Recent scientific knowledge supporting the adaptation of rules for the organization of road cycling competitions in the context of the COVID-19 pandemic

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References

This document is a review of the scientific knowledge on vaccine protection against the COVID-19 virus (i.e. SARS-CoV-2) updated to the end of December 2021. The objective of this review is to define the practical conditions for the organization of cycling competitions during the year 2022, still under pressure from the Covid-19 pandemic.

SARS-CoV-2 consists of a nucleocapsid (N) protein surrounded by an envelope containing three membrane proteins: spike (S, divided into two functional subunits, S1 and S2), membrane (M), and envelope (E) proteins. Among the four coronavirus structural proteins, S and N proteins are the main immunogens. The S protein facilitates the viral attachment and host cell entry by engaging its cognate receptor the angiotensin-converting enzyme-2 (ACE2). This interaction is mediated by the Receptor Binding Domain (RBD), a small 25 amino acids patch located in the S1 subunit. The RBD is highly immunogenic and elicits specific antibodies (Abs) that are strongly correlated with SARS-CoV-2 neutralization and prevention of COVID-19.

Despite significant efforts leveraging non-pharmaceutical interventions (NIPs) such as use of facemasks, physical distancing, community stay-at-home measures, quarantine, and isolation, spread has continued throughout much of the world. One of the main issues related to COVID-19 prevention is the duration and the protective capacity of the immune response to either infection or vaccination, especially taking into consideration the appearance of SARS-CoV-2 variants.

Herd immunity is critical for long-term control of the pandemic, and COVID-19 vaccination was initially suggested as the only viable path to reach herd immunity rather than by natural infection (Rasmusen, 2020). Although the concept of herd immunity remains a matter of debate for this respiratory viral infection, one potential effect of extensive vaccination is reducing transmission, one objective necessary to reduce virus circulation and reach herd immunity. The control of the pandemic is mainly dependent on the initial prevalence of infection, the characteristics of vaccines, the extent of the herd immunity and the strength of NPIs, i.e. mainly the use of face masks, physical distancing, etc.

The variables that may affect the establishment of effective herd immunity are,

- **vaccine efficacy**,
- **vaccine coverage** of the population, and **herd immunity**
- **longevity of the immunity** (i.e., neutralizing antibodies and memory cells),
- possibility of **third (booster) dose**,
- **viral transmission** by immunized athletes,
- and the degree to which **new variants are able to bypass immune responses from previous vaccination and or infection**.

1) Vaccine efficacy against the wild type strain of the virus

COVID-19 vaccines have been focused on the spike protein as the main vaccine antigen since it mediates the entrance into host cells. The COVID-19 vaccines are based on or encode the full-length S protein.

A- mRNA-based Vaccines

The mRNA vaccines are potentially more attractive because of their advantages as a pandemic-response strategy, given their flexibility and efficiency in immunogen design.

Safety and efficacy data from the Pfizer/BioNTech vaccine showed 95% effectivity in preventing COVID-19 due to the wild-type virus, and an efficacy between 90% and 100%,

with only very few adverse events, such as pain at the injection site, fatigue, or headaches (Polack et al., 2020). This vaccine elicited strong antibody responses; one week after the second dose, the geometric mean of the 50% neutralization titers of SARS CoV-2 serum was up to 3.3-fold higher than that observed in samples from individuals who recovered from COVID-19.

The Moderna vaccine that encodes the full-length S protein of the SARS-CoV-2 shows 94.1% efficacy in preventing COVID-19 with the wild-type form of the virus, including severe COVID-19 diseases, with rare serious adverse events (Baden et al., 2021).

B- Adenovirus-Based Vaccines

The adenovirus-based vaccine is a strategy based on adenovirus vectors, which carry a codon-optimized gene encoding the full-length SARS-CoV-2 S protein. The S protein is able to boost the immune response without the need for adjuvants.

The ChAdOx1 nCoV-19 vaccine (Astra-Zeneca, AZ vaccine) elicits a rapid production of Abs. Data derived from phase I/II showed that immunization with the AZ vaccine provoked the production of Abs against SARS-CoV-2 S protein that peaked by day 28 and elicited the neutralizing antibody in all participants after a second dose (Ewer et al., 2021). The overall vaccine efficacy was estimated to 66.7% (Voysey et al., 2021).

The Ad26.COV2.S vaccine (Johnson & Johnson, J&J vaccine) is known to trigger a strong humoral response in the majority of vaccine recipients, with the presence of S-binding and neutralizing antibodies (NAbs) in more than 90% of participants, regardless of age group or vaccine dose (Sadoff et al., 2021a). In a phase III trial, a single dose of J&J vaccine showed 67% efficacy, but 85% efficacy in preventing against severe-critical disease, including hospitalization and death (Sadoff et al., 2021b).

In summary, the authorized mRNA vaccines have demonstrated 94 to 95% efficacy in preventing COVID-19 related to the wild type strain of the virus (with the initial two-dose program). Full vaccination using Adenovirus-Based vaccines showed 66 to 67% efficacy against SARS-CoV-2 infection and higher efficacy in preventing severe forms of the disease.

2) Current vaccine coverage of the Teams

A peloton vaccination coverage survey was conducted from October to November 2021 with UCI-WorldTeams (WTT), UCI Women's WorldTeams (WTW), and UCI-ProTeams (PRT). The response rate was satisfactory, ranging from 100% of WTW to 79% for PRT teams.

The results show a great heterogeneity in the vaccination coverage of the teams; the vaccination coverage varies from 40 to 100%, according to the teams. However, for 75% of the teams, more than 80% of the personnel are totally vaccinated (riders and staff). For the vast majority of teams, the vaccination coverage of staff exceeds that of riders, 85% vs. 79%, respectively. Vaccination protection of WTW teams is better than that of WTT and PRT teams (97%, vs 79 and 86%, respectively).

Considering all the teams, we estimate that the vaccination coverage of the peloton is currently 82.7%.

Herd immunity is a crucial determinant for public-health policymakers to contain and potentially eradicate an infectious disease. It plays an important role in controlling the pandemic once a sufficiently high proportion of the population gains immunity through vaccination or infection. The herd-immunity threshold is the proportion of a population that must be vaccinated to stop an infectious disease from spreading.

However, the utility of the herd-immunity threshold becomes lower as the pandemic progresses. As we build immunity to SARS-CoV-2, through either vaccination or infection, the risk of severe illness markedly decreases.

Therefore, even without mentioning herd immunity, we can consider that the vaccination coverage of the peloton is an excellent factor to limit the spread of the virus and the risk of COVID-19.

In conclusion, the current vaccination coverage of the peloton can make us confident about the potential low circulation of the SARS-CoV-2 (low circulation, but not with zero risk of infection). It is remarkable to note that the vast majority of vaccinated riders and staff members were vaccinated with the most effective vaccines, i.e. mRNA vaccines.

3) Longevity of the immune protection against the wild strain and variants of concern, with either infection or vaccination

The aim of vaccination is to generate immune memory, namely the pool of blood cells including high-affinity memory B cells (MBCs) and long-lived plasma cells with their specific Abs. Differently from memory T cells, MBCs have the ability to improve their specificity. These cells with high affinity for recombinant S protein produce specific Abs able to neutralize the virus.

Like B cells, which produce antibodies, T cells play a pivotal role in the immune response to viral infection, not only in cell-mediated immunity, but also in synergizing with MBCs in antibody production. When the SARS-CoV-2 virus, which infects epithelial cells such as those found in the airways, replicates inside the cells, it causes the host cell to release specific molecules recognized by macrophages and causing them to produce chemokines; memory T cells are then recruited to the site of infection by these chemokines and promote further inflammatory response, especially through interferon-gamma (IFNγ) production. Several types of memory T cells are involved in this response, CD4+ helper/inducer T cells, CD8+ cytotoxic/suppressor T cells, which directly recognize viral peptides presented at the surfaces of infected cells, causing apoptosis.

A- Immune response during SARS-CoV-2 infection

Protective immune responses against SARSCoV-2 infection consist of two main parts, humoral immunoglobin (IgA and IgG) and T cell responses.

1- Humoral responses to SARS-CoV-2 infection.

Several studies have shown the appearance of neutralizing and protective anti-SARS-CoV-2 antibodies after infection, especially anti-S IgG, which protect convalescent COVID-19 patients against infection by the Alpha variant in the following 13 months (for review, see Altawalah, 2021; Galais et al., 2021).

During viral infections, viruses elicit a broad spectrum of antiviral Ab responses, i.e. neutralizing Abs (NAbs), and non-neutralizing Abs. NAb levels against the SARS-CoV-2 RBD of the S and the N proteins are highly predictive of protection against infection and clinical disease (Khoury et al. 2021). Available data support the concept that NAbs may serve as a biomarker that can ensure a proper protection of individuals. By 10–11 days after onset of COVID-19 symptoms, greater than 90% of patients develop specific immunoglobulin M (IgM) and immunoglobulin G (IgG) (Altawalah, 2021; Post et al., 2020; Thomas et al., 2021) (Figure 1). Within 17 to 19 days of symptom onset, 100% of patients are tested positive for specific IgG, while the fraction of patients with specific IgM peaks at 94.1%, and then shows a slight

decrease in the less than 3 weeks that followed. Furthermore, the immunoglobulin A (IgA) response increased since 6–8 days, peaks at 20–22 days and is stronger and more persistent than the IgM response. Serum concentrations of specific IgA decrease one month after symptom onset but contribute to virus neutralization in saliva for a longer period of time (days 49 to 73 after symptoms).

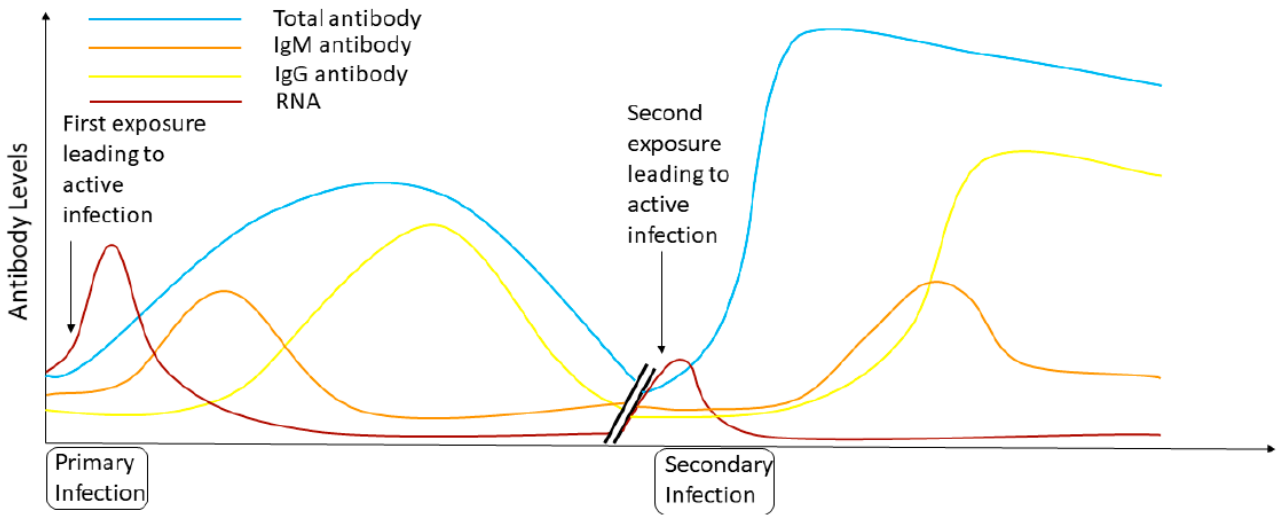


Figure 1. IgG/IgM/IgA/ Ab responses over time in humans following both primary and possible secondary infections with SARS-CoV-2 and associated variants.
(from Thomas et al., 2021).

The IgG, IgA and IgM titers are at least partly related to the severity of the disease. Striking differences were shown between asymptomatically infected individuals and symptomatic COVID-19 patients concerning the strength and persistence of SARS-CoV-2 specific responses of IgG recognizing the RBD of the S protein (Wu et al., 2021). Irrespective of sex, age, and body mass index, the symptom occurrence during the early SARS-CoV-2 infection phase was significantly positively correlated with stronger and more sustained anti-RBD IgG levels. The same difference was evident concerning the level of neutralizing antibodies. However, it is clear that despite such difference between asymptomatic and symptomatic forms of COVID-19, a considerable fraction of asymptomatic natural infections stimulate humoral immune responses conferring the ability to resist reinfections (Wu et al., 2021).

An important point to note is that higher titers of anti-S1 and anti-N IgG and IgM titers positively correlate with age (Jiang et al., 2020). This finding suggests that Ab titers are better maintained in athletes. Moreover, longitudinal studies have demonstrated that NAbs are more robust with severe clinical manifestations than after asymptomatic infections. Therefore, asymptomatic COVID-19 patients have a weaker immune response and faster and greater reduction of IgG titer (Long et al., 2020).

It has been shown that viral-specific RBD-IgG, Spike-IgG, and serum neutralization capacity declined quickly within 6 months (Feng et al., 2021; He et al., 2021; Figueiredo-Campos et al., 2020). However, a large study in relatively young subjects compared to the majority of other studies showed the persistence of S or N Ab levels and viral neutralization activity for up to 6 months after mild SARS-CoV-2 infection (Schuler et al., 2021). Fortunately, all three parameters remain stable after the first 6 months and for up to 1 year. It seems that viral-specific IgG could keep current levels for some time, and several longitudinal studies have shown that most patients have detectable SARS-CoV-2 Ab responses up to 13 months

after infection (Gallais et al., 2021; Yoo, 2021; Gaebler et al., 2021). S-IgG antibodies and, most importantly, NAbs persist in most subjects for at least a year following SARS-CoV-2 infection (Haveri et al., 2021). The NAb against the wild type strain of the virus persisted in 89% and S-IgG in 97% of subjects for at least 13 months after infection. The concentration of N-IgG, on the contrary, declined among a large proportion of subjects. Although there was no overall difference between genders, especially males with mild disease had markedly lower NAb titers for all viruses compared to individuals who recovered from severe disease (Haveri et al., 2021).

NAbs responses are likely the best available correlate of protection against re-infection. Sera from a cohort of 124 individuals with RT-PCR confirmed SARS-CoV-2 infections were tested for neutralization tests and S-RBD Ab (Lau et al., 2021). It was estimated that PRNT50 antibody (i.e. the reference method to measure the immune response to vaccination or to natural infection) remained detectable for around 1,717 days after symptom onset and that levels conferring 50% protection will be maintained for around 990 days post-symptom onset, in symptomatic patients. The data suggest that symptomatic COVID-19 disease with the -type virus is followed by relatively long-lived protection from re-infection by antigenically similar viruses.

2- Memory T-cell responses to SARS-CoV-2 infection.

If most studies suggest that NAbs levels begin to decline after roughly six to eight months, it has been suggested that memory B cells can produce antibodies in case of reinfection, and T cells can eliminate virus-infected cells (Phillips, 2021). While most studies focus on protective serum IgG analysis for its ready availability, a potent T cell immune protection will target viral containing cells, restrict viral spread in vivo, accelerate viral clearance, and alleviate disease burden. It has been shown that the T cell responses to N, S1, and S2 peptides, are kept stable until 12 months with only a slight initial decline indicating the possible existence of long-lasting memory T (Feng et al., 2021). These findings show that SARS-CoV-2 specific T cell response could be relatively stable for the long term.

Therefore, the decline of antibody levels does not negate the protective potential because of the importance of cellular responses against SARS-CoV-2 infection (Dan et al., 2021; Hartley et al., 2020; Rodda et al., 2021). The cellular immunity is not similarly affected by mutations in the RBD site and is likely to provide long-term protection against severe disease (Geers et al., 2021).

In conclusion, during and after viral infections with the wild type strain of the virus, the NAbs and Immunoglobulins titers are related to the severity of the disease and are better maintained in young people. After natural infection, the degree of subsequent protection will depend on the length of time after the initial exposure since immune responses wane with time The viral neutralization activity persists for up to 6 months and detectable Ab responses up to 13 months after mild infection with either the wild type virus or Alpha variant.

B- Immune responses after COVID-19 Vaccination

1- Humoral responses to SARS-CoV-2 vaccination.

The vaccines currently approved by WHO are either mRNA to specific SARS-CoV-2 antigens, viral-vector-based, or inactivated-virus-based vaccines. All these vaccines have shown seroconversion and efficient protection against SARS-CoV-2. One open question is the duration of the protective immunity after vaccination. Most attention has been concentrated on the level of specific antibodies, which increase in response to the vaccine, but decline after a few months. The reduction of specific antibody levels is perceived as incipient loss of protection. However, the most important protection from infection is represented by the

synergistic action of memory B cells (MBCs, which do not produce NAb) and memory plasma cells (which produce NAb).

Humoral responses to mRNA-based vaccines

A two-dose regimen of the Pfizer vaccine elicited robust immune protection against COVID-19 in persons aged >16 years (Polack et al., 2020). This vaccine elicits strong Ab responses; one week after the second dose, the geometric mean of the 50% neutralization titers of SARS-CoV-2 serum was up to 3.3-fold higher than that observed in samples from individuals who recovered from COVID-19. The dynamics of Ab response up to six months after the full vaccination with two doses of the Pfizer vaccine was examined in 122 individuals (Naaber et al., 2021). The results show strong S-RBD antibody responses one week after the second dose, with the capacity to block the ACE2-Spike protein interaction of the current variants of concern (VOCs) (Alpha, Beta, Gamma, Delta and Omicron). However, the antibody levels significantly decline at 3 and 6 months after the second dose. At 6 months after the second dose, the S-RBD Ab levels were comparable to those after the first dose of vaccine or the SARS-CoV-2 natural infection. Moreover, this study showed a negative correlation between antibody responses and the age of vaccinated individuals (Figure 2), supporting the notion that age is an important factor that influences vaccine responses. It was confirmed that few days after a Pfizer vaccine cycle, specific antibodies peak in the serum thanks to the activity of short- and long-lived plasma cells (Mortari et al., 2021). But the decay of short-lived plasma cells causes the reduction of serum antibodies.

The Moderna vaccine induces anti-SARS-CoV-2 immune responses after the first vaccination, and the neutralizing antibody titers induced by the two-dose schedule are similar to those found in convalescent serum specimens. The Moderna vaccine shows 94.1% efficacy in preventing COVID-19 disease (for review, see Altawalah, 2021).

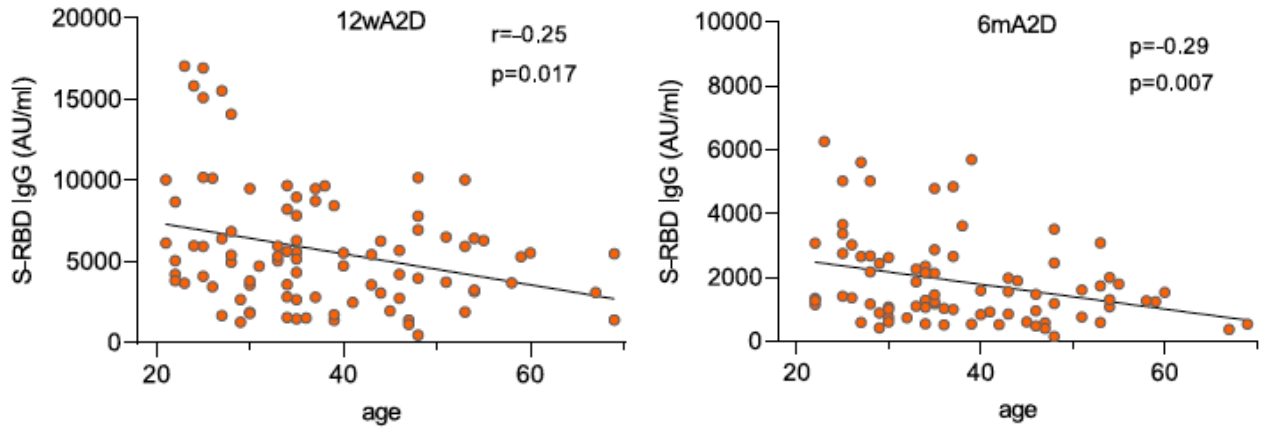


Figure 2. Post-vaccination Ab responses correlate negatively with age. Spearman correlation analysis between age and S-RBD IgG levels 12 weeks (12wA2D), and 6 months (6mA2D) after the second dose of the Pfizer vaccine (from Naaber et al., 2021).

It was recently shown that in individuals who had not previously been infected with SARS-CoV-2, a single dose of either the Pfizer or the AstraZeneca vaccine induced a detectable level of NAbs against the Delta variant. Despite the positive response to vaccines, their effectiveness was notably lower for the Delta variant than for the Alpha variant after one dose of the AstraZeneca or the Pfizer vaccine (Lopez-Bernal et al., 2021).

One interesting issue concerns the vaccination of individuals with prior COVID-19.

Recent studies have demonstrated that individuals with prior SARS-CoV-2 infection had increased levels of SARS-CoV-2 S-RBD and NAbs after vaccination, compared with individuals with no previous infection (Bradley et al., 2021; Saadat et al., 2021). Individuals with recent SARS-CoV-2 infection before vaccination have significantly higher specific Abs against Spike proteins S1, S2 and RBD at baseline and after primary immunization (at week 3) compared to individuals with no history of infection. After the second dose of the Pfizer vaccine both groups had a decreased antibody levels to the S1, S2 proteins and RBD, but levels remained significantly higher in those with a recent history of infection before vaccination compared to those without prior infection.

Moreover, when individuals are stratified into two age groups, individuals who were 18-49 years old have significantly higher blocking antibody titers at week 3 and week 28 compared to older individuals who were 50+ years old (Figure 3). A longer antibody half-life was shown in individuals with prior COVID-19 before vaccination compared with individuals with no infection history, and in individuals aged 18-49 compared with older individuals.

These findings are consistent with those obtained in a cohort study comprising 231 healthcare professionals who received the two-dose regimen of the Pfizer vaccine (Bayart et al., 2021). At day 180, a significant decline in NAbs and IgG against the N and S proteins of SARS-CoV-2 was observed in seronegative (i.e. individuals with no previous COVID-19 history) (-55.4% with total antibody assay; -89.6% with IgG assay) and seropositive individuals (-74.8% with total antibody assay; -79.4% with IgG assay). The estimated half-life of IgG from the peak humoral response was 21 days in seronegative and 53 days in seropositive individuals. The estimated half-life of total antibodies was longer and ranged from 68 days to 114 days in seronegative and seropositive individuals, respectively. The decline of NAbs was more pronounced (-98.6%) and around 45% of the subjects tested were negative at day 180. These results strongly suggest that vaccination of previously infected individuals is likely to be protective against a large array of circulating viral strains, including the Delta variant (Planas et al., 2021a).

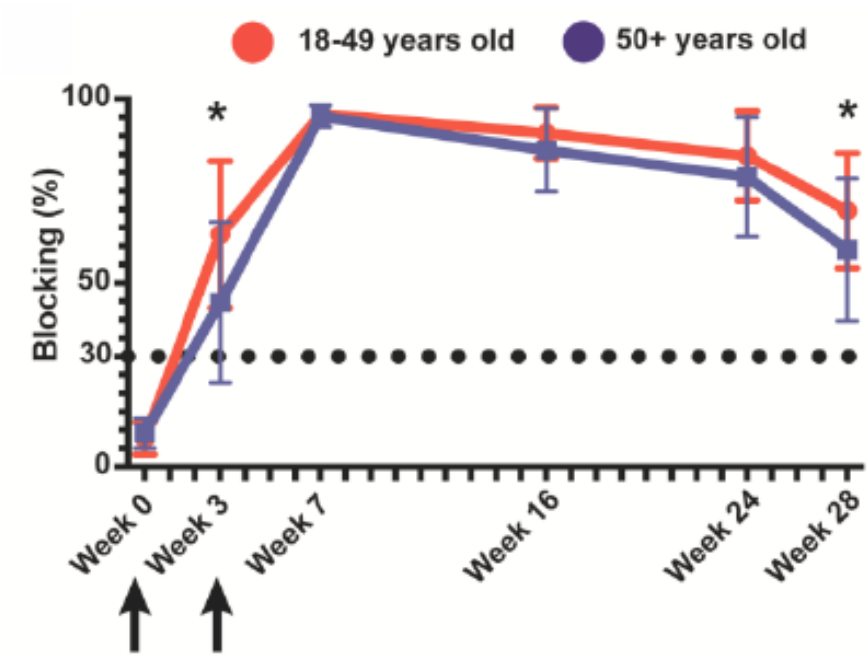


Figure 3. IgG Ab levels against SI, S2 subunits and RBD after SARS-CoV-2 mRNA vaccination. Immunization timing with COVID-19 mRNA vaccine indicated with arrows. Individuals with no history of infection prior to vaccination were stratified by age (18-49 years old, red line; 50+ years old, blue line) (from Fraley et al., 2021).

Taken together, these data show that the Ab titers in response to mRNA vaccines are higher in previously infected individuals compared to seronegative subjects and suggest that the duration of protective antibody immunity may be influenced by prior infection history.

Humoral Response to Adenovirus-Based Vaccines

Immunization with the AZ vaccine provokes the rapid production of Abs against SARS-CoV-2 S protein that peaked by day 28 and elicited the neutralizing antibody in all participants after a booster dose. An overall vaccine efficacy of 66.7% was previously reported (for review, see Altawalah, 2021).

A single dose of the Johnson & Johnson vaccine triggers also a strong humoral response in the majority of vaccine recipients, with the presence of S-binding and NAbs in more than 90% of participants, regardless of age group. Interestingly, binding and NAbs were detected by day 57 in 100% of vaccine recipients after a single immunization (for review, see Altawalah, 2021).

2- T-cell responses to SARS-CoV-2 vaccination.

Three months after 2 doses of the Pfizer vaccine, 87% of vaccinated individuals develop either CD4+ or CD8+ T cell responses, with similar prevalence in both T cell subsets (74% for CD4+ and 73% for CD8+), in agreement with phase I/II clinical trials with mRNA vaccines (Naaber et al., 2021). Induction of functional T cells occurs but with variable results in aged individuals, not in young people. This study suggests that two doses of Pfizer vaccine induce a strong antibody and T cell responses to the RBD region of the S protein.

In conclusion, the humoral responses to mRNA vaccines suggest an effective protection against the currently know VOCs, including the Delta variant. However, as after natural infection, the degree of immune protection with vaccination will depend on the length of time after vaccine injections since immune responses wane with time. The serum Ab levels decrease between 3 to 6 months, with a relative preservation in young people. Interestingly, vaccination of previously infected individuals is likely to be more protective against a large array of circulating viral strains, including the Delta variant, compared with individuals with no infection history. Full vaccination with Pfizer vaccine induces T-cell responses consistent with potent T-cell immune protection that targets virus-containing cells.

C- SARS-CoV-2 variants and vaccination efficacy

Over the last two years, the COVID-19 pandemic has produced successive waves of SARS-CoV-2 variants that outcompete earlier variants and demonstrate partial resistance to neutralizing antibodies (NAbs) induced by either natural infection or vaccination. The neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies could be affected by SARS-CoV-2 mutations, resulting in a mild-to-significant loss of vaccine efficacy. Moreover, these viral mutations might considerably affect the viral transmission, treatment effectiveness, and diagnostic procedures.

Variants of SARS-CoV-2 are emerging as an important key in determining whether COVID-19 vaccines could be sufficiently effective against COVID-19. To date, the WHO designated Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) as variants of concern (VOCs). Variants are classified as VOCs when they have a significant impact on transmissibility, severity and/or immunity. Since novel mutants mainly occur in the RBD domain, they could potentially escape the neutralization protection acquired either through natural infection or vaccination, although elicited T-cell responses can also contribute to protection from severe disease (Planas et al., 2021a; Hacisuleyman et al., 2021).

1- Alpha and Beta variants.

The possibilities that variants may reduce the vaccine effectiveness have been highlighted. It has been shown that neutralizing antibodies in convalescent plasma from individuals who have COVID-19 are less capable of recognizing the Alpha variant (identified in South Africa), than variants that circulated earlier during the pandemic (Xie et al., 2021; Cele et al., 2021a). The AZ vaccine showed reduced neutralization activity against the Alpha variant (B.1.1.7 variant) in comparison with a non-B.1.1.7 variant in vitro. However, from a clinical point of view, the vaccine has shown satisfactory efficacy against this variant (74.6%) (Emary et al., 2021).

Reduced NAb levels as compared to the wild-type virus have been shown against VOCs, especially against the Beta variant, after vaccination (Anichini et al., 2021; Jalkanen et al., 2021). A multicenter controlled trial showed that two doses of AZ vaccine did not confer adequate protection against mild-to-moderate COVID-19 due to Beta variant (Madhi et al., 2021). In comparison with the Pfizer vaccine, NAbs against all SARS-CoV-2 variants were reduced, with 2.4-fold decrease against Alpha and 2.5-fold decrease against Beta and Delta variants (Wall et al., 2021). Consistently, vaccination with the current vaccines showed a reduction in NAb levels against VOCs, compared with the wild-type virus, especially against the Beta variant (Planas et al., 2021a; Geers et al., 2021; Anichini et al., 2021; Jalkanen et al., 2021).

However, a more recent study showed that Alpha and Beta variants could partially escape humoral immunity induced by wild type SARS-CoV-2 infection or Pfizer vaccination, but not T-cell responses in COVID-19 convalescent donors and vaccinated individuals (Geers et al., 2021). Such results are important to reinforce the role of memory B cells and T cells in protecting against circulating SARS-CoV-2 variants (Wang et al., 2021). If the viral-specific T cells could not block virus entry into the cells, they still could kill the intracellular virus by directly destroying the virus-infected cells that present viral peptides.

The Beta variant that circulated in South Africa in late 2020 to mid-2021 is among the least neutralization-sensitive VOCs, but nonetheless remains susceptible to mRNA vaccines with only a modest reduction in efficacy, especially against serious illness and death (Abu-Raddad et al., 2021).

Taken together, the current studies show reduced NAb levels against the first variants declared as VOCs after vaccination, especially against the Beta variant, as compared to the wild-type virus.

2- the Delta variant.

In mid-June 2021, the Delta variant (B.1.671.2) became the predominant SARS-CoV-2 variant in most countries. Five studies estimated the basic reproductive number for the Delta variant, the dominant viral strain in December (Liu et al., 2021). The basic reproductive number (R_0) for the Delta variant ranges from 3.2 to 8, with a mean of 5.08, a much higher value than the R_0 of the ancestral strain (R_0=2.79). However, R_0 was estimated at a time when most countries still enforced lockdown measures, and there is a risk that the real reproductive number may be even higher than the estimated 5.08 (Liu et al., 2021).

A similar reduction in NAb titers has also been reported against the Delta variant from convalescent sera collected 3–12 months post symptoms or after vaccination (Edara et al., 2021). Public Health England has determined that two doses of either the Pfizer–BioNTech or the Oxford–AstraZeneca vaccines are 88% and 60% effective, respectively, at preventing symptomatic disease caused by the Delta variant (Lopez-Bernal et al., 2021). Individuals who were fully vaccinated with the Pfizer vaccine had 93% overall effectiveness against infection with the Delta variant 1 month after being fully vaccinated, but fell to 53% up to 5 months

after being fully vaccinated (Figure 4) (Tartof et al., 2021). In the same study, effectiveness against non-Delta variants was 97% and 67% within 1 month and 5 months after being fully vaccinated, respectively. One interesting finding of this study was that effectiveness against COVID-19-related hospital admissions was 90% after a mean time since being fully vaccinated of 3·4 months (Tartof et al., 2021). Although the efficacy of mRNA vaccine against infection is lower for the Delta variant compared to other SARS-CoV-2 variants, the efficacy against hospitalization remains very high during the six months at the level of 93%. In another study, the two-dose effectiveness against the Delta variant was estimated to be 60% and 88% for the AstraZeneca and the Pfizer vaccine, respectively (Lopez-Bernal et al., 2021).

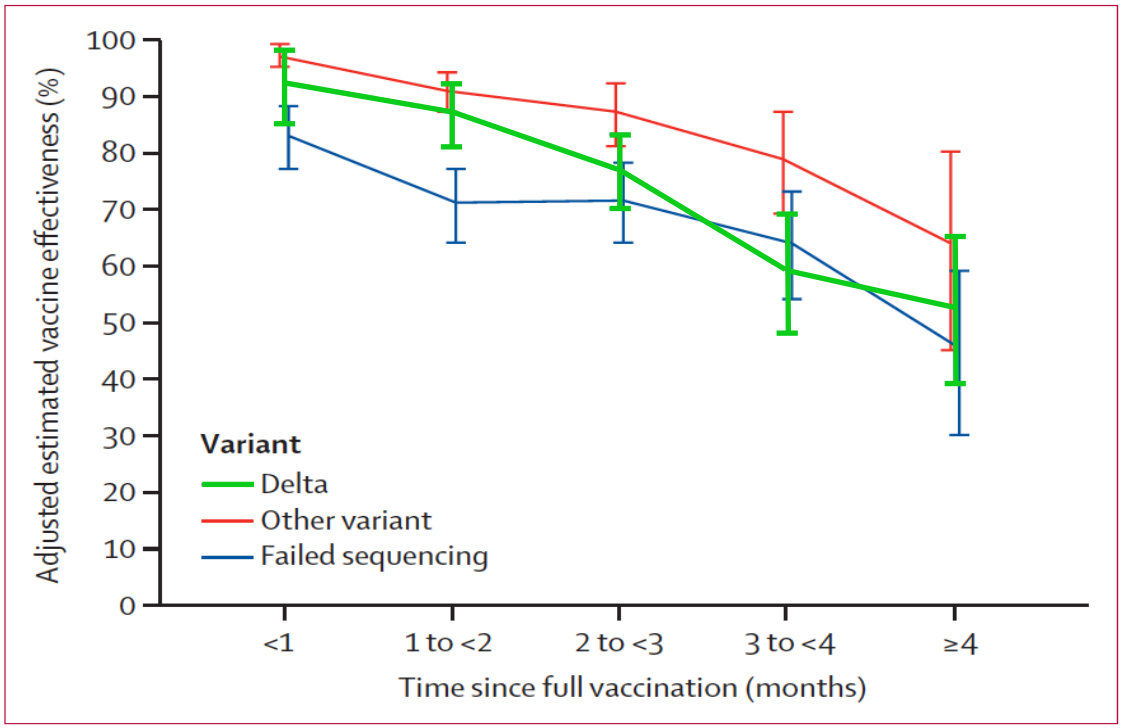


Figure 4. Adjusted estimated Pfizer vaccine effectiveness against SARS-CoV-2 infection by variant. (from Tartof et al., 2021).

The vaccine effectiveness was recently examined against the now predominant Delta variant of SARS-CoV-2 (Lopez-Bernal et al., 2021). It was found that the effectiveness after one dose of either Pfizer or AZ vaccine was notably lower among persons with the Delta variant (30.7%) than among those with the Alpha variant (48.7%), and similar results for both vaccines. However, after 2 doses of either vaccine there were only modest differences in vaccine effectiveness with the Delta variant.

A large-scale study aimed at examining the risk of COVID-19 after full vaccination was recently published (Israel et al., 2021). The cohort was based on 83,057 individuals aged at least 18 years who received repeated RT-PCR tests, at least 3 weeks after the second Pfizer vaccine injection (and with no evidence of previous COVID-19 infection). Compared with the initial 90 days after the second vaccine dose, the rate of positive PCR tests increased with time in all age groups. Adjusted odds ratio for infection are significantly increased compared with the reference of the first three months after vaccination in the age-group 18-39 years: 2.04 for 90-119 days after the second vaccine dose, 4.48 for 120-149 days, 11.11 for 150-179 days, and 16.83 for ≥180 days (Figure 5). Throughout this study, most of the new infections were caused by the Delta variant.

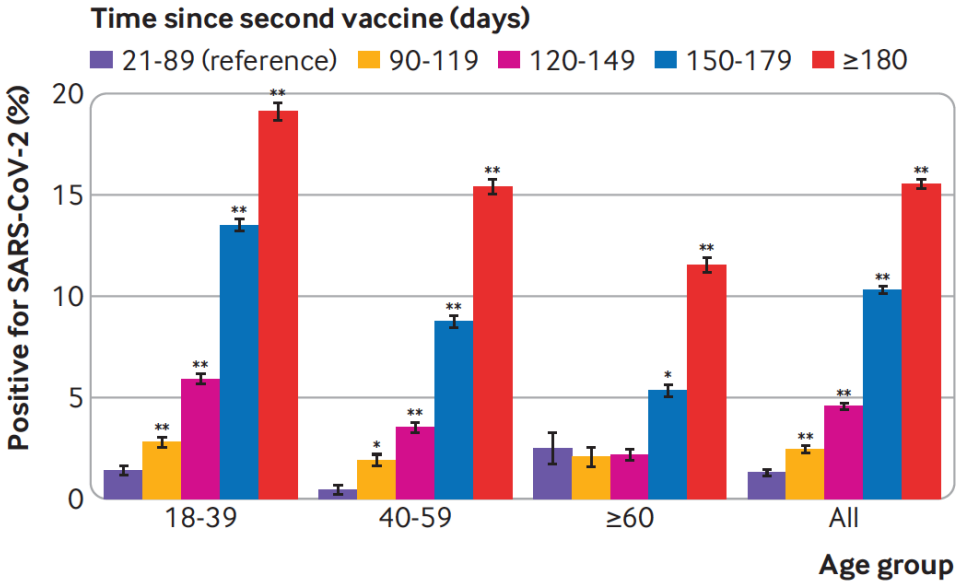


Figure 5. Comparison of percentage of positive RT-PCR tests, according to time elapsed since the second vaccine dose. * P<0.01, ** P<0.001. (from Israel et al., 2021).

These results are predictive of the immune protection in vaccinated individuals against infection and clinical consequences. Findings confirm that the Pfizer vaccine provided excellent protection in the initial weeks after vaccination, but suggest that protection against infection wanes for some individuals with time.

Together, these studies suggest that the Delta VOC is a modest neutralization-escape variant, being 2-3 fold less susceptible than the Alpha variant to neutralization by the Moderna vaccine-induced antibodies and having little impact on Moderna vaccine efficacy (Bruxvoort et al., 2021). Two doses of Moderna vaccine were highly effective against infection with all SARS-CoV-2 variants, especially against hospital admission. The estimated vaccine effectiveness against symptomatic disease with the Delta variant was approximately 88% with two doses of the Pfizer vaccine and approximately 67% with two doses of the AZ vaccine. However, vaccine effectiveness against infection with the Delta variant moderately declined with increasing time since vaccination.

3- the Omicron variant.

The recent emergence of the Omicron VOC, the most recent SARS-CoV-2 variant (B.1.1.529), has been postulated to be a serious threat which can worsen the prevailing situation.

Omicron has been first detected in Botswana (South Africa) on 24 November 2021, and has now been found in dozens of countries around the world (Garcia-Beltran et al., 2022). The US Centers for Disease Control and Prevention has highlighted 32 amino acid substitutions, three deletions, and one insertion in both the RBD domain of the S1 and S2 subunits of the S protein (Figure 6). Only 16 mutations in the S protein were identified in the highly infectious Delta variant.

At the time of writing this report, we have only few information concerning this new variant. However, Omicron variant has spread very quickly in South Africa, in a population where 60-80% already show serological evidence of previous infection or vaccination, suggesting that this variant is able to break through natural and vaccine-induced immunity. It is believed that the Omicron variant could be three times more infectious than the original SARS-CoV-2 strain (Gao et al., 2021). Some deletions and mutations are well known for

increasing viral transmissibility and RBD affinity. The combination of several mutations might also enhance the virus's ability to bind to the host receptor Angiotensin-converting enzyme 2 (ACE2) (Dhawan et al., 2022). There is concern that Omicron will lead to increased infection of individuals who have received vaccines (whose antigens are based on the original S sequence).

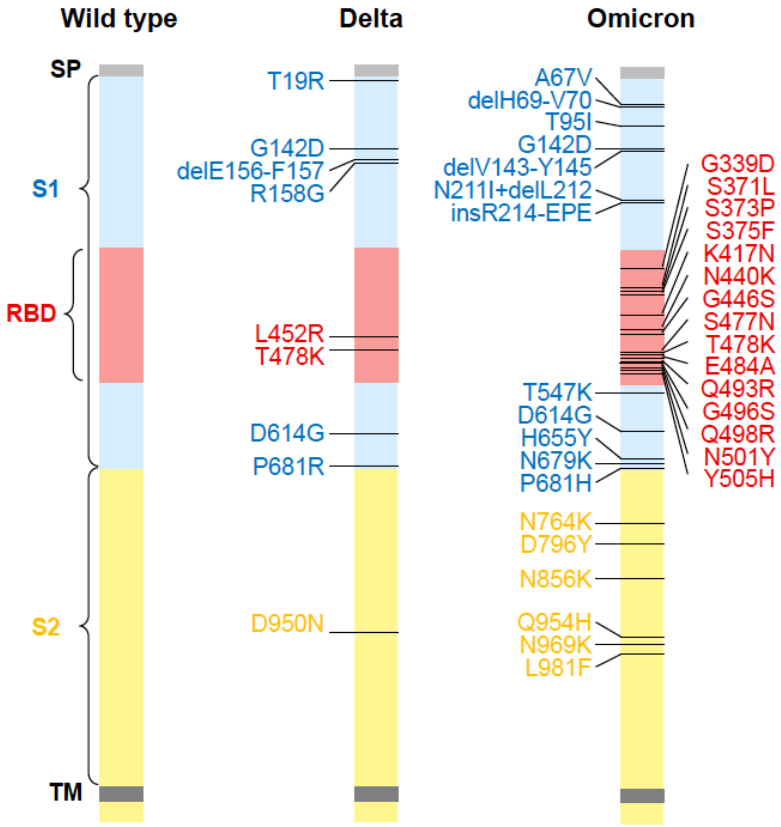


Figure 6. Schematic of SARS-CoV-2 spike protein structure and mutations of recent VOCs. The regions within the spike protein are abbreviated as follows: SP, signal peptide; RBD, receptor binding domain; S1 and S2, S protein subunits; TM, transmembrane domain. (from Garcia-Beltran et al., 2022)

Human antibodies produced by the immune system targets mainly the S protein, and Omicron is now viewed as a "worrying type" of coronavirus due to the heavy mutation in the S protein. Omicron may have the ability to impair the effectiveness of vaccines as the number of mutations on the S protein of this variant theoretically suggests that the efficacy of antibodies produced by vaccinations will be diminished. Whether the Pfizer vaccine, which was previously shown to have 95% efficacy against the SARS-CoV-2 wild type will effectively neutralize infection with the Omicron VOC variant is unclear.

The efficacy of the Pfizer vaccine against the Omicron variant was first tested versus virus with the ancestral D614G mutation using 14 plasma samples from 12 participants (Cele et al., 2021b). A 41-fold decline in NAb against Omicron was reported. However, the immune escape was incomplete, with previously infected participants showing higher neutralization titers with Omicron. One interesting finding of this study is that previous infection followed by vaccination or booster is likely to increase the neutralization level and likely confer improved protection against Omicron infection (Cele et al., 2021b). A substantial decrease in neutralization titer was reported in recipients of homologous AZ or Pfizer vaccines, with evidence of some recipients not neutralizing at all. This reduction in neutralization titer was

observed 28 days after the second immunization, and will probably be more pronounced at later time points. Then, Omicron is more likely than previous variants to reinfect people who have previously had COVID-19; 9.5% of people infected had a personal history of past infection (Mahase, 2021c).

The NAb titers to Omicron are 41-84 times lower than NAb titers to virus with the D614G mutation after 2 doses of the Moderna vaccine (Figure 7) (Doria-Rose et al., 2022). However, a third dose of Moderna vaccine induces an approximate 12-fold improvement in Omicron neutralization such that the variant was now only 6.5- and 3.4-fold less neutralization-susceptible, respectively. Thus, the third-dose provided improvement in neutralization of both the Omicron and Beta variants and may substantially reduce the risk of symptomatic breakthrough infections (Doria-Rose et al., 2022).

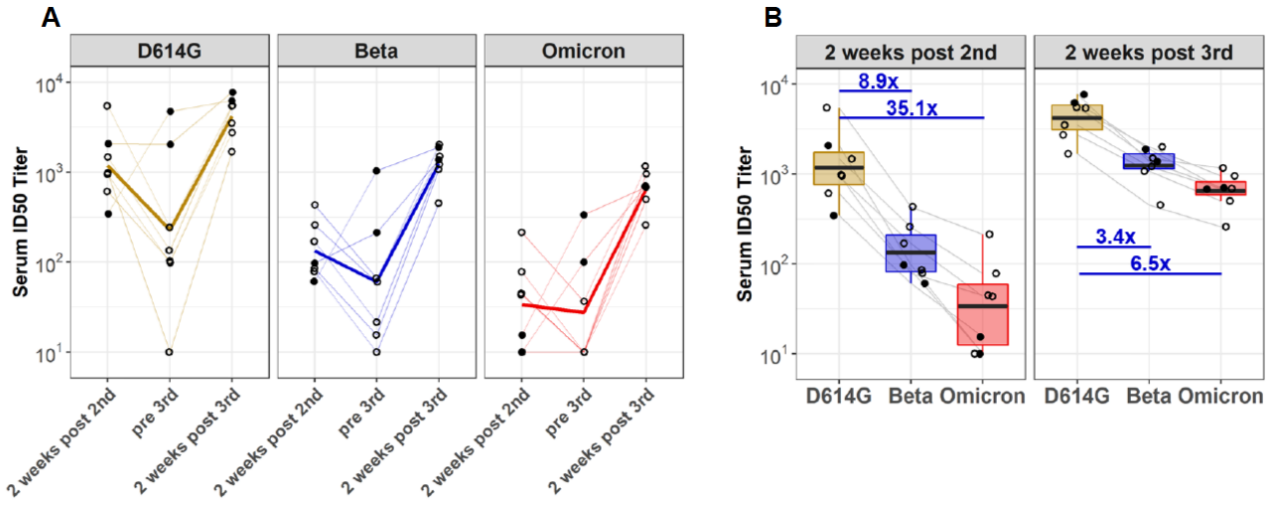


Figure 7. Longitudinal assessment of waning and recall neutralizing antibody responses in recipients of three doses of the Moderna vaccine. **A.** ID50 neutralization titers of serum samples from recipients of three doses of the Moderna vaccine assayed against D614G, Beta and Omicron. **B.** ID50 titers for the two peak immune time points. Horizontal blue lines express the geometric mean fold reduction in ID50 compared to D614G. Solid circles, two participants who were infected 5-6 months after second dose. Open circles, uninfected participants. (from Doria-Rose et al., 2022)

Neutralization assays with wild-type, Beta, Delta, and Omicron variant isolates were performed with the use of serum samples obtained from two groups of 20 health care workers, one who had received two doses of the Pfizer vaccine (mean, 165.6 days since receipt of the second dose), and the other one who had received three vaccine doses (mean, 25 days since receipt of the third dose) (Nemet et al., 2021). The importance of a third vaccine dose was confirmed in this study, with a 100-fold higher neutralization efficiency against the Omicron VOC after the third dose than after the second dose (Figure 8). However, even with three vaccine doses, neutralization against Omicron remained lower (by a factor of 4) than that against the Delta VOC.

The neutralization potency of sera from Moderna, Pfizer, and J&J vaccine recipients against wild type, Delta, and Omicron VOCs was recently measured (Garcia-Beltran et al., 2022). Individuals received a third dose of mRNA vaccine more than 6 months after primary vaccination series. All three primary vaccine series resulted in low-to-absent neutralization of Omicron (Figure 9). However, the third dose of mRNA vaccine recipients exhibited potent neutralization against Omicron, despite exhibiting wild type neutralization titers similar to

those in recently vaccinated (non-boosted) individuals. Taken together, these results highlight that Omicron VOC evades vaccine-induced neutralizing immunity under current vaccine regimens. Notwithstanding, our finding of potent cross-neutralizing immunity against Omicron in boosted individuals suggests that existing mRNA vaccines may overcome evasion of humoral immunity by VOCs.

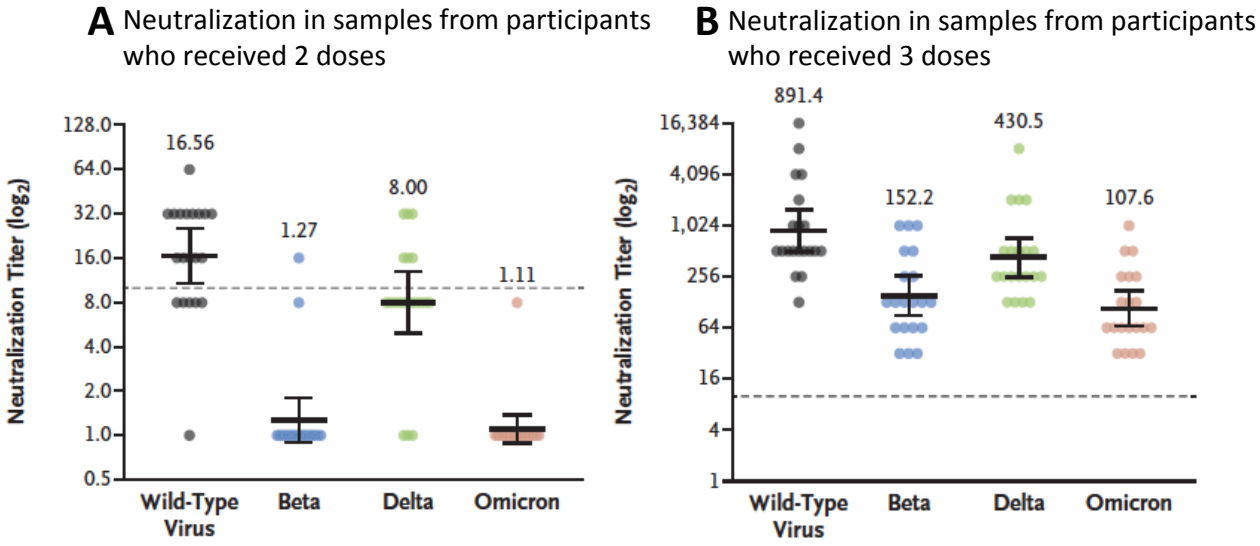
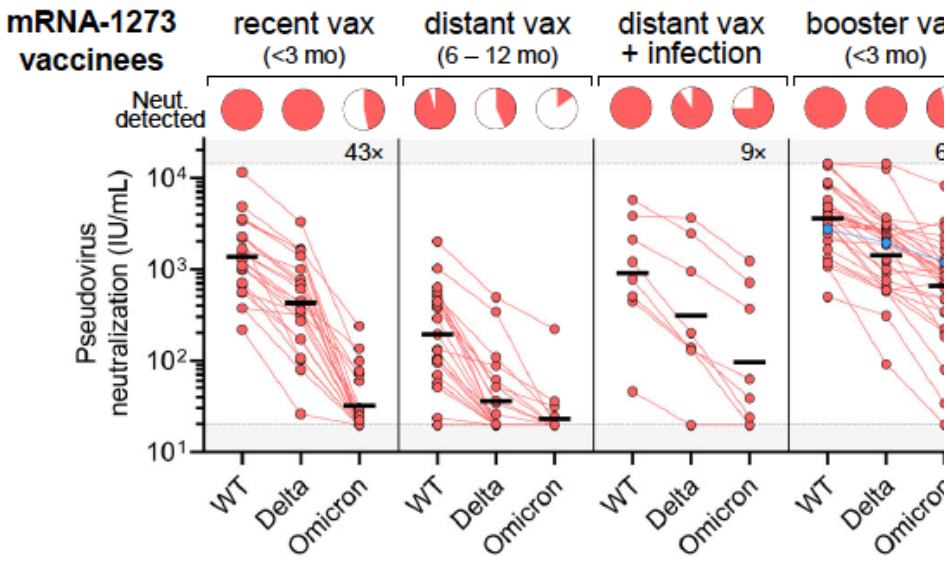


Figure 8. Neutralization efficiency against Wild-Type Virus and the Beta, Delta, and Omicron VOCs. Serum samples were obtained from 20 health care workers who had received 2 doses of the Pfizer vaccine (A) and from 20 who had received 3 doses (Panel B). Dashed lines in Panels A and B indicate the cutoff titer. (from Nemet et al., 2021)

Preliminary data from UK have shown similar results, with reduced effectiveness against symptomatic infection after two doses of AZ or Pfizer vaccines, suggesting a result of increased breakthrough infections in previously infected or double vaccinated individuals, which could drive a further wave of infection (UK Health Security Agency).



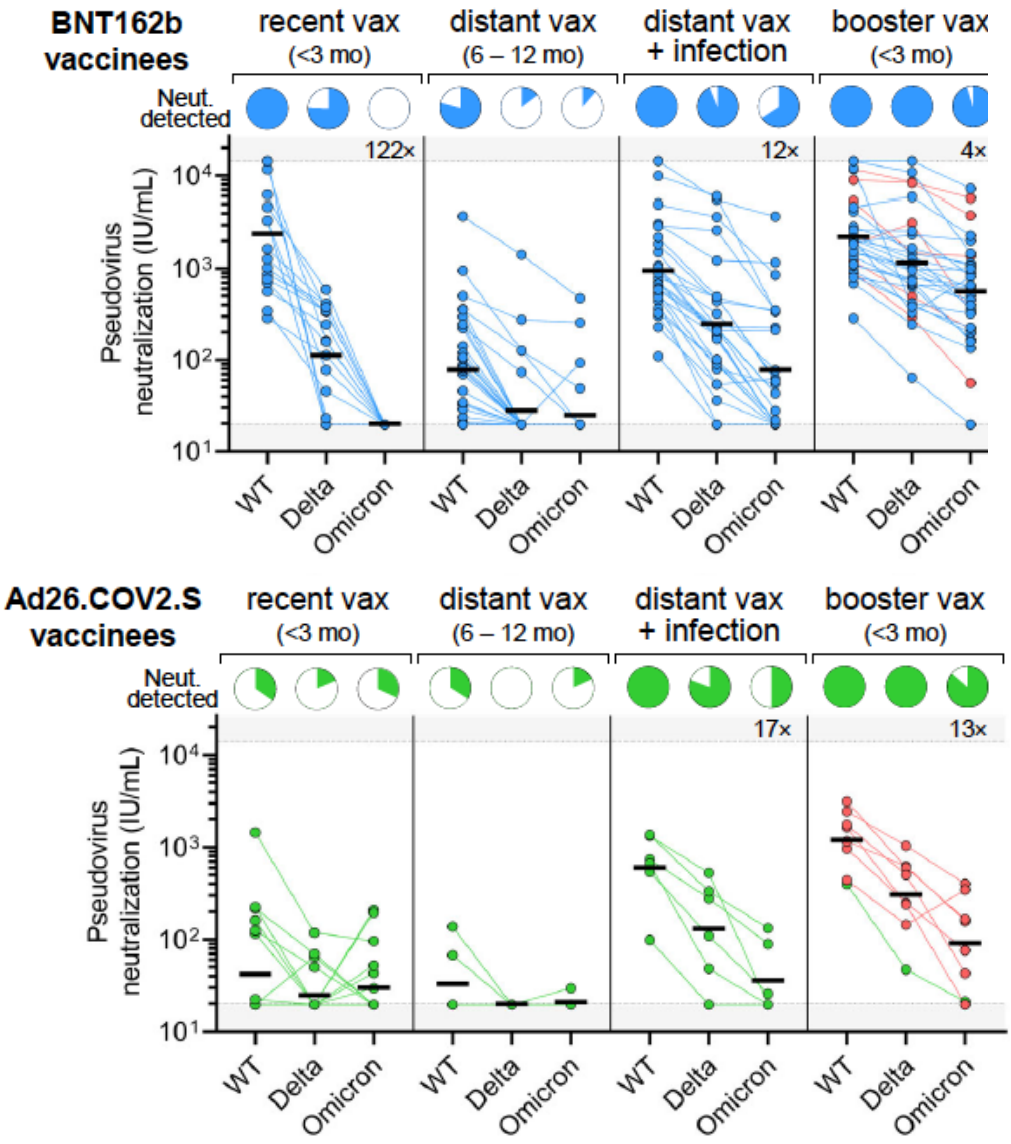


Figure 9. Neutralization titers of wild type (WT), Delta, and Omicron pseudoviruses, determined for people who received primary vaccination series with Moderna (mRNA-1273, top panel; in red), Pfizer (BNT162b2, middle panel; in blue), or J&J vaccines (d26.COV2.S, bottom panel; in green). Dark horizontal lines for each group denote geometric mean titer. Pie charts show the proportion of vaccinees within each group that had detectable neutralization against the SARS-CoV-2 pseudovirus. Fold-decrease in geometric mean neutralization titer of Omicron relative to wild type within a subgroup is shown as a number with '×' symbol within the gray region. Within 'booster vax' subgroups (far right), boosters were homologous (same vaccine) except for 1 of 33 Moderna vaccinees that crossed-over to Pfizer (top panel; in blue), 6 of 30 Pfizer vaccinees that crossed-over to Moderna (middle panel; in red), and 7 of 8 J&J vaccinees crossed-over to Moderna (bottom panel; in red).
(from Garcia-Beltran et al., 2022)

In conclusion, the current scientific knowledge demonstrates that Omicron drastically escapes vaccine-induced immunity after primary vaccination series with Moderna, Pfizer, AZ or J&J vaccines and exhibits increased infectivity, raising the potential for increased transmissibility (Garcia-Beltran et al., 2022; Doria-Rose et al., 2022). Despite escape from humoral immunity, Omicron breakthrough infections may result in attenuated disease

severity in vaccinees due likely to cellular and innate immunity. However, neutralization remains the leading correlate of protection from infection. The available clinical studies clearly demonstrate that receiving a third dose of an mRNA-based vaccine effectively yields a potent cross-neutralizing response against Omicron. These findings support the need for rapid vaccination of team members (riders and staff) with a third dose of mRNA-based vaccine to curtail the emergence and spread of Omicron within the peloton.

On the other hand, the current data on new emergent VOCs highlight the challenges facing all vaccines whose designs were finalized early in the pandemic and based on the sequence of the first-reported virus from Wuhan (i.e. wild-type SARS-CoV-2) (Garcia-Beltran et al., 2021).

D- immunization after infection with SARS-CoV-2 variants

SARS-CoV-2 is constantly mutating yet most changes have little or no impact on its virulence (Lauring and Hodcroft, 2021). However, some amino-acid substitutions are causing concerns regarding viral transmissibility, and potential escape from natural and vaccine-induced immunity. Reduced NAb levels as compared to the wild-type strain of the virus have been shown against the Beta variant 9 and 12 months after infection (Planas et al., 2021a). A similar reduction in NAb titers has also been reported against the Delta variant from convalescent sera collected 3–12 months post symptoms (Edara et al., 2021). The humoral protection mediated by NAbs may be impaired against the three main VOC strains Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2), especially when the Ab responses followed a mild disease (Haveri et al., 2021).

Sera collected from convalescent individuals up to 12 months after the onset of Covid-19 symptoms were fourfold less potent against the Delta variant relative to the Alpha variant (Planas et al., 2021b). The now dominant Delta variant partially—but notably—escapes neutralizing monoclonal antibodies and polyclonal antibodies elicited by previous infection with SARS-CoV-2.

In conclusion, the immune protection by NAbs against the three main VOCs may be impaired, especially after mild disease. The Delta variant only partially escapes NAbs induced by previous infection. Fortunately, it seems that the cell immunity could be relatively stable for the long term, ensuring long-term protection against COVID-19.

4) Effects of COVID-19 vaccination on SARS-CoV-2 transmission

Controlled clinical trials and clinical studies have provided clear evidence of the effectiveness of authorized COVID-19 vaccines in preventing symptomatic COVID-19, especially the severe forms of the disease. However, the impact of COVID-19 vaccines on asymptomatic SARS-CoV-2 infection and transmission risk are less known. The effects of COVID-19 vaccines on transmission are a composite of their effect on becoming infected (because someone not infected cannot transmit) and their effect on the infectiousness of those who get infected despite vaccination (Lipsitch and Kahn, 2021). These components have been called the vaccine efficacy for *susceptibility to infection*, and vaccine efficacy for *infectiousness*.

A- Risk of asymptomatic forms of COVID-19 in vaccinated individuals *(vaccine efficacy for susceptibility to infection)*

The Pfizer vaccine is effective at preventing SARS-CoV-2 infection, including asymptomatic forms of the disease, even after one single dose of vaccine (Chodick et al., 2021). During the clinical trial to approve the Moderna vaccine, SARS-CoV-2 PCR was performed in asymptomatic individuals 28 days from the first dose, just prior to the second dose (Baden et al., 2021); a 62% reduction in the risk of asymptomatic infection in the vaccine group was reported, compared to the placebo group.

Compared to unvaccinated patients, the risk of asymptomatic SARS-CoV-2 infection was decreased by 79% among those >10 days after 1st dose of a mRNA vaccine, either Pfizer or Moderna vaccines ($p<0.0001$), and after adjustment for potential confounding factors (Tande et al., 2021). After similar adjustment, the authors observed an 80% reduction in the risk of a positive PCR test among test performed in persons who had received 2 doses of a mRNA vaccine, compared to those who were not vaccinated. Results announced by Johnson & Johnson from clinical trials suggest that its vaccine is 74% effective against asymptomatic infections. Among individuals who received two doses of the AZ vaccine 12 or more weeks apart, there was a 47% reduction in asymptomatic infection when measured ≥14 days after the second dose (Voysey et al., 2021).

In summary, taken together all these results clearly suggest that current vaccines, especially mRNA vaccines, reduce the transmission of SARS-CoV-2 and its known variants, including the Delta variant. Current vaccines validated in most countries are effective against asymptomatic infections.

B- Potential viral transmission by vaccinated individuals *(vaccine efficacy for infectiousness)*

It has been shown that vaccination with the Pfizer vaccine reduces the amount of virus found in infected individuals by up to 4.5-fold (Levine-Tiefenbrun et al., 2021). The Ct distribution of positive PCR tests from days 12–37 after vaccination was significantly increased in comparison with that of matched unvaccinated control group. These results suggest that breakthrough infections (i.e. a SARS-CoV-2 infection occurring after full vaccination, at least 14 days after the second dose of mRNA vaccines) have significantly reduced viral loads at the time of testing, potentially affecting viral shedding and contagiousness as well as the severity of the disease. However, this study did not take into account the predominant type of SARS-CoV-2 variant during the period.

A strong negative association was shown between the vaccination rate at the community level and the risk of infection for unvaccinated members (Milman et al., 2021). Therefore, high vaccination rates are associated with lower infection rates at later time points among the unvaccinated cohort. Consistent with this finding, a study by Public Health England has found that even a single dose of either the Pfizer or AZ vaccine reduced the spread of SARS-CoV-2 from infected individuals to household members by up to 50% (Mahase, 2021a).

However, the spread of viral variants could complicate the picture still more. If vaccines are less able to decrease the viral load in individuals infected with a variant, they might also be less able to block transmission. Although the vaccine effectiveness against symptomatic forms was largely sustained against the known VOCs, preliminary evidence suggested that the efficacy against asymptomatic infection is reduced in the face of these variants. Vaccination confers protection against transmission of SARS-CoV-2 from vaccinated individuals, albeit somewhat less for the Delta than for the Alpha variant (De Gier et al., 2021). Effectiveness of full vaccination of the COVID-19 cases against transmission to unvaccinated

and to fully vaccinated household contacts, was estimated as 40% and 63%, respectively. As expected, the vaccine effectiveness against transmission to unvaccinated contacts is lower than to vaccinated contacts, with the latter already largely protected from infection, and especially from severe disease by their own vaccine-induced immunity.

In summary, current studies show that vaccination confers protection against transmission of SARS-CoV-2 from vaccinated individuals to unvaccinated and to fully vaccinated household contacts, albeit somewhat less for the Delta than for the Alpha variant. High vaccination rates are associated with lower infection rates among the unvaccinated cohort.

C- Vaccination and protection for those who are not vaccinated

Whether vaccination reduces transmission at the population level, thereby conferring protection for those who are not vaccinated is an important issue to address (Kadkhova, 2021; Fontanet and Cauchemez, 2020).

It is believed that a higher viral density of SARS-CoV-2 in the upper respiratory tract of people infected with the virus increases viral transmission. If vaccines reduce viral density in those who are infected despite vaccination, this would likely lead to lower infectivity and less transmission. During breakthrough Delta variant infections in vaccinated people, peak viral loads showed a faster decline in vaccinated compared with unvaccinated people, although peak viral load values were similar for unvaccinated and vaccinated people (Wilder-Smith et al., 2021).

Another recent study confirmed that COVID-19 vaccination reduces the risk of Delta variant infection and also accelerates viral clearance in the context of the predominance of this VOC (Singanayagam et al., 2021). However, this study also highlighted that the vaccine effect on reducing transmission to household contacts is markedly decreased in the context of Delta variant circulation, in comparison with Alpha variant circulation. Fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection to household contacts, including to fully vaccinated individuals. However, one interesting finding of this study is that the rate of viral load decline was faster for vaccinated individuals with Delta breakthrough infection than in unvaccinated cases with Alpha or Delta variants (Singanayagam et al., 2021). Even if this finding is less positive than for the Alpha variant, it is clearly in the direction of a reduction of the risk of spread of the Delta virus by the vaccinated individuals.

High vaccination rates are associated with lower infection rates at later time points among the unvaccinated cohorts. Then, higher vaccination coverage rates need to be achieved because indirect protection from vaccinated to unvaccinated people remains suboptimal, especially with the circulation of the Delta variant.

In conclusion, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases, but rate of viral load declines is faster for vaccinated individuals with Delta breakthrough infection than in unvaccinated cases with Alpha or Delta variants.

5- Rational for a third dose of vaccine

Initial reports have indicated that a third (booster) dose was effective in reducing the rates of confirmed infection and severe disease against the dominant Delta variant in the elderly population. Moreover, current evidence indicates that although two doses of vaccine

are less effective against the Omicron variant than against the previously dominant Delta variant, a third dose improves the immunization.

A- Against the Delta variant

Currently, the long-lasting effect of mRNA vaccines to protect against reinfections or severe COVID-19 disease remains unclear, but might not only depend on Ab responses but also on T cell immunity. The "physiological" drop of serum titers of anti-S1, anti-N IgG and IgM titers as well as NAbs is seen as a sign of vaccine failure and loss of protection. In response to this anxiety, the necessity of a third vaccine dose has been suggested. Although three months after the first dose serum-specific Ab and NAbs levels decline, it was clearly shown that MBCs generated in response to vaccination continue to improve their specificity and increase in numbers (Figure 10) (Mortari et al., 2021).

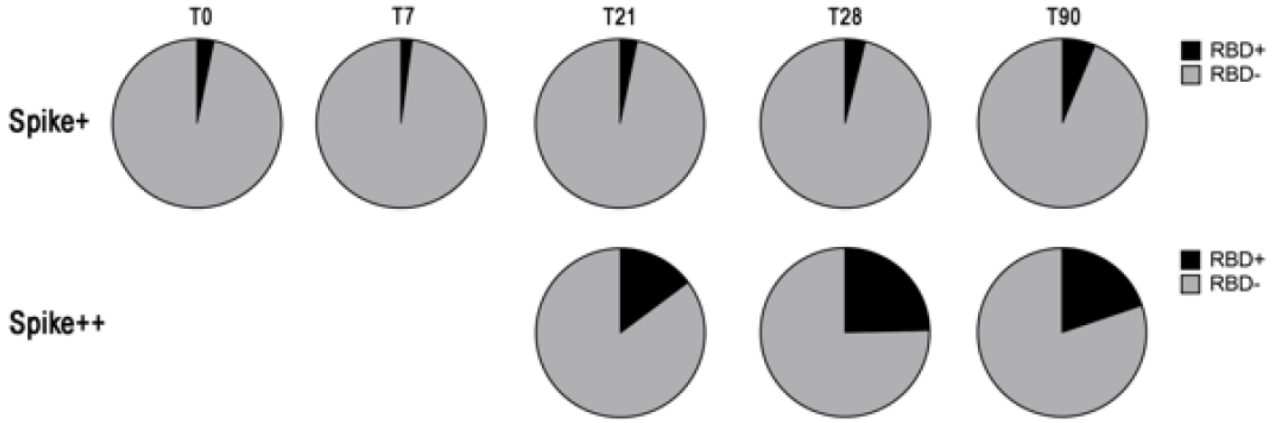


Figure 10. Spike-specific memory B cells. Pie charts show the average percentages of RBD+ and RBD- among MBCs specific for the recombinant spike protein over time (T0, T7, T21, T28 and T90 days). MBCs with low (S+) or high affinity (S++) for recombinant spike were identified. (from Mortari et al., 2021).

Using kinetics models, the drop of IgG below the positivity threshold was estimated to be reached after 229 days for seronegative and after 529 days for seropositive individuals (Bayart et al., 2021). Regarding total antibodies, these times range from 470 to 830 days in seronegative and from 507 to 718 days in seropositive subjects. Taken together, these data could already support the notion that a third vaccine dose would be likely needed 12 months following the first shot.

The aim of a third vaccine dose ("booster dose") is to keep an effective humoral response to protect vaccinated subjects against the wild-type SARS-CoV-2, but, more importantly, against the VOCs. Some VOCs have demonstrated an immune escape and these suggested models may even be optimistic since higher NAb titers may be needed to provide a similar degree of protection than the one reported during the state III development of these vaccines (Rubin, 2021).

Despite the call of the WHO and several authors ((WHO, 2021) to temporarily halt the administration of COVID vaccine boosters, some countries have already decided to administer such booster doses. In Israel and France, a third dose of the mRNA vaccine is given to people over 50 or 65 and to other vulnerable persons, and now to all people over 18. Indeed, at the time of the editorial published in Nature (WHO, 2021), 58% of people in high-income countries had received at least one vaccine dose compared to 1.3% in low-income countries.

What is important to keep in mind, is that the robustness of vaccine-induced protection does not depend only on the amount of serum antibodies but mostly on the persistence of MBCs able to migrate to the site of infection, locally produce antibodies and remodel in response to viral variants. Additional studies remain necessary to investigate the duration and resilience of the immune memory, both B- and T-cell memory, induced by the available vaccines, and according to the new VOCs.

As reported above, a drop in Ab levels slowly over time after vaccination is expected. However, there is insufficient data to suggest that this drop correlates with a decline in protection against the COVID-19 virus, including the Delta VOC. As a result, the correlate of protection and a protective threshold of the Ab levels for the COVID-19 vaccine is currently unknown (Shekhar et al., 2021). Due to the lack of reliable correlate between protection and Ab threshold, it is difficult to draw conclusions about the need for a third dose of vaccine in the general population, and especially in athletes in whom the Ab decline will be less than in the adult or elderly population.

Third doses of the vaccines administered more than six months after vaccination can potentially boost the neutralizing antibody titers, including targets against the Delta variant (Figure 11) (Mohamed et al., 2021)-. In a case-control study involving 306710 adults 40 years and older, analyses showed that a third dose of the Pfizer vaccine was associated with a lower odds of SARS-CoV-2 infection and hospitalization, the Delta variant being the dominant strain in the country at the time of study (Odds is a measure of the likelihood of SARS-CoV-2 infection and hospitalization) (Patalon et al., 2021). Compared to those who had not received the booster dose, there was a 86% reduction in the odds of testing positive for SARS-CoV-2 Delta variant in individuals who received the third doses. These results are consistent with another report, and indicate that the booster dose is effective in reducing the rates of confirmed infection and severe disease due to the Delta variant in elderly people (Bar-on et al., 2021a).

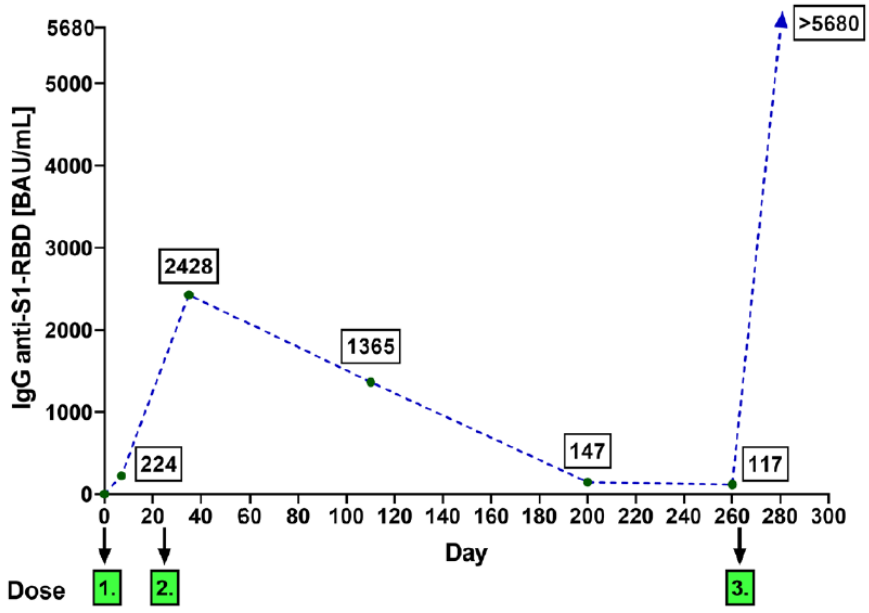


Figure 11. An example of dynamics of serum neutralizing IgG anti-S1-RBD Ab levels induced by administration of Pfizer vaccine. Note the decreasing levels over the course of 8 months after a second dose and a significant rise after a third (booster) dose.
(from Mohamed et al., 2021).

The protection level of the booster dose was recently examined in younger age groups (Bar-On et al., 2021b). The mean rate of confirmed infection with the Delta variant was lower in the booster group than in the non-booster group by a factor 17.2 among those 16 to 29 years of age, and 9 among those 30 to 39 years of age (Figure 12).

Information from clinical trials suggests that vaccine-related side effects of the third dose were similar to those observed after the first and second doses of vaccines (Shekhar et al., 2021). The safety profile and potential additional protection of a third dose must be weighed against the global scarcity of the vaccine to identify the most vulnerable populations who may benefit from a third dose.

According to several international agencies, the third dose was recommended for adults aged 65 and up, those who live in long-term care facilities, have underlying medical issues, or work or live in high-risk environments. For example, individuals at an increased risk for COVID-19 exposure and transmission because of occupational settings are eligible for a third dose of the COVID-19 vaccine (CDC, 2021).

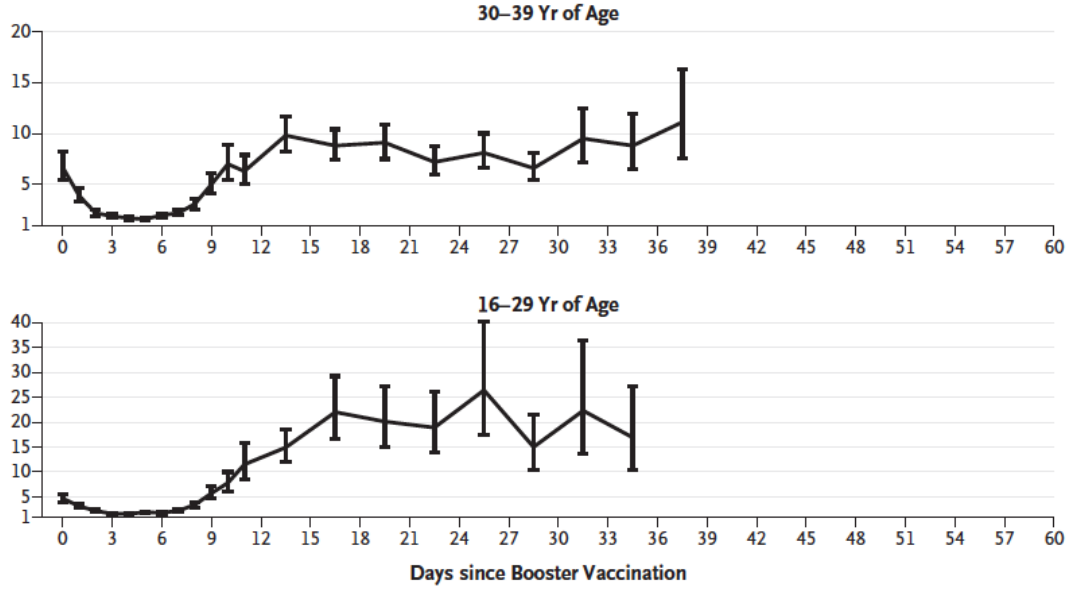


Figure 12. Reduction in rate of confirmed infection in the booster group as compared with the nonbooster group. Shown is the factor reduction in the rate of confirmed infection among participants who received a third (booster) dose of the Pfizer vaccine as compared with those who did not receive a booster dose. (from Bar-On et al., 2021b).

B- Against the Omicron variant

Following the Omicron emergence, significant adjustments have been made in national immunization programs, including the recommendation for a third dose of vaccine in large populations to avoid any potential repercussions. The main objective is to prevent high COVID-19 hospitalization rates. The hypothesis is that possessing a high starting neutralization titer against early viral strains gives a higher level of Omicron neutralization, which could be obtained by deploying third doses of vaccine.

As reported in paragraph #3-C-*3*, although Omicron escapes vaccine-induced immunity after primary vaccination series, there is some reassurance that a third dose of a COVID-19

vaccine does indeed increase vaccine effectiveness against this VOC. Evidence indicates that although two doses of vaccine are less effective against Omicron than against the previously dominant Delta variant, a third dose improves the immunization. But this extra protection may wane more rapidly against omicron than delta, being about 15-25% lower from 10 weeks after the third dose (Mahase et al., 2021b).

However, it is necessary to keep in mind that providing immunizations to those who have not had a single dose is more vital than the implementation of third dose protocols. This unvaccinated mass includes the vast majority of people in Africa, whose vaccination rates are far lower than in other regions of the world, thus favoring the emergence of variants (Dhawan et al., 2022).

In conclusion, third or subsequent doses of COVID-19 vaccines can potentially boost the NAb titers against SARS-CoV-2 and its variants, including VOCs, especially in immuno-compromised individuals or individuals with underlying comorbidities or who are at an increased risk for COVID-19 exposure and transmission. Recent data demonstrate the protective effect of the third dose of mRNA vaccine against the Delta variant, 5-6 months after the second dose of vaccine, including in young age groups (16 years and older) (Bar-On et al., 2021b). The potential use of this third dose is now enhanced since the appearance of Omicron variant, indeed we have now enough evidence to support the use of such third dose in order to increase the vaccine efficacy.

However, it is essential to consider appropriate use criteria for the third doses of COVID-19 vaccines without compromising global immunization efforts and exacerbating global vaccine inequality (WHO, 2021).

The third dose of vaccine may provide a way to control the SARS-CoV-2 transmission in the peloton. Further studies are needed to determine the longer-term effectiveness of such third doses against current and emerging variants.

6) Additional concerns supporting new COVID-protocols during cycling events

A- Why detect asymptomatic forms of COVID-19

Ongoing infection and subsequent transmission from asymptomatic individuals is a significant contributing factor to the ongoing pandemic. Disrupting the rate of asymptomatic transmission is critical to prevent symptomatic forms of the disease.

1- How common is asymptomatic infection?

First of all it is important to clearly define the term “asymptomatic”. An asymptomatic case is one with laboratory-confirmed SARS-CoV-2 infection as determined by PCR and/or serology but with no symptoms whatsoever for the duration of infection. Meta-analyses and studies of large cohorts have shown that around 20–40% of individuals infected with SARS-CoV-2 have asymptomatic disease (Buitrago-Garcia et al., 2020; Tsitilonis et al., 2021). Whether there is an age influence on the prevalence of asymptomatic disease? The assumption is that children and adolescents are more likely to be asymptomatic following infection (Tsukagoshy et al., 2021). The prevalence of asymptomatic carriers of the virus was estimated in a large cohort of 106,000 adults (Ward et al., 2021); in this study, 5,544 tested positive, of whom one-third had reported no symptoms, more than half of those older than 65 years. A systematic review and meta-analysis of 350 studies concluded that asymptomatic presentation in elderly people occurred in 19.7% of cases, compared with 46.7% in children (Sah et al., 2021). Although this issue remains debated, these data on very large populations

seem to show that the prevalence of asymptomatic carriers would be more important in young subjects.

2- Transmission by asymptomatic individuals.

The degree to which individuals with asymptomatic infection can transmit SARS-CoV-2 is an essential question because this has profound consequences for health strategy during cycling events. The general finding is that individuals with symptomatic and asymptomatic infections with the Delta variant have a comparable peak of viral load, supporting the idea of a similar potential for transmission. However, virus clearance may be faster in vaccinated individuals (Singanayagam et al., 2021) as well as during asymptomatic infections, suggesting a shorter period of transmission (Cevik et al., 2021).

In summary, individuals with asymptomatic infections have consistently been shown to shed the virus and accounts for substantial transmission, event if the period of transmission is shorter. This finding supports measures to detect and screen for healthy carriers within the peloton.

B- Vaccinated individuals as healthy carriers of the virus

The first obstacle posed by the immune system to mucosal infection is secretory IgA (SIgA) (for review, see Mortari et al., 2021). SIgA plays a fundamental role in the protection from respiratory viruses by blocking their attachment to epithelial cells. It has been shown that adult patients with COVID-19 have high levels of specific and neutralizing SIgA in the saliva. The absence of IgA in the saliva of vaccinated individuals suggests that the vaccine is not sterilising because it is unable to generate preventive mucosal immunity (Mortari et al., 2021). The lack of direct mucosal protection explains why vaccinated individuals can have a positive nasopharyngeal swab. In most cases, however, the infection remains asymptomatic or mild. Part of their defense may be due to spike-specific IgG and IgA antibodies exudated to the tissues. An important role may also be played by MBCs that migrate to the infected areas, produce IgA antibodies and become resident MBCs. Thanks to the combined action of antibodies and MBCs, the evolution of the disease is immediately blocked. For this reason, the viral load in vaccinated individuals who present a positive nasopharyngeal swab can be so low to be unable to transmit the disease to others (Levine Tiefenbrun et al., 2021).

C- How to detect asymptomatic carriers of the virus?

Testing for SARS-CoV-2 relies on testing for evidence of active infection through the detection of viral nucleic acids or viral antigens. But the detection of healthy carriers of the virus requires the use of tests with high sensitivity and specificity. It is a burning question whether the tests for SARS-CoV-2 are sensitive and specific enough to detect the new VOCs.

1- Molecular testing.

Molecular testing involves the detection of viral nucleic acid, after amplification, and test results can determine whether or not a patient has an active infection that may be transmissible depending on the viral load. In general, molecular testing should target conserved sites (i.e. the genomic sequences least likely to accumulate mutations over time). From the beginning of the pandemic, an unprecedented number of viral genomes are available and candidate conserved sites suitable for molecular diagnostics should be identified.

Most technologies utilize Polymerase Chain Reaction (PCR), the gold standard method for viral nucleic acid detection due to its high sensitivity and specificity. Importantly, PCR-

based tests are amenable to providing semi-quantitative results pertaining to viral load. Early in the pandemic, there were no genotyping or variant-specific tests needed due to the lack of functional variation in the SARS-CoV-2 genome. Importantly, since variant testing is not the primary aim of diagnostic testing for COVID-19, standard testing approaches that provide reproducible results by targeting both conserved sequences within the genome and antigenic regions in viral proteins are most desired. The widely used PCR tests continue to detect the SARS-CoV-2 infection, including with Omicron (WHO, Nov 2021).

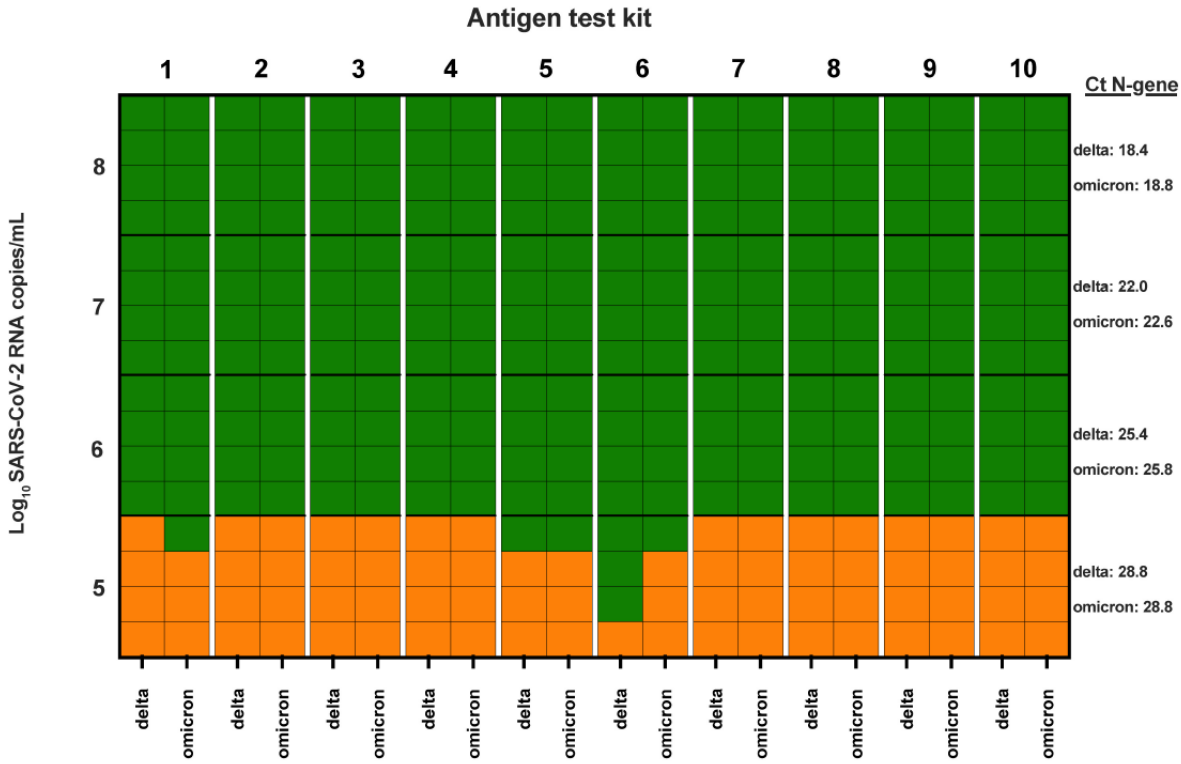


Figure 13. Analytical sensitivity of lateral flow devices against SARS-CoV-2 delta and omicron variants. Ten lateral flow devices were tested against 10-fold dilutions (1:100 to 1:100,000) of SARS-CoV-2 delta and omicron variants in quadruplicate. Green boxes indicate where SARS-CoV-2 antigen was detected and orange boxes indicate where a negative result was observed. Mean Ct values of three replicates for each dilution were calculated using in-house RT-PCR for N gene. The registered test name of the lateral flow devices included were; (1) Panbio™ COVID-19 Ag Rapid Test Device (Nasal); (2) NowCheck COVID-19 Antigen Test; (3) Roche SARS-CoV-2 Rapid Antigen Test; (4) STANDARD™ Q COVID-19 Ag Test; (5) Surescreen Diagnostics COVID-19 Antigen Rapid Test Cassette; (6) VivaDiag™ SARS-CoV-2 Ag Rapid Test; (7) Wantai SARS-CoV-2 Ag Rapid Test (Colloidal Gold); (8) Testsea SARS-CoV-2 Antigen Test Kit; (9) InnoScreen COVID-19 Antigen Rapid Test Device; (10) LYHER Novel Coronavirus (Covid-19) Antigen Test Kit (Colloidal Gold). (from Seerain et al., 2021).

2- Antigen tests and lateral flow assays.

An additional approach used for testing for SARS-CoV-2 infection involves technologies that are able of detecting viral antigens. These antigen tests can rapidly detect various viral proteins, including the SARS-CoV-2 S and N proteins. However, the sensitivity of this technique is lower when compared to molecular tests that utilize an amplification step. Their ability to quickly detect individuals with high viral loads provides clinical health utility. As

new variants arise, including the recent emergence of the Omicron VOC, the performance of antigen tests was recently assessed (Deerain et al., 2021). The ability of 10 antigen tests to detect Delta and Omicron variants was recently studied. The analytical sensitivity of the 10 antigen kits was similar for both Delta and Omicron variants (Figure 13). All 10 antigen kits were able to detect Delta at Ct=25.4, and Omicron at Ct=25.8. None of the 10 kits consistently detected either Delta or Omicron at lowest dilutions (Ct=28.8). These results provide valuable data on the ability of antigen tests to detect the Omicron VOC (Deerain et al., 2021), and are consistent with other work demonstrating the effectiveness of antigen tests to previous VOCs (Bekliz et al., 2021). However, the sensitivity of these antigen tests remains limited, detecting only moderate to high viral load infections.

D- The disease severity of the last SARS-CoV-2 variants

1- the Delta variant

The Delta variant of SARS-CoV-2 has been clearly shown to be highly transmissible, but it is questionable whether it causes more severe disease in adults. Analysis of data from 14 states in USA found no significant increases in the proportion of hospitalized COVID-19 patients with severe outcomes during the Delta period (Taylor et al., 2021). The proportion of hospitalized unvaccinated COVID-19 patients aged 18–49 years significantly increased during the Delta period, and the lower vaccination coverage in adults aged 18–49 years likely contributed to the increase in hospitalized patients during the Delta period. Using a meta-analysis, it was shown that all VOCs increase the risk of hospitalization, ICU admission, and death compared with the wild-type virus (Lin et al., 2021). Moreover, the Delta variant carried a much higher risk for hospitalization, ICU admission, and death than other VOCs (Figure 14). This finding is consistent with the main results of a recent study showing that persons infected with the Delta variant are more likely to be hospitalized (27.3% vs 20.0%) or to experience more severe disease outcomes (Butt et al., 2021).

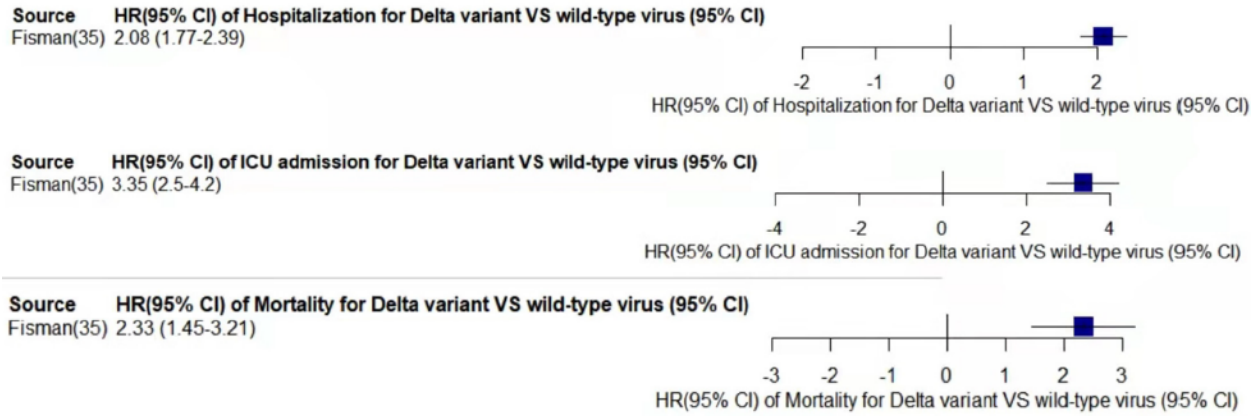


Figure 14. Pooled hazard ratio of hospitalization, ICU admission, and mortality for patients infected with Delta variant compared to those infected with the wild-type SARS-CoV-2. (from Lin et al., 2021)

It is suggested that the Omicron variant has a significant transmission advantage, significant immune escape, or both, or some other fitness advantage over the Delta variant (Mahase, 2021b). Despite the only few information published to date, it has been suggested that although Omicron is more transmissible than Delta, it causes less severe disease.

A matter of concern is the worrying number of infections in people who have either been vaccinated or experienced previous SARS-CoV-2 infection. But one of the key questions is "how severe are those Omicron infections?" To date, we have little information to clearly answer this essential question. However, recent reports from South Africa have consistently noted that the rate of hospitalization as a result of Omicron infections is lower than that for infections caused by the Delta variant. The hospitalization risk has been estimated to be 29% lower than with previous variants (Ledford, 2021). In UK, someone infected with the Omicron variant is estimated to be between 31% and 45% less likely to attend emergency care than if they had been infected with the Delta variant, and 50-70% less likely to be admitted to hospital (Mahase 2021c). In South Africa, the latest research has found that people who were given a diagnosis of Omicron infection in October and November were 80% less likely to be admitted to hospital than people with other variants (Wolter et al., 2021). The first information provided by South African physicians leads to suggest that symptoms of COVID-19 patients infected with the Omicron variant were mild so far and could be treated at home.

2- the Omicron variant

The clinical severity of hospital admissions was analyzed in an hospital in South Africa during the Omicron wave and compared with previous waves (Abdullah et al., 2021). There was decreased severity of disease during the Omicron wave, with fewer deaths (4.5% of patients admitted to the hospital, vs 21.3% during previous waves), ICU admissions (1% of patients admitted to the hospital, vs 4.3% during previous waves), and a shorter length of stay (4 days for patients admitted to the hospital, vs 8.8 days during previous waves). The results suggest a complete decoupling of case and death rates, suggesting that Omicron may be a harbinger of the end of the epidemic phase of the Covid pandemic and its entry into the endemic phase.

To date (i.e. 6 January 2022), the three first clinical studies in England, Scotland and South Africa have found the risk of admission to hospital to be between 15% and 80% lower with Omicron than with Delta variant (Christie, 2021). The first clinical studies suggest a decoupling between the incidence rates of COVID-19 cases and death rates.

In short, the Delta variant carries a much higher risk for hospitalization, ICU admission, and death than other VOCs. Concerning the Omicron variant now predominant in most countries, it has been suggested that although it is more transmissible than Delta, it causes less severe disease. Based on current information from several clinical studies, we do not see obviously increased severity and fatality in COVID-19 patients by Omicron yet, and the available clinical data clearly suggest a reduced severity of Omicron compared to previous VOCs.

7) Conclusions

The current published literature clearly shows that vaccination with the authorized mRNA and AZ vaccines demonstrate high efficacy in preventing COVID-19 induced by the SARS-CoV-2 wild type strain, with only minor and rare side effects. The humoral responses to mRNA vaccines suggest an effective protection against the currently know VOCs, including the now dominant Delta variant. The serum Ab levels decrease between 3 to 6 months, with a relative preservation in young people. Full vaccination with mRNA vaccines induces T-cell responses consistent with potent T-cell immune protection and (likely) long-term protection against COVID-19. The vaccine effectiveness against the Delta variant wanes during the 6 months after full vaccination, but effectiveness against COVID-19-related hospital admissions and severe forms of the disease don't wane. The current medical knowledge demonstrates

that Omicron partly escapes the vaccine-induced immunity after the primary vaccination series. This SARS-CoV-2 variant exhibits increased infectivity, raising the potential for increased transmissibility. However, Omicron breakthrough infections may result in attenuated severity of the disease in vaccinees compared to previous VOCs, at least partly due to previous cellular and innate immunity.

Full vaccination reduces onward transmission of SARS-CoV-2 from individuals with breakthrough infection. However, reductions in transmission are lower for all vaccines for the Delta variant, compared to Alpha. The now dominant Omicon variant is more transmissible and associated with reduced vaccine efficacy, but interestingly, the severity of the forms is greatly reduced, especially in vaccinated subjects. Vaccines continue to provide protection against infection with Delta and Omicron variants, but to a lesser degree than with Alpha. All clinical studies clearly conclude that full vaccination remains highly effective in preventing severe disease, also for the Delta and Omicron variant.

As full vaccination remains highly effective in preventing severe forms of the disease, high vaccination coverage remains the key to control the COVID-19 pandemic. Recent data showed that receiving a third dose of a mRNA-based vaccine effectively yields a potent cross-neutralizing response against Delta and Omicron variants. The administration of the third dose of mRNA vaccine, including in the young population, may contribute to reduce the rate of confirmed infection by the last Delta and Omicron variants in the peloton. However, the extension of the third dose to the young population depends on decisions by national health authorities.

Paradoxically, vaccination could also increase transmission due to behavioral effects, as vaccinated individuals may be less mindful of NPIs and social-distancing measures (Aschwanden et al., 2021). Although current vaccines remain effective at preventing severe disease and deaths from COVID-19, vaccination alone is not sufficient to prevent the transmission of the Omicron variant (and more broadly transmission of VOCs associated with high transmissibility) where exposure is close and prolonged, such as within cycling teams. Non-pharmaceutical interventions will continue to play a crucial part in keeping cases down. The whole point is to break the transmission path, and limiting social contact and continuing protective behaviors such as masking can help to reduce the spread of new variants.

8) Suggested adjustments of UCI Covid-19 protocols for the 2022 season

Considering,

- the high efficacy of current vaccines, especially RNA vaccines, in preventing COVID-19, with in particular,
    - persistent effectiveness against severe forms of the disease,
    - less decline in vaccine efficacy over time in young adults than in the general population.
- the high efficacy of third vaccine doses on the neutralizing responses against Omicron variant (currently dominant variant).
- our current knowledge on the longevity of the humoral immunity (i.e. lesser decrease of the humoral immunity in young people and very likely maintenance of the T-cell immunity over time).
- the high immunization coverage of the peloton (at least 82.5%), despite a high heterogeneity in the vaccination coverage between the teams.
- the persistent risk of viral transmission from vaccinated people, especially with asymptomatic infections.
- the rapid spread of the last VOC, i.e. the Omicron strain, that despite escape from humoral immunity, may result in attenuated disease severity in vaccinees.

The following measures are suggested,

1) As in past years, **local and national rules and laws prevail** over the requirements and recommendations set out in the present document.

However, if the national or regional rules are less strict than the UCI rules, the latter will apply.

2) Improving the immunization coverage of the peloton

To date, given the current variants identified, COVID-19 vaccines reduce the spread of the virus and its known variants from infected individuals. As full vaccination remains highly effective in preventing severe COVID-19, also with the Delta variant, a high immunization coverage remains the key to control the COVID-19 pandemic within the peloton and prevent SARS-CoV-2 infection.

Therefore, teams that do not yet have sufficient vaccination coverage must make an effort to convince riders and staff who have not yet been vaccinated. This measure is a guarantee of safety during training-camps and races. The importance of high immunization coverage is emphasized, especially for teams with low immunization coverage (some teams have a 95-100% vaccination rate, but few teams have only 40-45% protection).

Considering the rapid spread of VOCs, which partially escape vaccine immunization, a better immune protection of the peloton requires a third vaccine dose. Although additional studies are needed, booster vaccination programs have shown their effectiveness in young people. If the UCI recommends its application among riders and staff, its application remains dependent on the national health authorities.

3) Procedures for entering team bubbles

A) 1-day races and stage races of less than 7 stages

A UCI-health pass will be implemented. Before each road race, the health pass will be issued in case of either,

- proof of full course of vaccination with a vaccine authorized for use in European Union, approved by the European Medicines Agency,
  * 7 days after the 2nd injection for two-dose vaccines (Pfizer, Moderna, AstraZeneca);
  * 28 days after the injection for single-dose vaccines (Johnson & Johnson/Janssen);
  * 7 days after the injection for people who have previously had COVID-19 (only 1 injection needed);
- proof of a negative PCR test less than 48 hours before the race.

B) Grands Tours and stage races of more than 6 stages

One negative PCR test for SARS-CoV-2 will be mandatory 4 days (or 5 days) before the Event. If this COVID test is negative, a second PCR test will be carried out no more 2 days (or 3 days) before the Event.

PCR tests performed as part of mandatory entry procedures in countries (which have adopted this measure) can be used as pre-event tests. The objective is to optimize the testing program by avoiding unnecessary repetition.

4) Ensure the protection of the team bubbles and the peloton bubble

Although current vaccines are effective at preventing symptomatic and asymptomatic forms of COVID-19, vaccination alone is not sufficient to prevent the SARS-CoV-2 transmission including the Delta variant where exposure is close and prolonged, such as within cycling teams.

Non-pharmaceutical interventions and social distancing measures remain critical for limiting COVID-19 cases. Therefore, preventive measures (social distancing, personal hygiene, hand-washing, etc.) and improving vaccination coverage are essential for COVID prevention during road cycling events. All the non-pharmaceutical interventions comprising physical distancing mask wearing, and more generally all protective measures of the teams bubbles will be updated, and controlled with even more rigor.

5) Relevance of the third dose of vaccine for in the peloton

As explained above, it is currently very difficult to determine the efficacy and stability over time of the immune protection (i.e. humoral and cellular immunity) against the latest VOCs of the virus in young and trained subjects. MBCs and memory T cells ensure local and systemic protection after re-encounter with SARS-CoV-2 antigens but the neutralization stability over time remains unknown, especially with the last variants.

Very recent data demonstrate the protective effect of third or subsequent doses of COVID-19 vaccines on the NAb titers against SARS-CoV-2 and its main variants, especially in individuals who are immuno-compromised or at an increased risk for SARS-CoV-2 exposure and transmission. The protective effect of the third dose of mRNA vaccine has been demonstrated against the Delta variant, including in young age groups (16 years and older) (Bar-On et al., 2021b), and now against the Omicron variant (Mahase, 2021b; Garcia-Beltran et al., 2022). Such booster dose may provide a way to control the SARS-CoV-2 transmission in the peloton.

Therefore, a 3rd dose of mRNA vaccine is highly recommended by UCI, depending on the availability in the different countries, especially in team members and officials aged >50 years, immuno-compromised and/or at high risk for COVID-19.

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