The New York Times

R0, the Messy Metric That May Soon Shape Our Lives, Explained

'R-naught' represents the number of new infections estimated to stem from a single case. You may be hearing a lot about this.

The New York Times

Omicron's Radical Evolution

Thirteen of Omicron's mutations should have hurt the variant's chances of survival. Instead, they worked together to make it thrive.

SARS-CoV-2

Modelling in real time

Modelling to improve our understanding and to project future scenarios has contributed greatly to our collective knowledge during the COVID-19 pandemic.

Mathematical biology is the news, but what are these models? How are they made? How are they analysed? And how can they be interpreted and used?

SARS-CoV-2

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Biology 301 course goals

By the end of term, you will be able to:

- read and interpret models
- construct & analyse models
- simulate & predict using models

SARS-CoV-2

Modelling in real time

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Mathematical biology is the news, but what are these models? How are they made? How are they analysed? And how can they be interpreted and used?

Lecture goals

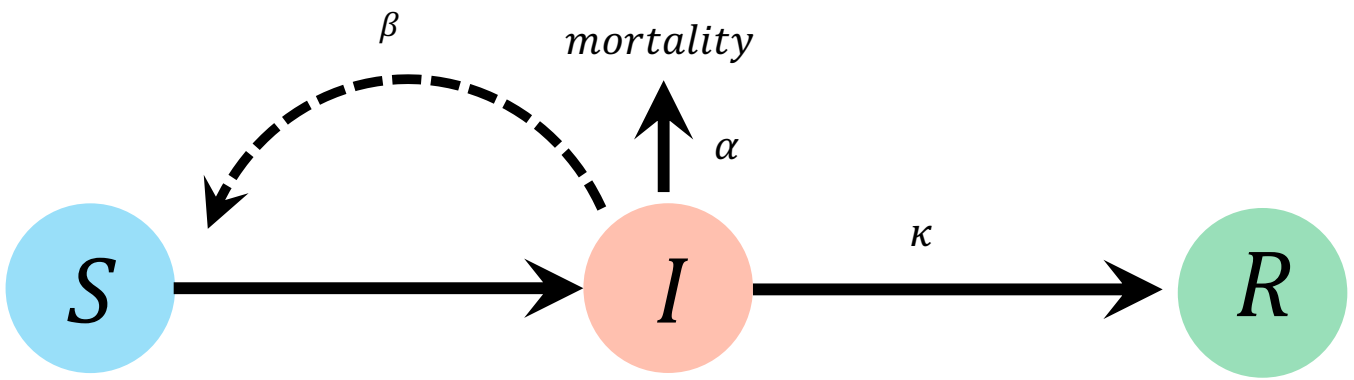
To illustrate modelling approaches that I've used during the COVID-19 pandemic and to give you a preview of techniques that you'll learn this term.

[This is for inspiration only; no need to memorize!!]

SIR Model

Variables
S: susceptible
I: infected (infectious)
R: recovered (not infectious)

Parameters
β: transmission rate
κ: recovery rate
α: mortality rate ("virulence")



$$\frac{dI}{dt} = \underbrace{\overbrace{\beta S I}^{\text{transmission}} - \overbrace{\kappa I}^{\text{recovery}} - \overbrace{\alpha I}^{\text{death}}}_{\text{rate of change in infections}}$$

When will a disease spread?

SIR Model

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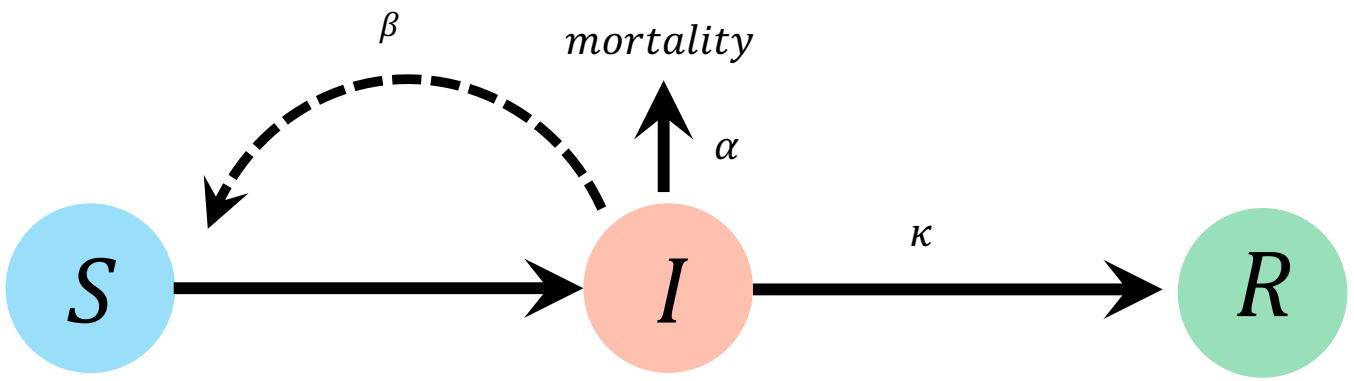
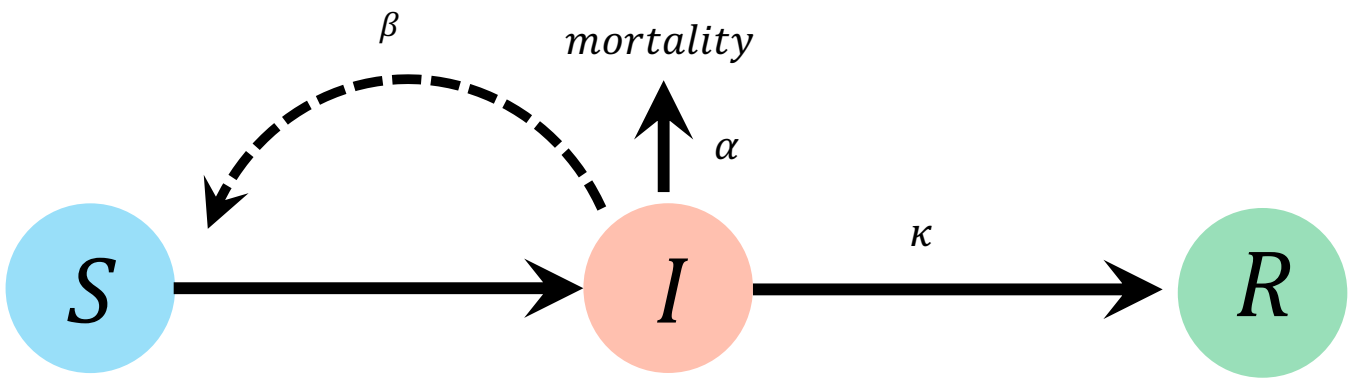


$$\frac{dI}{dt} = \underbrace{\overbrace{\beta S I}^{\text{transmission}} - \overbrace{\kappa I}^{\text{recovery}} - \overbrace{\alpha I}^{\text{death}}}_{\text{rate of change in infections}}$$

Derived by hand: when $R_0 = \frac{\beta}{\kappa+\alpha} > 1$ (defining S,I,R as proportions)

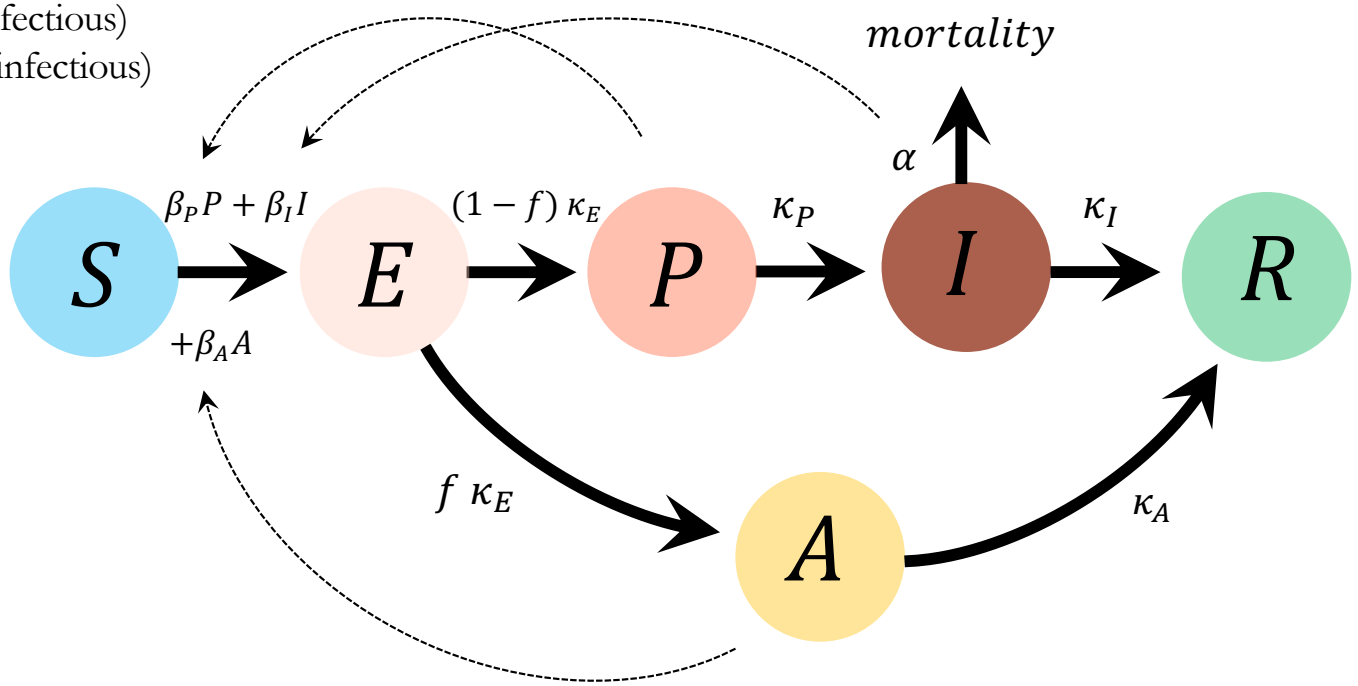
R_0: the expected number of new infections (β) over the infectious period of the disease ($\frac{1}{\kappa+\alpha}$) for a single infected individual in a fully susceptible population.

What about more realistic models for COVID-19?



Variables
S: susceptible
E: exposed (not infectious)
A: asymptomatic (less infectious)
P: pre-symptomatic (infectious)
I: symptomatic (infectious)
R: recovered (not infectious)

SEAPIR Model



R_0 ???

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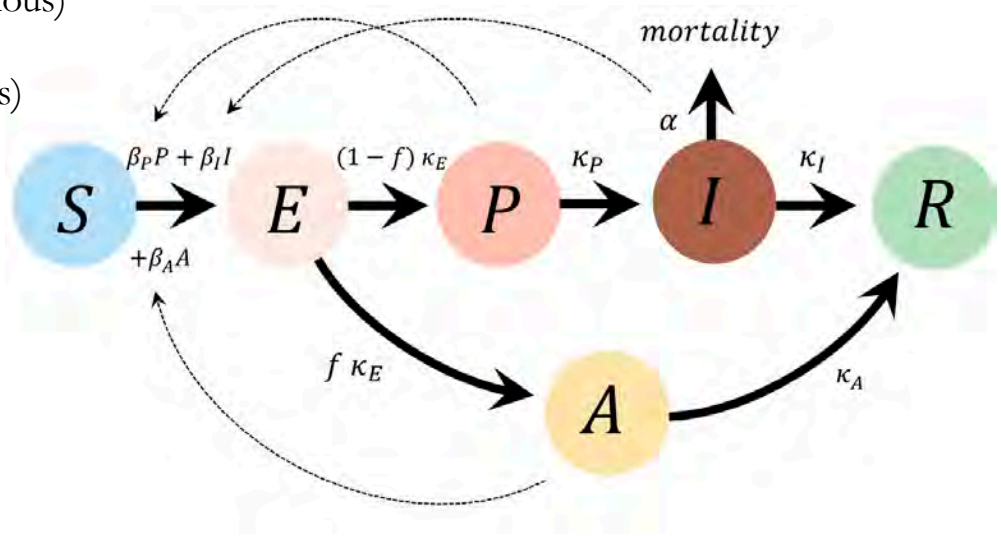


Derived by Maxima: $R_0 = f\left(\frac{\beta_A}{\kappa_A}\right) + (1-f)\left(\frac{\beta_P}{\kappa_P} + \frac{\beta_I}{\kappa_I+\alpha}\right)$ (defining S, E, A, P, I, R as proportions)

R_0: the expected number of births that occur during each phase of the infection, accounting for the fraction that go through the asymptomatic and the symptomatic routes.

SARS-CoV-2

Modelling in real time

Act 1: A Pandemic Tool

Act 2: An Evolving Pandemic

Act 3: Vaccines and Shifting Selection

→ Using tools from biology 301

SARS-CoV-2

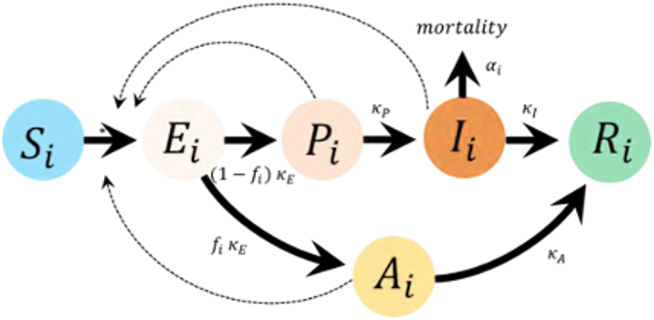
Modelling in real time

Act 1: A Pandemic Tool

Models allow exploration of alternative futures

The spread of SARS-CoV-2 depends on multiple factors:

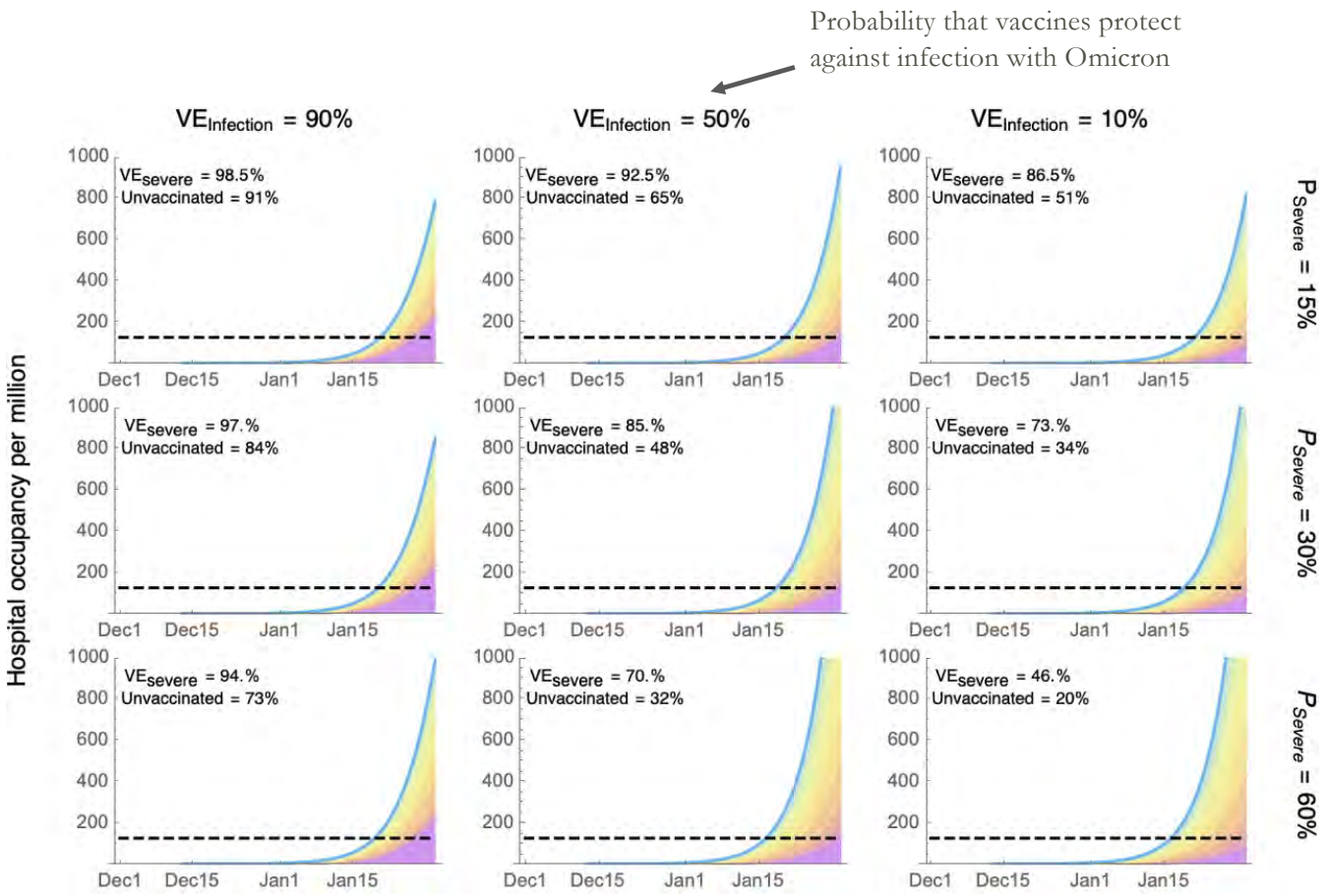
- Viral characteristics (incubation period, transmission rates, asymptomatic rates, etc.)
- Host characteristics (age, employment, etc.)
- Behavioural and policy responses (masking, social distancing, updating ventilation, etc.)
- Immunity through vaccination or prior exposure



Models allow us to knit together these threads and predict possible outcomes

Source: S. Otto. Based on model in Day et al. (2020)

Models allow exploration of alternative futures



In December 2021, for example, it was unclear how the Omicron wave would impact hospitals.

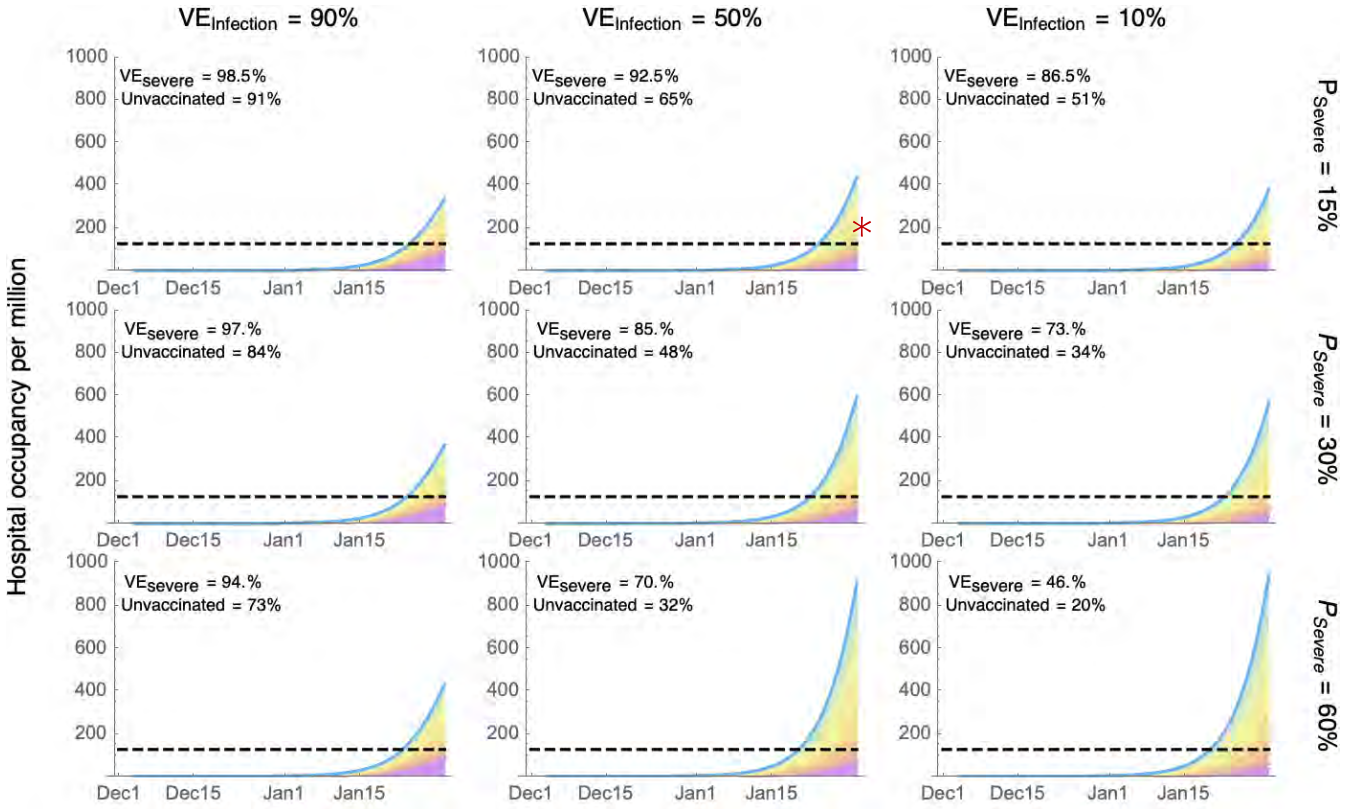
Models could explore outcomes across a variety of unknown parameters.

Source (S. Otto). https://covarrnet.ca/modelling-resources/ (December 17, 2021)

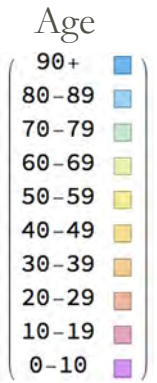
Models allow exploration of alternative futures

Probability that vaccines protect against infection with Omicron

Omicron half as severe



Probability of a severe case among infected individuals who are vaccinated compared to unvaccinated.



Source (S. Otto). https://covarrnet.ca/modelling-resources/ (December 17, 2021)

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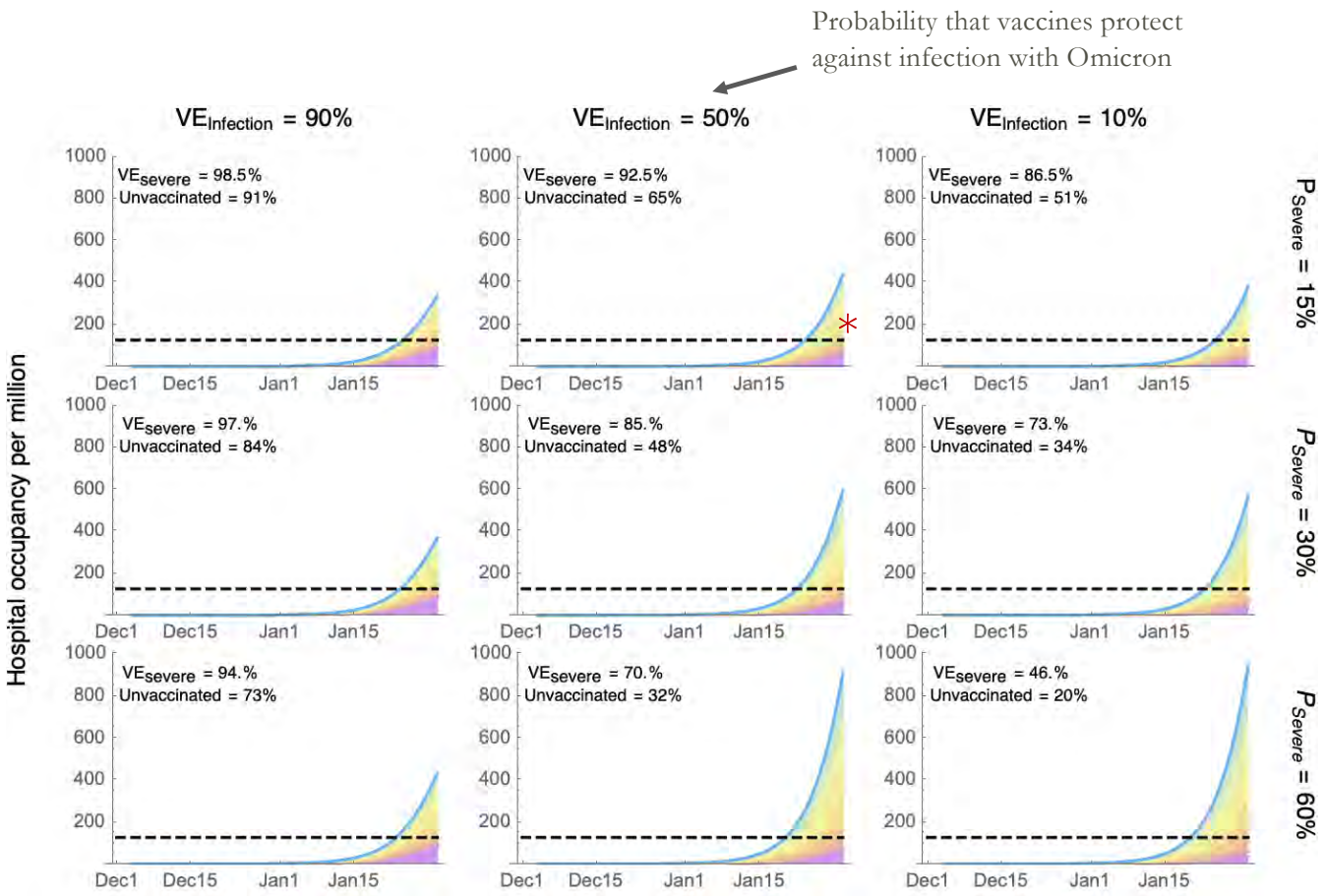
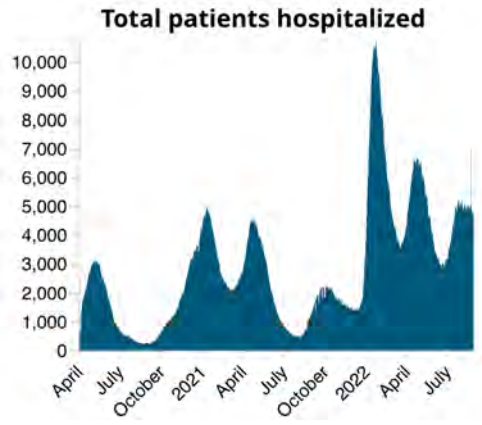


Omicron half as severe

- Fortunately, Omicron was ~half as severe among unvaccinated & vaccines provided strong protection against severe disease



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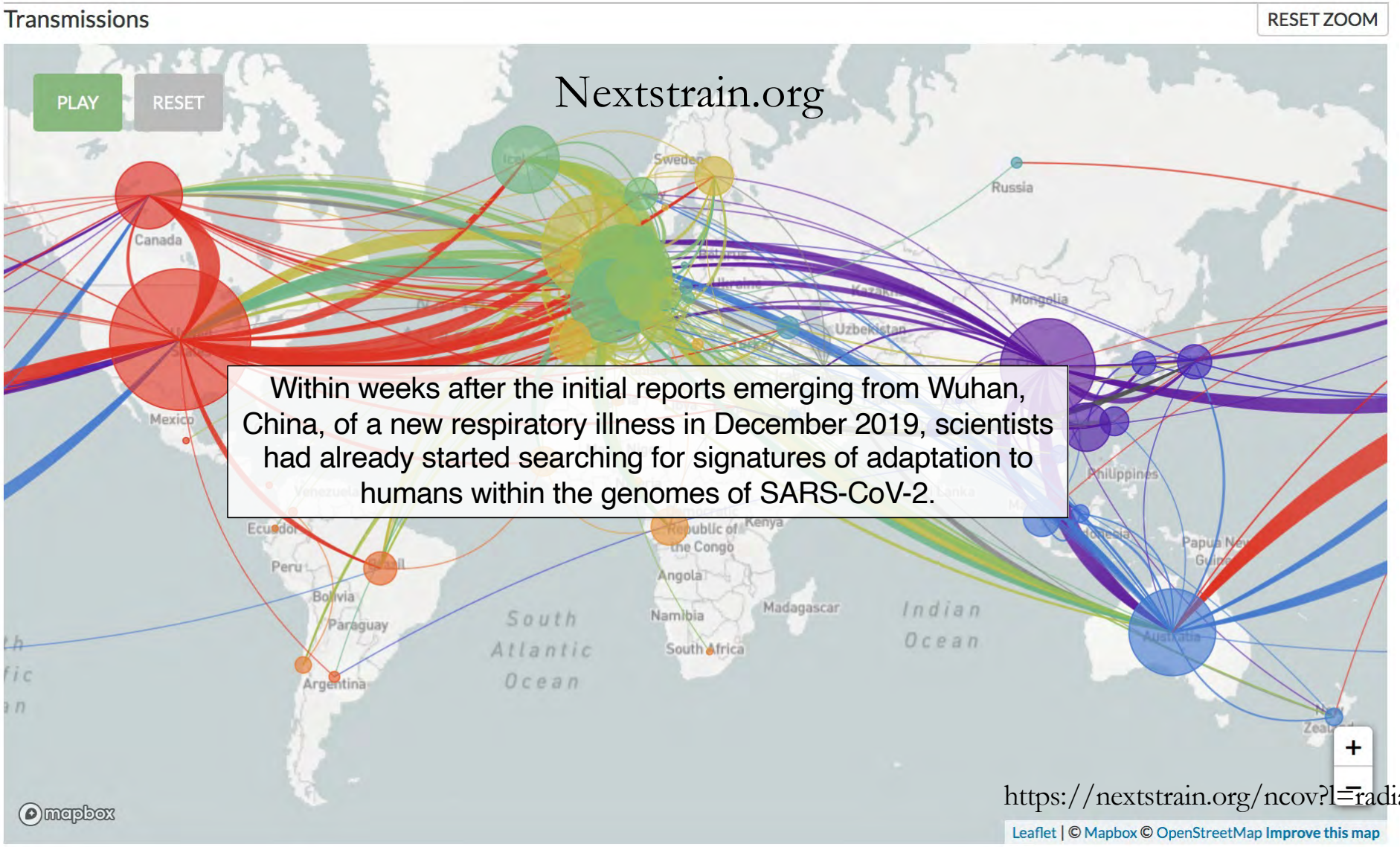
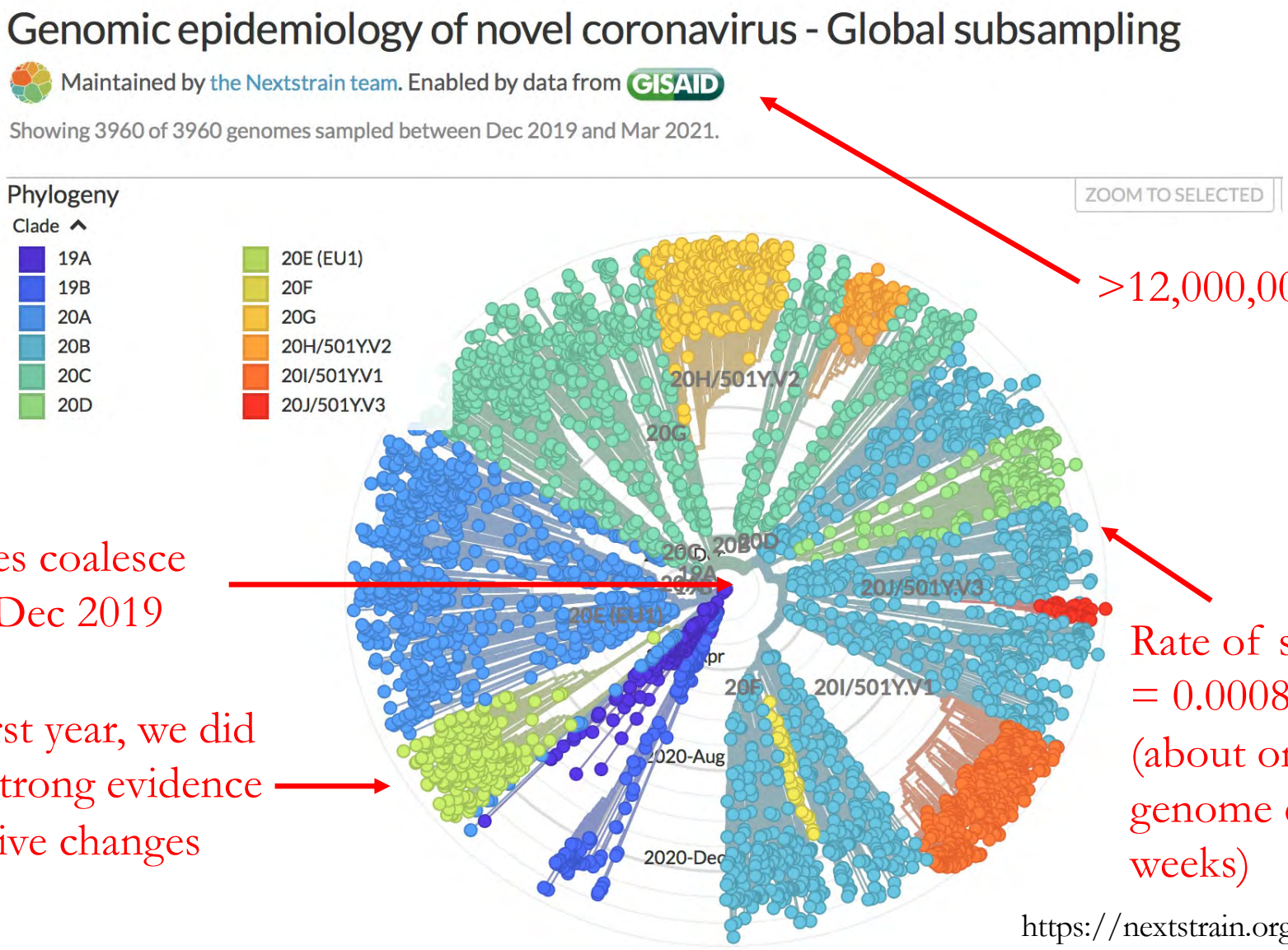
SARS-CoV-2

Modelling in real time

Act 2: An Evolving Pandemic


Transmissions
RESET ZOOM
PLAY
RESET
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
Canada
Mexico
Russia
Mongolia
Uzbekistan
Philippines
Ecuador
Peru
Bolivia
Paraguay
Argentina
Angola
Namibia
South Africa
Madagascar
Kenya
South Atlantic Ocean
Indian Ocean
mapbox
Leaflet | © Mapbox © OpenStreetMap Improve this map



>12,000,000 genomes!!

Sequences coalesce in Nov/Dec 2019

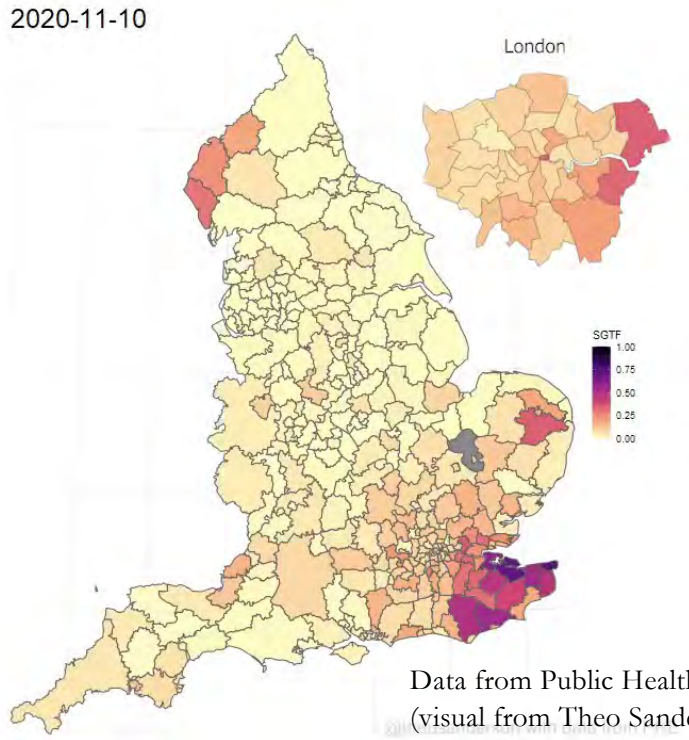
In the first year, we did not see strong evidence of selective changes

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

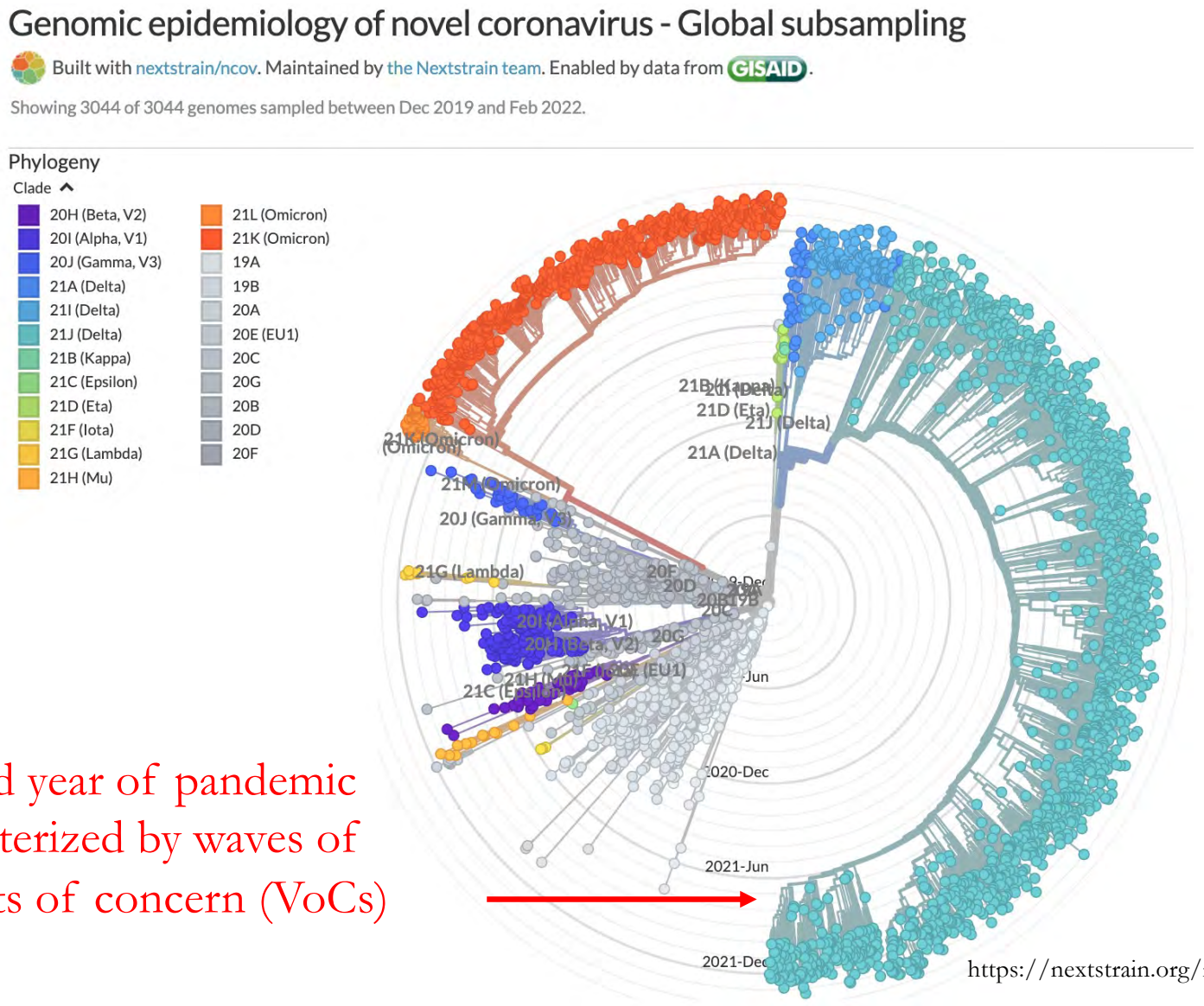
https://nextstrain.org/ncov?l=radial

Variants of Concern

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



Data from Public Health England
(visual from Theo Sanderson)



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

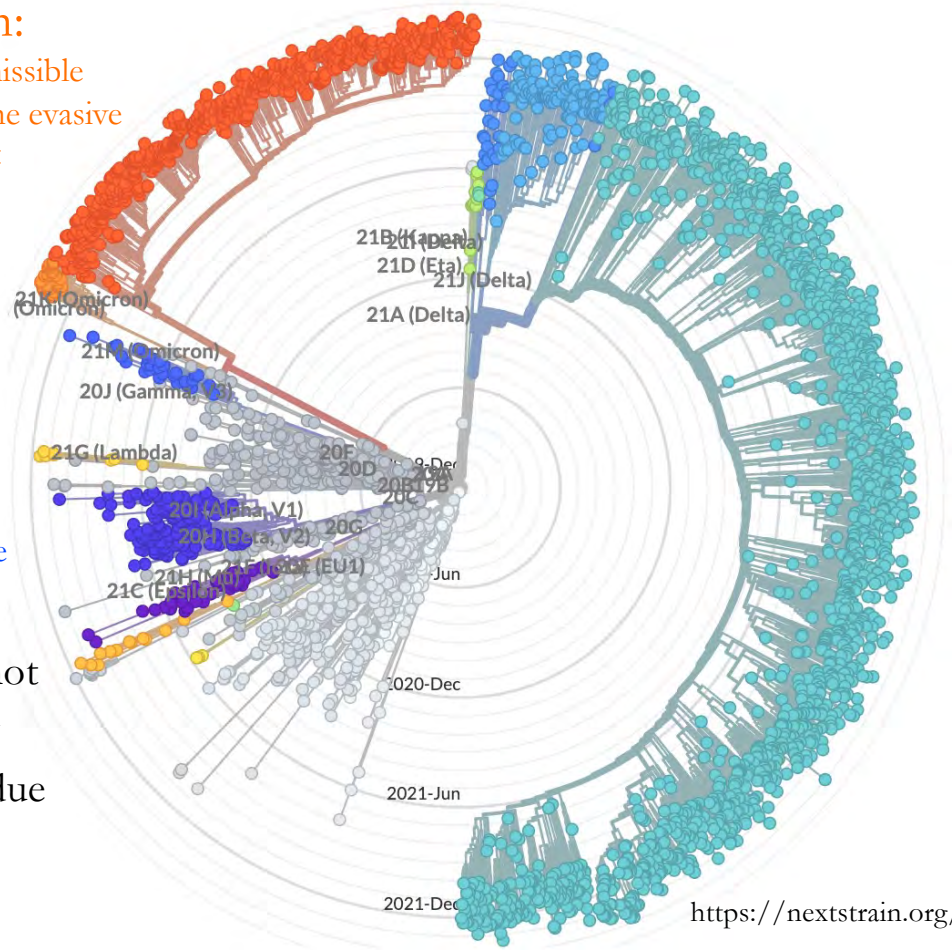
https://nextstrain.org/ncov?l=radial

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.

Omicron:
More transmissible
More immune evasive
Less virulent



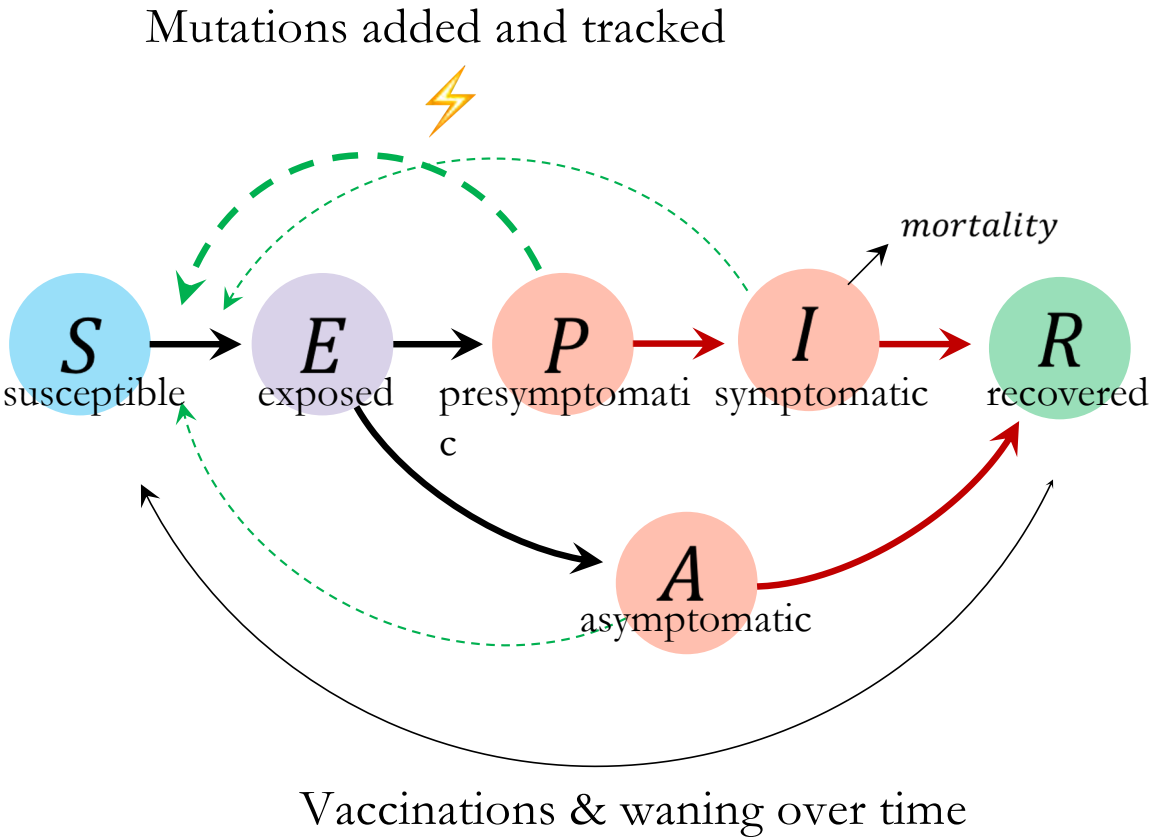
Delta:
More transmissible
More virulent

Alpha:
More transmissible
More virulent

Most VOCs emerged from earlier lineages, not currently common strains. This evolutionary history of "leap-frogging" is thought to be due to emergence of major new variants from persistent infections.

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

How does selection on SARS-CoV-2 variants?



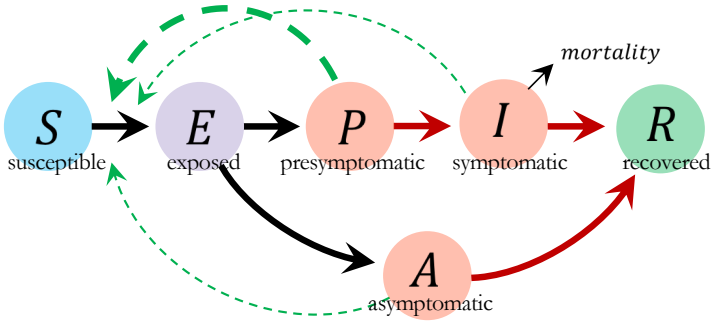
Current Biology

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 ($S \sim$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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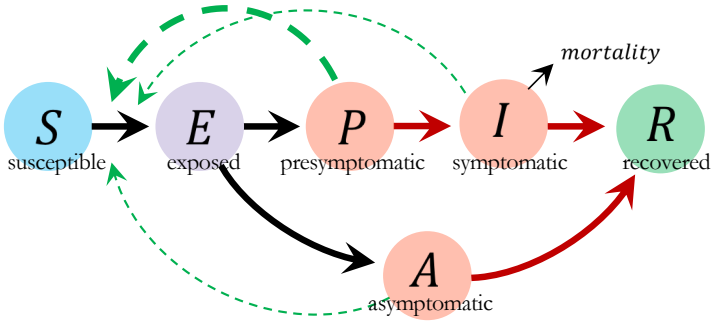
⚡ Add mutations (*) and track spread of new lineage



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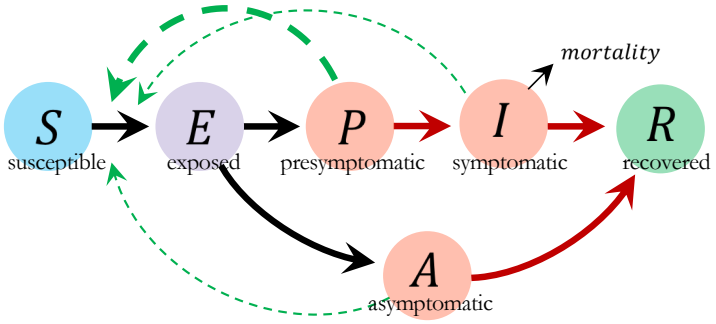
⚡ Add mutations (*) and track spread of new lineage

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

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



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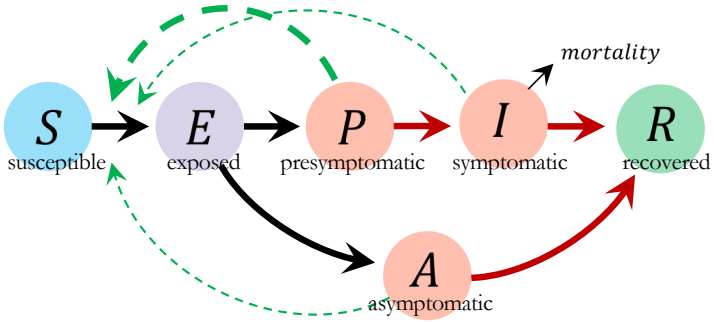
SEAPIR Model

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

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



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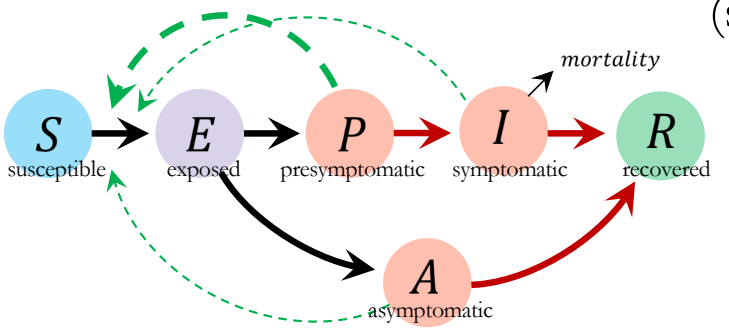
Mutant effects

Right eigenvector (strictly positive)

Differences in left eigenvectors
Compares "reproductive values"

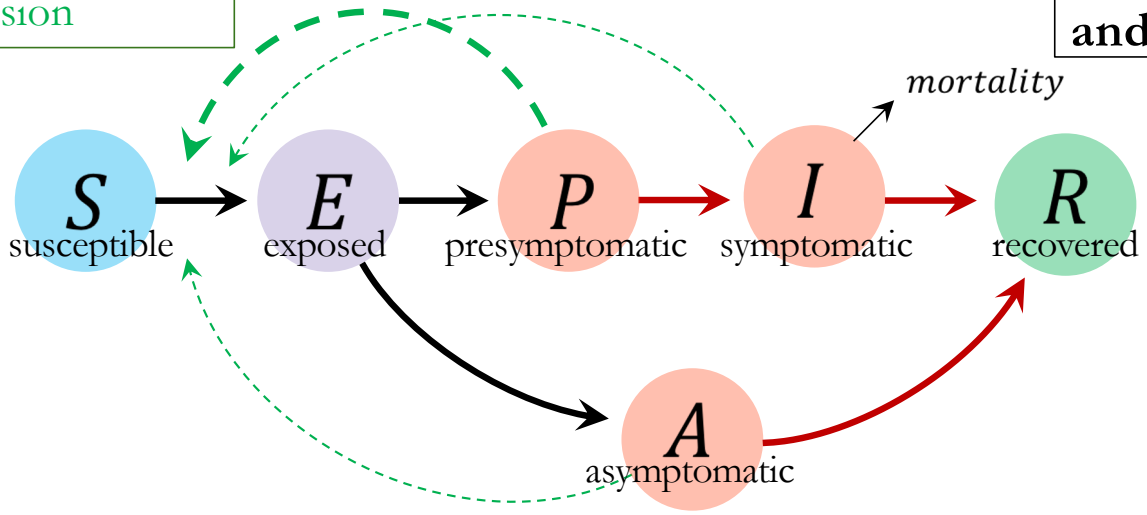


What selection pressures act on SARS-CoV-2 in a largely susceptible population?

Higher transmission

- Intrinsic transmissibility
- Immune evasion

Negligible direct selection on severity and mortality



Current Biology

Day et al. (2020)

Prolonged infectivity:

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

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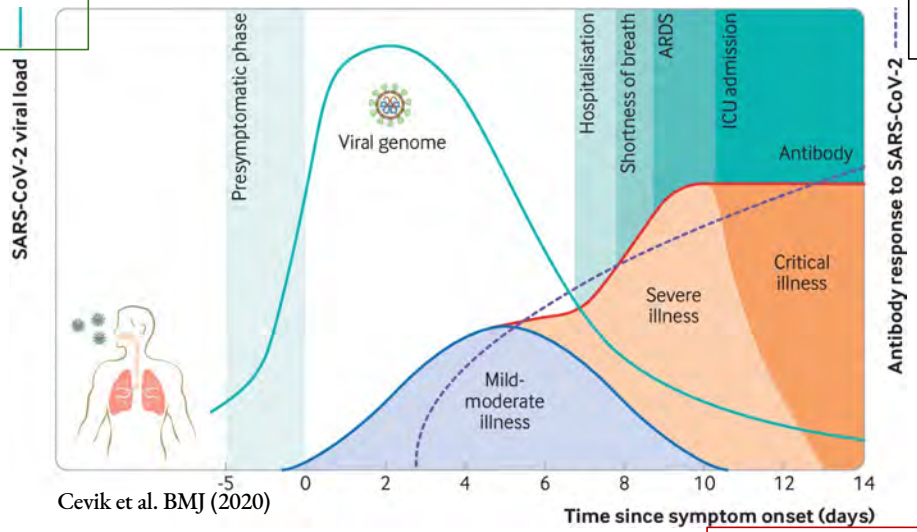

Cevik et al. BMJ (2020)

Current Biology

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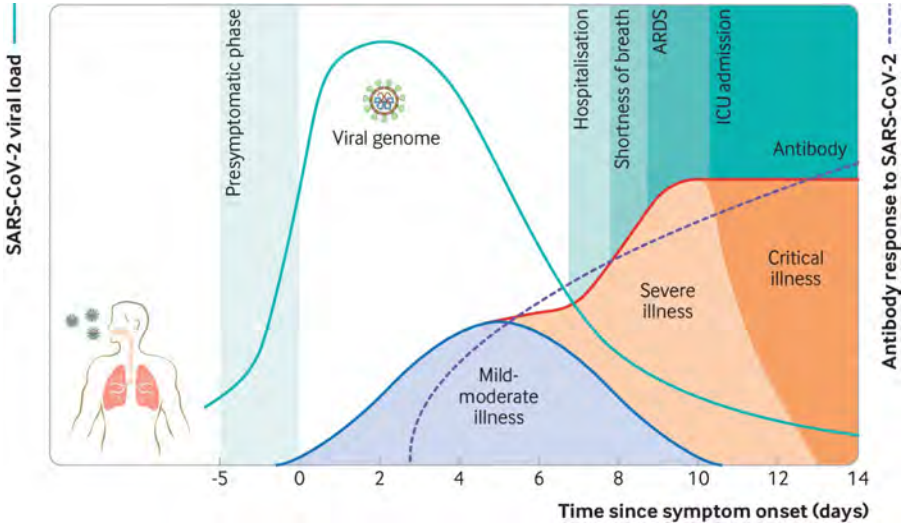
What selection pressures act on SARS-CoV-2 in a largely susceptible population?

"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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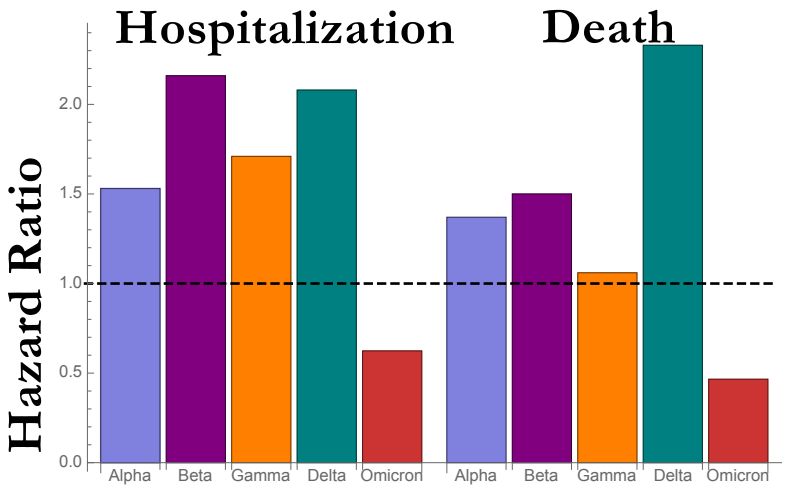


Current Biology

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)

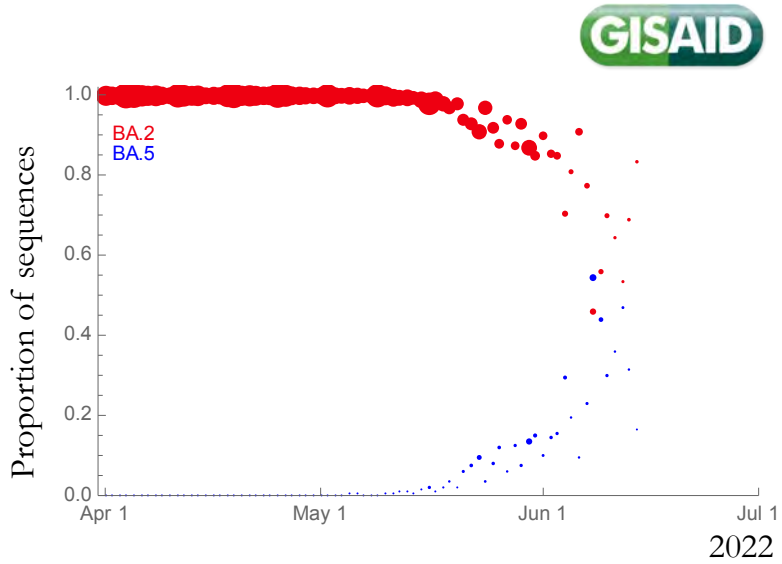
Evolution in action

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:

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



Selection, *s*: Differences among types in the ability to survive or reproduce (for a virus, to evade immunity and transmit), which cause evolutionary changes in frequency of those types.

Evolution in action

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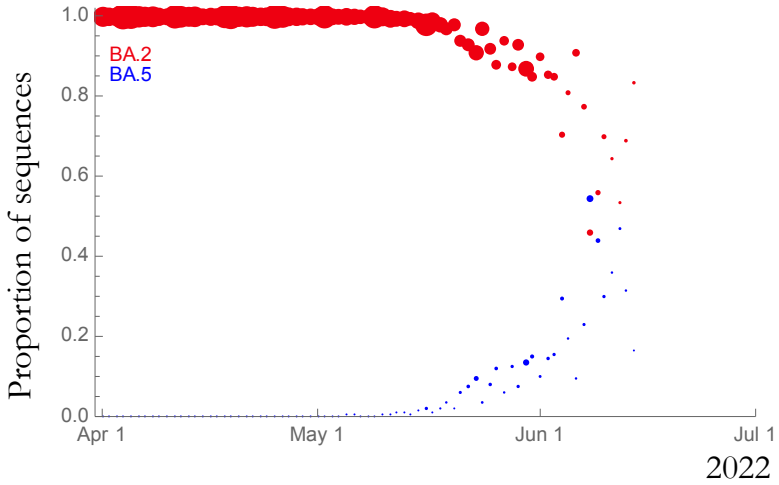
with n_t sequences at time t and an observed number of each type (j, k), the likelihood of observing the data is binomial:

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

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



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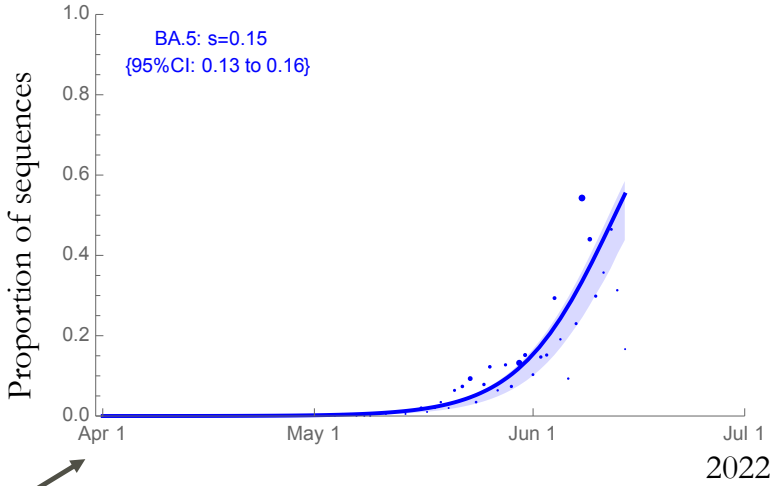


Estimate selection by maximizing the likelihood

Plus: get CI & allow for multiple variants

Evolution in action

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

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

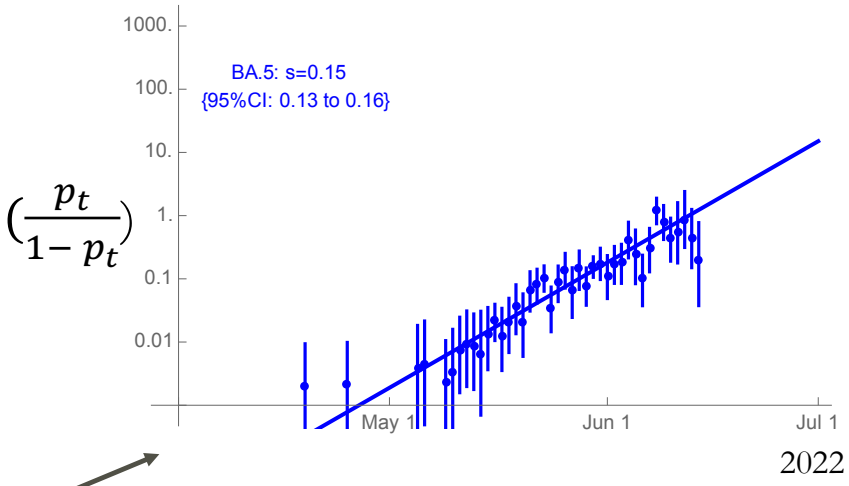
which can be solved:

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

Or rearrange:

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

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

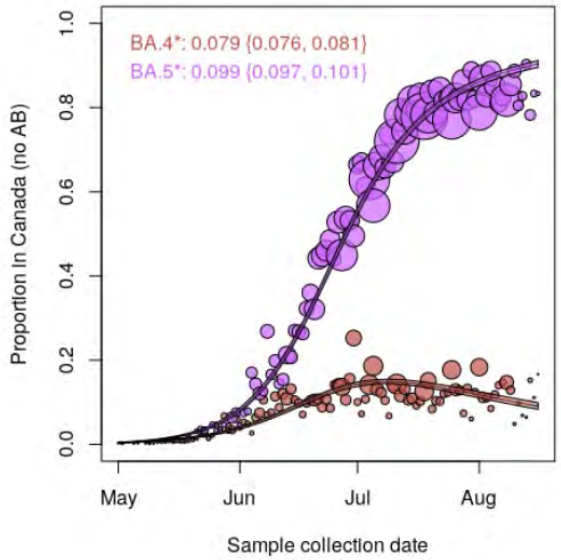


Predicts a linear relationship with constant slope s if selection is constant

Coronavirus Variants Rapid Response Network

Réseau de réponse rapide aux variants du coronavirus

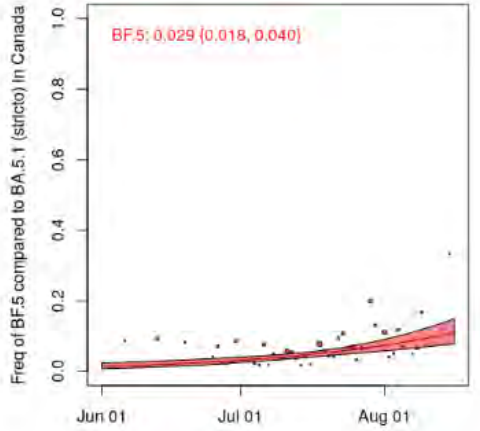
We use this method to estimate selection and monitor spread of variants in CoVaRR-Net, a network of researchers from institutions across the country created to assist in the Government of Canada's overall strategy to address the potential threat of emerging SARS-CoV-2 variants.

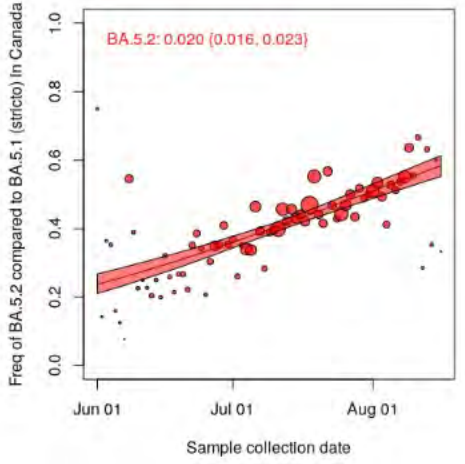


Monitor growth of variants

In Canada:

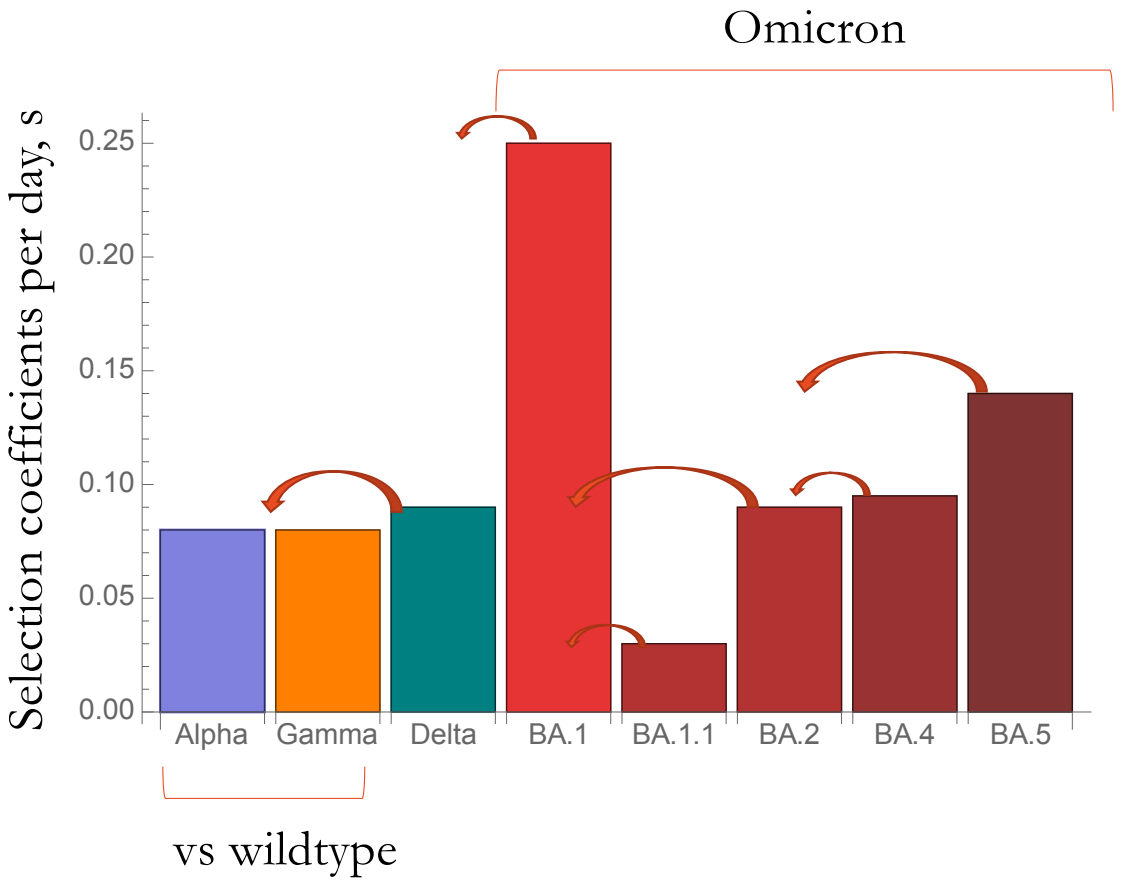
- BA.5 now dominating
- Some sub-variants show a minor growth advantage (e.g., BA.5.2 and BF.5 over BA.5.1)





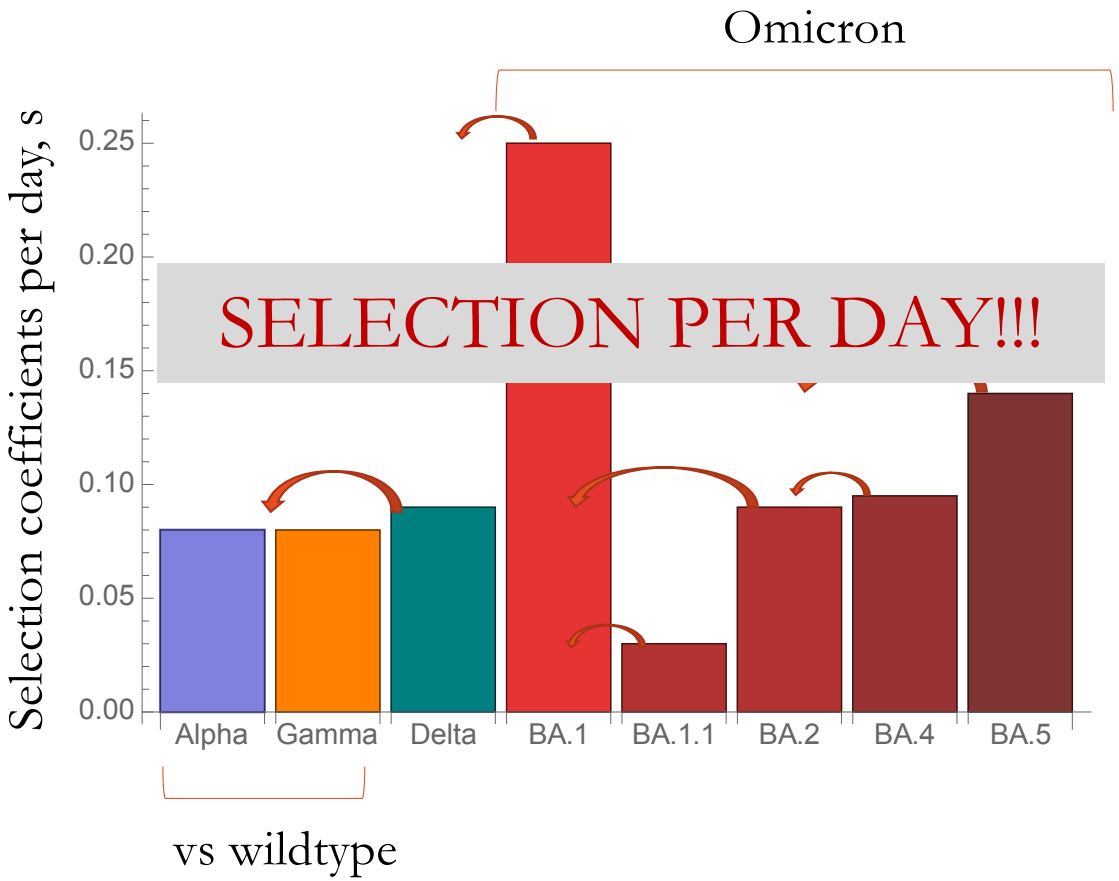
https://covarrnet.ca/modelling-resources/

Evolution in action



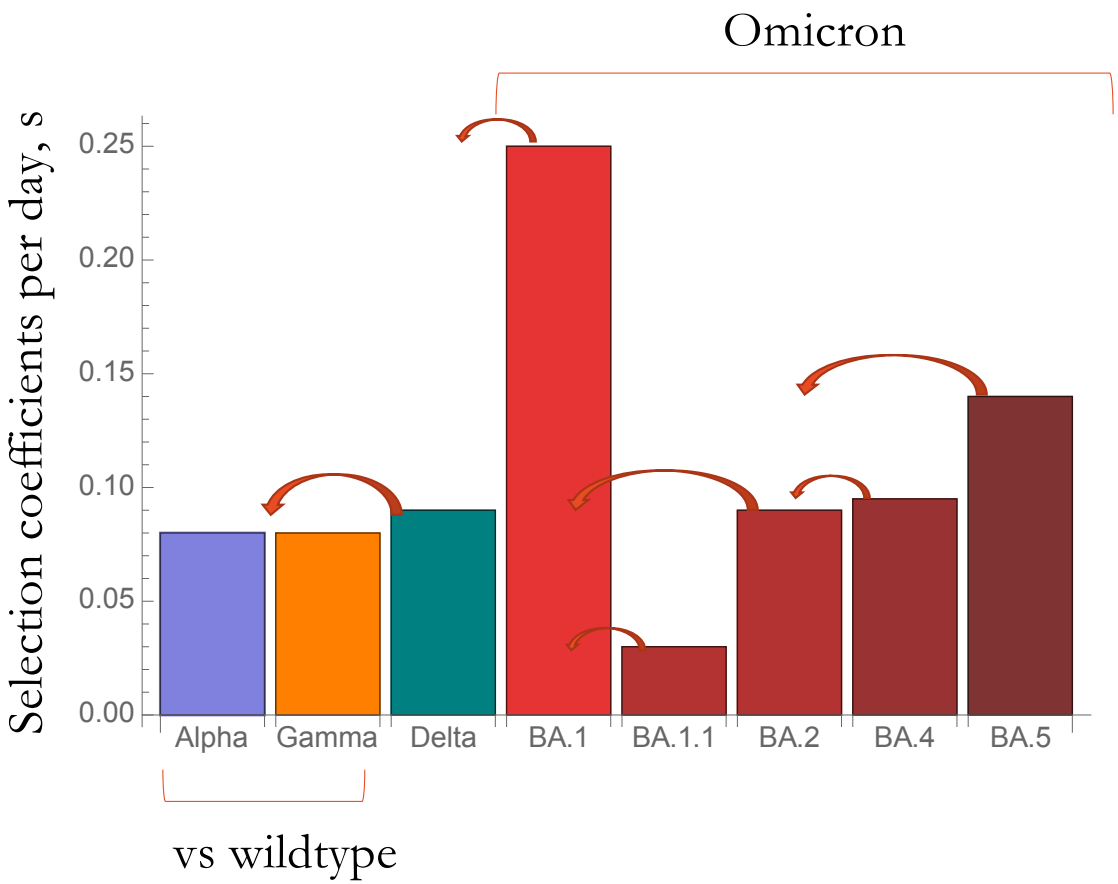
BC COVID-19 Modelling Report
(2June2021, 6August2021, 17Feb2022, 18May2022, next one)

Evolution in action



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

Evolution in action



Days to double in frequency relative to reference strain

$s = 25\% \rightarrow 2.7$ days

$s = 15\% \rightarrow 4.6$ days

$s = 10\% \rightarrow 7$ days

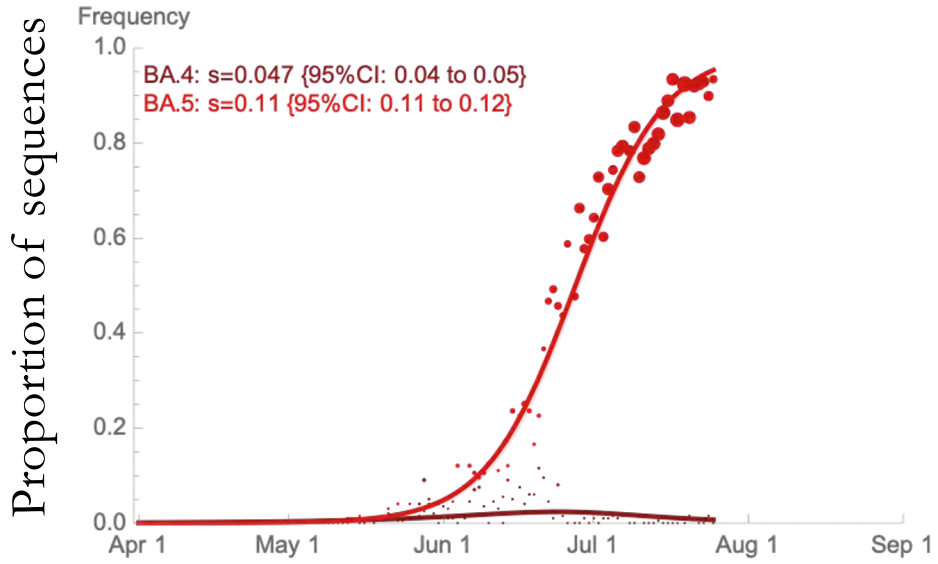
$s = 5\% \rightarrow 14$ days

$s = 1\% \rightarrow 70$ days

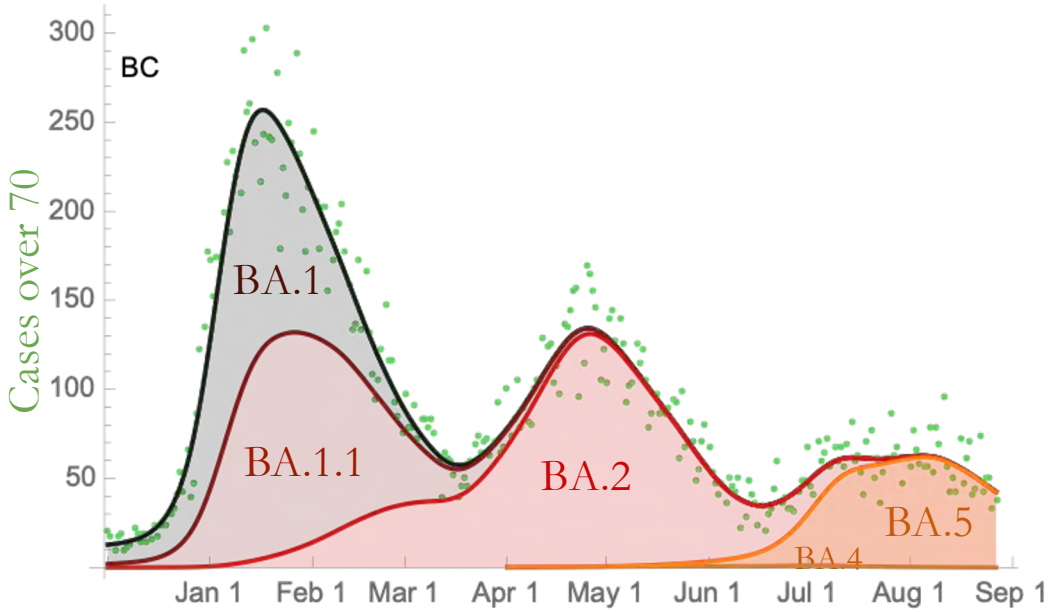
BC COVID-19 Modelling Report
(2June2021, 6August2021, 17Feb2022, 18May2022, next one)

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 (more consistently tested) allows us to estimate growth in numbers of each Omicron sublineage.



→ Estimated numbers of BA.5 have peaked, but wave is prolonged (likely due to waning immunity)

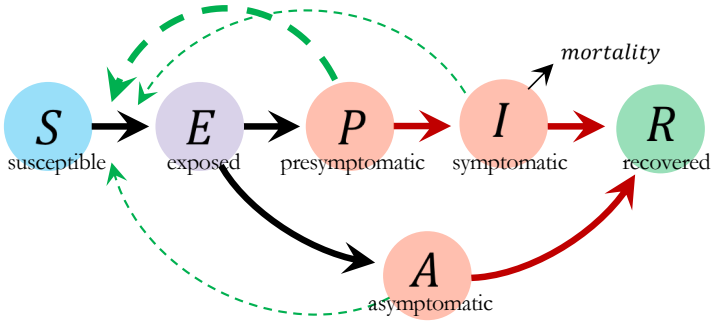
Source (S. Otto) Canadian metadata was downloaded from GISAID for the Omicron GRA clades. A model of selection was fit to the numbers of each type using maximum likelihood based on a trinomial distribution given the expected frequencies on each day. Hessian matrix used to obtain confidence intervals.

SEAPIR Model

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

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

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



SEAPIR Model

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

$$\frac{d\lambda}{dz} = S\, v_E \left(\Delta\beta_P\, u_P + \Delta\beta_I\, u_I + \Delta\beta_A\, u_A\right) - \left(\Delta\alpha + \Delta\kappa_I\right) u_I v_I - \Delta\kappa_A\, u_A v_A - \Delta f\, \kappa_E\, u_E \{v_P - v_A\}$$
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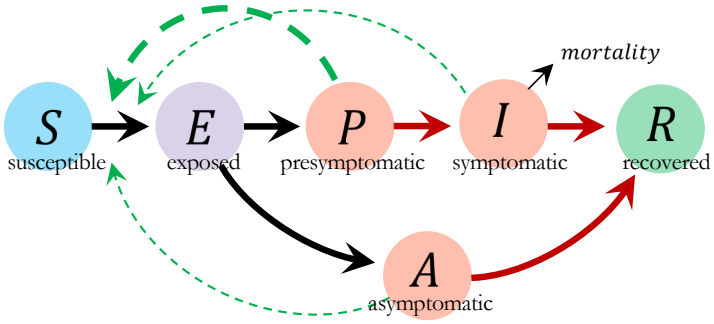
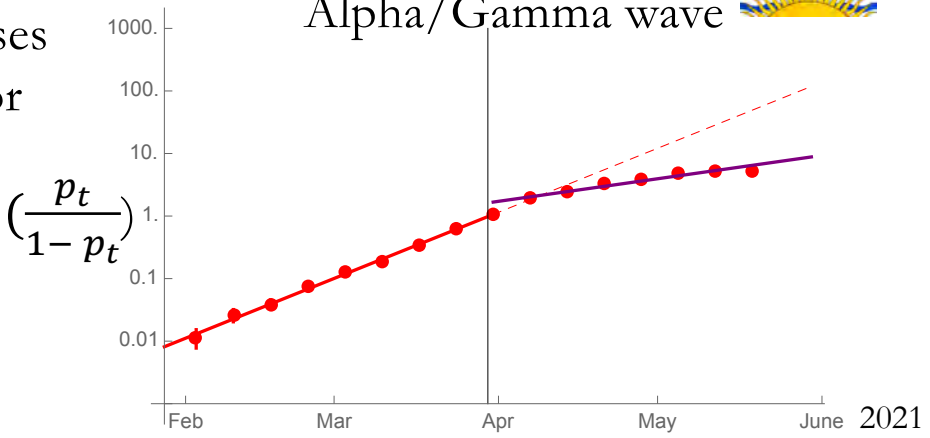
Selection should weaken for a variant that increases transmission if susceptibles are protected and/or transmission is limited.



Alpha/Gamma wave



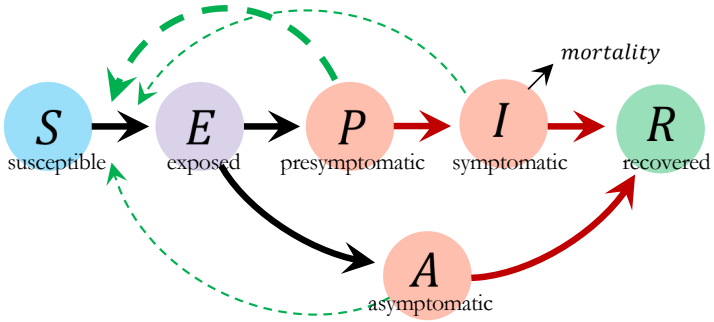
BC's 'circuit breaker' on 30 March 2021
(vertical line: closing indoor dining, gym closures, travel within the province restricted;
See Otto et al. 2022 Current Biology)

SEAPIR Model

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

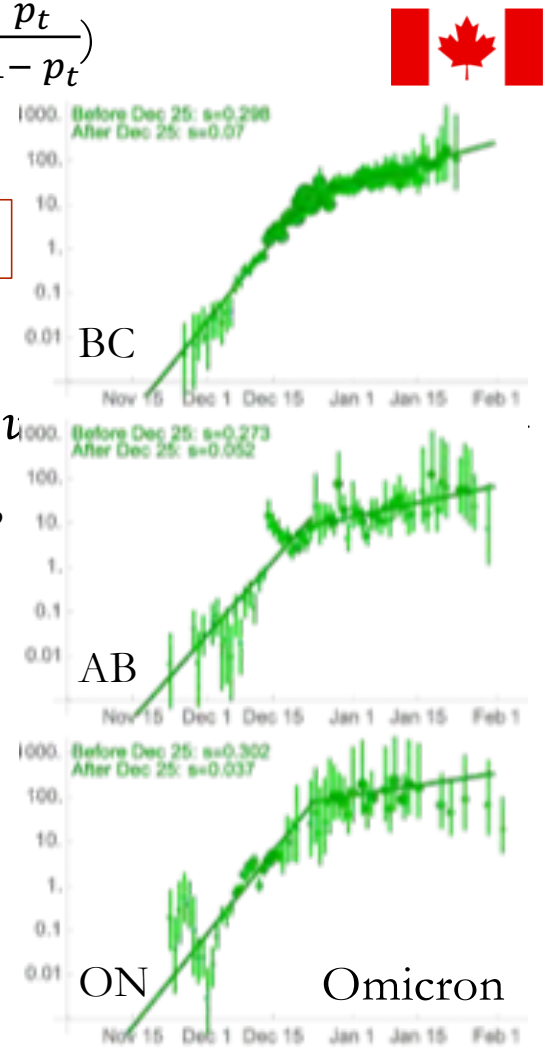
$$\frac{d\lambda}{dz} = S\, v_E \left(\Delta\beta_P\, u_P + \Delta\beta_I\, u_I + \Delta\beta_A\, u_A\right) - (\Delta\alpha + \Delta\kappa_I)\, u_I v_I - \Delta\kappa_A\, u_A \iota$$
$$+\Delta\kappa_E\, u_E \{(v_P(1-f) + f\, v_A) - v_E\} - \Delta\kappa_P\, u_P \{v_P$$

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



Collective concern

$\left(\frac{p_t}{1-p_t}\right)$



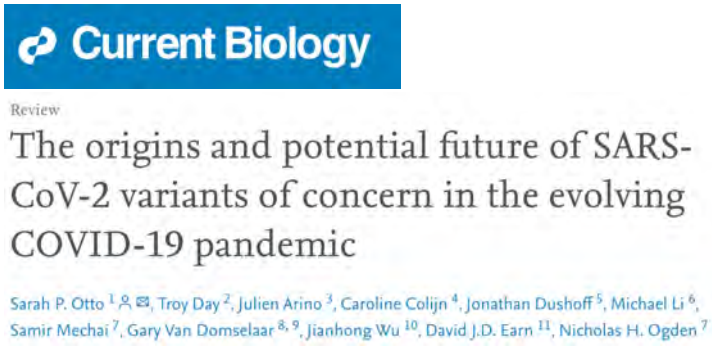
2022

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

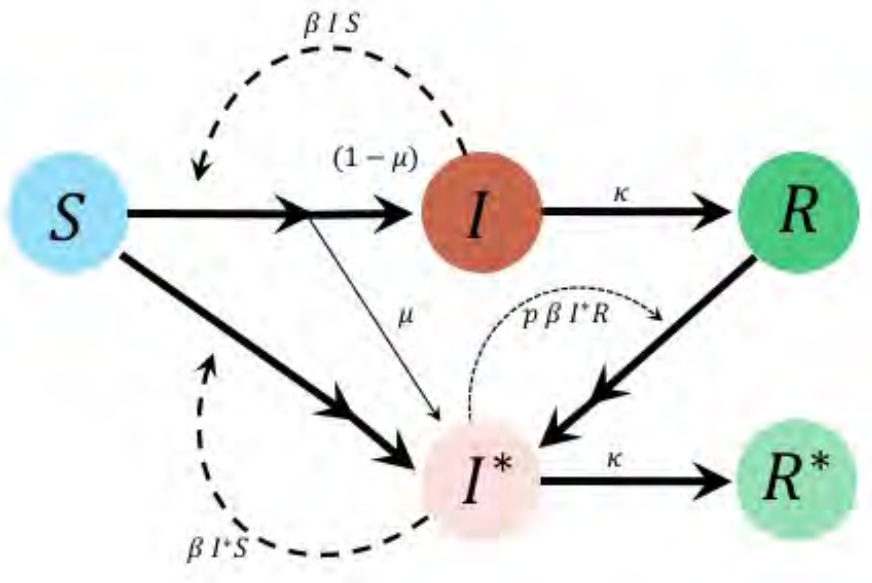
SARS-CoV-2

Modelling in real time

Act 3: Vaccines and Shifting Selection



Selection during vaccination roll out

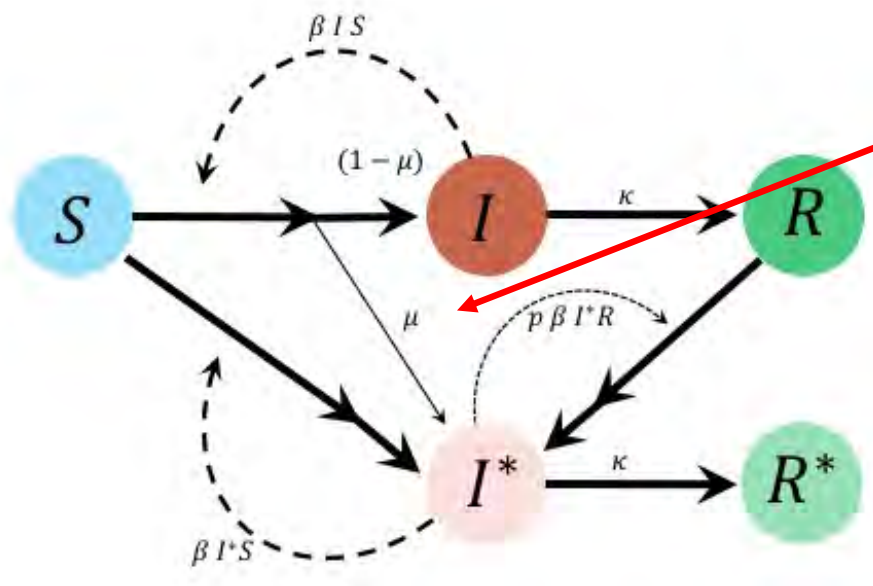


S: susceptible
I: symptomatic (infectious)
I*: escape mutation
R: resistant (not infectious)
R*: resistant to escape mutation

$$\frac{dI}{dt} = (1-\mu)\,\beta\,S\,I - \kappa\,I$$

$$\frac{dI^*}{dt} = \mu\,\beta\,S\,I + \beta\,S\,I^* + p\,\beta\,R\,I^* - \kappa\,I^*$$

Selection during vaccination roll out



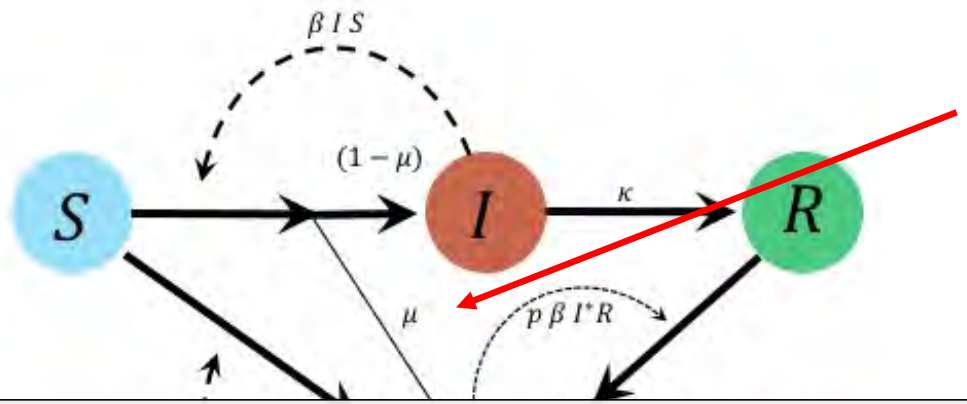
Time until first escape mutation is exponentially distributed with a mean of $1/(\mu\ \beta\ S\ I)$ serial transfers.

S: susceptible
I: symptomatic (infectious)
I*: escape mutation
R: resistant (not infectious)
R*: resistant to escape mutation

$$\frac{dI}{dt} = (1-\mu)\,\beta\,S\,I - \kappa\,I$$

$$\frac{dI^*}{dt} = \mu\,\beta\,S\,I + \beta\,S\,I^* + p\,\beta\,R\,I^* - \kappa\,I^*$$

Selection during vaccination roll out



Time until first escape mutation is exponentially distributed with a mean of $1/(\mu\ \beta\ S\ I)$ serial transfers.

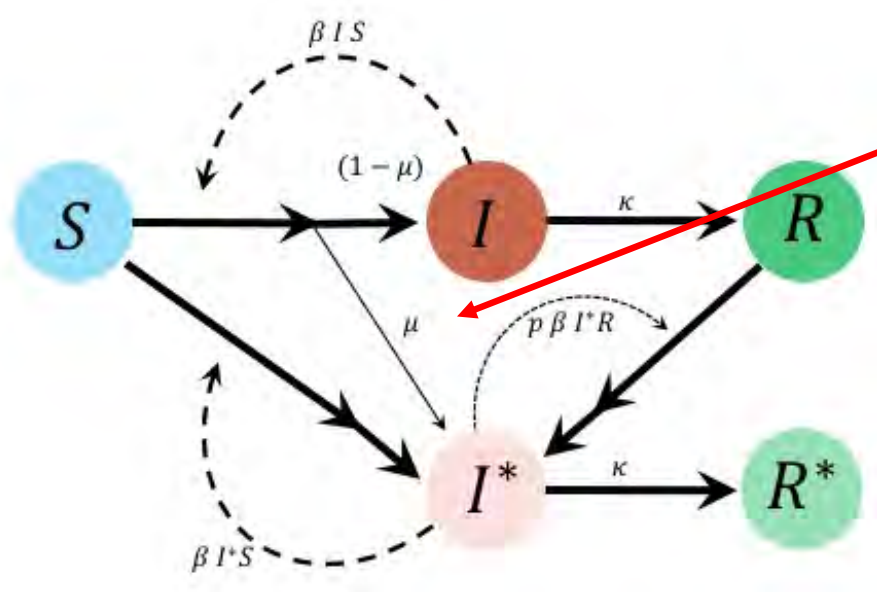
Key messages

- We can slow the **appearance** of escape mutations by effective control measures (lower β), reducing circulating cases (lower I), and vaccinating as many people as we can (lower S).
- We should also carefully monitor immunosuppressed patients and track potential mutators (e.g., changes to the ExoN proofreading function) (avoid higher μ).

S: susceptible
I: symptomatic (infectious)
I*: escape mutation
R: resistant (not infectious)
R*: resistant to escape mutation

$$\frac{dI^*}{dt} = \mu\ \beta\ S\ I + \beta\ S\ I^* + p\ \beta\ R\ I^* - \kappa\ I^*$$

Selection during vaccination roll out



Time until first escape mutation is exponentially distributed with a mean of $1/(\mu\ \beta\ S\ I)$ serial transfers.

R_t of escape mutants higher by $p\ \beta\ R/\kappa$

S: susceptible
I: symptomatic (infectious)
I*: escape mutation
R: resistant (not infectious)
R*: resistant to escape mutation

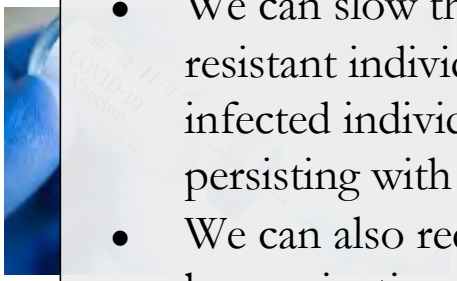
$$\frac{dI}{dt} = (1-\mu)\,\beta\,S\,I - \kappa\,I$$

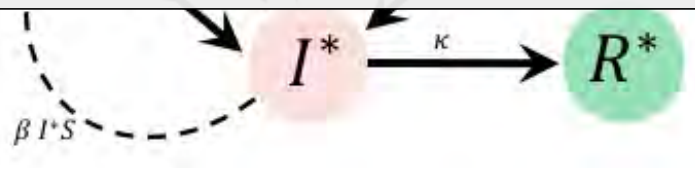
$$\frac{dI^*}{dt} = \mu\,\beta\,S\,I + \beta\,S\,I^* + p\,\beta\,R\,I^* - \kappa\,I^*$$

Selection during vaccination roll out

Key messages

- We can slow the **spread** of escape mutations by reducing contacts between cases and resistant individuals (*I** and *R*), boosting resistance where possible by vaccinating naturally infected individuals and by completing recommended vaccine doses (reducing p), and persisting with public health measures that reduce transmission in general (reducing β).
- We can also reduce the impact of escape mutations by reducing circulating cases (lower *I**) by vaccinating as many people as we can (lower *S*).





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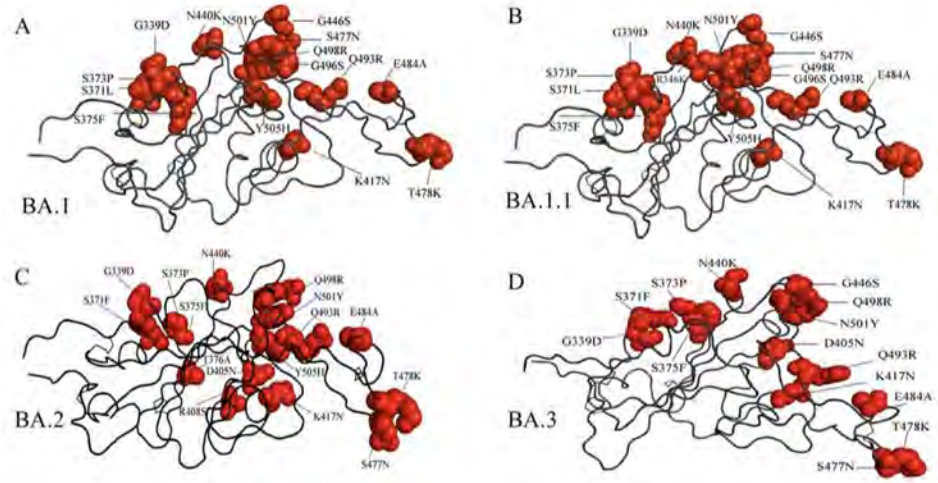
Time until first escape mutation is exponentially distributed with a mean of $1/(\mu\ \beta\ S\ I)$

R_t of escape mutants higher by $p\ \beta\ R/\kappa$

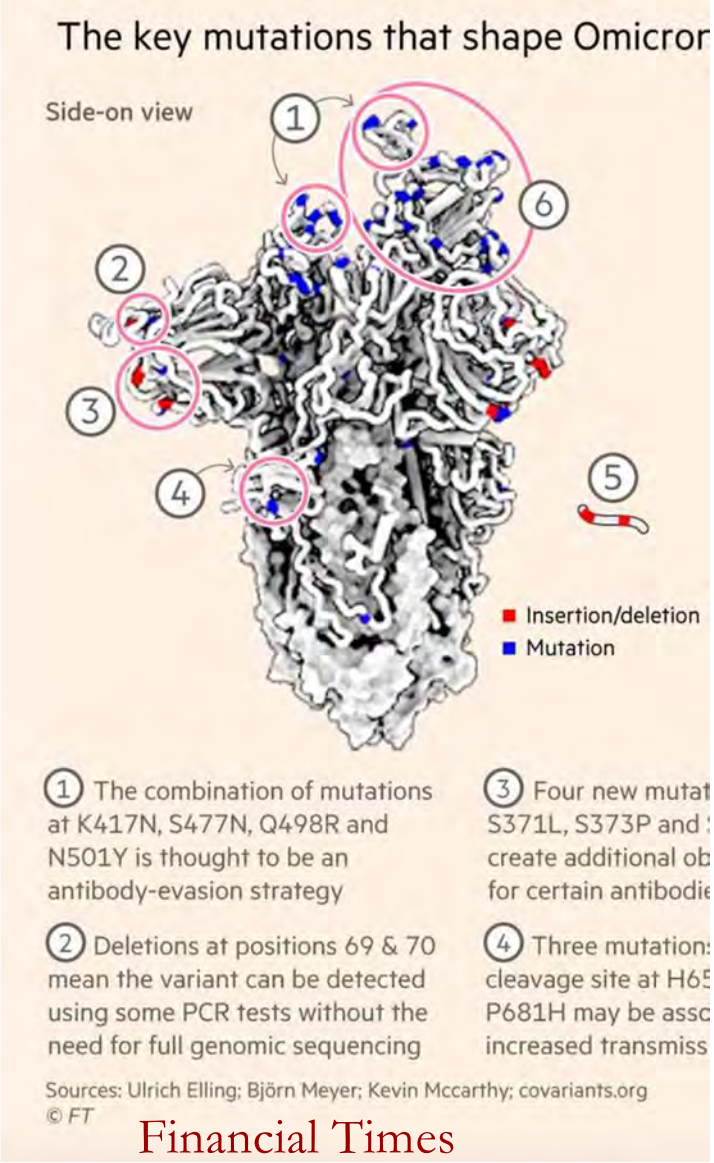
Omicron: First major VOC to evade immunity

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



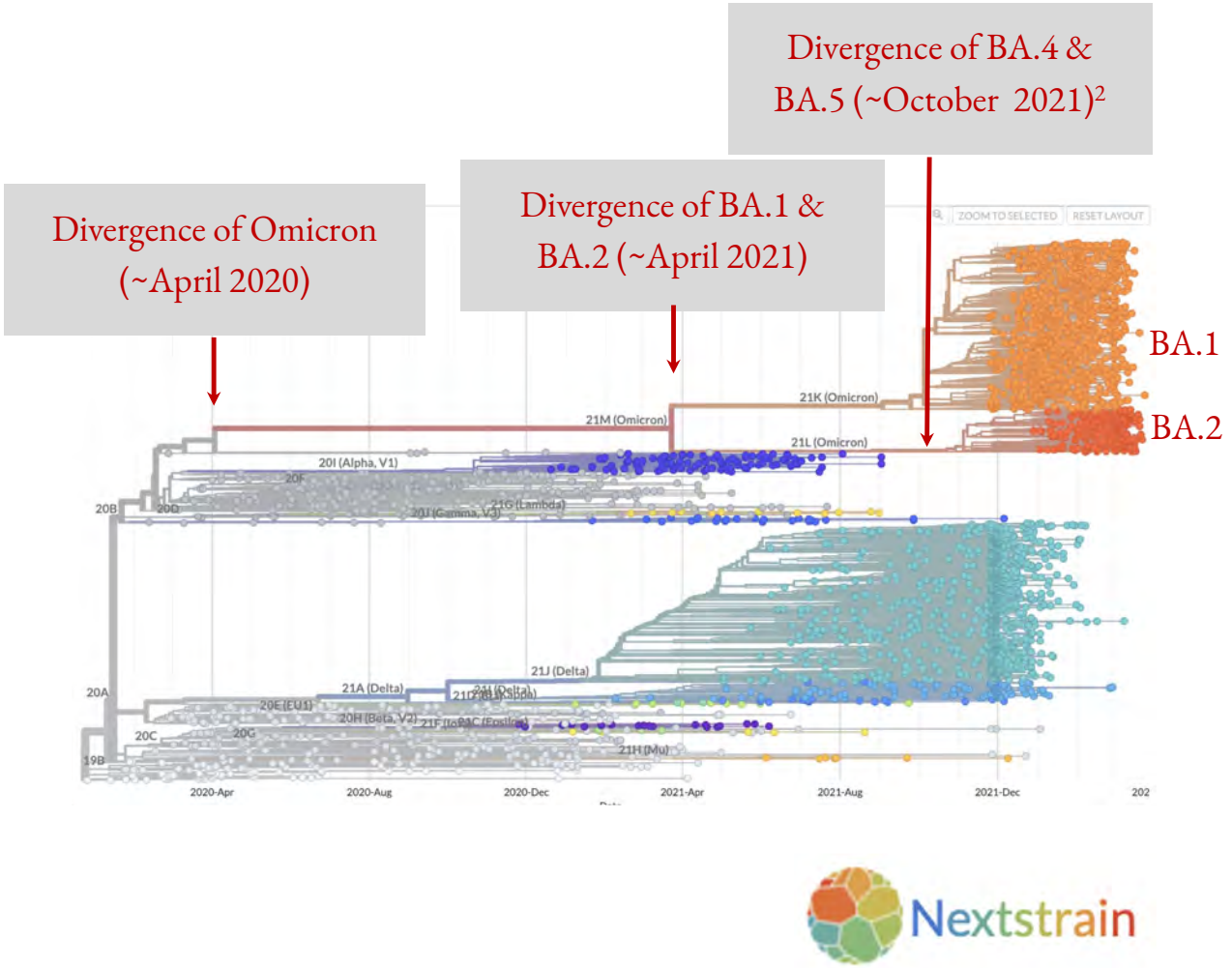
Receptor Binding Domain
with residue mutated relative to the wild-type

Kumar et al. (2022) J Med Vir



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.



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

Omicron Sub-Lineages

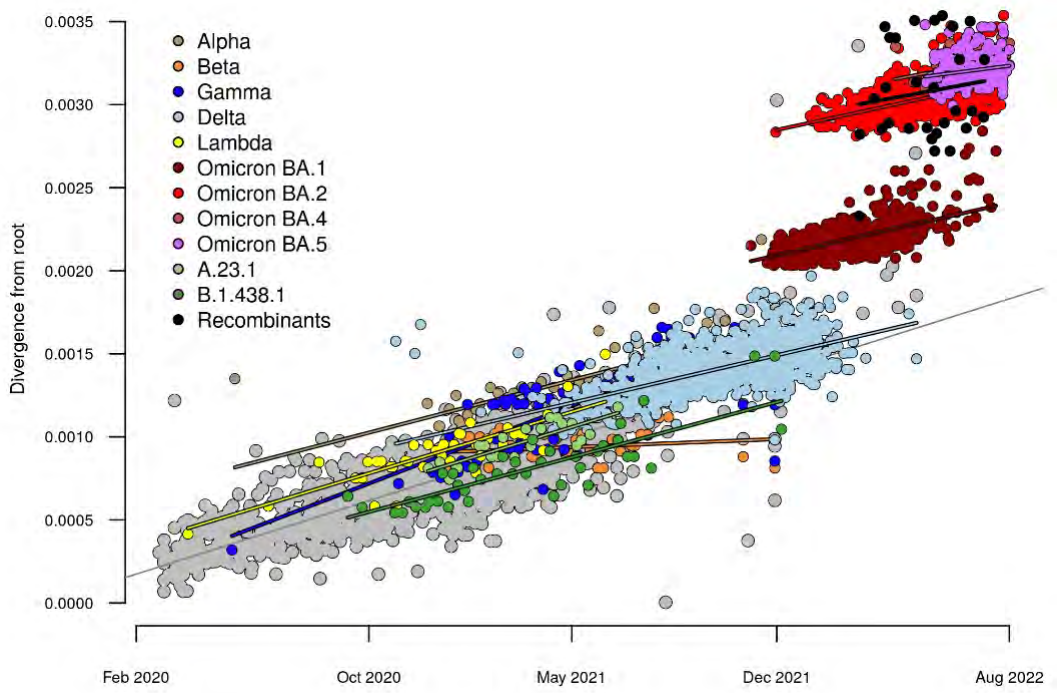
Coronavirus Variants Rapid Response Network

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:

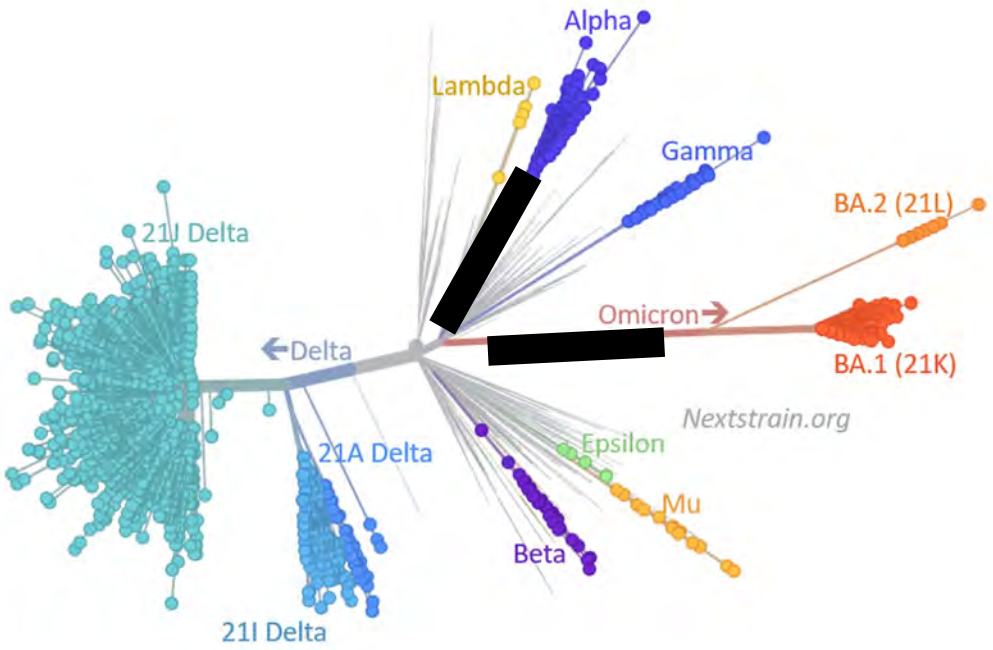
- more than expected number of mutations
- disproportionate number of changes in spike
- a long period of evolutionary divergence "out of sight" of global surveillance
- evidence that recombination was involved[1,2] in the generation of at least one of BA.1-BA.5



[Source: CoVaRR-Net, Art Poon]

[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

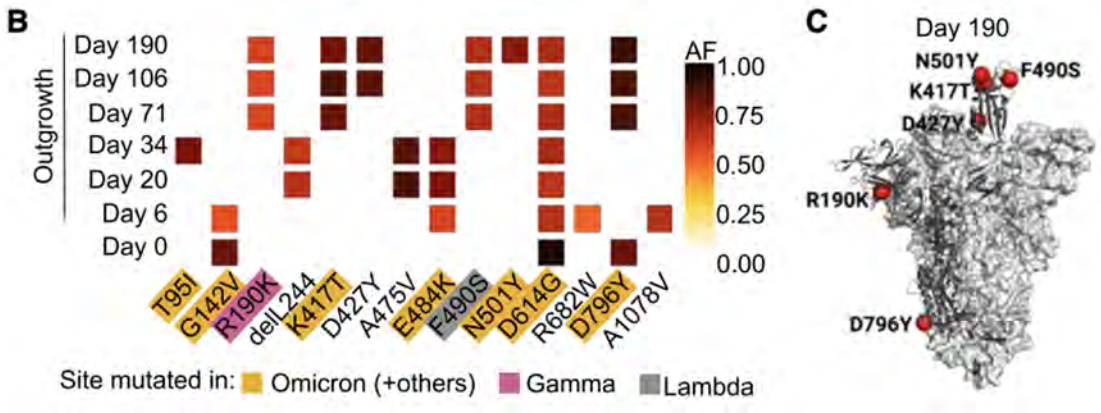
CellPress
OPEN ACCESS

Cell Host & Microbe

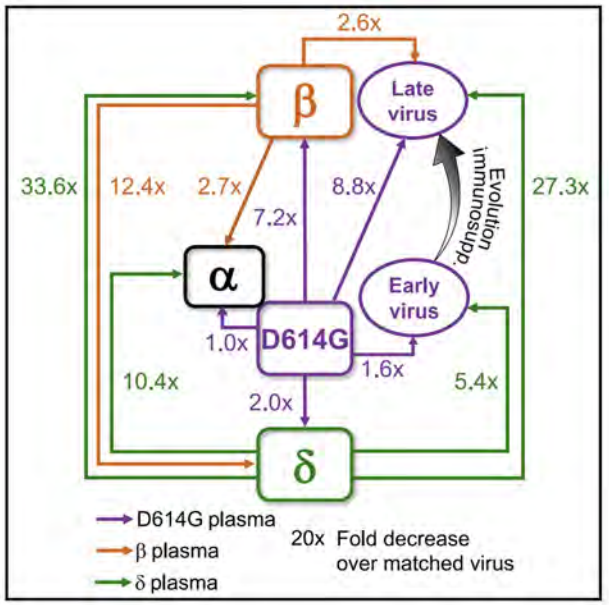
Brief Report

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

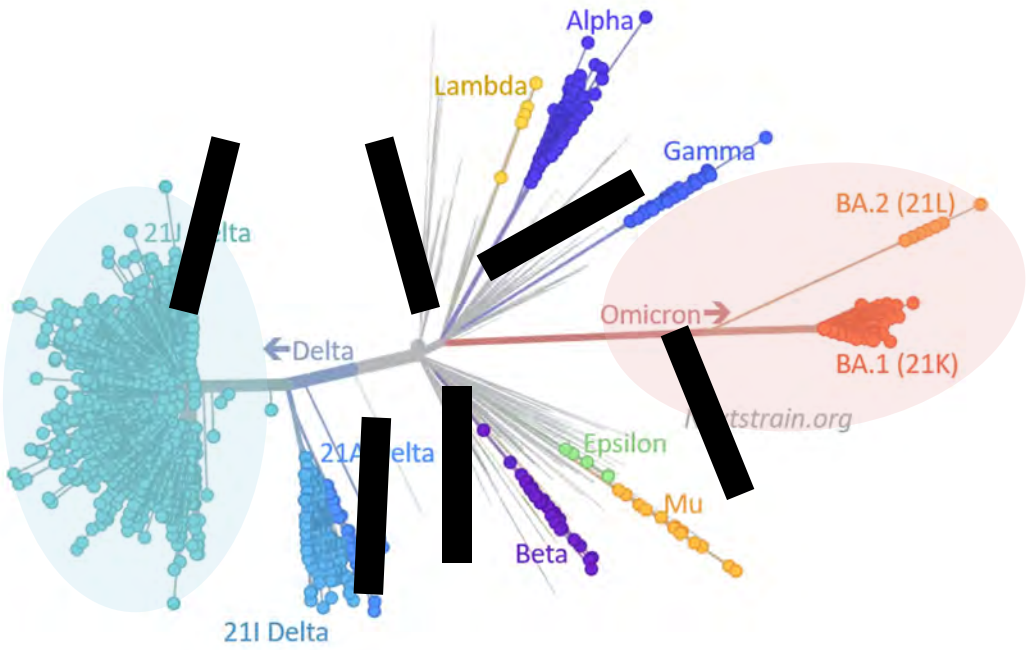
Sandile Cele,[1,2] Farina Karim,[1,2] Gila Lustig,[3] James Emmanuel San,[4] Tandile Hermanus,[5,6] Houriiyah Tegally,[4,7] Jumari Snyman,[1,8] Thandeka Moyo-Gwete,[5,6] Eduan Wilkinson,[4,7] Mallory Bernstein,[1] Khadija Khan,[1,2] Shi-Hsia Hwa,[1,8] Sasha W. Tilles,[10] Lavanya Singh,[4] Jennifer Giandhari,[4] 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,[1,2] 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.5)

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

SARS-CoV-2

Modelling in real time

Biology 301 course goals

By the end of term, you will be able to:

- read and interpret models like these
- construct & analyse models like these
- simulate & predict using models like these