COVID-19 Vaccines in Patients With Chronic Liver Disease

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The COVID-19 pandemic has caused mayhem globally since the beginning of 2020. Owing to the immune dysfunction inherent to cirrhosis and the poor general condition, patients with chronic liver disease (CLD) are at higher risk of mortality and morbidity due to COVID-19. Recently, a number of vaccines against SARS-Cov-2 have been approved for emergency use around the globe. Although the phase 2/3 trials of these vaccines show them to be safe and effective in the general population, data in patients with CLD are scarce. The number of patients with CLD enrolled on these trials is small, and no liver-related adverse effects have been reported yet. Various liver societies have come up with guidelines on vaccination in this population and recommend vaccination on a priority basis. Trials to assess the safety and efficacy of the COVID vaccines are underway and are likely to provide valuable insight into this matter. (J Clin Exp Hepatol 2021;11:720–726)

The year 2020 was marked by a global pandemic that devastated developed and developing nations alike. Severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) infection spread all over the world relentlessly, causing coronavirus disease 2019 (COVID-19), which resulted in significant morbidity and mortality. Patients with pre-existing comorbidities and chronic illnesses were more vulnerable to disease and death caused by the virus. Patients with chronic liver disease (CLD) were noted to have higher mortality and decompensation after SARS-Cov-2 infection. However, the year also saw unprecedented scientific progress and human endeavour, which culminated in the discovery of a number of vaccines, which are currently being administered to the global population in a phased manner. Our understanding of the risks and benefits of the COVID-19 vaccine in patients with CLD is still evolving. This review aims at summarizing the currently available evidence regarding COVID-19 vaccines in this population.

RISK OF SARS-COV-2 INFECTION IN CLD

Patients with CLD have a greater risk of adverse outcome with SARS-Cov-2 infection than the general population. International registry-based data from 745 patients from 29 countries with CLD showed that mortality after SARS-Cov-2 infection was four times patients with cirrhosis compared with the non-cirrhotic population. Age, increasing Child-Pugh class and alcohol as the aetiology of cirrhosis were independent predictors of mortality in this cohort. Moreover, half of the patients with decompensation after SARS-Cov-2 infection had acute on chronic liver failure (ACLF), a condition that inherently carries a higher short-term mortality.[1] Various mechanisms have been postulated for this increased mortality in CLD patients. Cirrhosis-associated immune dysfunction, characterized by immune dysregulation leads to persistent systemic inflammation and increased susceptibility to infections.[2] Endotoxemia associated with cirrhosis leading to an exaggerated immune response and alteration in gut microbiota leading to immune dysregulation may contribute to the increased disease severity and mortality.[2] A related consequence of the alterations in the immune system in cirrhosis is vaccine hyporesponsiveness to non-COVID vaccines. Immunogenicity to hepatitis A virus and hepatitis B virus vaccines decreases with increasing severity of cirrhosis and can be addressed by administering higher vaccine doses.[3]

The APCOLIS study from Asia reported outcomes of CLD patients with confirmed COVID infection. Of 228 patients, 20% cirrhotics presented as ACLF and mortality was noted in 43% of the decompensated cirrhotics. The complications increased with the severity of liver disease.[4]

COVID VACCINES UNDER DEVELOPMENT

The vaccines against SARS-Cov-2 can be categorized based on the platform they are developed on into mRNA vaccines, adenovirus vector vaccines and whole virion inactivated vaccines.

Keywords: COVID-19 vaccines, cirrhosis, liver diseases
Received: 7.4.2021; *Accepted:* 13.6.2021; *Available online 19 June 2021*
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Abbreviations: ACLF: acute on chronic liver failure; CLD: chronic liver disease; COVID-19: coronavirus disease 2019; HCC: hepatocellular carcinoma; SARS-Cov-2: severe acute respiratory syndrome coronavirus-2
https://doi.org/10.1016/j.jceh.2021.06.013

mRNA-based vaccines

mRNA-based vaccines involve the delivery of synthetic mRNA into the cytoplasm of the host, which uses the host ribosomes to translate into antigenic proteins that induce immunity against the virus.[3] Pfizer BioNTech vaccine (BNT162b2) and Moderna vaccine (mRNA-1273) belong to this class and contain mRNA that codes for the spike protein used by the virus to gain entry into the host.

Adenovirus vector vaccines

These involve the use of a replication incapable adenovirus as a vector to introduce the DNA coding for the spike protein into the host cells.[3] The AstraZeneca-University of Oxford vaccine (ChAdOx1 nCoV-19) and Johnson and Johnson vaccine belong to this category (JNJ-78436735).

Whole virion inactivated vaccine

The Bharat Biotech vaccine (BBV152) belongs to this category and contains β-propiolactone-inactivated whole virion.[5]

SAFETY AND EFFICACY OF THE INDIVIDUAL VACCINES

1. **Pfizer-BioNTech vaccine (BNT 162b2)**

The BNT 162b2 is an mRNA vaccine, which is administered as two doses of 30 μg each via the intramuscular route 21 days apart.[6] The vaccine is available in multidose vials and needs to be stored at $-60°$ to -80 °C,[3] which may prove to be a logistic hurdle in developing countries. It was authorized for emergency use by the FDA based on the ongoing phase 1/2/3 randomized placebo-controlled trial published in December 2020. In the trial, 43,448 volunteers were randomized to the vaccine arm and placebo arm in a 1:1 ratio. The vaccine demonstrated 95% efficacy in preventing COVID-19 when compared with placebo, which was maintained for subgroups defined by age, sex, body mass index, ethnicity and comorbidities. Among adverse events, local site reactions were the most frequent. Systemic symptoms like fever, joint pains and chills occurred more commonly in the young patients and were more common after the second dose.[7]

The above trial included 214 patients with mild liver disease and only three patients with moderate or severe liver disease. Patients with hepatitis B and hepatitis C infection were included, although the virological status and disease severity of these patients is not known. Patients on immunosuppressive medication were excluded. Hence, there is a paucity of available data on patients with liver disease.

2. **Moderna vaccine (mRNA-1273)**

The mRNA-1273 is also an mRNA vaccine that is administered in two doses of 100 μg each 28 days apart. It was licensed for use by the FDA based on an ongoing phase 3 randomized placebo-controlled trial published in December 2020, wherein 30,420 volunteers were randomized into the vaccine and placebo groups in a 1:1 ratio. The vaccine demonstrated an efficacy of 94.1% in preventing COVID-19. Severe COVID-19 occurred only in the placebo group with one fatality. Vaccine-related serious unsolicited adverse events occurred more commonly in the vaccine group but none resulted in fatality or study discontinuation. The unsolicited systemic and local reactions occurred more commonly after the second dose and in younger individuals.[8]

The trial included a total of 196 patients with liver disease (distributed almost equally between vaccine and placebo group), although the liver disease was not defined. Patients on systemic immunosuppressive medication were excluded from the trial. Efficacy and safety data were not available separately for the patients with liver disease.[8]

3. **ChAdOx1 nCoV-19 vaccine (AZD1222)**

The ChAdOx1 nCoV-19 vaccine (AZD1222), developed by the University of Oxford, contains replication-deficient chimpanzee adenovirus as a vector carrying the gene encoding for the SARS-Cov-2 spike glycoprotein. The storage requirements are less stringent than for mRNA vaccines and can be stored between 2 and 8 °C.[9] It is manufactured by AstraZeneca and Serum Institute of India (SII). The AstraZeneca manufactured vaccine was licensed for emergency use in the United Kingdom (UK) in December 2020.[3] The drug controller general of India (DCGI) gave its approval for use of the vaccine in India, manufactured by SII under the trade name COVISHIELD™.[9] The vaccine is administered in two intramuscular doses of 0.5 ml each, 4–6 weeks apart. Antibody responses peaked on day 28 in patients who received a single dose and on day 56 in patients who received a booster dose 28 days after the first dose.[10] The approval was granted based on a pooled interim analysis of four randomised controlled trials, done in UK, Brazil and South Africa, which together recruited 23,848 participants and 11,636 participants were included in the interim analysis. The trial demonstrated overall vaccine efficacy of 70.1%. Ten cases of COVID were reported after 21 days of vaccination and all were in the control arm included two cases of severe COVID and one death. Adverse events were noted in 175 cases, with only three possibly vaccine-related events.[11]

The four trials mentioned earlier largely excluded the patients with liver disease. The trials conducted in UK and Brazil excluded patients with "severe" liver disease, although the criteria for severity were not clarified. Furthermore, they also excluded volunteers on immunosuppressive medications and those with alcohol dependency. The trial conducted in South Africa mentions liver function tests (LFTs) abnormalities, Australian antigen positivity, CLD and alcohol abuse as exclusion criteria.

Liver function abnormalities were noted in only two patients (one each in vaccine and control groups).[11]

According to the interim report of an Indian phase 2/3 randomised placebo-controlled trial that recruited 1600 volunteers, seroconversion for anti-S IgG antibody was noted in 100% of participants who received COVISHIELD after 57 days of the second dose. Again, separate data are not available for patients with liver disease.[9]

4. **BBV152 vaccine**

The BBV152 is a whole virion inactivated vaccine, manufactured by Bharat Biotech under the trade name COVAXIN™. It was licensed for emergency use by the DCGI in January 2021. Two doses of the vaccine 28 days apart are recommended via the intramuscular route, each dose containing 6 μg of the whole virion inactivated coronavirus antigen.[12]

In a phase 2 trial of the vaccine, 380 patients were enrolled and randomised equally into two groups, both of which received the BBV152, but at different doses (3 μg and 6 μg). The primary outcomes were SARS-Cov-2 wild type neutralising antibody titres and seroconversion rates on day 56 and both were higher in the 6 μg group. This dose was chosen for the phase 3 study. The trial excluded patients on immunosuppressive medications and those with CLD.[13]

Interim results of the phase 3 trial were announced in a press release by the Indian council for medical research claiming a vaccine efficacy of 81%.[14] A study also showed the BBV152 vaccine to be effective against the UK variant of SARS-Cov-2.[15]

Table 1 summarizes currently available data on different COVID vaccines in patients with liver disease.

INTERVAL BETWEEN TWO DOSES OF THE VACCINE

The COVID-19 vaccination programme started in India on January 16, 2021, wherein citizens were vaccinated with COVISHIELD™ and COVAXIN™. Initially, the recommended interval between the two doses was 4–6 weeks. The Govt of India announced on March 22, 2021, that the interval is increased to 6–8 weeks for COVISHIELD™ in view of recent literature showing increased efficacy with this interval. The schedule for COVAXIN™, however, remains unchanged from before.[16]

It is not recommended at present to measure antibody titres after vaccination.[3]

CONCERNS REGARDING THE USE OF COVID VACCINES IN CLD PATIENTS

As summarised earlier, data regarding COVID vaccines in CLD patients are sparse. As patients with CLD have decreased immunogenicity to non-COVID vaccines, it is not yet clear whether the COVID vaccines will induce sufficient and durable immune response to the virus similar to individuals without CLD. The role of increasing severity of liver disease in determining the immune response to COVID vaccine also remains unclear at present. Although the trials conducted did not report significant hepatotoxicity, the number of liver disease patients enrolled were too less to conclude unequivocally regarding safety of the vaccines in this population. It is likely that more data in patients with CLD will emerge with postmarketing surveillance. However, currently, many trials are on-going, worldwide, in patients with liver disease as summarized in Table 2.

Nevertheless, despite all the aforementioned recommendations, in view of the higher risk of COVID-19–related mortality in CLD patients, EASL and AASLD recommend prioritisation of COVID-19 vaccination in patients with advanced liver disease as well as those with immune-mediated liver disease on immunosuppression.[3,17]

Patients with CLD on antivirals or immunosuppressive medications should not withhold their medications around the time of vaccination. But patients with recent fever are recommended not to get vaccinated till the infection is controlled.[3]

SPECIAL POPULATIONS

1. **Liver transplant recipients and donors**

All the trials conducted on COVID vaccines excluded patients on immunosuppressive medications, thereby raising certain concerns in the post-transplant setting. It remains to be seen whether vaccine efficacy and durability of immune response will be similar to the general population in the post-transplant patients on immunosuppression. Furthermore, as the immunosuppression is highest immediately post-transplant, the timing of vaccination in relation to the transplant is unclear. Also, any worsening of LFTs after vaccination may be difficult to interpret in post-transplant patients.

AASLD recommends COVID-19 vaccination in all patients who have undergone liver transplantation, preferably at least 3 months after liver transplant, once the immunosuppression has been reduced. Patients with ongoing acute rejection are recommended to get vaccinated after rejection has been tackled. It does not recommend lowering of immunosuppression to increase the immunogenicity of the vaccine. Any rise in LFT should be thoroughly investigated to rule out rejection.[3]

Although it is better to receive the vaccine before liver transplant, deceased donor transplant should not be delayed due to vaccination. However, donors and recipients of live-related liver transplant should preferably receive the second dose of the vaccine at least two weeks before transplant.[3]

2. **Patients with hepatocellular carcinoma (HCC)**

According to the AASLD recommendations, patient with HCC should be considered for vaccination. It is not recommended to interrupt locoregional or systemic therapy for HCC for the purpose of vaccination.[3]

Table 1 Summary of Existing Data on COVID-19 Vaccines in Patients With Liver Disease.

Name of vaccine	Type of vaccine	Data in general population	Data in patients with liver disease
Pfizer-BioNTech vaccine (BNT 162b2)[7]	mRNA vaccine	Efficacy: 95% compared to placebo Adverse events: Total AR = 26.7% Most common AR = pain at the injection site, fatigue and headache Serious AR = 0.6% Including shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia and right leg paraesthesia	214 patients with mild liver disease and 3 patients with moderate and severe liver disease included Liver transplant recipients and autoimmune liver disease on steroids excluded Results not reported separately
Moderna vaccine (mRNA-1273)[8]	mRNA vaccine	Efficacy: 94.1% compared to placebo Local AR: 84.2%–88.6% Most common AR: local pain Systemic AR: 54.9–79.4% Most common: fatigue, myalgia, arthralgia Serious AR-1%	196 patients included Patients on immunosuppression excluded Results not reported separately
ChAdOx1 nCoV-19 vaccine (AZD1222)[11]	Adenovector virus vaccine	Efficacy: 70.4% Serious AR: 0.7%	The study included four different trials conducted in different centres Excluded liver function tests abnormalities, Australian antigen positivity, chronic liver disease, alcohol abuse, patients on immunosuppression. Liver function abnormality: 2 patients Results not reported separately for patients with liver disease
BBV152 vaccine[14]	Whole virion inactivated vaccine	Seroconversion achieved in 92.9–98.3%	Phase 2 data were published Local AR: 3.7–4.7% Systemic AR: 5.8–7.4% Patients with chronic liver disease and those on immunosuppression were excluded

Table 2 On-Going Trials on COVID-19 Vaccines in Patients With Liver Disease.

Brief title	Investigators	Study population	Intervention	Characteristics	Outcome
Antibody Response to COVID-19 Vaccines in Liver Disease Patients NCT04775069[18]	Humanity and Health Medical Group Limited, Hong Kong	Chronic liver disease	Vaccines: a. BNT162b2 b. CoronaVac c. AZD1222	• Phase 4 • Non-randomized • Open Label	Antibody response
Safety and Efficacy of a Non-replicating ChAdOx1 Vector Vaccine AZD1222 (COVISHIELD), for Prevention of COVID-19 in Patients With Liver Cirrhosis NCT04794946[20]	Institute of Liver & Biliary Sciences, New Delhi, Delhi, India	Liver cirrhosis	COVISHIELD	• Phase 3 • Non-randomized • Open-label	• Proportion of patients with antibody titres • Proportion of patients with adverse events • Profile of immune cells and cytokine signatures after vaccination • Incidence of first case of SARS-CoV-2 RT-PCR positive symptomatic illness and first case of RT-PCR proven severe illness after vaccination
Vaccine Response to COVID-19 Vaccines in Patients Using Immunosuppressive Medication NCT04798625[21]	• Akershus University Hospital, Lùrenskog, Norway • Diakonhjemmet Hospital, Oslo, Norway	Patient on immunosuppressives • Rheumatoid arthritis • Psoriatic arthritis • Spondyloarthritis • Crohn disease • Ulcerative colitis • Autoimmune hepatitis • Liver transplant; complications	COVID-19 vaccine (not specified)	• Prospective observational study	• Serological response • Cellular response • Adverse events • BASDAI • Partial Mayo score • Harvey-Bradshaw index (HBI)
A Study to Evaluate Vaccines Against COVID-19 in the Real World NCT04775056[22]	Humanity & Health Medical Group, Hong Kong	• Chronic liver disease • Hepatic carcinoma	COVID-19 vaccine (not specified)	• Prospective observational study	• Immunogenicity index-seroconversion rates of neutralizing antibody • Safety index-incidence of adverse reactions • Immunogenicity index-seropositive rates of neutralizing antibody

The data regarding safety and efficacy of COVID-19 vaccines in CLD are sparse. However, there is sufficient data regarding the increased COVID-19–related mortality in this population. Presently, clinical trials are ongoing to measure the immunogenicity and safety of the available COVID vaccines in patients with CLD.[18] Registries like the SECURE-cirrhosis and COVID-Hep are also constantly yielding such data on a large scale.[19] But, considering the devastation already caused by the pandemic, we cannot afford to wait till such data come out.

The data on vaccines, although limited, do not report significant liver-related adverse event in the vaccinated population. There is also a lack of head-to-head trials as to which vaccine is superior in patients with liver disease. Such information is difficult to deduce from the existing literature, as vaccine trials largely excluded patients with significant hepatic impairment. Hence, in view of the high rate of complications and decompensation caused by COVID-19 in CLD, we feel that all patients with CLD should undergo vaccination. We do not have enough data to recommend any particular vaccine over the other. The international liver societies also recommend prioritised vaccination of patients with CLD. Studies in the future are likely to improve our understanding of the subject and vaccination may be tailored for CLD patients, but till then the fight must continue with whatever weapons we have.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Initial draft prepared by AS, AK and modified by IP. Review and approval of final draft were done by RG.

CONFLICTS OF INTEREST

The authors have none to declare

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J Hepatol*. 2021;74:567–577. https://doi.org/10.1016/j.jhep.2020.09.024.
2. Marjot T, Webb GJ, Barritt AS, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol*. 2021:1–17. https://doi.org/10.1038/s41575-021-00426-4 [Epub ahead of print].
3. Fix OK, Blumberg EA, Chang K, et al. AASLD expert panel consensus statement: vaccines to prevent COVID-19 infection in patients with liver disease. *Hepatology*. 2021 https://doi.org/10.1002/hep.31751 [Epub ahead of print].
4. Sarin SK, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; the APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int*. 2020;14:690–700. https://doi.org/10.1007/s12072-020-10072-8.
5. Ella R, Vadrevu KM, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis*. 2021;S1473–3099:30942–30947. https://doi.org/10.1016/S1473-3099(20)30942-7 [Epub ahead of print].
6. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting FDA Briefing Document. Pfizer-BioNTech COVID-19 Vaccine. Accessed April 1, 2021, https://www.fda.gov/media/144245/download.
7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383:2603–2615.
8. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403–416.
9. [package insert on the Internet]. *COVISHIELD™ (ChAdOx1 nCoV- 19 Corona Virus Vaccine)*. Pune (India): Serum Institute Of India Pvt. Ltd; 2021 https://www.seruminstitute.com/pdf/covishield_ChAdOx1_nCoV19_corona_virus_vaccine_insert.pdf.
10. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial [Internet] *Lancet*. 2020;396:467–478. https://doi.org/10.1016/S0140-6736(20)31604-4.
11. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99–111.
12. [package insert on the Internet]. *COVAXIN™ (Whole Virion Inactivated Corona Virus Vaccine)*. Bharat Biotech International Ltd; 2021 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NjkxNQ==.
13. Ella R, Reddy S, Jogdand H, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *Lancet Infect Dis*. 2021;S1473–309900070-0 https://doi.org/10.1016/S1473-3099(21)00070-0 [Epub ahead of print].
14. Indian council of medical research. Phase 3 Clinical Trial of COVAXIN, developed by ICMR & Bharat Biotech, shows 81% efficacy [press release](2021 Mar 3) [Accessed 2021 Mar 24]. https://www.icmr.gov.in/pdf/press_realease_files/Press_Release_ICMR_03_March_2021.pdf.
15. Sapkal GN, Yadav PD, Ella R, et al. *Neutralization of UK-variant VUI-202012/01 with COVAXIN Vaccinated Human Serum* [Internet]. bioRxiv; 2021 Jan 1, 2021.01.26.426986. Available from: http://biorxiv.org/content/early/2021/01/27/2021.01.26.426986.abstract.
16. Ministry of Health and Family Welfare, Govt of India[Internet]. India:-MOHFW;c2021. Frequently asked questions; 2021 Mar 25 [Accessed 2021 Mar 31]; https://www.mohfw.gov.in/covid_vaccination/vaccination/faqs.html#vaccine-registration.
17. Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. *J Hepatol*. 2021;74:944–951. https://doi.org/10.1016/j.jhep.2021.01.032.
18. Humanity & Health Medical Group Limited. *A Prospective Study Comparing the Antibody Response of Subjects with Chronic Liver*

Disease to mRNA, Inactivated Virus and Adenovirus Vector COVID-19 Vaccines. March 15- 2021, Dec 31; 2021. Identifier NCT04775069 https://clinicaltrials.gov/show/NCT04775069.
19. Marjot T, Webb GJ, Barritt AS, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. *Lancet Gastroenterol Hepatol*. 2021;6:156–158.
20. Institute of Liver and Biliary Sciences, India. *Safety and Efficacy of a Non-replicating ChAdOx1 Vector Vaccine AZD1222 (COVISHIELD), for Prevention of COVID-19 in Patients with Liver Cirrhosis*. March 19- 2022, March 19; 2021. Identifier NCT04794946 https://clinicaltrials.gov/ct2/show/record/NCT04794946.
21. Guro Lùvik Goll, Diakonhjemmet Hospital. *A Norwegian Study of Vaccine Response to COVID-19 Vaccines in Patients Using Immunosuppressive Medication within Rheumatology and Gastroenterology: The Nor-vaC Study*. Feb 15- 2026, Feb 15; 2021. Identifier NCT04798625 https://clinicaltrials.gov/ct2/show/record/NCT04798625.
22. Humanity & Health Medical Group Limited. *March 15- 2021, March 31). A Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of Vaccines against COVID-19 in the Real World*; 2021. Identifier NCT04775056 https://clinicaltrials.gov/ct2/show/record/NCT04775056.