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Waning Immunity, Breakthrough Infection and Booster Dose in COVID-19

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Caution: Summary is a preliminary report of work by Pandemic Scientific Response team. It will be continuously updated in accordance to the unfolding of events and emerging of scientific evidence.

In Brief

- Infection with SARS-CoV-2 and vaccination against it confer good protection (up to 99% from death) from COVID-19 in the following months.
- Seroconversion against at least one antigen was detectable at 12.6 days post-onset of symptoms (POS) or 10-15 days after one dose of vaccination.
- The IgM and IgA peak between **20-30 days** POS, IgG peaks between **30-40 days**. At these peaks of antibody titres, **60%** achieved the highest neutralization potency, and this proportion reduced to about **16% after about 2 months** POS.
- Prior SARS-CoV-2 infection, more severe symptoms (fatigue, fever and chills) and COVID-19 causes higher SARS-CoV-2-neutralizing antibody titres. Different types of vaccine (Moderna> Pfizer-BioNTech> Oxford-AstraZeneca), age< 65 years, female, and vaccination strategy (heterologous > homologous) induce higher antibody titres.
- Antibody titres and neutralising response wane over time. The IgM and IgA approach baseline after **2 months** and to the levels similar to the uninfected at **3 months** POS; the Spike IgG half-life is about **4.5 months** (95% CI: 3-11 months) and may become undetectable after **1 to 4 years**.
- SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3 to 5 months which means would be undetectable by **1.5 to 2 years**.
- The longevity of the immune depends on the peak titre and responses attained, and the same factors mentioned above.
- Antibody protection from COVID-19 is good within the 6 months after vaccination or infection. Although cellular immunity last longer but the mechanisms of its protection has yet to be defined in humans.
- The risk of reinfection increases with the time after full vaccination increases. The risk of reinfection increases at about 30-40% every month after vaccination disregards of different age and risk groups (when Delta variant predominates).
- Risk of reinfection is substantial **after 6 months** post vaccination/infection due to waning immunity and new variants. Heightened alert and precautions are needed including strict adherence to double masking, social distancing, SOPs of avowing the 3Ws and practising the 3Cs, or a booster dose is required.
- Pfizer suggests a booster with the 3rd dose within 12 months of the full 2-dose vaccination; US considers 8 months and Israel has vaccinated people age > 50-year-old after 6 months of full vaccination.
- This response draws on data on the Moderna, Pfizer-BioNTech, Oxford-AstraZeneca Johnson-Johnson and CoronaVac (Sinovac) vaccines.
- Antibody testing could identify who has had COVID-19 in the past but it cannot tell us for sure whether we are protected from future infection because such protective antibody titre is unknown and immunity depends on many other factors.

UNIT PENYELIDIKAN KLINIKAL
Hospital Pengajar Universiti Putra MalaysiaPersiaran Mardi - UPM
43400 Serdang
Selangor Darul Ehsan
MALAYSIA

Untuk maklumat lanjut, sila lawati: **penyelidikan@hpupm**
03-9769 9763 / 9762 / 9761
cru_hpupm@upm.edu.my

Full Summary

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Summary

The infection rate of SARS-CoV-2 in the community is about **10%**. Out of this, the incidence of mild to moderate symptomatic COVID-19 is about **80%** (up to categories 2 with or without mild pneumonia), about **15%** progress to severe respiratory disease (categories 3 and 4) and **5%** develop acute respiratory distress syndrome (ARDS), lung failure, septic shock or multi-organ failure (category 5)[1]. For those who survive (> 95%), the median recovery time from symptomatic mild cases was approximately two weeks and for patients with the severe or critical disease was three to six weeks[1]. Recovery from a severe stage of disease may be slow as symptoms such as cough, fatigue and that of the Long COVID syndrome (up to 50% of the survivals) may continue for weeks and months due to lung damage and multi-organ involvement[1].

The appearance of the more transmissible Delta variant SARS-CoV-2 has caused surges of COVID-19 cases in many countries. To many, the pandemic has become the pandemic of the unvaccinated[2]. Increasingly, it was observed that those who were fully vaccinated were also infected and hospitalised with severe diseases[3]. There have been hundreds of reinfections reported with positive test on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) after recovery and discharge from hospitals in several countries[1]. This raises the issue of breakthrough infections due to the waning beside other factors including the new variant Delta.

Immune Response

Neutralizing antibodies post-infection and vaccination block the entry of viruses into the target cells through neutralisation by binding pathogens and clear virus-infected cells via opsonisation to immune cells to facilitate phagocytosis, degranulation, and antibody dependent cell mediated cytotoxicity by phagocytes and natural killer cells as well as other immune components such as inflammatory cascades[1]. The binding of the antibodies to the virus inhibits the viral spike protein from interacting with the cellular ACE2 receptor. This limits viral replication within the host at the point of entry before infection of host cells [4]. The quantity and quality of neutralizing antibodies against SARS-CoV-2 is highly variable in COVID-19 patients[1-9]. Recovery process and long-term protection require contribution of multiple immunologic factors and components that last.

Studies are accumulating on the immune responses but scarce on the immune protective activity and durability after vaccination and COVID-19[1,4]. The reports observed immune responses varied according to the different vaccines, vaccination strategies (homologous or heterologous), severity of COVID-19, age groups, gender, as well as heterogeneity of immune memory, with different patterns of immune memory in different individuals over time[5-9]. Majority (**64%**) of COVID-19 people were positive for all five of immune memory compartments receptor-binding domain (RBD) IgG, RBD memory B cells, Spike IgA, total SARS-CoV-2-specific CD8+ T cells, and total SARS-CoV-2-specific CD4+ T cells at 1 to 2 months post-onset of symptoms (POS). Incomplete responses were largely of the CD8+ T cell memory and/or poor IgA responses. At 5 to 8 months POS, the proportion of individuals positive for all five of these immune memory compartments had dropped to **43%**. Nevertheless, **95%** of individuals were still positive for at least three out of five SARS-CoV-2 immune memory responses.

SARS-CoV-2 CD4+ T and SARS-CoV-2 CD8+ T cell memory was largely stable over time. Next would be the memory B cells with no apparent half-life at 5 to 8 months post-infection from one study[8], followed by Spike and RBD IgG, and Spike IgA. However, even the two mostly stable over time RBD IgG and SARS-CoV-2 CD4+ T cell memory, their relationship variation spanned over about 1000-fold range. Therefore, any predictive power of circulating RBD IgG for assessing T cell memory was poor because of the heterogeneity between individuals. In sum, heterogeneity of immune responses is a defining feature of COVID-19 and this includes variation of the immune memory to SARS-CoV-2 in almost all recovered people with complex relationships between the different immune memory compartments.

In human infected with COVID-19, rapid seroconversion within 3-5 days from the responses of memory B and T cell were associated with less COVID-19 disease severity[8]. Analysis of the relationship between neutralizing antibody titre and protection using data from vaccination and convalescent studies suggests that

- a neutralizing titre equivalent to **20%** of the average convalescent titre is sufficient to provide **50% protection from symptomatic COVID-19**;
- a lower neutralization titre of **3%** of the average convalescent antibody titre was associated with **50% protection from severe COVID-19**.

Booster Dose

Unfortunately, in real life and clinically, the protective effects of these immune components do not seem to hold up over time with the new SARS-CoV-2 variants such as the Delta seem to escape. There is accumulating evidence suggesting the importance of T-cell-mediated immunity and responses when the antibody responses wane. Nevertheless, available data and reasonable interpretations indicated that the antibodies are the only component of immune memory that can provide truly sterilizing immunity while the mechanisms of protective immunity of the memory cells against SARS-CoV-2 or COVID-19 **are yet to be defined in humans**.

In the attempt to curb the surge in COVID-19, many countries have considered the third or an extra booster vaccine dose including Israel[3]. Israelite government has started administering the third booster vaccination on 30 July for her people ≥ 60-year-old and, then to those ≥ 50-year-old, and very recently to all 30-year-old and above[10]. This comes after about 6-8 months after full vaccination. This was reported to be based on their nationwide high-quality data that shows waning protection[11] where those who were vaccinated in January 2021 had **2.3 times** (CI 1.80-3.01) higher risk of infection compared to those vaccinated in April 2021 after matching for high-risk individuals (e.g., healthcare personnel and persons with comorbidities) and those over the age of 60, sex, city of residence and socioeconomic status, and adjusted for underlying comorbidities, including obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer, COPD, IBD and immunosuppression conditions. Even so, the overall effectiveness of Pfizer-BioNTech against severe COVID-19 when the Delta variant predominated Israel was still above 80% among the worst protection group of those age between 80-89 year-old[12,13].

They also found that boosters might have broader value including a prompt surge in antibodies lining the nose and throat against infection. Additionally, the Israeli preliminary data indicated that people over age 60-year-old who have received a third dose were half as likely as their twice-vaccinated peers to be hospitalized[3]. Out of more than 4500 patients who received the boosters, 88% had side effects similar to after the second dose.

The UK's Joint Committee on Vaccination and Immunisation (JCVI) has proposed the following two stages of COVID-19 booster and influenza vaccination programme in the coming winter year 2021-2022 [14].

Stage 1. The following persons should be offered a third dose COVID-19 booster vaccine and the annual influenza vaccine as soon as possible from September 2021:

- adults aged 16 years and over who are immunosuppressed
- those living in residential care homes for older adults
- all adults aged 70 years or over
- adults aged 16 years and over who are considered clinically extremely vulnerable
- frontline health and social care workers

Stage 2. The following persons should be offered a third dose COVID-19 booster vaccine as soon as practicable after stage 1, with equal emphasis on deployment of the influenza vaccine where eligible:

- all adults aged 50 years and over
- adults aged 16 to 49 years who are in an influenza or COVID-19 at-risk group
- adult household contacts of immunosuppressed individuals

Adapted from JCVI interim advice: potential COVID-19 booster vaccine programme winter 2021 to 2022. Independent report. Published 30 June 2021.

Antibody Waning After Vaccination

Initial comparisons between the post-vaccination and infection in the first month showed similar durability of both neutralizing and binding antibody responses[4]. At the peak of response to the second vaccine dose (2 weeks), cross-reactive neutralizing responses to all variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.429), Iota (B.1.526), and Delta (B.1.617.2) have been observed[15].

A cross-sectional study of 605 UK adults on June 14–15, 2021, where 321 (53%) were women, the median age was 63 years (IQR 58–67), and three different categories of vulnerable group: 186 (31%) as clinically vulnerable, 117 (19%) as clinically extremely vulnerable, and 302 (50%) as not clinically vulnerable. A total of 197 (33%) samples were taken 14–154 days after second vaccine dose (median 42 days [IQR 30–53]) from BNT162b2 vaccinees and 405 (67%) were from ChAdOx1vaccinees. The median interval between first and second doses was 77 days (IQR 70–78).

The results observed waning of S-antibody levels in infection-naive individuals over a 3-10 weeks period after a second dose of either ChAdOx1 (5-fold reduction) or BNT162b2 (2 fold reduction).

- For BNT162b2, S-antibody levels reduced from a median of **7506 U/mL** (IQR 4925–11 950) at 21–41 days, to **3320 U/mL** (1566–4433) at 70 or more days.
- For ChAdOx1, S-antibody levels reduced from a median of **1201 U/mL** (IQR 609–1865) at 0–20 days to **190 U/mL** (67–644) at 70 or more days[7].

These data are consistent with the decline in Spike-antibody and neutralising antibody levels observed after infection (see below)[5], although memory B-cell populations appear to be maintained.

Across both vaccine types, women had higher initial S-antibody levels than men at 21–42 days after complete vaccination; also ending with higher levels at 70 days or more. Similarly, those aged 18–64 years had higher levels at 21–42 days compared to those aged 65 years and older, with correspondingly higher levels at 70 or more days[7].

These observations were also noted in a US study among the healthcare workers (n=954)[9]. Reporting clinically significant symptoms (fatigue, fever and chills), age younger than 60 years, female, recipient of Moderna vaccine, and prior SARS-CoV-2 infection were independently associated with higher median IgG measurements (enzyme-linked immunosorbent assay and not neutralizing antibody titers), after adjusting for time after dose 2.

A randomized controlled trial of CoronaVac (Sinovac) showed similar results of waning immunity up to 6 months post 2 doses and enhanced immunity with a 3rd booster dose (see table below)[16]. The participants (n= 600 ended in n=560) had mean age of about 42-year-old, with almost equal representation of the 2 genders, randomized to medium-dose group (**3 µg**), a high-dose group (**6 µg**), or a placebo group in the ratio of 2:2:1 within 4 different schedules of 3 doses:

1. ***Schedule One*** the first two doses on days 0 and 14, and a third dose 1 month after the second dose (day 42);
2. ***Schedule Two*** the first two doses on days 0 and 14, plus a third dose 6 months after the second dose (day 194);
3. ***Schedule Three*** the first two doses on days 0 and 28, and a third dose 1 month after the second dose (day 56);
4. ***Schedule Four*** the first two doses on days 0, and 28, plus a third dose 6 months after the second dose (day 208).


Photo by Saifullizan Tamadi/ NSTP

CoronaVac (Sinovac)	The geometric mean titers (GMTs) of neutralizing antibodies to live SARS-CoV-2* were quantified using a micro cytopathogenic effect assay				
	V2+14 days	**V2+28 days**	**V3+0 day V3+14 days V3+28 days**		**V3+6 months post 3rd dose)**
Schedule One 3 μg	**27.0** (28 days)	**22.2** (V3+0 day, 42 days)	**45.8** (V3+28 days, 70 days)		**9.2** (222 days)
Schedule One 6 μg	**40.8** (28 days)	**29.1** (V3+0 day, 42 days)	**74.2** (V3+28 days, 70 days)		**13.6** (222 days)
Schedule Two 3 μg	**28.2** (28 days)	**25.6** (42 days)	**4.1** (V3+0 day, 194 days)	**137.9** (V3+14 days, 208 days)	
Schedule Two 6 μg	**29.2** (28 days)	**31.1** (42 days)	**4.8** (V3+0 day, 194 days)	**175.1** (V3+14 days, 208 days)	
Schedule Three 3 μg		**39.6** (56 days)	**49.7** (84 days)		**10.0** (236 days)
Schedule Three 6 μg		**58.4** (56 days)	**51.9** (84 days)		**10.2** (236 days)
Schedule Four 3 μg		**49.1** (56 days)	**6.7** (V3+0 day, 208 days)	**143.1** (V3+28 days, 236 days)	
Schedule Four 6 μg	**175.1** (uncertain timing)	**73.6** (56 days)	**7.1** (V3+0 day, 208 days)	**215.7** (V3+28 days, 236 days)	

* live SARS-CoV-2= virus strain SARS-CoV-2/human/CHN/CN1/2020, GenBank number MT407649.1

Seropositivity in all four schedules was above **90.0%** on day 28 after both the second dose and third dose. On day 180 (6 months) after the third dose, seropositivity remained above **60%** for Schedule One and Schedule Three, but only **16.9%** in schedule 2 and **35.2%** in Schedule Four[16].

Most adverse reactions reported were grade 1 in severity[16]. After the third dose, there were **7.9%** and **3.1%** for Schedule One and Schedule Three, lower than the overall incidence of adverse reactions within 28 days after three doses for Schedule One (**33.3%**) and Schedule Three (**22.0%**). There were no significant differences among the 3 μg, 6 μg, and placebo groups for all schedules. A total of fourteen serious adverse events among nine participants were reported but none of these were related with vaccination.

Antibody Waning After SARS-Cov-2 Infection

Similarly, antibody responses to human coronaviruses including SARS-CoV-2 have been reported to wane over time[5-7]. A wide range of SARS-CoV-2-neutralizing antibody titre has been reported after infection and these vary depending on the length of time from infection and the severity of disease.

A UK study of 59 individuals and 6 HCWs, 78.5% male with an average age of 55.2 years (range 23–95 years)[5] with a severity score assigned to patients based on the maximal level of respiratory support required during their period of hospitalization. This cohort included the full breadth of COVID-19 severity, from asymptomatic infection to those requiring extracorporeal membrane oxygenation (ECMO) for severe respiratory failure. Comorbidities included diabetes mellitus, hypertension and obesity. Sequential samples were collected at timepoints between 1 and 94 days post onset of symptoms (POS). It highlights the transient nature of the neutralizing antibody response towards SARS-CoV-2 infection in some individuals.

Photo by Luqman Hakim Zubir/ NSTP

In some individuals who develop modest neutralizing antibody titres after infection at the ID50 (serum dilution that inhibits 50% infection) in the 100–300 range), titres become undetectable (ID50 < 50) or are approaching baseline after about 50 days[5]. In contrast, individuals with high peak ID50 for neutralization maintain neutralizing antibody titres in the 1,000–3,500 range >60 days POS[5].

When the IgG, IgM and IgA response against S glycoprotein, RBD and N protein were measured by enzyme-linked immunosorbent assay (ELISA) over multiple timepoints,

- the cumulative frequency of IgG responses against S, RBD and N antigens were observed in **92.3%**, **89.2%** and **93.8%** of individuals, respectively[5].
- The frequency of individuals generating an IgM response was similar to that with IgG, with **92.3%**, **92.3%** and **95.4%** seropositive against S glycoprotein, RBD and N protein, respectively[5].
- The frequency of individuals with an IgA response to RBD and N protein was lower, with only **72.3%** and **84.6%** seropositive, respectively, whereas the IgA to S glycoprotein frequency was similar to that of the IgM and IgG[5].

The average time to detectable neutralization for S glycoprotein IgA and S glycoprotein IgM was **14.3 days** POS (range 3–59 days) [5]. Longitudinal analysis across sequential samples highlighted the rapid decline in the IgM and IgA response to all three antigens after the peak optical density (OD) between 20 and 30 days POS for IgM and IgA, respectively. For some individuals, the IgM and IgA responses were **approaching baseline >60 days**. In contrast, the IgG OD (as measured at 1:50 dilution) **remained high in most individuals up to 94 days** POS.

However, differences were apparent when patients were stratified by disease severity and when half-maximal binding (EC50) was measured. More severe diseases enhance the magnitude of the neutralizing antibody response but does not alter the kinetics, which are the mean time taken to measure detectable neutralizing antibody titres and the mean time to reach peak neutralization[5].

The neutralization potency increased with increasing days POS reaching a peak neutralization titre (range 98–32,000) on average **23.1 days** POS (range 1–66 d) [5].
At peak neutralization, 7.7% had low (50–200), 10.8% medium (201–500), 18.5% high (501–2,000) and 60.0% potent (2,001+) neutralizing titres.

- For serum samples collected after 65 days POS, the percentage of donors with potent neutralizing antibodies (ID50 2,001+) had reduced to **16.7%**[5].

After the peak in neutralization, a waning in ID_{50} was detected in almost all cases at >40 days POS[5]. For some individuals with severity score 0, where peak neutralization was in the ID_{50} range 100–300, neutralization titres became **undetectable (ID_{50} < 50) by day 34-39**. In another study among the long-term care community, the peak IgG seropositivity was recorded at 30–45 days after the time of diagnosis and 91% still showed seropositivity but at lower levels at 6 months[6].

Longevity of Neutralizing Antibody Response and Cellular Immunity

1. Antibody Response

Among 188 (80 male, 108 female) Americans with a wide range of COVID-19 (asymptomatic, mild, moderate and severe) reported that the IgG to the Spike protein was relatively stable up to **8 months**[8]. However, the Spike IgG titers were heterogeneous among subjects: the Spike IgG half-life was **140 days** (95% CI: 89-325 days), the Nucleocapsid IgG half-life was **68 days** (95% CI: 50-106 days), and RBD IgG titers estimated half-life was **83 days** (95% CI: 62-126 days) [8].

In another review[4], Spike-specific IgG antibodies half-life was **100–230 days**; and IgM **55 days** and IgA1 spike-binding antibodies **42 days** in the early period after infection (before day 70 post-infection). However, the half-lives IgM and IgA responses decline to 118 days and >1,000 days, respectively, beyond 70 days after infection.

In another study, Spike IgA fit a short one-phase decay model with an extended plateau phase (initial half-life of **14 days**) [8]. Whereas the RBD IgA had an estimated initial half-life of **27 days**, decaying by about 90 days to levels indistinguishable from uninfected controls.

2. Cellular Immunity

Memory B cells provide an additional humoral immunity that is more durable. They provide the rapid recall and production of antibodies following a re-encounter with the pathogen[4]. However, the kinetics of recall and protective potential of memory B cells in SARS-CoV-2 immunity have yet to be determined or proven. Similarly, the protective effect of T cell-mediated immunity on SARS-CoV-2 is not well understood. There is some evidence linking robust T cell responses to mild disease outcome[4]. Whereas CD4+ T helper cells exert direct antiviral effector functions of T cells, also promote antibody responses by supporting the development of germinal centre B cells.

Studies observed that memory B cell frequencies were higher in hospitalized cases. This indicates that this long-term humoral immunity to SARS-CoV-2 is higher in individuals who experienced a more severe COVID-19 disease course. Contrastingly, the memory CD8+ T cell and CD4+ T cell frequencies were not higher in hospitalized cases compared to non-hospitalized cases[8].

Spike-specific memory B cells were more abundant at 6 months than at 1 month after symptom onset[8]. SARS-CoV-2 Spike-specific memory B cells increased over the first ~120 days POS and then plateaued. RBD-specific memory B cells (10-30% of Spike-specific memory B cells) appeared as early as 16 days POS, and the frequency steadily increased in the following 4-5 months[8]. Spike and RBD-specific memory B cell frequencies were also higher in hospitalized cases (~1.7-fold and ~2.5-fold, respectively).

The percentage of subjects with detectable circulating SARS-CoV-2 memory CD8+ T cells at 1-month POS (20-50 days) was **70%** (40/57). The proportion of subjects positive for SARS-CoV-2 memory CD8+ T cells at ≥ 6 months PSO was **50%** (18/36). SARS-CoV-2 memory CD8+ T cells declined with an apparent half-life of **125 days** in the full cohort and half-life **190 days** among 29 paired samples[8].

Circulating SARS-CoV-2 memory CD4+ T cell responses were quite robust with 42% (24/57) of COVID-19 cases at 1-month PSO had > 1.0% SARS-CoV-2-specific CD4+ T cells. SARS-CoV-2 memory CD4+ T cells declined with an apparent half-life of **94 days** in the full cohort and half-life **64 days** among 36 paired samples. The percentage of subjects with detectable circulating SARS-CoV-2 memory CD4+ T cells at 1-month PSO (20-50 days) was **93%** (53/57). The proportion of subjects positive for SARS-CoV-2 memory CD4+ T cells at ≥ 6 months PSO was **92%** (33/36)[8]. SARS-CoV-2-specific $CD4^+$ T cells and $CD8^+$ T cells declined with a half-life of 3 to 5 months[8].

Antibody Testing

Antibody tests look for a variation in IgA, IgG, and IgM antibodies either as a separate or combined measurement. IgM rises soonest and typically declines after infection while IgG and IgA persist and reflect longer term immune response. Antibody tests can be done in laboratory settings using enzyme linked immunosorbent assays or chemiluminescence immunoassays (CLIA) usually using venous blood samples or by the point of care tests that use disposable devices called lateral flow assays of finger prick blood.

The diagnostic accuracy of these tests varied depending on the timing of the tests according to the onset of COVID-19 symptoms. The maximum sensitivity for combined IgG or IgM tests was 96% at days 22-35 POS and was 88.2% at days 15-21 POS for IgG. Tests accuracy data beyond 35 days was lacking[17].

Although antibodies are an essential component of the immune response, there are B and T cell immunity and together providing specific protection and memory against future infection. However, testing for the presence of antibodies as an indication of the extent to which SARS-CoV-2 antibodies provide future immunity and protection from repeat infection is yet recommended because longitudinal studies are lacking of what is the considered protective antibody titre. Therefore, antibody testing should not be used in reassurance, to relay anxiety public health advice to individuals nor influencing reopening of workplaces[17,18].

Photo source: Imperial College London website

Universal Vaccines of Potent Antibodies Against SARS-CoV-2 Future Variants?

A research team in US discovered 2 most potent antibodies, dubbed A23-58.1 and B1-182.1 from the convalescent serum samples of people recovered from the first wave of SARS-CoV-2 infection[19]. These two überantibodies envelope a hook-like structure on the RBD tip in its up position skirted around key locations lower on the tip that appear to be mutational hotspots for the virus. In so structured, the antibodies would be always potent and effective all kind of coronaviruses including SAR-CoV-2 and variants. However, the researchers recognized that this work of developing a vaccine against a particular viral protein epitope is not a simple leap and require different strategies to achieve the goal (no elaboration was given).

Alternatively, higher vaccine-induced antibody titres to SARS-CoV-2 could be achieved through repeated boosting or a more immunogenic vaccine formulations would require. Certainly, expanding the breadth of neutralization against different antigenic variants will be an important requirement of next-generation vaccines.

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