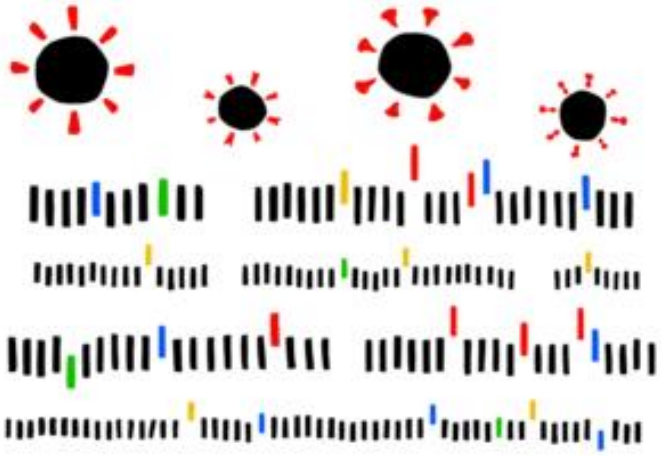
SARS-CoV-2 genetic variants and Vaccine Update



(from COG UK blog)

ISBT TTID Working Party (Virology)
11th March 2021

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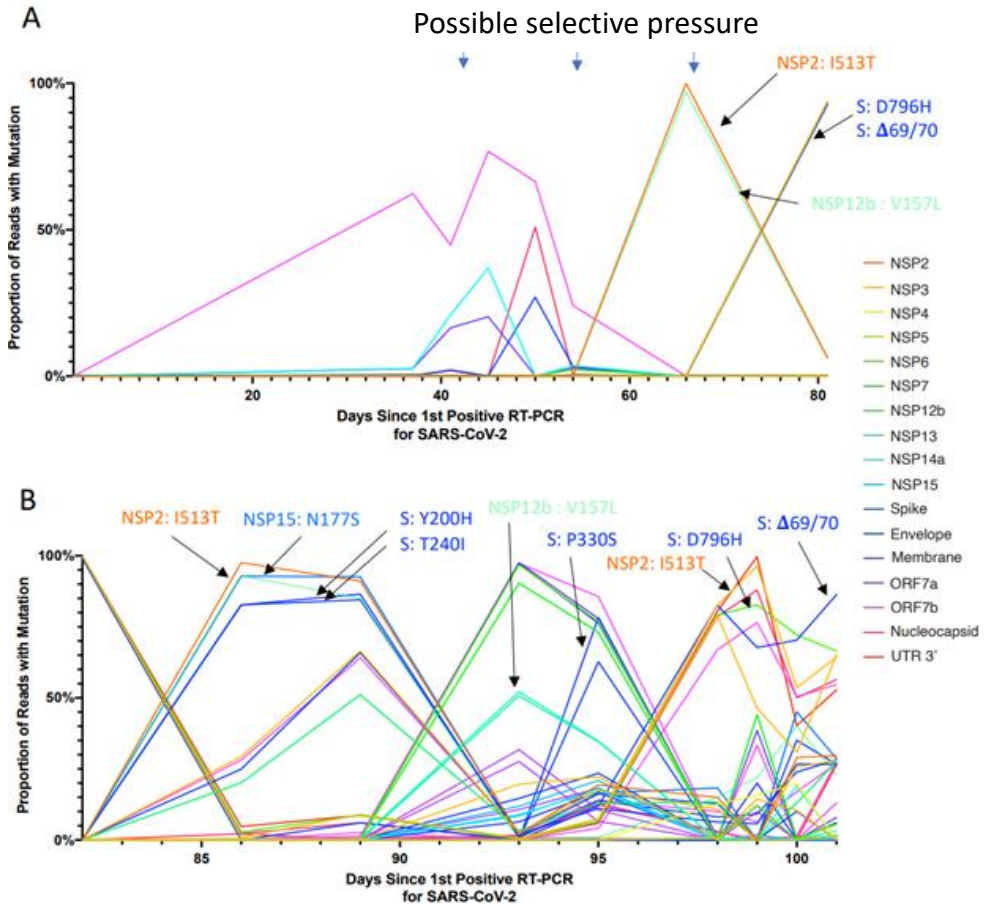
Potential advantages conferred by genetic changes

- 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?

- 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:
- 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

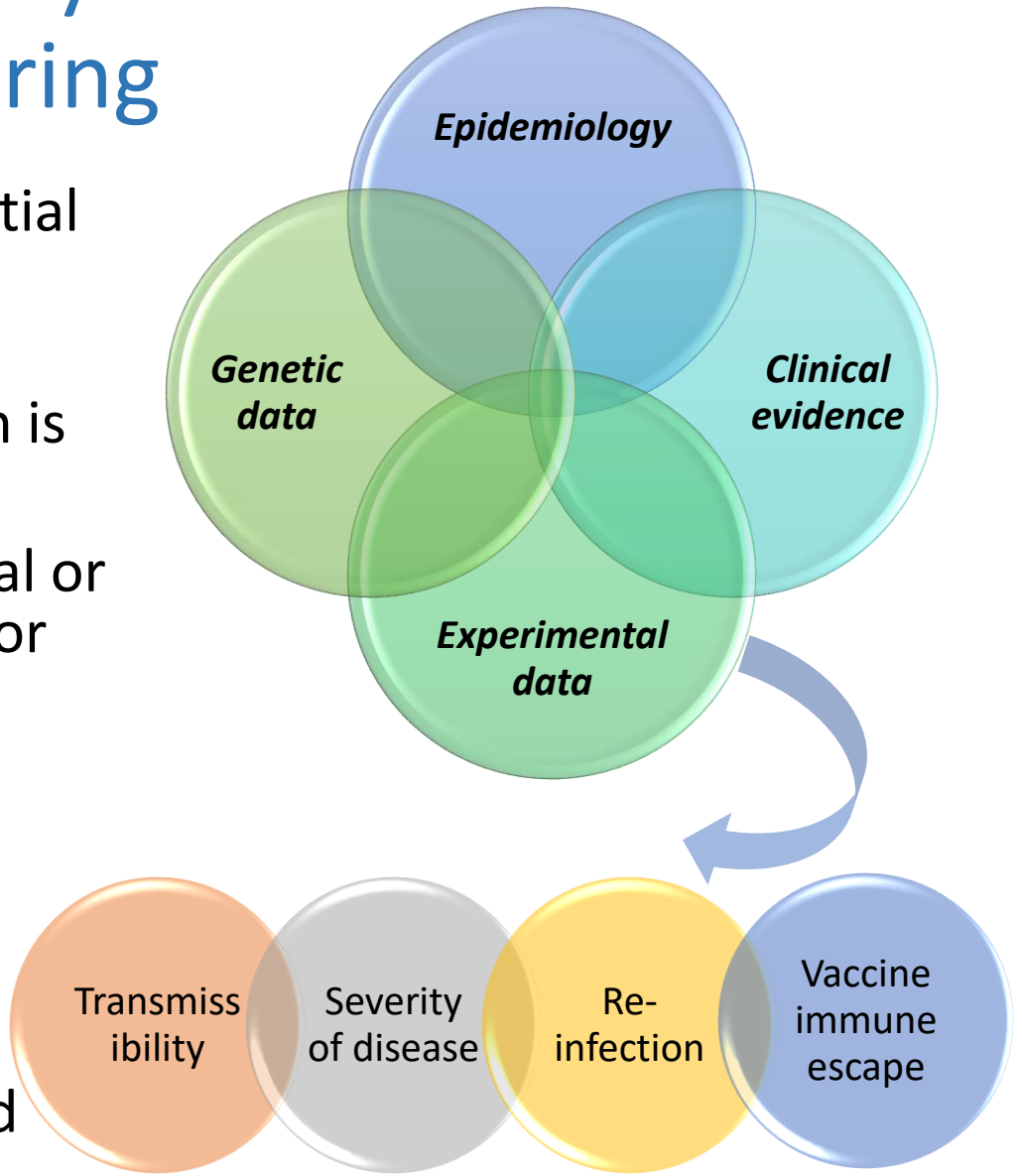
- Trends in the **frequency of specific viral variants**. If these are appearing more often in the population than other variants, there are several explanations that need to be investigated
  - One possible reason is that a virus with a specific mutation or combination of mutations may spread more rapidly in the population as a result of increased infectivity or transmissibility

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

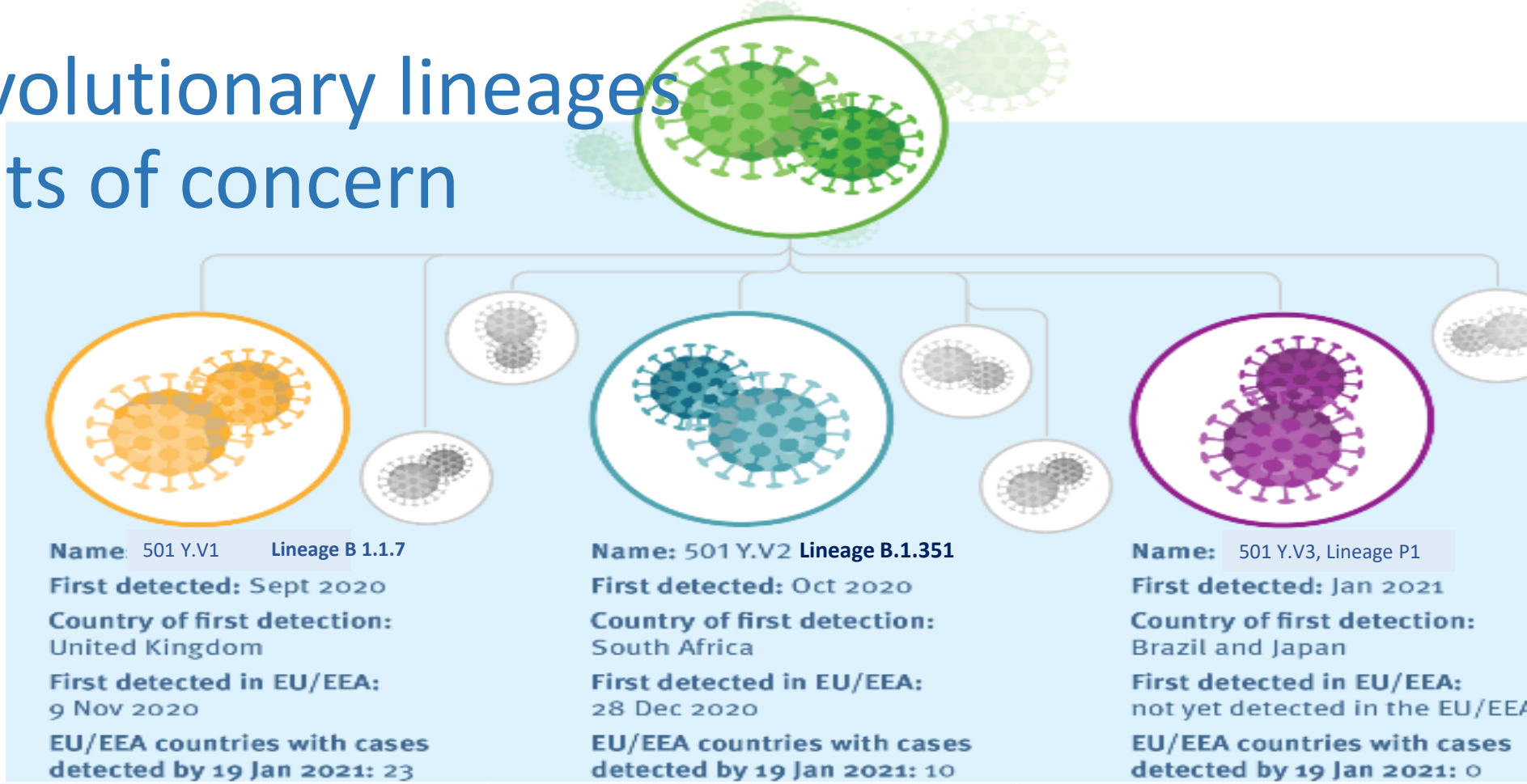
- **Genomic surveillance** detect variants that are evading the immune system elicited by past infection or vaccination

Mutations of interest- How are they identified and selected – role of genomic monitoring

- The spatial spread of SARS-CoV-2 highlights the potential for rapid virus dissemination through national and international travel
- Continued genomic monitoring of lineages of concern is required
- 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

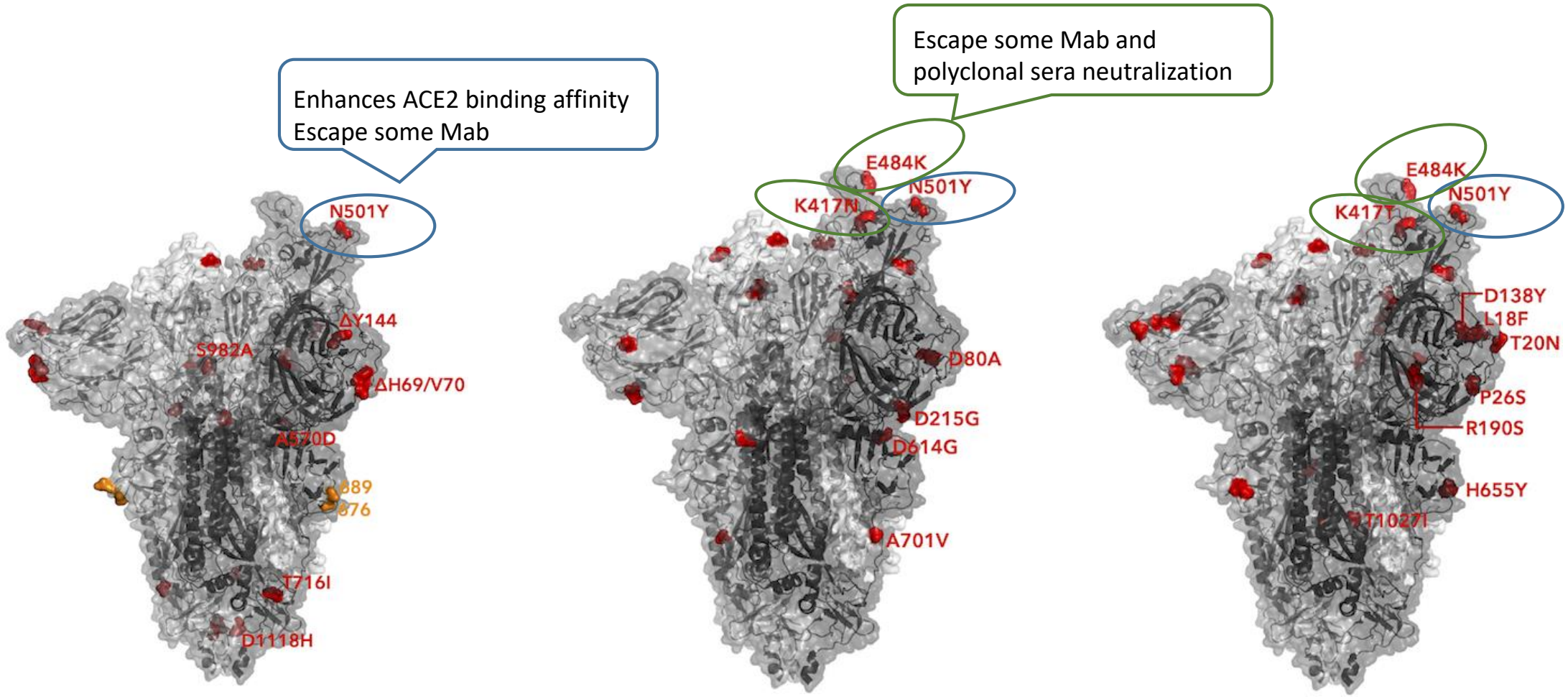


SARS-CoV-2 evolutionary lineages
Current variants of concern



Notable mutations	N501Y; P681H 69-70 del	N501Y; K417N; E484K	N501Y; E484K; K417T
Transmissibility	Increased	Increased	Possibly increased
Pathogenicity	Not increased	Not increased	No evidence to date
Significant antigenic escape from natural or vaccine induced immunity	No	Under investigation Immune escape reported	Under investigation Immune escape reported

Global Variants of Concern being monitored by UK Public Health Authorities



Lineage :	B.1.1.7	B.1.351	P.1

SARS-CoV2 variants : UK distribution and data

1 death

No hospitalization
No deaths
1 vaccinee 5 days prior

Surveillance overview

UK total distribution

Variant	Other names by which this variant may be known*	Country in which first detected	Genomically confirmed cases**	Genomically probable cases**	Total genomically confirmed and probable cases	New cases since last update
VOC-202012/01	B.1.1.7	England, UK	-	-	115,558	+7,291
VOC-202012/02	501Y.V2 B.1.351	South Africa	227	83	310	+15
VUI-202101/01	P2 (descendent of B.1.1.28)	Brazil	47	0	47^^	+4
VOC-202101/02 ¥¥¥	P1 (descendent of B.1.1.28)	Japan ex Manaus, Brazil	5	1	6	-
VUI-202102/01	A.23.1 with E484K	England, UK	59***	18	77***	-1
VOC-202102/02	B.1.1.7 with E484K	England, UK	35	0	35	+1
VUI-202102/03	B.1.525 (previously designated UK1188)	England, UK	78	29	107¥	+21
VUI-202102/04	B1.1.318	TBC	20	0	20^^^	+4

B.1.1.7- Biological profile

- Variants emerging in a range of geographical locations seem to share certain mutations — possible evidence that the changes aid transmission
- Growth kinetics show that B.1.1.7 variant grows well and better in human airways cells in comparison to previous isolates
- Antigenic distance between older circulating strains and new variant is being checked against sera from previously infected or vaccinated individuals
- Cross neutralizing antibodies is being detected
- Not associated with significant antigenic escape from
  - naturally-acquired immunity
  - vaccine-acquired immunity
- Case control study for comparison of disease severity and death is difficult as most cases are infected with the B1.1.7 variant
- B.1.1.7 RNA positivity seems to be longer than with previous strains (13.3 days vs 8.2 days)
- This could allow longer period of infectivity, making it “more infectious”

E484K in variants of concern

- Mutation of concern with regards to antigenic change and increased receptor binding avidity
- Potentially more concerning when combined with N501Y
- It arises in the presence of convalescent and vaccine-derived antisera
- Present in multiple variants of concern including the B.1.351 and P.1 lineages
- Identified as a long-term adaptation in different immunocompromised patient studies

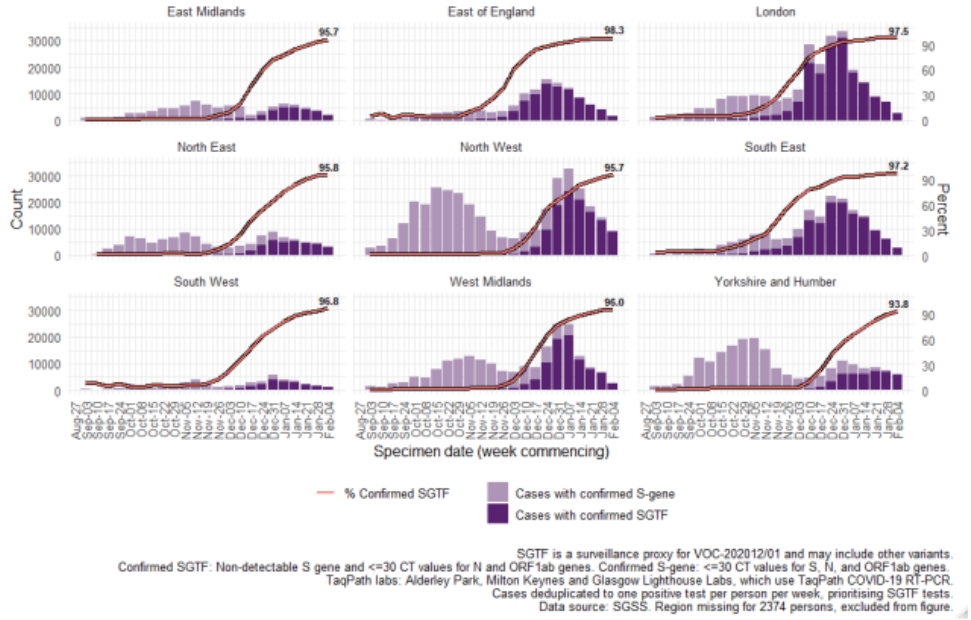
Performance of diagnostic assays

Assay Assurance

Impact on diagnostics

- The S-gene deletion corresponding to residues Δ69-70, in the spike protein causes reproducible **T**arget amplification **F**ailure in some assays (**S**-**g**ene **t**arget **f**ailure, SGTF)
  - ThermoFisher TaqPath assay used in UK
- The S-gene target failure is unlikely to cause an overall false-negative result for SARS-CoV-2 as the S-gene is generally not used by itself for detection of the virus

Figure 7. Weekly number and proportion of England Pillar 2 COVID-19 cases with SGTF among those tested with the TaqPath assay and with S gene detection results, by region of residence (3 September 2020 to 10 February 2021)



SGTF is a surveillance proxy for VOC-202012/01 and may include other variants.
Confirmed SGTF: Non-detectable S gene and <=30 CT values for N and ORF1ab genes. Confirmed S-gene: <=30 CT values for S, N, and ORF1ab genes.
TaqPath labs: Alderley Park, Milton Keynes and Glasgow Lighthouse Labs, which use TaqPath COVID-19 RT-PCR.
Cases deduplicated to one positive test per person per week, prioritising SGTF tests.
Data source: SGSS. Region missing for 2374 persons, excluded from figure.

Monitoring of RNA amplification methods

- How to identify issues with assays
  - Target drop out
  - Poor amplification efficiency
  - Significant (>3 CTs) shifts in average CT values (or equivalent)
  - Increased disparity between screening and confirmatory assays
  - Disparity in gene targets
  - Increase in equivocal results
- How to identify sequences of concern
  - Assays targeting single nucleotide polymorphisms (SNP) for screening
  - Melting curve analysis to detect specific SNIPs
  - Multiplex target amplification

Risk Level	Risk Rating	Description
Level 1		Uses target and these are in areas of key gene changes
Level 2		Uses target but these are not in areas of key gene changes
Level 3		Does not use target genes

Guidance

SARS-CoV-2 lateral flow antigen tests: evaluation of VOC1 (Kent, UK) and VOC2 (South Africa)

Published 12 February 2021

Rapid antigen detection tests validated in the UK

All targeting the nucleocapsid protein which has two amino acid changes for B.1.1.7 (D3L and S235F), still meet minimum performance criteria for this variant

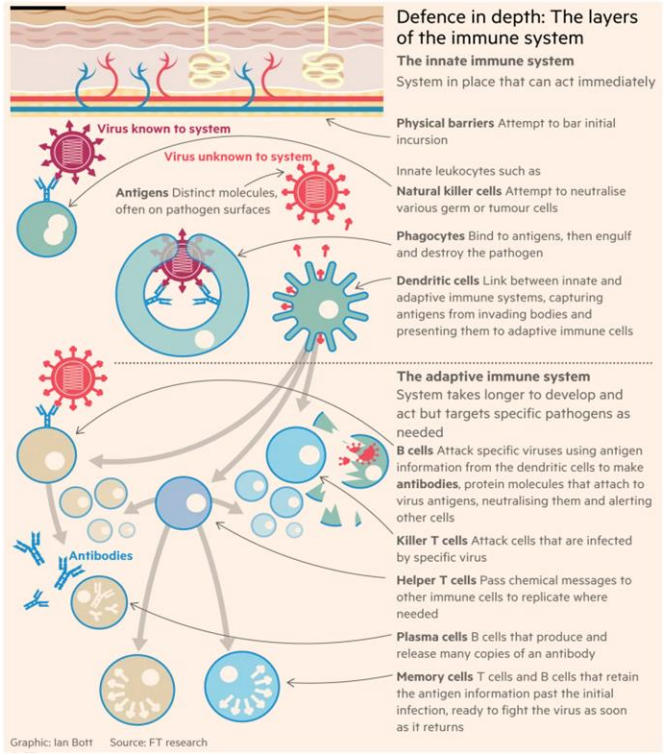
Variant of concern, virus titre and detection level

	VOC1	Kent, UK	VOC2	South Africa
Lateral Flow Device	**10^4 pfu/ml**	**10^3 pfu/ml**	**10^4 pfu/ml**	**10^3 pfu/ml**
Fortress	Detected	Detected	Detected	Detected
Roche SD Biosensor swab	Detected	Detected	Detected	Detected
Abbott Panbio	Detected	Detected	Detected	Detected
Innova	Detected	Detected	Detected	Detected
Surescreen	Detected	Detected	Detected	Detected
Orient Gene	Detected	Detected	Detected	Detected

Immune escape: Re-infection Vaccines and Therapeutics

- Do sera from people who have been infected and recovered from the original SARS-CoV-2 strain neutralise new variants
- Do vaccines based on the original Wuhan strain work against other strains
- Do monoclonal preparations neutralize new variants

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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Accelerated Article Preview

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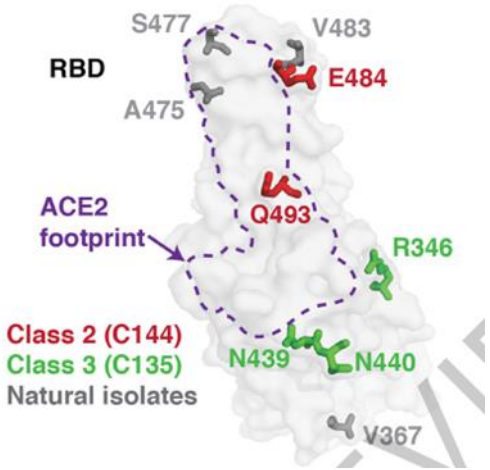
Christian Gaebler, Zijun Wang, Julio C. C. Lorenzi, Frauke Muecksch, Shlomo Finkin, Minami Tokuyama, Alice Cho, Mila Jankovic, Dennis Schaefer-Babajew, Thiago Y. Oliveira, Melissa Cipolla, Charlotte Viant, Christopher O. Barnes, Yaron Bram, Gaëlle Breton, Thomas Hägglöf, Pilar Mendoza, Arlene Hurley, 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

Impact on vaccine efficacy

- The reduction in neutralization that might indicate the need for a strain change has not been established for COVID-19 vaccines

- No evidence to date of significant evasion of B.1.1.7 variants to vaccine
- Significant boost in specific memory B cell frequency, IgG and IgA to RBD, against the initial and the variant strains can be seen with vaccination
- It is possible that vaccine efficacy could be preserved, despite detectable loss 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
  - Beyond anti-RBD neutralizing antibodies

Public Health England | Public Health Scotland | HSC Public Health Agency | GIG CYMRU NHS 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	Incidence infection per 100,000
Seropositive at enrollment (32%)	44	15 (34%)	6.7%
Seronegative at enrollment (68%)	409	249 (79%)	22.4%

Public Health England | Public Health Scotland | HSC Public Health Agency | GIG NHS Public Health Wales

SIREN
SARS-CoV2 Immunity & Reinfection Evaluation

Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study)

30 Pages • Posted: 22 Feb 2021

Victoria Jane Hall
Public Health England Colindale; University of Oxford - NIHR Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance

- A single dose of BNT162b2 vaccine demonstrated vaccine effectiveness of 72% (95% CI 58-86) 21 days after first dose
- 86% (95% CI 76-97) seven days after two doses
- As infection is being prevented, this suggests that vaccine has a role in interrupting transmission
- Protection against B.1.1.7 VOC

Pfizer Biontech Vaccine efficacy in UK vaccine roll out Real-world data

- High levels of protection from first dose in the >80y, including the B.1.1.7 variant
- 57% effective in preventing symptomatic disease
- Reduction of disease severity and death compared to unvaccinated individuals
    - Risk of hospitalization reduced by 40%
    - Risk of death reduced by 56% at least 14 days after 1st dose

- AZ vaccine efficacy being monitored, data soon to be available
    - Evidence that booster delay to 12 weeks will elicit stronger response

Alternative strategies and second-generation vaccines

- Booster dose with vaccine offering better match to prevalent variant
- Using different vaccines for priming and boosting
- Combination vaccines against different strains
- Different antigen target
- Protection against infection and person-to person transmission
- Vaccines to elicit mucosal immunity

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
- We should vaccinate as many people as possible
- The more virus circulates, the more risk of selecting new strains
- Preparedness for tackling escape variants is under way

Thank you