SARS-CoV-2

An evolving pandemic

Sarah (Sally) Otto
Department of Zoology
University of British Columbia

BC COVID-19 Modelling Group

The BC COVID-19 Modelling Group works on rapid response modelling of the COVID-19 pandemic, with a special focus on British Columbia and Canada.

The interdisciplinary group, working independently from Government, includes experts in epidemiology, mathematics, and data analysis from UBC, SFU, UVic, and the private sector, with support from the Pacific Institute for the Mathematical Sciences.

https://bccovid-19group.ca

Weekly meetings

- Review relevant articles
- Expert presentations
- Present new models for feedback
- Request help with projects
- Provide advice

Slack channel

- News updates
- Communications channel
- Community building

Public reports

- https://bccovid-19group.ca

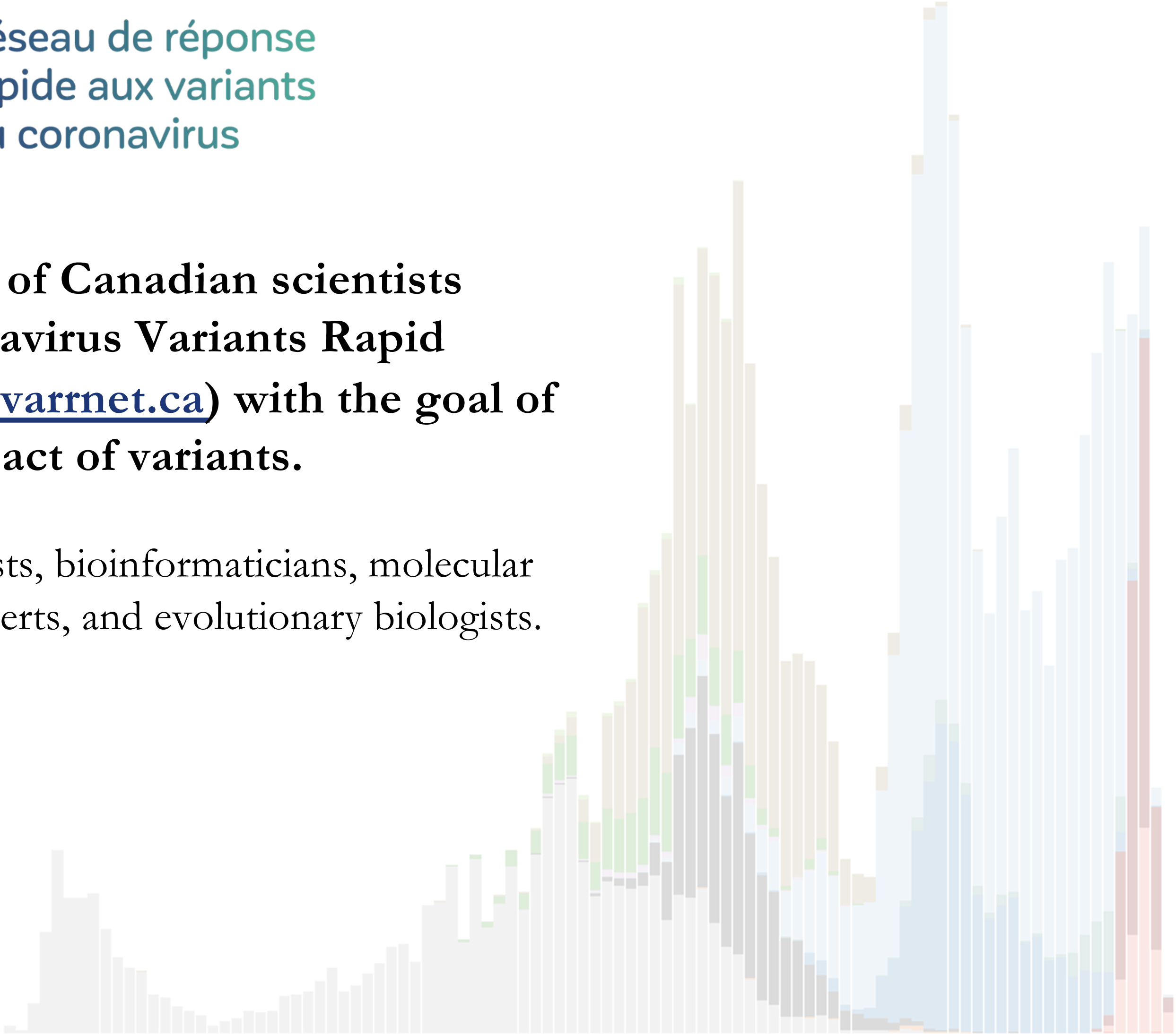
Independent and freely offered advice,
using a diversity of modelling approaches.

Coronavirus Variants
Rapid Response
Network

Réseau de réponse
rapide aux variants
du coronavirus

A year later, a broader network of Canadian scientists launched CoVaRR-Net (Coronavirus Variants Rapid Response Network, https://covarrnet.ca) with the goal of tracking and assessing the impact of variants.

Network brings together immunologists, bioinformaticians, molecular & cellular biologists, public health experts, and evolutionary biologists.



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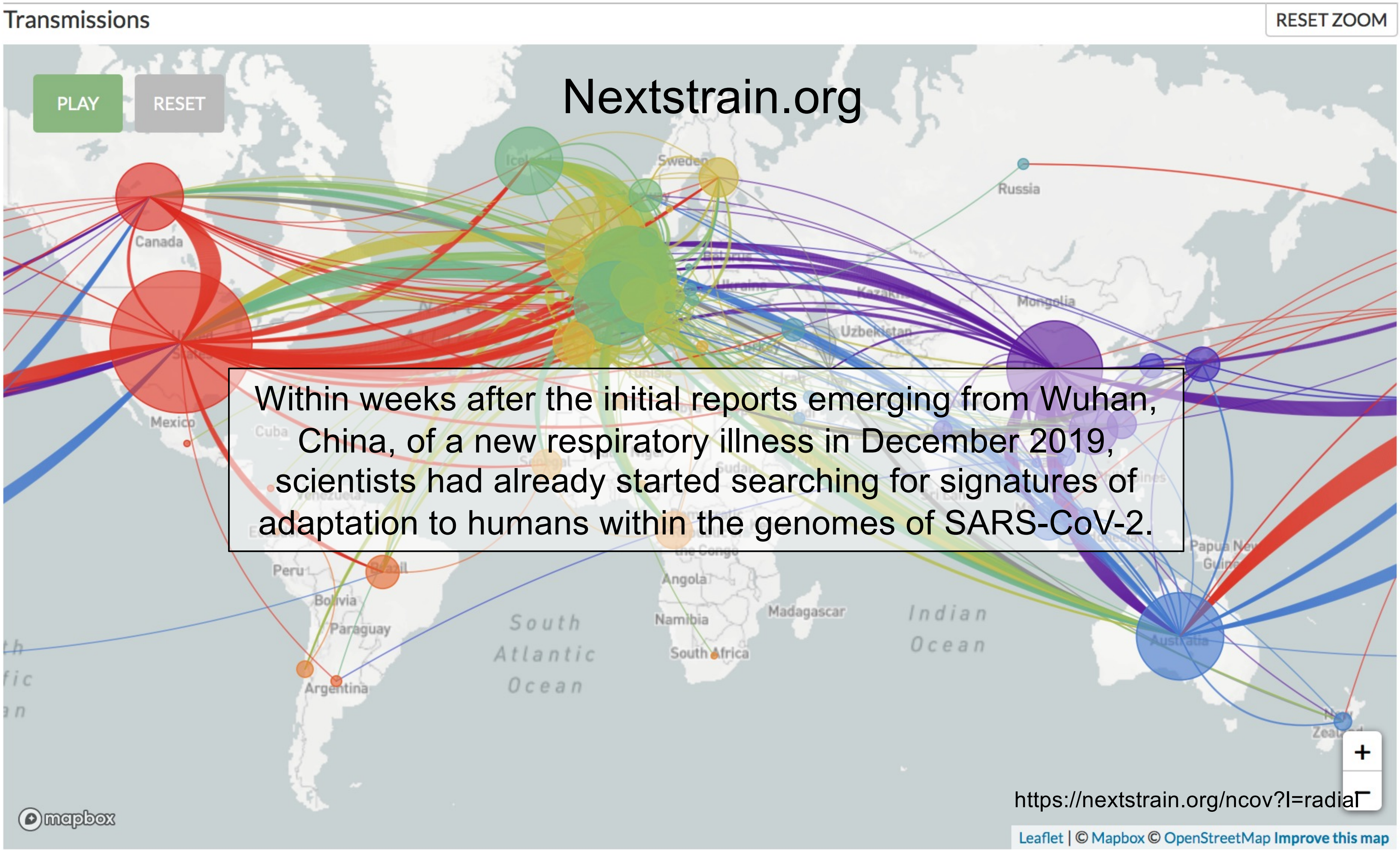
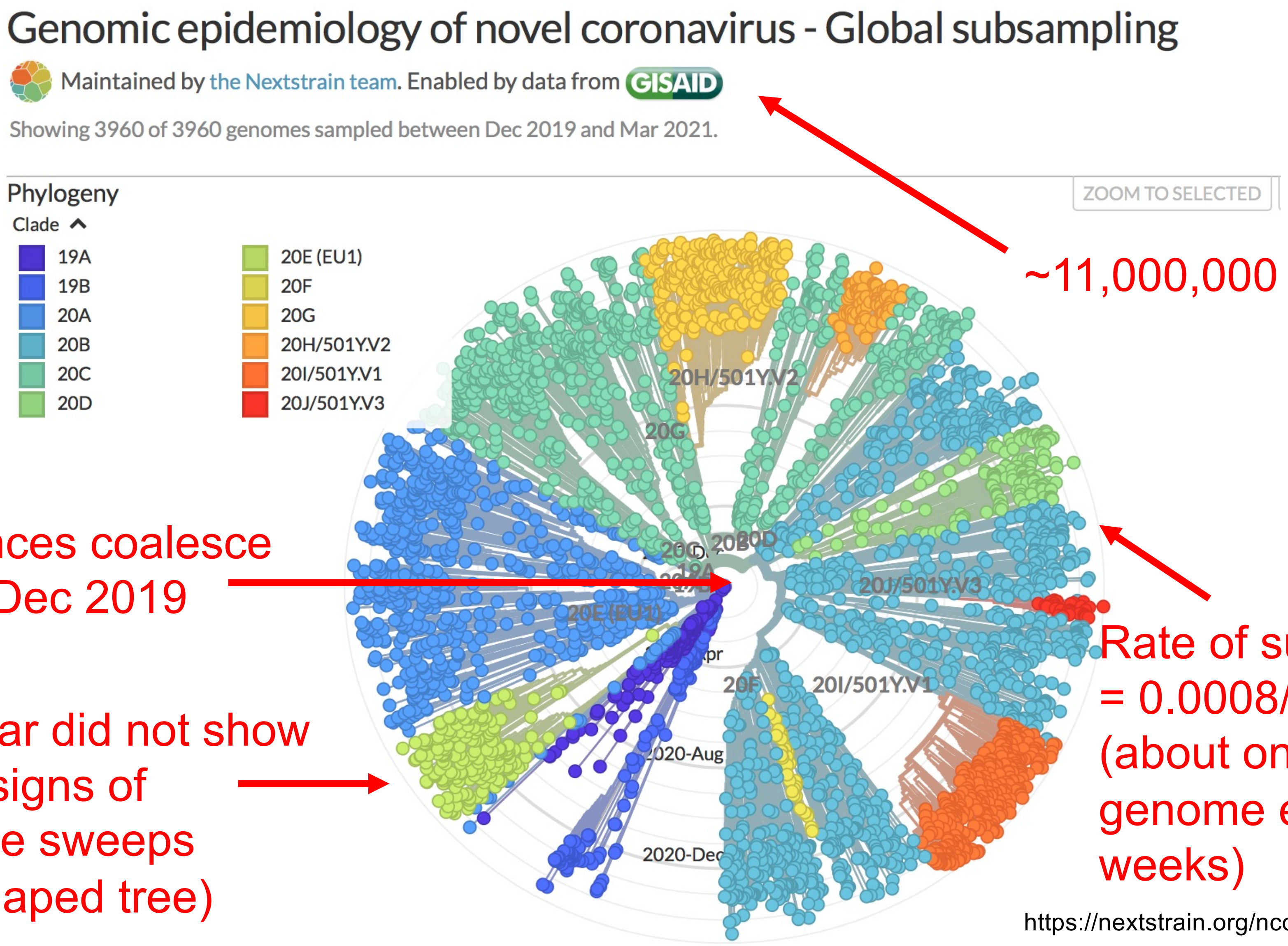
Evolution…of how we conduct science to aid action

Nextstrain.org



Within weeks after the initial reports emerging from Wuhan, China, of a new respiratory illness in December 2019, scientists had already started searching for signatures of adaptation to humans within the genomes of SARS-CoV-2.

https://nextstrain.org/ncov?l=radial



Genomic epidemiology of novel coronavirus - Global subsampling

Maintained by the Nextstrain team. Enabled by data from GISAID

Showing 3960 of 3960 genomes sampled between Dec 2019 and Mar 2021.

Phylogeny

~11,000,000 genomes!!

Sequences coalesce in Nov/Dec 2019

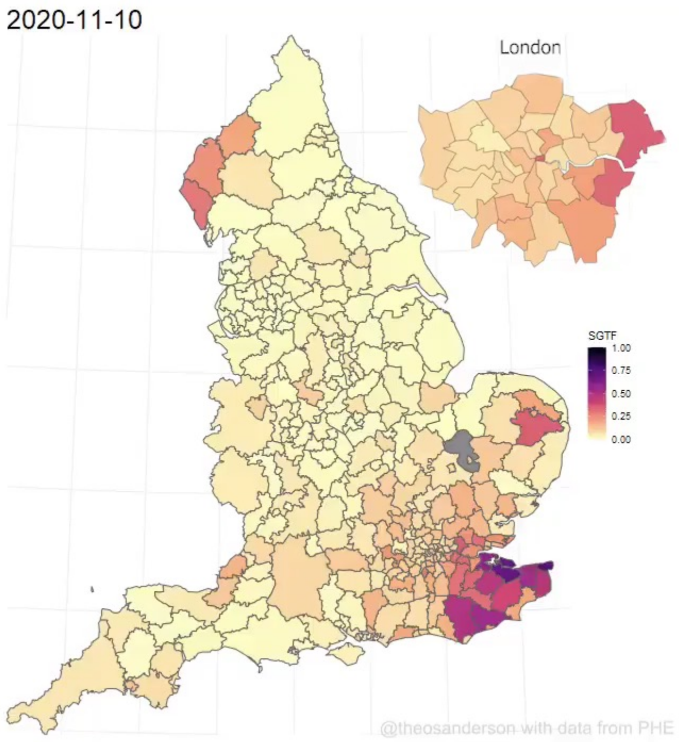
First year did not show strong signs of selective sweeps (star-shaped tree)

Rate of substitution: = 0.0008/bp/year (about once per genome every two weeks)

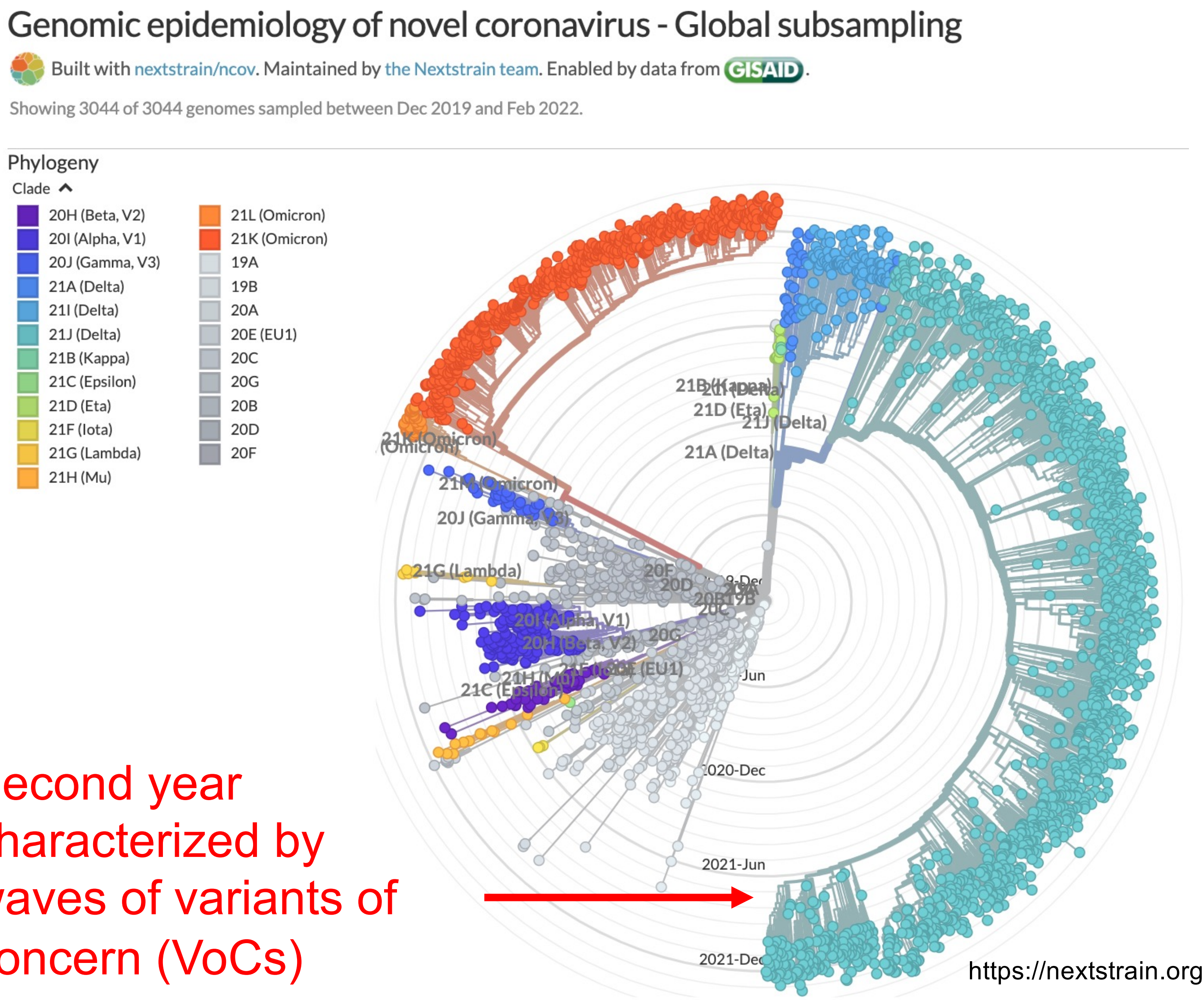
https://nextstrain.org/ncov?l=radial

Variants of Concern

Public Health England (Dec. 21, 2020) reported a Variant of Concern (VOC) B.1.1.7 that had increased in frequency across multiple weeks and across multiple health authorities.



Data from Public Health England
(visual from Theo Sanderson)



Genomic epidemiology of novel coronavirus - Global subsampling

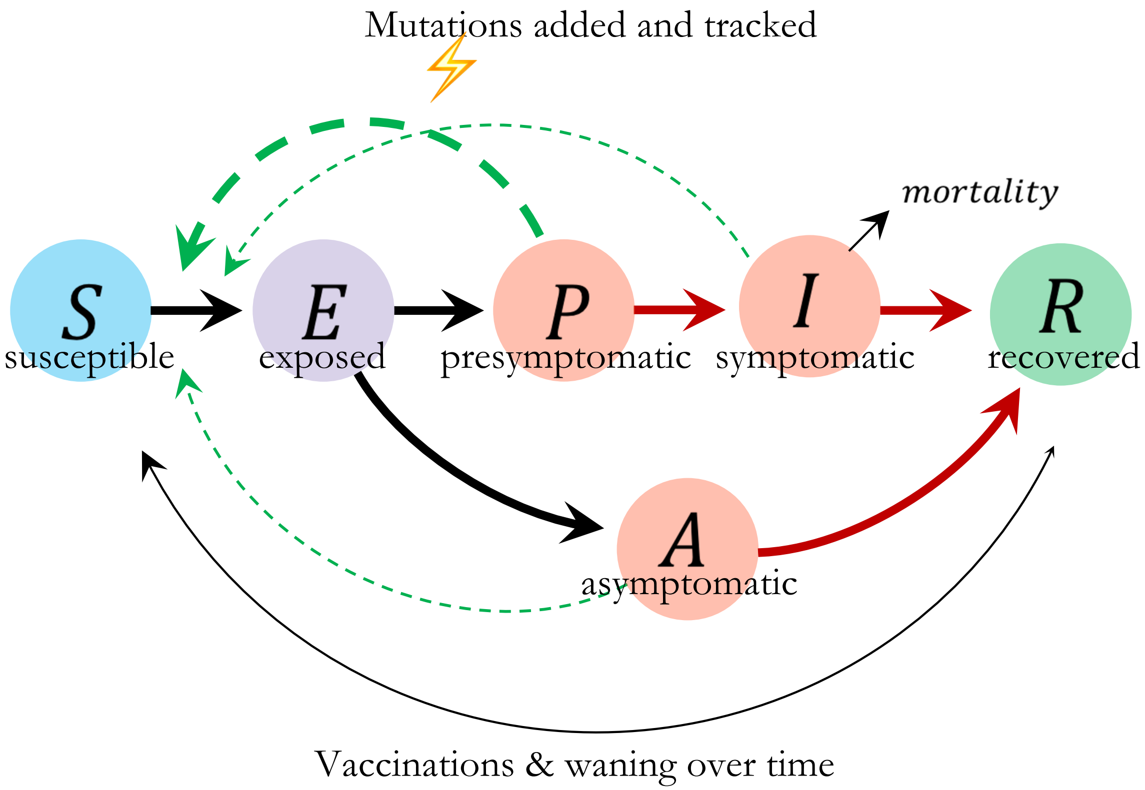
Built with nextstrain/ncov. Maintained by the Nextstrain team. Enabled by data from GISAID.

Showing 3044 of 3044 genomes sampled between Dec 2019 and Feb 2022.

Second year characterized by waves of variants of concern (VoCs)

https://nextstrain.org/ncov?l=radial

Modelling selection on SARS-CoV-2



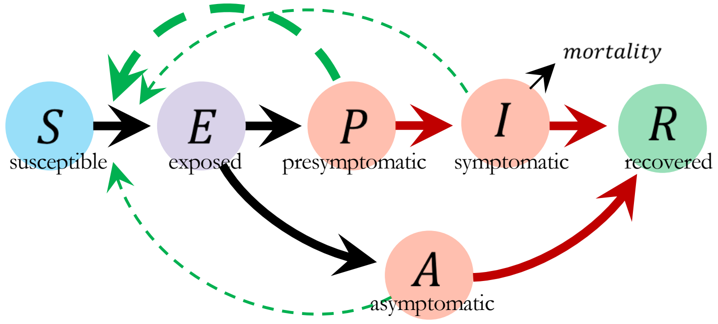
Current Biology

Day et al. (2020)

Otto et al. (2022)

SEAPIR Model

Non-linear set of equations is approximately linear when susceptible class is not changing rapidly (S~constant)



$$\frac{dS}{dt} = -S \sum_{*} (\beta_P^* P^* + \beta_I^* I^* + \beta_A^* A^*)$$

$$\frac{dE^*}{dt} = S(\beta_P^* P^* + \beta_I^* I^* + \beta_A^* A^*) - \kappa_E^* E^*$$

$$\frac{dA^*}{dt} = f^* \kappa_E^* E^* - \kappa_A^* A^*$$

$$\frac{dP^*}{dt} = (1 - f^*)\kappa_E^* E^* - \kappa_P^* P^*$$

$$\frac{dI^*}{dt} = \kappa_P^* P^* - (\alpha^* + \kappa_I^*) I^*$$

$$\frac{dR}{dt} = \sum_{*} (\kappa_I^* I^* + \kappa_A^* A^*)$$

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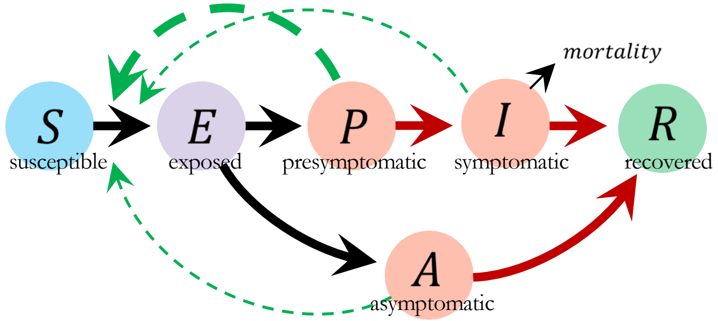
Non-linear set of equations is approximately linear when susceptible class is not changing rapidly (S~constant)

⚡ Add mutations (*) and track spread of new lineage



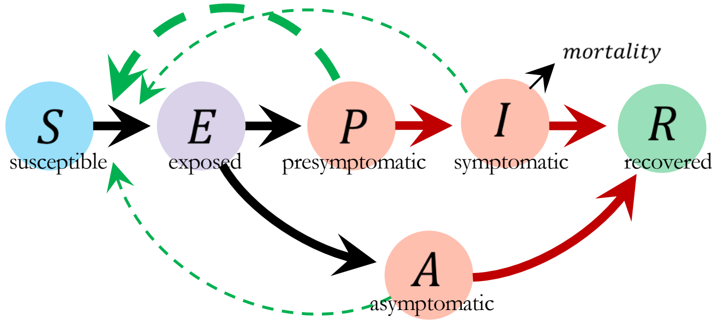
SEAPIR Model

Non-linear set of equations is approximately linear when susceptible class is not changing rapidly ($S \sim$constant)

⚡ Add mutations (*) and track spread of new lineage

Calculate selection on life-history traits by effect of mutations on the spread of the disease (λ, leading eigenvalue):

$$\boxed{\frac{d\lambda}{dz} = \vec{v}^{T}\,\frac{d\mathbf{M}}{dz}\,\vec{u}}$$



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SEAPIR Model

What selection pressures are acting on SARS-CoV-2?

$$\frac{d\lambda}{dz} = S\, v_E\, (\Delta\beta_P\, u_P + \Delta\beta_I\, u_I + \Delta\beta_A\, u_A) - (\Delta\alpha + \Delta\kappa_I)\, u_I v_I - \Delta\kappa_A\, u_A v_A - \Delta f\ \kappa_E\, u_E\, \{v_P - v_A\}$$
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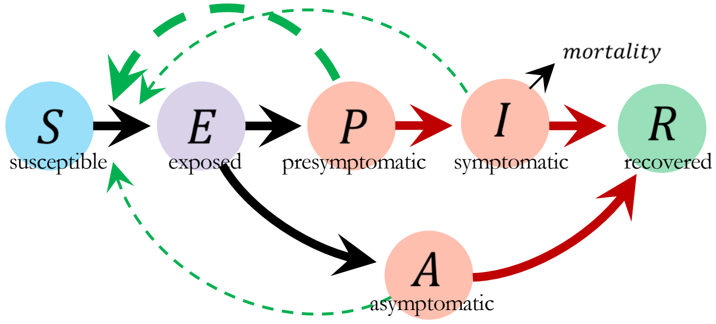

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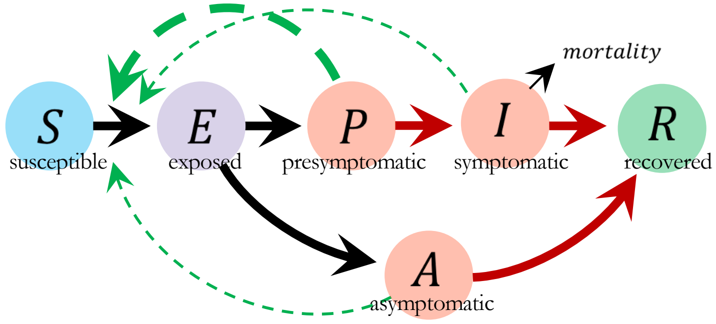
Mutant effects

Right eigenvector
(strictly positive)

Differences in left eigenvectors
Compares “reproductive values”

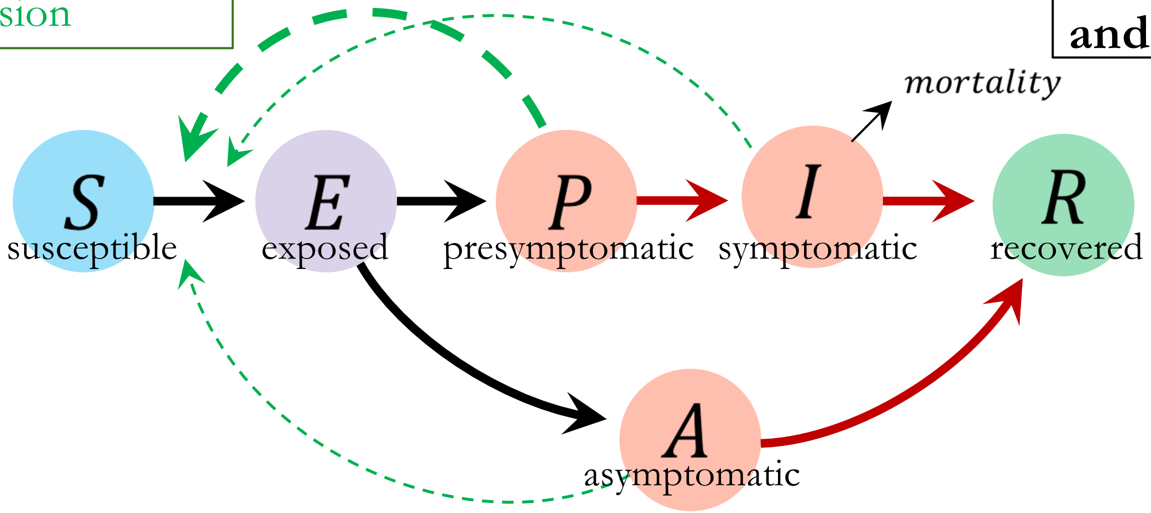


What selection pressures act on SARS-CoV-2 in a largely susceptible population?

Higher transmission

- Intrinsic transmissibility
- Immune evasion

Negligible direct selection on severity and mortality



Prolonged infectivity:

- Earlier infectivity favoured if cases rising
- Later infectivity favoured if cases declining

Current Biology

Day et al. (2020)

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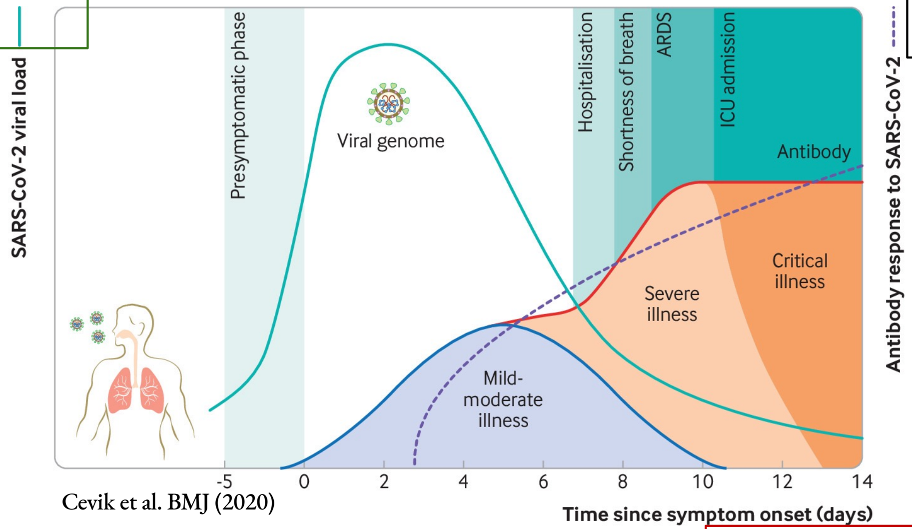


Cevik et al. BMJ (2020)

Negligible direct selection on severity and mortality

Current Biology

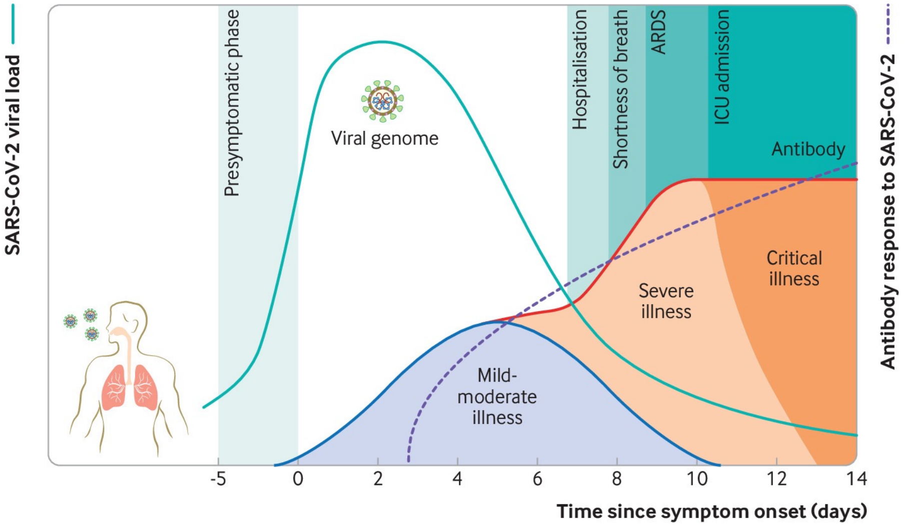
[Day et al.](#) (2020)

Prolonged infectivity:
- Earlier infectivity favoured if cases rising
- Later infectivity favoured if cases declining

What selection pressures act on SARS-CoV-2 in a largely susceptible population?

“Virulence evolution will be driven largely by the indirect effects of pleiotropy…”

- Mutations might “couple a higher transmission rate with higher mortality (**positive pleiotropy**)…if mutations increase viral replication rates.”
- Alternatively, mutations might alter “tissue tropism such that the disease tends to preferentially infect cells of the upper respiratory tract, rather than the lower respiratory tract. Such infections could lead to a higher transmission rate but be less virulent (negative pleiotropy)”



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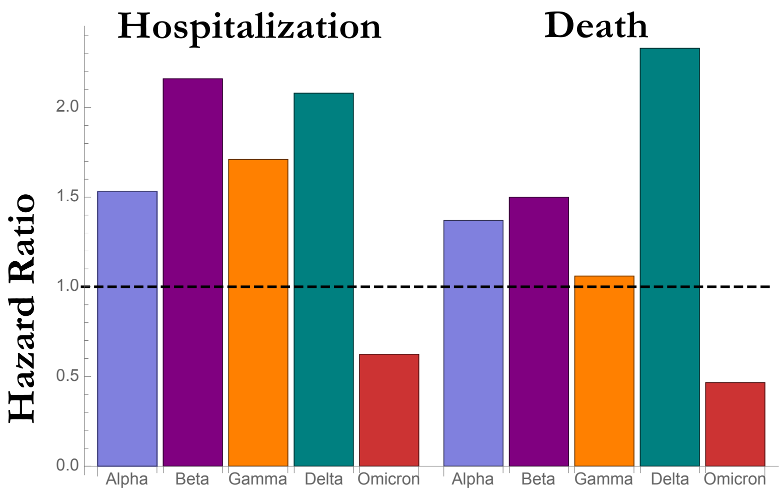


Current Biology

Day et al. (2020)

Based on:
Lin et al. (2022) for Alpha, Beta, Gamma, Delta vs wildtype
Nyberg et al. (2022) for Omicron vs Delta (rescaled using above to wildtype)

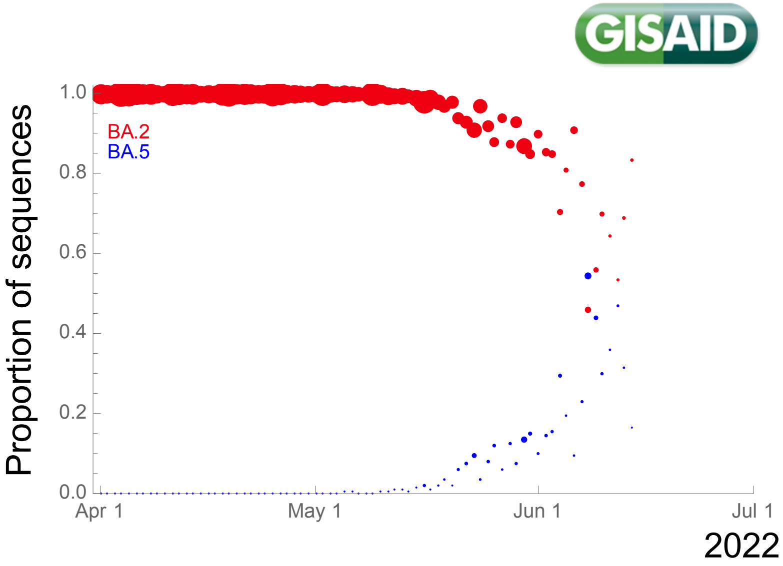
Evolution in action

We can estimate selection using classical population genetics models for the change in frequency (p) of a variant due to selection (s):

$$\frac{dp}{dt} = s\,p\,(1-p)$$

which can be solved:

$$p_t = \frac{e^{st}\,p_0}{1-p_0+e^{st}\,p_0}$$



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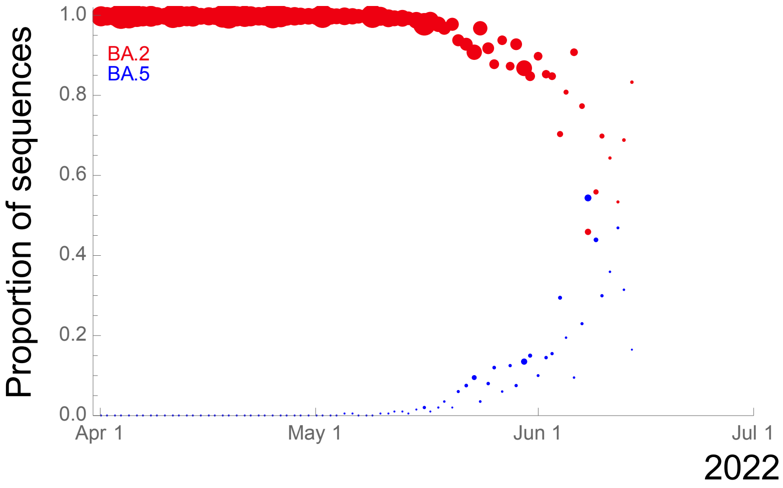
with n_t sequences at time t and an observed number of each type (j, k), the likelihood of observing the data is binomial:

$$\text{likelihood}(data_t) = \binom{n_t}{j}\, p_t^j\, (1 - p_t)^k$$

$$\ln L(all\ data) \propto \textstyle\sum_t j \ln(p_t) + k \ln(1 - p_t)$$



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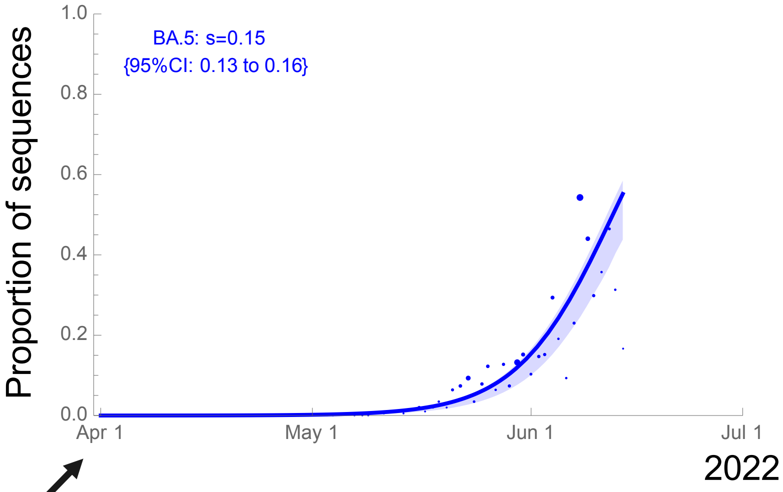

Estimate selection by maximizing the likelihood

Plus: get CI & allow for multiple variants

Evolution in action

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$$\frac{dp}{dt} = s\,p\,(1-p)$$

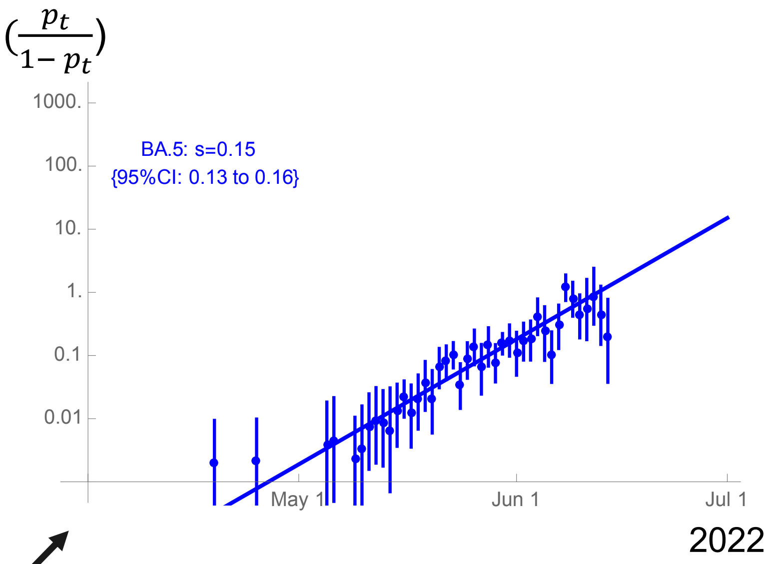
which can be solved:

$$p_t = \frac{e^{st}\,p_0}{1 - p_0 + e^{st}\,p_0}$$

Or rearrange:

$$\text{Step 1: } \frac{p_t}{1-p_t} = \frac{e^{st}\,p_0}{1-p_0}$$

$$\text{Step 2: } \ln\!\left(\frac{p_t}{1-p_t}\right) = s\,t + \ln\!\left(\frac{p_0}{1-p_0}\right)$$



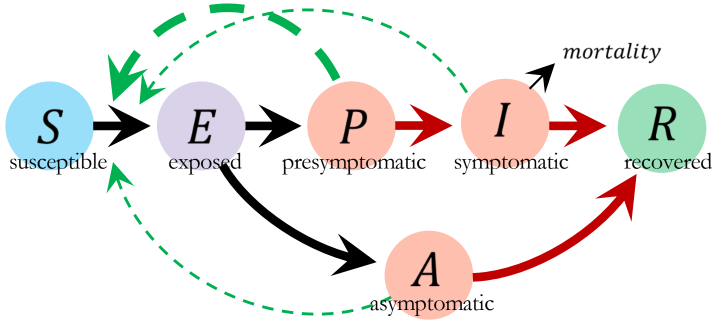
Predicts a linear relationship with constant slope *s* if selection is constant

SEAPIR Model

What selection pressures are acting on SARS-CoV-2?

$$\frac{d\lambda}{dz} = \boxed{S\, v_E \,(\Delta\beta_P\, u_P + \Delta\beta_I\, u_I + \Delta\beta_A\, u_A)} - (\Delta\alpha + \Delta\kappa_I)\, u_I v_I - \Delta\kappa_A\, u_A v_A - \Delta f\ \kappa_E\, u_E\, \{v_P - v_A\}$$
$$+ \Delta\kappa_E\, u_E\, \{(v_P(1-f) + f\, v_A) - v_E\} - \Delta\kappa_P\, u_P\, \{v_P - v_I\}$$

Selection should weaken for a variant that increases transmission
if susceptibles are protected and/or transmission is limited.



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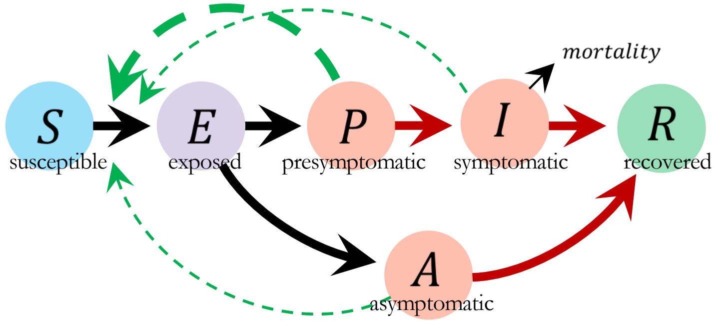

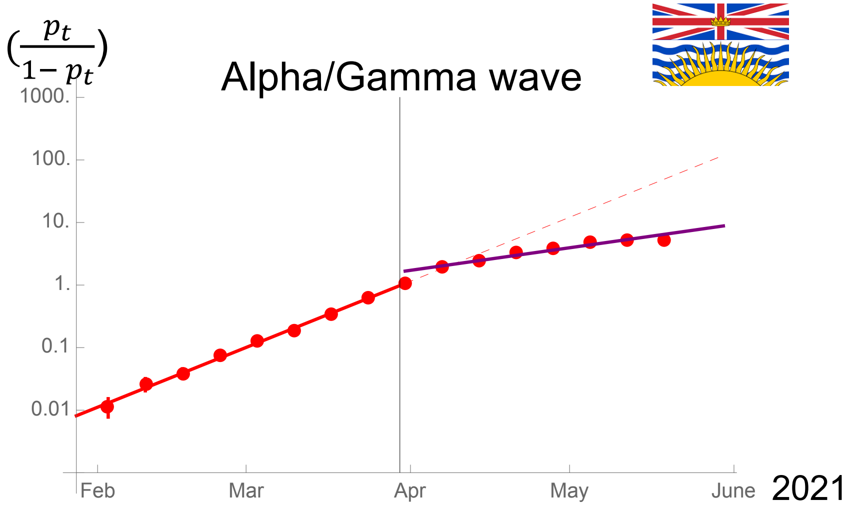

BC's 'circuit breaker' on 30 March 2021

(vertical line: closing indoor dining, gym closures, travel within the province restricted; See Otto et al. 2022 Current Biology)

SEAPIR Model

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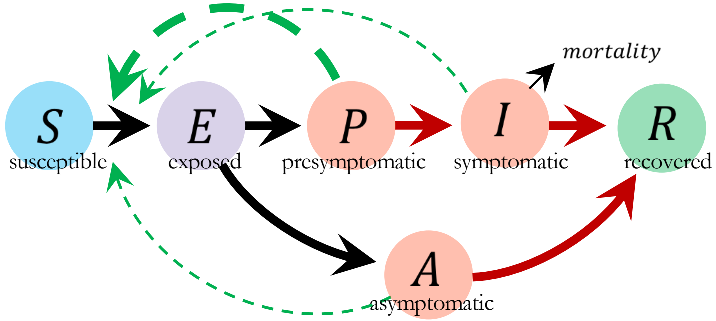
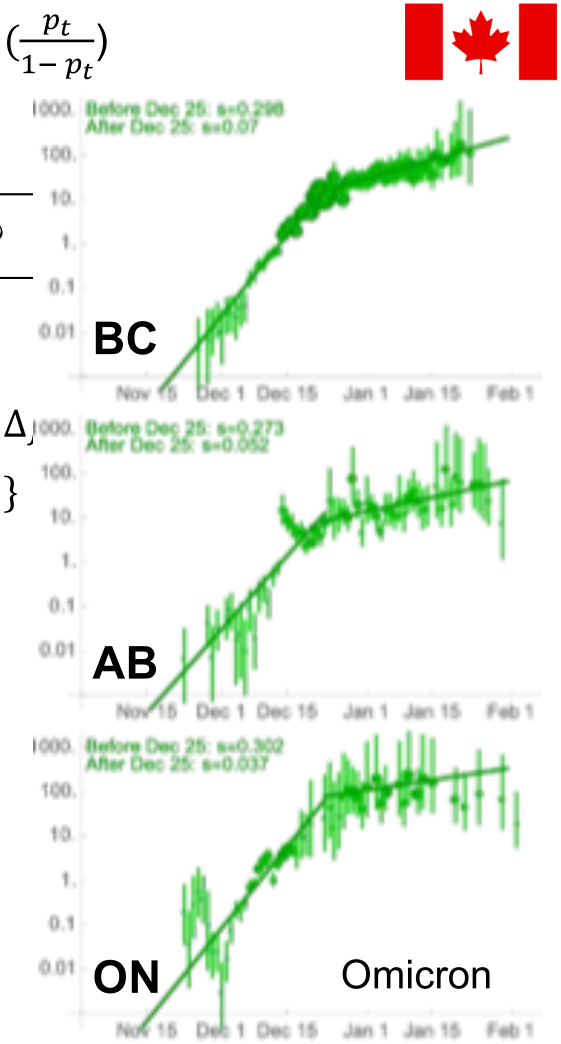


Collective concern

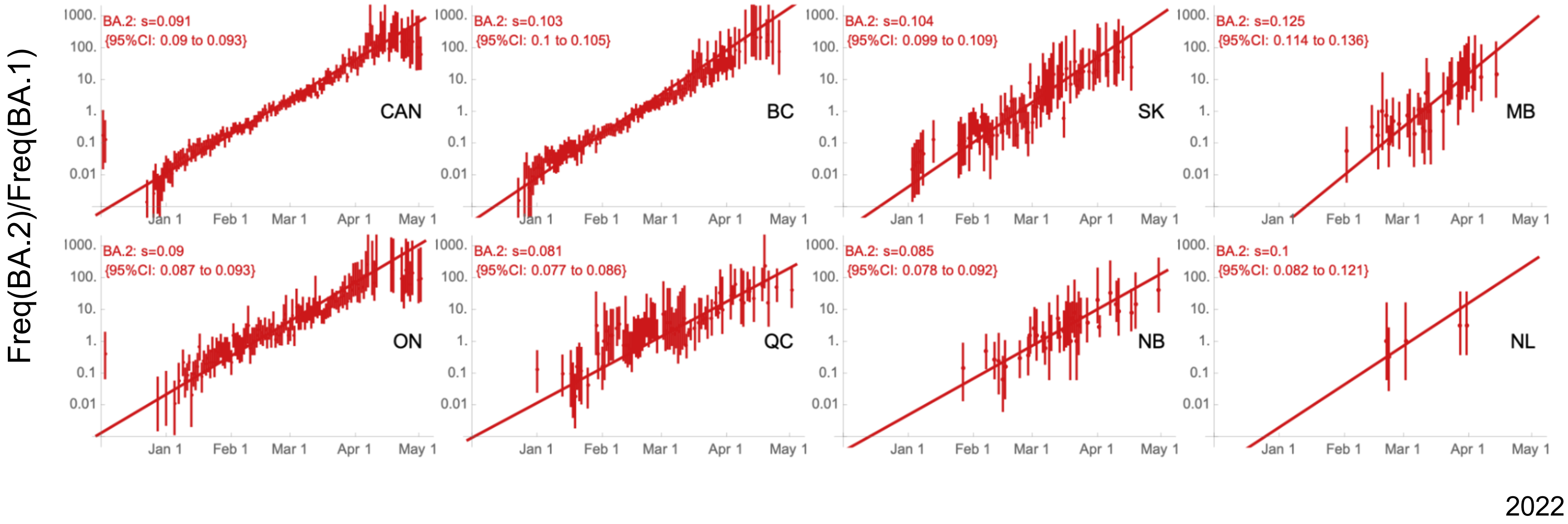


2022

BC COVID-19 Modelling Report (Feb 17, 2022)

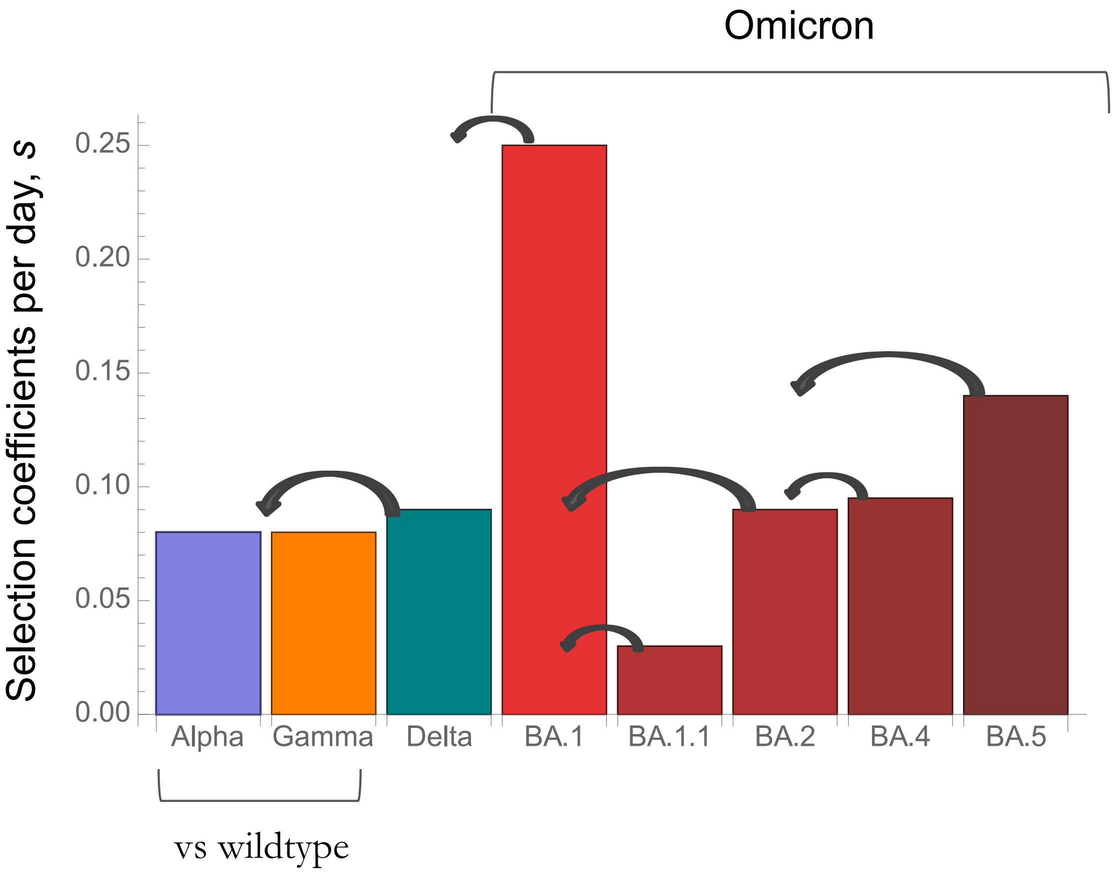
Evolution in action

Omicron’s BA.2 vs BA.1



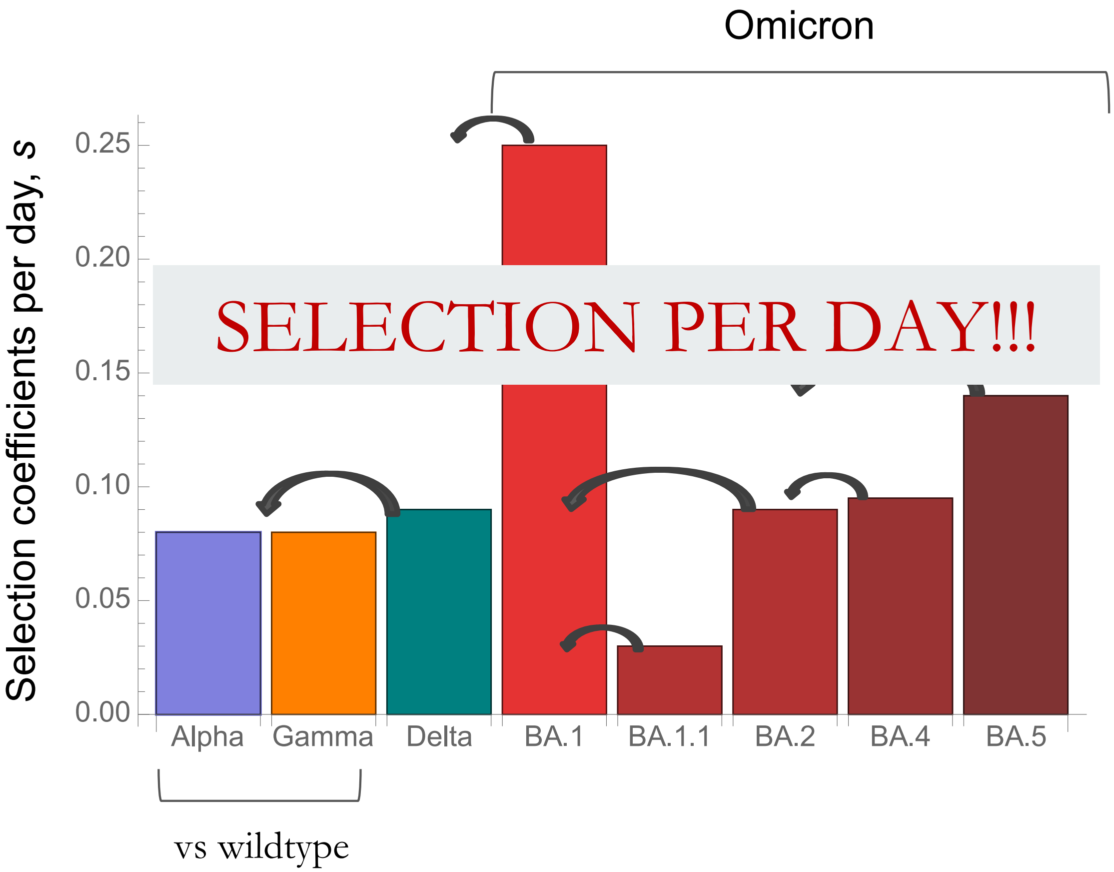
BC COVID-19 Modelling Report (May 18, 2022)

Evolution in action



BC COVID-19 Modelling Report
(2June2021, 6August2021, 17Feb2022, 18May2022, next one)

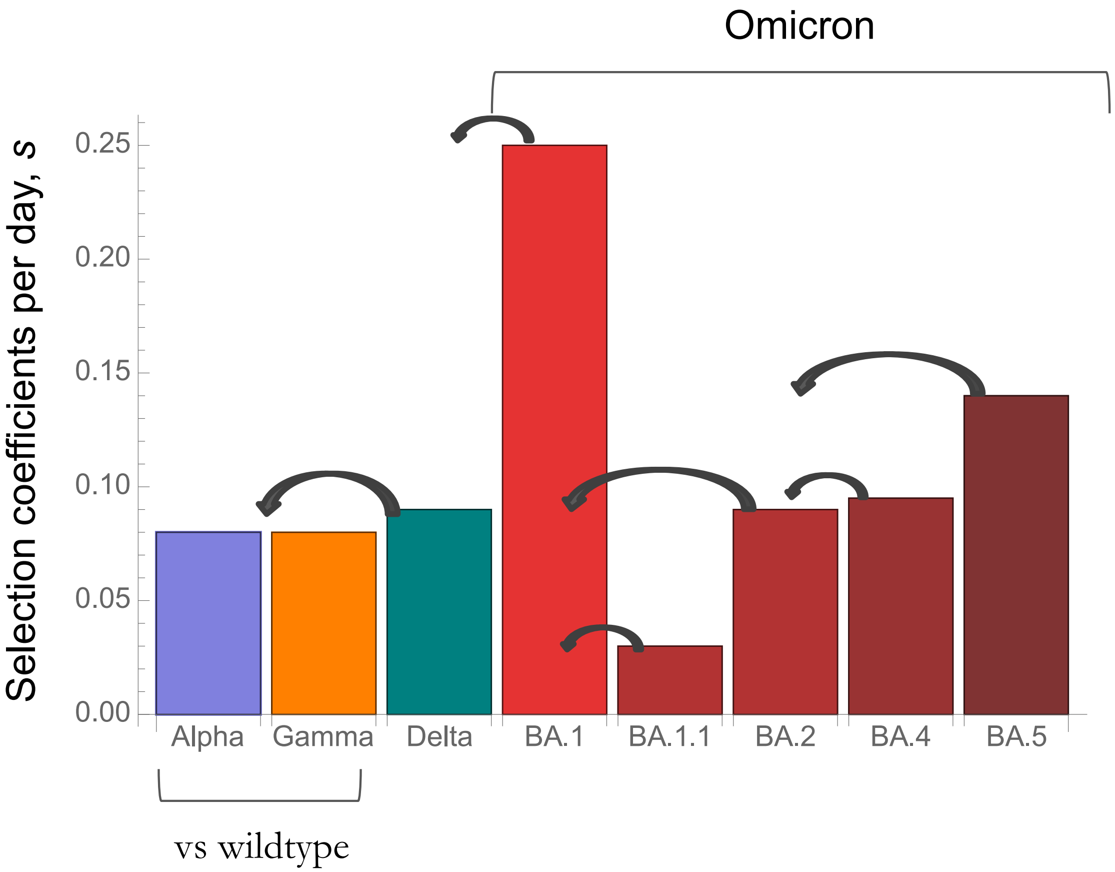
Evolution in action



SELECTION PER DAY!!!

BC COVID-19 Modelling Report
(2June2021, 6August2021, 17Feb2022, 18May2022, next one)

Evolution in action



Days to double in frequency relative to reference strain

s = 25% → 2.7 days

s = 15% → 4.6 days

s = 10% → 7 days

s = 5% → 14 days

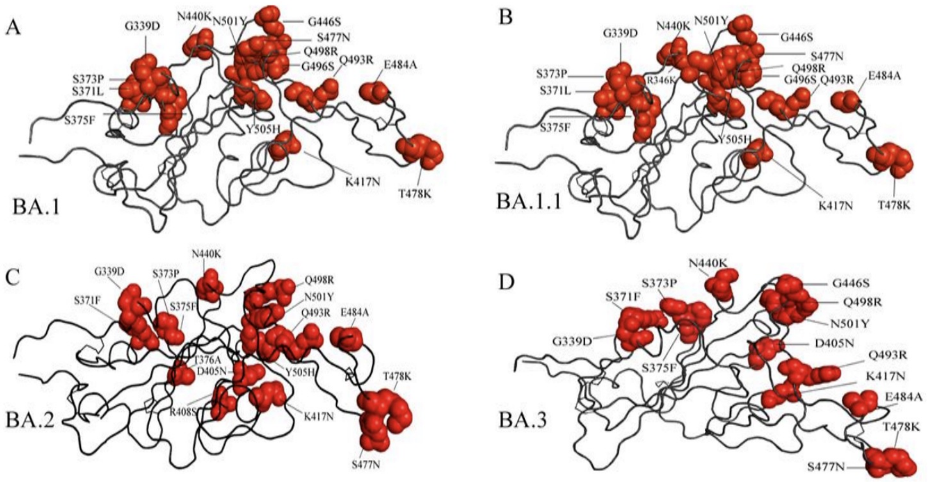
s = 1% → 70 days

BC COVID-19 Modelling Report
(2June2021, 6August2021, 17Feb2022, 18May2022, next one)

Omicron: First major VOC to evade immunity

Three times more spike mutations than all other VOC had when they arose.

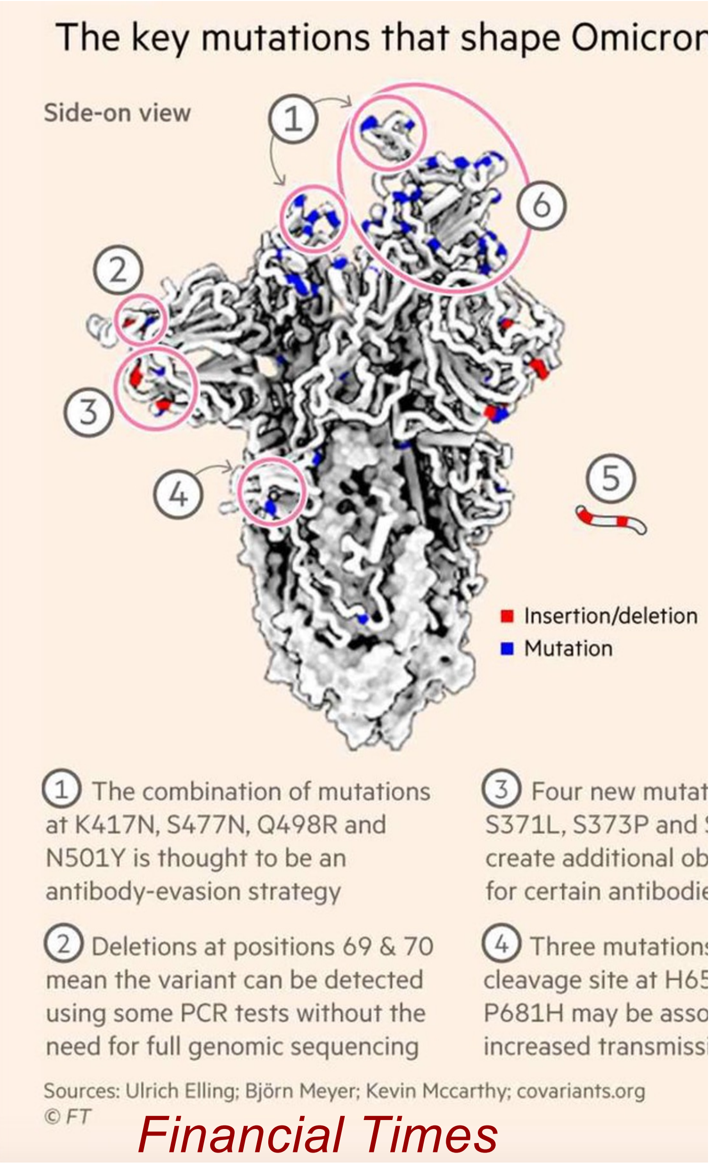
Many mutations are known or predicted to reduce efficacy of neutralizing antibodies and increase ACE2 binding.



Receptor Binding Domain

with residue mutated relative to the wild-type

Kumar et al. (2022) J Med Vir



The key mutations that shape Omicron

① The combination of mutations at K417N, S477N, Q498R and N501Y is thought to be an antibody-evasion strategy

② Deletions at positions 69 & 70 mean the variant can be detected using some PCR tests without the need for full genomic sequencing

③ Four new mutat S371L, S373P and create additional ob for certain antibodie

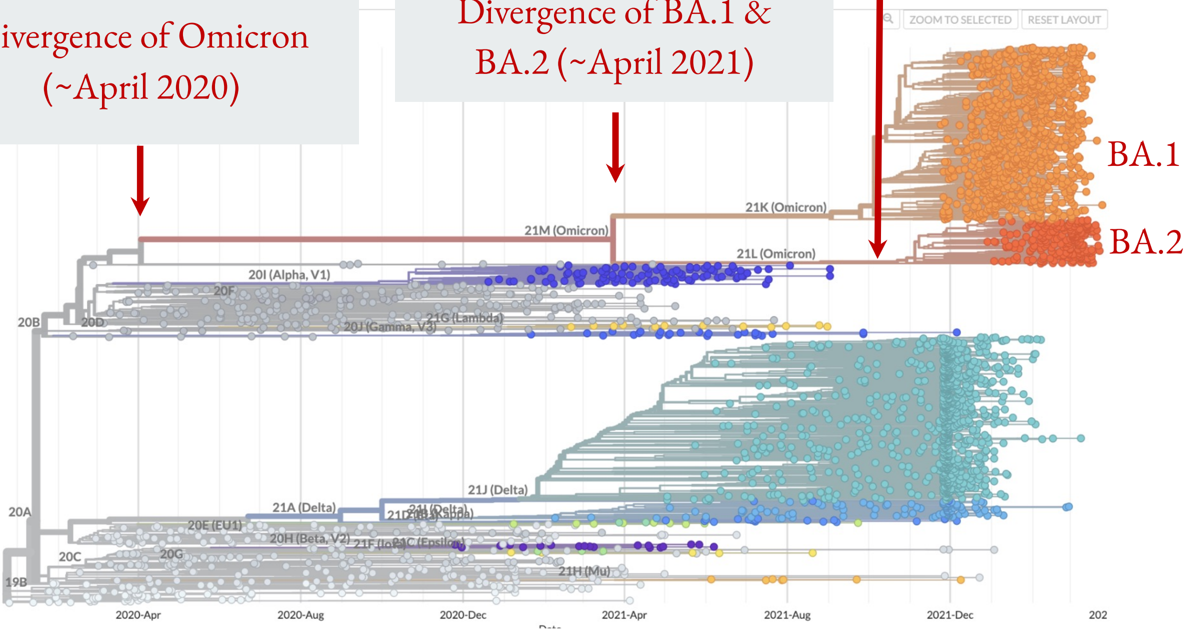
④ Three mutations cleavage site at H65 P681H may be asso increased transmissi

Sources: Ulrich Elling; Björn Meyer; Kevin Mccarthy; covariants.org

Financial Times

Omicron

First detected in mid-November 2021[1], Omicron shows a substantially older evolutionary history, diverging from other VOC near the beginning of the pandemic.



Divergence of Omicron (~April 2020)

Divergence of BA.1 & BA.2 (~April 2021)

Divergence of BA.4 & BA.5 (~October 2021)[2]

Nextstrain

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[1] Viana et al. (2022)
[2] Tegally et al. (2022)

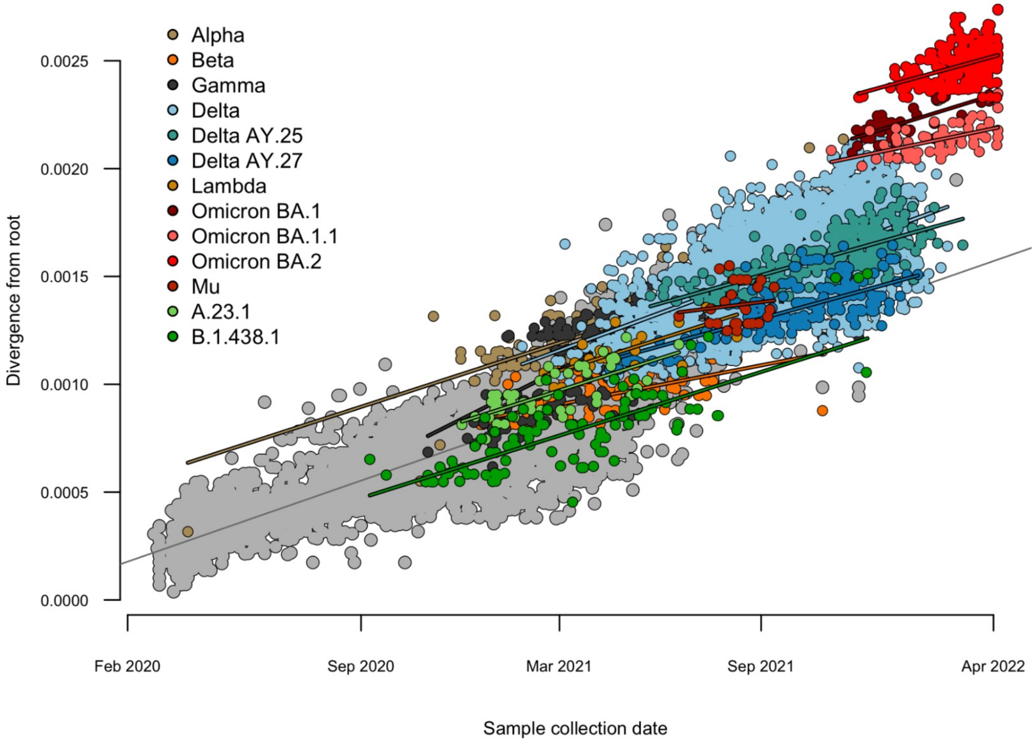
Omicron Sub-Lineages

Coronavirus Variants Rapid Response Network
Réseau de réponse rapide aux variants du coronavirus

The mutation rates per unit time (slopes) are similar, but Omicron appears to have had a history of elevated mutation (a pulse raising the intercept).

Unusual evolutionary features of Omicron:

- more than expected number of mutations
- disproportionate number of changes in spike
- a long period of evolutionary divergence "out of sight" of global surveillance
- evidence that recombination was involved[1,2] in the generation of at least one of BA.1-BA.5



[Source: Art Poon]

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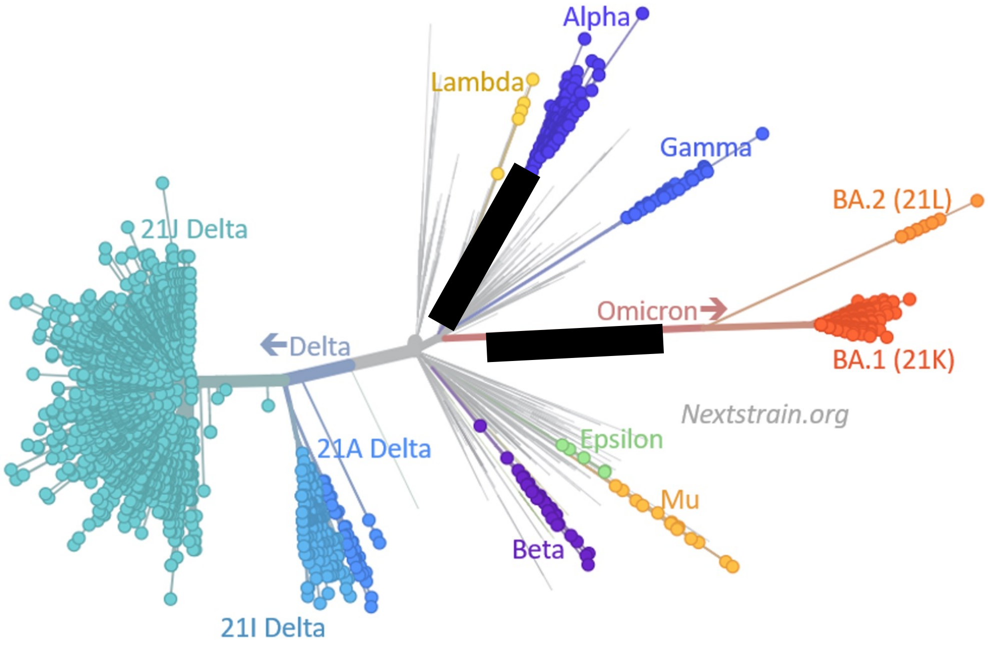
[1] Viana et al. (2022)
[2] Tegally et al. (2022)

Unusual evolutionary features of VOC



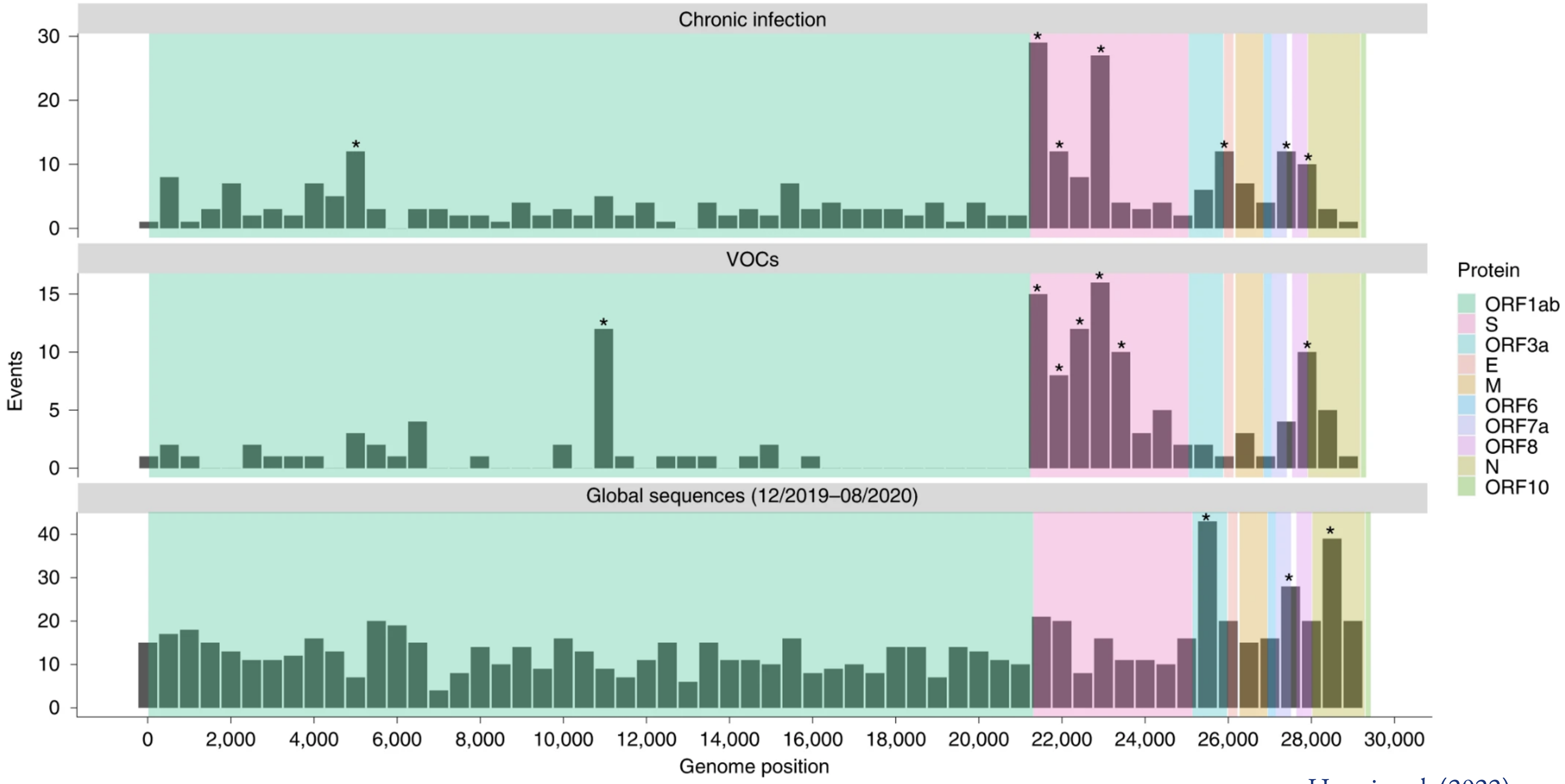
Black box: Passage through immunocompromised individual(s) with persistent infections[1] may account for these unusual features:

- High and prolonged viral replication (more mutations)
- Relaxed and/or altered immune environment, allowing mutations to accumulate in antigenic regions
- Hidden from surveillance efforts
- Higher potential for recombination[2]

[1] e.g., 335 days in a lymphoma patient; >9 months in an HIV patient

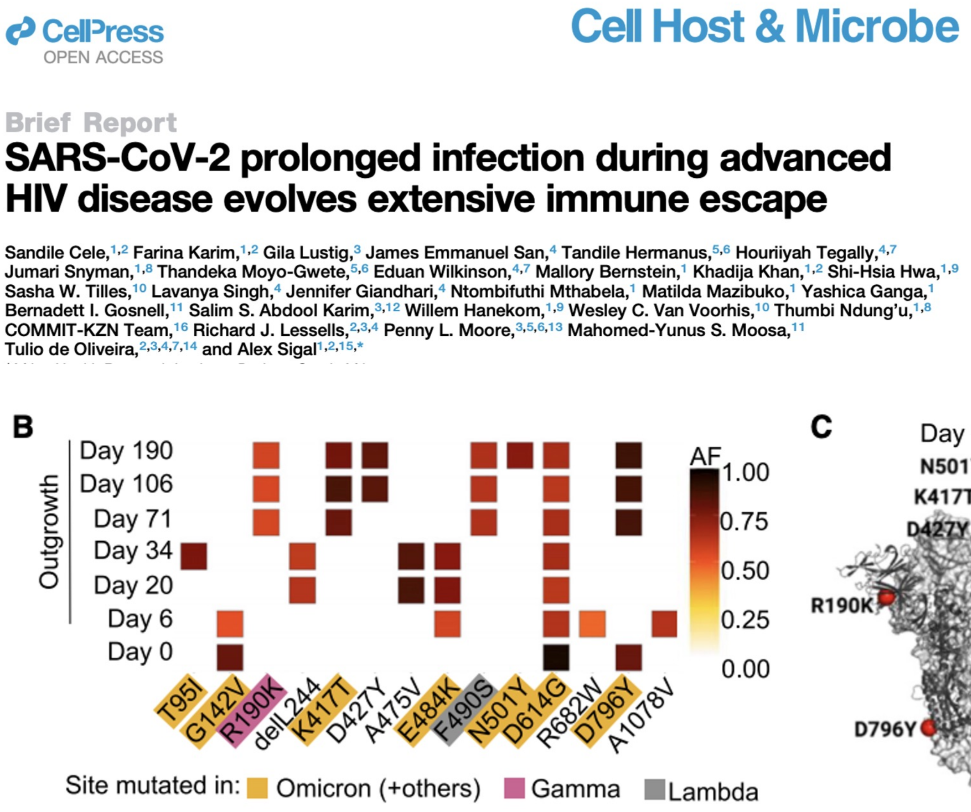
[2] Recombination detected in a lymphoma patient infected for 14 months, initially infected with B.1.160 then with Alpha (Burel et al.)

Unusual evolutionary features of VOC



Harari et al. (2022)

Unusual evolutionary features of VOC



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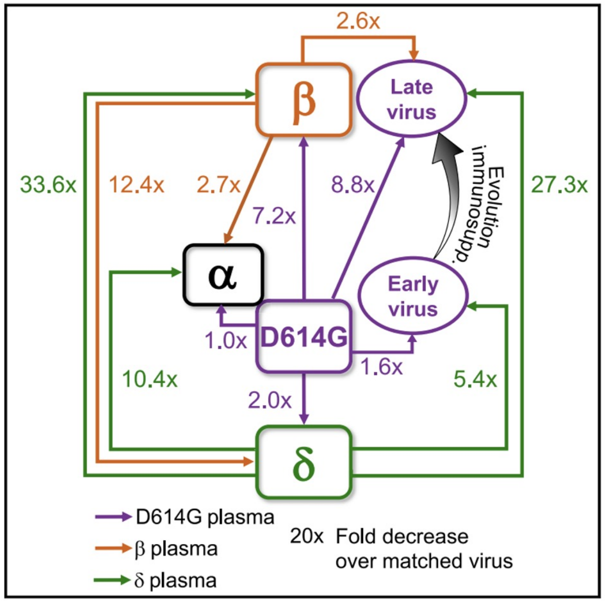
Cell Host & Microbe

Brief Report

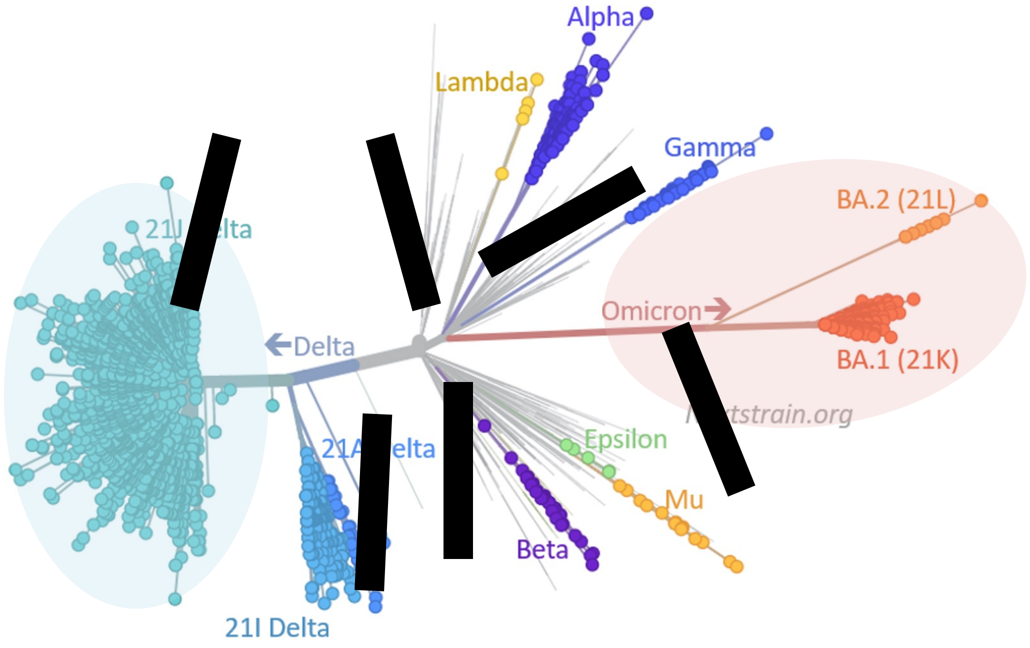
SARS-CoV-2 prolonged infection during advanced HIV disease evolves extensive immune escape

Sandile Cele,[1,2] Farina Karim,[1,2] Gila Lustig,[3] James Emmanuel San,[4] Tandile Hermanus,[5,6] Houriiyah Tegally,[4,7] Jumari Snyman,[1,8] Thandeka Moyo-Gwete,[5,6] Eduan Wilkinson,[4,7] Mallory Bernstein,[1] Khadija Khan,[1,2] Shi-Hsia Hwa,[1,9] Sasha W. Tilles,[10] Lavanya Singh,[4] Jennifer Giandhari,[4] Ntombifuthi Mthabela,[1] Matilda Mazibuko,[1] Yashica Ganga,[1] Bernadett I. Gosnell,[11] Salim S. Abdool Karim,[3,12] Willem Hanekom,[1,9] Wesley C. Van Voorhis,[10] Thumbi Ndung'u,[1,8] COMMIT-KZN Team,[16] Richard J. Lessells,[2,3,4] Penny L. Moore,[3,5,6,13] Mahomed-Yunus S. Moosa,[11] Tulio de Oliveira,[2,3,4,7,14] and Alex Sigal[1,2,15,*]

Example of an immunocompromised patient with persistent (190 day) COVID infection, which evolved substantial escape from neutralization.



Evolution: Emergence of new variants



Most mutations will arise in prevailing lineages:

- Increases in transmissibility & immune escape (e.g., BA.4 & BA.)

Major shifts may well arise outside of these lineages (less likely to elicit an immune response)

- Immunosuppressed individuals
- Human -> animal -> human zoonoses

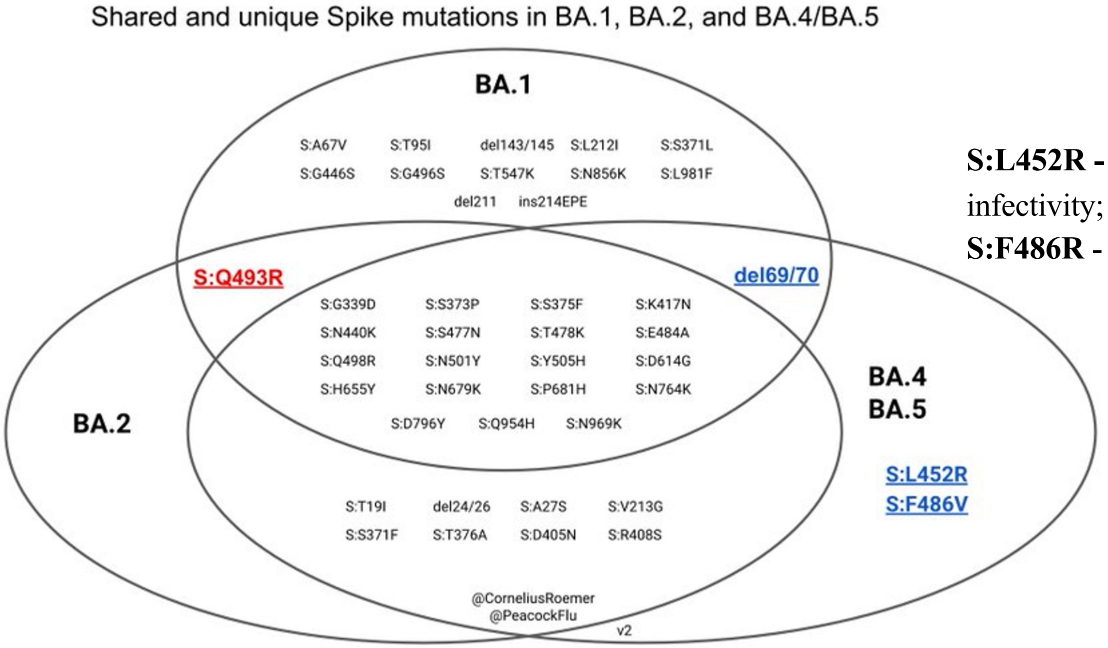
New variants may be more (e.g., Alpha and Delta) or less (e.g., Omicron) severe.

Globally: Since May 1, 2022, Delta (37), Alpha (2), and a variety of other non-VOC lineages remain in circulation (0.2%).

GISAID

Sub-variants BA.4 & BA.5

→ Very similar to BA.2, but called BA.4 and BA.5 because they lack some of the mutations characteristic of BA.2 (like S:Q493, NSP4 L438 and Orf6 D61). Diverged earlier?



S:L452R - increased ACE2 binding and infectivity; reduced antibody recognition

S:F486R - a key site for evasion of antibodies

Tegally et al. (2022)

Omicron Sub-Lineages

covSPECTRUM

Enabled by data from GISAID

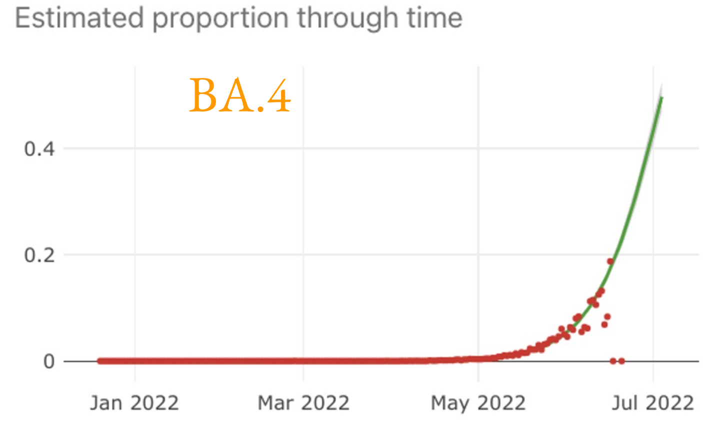
Early data from South Africa suggests an 8% per day selective advantage for BA.4 and 12% for BA.5 (Tegally et al. 2022), relative to BA.2.

Spread may result from a combination of **higher inherent transmissibility** and **immune evasion** (Khan et al. 2022; Hachmann et al.).

Together, BA.4 & BA.5 are estimated to comprise >70% of global sequences by today

Global proportion

Estimated proportion through time



s = 9% per day

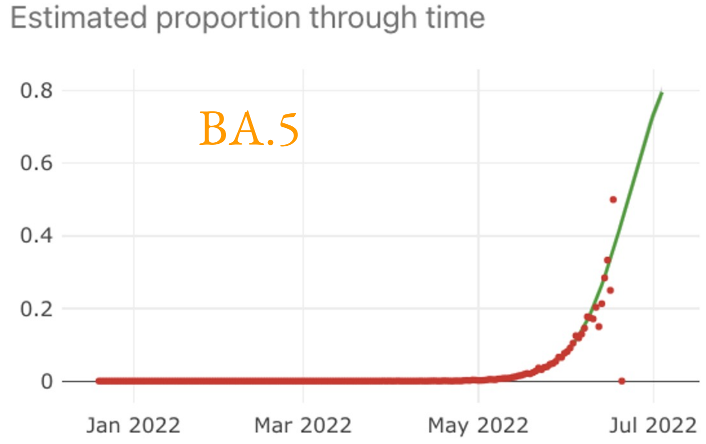
83% per week

Current adv.

79-86%

Confidence int.

Estimated proportion through time



s = 12% per day

122% per week

Current adv.

117-126%

Confidence int.

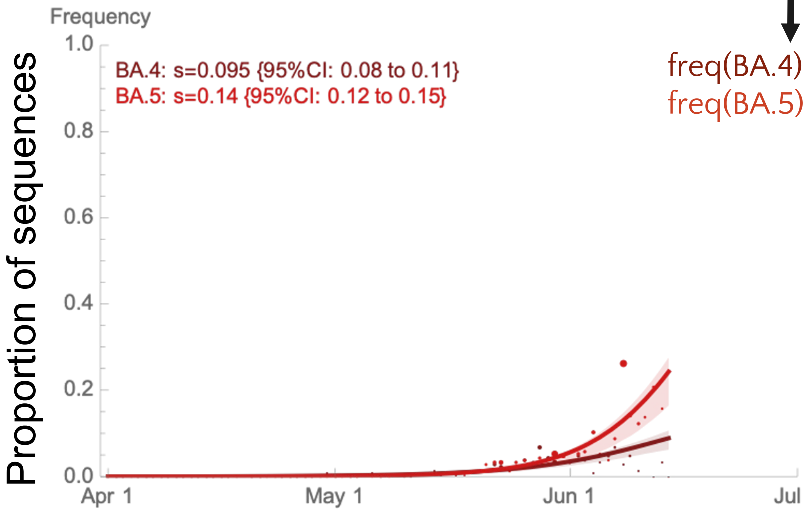
Omicron sub-lineages in Canada

GISAID data shared by Public Health labs across Canada allow us to track the spread of Omicron sublineages over time.

→ BA.4 is spreading rapidly at a rate of s=9.5% per day relative to BA.2#

→ BA.5 is spreading slightly faster with s=14% per day relative to BA.2#

These lineages should now (or soon) dominate the COVID-19 picture in Canada.



July 1, 2022 projection

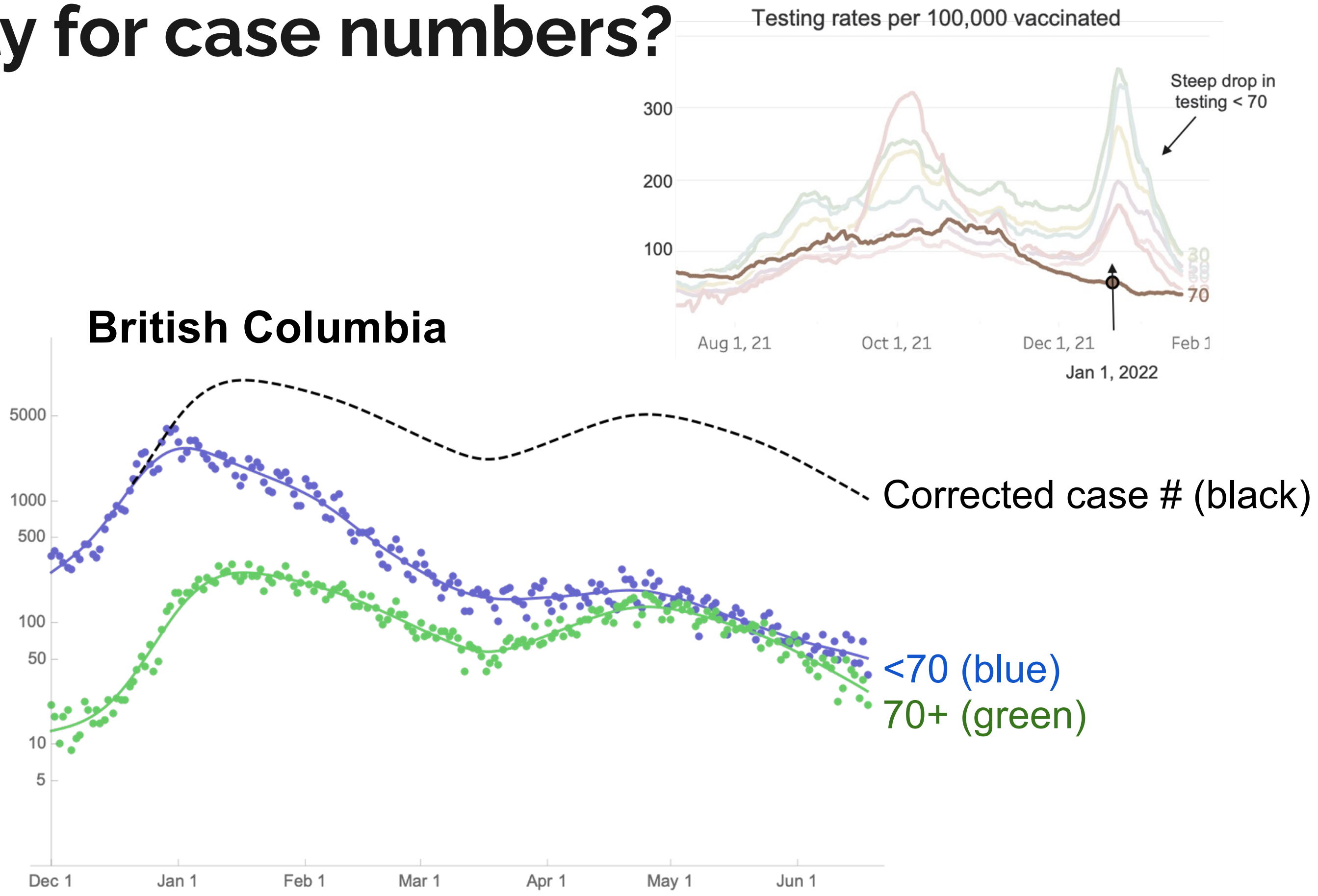
freq(BA.4): 13%
freq(BA.5): 69%

Source (S. Otto) Canadian metadata was downloaded from GISAID for the Omicron GRA clades (Alberta sequences were removed as AB first identifies variants and preferentially sequences some subtypes). A model of selection was fit to the numbers of each type using maximum likelihood based on a trinomial distribution given the expected frequencies on each day. Hessian matrix used to obtain confidence intervals.

What does this imply for case numbers?

We'll use case numbers observed in individuals aged 70+ to assess trends, as they have been more consistently tested.

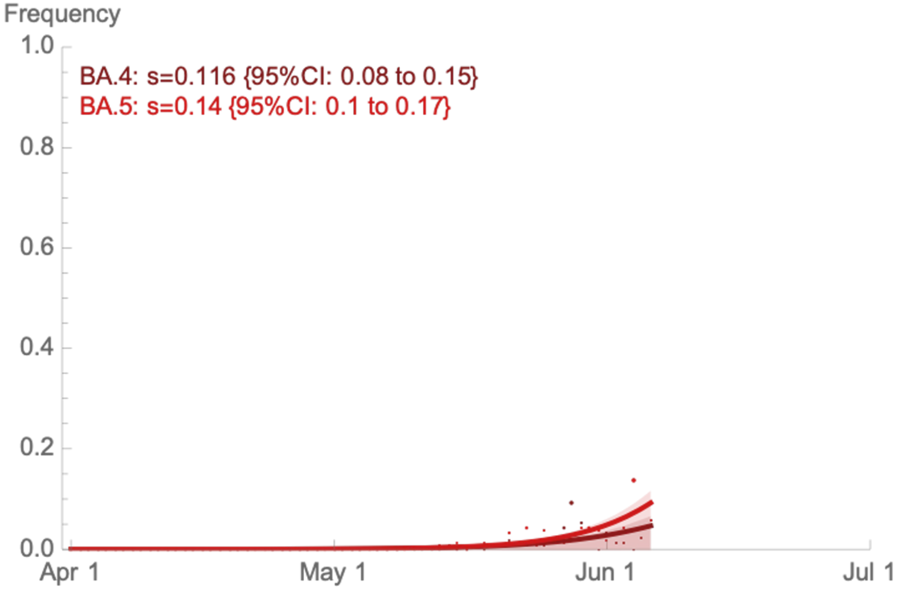
Cases among the 70+ age group are **significantly decreasing***.



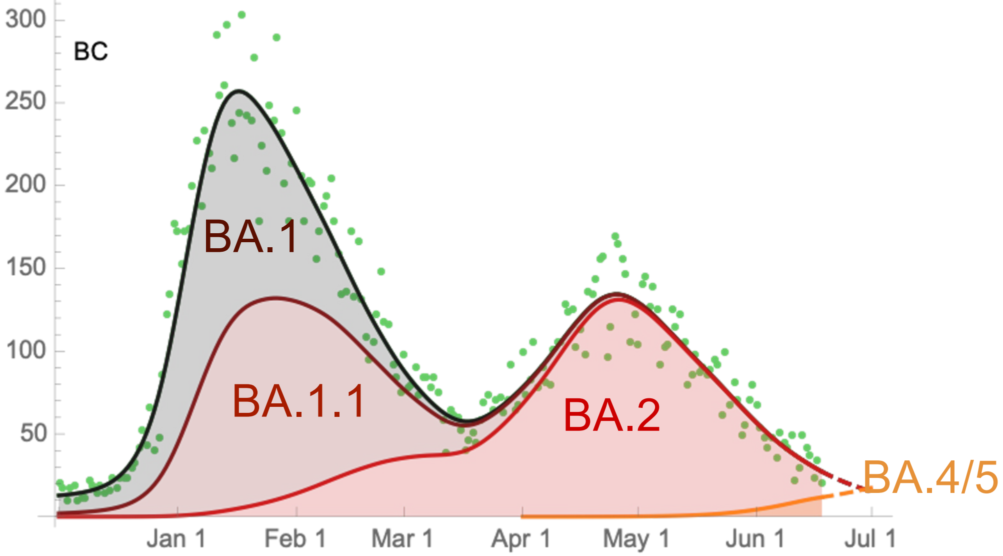
Source (S. Otto) New cases per day in 10-year age groups were downloaded from the BCCDC COVID-19 data portal. Cubic spline fits to log-case data were obtained (curves) for those 70+ (green) or <70 (blue). *Linear regression through log case counts among 70+ from last 14 days of data.

What does this imply for case numbers?

Fitting models of selection allows us to estimate frequency changes among variants.



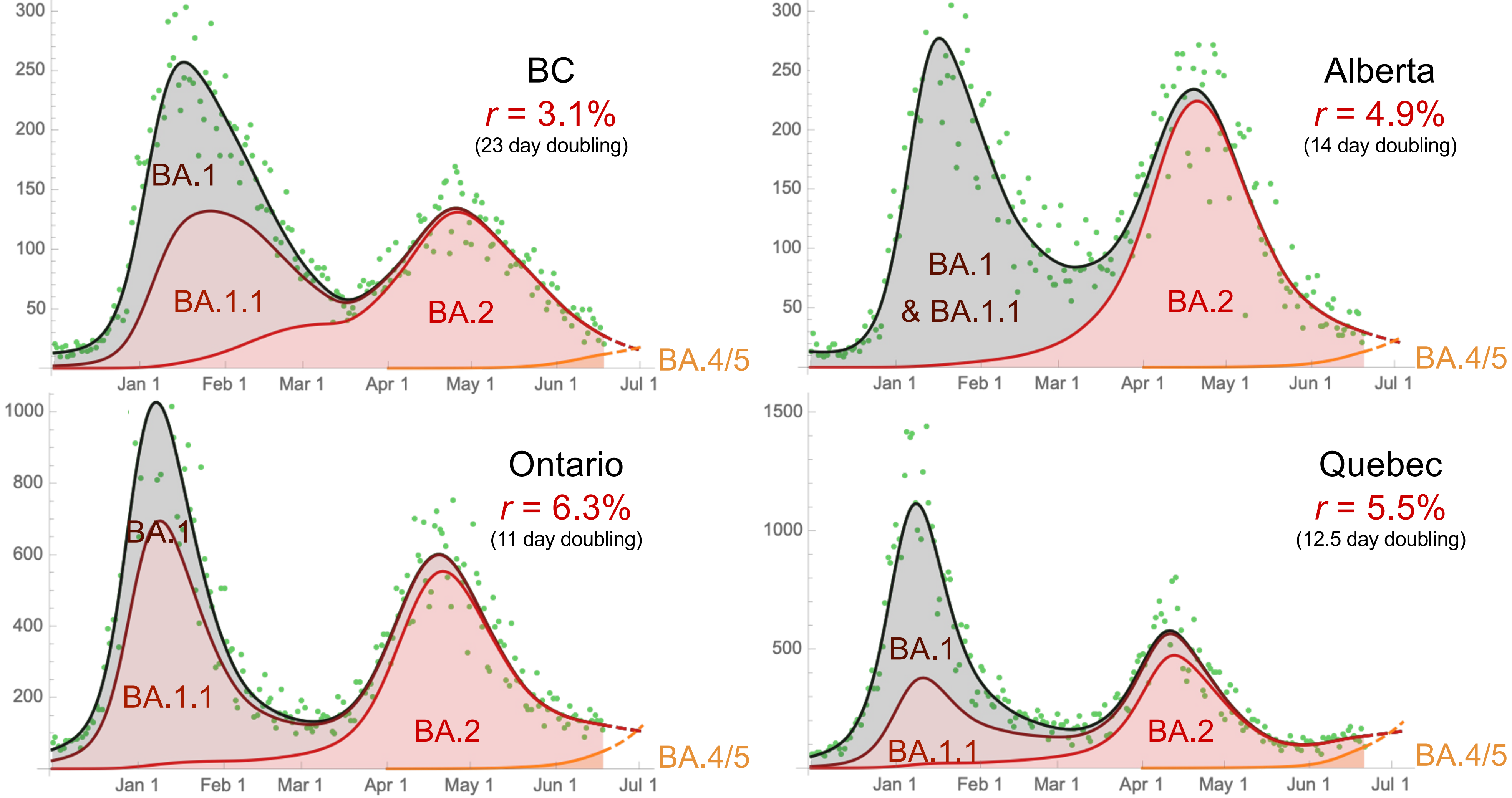
Multiplying by the # of cases in those over 70 allows us to **estimate** growth in numbers of each Omicron sublineage.



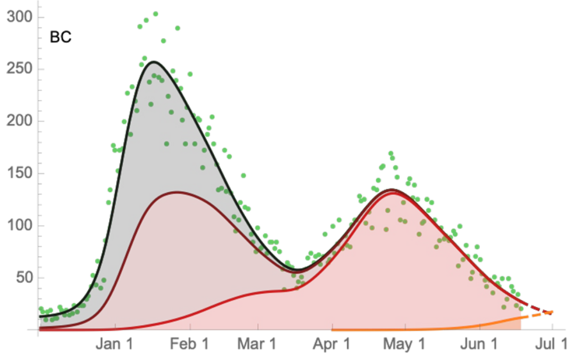
→ While numbers of BA.1 and BA.2 are declining, **estimated numbers of BA.4 & BA.5 (grouped together) are rising (*r* = +3.1%) in British Columbia.**

Source (S. Otto) Canadian metadata was downloaded from GISAID for the Omicron GRA clades. A model of selection was fit to the numbers of each type using maximum likelihood based on a trinomial distribution given the expected frequencies on each day. Hessian matrix used to obtain confidence intervals.

Daily growth rates



The Third Omicron Wave

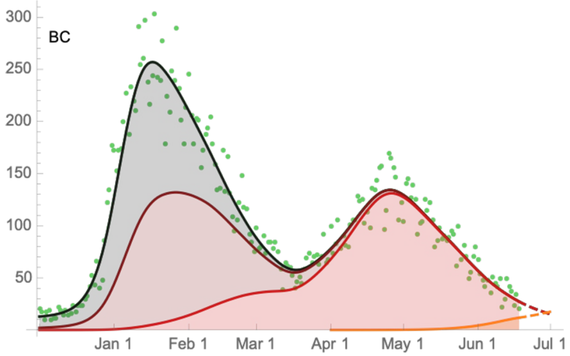


The above projections indicate that **case numbers should start rising around July 1**, driven by a BA.4 & BA.5 wave.

This third Omicron wave should **peak about 4-8 weeks** afterwards.

Fairly high confidence

The Third Omicron Wave



The above projections indicate that **case numbers should start rising around July 1**, driven by a BA.4 & BA.5 wave.

This third Omicron wave should **peak about 4-8 weeks** afterwards.

Fairly high confidence

The **height & impact of this peak is challenging to predict**, depending on the interplay of many factors:

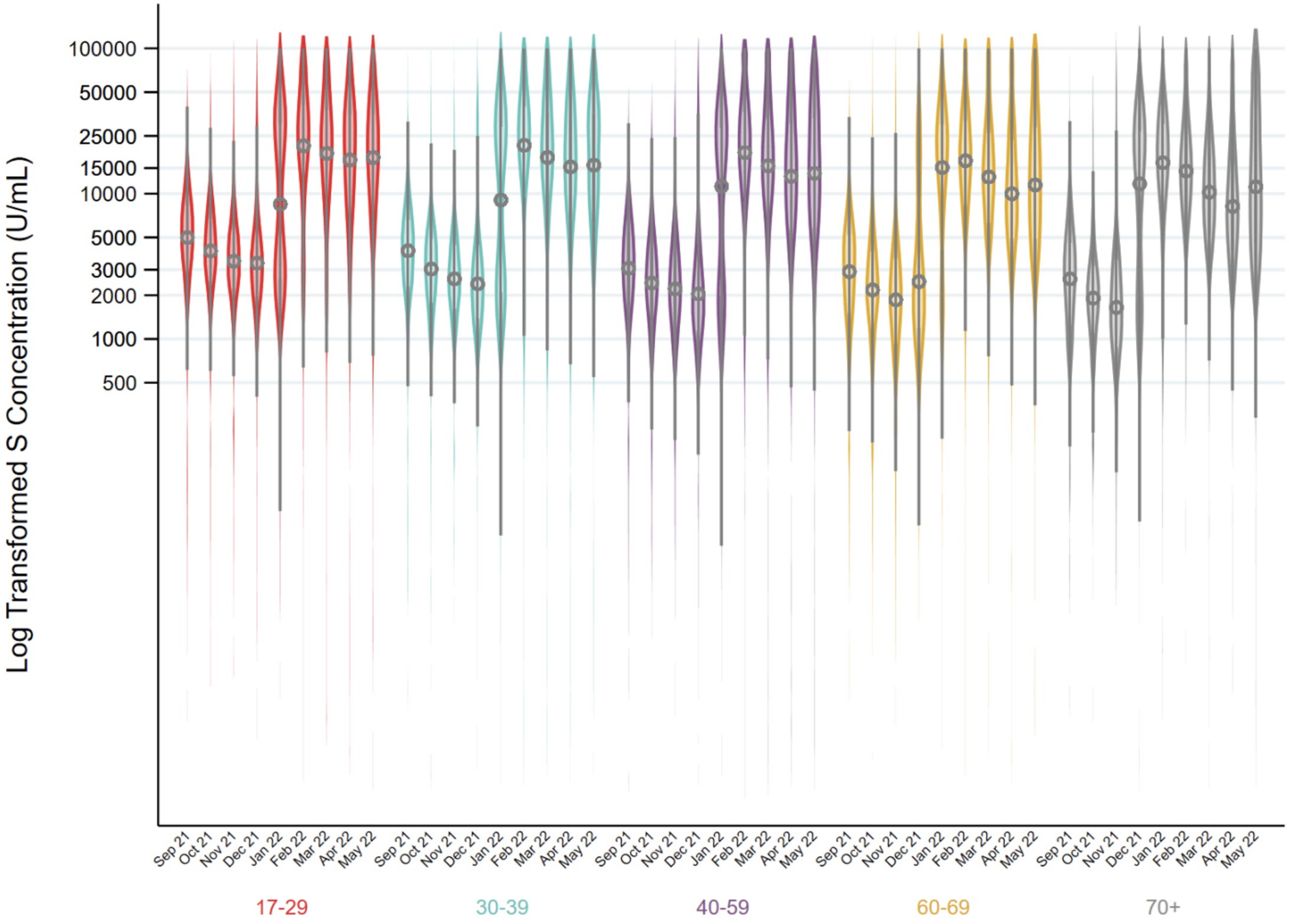
1. **Antibody levels**
2. **Efficacy of neutralizing antibodies**
3. **Virulence** of BA.4 & BA.5
4. **Public health measures**

No confidence

Factors determining the height of the BA.4/BA.5 wave

1. Antibody levels

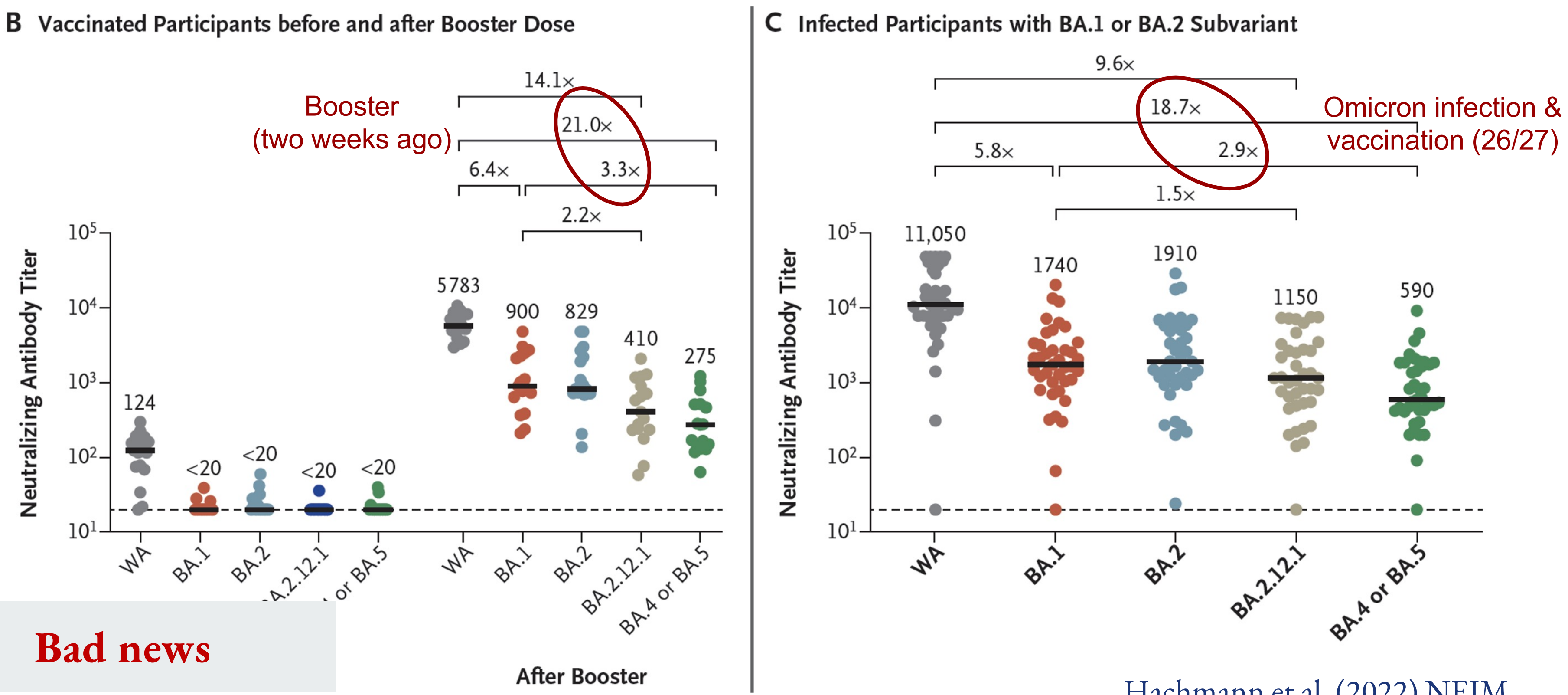
The COVID-19 Immunity Task Force & Canadian Blood Services data suggests high standing levels of spike antibodies in all age groups (blood donations through mid-May 2022).



Good news

Factors determining the height of the BA.4/BA.5 wave

2. Efficacy of neutralizing antibodies: The ability of these antibodies to neutralize SARS-CoV-2 and prevent infection is substantially compromised for BA.4 & BA.5.



Booster (two weeks ago)

Omicron infection & vaccination (26/27)

Bad news

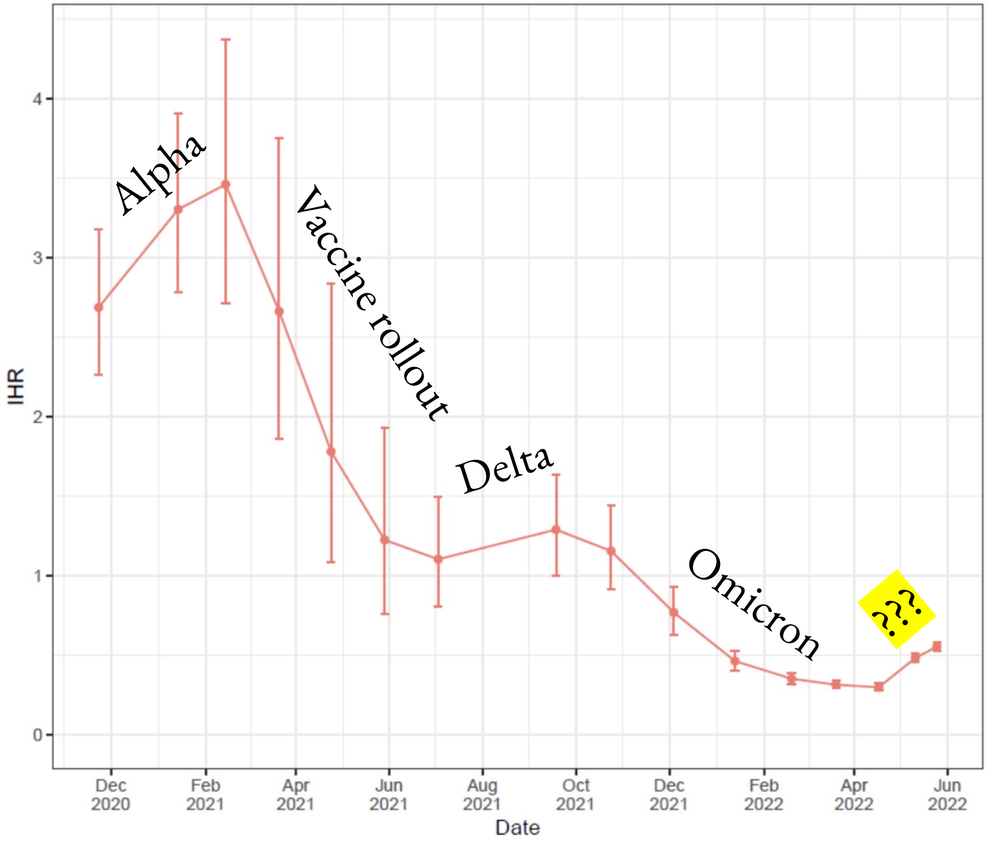
[Hachmann et al, (2022) NEJM](#)

Factors determining the height of the BA.4/BA.5 wave

3. Virulence: Currently have no clear indication of the relative virulence of BA.1-BA.5

In its 43 technical briefing, the UK Health Security Agency reported model estimates of hospitalization rate per infection (IHR) over time.

Recent data shows an uptick: BA.4 & BA.5 or waning immunity?

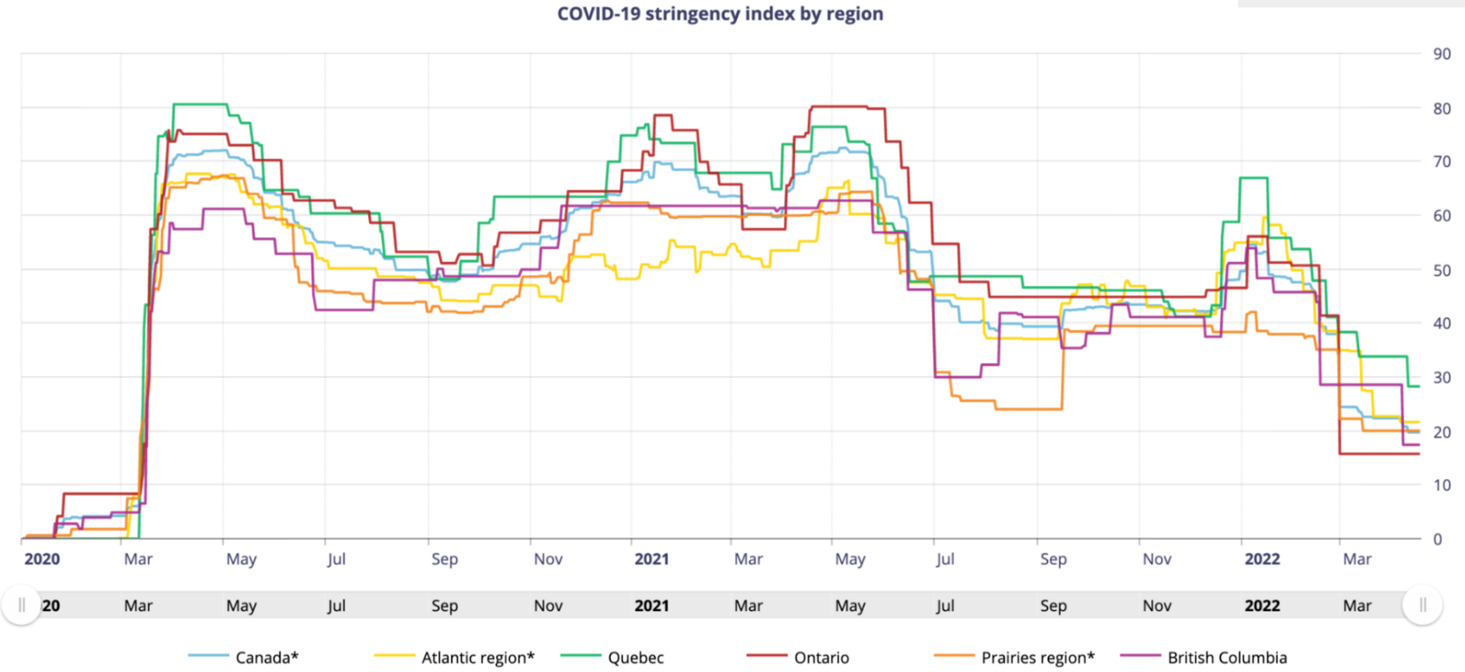


Uncertain news

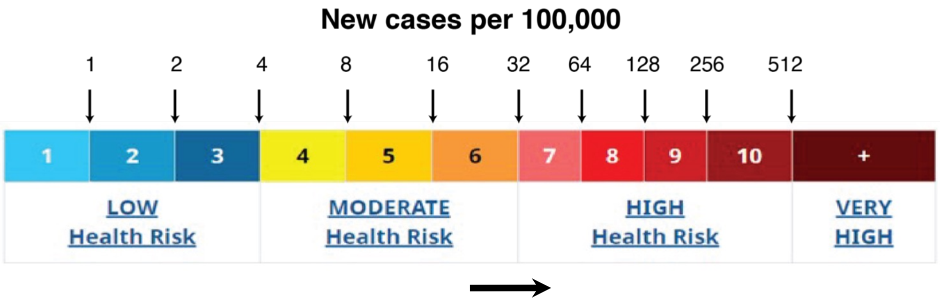
Factors determining the height of the BA.4/BA.5 wave

4. Public health measures: Lowest since the pandemic began and little appetite

BANK OF CANADA
BANQUE DU CANADA



Not great news



Prepare the public: We are at the start of the BA.4/BA.5 wave

Encourage boosters: Don't wait for the bivalent vaccines (Wuhan & Omicron)

- Omicron-specific booster from Moderna shows just a **slight** difference relative to prototype booster, which may have little real-world relevance to vaccine effectiveness (e.g., only 1.75 difference in neutralizing geometric mean titer ratio between boosting with mRNA-1273.214 vs mRNA-1273 [Moderna June 8 2022 press release].
- Prioritize bivalent vaccine for immunologically naive individual

Globally prioritize treatment of those suffering persistent infections

- 2-3% of population immunosuppressed
- 40M+ living with HIV/AIDS

The BC COVID-19 Modelling Group works on rapid response modelling of the COVID-19 pandemic, with a special focus on British Columbia and Canada.

The interdisciplinary group, working independently from Government, includes experts in epidemiology, mathematics, and data analysis from UBC, SFU, UVic, and the private sector, with support from the Pacific Institute for the Mathematical Sciences.

https://bccovid-19group.ca

Thank you

NSERC
CRSNG

UBC

Coronavirus Variants
Rapid Response
Network

Réseau de réponse
rapide aux variants
du coronavirus