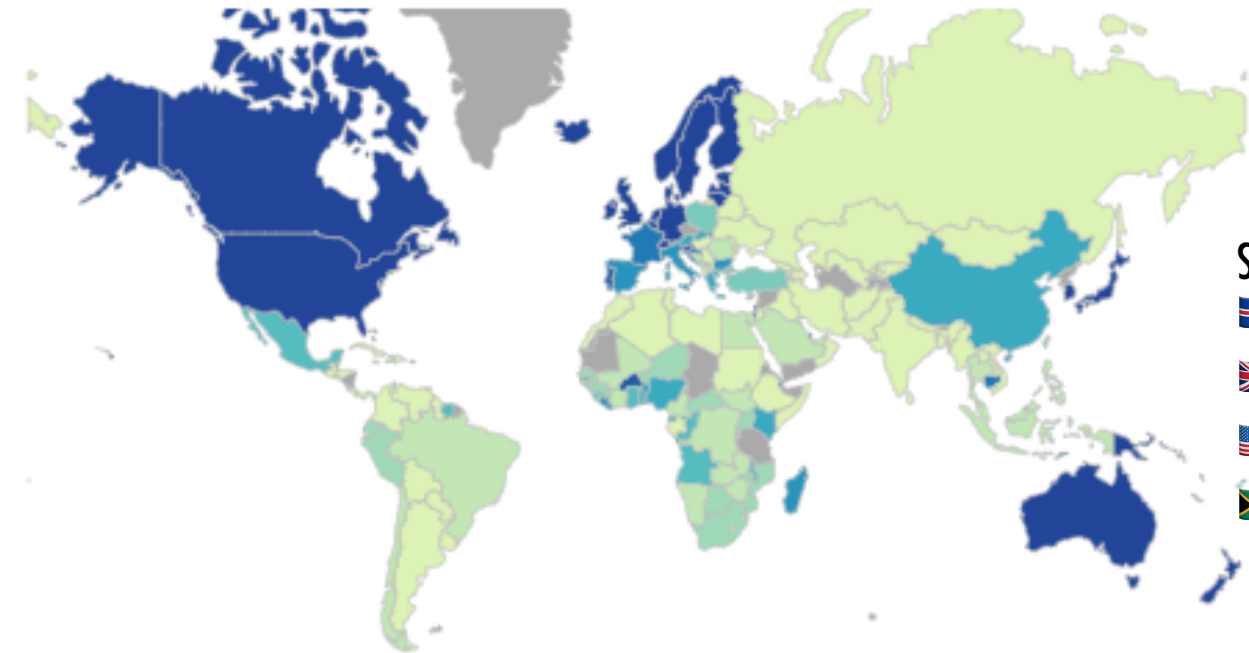
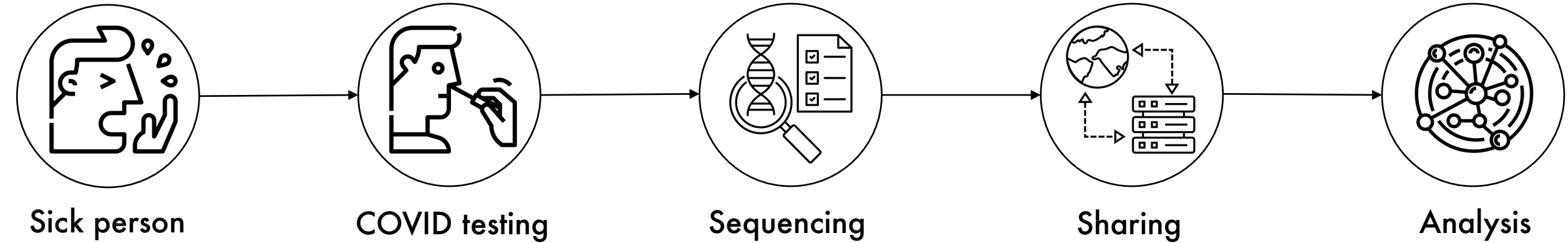
○

*little* ○





ομικρόν

Omicron

# PANDEMIC SURVEILLANCE: Individual Patient to Big Data



Sequences/1000 cases

-  455 (45.5%)
-  117 (11.7%)
-  30 (3%)
-  5.4 (0.5%)

 GISAID

 GenBank

 Nextstrain

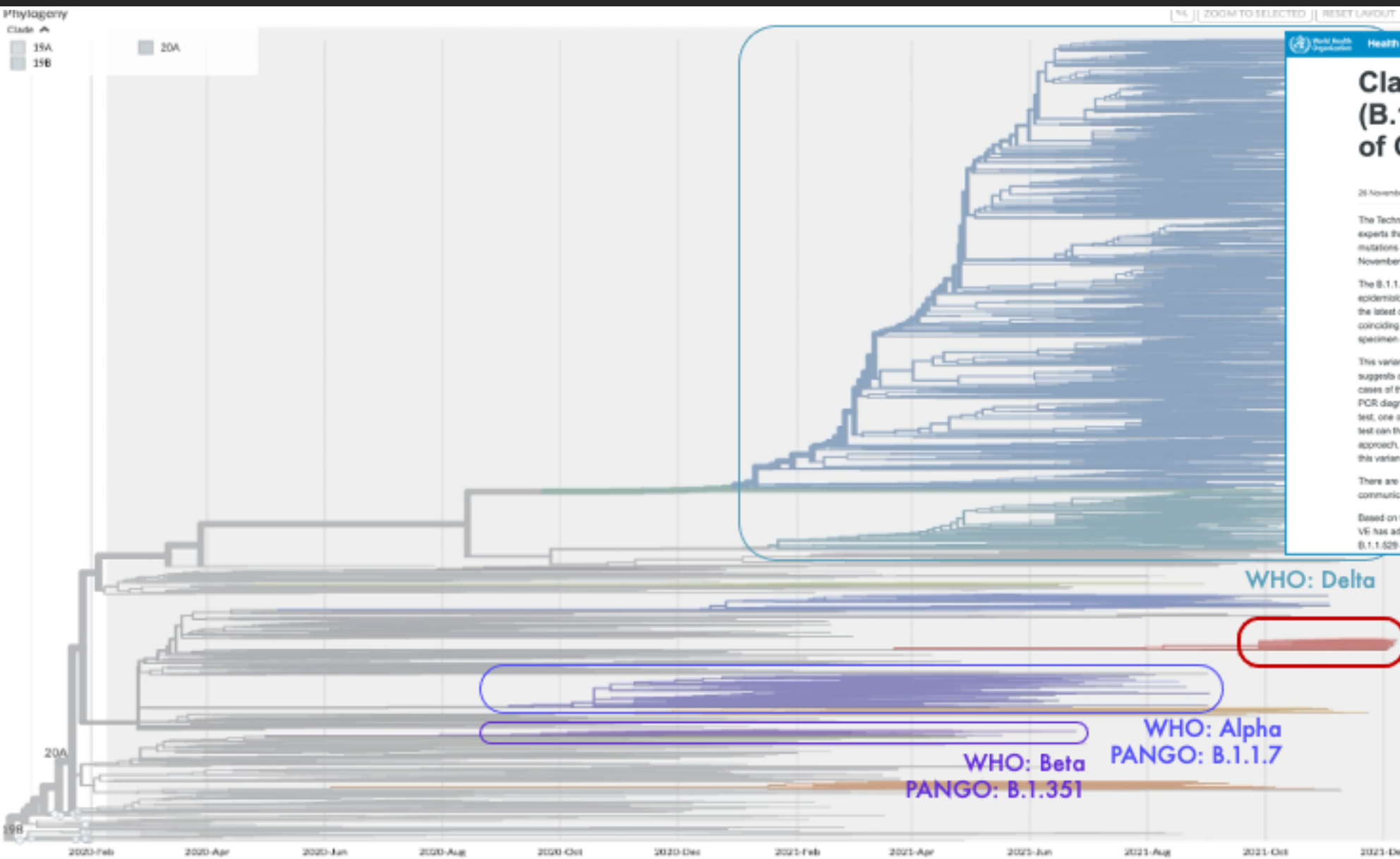
 CoVariants

 Cov-lineages.org

*in silico* structure models  
immune epitope prediction

Epidemiologic modeling

# ORIGINS: Evolution of Omicron



## Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern

26 November 2021 | Statement | Reading time: 2 min (814 words)

The Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) is an independent group of experts that periodically monitors and evaluates the evolution of SARS-CoV-2 and assesses if specific mutations and combinations of mutations alter the behaviour of the virus. The TAG-VE was convened on 26 November 2021 to assess the SARS-CoV-2 variant: B.1.1.529.

The B.1.1.529 variant was first reported to WHO from South Africa on 24 November 2021. The epidemiological situation in South Africa has been characterized by three distinct peaks in reported cases, the latest of which was predominantly the Delta variant. In recent weeks, infections have increased steeply, coinciding with the detection of B.1.1.529 variant. The first known confirmed B.1.1.529 infection was from a specimen collected on 8 November 2021.

This variant has a large number of mutations, some of which are concerning. Preliminary evidence suggests an increased risk of reinfection with this variant, as compared to other VOCs. The number of cases of this variant appears to be increasing in almost all provinces in South Africa. Current SARS-CoV-2 PCR diagnostics continue to detect this variant. Several labs have indicated that for one widely used PCR test, one of the three target genes is not detected (called S gene dropout or S gene target failure) and this test can therefore be used as marker for this variant, pending sequencing confirmation. Using this approach, this variant has been detected at faster rates than previous surges in infection, suggesting that this variant may have a growth advantage.

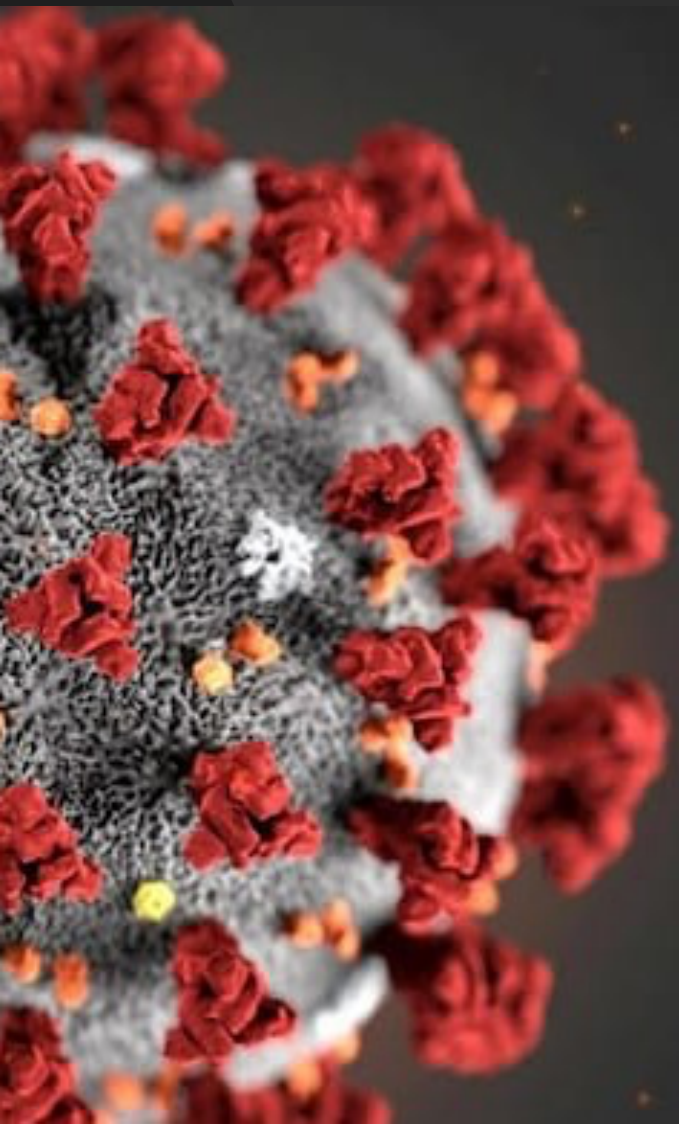
There are a number of studies underway and the TAG-VE will continue to evaluate this variant. WHO will communicate new findings with Member States and to the public as needed.

Based on the evidence presented indicative of a detrimental change in COVID-19 epidemiology, the TAG-VE has advised WHO that this variant should be designated as a VOC, and the WHO has designated B.1.1.529 as a VOC, named Omicron.

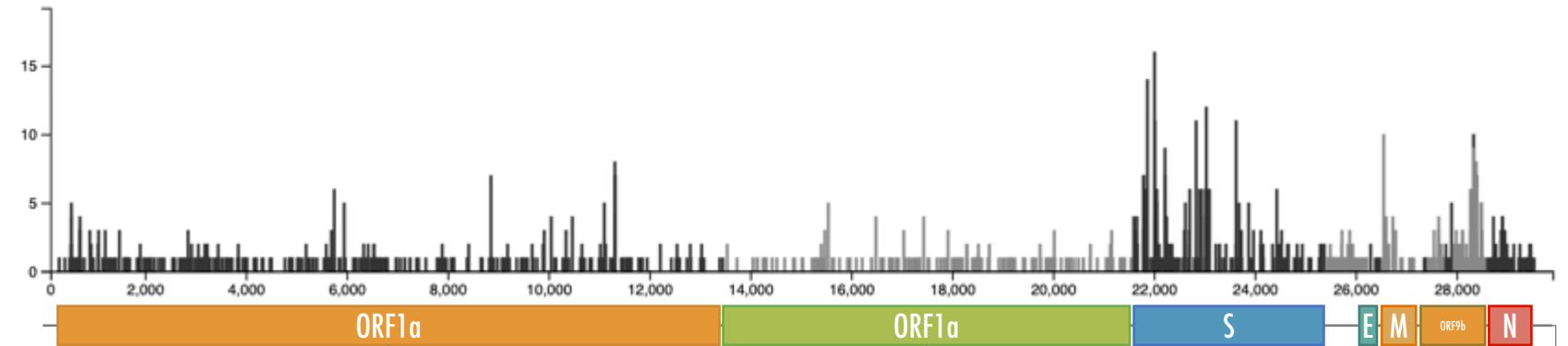
Nextstrain Clade: 21K  
PANGO lineage: B.1.1.529  
WHO: Omicron



# MUTATIONS: large number of spike protein mutations



AA mutation events



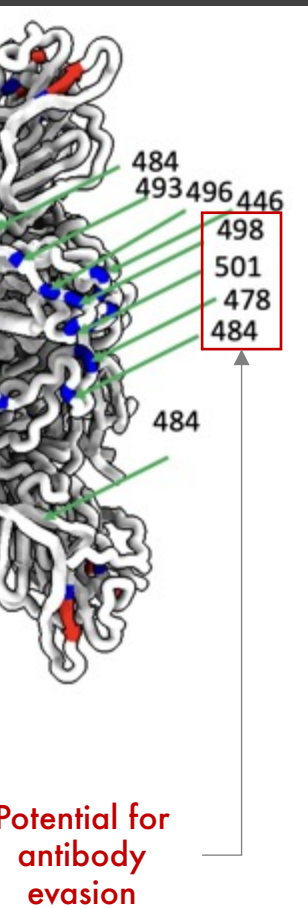
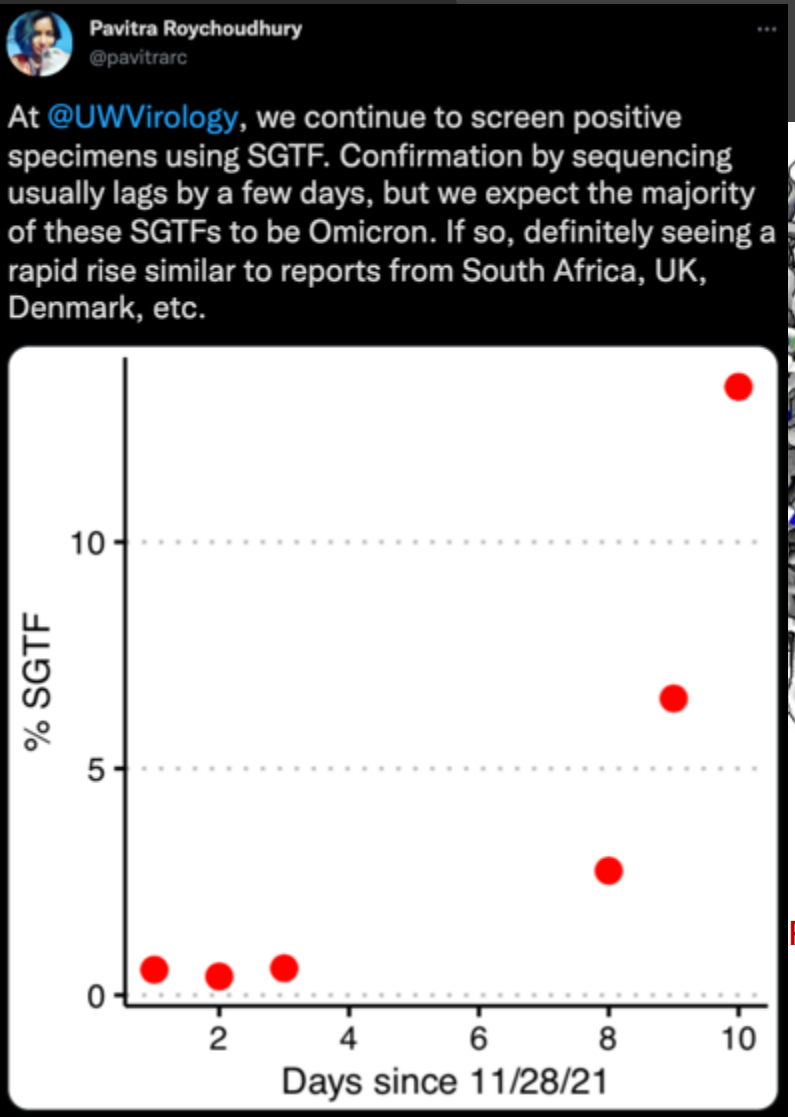
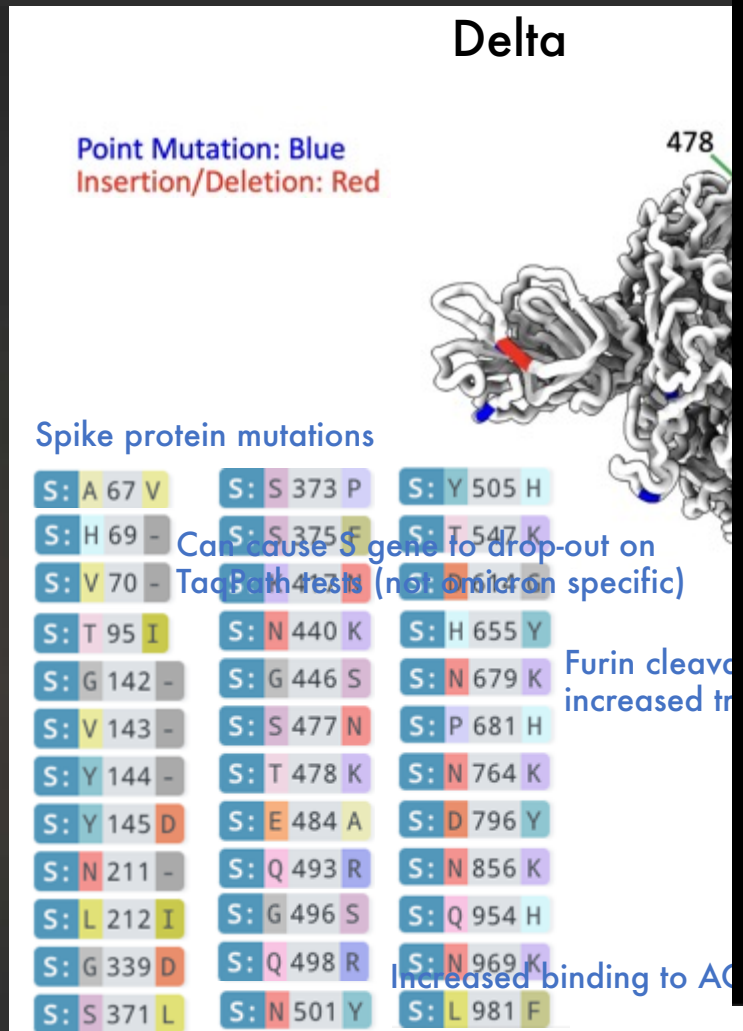
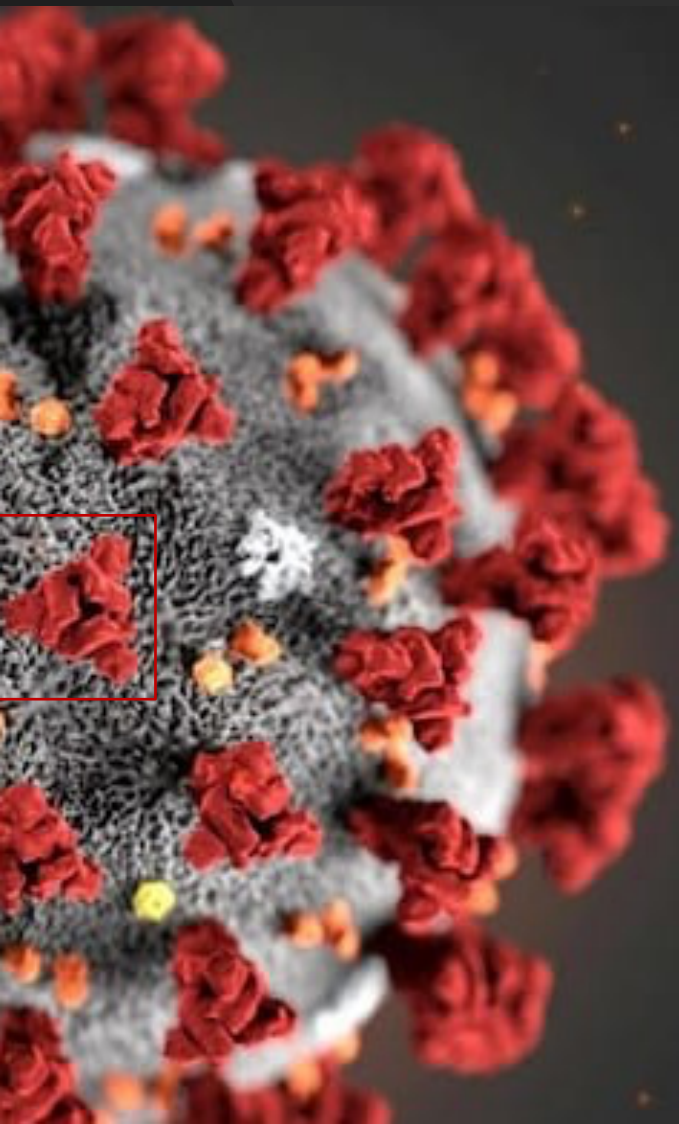
- ORF1a: K 856 R
- ORF1a: S 2083 -
- ORF1a: L 2084 I
- ORF1a: A 2710 T
- ORF1a: T 3255 I
- ORF1a: P 3395 H
- ORF1a: L 3674 -
- ORF1a: S 3675 -
- ORF1a: G 3676 -
- ORF1a: I 3758 V

- ORF1b: P 314 L
- ORF1b: I 1566 V
- ORF9b: P 10 S
- ORF9b: E 27 -
- ORF9b: N 28 -
- ORF9b: A 29 -

- S: A 67 V
- S: H 69 -
- S: V 70 -
- S: T 95 I
- S: G 142 -
- S: V 143 -
- S: Y 144 -
- S: Y 145 D
- S: N 211 -
- S: L 212 I
- S: G 339 D
- S: S 371 L
- S: S 373 P
- S: S 375 F
- S: K 417 N
- S: N 440 K
- S: G 446 S
- S: S 477 N
- S: T 478 K
- S: E 484 A
- S: Q 493 R
- S: G 496 S
- S: Q 498 R
- S: N 501 Y
- S: Y 505 H
- S: T 547 K
- S: D 614 G
- S: H 655 Y
- S: N 679 K
- S: P 681 H
- S: N 764 K
- S: D 796 Y
- S: N 856 K
- S: Q 954 H
- S: N 969 K
- S: L 981 F

- E: T 9 I
- M: D 3 G
- M: Q 19 E
- M: A 63 T
- N: P 13 L
- N: E 31 -
- N: R 32 -
- N: S 33 -
- N: R 203 K
- N: G 204 R

# MUTATIONS: several mutations may enhance transmission



Zahradnik et al [2021 Nature Microbiology](#)  
Yu et al [Pre-print. 2021. BioRxiv](#)

Visualization by Ulrich Elling @EllingUlrich  
Sequences & Mutations via [CoVariants](#)

# MUTATIONS: despite mutations CD8+ T-cell responses appear preserved

Figure 1:  
Spike

MFVFLVLLPLVSSQCVNITTRTQLPPAYTNSFTRGVVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTN  
GTRFDNPVLPNDGVYFASTEKNIIRGWIFGTTLDSTKQSLIVNNAATNVVIVKVEFCNDPFLGVVYHK  
NNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFNIDGYFKIYSKHTPIINLVRDLPQG  
FSALEPLVDLPIGINITRFQTLALHRSYLTPGDSSSGWTAGAAAYVGYLQPRTFLLKYNENGTITDAVDCALDP  
LSEKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNS  
ASFTFKCYGVSPTKLNLDLCTNVYADSFVIRGDEVQRQIAPGGQTGKIADYNYKLPDDFTGCVIAWNSNLDLSDK  
VGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFEL  
LHAPATVCGPKSTNLVKNKCVNFNGLTGTGVLTESNKKFLPFQQFGRDIADTDAVRDPQTLEILDITPCSF  
GGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSEYCDI  
PIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNISIAIPTNFTISVTTEILPVSMTKTSVDCTM  
YICGDSTECNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKR  
SFIEDLLFNKVTLADAGFIKQYGDCLGDIARDLCAQKFNGLTVLPLLTDEMIQYTSALLAGTITSGWTFGA  
GAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDLSSTASALGKLQDVVNQNAQALNTL  
VKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGOS  
KRVDFCGKGYHLMSPQSAPHGVVFLHVTVVPAQEKNTTAPAICHGDKAHFPREGVFVSNGTHWVFTQRN  
FYEPQIITDNTFVSGNCDVVIGIYVNTVYDPLQPELDSFKEELDKYFNHTSPVDLGDISGINASVVNIQKEI  
DRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFD  
EDDSEPVKGVKLHYT

## Minimal cross-over between mutations associated with Omicron variant of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals

Andrew D Redd<sup>1,2#</sup>, Alessandra Nardin<sup>3</sup>, Hassen Kared<sup>3</sup>, Evan M Bloch<sup>4</sup>, Brian Abel<sup>3</sup>, Andrew Pekosz<sup>5</sup>,  
Oliver Laeyendecker<sup>1,2</sup>, Michael Fehlings<sup>3</sup>, Thomas C Quinn<sup>1,2</sup> and Aaron AR Tobian<sup>4</sup>

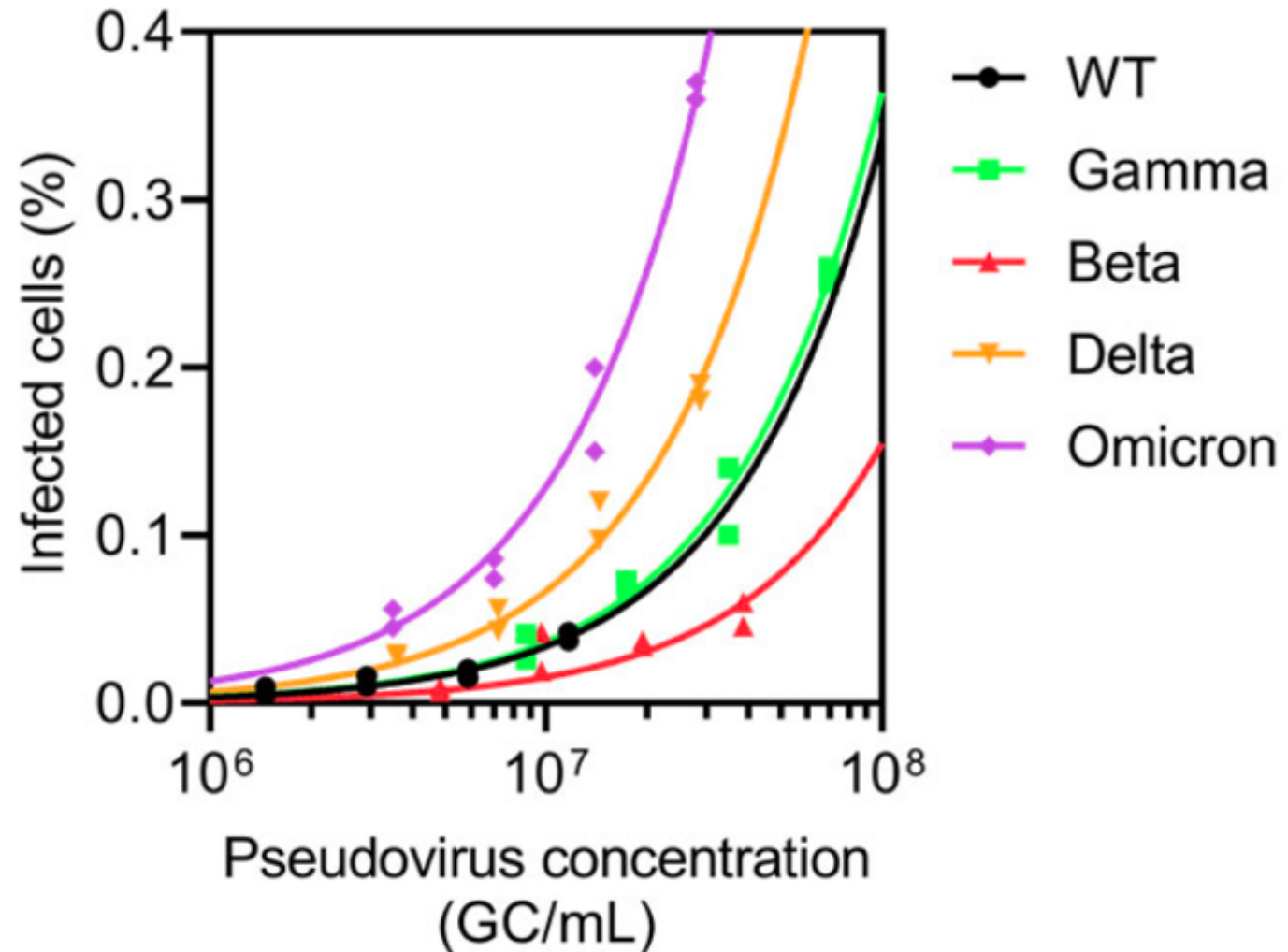
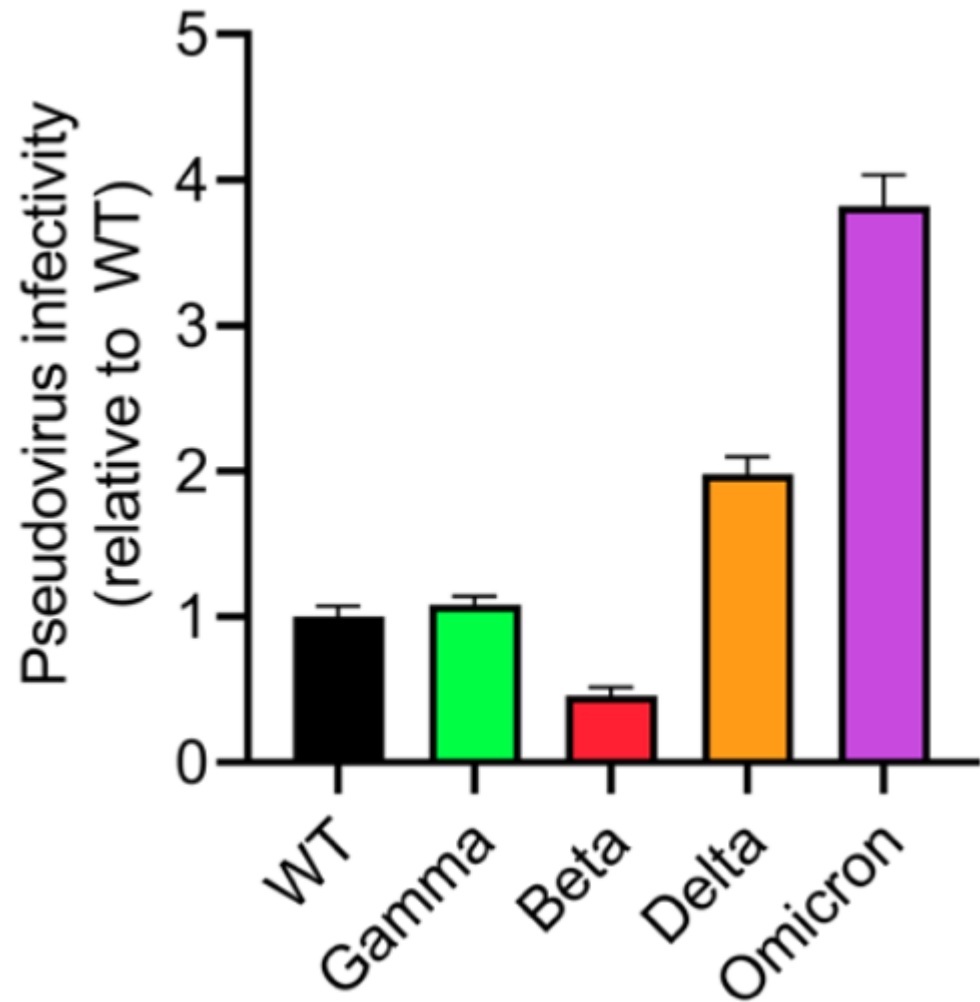
### Discussion:

This study demonstrates that despite the substantial number of mutations in the Omicron VOC, in this population only one low-prevalence CD8+ T-cell epitope from the Spike protein contained a single amino acid change. No other mutations were associated with our previously identified epitopes. These data suggest that virtually all individuals with existing anti-SARS-CoV-2 CD8+ T-cell responses should recognize the Omicron VOC, and that SARS-CoV-2 has not evolved extensive T-cell escape mutations at this point.

Omicron mutations  
T-cell epitopes

- 7/8 T-cell epitopes completely unmutated in Omicron
- The one TCR that reacted to the 8<sup>th</sup> epitope was low abundance

# MUTATIONS: greater infectivity in ACE2 expressing cells in vitro



# EPIDEMIOLOGY: a super-spreader event in Norway

December 3, 2021

10:05 AM PST

Last Updated 13 days ago

Europe

**Omicron outbreak at Norway  
Christmas party is biggest  
outside S. Africa -authorities**



Louise Restaurant & Bar at Aker Brygge is pictured after a person visiting it for a Christmas dinner was diagnosed with the omicron variant of coronavirus disease (COVID-19) in Oslo, Norway, December 2, 2021. Ole Berg-Rusten /NTB/via REUTERS

OSLO, Dec 3 (Reuters) - At least 13 people in Oslo have been infected with the Omicron variant of the coronavirus following a corporate Christmas party described as a "super spreader event", and their numbers could rise to over 60 cases, authorities said on Friday.

"This party has been a super spreader event," Preben Aavitsland, a senior physician at the Norwegian Institute of Public Health, told Reuters by email.

"Our working hypothesis is that at least half of the 120 participants were infected with the Omicron variant during the party. This makes this, for now, the largest Omicron outbreak outside South Africa."

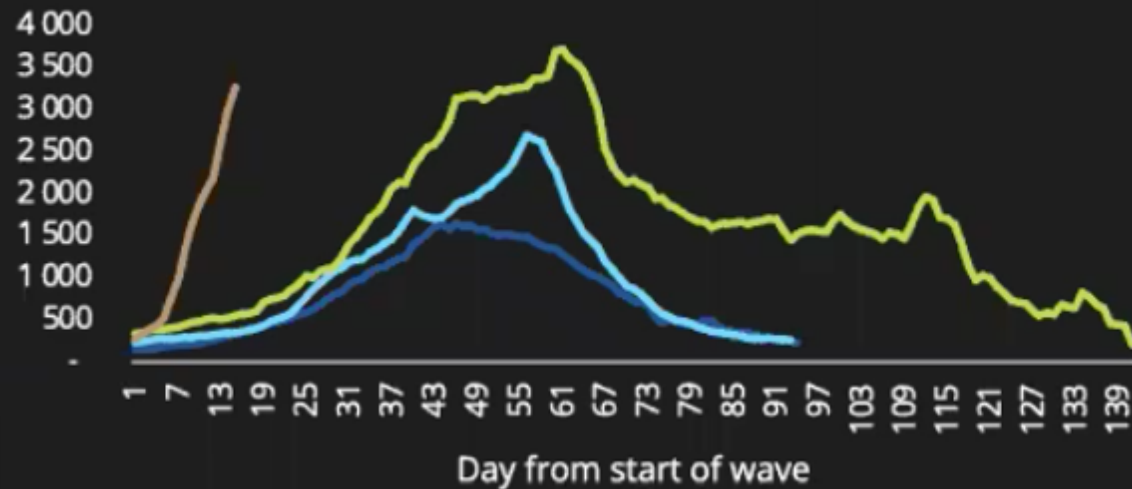
- A person returning from South Africa attended a corporate Christmas party in Oslo on November 26
- The person was asymptomatic at the time
- 80-90 of the 120 attendees became infected
- Other people at the restaurant (but not at the same party) also became infected
- All attendees were fully vaccinated
- None required hospitalization



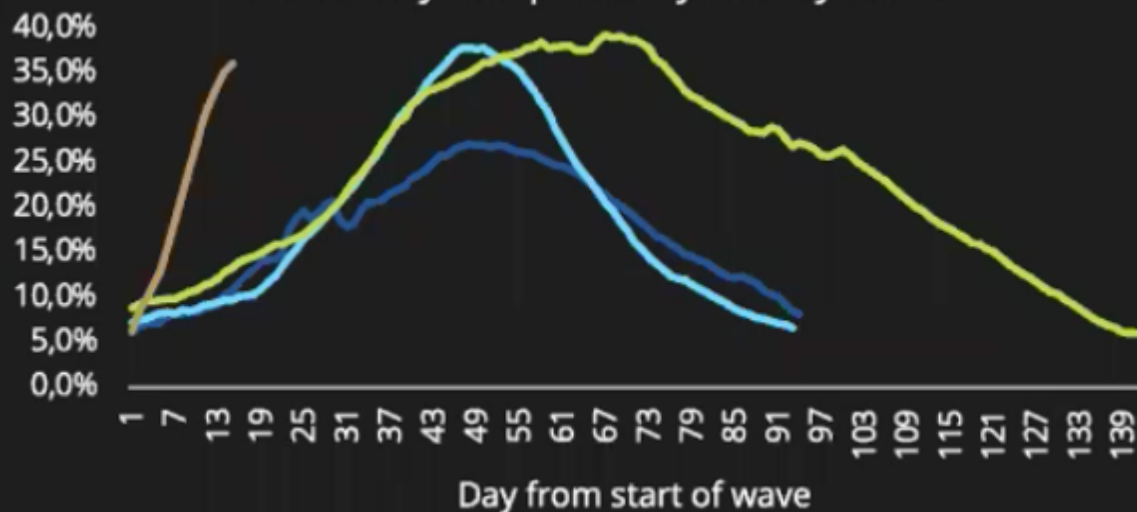
THOMSON REUTERS

# EPIDEMIOLOGY: faster spread than prior variants

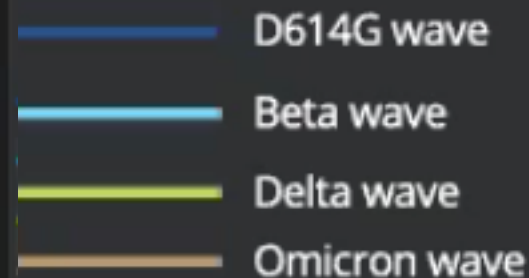
DH daily cases (7-day average) by wave



DH weekly test positivity rate by wave



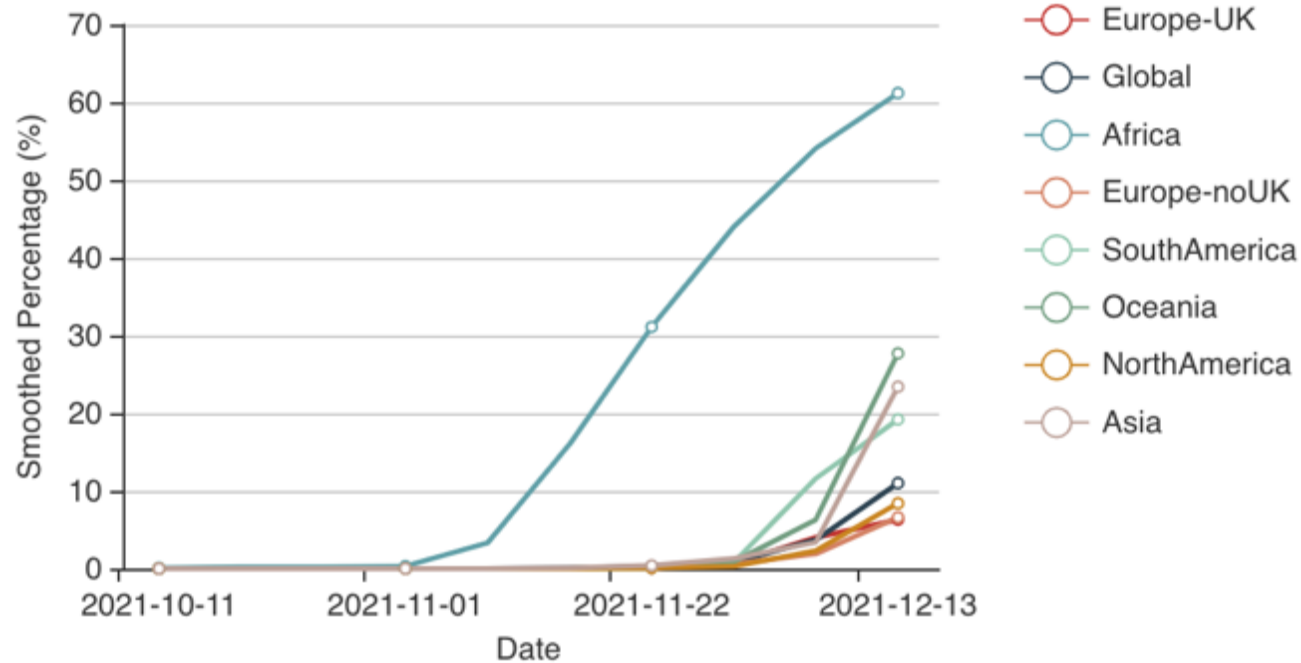
- Discovery Health is South Africa's largest private health insurer
- Data from 211k COVID test results, of which 78k were positive and 19k were positive during the "Omicron period" (15-Nov-21 to 07-Dec-21)
- Conclusion: **Faster increase** in new infections & test positivity with omicron than with the prior variants



# EPIDEMIOLOGY: faster spread than prior variants

Relative Variant Genome Frequency per Region  
(exponentially smoothed alpha=0.3)

Click Legend to show/hide series



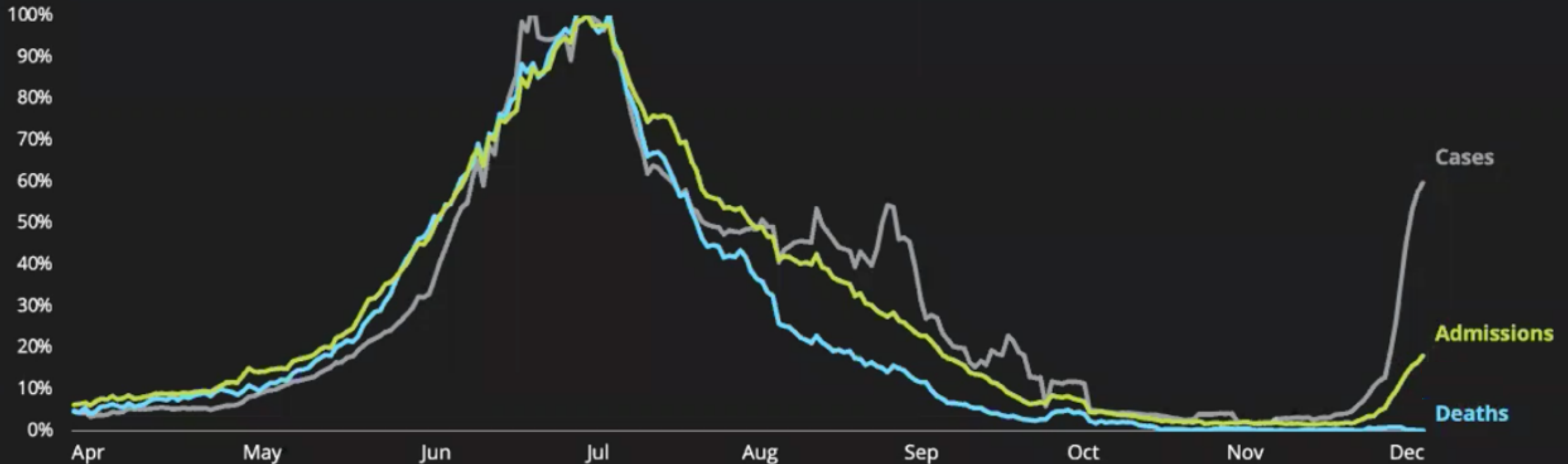
Omicron has been detected in **69 countries**

**>60% of isolates** in Africa are Omicron

Rapid increase in cases prevalence worldwide

# CLINICALLY: infection curve uncoupled from admissions & deaths

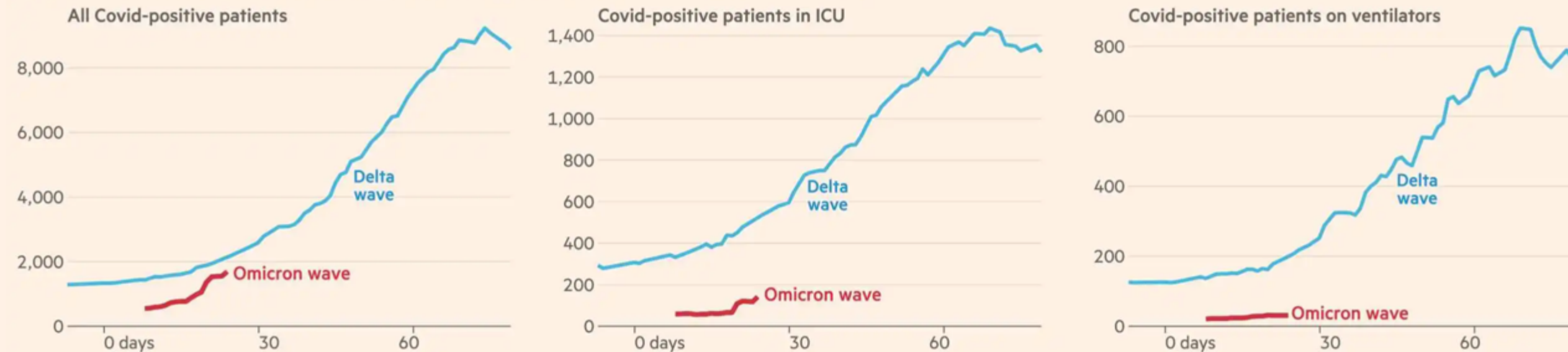
Cases, admissions and deaths indexed to the Delta wave, each as a share of Delta peak (%)





# CLINICALLY: fewer patients in ICUs or on mechanical ventilation

Number of Covid-positive patients requiring different levels of care, by days since each wave began



\*Start of wave defined as when 7-day average of cases rose for 7 successive days  
Source: FT analysis of data from South Africa's National Institute for Communicable Diseases  
FT graphic by John Burn-Murdoch / @jburnmurdoch

- Although the number of COVID positive patients in Gauteng is approaching the level from the Delta wave, the number in ICUs or on ventilators is much lower

# CLINICALLY: anecdotally a milder course ... at least if vaccinated

## Out-of-hospital acute care

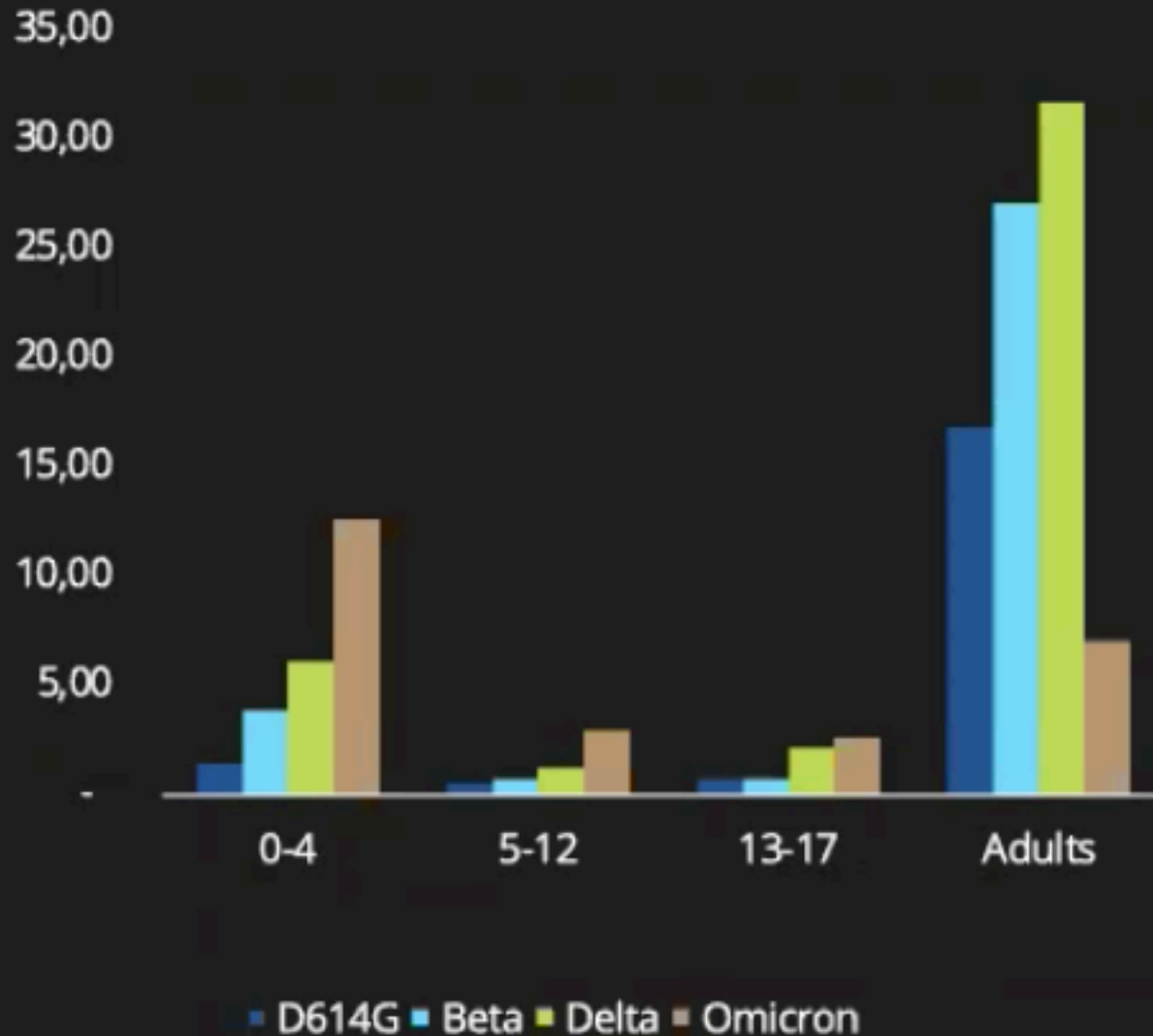
- **Higher reinfections and breakthrough infections** than other waves, including vaccinated
- **Shorter incubation period** of 3-4 days
- **Milder illness** with reported **recoveries within 3 days**
- **Scratchy/sore throat** most common early symptom, like other waves
- Typical features include **nasal congestion, dry cough and myalgia, especially lower back pain**

## Admissions

- Most **hospitalised patients** for Covid-19 related disease are **unvaccinated**
- High number of hospitalisations in Gauteng for non-Covid care, present with Covid as an **incidental finding on admission**
- **Less respiratory distress** on presentation
- Proportion of **High care and ICU admissions lower** compared to previous waves
- Significantly lower proportion of admitted patients requiring oxygen support
- Most hypoxic **patients requiring oxygenation are unvaccinated**
- **16% of ICU admissions are vaccinated** (raw data)

# CLINICALLY: more hospital admissions among children

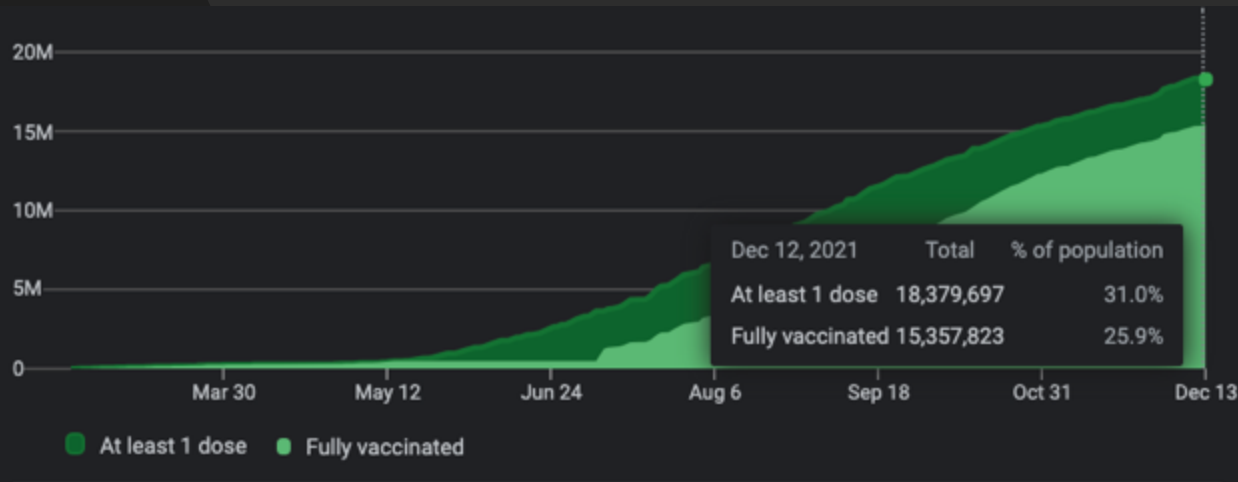
COVID19 admissions per 1,000 person years



- Unlike prior waves, children under 5 yo have higher risk of admission than adults

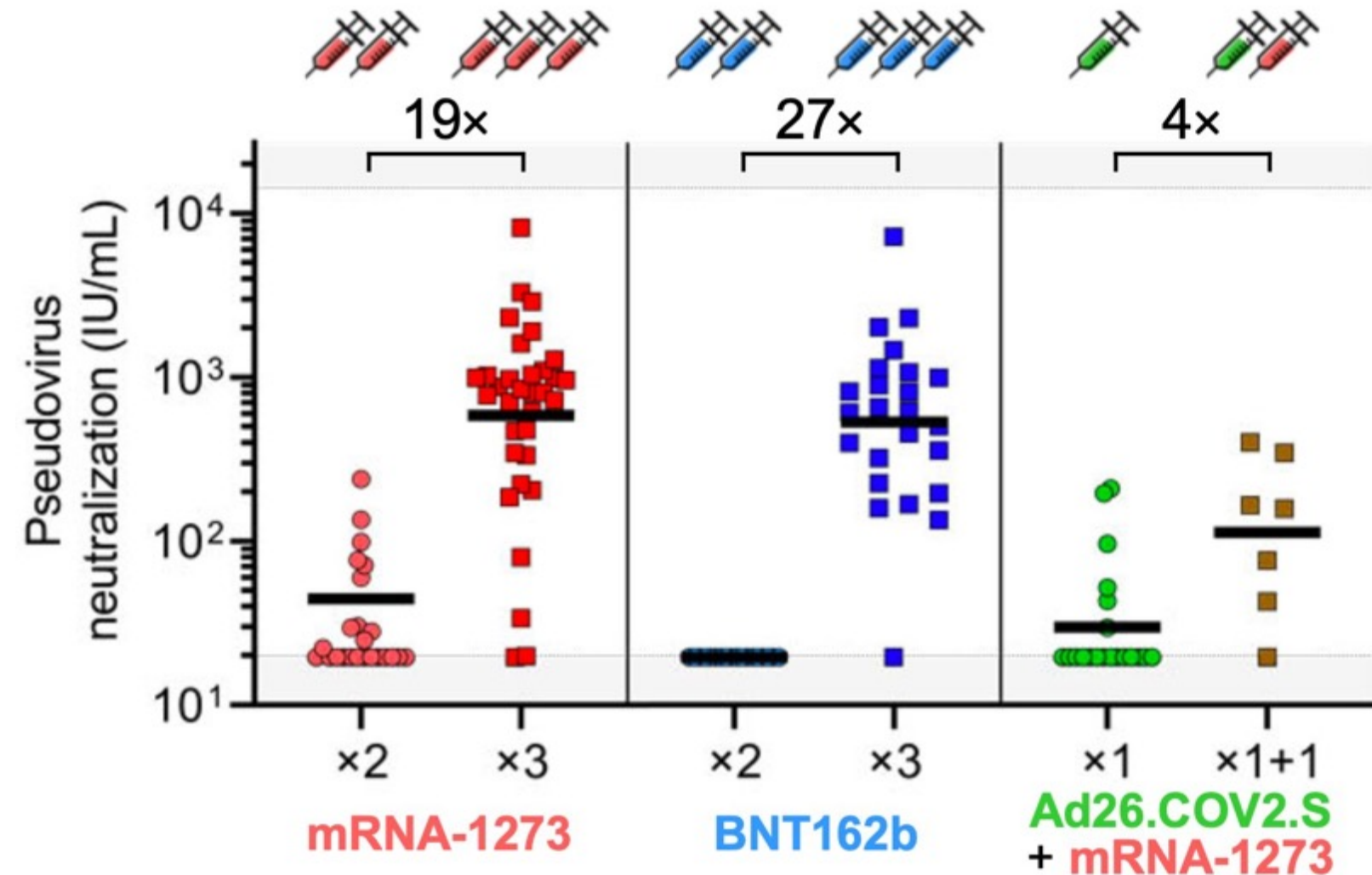
# IS OMICRON "MILD" or ~~ARE THE VACCINES WORKING?~~ is immunity

- Only **26%** of South Africa is fully vaccinated but **72%** of people in Gauteng are seropositive, suggesting high levels of prior immunity.



- Most hospitalized patients are unvaccinated
- Most ICU patients are unvaccinated
- Greater proportion of children hospitalized than seen in prior waves of the pandemic
- According to Discovery Health models, 2 doses of Pfizer vaccine provided:
  - 33% protection against infection
  - **70% protection against hospitalization**

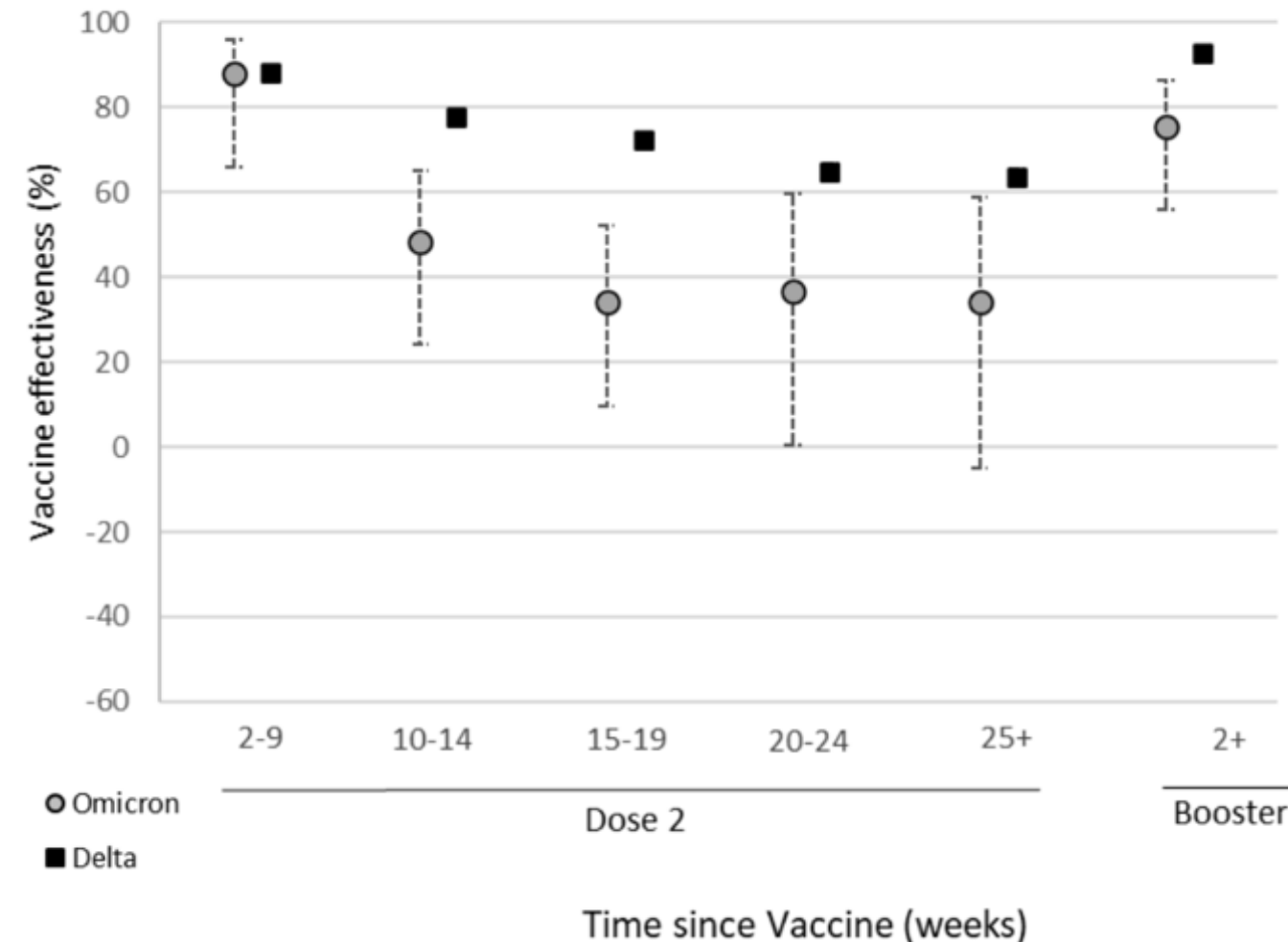
# VACCINES: evidence of neutralizing antibodies against Omicron



- Measured potency of sera from vaccinated patients against WT, delta, & omicron pseudoviruses *in vitro*
- Neutralization of omicron was undetectable in most vaccinated individuals, but individuals with boosted mRNA vaccines exhibited potent neutralization

# VACCINES: evidence of vaccine effectiveness against Omicron

Two doses of BNT162b2 with a BNT162b2 booster dose



- Case-control study based on COVID test results from UK labs cross-referenced against national vaccine registries
- Vaccine effectiveness against symptomatic diseases by period after Pfizer vaccination shows
  - High but waning effectiveness for Delta, improved with booster
  - More rapid waning of effect for omicron, significantly improved with booster

$$VE = (1 - \text{odds of vaccination in cases}) / (\text{odds of vaccination in controls})$$

# SUMMARY: keep calm & carry on

- **MOLECULAR:** Omicron (B.1.1.529) has spike protein mutations that **enhance infectivity/transmission**, unclear immune evasion
- **EPIDEMIOLOGIC:** Omicron has rapidly spread throughout Africa & worldwide, it is already here & **will likely become dominant strain**
- **CLINICAL:** Omicron may cause less serious disease, at least in those with prior immunity. **Vaccination remains effective** at preventing serious illness
- Emphasizes the importance of collaboration & information sharing



"YOU FEAR THE LEAST  
WHAT YOU KNOW  
THE MOST ABOUT"

-JOHN GLENN

(1921-2016)



thank you



KEEP CALM

AND

OMICRON

Thank you

A white, torn paper effect runs horizontally across the bottom of the image, with a jagged, irregular edge that gives the impression of a piece of paper being pulled away from a black background.