SARS-CoV-2 genetic variants

Practical implications

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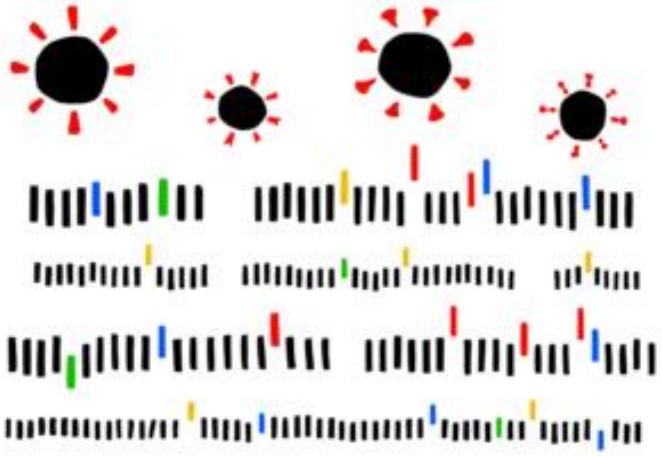
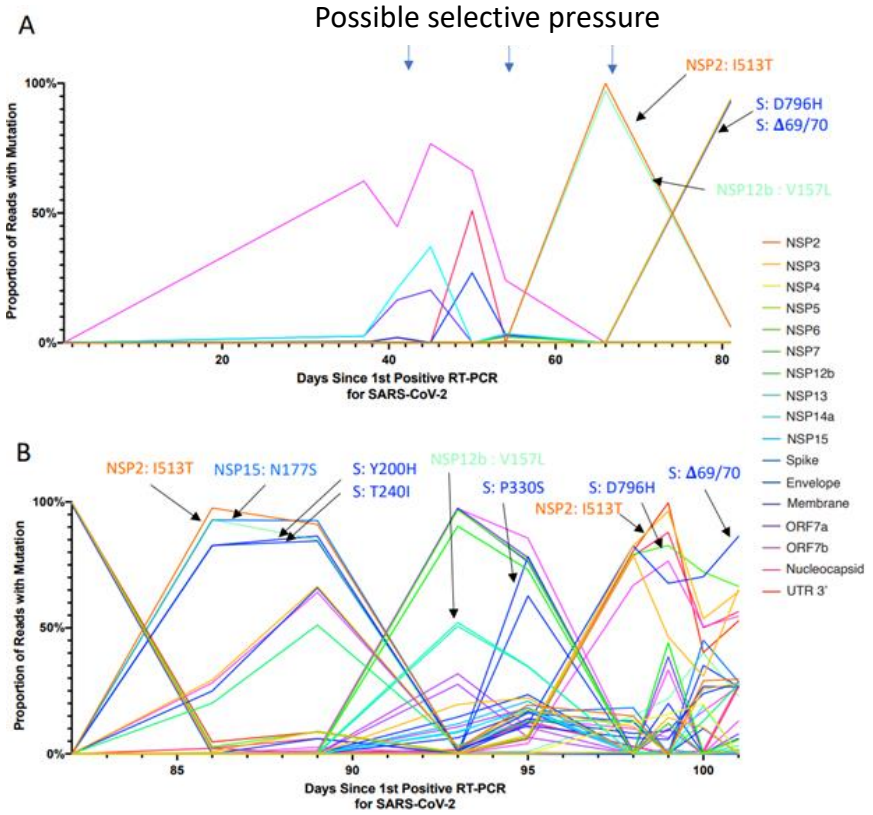


(from COG UK blog)

Potential advantages conferred by genetic changes

- Virus evolution is a naturally occurring phenomenon
- Some genetic changes do not lead to phenotypic changes and some may impair virus fitness
- Increased transmissibility
- Altered pathogenicity
- Escape from immune response conferred by previous infection
- Escape from vaccine-elicited immune response
- Escape from passive antibody therapy (monoclonals and CP)



Kemp et al, 2020

How do we choose which mutations or variants to track?

It may be difficult to predict whether any given mutation is important when it first emerges, against a backdrop of the continuous emergence of new mutations. Approaches to identify mutations of interest:

1. Mutations of **theoretical concern**, e.g. identified as potentially important in laboratory experiments but have not arisen in people yet but if they did, we would want to rapidly understand if this was important in humans

2. Trends in the **frequency of specific viral variants**. If these are appearing more often in the population than other variants, there are several explanations that need to be investigated

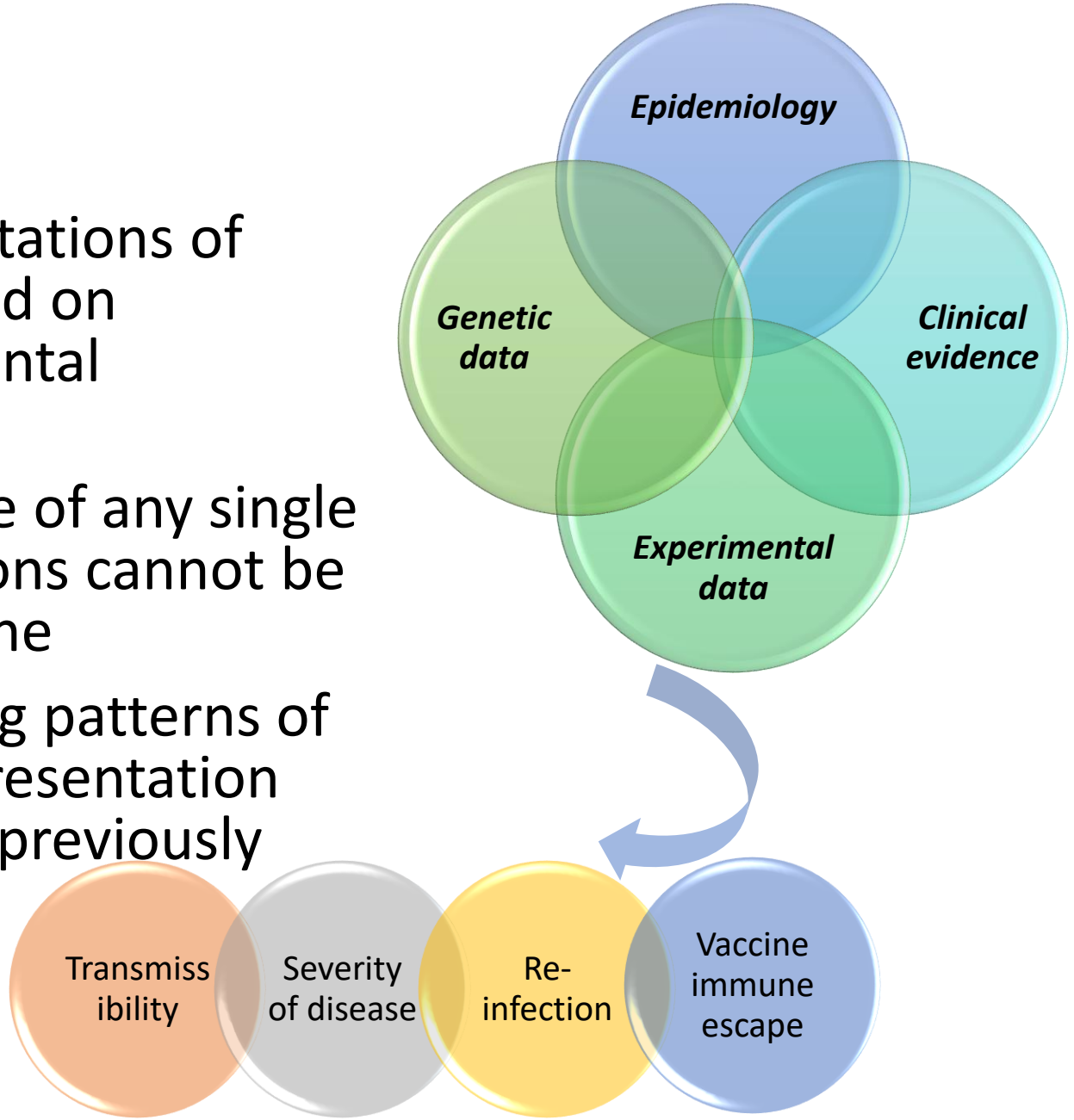
    One possible reason is that a virus with a specific mutation or combination of mutations may spread more rapidly in the population as a result of increased infectivity or transmissibility

3. **Public Health surveillance** can detect **patterns of infection** and **more severe cases of infection**, and look for supporting sequencing data

4. **Genomic surveillance detect variants that are evading the immune system elicited by past infection or vaccination**

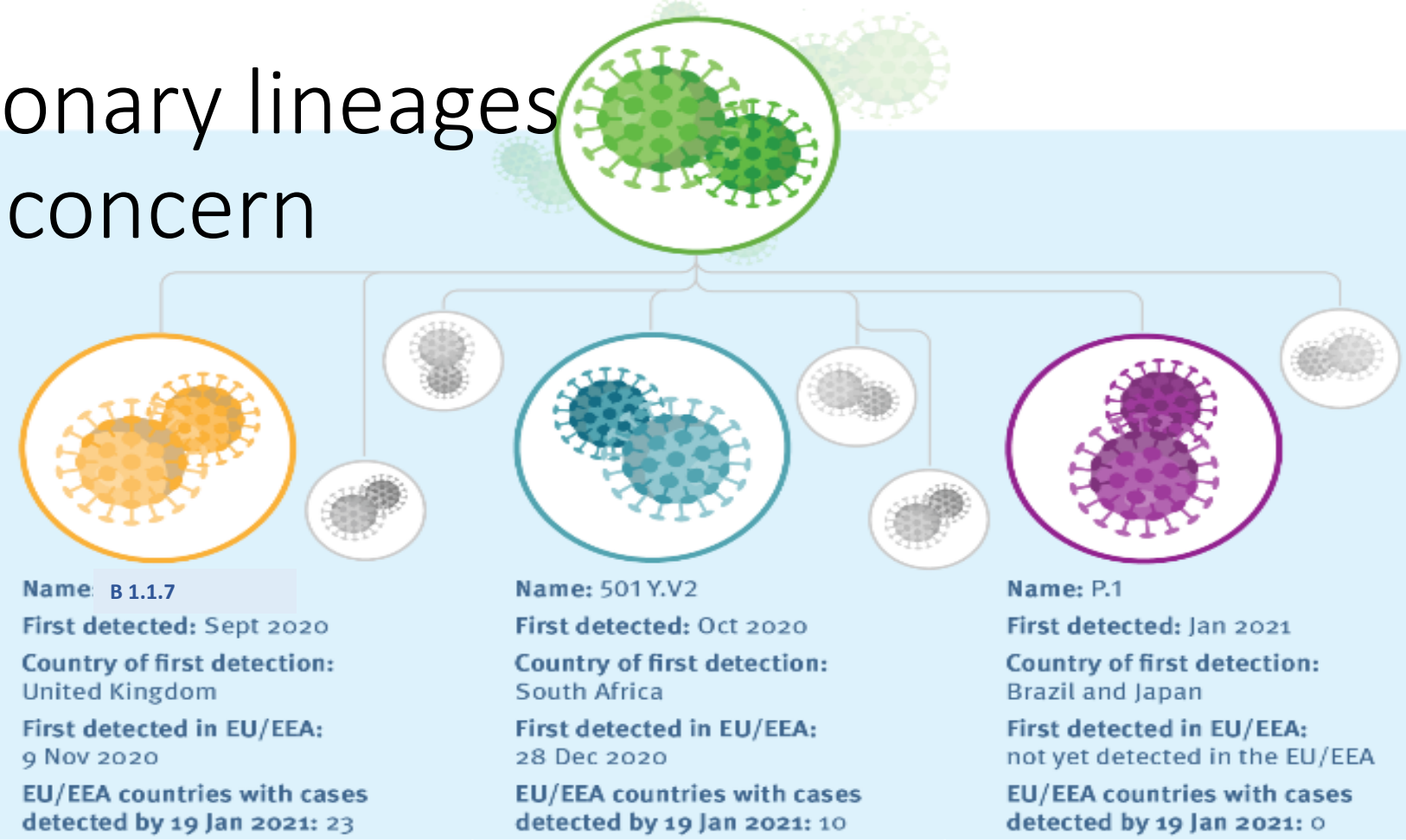
Mutations of interest

- Focus on SARS-CoV-2 spike gene mutations of potential or known importance based on epidemiological, clinical or experimental observations
- Clinical and public health importance of any single mutation, or combination of mutations cannot be determined from sequence data alone
- In practice: identifying cases, tracking patterns of transmissions, linking with clinical presentation and outcome including infections in previously vaccinated or infected people



SARS-CoV-2 evolutionary lineages
Current variants of concern

- Genetic variants have been observed globally
- Viruses, particularly RNA viruses, evolve naturally through mutations
- Some of these changes may increase virus fitness and provide selective advantage
- Close monitoring is required



Notable mutations	N501Y; P681H 69-70 del	N501Y; K471N; E484K	N501Y; E484K; K417T
Transmissibility	Increased	Increased	Possibly increased
Pathogenicity	Possibly increased	No evidence to date	No evidence to date
Antigenicity	No evidence to date	Under investigation	Under investigation Immune escape reported

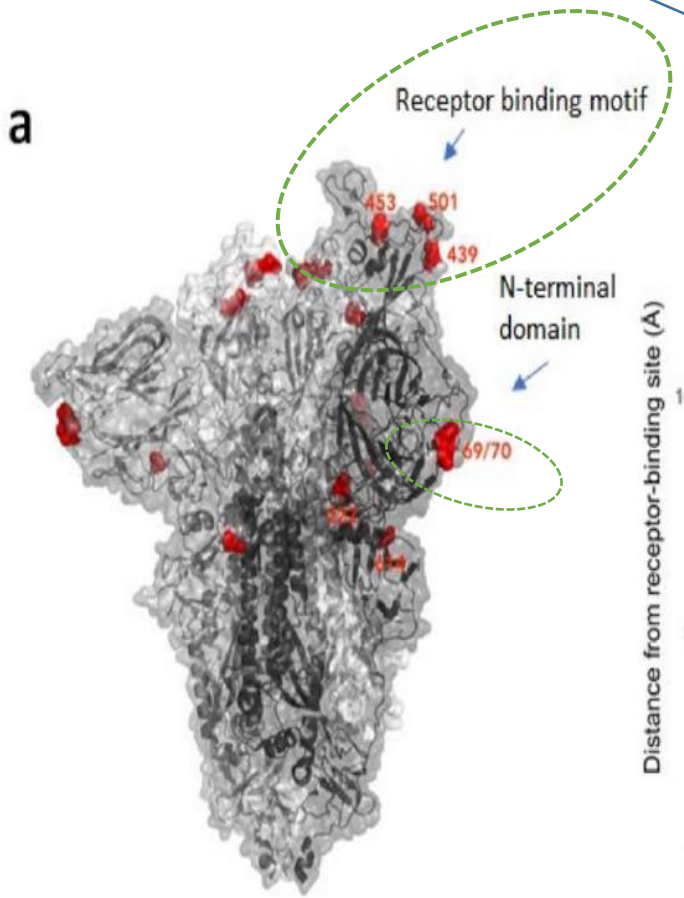
Potential significance of mutations an deletions

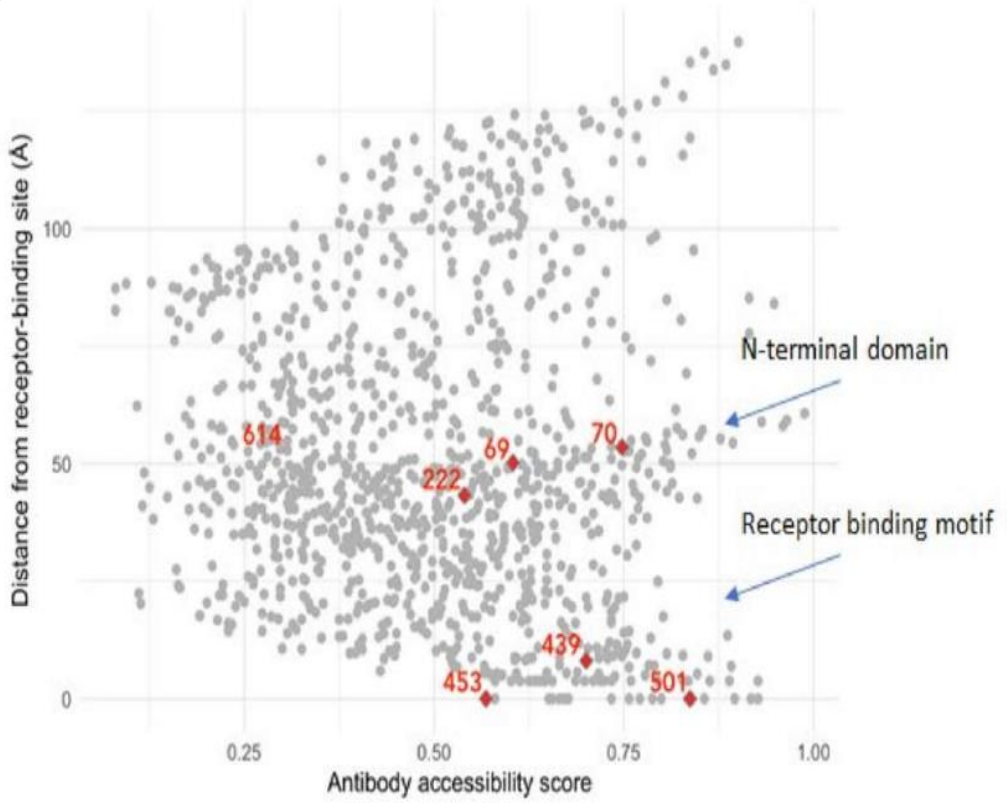
Table 1 | Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineage.

gene	nucleotide	amino acid
ORF1ab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 deletion
spike	21765-21770 deletion	HV 69-70 deletion
	21991-21993 deletion	Y144 deletion
	A23063T	N501Y
	C23271A	A570D
	C23604A	P681H
	C23709T	T716I
	T24506G	S982A
	G24914C	D1118H
Orf8	C27972T	Q27stop
	G28048T	R52I
	A28111G	Y73C
N	28280 GAT->CTA	D3L
	C28977T	S235F

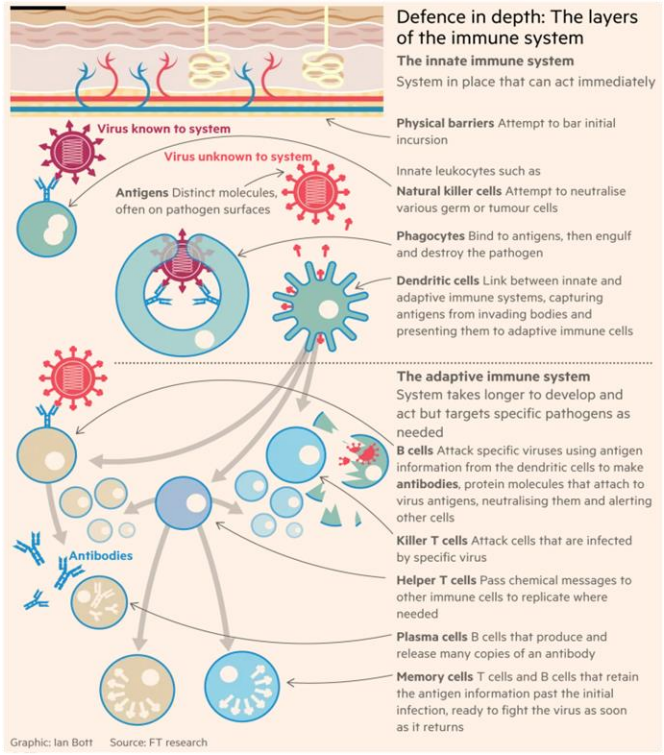
439K and 453F associated with increased ACE2r affinity and escape from some monoclonal antibodies and sera from people who recovered from SARS-CoV-2 infection

Molecular and serological assays





More to immune response than measurable antibodies…



nature

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Accelerated Article Preview

Evolution of antibody immunity to SARS-CoV-2

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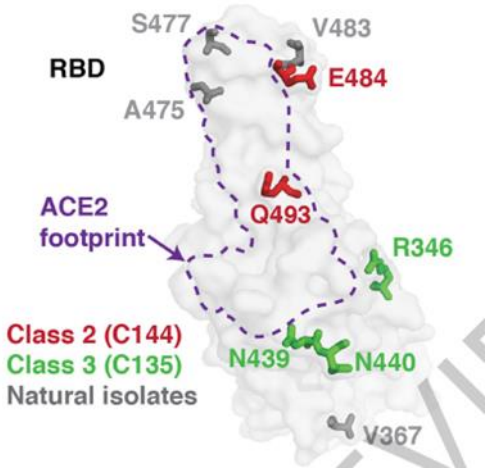
Christian Gaebler, Zijun Wang, Julio C. C. Lorenzi, Frauke Muecksch, Shlomo Finkin, Minami Tokuyama, Alice Cho, Mila Jankovic, Dennis Schaefer-Babajew, Thiago Y. Oliveira, Melissa Cipolla, Charlotte Viant, Christopher O. Barnes, Yaron Bram, Gaëlle Breton, Thomas Hägglöf, Pilar Mendoza, Arlene Hurley, Martina Turroja, Kristie Gordon, Katrina G. Millard, Victor Ramos, Fabian Schmidt, Yiska Weisblum, Divya Jha, Michael Tankelevich, Gustavo Martinez-Delgado, Jim Yee, Roshni Patel, Juan Dizon, Cecille Unson-O'Brien, Irina Shimeliovich, Davide F. Robbiani, Zhen Zhao, Anna Gazumyan, Robert E. Schwartz, Theodora Hatziioannou, Pamela J. Bjorkman, Saurabh Mehandru, Paul D. Bieniasz, Marina Caskey & Michel C. Nussenzweig



- Time points 1- and 6-months post illness onset (proven infection)
- Antibody levels to RBD in SARS-CoV-2 spike protein decrease with time, in parallel with neutralizing activity but remain detectable
- The number of RBD-specific memory B cells is unchanged
- There is continued evolution of the humoral response, broader and stronger specificity, consistent with antigen persistency and germinal center activity
- Memory responses are required for protection from re-infection and are essential for vaccine effectiveness
- Individuals who have been infected with SARS-CoV-2 could mount a rapid and effective response to the virus upon re-exposure

Re-infection

Public Health England | Public Health Scotland | HSC Public Health Agency | GIG CYMRU NHS Wales – Iechyd Cyhoeddus Cymru Public Health Wales

SIREN
SARS-CoV2 Immunity & Reinfection Evaluation

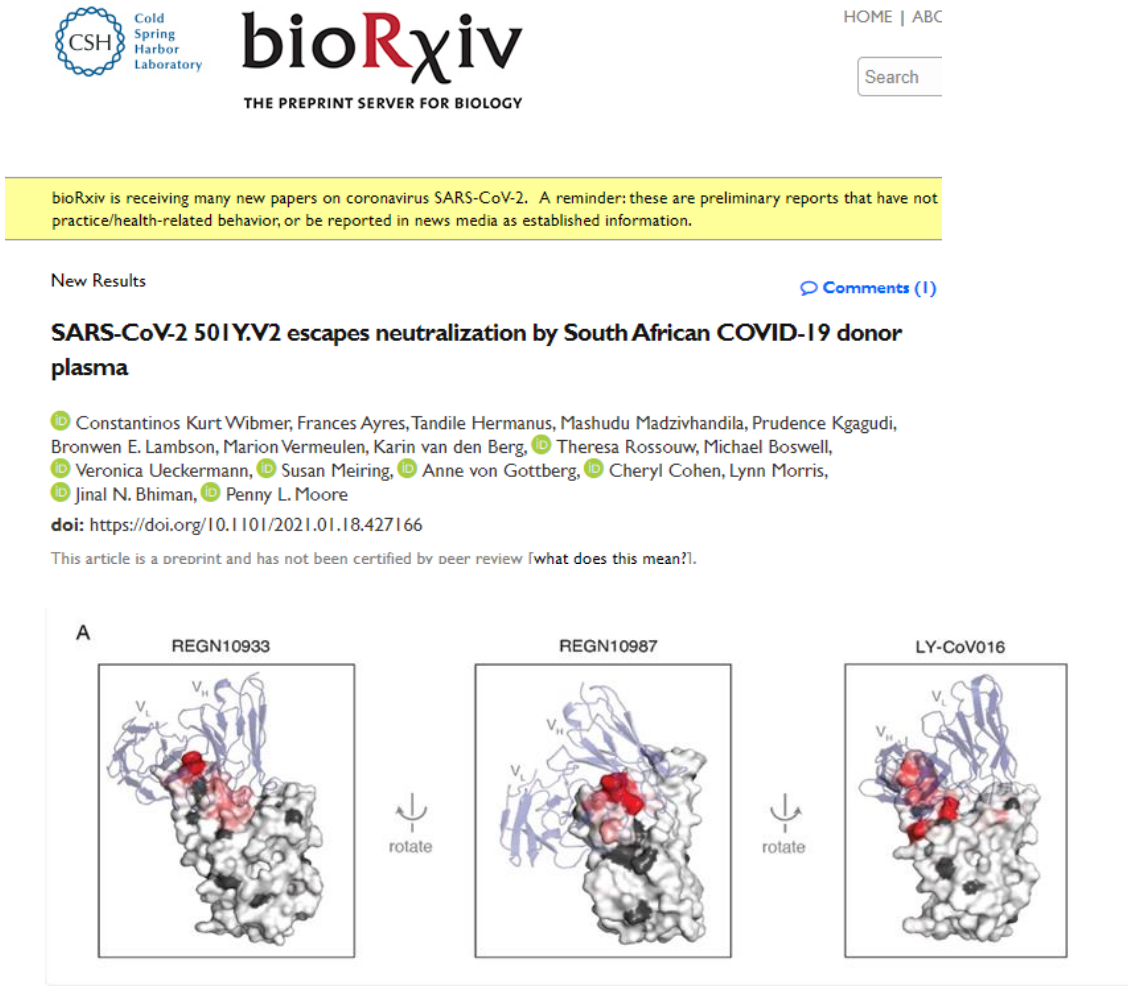
SARS-CoV-2 Immunity and Reinfection EvaluatioN- Preliminary report

- 18th June to 9th Nov , n=20,787 from 102 sites in England
- Naturally acquired immunity confers 83% protection against re-infection compared to people who have not been infected
- This lasts for at least 5 months from first onset of illness, i.e. minimum interval between infection episode was 5 months
- No correlates can be drawn in relation to vaccine response, which will be monitored
- Data suggests re-infection and significant virus shedding still occurs
- 2 probable
  - Symptomatic
  - High viral load, culture positive
  - Serological boosting
  - Support from sequencing

N=20787	Infection	Symptomatic	Cumulative Incidence of infection per 1,000
Seropositive at enrollment (32%)	44	15 (34%)	6.7%
Seronegative at enrollment (68%)	409	249 (61%)	22.4%

Level of cross protective immunity from previous infection to SARS-CoV-2 501Y.V2

- Question: does serum from people who have been infected with SARS-CoV-2 neutralize new variants?
- Changes in RBD leads to escape from therapeutic monoclonal Ab and convalescent plasma
- Deletion in the N terminal domain impairs neutralization
- Polyclonal Ab from convalescent plasma had significantly lower neutralization effect
- **Non-neutralizing Ab retain biding capacity to variant RBD**



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bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not practice/health-related behavior, or be reported in news media as established information.

New Results

Comments (1)

SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma

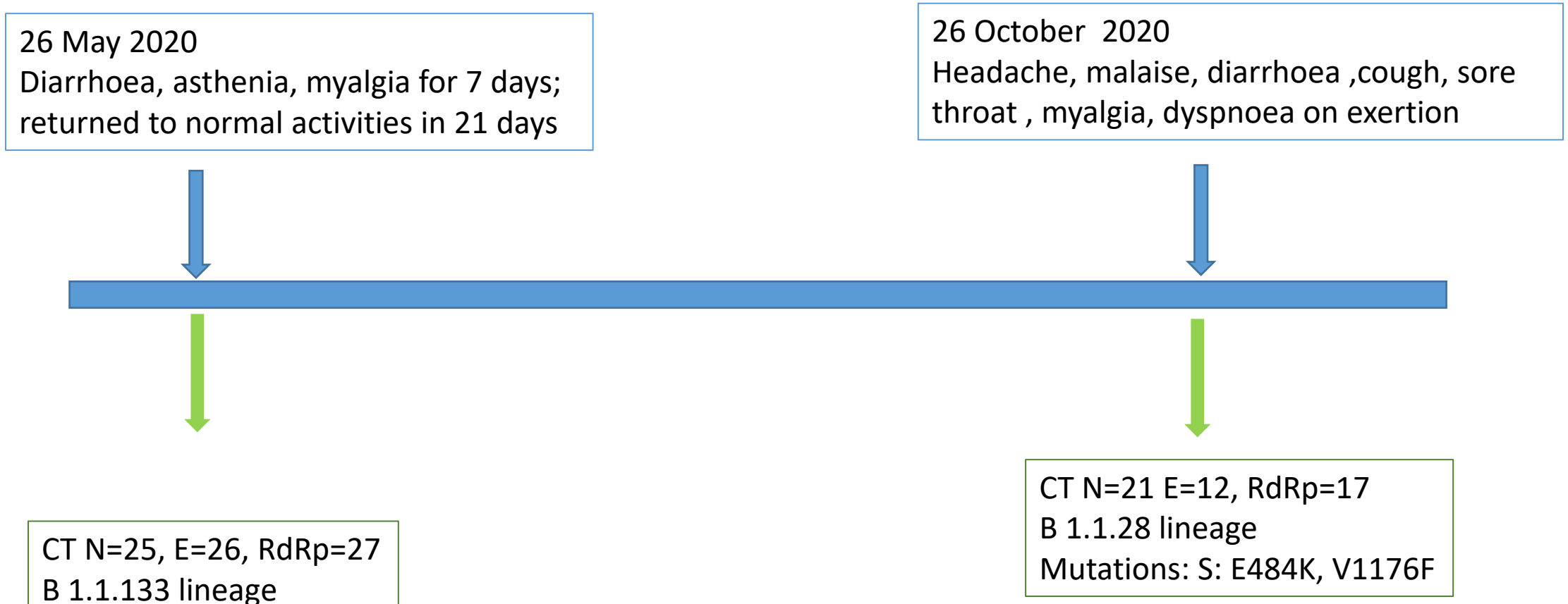
Constantinos Kurt Wibmer, Frances Ayres, Tandile Hermanus, Mashudu Madzivhandila, Prudence Kgagudi, Bronwen E. Lambson, Marion Vermeulen, Karin van den Berg, Theresa Rossouw, Michael Boswell, Veronica Ueckermann, Susan Meiring, Anne von Gottberg, Cheryl Cohen, Lynn Morris, Jinal N. Bhiman, Penny L. Moore

doi: https://doi.org/10.1101/2021.01.18.427166

This article is a preprint and has not been certified by peer review [what does this mean?].

Star T et al, bioRxiv 2020

Illustrative case of reinfection with a variant (P.2)



Nonaka et al , 2021

Immune escape
Vaccines and Therapeutics

B.1.1.7 lineage and BNT162b62 vaccine

- Pseudoviruses bearing the SARS-CoV-2 spike of the Wuhan reference strain *vs* B.1.1.7 lineage
- Sera from 16 BNT162b62 vaccine trial participants
- BNT162b2-immune sera neutralized SARS-CoV-2 (USA/WA-1/2020 15 background strain) with an introduced N501Y mutation as efficiently as SARS-CoV-2 without the mutation
- This, together with combined data on humoral and cellular responses to this vaccine indicate that **it is unlikely the B.1.1.7 lineage will escape the BNT162b62 –induced protection**

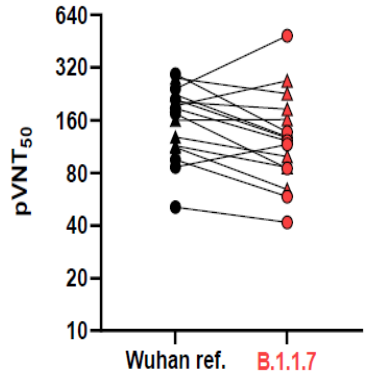


Fig. 1. 50% pseudovirus neutralization titers of 16 sera from BNT162b2 vaccine recipients against VSV-SARS-CoV-2-S pseudovirus bearing the Wuhan or lineage B.1.1.7 spike protein. N=8 representative sera each from younger adults (aged 18 to 55 yrs; indicated by triangles) and older adults (aged 56 to 85 yrs; indicated by circles) drawn at day 43 (21 days after dose 2) were tested.

Muik A, et al bioRxiv 2021

B.1.1.7 and 501Y.v2 lineages and the Moderna vaccine

Moderna COVID-19 Vaccine Retains Neutralizing Activity Against Emerging Variants First Identified in the U.K. and the Republic of South Africa

January 25, 2021

Out of an abundance of caution, Moderna launches clinical program to boost immunity to emerging variants

Manuscript posted to preprint server; company to host conference call once manuscript is available

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 25, 2021-- Moderna Inc. (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines, today announced results from in vitro neutralization studies of sera from individuals vaccinated with Moderna COVID-19 Vaccine showing activity against emerging strains of SARS-CoV-2. Vaccination with the Moderna COVID-19 Vaccine produced neutralizing titers against all key emerging variants tested, including B.1.1.7 and B.1.351, first identified in the UK and Republic of South Africa, respectively. The study showed no significant impact on neutralizing titers against the B.1.1.7 variant relative to prior variants. A six-fold reduction in neutralizing titers was observed with the B.1.351 variant relative to prior variants. Despite this reduction, neutralizing titer levels with B.1.351 remain above levels that are expected to be protective. This study was conducted in collaboration with the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The manuscript has been submitted as a preprint to *bioRxiv* and will be submitted for peer-reviewed publication.

The two-dose regimen of the Moderna COVID-19 Vaccine at the 100 µg dose is expected to be protective against emerging strains detected to date. Nonetheless, Moderna today announced its clinical strategy to proactively address the pandemic as the virus continues to evolve. First, the Company will test an additional booster dose of its COVID-19 Vaccine (mRNA-1273) to study the ability to further increase neutralizing titers against emerging strains beyond the existing primary vaccination series. Second, the Company is advancing an emerging variant booster candidate (mRNA-1273.351) against the B.1.351 variant first identified in the Republic of South Africa. The Company is advancing mRNA-1273.351 into preclinical studies and a Phase 1 study in the U.S. to evaluate the immunological benefit of boosting with strain-specific spike proteins. Moderna expects that its mRNA-based booster vaccine (whether mRNA-1273 or mRNA-1273.351) will be able to further boost neutralizing titers in combination with all of the leading vaccine candidates.

- Neutralizing titres detected against variants B1.1.7 and B1.351, with no significant difference in relation to prior variants
- Titres against B 1.351 were lower but still above levels that would be considered protective
- 2 dose regimens expected to be effective against current strains
- 3rd dose being investigated (mRNA-1273) for benefit of boosting with strain-specific spike protein
- This strategy could be used to boost neutralizing Ab titres in combination with all leading vaccine candidates

Ongoing work on the B.1.1.7 variant

- Growth kinetics being studied
- Grows well and better in human airways cells in comparison to other previous isolates
- Neutralisation work is under way
- Cross neutralising Ab is being detected
- Ag distance between older circulating viruses and these new variants, using post vaccination sera and sera from previously infected people
- Case control study for disease severity and death
  - Limitations as most cases are infected with the B1.1.17 variant

Final remarks on pre-existing immunity and vaccine efficacy

- The reduction in neutralization that might indicate the need for a strain change has not been established for COVID-19 vaccines
- Ongoing evolution of SARS-CoV-2 necessitates continuous monitoring of the significance of changes for maintained protection by currently authorized vaccines
- The true impact of the variants of concern on the vaccinated population must be measured outside of a laboratory context – and in the presence of other natural human immune responses
- It is possible that vaccine efficacy could be preserved, even with substantial losses of neutralization by vaccine-elicited sera
  - Immune response against several epitopes with activation of B and T cells with multiple potential mediators of protection elicited by vaccines
  - Binding of virus by non-neutralizing antibodies is preserved and may have a role
  - Other innate components of the immune system plus residual vaccine effect

Take home messages

Note:
Rapidly changing scene
Need to follow scientific developments

- Currently highly effective vaccines are predicted to tolerate some variation in the virus
- If not completely protective against new circulating strains, may still give enough response to make any new infection much less serious
- The more virus circulates, the higher the risk of selecting new strains
- Robust laboratory, genetic, clinical and epidemiological data must be collected to inform public health strategies

Thank you