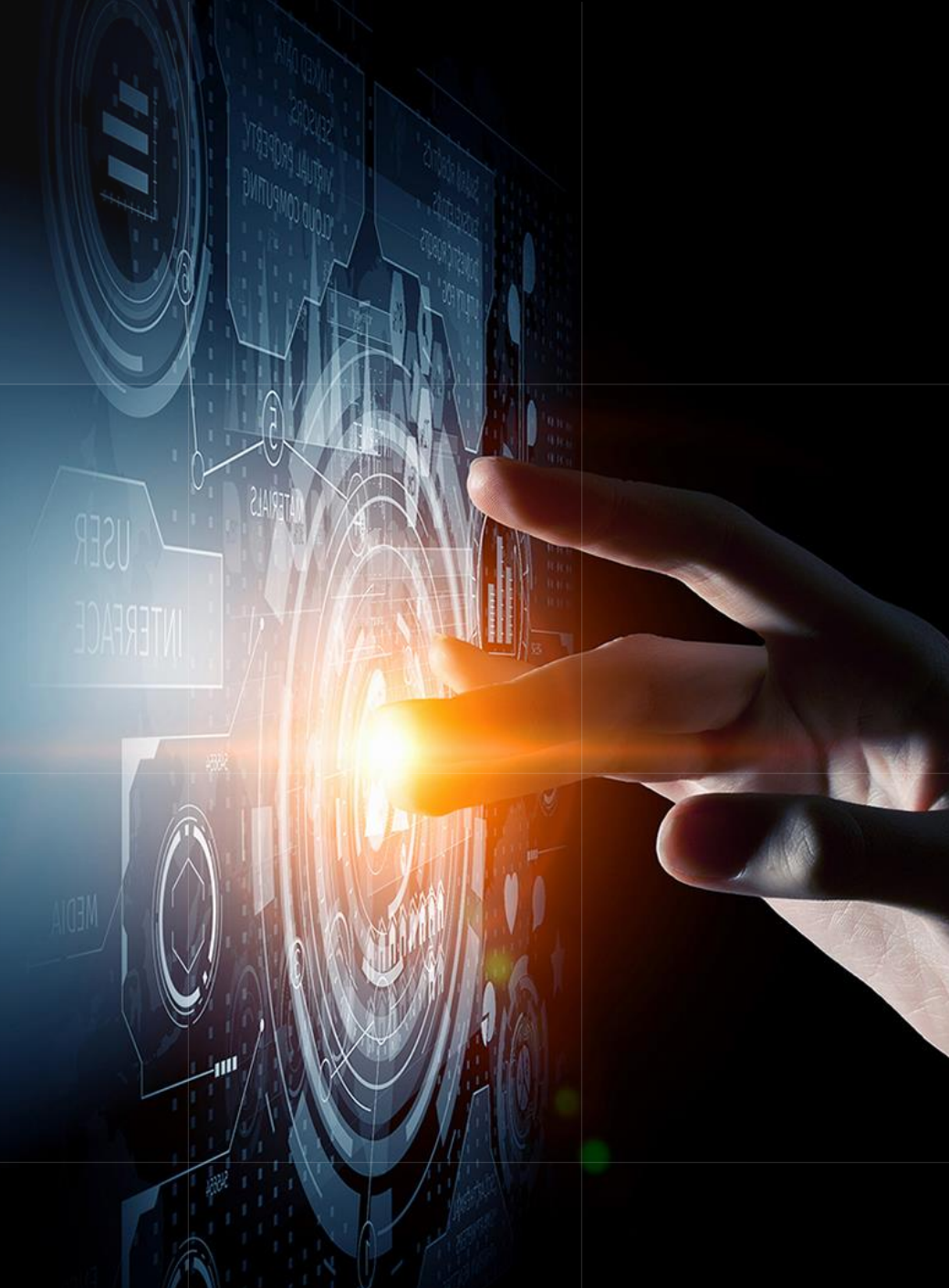


COVID-19 update

February 2021



COVID-19 update

Gradually turning the corner

This presentation provides information on the roll out of vaccine programs following the clinical trial announcements from Pfizer, Moderna and AstraZeneca in November 2020.

We also look at the emergence of more transmissible strains of the virus (SARS-CoV-2).

The COVID-19 pandemic has continued across the globe, but there are some signs that things are improving, at least in the developed world.

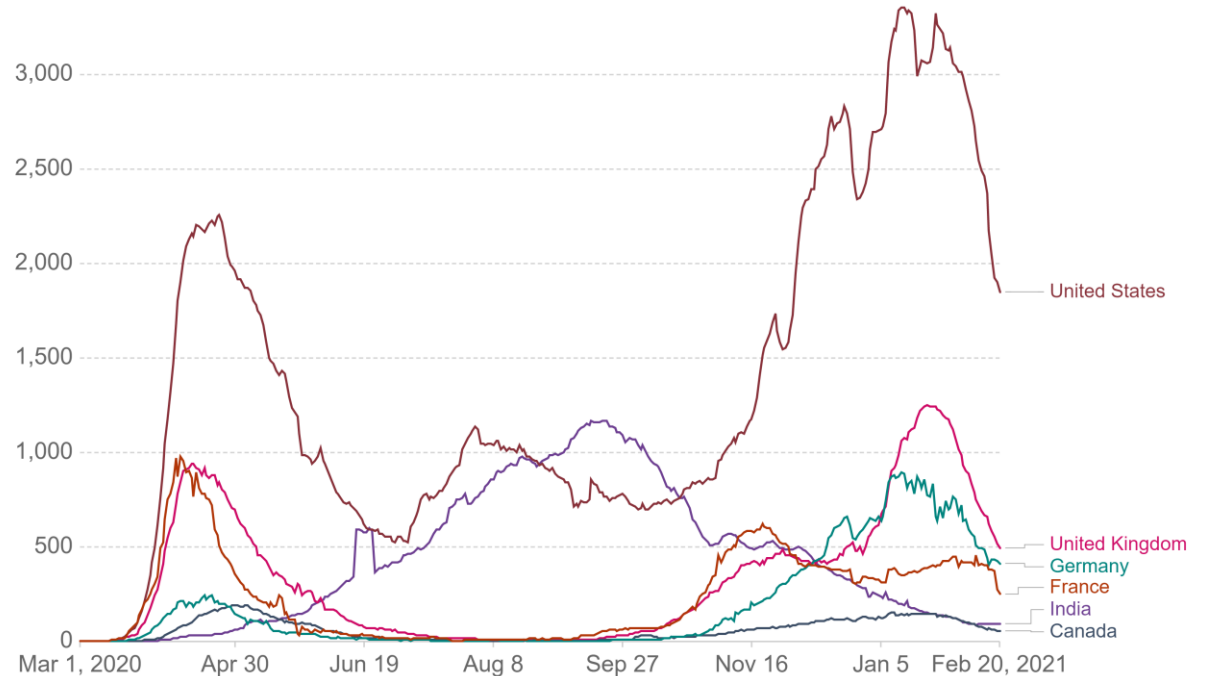
- Death rates are clearly improving in many countries.

A number of countries have begun vaccination programs, but these are unlikely to have had much effect on the course of the pandemic at this point.

- The main impact to date will be from more traditional measures, such as lockdowns and social distancing.

Daily new confirmed COVID-19 deaths

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.



Source: Johns Hopkins University CSSE COVID-19 Data – Last updated 21 February, 19:04 (London time)

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Vaccine roll out

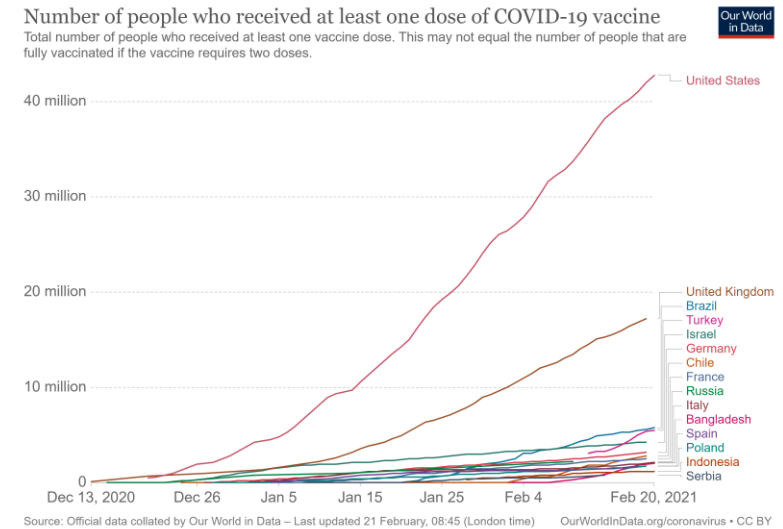
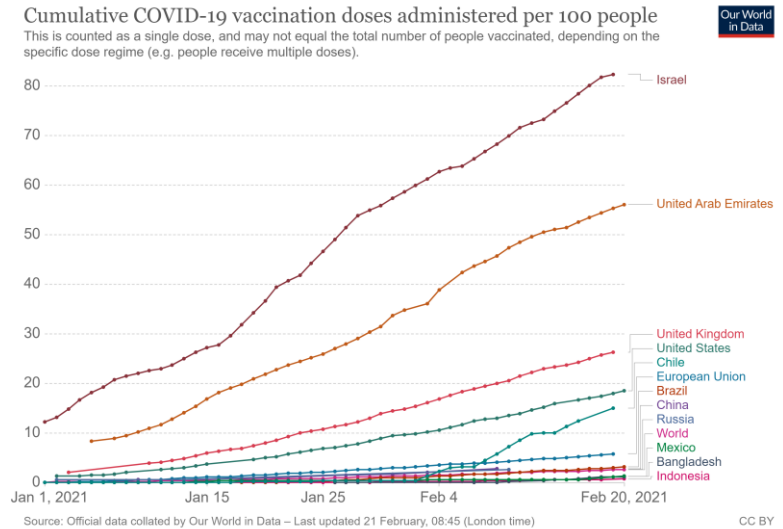
Vaccine approvals have been granted in numerous countries to a range of different vaccines.

- The three initial vaccines with Phase III trial data (Pfizer, Moderna and AstraZeneca) have the most approvals, but another eight have approvals in at least one country.
- Approved vaccines are a range of different types including RNA, non-replicating viral vector, inactivated and recombinant protein vaccines.¹

In line with the approvals, vaccine roll outs have begun in many countries.

- Per capita, Israel's roll out has been the fastest, but the UK has been relatively quick, particularly for the vulnerable age groups.
- The US started slow, but it has gained pace.
- However, the roll out has been slow in many places, notably Europe. Operational issues, regulatory approvals, vaccine refusal and vaccine supply are all factors that have slowed the vaccine roll out.

1. <https://vk.ovg.ox.ac.uk/vk/types-of-vaccine> provides a useful overview of the different vaccines types



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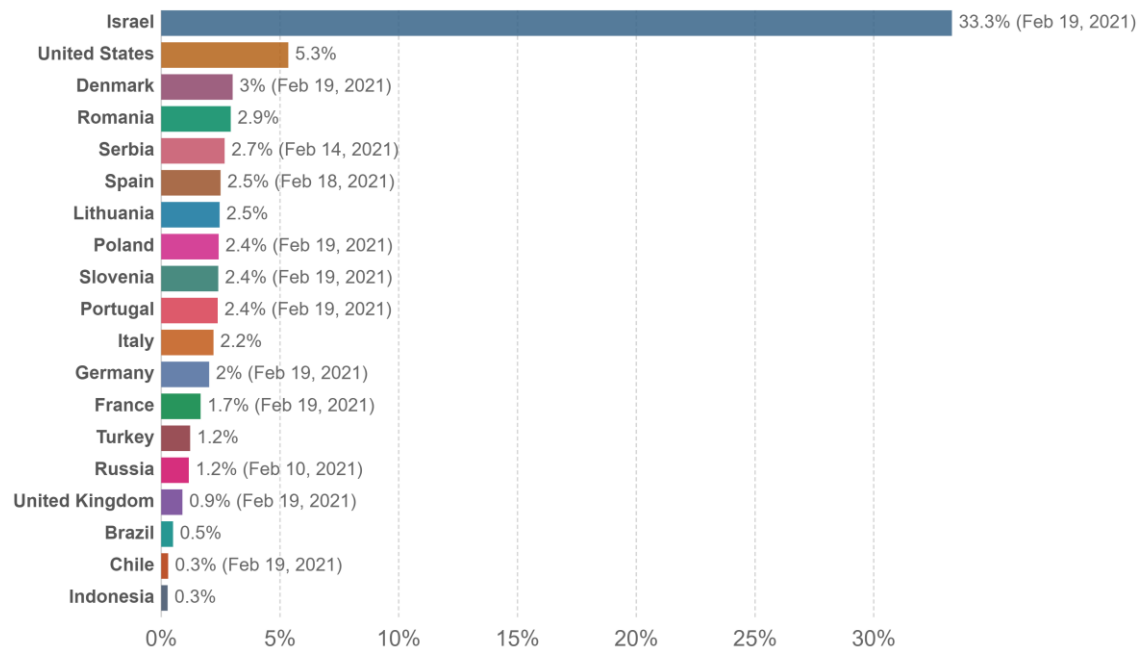
Vaccine roll out

As the vaccine regimes typically require two spaced doses, the level of fully vaccinated individuals per country varies from those simply receiving a single dose.

- Notable is how low the UK is on the list compared how many people have received a single dose.
 - This is due to its strategy of vaccinating as many people as possible with a single dose, by spacing out the two doses by around 12 weeks (instead of the recommended 3 weeks).
 - This strategy will allow a lower level of protection for a larger number of people until they receive their second dose.
 - This approach is controversial and notably, both the US and German governments have stated they will not follow this “delayed second dose” strategy.
 - There are some concerns that this strategy could result in more “escape mutants” (discussed later in this paper).

Share of the population fully vaccinated against COVID-19, Feb 20, 2021

Share of the total population that have received all doses prescribed by the vaccination protocol. This data is only available for countries which report the breakdown of doses administered by first and second doses.



Source: Official data collated by Our World in Data – Last updated 21 February, 08:45 (London time) OurWorldInData.org/coronavirus • CC BY

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Vaccine hesitancy may be problematic

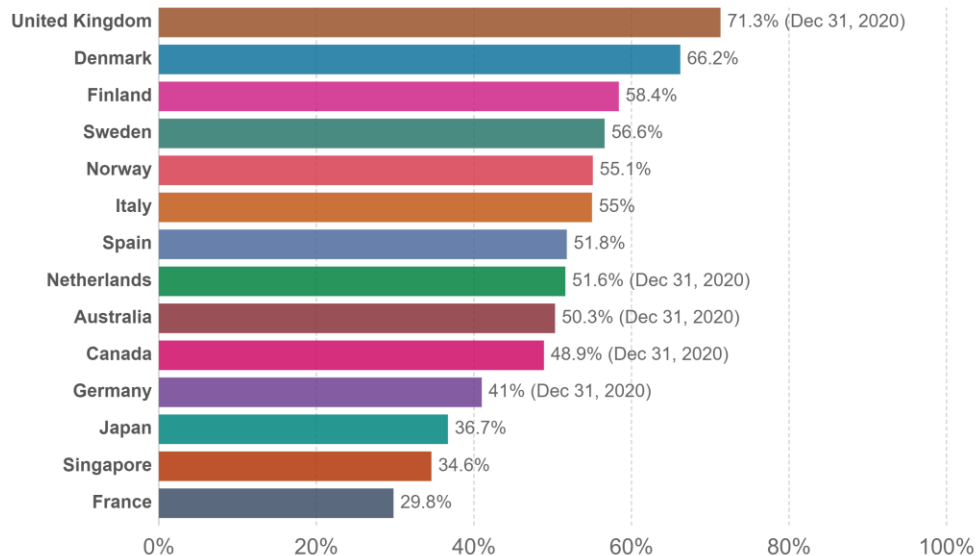
The pace of the roll out is important, but how much faster can it go and how long can it be sustained for?

- We would expect the roll out to speed up to a certain point as new countries start their programs, operational aspects are improved, new vaccines become available and manufacturing gains speed.
- But a vaccination program is still dependant on the willingness of the population to take the vaccine.
 - Surprisingly, there are reports of high levels of vaccine refusal in front line health workers in the US, as an example.
 - The chart to the right shows a high reluctance in many countries to being vaccinated. If these reflect final vaccination rates, it seems unlikely herd immunity will be achieved anywhere.
- Once the pool of “early adopters” is exhausted, the pace of vaccination programs may fall off.

Share who would get a COVID-19 vaccine if it was available to them this week, Jan 14, 2021

Our World
in Data

Share of survey respondents who agree with the statement: "If a COVID-19 vaccine were made available to me this week, I would definitely get it."



Source: Imperial College London YouGov Covid 19 Behaviour Tracker Data Hub – Last updated 18 January 2021, 09:52 (London time)
Note: Months containing fewer than 500 survey respondents are excluded. Respondents were presented with a 1 to 5 scale, ranging from "Strongly agree" (1) to "Strongly disagree" (5). We consider responses of 1 or 2 to be in agreement with the statement.
OurWorldInData.org/covid-vaccinations • CC BY

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Other points of note regarding vaccines

Some fears around vaccine nationalism have been realised.

- Following delays in AstraZeneca delivering its vaccine to the EU due to manufacturing delays, the EU passed regulations to block vaccine exports without explicit approval.
- This was always considered a risk, as it seemed probable that countries would try to protect their own populations as a priority over others.

Post the initial exuberance, there has been more focus on the details of each vaccine, their clinical trials and side effects. Some examples include:

- AstraZeneca has received criticism due to mistakes in its trial program. Notably, it turned out that one of the two dosing regimens used in its trials was due to a dosing mistake.
- Some countries have restricted the use of some vaccines for various reasons:
 - Norway has limited the AstraZeneca vaccine to under-65-year-olds citing lack of data on efficacy in older age cohorts.
 - South Africa stopped the usage of the AstraZeneca vaccine due to claims it wasn't effective against the circulating local strains of the virus.
- A study of the Moderna vaccine has shown a rapid decline in neutralising antibodies after vaccination. This has raised questions regarding the duration of protection, particularly in older people. However, it should be noted that a protective immune response is much more complex than simply generating antibodies.

Trial data continues to be released.

- For example, Novavax released phase III trial data at the end of January 2021 showing its vaccine (NVX-CoV2373) had a 89.3% efficacy, with the trial populations having a high exposure to the UK variant of the virus. This vaccine has the same target as the previously approved vaccines (the S-protein), but uses a different technology (purified protein). It is stable at refrigerator temperatures.

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The UK strain is becoming the dominant strain globally

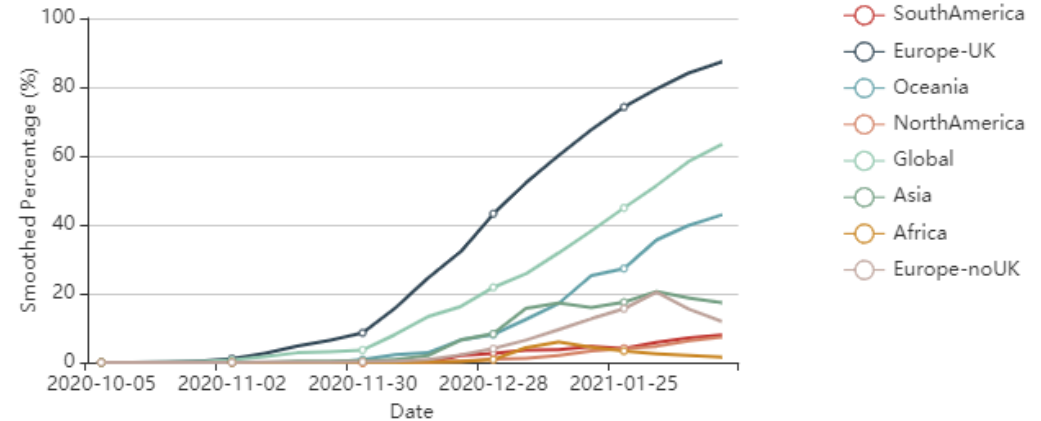
There are concerns around more virulent and transmissible strains arising from viral mutation.

- More highly transmissible strains have arisen (notably the B.1.1.7 UK variant and the B.1.351 South African variant).
 - Some reports indicate the UK variant may be more virulent (i.e. more damaging or deadly to their host).
 - The chart to the right shows how quickly the UK variant is spreading globally.
 - The UK variant emerged with a large number of characteristic mutations. One theory is the strain arose in an immunocompromised patient, as similar rapid changes have been seen in other such patients.

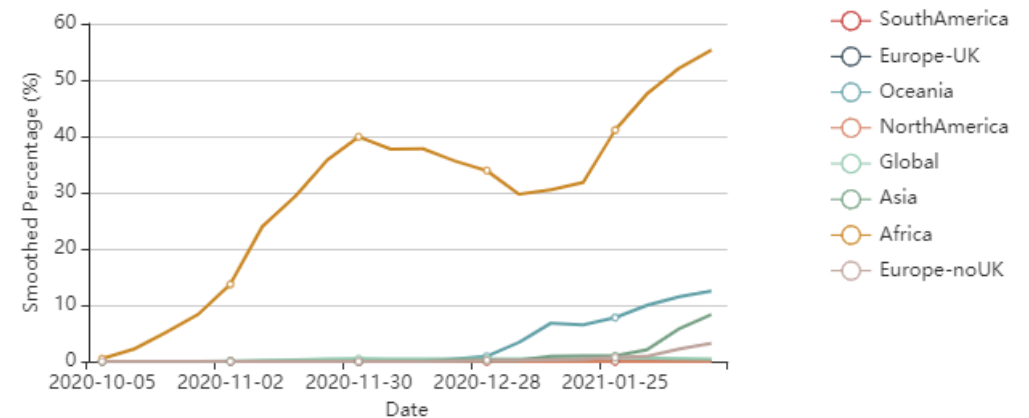
Claims of current vaccine efficacy against these strains has been mixed.

- Initial claims were that they should remain effective, but further studies are indicating some of the vaccines may have reduced efficacy. This will likely vary by the exact strain. It ultimately depends on where the mutations occur in these strains and if these mutations change the parts of the virus recognised by the immune system (called epitopes).
- South Africa has stopped the roll out of the AstraZeneca vaccine due to concerns it is not effective against the B.1.351 variant. Some studies have suggested all the current vaccines may be less effective against this strain.

Frequency of B.1.1.7 by region



Frequency of B.1.351 by region



Source: GISAIID

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The virus will continue to mutate and adapt

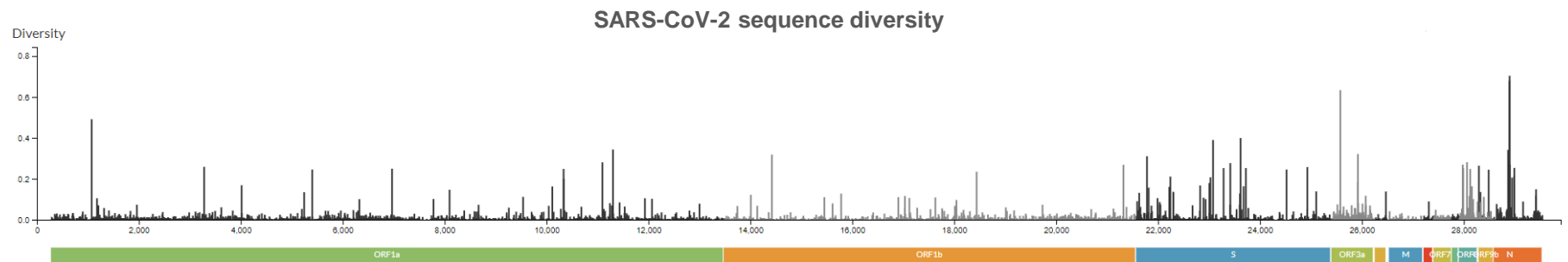
While SARS-CoV-2 doesn't mutate as fast as some viruses, it still mutates fairly quickly – the chart below shows the regions of the genome where mutations have been identified. Mutation is the raw material needed for adaptation.

SARS-CoV-2 appears to be of bat origin. This means when it emerged, it was adapted to its bat host and not to humans.

- Adaptation to its new host will enhance its survival, hence mutations that help it adapt will undergo positive selection.
- As an example, the receptor the virus needs to infect its host (known as ACE2) is not identical between bats and humans. There is evidence that some of the S-protein mutations being observed help the S-protein bind better to human ACE2.

This adaptation process also applies to the virus' susceptibility to human immunity.

- In particular, the vaccination program will create a large selection pressure on the virus population (specifically on its S-protein). New strains that arise that can evade the vaccine generated immunity are called "escape mutants". It is possible that strains will arise that can partially or fully evade current vaccines. The chance of this occurring is increased with a slower vaccine roll out.
- Many of the current vaccines should be able to be modified for new strains relatively easily, but vaccine evasion will be problematic as previously vaccinated individuals could be vulnerable to the new strain. There will also be regulatory hurdles to manage.



Source: Hadfield et al, Nextstrain: real-time tracking of pathogen evolution, Bioinformatics (2018), Sagulenko et al, TreeTime: Maximum-likelihood phylodynamic analysis, Virus Evolution (2017)

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Summary

- Following the phase III trial announcements for the Pfizer, Moderna and AstraZeneca vaccines in November 2020, the situation has been moving quickly, with many countries implementing vaccination programs.
 - The pace of the roll out has been variable, driven by many factors including operational issues, regulatory approvals, vaccine refusal and vaccine supply.
- The pace of the roll out will likely increase as operational challenges are overcome, vaccines become more available and more countries start their programs.
 - However, vaccine hesitancy is high in many countries, which may eventually slow the roll out.
- New strains of the virus have emerged that appear to be more transmissible.
 - The UK variant (B.1.1.7) appears to be spreading at a rapid pace globally.
 - There is some evidence that existing vaccines may be less effective against the South African variant (B.1.351).
 - Emergence of these strains reflects ongoing adaptation of an animal virus to its new host (humans).
- It is possible that further strains will arise that can partially or fully evade the current vaccines. The risk is increased with a slower vaccine roll out. Many of the vaccines should be easily adaptable to new strains, but this still raises challenges around regulatory processes, manufacturing and distribution of new vaccine and loss of effective immunity in the already vaccinated population.

Author:

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Previously Martin has worked in technology commercialisation at the University of Melbourne and the Bio21 Institute, and virology research at Murdoch University. Immediately prior to joining Frontier, Martin worked at Starfish Ventures, an Australian venture capital fund manager focused on high growth life sciences, information technology, and clean technology companies.

Martin has a Master of Applied Finance through Macquarie University, a PhD in Molecular Cell Biology, and a Bachelor of Science with first class honours in Microbiology.





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