XVI CURSO EN AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

Vigo, January 28 and 29, 2022

COVID-19 Pandemic Update: The Omicron wave!

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Hospital Universitari

UNIVERSITAT DE BARCELONA

In Wuhan, China started the outbreak of a novel Coronavirus (COVID-19) in Dec. 2019

Normile D. Science. Jan. 3, 2020 , 10:35 AM

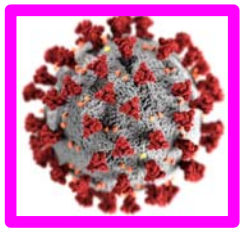
Widespread rapid dissemination in our hyper-connected world creates real-time challenges to prediction analyses

2020-2021


VACCINE
Pfizer
BIONTECH
Coronavirus COVID-19
VACCINE
moderna

2020-2022?

… Omicron!



COVID-19 Pandemic Update: The Omicron wave!

- Current epidemiology
- Virological characteristics
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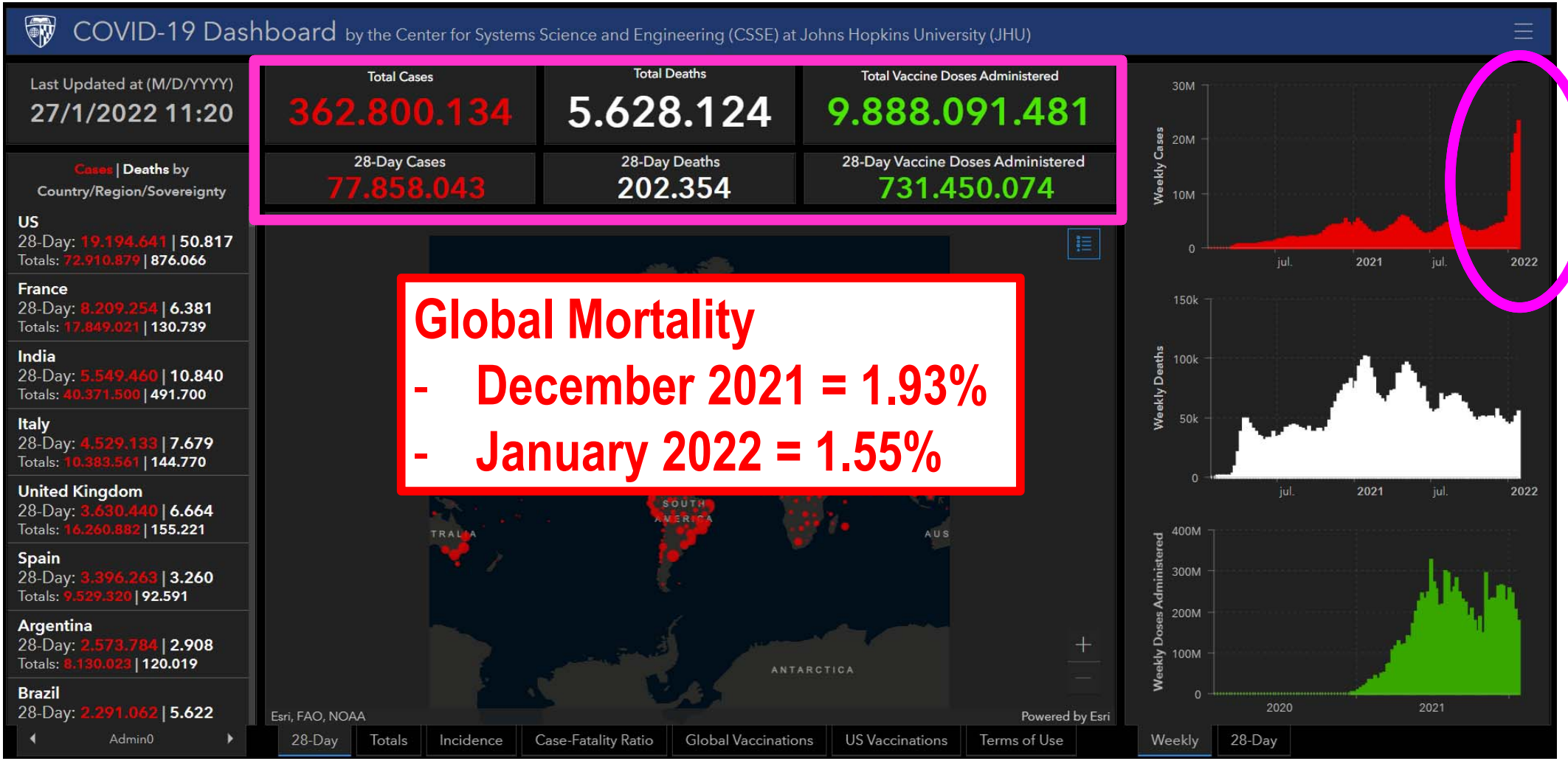
- Take-home messages

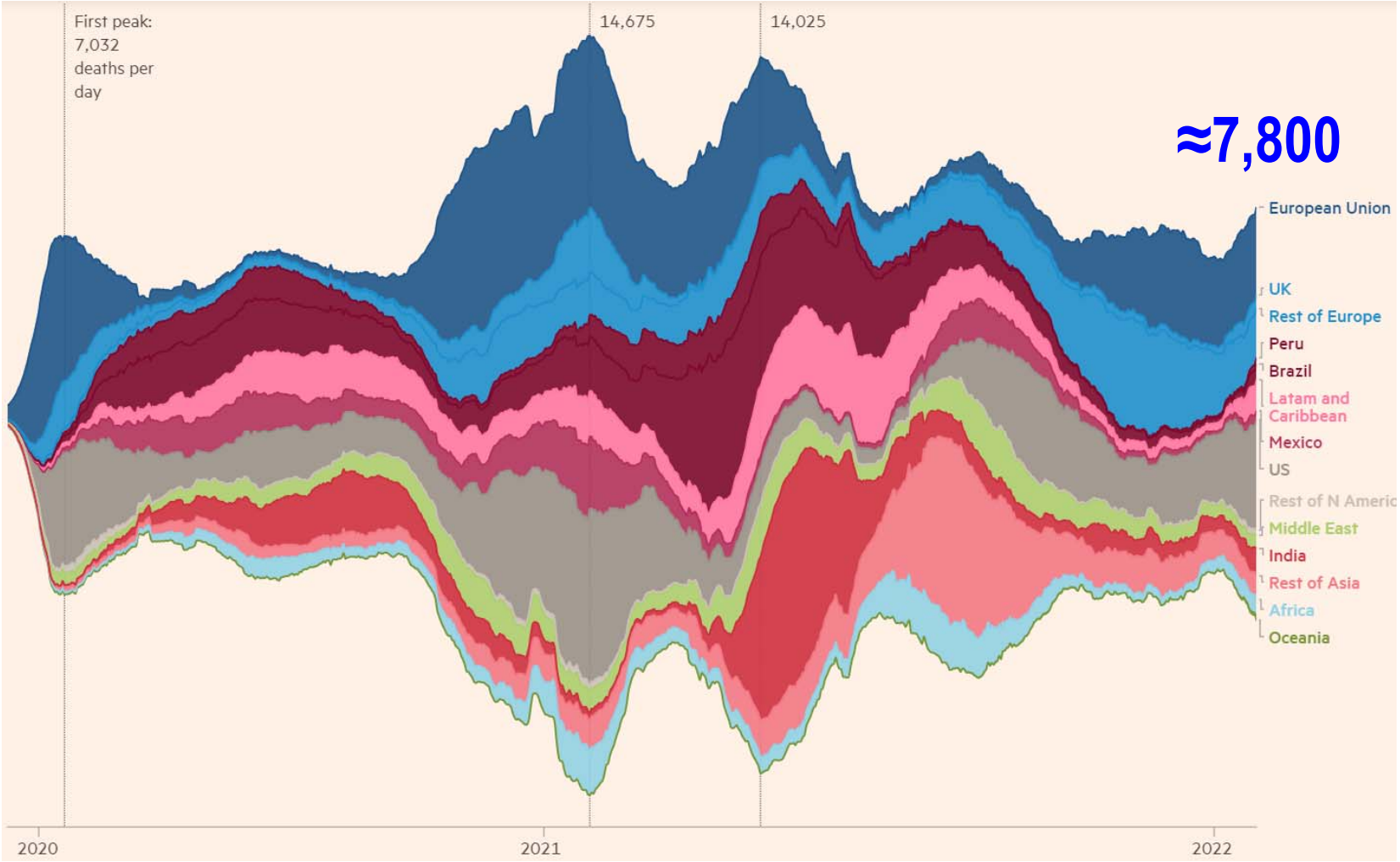
January 28th 2022

COVID-19 Global Cases



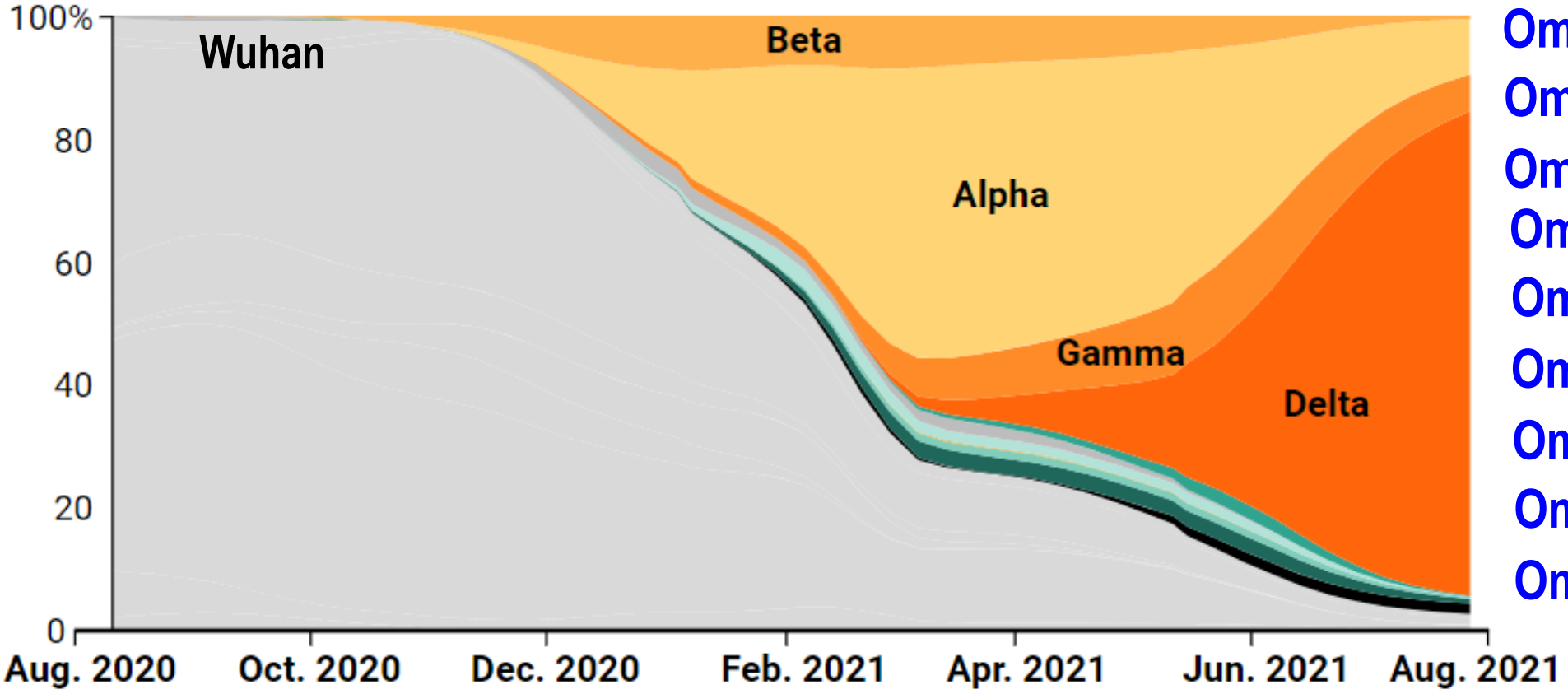
https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6; accessed on January 27th 2022

Global COVID-19: Almost 8,000 daily deaths!



https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938?shareType=nongift – January 27th 2022

SARS-CoV-2 VoC in the World: Omicron will replace them!



Omicron!
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Omicron!
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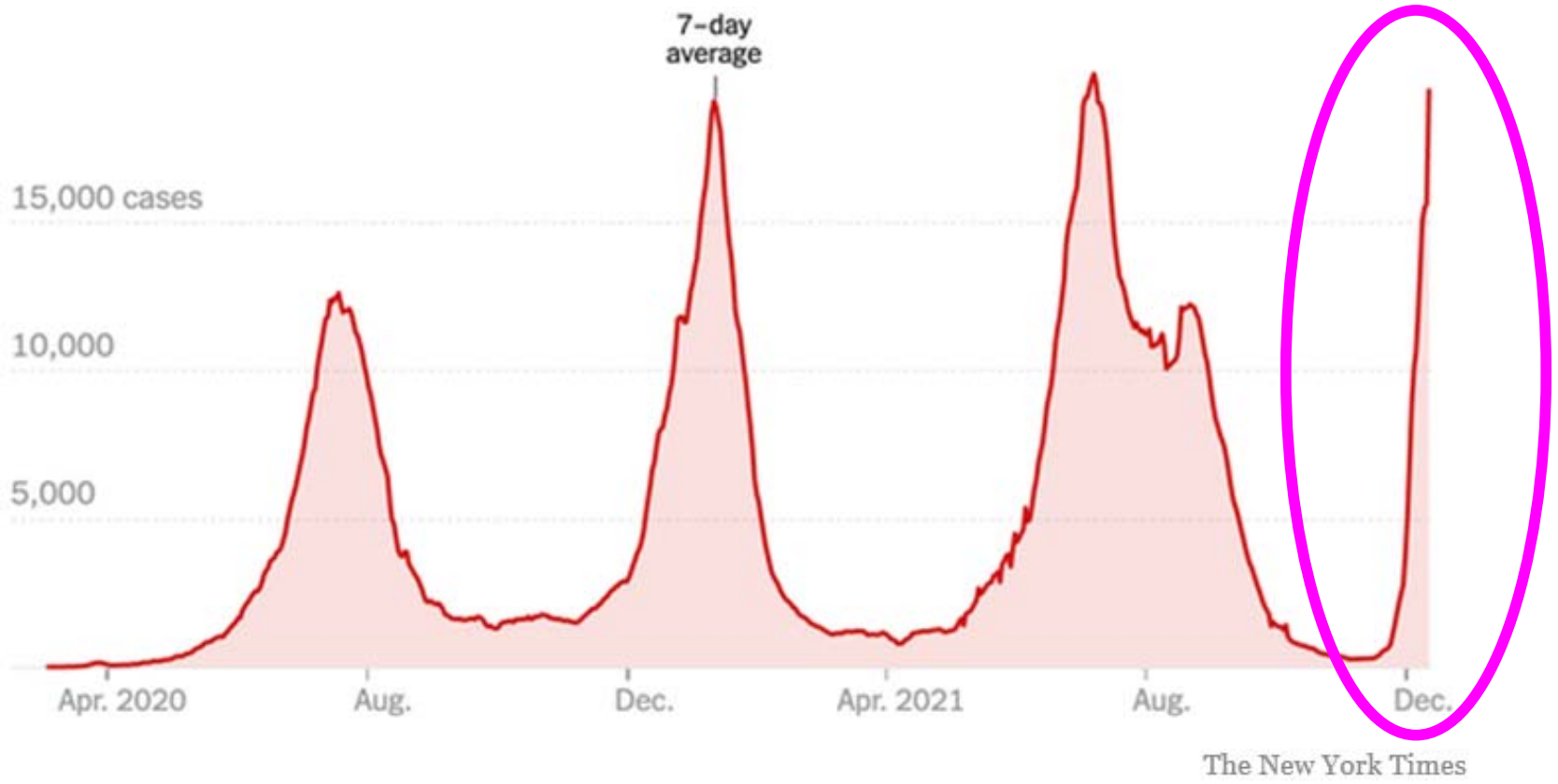
Omicron!
Omicron!
Omicron!

SARS-CoV-2 variants began to emerge in 2020. Alpha surged in many countries in early 2021, then was largely replaced by Delta. Two other variants of concern, Beta and Gamma, account for a smaller number of cases.

Kupferschmidt K. Science, Aug 20th 2021; 373:844-849.

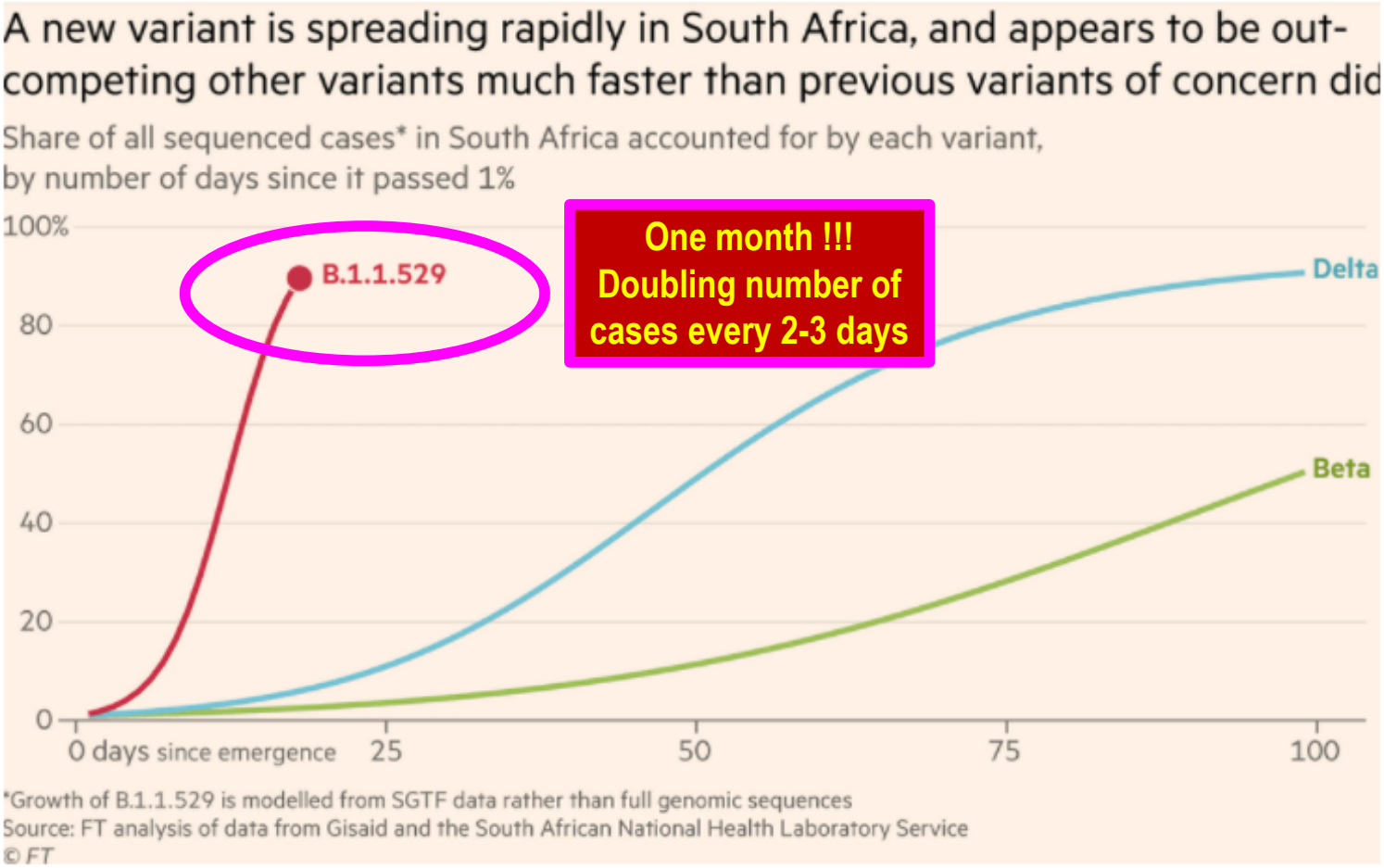
The Omicron variant was detected in southern Africa in Nov. 2021, and predominates in South Africa and Botswana



Omicron >90%!

The New York Times. December 13th 2021.

The Omicron variant (B.1.1.529) is much more transmissible than the previous variants of concern (Beta, Delta) !!!



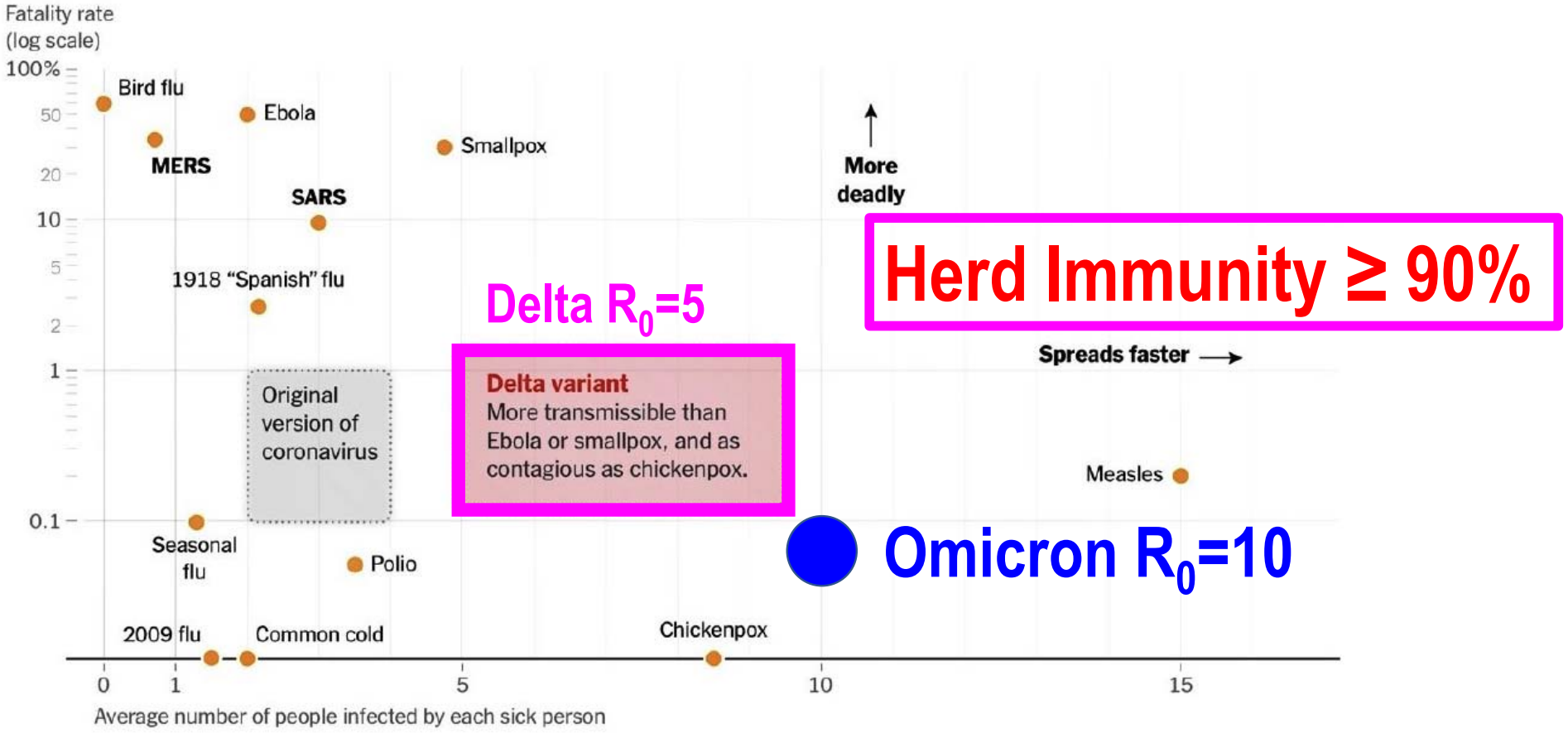
https://timmermanreport.com/2021/11/omicron-variant-the-latest-twist-in-the-pandemic/; November 26th 2021; Burki TK. Lancer Respir Med. Dec 17, 2021

The Omicron variant was detected in southern Africa in Nov. 2021 and has been already detected in ≈100 countries = New Global Wave

Once introduced in a given country, Omicron will replace Delta variant in ≈ One month!

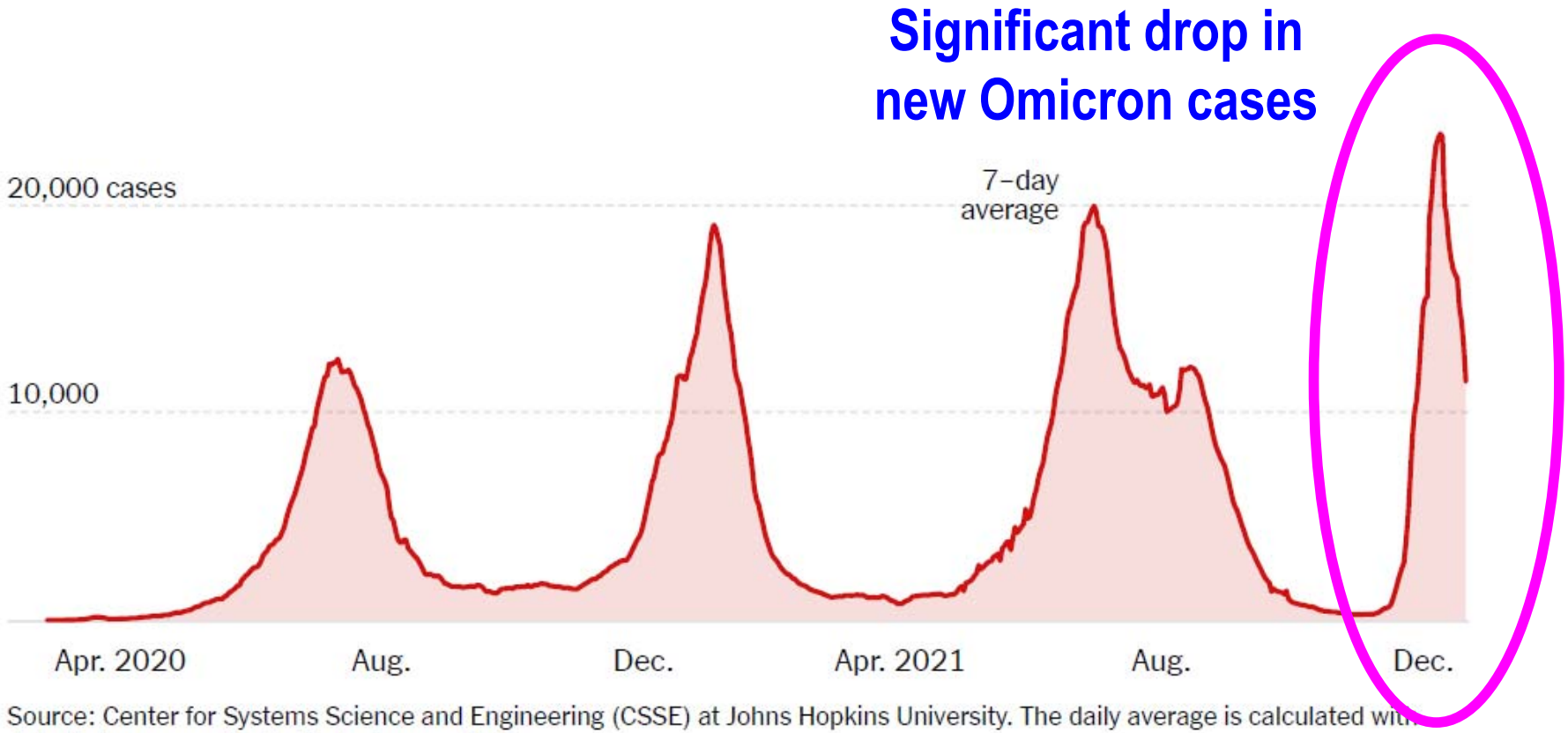
https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html; December 27th 2021.

Omicron variant (R_0= 10): Highly transmissible! More than Chickenpox and closer to Measles



https://www.nytimes.com; https://www.nature.com/articles/d41586-021-02259-2; Liu Y et al,. J Travel Med. Oct 11 2021; Burki TK. Lancer Respir Med; Dec 17, 2021

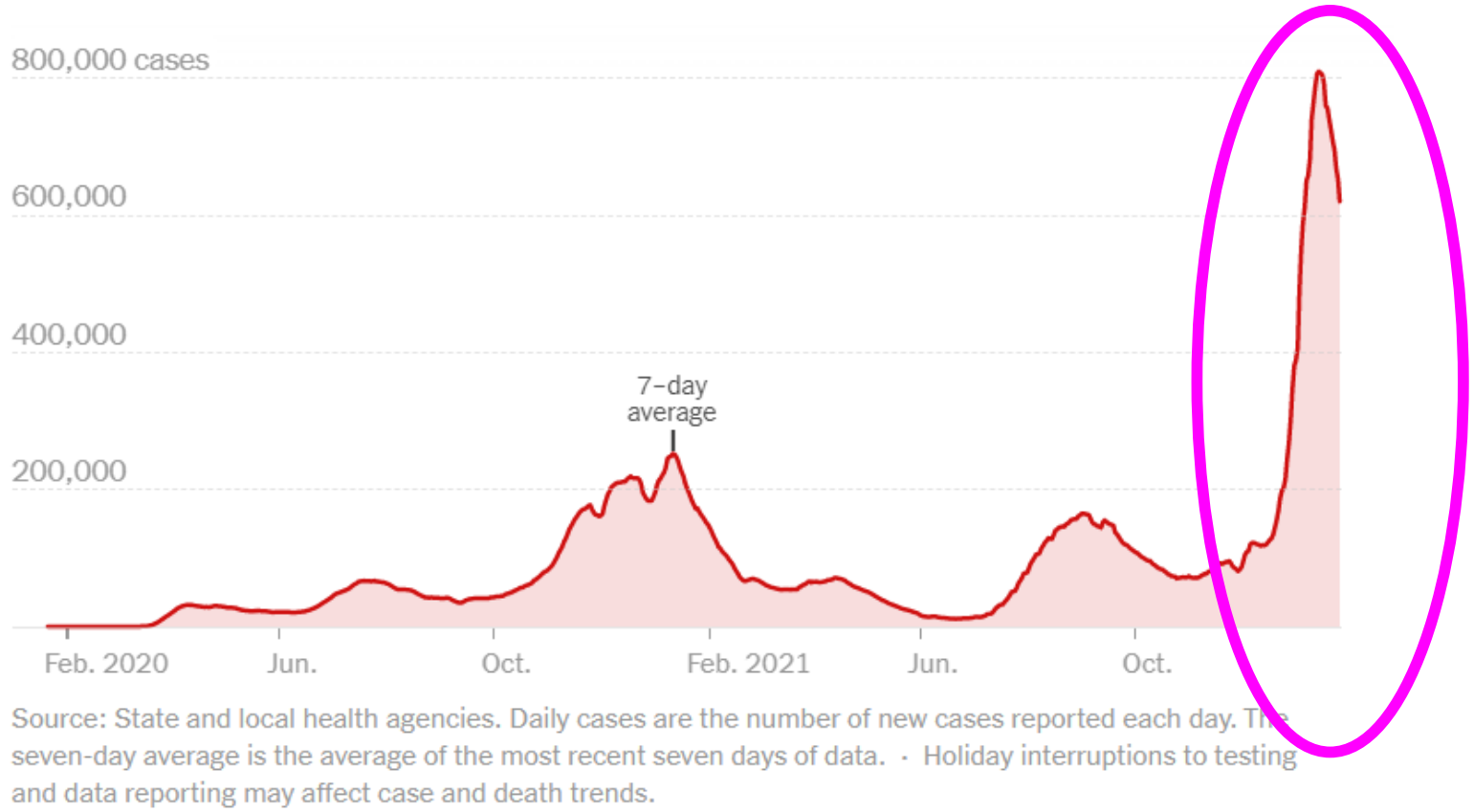
South Africa's huge Omicron wave appears to be decreasing just as quickly as it grew!



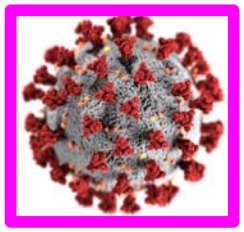
Source: Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. The daily average is calculated wit… data that was reported in the last seven days.

https://www.nytimes.com/live/2021/12/30/world/omicron-covid-vaccine-tests?campaign_id=154&emc=edit_cb_20211230&instance_id=49063&%E2%80%A6. Dec 31, 2021

Omicron wave appears to be decreasing just as quickly as it grew also in USA!



https://www.nytimes.com/live/2021/12/30/world/omicron-covid-vaccine-tests?campaign_id=154&emc=edit_cb_20211230&instance_id=49063&%E2%80%A6. Dec 31, 2021



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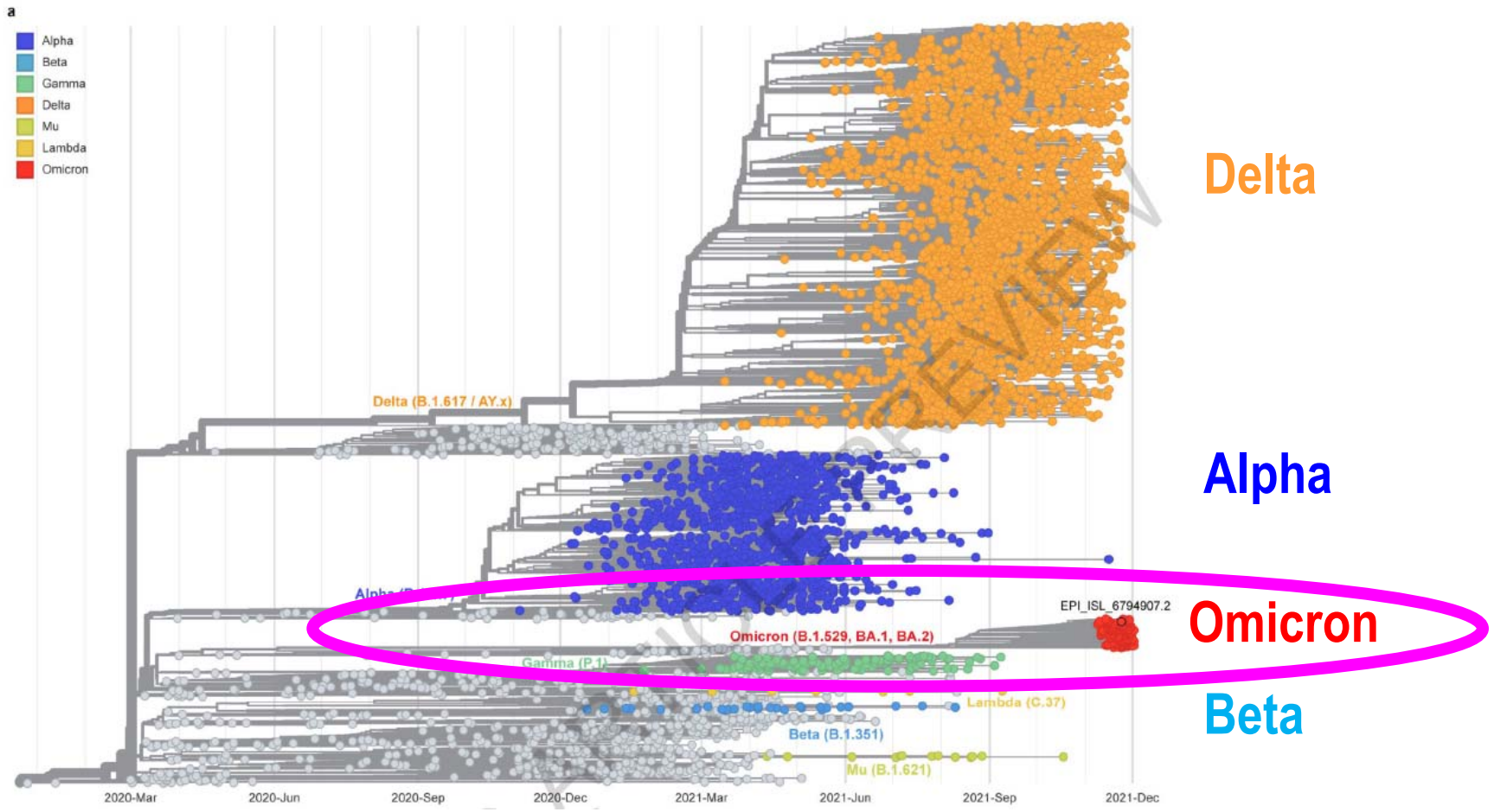
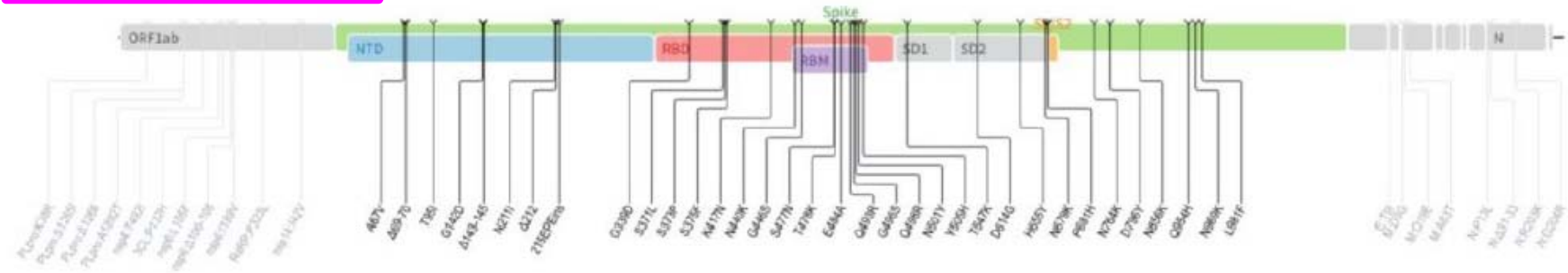
SARS-CoV-2 global phylogeny highlighting the new Omicron lineage



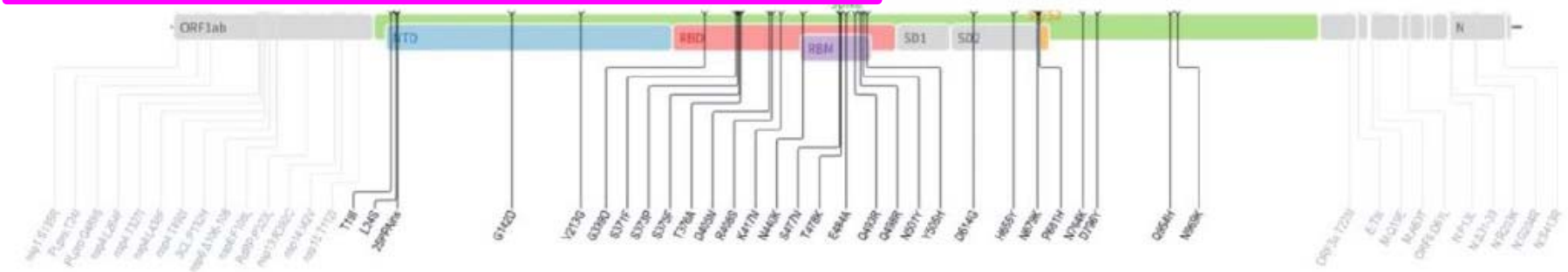
Planas D. Ho D et al. Nature. December 23, 2021.

Omicron (B.1.1.529) variant has lineages: BA.1 and BA.2

Omicron BA.1 lineage



Omicron BA.2 lineage; no 69/70 deletion, fewer mutations



https://github.com/cov-lineages/pango-designation/issues/361; https://outbreak.info/situation-reports?pango=BA.1; accesed Dec 27 2021; https://outbreak.info/situation-reports?pango=BA.2; accessed Dec 27 2021.

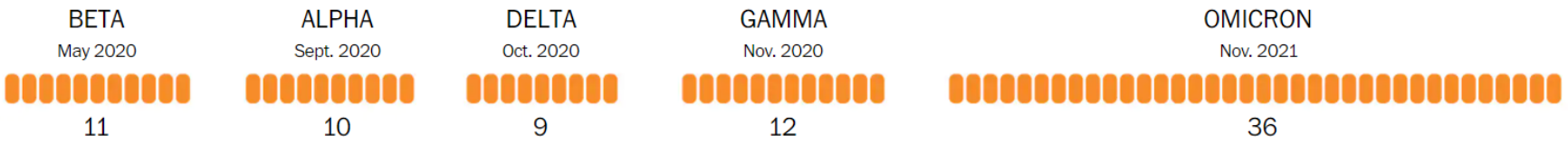
The Omicron variant (B.1.1.529) has more than 50 mutations, 36 in the Spike protein

Understanding omicron's many mutations

The virus's spikes have far more changes than we've seen in any previous variant, and researchers are racing to figure out how they affect it — and us

By Bonnie Berkowitz and Aaron Steckelberg

December 16, 2021 at 2:03 p.m. EST



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

https://www.washingtonpost.com/health/2021/12/16/omicron-variant-mutations-covid Dec 16th 2021; https://github.com/cov-lineages/pango-designation/issues/361; https://outbreak.info/situation-reports?pango=BA.1; accessed Dec 27 2021; https://outbreak.info/situation-reports?pango=BA.2; accessed Dec 27 2021.

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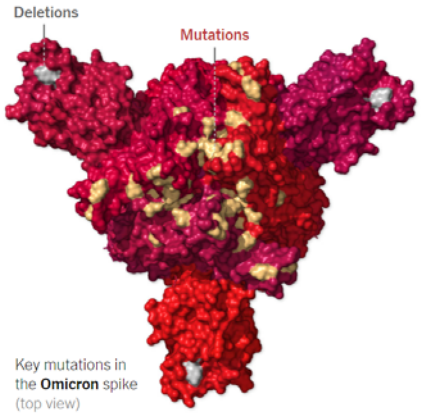
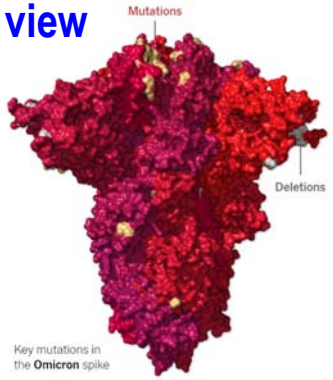
Top view



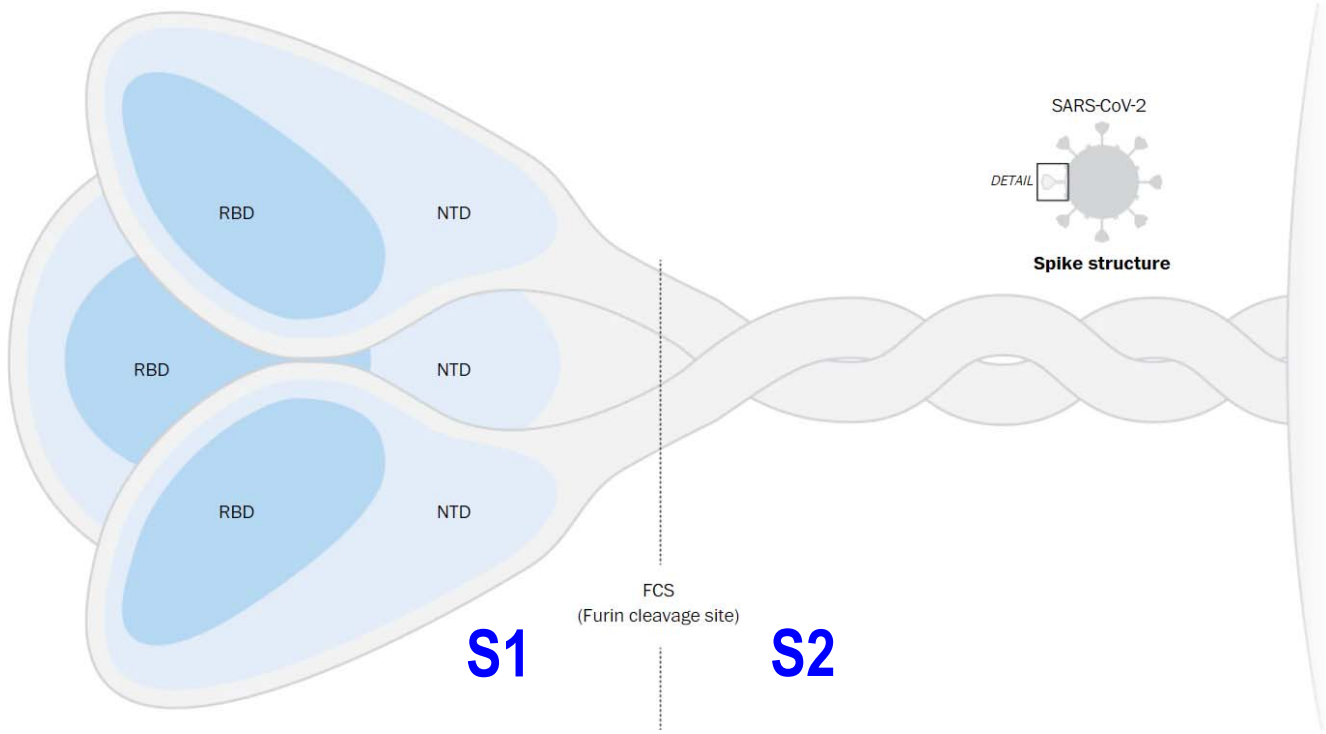
Side view



S1

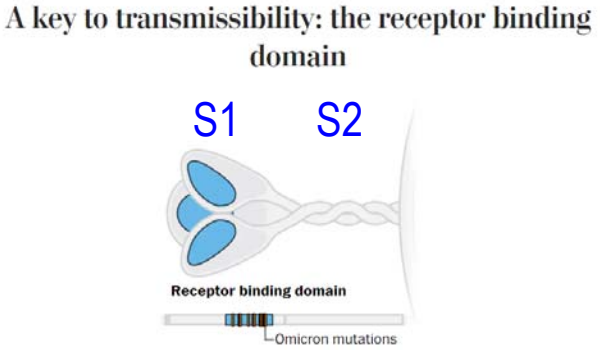
S2

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.

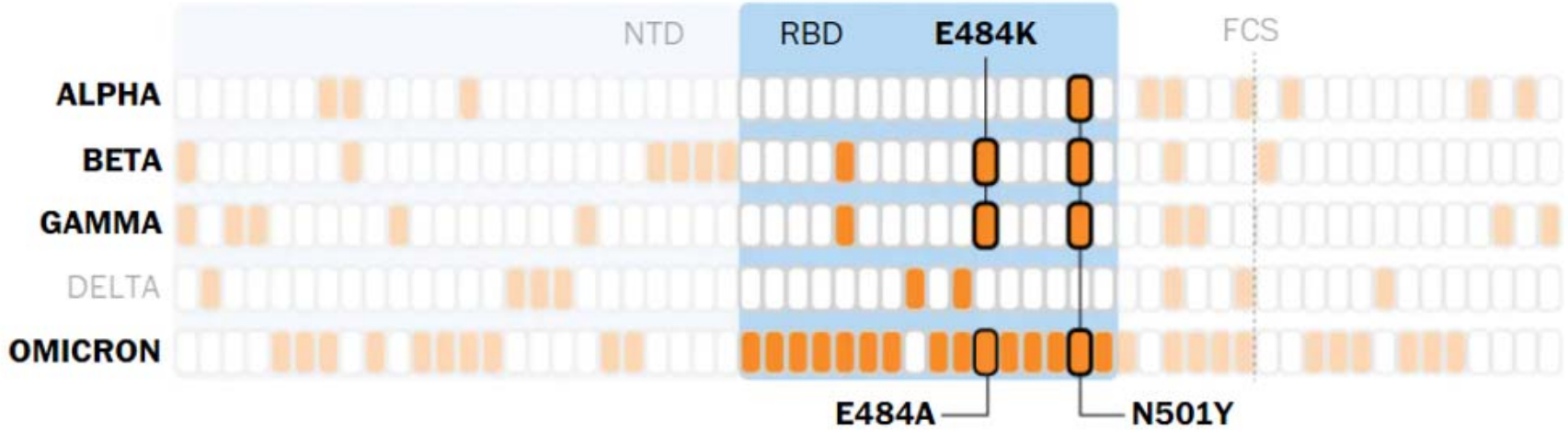


https://timmermanreport.com/2021/11/omicron-variant-the-latest-twist-in-the-pandemic/; November 26th 2021; and https://www.washingtonpost.com/health/2021/12/16/omicron-variant-mutations-covid Dec 16th 2021; https://github.com/cov-lineages/pango-designation/issues/361; https://outbreak.info/situation-reports?pango=BA.1; accessed Dec 27 2021; https://outbreak.info/situation-reports?pango=BA.2; accessed Dec 27 2021

The Omicron variant (B.1.1.529)
Mutations in the receptor binding domain (RBD)



Multiple RBD (including **E484A**) and NTD mutations (**and deletion 69/70 in BA.1 lineage;** Lack of S gene amplification by the TaqPath method of Thermofisher) are associated with **resistance to neutralizing antibodies and therapeutic monoclonal antibodies**



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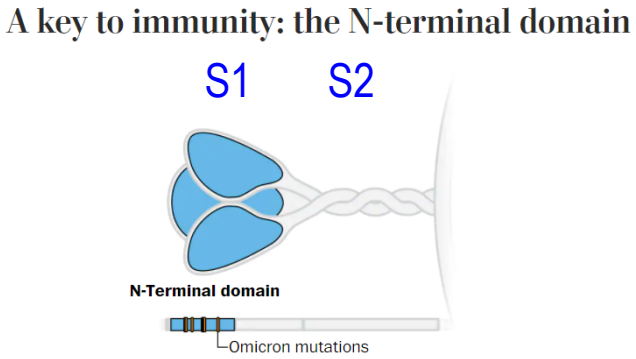
The Omicron variant (B.1.1.529)
Mutations in the N-terminal domain (NTD)



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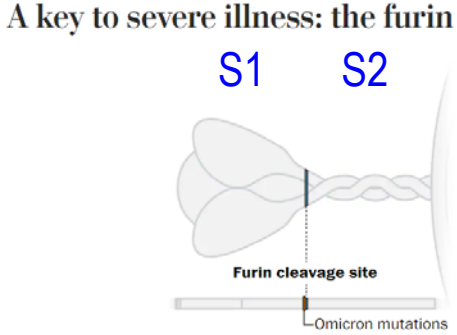
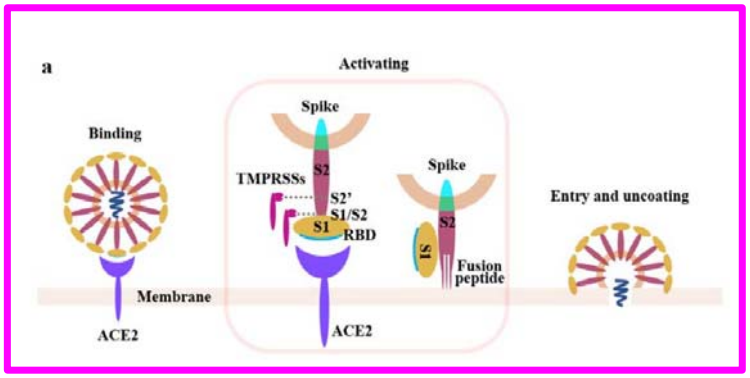
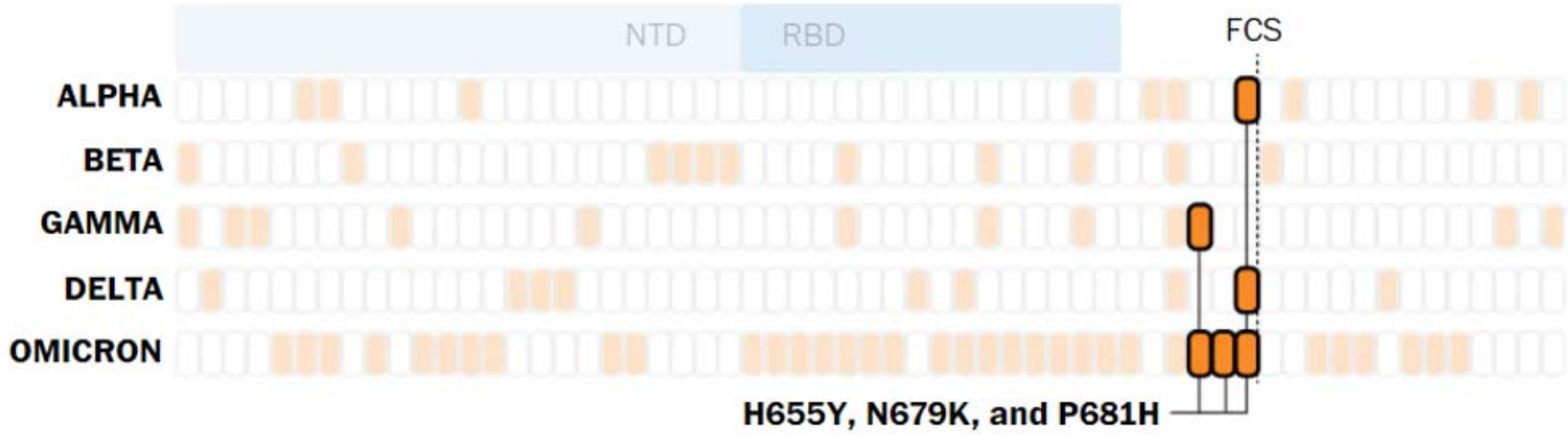
The Omicron variant (B.1.1.529)
Mutations in the Furin cleavage site (FCS)





A cluster of mutations (**H655Y + N679K + P681H**) near the furin cleavage site (FCS, S1-S2) are associated with more efficient cell entry → **enhancing transmissibility** (Yu et al., 2021).



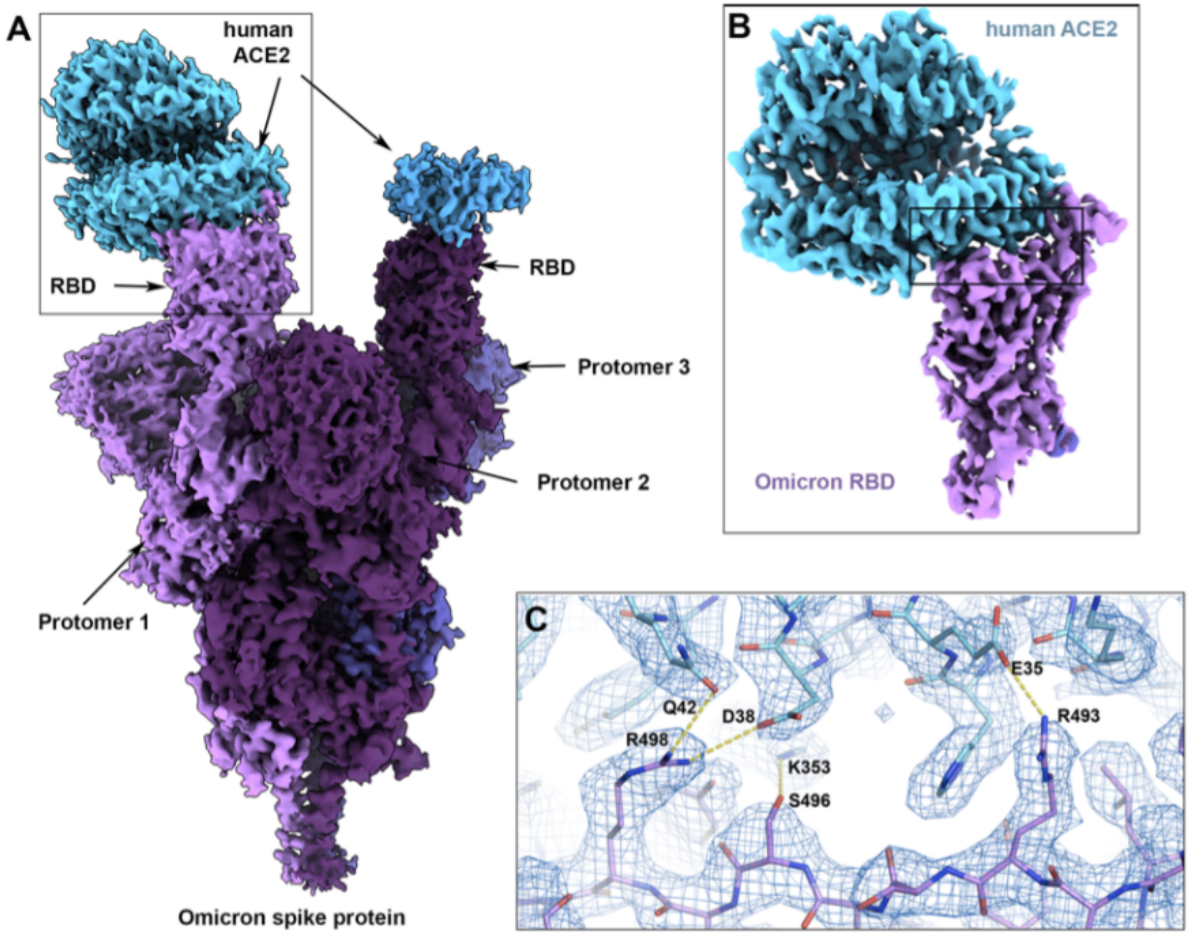
https://timmermanreport.com/2021/11/omicron-variant-the-latest-twist-in-the-pandemic/; Nov. 26th 2021; and https://www.washingtonpost.com/health/2021/12/16/omicron-variant-mutations-covid Dec 16th 2021; De Wit Nature Rev Microbiol, 2016; Fung S et al. Annu Rev Microbiol. 2019. 73:529–57; Zhou P et al, Nature, 2020; Yan R et al. Science. 2020; Meng T et al. bioRxiv. doi.org/10.1101/2020.02.08.926006; https://github.com/cov-lineages/pango-designation/issues/361; https://outbreak.info/situation-reports?pango=BA.1; accessed Dec 27 2021; https://outbreak.info/situation-reports?pango=BA.2; accessed Dec 27 2021

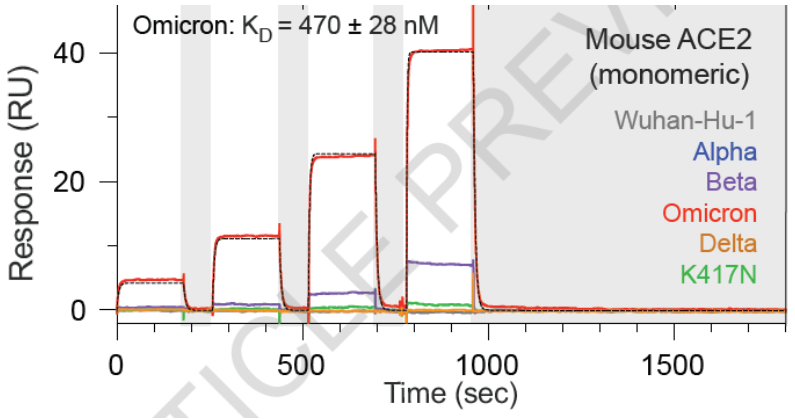
The Omicron variant (B.1.1.529)
Other Spike and Nucleocapsid mutations

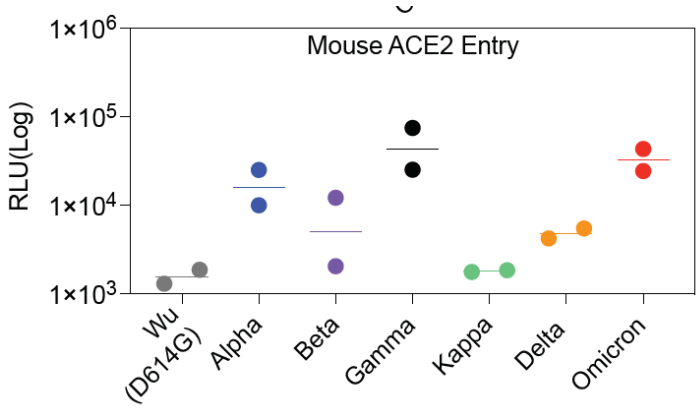
- **Spike Q498R and N501Y,** also seen in other variants, **increase affinity ACE2 receptor** (Zahradnik et al., 2021).
- **Spike NSP6 deletion** (Δ105-107), similar to deletion to Alpha, Beta, Gamma, Lambda, may be associated with **evasion of innate immunity** (interferon antagonism) and could also **enhance transmissibility** (Benvenuto et al., 2021).
- **Nucleocapsid R203K + G204R mutations**, also seen in Alpha, Gamma and Lambda variants, are associated with **increase the expression of sub-genomic RNA** (Leary et al., 2020) and **increase of viral load and increase infectivity** (Mourier et al., 2020).

https://timmermanreport.com/2021/11/omicron-variant-the-latest-twist-in-the-pandemic/; November 26th 2021; and https://www.washingtonpost.com/health/2021/12/16/omicron-variant-mutations-covid Dec 16th 2021; https://github.com/cov-lineages/pango-designation/issues/361; https://outbreak.info/situation-reports?pango=BA.1; accessed Dec 27 2021; https://outbreak.info/situation-reports?pango=BA.2; accessed Dec 27 2021

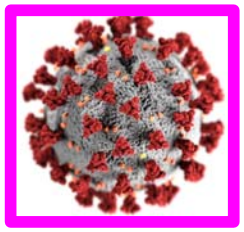
Cryo-EM structure of the Omicron spike protein-ACE2 complex







Manar D et al. bioRxiv preprint December 21, 2021; Cameroni E et al. Nature. December 23, 2021



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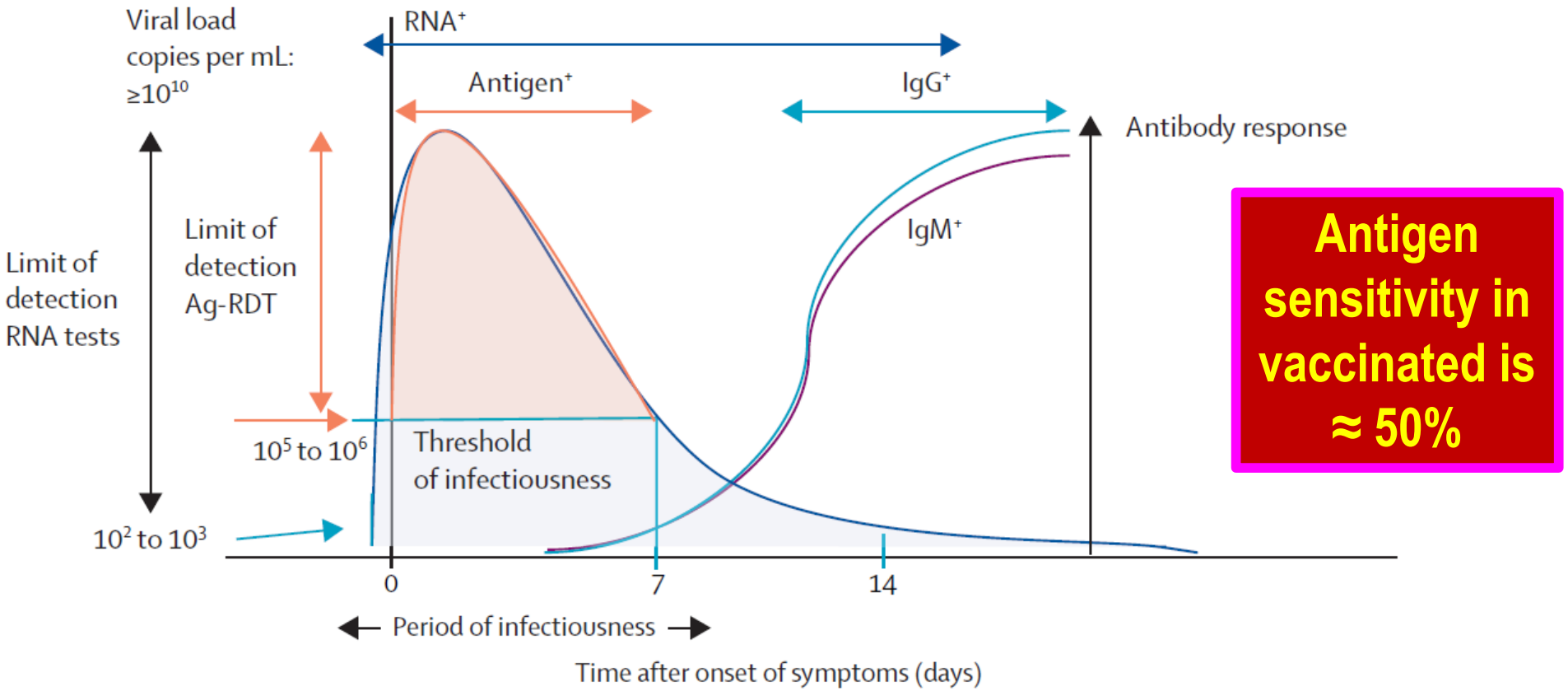
January 28th 2022

Timelines for optimal use of different diagnostic tests for COVID-19 detection and host response



Antigen sensitivity in vaccinated is ≈ 50%

Peeling RW et al. Lancet. Dec. 20th 2021; *Bergwerk M et al. N Engl J Med Oct 14th 2021;385:1474-84

Antigen RDT performance against Omicron is OK

- Antigen detection RDT detect the **nucleocapsid (N) protein** of SARS-CoV-2 (not the Spike [S] protein). Omicron's nucleocapsid protein has a single unique mutational difference from other SARS-CoV-2 variants, a deletion at aa31-33, that does not affect diagnostic performance.
- The UKHSA performed an study evaluating these five lateral flow devices for RDT using different dilutions: Acon Flow Flex 'self-test'; Innova Biotime 'self-test and professional use test'; Orient Gene 'self-test'; SureScreen 'professional use test'; SureScreen 'self-test'
- **Performance was optimal and similar to Delta variant with no false negative assay results.**

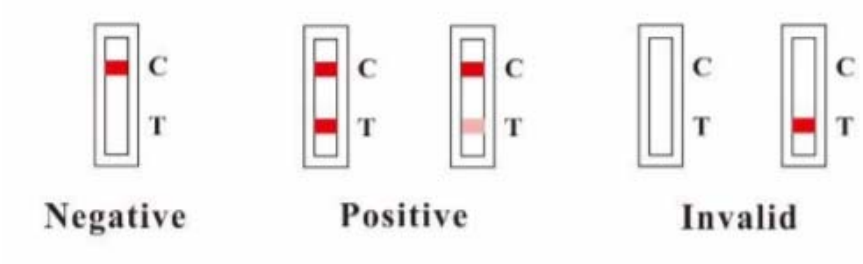


Table 2: Laboratory testing results for the sensitivity of 5 lateral flow devices (in or near deployment) for Omicron (contrived samples, sourced from UK patients Passage 2)

LFD / Date	Variant	Dilution	Viral titre FFU/ml	Viral Copy number	Number of samples tested	Number of negative results	Number of positive results
Acon Flowflex 09/12/2021	Omicron	1/80	1250	4,070,000	5	0	5
		1/800	125	280,000	5	0	5
		1/8,000	12.5	30,000	5	0	5
	Wild type	-	100	460,000	15	0	15
Innova Biotime 09/12/2021	Omicron	1/80	1250	4,070,000	5	0	5
		1/800	125	280,000	5	0	5
		1/8,000	12.5	30,000	5	0	5
	Wild-type	-	100	290,000	15	1	14
Orientgene 09/12/2021	Omicron	1/80	1250	4,070,000	5	0	5
		1/800	125	280,000	5	0	5
		1/8,000	12.5	30,000	5	0	5
	Wild-type	-	100	290,000	15	0	15
SureScreen Professional Test 09/12/2021	Omicron	1/80	1250	4,070,000	5	0	5
		1/800	125	280,000	5	0	5
		1/8,000	12.5	30,000	5	0	5
	Wild-type	-	100	580,000	15	0	15
SureScreen Self Test 09/12/2021	Live Omicron	1/80	1250	4,070,000	5	0	5
		1/800	125	280,000	5	0	5
		1/8,000	12.5	30,000	5	0	5
	Wild-type	-	100	560,000	15	0	15

UKHSA. Technical briefing #32. December 17, 2021

RT-PCR commercial assays against Omicron = OK

- **Amplification of several SARS-CoV-2 genes by RT-PCR (2-3 genes)**
  - ORF1a, ORF1b, **S**, E, M and/or N genes
  - Lack of S gene amplification (SGTF) by the Thermo Fisher TaqPath assay is key!

Table 2. **List of available assays/protocols for identification of SARS-CoV-2 Omicron variant (not exhaustive)**

Commercial or in-house assay	Spike gene amino acid substitution	Methodology	References
TIB MolBiol	S371L/S373P	Melting curve	[15,16]
TIB MolBiol	ins214EPE	Melting curve	[15,16]
TIB MolBiol	E484A	Melting curve	[15,16]
Thermo Fisher TaqPath	ΔH69/V70	SGTF	[20]
Seegene	E484A, N501Y, ΔH69/V70	RT-PCR	[21]
JRC	Multiple targets	RT-PCR - currently being validated	[18]
Israel Ministry of Health Central Virology Laboratory (CVL) and Israel Institute for Biological Research (IIBR)	nsp6 (Orf1a)	RT-PCR assay – as of 16 December 2021	[10]
University Hospital Geneva	Two partial S gene regions	RT-PCR and Sanger sequencing	[22]
Smorodintsev Research Institute of Influenza (St. Petersburg, Russia)	ORF1 deletion	RT-PCR	[23]
SSI, Denmark	Omicron specific 4-target PCR	RT-PCR	[19]

https://www.ecdc.europa.eu/sites/default/files/documents/Methods-for-the-detection-and-characterisation-of-SARS-CoV-2-variants-first-update.pdf

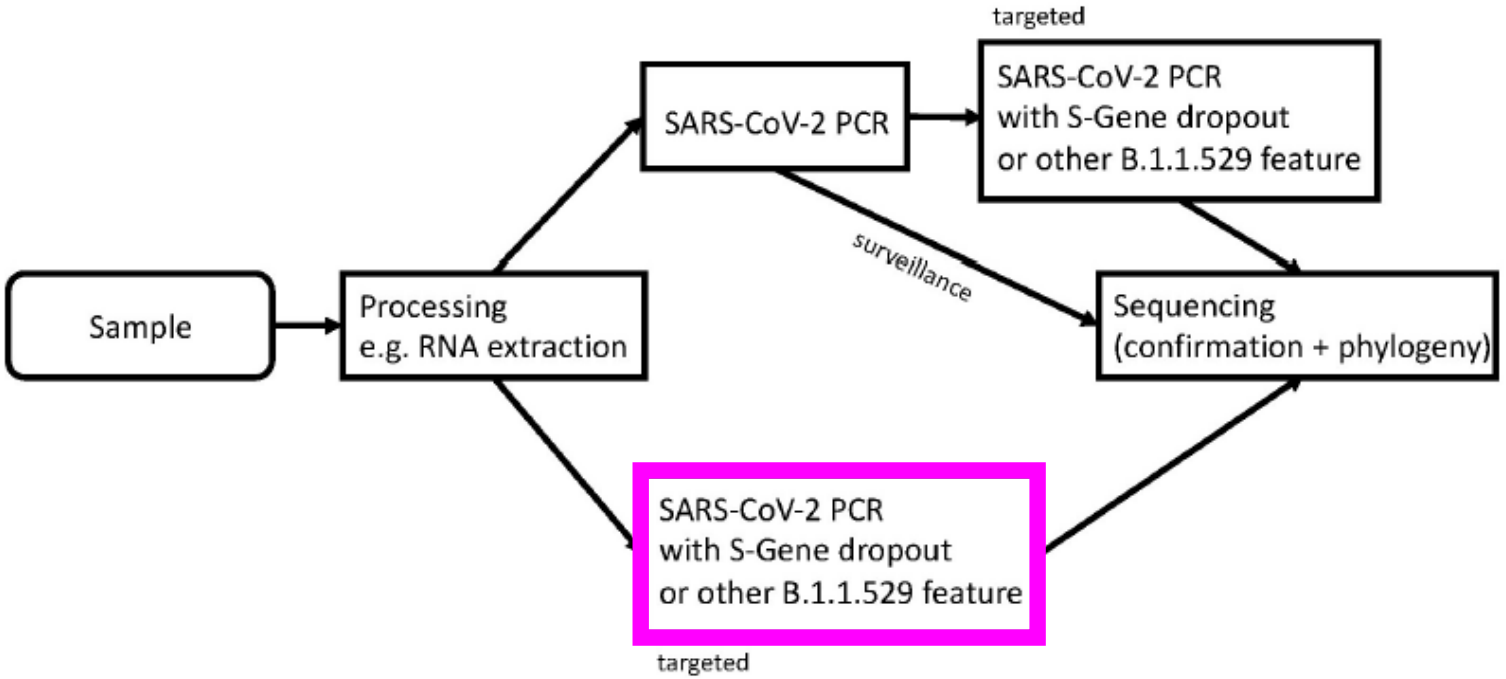
RT-PCR commercial assays against Omicron = OK

		Targets						Reported impact of VOC on signal detection of the S-gene target	
Supplier in Switzerland and Liechtenstein	Test-kit	ORF1ab	RdRp	S	E	M	N	Alpha (B.1.1.7)	Omicron (B.1.1.529)
Abbott	Abbott RealTime SARS-CoV-2 (#09N77-096)	0	1	0	0	0	1	No S-gene target	No S-gene target
Abbott	ALINITY m SARS-COV-2 ASSAY (#09N78-095)	0	1	0	0	0	1	No S-gene target	No S-gene target
Altona	Altona "RealStar® SARS-CoV-2 RT-PCR" (#821005)	0	0	1	1	0	0	No impact	No impact
Axon Lab / Cepheid	Gene Xpert® Xpress SARS-CoV-2 (#12039255)	0	0	0	1	0	1	No S-gene target	No S-gene target
Axon Lab	BioGX SARS-CoV-2 kit (#444213)	0	0	0	0	0	2	No S-gene target	No S-gene target
Axon Lab	EASY® SARS-CoV-2 Kit (#RT020)	0	1	0	0	0	1	No S-gene target	No S-gene target
Axon Lab	Hi-PCR® Coronavirus (SARS-CoV-2) Probe PCR Kit (#MBPCR242)	0	1	0	0	0	0	No S-gene target	No S-gene target
Axon Lab	NaGene Multiple Real-Time PCR kit for Detection of 2019-nCoV	1	0	0	0	0	1	No S-gene target	No S-gene target
Axon Lab	Progenie Coronavirus 2019-nCoV Assay (#CORO-UX 5.2)	0	0	0	0	0	1	No S-gene target	No S-gene target
Becton Dickinson	ViaSure SARS-CoV-2 (N1+N2) Real Time PCR (#444215)	0	0	0	0	0	2	No S-gene target	No S-gene target
Becton Dickinson	ViaSure SARS-CoV-2 S gene Real Time PCR (#444212)*	0	0	1	0	0	0	Detection compromised*	Not available in EU/CHE*
Becton Dickinson	ViaSure SARS-CoV-2, Flu (A+B) & RSV Real Time PCR Detection Kit (#444217)	0	0	0	0	0	2	No S-gene target	No S-gene target
bioMerieux	BIOFIRE® COVID-19 test (#423744)	1	0	0	0	0	0	No S-gene target	No S-gene target
bioMerieux	BIOFIRE® FILMARRAY® Respiratory Panel 2.1+ (RP2.1+) (#423740)	0	0	1	0	1	0	No impact	No impact
bioMerieux	SARS-COV-2 R-GENE® (#423720)	0	1	0	1	0	1	No S-gene target	No S-gene target
Bühlmann	Seegene Allplex™ 2019-nCov (#RP10243X) (older Kit)	0	1	0	1	0	1	No S-gene target	No S-gene target
Bühlmann	Seegene Allplex™ SARS-CoV-2 (#RV10248X) (newer kit)	0	1	1	1	0	1	2x 1-mer mismatch**	No impact
Bühlmann	Seegene Allplex™ SARS-CoV-2/Flu A/Flu B/RSV Assay (#RV10259X)	0	1	1	0	0	1	1x 1-mer mismatch**	Mismatch (delayed Ct/drop out possible)
DiaSorin	Simplexa™ COVID-19 Direct (#MOL4150)	1	0	1	0	0	0	No impact	No impact
Ender diagnostics	Ender MASS	1	0	0	0	0	0	No S-gene target	No S-gene target
Hologic	Panther® Fusion SARS-CoV-2 (#AW-21159-001)	2	0	0	0	0	0	No S-gene target	No S-gene target
Hologic	Aptima® SARS-CoV-2 Assay (#PRD-06419)	2	0	0	0	0	0	No S-gene target	No S-gene target
Hyris	SARS-CoV-2 human diagnostics (#bKTH-SCV2.02)	0	0	0	0	0	2	No S-gene target	No S-gene target
FRIZ Biochem	COVID-19 direct RT-PCR (#FBC101)	0	0	0	1	0	1	No S-gene target	No S-gene target
Lubioscience	2019-nCoV CDC EUA Kit (#10006606)	0	0	0	0	0	2	No S-gene target	No S-gene target
Mikrogen Diagnostik	ampliCube Coronavirus SARS-CoV-2 (#50143, #50144)	1	0	0	1	0	0	No S-gene target	No S-gene target
Qiagen	QiaStat-Dx Respiratory SARS-CoV-2 Panel (#691223)	0	1	0	1	0	0	No S-gene target	No S-gene target
Qiagen	NeuMoDx SARS-CoV-2 Assay (#300800)	1	0	0	0	0	1	No S-gene target	No S-gene target
Qiagen	SARS-CoV-2 N1+N2 Assay Kit (#222015 or #222017)	0	0	0	0	0	2	No S-gene target	No S-gene target
Roche Diagnostics	cobas® 6800/8800 SARS-CoV-2 (#09175431190)	1	0	0	1	0	0	No S-gene target	No S-gene target
Roche Diagnostics	cobas® 6800/8800 SARS-CoV-2 & Influenza A/B (#09233474190)	1	0	0	1	0	0	No S-gene target	No S-gene target
Roche Diagnostics	cobas® Liat SARS-CoV-2 & Influenza A/B (#09211101190)	1	0	0	0	0	1	No S-gene target	No S-gene target
Sansure	Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (#S3104E)	1	0	0	0	0	1	No S-gene target	No S-gene target
Siemens Healthineers	FTD SARS-CoV-2 qPCR Test (#11416302)	1	0	0	0	0	1	No S-gene target	No S-gene target
TECOmedical	PathoFinder RealAccurate® Quadruplex SARS-CoV-2 PCR Kit (#PF0971C-R)	0	1	0	0	0	1	No S-gene target	No S-gene target
TECOmedical	Eurobio Scientific EurobioPlex SARS-CoV-2 Multiplex (#EBX-041-192)	0	2	0	0	0	1	No S-gene target	No S-gene target
Thermo Fisher	TaqPath™ COVID-19 Combo Kit (#A48067)	1	0	1	0	0	1	S-gene drop out	S-gene drop out
Thermo Fisher	TaqPath™ COVID-19, FluA/B, RSV (#A49867)	0	0	1	0	0	1	No impact	No impact
TibMolBio	LightMix® Modular Sarbecovirus SARS-CoV-2 (#50-0776-96)	0	1	0	1	0	1	No S-gene target	No S-gene target

- The most frequently used SARS-CoV-2 PCR tests target many genomic loci, including the the **N gene** (N = 32), **ORF1ab region** (N = 16), the **RdRp gene** (N = 13), the **E gene** (N = 11), **the S gene (N = 8)**, and, in one case, the **M gene (N=1)**.
- **Only two of the eight assays targeting the S gene** appear to show S-gene dropout with the Omicron variant (Thermo Fisher TaqPath).
- Given the many SNPs localized on the sequence encoding for the S protein, and concentrated on the RBD in particular, it is likely that some of the serology assays utilizing the wildtype S protein may exhibit decreased sensitivity.

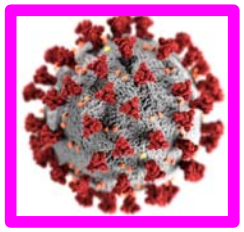
Metzger CMJA et al. Swiss Med Wkly. 2021 Dec 10;151:w30120.

Workflow for Screening and Confirmation of the SARS-CoV-2 Omicron variant



- **"Surveillance"** indicates the routine workflow for how Omicron variants could be detected by the sequencing surveillance program coordinated via CRIVE and the FOPH.
- **"Targeted"** indicates a suspected case of an Omicron variant which should be confirmed via sequencing.

Metzger CMJA et al. Swiss Med Wkly. 2021 Dec 10;151:w30120.



COVID-19 Pandemic Update: The Omicron wave!

- Current epidemiology
- Virological characteristics
- Diagnosis
- **Clinical manifestations and disease severity**
- Efficacy of antivirals and anti-inflammatory drugs
- Vaccines efficacy and boosters
- Take-home messages

January 28th 2022

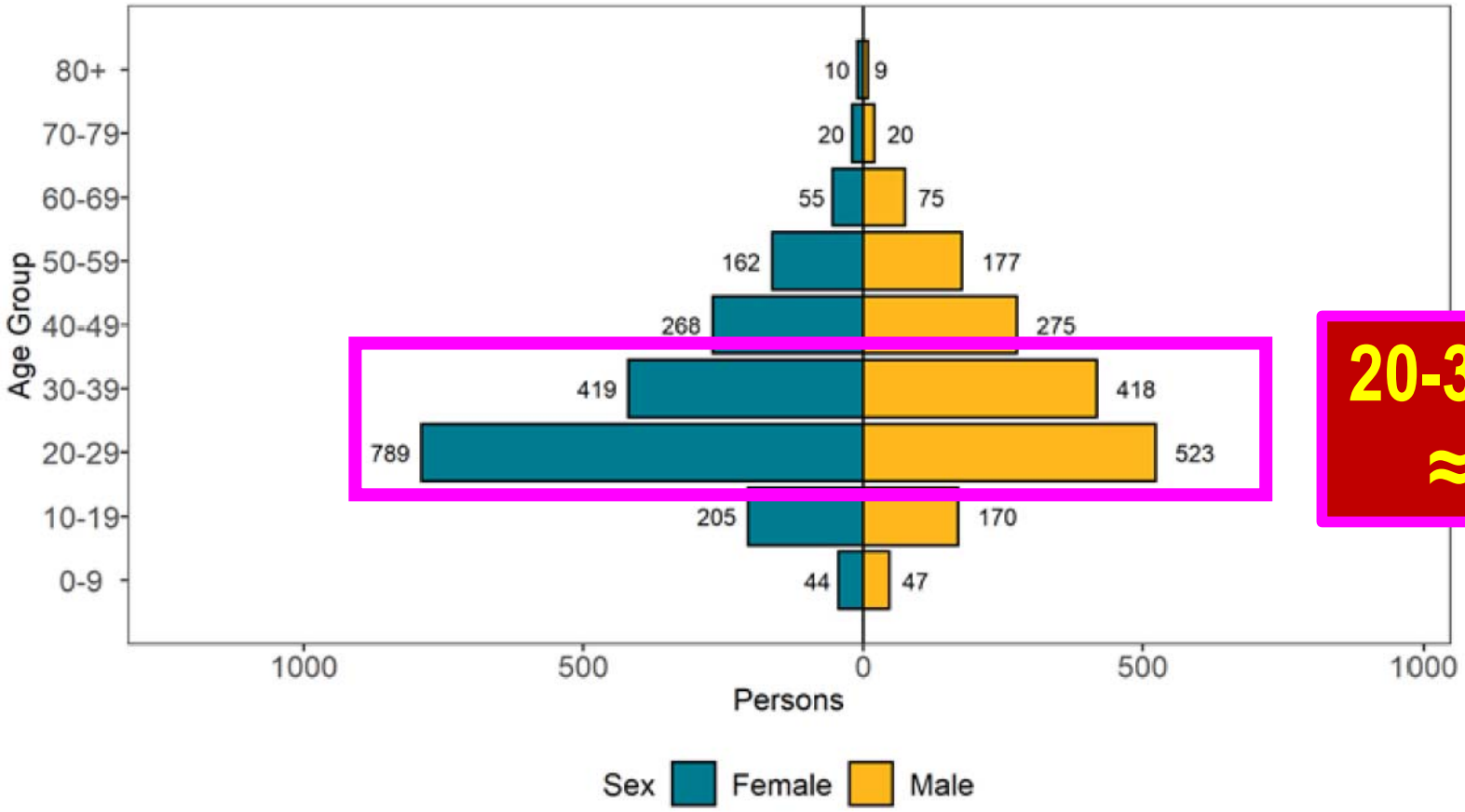
What are the clinical manifestations of Omicron?

- **Shorter incubation period** (2-3 days *vs.* 4-6 days in other variants)
- More or less similar clinical manifestations. Subtle differences.
- Preliminary data from South Africa: **Scratchy or sore throat along with nasal congestion, a dry cough and muscle pain**, especially low back pain. Omicron causes **less loss of taste and smell** than other variants (48%/41% vs. 23%/12%, respectively).
- Clinical manifestations can vary depending on **whether people are vaccinated** (headaches, body aches and fever) **or not** (flu-like syndrome).

→ **Reinfections, 9-10%** (Alpha and Delta variants previous infections)

https://www.nytimes.com/2021/12/21/well/live/omicron-variant-symptoms-covid.html, Accessed Dec 21, 2021

Cases of Omicron in England by age and sex as of 12 December 2021



20-39 years ≈ 60%

UKHSA. Technical briefing #32. December 17, 2021

Secondary Attack Rates higher with Omicron

	Delta	Omicron
- Households, %	10.1	13.6
- Non-households, %	2.8	7.6

UKHSA. Technical briefing #33. December 23, 2021

The Omicron variant (B.1.1.529) may be milder than the previous variants of concern (Beta, Delta) in South Africa!

Variants	Hospitalization Rates* First 3 weeks of the 4 waves in South Africa
- Beta	131
- Delta	101
- Omicron	38

*Rates per 1,000 admissions

https://www.nytimes.com/2021/12/14/world/africa/omicron-south-africa-study.html; December 14th 2021;
Dyer O. BMJ December 16th 2021; 375 doi: https://doi.org/10.1136/bmj.n3104

The Omicron variant (B.1.1.529) may be milder than the previous variants of concern (Beta, Delta) in South Africa!

	No. (%) of patients				
	Wave 1[a]	Wave 2	Wave 3	Wave 4	*P* value
COVID-19 patients treated	3875	4632	6342	2351	
COVID-19 patients admitted	2628 (67.8)	3198 (69.0)	4400 (69.3)	971 (41.3)	<.001
Age, median (IQR), y	53 (21.75)	54 (21)	59 (24)	36 (32)	<.001
Sex, female/male	1337/1291	1657/1541	2035/2365	590/381	<.001
Patients with comorbidities[b]	1472 (56.0)	1868 (58.4)	2311 (52.5)	227 (23.3)	<.001
Acute respiratory condition on admission	1909 (72.6)	2783 (87.0)	4013 (91.2)	307 (31.6)	<.001
Vaccination status[c]					
Vaccinated	No vaccine available	No vaccine available	No register available	235 (24.2)	
Not vaccinated				645 (66.4)	
Vaccination status unknown				91 (9.4)	

Maslo C et al. JAMA Dec. 30 2021

The Omicron variant (B.1.1.529) may be milder than the previous variants of concern (Beta, Delta) in South Africa!

	No. (%) of patients				
	Wave 1 (n = 2628)	Wave 2 (n = 3198)	Wave 3 (n = 4400)	Wave 4[b] (n = 971)	*P* value
Receiving oxygen therapy	2119 (80.3)	2624 (82.0)	3260 (74.0)	171 (17.6)	<.001
Receiving mechanical ventilation	431 (16.4)	259 (8.0)	548 (12.4)	16 (1.6)	<.001
Admission to intensive care	1104 (42)	1172 (36.6)	1318 (29.9)	180 (18.5)	<.001
Length of stay, median (IQR), d	8.0 (9)	7.8 (8)	7 (9)	3 (3)	<.001
Deaths	520 (19.7)	790 (25.5)	1284 (29.1)	27 (2.7)	<.001

Maslo C et al. JAMA Dec. 30 2021

The hospitalization rates caused by Omicron variant (B.1.1.529) in UK seems to be similar to Delta

Hospitalization Rates
Nov. 29 to Dec 11, 2021

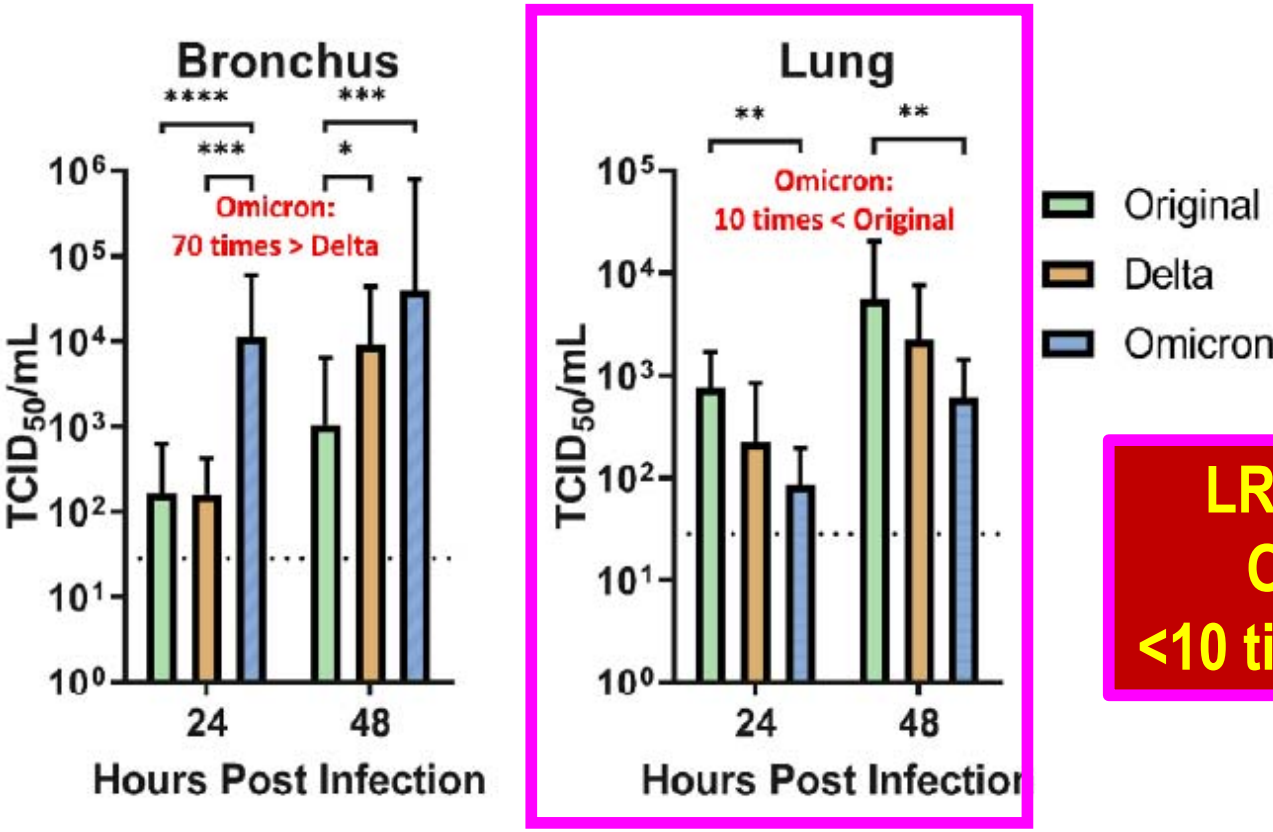
Variants	
- Delta (N=207,555)	2.8%
- Omicron (N=1,392)	1.7%*

*Admission RR 0.95 (0.61-1.47)

Ferguson et al. Dec. 2021

Omicron replicates much more in the bronchi than the Delta variant but much less than Wuhan in the lung

URT (Bronchi): Omicron >70 times Delta

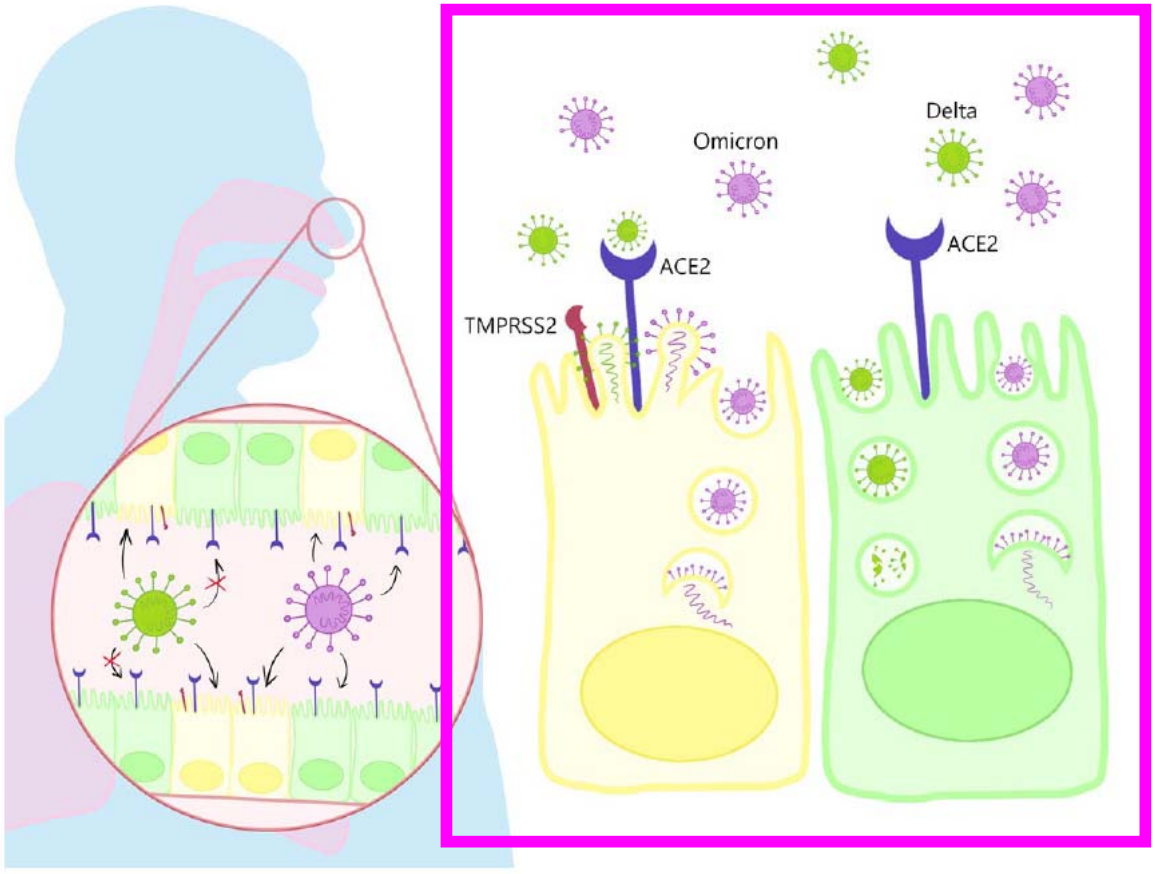


LRT (Lung): Omicron <10 times Wuhan

https://www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection Dec 15 2021

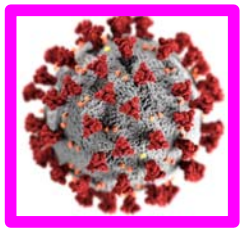
Kozlov M. Nature. January 13, 2022

Proposed model for Omicron's altered entry pathway leading to more rapid replication in the nasal epithelium



Omicron shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry

Peacock TP et al. bioRxiv preprint January 3, 2022 doi: https://doi.org/10.1101/2021.12.31.474653.



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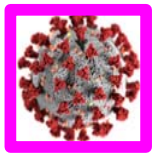
January 28th 2022



	Community	Hospital - Ward	Hospital - ICU
Disease stages	Asymptomatic/Mild Stages 1-2	Moderate/Severe Stages 3-5	Critical (MV, ECMO) Stages 6-7

Treatment

- Early antiviral therapy
- Proper timing anti-inflammatory drugs
- Prophylactic heparin

Isolation, at least 10-14 days

Symptomatic treatment
Close monitoring for early detection of progression. In older and high risk persons consider:

- **Parenteral mAbs* (OPAT)**
- **Molnupiravir, oral 5-d**
- **Nirmatrelvir/rtv, oral 5-d**
- **Remdesivir (OPAT), IV 3-d**

Remdesivir, IV, 5 days
Stages 4 (no oxygen) & 5 (low-flow oxygen supply)
Stage 6 plus **Baricitinib/Tofacitinib**, oral, 14 days

Parenteral mAbs, single dose
Only in seronegative persons

Dexamethasone, IV/oral, 10 days.
Stages 5-7, low/high-flow oxygen supply, MV and ECMO

Tocilizumab, single IV dose

Low molecular weight heparin, SC
During the entire hospitalization period

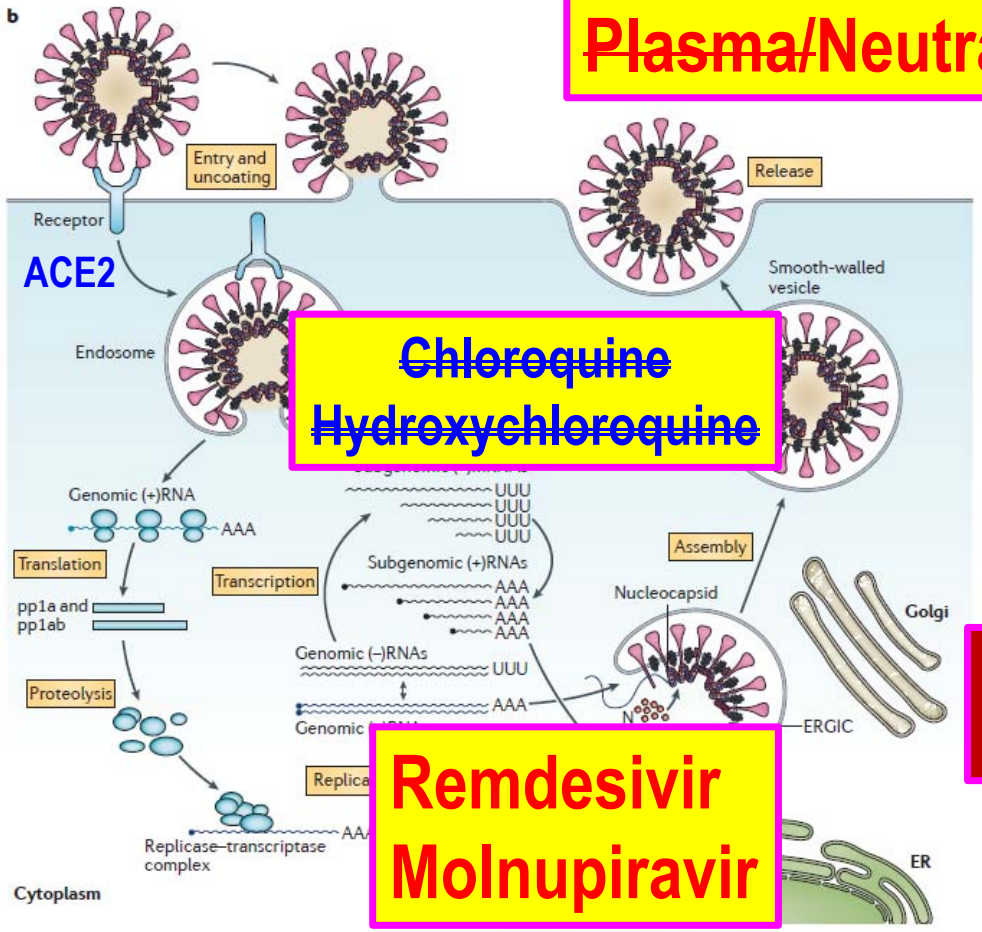
Dr. JM Miro, personal opinion. December 2021.
* Seronegative persons. No experience in vaccinated patients.

Activity of antiviral drugs against Omicron

SARS-CoV-2 life cycle: Antiviral targets

Entry inhibitors
hrACE2 – APN01

~~**Plasma/Neutralizing Antibodies**~~



~~**Chloroquine**~~
~~**Hydroxychloroquine**~~

~~**Interferon-beta**~~

~~**Ivermectin**~~

~~**Lopinavir/rtv**~~
Nirmatrelvir/rtv

Remdesivir
Molnupiravir

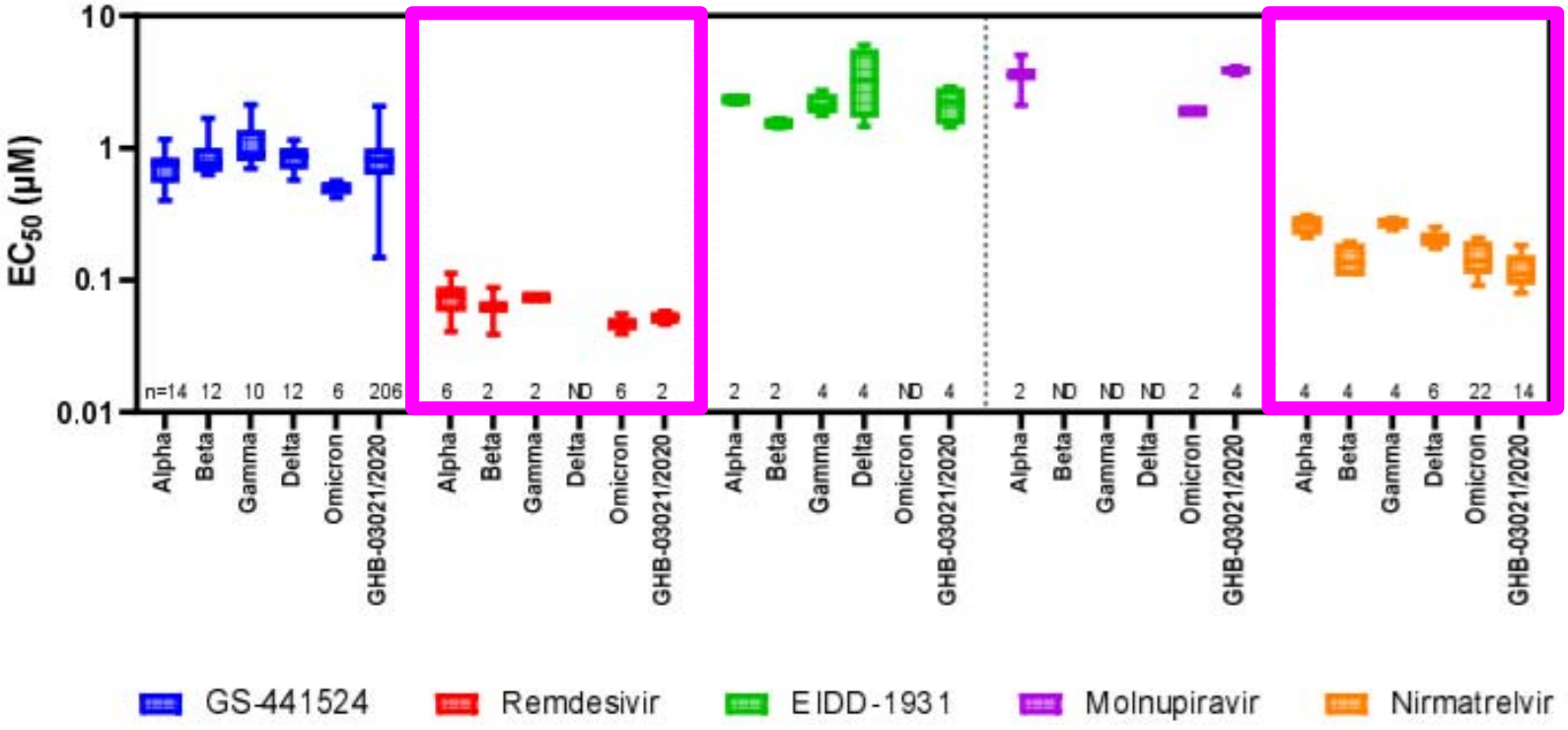
Potential for combining several antiviral drugs

* Interferon induces hundreds of genes which can act on various parts of the lifecycle from potentially degrading viral RNA (OAS, RNASL) to inhibiting virus egress (BST-2)

De Wit Nature Rev Microbiol, 2016; Sanders JM, et al. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019.

Antivirals remain active against Omicron!

Rega Institute, Laboratory of Virology and Chemotherapy, Leuven, Belgium



https://twitter.com/neyts_johan/status/1470887399341412361 Dec 16 2021; https://www.nytimes.com/article/omicron-coronavirus-variant.html Dec 16 2021

Vangeel L et al. bioRxiv preprint January 15, 2022 doi: https://doi.org/10.1101/2021.12.27.474275

Remdesivir - Outpatient COVID-19 Treatment Trial

- Phase 3 (GS-US-540-9012) double-blind, randomized, placebo-controlled trial compared the efficacy and safety of **3 days of remdesivir (N=279)** to standard of care (N=283) in **non-hospitalized, high-risk participants with confirmed COVID-19**
- 562 participants were randomly assigned 1:1 to receive intravenous (IV) RDV (200 mg on day 1, 100 mg on days 2 to 3) or placebo.
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- Overall, 52% were male, 44% were Hispanic/Latino ethnicity and **30% were ≥ 60 years old**. **The most common comorbidities were diabetes mellitus** (62%), **obesity** (56%; median BMI, 30.7) and **hypertension** (48%).

	Remdesivir N=279	Placebo N=283	*P*-value
- Hospitalization/all-cause death	0.7%	5.3%	0.008
- Medical visits/all-cause death	1.6%	8.3%	0.002
- Grade ≥3 TRAEs	3.6%	7.1%	-

*Median baseline SARS-CoV-2 RNA nasopharyngeal viral load was 6.2 log copies/mL.
There was no difference between arms in time-weighted average change in nasopharyngeal viral loads from baseline up to day 7.

No deaths occurred in either arm by day 28.

→ Remdesivir reduced hospital admission/death by 87%.

Gottlieb RL, et al. N Engl J Med. Dec 22, 2021.

Molnupiravir: MOVe-OUT RCT showed promising results

First 762 patients!

	Molnupiravir N=385	Placebo N=377	*P*-value
Outcomes at 29 days			
- Hospitalization/death	7.3%	14.1%	<0.001
- Mortality	No deaths	8 deaths	

→ **Molnupiravir reduced the risk of hospitalization/death by 50%.**

Caraco Y et al. 31st ECCMID July 9-12 2021 P#4700; MSD Press release October 1st 2021;
Bernal AJ et al, N Engl J Med. Dec 16, 2021; doi: 10.1056/NEJMoa2116044.

Molnupiravir: MOVe-OUT RCT showed promising results

Final 1,433 patients!

	Molnupiravir N=709	Placebo N=699	*P*-value
Outcomes at 29 days			
- Hospitalization/death	6.8%	9.7%	0.022
- Mortality	One death	9 deaths	

→ **Molnupiravir reduced the risk of hospitalization/death by 30%.**

Outcomes 2nd 646 patients			
- Hospitalization/death	6.2%	4.7%	0.395
- Mortality	One death	One death	

?

Bernal AJ et al, N Engl J Med. Dec 16, 2021; doi: 10.1056/NEJMoa2116044.

Oral Nirmatrelvir/ritonavir (Paxlovid) – Phase 2/3 EPIC-HR

- **EPIC-HR** (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients) is a multinational randomized, double-blind study of **non-hospitalized adult patients** with COVID-19, who are at high risk of progressing to severe illness.
- 2,246 eligible participants with at least **one underlying medical condition** and a **mild/moderate confirmed diagnosis of SARS-CoV-2 infection (within 5 days)** were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally **every 12 hours** for **5 days.**
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- **The study was stopped** after the first interim analysis with 1,219 adults enrolled by September 29, 2021 was performed.

	Nirmatrelvir N=1,039	**Placebo** N=1,046	*P*-value
At 28 days			
- Hospitalization/death	0.8%	6.3%	<0.001
- Death	No deaths	12 deaths	-
- D/C due to TRAEs	2.1%	4.2%	-

→ PF07321332/ritonavir reduced hospital admission/death by 87%.

A Phase 2/3 EPIC-SR (Standard-Risk Patients) RCT started in August 2021.

https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

Pfizer press releases, November 5th & December 14th 2021

Activity of neutralizing monoclonal antibodies and convalescent plasma against Omicron

The Omicron variant is resistant to most neutralizing monoclonal antibodies under EUA except Sotrovimab

Fold reducing neutralizing susceptibility to neutralizing antibodies under EUA

	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	REG
Alpha	1 11	16 9	1.2 4	1 17	0.6 17	1 8	1.0 6	1.7 5	0.8 4	3* 13	1.4
Beta	>100 13	>100 11	>100 5	70 21	0.6 20	1.3 11	1 5	6.3 5	1.3 4	1 12	27 2
Gamma	>100 9	>100 9	>100	>100 15	0.4 14	1 5	0.5 5	6.4 4	0.7	1.2 10	81 2
Delta	>100 10	0.6 10	1 2	0.8 10	1.5 10	1 3	3.5 2	1.3 2	0.6	1.2 6	54 2
Omicron	>100 4	>100 3	>100	>100 4	>100 4	>100 3	>100 4	>100 4	>100 2	3 4	>100

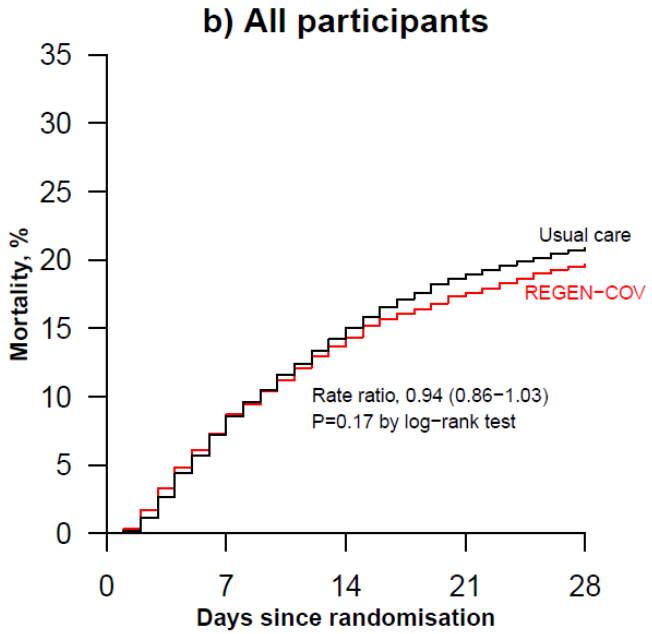
Monoclonal antibody (mAb) abbreviations: BAM: Bamlanivimab/LY-CoV555, CAS: Casirivimab/REGN10933, IMD: Imdevimab/REGN10987, CAS/IMD: Casirivimab+imdevimab/REGN-COV2, ETE: Etesevimab/LY-CoV016/JS016/CB6, CIL: Cilgavimab/COV2-2130/AZD1061, TIX: Tixagevimab/COV2-2196/AZD8895, TIX/CIL: Tixagevimab+Cilgavimab, BAM/ETE: Bamlanivimab+Etesevimab, SOT: Sotrovimab/Vir-7831/S309, REG: Regdanvimab/CT-P59.

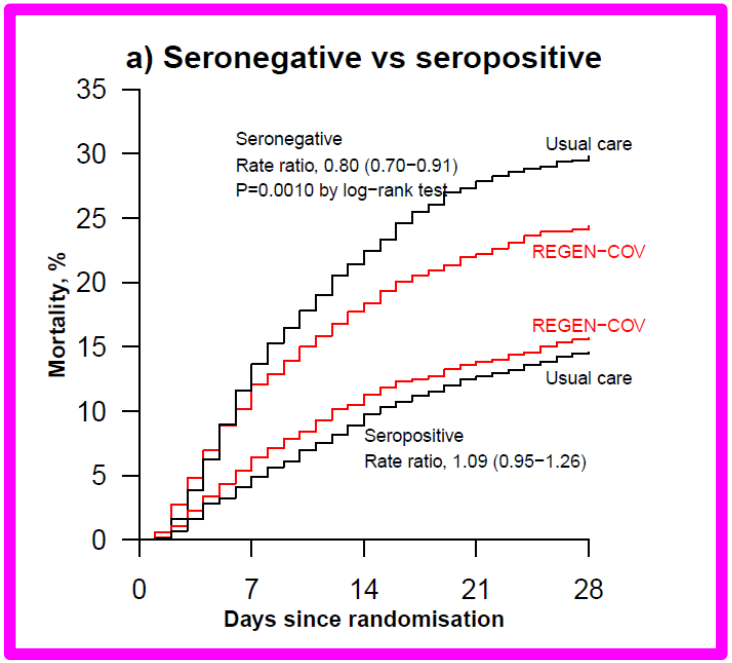
Stanford University
CORONAVIRUS ANTIVIRAL & RESISTANCE DATABASE
A Stanford HIVDB team website. Last updated on 12/25/2021, 8:52:45 PM.

https://covdb.stanford.edu/page/susceptibility-data/; December 27th 2021

Casirivimab & Imdevimab Reduced 28-day Mortality in Hospitalized Baseline Seronegative Patients: RECOVERY RCT

- Randomized, controlled, open-label platform trial. Eligible and consenting patients were randomly allocated (1:1) to either usual SoC (usual care group) or usual care plus a single dose of **REGEN-COV 8g (casirivimab 4g and imdevimab 4g) by IV infusion (REGEN-COV group).**
- Primary endpoint was **28-day mortality** assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population.
- Between 18 September 2020 and 22 May 2021, **9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone**, including 3153 (32%) seronegative patients 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status.





… Mortality increased in seropositives!

RECOVERY RCT. medRxiv June 16, 2021 (NCT04381936)

Monoclonal Antibodies (mAbs) in Non-Hospitalized Patients

Early Treatment in Patients with High Risk of Progression

	mAb	PBO	*P*-value
	Hospitalization rates at 28 days		
Bamlanivimab (iv single dose)			
- Chen P et al (N=552; 3:1)*	1.6%	6.3%	0.017
Casirivimab p			
- Weinreich DM			<0.001
Bamlanivimal			
- Dougan M et al. (N=1,035; 1:1)***	2.1%	7%	<0.001
Sotrovimab (im single dose)			
- Gupta A et al. (N=1,057; 1:1)****	1.1%	5.7%	<0.001

mAbs reduce hospitalization/death rates by 65%-80%!!

* 452 patients were assigned to receive a single IV infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo
** 266 patients received a single IV infusion of 2,400 milligrams casirivimab and imdevimab (1,200 mg of each), 267 received 8,000 mg casirivimab and imdevimab (4,000 mg of each), and 266 received a placebo, within three days of obtaining a positive SARS-CoV-2 viral test.
*** 1,035 patients were randomized to a single IV infusion of either a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) or placebo within 3 days after a laboratory SARS-CoV-2 infection.
**** Single IV infusion of 500 mg or placebo. Sotrovimab has a double mechanism of action: neutralization plus inducing ADCC (NK cells) and ADCP (macrophages).

Chen P et al. NEJM Oct 28 2020; Weinreich DM et al. NEJM, Sep 29 2021; Dougan M et al. NEJM July 14, 2021; Gupta A et al. NEJM Oct 27, 2021.

PEP trials with Monoclonal Antibodies (mABs)

- **Randomized, double-blind, placebo-controlled trials for prevention of SARS-COV-2 infection** in **residents and staff** of skilled nursing and assisted living facilities where at least 1 case of SARS-CoV-2 infection had been confirmed in the previous 7 days or in asymptomatic **household contacts** of people with COVID-19 documented within the previous 4 days and returning home.
- **mABs can offer immediate protection** for exposed or **unvaccinated, partially vaccinated or IS individuals in high risk settings** (in contrast to vaccines that take 7-14 days after 2nd dose to offer protection).

	mAB	PBO	*P*-value
BLAZE			
- Bamla			<0.001
R10933			
- Casirivimab/imdevimab (1,200 mg **SC**)		symptomatic COVID-19	<0.001

Only Sotrovimab (EUA) is active against Omicron!

*Nursing home residents; **Reduction of SARS-CoV-2 infection, shortened time of viral shedding and shortened time of high viral load (>10^4 copies/mL) shedding **suggesting a benefit for reduced transmission**.

Lilly press release, January 27, 2021; REGENERON press release, April 12, 2021; Cohen MS et al. JAMA. 2021 Jul 6; 326:46-55.

The Omicron variant is resistant to neutralizing antibodies from convalescent plasma (CP)

Convalescent Plasma (CP)

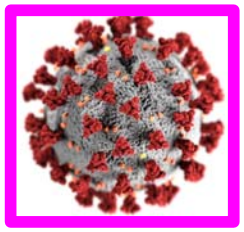
	CP Studies (#)	CP Samples (#)	CP <3-fold (S) (%)	CP 3-10-fold (I) (%)	CP ≥10-fold (R) (%)
Alpha	58	2145	81%	12%	7%
Beta	65	2353	26%	47%	27%
Gamma	30	1136	50%	40%	10%
Delta	19	530	50%	31%	19%
Omicron	5	103	2%	24%	74%

High rates of Omicron reinfections in patients with previous Alpha & Delta infections!

Stanford University
CORONAVIRUS ANTIVIRAL & RESISTANCE DATABASE
A Stanford HIVDB team website. Last updated on 12/25/2021, 8:52:45 PM.

https://covdb.stanford.edu/page/susceptibility-data/; December 27th 2021

It is not expected any loss of activity of anti-inflammatory or anticoagulant drugs, so these treatments should not be modified.

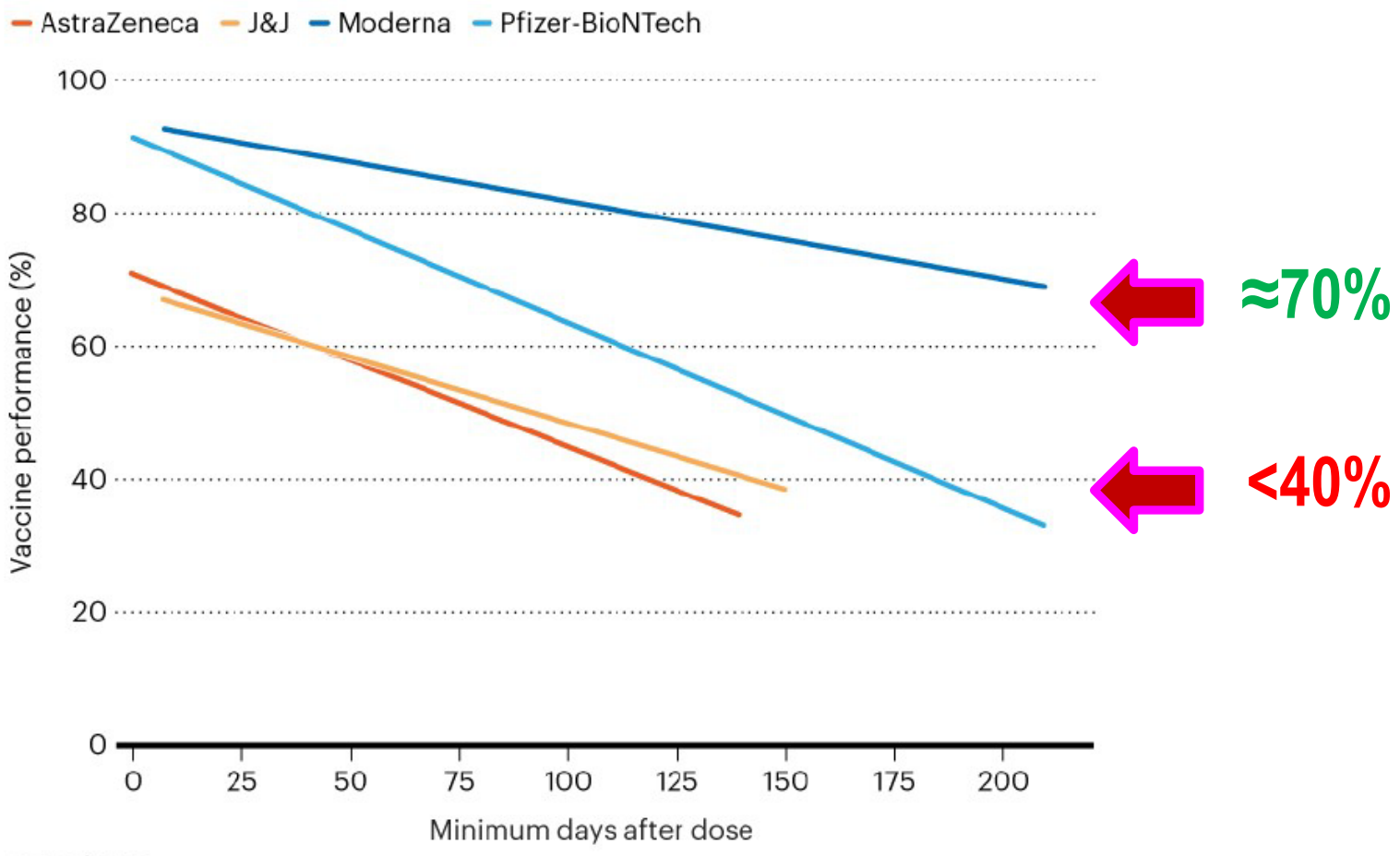


COVID-19 Pandemic Update: The Omicron wave!

- Current epidemiology
- Virological characteristics
- Diagnosis
- Clinical manifestations and disease severity
- Efficacy of antivirals and anti-inflammatory drugs
- **Vaccines efficacy and boosters**
- Take-home messages

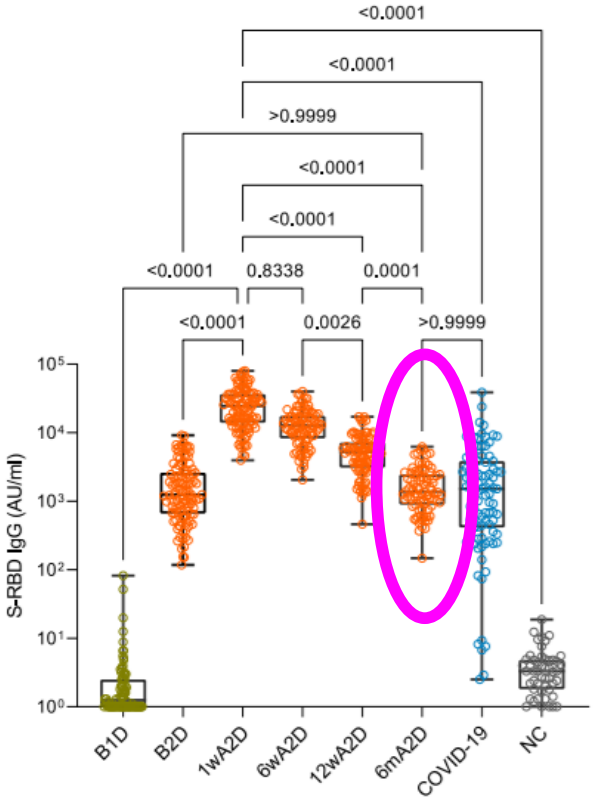
January 28th 2022

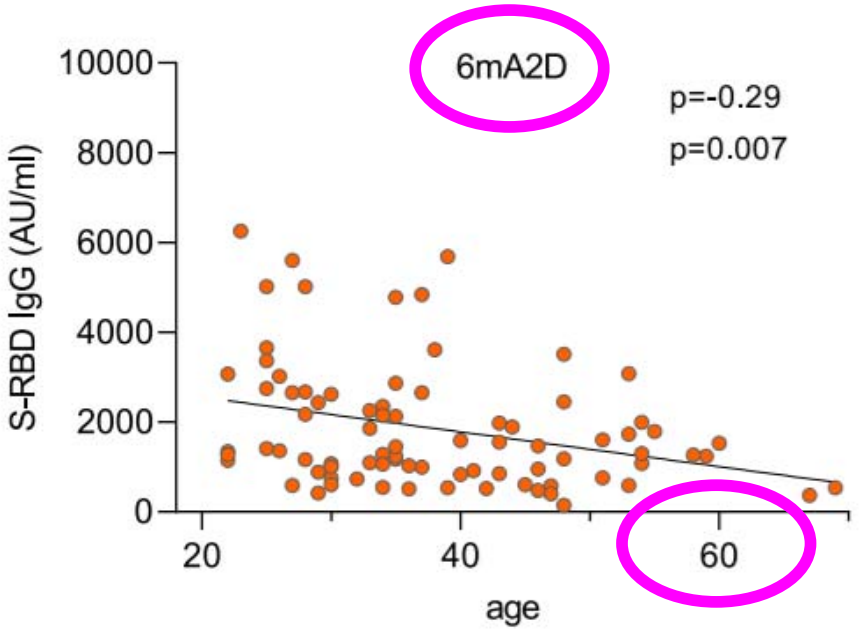
Waning Immunity: Vaccine efficacy against Delta in the months following the second dose



Mallapaty S et al. Nature. December 2021; 600:580-583.

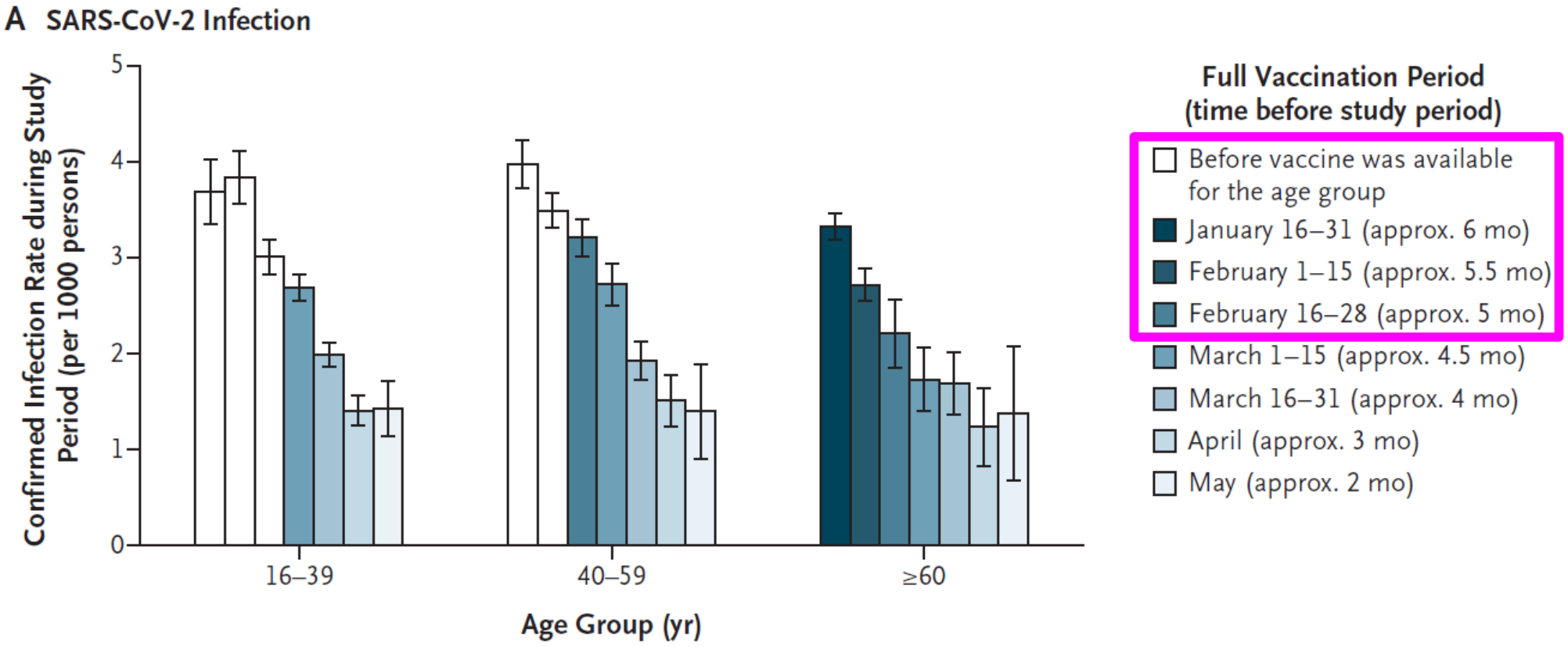
Waning antibody responses in individuals vaccinated with Pfizer-BioNTech vaccine is more pronounced at 6 mo. and in those over 60 years of age





Naaber P et al. The Lancet Regional Health - Europe. 6 September 6 2021.

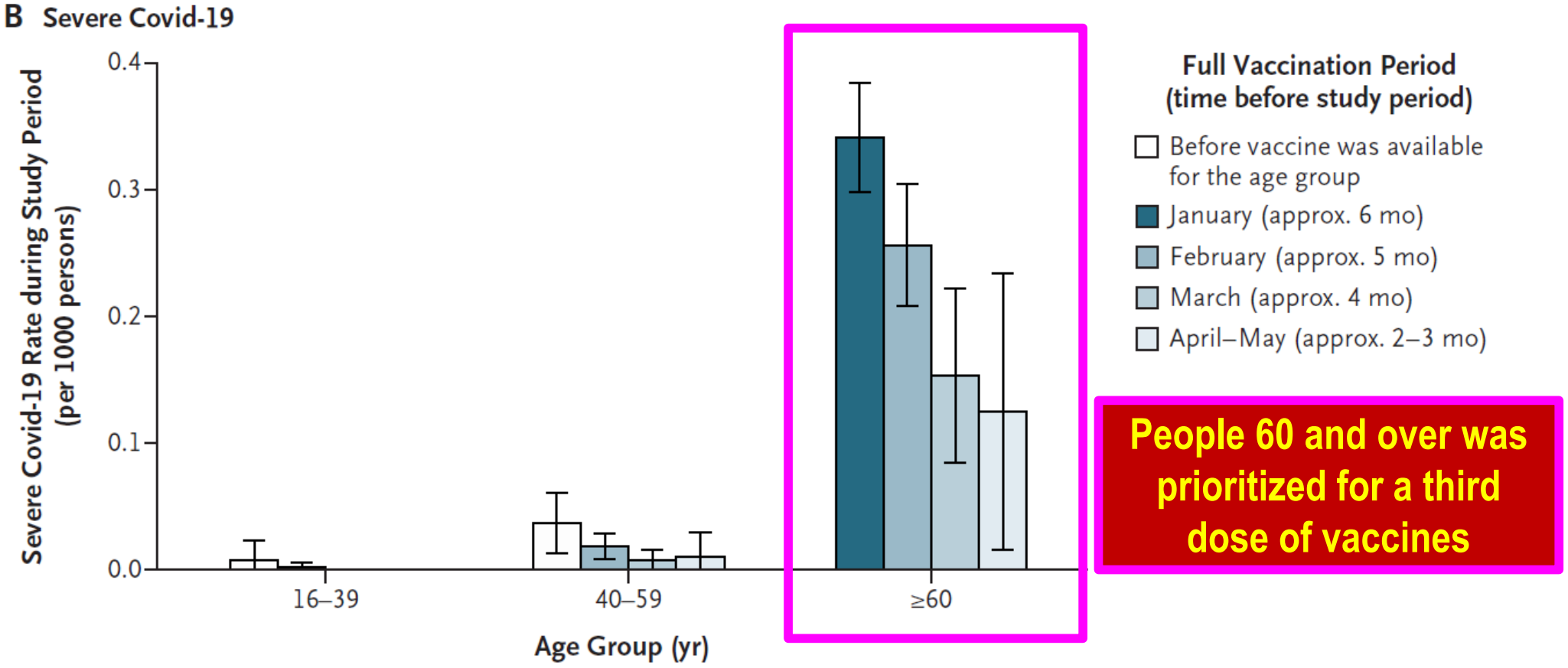
The effects of waning antibodies neutralization titer on clinical outcomes: SARS-CoV-2 infection increased regardless age



Most infections were due to the Delta variant

Goldberg Y et al., NEJM October 27, 2021.

The effects of waning antibodies neutralization titer on clinical outcomes: Severe COVID-19 mainly diagnosed ≥60 yr.

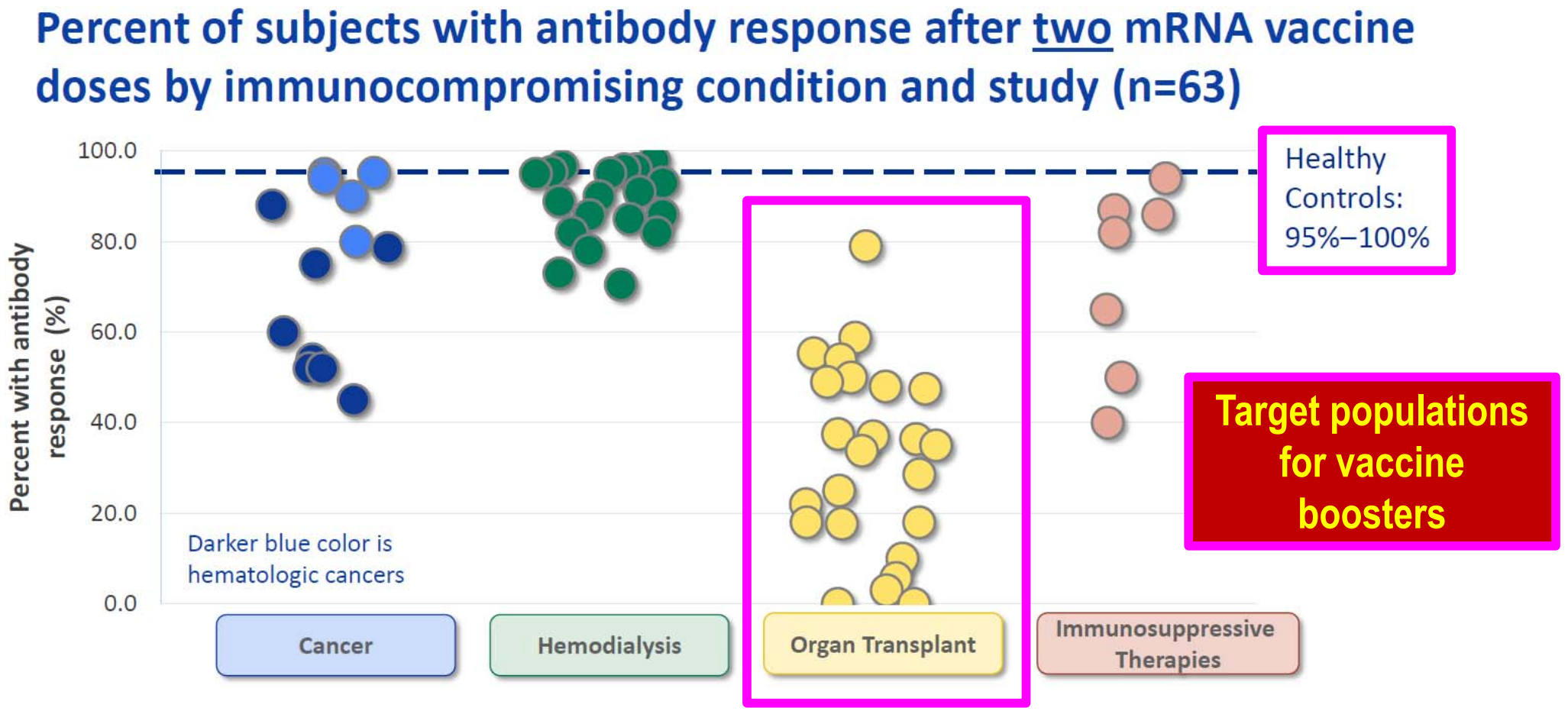


People 60 and over was prioritized for a third dose of vaccines

Most infections were due to the Delta variant

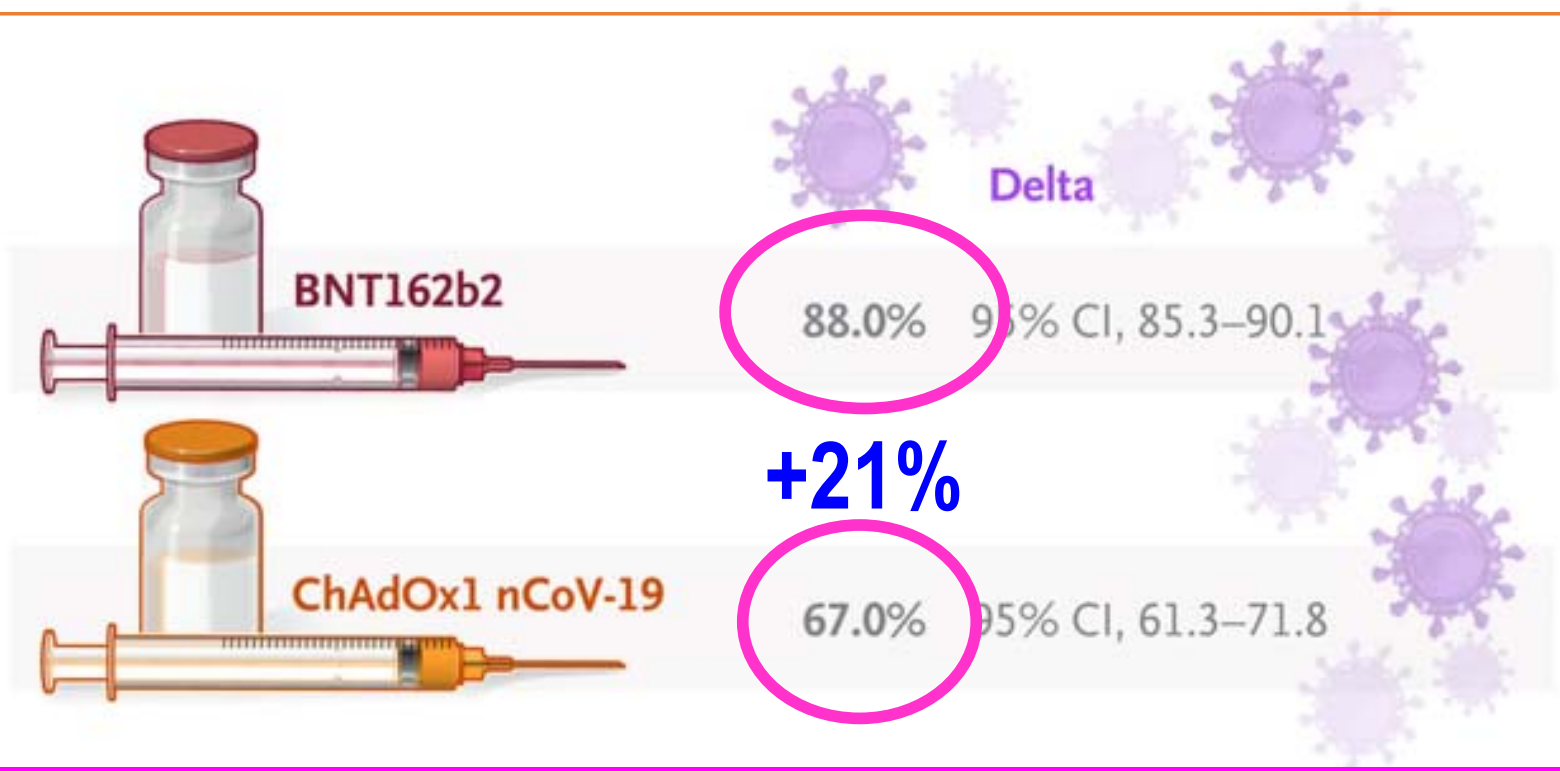
Goldberg Y et al., NEJM October 27, 2021.

Immunosuppressed patients have a much worse immune response to COVID-19 vaccines than healthy individuals



Oliver S. ACIP Meeting. July 22, 2021. https://www.cdc.gov/coronavirus.

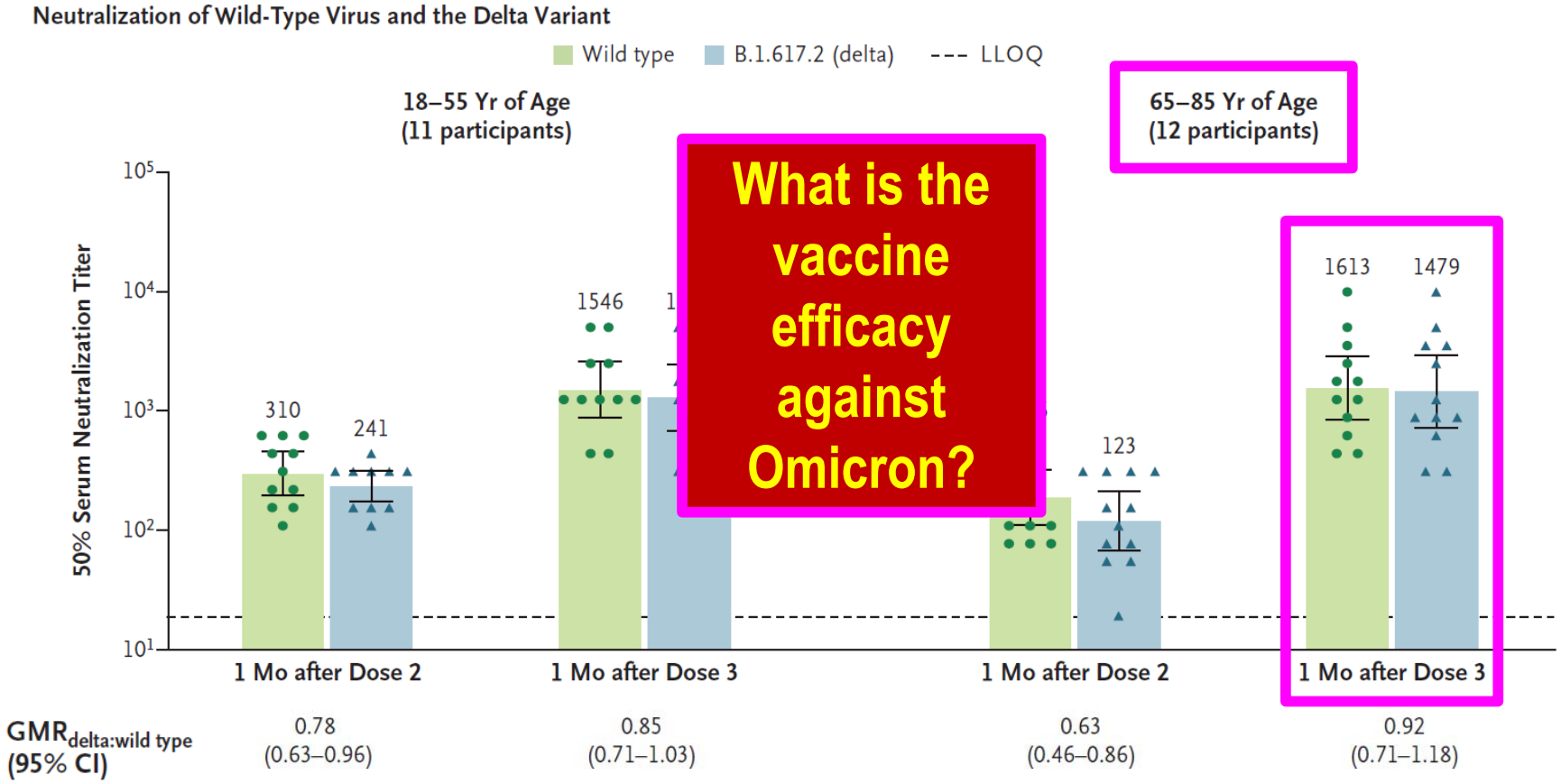
BNT162b2 & ChAdOx1 nCoV-19 vaccine efficacy against Delta variant after the 2nd dose



- Fully vaccinated individuals with **breakthrough Delta infections** have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts, although they have an accelerated viral clearance.

Lopez-Bernal J et al. N Engl J Med. August 12, 2021; 385:585-594; Singanayagam A et al,. Lancet Infect Dis. October 28, 2021.

Neutralization of the Delta Variant Increased with a 3rd mRNA BNT162b2 Vaccine Dose regardless Age



GMFR = Geometric mean fold rises in titers

Falsey AR et al., N Engl J Med. Oct 21 2021; 385:1627-1629.

BNT162b2 & ChAdOx1 nCoV-19 vaccine efficacy against Omicron variant after the 1st, 2nd & 3rd doses

	Delta	Omicron
ChAdOx1-S		
- 2nd dose, 2 weeks	76%	-
- 2nd dose, 6 months	**42%**	**6%** ←
- Third dose*, 2 weeks	94%	71%
BNT162b2		
- 2nd dose, 2 weeks	88%	88%
- 2nd dose, 6 months	**63%**	**34%** ←
- Third dose, 2 weeks	93%	76%

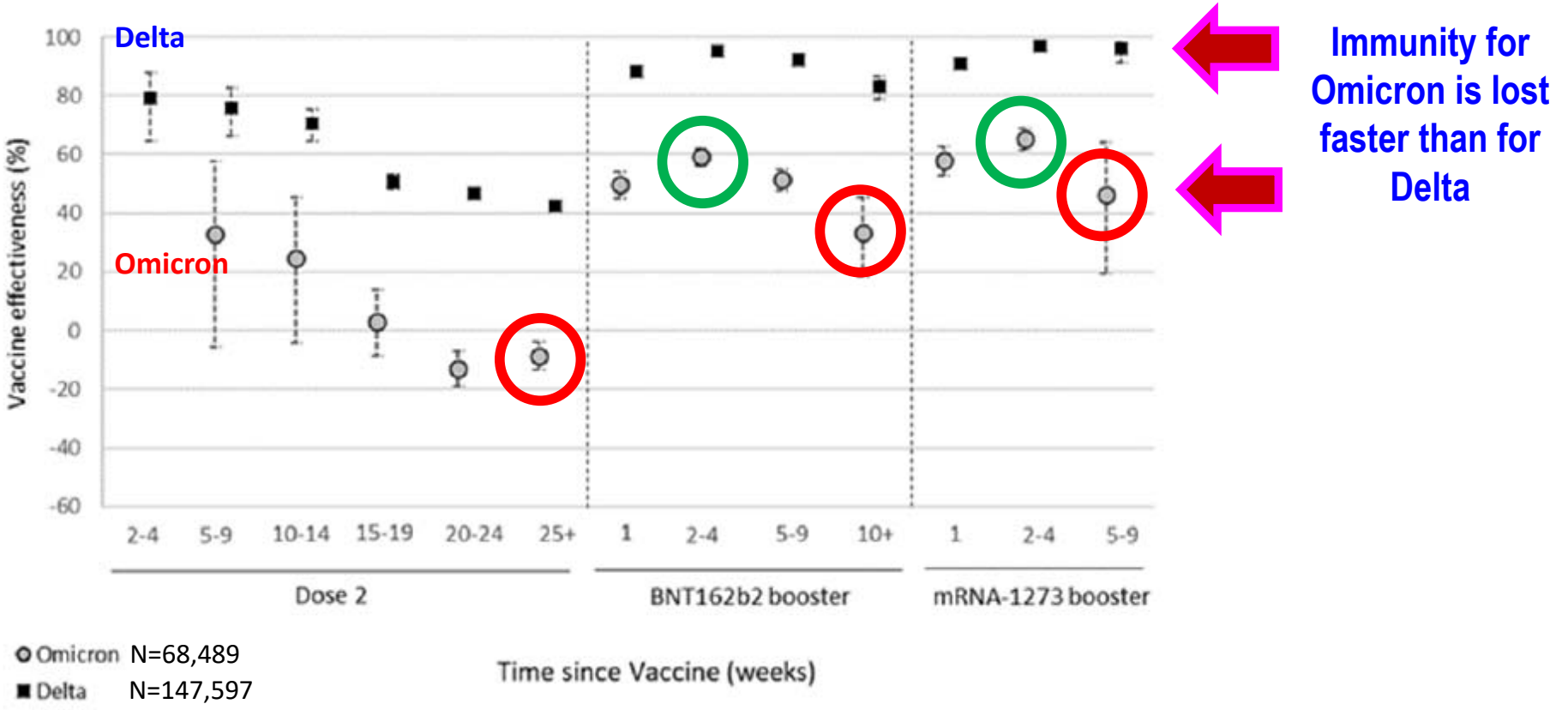
A 3rd dose should be prioritized!

*Boosting with Pfizer (BNT162b2)

Andrews N, Lopez-Bernal J et al. medRxiv, December 14th 2021

Vaccine effectiveness against Omicron symptomatic disease after the booster dose according to the type of vaccination

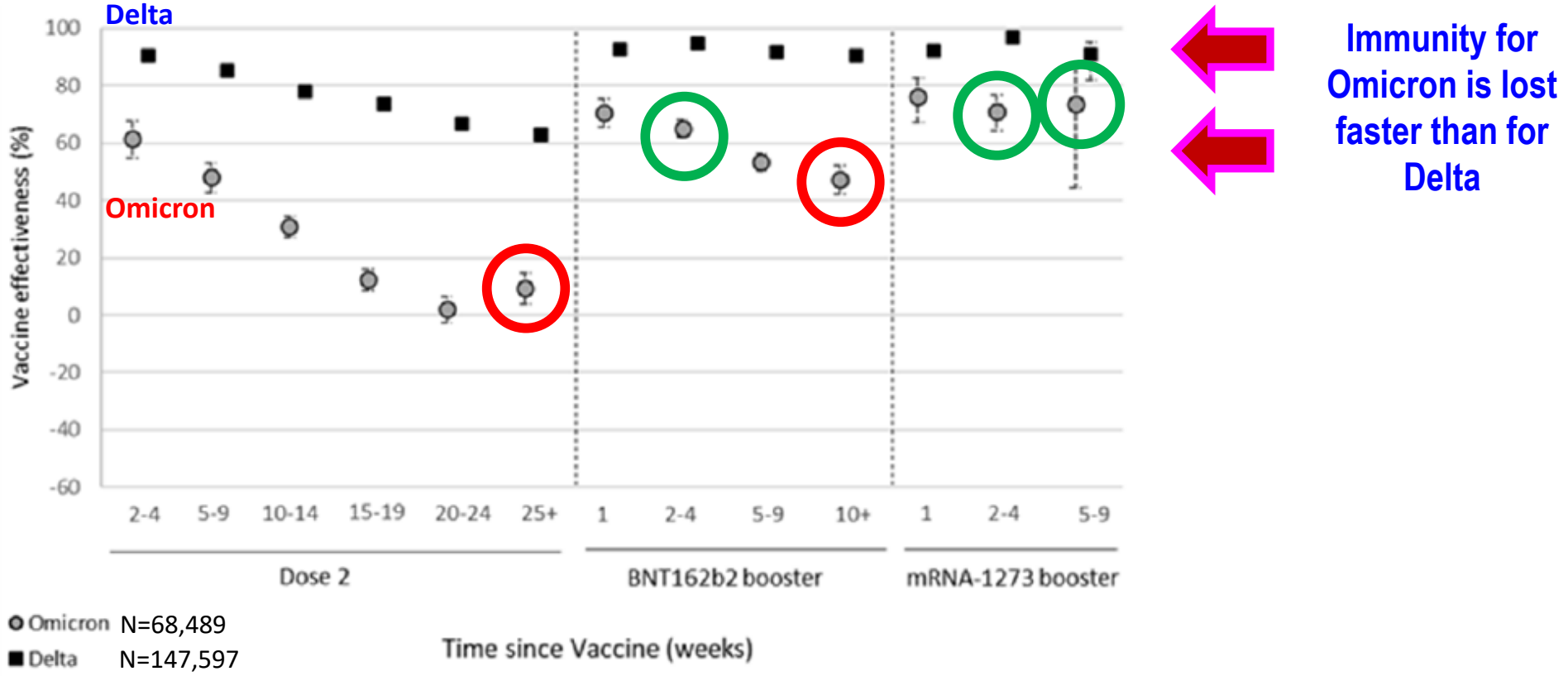
Two doses of Astra-Zeneca with a Pfizer or Moderna booster dose



UKHSA. Technical briefing #33. December 23, 2021.

Vaccine effectiveness against Omicron symptomatic disease after the booster dose according to the type of vaccination

Two doses of Pfizer with a Pfizer or Moderna booster dose



UKHSA. Technical briefing #33. December 23, 2021.

Vaccine effectiveness against Omicron symptomatic disease after the booster dose according to the type of vaccination

Primary vaccination	Booster	Efficacy at 2-4-wk	Efficacy at +10-wk
- Astra-Zeneca	Pfizer	60%	35%
- Astra-Zeneca	Moderna	60%	45%
- Pfizer	Pfizer	70%	45%
- Pfizer	Moderna	70%	70%*

Booster wanes at 10 weeks?
Will we need additional boosts?

*Efficacy at 5-9 weeks

UKHSA. Technical briefing #33. December 23, 2021.

Risk of dying from COVID-19 per 10,000 cases by Age, Sex and Vaccination status in Australia - January 2022 – Omicron 90%

70+
No *vs.* **3**

x 20

x 25

IMMUNISATION COALITION

RISK OF DYING FROM COVID-19

Estimated deaths per 10,000 COVID-19 cases by age, sex, and vaccination status
Australia, January 2022. Version 2.0.
(based on circulating variants = 90% omicron and 10% delta)
AZ=AstraZenca COVID-19 vaccine. Pfz = Pfizer COVID-19 vaccine. Mod = Moderna COVID-19 vaccine.

THE UNIVERSITY OF QUEENSLAND AUSTRALIA
Flinders UNIVERSITY

Gender	Age group (years)	Not vaccinated	1 dose of AZ (3 weeks ago)	2 doses of AZ (2nd dose less than 2 mths ago)	2 doses of AZ (2nd dose 2 to 4 mths ago)	2 doses of AZ (2nd dose 4 to 6 mths ago)	2 doses of AZ + Pfz or Mod booster (2 mths ago)	1 dose of Pfz (3 weeks ago)	2 doses of Pfz (2nd dose less than 2 mths ago)	2 doses of Pfz (2nd dose 2 to 4 mths ago)	2 doses of Pfz (2nd dose 4 to 6 mths ago)	2 doses of Pfz + Pfz or Mod booster (2 mths ago)
Male	12-19	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	20-29	0.3	0.1	0.1	0.1	0.2	<0.1	0.1	0.1	0.1	0.1	<0.1
	30-39	1.4	0.4	0.4	0.4	0.6	0.1	0.3	0.2	0.2	0.4	0.1
	40-49	4	1.0	0.7	0.8	1.3	0.2	0.8	0.4	0.4	0.8	0.2
	50-59	11	3	2	2	4	0.4	2	1.0	1.0	2	0.4
	60-69	38	9	6	7	12	1.4	7	3	3	7	1.4
	70+	362	98	74	80	134	18	75	42	42	83	18
Female	12-19	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	20-29	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	30-39	0.4	<0.1	<0.1	<0.1	0.1	<0.1	0.1	<0.1	<0.1	<0.1	<0.1
	40-49	1.6	0.4	0.3	0.3	0.6	0.1	0.3	0.2	0.2	0.3	0.1
	50-59	7	2	1.5	1.6	3	0.4	1.4	0.8	0.8	1.6	0.4
	60-69	22	7	6	6	10	1.4	5	3	3	6	1.4
	70+	322	77	55	61	106	13	62	31	31	63	13

Estimated deaths per 10,000 cases
- Less than 0.1
- 0.11 to 1.0
- 1.1 to 10
- 10.1 to 50
- 50.1 to 150
- More than 150

*****IMPORTANT NOTES*****
* Chart only shows risk of dying from COVID-19, but there are other potential long-term complications, such as Long COVID.
* Each dose of vaccine takes about 2 weeks to work.
* Calculations based on circulating variants = 90% omicron and 10% delta. Results might differ for other variants.
* Calculations based on population-level data and do not take into account individual comorbidities.
* Case fatality rates for Omicron based on reported cases & deaths in Australia during Omicron circulation, but true case numbers are unknown because of limited testing. Chart will be updated as more data become available.
* Deaths likely to be higher in people with serious medical problems and in vulnerable groups.
* Deaths likely to be higher if health systems are overwhelmed.
* There are only minor differences between the effectiveness of Pfizer and Moderna boosters against death. Both are highly effective.

Estimates based on CoRiCal (COVID-19 Risk Calculator):
https://corical.immunisationcoalition.org.au.
Questions & feedback to Prof Colleen Lau,
University of Queensland: colleen.lau@uq.edu.au

70+
2 +6 *vs.* **3**

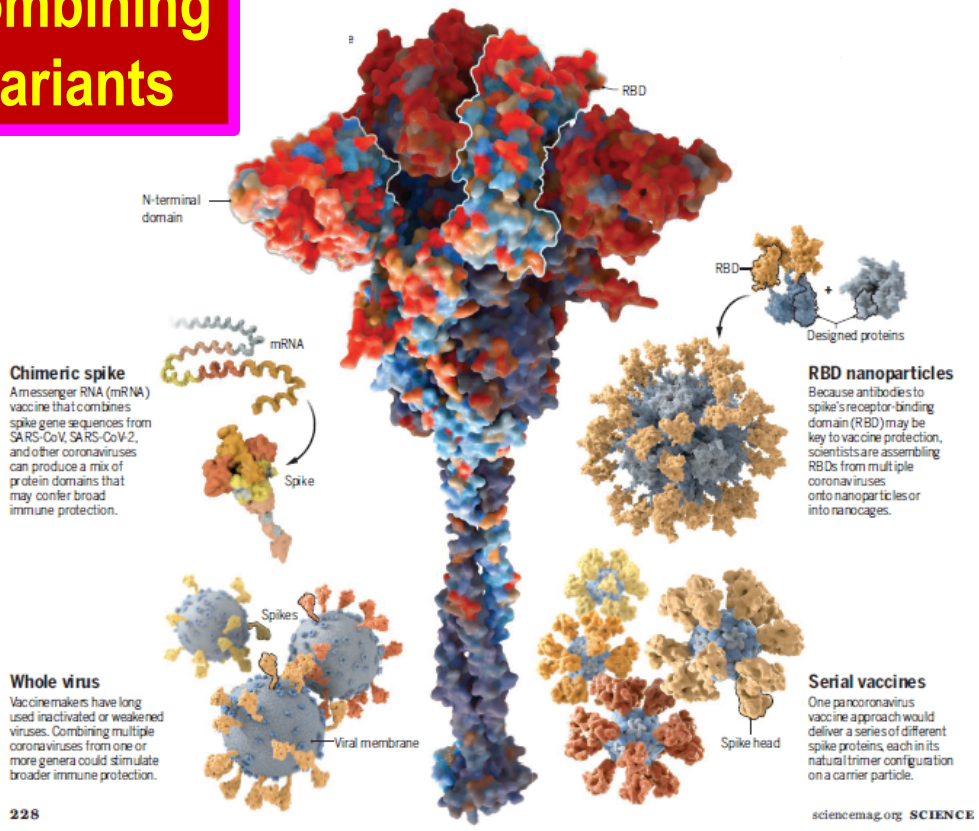
x 5-7

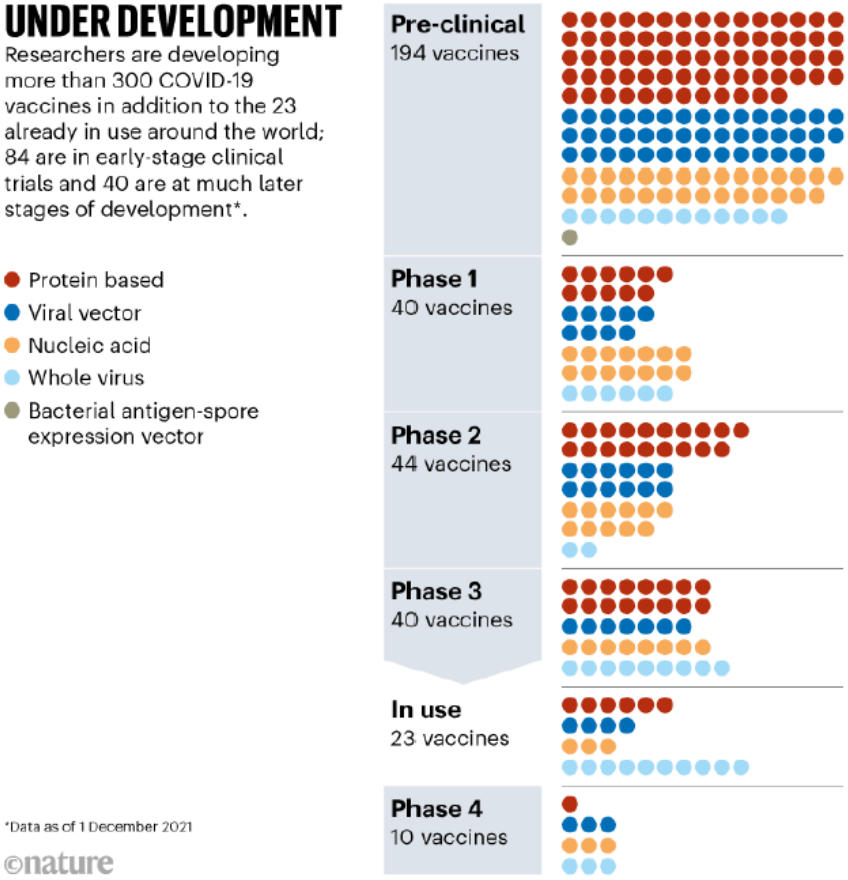
x 5-7

http://www.health.gov.au/resources/publications/coronavirus-covid-19-at-a-glance-26-january-2022

The new generation of SARS-CoV-2 vaccines must include VoC mutations: The Dream Vaccine

Combining variants



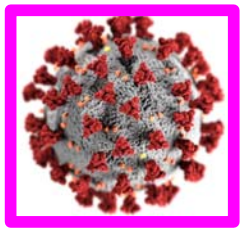


Cohen J. Science. 2021; 372: 227-231; Mallapaty S et al. Nature. December 2021; 600:580-583.

What plan do we have for Omicron?: Vaccination plus Facial Masks, Hand Washing, Social Distance & Non-Pharmacological Prevention Measures!

Rail commuters wearing white protective masks, one with the additional message “wear a mask or go to jail,” during the 1918 influenza pandemic in California. Vintage Space/Alamy

https://www.nytimes.com/2020/08/03/us/mask-protests-1918.html



COVID-19 Pandemic Update: The Omicron wave!

- Current epidemiology
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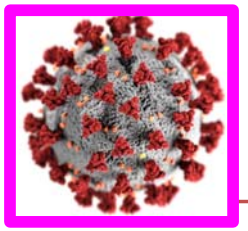
- Clinical manifestations and disease severity
- Efficacy of antivirals and anti-inflammatory drugs
- Vaccines efficacy and boosters
- **Take-home messages**

January 28th 2022

Take-home messages

- The Omicron variant is spreading very fast World wide (100 countries) replacing Delta variant in one month once introduced in a given country.
- Omicron has more than 50 mutations, 36 in the Spike, which give it the highest transmissibility seen ever (R_0 = 10).
- Omicron also infects vaccinated and previously infected persons. It is not known whether the disease is more serious than that caused by other SARS-CoV-2 variants.
- Antiviral drugs maintain activity against Omicron. However, most monoclonal antibodies under EUA are ineffective except for Sotrobimab.
- The efficacy of a full vaccination regimen is very low at 6 months. A third dose of a mRNA vaccine increases Omicron disease protection to 70%, although immunity wanes rapidly.
- Non-pharmacological prevention measures urgently need to be implemented to mitigate the expansion of Omicron and avoid collapse of the healthcare system.



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A. Vilella
A. Vallano

To all front-line health-care workers

To our patients and their families

Jan 28th 2022