COVID-19: Of Variants & Vaccines

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Hopeful…

The WHO declared a Public Health Emergency of International Concern around 2019-nCoV because of the spread of the virus outside of China, describing it as an "unprecedented outbreak".

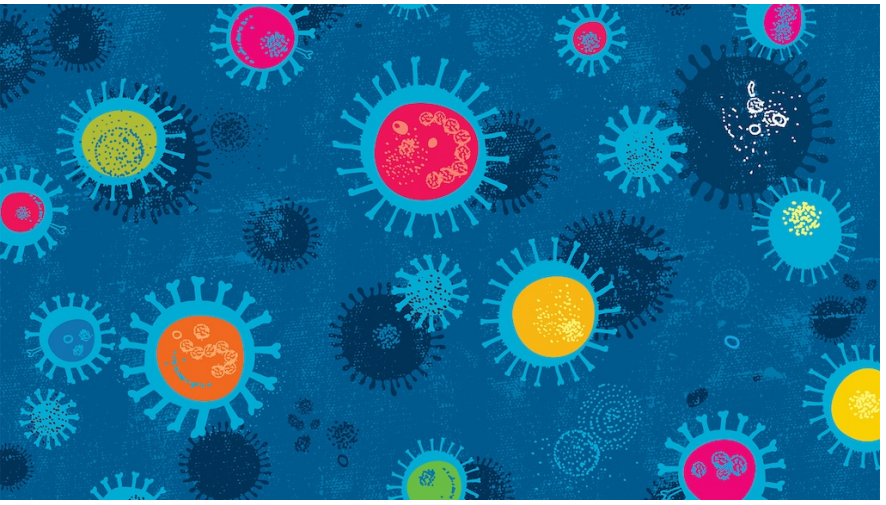
– January 30, 2020

World Health Organization

Not so Hopeful…

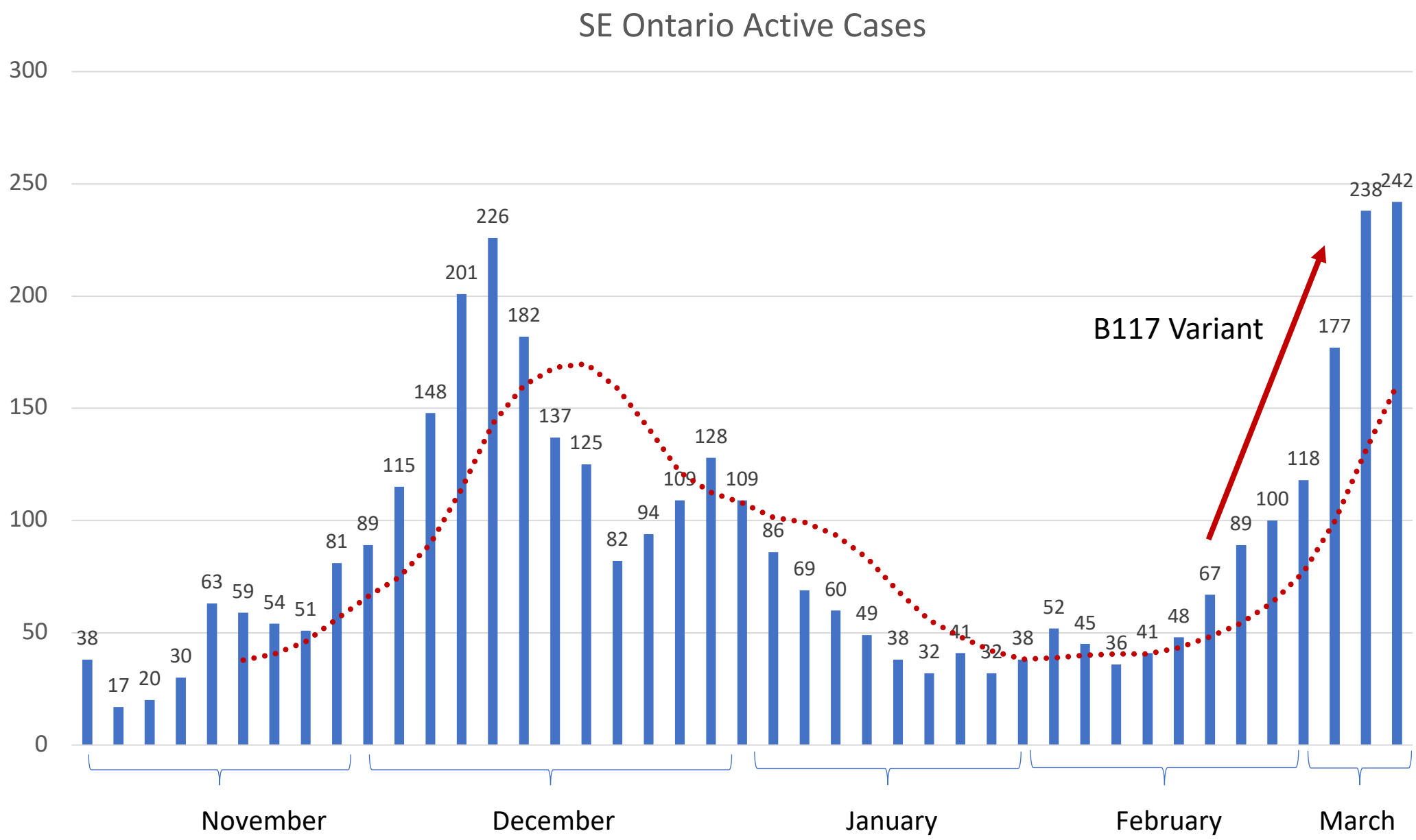
The WHO declared a COVID-19 a pandemic.

– March 11, 2020



Outline

- Where we are right now
- Variants
- Vaccines and Variants


SE Ontario Active Cases
300
250
200
150
100
50
0
38
17
20
30
63
59
54
51
81
89
115
148
201
226
182
137
125
82
94
109
128
109
86
69
60
49
38
32
41
32
38
52
45
36
41
48
67
89
100
118
177
238
242
B117 Variant
November
December
January
February
March

Ontario Effective Reproduction Number

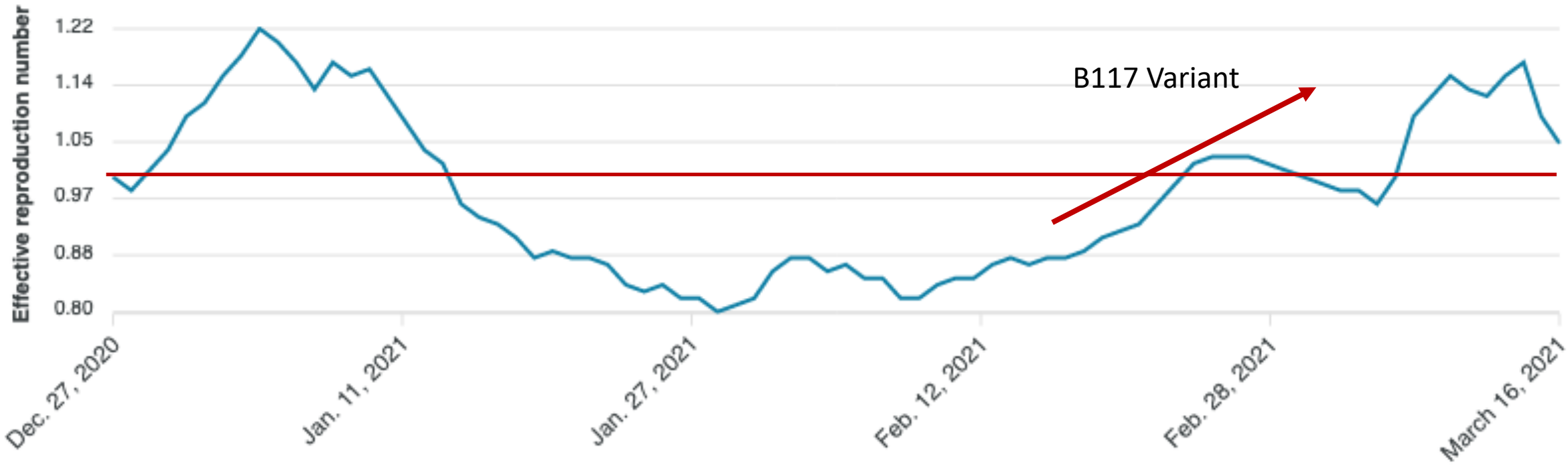


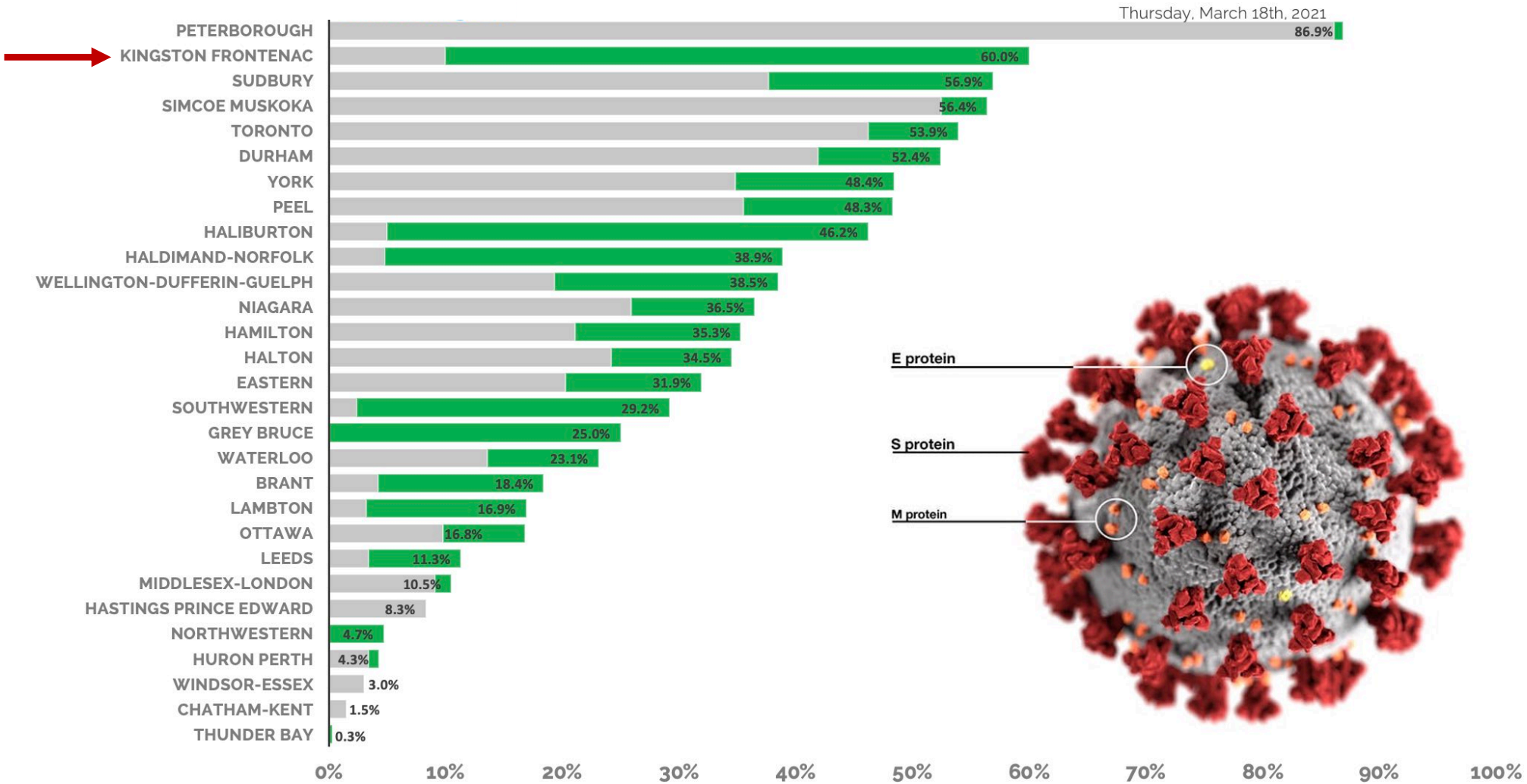
Table 7. Summary of confirmed COVID-19 cases with a mutation or VOC detected: Ontario

Variant	Change in cases March 22, 2021	Change in cases March 23, 2021	Cumulative case count up to March 23, 2021
Lineage B.1.1.7	19	30	1,389
Lineage B.1.351	-1	3	50
Lineage P.1	1	10	47
Mutation detected (lineage not determined)*	666	909	14,803

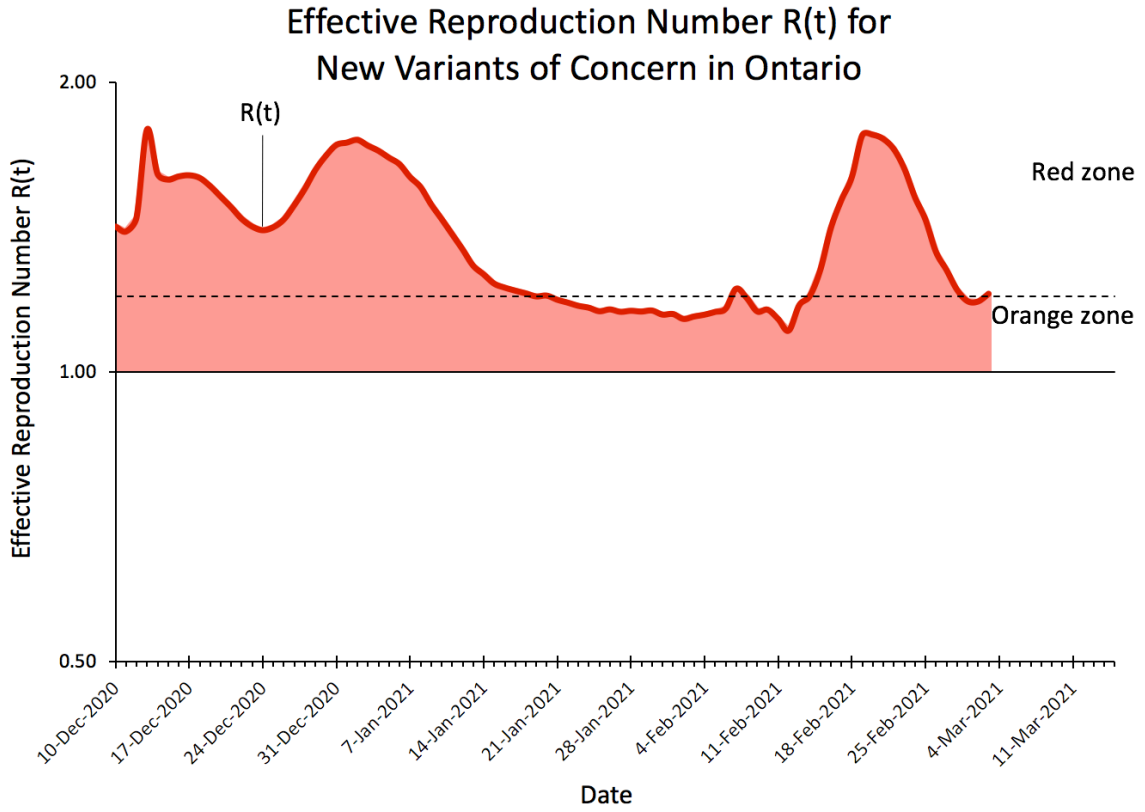
93.4% →

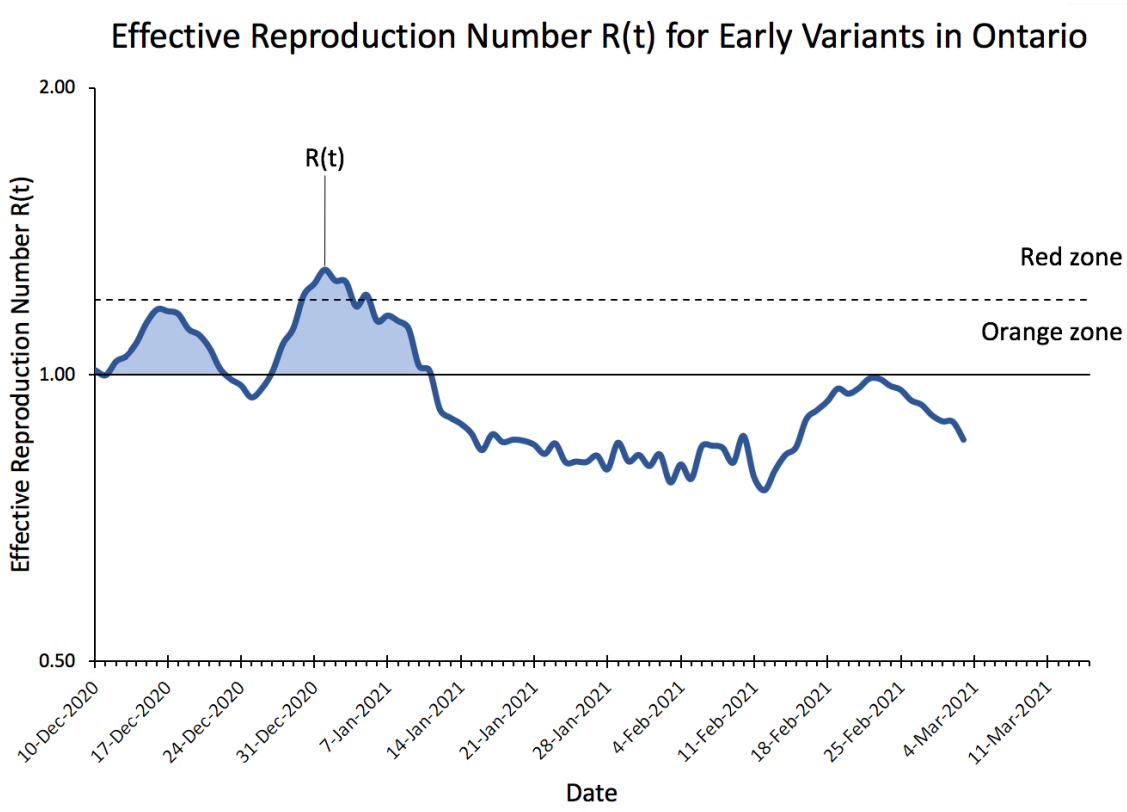
Date March 23, 2021

Percentage of Weekly Specimens in Ontario Positive for the N501Y Spike Gene Mutation and Week-on-Week Growth

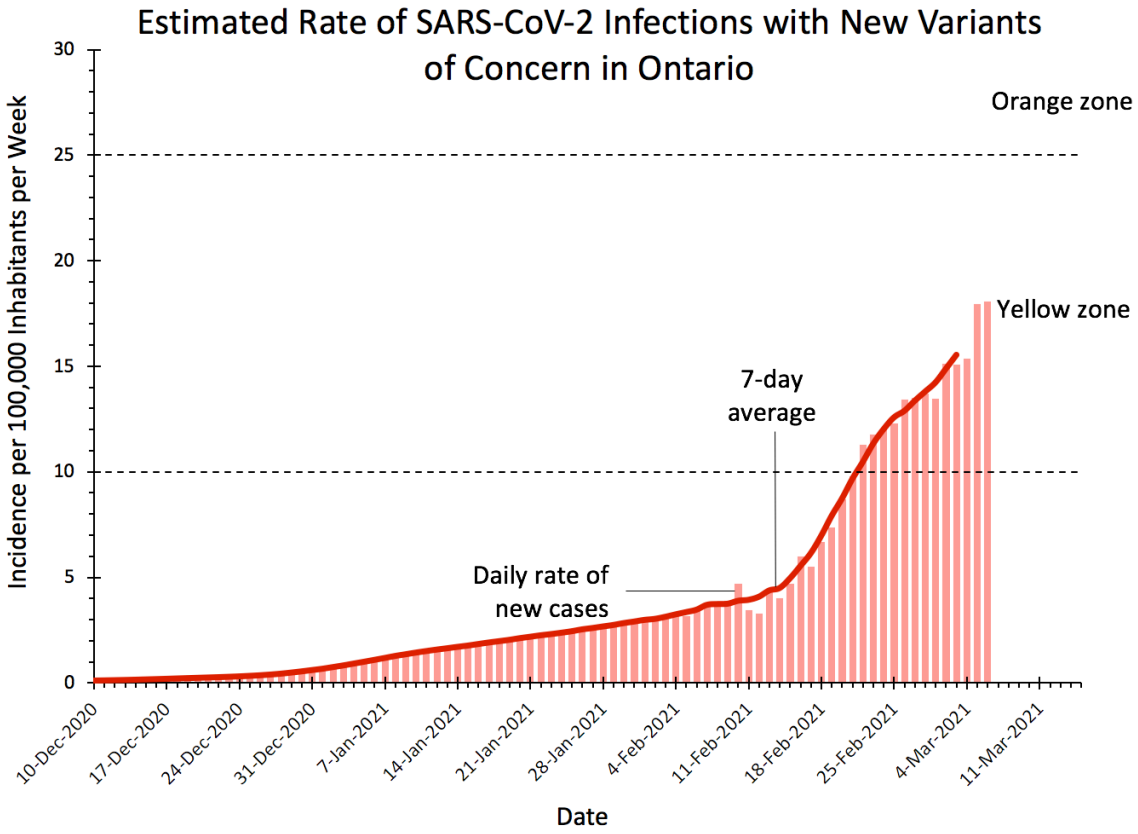


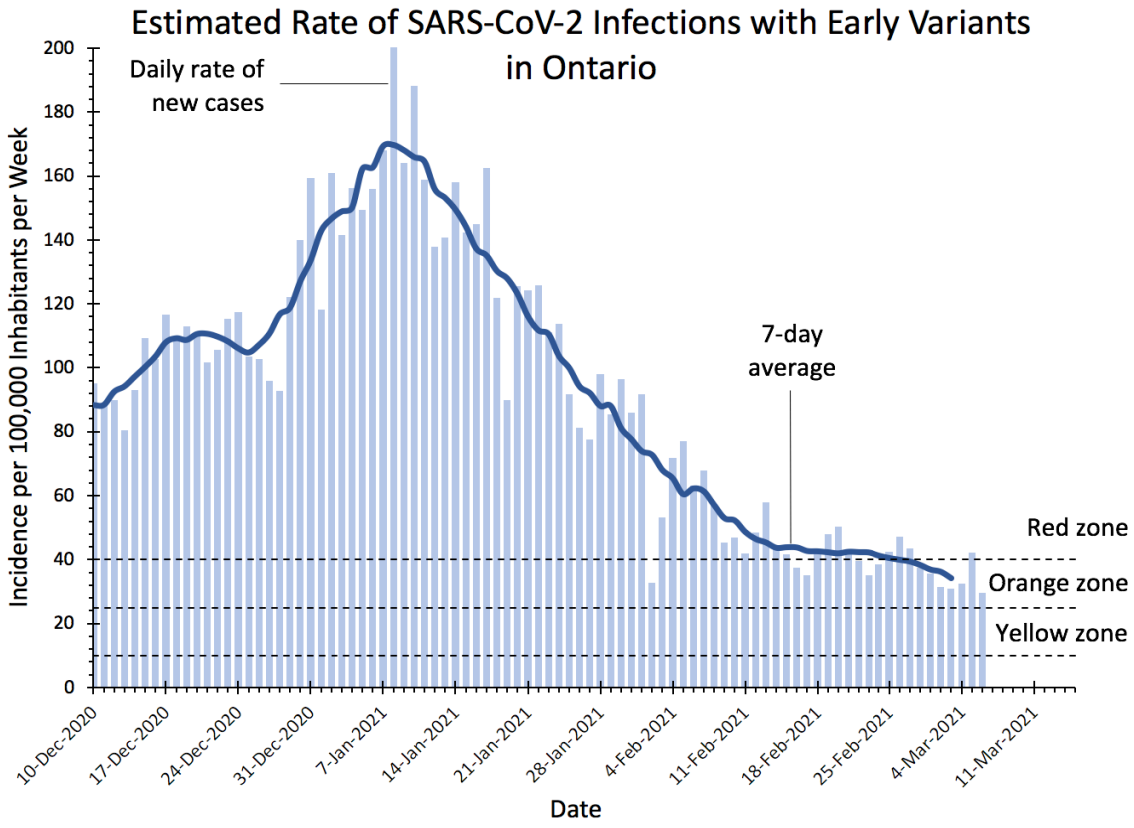
New variants of concern spread more easily than early variants



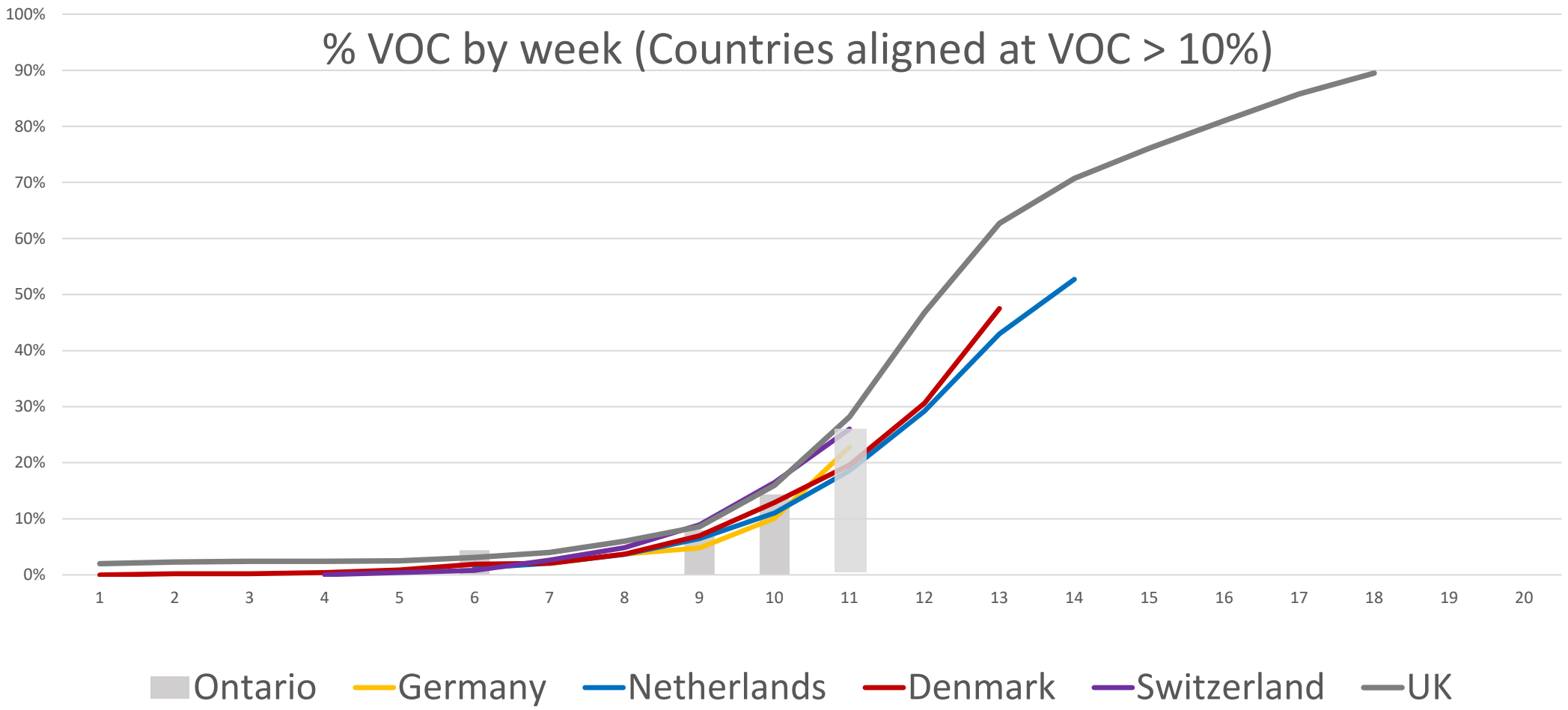


New variants of concern spread more easily than early variants





Weekly growth in Variants of Concern in Ontario matches other countries.



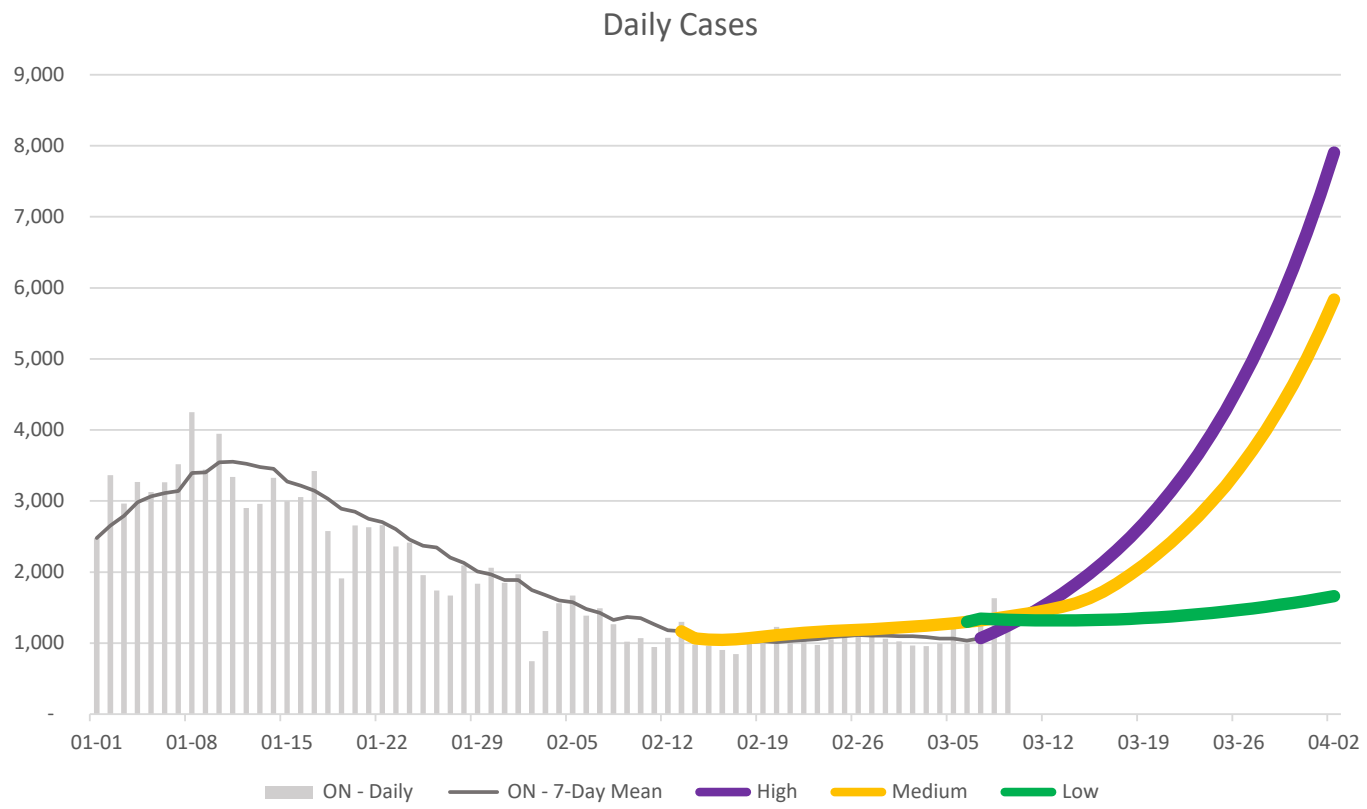
Data: PHO (Ontario), Robert Koch Institute (RKI), Rijksinstituut voor Volksgezondheid en Milieu (RIVM), Danish Covid-19 Consortium, SARS-CoV-2 Variants of Concern in Switzerland, Public Health England

Case projections depend heavily on spread of variants

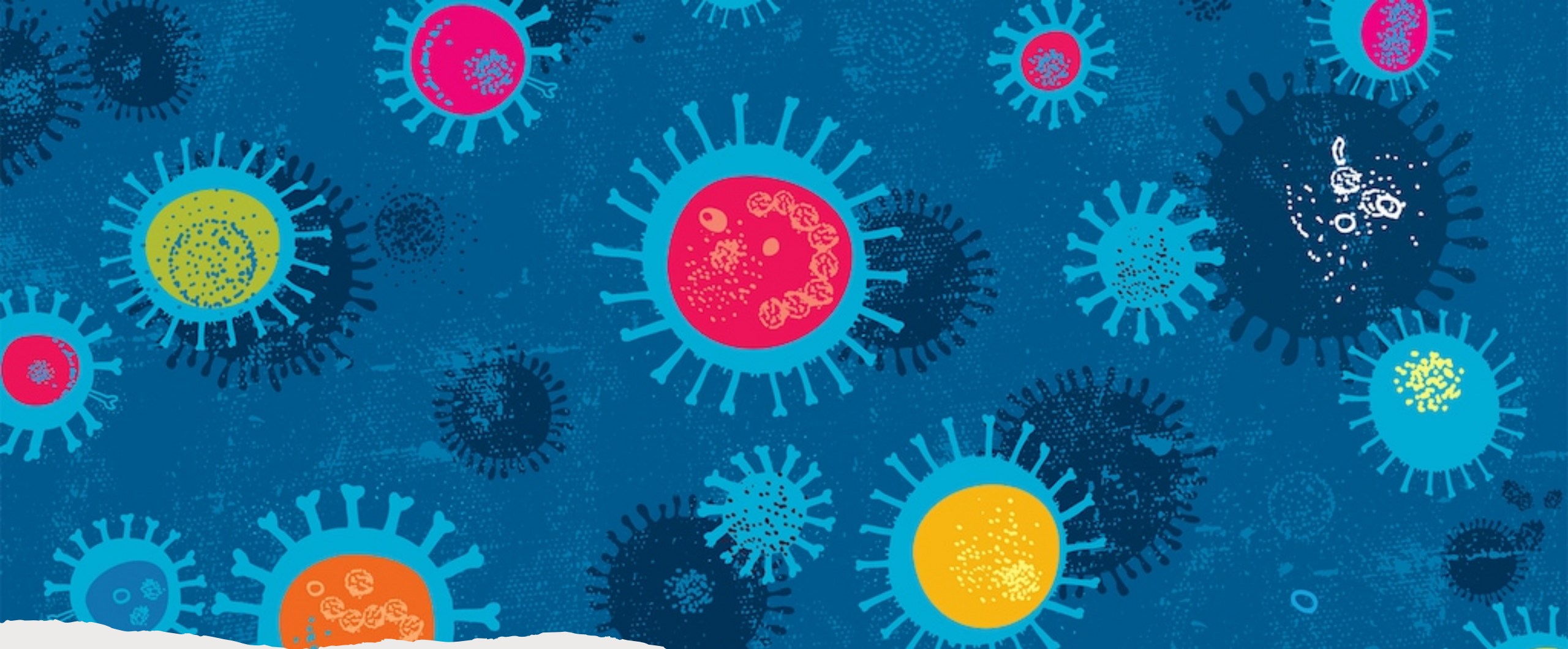
Scenarios based on 5 models, 3-5 scenarios each.

Optimistic scenario reflects:

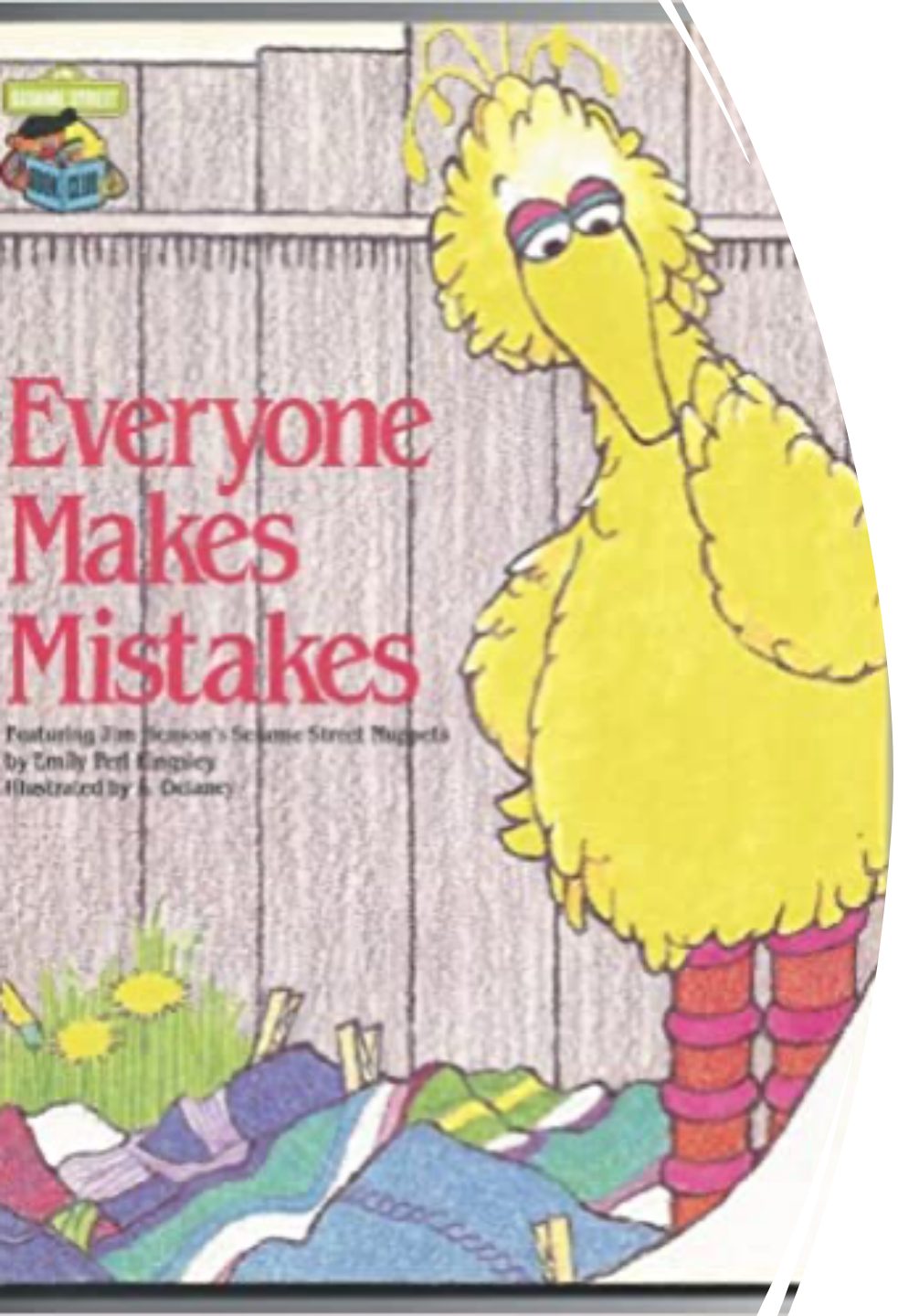
- Modeling approach
- Low increase of VOCs over time
- Low transmissibility of VOCs
- Degree and timing of relaxing public health measures



Predictions informed by modeling from COVID-19 ModCollab, Fields Institute, McMasterU, PHO, YorkU
Data (Observed Cases): covid-19.ontario.ca



SARS-CoV-2 Variants

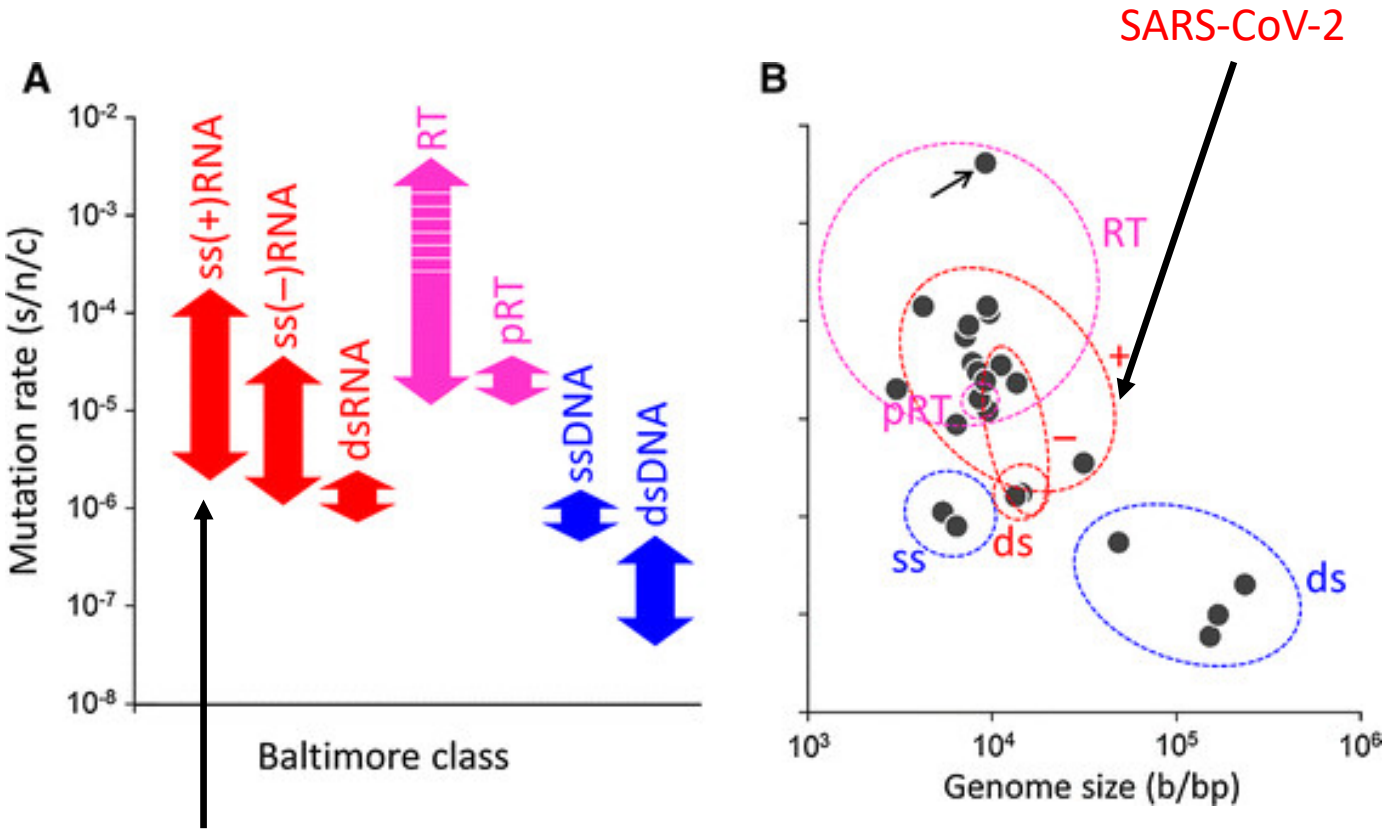


What generates Variants of SARS-CoV-2?

Viruses, just like people, make mistakes.

What generates Variants of SARS-CoV-2?

- <u>All viruses can develop mutations during viral replication</u>
- The likelihood of mutation arising is related to overall rates of viral replication
  - The more viral replication cycles the more likely the occurrence of random mutations
- Right now there is a lot of viral replication with COVID-19 worldwide

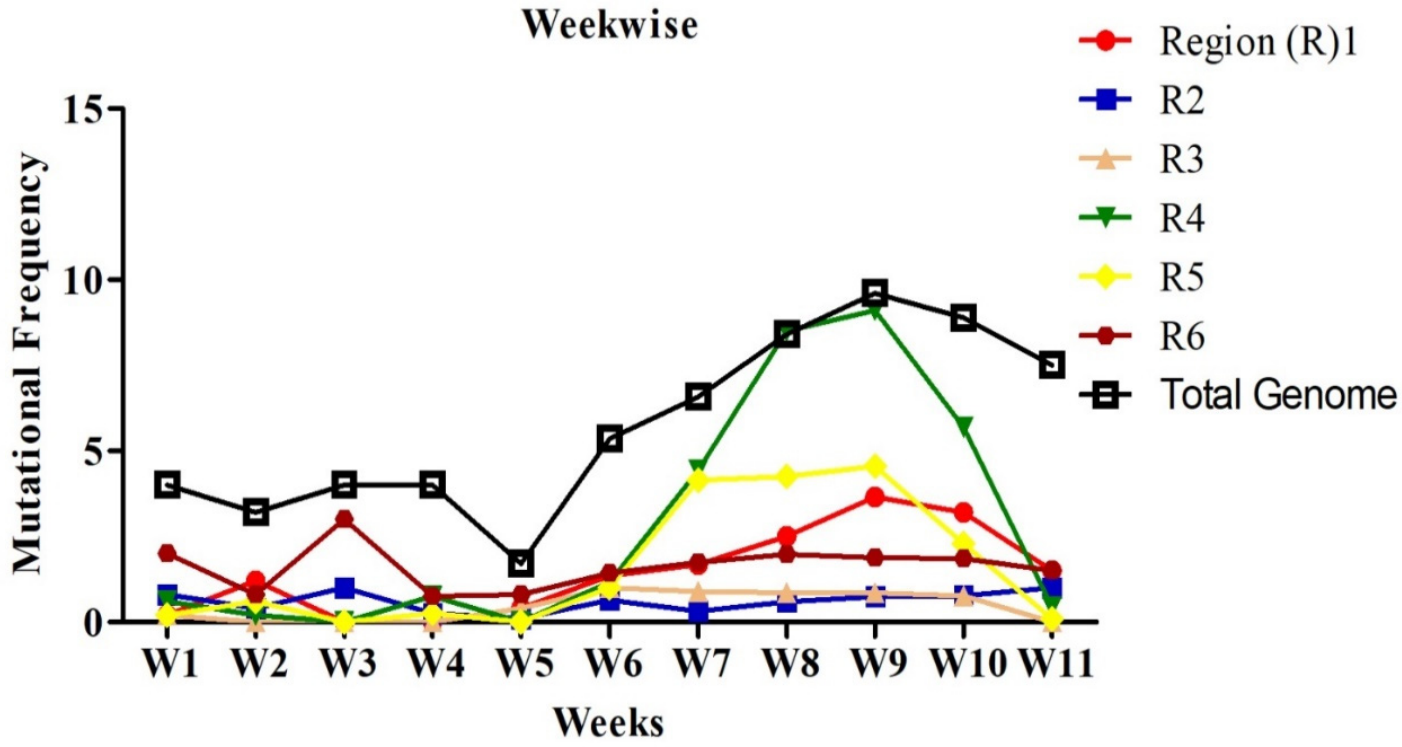


SARS-CoV-2 in in this group of viruses

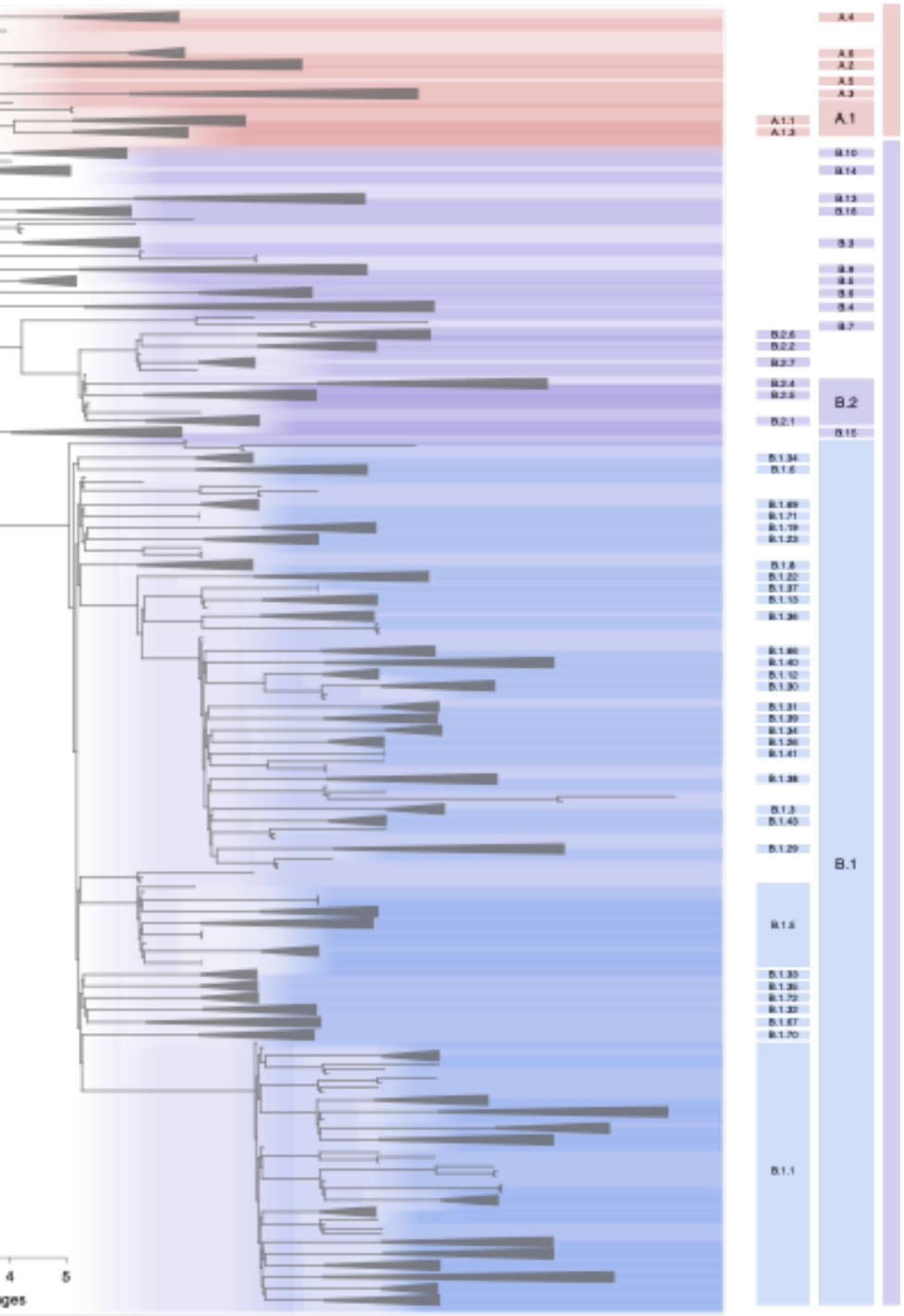
Source: R Sanjuán & P Dominog-Calap Cell. Mol. Life Sci. (2016) 73:4433–4448

Mutational Frequencies of SARS-CoV-2

- Nucleotide mutational frequency of six genomic segments of SARS-CoV-2 over an 11-week period
- R5 (in yellow)is the genomic sequence that encompasses the Spike Protein of SARS-CoV-2



Source: N Kaushal et al Pathogens 2020, 9, 565; doi:10.3390/pathogens9070565

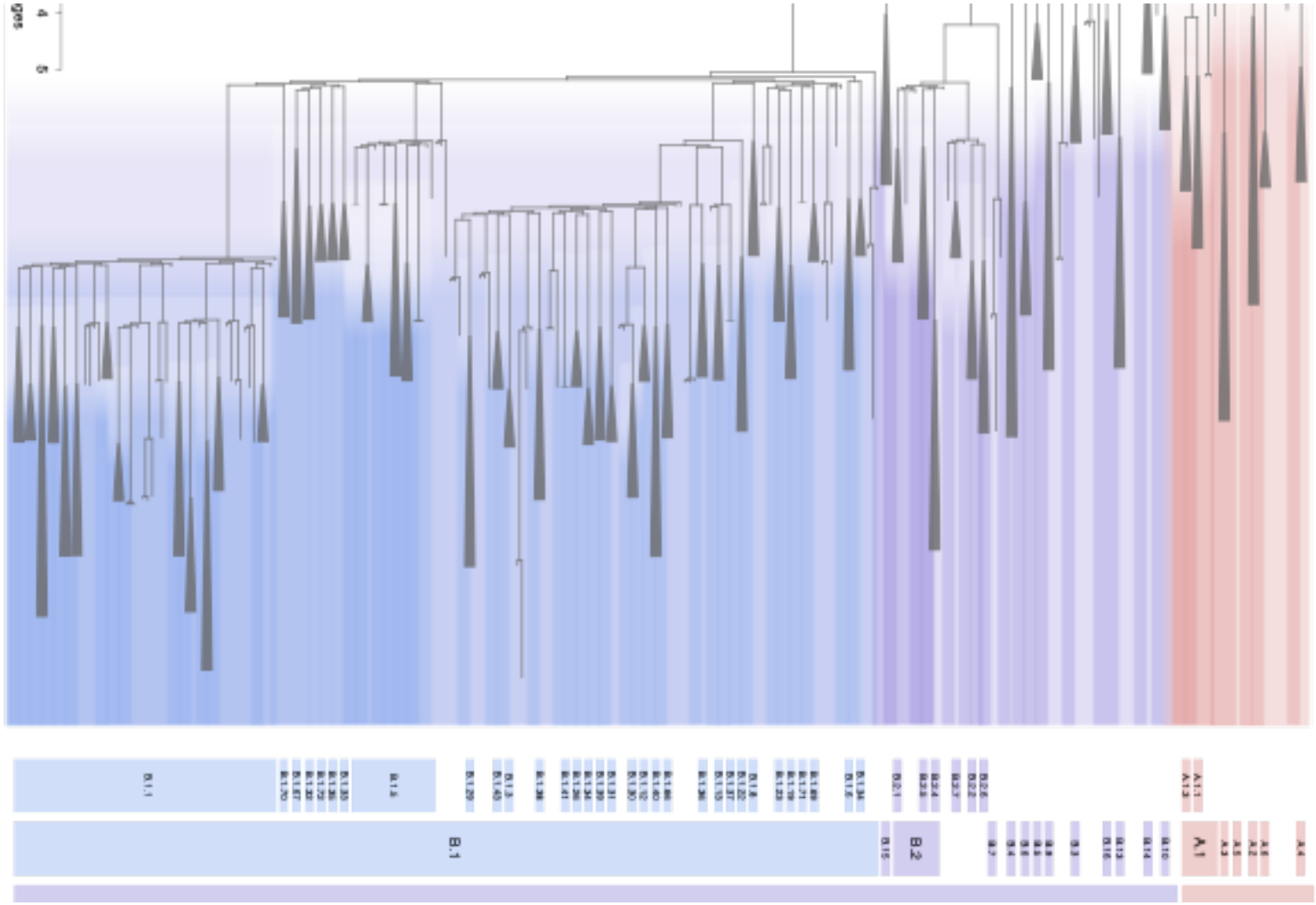


VOC Evolution & Nomenclature

Lineage	Genomes	Date range	Comments
A	223	5 January–27 April 2020	The root of the pandemic lies in this lineage. Many Chinese sequences with global exports
B	1,713	24 December 2019–3 May 2020	The base of this lineage lies in China, with extensive global travel between multiple locations
B.1	7,438	24 January–10 May 2020	Comprises the large Italian outbreak; it now represents many European outbreaks, with travel within Europe and from Europe to the rest of the world
B.1.1	6,286	15 February–9 May 2020	Major European lineage; exports to the rest of the world from Europe

Source: A Rambaut et al Nature Micro https://doi.org/10.1038/s41564-020-0770-5

The SARS-CoV-2 Family Tree



Source: A Rambaut et al Nature Micro https://doi.org/10.1038/s41564-020-0770-5

Why are we concerned about Variants?

- Possible consequences of emerging mutations

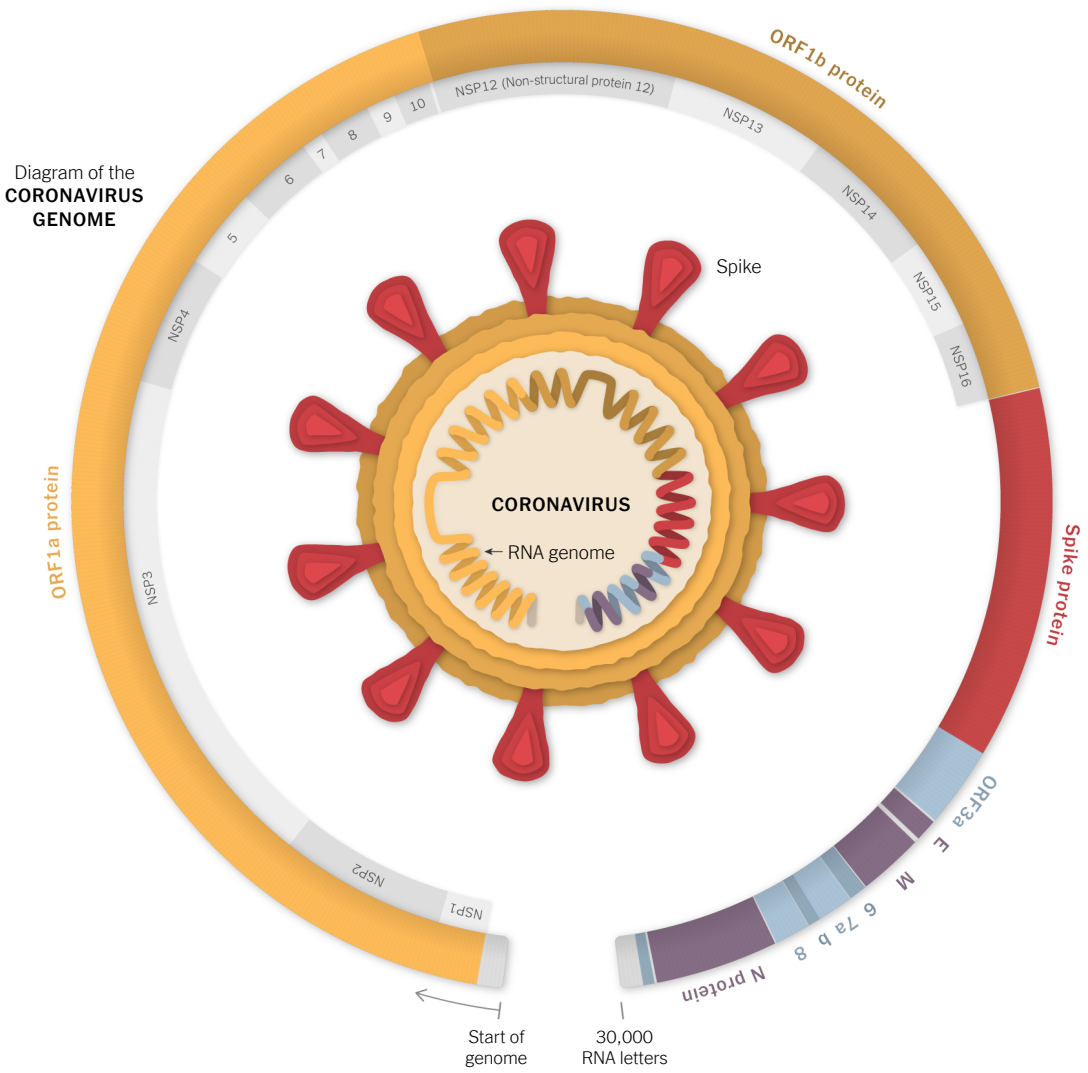
1. Increased transmissibility
2. Increased virulence
3. Decreased protection from current vaccines or previous natural infection

Current SARS-CoV-2 Variants of Concern (VOC)

- The chief variants of concern presently are:
  - B.1.1.7 (UK variant) 🇬🇧
  - B.1.351 (South African variant) 🇿🇦
  - B.1.128 (Brazilian variant) 🇧🇷
  - B.1.427/429 (California variant) 🇺🇸
  - B.1.525/526 (New York variant) 🇺🇸

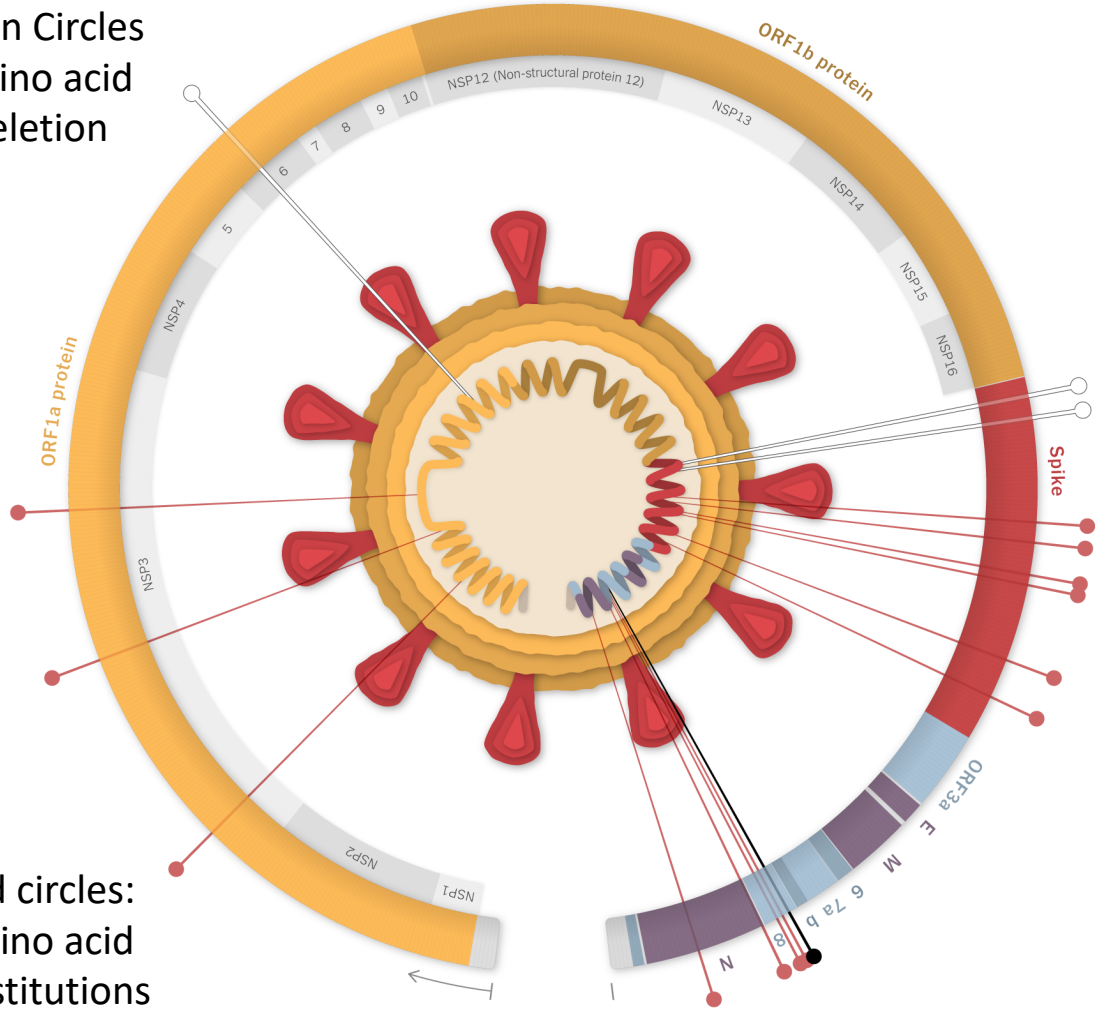
Variant Name	Amino Acid Changes in Spike
20E (EU1)	A222V-D614G
20A.EU2	S477N-D614G
N439K-D614G	N439K-D614G
Mink Cluster 5 Variant	ΔH69ΔV70-Y453F-D614G-I692V-M1229I
B.1.1.7 (a.k.a., 20I/501Y.V1, VOC 202012/01)	ΔH69ΔV70-ΔY144-N501Y-A570D-D614G-P681H-T716I-S982A-D1118H
B.1.351 (a.k.a., 20H/501Y.V2)	L18F-D80A-D215G-ΔL242ΔA243ΔL244-R246I-K417N-E484K-N501Y-D614G-A701V

WT-SARS-CoV-2



B117-SARS-CoV-2

Open Circles
Amino acid
deletion

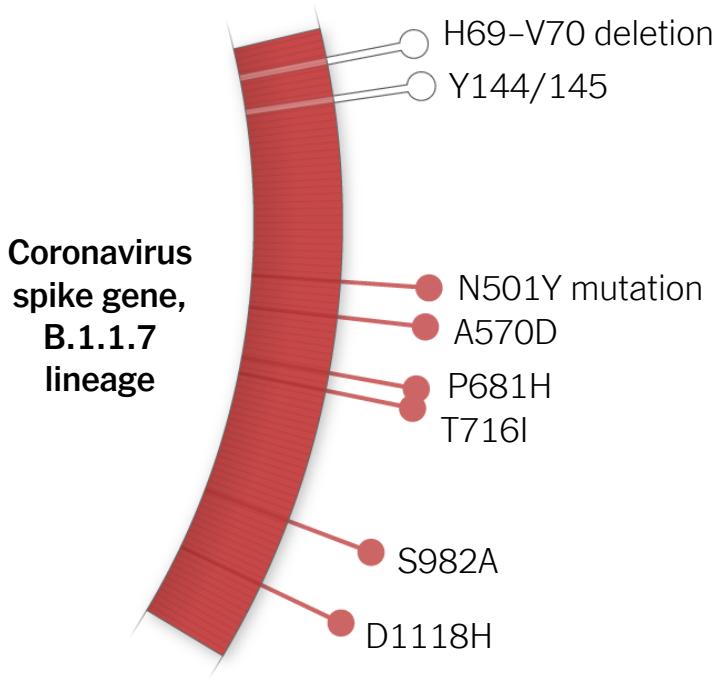


Red circles:
Amino acid
Substitutions

Connecting rays:
MUTATIONS

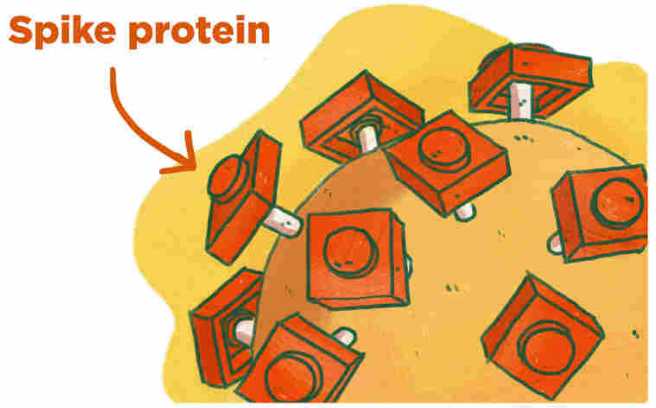
Spike Protein Mutations

- N501Y is the most common
  - Increases avidity for ACE2 receptor
  - Likely main reason for increased transmissibility
- Deletions like H69-70 and other mutations like E484K likely contribute to decrease binding by neutralizing antibodies to spike protein
- Other mutations being studied as to their implications
  - K417N
  - L452R

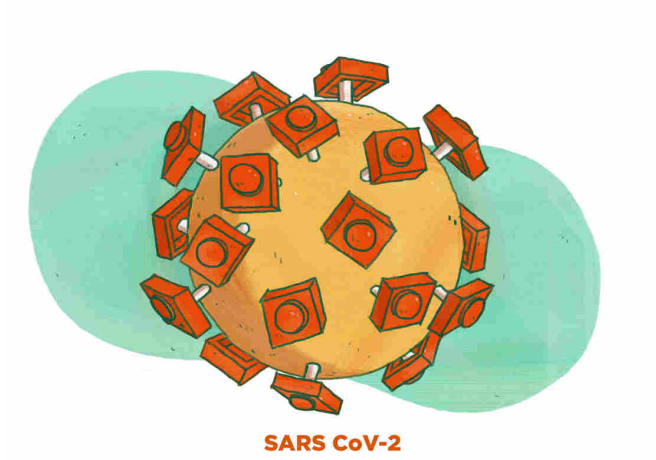


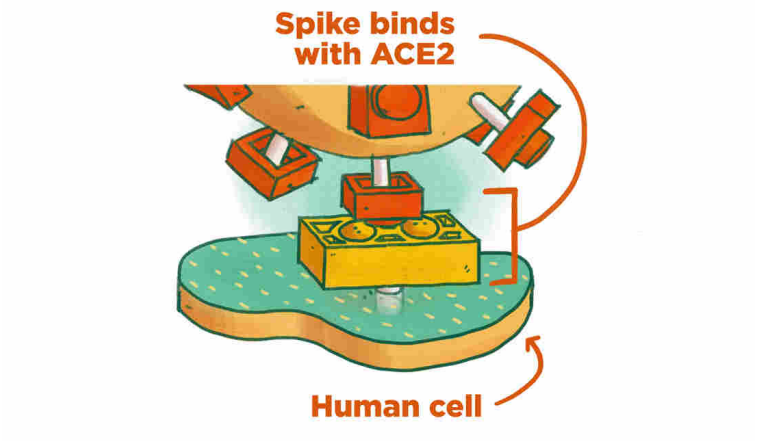
Why are mutations in the Spike Protein so important?

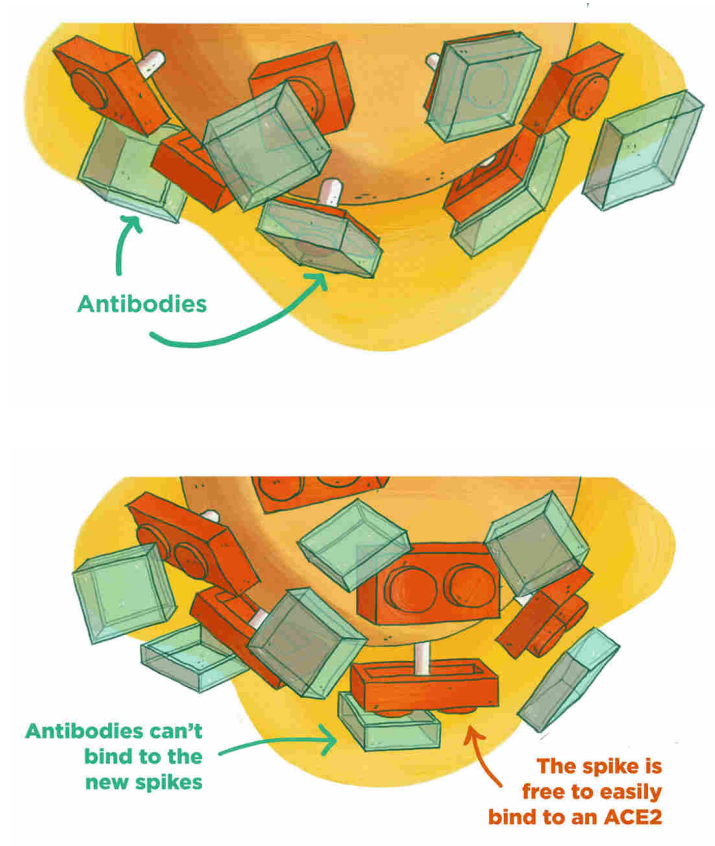
- Viral receptor that allows for binding to ACE2, the human cell receptor
  - If mutations in the spike protein increase that binding affinity, this could lead to ⬆️ transmissibility of COVID-19
- Our current vaccine strategy is to produce antibodies against the spike protein in the vaccine recipient
  - If mutations in the spike protein reduce the binding of antibodies to the site of their attachment, vaccine-induced immunity might be reduced to our current COVID-19 vaccines



How Spike Protein Changes Affect Interactions with ACE2 and Antibodies



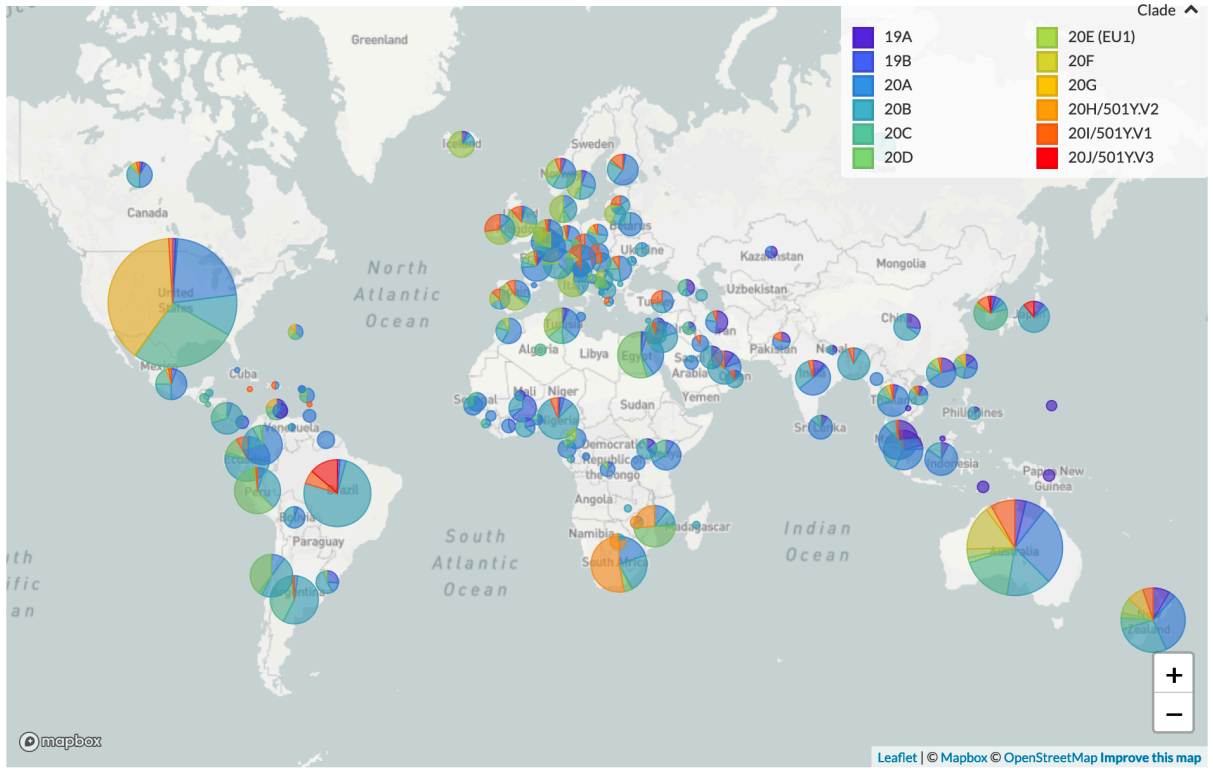




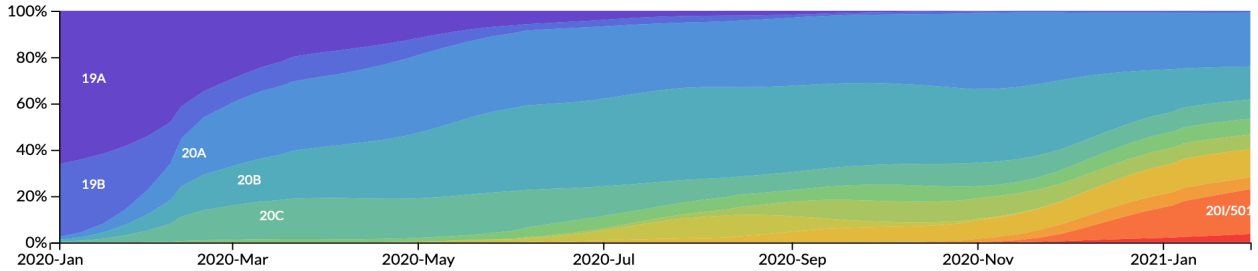
Source: NPR

Why are we concerned about Variants?

- Worldwide spread following their emergence
  - More variants are continuing to arise with uncontrolled numbers of cases around the world
- Without control on the numbers of cases, variants with better fitness will eventually predominate over the wild type strain of SARS-CoV-2



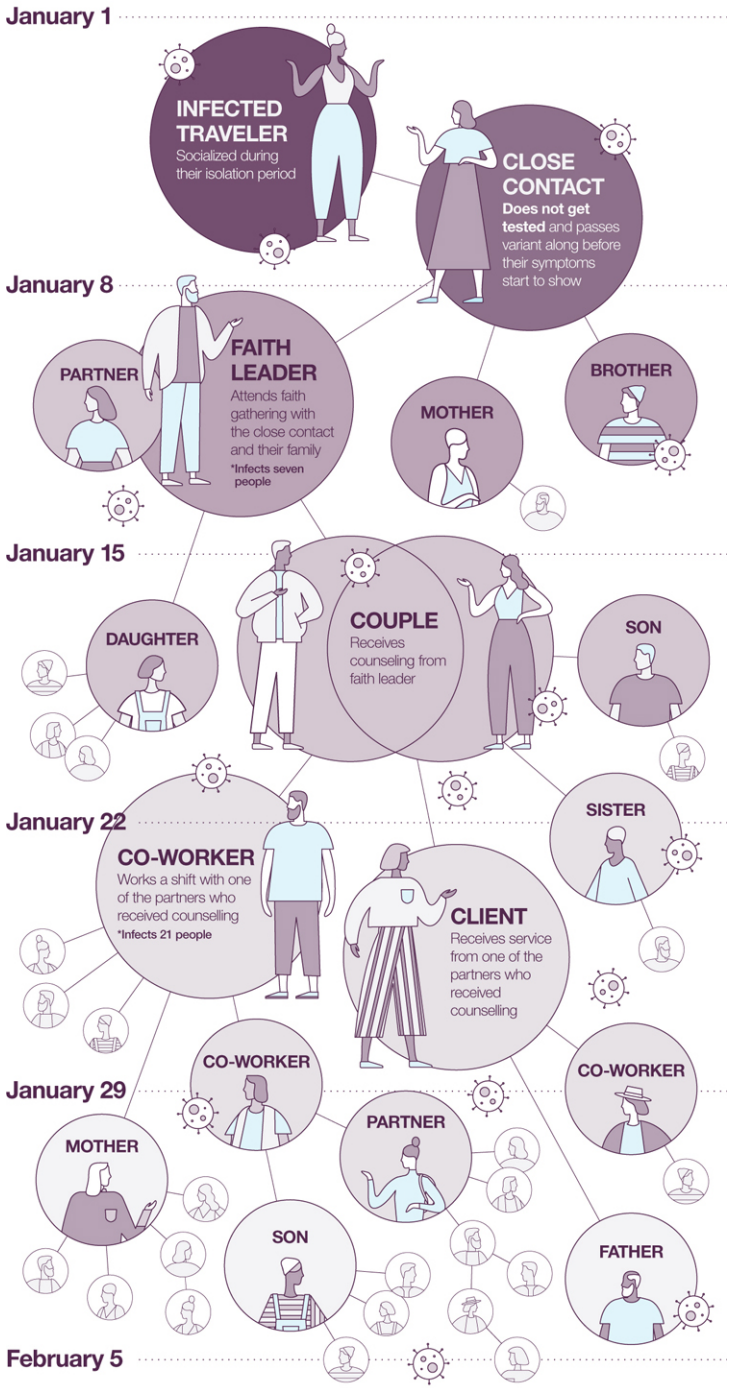
Frequencies (colored by Clade)



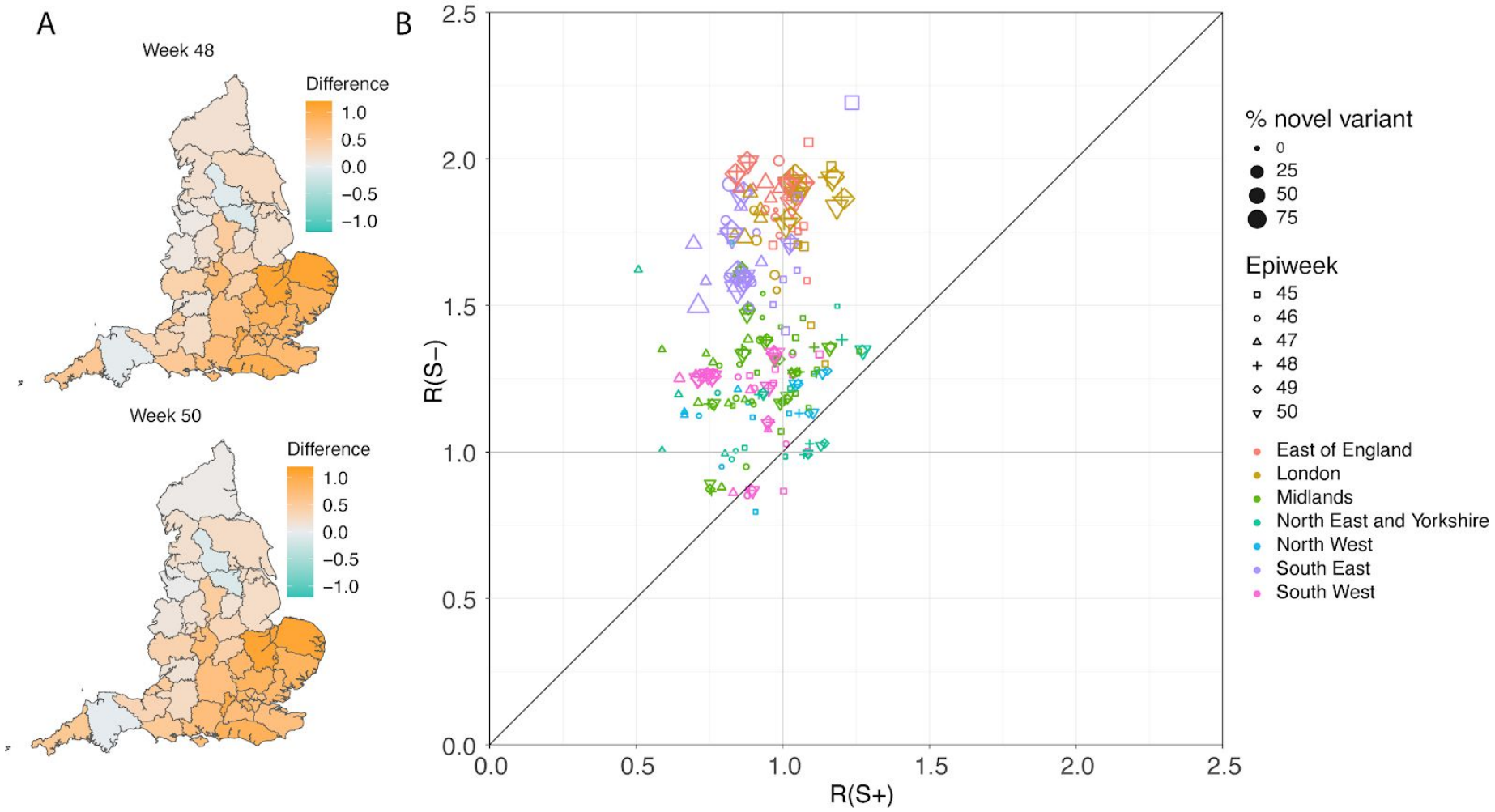
Source: https://nextstrain.org/ncov/global

Alberta COVID-19 Variant Case

- One case of SARS-CoV-2 variant B.1.1.7 imported from an international traveler to the province on January 1, 2021 led to 42 cases
- There have now been 1,886 cases found in Alberta



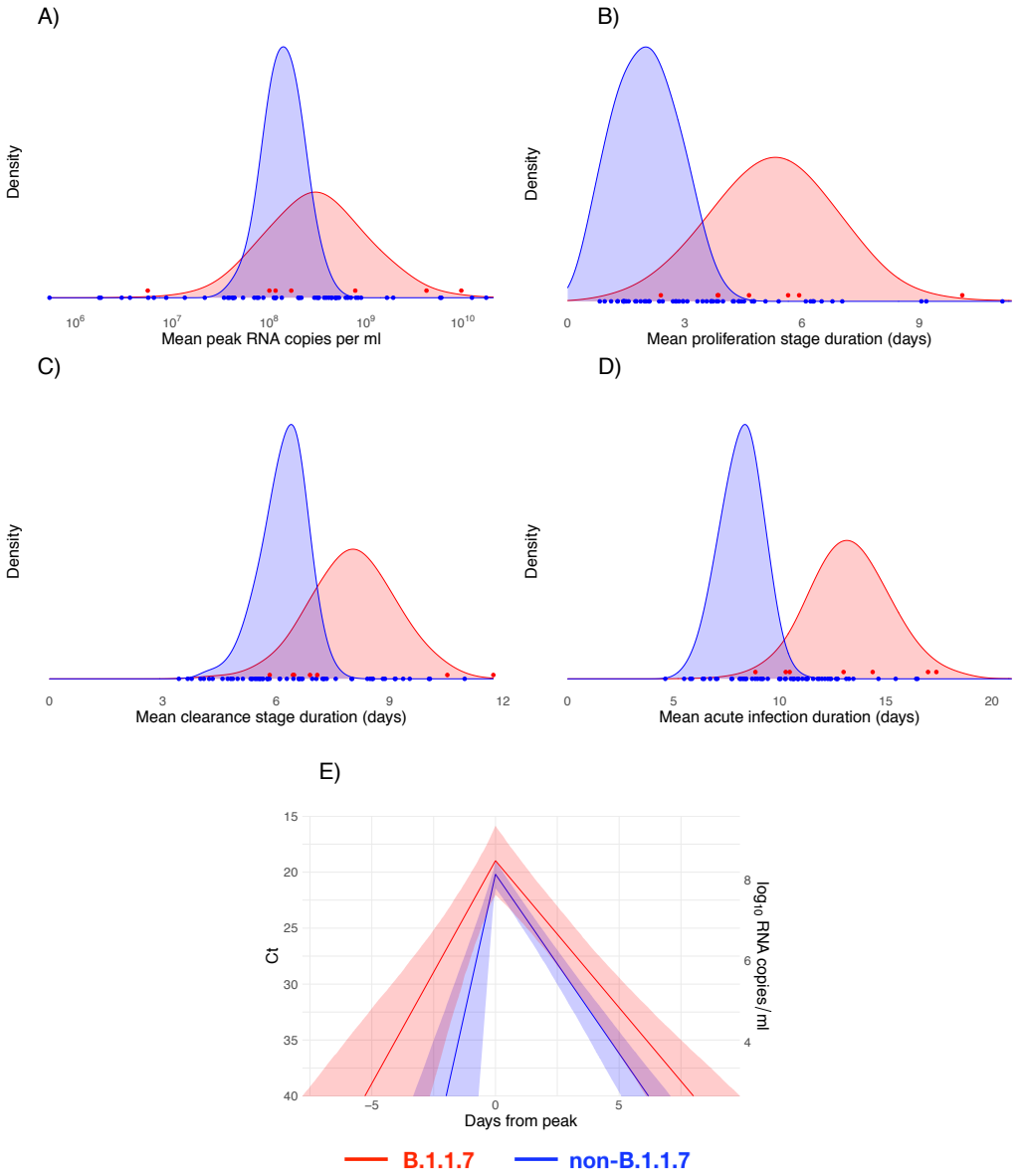
Transmission of SARS-CoV-2 Lineage B.1.1.7 in England



Source: E Volz et al Preprint https://doi.org/10.1101/2020.12.30.20249034

B.1.1.7 Infectiousness

- Mean duration of the proliferation phase
  - B117 = 5.3 days
  - Non-B117 = 2.0 days
- Mean duration of the clearance phase
  - B117 = 8.0 days
  - Non-B117 = 6.2 days
- Mean overall duration of infection (proliferation plus clearance)
  - B117 = 13.3 days
  - Non-B117 = 8.2 days
- Peak viral RNA Ct = 19.0 vs 20.2



Source: S Kissler et al https://nrs.harvard.edu/URN-3:HUL.INSTREPOS:37366884

VOC Transmissibility

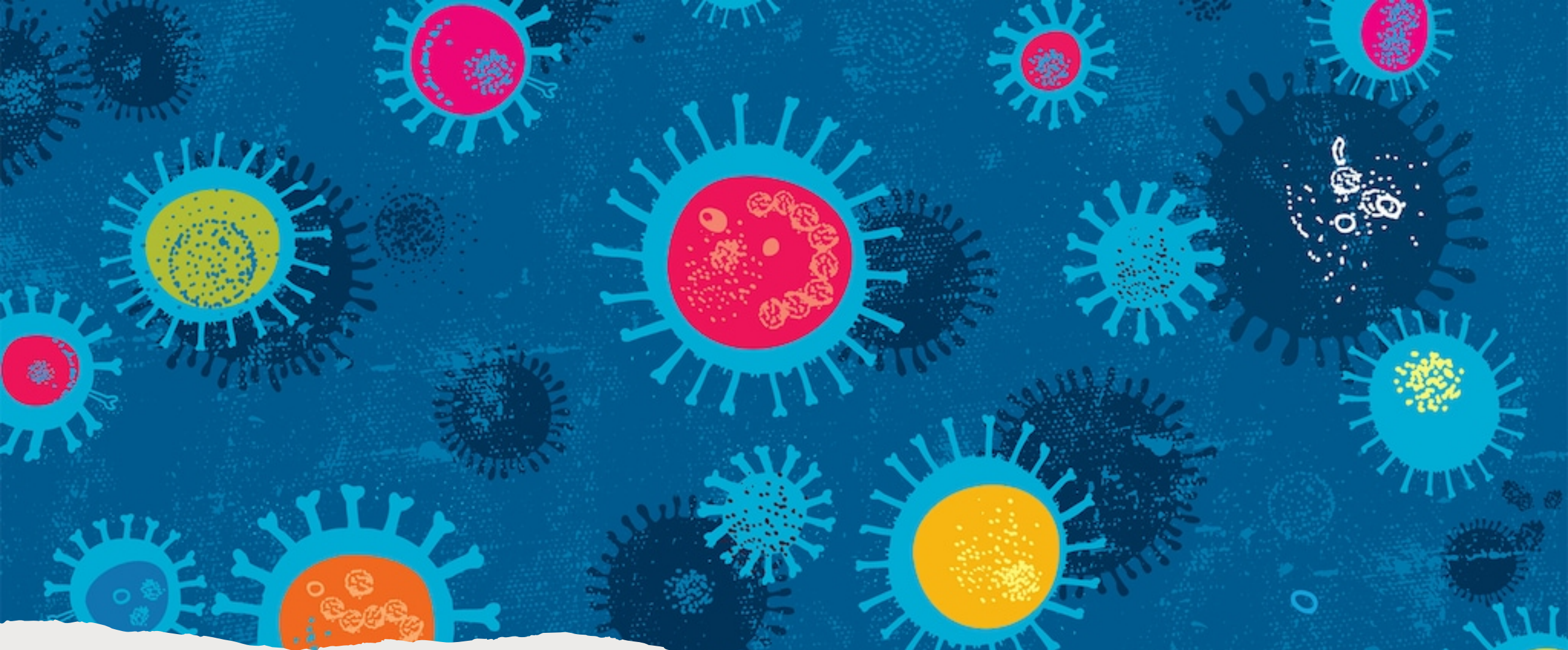
- B.1.1.7 – 40-50% more transmissible[1]
- B.1.427/B.1.429 – 20% more transmissible[2]
- B.1.351 – 50% more transmissible[3]
- B.1.128 - ?
- B.1.525/B.1.526 - ?

Sources:

1. NextTag
2. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. MedRxiv 2021. doi: https://doi.org/10.1101/2021.03.07.21252647
3. Mahase E. Covid-19: what new variants are emerging and how are they being investigated? BMJ. 2021;372:n158. Available from: https://doi.org/10.1136/bmj.n15

Variants: Bottom Line

- B.1.1.7, the VOC originally identified in the UK is now dominating the trajectory of the pandemic curve in NA & Europe
- B.1.1.7 is associated with:
  - Increased transmission
  - Increased risk of hospitalization, ICU admission and death
- In general, there is a 10-day time lag until the full risk increase becomes apparent after the initial rise in cases



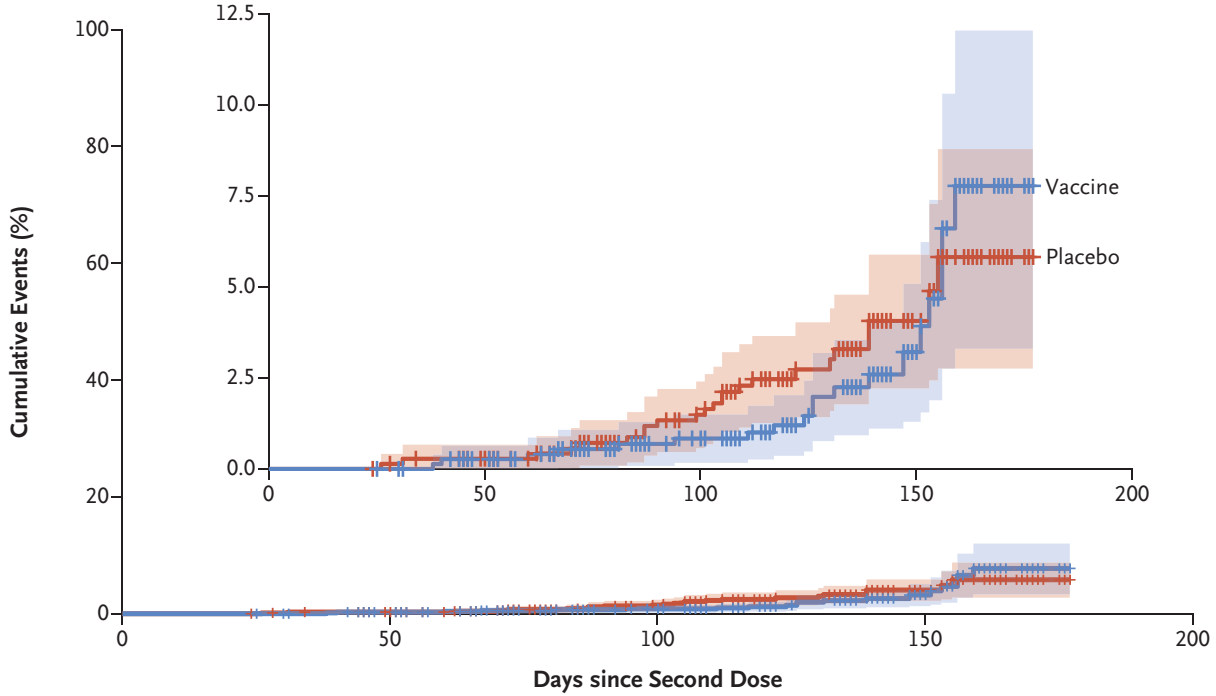
SARS-CoV-2 Variants and Immune Escape

South Africa AZ Vaccine Suspension

- Based on a study of around 2,000 participants whose median age was 31
- AstraZeneca vaccine had been showing a 75% efficacy against mild to moderate COVID cases until the B.1.351 strain became dominant in South Africa
- After that, the efficacy dropped to just 22% percent, based on 42 symptomatic cases
- However, the number of cases involved was too small to draw firm conclusions

South Africa AZ Vaccine Study

- MC DBRCT in South Africa of HIV- subjects
- Participants 18-65 years of age (mean age =31)
  - Placebo = 1010
  - Vaccine = 1011
- A 2-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate COVID-19 due to the B.1.351 variant



No. at Risk					
Vaccine	750	738	674	137	0
Placebo	717	707	632	124	0
Cumulative No. of Events					
Vaccine	0	2	6	14	19
Placebo	0	2	10	21	23

Source: S Mahdi et al NEJM 2021 DOI: 10.1056/NEJMoa210221

Other Preliminary Reports on Vaccine Effectiveness vs. B.1.351

- Preliminary data from J&J/Janssen® single-dose vaccine suggested it was 72% effective against moderate to severe COVID-19 in the U.S. compared with 57% effective in South Africa
- Novavax® said the efficacy of its vaccine in studies from the U.K. was 89% compared to 60% in South Africa

A participant in the South African trial of the AstraZeneca–University of Oxford COVID-19 vaccine has blood drawn before receiving her second dose. AP PHOTO/JEROME DELAY

South Africa suspends use of AstraZeneca's COVID-19 vaccine after it fails to clearly stop virus variant

Efficacy of Pfizer-BioNTech Vaccine vs. Variants

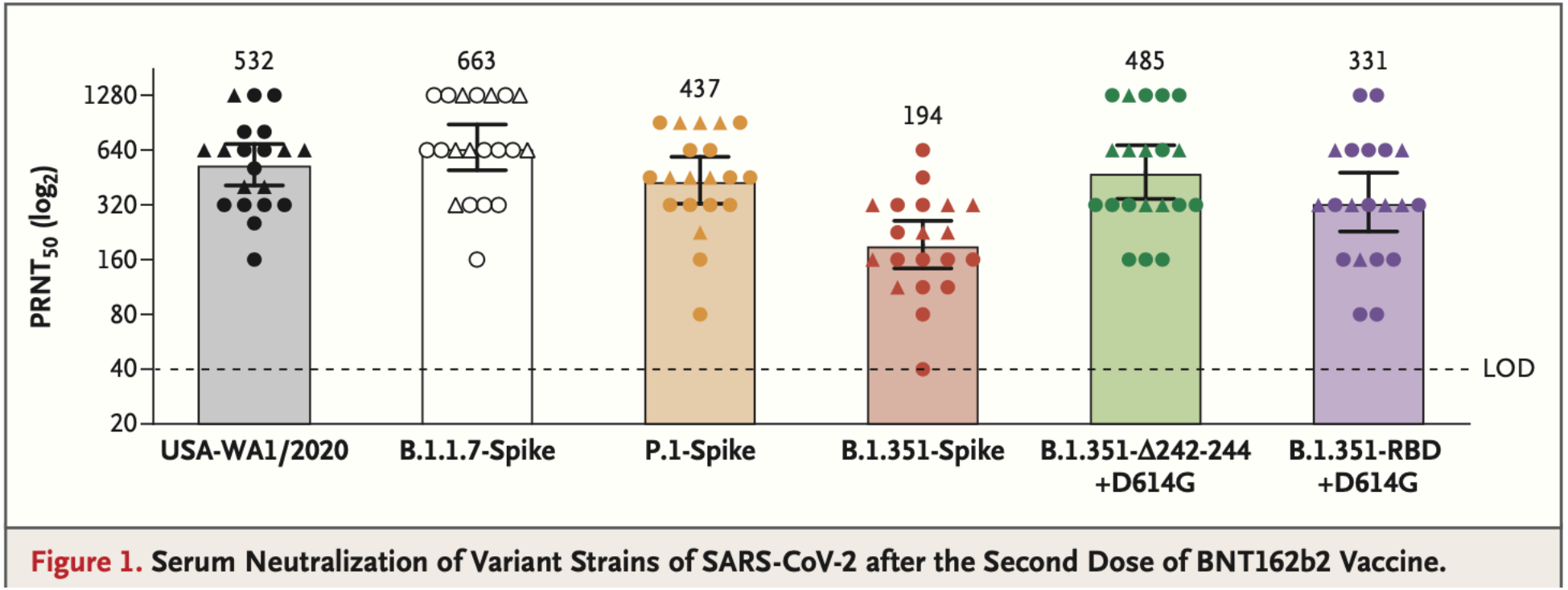
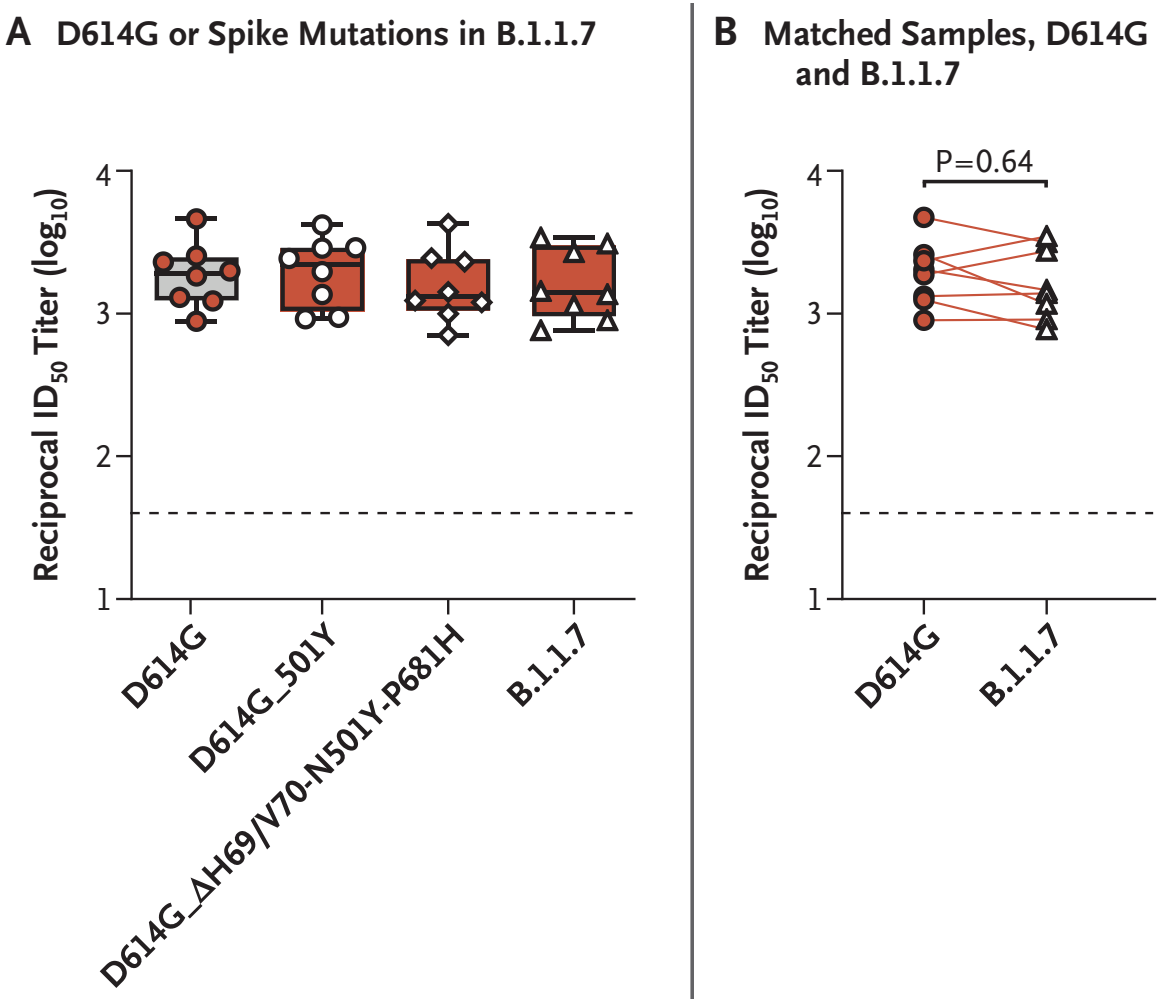


Figure 1. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

- 20 serum samples obtained from 15 participants in the RCT
- 2 or 4 weeks after the administration of the 2nd dose of BNT162b2

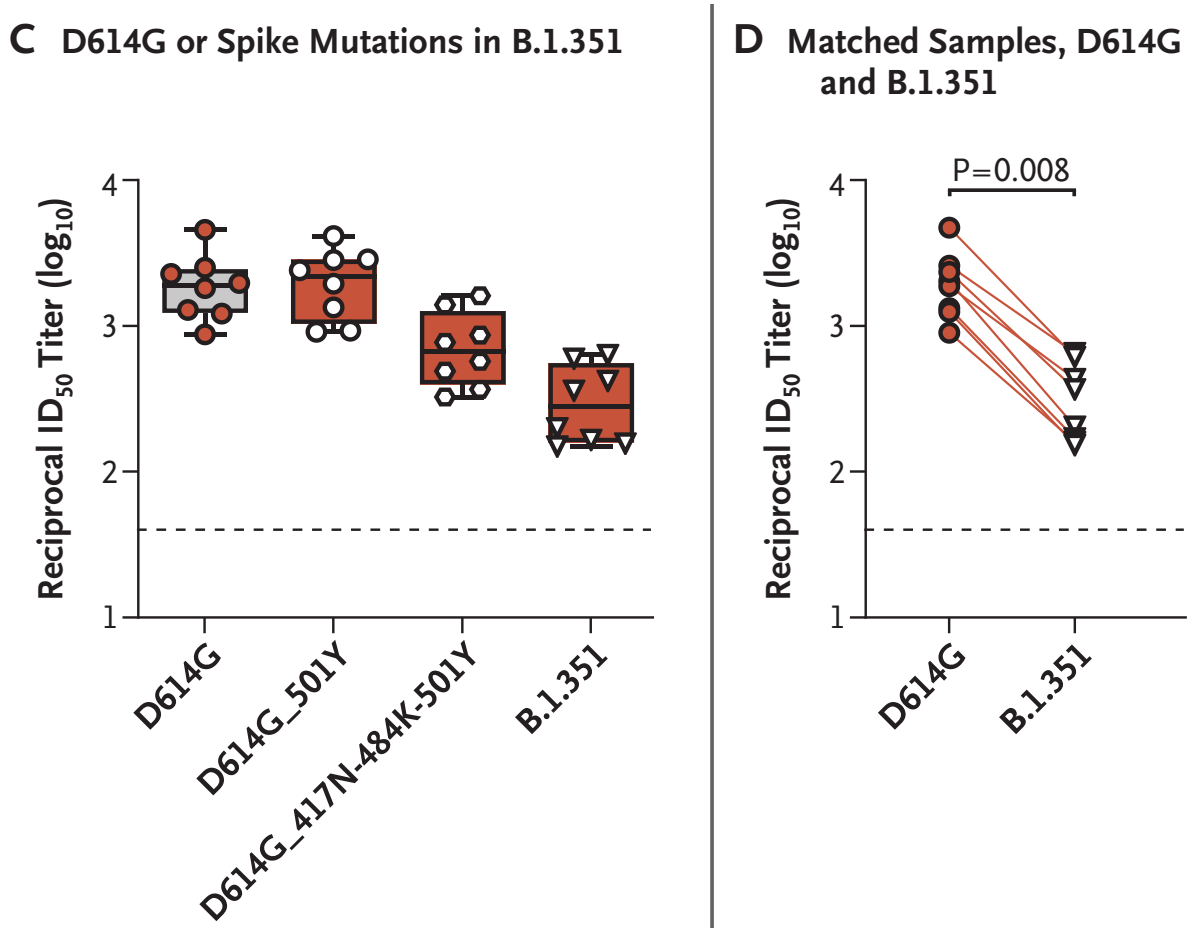
Source: Y Liu et al NEJM 2021 DOI: 10.1056/NEJMc2102017

Moderna Neutralizing Antibody Titres from Vaccine Recipients to B.1.1.7



Source: K Wu et al NEJM 2021 DOI: 10.1056/NEJMc2102179

Moderna Neutralizing Antibody Titres from Vaccine Recipients to B.1.351



Source: K Wu et al NEJM 2021 DOI: 10.1056/NEJMc2102179

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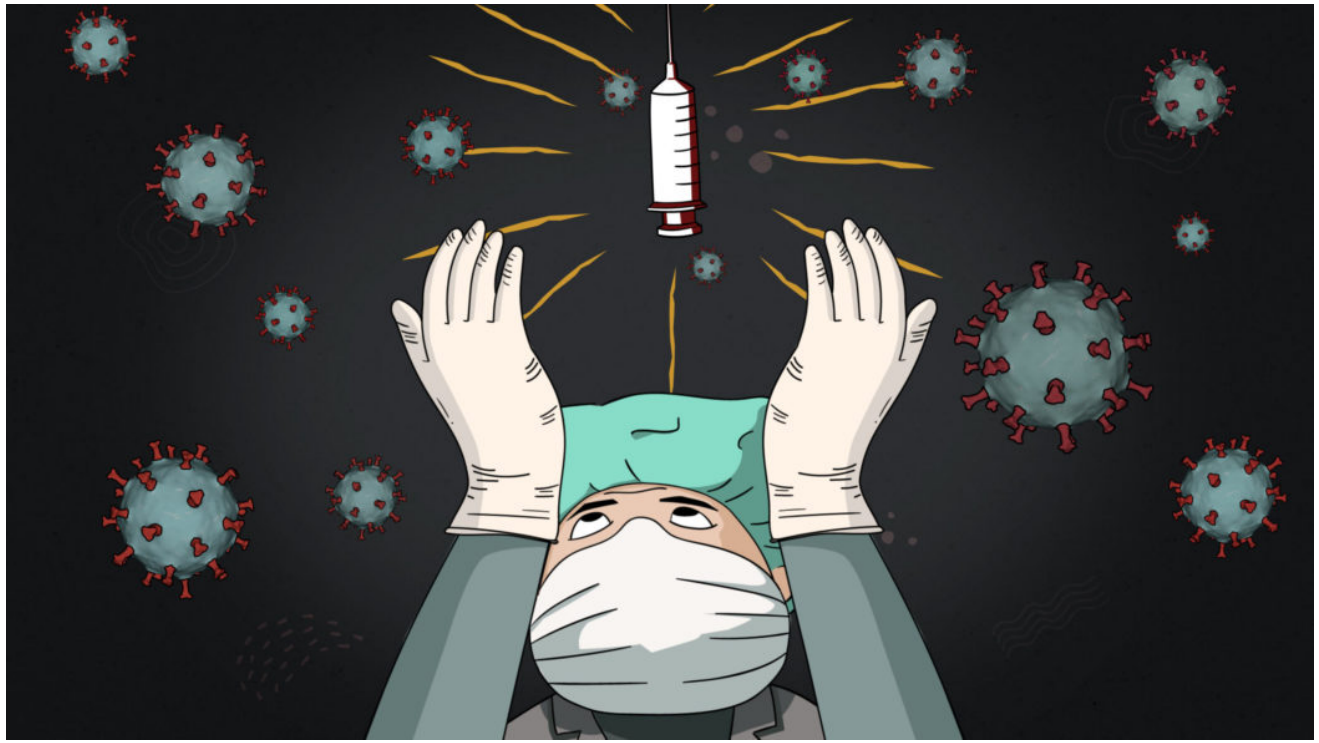
- Possible consequences of emerging mutations

1. Increased transmissibility ✅
2. Increased virulence ✅
3. Decreased protection from current vaccines or previous natural infection ❓



COVID-19 Vaccines

Vaccine-induced Immunity to SARS-CoV-2

1. Protective immunity ✅
   - Immunity protects the individual from more severe disease
2. Sterilizing immunity ❓→✅
   - Immunity confers protection from infection
3. Transmission immunity ❓→✅
   - Immune individuals do not transmit infection
   - Herd immunity when sufficient numbers vaccinated

Good

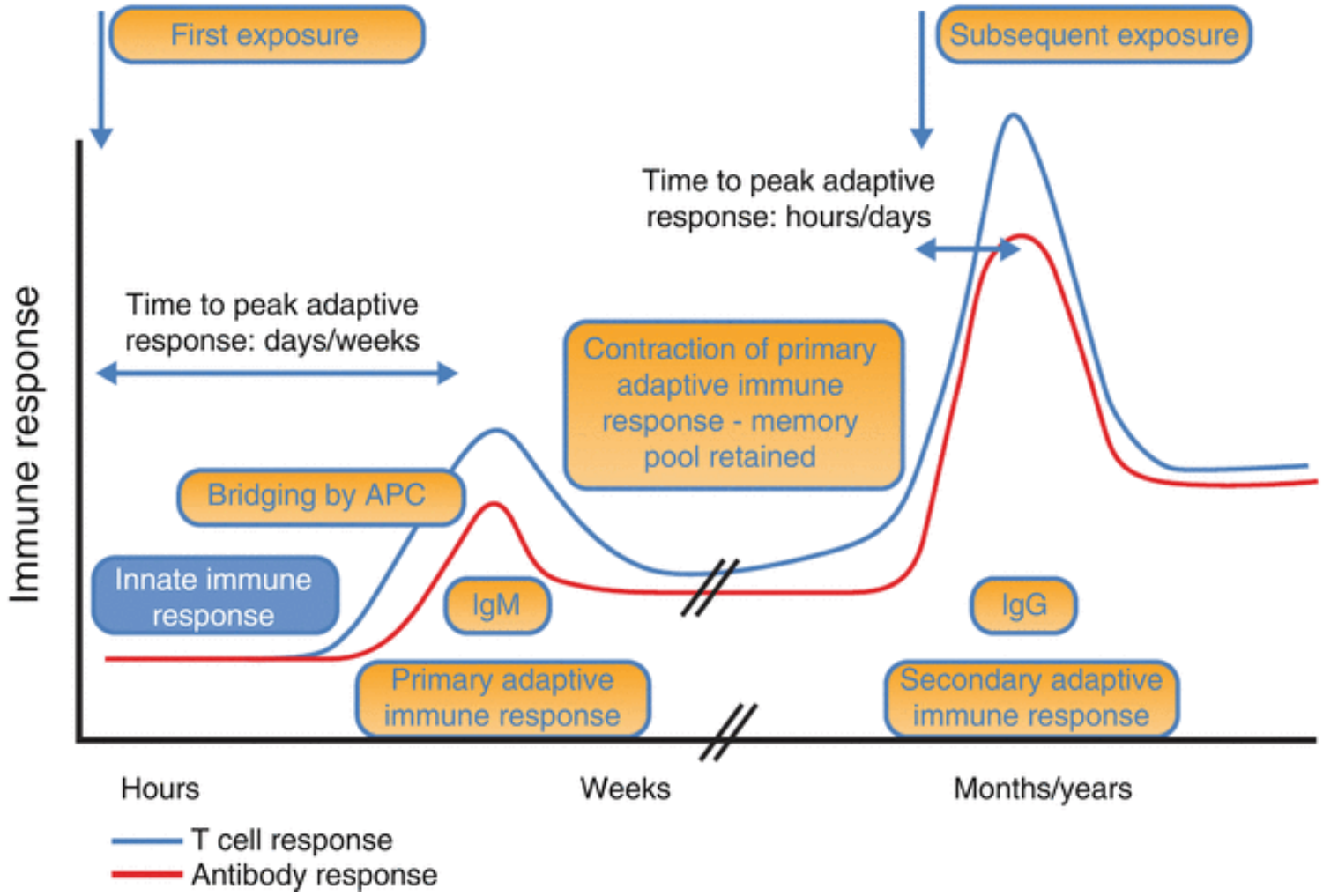
↓

Better

↓

Best

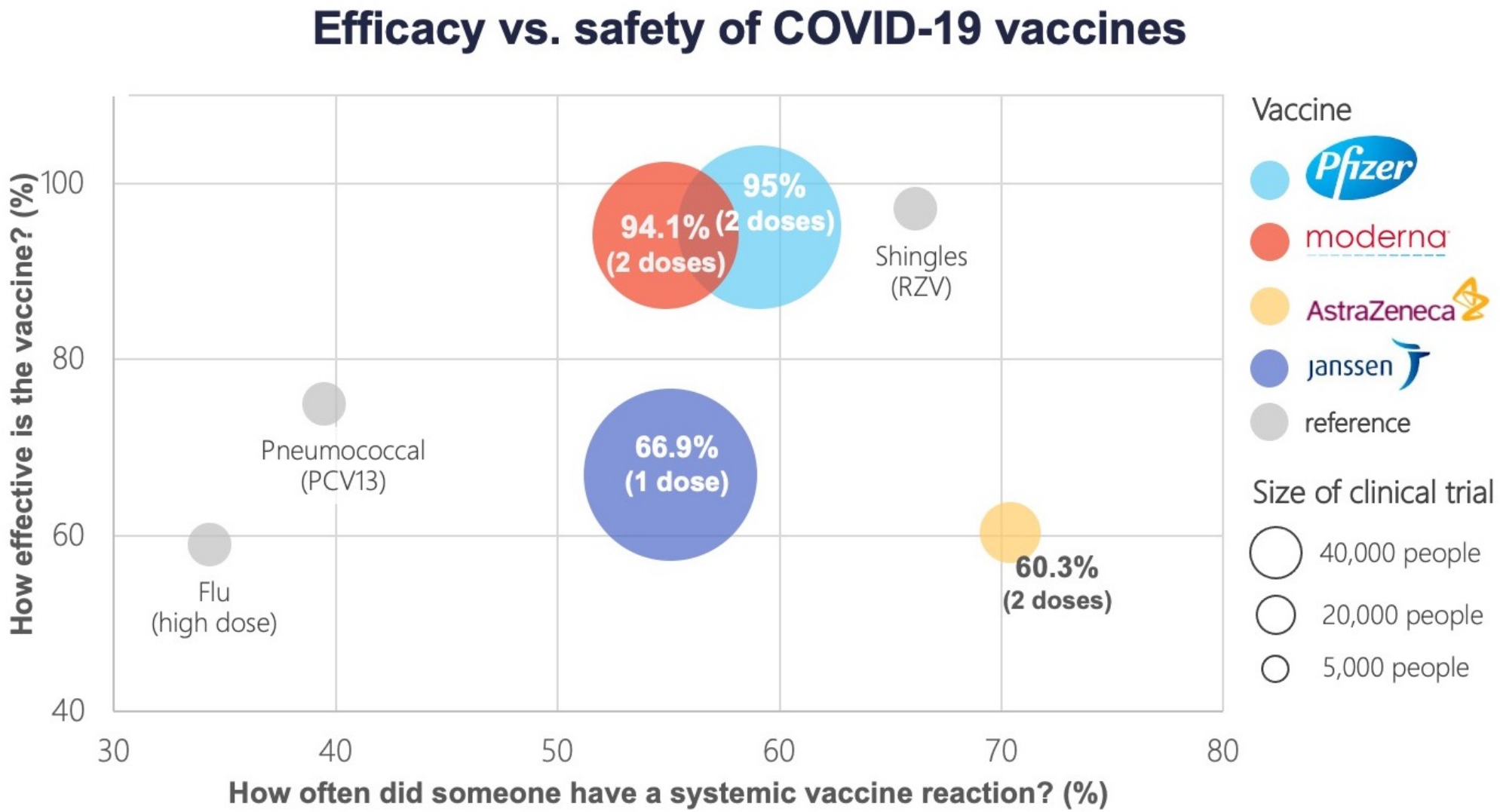
Dynamics of the Adaptive Immune Response to Vaccines



Comparison of COVID-19 vaccines currently available in Canada

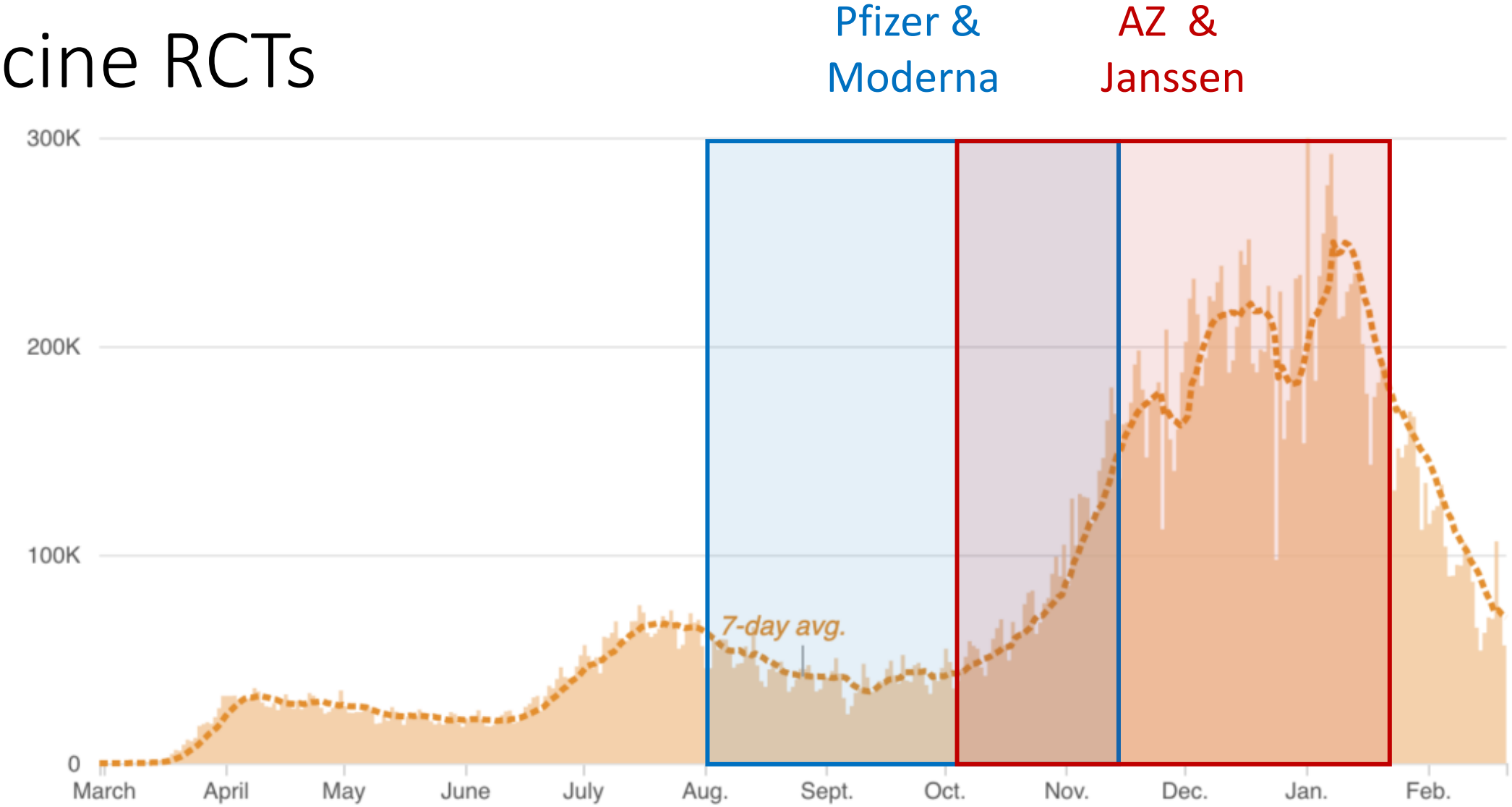
	Pfizer	moderna	AstraZeneca	janssen
	Authorized in Canada on: 9-Dec-2020	Authorized in Canada on: 23-Dec-2020	Authorized in Canada on: 26-Feb-2021	Authorized in Canada on: 5-Mar-2021
Type of vaccine	mRNA	mRNA	Non-replicating viral vector	Non-replicating viral vector
Authorized groups	≥16 years of age	≥18 years of age	≥18 years of age Not recommended for individuals ≥ 65 years of age	≥18 years of age
Dosing	2 doses 0.3 mL (30 µg of mRNA)	2 doses 0.5 mL (100 µg of mRNA)	2 doses 0.5 mL (5×10^{10} viral particles)	1 dose 0.5 mL (5×10^{10} viral particles)
Schedule	3 weeks apart Up to 4 months	4 weeks apart Up to 4 months	4-12 weeks apart Up to 4 months	N/A
Storage	Ultra-cold freezer (-80°C to -60°C)	Standard freezer (-25°C to -15°C)	Standard refrigerator (2°C to 8°C)	Standard refrigerator (2°C to 8°C)

Source: C Chambers at https://healthydebate.ca/2021/03/topic/comparing-vaccines/?utm_source=mailpoet&utm_medium=email&utm_campaign=what-you-need-to-know-about-vaccines_6



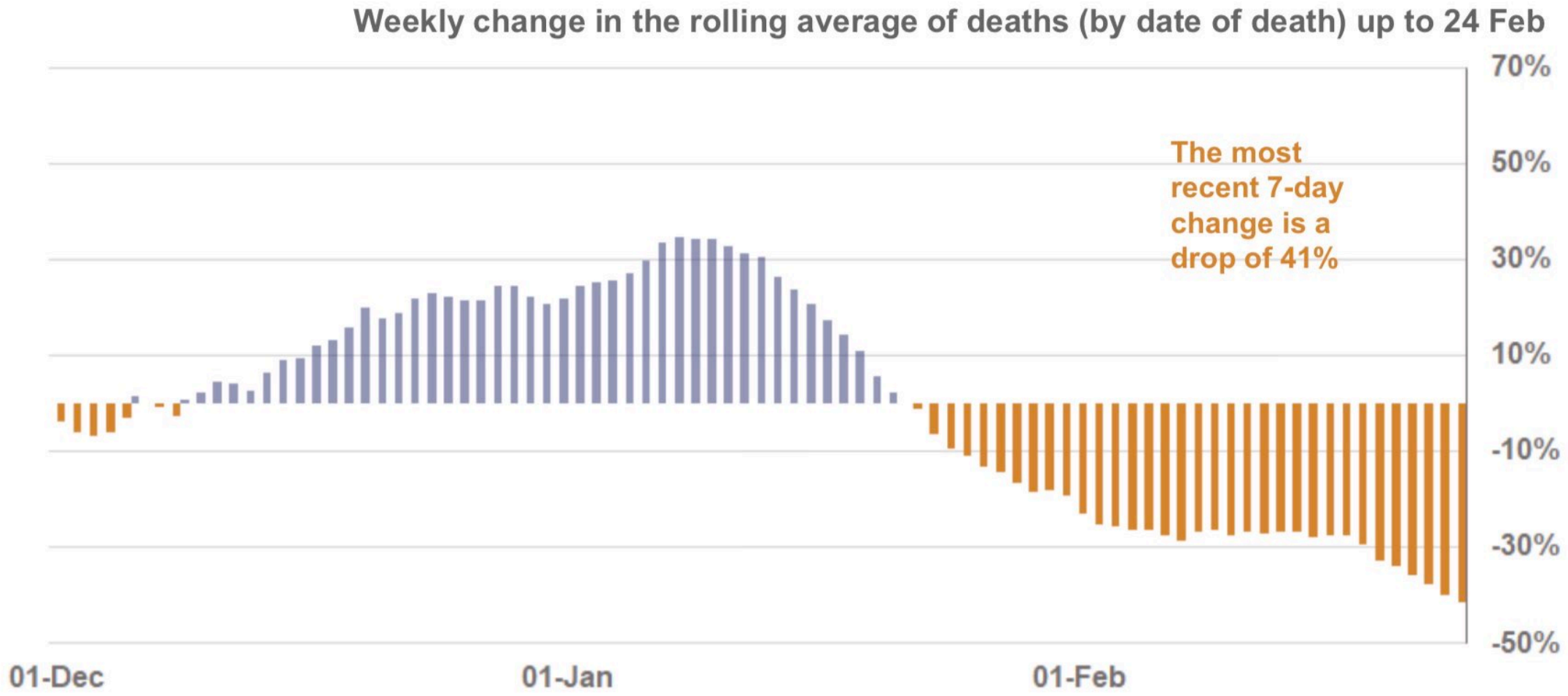
Source: C Chambers at https://healthydebate.ca/2021/03/topic/comparing-vaccines/?utm_source=mailpoet&utm_medium=email&utm_campaign=what-you-need-to-know-about-vaccines_6

Time Periods for Vaccine RCTs



Company	Platform	Dose	Non-clinical results	# who got vaccine	Protection from hospitalization from COVID-19	Protection from COVID severe dz (some at home)	Efficacy against milder COVID
moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~15,000	97% (1 in vaccine arm after 2nd dose hospitalized)	97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)	94.1%
Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine- 1 initially severe but not)	95%
Johnson & Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; challenge protection (macaque)	~22,000 US, Latin America, S. Africa	100%	85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)	72% US; 61% Latin America; 64% S. Africa (96% B1.351)
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~8588	100%	100% (15 in placebo – all hospitalized; 0 in vaccine)	70% overall; 76% 1 dose; S. Africa trial halted for mild
NOVAVAX Creating Tomorrow's Vaccines Today	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; challenge protection (macaques)	~8833 (Phase 3 UK; 2b SA)	100%	100% (10 severe in placebo in UK/SA; 0 in vaccine)	96.4% UK; 89% B117 UK; 55% SA (94% B1351)
Sputnik V	Ad26 and Ad5 adenovirus/DNA	2	NAbs; IFN-γ secretion PMBCs, cellular response	~14964	100%	100% (20 in placebo; 0 vaccine)	91.6%
sinovac	Inactivated virus	2	Antibodies (T cells next)	~12500	100%	83% (tx needed)	50.7% across

The rate of change of the number of deaths of people who had a positive test result for COVID-19 in the UK



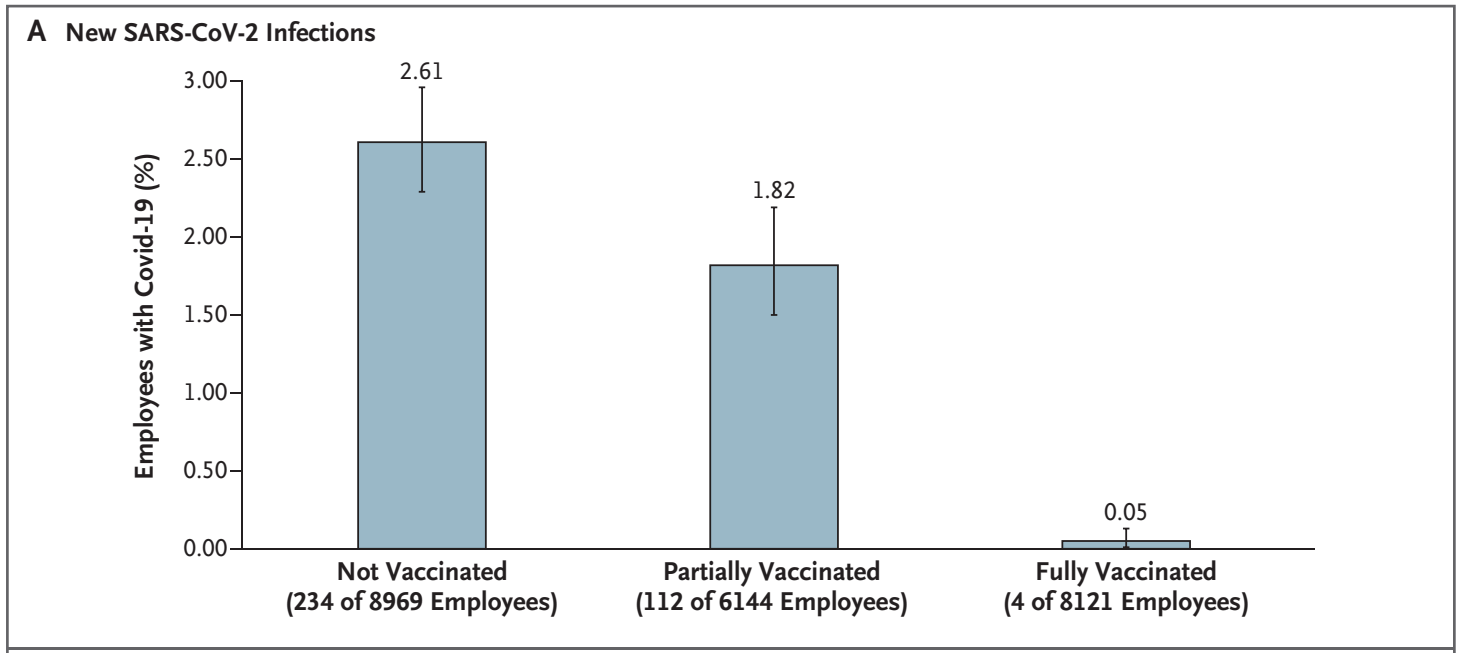
COBR
Cabinet Office Briefing Rooms

Source: https://coronavirus.data.gov.uk/
Further details on data sources can be found here:
https://www.gov.uk/government/collections/slides-and-datasets-to-accompany-coronavirus-press-conferences

STAY HOME › PROTECT THE NHS › SAVE LIVES

Vaccine Effectiveness in Acute Care HCWs

1.



2.

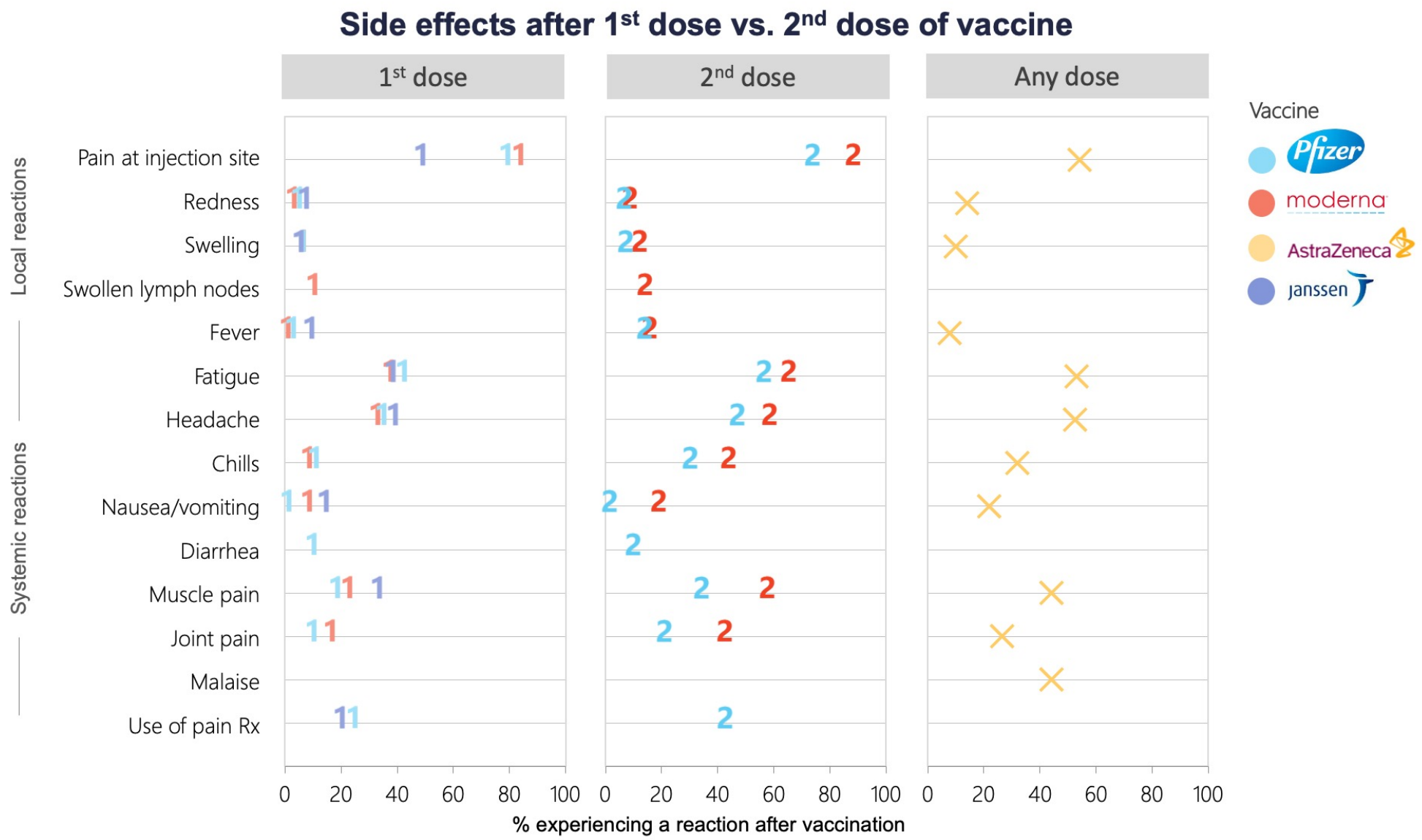
Table 1. New SARS-CoV-2 Infections among Vaccinated Health Care Workers from December 16, 2020, through February 9, 2021.

Days after Vaccination	Vaccinated Persons		
	With New Infection (N=379)	Tested (N=14,604)*	Eligible for Testing (N=36,659)†
	number		*number (percent)*
Dose 1			
Days 1–7	145	5794	35,673 (97.3)
Days 8–14	125	7844	34,404 (93.8)
Days 15–21	57	7958	32,667 (89.1)
Day 22 or later, before dose 2	15	4286	32,327 (88.2)
Dose 2			
Days 1–7	22	5546	23,100 (63.0)
Days 8–14	8	4909	16,082 (43.9)
Day 15 or later	7	4167	14,990 (40.9)

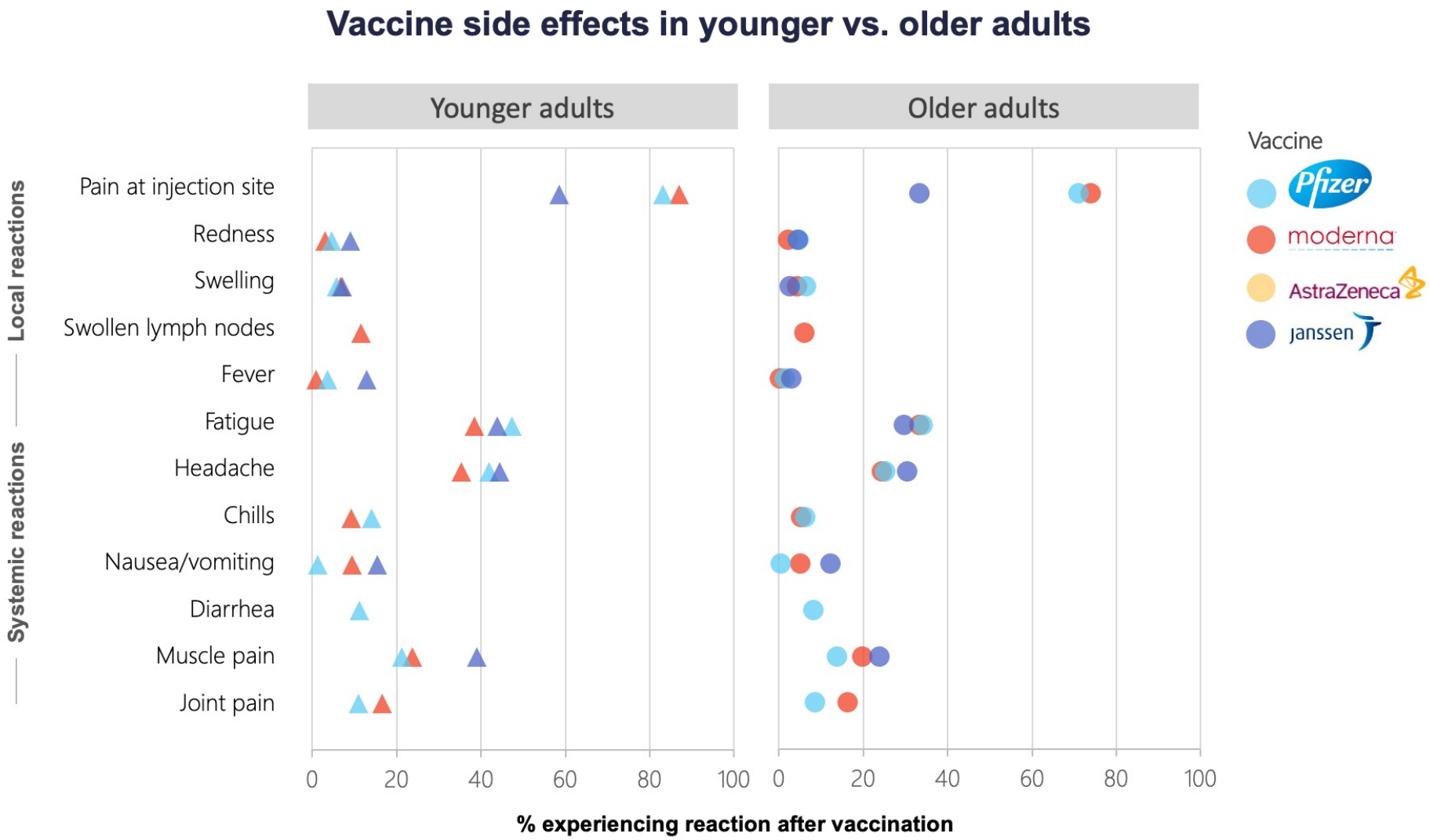
Sources:

1. W Daniel et al NEJM 2021 DOI: 10.1056/NEJMc2102153
2. J Keehner et al NEJM 2021 DOI: 10.1056/NEJMc2101927

Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)		
Setting	Finding of xx% reduction in asymptomatic or infections including asymptomatic	Reference
Healthcare workers in England	**86%**	**Hall SSRN, February 22, 2021**
Healthcare workers in Israel	**75%**	**Amit, Lancet, March 6, 2021**
Patients in Mayo Clinic health system	**88.7%**	**Pawlowski medRxiv, February 27, 2021**
Israel Ministry of Health (nationwide) Israel general population (Pfizer)	**94%** **90%**	**Pfizer press release, March 11, 2021** **Dagan NEJM, February 24, 2021**
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	**80%**	**Tande Clin Inf Dis, March 10, 2021**
Healthcare workers in Cambridge University Hospitals	**75%**	**Weekes Authorea, February 24, 2021**
Nasal viral load values are most important determinant of transmissibility (Lancet study); Nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if want to test symptomatic)		



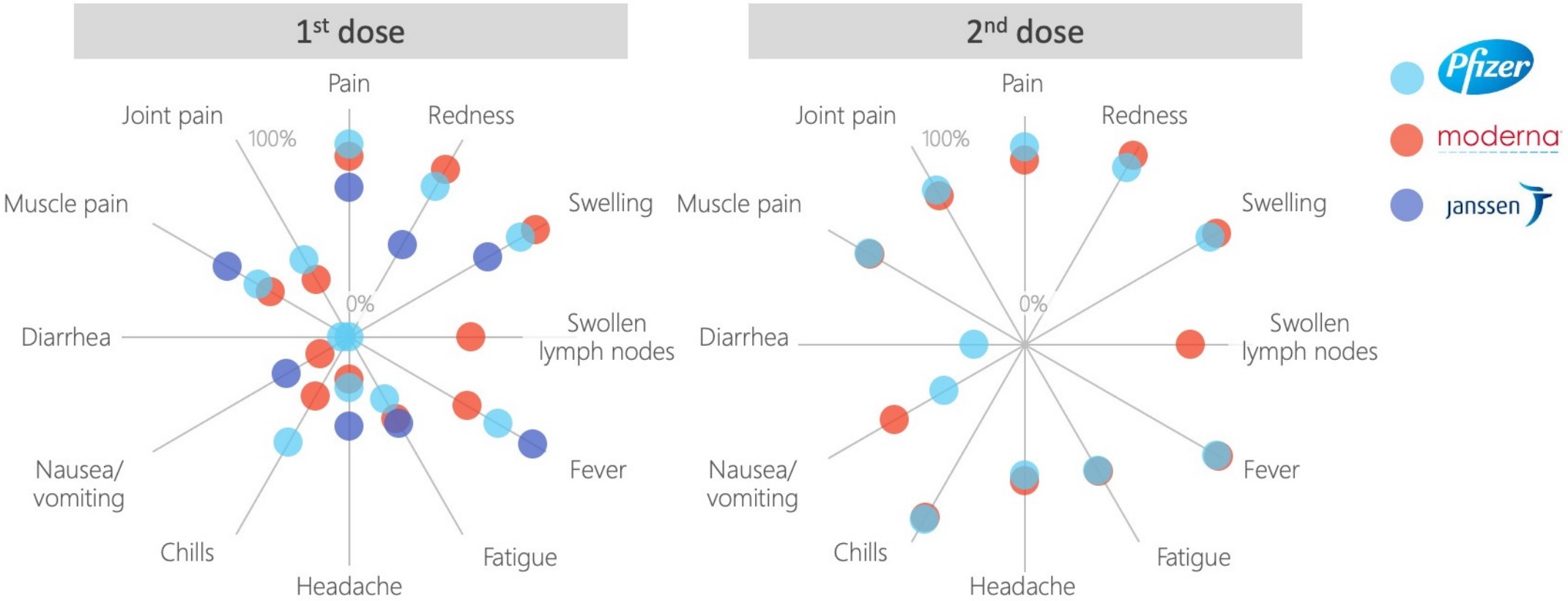
Source: C Chambers at https://healthydebate.ca/2021/03/topic/comparing-vaccines/?utm_source=mailpoet&utm_medium=email&utm_campaign=what-you-need-to-know-about-vaccines_6



Source: C Chambers at https://healthydebate.ca/2021/03/topic/comparing-vaccines/?utm_source=mailpoet&utm_medium=email&utm_campaign=what-you-need-to-know-about-vaccines_6

Side effects caused directly by the COVID-19 vaccine

% of reactions attributable to vaccination



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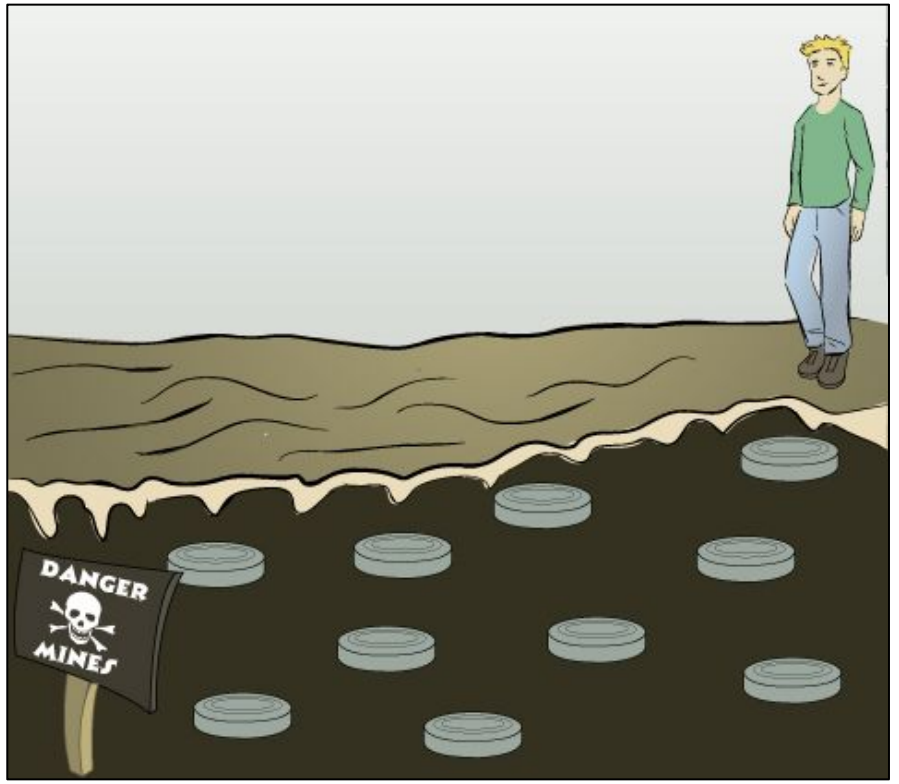
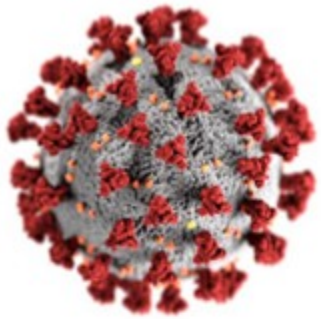
Summing up

- Where we are
  - Right now we're in a 3rd wave and in Ontario, a high % of SARS-CoV-2 variants
- Variants
  - A cause for concern due to increase in transmissibility and virulence
- Vaccines
  - They're effective and safe with more on the horizon





COVID 19 Prevention Toolbox

Our best ways to prevent contacting COVID 19 is by using the tools we have available.

Risks may vary based on your ability to maintain a 2-metre physical distance from others; the use of non-medical masks by you and others; and the measures in place to reduce exposure in the setting you are in. Generally, the risk of exposure will increase with prolonged duration and in closed indoor or crowded settings or close contact situations, particularly if activities involve forceful exhalation (talking loudly/shouting, singing, coughing). Individuals who receive the vaccine are 20 times less likely to contact COVID 19.