SAGE Vaccine Updates Group

Considerations on when and how to update SARS-CoV-2 vaccines

Purpose and Scope of this Paper

The objective of this paper is to inform and support short term decisions on vaccine updates. This paper serves as a guide for how antigenic evolution of the virus might impact vaccine decisions. In the longer term, a vaccine strategy for different potential future scenarios might be required – SARS-CoV-2 might become an endemic antigenically variable virus in humans or it might recede in the face of large-scale population immunity. A long-term vaccine strategy should be developed to effectively respond to any potential scenario. In the short term, however, there are urgent questions concerning the potential need for an update in the formulation of existing SARS-CoV-2 vaccines to respond to the emergence of new SARS-CoV-2 variants which this paper seeks to inform. This paper summarizes the current evidence of antigenic evolution of SARS-CoV-2 and gathers information about the impact of this evolution on the efficacy of current vaccines containing spike protein from an original Wuhan-like wildtype strain.

Executive Summary

How will we know when to update the vaccine?

Ideally to know when to update the vaccine we need:

1. A correlate of protection: something that can be measured that indicates if a person is protected or not.
2. A reliable assay to measure the correlate, preferably one that is easy to perform.
3. A good survey of the population immunity using this measurement.
4. Knowledge of how stable the immune correlate is over time.
5. Measurements of this parameter against multiple independent isolates of each variant of concern and/or interest.
6. To develop a vaccine strain selection and update process. To begin with this might adapt what it can from existing processes such as that for the annual influenza vaccine strain update, but it must also recognize the current uncertainty around SARS-CoV-2 antigenic variation and immunity, and that we don't yet know how the antigenic evolution will proceed and how many distinct variants, if any, will co-circulate.

Given we don't yet have full knowledge, where are we today?

- With respect to a correlate of protection, there is some data, and we can fall back on what we know has worked for other pathogens
- We can measure serum antibody titres in a live virus neutralization assay and this is accepted as the most reliable correlate thus far
- We can estimate what neutralizing antibody titres are protective in practice.

What variants do we need to consider today, and what do we know about their antigenic difference from current vaccine immunogen?:

- There are 3 variants of concerns, two of which have consistently measurable antigenic distance from the progenitor Wuhan like virus (B.1.351 South African VOC and P.1 Brazilian VOC).
- There is laboratory and real world data that they might be antigenically different enough to warrant concern over VE.
- There is other data that indicate some current vaccines may still confer adequate protection.
- In summary, there is preliminary data both for and against a need to update vaccines in the short term and this decision will depend on whether vaccines are being used to protect against severe disease, or transmission for which a higher titre or better matched immune response may be required.

Recommendations:

- Further work to define and refine the estimate of correlates of protection.

- Pursue small scale trials with a third dose of homologous and variant vaccine in a representative population sample.

- Ensure a good survey of population immunity, including immunity to variants, over time to both infection and vaccination.

- Develop and validate surrogate tests and reagents to measure correlates of protection and quantify antigenic differences between variants.

- Invest in establishing surveillance in the traditional sense of global sharing of isolates and sera, as well as leveraging the genomic data to test variants.

Reports of potential antigenic escape

Numerous studies now report that certain variants of SARS-CoV-2 display differences in antigenic properties, pathogenicity and transmissibility from the original Wuhan strain (Baum *et al.*, 2020; Chand and Others, 2020; Davies *et al.*, 2021; Greaney *et al.*, 2021).

Three main variants of concern show substitutions in a key antigenic site, the receptor binding domain

The UK variant B.1.1.7 harbours an amino acid substitution N501Y in the Spike protein RBD that has been associated with loss of recognition by some monoclonal antibodies.

The B.1.351 variant has emerged in South Africa with a signature set of mutations across the virus genome including 9 in S gene, including three changes across the RBD that have been associated with evasion of antibody: E484K, N501Y and K417N. Substitution at 484K has been associated with high receptor avidity and antibody evasion.

The SARS-CoV-2 lineage P.1 emerged in Manaus City, Amazonas state, Brazil with a signature set of 17 unique amino acid changes, including the trio of substitutions (E484K, K417T, and N501Y) which are common/similar to those in the B.1.351 variant (B.1.351 has 417N). These variants have arisen independently, but with some common features and mutations indicative of convergent evolution.

Laboratory studies find a drop in neutralization of variants

Numerous laboratory studies have measured a fall in neutralization titres of sera containing antibodies raised against original Wuhan like virus against these variants. (Chen *et al.*, 2021), (Rees-Spear *et al.*, 2021), (Li *et al.*, 2021),(Garcia-Beltran *et al.*, 2021)

Most studies find **small reductions in neutralising antibody titres of polyclonal sera against the UK variant B.1.1.7** (Emary *et al.*, 2021) (around 3-fold), compared to WT/D614G virus but **larger decreases against the two other variants of concern, P.1 originating from Manaus, Brazil and B.1.351 originating from South Africa** (Madhi *et al.*, no date; Liu *et al.*, 2021) with the loss of titre for B.1.351 being the most dramatic. The results for different types of laboratory studies with post-vaccination (Table 1) and post-infection (Table 2) sera are summarised below. **This shows, in general, a decrease of up to 10-fold against B.1.351 with both vaccinee and convalescent sera, and similar results from pseudotype and live virus assays.**

Table 1: Summary of antibody neutralization studies of B.1.351 and B.1.1.7 using **vaccinee** sera

PV or live virus	**Number of sera**	**Fold reduction of B.1.351 compared to homologous**	**Notes**	**Fold reduction of B.1.1.7 compared to homologous**	**Citation**
PV (VSV)	22	8.6 fold Moderna 6.5 fold Pfizer	12 Moderna 10 Pfizer 2 doses	2.8 fold Moderna 2.0 fold Pfizer	(P. Wang *et al.*, 2021)
Recombinant live virus	22	12.4 fold Moderna 10.3 fold Pfizer	12 Moderna 10 Pfizer 2 doses	+1.6 fold Moderna +1.3 fold Pfizer	(P. Wang *et al.*, 2021)
PV (lentivirus)	20	1.3-3 fold (triple mutant, not B.1.351)	14 Moderna 6 Pfizer 2 doses	Not done	(Z. Wang *et al.*, 2021)
Recombinant live virus	20	2.7 fold	Pfizer, 2 doses, whole S more than RBD alone	+1.25 fold	(Liu *et al.*, 2021)
PV (VSV)		6.4	Moderna 2 doses,	No sig change	(Wu *et al.*, 2021)
Recombinant live virus	24	10 fold	Pfizer	Few sera lost activity,2 fold max	(Diamond *et al.*, 2021)
Live virus	25	2/25 lost activity (estimated at <10 fold)	Pfizer 2 doses	0/25 lost activity	(Skelly *et al.*, 2021)
PV (lentivirus)	10	~3 fold but still all neutralizing	Pfizer single dose after previous infection	Not done	(Stamatatos *et al.*, 2021)

Table 2: Summary of antibody neutralization studies of B.1.351 and B.1.1.7 using **convalescent** sera

PV or live virus	Number of sera	Fold reduction of B.1.351 compared to homologous	Notes	Fold reduction of B.1.1.7 compared to homologous	Citation
Live virus	14	8.4 fold		Not done	(Cele *et al.*, 2021)
PV (lentivirus)	44	48% lost all neut activity (most others substantially reduced)	Effect on whole S greater than RBD,	Not done	(Wibmer *et al.*, 2021)
PV	20	22 fold		11/20, 3 fold loss	(P. Wang *et al.*, 2021)
Live recombinant virus	20	9.4 fold		+1.4 fold	(P. Wang *et al.*, 2021)
Live recombinant virus	19	4.5 fold		No sig difference	(Diamond *et al.*, 2021)
Live virus	9	7/9 undetectable	10 fold reduction of NIBSC reference serum	2/9 undetectable	(Skelly *et al.*, 2021)
PV (lentivirus)	10	Overall ~6.5 fold Of 9 Wuhan-neutralizing sera, only 5 neutralized B.1.351		Not done	(Stamatatos *et al.*, 2021)

Real world experience indicates that loss of neutralization can lead to loss of protection

UK variant B.1.1.7

In a study of UK care homes, eleven individuals who experienced confirmed re-infection with the Wuhan like or B.1.1.7 variant had no or low levels of neutralising antibody prior to re-infection, but then significantly boosted anti S binding and neutralising antibodies to both 2020 strains and B.1.1.7 upon reinfection (PHE unpublished data, NERVTAG 5th March). Whilst re-infections with both Wuhan like and B.1.1.7 variant are rare, this provides real world data suggesting that low levels of neutralising antibodies confer susceptibility to re-infection. These findings also suggest that there is little antigenic difference between B.1.1.7 and earlier viruses, and that antibodies to earlier viruses will continue to provide protection against this emerging variant.

Two other variants of concern, P.1 originating from Manaus, Brazil and B.1.351 originating from South Africa

However, the emergence of diverse variants in different parts of the world does not provide an equally reassuring picture. Of concern, vaccine clinical field studies in S. Africa conducted since the emergence of B.1.351 showed that during the first 60 days of follow-up, the incidence of Covid-19 observed in baseline seronegative placebo participants (5.3% [95% CI: 4.3 to 6.6]; 33 mild and 47 moderate cases out of 1516 participants) was comparable to the incidence in baseline seropositive placebo participants (5.2% [95% CI: 3.6 to 7.2]; 14 mild and 21 moderate cases out of 674 participants), suggesting that prior infection, with 2020 prototype SARS-CoV-2, did not reduce the risk of subsequent COVID-19 illness likely due to the B.1.351 variant (Shinde *et al.*, 2021). Laboratory studies investigating the inhibition of B.1.351 viruses by antisera raised to prototype viruses demonstrates a minimum of 4-fold reduction(Diamond *et al.*, 2021), with other laboratory studies indicating greater fold reduction, depending on methodology used.

The P.1 Brazil variant demonstrates a six fold or more reduction in neutralisation by sera from people infected in the first wave (de Souza *et al.*, 2021). Neutralization assays with pseudoviruses of SARS-CoV-2 containing the key RBD substitutions showed inhibition by antibodies present after natural infection and elicited by the BNT162b2 vaccine, but the neutralization potency was reduced at least 4 fold compared with titres against Wuhan like PV. Some reports of reinfections in Brazil and the emergence of the P.1 and related P.2 variants in the face of a high seropositivity rate after the first wave, suggest that the substitutions present in these variants enable escape from antibodies raised to first wave virus.(Nonaka *et al.*, 2021) (paola, 2021)(paola, 2021; Sabino *et al.*, 2021)

These data suggest that where there is significant antigenic distance, lower levels of antibody after natural infection may not provide protection.

A recent study shows that sera of individuals infected with common cold coronavirus HCoV-229E in the 1980s and 1990s had a neutralization antibody capacity reduced at least 4-fold against contemporary HCoV-229E isolates (Eguia *et al.*, 2020). This might mean that this seasonal common cold coronavirus has undergone antigenic evolution driven by natural immunity and that variants with more than 4-fold antigenic difference had a selective advantage that drove their evolution; however, this is by no means certain.

The concordance between lack of neutralising antibodies in individuals prior to re-infection with prototype or B.1.1.7 variants and also the significantly reduced cross neutralisation *in vitro* and lack of protection against infection *in vivo* against B.1.351 variants supports the hypothesis that **neutralising antibody titres may serve as a proxy for a correlate of protection**. Where there is little antigenic difference between viruses such as between older 2020 strains and B.1.1.7, this is seen as a less than four-fold variation in inhibition by post-infection sera, and cross protection is evident. On the other hand, a greater than fourfold variation in neutralising antibody is indicative of much more significant antigenic distance, and correlates with a clinical infection outcome. This suggests that a quantitative threshold of protective levels of antibody may be predicted, though this is at present confounded by technical differences in the way in which this may be measured.

This correlation between measured antibody and infection outcome is encouraging from the perspective of predicting the protective effectiveness of vaccine induced immunity at a population level.

How well do the current vaccines protect against South Africa and Brazil variants?

In the UK during the vaccine rollout in January and February 2021, the vast majority of circulating viruses (>70%) have been the B.1.1.7 variant. Vaccine effectiveness results were extremely good over this period, and indeed were comparable to those reported from Phase II/III trials conducted last year before the emergence of B.1.1.7 (Lopez Bernal *et al.*, 2021). For example, a recent Scottish study reported a substantial (90%) reduction in hospitalization rate in vaccinees receiving the AstraZeneca adenovirus-vectored or the Pfizer mRNA vaccines compared to controls, even after a single dose. (Torjesen, 2021). When examining the results from randomised clinical trials, shown in Figure 1, both the AstraZeneca adenovirus-vectored and Novavax protein subunit vaccine efficacy showed non-significant decreases of about 10% between non-B.1.1.7 and B.1.1.7.

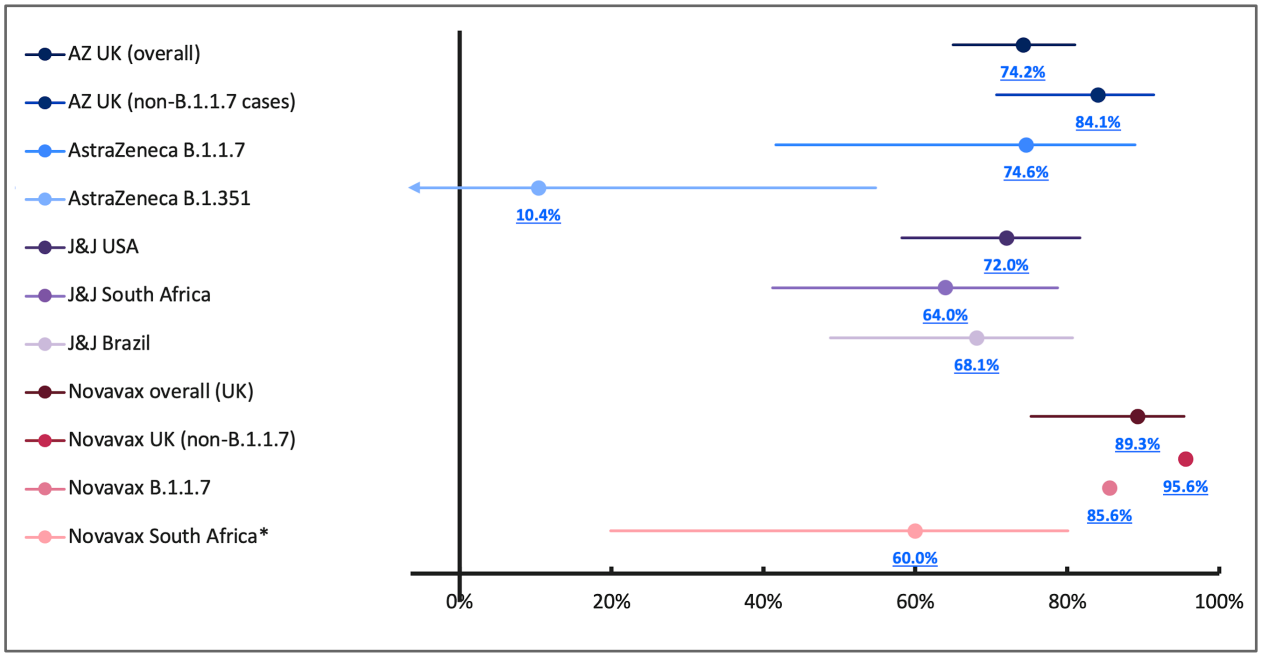

Figure 1: Randomised clinical trial results for vaccine candidates stratified by variant or geographic location, where this data was available - Figure generated by Airfinity. (Voysey et al, Emary et al, Madhi et al, FDA submission, Shinde et al, (Mahase, 2021a) et al)

Only one randomised controlled trial has directly measured vaccine effectiveness against B.1.351 (Madhi *et al.*, no date). This small study of adults under 65 years (median age 31 years) showed a vaccine efficacy of the AstraZeneca adenovirus-vectored vaccine of 10.4% (95%CI: −76.8; 54.8) against mild-moderate disease. The study was underpowered to detect an effect on severe disease. Additionally, there are two studies conducted in South Africa when the proportion of

B.1.351 was high (over 90%) that did not provide variant specific estimates of vaccine efficacy. These studies reported smaller decreases in vaccine efficacy. The J&J adenovirus-vectored vaccine had a vaccine efficacy against moderate-severe/critical disease of 72.0% (95%CI: 58.2; 81.7) in the USA and 64.0% (95%CI: 41.2; 78.7) in South Africa (VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE, 2021). Novavax, a vaccine comprised of expressed spike protein presented on nanoparticles, interim results show a vaccine efficacy against PCR-confirmed symptomatic infection (mild, moderate or severe) in South Africa of only 60.1% (95%CI: 19.9; 80.1) (Shinde *et al.*, 2021) in comparison with 89% in the UK. (Mahase, 2021a). Overall, this suggests a modest decrease in vaccine efficacy against B.1.351 infection. From analysis of clinical trial results and laboratory studies, a provisional conclusion is that as the neutralising antibody (NAb) titres fall against variants, we can expect a decrease in vaccine efficacy. (Khoury *et al.*, 2021)The extent of the decrease will depend on type of vaccine, starting antibody titre after immunization, time after immunization and antigenic distance of the variant vs the vaccine immunogen. As more trials and real-world effectiveness data accrue in different geographical regions, the relationship between NAb titres and field measurements of VE against antigenically distinct variants will become clearer.

No trials reported variant specific estimates relevant to P.1. The J&J adenovirus-vectored vaccine trial reported a similar vaccine efficacy of 68.1% (95%CI: 48.8; 80.7) compared with 72.0% (95%CI: 58.2; 81.7) in the USA. 70% of sequenced cases in Brazil were from the P.2 lineage (which has E484K).

Another way to understand whether variants are escaping from vaccine-induced immunity is to monitor for enrichment of variant cases in vaccine breakthrough. The SIREN study is well placed to do this and its design enables both symptomatic and asymptomatic infections post-immunisation to be detected. Data from vaccine breakthrough in SIREN are expected imminently. (Hall *et al.*, 2021) Separately, hospitalized COVID-19 cases in the small number of individuals who have received vaccine can be sequenced by COG-UK to observe potential enrichment of B.1.1.7 infections and the appearance of further novel amino acid substitutions in Spike associated with immune escape induced by a partially protective vaccine. It will be important to ensure that pipeline is in place

A key consideration for any vaccine programme is the duration of immunity arising from vaccination and the necessity for re-vaccination. An easily measured and quantitatively assessed correlate of protection arising from natural infection provides the simplest way of doing this for an individual or at a population level, and will inform the extent to which vaccination recapitulates naturally acquired immunity.

Correlates of Protection

Immunological correlates of protection are usually established through direct observation, linking the occurrence of clinical disease with measurements of specific target antibodies to determine the titres which appear to correlate with protection against infection. One of the best-known examples of this are studies in the early 1970s demonstrating protection from influenza re-

infection. Haemagglutinin Antibody titres (HI) titres between 18-36 pre-challenge were associated with 50% protection from infection, giving rise to the concept of a protective antibody titre. Meta-analysis 40 years later incorporating many diverse influenza strains and studies re-confirmed the continuing relevance of this general approach (Coudeville *et al.*, 2010; Dunning *et al.*, 2016). HI or receptor binding antibody titres, a conveniently measured surrogate for virus neutralising antibodies, remain the benchmark for immunogenicity assessments of influenza vaccines and underpin serological assessments of vaccine efficacy

Over 90% of individuals infected with SARS-CoV-2 develop antibodies about one week after symptoms onset, persisting for at least several months (Overbaugh, 2020; Wajnberg *et al.*, 2020). The majority of people who make antibody responses, also make neutralising antibody responses (Harvala *et al.*, 2020)(Muecksch *et al.*, no date). High levels of neutralising antibodies targeting SARS-CoV-2 Spike protein offer considerable protection against SARS-CoV-2 reinfection, in keeping with data from common human coronaviruses and non-human primate models and vaccine studies (Muecksch *et al.*, no date), (Huang *et al.*, 2020; Yu *et al.*, 2020; Voysey *et al.*, 2021). Whilst the exact length of immunity conferred by natural infection is still unknown, neutralising antibodies against SARS-CoV-2 spike protein are detectable for at least five months after primary infection (Wajnberg *et al.*, 2020)(PHE NERVTAG March 5th 2021)

Longitudinal cohort studies with regular testing have provided information on rates of reinfection in the 12-18 months since SARS CoV 2 emerged into the human population. Estimates derived from different studies including health care workers (HCW)(Hall *et al.*, 2020), police and firemen (Lumley *et al.*, 2020; Wyllie *et al.*, 2020) and elderly in care homes (Ladhani *et al.*, 2020) give a rate of re-infection of <5% over this period (Table 1 SAGE 10/12/2020) (Mahase, 2021b). Reinfection rates for children are as yet unknown. Establishing whether reinfection is typically symptomatic or asymptomatic, whether reinfected individuals are infectious to others and the expected duration of SARS-CoV-2 immunity from infection requires further work.

Whether re-infection occurs as a result of waning immunity following primary infection, or follows an inadequate immune response to primary infection, or is due to antigenic evolution, have different implications for re-vaccination strategies. A protective response which declines to a threshold, at which re-infection can occur, may result from waning of humoral immunity, whereas failure to mount an adequate response following primary infection, making an individual vulnerable to re-infection, suggests a clinical phenotype where response to primary infection varies according to disease severity or other unknown variables. These scenarios have different implications for understanding protective immunity, which is a crucial parameter to predict the future dynamics of SARS-CoV-2 circulation and timing of vaccine campaigns.

A few studies have reported that individuals with SARS-CoV-2 antibodies following infection are at lower risk of clinical reinfection than antibody negative individuals (Addetia *et al.*, 2020; Houlihan *et al.*, 2020; Lumley *et al.*, 2021). Field studies in UK settings with highly vulnerable elderly individuals, a key target group for vaccines, demonstrate that the protective efficacy of antibodies to similar SARS-CoV-2 variants is over 95% (Jeffery-Smith *et al.*, 2021). Studies in January 2021 following outbreaks of B.1.1.7 variant virus in care homes show similar levels of clinical protection against infection, despite the multiple changes in viral S protein in the B.1.1.7 variant (PHE unpublished data, NERVTAG 5th March). These clinical findings correlate with the laboratory assessments of neutralisation *in vitro* of B.1.1.7 compared with 2020 viruses,

measured by live virus or pseudovirus where the technically different approaches to this measurement are broadly concordant, and suggest minor differences in antibody titres to these viruses (Tables 1 and 2).

Towards reliable neutralization assays for measuring antigenic difference and a correlate of protection

The ability to determine whether an individual immunised by vaccination or infection is resistant to subsequent infections or disease is a crucial step in monitoring the effectiveness of vaccine programmes as exemplified for influenza, above. The development of assays to monitor the effectiveness of SARS-CoV-2 vaccines and to estimate overall population immunity would be a significant step in the national and global vaccine program. However, the ability to monitor and predict immunity using laboratory-based tests currently faces numerous conceptual and practical diagnostic problems that need to be addressed.

Levels of virus neutralising antibodies elicited by SARS-CoV-2 immunisation detected in laboratory assays likely represent a useful correlate of protection from infection. This operational assumption is predicated by analogy with previous evaluations of immune correlates of vaccines against yellow fever, influenza and many other diseases. Although potent T cell responses and non-neutralizing antibodies against SARS-CoV-2 are also induced by immunisation with virus, vectors, proteins and mRNAs (Ewer *et al.*, 2021), it is generally considered that virus neutralising antibody titres represent a reliable and readily measured metric of protection from infection. The SARS-CoV-2 spike protein would be the most useful target of laboratory assays, as infections and all current vaccines will or aim to yield virus neutralising antibodies directed against spike. Tests for antibodies against other proteins such as N may be useful to differentiate previously infected individuals from vaccinated individuals, to investigate how prior immunity affects (vaccine-induced) immune responses to SARS-CoV-2.

Assay methods. Classical virus neutralisation assays are likely the most appropriate starting metric of in vivo protection, despite their often cumbersome nature and requirement for a containment level 3 laboratory. Virus neutralising antibody responses are quantified by pre-incubation of a dilution series of test serum/plasma with a defined amount of infectious SARS-CoV-2, followed by plating out on susceptible cells to determine the maximum antibody dilution that inhibits infection. Such assays should be performed in cell lines expressing appropriate viral receptors and host-cell factors. Given that exchange of viruses and antisera between laboratories around the world is becoming problematic, e.g. due to privacy laws and Nagoya regulations, appropriately validated surrogate methods may be developed. Virus pseudotypes or virus-like particles, in which a reporter virus is decorated with the SARS-CoV-2 spike protein for entry provides an alternative method for measurement of virus neutralising antibody titres. Such assays do not require high containment levels and synthetic spike genes can be synthesised and investigated rapidly. However, pre-validation of these assays and their correlations with neutralising antibody titres determined in virus neutralisation assays is essential. For example, titres determined in pseudotype assays may be influenced by differences in spike density and spike conformation in pseudovirus particles compared to native virions. Other surrogate assays

such as ELISAs using recombinant spike protein as antigen (eg. EuroImmun, Roche), or pseudo-neutralisation assays where sera are evaluated for their ability to block in vitro spike-ACE2 binding (eg. Genscript) (Harvala, Robb, et al., 2020) may also be aligned with classical virus neutralisation assays in the future.

Standards and controls. Human antisera from previously exposed or vaccinated humans should remain the gold standard for the above tests. Human antisera have advantages of representing relevant epitope specificities, and can be produced in large volumes enabling the establishment of a permanent long-term standard and assignment of a fixed unitage of neutralisation. They can also be directly used in surrogate (e.g. pseudotype) assays. A potential disadvantage is the possibility of undocumented past exposure to multiple antigenic variants of SARS-CoV-2 although this is unlikely in samples collected in 2020. There may additionally be limited availability of antisera against emerging variants, especially when such variants emerge elsewhere in the world. Antisera raised in susceptible animals (eg. hamsters, mice, ferrets, guinea pigs, rabbits) may be useful in terms of their defined exposure to a defined virus, an optimised time course for antibody development and lack of pre-existing exposure to the virus or variants. Disadvantages are the existence of potential different antibody repertoires that may not match effects of specific amino acid changes in the spike gene on neutralisation susceptibility. Serum volumes from individual immunised animals would be limited and may necessitate ongoing replacement and re-calibration of controls. Such antisera may also be distributed as useful standards. Careful evaluation of the optimal animal antisera to serve as a surrogate for resource-limited human antisera is needed to assist the vaccine selection program.

Finally, as regards assay standardisation, testing comparability between laboratories and the use of assay standards and controls is essential in monitoring and for the longer-term establishment of what constitutes a protective level of vaccine-induced antibody. International assay standardisation may be achievable following programmes designed for other infectious diseases, with the support of existing national and international authorities (e.g. NIBSC).

Costs and benefits of a vaccine update, when to update

There are risks associated with updating the current COVID-19 vaccines especially in the face of the mass production and global distribution already required to achieve a level of immune protection afforded by current vaccines throughout the world. A degree of assurance will be required to switch manufacturing, distribution and immunisation campaigns for a variant vaccine. Such assurance is provided in the seasonal influenza vaccine update decision making of the WHO, but does not exist for SARS-CoV-2 variant vaccine updates.

With the current levels of neutralizing antibody activity in the sera of immunised individuals to Wuhan like SARS-CoV-2 and with only limited clinical vaccine efficacy (VE) data to suggest the ~10-fold decrease in neutralizing antibody levels to variants of SARS-CoV-2 has an effect of decreasing VE, there is an argument for "If it's not broken don't fix it": Current SARS-CoV-2 vaccines have shown remarkably good effectiveness and very minor adverse effects, and it would be desirable to preserve these features. It is possible that a third boost with the same vaccine

administered initially or with an alternative (by vaccine manufacturer) currently licensed SARS-CoV-2, will be sufficient to preserve vaccine efficacy in the face of current variants, a strategy that requires the urgent support of clinical data.

Similarly, there are risks associated with not updating the current vaccines in the face of ongoing virus evolution. The main risk is that the current vaccine may be a suboptimal choice because of antigenic evolution of circulating variants. In this case the number of infections and severity of disease among vaccinees might well be higher than it would have been with an updated vaccine that protected against the new variants. Indeed, current vaccine effectiveness to date may be largely attributable to an absence of significant antigenic variation in SARS-CoV-2 variants circulating in the UK and elsewhere in 2020 and early 2021, and to the fact that it was a first vaccine for naive recipients. Preparedness, based on known SARS-CoV-2 variants of concern such as B.1.351 and P.1 is therefore being pursued by some vaccine manufacturers, to the level of pre-clinical development and in a limited number of cases human safety and immunogenicity clinical trials

The FDA (Center for Biologics Evaluation and Research, 2021), EMA (Buckingham, 2021) and MHRA (*Guidance on strain changes in authorised COVID-19 vaccines*, 2021) have all issued guidance on what regulatory authorities will most likely require to provide a license for an updated SARS-CoV-2 variant vaccine. Although some details differ between these guidance documents, the general thrust is to assume a highly similar or identical chemistry, manufacturing, and controls information (CMC) package, for a variant vaccine update to an existing licensed vaccine, and to work on the principle that safety and reactogenicity profiles will be similar to the licensed vaccines. The latter will require formal assessment as part of safety and immunogenicity studies in humans. Although pre-clinical animal immunogenicity and protection data are considered useful and supportive, the primary concern for the regulatory authorities will be evidence of immunogenicity in humans, for example, the MHRA discusses an example 300 person clinical study to inform about reactogenicity and immunogenicity. Dialogue with regulatory authorities is recommended, but it is clear that although the pathway to a variant vaccine update licensing can be rapid, this does not impact on the ‘demand side’ drivers and formal recommendation systems that will define when, where and how such a variant vaccine will be needed.

Decision making framework to ensure timely variant vaccine update supply

Rapid vaccine updates in the face of continuous virus antigenic change currently only happens for influenza virus, where the culmination of decades of research knowledge, a WHO assessment and strain recommendation system, an established regulatory system and a limited number of vaccine manufacturers is combined into a robust process where the scientific ‘push’ for vaccine updates is moderated by a transparent and global decision making process, giving ‘pull’ confidence to manufactures that an updated vaccine will be deployed if safe and immunogenic. For SARS-CoV-2, none of these is established or tested.

As described in this paper there is considerable scientific concern arising from monitoring of SARS-CoV-2 variation and its immunological consequences. There is an evolving regulatory framework, but as yet no clear rationale for transition from the current to an updated variant vaccine nor a robust mechanism for defining and deciding on the variant(s) of concern that should become the new vaccine.

Currently, there is evidence for co-circulation of many different genetic variants with early signs of some convergence around a more limited set of genetic variants that confer some immune escape. It is not clear however, if antigenically distinct variants may leave the recipient vulnerable to continual rounds of re-infection and thereby help sustain the circulation of multiple different antigenic variants or if global strain replacement will occur. In the former situation only a multivalent vaccine, or a platform designed to raise antibodies to relevant epitopes of various variants would be fully protective. Such a vaccine might be able to broadly protect against more than one variant, but of course yet another variant could evolve after vaccine choice and escape vaccine immunity. In the latter, single 'dominant' variant vaccine updates may suffice. In both instances there is a risk that by the time the pattern is observed it may be too late to update a vaccine at scale.

The early success of SARS-CoV-2 vaccination programme has required public/private partnerships at a scale and speed never seen before. This is likely to be required again for variant vaccine updates. Companies and different national science programmes are working somewhat independently, and the WHO is currently undertaking consultation and coordination. Whilst this is all individually necessary it may not be sufficient to achieve the rapid update, manufacture and rollout of a variant vaccine. There is a need to understand what can be borrowed from the influenza vaccine update programme, what datastreams need consolidating and expanding and how direction can be given to diverse vaccine manufacturers to ensure appropriate coordination.

In the UK, five areas of SARS-CoV-2 academic and public health science are contributing to national and international assessment of virus variants. These involve genetic surveillance (COVID-19 Genomics UK Consortium [COG-UK], the National Variant Assessment Program [NVAP] and the PHE Variant Technical Group), virus genotype to phenotype characterisation ('G2P-UK' National Virology Consortium), immunology (*UK Coronavirus* Immunology Consortium), structural biology and epidemiology. These are linked to different national cohort studies of infection rates and disease outcome. Together with international collaborations and relationships, the UK is an opinion leader in SARS-CoV-2. Leadership and experts from these groups contribute their advice to the Vaccine Update Expert Advisory Group (VUEAG) which assesses current knowledge and makes recommendations of potential vaccine update genotypes to the deputy CMO. These recommendations are then passed to the Vaccine Task Force to inform future vaccine procurement processes and to guide vaccine variant selection for the new partnership between the UK government and vaccine manufacturer CureVac, established to rapidly develop new vaccines in response to new COVID-19 variants if required (https://www.gov.uk/government/news/new-vaccines-partnership-to-rapidly-respond-to-new-virus-variants). This process is sustainable but ultimately should be replaced by an international forum to achieve the same aims globally.

What can be learned from influenza about vaccine updates in a circumstance of uncertainty

In seasonal influenza, situations also arise in which the population is exposed partly to the variant covered by one or more prior vaccinations and also partly to a new variant, posing the question whether the vaccine should be updated. In the case of influenza, there is a clear benefit to updating towards the new variant, because it has been shown that in influenza, humans retain some memory B cells and some antibody to variants they have previously been exposed to, and upon vaccination with a new variant there is a titre increase both to the new variant and to the older variants, a phenomenon referred to as *backboost*.

The backboost can be clearly seen using antibody landscapes, a method to assess and visualize specific antibody protection to influenza in individuals and populations (Fonville *et al.*, 2014), Antibody levels to multiple antigenic variants are plotted on an antigenic map to form an antibody landscape or immunity profile. Using antibody landscapes, the backboost phenomenon can be clearly seen: vaccination with an influenza variant raises antibody levels not only to the variant itself, but also to a broad range of an individual's prior immunity.

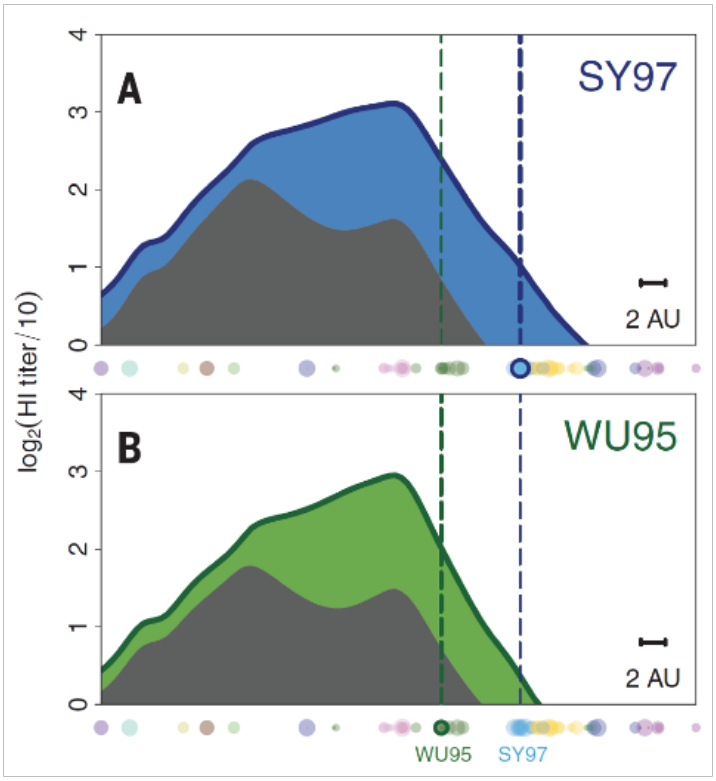

Figure 2
The grey areas in these figures show antibody landscapes, the immunity level or antibody titre, for various strains representative of approximately 50 years of evolution of the influenza subtype A/H3N2.

(A) The blue area shows the boost in titres after vaccination with a strain from an antigenically more advanced cluster not yet circulating widely (in blue).
(B) The green area shows the boost in titres after vaccination with a strain from the cluster circulating at the time (in green).

The vertical dotted lines indicate the position of the (blue) and (green) wildtype vaccine viruses. As can be seen, the more advanced vaccination provides higher protective titres to strains in both the old and the new cluster.

While the backboost phenomenon has been demonstrated for influenza, it has not been tested in other antigenically variable pathogens. **It is important to test whether vaccination with SARS-CoV-2 also boosts pre-existing immunity against previous variants**, as this knowledge is decisive in cases where an older and an antigenically different newer variant co-circulate.

To what extent SARS-CoV-2 vaccination can be modelled on influenza vaccination remains to be seen, because observations need to accumulate for aspects of SARS-CoV-2. For influenza it has become apparent over the decades that antigenic change is quite uniform globally, typically sweeps the globe in a year, previous antigenic clusters go extinct, and there is usually just a single antigenic cluster of each (sub)type circulating.

It is not clear yet how much SARS-CoV-2 will follow these patterns, although the global replacement of the original SARS-CoV-2 strain by the D614G mutant in mid-2020, and the more recent emergence and replacement of that mutant by B.1.1.7 in the UK and perhaps elsewhere in the forthcoming months suggests that large scale population replacements in SARS-CoV-2 are clearly possible if not geographically synchronous. Until SARS-CoV-02 transmission and population dynamics and effects of containment are better understood it is prudent to prepare for heterogeneous antigenic variation.

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