Emergent COVID-19 strains & UK-approved vaccines

7 Jan 2021

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Emergent viral variants

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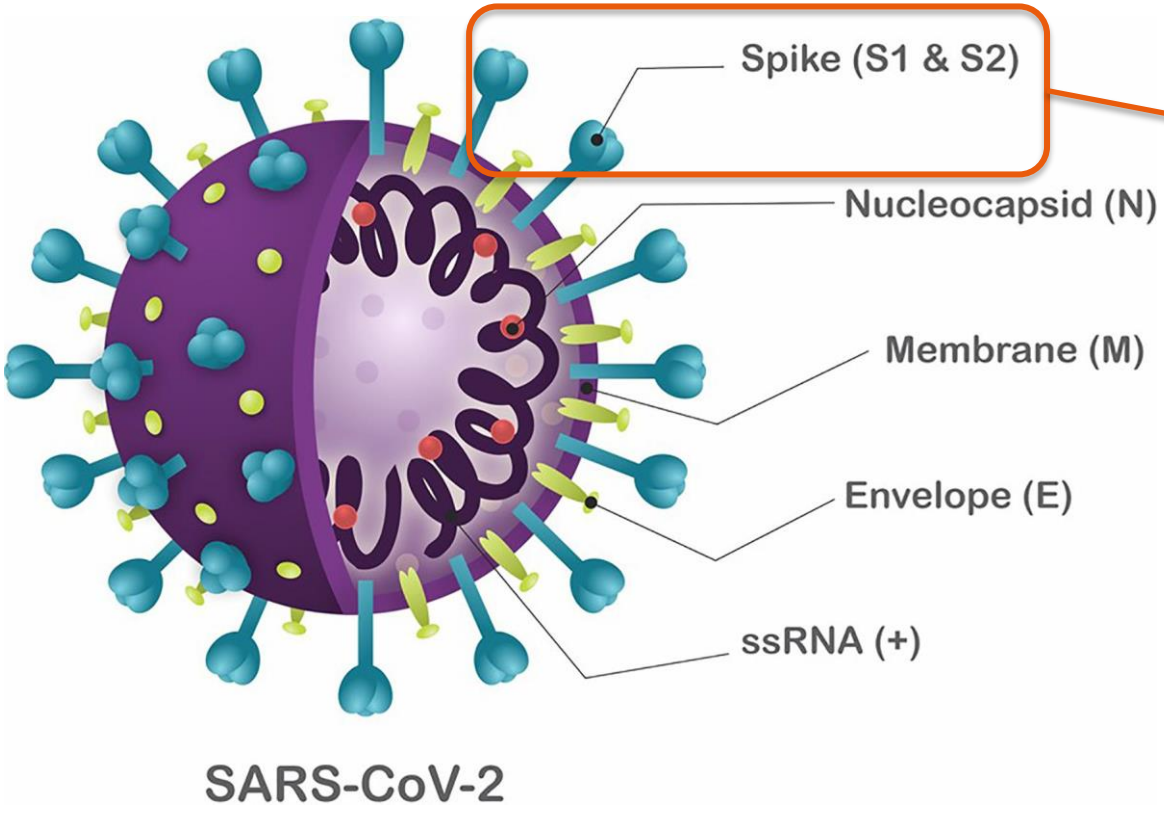
Which SARS-CoV-2 mutations do we worry about?



Mechanism of cellular entry
as spike proteins bind to ACE2-expressing epithelial tissue

- Nose and throat
- Lungs and bronchi
- Heart
- Blood vessels
- Liver
- Kidneys
- GI tract
- Brain
- …

Main antigenic target for…

- Vaccines
- Antiviral treatments

Source: Santos et al, Front. Microbiol., 13 August 2020 | https://doi.org/10.3389/fmicb.2020.01818

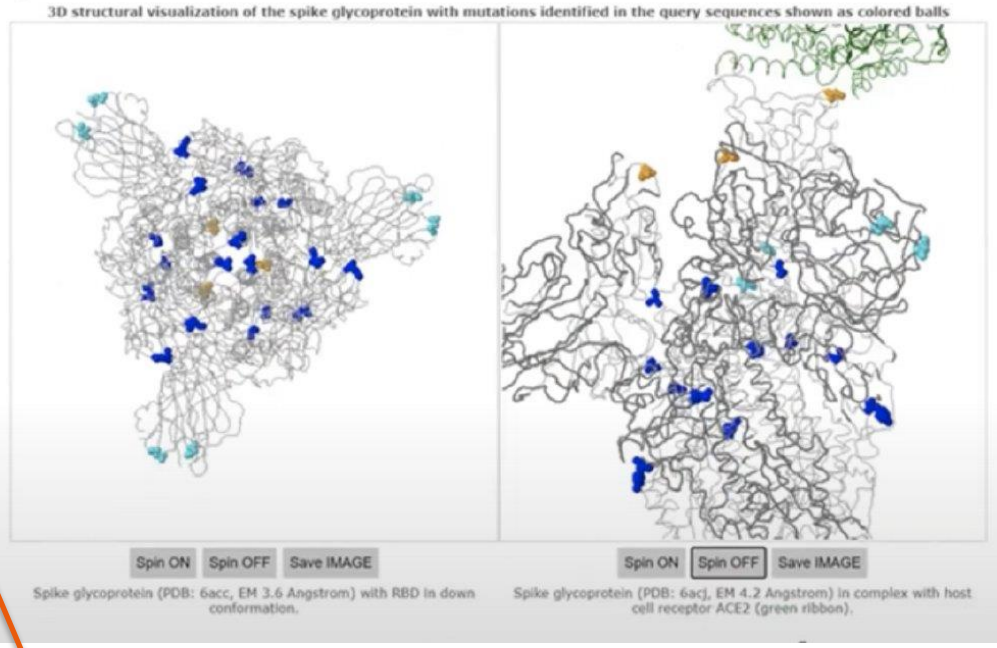
So how has SARS-CoV-2 RBD mutated in England?

17 mutations, 8 of which are in the spike. 3 most concerning: **N501Y** (shared with **501Y.V2** in South Africa), **69-70del**, and **P681H**

- UK's newest fast growing lineage, B.1.1.7:

Defined by multiple spike protein mutations: 69-70del, 144-145del, N501Y, A570D, D614G, P681H, T716I, S982A & D1118H.

Image from report by Sebastian Maurer-Stroh at GISAID.



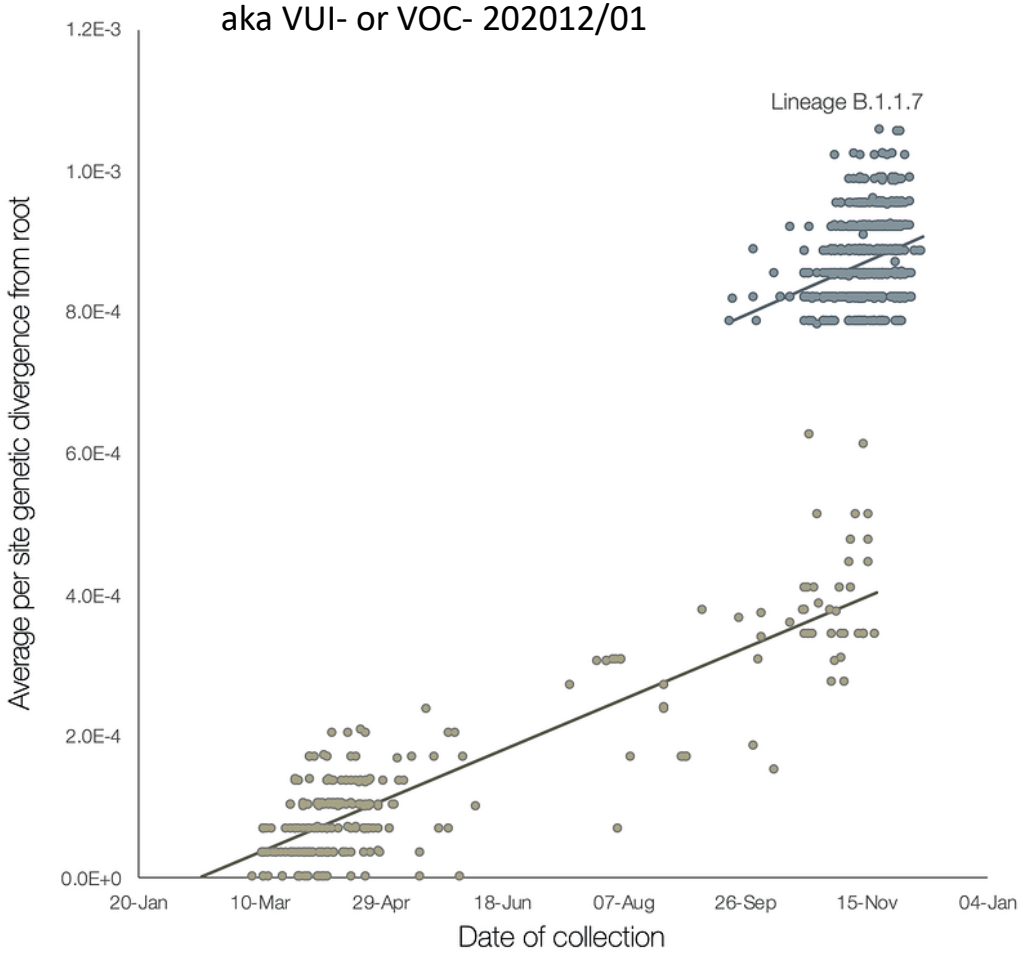
strong circumstantial overlap with "S gene dropout", which is detectable on standard PCR tests

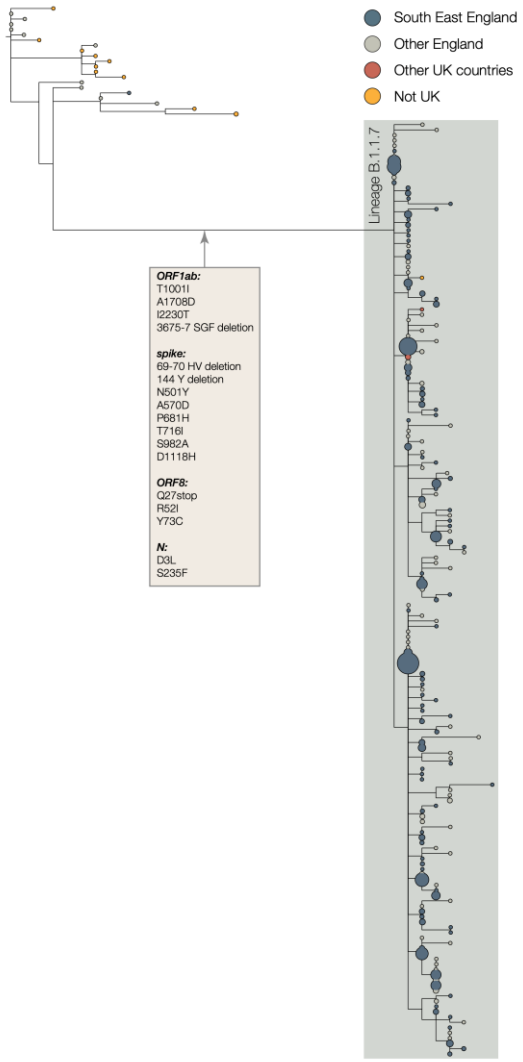
Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208, and Kai Kupferschmidt, https://science.sciencemag.org/content/371/6524/9

So how has SARS-CoV-2 RBD mutated in England?

B117 variant is **very** genetically distinct

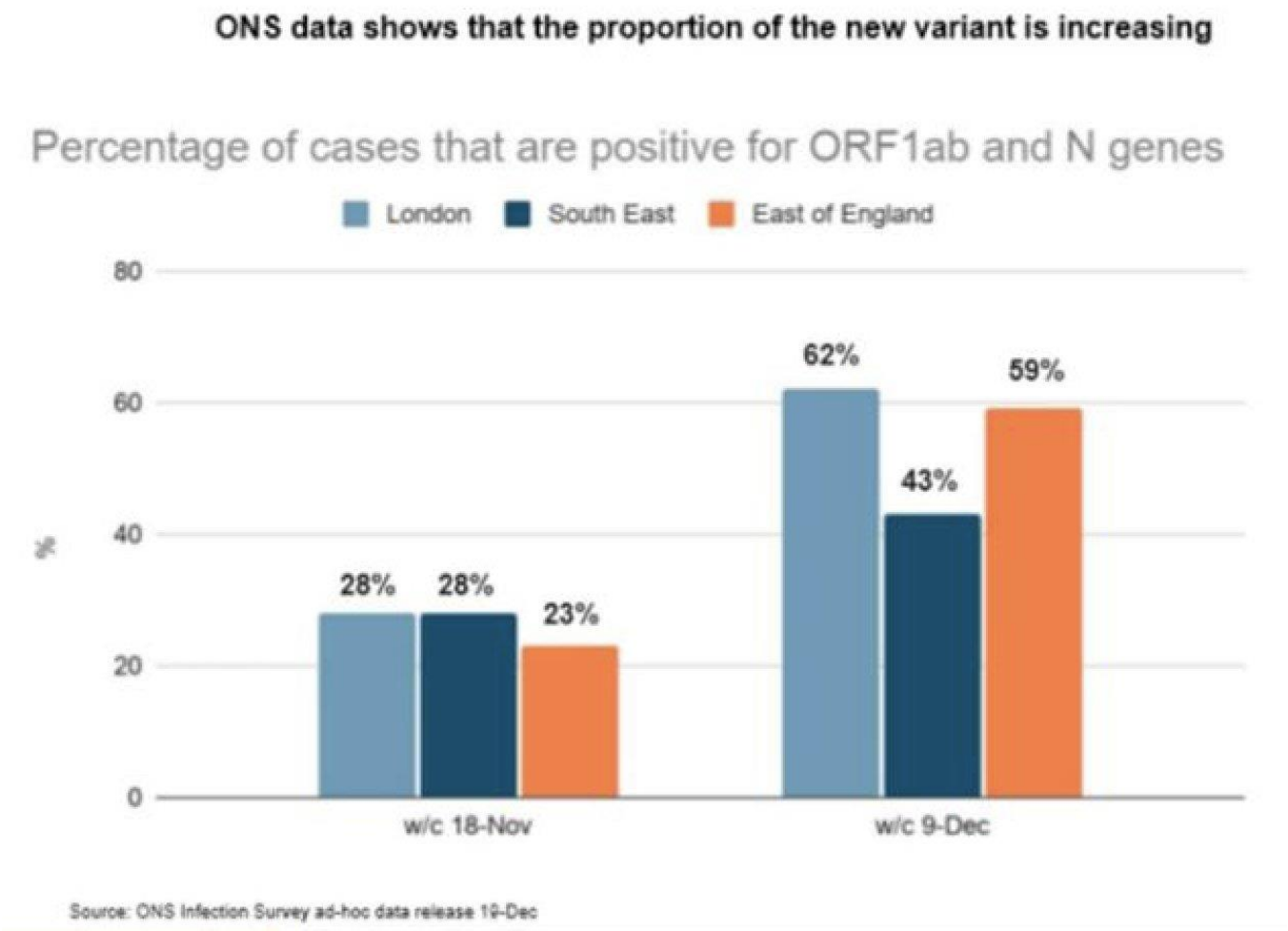
aka VUI- or VOC- 202012/01





Source: Rambaut et al, https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

In a matter of weeks, B117 become THE STRAIN



Source: ONS, https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/adhocs/12690percentageofcovid19casesthatarepositivefororf1abandngenes

Statistical modelling finds B117 linked with higher R_t

Methods and tables

Our logistic beta-binomial model of VOC 202012/01 growth is as follows:

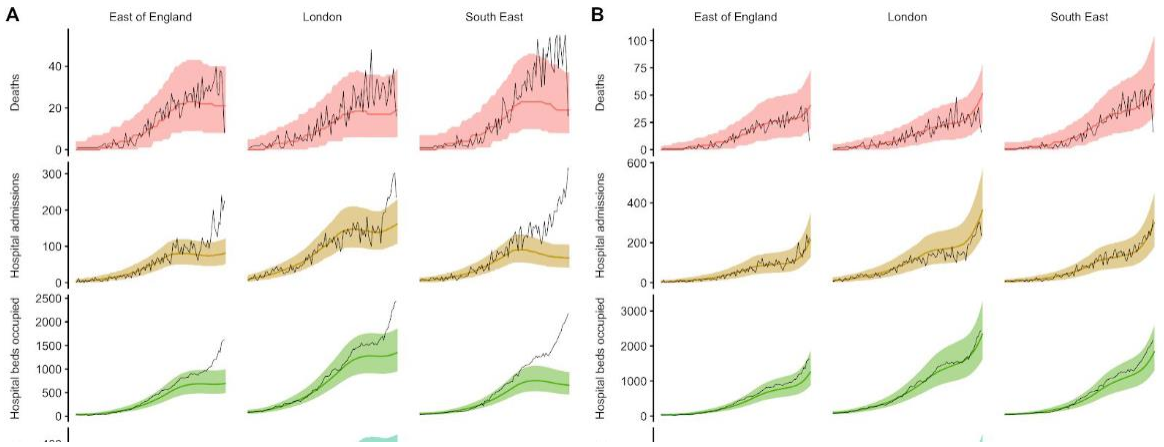
$$slope \sim normal(mean = 0, sd = 1)$$
$$intercept \sim normal(mean = 0, sd = 1000)$$
$$falsepos \sim beta(\alpha = 1.5, \beta = 15)$$
$$conc \sim normal(mean = 0, sd = 500) \geq 2$$

$$f(t) = \frac{\exp[slope \times (t - intercept)]}{1 + \exp[slope \times (t - intercept)]}$$
$$s(t) = f(t) + \big(1 - f(t)\big) \times falsepos$$

$$k_t \sim beta\text{-}binomial(n = n_t, \alpha = s(t) \times (conc - 2) + 1, \beta = (1 - s(t)) \times (conc - 2) + 1)$$

A = model fit without increased R_t

B = model fit WITH increased R_t



Consensus estimate among modellers:
R for B117 is **~50-70% higher**

Source: Davies et al, LSHTM CMMID, https://cmmid.github.io/topics/covid19/uk-novel-variant.html

In COVID, higher R_t is **much worse** for public health

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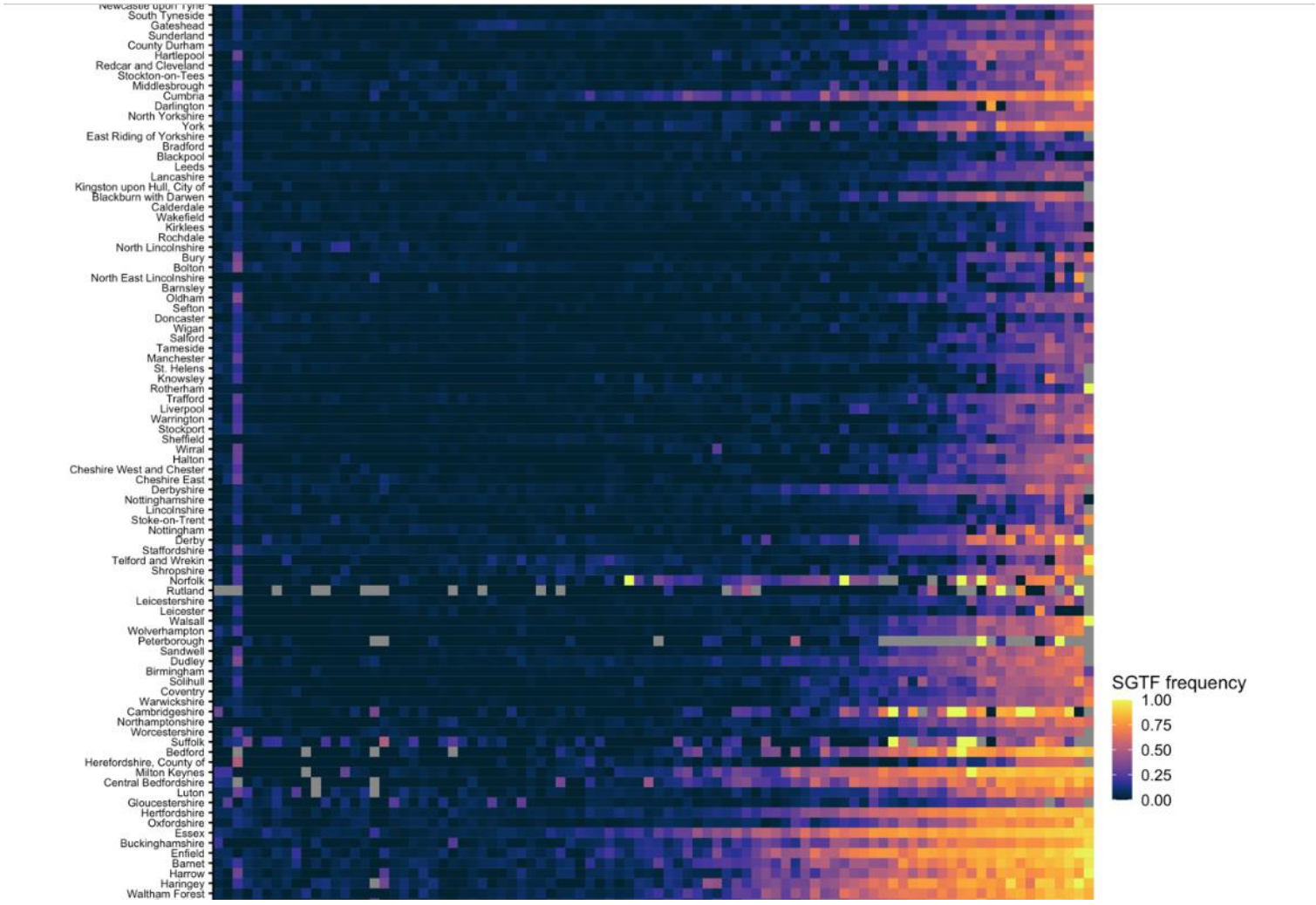
baseline stats	**R_t = 1.4** serial interval (time between infections) = 6 days **hospitalisation rate = 10%** **infection fatality rate (IFR) = 1%** 100 cases	
scenario	**R_t** increases by 50% to **2.1**	**hospitalisation and IFR** increase by 50% (to **15% and 1.5%**)
after 30 days (or five generations of infection)	4,084 cases = 100 x 2.1^5 cases ~408 hospitalisations (10%) **~41 deaths** (1%)	538 cases = 100 x 1.4^5 cases ~81 hospitalisations (15%) **~8 deaths** (1.5%)

!!! exponential growth and harms from R_t … especially with asymptomatic transmission

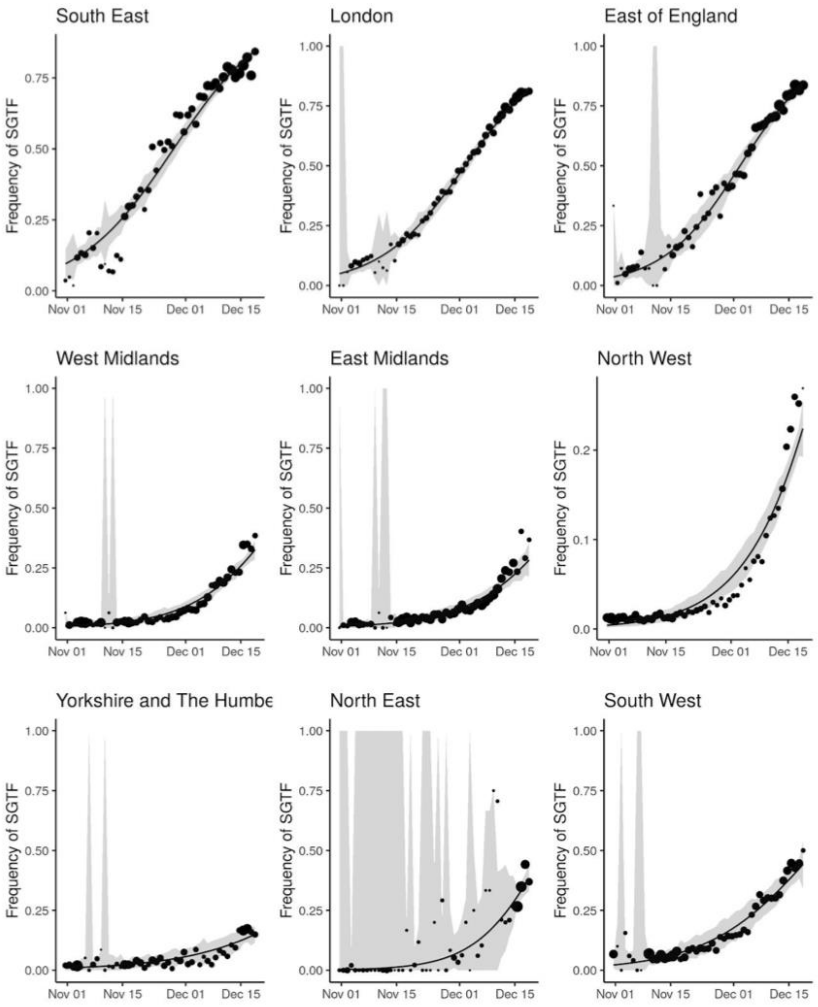
Source: Personal analysis, inspired by an Adam Kucharski tweet? at some point

Despite “Tier” strategy, B117 has spread over UK



Source: Davies et al, LSHTM CMMID, https://cmmid.github.io/topics/covid19/uk-novel-variant.html

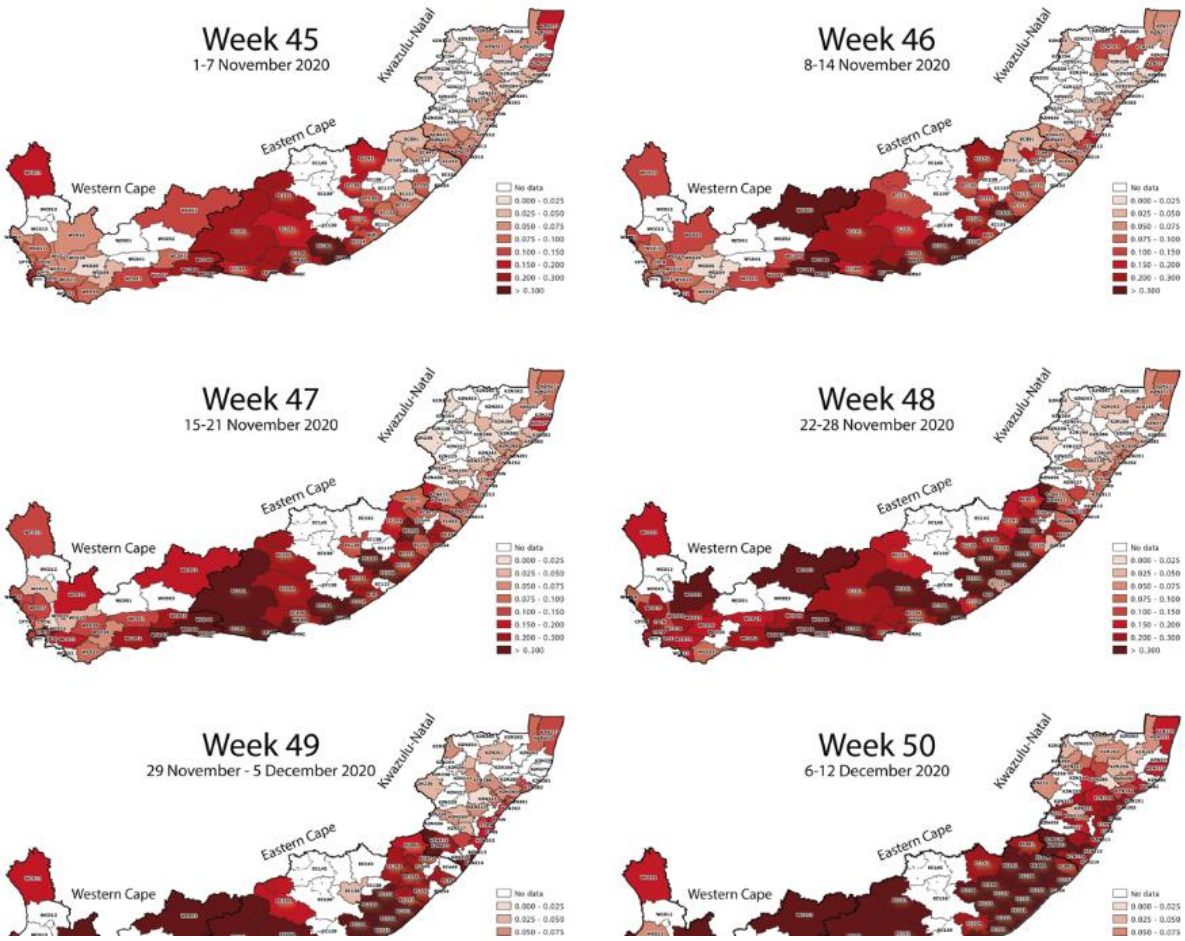
B117 on a worrying rise throughout England



Source: Volz et al, Imperial MRC GIDA, https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-42-sars-cov-2-variant/

South Africa variant 501Y.V2 is similar but distinct

Common **N501Y** mutation with B117, and also had spread quickly from in Q4 2020



Source: Tegally et al, https://www.krisp.org.za/manuscripts/MEDRXIV-2020-248640v1-de_Oliveira.pdf

Why B117 is likely to be much more problematic

- **London/SE England is much more of a global travel hub than SA coast** (especially as Gauteng is apparently not yet as colonised as Cape provinces)
- **Likely B117 presence in the USA since Oct-Nov 2020**, with confirmed cases detected in 5+ states, and suspicious S-gene dropout increasing in reanalysis of 2mln RT-PCR samples suggesting broad community transmission
    - First cases in CO national guard staffing a care home, but without travel history → community transmission
- **B117 has already been detected in 15+ further countries** (France, Italy, Germany, Spain, Sweden, Switzerland, Denmark, the Netherlands, Canada, Australia, Japan, Singapore, India, Lebanon and UAE)… and counting, e.g. Luxembourg
- **Some detection** (n<5 patients) **of 501Y.V2 exports from SA:** Finland, UK, Zambia
- **B117 was NOT yet predominant in areas of high UK transmission in early December 2020:** South Wales, North West, Northern Ireland, etc.
- **Urgent genomic surveillance** necessary globally for both strains

Sources: Personal analysis, Europe CDC at https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-risk-related-to-spread-of-new-SARS-CoV-2-variants-EU-EEA.pdf and *USA Today* overview at https://eu.usatoday.com/story/news/health/2020/12/29/colorado-reports-first-known-us-case-new-covid-strain-uk/4079697001/

B117 is likely also becoming predominant in USA

COVID-19-positive tests exhibiting this pattern during the first week. The rate of positive samples with S gene dropout has grown slowly over time, with last week exhibiting the highest level yet at 0.5% of COVID-19-positive tests that are consistent with the H69del/V70del variant.

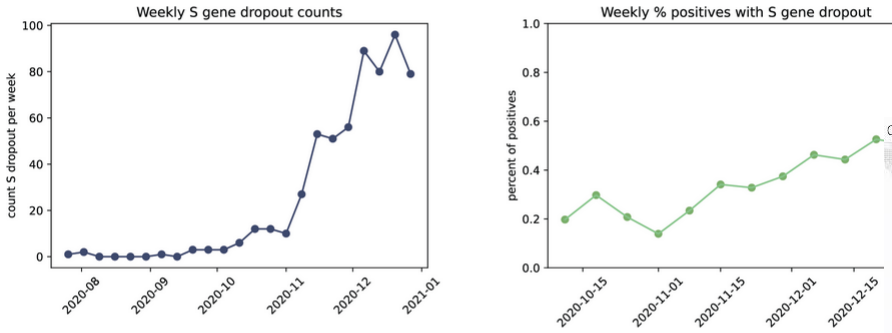


Figure 1. Weekly observations of S gene dropout. The raw number of tests per week with S gene dropout (lef well as normalized by the number of positive tests (right), indicates that the presence of the H69del/V70del, potentially other S gene variants, is increasing in our tested population.**Updated 12/28/2020

Since we test samples from all 50 states in our laboratory, we examined the nationw distribution of these S gene dropout positive samples as well as state-level trends. \ have observed S gene dropout positive samples in 19 states so far. Focusing on the 1 states for which we have sufficient sample size to assess the frequency of this rare event (n>1000 SARS-CoV-2-positive samples), we see a recent expansion in the Eastern part of the US, concentrated in MA, OH, and FL.

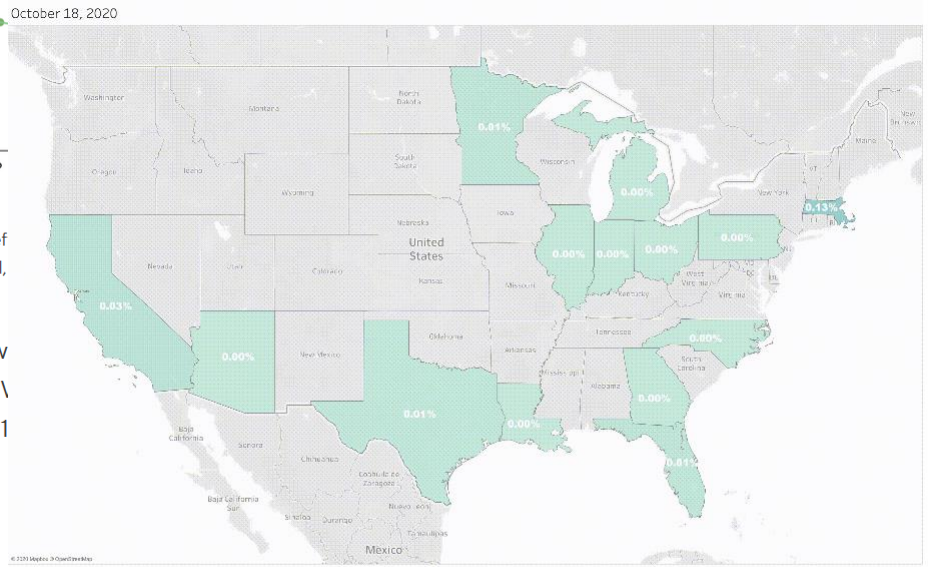


Figure 2. US cumulative distribution of S gene dropout-positive SARS-CoV-2 tests as of Dec 21, 2020. Values ndicate percent of positive tests with S gene dropout. To ensure that low sample sizes do not skew frequencies, only states with more than 1,000 SARS-CoV-2 positive tests are shown. (Additional states with S gene dropout, but with <1K positives in our dataset thus far are: AL, ME, NH, NY, RI, VA.) States with insufficient data are shown in gray.

Source: Washington et al, https://blog.helix.com/sars-cov2_uk-variant/. See also context at https://twunroll.com/article/1341955114043662336 and https://www.medrxiv.org/content/10.1101/2020.12.24.20248814v1.full.pdf. S gene deletion very likely but not certain to overlap with H69del/V70del seen in B117.

A precautionary principle makes sense

We should be concerned and careful about anything that drives selective evolution for higher transmissibility. This is analogous to patients not finishing antibiotic prescriptions, and the consequent rise of antimicrobial resistance.

> During the first wave of Covid-19 in Britain, many scientists – myself included – said the government should be pursuing a "maximum suppression" or "zero Covid" strategy. One of the many reasons for this was to stop natural selection doing its work. When a virus is allowed to spread, spending time in different hosts, it evolves and mutates…
>
> … The new variant seems to be accelerating transmission. Many have asked whether this will affect the efficacy of a vaccination programme – but this is something scientists could likely fix reasonably quickly by adjusting the RNA coding of the new vaccines. It's not possible to tell yet whether the new variant of the virus will change the severity of Covid-19 in those who catch it…
>
> **What's certain is that the greater the number of people who are infected, the more chance a virus has to evolve. - Anthony Costello, UCL** (1)

antibody escape: Some preliminary evidence that mutations seen in Brazil and South Africa lineages are resistant to convalescent plasma treatment, indicating diverse antibodies to 'wild-type' virus are less effective at combating the mutated strain (2)

Sources : (1) Anthony Costello, https://www.theguardian.com/commentisfree/2020/dec/22/uk-government-blamed-covid-19-mutation-occur. (2) Greaney at al, https://www.biorxiv.org/content/10.1101/2020.12.31.425021v1.

… but don't panic

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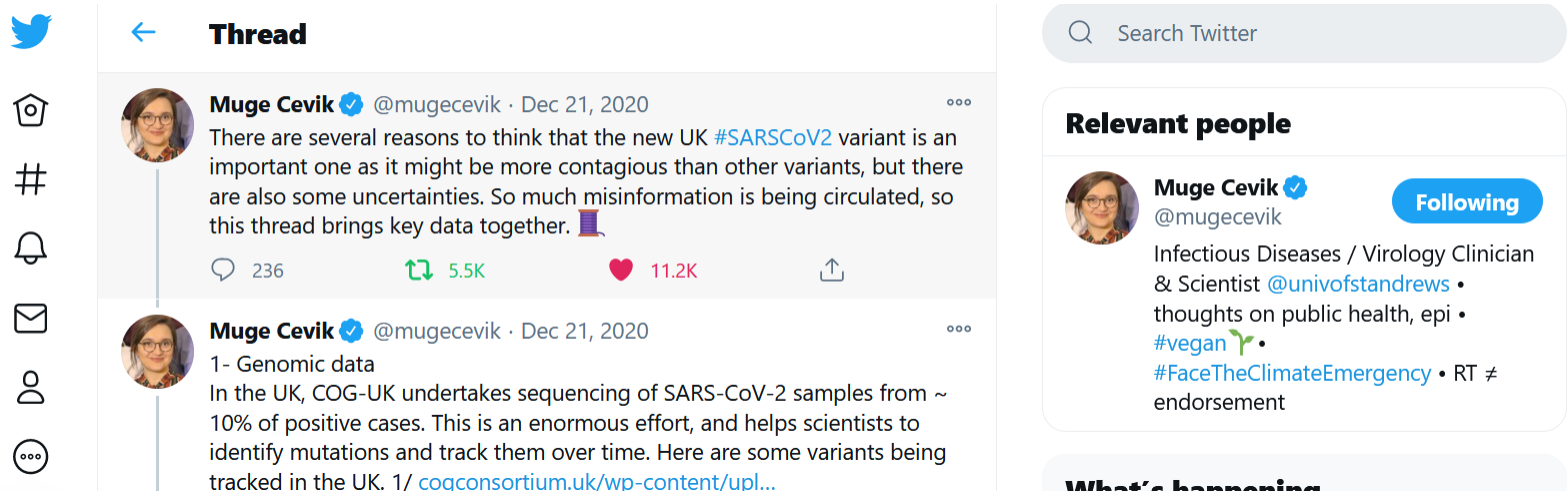
"" The biggest worry for vaccines about the new UK variant is the N501Y mutation in the receptor binding domain. This is also a mutation that appears when SARS-CoV-2 is mouse adapted. A paper looking at that found that an **experimental RBD-based vaccine still worked**. I am not 100% sure the vaccine was based on N501, but I assume so. That would already be some good news. In general, I am not to worried about the impact of the new variant on vaccines. **Florian Krammer, Mount Sinai School of Medicine.**

Whereas some mutations have been shown to let the virus evade monoclonal antibodies, **vaccines and natural infections both appear to lead to a broad immune response that targets many parts of the virus**, says **Shane Crotty of the La Jolla Institute for Immunology**. "It would be a real challenge for a virus to escape from that." The measles and polio viruses have never learned to escape the vaccines targeting them, he notes: "**Those are historical examples suggesting not to freak out**."

At a 22 December press conference, **BioNTech CEO Uğur Şahin** pointed out that the U.K. variant **differed in only nine of more than 1270 amino acids of the spike protein** encoded by the messenger RNA in the very effective COVID-19 vaccine his company developed with Pfizer. "**Scientifically it is highly likely that the immune response by this vaccine also can deal with the new virus**," he said. Experiments are underway that should soon confirm that, Şahin added. (2)

Sources : 1. Florian Krammer, https://twitter.com/florian_krammer/status/1341387794493693953. 2. Kai Kupferschmidt, https://science.sciencemag.org/content/371/6524/9

For more detailed synthesis, follow Muge Cevik



Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208

UK-approved vaccines

Content update pending for **9 Jan 2021**

Nb Moderna vax just approved in UK

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Three vaccines now authorised in the UK, and elsewhere

mRNA #1 (BNT162b2) *Pfizer/BioNTech*	mRNA #2 (mRNA-1273) *Moderna*	adenovirus #1 (ChAdOx-1) *AstraZeneca/Oxford*

Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208

How do the approved vaccines work?

Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208

mRNA #1 (Pfizer/BioNTech) trial results

Source: 1. Polack et al, https://www.nejm.org/doi/full/10.1056/NEJMoa2034577. 2. Pfizer/BioNTech trial registration, https://clinicaltrials.gov/ct2/show/NCT04368728

mRNA #2 (Moderna) trial results

Source: 1. FDA Briefing Doc, Moderna COVID-19 Vaccine, https://www.fda.gov/media/144434/download. 2. Moderna trial registration, https://clinicaltrials.gov/ct2/show/NCT04470427.

adenovirus #1 (AZ/Oxford) trial results

Sources: 1. Ramasamy et al, https://doi.org/10.1016/S0140-6736(20)32466-1. 2. Folegatti et al, https://doi.org/10.1016/S0140-6736(20)31604-4. 3. https://covid19vaccinetrial.co.uk/interim-efficacy-results.

What are the pros and cons of each vaccine?

mRNA #1 (BNT162b2) *Pfizer/BioNTech*	mRNA #2 (mRNA-1273) *Moderna*	adenovirus #1 (ChAdOx-1) *AstraZeneca/Oxford*

Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208

Why the controversy over 21/28 days vs. 12 weeks between vaccine doses?

mRNA #1 (BNT162b2) *Pfizer/BioNTech*	mRNA #2 (mRNA-1273) *Moderna*	adenovirus #1 (ChAdOx-1) *AstraZeneca/Oxford*

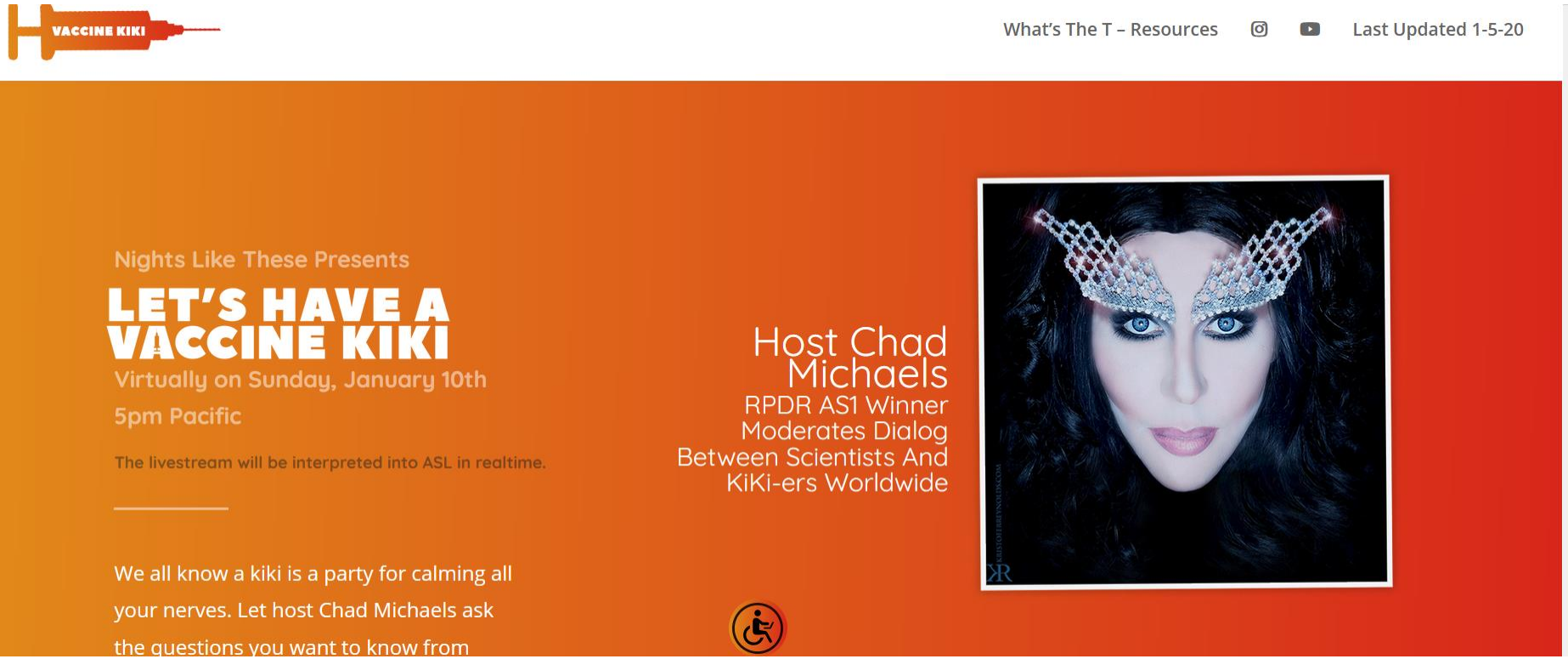
Source: Muge Cevik, https://twitter.com/mugecevik/status/1341094894757171208

Let's talk about variants, vaccines, and everything

mRNA platforms
- Pfizer/BioNTech
- Moderna

adenovirus platforms
- Oxford/AstraZeneca ChAdOx-1

… and all the rest!



https://vaccinekiki.com/

UTC: Mon 11 Jan @1am (will be recorded)

Thank you

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