How long will vaccines continue to protect against COVID?

Wendy Barclay, Paul Kellam, Paul Moss, Jamie Lopez-Bernal, Mary Ramsey and Maria Zambon.

Executive summary

1. It is highly likely that vaccine induced immunity to SARS-CoV-2 infection, and potentially severe disease (but probably to a lesser extent) will wane over time.
2. This is likely to be first detected by vaccine failures in vulnerable cohorts (for example a high rate of infections in people vaccinated over time, including hospitalized cases).
3. It is therefore likely that there will be vaccination campaigns against SARS-CoV-2 for many years to come, but currently we do not know what will be the optimal required frequency for re-vaccination to protect the vulnerable from COVID disease.
4. Different vaccines may induce different sorts of immunity, which may have different duration. Absolute correlates of protection are yet to be determined, but the only ready measure that can be used at scale is of serum antibody.
5. Even if antibody levels after vaccination wane to allow significant numbers of infections, this might have an effect of boosting the primed immune system of vaccinees who would experience mild or asymptomatic infections. In turn this could result in a broader immune response than expected if vaccines induced a sustained sterilizing immune response. Measurements of immune responses in persons who are infected following vaccination will be important to understand this.
6. Current studies (PHE and National core studies) have assembled longitudinal cohorts but are only funded or planned to continue for 12-18 months, and waning may be important in the time frame of 2-5 years. There is a need to decide what further longitudinal studies are required, and to what extent they can build on existing funded studies which could be extended, or whether de novo studies will be needed.
7. We strongly recommend that funding is maintained to allow some of the current cohorts to be followed for longer times periods, and to included subsets who remain unboosted.
8. Maintaining focussed studies with cohorts of individuals in whom waning may happen sooner are particularly important since these groups may act as ‘canaries’ in signalling the time point beyond which waning vaccine immunity might become an issue. It will be important to relate immunological information to parallel studies of disease outcome, particularly those for severe disease.
9. These studies should continue to include a collaboration of public health, academia and clinical scientists working together with support for the appropriate data linkage, to measure VE in the real world and to understand mechanisms of protection and waning.

Background

Several different vaccines against SARS-CoV-2 have been developed over the last 18 months. Eleven of these have received emergency use approval in multiple countries and eight have been licensed in a smaller number of countries. Billions of doses have been rolled out to the populations of wealthy countries but in low and middle income countries vaccination rates remain lower.

Two novel vaccine platforms representing 3 approved vaccines have been used in the UK and both use the SARS-CoV-2 Spike as the immunogen. The Oxford/AstraZeneca ChAdOx1 vaccine uses a chimpanzee adenovirus as a non-replicating vector to deliver a Spike protein immunogen. The Pfizer/BioNTech and Moderna vaccines use modified mRNAs to direct expression of the Spike protein. In other parts of the world, different platforms have been used including whole virus inactivated vaccines, Spike proteins expressed in insect cells and different viral vectors.

So far, the results from clinical trials and from real world use of these vaccines have exceeded original expectations.

Vaccines are highly effective in protecting against severe disease and death. Real world data show with high confidence that both types of vaccine in use in the UK protect with 95% or greater effectiveness against severe disease caused by the alpha variant that dominated the UK second wave in early 2021.

Most vaccines in use against pathogens today do not produce *sterilizing immunity*, and this includes the vaccines being used against COVID. In other words, vaccine recipients can still be infected. However, their vaccine-primed immune systems have enhanced capacity to clear the pathogen quickly and disease is thus abrogated or minimized. Real world data shows the ability of COVID vaccines to protect against infection and onwards transmission is lower than against severe disease. ChAdOx1 vaccine effectiveness against infection is ~65%, and Pfizer 85%. Vaccine-induced protection (after a single dose) against onward transmission from identified symptomatic individuals is only around 50% according to the PHE HOSTED study, but when combined with the decrease in infections rates leads to a substantial impact on transmission in the population.

The real world VE data have been collected during the first 7 months of 2021 at a time when vaccines were first being rolled out and the UK was experiencing the second wave of COVID due to the alpha variant. A priority order for vaccination was used such that those at most risk were vaccinated earliest. This means there is now a diverse mix of immune experience for the population of the UK who vary in the time since their first or second vaccine dose, the type of vaccine they have received, whether they were infected before being vaccinated as well as in other factors that affect immunity such as age and comorbidity.

At the current time, around 46,318,000 people in the UK have received one dose of vaccine of which 36,099,000 have received a second dose.

It is not yet known how long vaccine-induced protection against COVID or against SARS-CoV-2 infection will last as, outside clinical trials, vaccines have been in use for < 9 months. In addition, as these vaccine platforms are also novel there is very little experience of the longevity of the protective immunity that they provide.

In the absence of a defined *immune correlate of protection* a range of immune parameters, principally antibodies and T cell responses, are being measured to monitor vaccine-induced immune response at the individual or population level. There is increasing data that the levels of neutralizing

antibody following vaccination correlates with the level of protection (Earle et al., 2021; Khoury et al., 2021).

However, antibody levels do not remain constant over time and the phenomenon of *antibody waning* might impact long-term vaccine efficacy. This is of particular concern in relation to protection against viral Variants of Concern (VOC) for which higher antibody levels (titres) are typically required for viral neutralisation.

Figure 1 illustrates how protection against the original virus immunogen and VOC might change over time in relation to antibody waning.

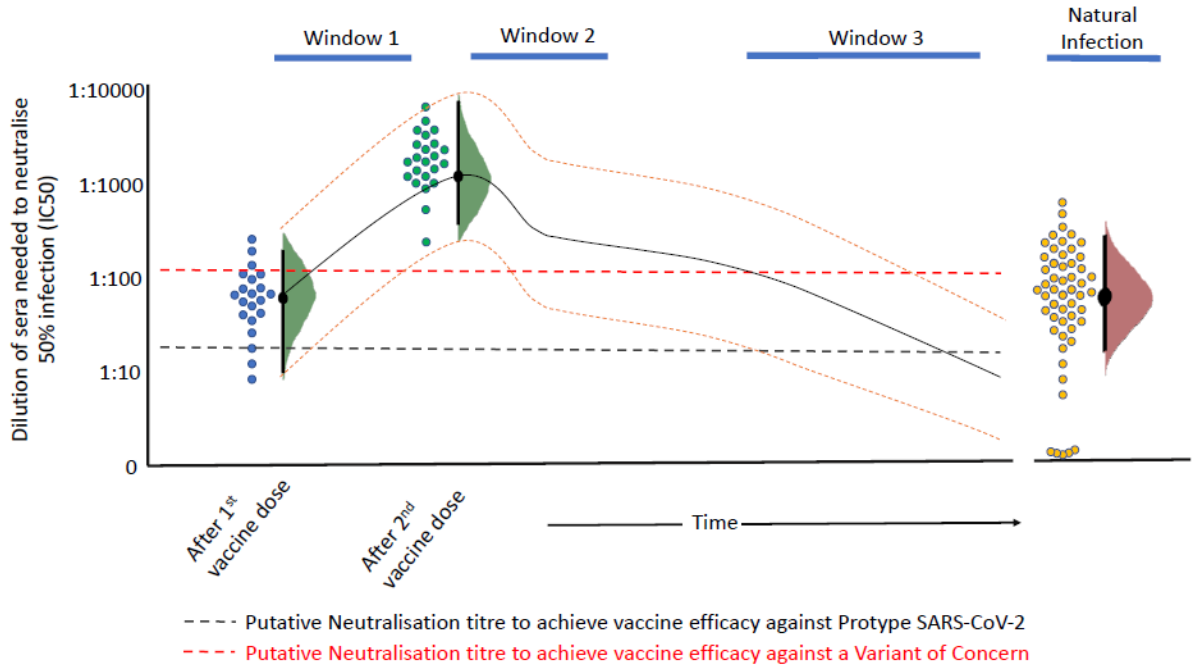

Figure 1 A representation of antibody immunity levels and durability that can be measured in the sera of people following their 1st and 2nd dose of vaccine.

Figure 1 Legend

The level of immunity is measure by the dilution of the sera that contains antibodies required to inhibit by 50% the infection of cells (neutralise) in the laboratory (IC50). After the 1st dose of the vaccine people make different levels of antibodies (blue dots), yielding a population distribution of neutralising antibodies levels (green distribution, with mean level represent by black dot). After the 2nd dose of vaccine, neutralising antibody levels are further boosted to give elevate individual responses (green dots) and a population distribution of neutralising antibodies levels (green distribution, with mean level represent by black dot). Over time from the 2nd vaccination, the levels of neutralising antibodies decline, more rapidly at first and then at a slower rate, but the dynamics are poorly understood at the individual or population level. The correlation between the level of immune response and vaccine efficacy is not known, but for other vaccines, detection of neutralising antibodies are a reasonable proxy for vaccine efficacy. The levels of neutralising antibodies required to neutralise the prototype 'Wuhan' like SARS-CoV-2 (grey dotted line) are different from the levels required to neutralise Variants of Concern (VOC; red dotted line), where mutations in the Spike gene decrease the potency of the neutralising antibody response, resulting in the need for a higher neutralising antibody level to achieve the same level of vaccine protection. As different people in the population have different levels of neutralising antibodies following two doses of vaccine, then the rate at which people become susceptible to infection by prototype 'Wuhan' like SARS-CoV-2 or a VOC is specific to a person within the vaccinated population. The average rate of change over time (black solid curve) and range (high-low, orange dashed curves) therefore yields three windows of concern: window 1, following the 1st vaccine dose, where most people are protected from infection by prototype 'Wuhan' like SARS-CoV-2 (above grey dashed line) but many are susceptible to infection by a VOC (below the red dashed line); window 2, following the 2nd vaccine dose, where most people are protected from infection by prototype 'Wuhan' like SARS-CoV-2 (above grey dashed line) and by a VOC (above the red dashed line), but where some people remain susceptible to infection by a VOC (below the red dashed line); window 3, immunity waning over time leading to many

people becoming susceptible to infection especially to VOCs. It should be noted however, the VE to asymptomatic, symptomatic, severe, and fatal infection are all different endpoints, each of which requires separate interpretation within this framework, and will most likely involve different component of the total immune response including vaccine induced cell mediated immunity. Each vaccine platform and regimen will have a slightly different prime and boost response for detectable antibody levels. For comparison, the level of antibody immunity likely achieved from natural infection is indicated (orange dots and distribution), including an indication of the small number of people below the level of detection for neutralising antibodies.

In this paper we summarize relevant studies that:

- address the potential durability of vaccine-induced immunity to COVID; and
- tabulate ongoing or planned studies that will complement this knowledge.

Informing VE longevity from studies on immunity to SARS CoV-2 after natural infection

Some information about how long vaccine protection will last might be gleaned from considering what we know about longevity of protection after natural infection. A recent paper from NERVTAG was presented to SAGE on 27th May:

Protection from re-infection with SARS-CoV-2 can last at least 7 months and in some studies up to one year. These findings are supported by reports of immune measures being detectable beyond 8 months in healthy people who have recovered from COVID.

Since antibody titres after vaccination are frequently higher than after infection, if waning rate were similar, a threshold level where protection would be lost might take longer to be reached after vaccination than after infection. On the other hand, natural infection induces a qualitatively different immunity than does vaccination: the response is broader (against more antigens) and varies in the relative contribution of different arms of the immune system . Thus it is possible that the clinical effectiveness of vaccine-induced immunity might wane more quickly.

Vaccine Effectiveness studies that consider longevity of protection:

Comprehensive population-based surveillance to measure VE in the real world in UK is underway, undertaken by PHE as part of their core remit using health service and surveillance data.

There are also a number of niche studies planned or underway that will enhance the observational data that are available for individual population groups (see summary in Appendix 1).

More detailed mechanistic studies into the immunology that underpins VE are funded by UKRI or other sources (see Appendix 4).

Real world data on waning VE

Data from PHE will assess the VE against symptomatic infection using pillar 2 data and against severe disease, hospitalization[1].

It might be expected that VE will remain high for severe disease but a fall off in VE over time against mild disease and infection might be expected. There are anecdotal reports from the ONS CIS in UK, and from Israel that support this concept.

The impact of waning immunity might be first detected in those with relative immune suppression and/or comorbidities.

Israel rolled out a comprehensive and early vaccine campaign employing Pfizer vaccine. A recent description of vaccine breakthroughs in 152 hospitalized but fully vaccinated patients in Israel shows poor outcomes in 38 and mortality rate of 22% (Nissimov et al., 2021). This cohort was characterized by a high rate of comorbidity and 60% were immunocompromised. It is likely that waning vaccine immunity will first be picked up by detecting increasing numbers of vaccine failures in immunocompromised, aged or otherwise comorbid individuals. In addition, as underlying mortality

[1] This section has been updated following SAGE 94 to reflect that confidence in the currently available data is low. An update on real world data on vaccine effectiveness over time from PHE is expected in the next two months and will be published.

is high in such groups many of the COVID-related deaths may be people dying with COVID rather than from COVID and therefore not preventable by vaccination.

Immunity waning is compounded by viral evolution

Measuring vaccine effectiveness waning in the real world is confounded by the fact that the virus is also mutating and antibody from an 'old' vaccine provides less protection against new variants. Indeed, it has been suggested that for the seasonal human coronavirus 229E, antigenic 'drift' variants emerged between 1984 and 1992, with an accumulated 17 mutations in the spike protein and 8 fold loss in neutralizing antibody efficacy (Eguia et al., 2021). The antigenic distance combined with waning immunity following natural infection gave the opportunity for the variant to emerge. If vaccine immunity wanes faster than that from natural infection and if vaccine immunity were to constitute the majority of immunity in the population, we might expect a shorter interval between drift variants for SARS-CoV2.

This outcome might also be influenced by the quality and quantity of immunity induced by any boosting with homologous or heterologous vaccines.

How can we predict or measure waning vaccine immunity?

One way to predict whether immunity is waning is to look for falls in the immune effectors such as antibody titres and T cell responses over time. Many studies are set up in the UK to do this (appendix 2) and some results from the publicly available literature are catalogued below.

However, it must be noted that antibody titres are expected to fall over time, and the basis of vaccine induced immunity is to provide initial high levels of antibodies and T cells and to prime the immune system for re-encounter with a pathogen, rather than necessarily to induce sustainable very high levels of antibody that are maintained by an individual for many years. Memory B cells that can make specific antibodies very rapidly after re-exposure cannot be measured in a simple serum sample. However, emerging data shows these are established after mRNA vaccination (Turner et al., 2021), and the large increase antibody titres following a vaccine second dose strongly supports the presence of a good memory B cell response.

The rate of antibody waning will likely be different for **different age groups** of the population and will likely depend on how high the initial antibody levels were, and which aspects of immunity are less robust in older individuals. Data so far points to starting antibody levels being somewhat lower for older people. Following vaccination with Moderna product mRNA01273, antibody levels were still robustly detected after 6 months but waning of neutralizing antibody was more evident in older age groups (Doria-Rose et al., 2021). Within the UK the DHSC-funded VIVALDI study is assessing antibody levels of staff and residents within Long Term Care Facilities (LTCF) and delivering monthly reports to assess waning. Within the community, the National Core Studies Immunity CAIRO cohort studies longitudinal immunity in donors aged 80-100+ years (Appendix 4).

However, if antibodies that can bind or neutralize the relevant spike protein of the circulating virus variant are still detected in sera of vaccinees, these individuals are highly likely to be protected at least from severe disease.

There are data from studies for each of the vaccines in use in UK and also for the Janssen Ad.26.COV2.S vaccine that assess the longevity of the antibodies induced by vaccines. The half-life of the antibodies from the Moderna study is estimated at 68-200 days (Doria-Rose et al., 2021).

The decline in antibody titres is more evident when a sensitive assay such as virus neutrlization is used, for example in the study from Barouch et al. NEJM 2021, Ad.26.COV2.s vaccine antibodies and T cell responses were measured at 8 months post vaccination but titres had fallen 1.8 fold between peak response on day 71 and the final time point measured on day 239 (Barouch et al., 2021).

For ChAdOx/AZ, a decline from initial peak after second dose can be measured, but at 200 days there are still robust antibody titres (Flaxman et al., 2021).

Similarly neutralizing antibody titres induced following second dose of Pfizer vaccine declined with time since second dose, and where neutralization is tested against antigenically distant variants such as beta (B.1.351) and delta (B.1.617.2) this becomes highly significant as shown in Figure 2.

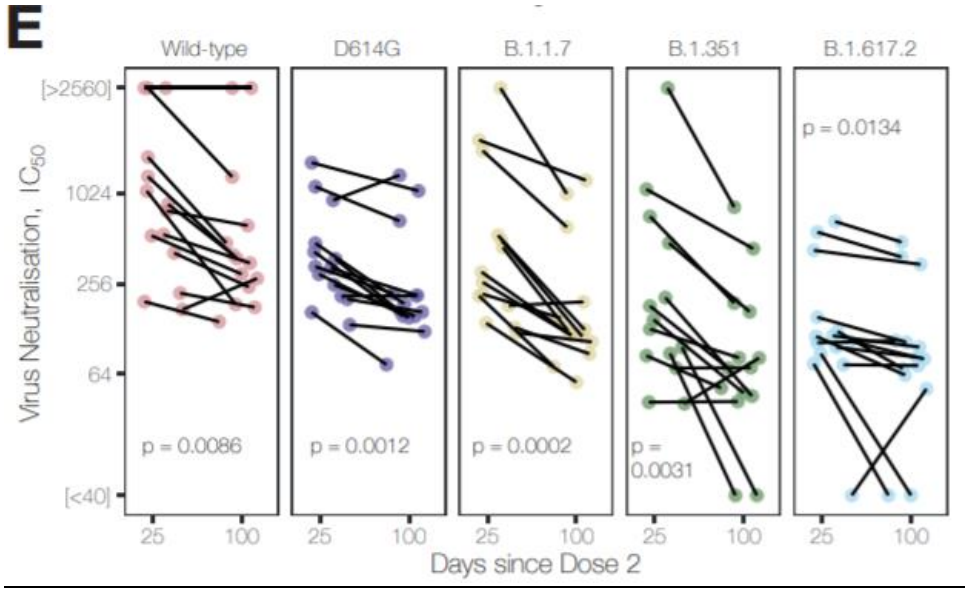

Figure 2 Neutralising antibody titres (taken from Flaxman et al., 2021)

Antibody waning measured in the community

Community based studies such as Virus Watch, the ONS CIS survey and REACT-2 can measure the prevalence of antibody at a population level. Virus Watch, a longitudinal community study in England and Wales recently reported a study of 605 adults with a mean age of 63 years (Shrotri et al., 2021). They found antibody waning following second dose of both Pfizer or AZ vaccine (Figure 3).

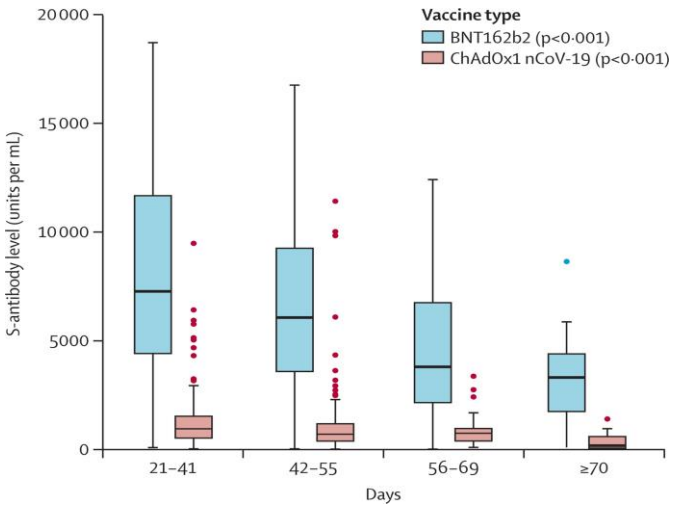

Figure 3 Levels of antibody against the spike glycoprotein of SARS-CoV-2 (S-antibody) at defined timepoints after second dose of vaccination (with extended dose intervals) in individuals with no previous infection, stratified by vaccine type p values derived from non-parametric tests for trend for each vaccine subgroup are given in parenthesis in the key (taken from Shrotri et al., 2021)

REACT-2 round 6 assessed the antibody positivity in the UK population after vaccination and found evidence of substantial waning after single dose vaccines, especially evident following one dose of Pfizer vaccine, and some waning after second dose OxAZ in the over 60s (see Figure 4). Further rounds of REACT-2 to assess whether the trend in falling seroprevalences continues have not been funded.

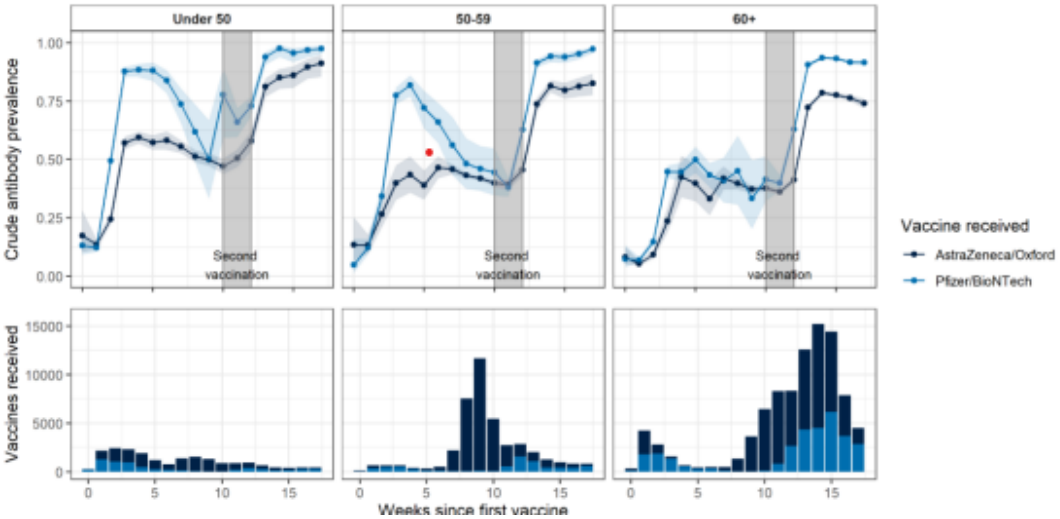

Figure 4 Antibody prevalence in the UK population measured by lateral flow tests in the community and normalized to time since vaccine first or second dose.

In contrast the latest ONS CIS study reports an increase in antibody prevalence over time in line with increased vaccinations (Figure 5). The antibody test used in the ONS study is more sensitive than that used by REACT-2, but did pick up the waning antibody levels between first and second dose in elderly individuals.

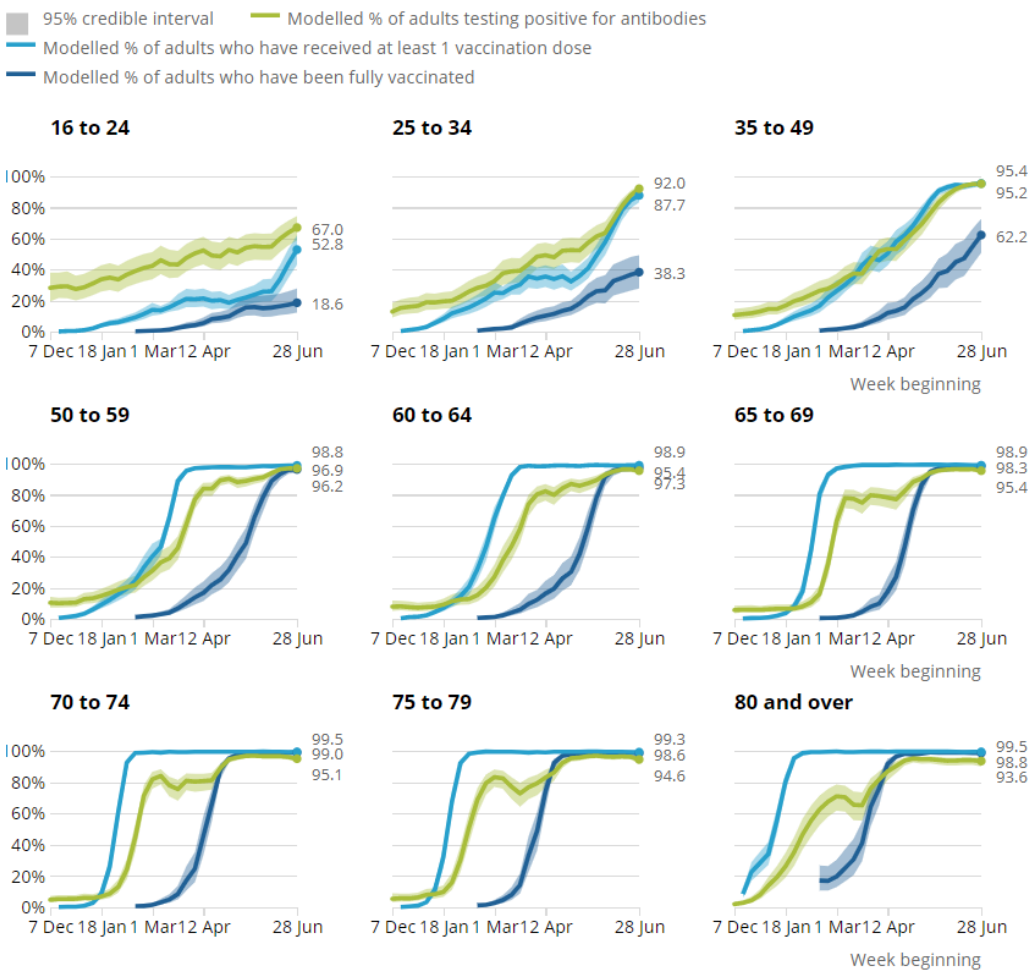

Figure 5 Results from ONS CIS Study

Taken together these data suggest that vaccine induced antibodies will wane over time but that after two doses of vaccine, levels remain high over at least several months and can still be robustly detected with sensitive assays. The effect of this amount of waning of VE will depend on the level of antibody required for protection against severe disease , symptoms or infection.

Is waning immunity following vaccination necessarily a bad thing?

A likely scenario is that as vaccine induced immunity to SARS-CoV-2 wanes over time, individuals will become infected. Because of the priming of the immune system and amnestic response will rapidly control viral load resulting in no or mild symptoms. Meanwhile the re-exposure will further boost the immune system and result in a broader immune response (see for example Cromer et al., 2021). Since we do not expect to eliminate SARS-CoV-2, the frequency of re-exposure will depend on levels of control of virus over coming months and years, and this may impact of how frequently we need to administer booster vaccinations. The severity of infection following vaccination will depend on the robustness and longevity of the initial vaccine induced response, and it will be prudent to monitor this in vulnerable groups. There is little information thus far on the immune responses of individuals who are infected following vaccination. However, the other way around, with vaccination after infection is found to have a very strong boost of the convalescent response even after a single vaccine dose suggesting that heterologous prime and boost mechanisms can be potent.