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Communication

Would new SARS-CoV-2 variants change the war against COVID-19?

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Abstract: The scientific, private and industrial sectors use a wide variety of technological platforms available to achieve protection against SARS-CoV-2, including vaccines. However, the virus evolves continually into new highly virulent variants, which might overcome the protection provided by vaccines and may re-expose the population to infections. Mass vaccinations should be continued in combination with more or less obligation mandatory non-pharmaceutical interventions. Therefore, the key questions to be answered are: (i) How to identify the primary and secondary infections of SARS-CoV-2? (ii) Why are neutralizing antibodies not long-lasting in both the cases of natural infections and post-vaccinations? (iii) Which are the factors responsible for this decay in neutralizing antibodies? (iv) What strategy could be adapted to develop long-term herd immunity? (v) Is the Spike the only vaccine candidate or a vaccine cocktail is better?

Keywords: SARS-CoV-2; COVID-19; variant; sublineage; transmission; immunity; infection; vaccination; non-pharmaceutical interventions;

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Can COVID-19 infection provide lifelong immunity?

Adaptive immune responses triggered by SARS-CoV-2 infections, including B and T lymphocyte cells response, can induce immunological memory during primary infection to prevent or decrease disease severity on repeated exposures to the same pathogen. On reinfection, antibodies produced by short-lived plasma cells derived from B lymphocytes bind to and block the recognized virus, and the long-lasting bone marrow plasma cells (BMPCs) become resident in the bone marrow and retain the ability to produce antibodies for decades [1].

The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study enrolled 8,278 SARS-CoV-2 seropositive and 17,383 seronegative healthcare workers in England between June 18, 2020, and December 31, 2020 [2]. The study demonstrated that individuals with a previous history of SARS-CoV-2 infection showed an 84% lower infection risk than the seronegative individuals, with median protective effect lasting 7 months following primary infection [2].

However, this "long-lasting" immunity may not protect against reinfection, and despite huge numbers of infections and deaths worldwide caused by SARS-CoV-2, herd immunity could not be achieved in communities with the previous infection of most of its population. One factor which affects protection against reinfections is the severity of primary infections. In severe SARS-CoV-2 infection, the immune response may be impaired, which will decrease affinity maturation, memory quality, and quantity [3]. In contrast, in cases of mild COVID-19 disease and quick recovery, the efficient antibody immune response that cleared symptoms rapidly remains stable for a long time after infection [4]. Another factor is the decrease/waning in antibody levels with time, which was demonstrated in seven individuals five months after SARS-CoV-2 infection [5].

Others have reported that circulating anti-spike IgG antibodies remain detectable one year after hospitalization of COVID-19 patients, and these higher antibody titers and disease severity were associated with increased durability of detectable antibodies [6]. Although the total circulating anti-SARS-CoV-2 antibodies wane over a few months, these antibodies could be detected up to one year after infection, even in mild COVID-19 patients [7]. The levels of circulating neutralizing antibodies correlate with the duration and infection severity but not with patient age [8]. The issue has many parameters not broadly discussed in most published articles, such as but not limited to patient age, symptomatic or asymptomatic phenotype, symptomatic grade, duration of sampling, type of sample, type of evaluation methodology used [9]. It has generated existing controversies regarding the durability of the acquired immunity.

Another concern about assessing long-lasting immunity after primary SARS-CoV-2 infection is the difficulty of identifying the precise incidence of SARS-CoV-2 reinfection [10,11]. Viral genome sequencing from primary and secondary infections is required to ensure that they are two separate events and repeated PCR testing is required to confirm reinfection. Individuals who have tested positive in PCR assays, should show a negative PCR result and then test positive after reinfection. Also, reinfections were difficult to track during the first wave of the COVID-19 pandemic due to the overloaded testing capacity [10,11].

SARS-CoV-2 mutations may be the most important explanation for the immunity loss due to the release of new variants that can be more transmissible and more efficient at avoiding the host immune system and evading immunity formed by primary infection. In fact, throughout the COVID-19 pandemic, many SARS-CoV-2 variants have appeared. Some are variants of interest (VOI) that may be associated with reduced efficacy of available treatments and vaccinations, and predicted increase in transmissibility or disease severity (e.g., B.1.427 (Kappa), B.1.525 (Eta), and B.1.617.1 (Kappa)), and some are variants of concern (VOC) that may cause increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralizing antibodies generated during previous infection or vaccination (e.g., Alpha (B.1.1.7), Beta (B.1.351), Delta

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(B.1.617.2 and its sub-lineages AY.1, AY.2, and AY.3), Gamma (P.1), and most recent Omicron ('Nu' B1.1.529)). The seriousness of this issue can be illustrated by the case in Manaus, Brazil, where SARS-CoV-2 infected more than 70% of the population by October 2020, which should have provided herd immunity. However, a surge of reinfection occurred in late December 2020, and early January 2021; i.e., about 7 months after the first wave [12,13]. The most likely explanation for the decrease in protective antibody levels and the reinfection of the population was the appearance of new more transmissible SARS-CoV-2 variants such as the B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and AY.1, AY.2, and AY.3 sub-lineages of Delta [12,13]. Another example is given by the Omicron variant, which was shown to systematically escape neutralization by the existing vaccines [14,15]. In general, accumulating evidence suggests that the existing vaccines might have limited protection against novel SARS-CoV-2 variants and infection with SARS-CoV-2 might show limited cross-variant immunity (e.g., see [16-25])

Novel mutations will appear as long as the virus continues to spread. This emphasizes the need for precautionary measures to reduce the risk of infection, such as mask-wearing, physical distancing, hand hygiene, and surface sanitation. Obviously, among the very important constituents of the successful strategies to control the pandemics are the existing and future anti-SARS-CoV-2 vaccines.

Can COVID-19 vaccines alone stop the pandemic?

Available SARS-CoV-2 vaccines stimulate an adaptive immune responses against different SARS-CoV-2 spike proteins and decrease both symptomatic and asymptomatic disease incidence with the development of immunological memory.

The prospective SIREN study among staff working in publicly-funded hospitals in England showed that the BNT162b2 mRNA vaccine could prevent both symptomatic and asymptomatic infection caused by the B1.1.7 (Alpha) variant by 70% (95% CI 55–85) 21 days after the first dose and 85% (74–96) 7 days after the second dose [26]. For the moment, the estimated time of lasting protection from severe disease after vaccination is up to 8 months, even with the decay of neutralizing antibody titers after this period [27].

Despite the high efficacy of available COVID-19 vaccines, SARS-CoV-2 viral infections can still occur in vaccinated individuals due to the decline in neutralizing antibody titers 7-8 months post-vaccination. Furthermore, the emerging new SARS-CoV-2 variants are one of the most important sources of post-vaccination infections [28]. The reported efficacy against the B.1.351 (Beta) variant first identified in South Africa is 57% against moderate-to-severe COVID-19, and 89% against severe COVID-19 for the Ad26.COV2.S vaccine, and zero percent against mild-to-moderate COVID-19 for the ChAdOx1 nCoV-19 vaccine [29]. Two cases out of 417 who had received the second dose of BNT162b2, or the mRNA-1273 vaccines, developed breakthrough infection two weeks after vaccination despite evidence of vaccine efficacy. Breakthrough infections correspond to cases when individuals test positive for COVID-19 after they being fully vaccinated against the disease [30]. Subsequent viral sequencing revealed the E484K, T95I, del142–144, and D614G mutations in SARS-CoV-2 causing those breakthrough infections [31].

Concerns about post-vaccination herd immunity also include the uneven distribution of vaccines among countries and within individual countries, and the age limit of vaccination (although vaccination is in progress in teenagers and the Moderna mRNA-1273 vaccine has been approved for vaccination of 12-17 years old). These factors make it more difficult to reach the levels of the vaccinated population needed to achieve herd immunity [32]. A preprint study reported sequencing of over 2,000 samples from COVID-19 patients below the age of 19 years and found more than 250 VOCs, with over 70% of the VOCs in children below the age of 12, including 33 cases of B.1.1.7 (Alpha) and 119 of B.1.429/B.1.427 (Kappa) variants [33].

Another thing to consider is the possibility of virus spread by fully vaccinated individuals without manifesting breakthrough disease. Data released by the CDC reported that vaccinated people infected by the SARS-CoV-2 Delta variant could carry viral loads

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similar to those of unvaccinated people (https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html). Currently, it is not recommended to test vaccinated people following exposure to infection. However, highly tested groups, such as professional sport teams, demonstrated that asymptomatic breakthrough infections among vaccinated people might be higher than reported.

A crucial question related to vaccine efficacy against current and emerging SARS-CoV-2 is whether we look at the wrong place? Most of the current vaccine development focuses on the spike protein as a target. Unfortunately, the virus mutates faster than humans engineer vaccines, so it might be a good idea to diversify the efforts. Obviously, the inactivated whole virus vaccines can generate a broad repertoire of antibody responses and the SARS-CoV-2-based vaccine from Sinopharm was approved by the WHO for emergency use in May 2021. Additionally, other initiatives such as the combination of spike, nucleoprotein and ORF3a sequences have elicited neutralizing antibodies and demonstrated strong CD8 T cell responses against SARS-CoV-2 in most immunized individuals (https://ir.gritstonebio.com/static-files/6a7c26ca-06a6-4295-bf76-83948a341397). This pan-vaccine approach could potentially be a way to outsmart the virus.

Breakthrough infections of SARS-CoV-2 variants and community herd immunity build-up

Natural infections

Many recovered patients have been reinfected worldwide, despite being among the population that had acquired immunity against the virus. However, the best-known example of breakthrough of a population with established herd immunity was observed in Manaus city (the capital of Amazonas state in northern Brazil) where from June 2020 to October 2020 the SARS-CoV-2 prevalence increased from 60% to more than 70%, a condition which may mirror achieving herd immunity [12]. By January 2021 Manaus had a huge resurgence in cases due to the emergence of a new variant known as P.1 (Gamma), which was responsible for nearly 100% of the new cases [13]. Although the population may have reached a high herd immunity threshold, there is still a risk of resurgence of new variants escaping protection. Sabino *et al*. attributed this to the waning of protective antibodies levels and emergence of new SARS-CoV-2 variants [12,13].

Vaccinations

On the personal level, recovered patients can be reinfected, and the vaccinated persons can contract new infection (despite being previously infected or not). For example, the CDC reported that Massachusetts (USA) has already fully vaccinated more than 4 million people (out of 7.03 million total) (56.899%). The total rate of fully vaccinated people in the Barnstable County is 76% [30], with the vaccination levels by age category being as follows: 86% (75+), 77% (50-64), 80% (30-49), 62% (20-29), 64% (16-19), and 43% (12-15) (https://www.wcvb.com/article/massachusetts-covid-breakthrough-cases-delta-variant-pandemic-vaccine-data-charts-maps/37089843). However, the Department of Public Health of Massachusetts reported 7,737 total COVID-19 breakthrough cases in fully vaccinated individuals as of Aug. 3, 2021. Among the breakthrough cases, 395 patients have been hospitalized, and 100 have died. Genomic sequencing of specimens from 133 patients revealed that this breakthrough was caused by the newly identified and highly transmissible SARS-CoV-2 variants. The B.1.617.2 (Delta) variant was identified in 119 (89%) patients, and one person was infected by the Delta AY.3 sublineage (1%). Since the youngest age group (12-15) showed the lowest coverage by one and/or two vaccine doses (43% vs. >60% in other age groups), these data indicated the need for higher vaccination levels in this group. Although many factors, such as hesitancy and shortage of vaccine supply (especially in the developing countries) [34], define low vaccination rates, vaccination is still the most important strategy to prevent severe illness, hospitalization, and death.

The emergence of breakthrough infections has urged many developed countries to call their citizens for additional vaccine booster doses (specifically for those older than 60

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years of age) from the same or newly approved vaccines (combined vaccines). However, it is not clear whether such boosting will help overcoming the viral infectivity and/or transmissibility, and/or emerging new variants. The COVID-19 pandemic incidences worldwide clearly indicate that it might not. Overall, it seems that this virus can overcome herd immunity (formed naturally and/or via vaccination), suggesting that it can prevail in the general population for a long time. Of note, young individuals may represent a live source for new infections, as most of them, when infected, are asymptomatic or show light to moderate symptoms.

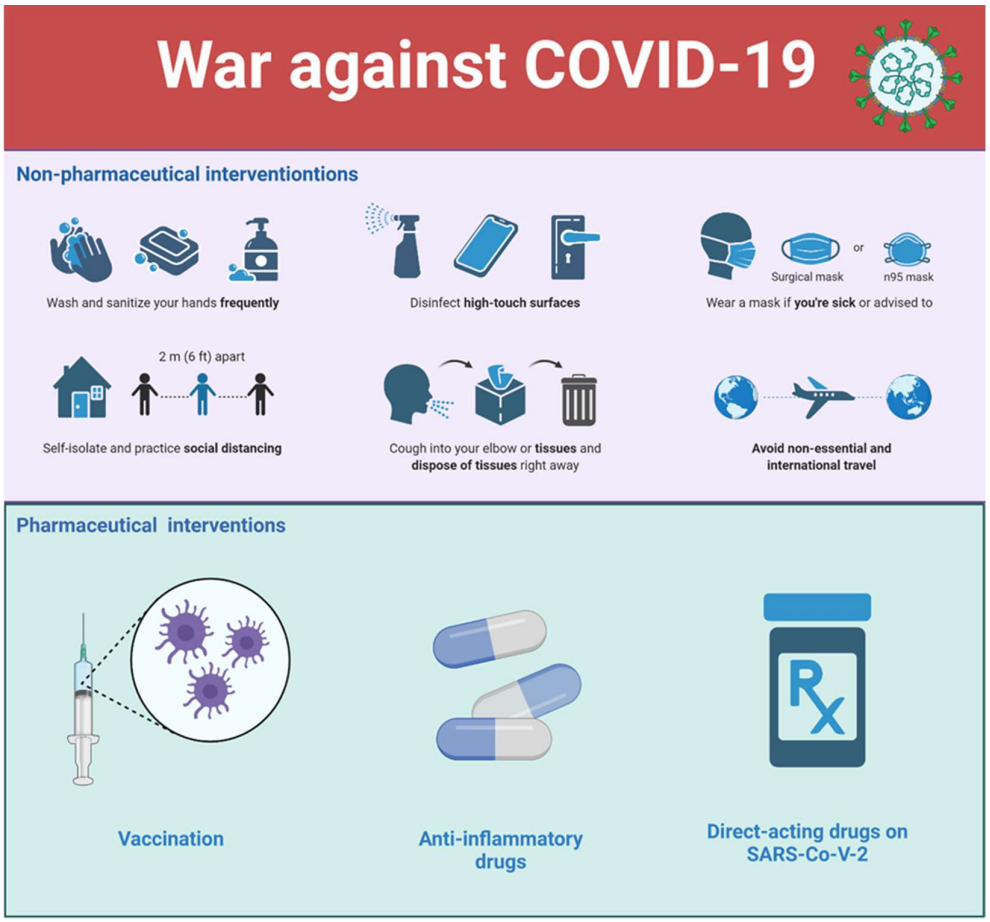

Figure 1. The war against COVID-19 includes multiple strategies. Both pharmaceutical and non-pharmaceutical interventions are needed now and may be needed for long time.

As the WHO has emphasized, 90-99% of individuals infected with the SARS-CoV-2 virus develop detectable neutralizing antibodies within four weeks after infection (WHO/2019-nCoV/Sci_Brief/Natural_immunity/2021.1), the levels of which decline during 6–12 months post-infection. In parallel, according to classical immunology, most vaccines can elicit durable immune responses. However, the open questions are: Why does herd immunity (from natural infection or vaccination) against SARS-CoV-2 decrease within 6-12 months? What are the mechanisms behind such a decay?

Taking all these facts into account, it is clear that the war against COVID-19 should be conducted at multiple levels (see **Figure 1**), and our efforts to end virus transmission, complications, lockdowns, and the world economy disruption should not be limited to only endorsing various approaches of vaccination (e.g., promoting different vaccines, encouraging booster doses, recommending combined vaccines, re-engineering existing vaccines to target emerging variants, etc.). However, one needs to place greater emphasis on

various hygienic precautions. Among such non-pharmaceutical interventions and protective precautionary actions continue to be important and mandatory use of protective masks, frequent disinfection of public areas, and social distancing, especially indoors should remain part of our daily life. One should keep in mind that when the non-pharmaceutical interventions are relaxed when the majority of the population has already been vaccinated, the probability of a new resistant strain emergence is greatly increased. Therefore, individuals should be encouraged to maintain the non-pharmaceutical interventions and transmission-reducing behaviors throughout the entire vaccination period [35]. Obviously, the development of novel drugs directly targeting the SARS-CoV-2 would significantly help reducing viral transmission. Furthermore, we need to understand better what represents a protective or fully protective immunity threshold for SARS-CoV-2 infection, and, similar to almost all approved vaccines for human beings, the world needs to achieve a consensus on the protective immunity threshold [36]. To this end, standard or consensus methods that would consider various correlations of different *in vitro* and *in vivo* data are needed to estimate the quality and quantity of protective immunity against this virus (WHO/2019-nCoV/Sci_Brief/Natural_immunity/2021.1) [9,37].

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