Setting up medium- and long-term vaccine strain selection and immunity management for SARS-CoV-2

Executive Summary

1. SARS-CoV-2 is evolving antigenically. Some variants are less well neutralized by antibodies raised to current vaccines, and the vaccine efficacy against these variants is lower than for matched virus.

2. Administration of further doses of the current vaccine, which is based on the spike protein from the Wuhan-like virus that emerged in 2019, might maintain and/or boost protection into winter 2021/22, but potentially less so for individuals with a less robust immune response, and less so if substantially antigenically variant viruses circulate widely. Eventually it is likely that the virus will display sufficient substantial antigenic variation and current vaccines will fail to protect against transmission, infection, or even against disease caused by newer variants.

3. Loss of vaccine effectiveness will result in further economic and social costs.

4. A solution is to update vaccines to keep pace with virus evolution, and the newer, more flexible vaccine platforms are particularly suitable for this approach.

5. Additional potential solutions are to invest in developing new vaccination strategies that could induce stronger T cell responses since T cell epitopes might vary less over time.

6. Another strategy would be to search for more broadly protective vaccines, including universal vaccine candidates, multivalent vaccines, and heterologous prime-boost strategies

7. We should also consider whether future vaccination policy will aim to immunize the whole population or only those at risk from severe disease, and how this might be impacted by the long-term accumulation of baseline immunity in the population and long-term evolution of the virus.

8. Effective vaccine updates require coordinated virus and immunity surveillance as well as an effective relationship between public health bodies and the vaccine manufacturers, and an integrated international approach that will integrate into the WHO.

9. Virus surveillance has been a strength of the UK so far, we are world-leading in SARS-CoV-2 genomics. But maintaining or enhancing our capabilities to amass virus sequences

on its own will not suffice because biological properties such as antigenic characteristics and population immunity levels need to be linked to the genetic data.

10. Recent evidence from the influenza vaccine-update system indicates that the vaccine choice can be improved through "immunity management", which takes into account the role of prior immunity in the population on vaccine effectiveness.

11. The UK is in a strong position to leverage classical and new horizon-scanning virus surveillance, existing influenza vaccine strain selection knowledge and expertise (both classical and innovative), and new generation vaccine technology for rational robust and optimized vaccine strain selection and vaccination strategies (described in sections 2, 3, and 4 of this document).

12. The current progress of the Vaccine Update Expert Advisory Group (VUEAG) and the Variant Technical Group (VTG) on vaccine updates and variant risk assessment respectively, has been excellent and can be expanded into this ideal path as described in section 5 of this document.

13. There is an opportunity for the UK to play a leading role to pave the way for a SARS-CoV-2 vaccine update system, in this document we outline the science and science infrastructure required.

Outline of the rest of the document

1. The challenge of vaccinating against antigenically-variable pathogens

2. Virus surveillance--classical and predictive horizon scanning

3. Immunity surveillance--monitoring population protection from SARS-CoV-2

4. Vaccine strain selection and immunity management--identifying the need for re-vaccination, when, and with what strain

5. Current state of variant assessment and vaccine updating for SARS-CoV-2 in the UK

Setting up medium- and long-term vaccine strain selection and immunity management for SARS-CoV-2

1) The challenge of vaccinating against antigenically-variable pathogens

When a pathogen causing considerable morbidity evolves antigenically and escapes host immunity, it may be necessary to decide whether re-vaccination is necessary, and if so, both when and with what strain. The pathogen might cause less severe disease due to some residual effective immunity at the individual level, and its circulation may slow or cease due to increasing herd immunity at the population level. But if sufficient mortality, morbidity and other costs affect the human population, a re-vaccination strategy, and vaccine strain selection process, needs to be in place to ensure protection is adjusted in step with pathogen evolution.

Seasonal influenza in humans is the classic example of such an antigenically-variable pathogen, and routine vaccine strain updates have been required since the 1940s to track the antigenic evolution of the virus, and at-risk individuals have to be revaccinated to extend protection. Although antigenic evolution of seasonal coronaviruses has not been evaluated in detail historically, recent data on human coronavirus 229E indicate that its antigenic properties change over time, resulting in immune escape (Eguia et al. 2021).

It is not known at this stage which aspects of antigenic evolution, immunity, and disease of influenza will be equivalent in SARS-CoV-2. This will continue to be revealed in the coming months and years. It is however worth reviewing what is known about the arms race between antigenically evolving influenza lineages and natural as well as vaccine-induced immunity in individuals and populations, as this has the potential to inform the SARS-CoV-2 vaccine strain selection process, although we must be careful to recognize the differences.

Lessons from influenza vaccine strain selection

A characteristic property of seasonal influenza and vaccination efforts is the annual nature of the epidemics. In temperate climates, seasonal influenza epidemics occur mainly during winter, while in tropical regions, influenza often occurs during the rainy season. Since the other coronaviruses endemic in humans, and respiratory viruses in general, are typically seasonal with higher incidence in winter, it is likely that SARS-CoV-2 will eventually also follow this pattern.

The first influenza vaccine, a live attenuated monovalent vaccine against influenza A virus, was developed soon after influenza virus was discovered in 1933. (Shimizu 1997) Since then, repeated updates to the vaccine strains have been necessary. In 1952, vaccine strain selection was formalized in a WHO strain selection process which has issued annual recommendations for the composition of the influenza vaccine, trivalent since 1978, and quadrivalent since 2012

(Barberis et al. 2016; Hannoun 2013; Li et al. 2016). Note, the multivalency of these vaccines is to vaccinate against different (sub)types of influenza, not different variants within a (sub)type.

Human seasonal influenza strains are monitored year round by national efforts in more than 130 countries, and processed in five WHO collaborating centres. A few thousand strains each year are sequenced and tested for phenotypic differences by the collaborating centres. These data are shared in close to real-time among the collaborating centres and four research institutions (University of Cambridge, University of Basel, The Fred Hutchinson Center, and University of Cologne) involved in the process for analyses of the evolution of the viruses. The WHO influenza vaccine composition committee meets in February each year to make a vaccine strain recommendation for the following Northern Hemisphere winter season, and in September to make a vaccine strain recommendation for the following Southern Hemisphere winter season. Three teleconferences are held before each vaccine strain selection meeting to consider 50-150 page reports on the virus' evolution submitted by each collaborating center and academic institution. Some countries have independent committees which review the WHO recommended vaccine strain and license the vaccine strain. Occasionally such countries deviate with a license for an alternative vaccine choice to better reflect circulating viruses in their territory, but most countries license the WHO recommended vaccine strain.

Whether SARS-CoV-2 vaccination should follow this bi-annual rhythm depends not only on the cyclicality of the incidence, but also on the magnitude of antigenic difference per year relative to the antibody levels from previous vaccination. It is possible that antibody levels from mRNA or other modern vaccines and infection are high enough to be protective over several years of subsequent antigenic evolution.

Most of the widely-used influenza vaccines are still grown in chicken eggs because this has been the most cost-effective large-scale production method, although this is gradually changing and the rapid scale-up of other vaccine platforms for SARS-CoV-2 may change this further.

Classical influenza vaccine strain selection

Since the beginning of influenza vaccination and until recently, the vaccine strain selection strategy has been primarily based on identifying a wildtype strain that was most antigenically similar or "representative" of the predominating, or clearly about-to-predominate, variants. These assessments are made by the WHO Global Influenza Surveillance and Response system, a remarkable and long-established highly-collaborative worldwide network that accurately phenotypes and genotypes thousands of viruses per year from around the globe. These viruses are typically tested against 8 or more ferret first-infection antisera raised against predominant strains and variants of interest. The data are interpreted by classical reading of the tabular data, and since 2004, by antigenic cartography (Smith et al. 2004). Antigenic cartography provides a graphical representation of antigenic distances on a single antigenic map which integrates all distance values by minimizing the error between conflicts that arise from multiple pairwise comparisons. In addition to these antigenic analyses by first-infection ferret sera, there are also titrations of variant viruses against human sera vaccinated with the previous years vaccine. Because human seasonal influenza viruses predominantly circulate as a single antigenic variant,

making the initial and primary vaccine choice with ferret sera is generally in concordance with the human sra titrations.

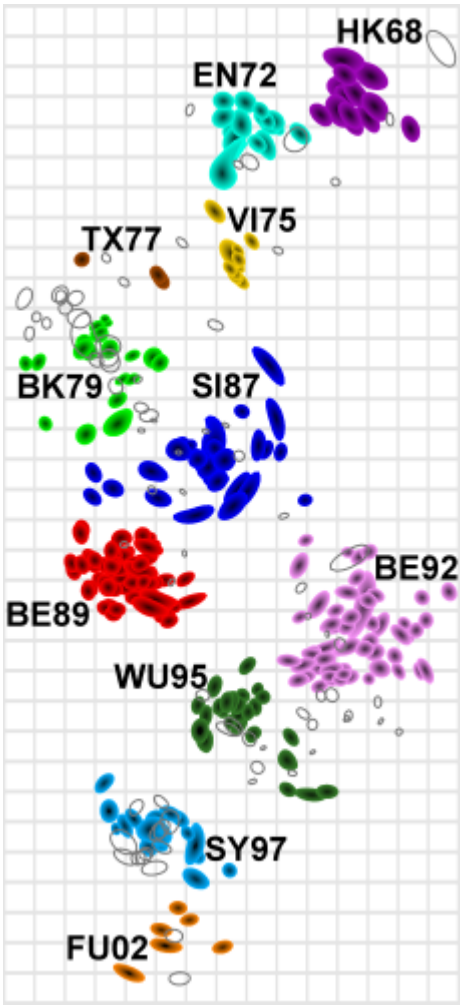

Figure 1 Antigenic map of influenza A (H3N2) virus from 1968 to 2003*. The relative positions of strains (colored shapes) and antisera (uncolored open shapes) were adjusted such that the distances between strains and antisera in the map represent the corresponding HI measurements with the least error. The periphery of each shape denotes a 0.5-unit increase in the total error; thus, size and shape represent a confidence area in the placement of the strain or antiserum. Strain color represents the antigenic cluster to which the strain belongs. Clusters were identified by a k-means clustering algorithm and named after the first vaccine-strain in the cluster—two letters refer to the location of isolation (Hong Kong, England, Victoria, Texas, Bangkok, Sichuan, Beijing, Wuhan, Sydney, and Fujian) and two digits refer to year of isolation. The vertical and horizontal axes both represent antigenic distance, and, because only the relative positions of antigens and antisera can be determined, the orientation of the map within these axes is free. The spacing between grid lines is 1 unit of antigenic distance—corresponding to a 2-fold dilution of antiserum in the HI assay. Two units correspond to 4-fold dilution, three units to 8-fold dilution, and so on.*

Continual innovation in the influenza vaccine strain selection process, and some remaining issues

The effectiveness of the influenza vaccine is about 50% on average (“CDC Seasonal Flu Vaccine Effectiveness Studies” 2020). Causes contributing to low vaccine effectiveness (VE) in influenza are egg-passaging adaptations in the hemagglutinin (HA) protein (the main antigenic component, analogous to the spike protein in SARS-COV-2) and antigenic mismatch occurring due to antigenic evolution during the eight months between vaccine strain selection and the target season. Also known is the repeated vaccination effect - individuals who have been frequently vaccinated against influenza in the past have a weaker response to a new influenza vaccine, both as measured in serology and in vaccine effectiveness studies (Belongia et al. 2017; Mosterín Höpping et al. 2016; Kwong et al. 2020).
Recent developments in the control of influenza that can also aid the control of SARS-CoV2 from the start are an increased focus on immune surveillance, namely:

- An increased role of VE estimates, and research on VE
- The realization of the effect of prior immunity on VE such as “the backboost” (see below) and the benefits of antigenically advanced vaccine strains, and
- Continued research on repeated vaccination effect, original antigenic sin, and immunologic imprinting.

In the next section we describe the immunological backboost, and how this can be leveraged in an “immunity management” process to broaden the coverage of vaccines.

Antibody Landscapes, the potential for backboost and advantages to antigenically advanced vaccination

One property of specific antibody immunity in influenza is that antibodies to influenza variants encountered at any time in life continue to circulate in humans. This has become apparent with the introduction of the antibody landscapes method (Fonville et al. 2014) which allows the visualization of residual antibodies to past strains. Constructing antibody landscapes to assess population immunity requires antigenic variant viruses (x-axis), sera from people, and an assay that relates sera reactivity (neutralization of the virus) (y-axis) to a clinical property, namely protection from infection or re-infection (Figure 2).

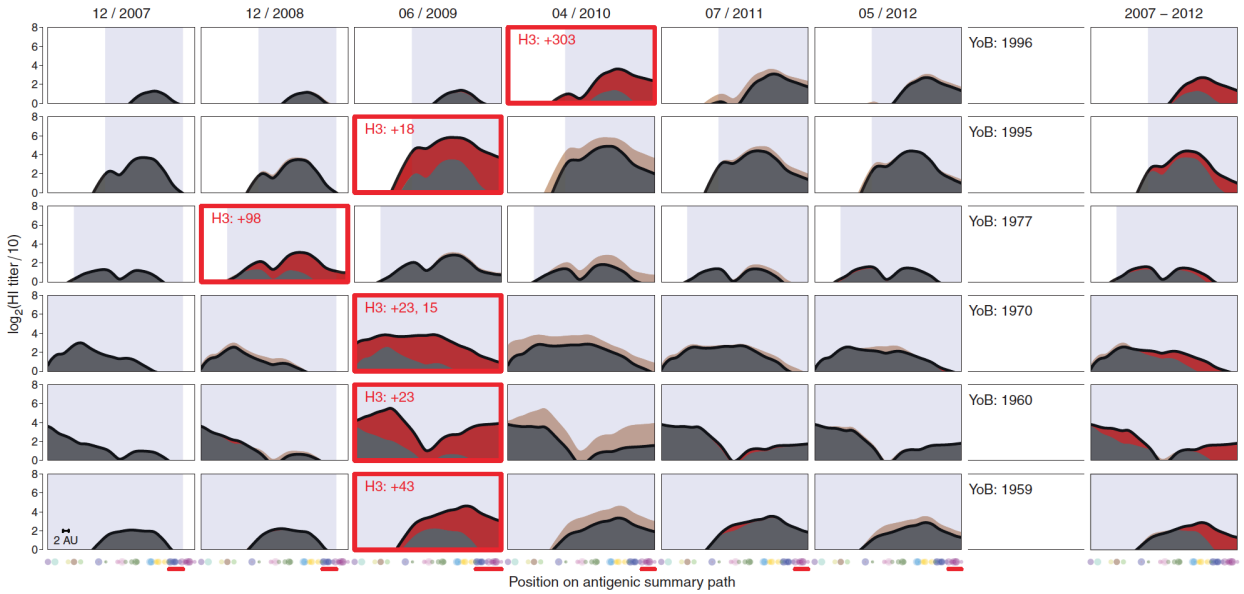

Figure 2 Antibody landscapes from 2007 to 2012 for six individuals. *Each row represents one individual and the dark gray areas represent the landscape height for each position on an antigenic summary path through the antigenic clusters from 1968-2009 along the x-axis. The first sample taken after a confirmed A/H3N2 influenza virus infection is marked with a red box, and the red number gives the days from the date of influenza-like illness–associated. The blue shaded rectangles indicate antigenic clusters that circulated during an individual’s lifespan until sample collection. Dots along the x axis indicate the subset of 30 viruses used to generate these landscapes; contemporary strains, probably causing the infection, are indicated with red horizontal bars. The rightmost column shows the difference between the landscape in 2012 compared with 2007. The scale bar indicates 2 antigenic units. YoB is year of birth. Thus, the graphs show each individual’s antibody reactivity to diverse viruses, with a substantial boost (in red) shortly after infection and a subsequent decline of antibodies (in brown) in time.*

In the case of influenza, an understanding of the serological protection of individuals and populations is particularly relevant to vaccine strain selection because the pre-existing antibody landscapes modulate the effect of the vaccine: those variants to which there are some antibodies prior to vaccination will respond to the vaccination with an increase even when the vaccine strain is a different variant. That means that if two variants are expected to circulate, then out of two equally immunogenic vaccine candidate strains, the one that is most antigenically distinct from pre-existing immunity will have the greater effect.

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 of the backboost.

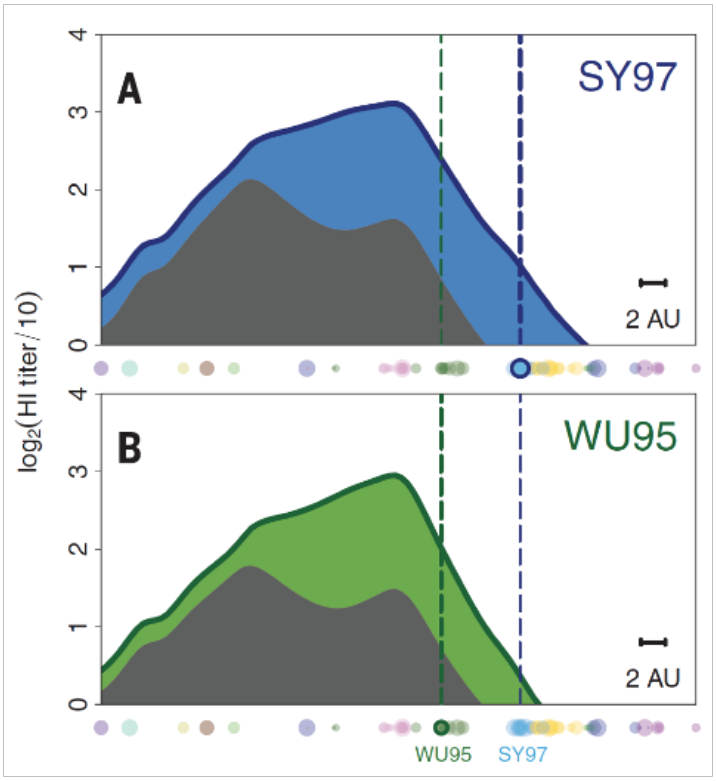

Figure 3 Population Landscapes
The grey areas in these figures show population antibody landscapes for samples of about 100 individuals, the immunity level or antibody titre, for various strains representative of approximately 50 years of evolution of the influenza subtype A/H3N2.

(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 SY97) and (green WU95) wildtype vaccine viruses. As can be seen, the more advanced vaccination (top) provides higher protective titres to strains in both the old and the new cluster, because of the backboost.

While the backboost phenomenon has been demonstrated for 8 different influenza vaccine strains that have been used between 1989 to 2010, it has not been tested in other antigenically-variable pathogens. It is known that antibody levels to seasonal human coronaviruses are affected by subsequent SARS-CoV-2 infection (Westerhuis et al. 2020), hence immune imprinting effects of subsequent infections and vaccinations with SARS-CoV-2 variants is likely. **It is important to test further whether vaccination with SARS-CoV-2 also boosts pre-existing immunity against previous variants**, as this knowledge is decisive in cases where an established and an antigenically different newer variant co-circulate. These data are due very soon from the Moderna trial of vaccination with B.1.351.

The backboost in practice: serological and vaccine effectiveness data

Influenza vaccine strain selection decisions in 2018 and 2019 allowed the prospective evaluation of the effect of vaccine updates to antigenically-variant stains. In both cases, serological analysis of vaccinated humans showed that the updated vaccines stimulated a strong response against the new variants against which they were targeted, and also an equally strong backboost response against older strains. The effect of the vaccine is also captured in estimates of vaccine effectiveness. Such estimates are only regularly measured by a small number of countries, and only for those subtypes of influenza that circulate in sufficient numbers. Previous variants to the vaccine strain remained dominant in Canada in season 2019/20 (fortunately, Canada does extensive vaccine effectiveness measurement). Vaccine effectiveness against these older strains was substantially higher (62%) than that seen in the previous six years in North America when a classical matched vaccine choice had been made. (Figure 4).

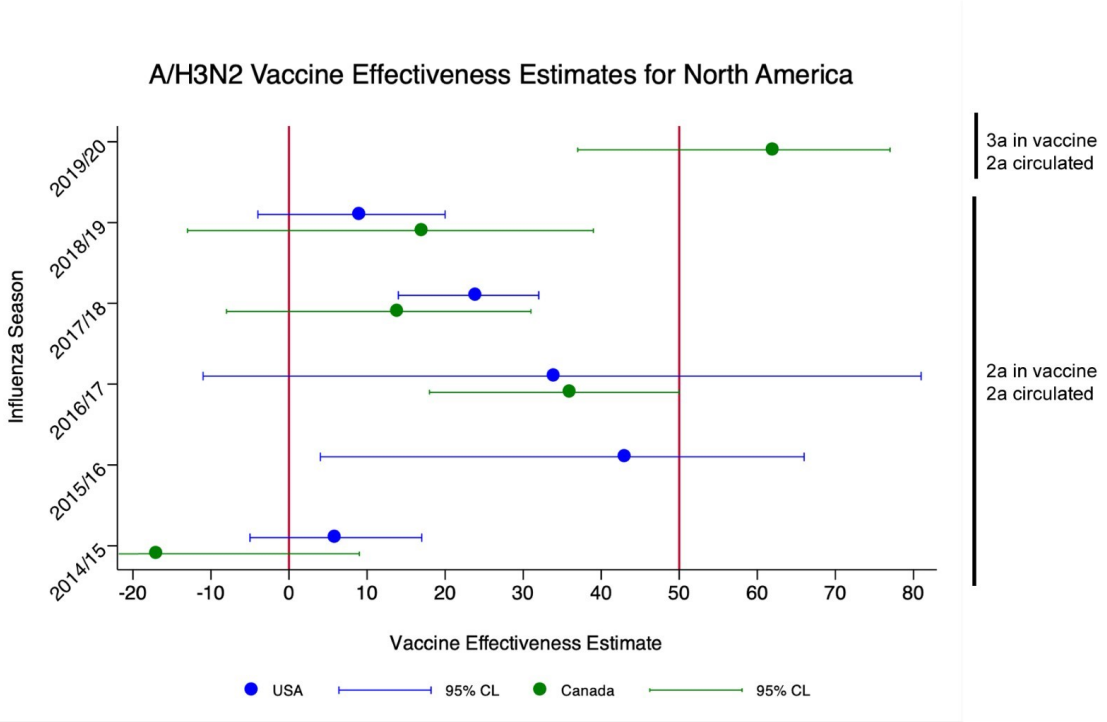

Figure 4 Seasonal VE estimates for A/H3N2 *virus for North America for seasons 2014/15 - 2019/20. VE estimates for the USA (in blue) are from the US Flu Vaccine Effectiveness Networks, estimates for Canada (in green) are from the Canadian Sentinel Practitioner Surveillance Network. Between the 2014/15 and 2018/19 Northern Hemisphere influenza seasons the VE did not reach 50% even though the vaccine strain was from the same lineage as the circulating strains, the 2a lineage. In season 2019/20 the vaccine contained an antigenically advanced 3a lineage strain. Even though in North America the 2a lineage continued to circulate in the winter of 2019/20, the vaccine with the antigenically advanced 3a lineage achieved a higher VE than in any of the previous five years of matched vaccine and circulating lineages.*

Other considerations

There are other effects observed in influenza serological immunity that relate to the interaction between past and novel exposure to virus. The order of exposure to different variants can result in very different immunity profiles. A second exposure generally boosts antibodies from the first infection. The phenomenon of “original antigenic sin” (OAS) first described in 1960 by Thomas

Francis Jr. (Francis 1960) also relates to the effect of a first exposure to subsequent exposures: pre-existing antibodies from past exposures are preferentially used and boosted upon subsequent exposures such that the repertoire of the polyclonal response is conditioned by the first exposure and the exposure history. This priming effect may also explain the repeated vaccination effect - individuals who have had multiple prior vaccinations to seasonal influenza respond to vaccination with a lower titre than individuals responding to the same vaccine with no prior vaccination history. If these interaction effects are also a feature of the immune response to SARS-CoV-2, we may find it difficult to induce an antibody response as robust as the first to updated vaccines in a population who have been infected with first wave virus or immunized with a Wuhan spike vaccine. Studies are urgently required to understand if human immune responses to repeated exposure to SARS-CoV-2 will be affected by OAS. Some relevant results imminently due from small-scale vaccine update trials such as those from Moderna, and from non-human primate studies in the USA.

To what extent SARS-CoV-2 vaccination can be modelled on influenza vaccination remains to be seen, because observations need to accumulate, or explicit testing be done, for SARS-CoV-2. Section 3 of this paper lays out proposed steps for the study and use of immune surveillance. 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 of the B.1.1.7 variant in the UK and elsewhere suggests that large-scale selective sweeps in SARS-CoV-2 are possible. Nevertheless, until SARS-CoV-2 transmission and population dynamics and effects of containment are better understood, it is prudent to prepare for heterogeneous antigenic variation.

Current evidence on the need for SARS-CoV-2 vaccine update.

SARS-CoV-2 variants have emerged that harbour mutations across the genome including in the spike protein, which is the major viral antigen and sole component of most COVID-19 vaccines (Peacock et al Journal of General Virology 2021). This prompts the concern that these variants will be less effectively controlled by current vaccines that employ a spike immunogen derived from the first wave Wuhan spike sequence.

There are currently four Variants of Concern (VOCs) in the UK and a number of Variants Under Investigation (VUIs). The VOCs include the B.1.1.7 UK variant that is the predominant circulating virus, as well as a variant which is a single amino acid derivative of B.1.1.7 with the E484K mutation. This mutation is known to enable escape from neutralization by many antibodies that target the receptor binding domain (RBD). The other two VOCs are the B.1.351 variant first identified in South Africa in autumn 2020, and the P.1 variant that originated in the Amazonas region of Brazil, reported in December 2020. Both emerged in parts of the world where seroprevalence was high following large first waves and also have the E484K mutation in the RBD.

Laboratory data confirm that the substitutions in the spike proteins of B.1.351 and P.1 result in a significant loss of neutralization by sera from people infected in the first wave, or vaccine

recipients (Zhou et al. Cell 2021; de Souza et al. Lancet 2021). Since there is no robust correlate of protection agreed as yet, the effect that such antigenic differences measured in the laboratory will have on vaccine effectiveness in the real world is still unclear. (Khoury et al. 2021; Earle et al. 2021)

Worryingly, increasing evidence from clinical trials and real-world use of vaccines confirms that current vaccines are less effective at protecting against infections and mild disease caused by the B.1.351 variant than they are against less antigenically evolved variants such as B.1.1.7, against which they show very high effectiveness. Trials in South Africa, where B.1.351 predominates, have shown lower efficacy than when the same vaccine candidates were tested in parts of the world where B.1.351 is scarce, such as the USA or UK. The AstraZeneca ChAdOx vaccine showed no efficacy against mild to moderate disease (although this was a very low-powered study (Madhi et al. 2021)). Novavax reported around 30-40% decreased efficacy of their vaccine and also found evidence of individuals in the placebo arm who were seropositive at the start of the trial becoming infected with B.1.351 during the trial period (Shinde et al. medrix). Efficacy of the Johnson and Johnson single-dose adenovirus vaccine fell from 72% in the USA to 57% in South Africa. A recent report from Israel indicates that, where vaccine breakthrough has occurred after vaccine roll out, the causative virus was eight times more likely to be the B.1.351 variant than other circulating strains (Kustin et al. 2021). However, vaccine protection against severe disease and death currently seems to be preserved against SARS-CoV-2 variants, but the pattern of loss of VE for B.1.351 across all other clinical criteria is noted. In light of these data, several manufacturers have already begun to produce trial lots of updated vaccines that present the B.1.351 spike protein in place of the Wuhan immunogen (“Tackling the Rise of Concerning COVID-19 Variants in the UK” 2021). No data has been released yet to demonstrate the immunogenicity of these updated vaccines in humans nor the ability of the antibodies they induce to cross-neutralize other variants--these data are however due very soon. However, it is likely that antibodies raised to a B.1.351 immunogen will cross-neutralize other variants to some extent: convalescent sera from individuals infected with B.1.351 were found to back-neutralize first-wave virus although the titres for heterologous back-neutralization were slightly less (1.6- to 7.2-fold drop) than for the homologous B.1.351 virus (Cele, Gazy, Jackson, Hwa, Tegally, Lustig, Giandhari, Pillay, Wilkinson, Naidoo, Karim, Ganga, Khan, Bernstein, et al. 2021). Since current VOCs are geographically dispersed, this raises the issue of whether different vaccines might need to be used in different parts of the world. For example, if B.1.1.7 remains the predominant virus in the UK, would UK vaccine effectiveness be compromised if a switch was made to update to B.1.351? Or, if B.1.1.7 spike was used as immunogen, instead of Wuhan-like spike, would the drop of protection against B.1.351 be as dramatic? Data from Dejnirattisai et al show that first wave convalescent sera neutralization of B.1.351 was 13-fold lower than for first wave virus whereas for B.1.1.7 convalescent sera the drop was only 4-fold (Dejnirattisai, Zhou, Supasa, Liu, Mentzer, Ginn, Zhao, Duyvesteyn, Tuekprakhon, Nutalai, Wang, Paesen, et al. 2021). If another variant (e.g., B.1.617 from India) predominated or co-circulated with B.1.1.7 in the UK, it is not obvious at the moment which variant based vaccine would most effectively cross protect.

Predicting future antigenic evolution of SARS-CoV-2

As the level of immunity from natural infections and vaccines increases, it is possible the virus will continue to evolve. Since eradication is extremely unlikely, this evolution will continue for years. The extent of antigenic variation that any virus undergoes is determined by a combination of factors:

1. The plasticity of the sequence of the major viral antigen. Virus variants carrying mutations that enable antibody escape can only emerge if the mutations do not confer a significant cost on viral fitness. For example, mutations that adversely affect the interaction of the virus with its receptor or the stability of the spike protein are unlikely to circulate. A classic paper from Palese et al showed that the measles virus H protein did not tolerate mutation to the same extent as the influenza HA protein (Fulton et al. 2015).

2. The polyclonality of the human immune response. It is relatively easy for variants of RNA viruses to emerge that have single or a small number of mutations that enable escape from a specific selective pressure such as an antiviral drug or a monoclonal antibody. However, the human immune response is polyclonal and most individuals generate antibodies that bind to several different parts of the viral antigen. Thus, variants with mutations in just one of the spike antigenic sites are unlikely to totally escape the polyclonal response, and for true antigenic escape the accumulation of multiple mutations across different antigenic sites will be necessary. However the human immune response against some viruses is rather focussed and this may result in a selective advantage for drifted mutants. For influenza it has been shown that only a small number of changes is required to throw off neutralization by convalescent sera (Lee et al. 2019) whereas the response to measles virus is more distributed (Muñoz-Alía et al. 2020).

Thus, measles virus does not vary antigenically, whereas influenza virus does. The situation for coronaviruses is less clear. Until recently it was not appreciated that seasonal coronaviruses undergo antigenic drift. Instead it was suspected that a fast-waning immune response left open the window for reinfections that are recorded every 4-5 years (Edridge et al Nature Medicine 2020). A study from Eguia has now shown that historical sequences of human coronavirus 229E have spike mutations that confer escape from the antibodies in human sera and that the virus evolves antigenically over time (Eguia et al. 2021). This highlights the possibility that SARS-CoV-2 will continue to accumulate mutations that eventually confer significant escape even from current-day potent vaccines. Indeed, Greaney et al. find that the polyclonal response to SARS-CoV-2 infection is focussed in some individuals but not in others, implying that drift variants might be selected for in some individuals (Greaney, Loes, Crawford, et al. 2021a).

Predicting which mutations might confer drift, and the concept of an antigenically advanced SARS-CoV-2 vaccine.

The Bloom laboratory has pioneered a methodology that can be used to predict antigenic escape mutations (Greaney, Loes, Crawford, et al. 2021b). Using a deep mutagenesis scanning approach they create single, double, and triple nucleotide mutants in a synthetic spike expressed in yeast and scan for mutants that are no longer bound by antibodies. Using this screen, they showed that the mutation E484K in the spike receptor binding domain (RBD) would likely be a potent escape mutation and indeed it is present in the most notable VOCs today. Currently the yeast library they

have screened expressed only the RBD proportion of spike and, as considered below, the NTD may also affect antigenicity, so further development of synthetic approaches to predict future drift are required. In addition, a similar yeast-expressed RBD library screen performed by Zahradniík et al. showed that selection of some mutations with large effects depended on accumulation of other mutations in the RBD. In particular those mutations that are present in the B.1.351 and P.1 spike RBDs primed for further selection of a mutation, Q496R, with extremely potent increase in RBD/ACE2 affinity to the extent that antibodies were highly unlikely to compete for ACE2 binding by affinity alone (Zahradník et al. 2021). Thus, the antigenic evolutionary potential of SARS-CoV-2 variants is currently not defined and further work in this area is highly recommended.

Current understanding of the antigenic properties of SARS-CoV-2

The spike protein is the major surface antigen of SARS-CoV-2 and every vaccine currently developed uses spike as the main antigen (although the whole-virus inactivated vaccines such as Sinovac, Covaxin, and the Valneva product contain the entire virus structural protein set). Structurally, the spike protein has two domains against which antibodies that protect against virus infection or disease are raised, RBD and NTD.

1. The RBD stretches from amino acid 329 to 529 in the S1 subunit. It can assume two conformations known as the ‘up’ and the ‘down’ conformations; only the up conformation is available to engage with the ACE2 receptors on the host target cell. Spike is a trimer and only a single monomer needs to be ‘up’ to bind to cells and initiate entry. Four different classes of antibody are described that react with this RBD domain with non-overlapping epitopes (Barnes et al. 2020). In other words, substitutions that allow escape of one such antibody class do not abrogate binding of another. Substitutions in the RBD occur in all current Variants of Concern, B.1.1.7, B.1.351 and the P.1 and P.2 Brazilian variants of the B.1.128 lineage. The Indian variant B.1.671.1 has two mutations in the RBD, L452R and E484Q (or L452R, T478K in B.1.617.2). Some of these mutations are known to affect antibody binding, although the spectrum of neutralisation decrease for polyclonal sera of these is reported to be low (2-fold decrease).

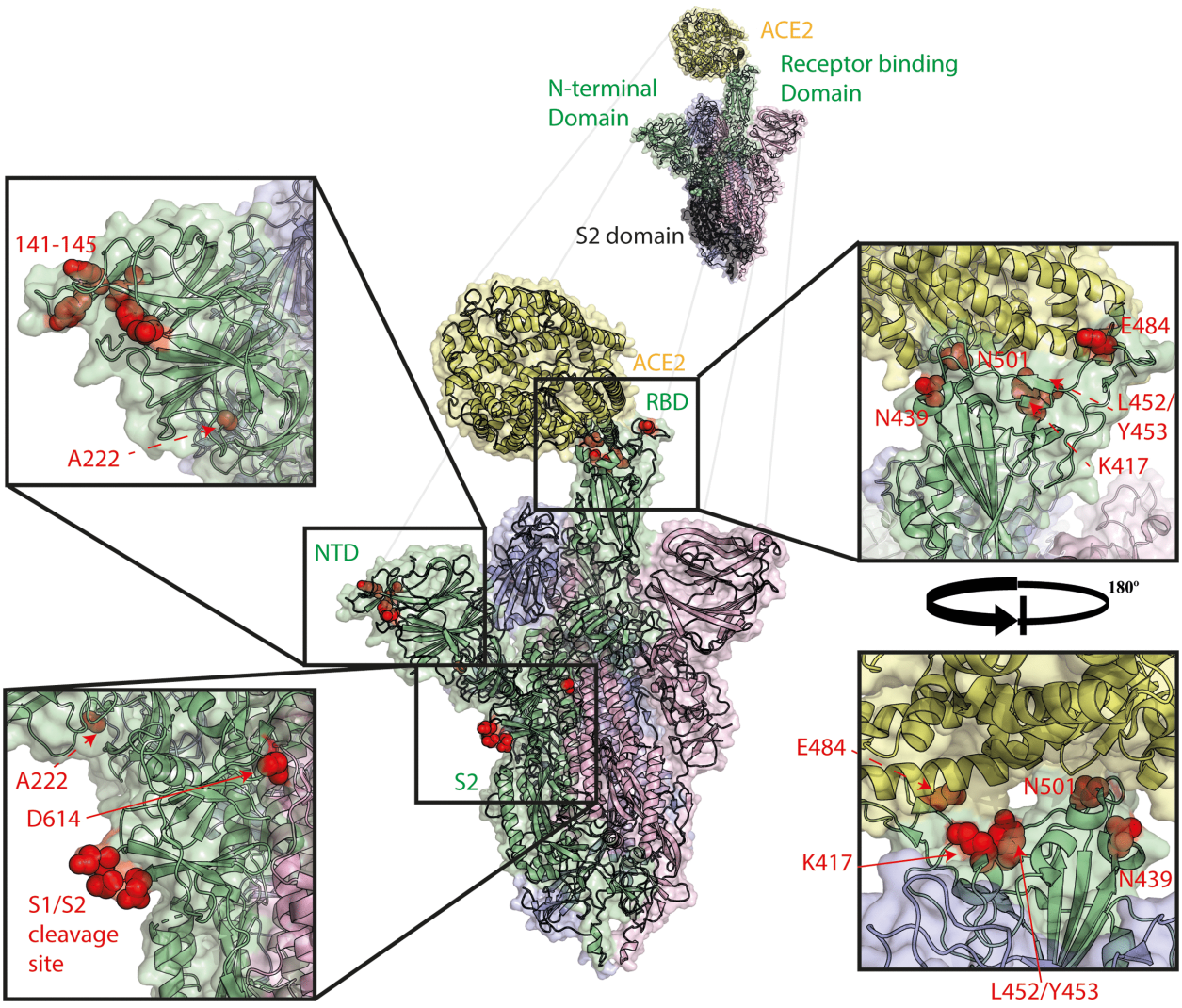

Figure 5 *Spike mutations of interest mapped to the spike trimer. Mutations shown in red, ACE2 shown in yellow, spike monomer in RBD 'up' conformation shown in green, spike monomers in RBD 'down' conformation shown in pink and blue. Structure made using PyMOL using PDBID 7A94. Figure from Peacock et al.(Peacock, Penrice-Randal, et al. 2021)*

Deep mutational scanning of RBD libraries expressed from yeast has enabled prediction of the likely substitutions that can enable immune escape and those that can increase affinity for the human ACE2 receptor. Often the same substitution confers both these properties, the best and most potent example being E484K (Greaney, Loes, Crawford, et al. 2021a; Starr et al. 2020; Schreiber et al. 2021).

2. The other antigenic domain of spike is the NTD, spanning residues 1 – 320 of the S1 subunit, with a series of external loops that together form what has been termed an antigenic supersite (McCallum et al. Cell 2021; Ceruitti et al. Cell Host Microbe 2021). Interestingly, all the current VOCs have deletions in various external loops and there are monoclonal antibodies that no longer recognise spike proteins with these deletions (McCarthy et al. 2021; Kemp et al. 2020).

Table 1 *showing RBD and NTD changes in VOCs and VUIs:*

VOC/VUI	RBD mutations	NTD mutations
B.1.1.7	N501Y	Δ69-70; Δ144
B.1.1.7/E484K	N501Y; E484K	Δ69-70; Δ144
P.1	N501Y; K417T; E484K	L18F; T20N; P26S; D138Y; R190S*
B.1.351	N501Y; K417N;E484K	L18F*; D80A; D215G; Δ242-244
B.1.671.1	L452R; E484Q	T95I*; G142D; E154K
B.1.617.2	L452R; T478K	T19R; G142D; Δ156-157/R158G; A222V*

*found in some, but not all of this lineage

The importance of the NTD for the antigenic properties of spike is overlooked by studies that concentrate on the RBD substitutions. However, the larger degree of immune escape of the VOC B.1.351 spike compared with spike of the P.1 VOC, even though the same amino acids are changed in their RBDs, shows that the NTD must contribute. SARS-CoV-2 spike has been recently shown to recruit a haem metabolite that can mask antigenic sites on the NTD (Rosa et al. 2021). The bound haem molecule locks the NTD into a conformation that bars antibody access. The authors suggest that producing a spike immunogen that cannot recruit the haem might increase its immunogenicity by allowing this site to be accessible to B cells. These structural data might be crucial for rational design of future synthetic vaccines.

Vaccine strain selection and immunity management strategies for SARS-CoV-2

In the next three sections of this paper we detail the two types of surveillance necessary to inform vaccine strain selection for SARS-CoV-2, virus surveillance (section 2) and immunity surveillance (section 3), and how they come together for vaccine strategy decisions (section 4). In section 5 we detail the current UK SARS-CoV-2 vaccine strain selection process, and how it can be refined into the medium- and long-term ideal.

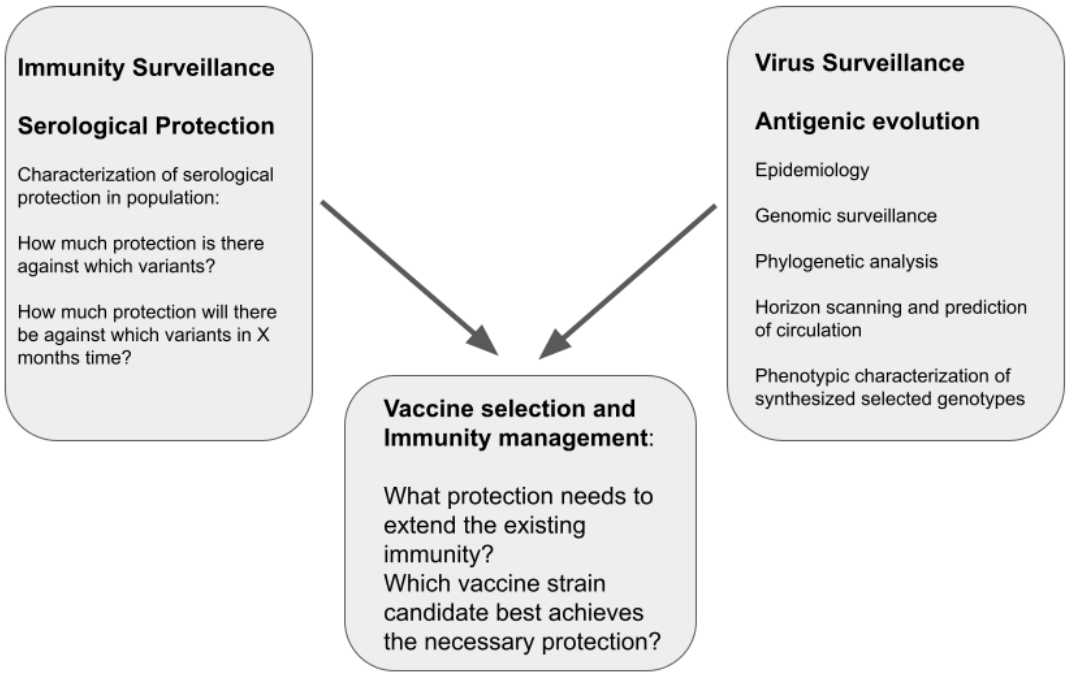

Figure 6 *Vaccine strain selection and immunity management are informed by continuous up to date information from immunity surveillance and virus surveillance.*

2) Virus surveillance--classical and predictive horizon scanning

The economic impact of the SARS-CoV-2 pandemic and associated risks warrant the implementation of a state of the art surveillance and control system. Just how vulnerable an immunized population is to a significant drop in protection rates in a given year depends on the relative size of the changes in antibody levels of titre waning per year and the magnitude of the antigenic advancement of newly emerging variants. The continued work on protection from SARS-CoV-2 will take shape as the virus evolves antigenically. Although protocols will continue to adjust flexibly, we distinguish between initial work that is necessary in response to the pandemic, and longer-term work that could be an ongoing response to this pathogen for as long as it is necessary.

Initial work

- Incrementally refine correlate(s) of protection (Scientific Advisory Group for Emergencies 2021).

- Identify appropriate assays for antigenic characterization of SARS-CoV-2 strains: unbiased, consistent, high throughput. The use of assays with live virus may be replaced with pseudotype virus assays and synthetic biology upon proper validation (Scientific Advisory Group for Emergencies 2021).

- Identify the best species for generating controlled sera for antigenic characterization of SARS-CoV-2 strains by comparing animal sera from candidate model species to human first infection sera. Compare and calibrate animal serum titrations based on human serum titrations.

- Assess the antigenic variation of emerging virus variants detected in global surveillance programs, using cross-titrations with live viruses and pseudotyped viruses against human sera and animal sera. Antigenic cartography may be useful for quantitative analysis and data visualization. (Smith et al. 2004)

- Epidemiology. An assessment is made continuously of the distribution of circulation of variants (antigenic, pathogenic, transmission, and drug susceptibility phenotypes). Also an anticipated distribution of circulation of variants is made.

Ongoing analyses of surveillance data

Currently, a variant needs to make up a significant proportion of geographic locations cases or have a mutation with known or suspected phenotypic effect before it is identified as transmitting within a population to initiate further detailed antigenic characterisation. Therefore, there can be a significant delay in characterising the phenotype of a variant. By identifying particular amino acid positions and substitutions that have not circulated widely and phenotyping them, we can build up our knowledge base of their likely effect in advance of them potentially circulating. With this knowledge, when a new variant of potential concern or interest emerges, its phenotypic

properties can be immediately predicted or estimated if it contains substitutions that have already been phenotyped. Subsequent phenotyping of the variant would check for additional epistatic effects. Further substitutions found to have a phenotypic effect can be used to expand lists of substitutions to monitor more closely.

There are several lines of evidence which can be used initially to identify potentially interesting substitutions in the spike protein:

- Substitutions associated with variants of concern (VOCs) and variants of interest (VOIs), and the associated epidemiological and virological evidence base.
- Substitutions that occur in multiple clades in the phylogenetic tree, suggestive of parallel evolution which occurs independently in different geographic locations, can be an indication of potential phenotypic advantage. When these substitutions are maintained, such parallel/convergent evolution may be suggestive of substantial natural selection.
- Deep mutational scanning results as done in the Bloom lab, which measure expression, binding, and antibody escape in a yeast expression system (Starr et al. 2020; Greaney, Starr, Gilchuk, et al. 2021; Greaney, Starr, Barnes, et al. 2021).
- Insights from structural biology and limited molecular modeling.

The long-term horizon scanning approach

- Continuously review sequences submitted in the UK and globally, along with the generation and analyse genome phylogenies , allows selection of strains that might potentially have altered antigenic properties on the basis of the location of the substitutions in the spike protein structure and their patterns of appearance. Where isolates of these circulating strains become available, they are sent to labs for antigenic characterization. Where sequences of interest are not available as wildtype virus, the spikes can be analysed using pseudotype assays, or the viruses can be created using reverse-genetic methods. Given the delays in exchange of variant virus isolates around the globe, it is advisable to build capacity for nucleic acid synthesis in the UK for ‘synthetic/reverse genetics' virus production.

- Horizon scanning for phenotypic changes through early detection of potential variants of concern allows the continued ranking of single amino acid substitutions occurring in spike proteins globally, taking into account information regarding parallel evolution, convergence, deep mutational scanning, the scientific literature, and structural information on the spike protein. This ranking supplies a selection of substitutions that are likely to cause antigenic change or changes in pathogenicity or transmissibility to watch out for in surveillance data. A selection of substitutions of interest can then be tested for their effect on antigenic properties.

- Once there is an established and validated correlate of protection, it will be possible to derive a protection antibody landscape showing the rate of protection to different variants in the population, one of the crucial inputs to vaccine strain selection.

Some of the necessary steps in a national protection strategy, as described above, require capacity building in various areas:

- Deep mutational scanning data of receptor interactions of the spike protein and potential escape from neutralizing antibodies, and other computational analyses of potential key antigenic sites can be used to prioritize a set of mutations of interest.

- Continued support international efforts to improve genomic surveillance

- Evaluation and analysis of genetic and antigenic data, to produce and curate a universally accessible updated antigenic map of SARS-CoV-2.

3) Immunity surveillance - Monitoring population protection from SARS-CoV-2

Surveillance of population immunity is crucial for the control of endemic viruses. In the case of influenza, vaccine strain selection has until recently focused primarily on virus surveillance, and has been able to achieve reasonable vaccine effectiveness because there is usually only one single cluster of each subtype of influenza typically circulating globally at any one time with relatively rapid transition between clusters.

However, in recent years the importance of human serological surveillance has been increasingly recognized in the control of influenza to further optimize vaccine strain selection. As described in section 1 above the backboost and immunity management has been effectively used to broaden the antigenic variants covered by the vaccine. Systematic surveillance of population immunity, and vaccine strain selection by immunity management, can optimize the control of SARS-CoV-2 from the beginning, and is potentially particularly important given the different antigenic variants that are currently emerging.

The worldwide human population already has a diverse mix of immune experience to SARS-CoV-2 that will complicate the interpretation of future vaccine trials. Some people have been infected, some with different virus variants, while others have been vaccinated with different types of vaccine and different dose numbers and timing. Some have been first infected and then vaccinated, and others have been vaccinated yet also infected after that. In addition, the maturation of the immune response over time may well alter the spectrum of specific antibodies present. Bloom et al. have shown that individuals show considerable differences in the spectrum of spike mutants they recognise and even the sera obtained from the same individual, but at different times after infection, differs in this respect, with some becoming more focussed over time and other less so. (Greaney, Loes, Crawford, et al. 2021a) How any of these differences will affect the population immunity to variants is unclear but will need recording and understanding if we are to intelligently select future vaccine updates.

It will be worthwhile determining how many individual serum samples are necessary for a representative population landscape. Because the importance of serological surveillance has only recently been recognized in influenza, the efficient size of a representative population landscape has not been formally assessed for influenza, although there are new programs to do so. It is worth studying what heterogeneity exists in a population, and whether an entire population can be usefully summarized in a single representative landscape, or if it makes sense to keep separate samples for certain population segments.

While the composition of an efficient representative population is assessed, it would make sense to sample sera from e.g., 100 individuals of each decade of age in a country with known infection and vaccination histories. For example, a total of 1,000 individuals who donate serum samples before and after vaccination, and for a number of months thereafter, and some samples from non-vaccinated individuals are a cost-effective and simple source for invaluable information and insight.

Some of the benefits of this serum collection and the resulting antibody landscapes are:

- Comparing the observed infection rate per age group to the titre levels of that age group contributes to understanding about the correlate of protection and can allow prediction of infection rates before they materialize.
- The representative antibody landscapes can serve to identify vulnerability to variants.
- Pre- and post-vaccination sampling serves to evaluate the serological effect of different vaccine products over time.
- Pre- and post-vaccination sampling also provides data to train predictive models that estimate the effect of vaccination with a given vaccine strain based on antigenic distance between each variant and the vaccine strain and prior immunity to each variant. It provides data for the study of the backboost in SARS-CoV-2.
- Serological data unlocks epidemiological insights. It allows us to test if a population antibody landscape reflects the past circulation that has been described by viral surveillance, and if it predicts circulation.

Currently, the original Wuhan seed strain of SARS-CoV-2 has branched into regional variants that vary phenotypically to various extents. When significant international air traffic resumes it is not clear if the distribution of variants will become more mixed and circulate where they have not been before, or whether they will continue to diverge regionally.

If we find that a population antibody landscape predicts circulation, analyzing sera from different parts of the world will help to answer these questions by predicting what will circulate in which part of the world based on regional serology.

Populations from different parts of the world can also serve to assess variations in vaccine effectiveness in different countries, the impact of population structure on epidemiology, etc.

There are two types of useful population sampling: general sampling by age groups that could be relatively random at various time points, and more controlled sampling pre- and post-vaccination.

Antibody waning over time after natural infection and vaccination with various vaccine platforms in diverse cohorts also needs to be studied carefully so that it can then be estimated for populations. Periodic titrations should assess antibody waning and the possibility of antibody boost through subclinical infections or exposures. These measurements would need to be complemented with analyses of the relationship between titres and probability of protection - does the protection threshold vary between a recent titre and a partially-waned titre from an older exposure?

4) Vaccine strain selection and immunity management: Identifying need for re-vaccination, when, and with what strain.

To assess when there needs to be a renewed vaccination, for whom, and with what variant, analyses of existing immunity in the population (section 3 above) needs to be combined with estimates of what antigenic variants are, or are about to circulate (section 2 above), to estimate the current, and anticipated future, protection rate of various vaccine strain choices. When the anticipated protection rate for the near future drops below some threshold there is a need for renewed vaccination, and the best vaccine candidate would be the one that would most reduce the expected vulnerability of the population.

But how to choose such an optimal vaccine strain? Ultimately, the optimal strain cannot be chosen, our understanding of vaccination against antigenically variable pathogens is not yet sufficiently complete. We can however make perfectly reasonable and good choices, not least of which by leveraging decades of individual and institutional experience in the WHO influenza vaccine strain selection process (as described in section 1). Such a choice can be further optimized, by leveraging the recent advances in influenza vaccinology employed by the WHO network by leveraging the immunological backboost and focusing on immunity management to broaden immunity (as described in section 1)--especially in circumstances that we are currently in with only partial knowledge of which variants might circulate next.

Next we show an example of such immunity management reasoning (Box 1), followed by a more formal description of the method, and then the pragmatics of evaluating different choices in small scale vaccine trials with a serological endpoint.

Immunity management, a formal description

The example in Box 1 immunity management applied to vaccine strain selection for an antigenically evolving pathogen with a typical situation in which more than one variant is circulating or might circulate with different probabilities or to different degrees. In the case of choice among various wild type strains for a vaccine the chosen strain should be the one that achieves the greatest expected post-vaccination protection rate.

Box 1: Example of optimising population protection

There are two potential vaccines with expected protection under three scenarios (Strain A, the current variant, continues to circulate Strain B, an antigenic variant circulates, or Strain C, a different antigenic variant circulates) as shown in the table below. Post-vaccination, vaccine B results in better protection against strain A than vice versa (due to a combination of pre-existing immunity to strain A and because vaccine B backboosts the immunity to strain A). Additionally, the vaccine to strain B provides better protection against strain B than would a vaccine to strain A. Thus, even though strain A is more likely to circulate, using strain B in the vaccine will overall provide greater population protection.

Vaccine	*Circulating variant*	*Probability of circulation*	*Post-vaccination protection against circulating variant*	*Expected total post-vaccination protection*
Strain A	*Strain A*	*50%*	*90%*	*0.5x0.9+ 0.4x0.4+ 0.1x0.1=* ***62%***
	Strain B	*40%*	*40%*	
	Strain C	*10%*	*10%*	
Strain B	*Strain A*	*50%*	*70%*	*0.5x0.4+ 0.4x0.9+ 0.1x0.4=* ***75%***
	Strain B	*40%*	*90%*	
	Strain C	*10%*	*40%*	

The basic calculations shown in Box 1 can be expanded to weigh the need for protection by the pathogenicity of the variants if pathogenicity varies.

The same rationale for choosing a strain with the highest expected protection rate given information on cross-protection and expected circulation probabilities can be formalized for any number of variants. Expected vaccine effectiveness is maximized by choosing antigenic vaccine location j (column “Vaccine” in Box 1) for which expected vaccine effectiveness is highest. Expected vaccine effectiveness in antigenic location j is based on vaccine effectiveness of a vaccine in antigenic location j on each potential antigenic location of virus circulation i (Column “Circulating variant”) by forming a weighted average based on the probability Pi of circulation (Column “Probability of circulation”) in each antigenic location i.

$$\text{Max } E(VE) \text{ where } E(VE(j)) = \Sigma\, VE_i(j) * P_i$$

In this formula VE stands for vaccine effectiveness but the value VEi(j) more generally captures the rate of protected individuals in antigenic location i after vaccination in antigenic location j. (The probability of circulation in this formula is estimated by various horizon scanning/prediction methods, the protection rates in any location given vaccination in another location are based on an antibody landscapes model using population pre-vaccination titres and distance between location j and vaccine strain location). Since overall the antibody response in potential antigenic locations of virus circulation is higher when the antigenic location of the vaccine is in an antigenic area of low pre-vaccination titres, the formula that maximizes vaccine effectiveness in the upcoming season also over the seasons creates a broad area of protection ahead of circulating strains. Note that use of this formula is not in opposition to the traditional strategy of vaccinating with the circulating cluster, but would always include the current cluster as a high-probability antigenic location of circulation and recommend vaccinating there in the cases where current cluster vaccination gives highest expected vaccine effectiveness.

Such a strategy would sculpt an antibody landscape that is an extension of the historical landscape. This type of advanced landscape could set apart the vaccinated from the unvaccinated population in an unprecedented way as the vaccinated would have antibodies against antigenic escape mutants. This broad front of antibody protection could be recalled with every subsequent vaccination, such that each new vaccination would maintain and protect the front landscape in a similar way as the less-effective historical landscape is maintained.

The pragmatics of vaccine strain selection: Small scale vaccine trials with serological endpoints.

We recommend, especially in the early years as we learn more about the evolution of, and immunity to, SARS-CoV-2: to trial various well-considered vaccine strain choices in humans. These trials can be small scale, and with a serological endpoint (assuming virus neutralization titers continue to be a reasonable correlate of protection). With the immunity surveillance from section 3, such a small trial can be reasonably generalized to expected (at-risk) population immunity.

The cost of such trials is not small, but the value of an extra 5 or 10% in vaccine effectiveness is substantial, and we estimate would more than offset the cost of the serological endpoint trials.

Such trials, in addition to testing the backboost, will also test asymmetry in neutralization such as that between B.1.351 and Wu-1 (Cele, Gazy, Jackson, Hwa, Tegally, Lustig, Giandhari, Pillay, Wilkinson, Naidoo, Karim, Ganga, Khan, Balazs, et al. 2021), and the breadth of immunity raised by B.1.1.7 compared to Wu-1. Similarly there may be other asymmetries and hidden benefits to different vaccine candidates as well as vaccine platforms that may best be revealed in small trials ahead of vaccine strain selection. In addition such trials can be used to test bi-, or multivalent formulations, heterologous prime-boost for naïve individuals, and take into account differences in the breadth of the immune response using various vaccine platforms. Some such trials are already underway, and we recommend further expansion of such trails.

Who decides - regulators' and manufacturers' say in vaccine strain choice.

The status quo in influenza is that manufacturers are bound to the strain choice approved for all markets, either using the WHO recommended strain or a strain chosen by a national regulatory body. This system suppresses competition on vaccine efficacy, it reduces the downside risk of manufacturers experimenting with alternative vaccine composition that may be found to be inferior at too late a stage when vaccine lots are already produced, resulting in a nation-wide vaccine shortfall. It also reduces the upside potential of a superior vaccine composition by stymying the incentive for research and development work that might usefully complement the academic research supported by governmental regulatory and funding bodies. It will need to be established how SARS-CoV-2 vaccines and vaccine strains are licensed. One possibility is that only vaccines containing the vaccine strain recommended by the regulator are licensed. Another possibility is to recommend a strain and publish alongside the titre level induced to relevant variants in the population by this strain, and license any vaccine which matches or improves upon these titre levels.

5) Current state of variant assessment and vaccine updating for SARS-CoV-2 in the UK

Research on the establishment of assays and correlates of protection will eventually yield a combined knowledge base on the antibody levels associated with natural infection, vaccination, titre waning per year, and the size of antigenic advancement of a variant mutation. However, with the current absence of a formal, data rich and experimental evidence based system to inform strategy, ad hoc variant assessment and vaccine update systems have emerged around the world. This is the case in the UK. Nevertheless, mapping of current efforts in the UK onto the ideal system for updating vaccines from the preceding section provides a gap analysis to highlight what is needed now.

The current approach in the UK is to fund various sources of data generation and basic research whilst simultaneously convening expert groups to assimilate different data streams and come to reasoned opinion about the risk posed by SARS-CoV-2 variants to humans (focusing on increased transmission and altered disease severity), and to medical interventions, for example decreased effectiveness of vaccines (vaccine escape) or drug treatments (drug resistance). The substrates for much of what is needed for the future already exist in the UK or through international partnership, but with some notable areas absent and/or requiring focused coordination.

A. Data

COVID-19 Genomics UK Consortium (COG UK) and the UK Health Security Agency (UKHSA)

COG-UK undertakes genome sequencing and analysis, specifically looking for lineages and variants of significance for experimental and epidemiological evaluation. COG-UK provides data that influences public health interventions and policy decisions, through innovative partnerships of NHS organisations, Public Health Agencies, lighthouse labs, and academic partners all providing samples, sequencing and analysis capacity, together with the central sequencing hub of the Wellcome Sanger Institute. It is likely that as the UK Health Security Agency becomes fully functional much of the activity for routine genomic surveillance for public health will fall under its remit. The UK Health Security Agency (UKHSA) is responsible for planning, preventing and responding to external health threats, and providing intellectual, scientific and operational leadership at national and local levels, as well as on the global stage. Through this, UKHSA intends to ensure the nation can respond quickly and at greater scale to deal with pandemics and future threats.

International SARS-CoV-2 genomics data resources

Pathogen genome sequencing is certain to continue to grow globally, not only for SARS-CoV-2 but also for a large range of other pathogens. Therefore the primary and critical output will be pathogen genome data linked to epidemiological characteristics (data, geolocation, and other phenotypic information). Sorting, curating, and analysis of these data is central to its utility. A number of internationally focused SARS-CoV-2 and Influenza virus programmes such as

NextStrain and GISAID are undertaking the synthesis and collation of SARS-CoV-2 genome data from around the world for analysis, specifically looking for lineages and variants of significance for experimental and epidemiological evaluation. However, specific UK focused pathogen genome sequencing and analysis is likely to involve metadata linking virus genomes to other epidemiologic or phenotypic data, not present in an international database and will fall under the remit of the UKHSA.

Structural biology of variation in the SARS-CoV-2 spike protein

Knowledge of the three-dimensional structure of virus proteins at atomic level is critical for vaccine and therapeutic drug development. Research at The Division of Structural Biology (STRUBI) and Dept Medicine (University of Oxford) and other UK structural biology groups are assessing the structural, virologic, and immunologic consequences of variants in the spike gene, characterising immune responses to SARS-CoV-2 variants following infection, vaccination and against monoclonal antibodies. The power of combining structural biology, virology and immunology has been shown by recent publications from Oxford [(Zhou et al. 2021), (Supasa et al. 2021), (Dejnirattisai, Zhou, Ginn, et al. 2021), (Dejnirattisai, Zhou, Supasa, Liu, Mentzer, Ginn, Zhao, Duyvesteyn, Tuekprakhon, Nutalai, Wang, López-Camacho, et al. 2021)], Glasgow [(Thomson et al. 2021)], and King's College London [(Graham et al. 2021), (Graham et al. 2021)].

Data assimilation and analytics

The amounts and types of data, from basic biology through to clinical implications and treatment efficacy is enormous. Traditionally, research excellence in academic and public health labs leads to the production and contextualising of data to reach conclusions. For SARS-CoV-2 the formation of expert groups to assimilate and reach opinion on diverse and rapidly-changing data provides methods to synthesise informally a consensus view for future actions. However, data analytics methods and collation of publicly-available data from many sources has been considerably aided by data analytics companies such as Airfinity. Airfinity provides such data collation and analysis for UK Government Departments, initially focusing on the more than 1200 therapies under investigation / development and more than 300 vaccines, but more recently developing data acquisition around SARS-CoV-2 variants.

What is missing for 'data' relative to the 'ideal'

Data integration is urgently needed where the focus is on readily updated phylogenies of SARS-CoV-2 where genetic variation is contextualised with structural and phenotypic informations from the literature, focusing on the impact of mutations and mutation combinations on monoclonal antibody and polyclonal sera escape from neutralisation. Such a data analytic framework should provide persistence of data streams (for example from COG-UK and GISAID) with flexibility to add unstructured data (Literature) and high-throughput phenotypic assay data (see D) assessing immunity. This would allow AI methods, modeling and research to be conducted to inform the construction of immunologic and virus variation landscapes to inform vaccine design and deployment strategies, aiming to remain ahead of virus immune escape evolution.

B. Antisera

UK COVID Immunology Consortium (UK-CIC)

The UK COVID Immunology Consortium (UK-CIC) is a nationally targeted effort to understand the immunology of SARS-CoV-2 and COVID-19, to identify how the immune system responds to SARS-CoV-2, focusing on why infection makes some people sick and not others, what constitutes effective immunity, and how long immunity lasts? UK-CIC brings together 20 UK immunology centres of excellence and, importantly, assesses cohorts of people who have been infected and/or vaccinated to obtain appropriate samples for analysis. The fruits of UK-CIC are beginning to emerge, with insights gained into vaccine immune responses for deployed vaccines in the UK (Publications | UK-CIC) .

What is missing for 'antisera' relative to the 'ideal'

Clinical trials and vaccine deployment have been run successfully in the UK, which together with the cohort studies such as the SARS-CoV-2 Immunity & REinfection EvaluatioN (SIREN) (https://publichealthmatters.blog.gov.uk/2021/03/11/the-siren-study-answering-the-big-questions/) and Vivaldi (https://www.ucl.ac.uk/health-informatics/research/vivaldi-study), a national study of COVID-19 infections in care homes, should provide a rich resource of age and time structured antisera before and after infection or vaccination.

There is a lack, however, of a coordinate serum BioBank, where sera from convalescent populations or vaccinees is linked to minimal epidemiological and patient data. Such BioBanks are now well established in the UK for genomics and these could be easily adapted for existing and future cohorts.

The UK also lacks co-ordinated *in vivo* animal model work, especially in small animal models such as the hamster and mouse, where variant pathogenesis and immune responses to infection and vaccination can be studied. *In vivo* models critical for variant assessment and vaccine candidate assessment where defined antisera can readily bridge between human samples, especially when a variant is not extensively circulating in the UK or, where human sera is limited.

A human and animal antisera BioBank should undertake the sourcing, ethics, and coordination of serum samples for immune landscape assessment against SARS-CoV-2 variants and provide a serum preparedness function for future epidemics and pandemics.

C. Viruses

UK Virology consortium for SARS-CoV2 genotype to phenotype assessment

Interpreting the phenotypic consequences of SARS-CoV-2 genetic variation is essential to understand the likely impact of variants. This work occurs globally and is supported in the UK in a consortium of 10 research institutions and COG-UK. This consortium is assessing the functional significance of virus evolution and mechanism of SARS-CoV-2 protein function across the genome, including the assessment of virus properties such as fitness, and the assessment of virus neutralisation as well as focusing on basic virology of the immune response, virus transmissibility, the severity of the disease it causes, and the effectiveness of vaccines and treatments. Importantly, Genotype-to-phenotype (G2P) is creating standardised versions of the SARS-CoV-2 variants with and without each mutation, so they can study the effects of each change individually (Rihn et al. 2021; Peacock, Goldhill, et al. 2021).

What is missing for 'viruses' relative to the 'ideal.

The provision of SARS-CoV-2 variant viruses either as virus isolates from clinical samples, as pseudotyped viruses where the spike gene from SARS-CoV-2 is synthesised based on the desired sequence, or where a replication-competent reverse genetics virus is derived directly from the full genome sequence are essential for assessing the phenotypic consequences of genetic variation, including escape from immunity. This is currently a slow process and often subject to restrictions on use or lack of ability to obtain an appropriate sample. A robust system for rapidly producing pseudotyped virus or reverse genetics replication-competent viruses would afford a step change in our ability to determine immune landscapes and virus phenotypes.

D. Vaccines and assays that need establishing

There is little well resourced, coordinated work on integrating vaccine candidates, immune responses to vaccines, and clinical or pre-clinical study samples with appropriate assays to relevant SARS-CoV-2 variant virus isolates. In the absence of such a focused data-rich environment, it is impossible to do anything other than convene expert groups to reach an opinion on vaccine variant updates. This is unsustainable and will inevitably lead to suboptimal choices of vaccine variant updates and immune management strategies for populations and individuals.

The Influenza virus WHO Collaborating Centres and Essential Regulatory Laboratories within Global Influenza Surveillance and Response System (GISRS) provides a framework for what is required but this must be updated and adapted for current technologies and geopolitical context. For technological advances, we are now in the position where virus isolates can be complemented and in some cases replaced with pseudotyped virus systems and reverse genetics or pure synthetic biologic generated virus stocks. Further the ability to genetically manipulate *in vitro* cell lines and *in vivo* animal models means optimal virus infection systems can be established rapidly. Finally, high-throughput, industrial scale robot screen systems can reduce staffing restrictions, increase scale, and throughput and provide a more standardised assay framework for serology studies.

In a world where easy and rapid movement of virus isolates and patient material in the form of antisera can be slow or impossible, national resilience is essential. The major areas that this can be achieved in a global context is in the production of reverse genetics (or synthetic biology) virus isolates, the production of animal antisera to vaccines, and variant infection and the establishment of high-throughput robust assays.

Further, providing a sample and data rich environment has the potential to act as a bridge to creating a vibrant academic, public health and industrial ecosystem for vaccine development, assessment and manufacturing in the UK.

E. Procedures to decision making and vaccine variant update recommendations

Two expert working groups provide variant assessment and vaccine update assessments in the UK.

Variant Risk Assessment framework (Chair Meera Chand, PHE/UKHSA)

The Variant Technical Group (VTG) is an expert group which forms part of the main public health incident structure. The VTG shares and considers data on novel variants and data escalated from the horizon scanning process, to recommend formal risk assessment for emerging or current Variants of Concern (VOC) and Variants under investigation (VUI) and regularly undertakes and reviews the risk assessments associated with these. Such VOCs and VUIs are critical points of classification for assessment of sustained vaccine and treatment effectiveness.

Vaccine update assessment framework (Chair Paul Kellam, VTF)

The UK Vaccine Task Force (VTF) was established in 2020 to identify promising SARS-CoV-2 vaccine candidates that would be able to save lives and, by working with manufactures, aid where possible the pathway to safety, efficacy, and licensing studies whilst simultaneously ensuring contractual security and the availability of industrial process to deliver diverse vaccines at scale to the UK and world populations. With the emergence of SARS-CoV-2 variants with the potential to reduce vaccine effectiveness the VTF established an Vaccine Update Expert Advisory Group (VUEAG) to provide opinion on SARS-CoV-2 genome variation data focused on the spike gene and phenotype data on the immunological consequences of such variation and through that make recommendations on vaccine variant updates required for the UK. Further, opinion-lead assessment is made of ‘real world’ and ‘clinical trial’ vaccine effectiveness against variant virus as the data becomes available.
It is likely that in the near future such assessment and recommendations will be made by international organisations such as the WHO, however, in keeping with similar systems for updating Influenza vaccines, this will likely draw on national experience and expertise such as VUEAG.

Progress to date and what is missing relative to the 'ideal'

The VTG meets weekly and assess national and international data to produce regulary technical reports and updates published. One component of the VTG is horizon scanning for variants occurring at low frequency that have a potential to alter the virus phenotype. Therefore between the VTG and the VUEAG the aim is to assess potential variants that could affect vaccine effectiveness as a means of preparedness.

The VUEAG meets ad hoc and provides recommendations of vaccine variant updates to the UK deputy Chief Medical Officer. To date, the VUEAG has recommended the B.1.351 as the highest-priority VOC for vaccine updates, with the B.1.1.7 plus E484K VOC as the second highest priority given current data. Further, the VUEAG has assessed potential combinations of mutations in the SARS-CoV-2 spike protein that could be candidates to produce rapid vaccine updates for testing *in vivo*. Using the methods and data resources of the Smith Laboratory (Cambridge University), members of VUEAG ranked potential mutation choices based on *in vitro* virus neutralisation data, *in vitro* data on receptor binding, and phylogenetic patterns of mutation distribution.

The fusion of the expertise on the VTG and VUEAG, together with persistent and curated dataflows, especially large scale SARS-CoV-2 variant naturalisation profiles to existing and variant convalescent or vaccine candidate antisera has the potential to evolve from the expert-led consensus system to a data rich, evidence-led vaccine update system.

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