R, a key metric to watch as COVID-19 restrictions are lifted

Reproduction number can help decision-makers know when it’s safe to loosen restrictions and when it’s not.

Emily Chung
CBC News • May 27, 2020

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
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?

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

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?

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

SIR Model

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

\[
\frac{dI}{dt} = \beta S I - \kappa I - \alpha I
\]
rate of change in infections

When will a disease spread?

CBC News
R, a key metric to watch as COVID-19 restrictions are lifted
Reproduction number can help decision-makers know when it’s safe to loosen restrictions and when it’s not

Emily Chung
CBC News/ May 17, 2020
**Variables**

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

**SIR Model**

- $dI/dt = \beta SI - \kappa I - \alpha I$

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

**Parameters**

- $\beta$: transmission rate
- $\kappa$: recovery rate
- $\alpha$: mortality rate ("virulence")

**$R_0$:** the expected number of new infections ($\beta$) 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

\[ β_P P + β_I I + β_A A \]

\[ (1 - f) \kappa_E \]

\[ \kappa_P \]

\[ \alpha \]

\[ \kappa_I \]

\[ \kappa_A \]

\[ f \kappa_E \]

\[ \text{mortality} \]

\[ R_0 \]
Variables
S: susceptible
E: exposed (not infectious)
A: asymptomatic (less infectious)
P: pre-symptomatic (infectious)
I: symptomatic (infectious)
R: recovered (not infectious)

SEAPIR Model

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
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.

Probability that vaccines protect against infection with Omicron

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

Source (S. Otto). [https://covarrnet.ca/modelling-resources/](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/](https://covarrnet.ca/modelling-resources/) (December 17, 2021)
Models allow exploration of alternative futures

Omicron half as severe

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

Probability that vaccines protect against infection with Omicron

Source (S. Otto). [https://covarrnet.ca/modelling-resources/](https://covarrnet.ca/modelling-resources/) (December 17, 2021)
SARS-CoV-2
Modelling in real time

Act 2: An Evolving Pandemic
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.
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

>12,000,000 genomes!!
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.
Second year of pandemic characterized by waves of variants of concern (VoCs)
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?

Mutations added and tracked

Susceptible $S$ → Exposed $E$ → Presymptomatic $P$ → Symptomatic $I$ → Recovered $R$

Asymptomatic $A$

Mortality

Vaccinations & waning over time

*Current Biology*

Day et al. (2020)
Otto et al. (2022)
Non-linear set of equations is approximately linear when susceptible class is not changing rapidly (S~constant)

\[
\frac{dS}{dt} = -S \sum_i (\beta_p^* P^* + \beta_i^* I^* + \beta_a^* A^*)
\]

\[
\frac{dE^*}{dt} = S(\beta_p^* P^* + \beta_i^* I^* + \beta_a^* A^*) - \kappa_E^* E^*
\]

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

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

\[
\frac{dl^*}{dt} = \kappa_p^* P^* - (\alpha^* + \kappa_I^*) I^*
\]

\[
\frac{dR}{dt} = \sum_i (\kappa_i^* I^* + \kappa_A^* A^*)
\]
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

\[
\begin{align*}
\frac{dS}{dt} &= -S \sum \beta_i^*P^* + \beta_i^*I^* + \beta_A^*A^* \\
\frac{dE^*}{dt} &= S(\beta_p^*P^* + \beta_i^*I^* + \beta_A^*A^*) - \kappa_E^*E^* \\
\frac{dA^*}{dt} &= f^*\kappa_E^*E^* - \kappa_A^*A^* \\
\frac{dP^*}{dt} &= (1 - f^*)\kappa_E^*E^* - \kappa_P^*P^* \\
\frac{dl^*}{dt} &= \kappa_P^*P^* - (\alpha^* + \kappa_i^*)l^* \\
\frac{dR}{dt} &= \sum \kappa_i^*l^* + \kappa_A^*A^*
\end{align*}
\]
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 ($\lambda$, leading eigenvalue):

$$\frac{d\lambda}{dz} = v^T \frac{dM}{dz} u$$

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

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

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

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

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

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

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

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

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

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

Mutant effects
Right eigenvector (strictly positive)
Differences in left eigenvectors
Compares “reproductive values”

\[
\begin{aligned}
S &\quad \text{susceptible} \\
E &\quad \text{exposed} \\
P &\quad \text{presymptomatic} \\
I &\quad \text{symptomatic} \\
R &\quad \text{recovered} \\
A &\quad \text{asymptomatic}
\end{aligned}
\]
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)
**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)
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)”

Day et al. (2020)
What selection pressures act on SARS-CoV-2 in a largely susceptible population?

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- 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)”

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 ($s$):

$$\frac{dp}{dt} = sp \left( 1 - p \right)$$

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

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:

\[
p_t = \frac{e^{st} \ p_0}{1 - p_0 + e^{st} \ p_0}
\]

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

\[
\text{likelihood(data}_t) = \binom{n_t}{j} \ p_t^j \ (1 - p_t)^k
\]

\[
\ln L(all \ data) \propto \sum_t j \ln(p_t) + k \ln(1 - p_t)
\]
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:

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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:

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\]

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

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 ($s$):

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

which can be solved:

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

Or rearrange:

Step 1: \(\frac{p_t}{1 - p_t} = \frac{e^{st} \cdot p_0}{1 - p_0}\)

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

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

Selection coefficients per day, $s$

Omicron

vs wildtype

BC COVID-19 Modelling Report
(2 June 2021, 6 August 2021, 17 February 2022, 18 May 2022, next one)
Evolution in action

Selection coefficients per day, $s$

- Alpha
- Gamma
- Delta
- BA.1
- BA.1.1
- BA.2
- BA.4
- BA.5

vs wildtype

Omicron

SELECTION PER DAY!!!
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?

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

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

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

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

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
(see Otto et al. 2022 Current Biology)

(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?

\[
\frac{d\lambda}{dz} = S v_E (\Delta\beta_P u_P + \Delta\beta_I u_I + \Delta\beta_A u_A) - (\Delta\alpha + \Delta\kappa_I) u_I v_I - \Delta\kappa_A u_A v_A
\]

\[
+ \Delta\kappa_E u_E \{(v_P(1-f) + f v_A) - v_E\} - \Delta\kappa_P u_P \{v_P
\]

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

Collective concern

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

\[
\frac{dI}{dt} = (1 - \mu) \beta SI - \kappa I
\]

\[
\frac{dI^*}{dt} = \mu \beta SI + \beta SI^* + p \beta R I^* - \kappa I^*
\]
Selection during vaccination roll out

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

\[
\begin{align*}
\frac{dI}{dt} &= (1 - \mu) \beta S I - \kappa I \\
\frac{dI*}{dt} &= \mu \beta S I + \beta S I^* + p \beta R I^* - \kappa I^*
\end{align*}
\]

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

\[ \frac{dI}{dt} = 1 - \mu \beta S I - \lambda I \]

\[ \frac{dI^*}{dt} = \mu \beta S I + \beta S I^* + p \beta R I^* - \lambda I^* \]

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 \(\beta\)), 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 \(\mu\)).
Selection during vaccination roll out

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

\[ \frac{dI}{dt} = (1 - \mu) \beta SI - \kappa I \]
\[ \frac{dI^*}{dt} = \mu \beta SI + \beta SI^* + p \beta R I^* - \kappa I^* \]

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 \( p \beta R/\kappa \)
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 \(\beta\)).
- We can also reduce the impact of escape mutations by reducing circulating cases (lower \(I^*\)) by vaccinating as many people as we can (lower \(S\)).

\[
\frac{dI}{dt} = (1 - \mu) \beta SI - \kappa I
\]

\[
\frac{dI^*}{dt} = \mu \beta SI + \beta SI^* + p \beta RI^* - \kappa I^*
\]

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

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

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

Financial Times
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

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

\(^1\) Viana et al. (2022)
\(^2\) Tegally et al. (2022)

[Source: CoVaRR-Net, Art Poon]
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

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%).
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