HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 2, 2234784
https://doi.org/10.1080/21645515.2023.2234784

Taylor & Francis
Taylor & Francis Group

ARTICLE COMMENTARY

Phase 4 clinical trials in the era of the Coronavirus Disease (COVID-19) pandemic and their importance to optimize the COVID-19 vaccination

Ana Eliza Garcia Ralise*, Tais Mendes Camargo*, and Fernando Augusto Lima Marson*

Laboratory of Molecular Biology and Genetics, São Francisco University, Bragança Paulista, Brazil

ABSTRACT

Since the appearance of SARS-CoV-2, the scientific community has worked relentlessly to gather enough information about the illness caused by this virus infection. Such great effort has resulted in increased scientific publication, including phase 4 clinical trials addressing the applicability of COVID-19 vaccines. In those trials that investigated the properties of the vaccine among participants with morbidities, mainly immunocompromised individuals, the safety was recommended, but in the presence of immunogenicity, such protection was considered of short and medium terms. It was also observed that a physically active lifestyle might increase the immunogenicity of the COVID-19 vaccination in patients with autoimmune rheumatic diseases and in immunocompromised patients. The coadministration of different types of vaccine such as the combination of the recombinant adenovirus type 5 (AD5)-vectored Convidecia as heterologous reinforcement vs. CoronaVac with homologous reinforcement in adults previously vaccinated with CoronaVac, as well as the coadministration of inactivated COVID-19 vaccine followed by the administration of the tetravalent influenza vaccine (Fragmented, Inactivated) and the pneumococcal vaccine 23 presented satisfactory immunogenicity. However, the heterologous reinforcement had better immunogenicity when compared to the homologous reinforcement. Simultaneous COVID-19 vaccination and vaccines against seasonal influenza did not raise safety issues, producing acceptable levels of adverse reactions and preserving the antibody responses against SARS-CoV-2. In the lot-to-lot consistency evaluation, CoronaVac was seen to induce an immune response considered relatively high, and the lots presented a similar profile of stability and immunogenicity, thus enabling their large-scale distribution. In brief, this article addressed, mainly, the importance of evaluating the immunological response in the COVID-19 vaccination in patients with specific health conditions (e.g., immunocompromised individuals) aiming at enabling adjustments to the vaccine calendar in national vaccination programs.

ARTICLE HISTORY
Received 17 May 2023
Revised 23 June 2023
Accepted 3 July 2023

KEYWORDS
COVID-19; clinical trial; phase 4 clinical trial; SARS-CoV-2; science; vaccination

Since the appearance of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the scientific community has worked relentlessly to gather enough information about the illness caused by this virus infection [Coronavirus Disease (COVID)-19]. Such great effort has resulted in increased scientific publication. After the virus first genetic sequence was published, the first diagnostic tests were developed followed by studies on possible therapeutic interventions and vaccines.[1–4] Simultaneously, the development of protection measures against this virus has been the focus of several studies worldwide, and vaccines have been considered the main targets for the development of a COVID-19 global protection model.[3,4]

Due to the impact caused by COVID-19, clinical trials outstood with countless publications,[5–7] which also raised the number of retractions.[6,8–10] Among clinical trials, in the short period of the COVID-19 pandemic, phase 4 clinical trials were published, mainly addressing the applicability of COVID-19 vaccines in the pandemic scenery.[11–25] The importance of phase 4 clinical studies is unquestionable, since they require previous approval and aim at evaluating the outcomes associated with several treatments in the clinical practice, which have been used in the general population, thus supporting the continuous search to enable an efficient and safe intervention in the COVID-19 context.[26,27]

Taking all that into consideration, this paper aimed to review and describe the main findings of phase 4 clinical trials related to COVID-19 vaccines. Data collection was carried out up to March 2023 on the PubMed-Medline platform by inserting the descriptor COVID-19 and the filters "Clinical Trial, Phase IV, Humans, English."

Among the clinical trials collected, 15 evaluated vaccines (nine clinical trials were developed in Brazil,[11,13–15,18–20,24,25] three in China,[16,21,22] two in Austria,[12,23] and one in the United Kingdom.[17] The clinical trials found had been published in a variety of journals with diverse impact factor (Table 1). The objectives, methods, results, and conclusions of the phase 4 clinical trials are presented below (Table 2).

Considering this scenery, in Brazil, phase 4 clinical trial investigated the vaccine properties against the COVID-19 among participants with morbidities (primary Sjögren syndrome,[13] individuals subjected to kidney transplant,[14]

CONTACT Fernando Augusto Lima Marson fernandolimamarson@hotmail.com; fernando.marson@usf.edu.br Laboratory of Molecular Biology and Genetics, University of São Francisco, Avenida São Francisco de Assis, 218. Jardim São José, Bragança Paulista, São Paulo 12916-900, Brazil.
*The authors contributed equally to this work.

Table 1. Description of phase 4 clinical trials on the Coronavirus Disease (COVID)-19 published in the PubMed-Database.

Author	Title	Clinical trial registry	Journal	IF	Country[a]
Shinjo et al.[11]	Systemic autoimmune myopathies: a prospective phase 4 controlled trial of an inactivated virus vaccine against SARS-CoV-2	NCT04754698	Rheumatology	7.046	Brazil
Schulz et al.[12]	CD19+IgD+CD27- naïve B cells as predictors of humoral response to COVID-19 mRNA vaccination in immunocompromised patients	NCT04858607	Frontiers in Immunology	8.786	Austria
Pasoto et al.[13]	Inactivated SARS-CoV-2 vaccine in primary Sjögren's syndrome: humoral response, safety, and effects on disease activity	NCT04754698	Clinical Rheumatology	2.980	Brazil
Medina-Pestana et al.[14]	Inactivated whole-virus vaccine triggers low response against SARS-CoV-2 infection among renal transplant patients: prospective phase 4 study results	NCT04801667	Transplantation	5.385	Brazil
Medeiros-Ribeiro et al.[15]	Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial	NCT04754698	Nature Medicine	87.241	Brazil
Li et al.[16]	Heterologous AD5-nCOV plus CoronaVac versus homologous CoronaVac vaccination: a randomized phase 4 trial	NCT04892459	Nature Medicine	87.241	China
Lazarus et al.[17]	Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal Influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial	ISRCTN14391248	Lancet	202.73	United Kingdom
Gualano et al.[18]	Association between physical activity and immunogenicity of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases	NCT04754698	Brain Behavior and Immunity	19.227	Brazil
Grenfell et al.[19]	Immunogenicity, effectiveness, and safety of inactivated virus (CoronaVac) vaccine in a two-dose primary protocol and BNT162b2 heterologous booster in Brazil (Immunita-001): A one year period follow up phase 4 study	None	Frontiers in Immunology	8.786	Brazil
Costa Clemens et al.[20]	Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study	RBR–9nn3scw	Lancet	202.73	Brazil*
Chen et al.[21]	Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV) coadministered with quadrivalent split-virion inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in China: A multicentre, non-inferiority, open-label, randomised, controlled, phase 4 trial	NCT04790851	Vaccine	4.169	China
Zhu et al.[22]	Lot-to-lot consistency, immunogenicity, and safety of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults: A randomized, double-blind, phase IV trial	NCT04894227	Human Vaccines e Immunotherapeutics	4.526	China
Wagner et al.[23]	SARS-CoV-2-mRNA booster vaccination reverses non-responsiveness and early antibody waning in immunocompromised patients – A phase four study comparing immune responses in patients with solid cancers, multiple myeloma and inflammatory bowel disease	EudraCT: 2021-000291-11	Frontiers in Immunology	8.786	Austria
Gualano et al.[24]	Physical activity and antibody persistence 6 months after the second dose of CoronaVac in immunocompromised patients	NCT04754698	Scandinavian Journal of Medicine & Science in Sports	4.645	Brazil
Saad et al.[25]	Interaction of TNFi and conventional synthetic DMARD in SARS-CoV-2 vaccine response in axial spondyloarthritis and psoriatic arthritis	NCT04754698	Joint Bone Spine	5.263	Brazil

Ad5-nCoV: Type 5 Adenovirus Vector – Novel Coronavirus; BBIBP-CorV: Beijing Bio-Institute of Biological Products Coronavirus Vaccine; BNT162b2: BioNTech 162b2; CD19: Cluster of Differentiation 19; CD27: Cluster of Differentiation 19; ChAdOx1: Chimpanzee Adenovirus-vectored Oxford #1; ComFluCoV: Combining Influenza and COVID-19 Vaccination; DMARD: disease modifying anti-rheumatic drug; EudraCT: European Union Drug Regulating Authorities Clinical Trials Database; IF: Impact factor; IgD: immunoglobulins D; ISRCTN: International Standard Randomised Controlled Trial Number; mRNA: messenger RiboNucleic Acid; NCT: National Clinical Trial number; RBR (REBEC): Brazilian Registry of Clinical Trials; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TNFi: Tumor necrosis factor inhibitors; UK: United Kingdom. *, the first author is from Italy, but the clinical trial was carried out in Brazil. [a], country indicates the main site of the trial when the clinical trial is a multi-country clinical trial.

Table 2. Characterization of the phase 4 clinical trials on the Coronavirus Disease (COVID)-19 published in the PubMed-MedLine focusing on the immunological response of the vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

Author	Population	Objective	Methods	Results	Conclusions
Shinjo et al.[11]	53 patients with systemic autoimmune myopathies and 106 individuals without autoimmune rheumatic disease or another immunosuppression condition.	(i) To evaluate the safety and immunogenicity of the Sinovac-CoronaVac vaccine in patients with systemic autoimmune myopathies in comparison to control individuals. (ii) To analyze the potential damaging effect on the disease parameters, comorbidities, and antibody response in the vaccine induced therapy.	Prospective controlled clinical trial. The vaccination protocol followed a vaccination calendar with two doses of the Sinovac-CoronaVac vaccine. First dose + blood collection (D0); second dose + blood collection (D28); and last blood collection (D69). The immunogenicity evaluation was carried out based on the seroconversion rate of IgG anti-SARS-CoV-2 antibodies (S1/S2) and the presence of neutralizing antibodies against SARS-CoV-2 (D28 and D69). Geometric mean titers of IgG S1/S2 antibodies and their factor increase on D28 and D69, as well as the neutralizing activity of SARS-CoV-2 neutralizing antibodies were analyzed (D28 and D69).	(i) The analysis of the IgG anti-SARS-CoV-2 (S1/S2) antibody response showed that after six weeks as of the second dose of the vaccine, seroconversion rates were moderate, but lower than those obtained by the control group (64.9% vs. 91.1%). (ii) Geometric mean titers of the IgG anti-S1/S2 antibodies were lower in patients with systemic autoimmune myopathies when compared to the control group. (iii) After complete vaccination, the positivity of SARS-CoV-2 neutralizing antibodies was moderate, but lower when compared to the control group (51.4% vs. 77.2%). (iv) Patients with positive results for SARS-CoV-2 neutralizing antibodies used less immunosuppressants than those without antibodies (73.7% vs. 100.0%). (v) Moderate/severe adverse events were not observed after vaccination and the frequency of mild events was similar among the groups, except for the presence of headaches, which was more frequent in patients with systemic autoimmune myopathies in the vaccine first dose (26.4% vs. 8.5%). No patient required hospitalization.	(i) The Sinovac-CoronaVac vaccine was safe and presented short-term moderate immunogenicity in patients with systemic autoimmune myopathies, which was reduced when compared to the control group. (ii) Immunosuppressive medication might have deleterious effects on the vaccine induced antibody production, which affects the positivity rate of SARS-CoV-2 neutralizing antibodies.
Schulz et al.[12]	120 patients with hematological neoplasia or other immunodeficiency causes and 79 healthy individuals.	To analyze the presence of B cell specific subsets in immunocompromised individuals after their COVID-19 vaccination with mRNA vaccines.	Monocentric prospective clinical trial. Blood was collected before the first vaccination (D0) with BioNTech/Pfizer or Moderna vaccines for the analysis of immunological markers. The second vaccination was on D21 or D28.	(i) In immunocompromised patients, the seroconversion rates and the levels of antibodies were lower than those observed in the control individuals (67.0% vs. 82.0%). (ii) The interval between the B cell depletion therapy and the COVID-19 vaccination played a crucial role in the seroconversion of immunocompromised patients. (iii) The abundance of circulating CD19+IgD+CD27 näive B cells was associated with better vaccine antibody response in different diseases and therapies.	(i) The humoral response to the mRNA COVID-19 vaccine was hampered in immunocompromised patients. (ii) The measurement of näive B cells CD19+IgD+CD27 might allow the prediction of the humoral response to the vaccination against COVID-19 in immunocompromised individuals.
Pasoto et al.[13]	51 patients with primary Sjögren syndrome and 102 control individuals.	To evaluate immunogenicity, safety, and impact of the Sinovac-CoronaVac vaccine on patients with primary Sjögren syndrome and on the antibody profile.	Prospective controlled study within a larger phase 4 clinical trial. Participants received the Sinovac-CoronaVac vaccine (D0 and D28). Adverse events and COVID-19 symptoms were monitored using a logbook for the record of symptoms and contact with the investigators. The systemic disease degree of activity was assessed in onsite appointments on D0, D28, and D69 employing the Sjögren syndrome systemic activity index. Blood samples were collected before each dose of the vaccine was administered (D0 and D28) and on D69. Serum responses of IgG anti-SARS-CoV-2 (S1/S2) and neutralizing antibodies were analyzed.	(i) Adverse events related to the vaccine were mild, with higher frequency of vomiting, muscle weakness, arthralgia, and back pain in patients with primary Sjögren syndrome than in the control group. (ii) The disease systemic activity index remained unchanged during the clinical trial. (iii) On D69, patients with Sjögren syndrome presented moderate seroconversion, which was lower than that of the control group (67.5% vs. 93.0%); the same occurred with geometric mean titers (22.5 vs. 59.6 AU/mL), geometric mean titer factor increased IgG anti-SARS-CoV-2 (S1/S2) antibodies (8.9 vs. 27.4), and frequency of neutralizing antibodies (52.5% vs. 73.3%). (iv) Longitudinal increase was observed in the geometric mean titers of IgG anti-SARS-CoV-2 (S1/S2) antibodies in both groups. (v) The disease activity had no impact on the humoral response to the vaccine.	(i) The Sinovac-CoronaVac vaccine was safe and presented moderate humoral response in patients with the Sjögren syndrome, even though it was reduced when compared to the control group. (ii) The current treatment with methotrexate negatively influenced the humoral response to the vaccine. (iii) The disease activity did not present deleterious effect on the humoral response to the vaccine and the systemic clinical activity index remained unchanged in the short term after vaccination. (iv) After vaccination, there was no induction of autoantibodies in patients with the Sjögren syndrome or in the control group, while few patients in both groups developed positive antinuclear antibodies.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Medina-Pestana et al.[14]	3,371 renal transplant patients who had received at least one dose of the CoronaVac vaccine.	To investigate the CoronaVac vaccine effect on renal transplant patients.	Monocentric, prospective and intervention clinical trial. A six-month follow-up of the patients of renal transplant after two doses of CoronaVac was carried out, with a 28-day interval, to evaluate reactogenicity, immunogenicity, and efficacy of that vaccine. Reactogenicity data was obtained using a pre-specified questionnaire applied on the day of the second dose. Blood samples were collected on the day of the first dose (D0) to evaluate the IgG antibody against SARS-CoV-2. In a subset of patients (immunogenicity cohort), additional samples were collected before the second dose (D1) and at least 28 days after the second dose (D2). In a sub-group of patients of the immunogenicity cohort, the association between the IgG value and the detection of anti-SARS-CoV-2 neutralizing antibodies was explored. The vaccine efficacy was evaluated based on the comparison of the COVID-19 incidence per 1,000 patients at risk three months before the clinical trial (group control, without vaccine) and the results of the observation carried out in the following three months.	(i) At least one adverse reaction was reported by 33.0% of the patients, which often included pain or local sensitiveness, headache, and myalgia. In addition, 1.0% of the participants reported fever. (ii) The seroprevalence of the IgG anti-SARS-CoV-2 antibody on D0 was 3.6%. (iii) IgG anti-SARS-CoV-2 antibodies were found in 15.2% of the patients on D1 and in 43.0% of the participants on D2. (iv) Antibody mean levels among respondents was 490 AU/mL after D1 and 319 AU/mL after D2. Among them, 15.0% presented antibody response after the first and second doses of the vaccine, 28.0% presented seroconversion only after the second dose, and 57.0% did not present antibody response. Independent risk factors associated with lack of seroconversion after the second dose were older age and those who received kidneys from deceased donors. (v) Among the 15 patients who did not show alterations in IgG values, there was no change in the proportion of patients with neutralizing activity. Among the 15 patients with higher variation in IgG values, the percentage of patients with neutralizing activity observed increased from 13.0% on D1 to 100.0% on D2. (vi) 7.0% of the patients developed SARS-CoV-2 infection after D1, 29.0% before D2, 12.0% in less than 15 days after the second dose, and 59.0% over 15 days after the second dose. The hospitalization, need for mechanical ventilation, and death rates in 28 days were 62.0%, 36.0%, and 30.0%, respectively. When compared to the 341 renal transplant patients that developed COVID-19 in three months prior to vaccination, the 135 individuals fully vaccinated presented lower percentage of patients with diabetes mellitus. There was increase in the need for hospitalization in the fully vaccinated group (59.0% vs. 49.0%).	(i) The CoronaVac vaccine presented low reactogenicity and a 15.0% increase in seroconversion after the first dose, which reached 43.0% after the second dose. (ii) The immunosuppressive regimen was not associated with seroconversion. (iii) Reduction was observed in the COVID-19 incidence as of two weeks after the second dose administration, when compared to the three-month period preceding the clinical trial. (iv) Low immunogenicity and reduced COVID-19 incidence were observed among renal transplant patients. (v) The global death rate remained unchanged.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Medeiros-Ribeiro et al.[15]	910 adult patients with autoimmune rheumatic diseases and 182 healthy adult individuals who had received two doses of the CoronaVac vaccine.	To evaluate prospectively the immunogenicity and safety of the CoronaVac vaccine in individuals with autoimmune rheumatic diseases.	Clinical prospective controlled trial carried out in a tertiary center. The vaccination occurred on the same day the participants joined the clinical trial. Patients and control group were monitored up to D79 after the vaccine first dose (D0) for immunogenicity analysis and the record of incident cases. Regarding incident cases, the participants were monitored for periods of 40 days before and after the complete vaccination: from D0 to D39 and from D40 to D79.	(i) A 15.0% reduction was observed in the seroconversion of the IgG anti-SARS-CoV-2 (S1/S2) antibody and in the presence of neutralizing antibodies in patients with autoimmune rheumatic diseases when compared to the control group on D69 after the vaccine second dose. (ii) Lower seroconversion rate was observed in patients with autoimmune rheumatic diseases (70.4% vs. 95.5%). (iii) Positive results for neutralizing antibodies were lower in patients with autoimmune rheumatic diseases when compared to the control group (56.3% vs. 79.3%). (iv) Only few participants developed IgG anti-SARS-CoV-2 antibodies after D28, with lower frequency and level observed in patients with autoimmune rheumatic diseases when compared to the control group (18.7% vs. 34.6%), while geometric mean titer factor increased (2.3 vs. 4.6) and seroconversion rates doubled after the vaccine second dose, with an over fivefold increase in the geometric mean titers in both groups. (v) No moderate/severe adverse effect related to the vaccine was reported. (vi) Patients with the IgG anti-SARS-CoV-2 antibody and with negative neutralizing antibodies after two doses of CoronaVac were older and were more frequently medicated with prednisone (59.9% vs. 31.1%), immunosuppressive drugs (81.9% vs. 54.5%), methotrexate (34.6% vs. 21.7%), mycophenolate mofetil (24.4% vs. 7.9%), and biological therapy (44.1% vs. 32.2%), mainly Abatacept and Rituximab. (vii) Similar frequency of SARS-CoV-2 infection was observed in patients with autoimmune rheumatic diseases and the control group (4.0% vs. 1.6%). (viii) Patients with autoimmune rheumatic diseases reported higher adhesion to social isolation (69.5% vs. 21.7%) with lesser contact with infected people in their households (4.6% vs. 15.5%), and less frequent use of public transport (47.7% vs. 81.7%) when compared to the control group. The number of people living in the same household was similar in both groups.	The clinical trial suggested safety and short-term reduced immunogenicity, which was acceptable in patients with autoimmune rheumatic diseases after vaccination with the CoronaVac vaccine

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Li et al.[16]	302 participants who had received the CoronaVac vaccine in the last 1 to 3 months, or two doses in the last 3 to 6 months before inclusion in the clinical trial.	To evaluate the safety and immunogenicity of the vaccine against COVID-19 with a recombinant adenovirus type 5 (Ad5)-vectored (Ad5-nCOV), Convidecia (CanSino Biologics), as heterologous reinforcement vs. the results obtained using the CoronaVac vaccine as homologous reinforcement in adult individuals previously vaccinated with CoronaVac.	Continuous observer blind randomized and parallel controlled clinical trial. Participants in the three-dose regime cohort were randomized in a 1:1 ratio to receive the third Convidecia dose (group A, heterologous reinforcement dose) or CoronaVac (group B, homologous reinforcement dose). Participants in the two-dose regime cohort were equally randomized to receive a second dose of Convidecia (group C, heterologous dose) or CoronaVac (group D, homologous dose). Two hundred and ninety-nine participants that received reinforcement were included in the safety analysis. Solicited adverse events were recorded in a check list included in the participant's record card, while unsolicited reported adverse events were collected spontaneously.	(i) Within 28 days, higher frequency of adverse reactions was reported in group A than in group B (34.4% vs. 4.9%); and higher frequency of adverse reactions in group C than in group D (25.5% vs. 8.0%). (ii) Adverse reactions were usually mild or moderate. (iii) The incidence of unsolicited adverse events on D28 after the vaccination was low in the groups evaluated. (iv) No thrombosis or anaphylaxis, or other adverse events related to the vaccine were observed in the groups up to D28 after the booster dose. (v) Increased levels of neutralizing antibodies against wild-type SARS-CoV-2 were observed after the booster dose in all groups. (vi) The post-vaccination geometric mean titers in different groups (groups A and C) were higher than those of homologous groups (groups B and D) in both three-dose and two-dose regime cohorts.	This clinical trial suggested that the heterologous reinforcement with Convidecia after the initial vaccination with CoronaVac is safe and provides higher immunogenicity than that offered by the homologous reinforcement.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Lazarus et al.[17]	126 participants per cohort (total = 756).	To evaluate the safety of the simultaneous administration of ChAdOx1 or BNT162b2 and another vaccine against the influenza virus suitable to the patients' age.	Multicenter, randomized, and controlled trial called ComFluCOV. A vaccine against the influenza virus was administered in association with the second dose of the COVID-19 vaccine. The clinical trial was designed to investigate the simultaneous administration of second doses of two vaccines against COVID-19 (ChAdOx1 - AZD1222; Oxford–AstraZeneca and BNT162b2; Pfizer–BioNTech) with vaccines against the influenza virus (with MF59C adjuvant, trivalent vaccine, quadrivalent cell based, and quadrivalent recombinant vaccines). Participants were recruited to one of the six cohorts defined by the six combinations of vaccines against COVID-19 and influenza. On D0, eligible volunteers who agreed to participate were randomly appointed and received the test vaccines (one against flu, suitable for the patients' age, or a placebo injection, along with their second dose of a COVID-19 vaccine). In the second visit, between 21 and 28 days later (D21), those that had received the vaccine against flu on D0 received a placebo injection and vice-versa. Participants had a final test visit between 42 and 56 days (D42) for safety evaluations.	(i) In the cohorts established, most systemic reactions were mild or moderate. The local systemic reaction and unsolicited reaction rates were similar among the groups. (ii) The concomitant administration of the two vaccines was considered non-inferior to the administration of the COVID-19 vaccine only in relation to the primary result of any systemic adverse reaction within seven days after D0 in four cohorts: ChAdOx1 plus quadrivalent cell vaccine against influenza [risk difference for the influenza vaccine minus placebo (-) 1.29%, 95%CI: (-) 14.70 to 12.10], BNT162b2 plus quadrivalent cell vaccine against influenza [6.17%, (-) 6.27 to 18.60], BNT162b2 plus trivalent vaccine against the influenza virus with MF59C adjuvant [(-)12.90%, (-) 34.20 to 8.37] and ChAdOx1 plus quadrivalent recombinant vaccine against the influenza virus [2.53%, (-) 13.30 to 18.30]. In the other two cohorts, the 95%CI superior limit exceeded the 0.25 non-inferiority margin. (iii) Four severe systemic reactions were observed in the trivalent influenza vaccine ChAdOx1 adjuvant plus MF59C cohort, they were reported by two participants vaccinated on D0. Three severe systemic reactions were observed in the BNT162b2 plus quadrivalent recombinant vaccine cohort. (iv) No differences were observed in the geometric mean rate of inhibition of hemagglutinin antibodies for any influenza strain 21 days after vaccination against the influenza virus plus a COVID-19 vaccine when compared to receiving the influenza vaccine alone (quadrivalent cell vaccine) and the trivalent vaccine with MF59C adjuvant cohorts or in the cohort that received ChAdOx1 plus the quadrivalent recombinant influenza vaccine. In the BNT162b2 plus the quadrivalent recombinant vaccine against the influenza virus cohort, the A/H1N1 geometric mean titers and both B strains were higher when administered with BNT162b2 in comparison to the quadrivalent recombinant vaccine against the influenza virus use only but were similar for A/H3N2. (v) Seroconversion rates ranged between 1.0% and 72.0% and tended to be lower in the trivalent vaccine against influenza plus MF59C adjuvant cohort than in any other cohort using quadrivalent vaccine against the influenza virus, and also lower for B strains than for A strains. (vi) Nine (1.0%) participants reported that they were not willing to receive simultaneous vaccines in the future, and 11 (3.0%) participants reported between 0.5 and two days off work after being vaccinated.	The simultaneous administration of six different combinations of vaccines against COVID-19 and influenza did not raise safety concerns, produced acceptable reactogenicity profile and preserved the responses of binding antibodies.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Gualano et al.[18]	898 participants with autoimmune rheumatic diseases diagnosed with rheumatoid arthritis, systemic erythematosus lupus, axial spondyloarthritis, psoriatic arthritis, primary vasculitis, primary Sjögren syndrome, systemic sclerosis, systemic autoimmune myopathies, and primary antiphospholipid syndrome and 197 participants without autoimmune rheumatic diseases.	To investigate whether physical activity is associated with increased immunogenicity of an inactivated COVID-19 vaccine (CoronaVac) in patients with autoimmune rheumatic diseases and individuals without autoimmune rheumatic diseases, and without preexisting immunogenicity to SARS-CoV-2.	Prospective cohort clinical trial within a single-arm, open vaccination trial. Participants received two CoronaVac doses (D0 and D28) and had their blood collected on D0, D28, and D69. Seroconversion rates of IgG anti-SARS-CoV-2 (S1/S2) antibodies were measured, as well as geometric mean titers of IgG anti-S1/S2, factor increase in geometric mean titers, frequency of neutralizing antibodies, and median neutralizing activity. Physical activity and sedentary behavior were evaluated using a questionnaire.	(i) Patients with autoimmune rheumatic diseases who were physically active (n = 494) were younger and used prednisone and biological therapy less frequently than those that were inactive (n = 404). (ii) Active and inactive individuals without autoimmune rheumatic diseases did not differ statistically in age, sex, and body mass index. (iii) After vaccination, the seroconversion frequency, geometric mean titers of IgG anti-S1/S2, factor increase of IgG anti-S1/S2 titers and neutralizing antibodies were higher in active patients with autoimmune rheumatic diseases vs. inactive. (iv) Older age, body mass index over 30 kg/m^2, and the use of prednisone, biological therapy, and immunosuppressive medication were the factors most frequently associated with low immunogenicity, while being physically active was associated with better immunogenicity. (v) Among the participants without autoimmune rheumatic diseases, higher seroconversion levels were observed. The associations between physical activity and neutralizing activity and antibodies were not significant between active and inactive individuals.	A physically active lifestyle might increase the vaccine immunogenicity against SARS-CoV-2 in patients with autoimmune rheumatic diseases.
Grenfell et al.[19]	1,587 individuals vaccinated with two CoronaVac and BNT162b2 booster doses after six months of the primary protocol.	To evaluate the efficacy of associating CoronaVac with BNT162b2 from the clinical and biological standpoints.	Transversal clinical trial on immunogenicity and safety (Immunita-001) of the CoronaVac two-dose regime (Sinovac/Butantan), followed by a heterologous reinforcement dose of mRNA vaccine (BNT162b2). Participants had already received the primary protocol in the first two months of 2021. The booster dose was administered six months later. Blood samples were collected 1, 2, 3, 6, 9, and 12 months after the second dose of the vaccine for immunogenicity analysis. Participants were monitored during the clinical trial regarding the appearance of COVID-19 symptoms, and when presenting them, they were tested with the reverse transcription-quantitative polymerase chain reaction and sequencing when positive. Adverse events in the first 15 days after vaccination were also reported.	(i) Decreased IgG anti-Spike titers were observed 80 days after the CoronaVac vaccine second dose and a 1.7 time increase after the BNT162b2 booster dose. (ii) 74.0% of the participants that did not receive a booster dose remained seropositive for a year, even if the IgG titers remained smaller in comparison to those who received the booster dose. (iii) The seropositivity rate was higher (98.0%) after 31–60 days and lower (69.0%) after 91–180 days after vaccination with CoronaVac. The BNT162b2 booster dose increased seropositivity to 96.0%. (iv) Participants with COVID-19 before the vaccination, presented increased seropositivity rate when compared to those who had not been previously infected. (v) Seropositivity in older participants was 15.0% lower than that observed in younger individuals on days 150–200 after vaccination with CoronaVac and restored after the BNT162b2 booster dose. (vi) Titers of neutralizing antibodies for the Omicron (13.0%) variant were lower in all points when compared to the Delta variant (33.0%). (vii) 20.5% of the participants presented some adverse effect after vaccination with CoronaVac and 53.1% after the BNT162b2 dose. (viii) There was no register of severe adverse events.	(i) Previous exposure to the SARS-CoV-2 resulted in increased seropositivity rate. (ii) The CoronaVac and BNT162b2 vaccines were safe and well tolerated among the participants of the clinical trial.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Costa Clemens et al.[20]	1,240 participants, 1,239 were vaccinated and 1,205 were eligible for inclusion in the primary analysis.	To evaluate whether a third dose of homologous vaccine or of a different one can increase immune responses.	Clinical trial on masked participants from two centers to evaluate safety and immunogenicity in adult patients who received two CoronaVac doses, six months before inclusion. The third, heterologous dose [recombinant adenovirus type-vectored (Ad26.CoV2-S, Janssen), mRNA vaccine (BNT162b2) or recombinant adenovirus type-vectored ChAdOx1 nCoV-19] was compared to the homologous vaccine. Blood samples were collected before vaccination and on D28 after vaccination.	(i) The third dose of all vaccines tested provided increased IgG response after two CoronaVac doses when administered six months after the second dose, which was higher with adenovirus type-vectored vaccines (Ad26.CoV2-s and ChAdOx1 nCoV-19) and the mRNA vaccine (BNT162b2) than the homologous regime response. (ii) The vaccines were safe and improved immune responses, which were higher with adenovirus type-vectored vaccines and the mRNA vaccine when compared to homologous vaccines. (iii) Booster doses with adenovirus type-vectored vaccines and mRNA vaccines induced high concentrations of neutralizing antibodies (94.0%). (iv) Five severe adverse events were recorded, three of those were possibly related to the vaccine (one to BNT162b2 and two to Ad26.CoV2-S).	The heterologous reinforcement resulted in more robust immune responses than the homologous reinforcement and might increase protection against infection by the viral agent.
Chen et al.[21]	1,152 participants, distributed in three groups of 384 people.	To evaluate the safety and immunogenicity of the coadministration of inactivated vaccine against SARS-CoV-2 (Sinopharm BBIBP-CorV) followed by the administration of a tetravalent influenza vaccine (Fragmented, Inactivated) and the pneumococcal 23 vaccine.	Multicenter, clinical, randomized, controlled, non-inferiority, open trial. Participants that had not been vaccinated against COVID-19, had no history of pneumonia, and had not been vaccinated against flu between 2020 and 2021 were recruited from the community. Participants were randomized in blocks: (a) one dose of the COVID-19 vaccine and one dose of tetravalent influenza vaccine, followed by a dose of the COVID-19 vaccine and one dose of the pneumococcal 23 vaccine (D28); (b) two doses of the COVID-19 vaccine (D0 and D28); (c) one dose of the tetravalent influenza vaccine (D0), followed by the pneumococcal 23 vaccine (D28). Three blood samples were collected on day 0 (to evaluate the antibodies related to the vaccine at baseline), day 28 before vaccination (to evaluate the SARS-CoV-2 neutralizing antibodies of the first dose or the antibodies against the influenza virus) and day 56 (to evaluate the SARS-CoV-2 neutralizing antibodies or the IgG anti-pneumococcal antibodies). Post-vaccination adverse events were monitored and recorded in the participants' record card.	(i) The seroconversion rate and geometric mean titer of SARS-CoV-2 neutralizing antibodies in the COVID-19 vaccine + vaccine against influenza/pneumococcal group (97.0% on D28 and 100.0% on D56) was not lower than that observed in the group that received only the COVID-19 vaccine (99.0% on D28 and 100.0% on D56). (ii) On D28, the group receiving COVID-19 vaccine + vaccine against influenza/pneumococcal did not present lower seroconversion rates or geometric mean titers of antibodies against the influenza virus for all strains than that of the group receiving only vaccine against influenza/pneumococcal, except for the seroconversion rate for the B/Yamagata strain (100.0% vs. 96.0%). (iii) No death or severe adverse event were observed.	(i) The coadministration of the COVID-19 vaccine and the tetravalent influenza and pneumococcal 23 vaccine was safe and showed satisfactory immunogenicity. (ii) All vaccines were well tolerated by the participants in this trial.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Zhu et al.[22]	1,080 healthy adult individuals, out of those, 1,072 individuals received two doses of vaccine, with 359 individuals in each lot of the vaccine.	To evaluate the lot-to-lot consistency of the CoronaVac vaccine immunogenicity and safety.	Double-blind clinical randomized trial. Participants were divided into three groups and received two doses of the CoronaVac vaccine (D0 and D28) from three different lots (A202103012, A202103013, and A202103014). On D0 and D56, the participants' blood samples were collected to measure neutralizing antibodies and the antibodies against the SARS-CoV-2 Spike receptor binding domain. Adverse events were observed onsite for at least 30 minutes after each vaccination and recorded in the participants' record card.	(i) Participants presented negative results for neutralizing antibodies before vaccination. (ii) The geometric mean titers of Lot 1, Lot 2, and Lot 3 were 75.2 (68.5, 82.6), 65.0 (59.0, 71.7) and 65.3 (59.4, 71.8), respectively, 28 days after all the doses of the vaccination had been completed. (iii) No statistical difference occurred in seroconversion or seropositivity rates (99.7%, 98.6% and 98.6%), geometric mean titers, and geometric mean increased between groups. (iv) After vaccination, seropositivity and seroconversion rates of the antibody against the SARS-CoV-2 Spike receptor binding domain were 100.0%, 100.0%, and 99.4%, respectively. (v) The incidence of adverse reactions was 19.2% (69/360), 13.9% (50/360), and 18.3% (66/360), respectively.	(i) The clinical trial indicated good lot-to-lot consistency of vaccines on commercial scale. (ii) CoronaVac vaccine might induce a relatively high immune response and guarantee stability and immunogenicity in the healthy population between 26 and 45 years old in different lots. (iii) The CoronaVac vaccine showed an acceptable safety profile.
Wagner et al.[23]	263 participants, 66 were in the control group and 197 received immunosuppressive/modulatory treatments (solid tumors, multiple myeloma, and inflammatory bowel disease), none had been previously vaccinated against COVID-19.	To evaluate the humoral and cell immune response after the first dose and the booster dose with mRNA vaccines against COVID-19 in a heterogeneous group of immunocompromised patients under different immunosuppressive/modulatory therapies.	Prospective, open clinical trial. Participants received two doses of an mRNA vaccine (BNT162b2 or mRNA-1273, Spikevax, Moderna Biotech), with an interval between three and four weeks, respectively. Serum samples were collected to measure antibody titers (before the first dose, on the day of the second dose, four weeks, five to six months after the second dose, and four weeks after having received the booster dose). Participants without antibody response four weeks after the second dose received the third dose earlier but were not included in the analysis of antibody response five to six months after the second dose.	(i) The antibody rate was lower after the first dose in patients being treated with immunosuppressive medication (50.0% in patients with multiple myeloma, 28.6% with solid tumor, and 3.8% with inflammatory bowel disease) when compared to the control group (1.5%). (ii) After the second dose, the antibody rate remained lower in the groups with multiple myeloma (17.1%) and solid tumors (1.6%) but presented positive results in patients with inflammatory bowel diseases. (iii) Four weeks after the second dose, lower antibody rates were identified in patients with multiple myeloma (552.5 BAU/mL) when compared to the control group (3,205.5 BAU/mL). (iv) Six months after the second dose, a high number of the immunocompromised patients became seronegative (18.0% of the patients with multiple myeloma, 10.0% with solid tumors, 4.0% with inflammatory bowel diseases). There were no seronegative patients in the control group. (v) The vaccination with mRNA-1273 resulted in higher levels of antibodies than that with BNT162b2.	Results stressed the need for immunomonitoring of the vaccine specific antibodies and the cell response to identify flaws in vaccination and define special vaccine schemes for patients with immunodeficiency.
Gualano et al.[24]	748 participants with autoimmune rheumatic diseases.	To investigate the association between physical activity and IgG anti-SARS-CoV-2 antibodies, remaining six months after two CoronaVac doses in patients with autoimmune rheumatic diseases.	Prospective cohort trial within a single-arm, open vaccination clinical trial. Persistent immunogenicity six months after the complete vaccination was evaluated using total seroconversion rates of IgG anti-SARS-CoV-2 (S1/S2) antibodies, geometric mean titers of IgG anti-SARS-CoV-2 (S1/S2) antibodies, and frequency of positive neutralizing antibodies. Physical activity was evaluated using a questionnaire.	(i) Participants were classified as physically active (421 participants) and inactive (327 participants). (ii) Physically active participants were significantly younger and showed lower frequency of chronic inflammatory arthritis. (iii) Active participants presented higher rates of seroconversion of total IgG anti-SARS-CoV-2 (S1/S2) antibodies (53.1% vs. 40.7%), higher positivity of neutralizing antibodies (31.2% vs. 22.0%), and higher geometric mean titers of IgG anti-SARS-CoV-2 (S1/S2) antibodies than inactive participants. (iv) The use of prednisone and biological medication was associated with low immunogenicity, even though active participants showed higher values.	Among immunocompromised patients with autoimmune rheumatic diseases, being physically active was associated with higher persistence of antibodies up to six months after the complete vaccination scheme with inactivated SARS-CoV-2.

(*Continued*)

Table 2. (Continued).

Author	Population	Objective	Methods	Results	Conclusions
Saad et al.[25]	A hundred and eighty-three participants with spondyloarthritis (including axial spondyloarthritis, ankylosing and non-radiographic arthritis, and psoriatic arthritis) with regular outpatient assistance in a rheumatology center and 183 participants without immunosuppression (control group). Out of the 183 participants in each group, seven with spondyloarthritis and 21 of the control group were excluded from the immunogenicity analysis for presenting positive reverse transcription followed by a polymerase chain reaction for SARS-CoV-2 (COVID-19) between the two vaccine doses (seven patients/five control individuals) or for missing the final appointment (16 control individuals).	To evaluate humoral immune responses to three doses of the CoronaVac vaccine in patients with spondyloarthritis and using disease modifying anti-rheumatic drugs and commonly targeted biological therapy in comparison to a control group.	Prospective, observational, cohort trial. Participants were paired according to their sex and age (patients with spondyloarthritis and control group) and were both vaccinated with CoronaVac vaccine following the two-dose scheme with a 28-day interval. They received a third dose on D210. Blood was collected on days 0, 28, and 69.	(i) The participants' immunogenicity analysis after the vaccine first dose (D28) revealed that the IgG rate (19.9% vs. 30.2%) and the positivity of neutralizing antibodies (21.0% vs. 35.2%) were reduced in patients with spondyloarthritis when compared to the control group. (ii) On D69, patients with spondyloarthritis showed increased IgG (80.2% vs. 95.7%) and moderate neutralizing antibody rate (61.6% vs. 82.7%), but lower than that of the control group. (iii) The analysis of IgG anti-SARS-CoV-2 (S1/S2) antibody rates evidenced lower titers in patients with spondyloarthritis (34.3 UA/mL) when compared to the control group (68.9 UA/mL). (iv) The mean activity of neutralizing antibodies was moderate among patients with spondyloarthritis when compared to the control group (61.4% vs. 66.7%). (v) The tumoral necrosis inhibiting factor reduced the immunogenicity in spondyloarthritis (73.3% vs. 96.0%). Sulfasalazine had a positive impact on the production of antibodies (85.7% vs. 96.0%). (vi) Specific drugs in monotherapy or in combination hindered immunogenicity.	(i) The levels of neutralizing antibodies were reported as predictive of protection against COVID-19. (ii) Patients with spondyloarthritis showed lower immunogenicity for IgG neutralizing antibodies after two doses of CoronaVac vaccines.

%, percentage; Ad26: adenovirus type 26; Ad5-nCoV: Type 5 Adenovirus Vector – Novel Coronavirus; A/H1N1: influenza A virus subtype H1N1; A/H3N2: influenza A virus subtype H3N2; AU/mL: international units per milliliter; BAU/mL: binding antibody units per milliliter; BBIBP-CorV: Beijing Bio-Institute of Biological Products Coronavirus Vaccine; BNT162b2: BioNTech 162b2; CD19: Cluster of Differentiation 19; CD27: Cluster of Differentiation 19; ChAdOx1: Chimpanzee Adenovirus-vectored Oxford #1; ComFluCOV: combination of vaccine against influenza and vaccine against COVID-19; D0: day zero (baseline) OR day of the first dose; D1: day one OR before second dose; D2: day two OR at least 28 days after the second dose; D21: day twenty-one; D28: day twenty-eight; D39: day thirty-nine; D40: day forty; D42: day forty-two; D56: day fifty-six; D69: day sixty-nine; D79: day seventy-nine; D210: day two hundred and ten; IgG: Immunoglobulin G; IgD: immunoglobulin D; Kg/m^2 kilogram per square meter; MF59C: oil-in-water emulsion adjuvant; mRNA: messenger RiboNucleic Acid; RNA: ribonucleic acid; S1: spike protein S1 domain; S2: spike protein S2 domain; vs.: versus.

patients with autoimmune rheumatic diseases,[15,18] immunocompromised patients, physical activity influence in the response to the vaccine,[24] axial spondyloarthritis and psoriatic arthritis).[25] When the reports were compared, they showed similar results in relation to the response to vaccines by patients with autoimmune diseases. Although the safety of vaccines was recommended for this group of individuals, in the presence of immunogenicity such protection was considered of short and medium term.[11,13,15] Lower immunogenicity might be a factor related to the use of immunosuppressor medication that could present deleterious effect on the vaccine induced antibody production, which directly affects the production of neutralizing antibodies against SARS-CoV-2.[11,13,15] In the same context, Schulz et al. (2021) and Wagner et al. (2022), developed a clinical trial in Austria focusing on the presence of specific subsets of the B cell in immunocompromised individuals after vaccination with the mRNA vaccines against COVID-19 and verified that the humoral response was hampered in this group of individuals, emphasizing the need for monitoring specific antibodies to the vaccine as well as the cell responses. This also aimed at identifying flaws in vaccination and defining possible special vaccination schemes targeting patients with immunodeficiency.[12,23]

In patients that had been subjected to kidney transplant, the COVID-19 vaccine was associated with a low number of adverse reactions.[14] At the same time, increased seroconversion rate, from 15.0% after the first dose to 43.0% after the second dose onwards, was observed. In that population, immunosuppressors were not associated with seroconversion and reduction in the COVID-19 incidence from two weeks after the second dose onwards when compared with the three-month period that preceded the inclusion of the research participants.[14] There was low immunogenicity in relation to the vaccine; however, reduced COVID-19 incidence was observed among those that were subjected to kidney transplant, while the global lethality remained unchanged.[14]

Among the phase 4 clinical trial included, two of them explored the use of vaccine combined with physical activity, and found out that a physically active lifestyle might increase the immunogenicity of the COVID-19 in patients with autoimmune rheumatic diseases[18] and in immunocompromised patients.[24] Being physically active was associated with an increased persistency of antibodies for six months after those individuals had completed all doses of the COVID-19 vaccination.[24] In addition, in the booster dose, after two CoronaVac vaccine doses, a heterologous reinforcement seems to have resulted in more robust immune responses than those observed with the homologous reinforcement, thus guaranteeing greater protection against COVID-19.[20]

Phase 4 clinical trial carried out in China on COVID-19 vaccines assessed the safety and immunogenicity in response to the vaccine, as well as the consistency between vaccine lots for the markers informed. All clinical trials developed in China included healthy individuals.[16,21,22] Among those clinical trials, two evaluated the coadministration of different types of vaccine such as the combination of the recombinant adenovirus type 5 (AD5)-vectored Convidecia as heterologous reinforcement vs. CoronaVac with homologous reinforcement in adults previously vaccinated with CoronaVac,[16] as well as the coadministration of inactivated COVID-19 vaccine [Sinopharm BBIBP-CorV (Beijing Bio-Institute of Biological Products Coronavirus Vaccine)] followed by the administration of the tetravalent influenza vaccine (Fragmented, Inactivated) and the pneumococcal vaccine 23.[21] Both clinical trials reported satisfactory immunogenicity.[16,21] However, the heterologous reinforcement was considered safe and with better immunogenicity when compared to the homologous reinforcement.[16] In the lot-to-lot consistency evaluation of commercial vaccines, CoronaVac was seen to induce an immune response considered relatively high, and the lots presented a similar profile of stability and immunogenicity, thus enabling their large-scale distribution.[22] Adopting the same reasoning, Lazarus et al. (2021) – from the United Kingdom, evaluated the safety and immunogenicity resulting from the simultaneous COVID-19 vaccination [ChAdOx1 (Chimpanzee Adenovirus-vectored Oxford #1) or BNT162b2 (BioNTech 162b2)] and vaccines against the seasonal influenza.[17] That clinical trial reported that the simultaneous administration of six different combinations of vaccines against the COVID-19 and influenza did not raise safety issues, producing acceptable levels of adverse reactions and preserving the antibody responses against SARS-CoV-2.[17]

It seems relevant to highlight that the data analyzed, and the considerations presented in this article added invaluable information about the "scientific marathon" in the search for new treatments to enable efficient and safe interventions in the COVID-19 context. This effort includes analysis of the viability of vaccines. In addition, this article can support the implementation of health policies, especially public policies related to the coordination of vaccination campaigns against the COVID-19 targeting individuals who present low immunological response (e.g., immunocompromised patients).

Limitations

Although the discussions presented in this article are highly relevant, some aspects cannot be neglected such as the differences between the samples investigated, number of participants included in the phase 4 clinical trial, scarcity of previous research on phase 4 clinical trials in COVID-19, and the disproportionate number of studies developed in certain countries in relation to other countries.

Conclusion

The COVID-19 pandemic led the scientific community to a continuous quest for efficient therapeutic approaches to face this disease, which resulted in the publication of countless scientific reports. Historically, phase 4 clinical trial have been highly relevant since they evaluate outcomes associated with several therapeutics in the clinical practice and their potential use in the general population. More recently developed, the COVID-19 studies unveil the importance of such intervention, mainly in populations that are considered to be at risk since some vaccines might not be tolerated by certain groups of individuals. Taking that into consideration, this article addressed the importance of evaluating the immunological response in the COVID-19

vaccination in patients with specific health conditions (e.g., immunocompromised individuals) aiming at enabling adjustments to the vaccine calendar in national vaccination programs, mainly those managed by the public health, which is the Brazilian model.

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

Ana Eliza Garcia Ralise http://orcid.org/0000-0003-3344-6589
Tais Mendes Camargo http://orcid.org/0000-0002-3804-280X
Fernando Augusto Lima Marson http://orcid.org/0000-0003-4955-4234

Authors' contributions

All the authors contributed equally to this study.

Consent for publication

All the authors have approved the manuscript and agreed with its submission.

References

1. Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis -a review of current methods. Biosens Bioelectron. 2021;172:112752. doi:10.1016/j.bios.2020.112752.
2. Majumder J, Minko T. Recent developments on therapeutic and diagnostic approaches for COVID-19. AAPS J. 2021;23(1):14. doi:10.1208/s12248-020-00532-2.
3. Fernandes Q, Inchakalody VP, Merhi M, Mestiri S, Taib N, Moustafa Abo El-Ella D, Bedhiafi T, Raza A, Al-Zaidan L, Mohsen MO, et al. Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics and vaccines. Ann Med. 2022;54(1):524–40. doi:10.1080/07853890.2022.2031274.
4. Hadj Hassine I. Covid-19 vaccines and variants of concern: a review. Rev Med Virol. 2022;32(4):e2313. doi:10.1002/rmv.2313.
5. Machin-Mastromatteo JD, Tarango J, Romo-González JR. 19 - impact of the COVID-19 pandemic on scientific production [Internet]. In: Baker D, Ellis L, editors. Libraries, digital information, and COVID. Chandos Publishing; 2021 [accessed 2023 Mar 23]. p. 183–98. https://www.sciencedirect.com/science/article/pii/B9780323884938000203.
6. Carvalho TA, Lima TM, Melani VF, Mendes MF, Pereira LR, Marson FAL. The scientific production during 2009 swine flu pandemic and 2019/2020 COVID-19 pandemic. Pulmonology. 2020;26(6):340–5. doi:10.1016/j.pulmoe.2020.07.009.
7. Valencise FE, Boschiero MN, Palamim CVC, Marson FAL. The COVID-19 impact on the scientific production on the 25 main death causes according to world region. Pulmonology. 2022;28(1):1–3. doi:10.1016/j.pulmoe.2021.05.011.
8. adminpmls2016. COVID-19 and clinical trials: past, present, and future [Internet]. J Precis Med. [accessed 2023 Mar 24]. https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/covid-19-and-clinical-trials-past-present-and-future/.
9. Valencise FE, Palamim CVC, Marson FAL. Retraction of clinical trials about the SARS-CoV-2 infection: an unaddressed problem and its possible impact on Coronavirus disease (COVID)-19 treatment. Int J Environ Res Public Health. 2023;20(3):1835. doi:10.3390/ijerph20031835.
10. Lasch F, Psarelli E-E, Herold R, Mattsson A, Guizzaro L, Pétavy F, Schiel A. The impact of COVID-19 on the initiation of clinical trials in Europe and the United States. Clin Pharmacol Ther. 2022;111(5):1093–102. doi:10.1002/cpt.2534.
11. Systemic autoimmune myopathies: a prospective phase 4 controlled trial of an inactivated virus vaccine against SARS-CoV-2 - PMC [Internet]. [accessed 2023 Mar 15]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8574538/.
12. Schulz E, Hodl I, Forstner P, Hatzl S, Sareban N, Moritz M, Fessler J, Dreo B, Uhl B, Url C, et al. CD19+IgD+CD27- Naïve B cells as predictors of humoral response to COVID-19 mRNA vaccination in immunocompromised patients. Front Immunol. 2021;12:803742. doi:10.3389/fimmu.2021.803742.
13. Pasoto SG, Halpern ASR, Guedes LKN, Ribeiro ACM, Yuki ENF, Saad CGS, da Silva CAA, de Vinci Kanda Kupa L, Villamarín LEB, de Oliveira Martins VA, et al. Inactivated SARS-CoV-2 vaccine in primary Sjögren's syndrome: humoral response, safety, and effects on disease activity. Clin Rheumatol. 2022;41(7):2079–89. doi:10.1007/s10067-022-06134-x.
14. Medina-Pestana J, Covas DT, Viana LA, Dreige YC, Nakamura MR, Lucena EF, Requião-Moura LR, Fortaleza CMCB, Foresto RD, Tedesco-Silva H, et al. Inactivated whole-virus vaccine triggers low response against SARS-CoV-2 infection among renal transplant patients: prospective phase 4 study results. Transplantation. 2022;106(4):853–61. doi:10.1097/TP.0000000000004036.
15. Medeiros-Ribeiro AC, Aikawa NE, Saad CGS, Yuki EFN, Pedrosa T, Fusco SRG, Rojo PT, Pereira RMR, Shinjo SK, Andrade DCO, et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. Nat Med. 2021;27(10):1744–51. doi:10.1038/s41591-021-01469-5.
16. Li J, Hou L, Guo X, Jin P, Wu S, Zhu J, Pan H, Wang X, Song Z, Wan J, et al. Heterologous AD5-nCOV plus CoronaVac versus homologous CoronaVac vaccination: a randomized phase 4 trial. Nat Med. 2022;28(2):401–9. doi:10.1038/s41591-021-01677-z.
17. Lazarus R, Baos S, Cappel-Porter H, Carson-Stevens A, Clout M, Culliford L, Emmett SR, Garstang J, Gbadamoshi L, Hallis B, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial. Lancet. 2021;398(10318):2277–87. doi:10.1016/S0140-6736(21)02329-1.
18. Gualano B, Lemes IR, Silva RP, Pinto AJ, Mazzolani BC, Smaira FI, Sieczkowska SM, Aikawa NE, Pasoto SG, Medeiros-Ribeiro AC, et al. Association between physical activity and immunogenicity of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases. Brain Behav Immun. 2022;101:49–56. doi:10.1016/j.bbi.2021.12.016.
19. Grenfell RFQ, Almeida NBF, Filgueiras PS, Corsini CA, Gomes SVC, de Miranda DAP, Lourenço AJ, Martins-Filho OA, de Oliveira JG, Teixeira-Carvalho A, et al. Immunogenicity, effectiveness, and safety of inactivated virus (CoronaVac) vaccine in a two-dose primary protocol and BNT162b2 heterologous booster in Brazil (Immunita-001): a one year period follow up phase 4 study. Front Immunol. 2022;13:918896. doi:10.3389/fimmu.2022.918896.
20. Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MBV, da Guarda SNF, de Nobrega MM, de Moraes Pinto MI, Gonzalez IGS, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study.

Lancet. 2022;399(10324):521–9. doi:10.1016/S0140-6736(22)00094-0.
21. Chen H, Huang Z, Chang S, Hu M, Lu Q, Zhang Y, Wang H, Xiao Y, Wang H, Ge Y, et al. Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV) coadministered with quadrivalent split-virion inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in China: a multicentre, non-inferiority, open-label, randomised, controlled, phase 4 trial. Vaccine. 2022;40(36):5322–32. doi:10.1016/j.vaccine.2022.07.033.
22. Zhu D, Hu Y, Jiang Z, Yang T, Chu K, Zhang H, Hu J, Meng X, Tan Z, Wu J, et al. Lot-to-lot consistency, immunogenicity, and safety of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults: a randomized, double-blind, phase IV trial. Hum Vaccin Immunother. 2022;18(6):2135929. doi:10.1080/21645515.2022.2135929.
23. Wagner A, Garner-Spitzer E, Schötta A-M, Orola M, Wessely A, Zwazl I, Ohradanova-Repic A, Weseslindtner L, Tajti G, Gebetsberger L, et al. SARS-CoV-2-mRNA booster vaccination reverses non-responsiveness and early antibody waning in immunocompromised patients – a phase four study comparing immune responses in patients with solid cancers, multiple myeloma and inflammatory bowel disease. Front Immunol. 2022;13:889138. doi:10.3389/fimmu.2022.889138.
24. Physical activity and antibody persistence 6 months after the second dose of CoronaVac in immunocompromised patients - Gualano - 2022 - Scandinavian Journal of Medicine & Science in Sports - Wiley Online Library [Internet]. [accessed 2023 Mar 15]. https://onlinelibrary.wiley.com/doi/10.1111/sms.14213.
25. Saad GSC, Silva SRM, Sampaio-Barros DP, Moraes CBJ, Schainberg CG, Gonçalves CR, Shimabuco AY, Aikawa NE, Yuki EFN, Pasoto SG, et al. Interaction of TNFi and conventional synthetic DMARD in SARS-CoV-2 vaccine response in axial spondyloarthritis and psoriatic arthritis. Joint Bone Spine. 2023;90(1):105464. doi:10.1016/j.jbspin.2022.105464.
26. Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: what is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol. 2007;47(9):1074–86. doi:10.1177/0091270007304776.
27. Cesana BM, Biganzoli EM. Phase IV studies: some insights, clarifications, and issues. Curr Clin Pharmacol. 2018;13(1):14–20. doi:10.2174/1574884713666180412152949.