Natural Infection Appears to Lack Selection Pressure for Immune Escape Variants: Iatrogenic Selection Pressures by Vaccines (and Perhaps, Therapeutic Neutralizing Monoclonal Antibodies) May Have Selected for the Alpha, Delta Immune Escape Variants

June 30, 2022

Dr. Marian Laderoute

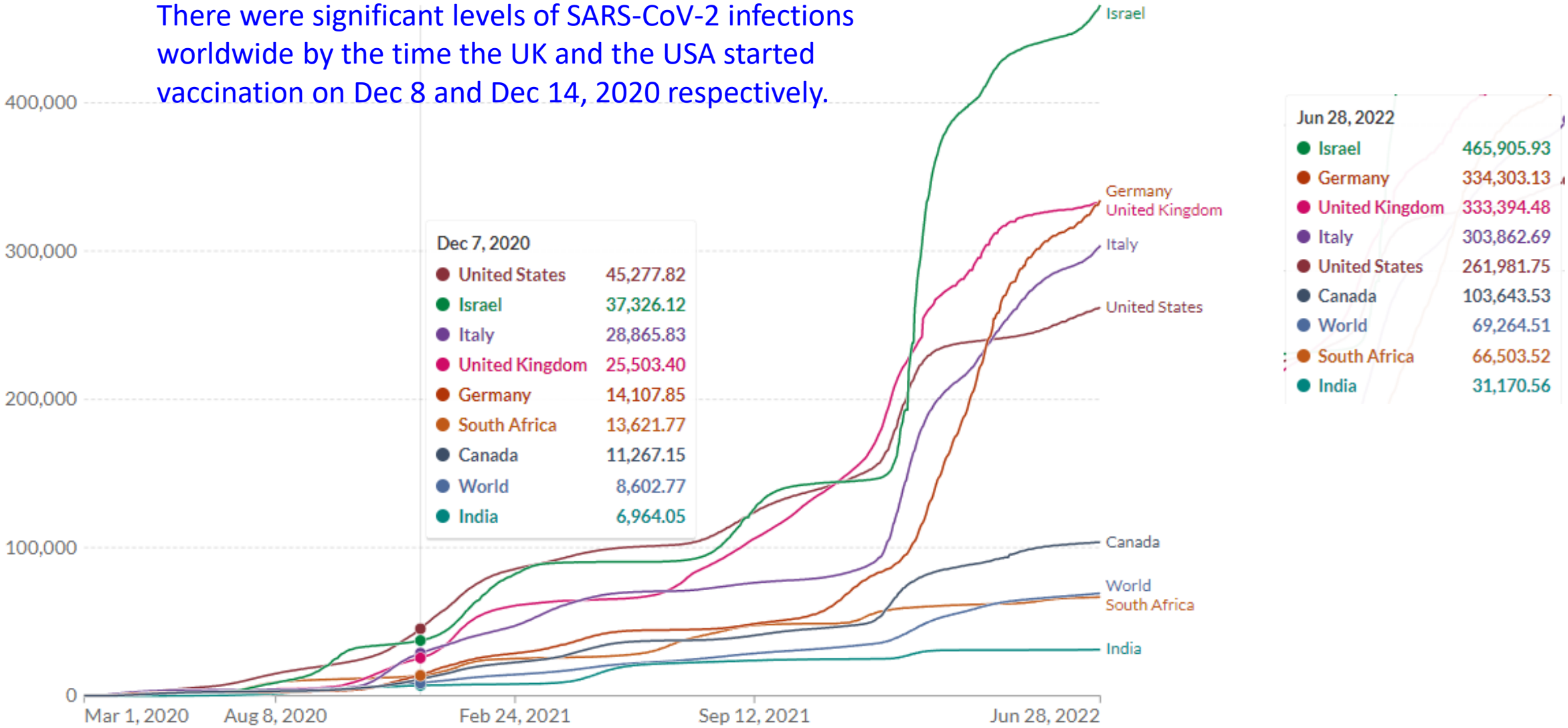
Cumulative confirmed COVID-19 cases per million people

Due to limited testing, the number of confirmed cases is lower than the true number of infections.

Our World in Data

LINEAR LOG

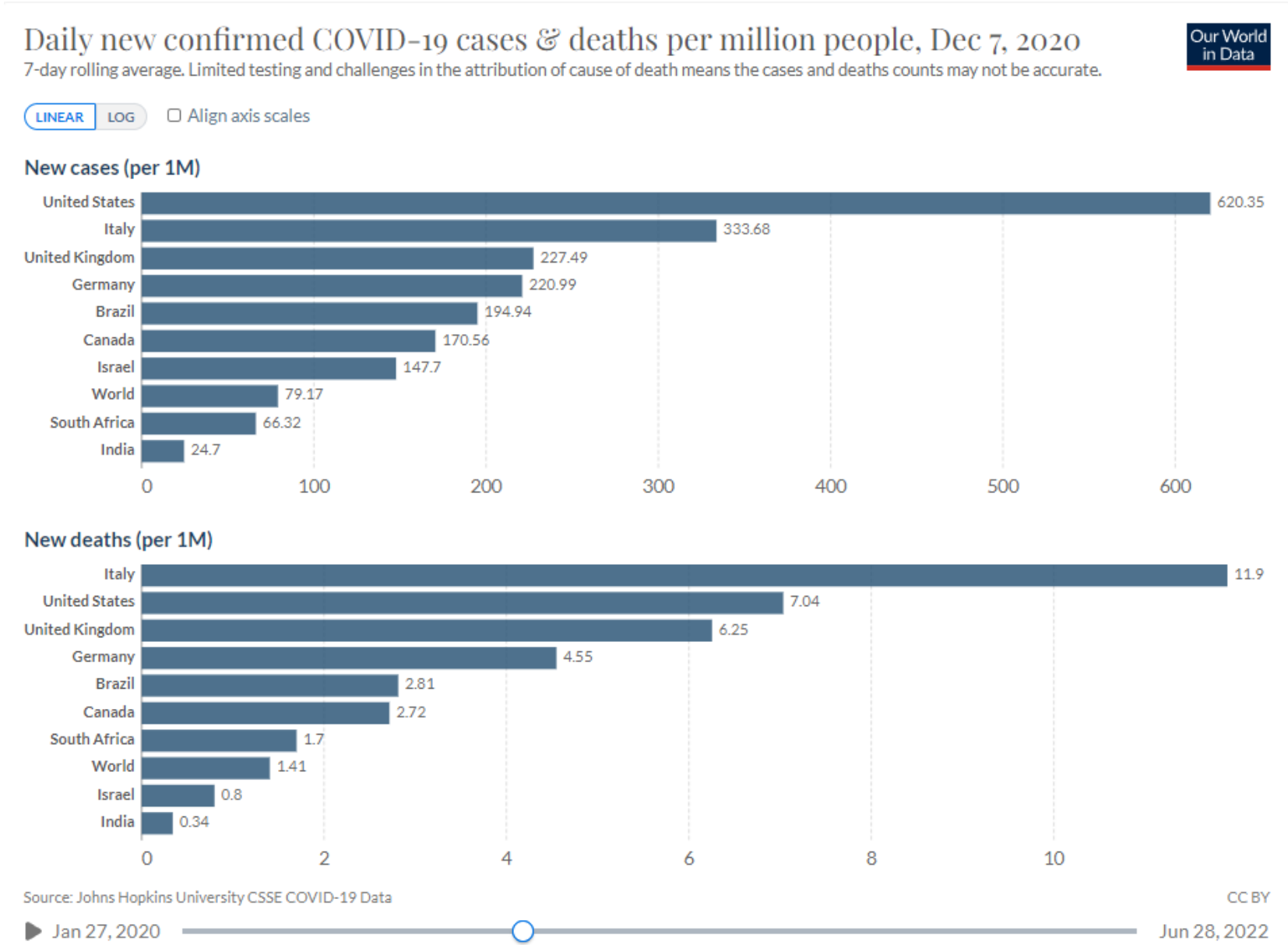
There were significant levels of SARS-CoV-2 infections worldwide by the time the UK and the USA started vaccination on Dec 8 and Dec 14, 2020 respectively.



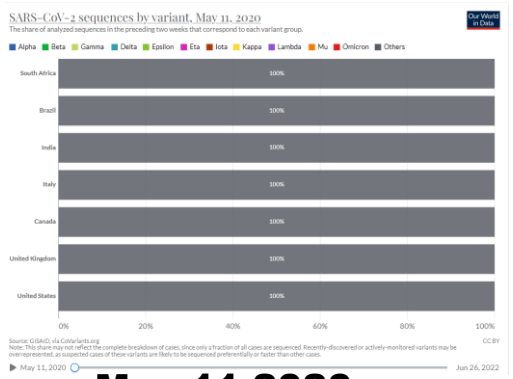
Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

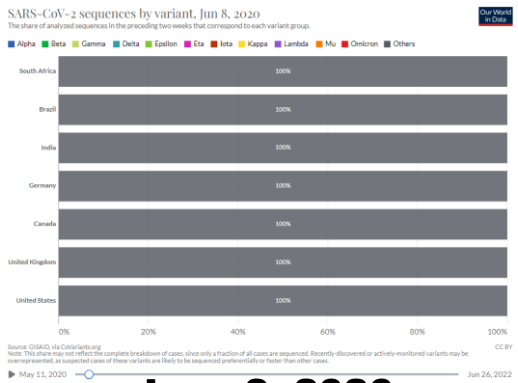
By December 7, there were significant levels of active symptomatic infection worldwide and deaths, but not much in terms of selection of immune escape variants (see next slide).



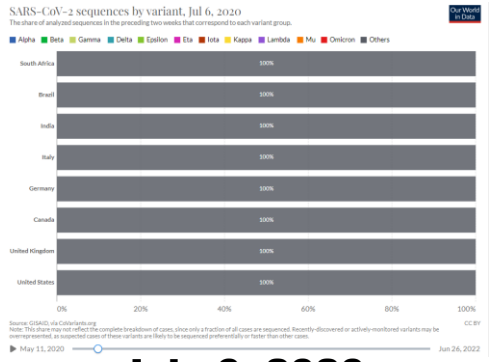
Vaccination against COVID-19 commenced in England on 8 December 2020, initially using the Pfizer-BioNTech mRNA vaccine. The Oxford-AstraZeneca vaccine was then added to the programme from 4 January 2021.



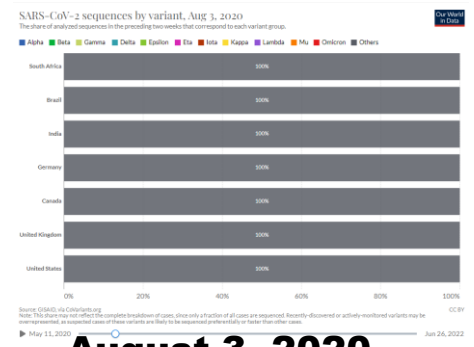
May 11 2020



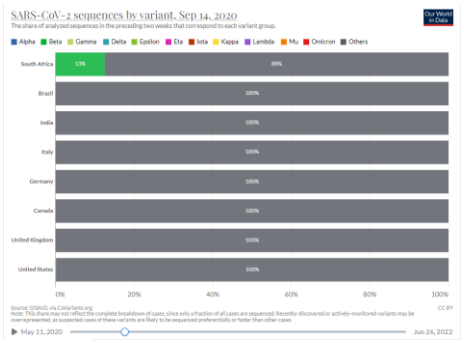
June 8, 2020



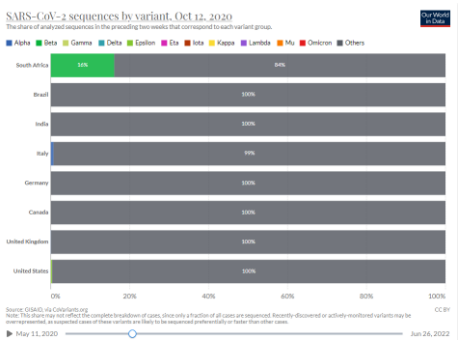
July 6, 2020



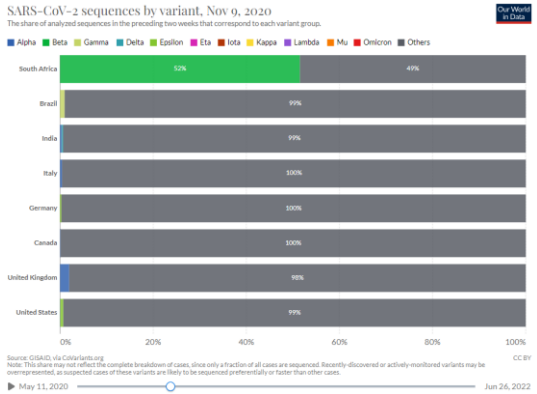
August 3, 2020



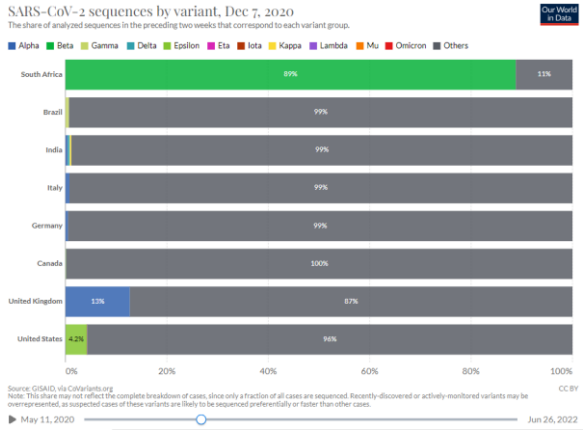
September 14, 2020



October 12, 2020



November 9, 2020



December 7, 2020

Assuming that the widespread transmission of SARS-CoV-2 began by December 2019 in China, which subsequently spread globally, it is remarkable that selection of immune escape variants did not occur during 2020 (about 12 months) **except where the mRNA vaccines were being tested in clinical trials** (e.g., South Africa, UK, USA). It is notable that the beta variant in South Africa was 52 % by November 9, 2020. It is unclear if this related to the high levels of HIV-1 infection in this population. (Grey bars indicate WT).

There was a notable lack of selection of immune escape variants over the first 12 months, implying SARS-CoV-2 Wuhan (WT) was fully adapted to humans at the time of its release favoring the lab-leak hypothesis.

bioRxiv preprint doi: https://doi.org/10.1101/2020.05.01.073262. this version posted May 2, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. It is made available under a CC-BY 4.0 International license.

SARS-CoV-2 is well adapted for humans.
What does this mean for re-emergence?

Shing Hei Zhan[1,2]*, Benjamin E. Deverman[3], Yujia Alina Chan[3]*

[1]Department of Zoology & Biodiversity Research Centre, the University of British Columbia, Vancouver BC, Canada.

[2]Fusion Genomics Corporation, Burnaby BC, Canada.

[3]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, United States of America.

*Correspondence to: zhan@zoology.ubc.ca, alinac@broadinstitute.org

SARS-CoV-2 is well adapted for humans. What does this mean for re-emergence?

Several reports have noted that SARS-CoV-2 appears genetically stable and not under much pressure to adapt, which bodes well for diagnostics, vaccine, and therapeutics development (1–4). How long a particular antiviral, antibody, or vaccine will be effective against SARS-CoV-2 depends greatly on how fast and how extensively the target gene or protein is evolving. To identify

The blue violin plots (Figure 1c) show the high levels of mutation in the first 3 months (Jan to Mar 2003) for SARS-CoV-1 spread in humans which was minimized thereafter (Feb-May 2003). In contrast, SARS-COV-2 showed far less mutation for its first 3 months (Jan to March 2020) consistent with it being fully adapted to humans.

bioRxiv preprint doi: https://doi.org/10.1101/2020.05.01.073262. this version posted May 2, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. It is made available under a CC-BY 4.0 International license.

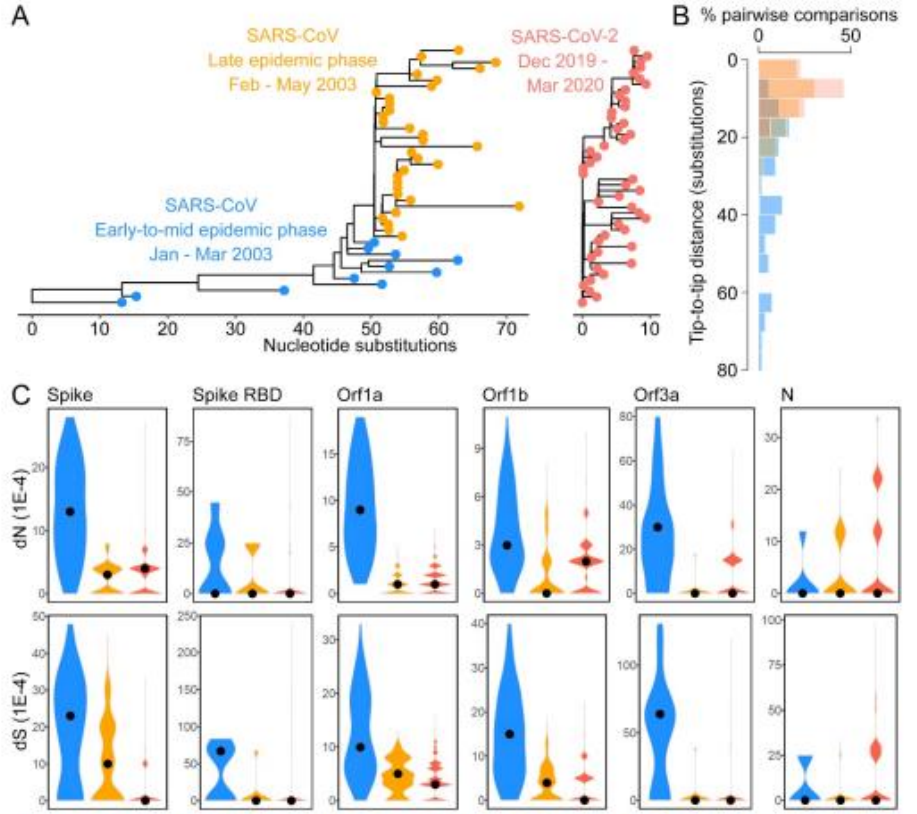
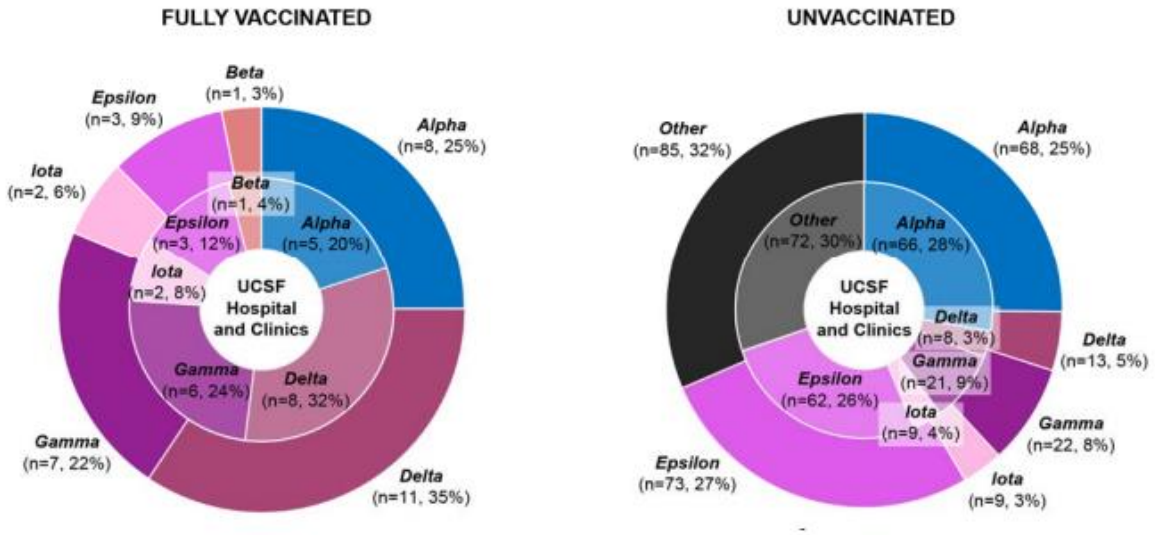
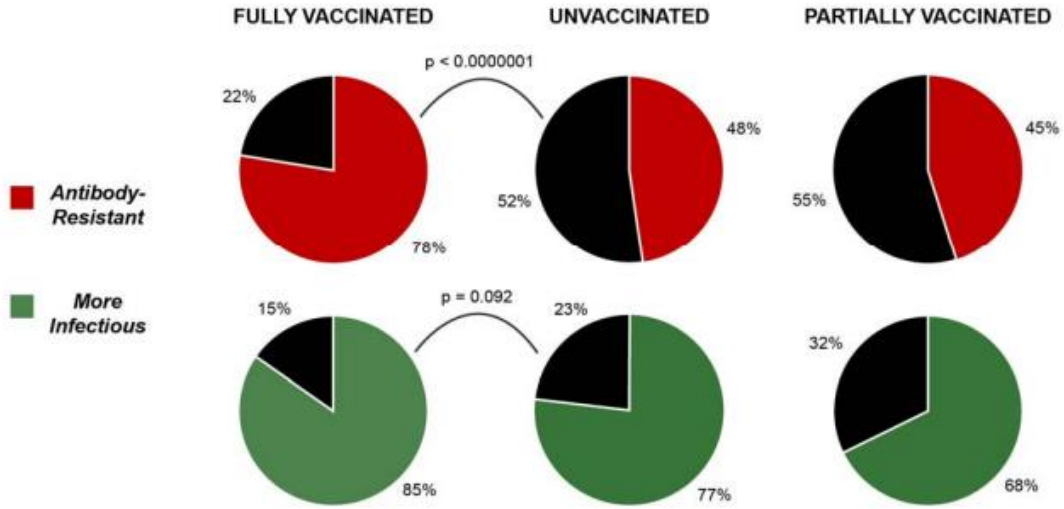


Figure 1. Comparison of the genetic divergence of SARS-CoV and SARS-CoV-2. (A) Maximum likelihood trees built with IQtree (19). We curated 11 early-to-mid epidemic SARS-CoV genomes, 32 late epidemic SARS-CoV genomes, and 46 SARS-CoV-2 genomes consisting of a December, 2019 Wuhan-Hu-1 isolate and 15 isolates from each month of January, February, and March, 2020. **(B)** Tip-to-tip distance of each tree: SARS-CoV-2 (red) is less polymorphic than early-to-mid epidemic (blue) SARS-CoV over similar 3-month periods based on the current sampling approach (resampling test, $p < 0.01$). **(C)** Distribution of pairwise non-synonymous (dN) and synonymous (dS) substitution rates in the Spike, S RBD, Orf1a, Orf1b, Orf3a, and N gene across 151 SARS-CoV-2 genomes: 50 from each month of January, February, and March, 2020, in addition to the Wuhan-Hu-1 isolate.

Given about a 3-4 week interval between the first dose and the second dose, and where the second dose is greatly implicated in the selection of variants whereas the first dose appears to protect against selection (Servellita V et al MedRxiv, August 25, 2021) :

SARS-CoV-2 Strains (Feb-June 2021)

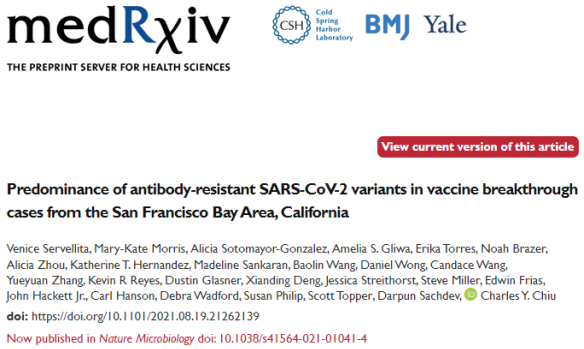




Servellita V et al MedRxiv, August 25, 2021

The inner circles represent the immunocompetent cases, and the outer circles include both immunocompetent and immunocompromised individuals.

Samples Collected February through June 2021


medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES

View current version of this article

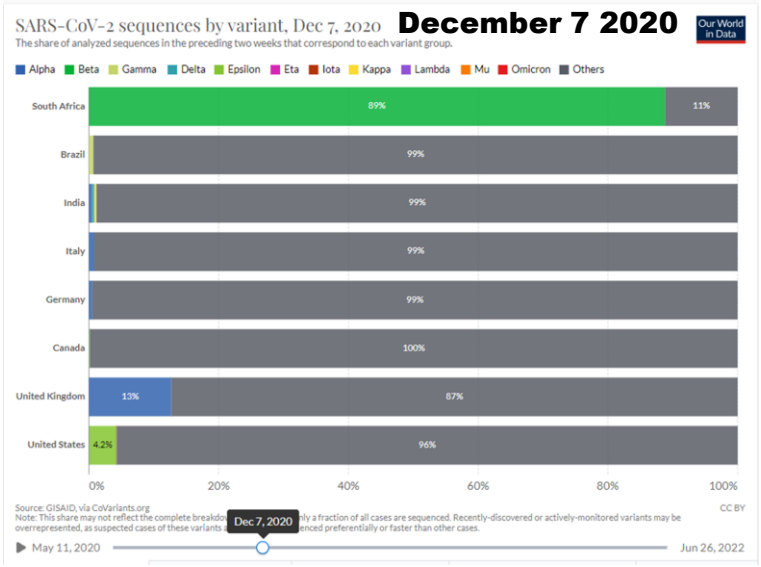
Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California

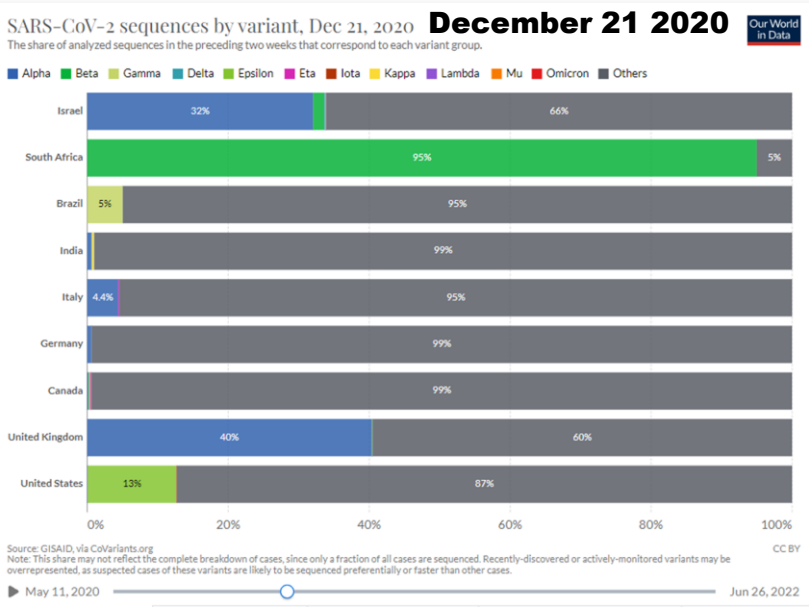
Venice Servellita, Mary-Kate Morris, Alicia Sotomayor-Gonzalez, Amelia S. Gliwa, Erika Torres, Noah Brazer, Alicia Zhou, Katherine T. Hernandez, Madeline Sankaran, Baolin Wang, Daniel Wong, Candace Wang, Yueyuan Zhang, Kevin R Reyes, Dustin Glasner, Xianding Deng, Jessica Streithorst, Steve Miller, Edwin Frias, John Hackett Jr., Carl Hanson, Debra Wadford, Susan Philip, Scott Topper, Darpun Sachdev, Charles Y. Chiu

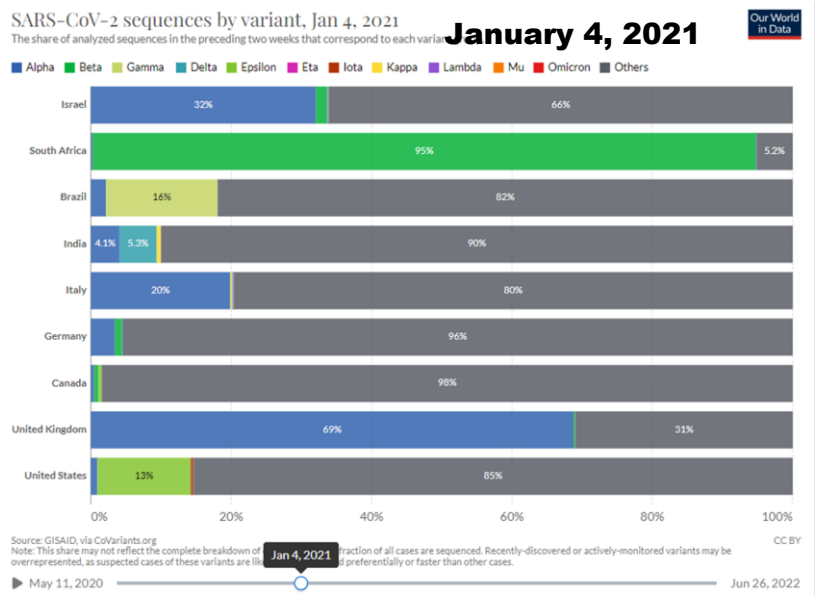
doi: https://doi.org/10.1101/2021.08.19.21262139

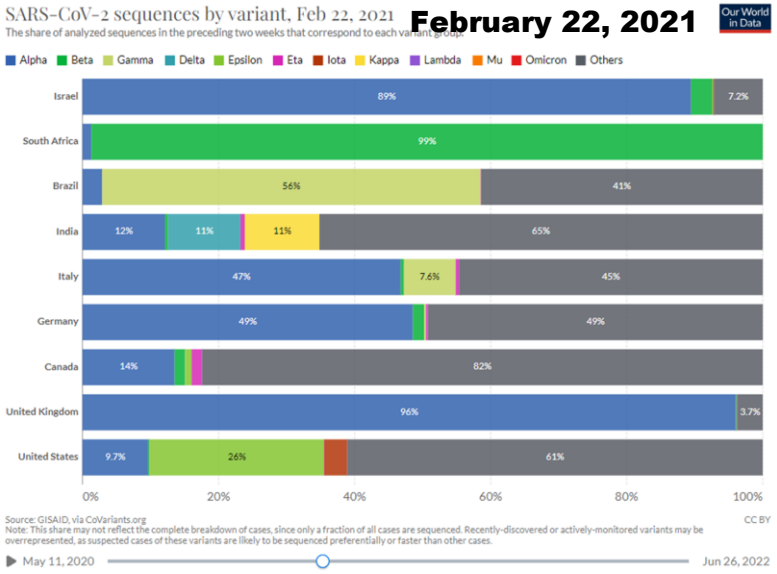
Now published in *Nature Microbiology* doi: 10.1038/s41564-021-01041-4

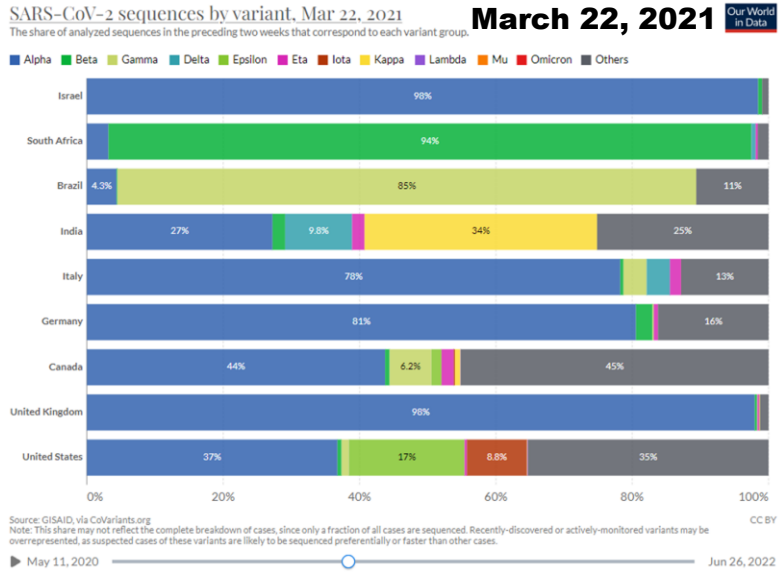
https://www.medrxiv.org/content/10.1101/2021.08.19.21262139v1

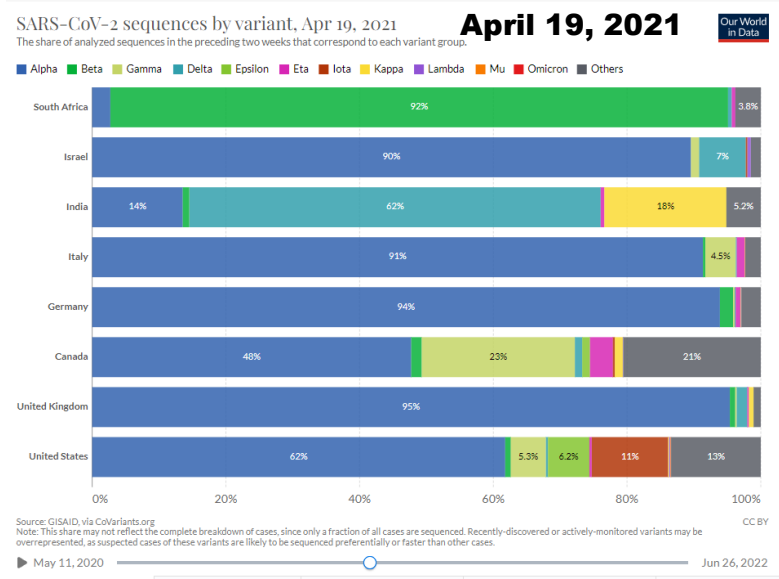




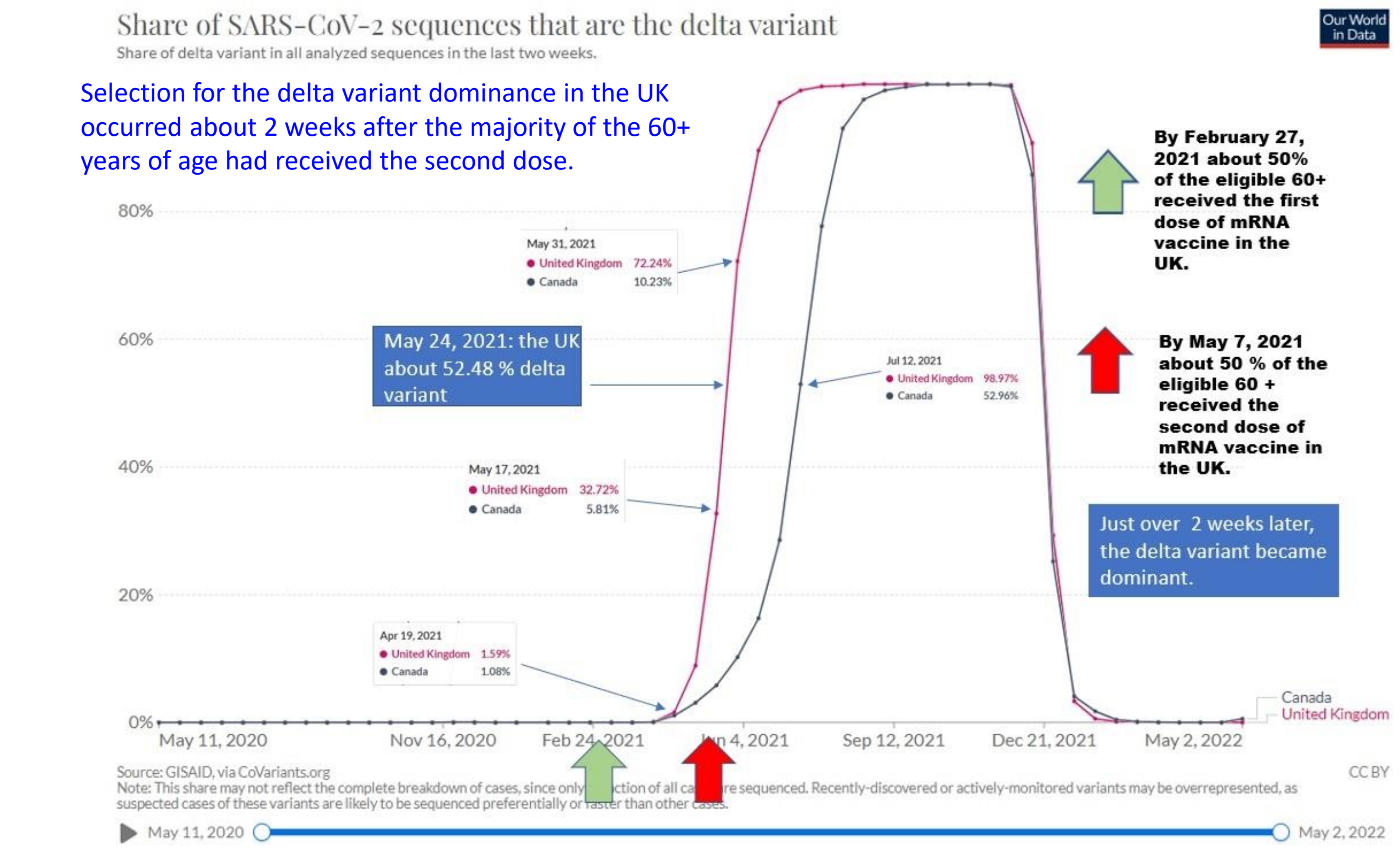




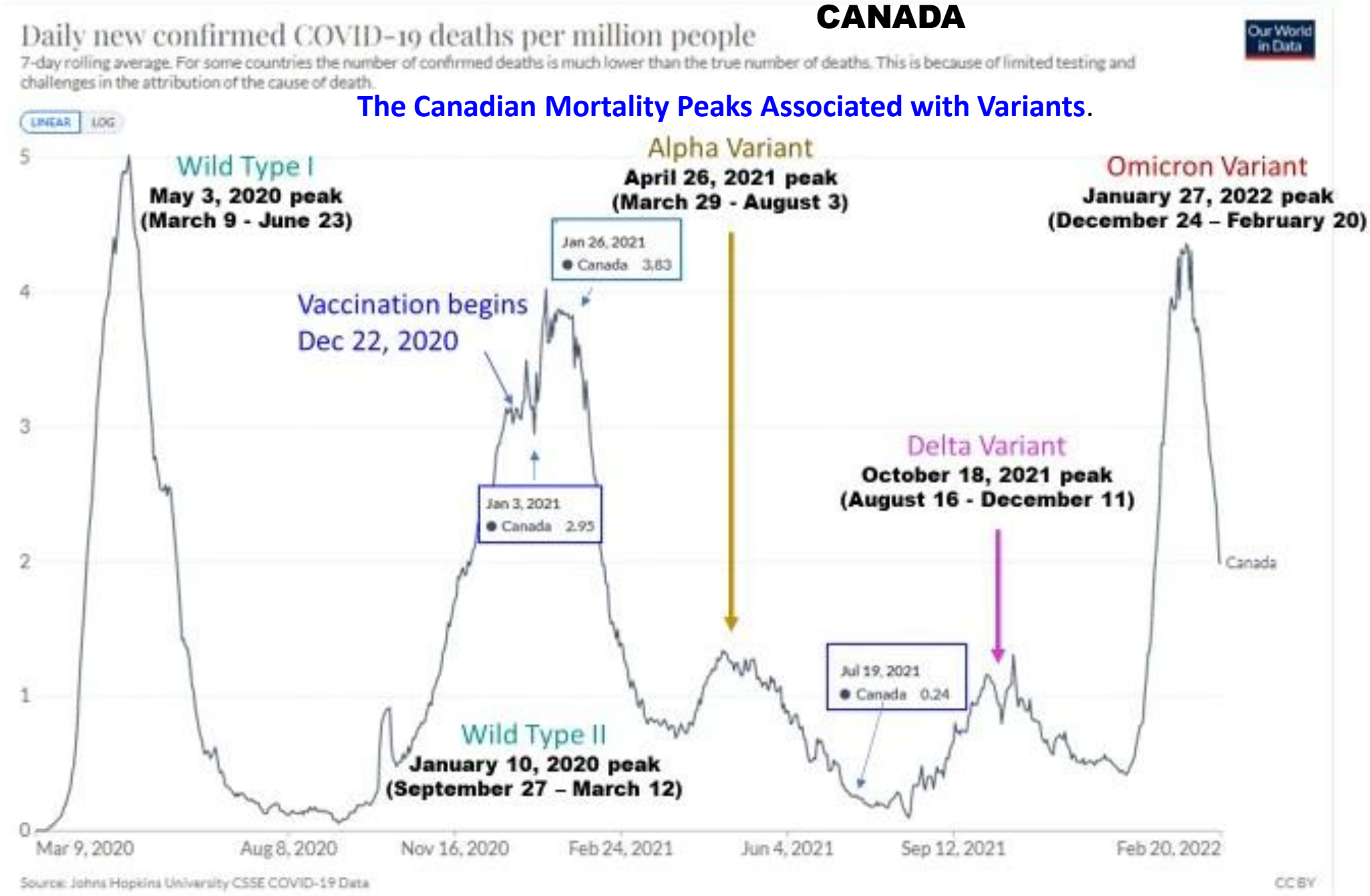




we find strong evidence for selection of immune escape variants by the vaccines, in various countries worldwide.


Share of SARS-CoV-2 sequences that are the delta variant
Share of delta variant in all analyzed sequences in the last two weeks.
Our World in Data
Selection for the delta variant dominance in the UK occurred about 2 weeks after the majority of the 60+ years of age had received the second dose.
By February 27, 2021 about 50% of the eligible 60+ received the first dose of mRNA vaccine in the UK.
By May 7, 2021 about 50 % of the eligible 60 + received the second dose of mRNA vaccine in the UK.
May 24, 2021: the UK about 52.48 % delta variant
Just over 2 weeks later, the delta variant became dominant.
May 31, 2021
United Kingdom 72.24%
Canada 10.23%
Jul 12, 2021
United Kingdom 98.97%
Canada 52.96%
May 17, 2021
United Kingdom 32.72%
Canada 5.81%
Apr 19, 2021
United Kingdom 1.59%
Canada 1.08%
80%
60%
40%
20%
0%
May 11, 2020
Nov 16, 2020
Feb 24, 2021
Jun 4, 2021
Sep 12, 2021
Dec 21, 2021
May 2, 2022
Canada
United Kingdom
Source: GISAID, via CoVariants.org
CC BY
May 11, 2020
May 2, 2022

CANADA


Daily new confirmed COVID-19 deaths per million people
7-day rolling average. For some countries the number of confirmed deaths is much lower than the true number of deaths. This is because of limited testing and challenges in the attribution of the cause of death.
Our World in Data
LINEAR
LOG
The Canadian Mortality Peaks Associated with Variants.
Wild Type I
May 3, 2020 peak
(March 9 - June 23)
Alpha Variant
April 26, 2021 peak
(March 29 - August 3)
Omicron Variant
January 27, 2022 peak
(December 24 – February 20)
Jan 26, 2021
Canada 3.83
Vaccination begins
Dec 22, 2020
Jan 3, 2021
Canada 2.95
Delta Variant
October 18, 2021 peak
(August 16 - December 11)
Jul 19, 2021
Canada 0.24
Canada
Wild Type II
January 10, 2020 peak
(September 27 – March 12)
5
4
3
2
1
0
Mar 9, 2020
Aug 8, 2020
Nov 16, 2020
Feb 24, 2021
Jun 4, 2021
Sep 12, 2021
Feb 20, 2022
Source: Johns Hopkins University CSSE COVID-19 Data
CC BY

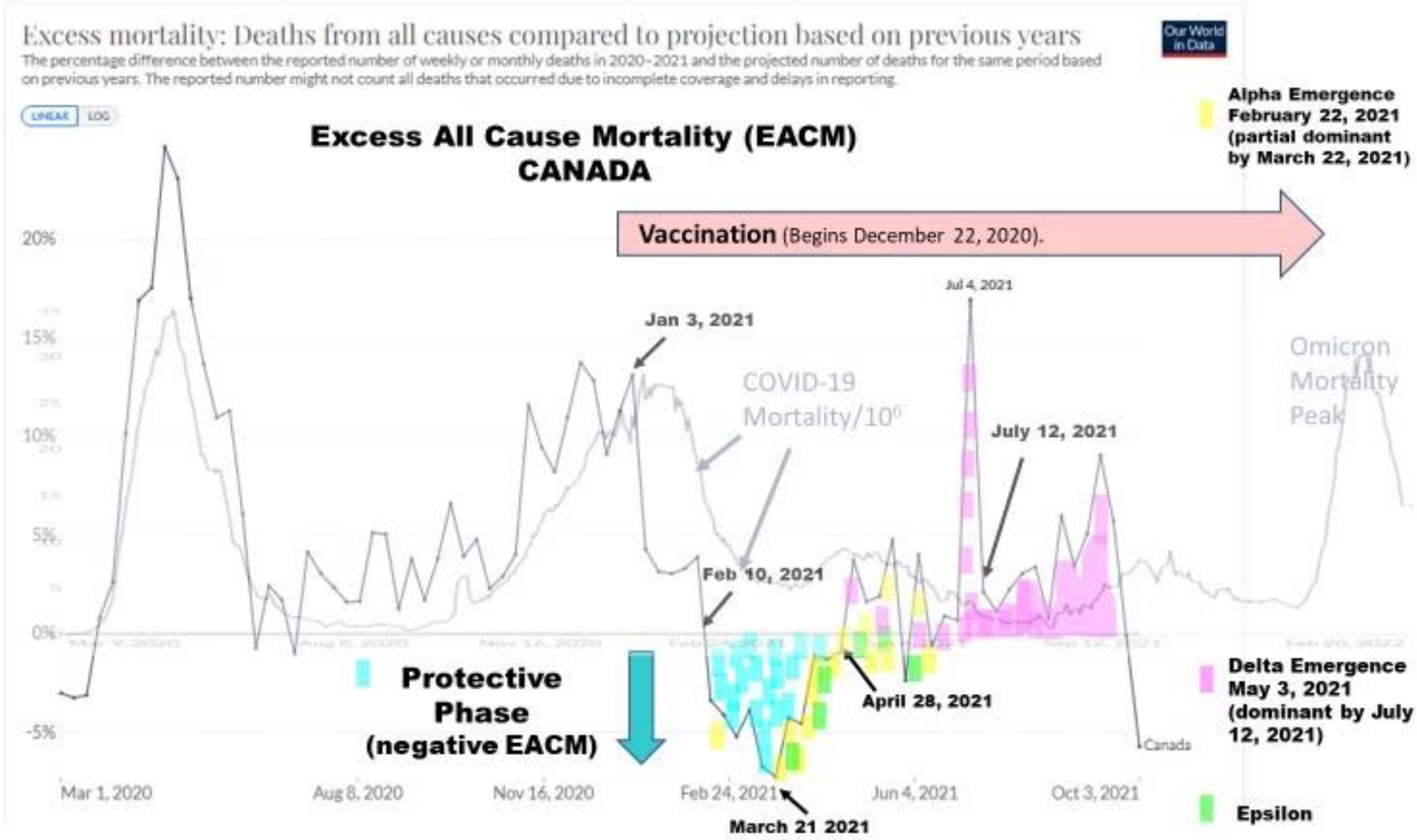
CANADA. Initial Emergence or Dominance (at >50% of Variants) Coincided with a Two Dose/One Dose Ratio of > 0.5 about 10 to 14 Days Prior or as Associated with the Loss of Trained Immunity Revealed by a Negative Excess All-Cause Mortality (EACM)

Two to One Dose Ratios for COVID-19 Vaccine Use In Canada

By Date in 2021 (from Our World in Data)

DATE	% At Least One Dose	% Two Doses	% One Dose	Two / One RATIO	EVENTS	NOTES
22-Dec	0.071	None	0.071	N/A		
29-Dec	0.19	None	0.19	N/A		
3-Jan	0.3	None	0.30	N/A		EACM Decreases
10-Jan	0.84	0.1	0.74	0.135		
17-Jan	1.5	0.6	0.9	0.667		EACM flattened
24-Jan	2.03	0.15	1.88	0.080		
31-Jan	2.3	0.3	2	0.150		
7-Feb	2.4	0.47	1.93	0.244		
8-Feb	2.4	0.5	1.9	0.263		
10-Feb	2.5	0.6	1.9	0.316		Enters Neg EACM
14-Feb	2.59	0.81	1.78	0.455	14 days prior	Feb 14-28
21-Feb	2.9	1.1	1.8	0.611	7 days prior	
22-Feb	3	1.2	1.8	0.667	Alpha emerges	
25-Feb	3.2	1.3	1.9	0.684		
26-Feb	3.4	1.4	2	0.700		
27-Feb	3.5	1.4	2.1	0.667	NACI Intervention on Feb 27?	
28-Feb	3.63	1.41	2.22	0.635		
7-Mar	4.85	1.52	3.33	0.456		Peak in -EACM
8-Mar	5.1	1.6	3.5	0.457		
11-Mar	5.67	1.59	4.08	0.390		
14-Mar	6.5	1.6	4.9	0.327		
15-Mar	6.8	1.6	5.2	0.308	14 days prior	
21-Mar	8.83	1.7	7.13	0.238	7 days prior	Lowest EACM

DATE	% At Least One Dose	% Two Doses	% One Dose	Two / One RATIO	EVENTS	NOTES
21-Mar	8.83	1.7	7.13	0.238	7 days prior	Lowest EACM
22-Mar	9.2	1.7	7.5	0.227	Alpha dominates	
28-Mar	11.81	1.81	10	0.181		Peak in -EACM
4-Apr	15.07	1.92	13.15	0.146		
11-Apr	19.04	2.19	16.85	0.130		Peak in -EACM
18-Apr	24	2.5	21.5	0.116	14 days prior	
19-Apr	25	2.5	22.5	0.111		
25-Apr	29.18	2.75	26.43	0.104	7 days prior	
26-Apr	30	2.8	27.2	0.103		
28-Apr	31	2.9	28.1	0.103		Exit Neg EACM
2-May	33.58	3.05	30.53	0.100	Delta emerges	
3-May	34	3.1	30.9	0.100		
9-May	39	3.4	35.6	0.096		
16-May	45	3.8	41.2	0.092		
17-May	46	3.9	42.1	0.093	Max alpha at 59%	
23-May	51	4.05	46.95	0.086		
30-May	56.69	5.45	51.24	0.106		
2-Jun	58.8	6.11	52.69	0.116		
11-Jun	63.87	10.82	53.05	0.204		
14-Jun	64.86	13.11	51.75	0.253		
20-Jun	66.29	18.85	47.44	0.397		
26-Jun	67.38	26.47	40.91	0.647	14 days prior	
4-Jul	68.31	35.02	33.29	1.052	7 days prior	50% Receive 2nd Dose
12-Jul	69.27	44.33	24.94	1.777	Delta Dominant	
19-Jul	69.99	50.61	19.38	2.611		50% Fully Vaxxed
25-Jul	71	55	16	3.438		
1-Aug	71	59	12	4.917		


Excess mortality: Deaths from all causes compared to projection based on previous years
The percentage difference between the reported number of weekly or monthly deaths in 2020–2021 and the projected number of deaths for the same period based on previous years. The reported number might not count all deaths that occurred due to incomplete coverage and delays in reporting.
Our World in Data
LINEAR
LOG
Excess All Cause Mortality (EACM)
CANADA
Alpha Emergence
February 22, 2021
(partial dominant
by March 22, 2021)
Vaccination (Begins December 22, 2020).
20%
15%
10%
5%
0%
-5%
Jan 3, 2021
Jul 4, 2021
COVID-19
Mortality/10⁶
July 12, 2021
Omicron
Mortality
Peak
Feb 10, 2021
April 28, 2021
Canada
Protective
Phase
(negative EACM)
Delta Emergence
May 3, 2021
(dominant by July
12, 2021)
Mar 1, 2020
Aug 8, 2020
Nov 16, 2020
Feb 24, 2021
Jun 4, 2021
Oct 3, 2021
March 21 2021
Epsilon

The E484K substitution known to confer immune escape was detected at the time of viral rebound by bamlanivimab treatment (but not before bamlanivimab treatment) of severely immunosuppressed individuals (10 day average to viral rebound with selected immune escape variants).

This data argues even in those with the highest COVID-19 risks & hospitalized for some time in the ICU, the selection of immune escape variants did not naturally occur without the selection pressure mediated by neutralizing monoclonal antibodies.

Jensen B, Luebke N, Feldt T, Keitel V, Brandenburger T, Kindgen-Milles D, Lutterbeck M, Freise NF, Schoeler D, Haas R, Dilthey A, Adams O, Walker A, Timm J, Luedde T. Emergence of the E484K mutation in SARS-COV-2-infected immunocompromised patients treated with bamlanivimab in Germany. Lancet Reg Health Eur. 2021 Sep;8:100164. doi: 10.1016/j.lanepe.2021.100164.

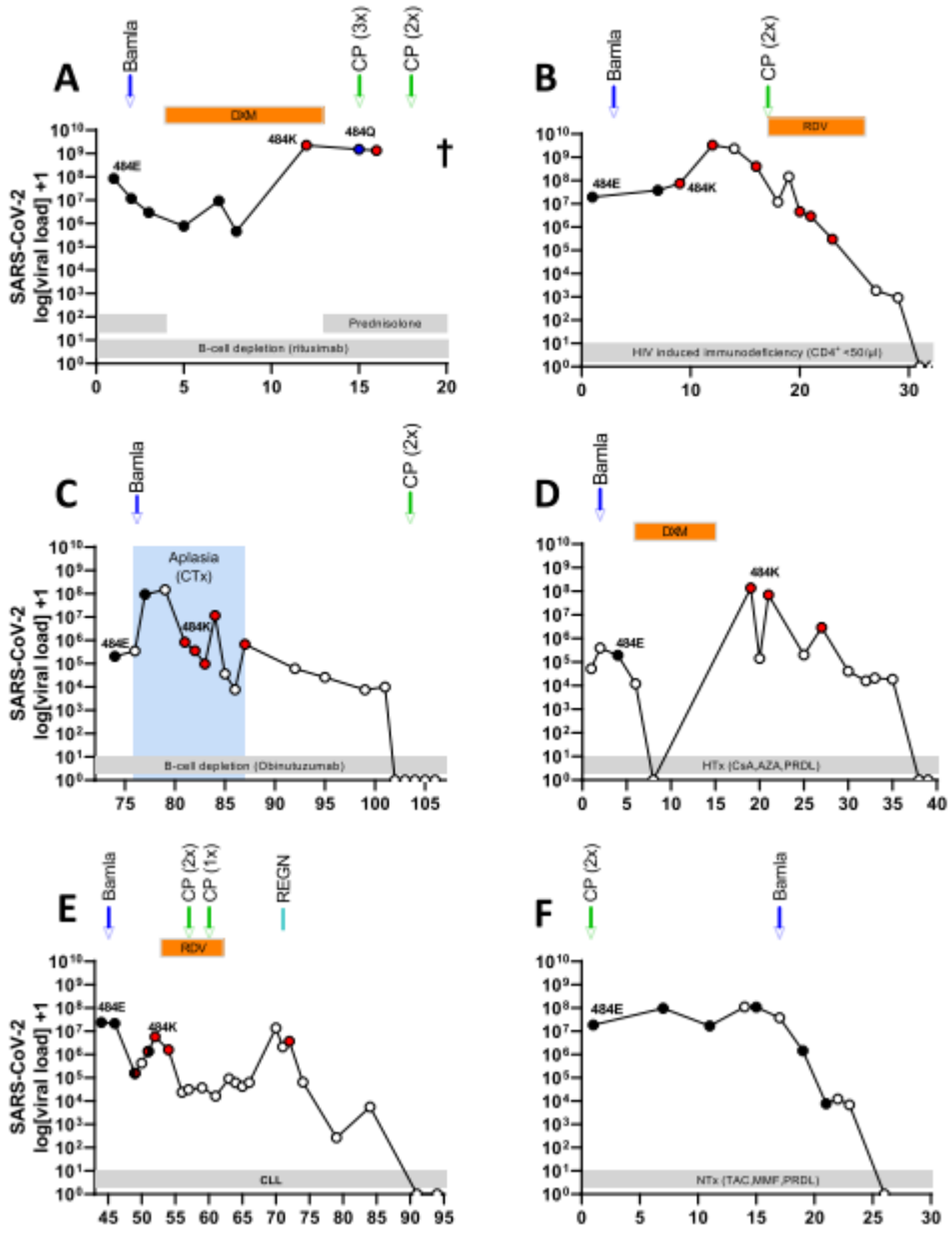


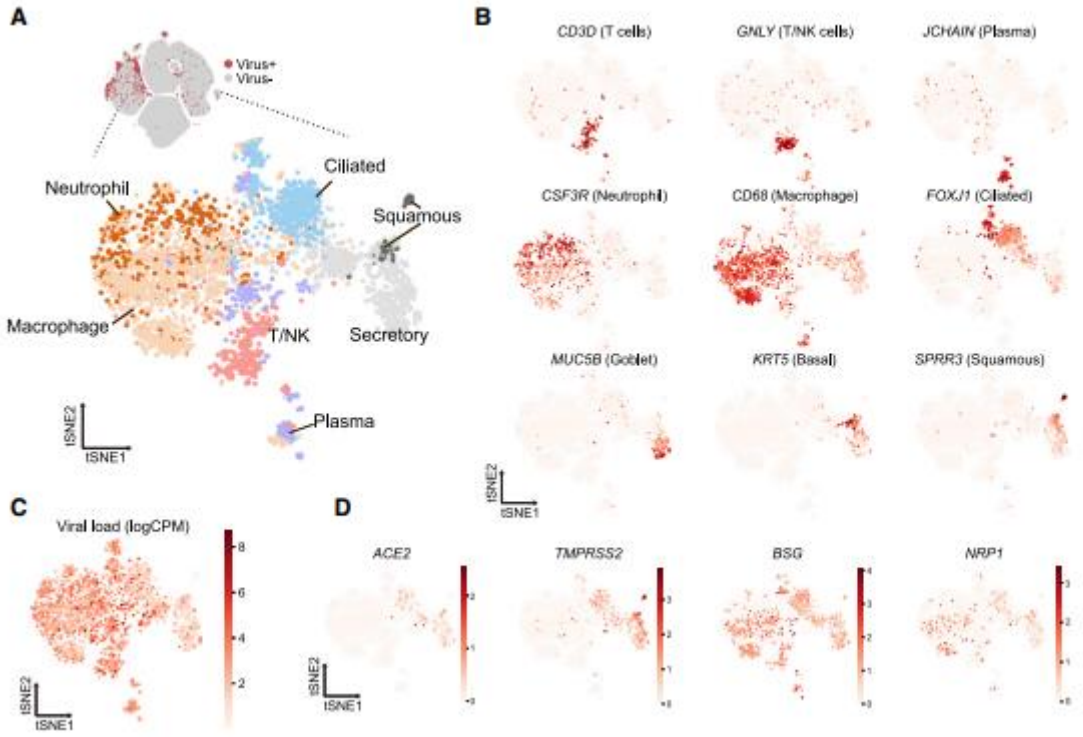
Fig. 1. Selection of E484K in SARS-CoV-2 infected patients with severe immunosuppression.

Why is there so little selection pressure during natural infection including moderate and severe COVID-19?

Ren X, Wen W, Fan X, Hou W, Su B, Cai P, et al. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. **Cell. 2021 Apr** 1;184(7):1895-1913.e19. doi: 10.1016/j.cell.2021.01.053. Epub 2021 Feb 3.

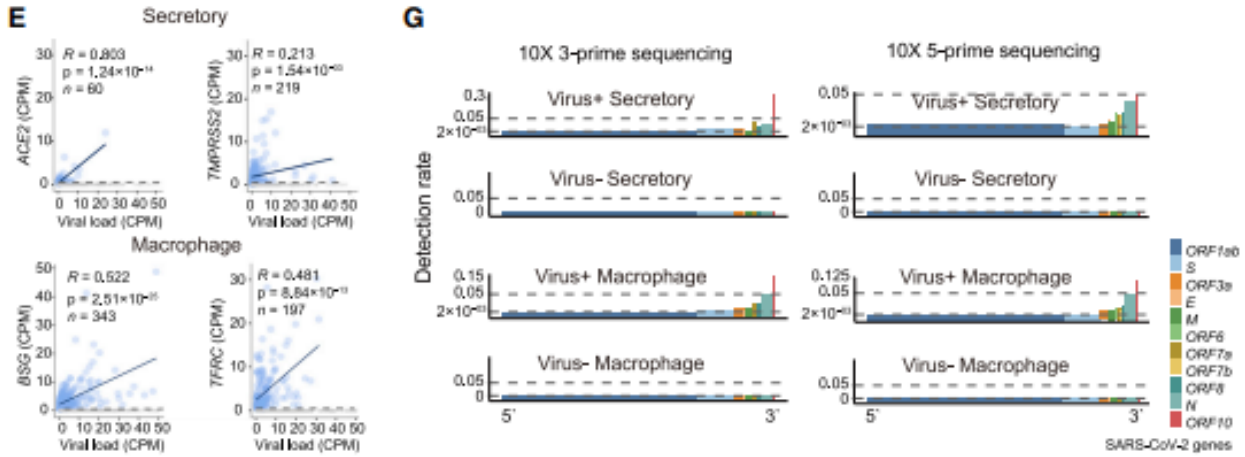
"The presence of SARS-CoV-2 RNA in various immune cell types, {in BALF} including neutrophils, macrophages, plasma B cells, T cells, and NK cells, was surprising to us initially, but the research community is beginning to appreciate this phenomenon. … In summary, the large scRNA-seq dataset covering diverse disease severity and stages has revealed multiple immune characteristics of COVID-19 that were not adequately appreciated previously. "

"**No cells from PBMCs** were detected as SARS-CoV-2 positive."



BALF and Sputum Samples

SARS-CoV-2 infected macrophages in BALF are ACE2 negative.

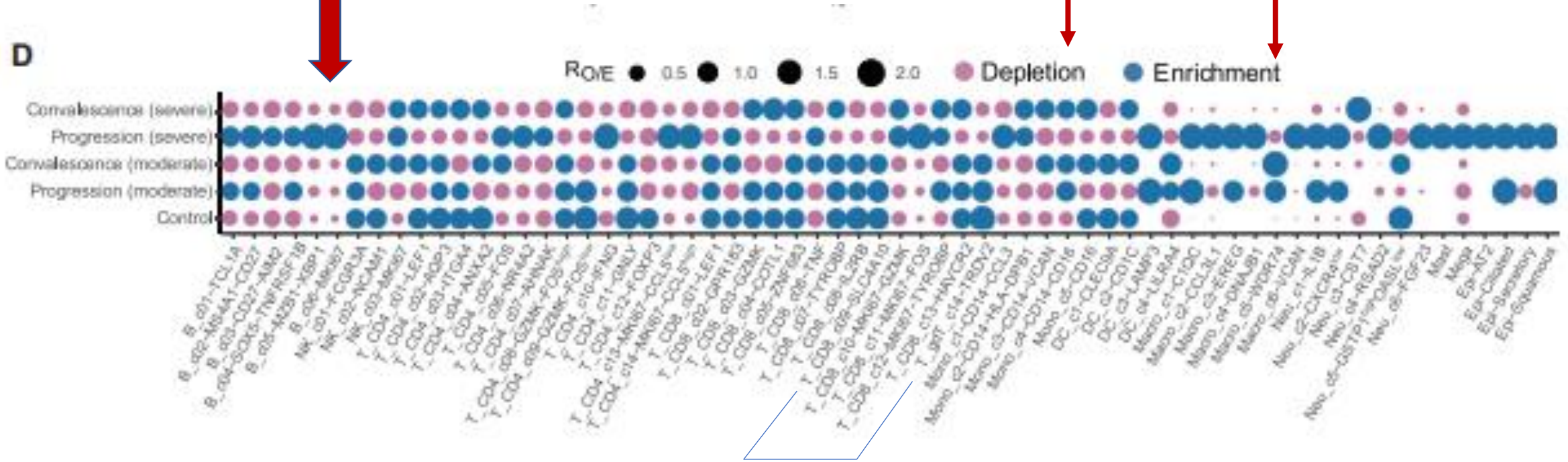


Virus **<u>productively</u> infects macrophages** associated with **BSG** and TFRC (transferrin receptor) upregulation.

Plasma B cells correlate with progression to severe

Moderate & Severe Recovery Associated "Mono_c4-CD14-CD16" *

Moderate (Recovery Associated) "Macro_c5-WDR74" (VDR+ HERV-K102 particle producing cells)



Innate T cells (**MALT** and **γ/δ T cells**) associated with recovery from moderate but depleted with progression to severe **(like Macro_c5-WDR74)**.

*Progenitor of Macro_c5-WDR74, is the Mono_c4-CD14-CD16 which is also **VDR+, IRF1+** and shares programming (transcription factors) with the recovery Macro_c5-WDR74 macrophages.

Ren X, Wen W, Fan X, Hou W, Su B, Cai P, et al. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. Cell. 2021 Apr 1;184(7):1895-1913.e19. doi: 10.1016/j.cell.2021.01.053. Epub 2021 Feb 3.

Schematic Demonstrating the spike:ACE2 to spike:BSG Switch: Associated with the Production of Spike Neutralizing Antibodies (NAbs) in BALF (evidence in Ren X et al, Cell 2021).

Spike: ACE2 Favored

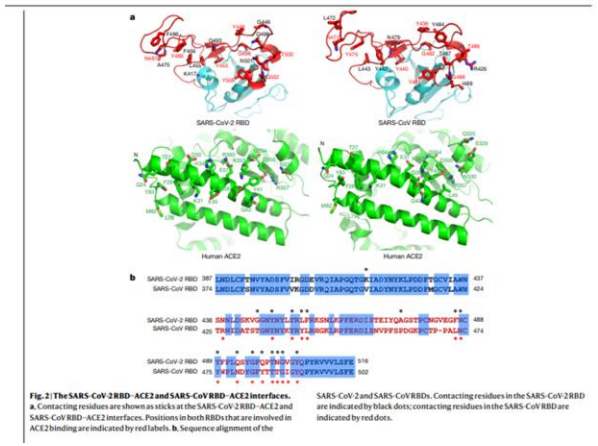
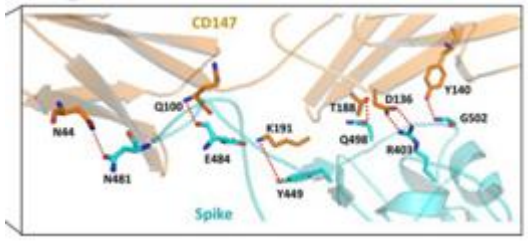


Fig. 2 | The SARS-CoV-2 RBD–ACE2 and SARS-CoVRBD–ACE2 interfaces. a. Contacting residues are shown as sticks at the SARS-CoV-2 RBD–ACE2 and SARS-CoVRBD–ACE2 interfaces. Positions in both RBDs that are involved in ACE2 binding are indicated by red labels. b. Sequence alignment of the SARS-CoV-2 and SARS-CoVRBDs. Contacting residues in the SARS-CoV-2 RBD are indicated by black dots; contacting residues in the SARS-CoVRBD are indicated by red dots.

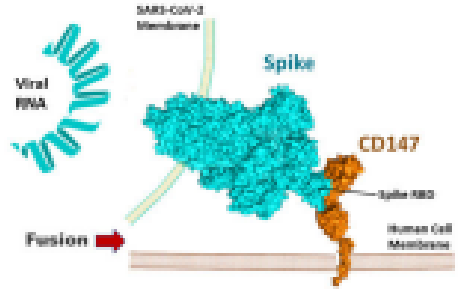
Lan J et al, Nature, 14 May 2020

Spike: CD147 (BSG) Favored Entry into Macrophages and other immune cell types [Ren X et al, Cell 2021]

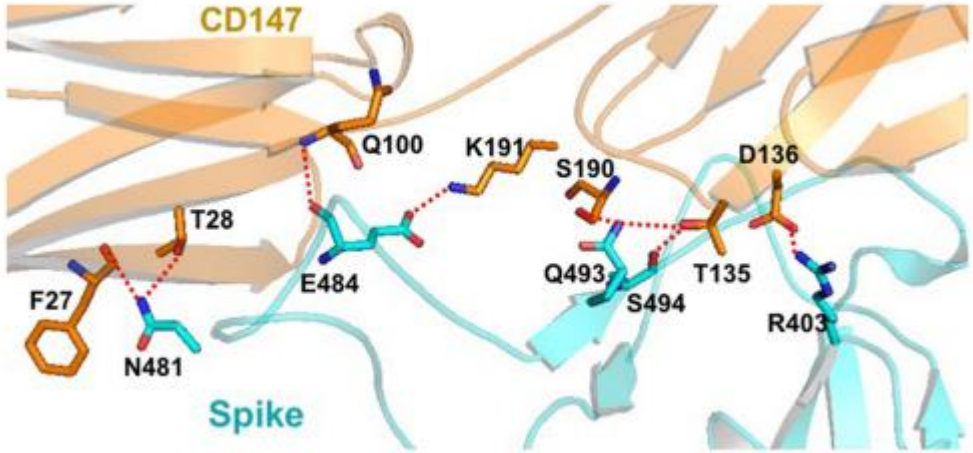


Helal MA et al, J. BioM Struct & Dynamics Sept 7 2020

Helal MA, Shouman S, Abdelwaly A, Elmehrath AO, Essawy M, Sayed SM, Saleh AH, El-Badri N. Molecular basis of the potential interaction of SARS-CoV-2 spike protein to CD147 in COVID-19 associated-lymphopenia. J Biomol Struct Dyn. 2022 Feb;40(3):1109-1119. doi: 10.1080/07391102.2020.1822208.



CD147 = BSG



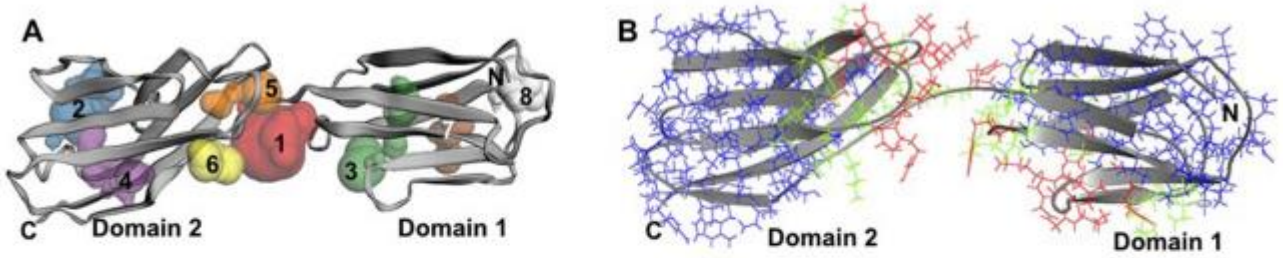
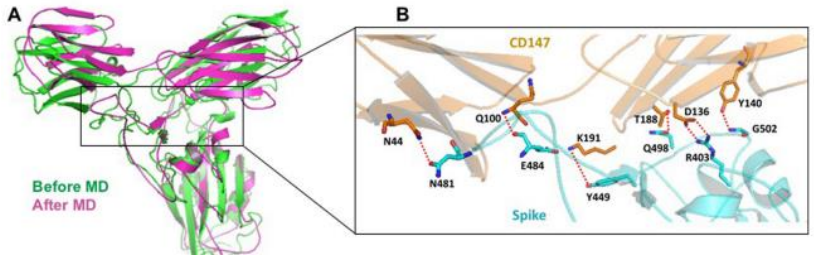


Figure 1. (A) Pockets detected on the surface of the CD147 receptor using the CASTp server. The protein is shown as a grey cartoon and the pockets are displayed as colored spheres. (B) Interacting residues of the CD147 as predicted by the CPROT tool. Predicted binding residues and surrounding residues are shown as red and green lines, respectively. Residues not participating in the interaction are shown as blue lines.

Table 1. Parameters of the interface of the interaction between the spike RBD and CD147 as predicted by the PDBePISA server and the Hawkdock MM/GBSA calculations.

Docking Server	Spike		CD147		Interface		
	Interface Residues	[a]Interface Surface, Å^2	Interface Residues	Interface Surface, Å^2	[b]Interface Surface, Å^2	[c]ΔG P-Value	MM/GBSA kcal/mol
HADDOCK	32	10,339	34	10,130	1,069	0.297	−68.00
ZDOCK	32	10,292	39	10,500	1,154	0.367	−66.77
HawkDock	36	10,259	29	10,284	1,042	0.181	−59.26

[a]**Total solvent accessible surface** area in square angstroms for each protein.
[b]**Interface area**, calculated as difference in total accessible surface areas of isolated and interfacing structures divided by two.
[c]**ΔiG P-value** indicates the P-value of the observed solvation free energy gain. The P-value measures the probability of getting a lower than observed ΔiG, when the interface atoms are picked randomly from the protein surface. $p < 0.5$ indicates interfaces with surprising (higher than would-be-average for given structures) hydrophobicity, implying that the interface surface can be interaction-specific.



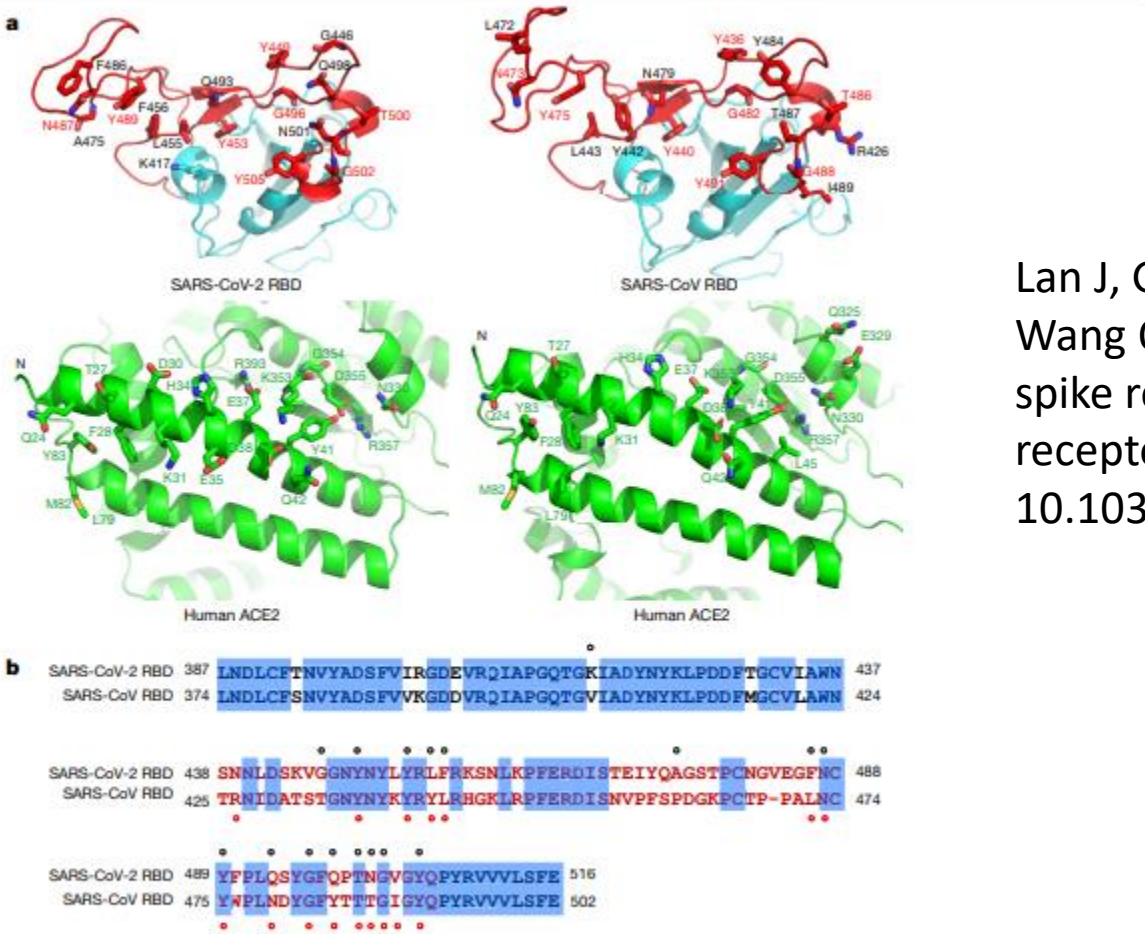


Fig. 2 | The SARS-CoV-2 RBD–ACE2 and SARS-CoV RBD–ACE2 interfaces. **a**, Contacting residues are shown as sticks at the SARS-CoV-2 RBD–ACE2 and SARS-CoV RBD–ACE2 interfaces. Positions in both RBDs that are involved in ACE2 binding are indicated by red labels. **b**, Sequence alignment of the SARS-CoV-2 and SARS-CoV RBDs. Contacting residues in the SARS-CoV-2 RBD are indicated by black dots; contacting residues in the SARS-CoV RBD are indicated by red dots.

Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020 May;581(7807):215-220. doi: 10.1038/s41586-020-2180-5. Epub 2020 Mar 30.

Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, Yu J, Shan S, Zhou B, Song S, Tang X, Yu J, Lan J, Yuan J, Wang H, Zhao J, Zhang S, Wang Y, Shi X, Liu L, Zhao J, Wang X, Zhang Z, Zhang L. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature. 2020 Aug;584(7819):115-119. doi: 10.1038/s41586-020-2380-z. Epub 2020 May 26.

Molecular interference of the spike RBD with ACE2 by a neutralizing antibody to spike RBD.

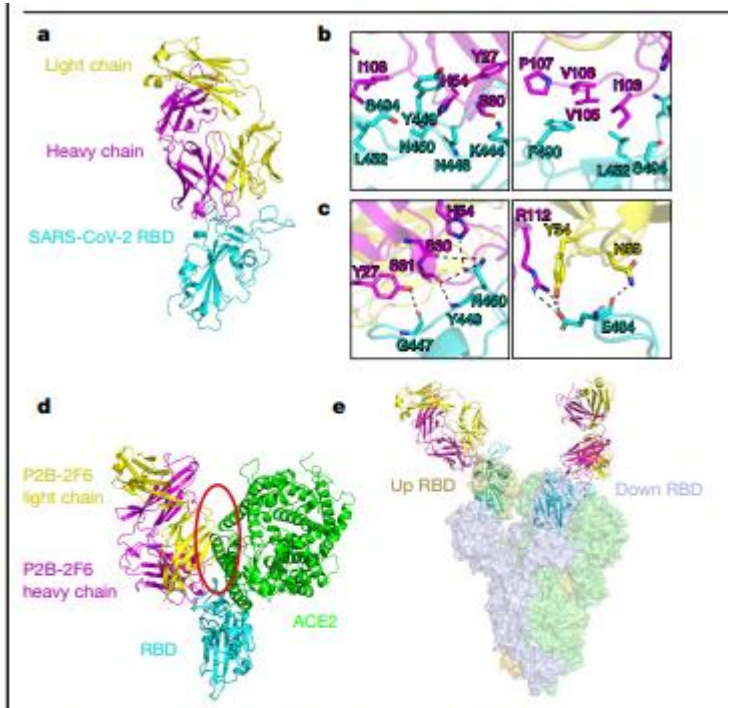


Fig. 4 | Crystal structure of P2B-2F6 in complex with SARS-CoV-2 RBD. **a**, Overall structure of P2B-2F6 Fab in complex with SARS-CoV-2 RBD. **b**, Hydrophobic interactions around SARS-CoV-2 RBD residues Y449, L452 and F490 at the binding interface. **c**, Hydrogen bonds and salt bridges at the binding interface. **d**, Structural superposition of the RBD–P2B-2F6 and RBD–ACE2 crystal structures (PDB ID: 6M0J) shows that clashes between ACE2 and P2B-2F6 would occur at the site within the red circle. **e**, The SARS-CoV-2 spike (PDB ID: 6VSB) is shown as a molecular surface, with protomers coloured light orange, blue or green. The RBD–P2B-2F6 complex could be aligned with both the up (light orange) and down (light blue) RBD in spike. The P2B-2F6 heavy chain is coloured magenta, P2B-2F6 light chain is yellow, SARS-CoV-2 RBD is cyan and ACE2 is green.

Since the blocking of spike:ACE2 (primary receptor) by neutralizing antibodies apparently reveals the spike:BSG (secondary receptor), there is no selection in moderate-severe BALF for SARS-CoV-2 immune escape variants during natural infection with the SARS-CoV-2 Wuhan strain (?).

This is consistent with little or no selection of immune escape variants globally within the first 12 months of the pandemic.

Therefore, if there is no selection for immune escape variants during natural infection, this means selection of the alpha/delta variants were largely due to COVID-19 vaccination with the second dose which strongly induces the neutralizing/enhancing antibodies to spike protein.

The evidence to date does not implicate the first mRNA dose in selection; rather there appears to be protection against selection associated with heterologous protection of trained immunity (which cannot select for variants as it DOES NOT RECOGNIZE SPIKE SPECIFIC SEQUENCES.

Presumably the treatment of COVID-19 patients with SARS-CoV-2 spike neutralizing antibodies may have also selected for the emergence of immune escape variants but to what extent remains unknown.

There is evidence that during the first 6 days following the second dose "2nd dose, partial" that 100% herd immunity is obtained with the alpha and delta variants (boosted trained immunity before NAbs to Spike are made) while VE (full vax) **drops below 50%.**

MONTH (crude VE)	1st Dose, Partial	2nd Dose, Partial	Fully Vaccinated
Dec 2020 WT	100%	100%	NA
Jan 2021 WT	44%	64%	77%
Feb 2021 WT	66%	83%	79%
Mar 2021 Mix	30%	53%	84%
Apr 2021 Alpha	57%	**100%**	78%
May 2021 Alpha	75%	**100%**	86%
June 2021 δ/α	12%	**100%**	56%
July 2021 Delta	36%	**100%**	44%
Aug 2021 Delta	81%	**100%**	48%

Table 5c. Monthly Comparison of Crude Rate Ratios to VE Estimated Using the Cox Model With Time-varying Vaccination Status, Age >12 Years

Month of Follow-up	Vaccination Status	People included	Person years	Cases	Cases / 100000py	Crude VE	Model VE	People included	Person years	Cases	Cases / 100000py	Crude VE	Model VE
December 2020	Unvaccinated	3436957	157175.1	68564	43622.7			676271	31216.4	7291	23356.3		
	1st Dose, Partial	5591	5.32	1	18788.1	57	67	269	0.22	0	0	100	N/A
	2nd Dose, Partial	30	0.23	0	0	100	N/A	8	0.02	0	0	100	N/A
	Fully Vaccinated	7	0.01	0	0	100	N/A	0	0	0	0	N/A	N/A
January 2021	Unvaccinated	3231179	252449.6	64556	25571.8			655115	50270.3	8036	15986		
	1st Dose, Partial	80243	1392.0	199	14295.7	44	46	9021	122.3	11	8996	44	31
	2nd Dose, Partial	60347	1045.7	68	6502.9	75	68	4317	70.3	4	5687	64	54
	Fully Vaccinated	47956	1458.4	32	2194.2	91	84	2933	82.3	3	3643	77	61
February 2021	Unvaccinated	2841630	194541.8	9517	4892.0			495977	25932.8	1143	4407.5		
	1st Dose, Partial	196527	3602.5	64	1776.5	64	56	125717	2241.9	34	1516.6	66	49
	2nd Dose, Partial	149385	2297	19	827.2	83	76	87393	1363.4	10	733.5	83	70
	Fully Vaccinated	155922	6458.1	52	805.2	84	79	60229	1287.0	12	932.4	79	62
March 2021	Unvaccinated	2438824	174938.5	2793	1596.6			254539	15851.8	195	1230.1		
	1st Dose, Partial	321359	6381.2	43	673.9	58	55	114581	2327.1	20	859.4	30	29
	2nd Dose, Partial	286784	4328.6	23	531.4	67	65	133164	2085.9	12	575.3	53	54
	Fully Vaccinated	376391	21008.56	45	214.2	87	85	183541	10454.2	21	200.9	84	82
April 2021	Unvaccinated	1807694	123125.2	1894	1538.3			151155	10750.8	98	911.6		
	1st Dose, Partial	300218	6424.8	39	607.0	61	59	23560	764.8	3	392.3	57	56
	2nd Dose, Partial	279347	3976.0	9	226.4	85	85	24958	338.2	0	0.0	100	N/A
	Fully Vaccinated	605447	39253.38	72	183.4	88	88	205780	15636.0	32	204.7	78	77
May 2021	Unvaccinated	1337876	101238.2	1000	987.8			123522	9612.1	61	634.6		
	1st Dose, Partial	247431	6069.8	21	346.0	65	67	15054	639.5	1	156.4	75	100
	2nd Dose, Partial	218973	3574.4	4	111.9	89	89	9816	158.7	0	0.0	100	N/A
	Fully Vaccinated	802314	58094.44	72	123.9	87	87	213845	17201.1	15	87.2	86	85
June 2021	Unvaccinated	1138928	86747.51	1174	1353.4			111988	8647.9	54	624.4		
	1st Dose, Partial	164182	5089.6	18	353.7	74	72	10543	546.8	3	548.6	12	9
	2nd Dose, Partial	129513	2061.6	2	97.0	93	92	4929	71.9	0	0.0	100	N/A
	Fully Vaccinated	912288	68029.57	180	264.6	80	80	217348	17093.5	47	275.0	56	54
July 2021	Unvaccinated	1042964	82847.71	7175	8660.5			105705	8482.3	244	2876.6		
	1st Dose, Partial	100649	4323.2	139	3215.2	63	63	8995	546.8	10	1829.0	36	36
	2nd Dose, Partial	63018	936.3	10	1068.1	88	87	2892	44.1	0	0.0	100	N/A
	Fully Vaccinated	960257	76665.8	1946	2538.3	71	71	218949	17860.6	287	1606.9	44	44
August 2021	Unvaccinated	959825	18179.9	3607	19840.6			100176	1907.5	156	8178.3		
	1st Dose, Partial	64901	1047.1	61	5825.6	71	70	7403	131.1	2	1525.4	81	80
	2nd Dose, Partial	15235	153.9	4	2599.9	87	86	764	7.6	0	0.0	100	N/A
	Fully Vaccinated	962774	18362.79	1015	5527.5	72	72	218497	4182.3	177	4232.2	48	46

Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021 Oct 16;398(10309):1407-1416. doi: 10.1016/S0140-6736(21)02183-8. Epub 2021 Oct 4.

Symptomatic Infection

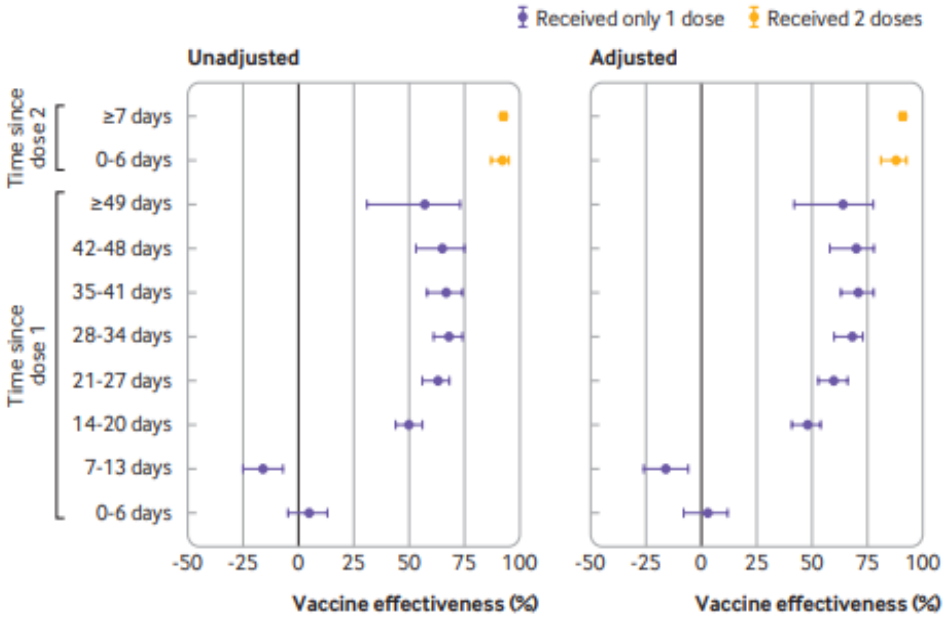


Fig 2 | Unadjusted and adjusted vaccine effectiveness estimates of covid-19 mRNA vaccines (BNT162b2, mRNA-1273) against laboratory confirmed symptomatic SARS-CoV-2 infection by various intervals, between 14 December 2020 and 19 April 2021 in Ontario, Canada. Models were adjusted for age, sex, public health unit region, biweekly period of test, number of SARS-CoV-2 tests in the three months before 14 December 2020, presence of any comorbidity increasing the risk of severe covid-19, receipt of influenza vaccination in current or previous influenza season, and fifths of neighbourhood level household income, number of people in each dwelling, proportion of people employed as non-health essential workers, and self-identified visible minority

Severe OutComes

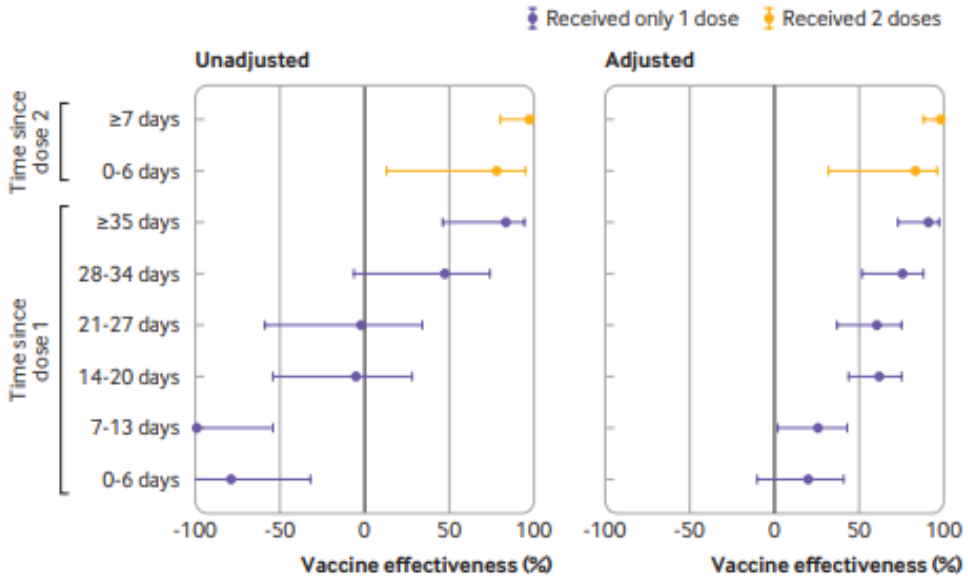


Fig 3 | Unadjusted and adjusted vaccine effectiveness estimates of covid-19 mRNA vaccines (BNT162b2, mRNA-1273) against severe outcomes (hospital admission or death) associated with laboratory confirmed symptomatic SARS-CoV-2 infection by various intervals, between 14 December 2020 and 19 April 2021 in Ontario, Canada. Models were adjusted for age, sex, public health unit region, biweekly period of test, number of SARS-CoV-2 tests in the three months before 14 December 2020, presence of any comorbidity increasing the risk of severe covid-19, receipt of influenza vaccination in current or previous influenza season, and fifths of neighbourhood level household income, number of people in each dwelling, proportion of people employed as non-health essential workers, and self-identified visible minority

DATA suggests SARS-CoV-2 infection acquired <u>at the time of vaccination</u> especially following dose 1, artificially reduces the first dose VE.

Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada: test negative design study. BMJ. 2021 Aug 20;374:n1943. doi: 10.1136/bmj.n1943.

1. HERD immunity may be achievable at 100% if one can boost trained immunity without stimulating adaptive immunity antibody responses (and if one can avoid infection at the vaccination clinic).
2. The COVID-19 vaccines seem to be solely responsible for the selection of immune escape variants.