HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2037384 (10 pages)
https://doi.org/10.1080/21645515.2022.2037384

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

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

Elham Jamshidi[a], Amirhossein Asgary[b], Paria Shafiekhani[c], Yasaman Khajeamiri[d], Kawthar Mohamed[e,f], Hadi Esmaily[d], Sahand Jamal Rahi[g], and Nahal Mansouri[h,i,j]

[a]Functional Neurosurgery Research Center, Shohada Tajrish Comprehensive Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [b]Department of Biotechnology, College of Sciences, University of Tehran, Tehran, Iran; [c]USERN office, Functional Neurosurgery Research Centre, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [d]School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [e]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; [f]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Manama, Bahrain; [g]Laboratory of the Physics of Biological Systems, Institute of Physics, École polytechnique fédérale de Lausanne (EPFL), Lausanne, Switzerland; [h]Division of Pulmonary Medicine, Department of Medicine, Lausanne University Hospital (CHUV), University of Lausanne (UNIL), Lausanne, Switzerland; [i]Research Group on Artificial Intelligence in Pulmonary Medicine, Division of Pulmonary Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland; [j]Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, École polytechnique fédérale de Lausanne (EPFL), Lausanne, Switzerland

ABSTRACT

It is unknown how long the immunity following COVID-19 vaccination lasts. The current systematic review provides a perspective on the persistence of various antibodies for available vaccines.Both the BNT162b2 and the mRNA-1273 induce the production of IgA antibodies, reflecting the possible prevention of the asymptomatic spread. The mRNA-1273 vaccine's antibodies were detectable until 6 months, followed by the AZD1222, 3 months, the Ad26.COV2.S and the BNT162b2 vaccines within 2 months.The BNT162b2 produced anti-spike IgGs 11 days after the first dose and peaked at day 21, whereas the AZD1222 induced a neutralizing effect 22 days after the first dose.These vaccines induce T-cell mediated immune responses too. Each one of the AZD1222, Ad26.COV2.S, mRNA-1273 mediates T-cell response immunity at days 14-22, 15, and 43 after the first dose, respectively. Whereas for the BNT162b1 and BNT162b2 vaccines, T-cell immunity is induced 7 days and 12 weeks after the booster dose, respectively.

ARTICLE HISTORY
Received 12 September 2021
Revised 13 January 2022
Accepted 31 January 2022

KEYWORDS
COVID-19; Vaccines; SARS-CoV-2; Immunogenicity; Humoral immunity; Cell-mediated immunity; Antibody persistence; Long-term protection; Long-term immunity

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 19th,2021.[1] 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.[2,3] Indeed, an ideal vaccine should elicit long-term protection.[4]

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, other 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.[5]

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.[6]

CONTACT Nahal Mansouri nahal.mansouri@chuv.ch Lausanne University Hospital(CHUV), University of Lausanne (UNIL), Rue du Bugnon 21, 1011, Lausanne, Switzerland

© 2022 The Author(s). Published with license by Taylor & Francis Group, LLC.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

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.[7] 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.[8]

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.[9]

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.[10] 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.[11,12] 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.[10] 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.[13]

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.[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? 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.[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 addressedissues 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)

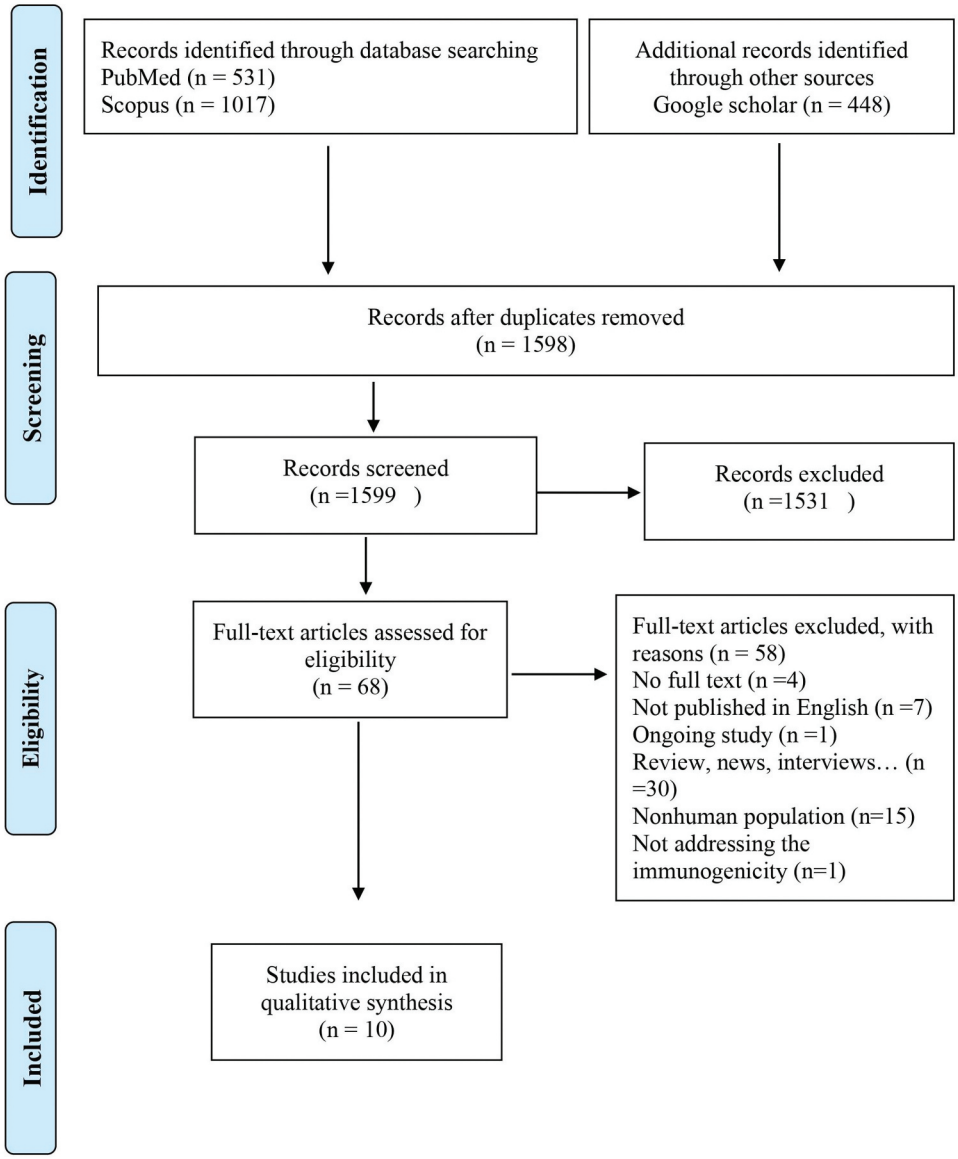

Figure 1. This diagram represents all systematic review phases with the number of excluded or included studies in each phase.

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.,[16,17] 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.[17,18]

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

Table 1. Studies characteristics.

First author, year	Country	Study type	Age groups	Sample size	Vaccine	Manufacturer
Ramasamy, M. N et al. 2020[18]	UK	phase 2/3 RCT	18–55 yr 56–69 yr70 yr ≥	Intervention group = 420 Placebo = 140	ChAdOx1 nCoV-19 (AZD1222)	Advent (Pomezia, Italy), COBRA Biologics (Keele, UK)
Merryn Voysey 2021[17]	Brazil, South Africa, and the UK	RCT	COV001 18–55 yr (UK trial), COV002 (UK) and COV003 (Brazil) 18 ≤ healthcare personnel, COV005 (South Africa) 18–65 yr	Intervention group = 8597 Placebo group = 8581	ChAdOx1 nCoV-19 (AZD1222)	Oxford–AstraZeneca (UK, Sweden)
J. Sadoff 2021[16]	Belgium and the USA	phase 1–2a RCT	18–55 yr, 65 yr ≥,	Intervention group = 642 Placebo group = 642	Ad26.COV2.S	Johnson & Johnson (USA)
Nicole Doria-Rose 2021[19]	England	phase 1 RCT	18–55 yr, 56–70 yr, 70 yr ≥	Intervention group = 33 Placebo group= NA	Moderna mRNA-1273	ModernaTX, Inc (USA)
Alicia T. Widge, 2020[20]	USA	Phase 1 trial	18–55 yr, 56–70 yr, 71 yr≥	Intervention group = 34 Placebo group = 41	Moderna (mRNA-1273)	ModernaTX, Inc (US)
Zijun Wang 2021[21]	USA	Cohort	29–69 yr	Intervention group = 20 Placebo group= NA	Moderna (mRNA-1273) Pfizer–BioNTech (BNT162b1)	ModernaTX, Inc and BioNTech (USA), Pfizer, Inc (Germany)
Mark J. Mulligan 2020[22]	USA	Cohort	19–54 yr	Intervention group = 36 Placebo group = 9	Pfizer–BioNTech (BNT162b1)	Pfizer, Inc(Germany) and BioNTech (USA)
Ugur Sahin 2020[23]	Germany	Cohort	20–56 yr	Intervention group = 60 Placebo group = 38	Pfizer–BioNTech (BNT162b1)	Pfizer, Inc(Germany) and BioNTech (USA)
Elisa Danese 2021[24]	Italy	Case series	44 yr, 39 yr, and 53 yr	3 people case series	Pfizer–BioNTech (BNT162b2)	Pfizer, Inc(Germany) and BioNTech (USA
Paul Naaber 2021[25]	Eswatini	Cohort	21–69 yr	Intervention group = 122 Placebo group = 147	Pfizer–BioNTech (BNT162b2)	Pfizer, Inc(Germany) and BioNTech (USA

Table 2. Quality assessment table.

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	6
Merryn Voysey[17]	1	0	1	0	0	0	0	1	3
J. Sadoff[16]	1	1	1	1	0	0	1	1	6
Nicole Doria-Rose[19]	1	1	0	0	0	0	0	0	2
Widge, Alicia T[20]	0	0	0	0	0	0	0	1	1
Zijun Wang[21]	0	0	0	0	0	0	0	0	0
Mark J. Mulligan[22]	1	1	1	1	0	1	1	1	7
Ugur Sahin[23]	0	0	1	0	1	1	1	1	5
Elisa Danese[24]	0	0	0	0	0	0	0	1	1
Paul Naaber[25]	0	0	0	0	0	0	1	1	2

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-

Table 3. Summary of immunologic profile following COVID-19 vaccines from selected publication.

		Dosage		IgG antibodies*			Neutralizing effects				
				Induction			Induction				
First Author, year	Vaccine	Amount	No.	1st dose	2nd dose	Persistence	1st dose	2nd dose	Persistence	T cell responses	Others
Ramasamy, M. N. 2020[18]	ChAdOx1 nCoV-19 (AZD1222)	low dose 0·22 mL) and standard dose (0·5 mL)	2 doses given 28 days apart	28 days after.	Increased After 28 days after the 2ne dose	On day 28, decreased with increasing age	Peaked after 28 days	No response	NA	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.
Merryn 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	NA	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.COV2.S	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.	Until day 71 from the 1st dose	Significant neutralization effect after 29 days and increased at day 57	There was no correlation between the magnitude of response and the 2nd dose.	Until day 71 from the 1st dose	Th1 responses were observed on day 15 at a dose-dependent and age-dependent manner, and no Th2 response was observed. CD8+ cell responses were similar with an exception to the ≥65 yr age group having higher response rates with low doses.	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*)

Table 3. (Continued).

		Dosage		IgG antibodies*			Neutralizing effects				
				Induction			Induction				
First Author, year	Vaccine	Amount	No.	1st dose	2nd dose	Persistence	1st dose	2nd dose	Persistence	T cell responses	Others
Zijun Wang, 2021[21]	mRNA-1273 and BNT162b1	Full dose regimen	2 shots, given 28 days apart	NA	Significant production 8 weeks after the 2nd dose	NA	No response	Significant neutralizing effect 3–14 weeks after the 2nd dose	NA	NA	–There was no significant difference in the results of both vaccines. –IgA was produced in the same manner but in fewer amounts compared to IgG.
Mark J. Mulligan 2020[22]	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	Little neutralizing effect 21 days after the 1st dose	Significant neutralizing effect 7 days after the 2nd dose	neutralizing effect further increased at day 35	NA	NA
Ugur Sahin 2020[23]	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	Modest neutralizing effect 21 days after the 1st dose	Further increased 7 days after the 2nd dose	Remained stable until day 43	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.
Elisa Danese 2021[24]	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	NA	NA	NA	NA	Anti-S1 IgA levels increased between 7 and 11 days after the 1st dose and further increased 7 days after the 2nd dose.
Paul Naaber 2021[25]	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)	No response	Significant neutralizing effect 7 days after the 2nd dose	Started to decline after one week but still detectable until 12 weeks (day 84)	CD4+ and CD8+ T-cell responses were induced in the majority of individuals12 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.

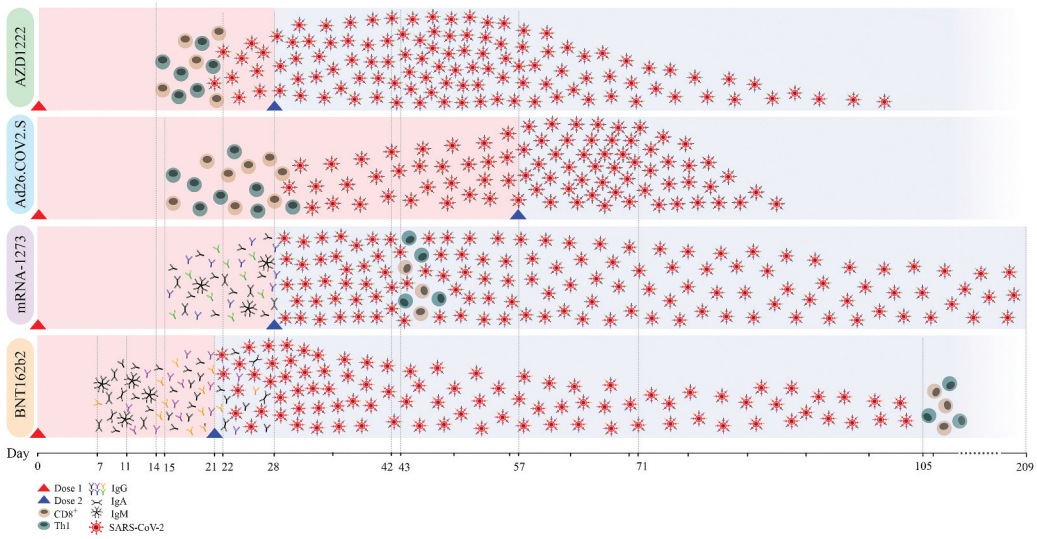

Figure 2. This figure illustrates the timeline of the immune responses induced by the AZD122, Ad26.COV.S,mRNA-1273, and BNT16b2 vaccines. the neutralizing effect was assessed by addingthe plasma of the vaccine recipients to SARS-CoV-2 spike antigens in vitro. TheBnt16b2 vaccine has the earliest detectable immune response by producing IgG,igm, and IgA at day 7; the neutralizing effect started at day 21 and continueduntil day 105. the mRNA-1273 vaccine immune response began at day 15, while theneutralizing effect started from day 28 and persisted until day 209. TheAd26.Cov.s immune response began with T-cell responses on day 15, while the neutralizingeffect started at day 28 and persisted until day 71. the AZD122 vaccine'simmune response began at day 15, while the neutralizing effect began at day 21 andlasted until day 90.

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 vacccines. 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 multifractional 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 EUL 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.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Nahal Mansouri http://orcid.org/0000-0002-8348-0737

References

1. WHO coronavirus (COVID-19) dashboard [Internet]. [accessed 2021 Sep 10]. https://covid19.who.int/
2. Copper FA, de Vázquez CC, Bell A, Mayigane LN, Vedrasco L, Chungong S, de Vázquez CC. Preparing for COVID-19 vaccine roll-out through simulation exercises. Lancet Glob Health. 2021; 9 (6):e742–3. doi:10.1016/S2214-109X(21)00051-6.
3. Burki TK. Challenges in the rollout of COVID-19 vaccines worldwide. Lancet Respir Med. 2021;9(4):e42–3. doi:10.1016/S2213-2600(21)00129-6.
4. Criteria for COVID-19 vaccine prioritization [Internet]. [accessed 2021 Sep 10]. https://www.who.int/publications/m/item/criteria-for-covid-19-vaccine-prioritization
5. Lai CKC, Lam W. Laboratory testing for the diagnosis of COVID-19. Biochem Biophys Res Commun. 2021;538:226–30. doi:10.1016/j.bbrc.2020.10.069.
6. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. Physiol Res. 2020;69:379–88. doi:10.33549/physiolres.934492.
7. Salehi-Vaziri M, Jalali T, Farahmand B, Fotouhi F, Banifazl M, Pouriayevali MH, Sadat Larijani M, Afzali N, Ramezani A. Clinical characteristics of SARS-CoV-2 by re-infection vs. reactivation: a case series from Iran. Eur J Clin Microbiol Infect Dis. 2021;40 (8):1713–19. doi:10.1007/s10096-021-04221-6.
8. Murchu EO, Byrne P, Carty PG, De Gascun C, Keogan M, O'-Neill M, Harrington P, Ryan M. Quantifying the risk of SARS-CoV-2 reinfection over time. Rev Med Virol. 2021:e2260. doi:10.1002/rmv.2260.
9. Giurgea LT, Memoli MJ. Navigating the Quagmire: Comparison and interpretation of COVID-19 vaccine phase 1/2 clinical trials. Vaccines (Basel) 2020;8(4):746 doi:10.3390/vaccines8040746.
10. Xing K, Tu X-Y, Liu M, Liang Z-W, Chen J-N, Li J-J, Jiang L-G, Xing F-Q, Jiang Y. Efficacy and safety of COVID-19 vaccines: a systematic review. Zhongguo Dang Dai Er Ke Za Zhi. 2021;23:221–28.
11. Yan Z-P, Yang M, Lai C-L. COVID-19 vaccines: a review of the safety and efficacy of current clinical trials. Pharmaceuticals. 2021;14(5):406. doi:10.3390/ph14050406.
12. Sagili Anthony DP, Sivakumar K, Venugopal P, Sriram DK, George M. Can mRNA vaccines turn the tables during the COVID-19 pandemic? Current status and challenges. Clin Drug Investig. 2021;41(6):499–509. doi:10.1007/s40261-021-01022-9.
13. Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: a systematic review. Phys Ther. 2008;88(2):156–75. doi:10.2522/ptj.20070147.
14. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12. doi:10.1016/0197-2456(95)00134-4.
15. Oremus M, Wolfson C, Perrault A, Demers L, Momoli F, Moride Y. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. Dement Geriatr Cogn Disord. 2001;12(3):232–36. doi:10.1159/000051263.
16. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med. 2021;384(19):1824–35. doi:10.1056/NEJMoa2034201.
17. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE et al. Single-Dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdox1 nCov-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881–91. doi:10.1016/S0140-6736(21)00432-3.
18. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, Voysey M, Aley PK, Angus B, Babbage G et al. Safety and immunogenicity of ChAdox1 nCov-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020;396(10267):1979–93. doi:10.1016/S0140-6736(20)32466-1.
19. Doria-Rose N, Suthar MS, Makowski M, O'-Connell S, McDermott AB, Flach B, Ledgerwood JE, Mascola JR, Graham BS, Lin BC et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. N Engl J Med. 2021;384 (23):2259–61. doi:10.1056/NEJMc2103916.
20. Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. 2021;384(1):80–82. doi:10.1056/NEJMc2032195.

21. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, Schaefer-Babajew D, Cipolla M, Gaebler C, Lieberman JA et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592:616–22. doi:10.1038/s41586-021-03324-6.
22. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Raabe V, Bailey R, Swanson KA et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589–93. doi:10.1038/s41586-020-2639-4.
23. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D et al. COVID-19 vaccine BNT162b1 elicits human antibody and T H 1 T cell responsesNature 2020 [accessed 2021 Jul 15]. 586 (7830):594–99. doi:10.1038/s41586-020-2814-7.
24. Danese E, Montagnana M, Salvagno GL, Peserico D, Pighi L, De Nitto S, Henry BM, Porru S, Lippi G. Comprehensive assessment of humoral response after Pfizer BNT162b2 mRNA Covid-19 vaccination: a three-case series. Clin Chem Lab Med. 2021;59 (9):1585–91. doi:10.1515/cclm-2021-0339.
25. Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, Haljasmägi L, Rumm P, Maruste R, Kärner J, et al. Declined antibody responses to COVID-19 mRNA vaccine within first three months. medRxiv [Internet] 2021 [cited 2021 Jul 15]. 2021.04.19.21255714. https://www.medrxiv.org/content/10.1101/2021.04.19.21255714v2.full
26. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ, Lee BW, Lolekha S, Peltola H, Ruff TA et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. Bull World Health Organ. 2008;86(2):140–46. doi:10.2471/blt.07.040089.
27. Banatvala J, Van Damme P, Oehen S. Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory. Vaccine. 2000;19:877–85. doi:10.1016/s0264-410x(00)00224-3.
28. Vaccine efficacy, effectiveness and protection [Internet]. [accessed 2021 Nov 22]. https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection
29. WHO issues emergency use listing for eighth COVID-19 vaccine [Internet]. [accessed 2021 Nov 22]. https://www.who.int/news/item/03-11-2021-who-issues-emergency-use-listing-for-eighth-covid-19-vaccine
30. Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol. 2021;21 (4):195–97. doi:10.1038/s41577-021-00526-x.
31. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261–79. doi:10.1038/nrd.2017.243.
32. Sayedahmed EE, Elkashif A, Alhashimi M, Sambhara S, Mittal SK. Adenoviral vector-based vaccine platforms for developing the next generation of Influenza vaccines. Vaccines (Basel). 2020;8. doi:10.3390/vaccines8040574.
33. Bleier BS, Ramanathan M Jr, Lane AP. COVID-19 vaccines may not prevent nasal SARS-CoV-2 infection and asymptomatic transmission. Otolaryngol–head Neck Surg. 2021;164(2):305–07. doi:10.1177/0194599820982633.
34. Alidjinou EK, Gaillot O, Guigon A, Tinez C, Lazrek M, Bocket L, Engelmann I, Hober D. SARS-CoV-2 infection long time after full vaccination is related to a lack of neutralizing antibodies. Diagn Microbiol Infect Dis. 2022;102(1):115565. doi:10.1016/j.diagmicrobio.2021.115565.
35. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, Planchais C, Porrot F, Robillard N, Puech J et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596:276–80. doi:10.1038/s41586-021-03777-9.
36. Noh JY, Jeong HW, Kim JH, Shin E-C. T cell-oriented strategies for controlling the COVID-19 pandemic. Nat Rev Immunol. 2021;21(11):687–88. doi:10.1038/s41577-021-00625-9.
37. Bange EM, Han NA, Wileyto P, Kim JY, Gouma S, Robinson J, Greenplate AR, Hwee MA, Porterfield F, Owoyemi O et al. CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer. Nat Med. 2021;27(7):1280–89. doi:10.1038/s41591-021-01386-7.