Longevity of immunity following COVID-19 vaccination: a comprehensive review of the currently approved vaccines

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1. Introduction

The current COVID-19 pandemic has affected millions of people across the globe. According to the World Health Organization (WHO), nearly 5.1 million deaths have been reported on November 19, 2021. Therefore, there is an essential need for vaccination campaigns to reduce COVID-19 mortality and its detrimental impacts on society. Most countries have started vaccination programs as a promising way for their citizens to limit the damages of COVID-19. According to the WHO plan, countries relying on COVID-19 Vaccines Global Access (COVAX) alone may hardly vaccinate more than 20% of their population. Indeed, an ideal vaccine should elicit long-term protection.

Furthermore, early diagnosis of COVID-19 is vital for controlling and managing the pandemic. Some of the COVID-19 diagnosis techniques, based on antigen detection, require nasopharynx sampling; alternative sampling methods like saliva have been used in various studies. Antibody detection methods are also common, which target the viral spike protein or the nucleocapsid. The detection technologies of antibodies against these two SARS-CoV-2 antigens also differ. Enzyme-linked immunosorbent assays (ELISA) and chemiluminescence immunoassays (CLIA) are commonly used as laboratory assays. Also, various techniques such as lateral flow immunoassays, fluorescence-label techniques, or colloidal gold are most widely performed. While the non-quantitative serological testing can be used for epidemiological surveys to detect the attack rate of the disease, the quantitative or the semi-quantitative methods are used for the prediction of the severity of the disease. The highest accuracy of the serological testing is reached between 3 and 4 weeks after the onset of the initial signs and symptoms with checking the total immunoglobulins or the IgG levels. Each one of the IgM and IgA levels are related to less accuracy.

The immune response to the SARS-CoV-2 virus causes a variety of clinical manifestations. While adaptive immune responses play a significant role against this virus, the innate immune cells somehow lead to disease progression. Macrophages, the major players of innate immunity, are associated with significant production of Interleukin-6; therefore, leading to excessive inflammation in COVID-19. In the adaptive immune response, while the T-cell mediated immune response is inhibited as the downregulation of MHC class I and II molecules occurs, the humoral immune system plays an essential role in controlling the COVID-19 disease. Although IgM and IgG antibodies appear to have similar dynamics, IgA response is more robust in comparison to IgM response.
There is a strong relation between cell-mediated immunity, the severity of infection and survival; while the severe COVID-19 infected individuals had increased levels of anti-receptor binding domain (RBD) antibodies the high potent neutralizing antibodies served as a predictor of survival.

COVID-19 immunity may not remain in individuals who previously had the infection. Mild COVID-19 cases usually reach antibody responses after 4 months, although most patients manifest this response during day 10 to day 21 post-infection. Neutralizing antibodies levels begin to decrease about 2 months after the acute phase of disease. On the other hand, some studies demonstrated that natural immunity obtained against SARS-CoV-2 does not wane until 10 months post-infection, and the risk of reinfection is shallow 7 months post-infection, considering the pivotal role of natural immunity in controlling the disease.

Due to the fast emergence of different COVID-19 vaccines with varying mechanisms of action, recognition of the immune response profile following each vaccine becomes more and more challenging, yet very important.

Insight on the onset and the duration of antibody response following each vaccine helps control the spread of the disease, institute timely isolation strategies, and improve the epidemiological outcomes of this pandemic.

The production of vaccine-induced antibodies causes the body to give an anamnestic immune response in exposure to SARS-CoV-2.

Many studies sought to demonstrate the efficacy and the quality of immunogenicity of COVID-19 vaccines. However, neutralizing antibodies can exist for more extended periods and therefore help reduce the transmission and mortality of COVID-19 longer. Although most studies have shown acceptable short-term efficacy of vaccines, information on long-term immunogenicity is still limited.

Furthermore, it is a considerable challenge to assess the effective duration of vaccine-induced immunity. More research is needed to investigate the long-term efficacy and safety of the vaccines and the impact of different factors on the longevity of the immune response. This systematic review provided a summary of immune response profiles, type of antibody response, the onset of humoral immunity, and its duration following each currently approved COVID-19 vaccine.

2. Methods

We performed this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Before starting the search in the databases to clarify the review process and avoid unintentional duplications, we registered the proposal of this systematic review in PROSPERO [CRD42021262005].

2.1. Search strategy

Three investigators independently looked for research papers related to the longevity of the immune response following COVID-19 vaccines. Articles in PubMed and Scopus were selected using, for example, the following search terms: “COVID-19 Vaccines”, “SARS-CoV-2 vaccine”, “2019-nCoV vaccine”, “2019-nCoV vaccines”, “immunity,” “immune process,” “immune Response,” immunity and “COVID 19 vaccine”, “immune Response” AND “COVID 19 vaccine”.

A similar search was performed in the Google Scholar search engine to identify preprints and unpublished articles. No time restriction was set, and all search results until May 9th, 2021, were imported. The results were then imported into the Rayyan software, created by Qatar Computing Research Institute.

2.2. Study selection

In this systematic review, we included English articles that evaluated the efficacy and duration of COVID-19 vaccine-induced immunity and for which the full text was available. Medical news, non-medical papers, reviews, letters, commentaries, conference abstracts, and pre-clinical studies were excluded.

Two Researchers independently screened the results and selected the appropriate articles derived from selected databases based on the inclusion criteria stated above.

Duplicates imported into Rayyan were then removed. Subsequently, the titles and abstracts were screened to exclude irrelevant studies and studies without associated full-text.

2.3. Data extraction

Systematic data extraction was implemented in the following manner: The first author name, year of publication, study type, country name, vaccine type, manufacturer, the interval between injections, intervention group number, placebo group number, vaccine efficacy, time to peak neutralizing antibody titers, time for optimal binding antibody responses, the duration of antibody detection in the blood, and antibody waning time. Each of the two investigators separately extracted data into the data collection sheet. Afterward, discrepancies between researchers were discussed and checked with the third reviewer to resolve the conflicts.

2.4. Quality assessment

We considered the modified JADAD scale or the Oxford quality scoring system to assess the methodological quality of the publications. We chose this scoring system as it is the preferred quality assessment tool for randomized control trials (RCT) and that most of the included studies were RCTs.

The JADAD scale mainly consists of six items which are described below in detail.

Item number 1: Was the study described as randomized? If yes, a score of 2 is given for acceptable randomization tools (e.g., computer-generated), and a score of 1 is given for inappropriate methods. If no, no score is given.

Item number 2: Was the trial stated as double-blind? If yes, a score of 2 is given for acceptable double-blinding methods (e.g., identical placebo), and a score of 1 is given for inappropriate methods. If no, no score is given.
Item number 3: Was there a description of dropouts and withdrawals? If yes, a score of 1, and if no, a score of 0 is given. Scores on the scale can range from 0 to 5, with higher numbers signifying higher quality. Studies with three or higher points are considered high quality, whereas those with less than three are considered low-quality trials.\textsuperscript{14}

The other four additional questions were included from the modified version of the JADAD scale: Was there a clear description of the inclusion/exclusion criteria? Was the method used to assess adverse effects described? Were the methods of statistical analysis described? Each positive response is worth one point, whereas a negative response earns no points—scores on the modified JADAD scale range from 0 to 8, with higher numbers indicating higher-quality trials. Scores of 1–3 denoted poor quality, while scores of 4–8 denoted excellent quality.\textsuperscript{15}

Two authors (P.Sh. and Y.Kh.) independently assessed the quality of each eligible paper, which was subsequently double-checked by a third reviewer (K.M.).

3. Results
3.1. Study selection
1996 studies were retrieved from the database search, of which 397 studies were duplicates, leaving us with 1599 results. We conducted title and abstract screening on the remaining articles, the number of 1531 studies then were excluded, as they addressed issues outside of our research question such as COVID-19 vaccine development, treatment, and therapeutic agents, COVID-19 prevalence, or hesitancy to vaccines. Among the remaining 68 studies, we excluded the Nonhuman population (n = 15), review articles, news and views (n = 30), Ongoing studies (n = 1), a primary language other than English (n = 7), unavailable full text (n = 4) and not addressing the immunogenicity (n = 1). Finally, 10 original articles related to the longevity of immunity following approved COVID-19 vaccines were included. (Figure 1)

![Figure 1](image-url)
### 3.2. Study characteristics

As summarized in Table 1, we classified studies according to their first author, year of publication, country, study type, age group, vaccine type, and manufacturer. Five of the studies were randomized clinical trials (RCTs), four were cohorts, and one case series. Four studies were conducted in the USA, three studies in the UK, and one study in Belgium, Italy, Germany, Brazil, South Africa, and Eswatini as either single or multinational trials.

There were two multinational studies conducted by J. Sadoff et al. and Merryn Voysey et al., Three studies investigated the immunogenicity of the BNT162b1 vaccine, two studies studied the BNT162b2 vaccine, two studies researched the mRNA-1273 vaccine, and one study compared the BNT162b1 and the mRNA-1273 vaccine. Two studies were conducted on the AZD1222 vaccine and one on the Ad26.COV2.S vaccine.

### 3.3. Study quality

As represented in Table 2, articles were divided into two groups, ≥5 and ≤3, according to the JADAD quality scale; 40% of the studies scored above 4, while 60% scored below 4. (Table 2)

### 3.4. Data synthesis

In this review, we demonstrate the immunogenicity of four approved vaccines, AZD1222, Ad26.COV2.S, mRNA-1273 BNT162b1, and BNT162b2. A thematic qualitative study assessing and summarizing the results of each individual vaccine was performed. We mainly represent the timeframe when antibody production following vaccines was detected and the duration the antibody response remained detectable. The key findings of the selected publications are summarized in Table 3, and a summary of the timeline of detected immune responses is indicated in Figure 2.

#### 3.4.1 The immunogenicity of the AZD1222 vaccine

AZD1222 induced two types of immune response; humoral immune response, including IgG production against the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) protein or the S protein itself neutralizing antibodies, and a cell-mediated spike specific T-cell response after the first and the second dose.

A single dose of AZD1222 could induce anti-RBD and anti-S IgG production after 28 days, and their titers peaked 28 days after receiving the second dose. This antibody level remained stable until day 56, then decreased gradually until day 90, after which it decayed log linearly in 6 months.

Neutralizing antibodies and T-cell spike-specific responses were induced around 14–22 days after the first dose. The T-cell spike-specific responses were not significantly enhanced by receiving the second dose and persisted until days 90.

#### 3.4.2 The immunogenicity of the Ad26.COV2.S vaccine

Neutralizing antibodies and anti-spike binding IgG titers were detected in more than 90% of participants 29 days after the first vaccination dose. Then these percentages were increased to

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### Table 1. Studies characteristics.

| First author, year | Country | Study type | Age groups | Sample size | Vaccine | Manufacturer |
|--------------------|---------|------------|------------|-------------|---------|--------------|
| Ramasamy, M. N et al. 2020 | UK | phase 2/3 RCT | 18–55 yr | Intervention group = 420 | ChAdOx1 nCoV-19 (AZD1222) | Advent (Pomezia, Italy), COBRA Biologics (Keele, UK) |
| Merryn Voysey 2021 | Brazil, South Africa, and the UK | RCT | 56–69 yr70 yr ≥ COV001 18–55 yr (UK trial), COV002 (UK) and COV003 (Brazil) 18 ≤ healthcare personnel, COV005 (South Africa) 18–65 yr | Placebo = 140 | | |
| J. Sadoff 2021 | Belgium and the USA | phase 1–2a RCT | 18–55 yr, 65 yr ≥ | Intervention group = 642 | Ad26.COV2.S | Johnson & Johnson (USA) |
| Nicole Doria-Rose 2021 | USA | Phase 1 trial | 18–55 yr, 56–70 yr, 70 yr ≥ | Intervention group = 133 | Moderna mRNA-1273 | ModernaTX, Inc (USA) |
| Alicia T. Widge, 2020 | USA | Cohort | 29–69 yr | Placebo group = NA | Moderna (mRNA-1273) | ModernaTX, Inc (US) |
| Zijun Wang 2021 | USA | Cohort | 19–54 yr | Intervention group = 36 | Pfizer-BioNTech (BNT162b1) | ModernaTX, Inc and BioNTech (USA), Pfizer, Inc (Germany) |
| Mark J. Mulligan 2020 | USA | Cohort | 20–56 yr | Placebo group = 38 | Pfizer-BioNTech (BNT162b1) | Pfizer, Inc (Germany) and BioNTech (USA) |
| Ugur Sahin 2020 | Germany | Cohort | 44 yr, 39 yr, and 53 yr | Intervention group = 122 | Pfizer-BioNTech (BNT162b2) | Pfizer, Inc (Germany) and BioNTech (USA) |
| Elisa Danese 2021 | Italy | Case series | 19–54 yr | Placebo group = 147 | Pfizer-BioNTech (BNT162b2) | Pfizer, Inc (Germany) and BioNTech (USA) |
more than 96% of the participants with detecting the highest titers in the 18–55 age group. These levels of antibodies remained stable until day 71.16

The T-cell responses were measured indirectly via the detection of interferons and interleukins. While T helper 1 cells (Th1) response, detected via the measurement of interferon-γ; IL-2; or both; was induced at day 15 from the first dose of vaccination with higher response rates in the high dose recipients and the 18–55 age group. No T helper 2 cells (Th2) were observed. The CD8+ T cells response was also present as the younger participants who received higher doses had higher response rates with an exception to the ≥65 years age group having higher response rates with low doses.16

3.4.3 The immunogenicity of the mRNA-1273 vaccine
The mRNA-1273 vaccine (Moderna) induced neutralizing antibodies, anti-spike, anti-RBD IgG, and IgM approximately 15 days after receiving the 2nd dose and persisted between 3 to 6 months after this dose.19–21

3.4.4 The immunogenicity of the BNT162b1 and BNT162b2 vaccines
Both the BNT162b1 and the BNT162b2 vaccines were produced by Pfizer–BioNTech companies.

The former induced low levels of neutralizing antibodies and anti-RBD-binding IgGs 21 days after the first dose. Then, seven days after receiving the second dose, both the neutralizing antibodies and anti-RBD-binding IgGs substantially increased in a dose-dependent manner. Fourteen days after the second dose, neutralizing antibody titers continued to rise. In comparison, the RBD-binding IgGs started to drop. 21 days after the second dose, both neutralizing antibodies and anti-RBD-binding IgGs dropped in all age groups and doses except for the 18–55 age group who received the 1 μg dose of the vaccine, which elicited a stable titer.22,23

BNT162b2 is an upgraded version of BNT162b1 with IgA production and better immunogenicity. While the production of neutralizing antibodies is induced three weeks after receiving the first dose, anti-RBD-binding, anti S1, and S2 IgGs are induced 11–21 days after the first dose. The production of anti S1 IgA is induced 7–11 days from the first dose.24,25

After receiving the second dose, anti-RBD-binding, anti S1, and S2 IgG, and IgM are induced at day 7 to reach a peak at day 14. The anti-S1 IgA hit a peak 7 days after the second dose. From day 14 to day 29 after the second vaccine dose, antibody titers gradually decreased; however, from day 29 to day 44, they reduced significantly and approached baseline levels. Thus, the BNT162b2 vaccine approximately provided two months of protection.24,25

4. Discussion
Vaccines direct the immune system toward providing immunity against infections. Various vaccines mainly aim for disease prevention and not necessarily full protection against specific infections.26 While the ‘sterilizing immunity’ provided by vaccines might wane in the long run, the protection against either the disease or the disease progression (severity) can remain for a longer period because of the immune memory.27 This might make vaccines good candidates against the death toll and the burden of the COVID-19 infection. However, the condition is a bit challenging when it comes to the COVID-19 vaccination. Initially, the effectiveness of these vaccines, meaning the efficacy of a vaccine for preventing the disease in real-world situations not under certain controlled conditions -as it represents the efficacy of vaccines- is still questionable.28 Although eight vaccines have the emergency use listing (EUL) of the WHO, which means they have reliable trials guaranteeing their 50% or more efficacy, their effectiveness is disputable mostly due to the emergence of new COVID-19 variants and the differences in the characteristics of vaccine recipients.28,29

Hence, knowing the relationship between the time and immunogenicity of various COVID-19 vaccines can take the world a step toward curbing this pandemic down.

Vaccines induce immunity via the utilization of two components, a pathogen-specific immunogen, and an adjuvant. The former component carries the viral protein, while the latter is in charge of activating innate immunity and providing a second signal for T cell activation. An ideal adjuvant precisely activates innate immunity and does not lead to systemic inflammation resulting in severe adverse effects.30 In mRNA vaccines, mRNA serves as both the pathogen-specific immunogen and the adjuvant. These vaccines contain purified, in vitro-

| First author | Was the research described as randomized? | Was the approach of randomization appropriate? | Was the study blinded? | Was the approach of blinding appropriate? | Was there a representation of withdrawals and dropouts? | Was there a presentation of the inclusion/exclusion criteria? | Was the approach used to assess adverse effects described? | Was the approach of statistical analysis described? | Total |
|--------------|------------------------------------------|-----------------------------------------------|-----------------------|------------------------------------------|---------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|-------|
| Ramasamy, M. N.18 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 |
| Merryn Voysey17 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 3 |
| J. Sadoff16 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 6 |
| Nicole Doria-Rose19 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Widge, Alicia T20 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| Zijun Wang21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mark J. Mulligan22 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| Ugur Sahin23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Elisa Danese24 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Paul Naaber25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
Table 3. Summary of immunologic profile following COVID-19 vaccines from selected publication.

| First Author, year | Vaccine | Dosage | IgG antibodies* | Neutralizing effects | T cell responses | Others |
|---------------------|---------|--------|-----------------|----------------------|-----------------|--------|
|                     |         |        | Induction       | Persistence          | Induction       |         |
|                     |         |        | 1st dose        | 2nd dose             | 1st dose        | 2nd dose | Persistence | T cell responses |         |
| Ramasamy, M. N. 2020/18 | ChAdOx1 nCoV-19 (AZD1222) | low dose (0.22 mL) and standard dose (0.5 mL) | 2 doses in a period of 28 days to 12 weeks apart | Increased after 28 days after the 2nd dose | On day 28, decreased with increasing age | NA | No response | Spike-specific T-cell responses measured with ELISpot peaked at 14 days after the first dose | There was no significant difference between the doses; however, 18–55 age groups had higher antibody amounts. |
| Meryn Voysey 2021/17 | ChAdOx1 nCoV-19 (AZD1222) | Low dose (2-2 × 1010 viral particles) standard dose (5 × 1010 viral particles) | 2 doses in a period of 28 days to 12 weeks apart | Significant Production at day 28 | Remained stable until day 90, then decayed log linearly over 6 months. | Significant neutralization effect 22 days after the 1st dose | NA | Maintained until day 90 from the 1st dose | The T cell responses are induced 14–22 days after the first dose | The vaccine efficacy is higher in those receiving a low dose vaccine plus a high dose one with a 12 weeks interval between the two doses. |
| J. Sadoff 2021/16 | Ad26.COV2S | low dose (5 × 1010 viral particles) or high dose(1 × 1011 viral particles) | 2 doses 57 days apart | Significant Production after 29 days and increased at day 57 | There was no correlation between the magnitude of response and the 2nd dose. | Significant neutralization effect after 29 days and increased at day 57 | Until day 71 from the 1st dose | No significant difference was observed among several vaccine doses or age groups in antibody neutralizing effects. |
| Nicole Doria-Rose, 2021/19 | mRNA-1273 | 100 μg regimen s | 2 doses 29 days apart | Significant Production at day 15 and further increased at day 29 | Increased 7 days after the second dose | Remained stable with minimal waning until day 209 | Significant neutralizing effect at day 29 | Further, increase in neutralization effect 14 days after the 2nd dose | Remained stable with minimal waning until day 209 | NA | NA |
| Alicia T Widge. 2020/20 | mRNA-1273 | 100 μg regimen s | 2 shots, given 28 days apart | Significant Production at day 29 | Increased 14 days after the second dose | Remained stable with minimal waning until day 119 | Significant neutralizing effect at day 29 | Further, increase in neutralization effect 14 days after the 2nd dose | Remained stable with minimal waning until day 119 | CD4+ T-cell responses, specifically Th1 was induced 43 days after the 1st dose | NA |

(Continued)
| First Author, year | Vaccine | Amount | Dosage | Antibodies* | Effects | Persistence | T cell responses | Others |
|-------------------|---------|--------|--------|-------------|---------|-------------|-----------------|--------|
| Zijun Wang, 2021  | mRNA-1273 and BNT162b1 | Full dose regimen | 2 shots, given 28 days apart | Significant production 8 weeks after the 2nd dose | No response | Significant neutralizing effect 3–14 weeks after the 2nd dose | Decreased since day 28 | NA |
| Mark J. Mulligan, 2020 | BNT162b1 | 10 μg, 30 μg, and 100 μg regimens | 2 shots, given 21 days apart | Significant production at day 28 | Further increased 7 days after the 2nd dose | Decreased since day 28 | Further increased 7 days after the 2nd dose | NA |
| Ugur Sahin, 2020 | BNT162b1 | 1 μg, 10 μg, 30 μg, and 50 μg regimens | 2 shots, given 21 days apart | Modest production 21 days after the 1st dose | Further increased 7 days after the 2nd dose | Remained stable until day 43 | Further increased 7 days after the 2nd dose | NA |
| Elisa Danese, 2022 | BNT162b2 | 30 μg regimen | 2 shots, given 21 days apart | Significant production at day 11 and further increased at day 21 | Increased 7 days after the second dose | Remained stable with minimal waning until day 65 | Functional and proinflammatory CD4+ T-cell responses, specifically Th1 and the CD8+ T-cell responses, were observed 7 days after the 2nd dose | Immunogenicity appeared in a dose-dependent manner. |
| Paul Naaber, 2021 | BNT162b2 | NA | 2 shots, given 21 days apart | Significant production 21 days after the 1st dose | Increased 7 days after the second dose | Started to decline after one week but still detectable until 12 weeks (day 84) | Significant neutralizing effect 7 days after the 2nd dose | CD4+ and CD8+ T-cell responses were induced in the majority of individuals 12 weeks after the second dose | NA |

NA: Not applicable, which means no data regarding this issue was available.

*Types of IgGs: Anti-spike IgG and anti-RBD IgGs.
transcribed single-stranded mRNA with modified nucleotides. They bind less effectively to toll-like receptors (TLR) and immune sensors; therefore, restricting the excessive production of type I interferon and its inhibitory impact on cellular translation.31

This scenario differs in adenovirus (AdV) vaccines, as both vaccine components—the immunogen and the adjuvant-exist and are not the same like mRNA vaccines. Both components are embedded in the viral component encoding the immunogen’s DNA. AdV particles stimulate innate immune cells like dendritic cells and macrophages via binding to multiple pattern-recognition receptors and in particular to TLR9 resulting in the production of type I interferon.32

Vaccine-induced type I interferon facilitates the differentiation of CD4+ and CD8+ effector T cells, leading to cytotoxic and inflammatory mediators and the CD4+ T follicular helper (TFH) cells that promote the differentiation of B cells into antibody-secreting plasma cells.30

While mRNA and AdV vaccines induce optimal immunogenicity theoretically, the situation might differ in the real world. Thus, in this review, we discuss immunogenicity and particularly the relation between the timing of receiving vaccine shots and the presence of detectable amounts of anti-SARS-CoV-2 antibodies and T cell responses.

Starting with mRNA vaccines, the BNT162b2 showed the quickest vaccine-induced immune response; 7 to 11 days, for anti-spike IgA, and 11 to 21 days, for anti-spike IgG, after receiving the first dose of vaccine.20,24,25

It is also worth mentioning, the mRNA-1273 and the BNT162b2 vaccines induced the production of the anti-spike IgAs, which might be effective in preventing the asymptomatic spread.33

However, the BNT162b2 and the Ad26.COV2.S have a short duration of antibody persistence of about 2 months after the second dose.24,25 Findings of several cohorts and clinical trials have demonstrated that both symptomatic and asymptomatic COVID-19 infection after vaccination are not unexpected because vaccines could not be 100% effective. Host immune responses and susceptibility of new variants of SARS-CoV-2 for infection could be the cause of this failure. Given that immune response is multifrational and complex, it depends on both humoral and cellular immunity and it varies from person to person.34 The antibody persistence time of the mRNA-1273 vaccine is about 180 days (six months), following the AZD122 vaccine with 90 days.17–19

Indeed the antibody response raised by vaccines is roughly affected by not only the time but also the emergence of new SARS-CoV-2 variants; therefore, to mitigate the spread of this infection in the long run, a more effective immune response is needed.35,36

The T-cell response can serve as an optimal response in the long run; as was shown by Bange et al, 2021 higher levels of CD8+ T cell-mediated immunity was linked to the improvement of survival and the reduction of fatality, disease severity, or viral load among the patients with hematological malignancy receiving anti-CD20 therapy with low titers of anti-SARS-CoV-2-specific IgG considering the protective effects of CD8+ T cell-mediated immunity.37

Moreover, T-cell response can fight better with SARS-CoV-2 new variants due to the variation of the HLA-specific T-cell epitopes among individuals and their wide distribution across proteins; thus, escaping from T-cell response is much harder.36

Fortunately, the vaccines studied in this review elicit T-cell immunity providing a backup mechanism coping with new SARS-CoV-2 variants and the waning of humoral immunity—each one of the Ad26.COV2.S, AZD1222, mRNA-1273 vaccines elicit T-cell responses respectively, 15 days, 14–22 days, and 43 days from receiving the first vaccination dose.

Lastly, the BNT162b1 and the BNT162b2 vaccines promote T-cell immunity respectively after 7 days and 12 weeks from receiving the second vaccination dose. Look at Table 3 and Figure 1.
Although the function of these T-cell responses is still debatable and more studies are needed to approve their effectiveness and function, their presence might provide hopeful promises toward mitigating the spread of this pandemic and controlling its burden.

5. Limitations

Various limitations surround this review. To begin with, the focus of this review is mainly on the mRNA and viral vector vaccines; other EUA vaccines are missed due to the lack of data. Moreover, the reported results of this study are not comparable between various vaccines due to study protocol variations; for instance, we cannot say that only BNT162b2 and mRNA-1273 produce IgA. Other vaccines might have this capability, but it was not reported because it was not a part of the study protocol. Furthermore, some of the included studies have small sample sizes resulting in enormous differences between the reported outcomes and the real-world outcomes, making them unreal and biased for the general population (Table 1).

6. Conclusion

AZD1222, Ad26.COV2.S, mRNA-1273, BNT162b1, and BNT162b2 vaccines have an acceptable immunogenicity and vaccine persistence of up to two months after the second dose (except for Ad26.COV2.S, which is administered at only one dose).

In summary, in this systematic review, we summarize key immunological data following four of the currently approved COVID-19 vaccines, while the immunogenicity of other vaccines is being explored at ongoing trials. More studies are needed on wider populations with various genetic and environmental backgrounds to emphasize and generalize these results.

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