

Omicron at Steady State

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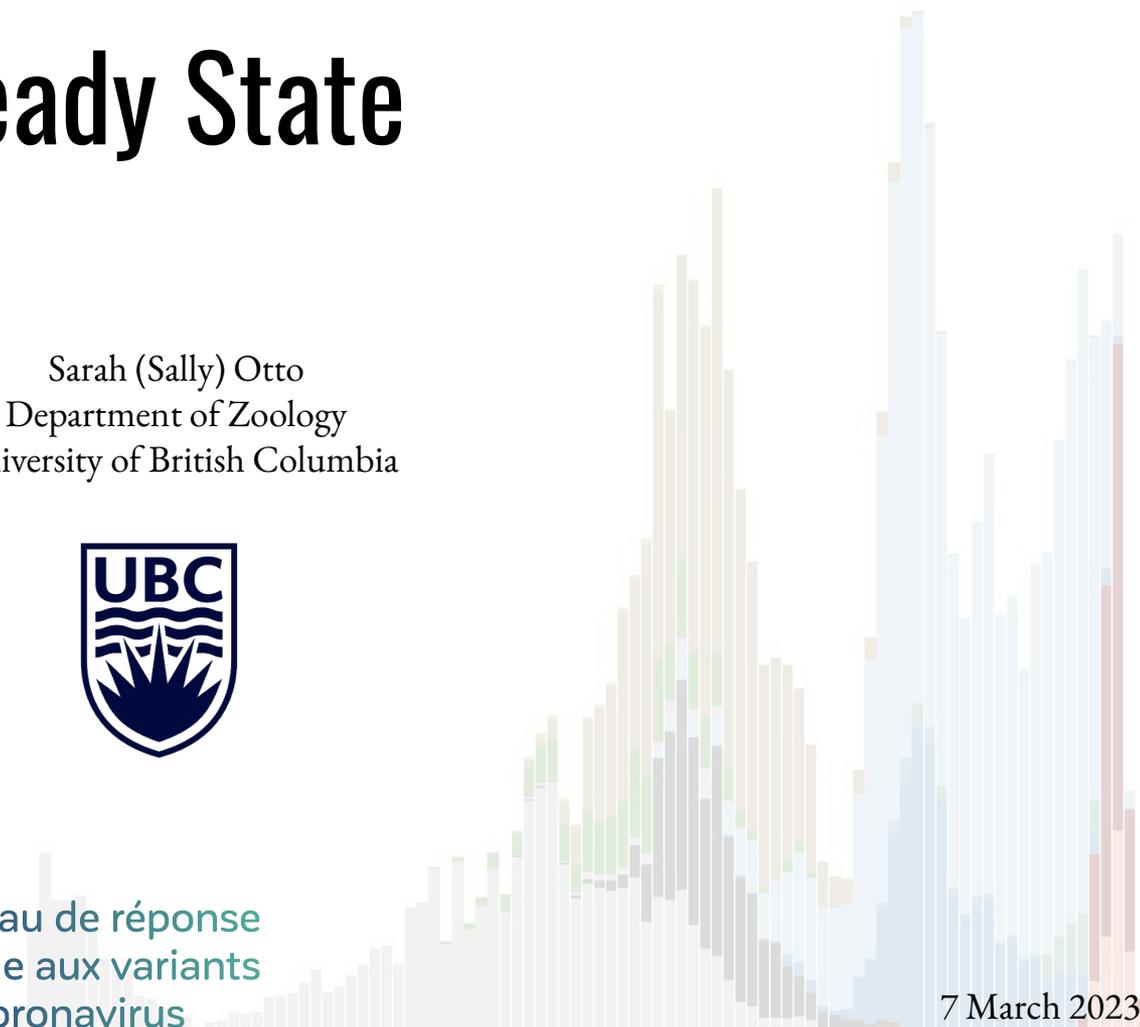


Coronavirus Variants
Rapid Response
Network



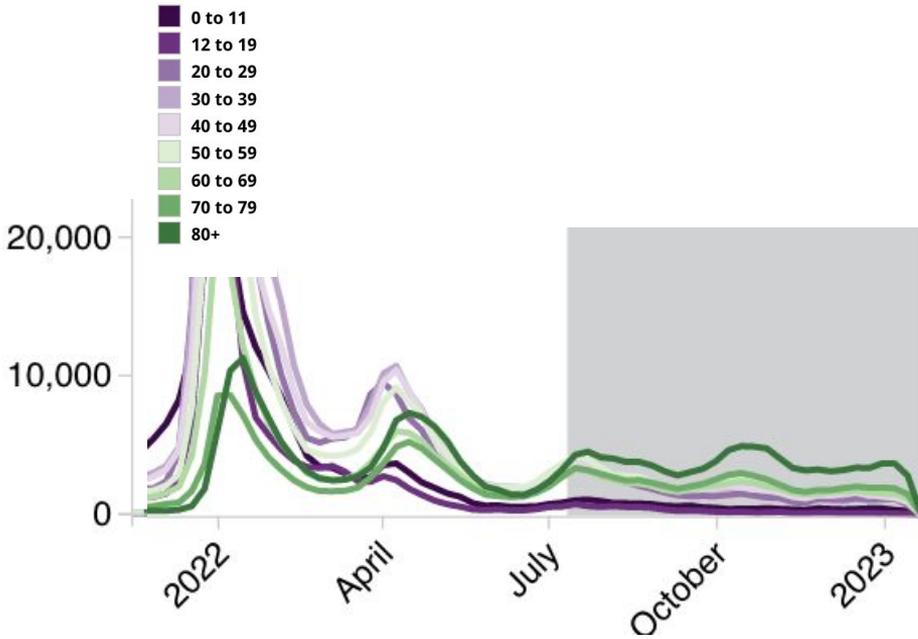
Réseau de réponse
rapide aux variants
du coronavirus

7 March 2023

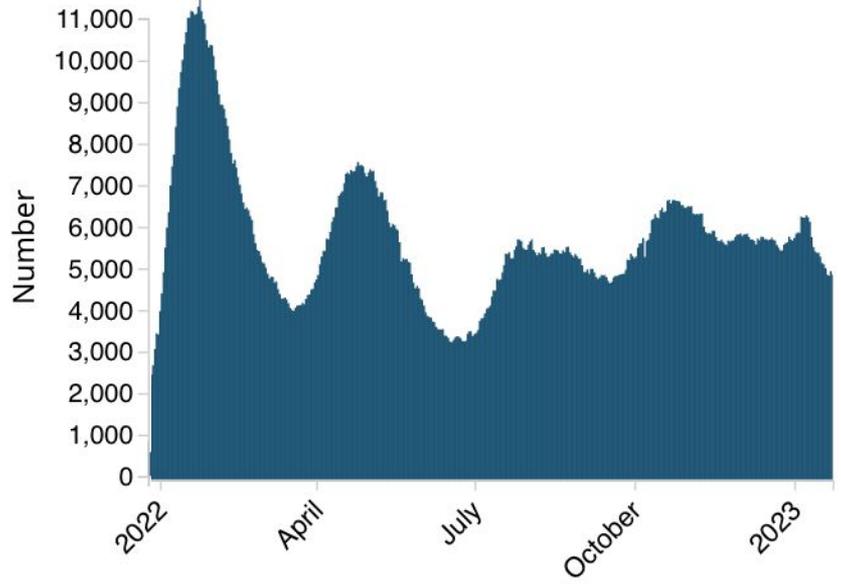


COVID-19 has held steady over last 8 months

Cases

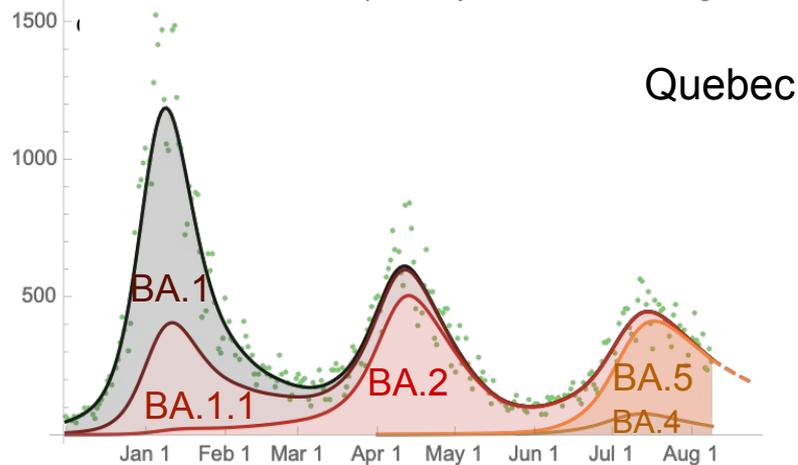
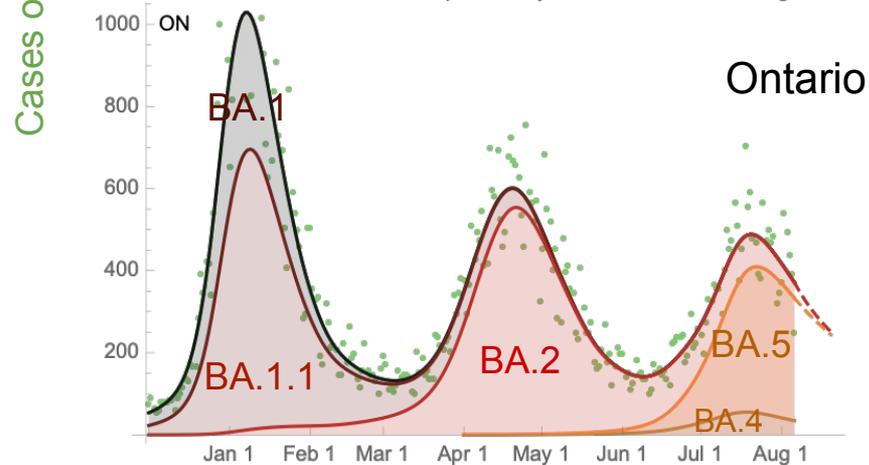
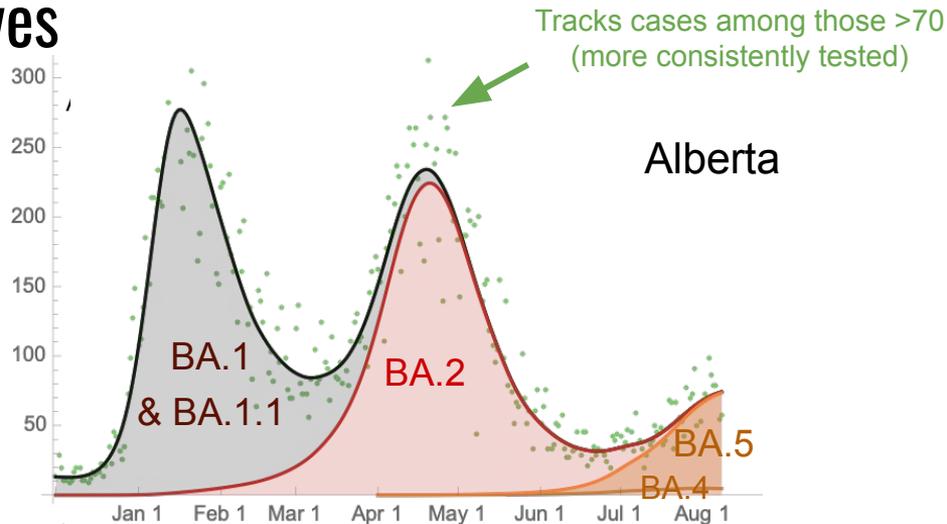
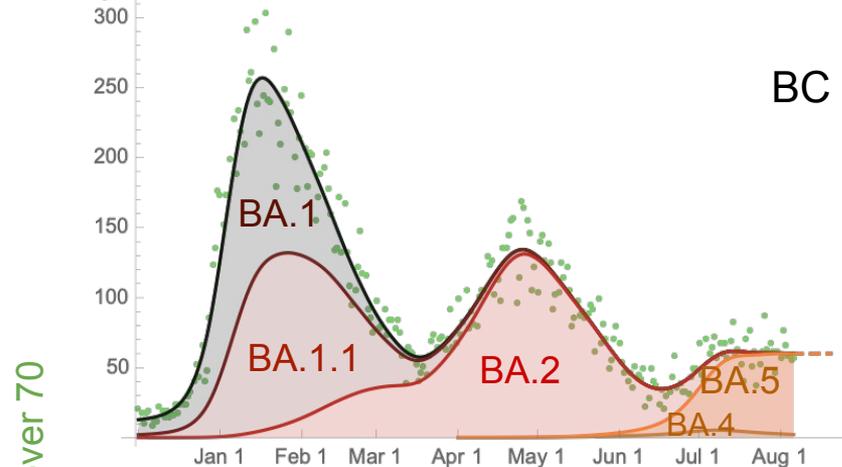


Hospital Occupancy

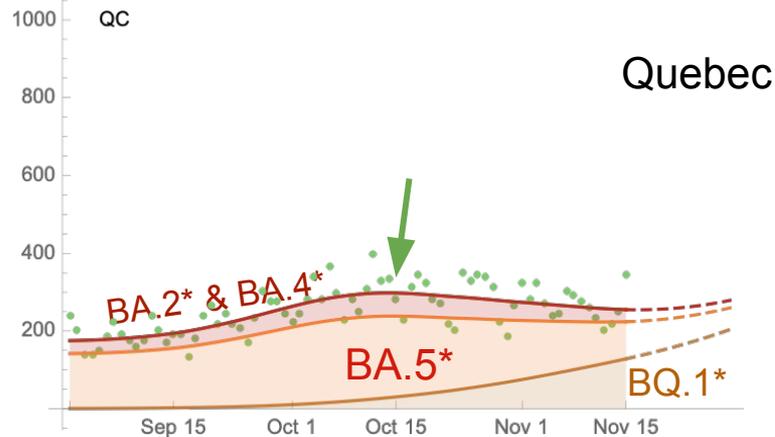
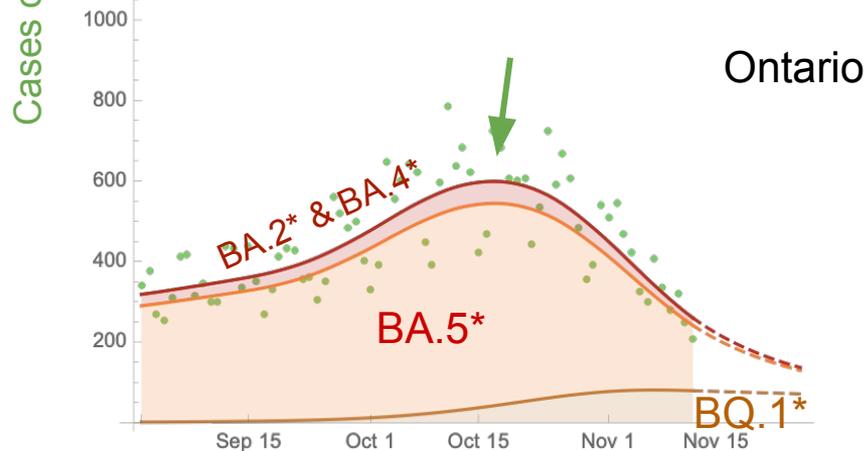
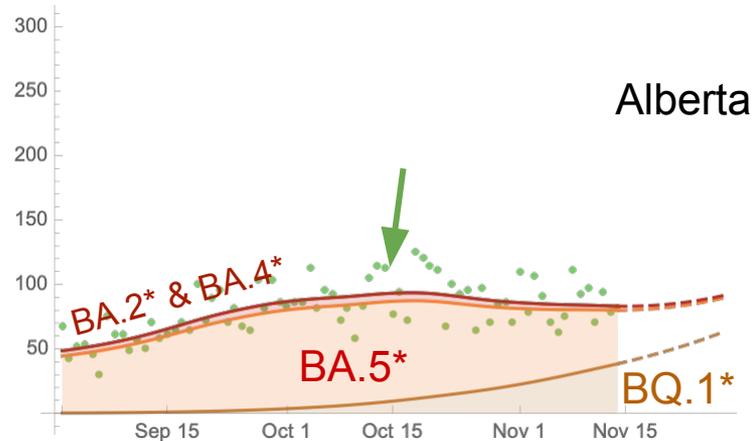
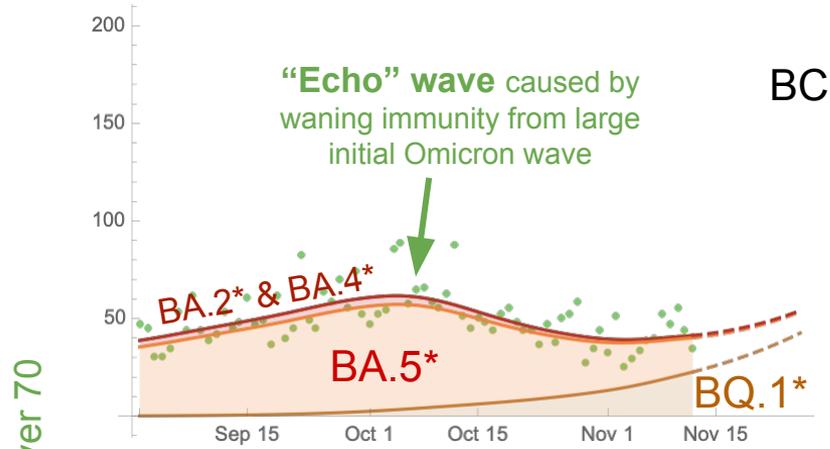


SOURCE: <https://health-infobase.canada.ca/covid-19/current-situation.html#graphHospVentICU>

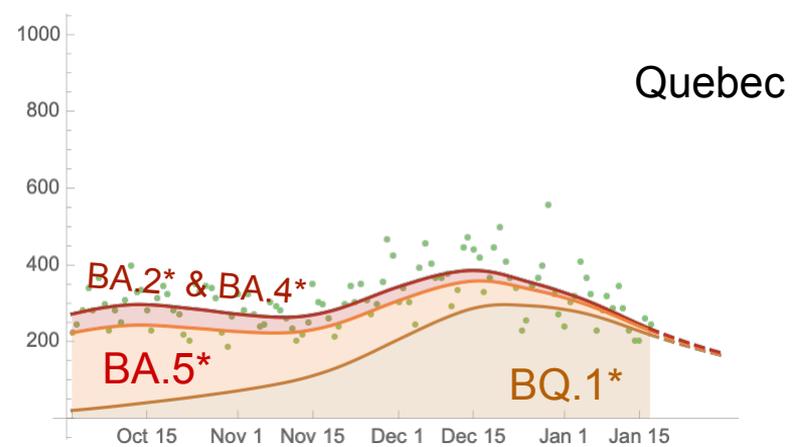
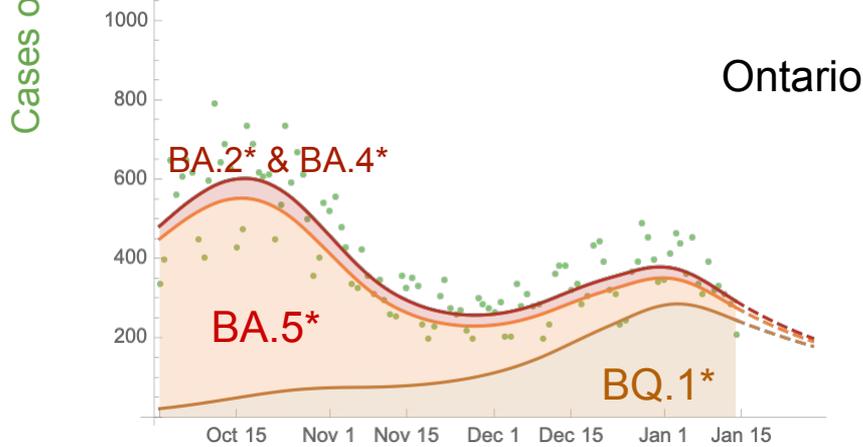
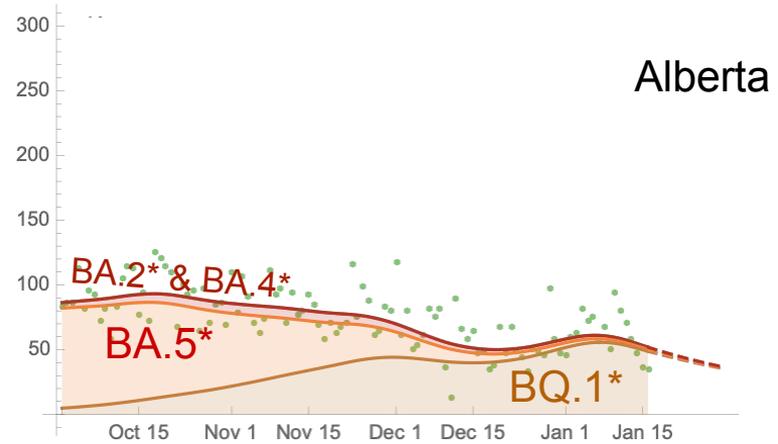
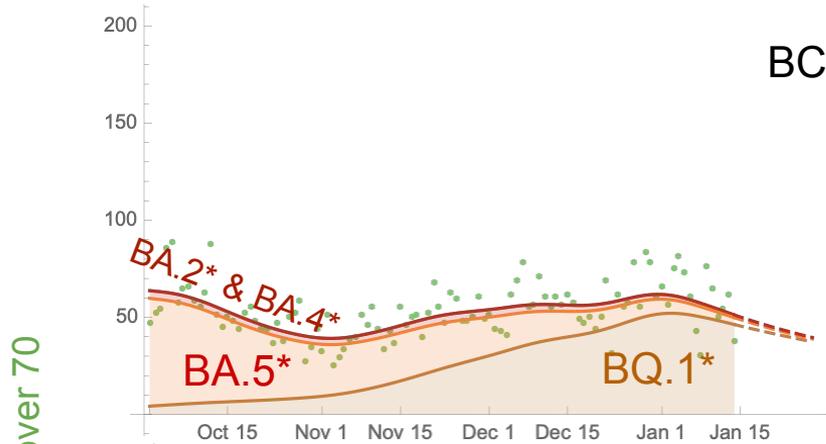
Early 2022: Distinct variant driven waves



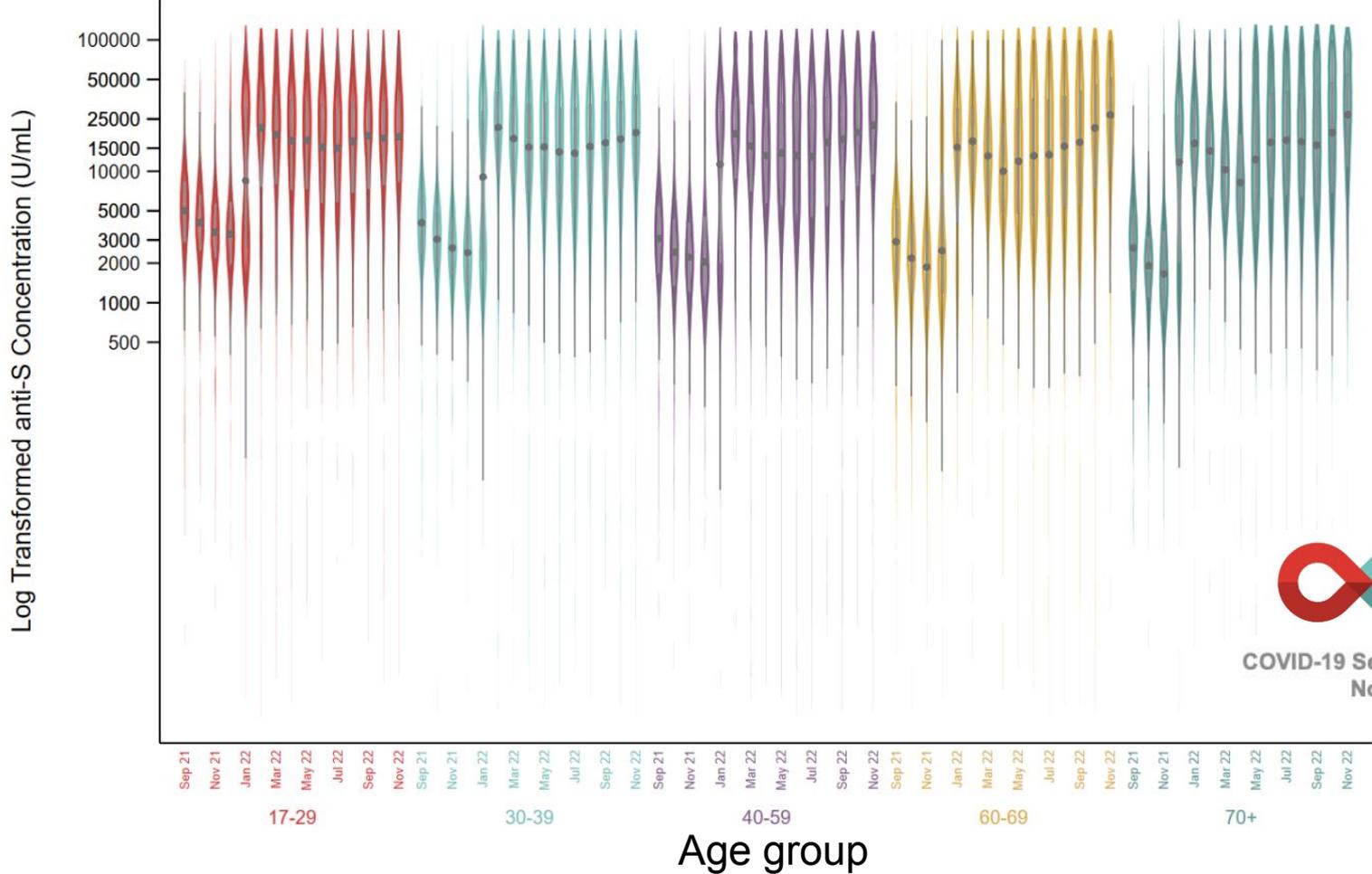
Fall 2022: Echo waves in fall not driven by variant



Winter 2022: Similar case levels despite further spread of variants

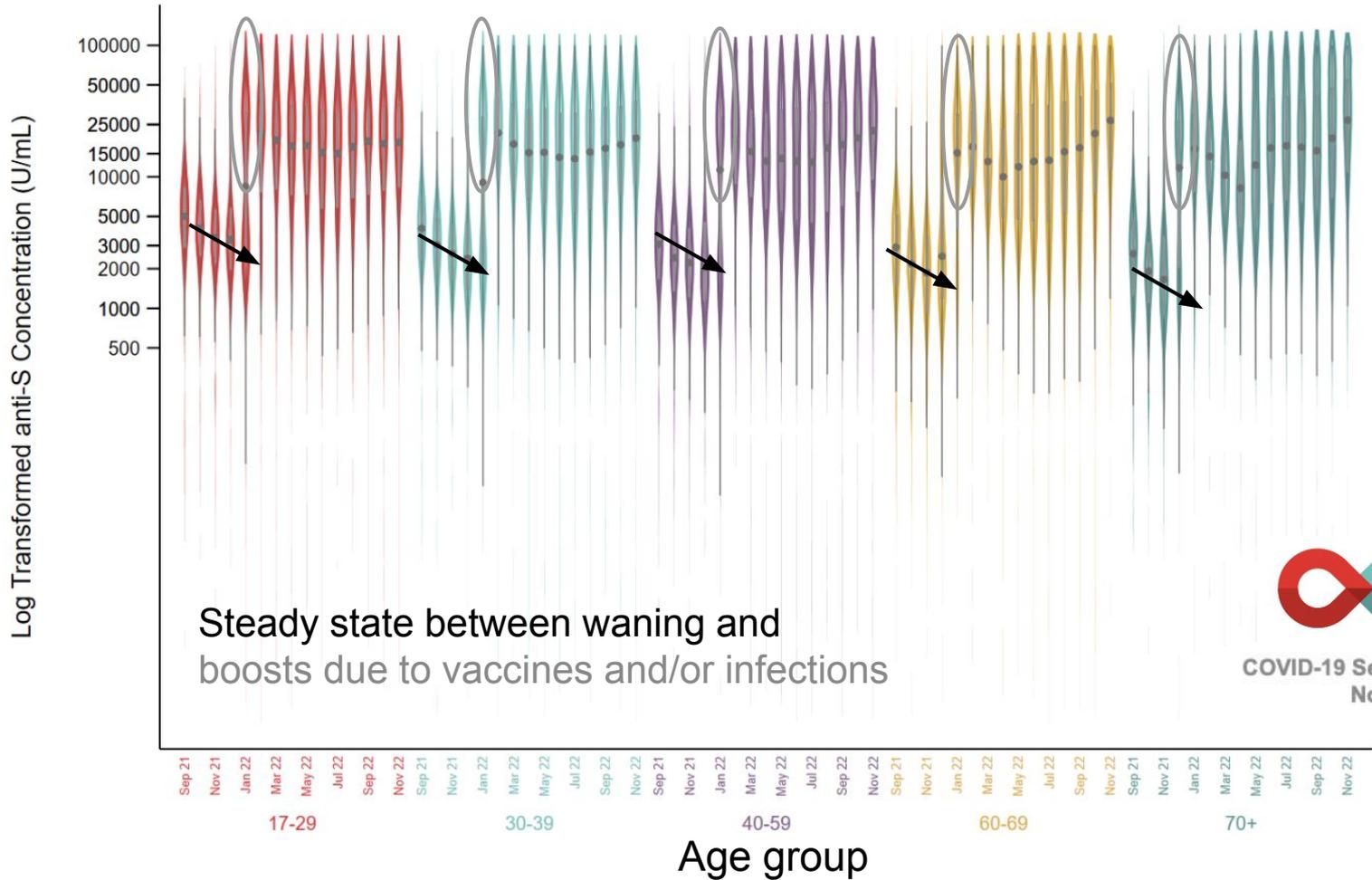


Canada-wide immunity is also approaching a steady state



COVID-19 Seroprevalence Report
November 2022 Survey

Canada-wide immunity is also approaching a steady state



Steady state between waning and boosts due to vaccines and/or infections



COVID-19 Seroprevalence Report
November 2022 Survey

Variants on the horizon in Canada



CoVaRR Net

Duotang

Duotang, a genomic epidemiology analyses and mathematical modelling notebook

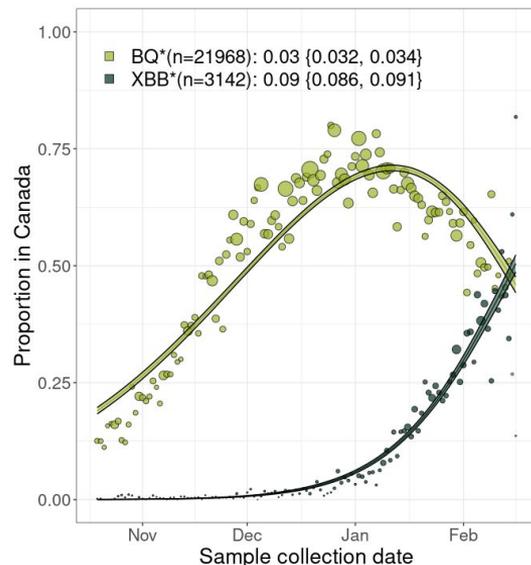
Pillar 6

06 March, 2023

We have built an automated analysis of frequency changes, estimating selection on variants across Canada.

Code ▾

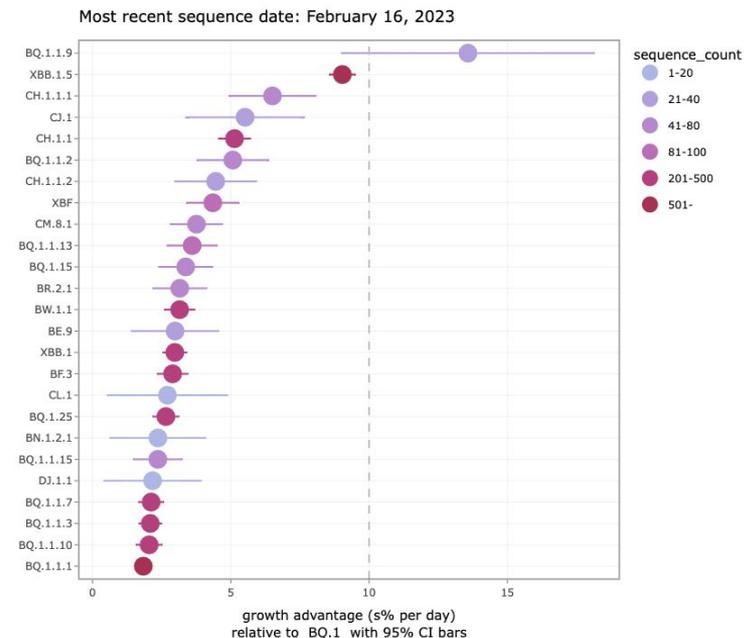
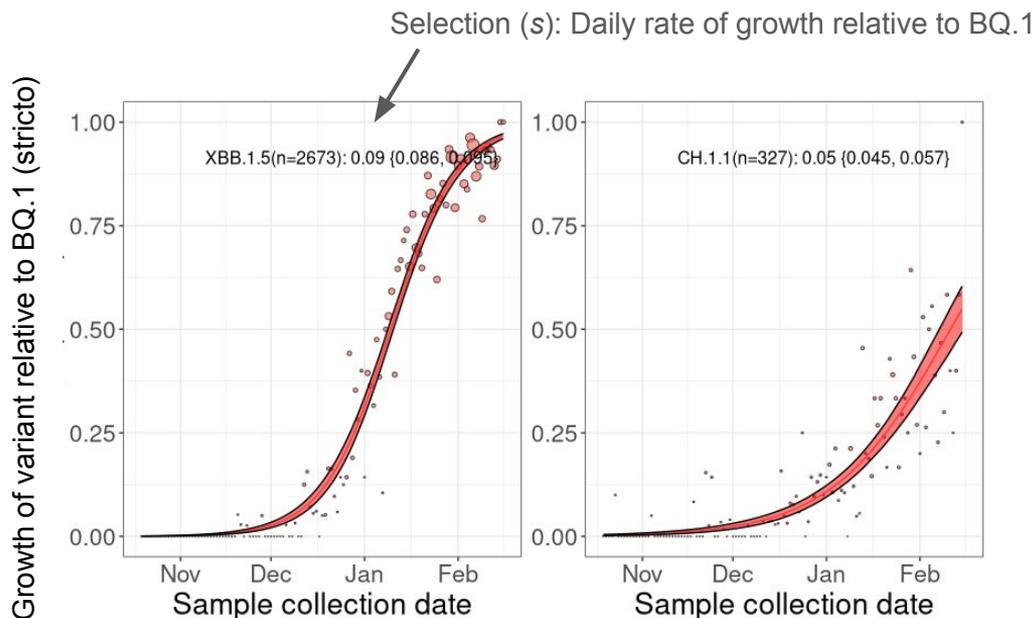
Code



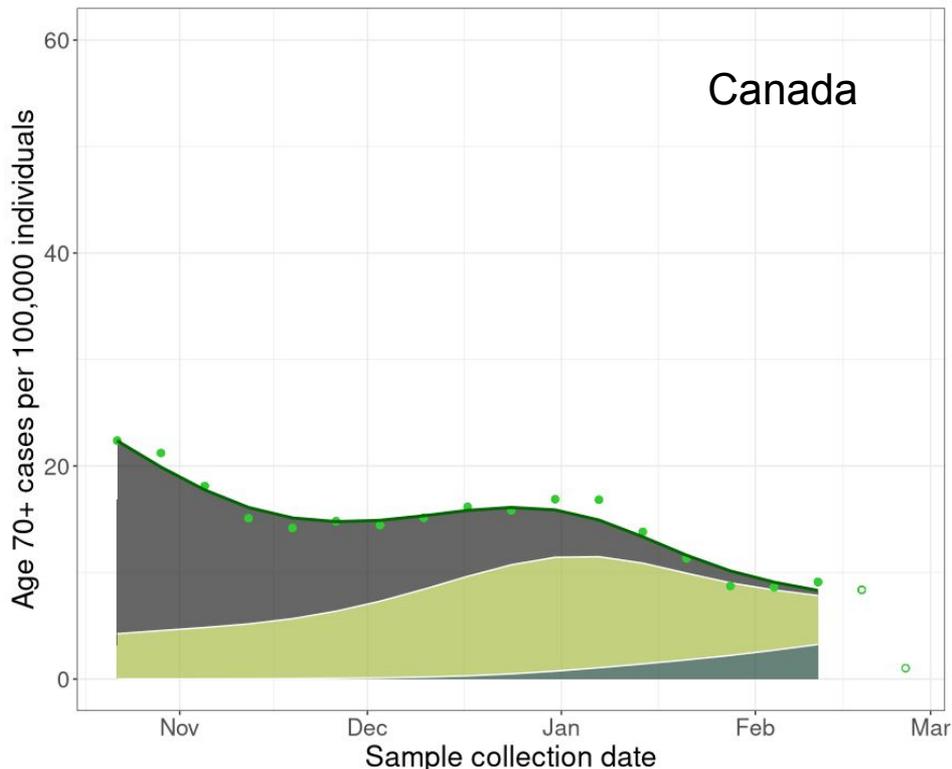
*Relative to the rest
Most recent data date: 2023-02-16

Variants on the horizon in Canada

429 named Omicron lineages have been circulating in Canada over the last three months. Measuring the selective advantage of each relative to BQ.1, the fastest growing lineages with sufficient data are the recombinant XBB.1.5 (s ~ 9% per day) and CH.1.1 (s ~ 5%).



Variants on the horizon in Canada



Cases over 70

Growth rate (r): Daily rate of growth in cases by variant

Variants

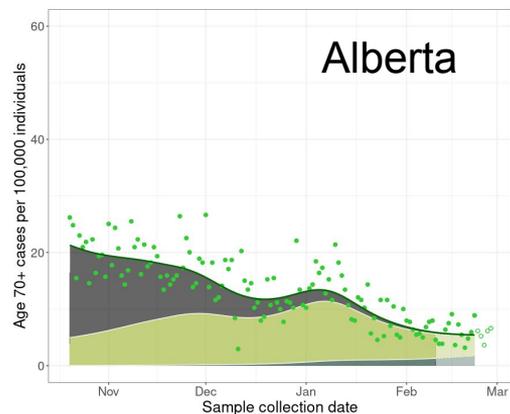
- The Rest (r = -7%)
- BQ* (r = -4%)
- XBB* (r = 1%)

Case Count (r = -1%)

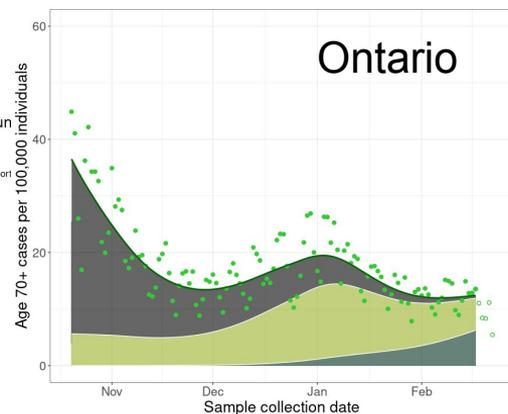
- Accurate (green dot)
- Under Reported (white dot)

Last day of genomic data (Darker colours) is 2023-02-18
Last day of accurate case counts (lighter colours) is 2023-02-11

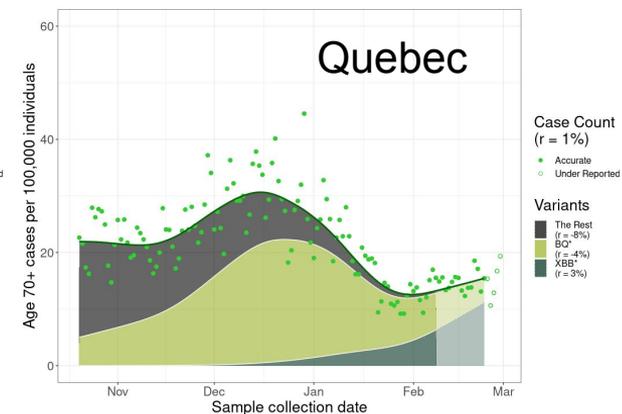
Variants on the horizon in Canada



Last day of genomic data (Darker colours) is 2023-02-10
 Last day of accurate case counts (lighter colours) is 2023-02-22



Last day of genomic data (Darker colours) is 2023-02-17
 Last day of accurate case counts (lighter colours) is 2023-02-17



Last day of genomic data (Darker colours) is 2023-02-08
 Last day of accurate case counts (lighter colours) is 2023-02-23

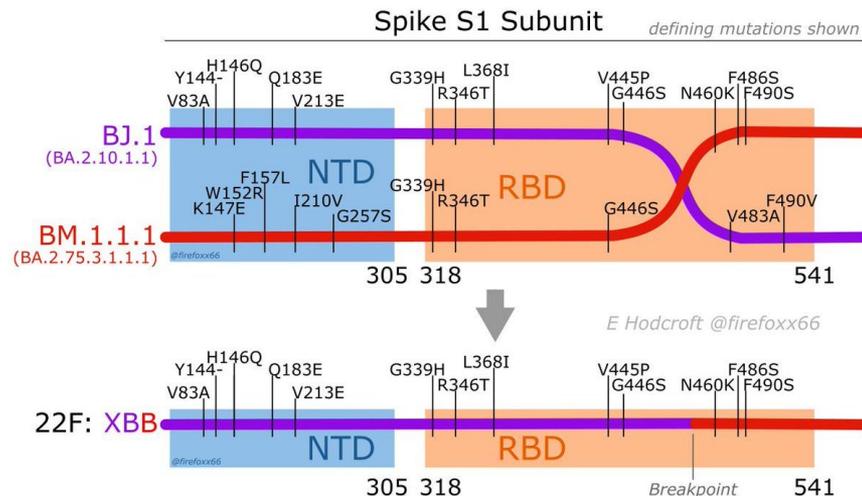
What is XBB.1.5?

XBB.1.5 is a descendant of XBB, a recombinant lineage between two BA.2* lineages. XBB.1.5 carries a change in the spike protein (S:F486P) that is rare, because the change from phenylalanine (F) to proline (P) requires two mutational steps.

All XBB and BQ.* lineages have strong immune evasion properties relative to BA.5*, but what gives XBB.1.5 the edge is thought to be superior binding to ACE2 receptors and so higher transmissibility ([Cao et al. 2023](#)).

Genomic signature of recombinant origin of XBB

(from Dr. Emma Hodcroft @firefox66)



Impact of variants

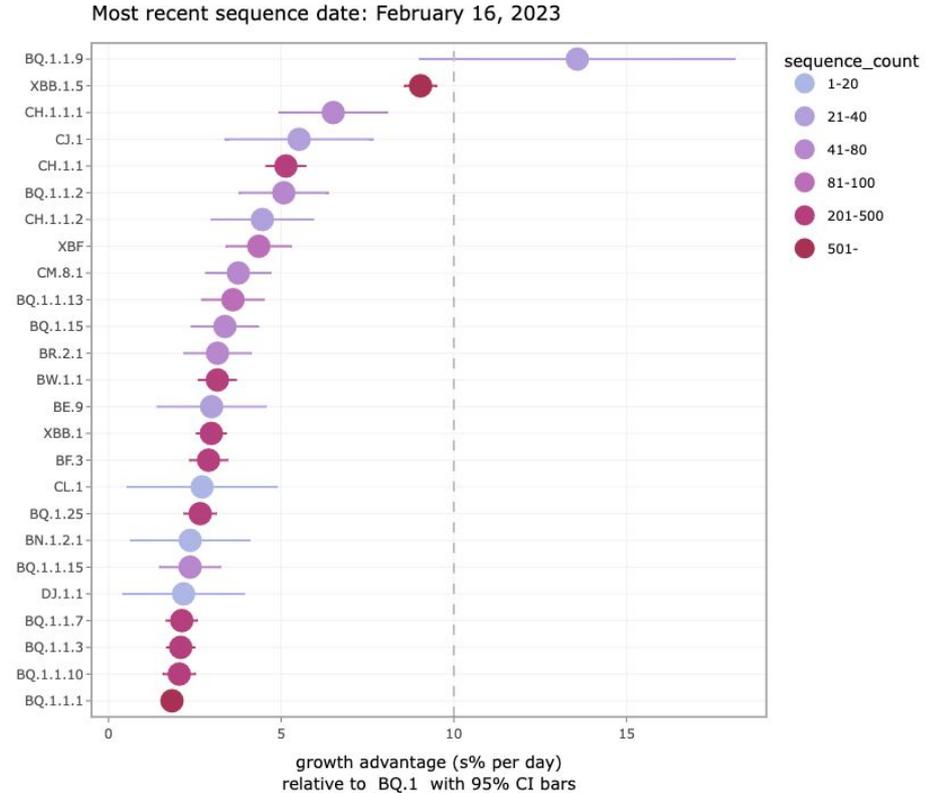
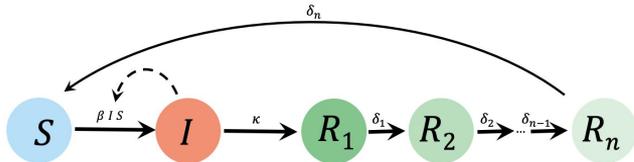
How will the spread of

a) Immune evasive variants (e.g., BQ.1*)

or more

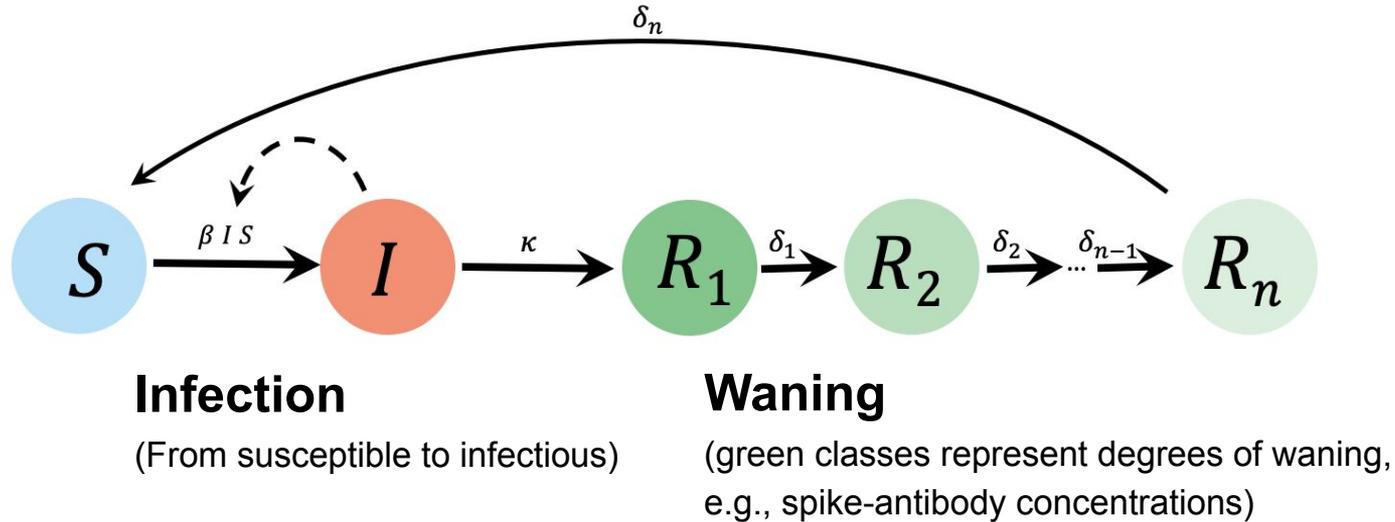
b) Transmissible variants (e.g., XBB.1.5)

alter the level of COVID-19?



COVID-19 levels

Models can help us explore the factors that affect the steady-state level of COVID-19 (e.g., variants, NPIs, vaccinations).

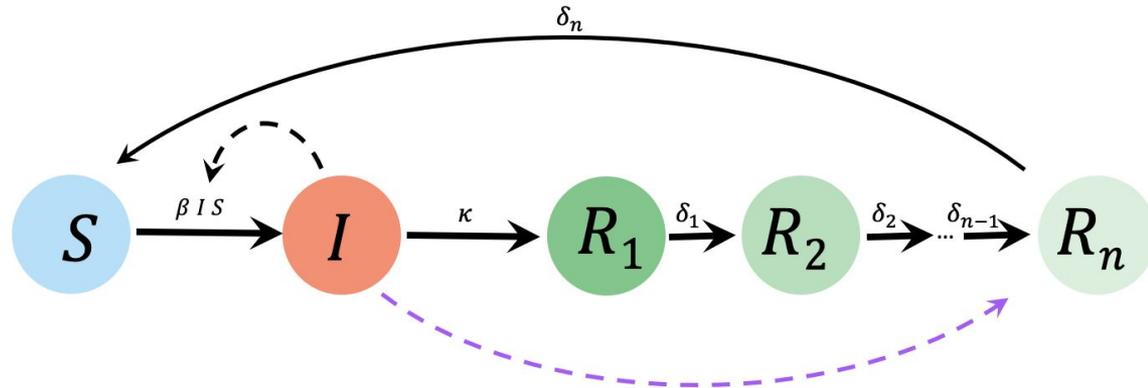


Impact of variants

a) Immune evasive variants

Immune evasive variants can spread by infecting individuals sooner (purple). The long-term impact depends on whether or not infections with the variant subsequently elicit strong recognition of that variant.

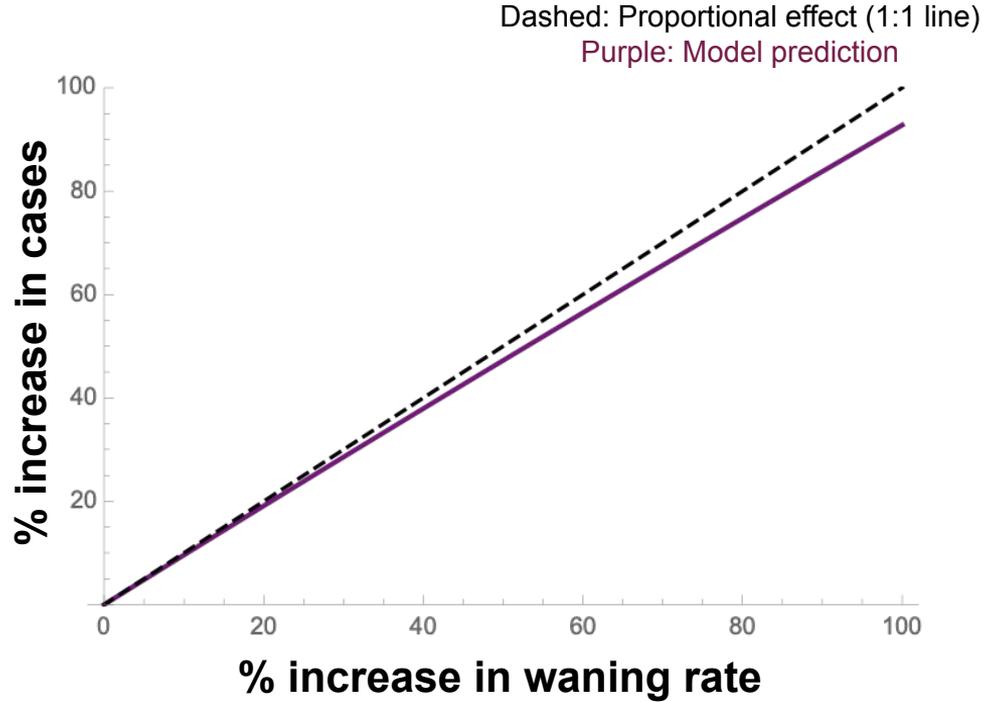
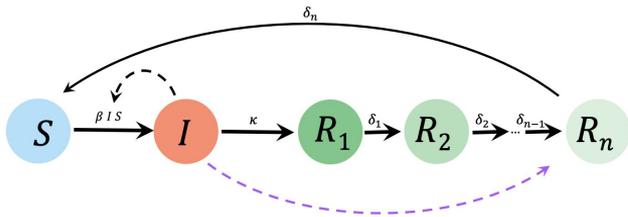
If immune evasiveness is **temporary** (immunity builds against the variant), the level of COVID-19 is **unaffected** in the long-term.



Impact of variants

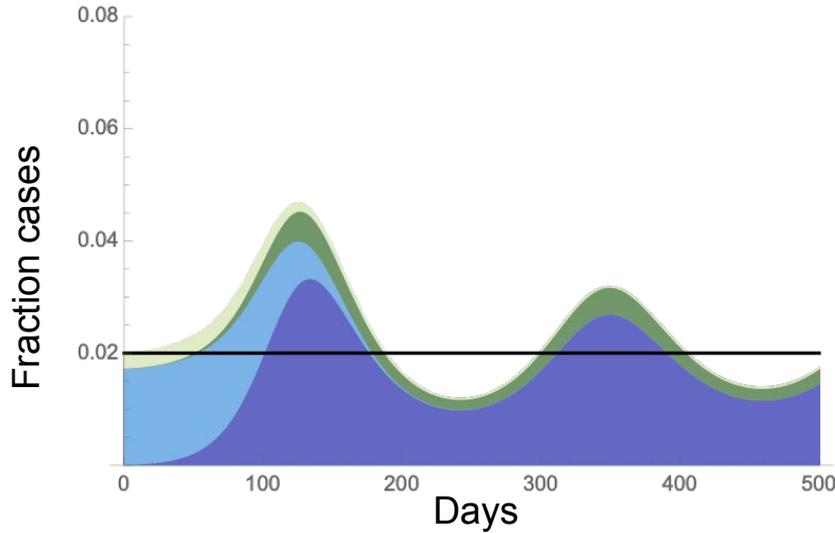
a) Immune evasive variants

If immune evasiveness is *permanent* (variant is always able to infect earlier), COVID-19 levels are expected to **rise in proportion** to the increased rate of waning.

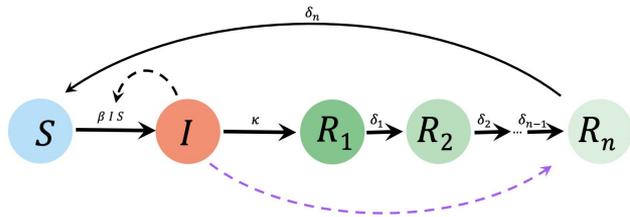
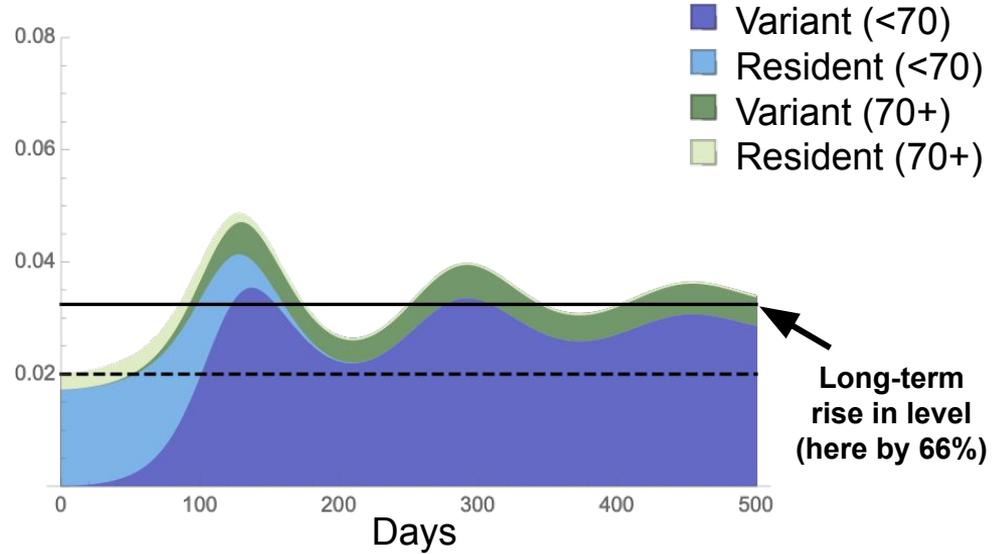


An immune-evasive variant wave

Temporarily immune evasive



Permanently immune evasive



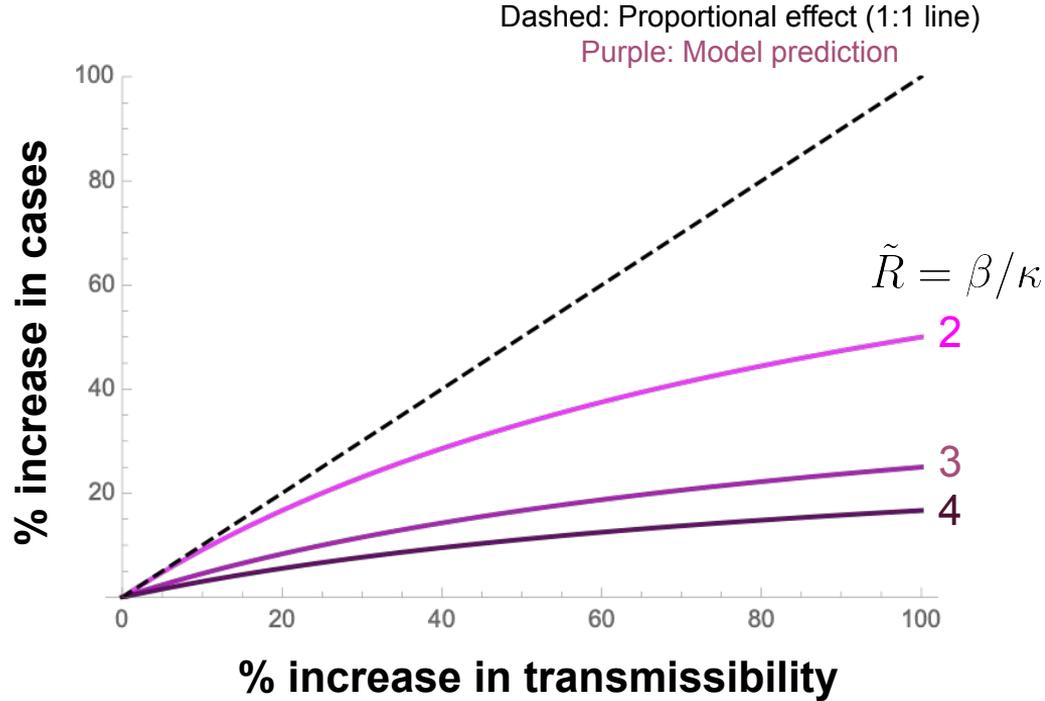
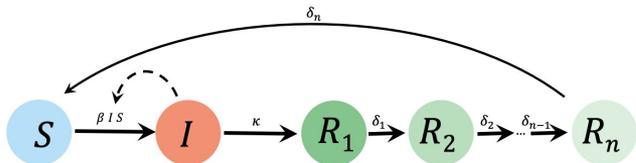
Simulation example: Resident allele wanes over ~6 months for <70 and ~4 months for 70+. Variant increases waning rate by 66% ($s = 5\%$ per day selective advantage). Infectious period lasts an average of 7 days. Transmission rate, β , is set to give a current infection rate of 1 in 50 (comparable to [COVID-19 Resources Canada](#): 1 in 32; [National Defence](#): 1 in 150).

Impact of variants

b) Transmissible variants

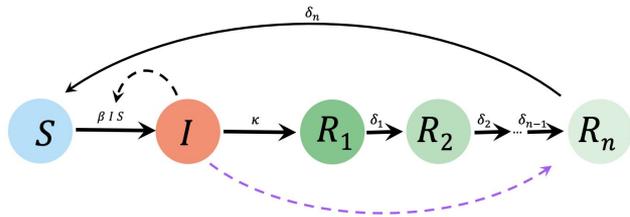
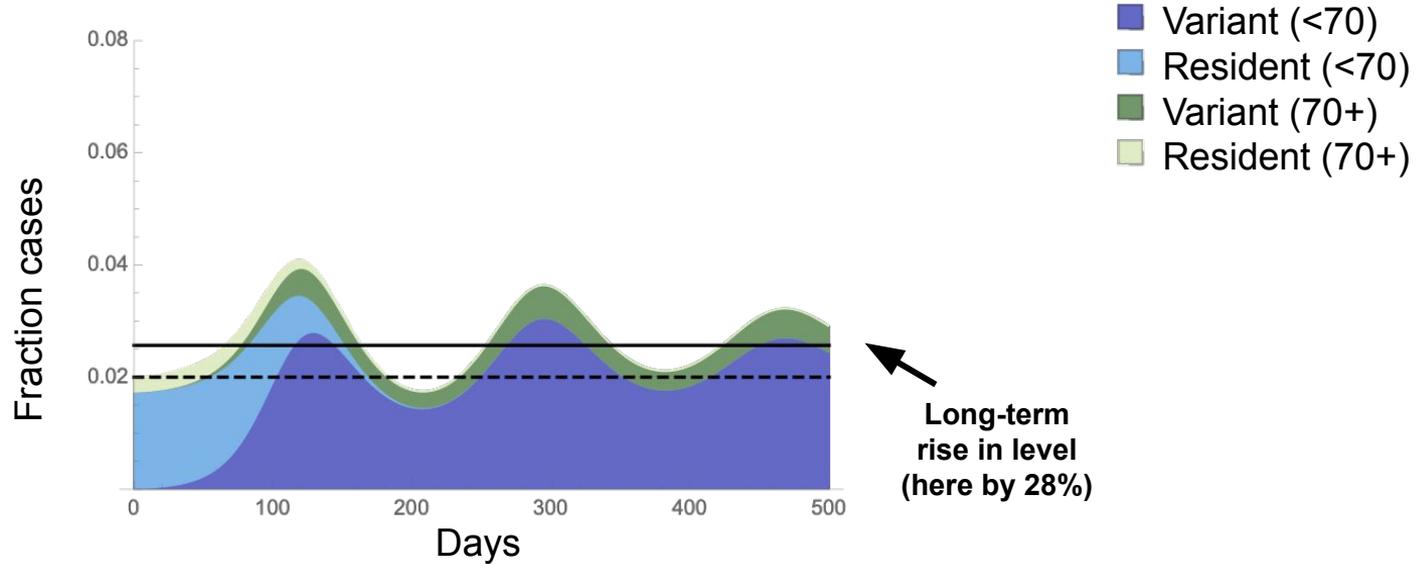
Lineages, like XBB.1.5, that are more transmissible (increasing β) rapidly deplete the susceptible pool and have an intermediate influence on cases.

Model result: If a variant increases transmission by a factor c , the steady state number of COVID-19 infections increases only by $\frac{c\tilde{R} - 1}{c(\tilde{R} - 1)}$



$\tilde{R} = \beta/\kappa$ is the effective reproductive number (# of new cases per infection) if everyone were susceptible today, given current measures and immune memory (estimated from current infection levels to be ~2-4).

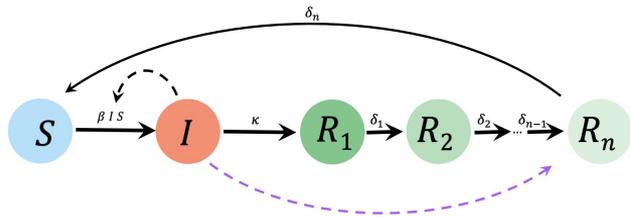
A more transmissible variant wave



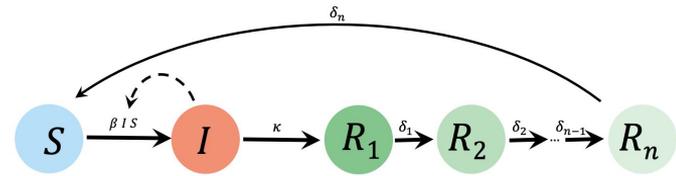
Simulation example: Variant increases transmissibility β by a factor 1.36, for a selective advantage of $s = 5\%$ per day. See other details on slide 15.

Impact of variants

The largest impact on standing levels of COVID-19 is expected from variants that are **permanently immune evasive**, then more **transmissible variants**, with the lowest impact expected for variants that are only **temporarily immune-evasive** because they elicit variant-specific antibodies.



Impact of public health measures



How would changes in

c) Vaccination rates

or

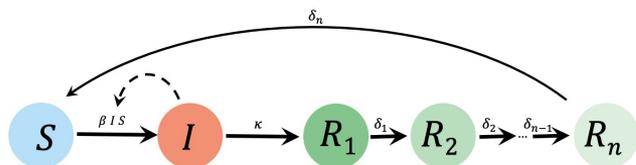
d) NPIs (e.g., masking or ventilation)

alter the level of COVID-19?

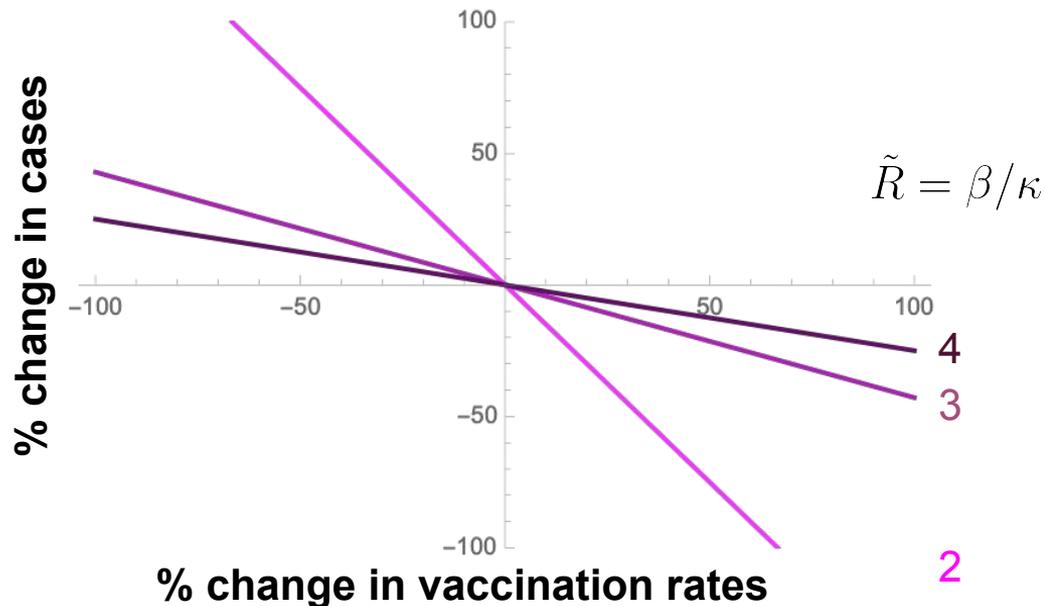
Impact of public health measures

c) Changing vaccination rates

Current rates of vaccination are ~1M per month. The steady-state level of COVID cases depends strongly on vaccine rates, given likely range of the effective reproductive number.



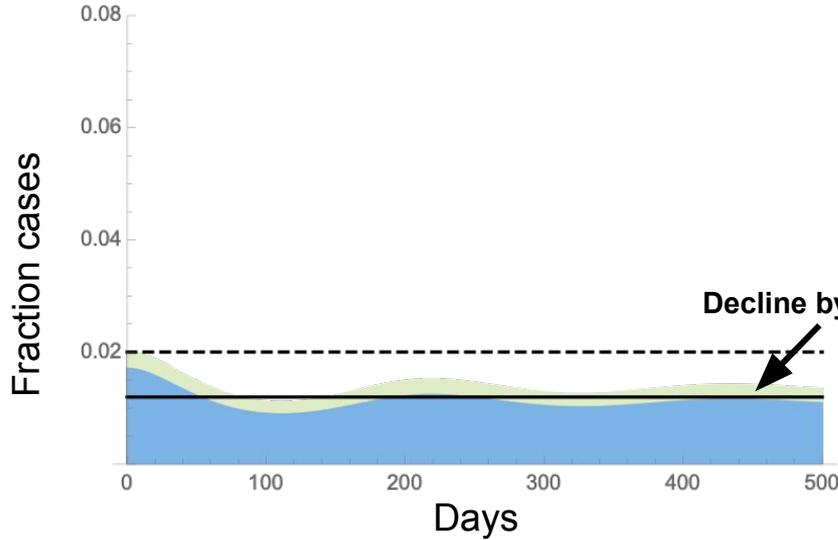
Purple: Model prediction



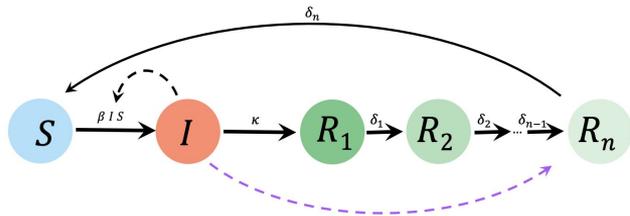
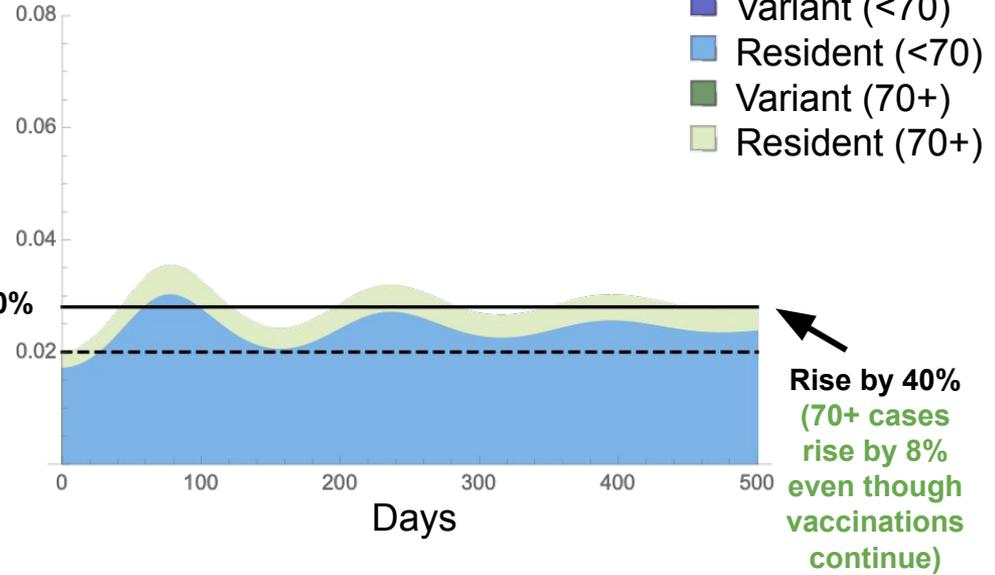
$\tilde{R} = \beta/\kappa$ is the effective reproductive number (# of new cases per infection) if everyone were susceptible today, given current measures and immune memory (estimated from current infection levels to be ~2-4).

Impact of public health measures

Doubling vaccination rates



Stopping vaccination in <70



Simulation example: Vaccination occurs at a rate of one million doses per month and are given to susceptible Individuals. See other details on slide 15.

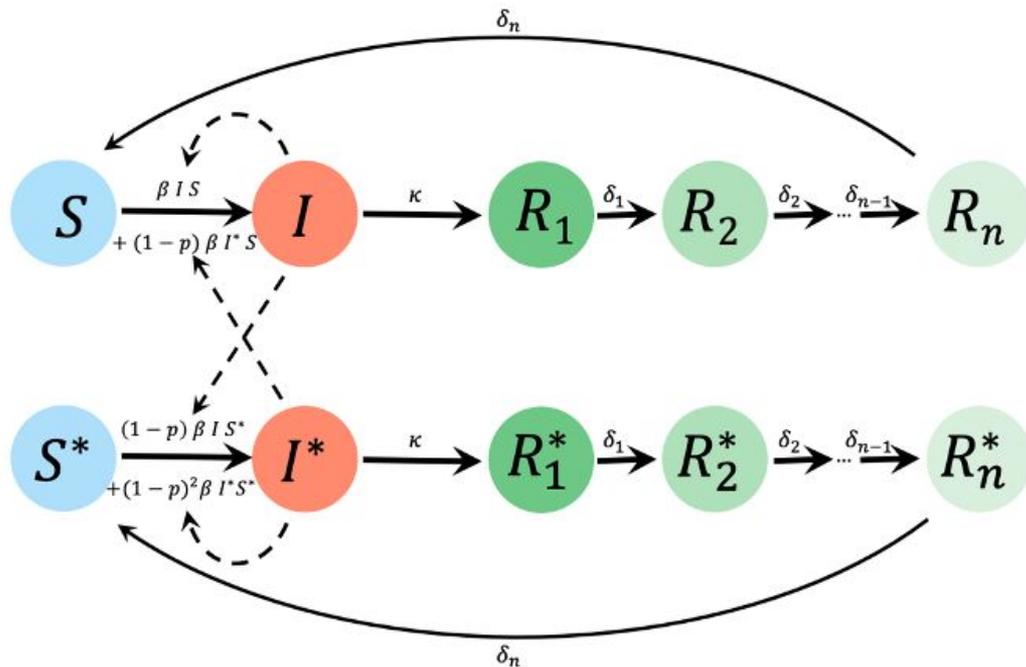
Impact of public health measures

d) Changing NPI uptake

NPIs (including masking and improved ventilation) that reduce the chance of transmission (by p) have both individual and population benefits.

The benefits depend on the efficacy of the measure.

For example, a metaanalysis of early masking studies suggest $p = 0.25$ (Leech et al. 2022), although the authors note that this underestimates the benefits of consistent use of high-quality masks.



Impact of public health measures

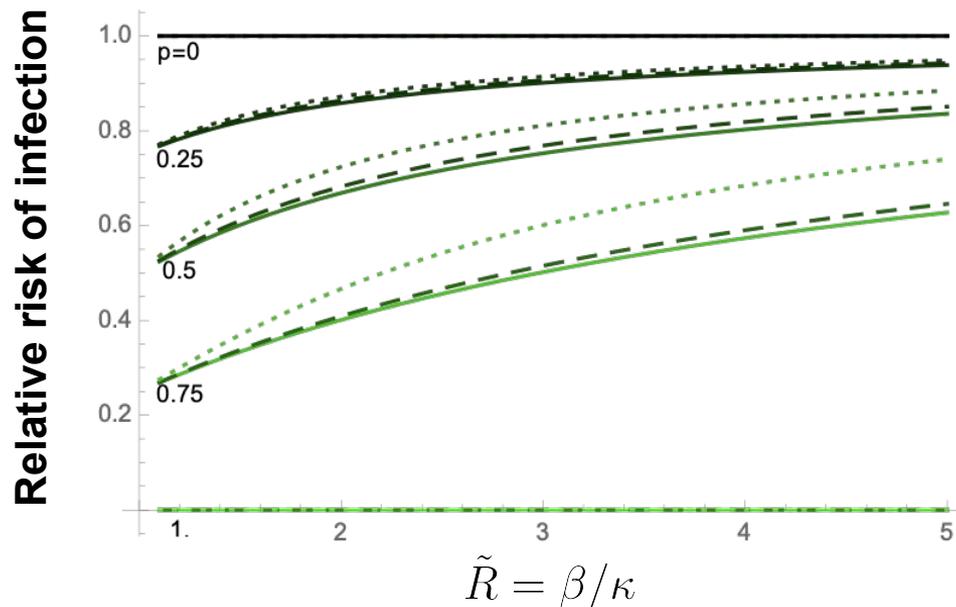
d) Changing NPI uptake

NPIs (including masking and improved ventilation) that reduce the chance of transmission (by p) have both **individual** and population benefits.

The benefits depend on the efficacy of the measure.

For example, a metaanalysis of early masking studies suggest $p = 0.25$ (Leech et al. 2022), although the authors note that this underestimates the benefits of consistent use of high-quality masks.

Fraction of population practicing
 $f = 10\%$ (solid)
 $f = 50\%$ (dashed)
 $f = 90\%$ (dotted)



$\tilde{R} = \beta/\kappa$ is the effective reproductive number (# of new cases per infection) if everyone were susceptible today, given current measures and immune memory.

* The benefits of avoiding infection decline as transmission rises because individuals experience more exposures.

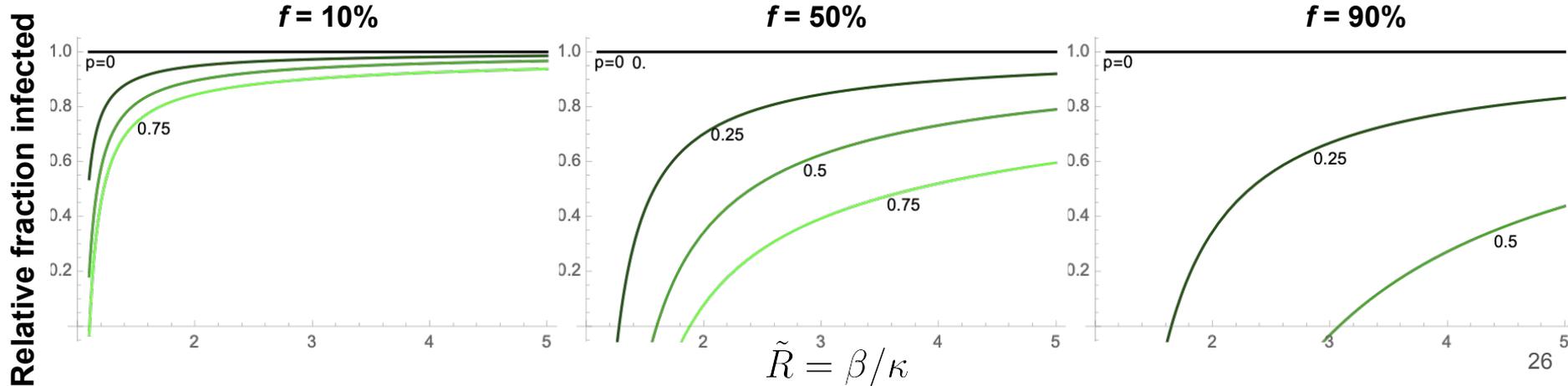
Impact of public health measures

d) Changing NPI uptake

At the **population** level, if the fraction participating in the NPI measure, f , is too low (left), the steady state number of cases remains high.

As participation rises (right), case numbers – and the health impacts that result – can be substantially reduced.

→ Focus on those measures, at those times, where more people will willingly comply.



Limiting the appearance of variants

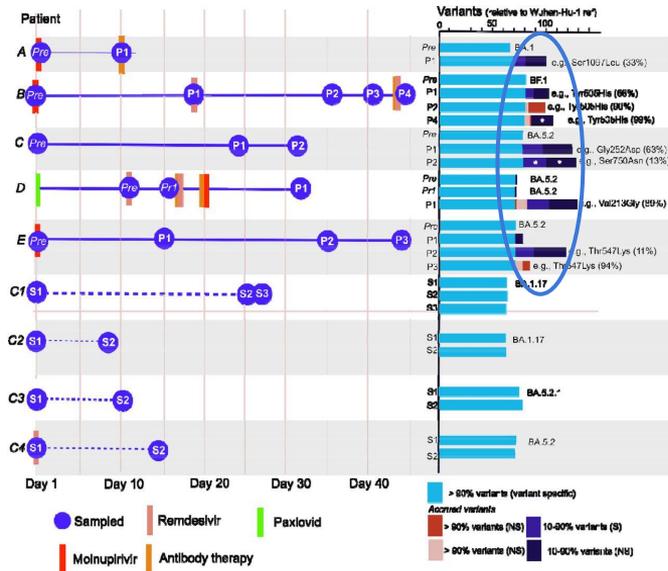
Policies to reduce appearance rate of variants:

- Reduce cases
- Detect and treat persistent infections
- Avoid mutagens when treating COVID-19, and urge other countries to halt use of Molnupiravir

Limiting the appearance of variants

Policies to reduce appearance rate of variants:

- Reduce cases
- Detect and treat long-term infections
- Avoid mutagens when treating COVID-19, and urge other countries to halt use of Molnupiravir



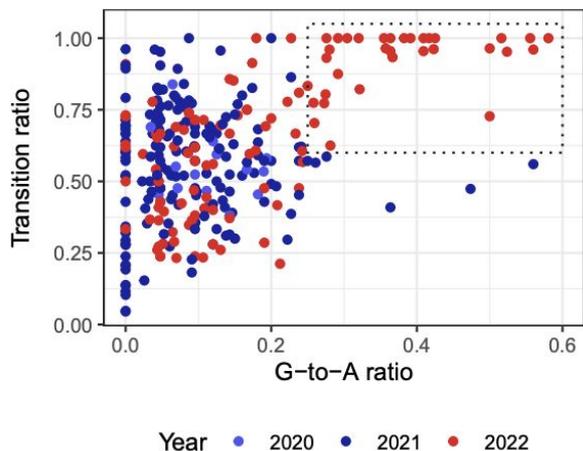
Patients with long-term infections accumulated dozens of additional mutations after Molnupiravir treatment

Samples prior to Molnupiravir and controls showed no such pattern (bearing only mutations they started with)

Limiting the appearance of variants

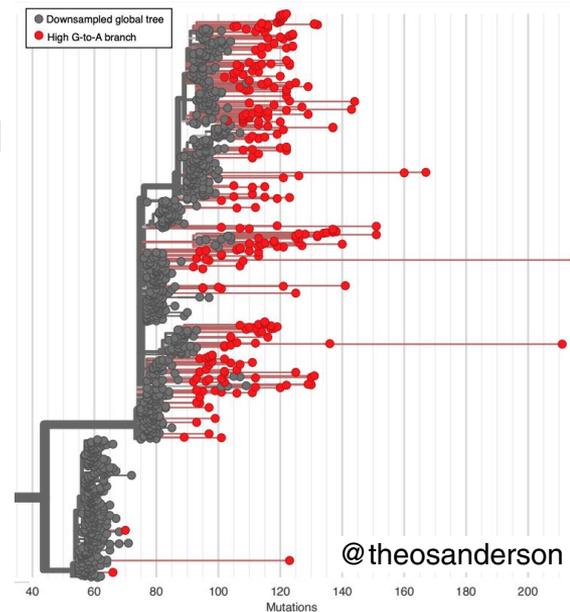
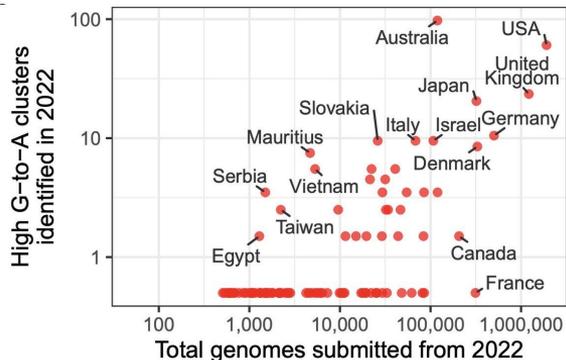
Policies to reduce appearance rate of variants:

- Reduce cases
- Detect and treat long-term infections
- Avoid mutagens when treating COVID-19, and urge other countries to halt use of Molnupiravir



[Sanderson et al. \(2023\)](#)

A signature of **Molnupiravir** is a higher G-to-A mutation rate, a signature found recently (in 2022, not 2021) and in countries that approved the drug.



Limiting the appearance of variants

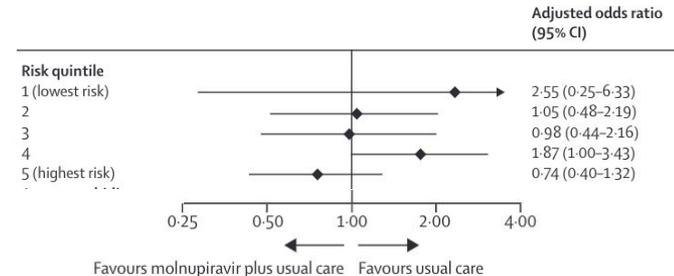
Policies to reduce appearance rate of variants:

- Reduce cases
- Detect and treat long-term infections
- Avoid mutagens when treating COVID-19, and urge other countries to halt use of Molnupiravir

Efficacy is modest at best.

A recent large randomized trial in the UK (PANORAMIC, [Butler et al. 2023](#)) found "Molnupiravir did not reduce the frequency of COVID-19-associated hospitalisations or death among high-risk vaccinated adults...(adjusted odds ratio 1.06 [95% Bayesian credible interval 0.81–1.41])"

- Call for global halt to this mutagen.



As we approach endemic COVID-19, we need to shift discourse from “bending the curve” to “**lowering the level**” of **COVID**.

We should expect few major peaks (unless a new variant arises that evades most immunity), but also no low troughs.

Public health and individual-level protective measures remain important, as they lower the level of cases and serious health impacts.

Thank you

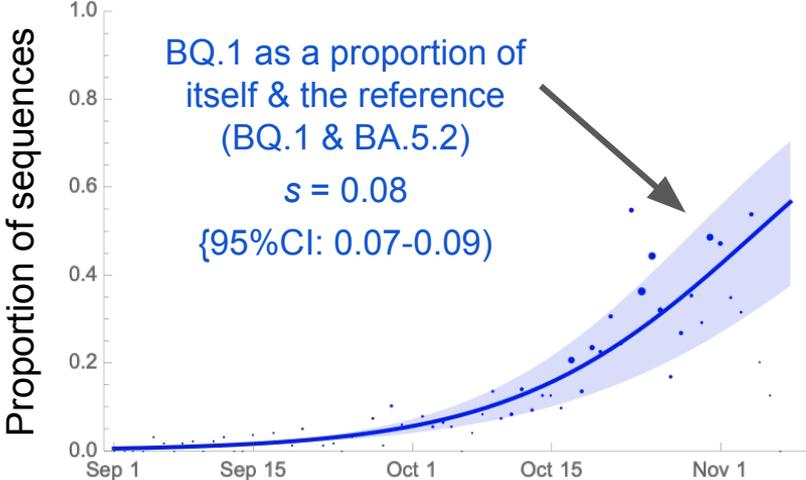


Appendix: Interpreting selection

What is selection (“s”) and what does it mean?

s measures the selective advantage per day of a variant relative to a reference strain (e.g., measuring the rate of spread of BQ.1 relative to BA.5.2)*.

This selective advantage may reflect a higher transmission rate or a greater ability to evade immunity or both.



* Selection per day, s, satisfies $p_T = \text{Exp}(s T) p_0 / (1 - p_0 + \text{Exp}(s T) p_0)$ where p_T is the frequency of a lineage of interest on day T, considering only itself and the reference (e.g., the # of BQ.1 divided by the # of BQ.1 and BA.5.2). s is estimated from the numbers of sequences over time by maximizing the likelihood of observing the data (see [methods](#)).

