A comparative study between vaccines against Covid-19 in phase III clinical trials

Um estudo comparativo entre vacinas contra Covid-19 em ensaios clínicos de fase III

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ABSTRACT
Objective: Compare different characteristics of the vaccines against Covid-19 in phase III clinical trials: type of vaccine, storage, route of administration, number of doses, interval between doses, countries tested, age group tested, seroconversion interval, general efficacy, country distribution, estimated number of participants, and pharmacodynamics. Methods: Phase III clinical trials were identified through the ClinicalTrials.gov database. The filters used were: coronavirus infection; vaccines; clinical trials; all studies; recruitment status (all); stage III; 06-06-2020 to 06-06-2021. 182 studies were found. After excluding studies with drug therapies and vaccines not exclusive to Covid-19, there remained 56 studies. Results: Our study compared 28 vaccines in phase III clinical trials. All vaccines with available data on general efficacy achieved values above 50%. More than half of the studies had at least 50,000 participants. The immunizing agents were tested in 37 countries and the predominant age group tested was >=18 years. As for storage 80% of vaccines with available data need to be refrigerated between 2-8 °C, while mRNA type vaccines require lower temperatures. Regarding types of vaccines, recombinant viral vectors constituted 50%. Within the vaccines approved for distribution, 7.14% were distributed to over 100 countries, in contrast, another 14.29% of the vaccines were distributed to only 1 country each. Conclusion: The analysis and understanding of our results can contribute to disseminate important information so that people do not perceive in a false manner that one vaccine works better than the other, reducing vaccine hesitancy. However, it is up to each nation to compare each immunizer and define the best choice that fits their needs.

Keywords: SARS-CoV-2, Vaccine-Preventable Diseases, Public Health.

RESUMO
Objetivo: Comparar diferentes características das vacinas contra Covid-19 em ensaios clínicos de fase III: tipo de vacina, armazenamento, via de administração, número de doses, intervalo entre doses, países testados, faixa etária testada, intervalo de sorocronversão, eficácia geral, país distribuição, número estimado de participantes e farmacodinâmica. Métodos: Os ensaios clínicos de fase III foram identificados por meio do banco de dados ClinicalTrials.gov. Os filtros utilizados foram: infecção por coronavírus; vacinas; testes clínicos; todos os estudos; status de recrutamento (todos); estágio III; 06-06-2020 a 06-06-2021. 182 estudos foram encontrados. Depois de excluir...
estudos com terapias medicamentosas e vacinas não exclusivas da Covid-19, permaneceram 56 estudos. Resultados: Nosso estudo comparou 28 vacinas em ensaios clínicos de fase III. Todas as vacinas com dados disponíveis sobre a eficácia geral alcançaram valores acima de 50%. Mais da metade dos estudos teve pelo menos 50.000 participantes. Os agentes imunizantes foram testados em 37 países e a faixa etária predominante testada foi > = 18 anos. Quanto ao armazenamento, 80% das vacinas com dados disponíveis precisam ser refrigeradas entre 2-8 °C, enquanto as vacinas do tipo mRNA requerem temperaturas mais baixas. Em relação aos tipos de vacinas, os vetores virais recombinantes constituíram 50%. Dentre as vacinas aprovadas para distribuição, 7,14% foram distribuídas para mais de 100 países, em contraste, outros 14,29% das vacinas foram distribuídas para apenas 1 país cada. Conclusão: A análise e compreensão dos nossos resultados podem contribuir para disseminar informações importantes para que as pessoas não percebam de forma falsa que uma vacina funciona melhor que a outra, reduzindo a hesitação vacinal. No entanto, cabe a cada nação comparar cada imunizante e definir a melhor escolha que se adapte às suas necessidades.

Palavras-chave: SARS-CoV-2, Doenças evitáveis por vacinas, Saúde pública.

1 INTRODUCTION

In December 2019, in Wuhan, China, the first case of the new Coronavirus (Sars-Cov-2) was registered. Initially documented by the responsible medical teams as “pneumonia of unknown cause”, and later on March 11, 2020, classified as the etiological agent of Covid-19 and officially declared a pandemic by the World Health Organization (WHO). Since then, over 173 million cases of Covid-19 contamination have been reported worldwide, with approximately 3 million deaths.

Despite the sanitary measures, such as social restrictions, mask-wearing, handwashing, and access to diagnostic tests, adopted by WHO, the pandemic is still a global public health problem, and the control of COVID-19 is a priority in public policies of health. In this sense, countries have been investing in the development of immunobiologicals very quickly. This intervention has been essential to control the disease, reduce incidence and mortality.

Currently, a significant variety of immunizers to combat Covid-19 are at different stages of research (phase I, II or III). Some of the vaccines approved for use around the world are: ChAdOx1 nCoV-19 (Oxford/AstraZeneca), BNT162b2 (BioNTech, Pfizer), BBIBP-CorV (Sinopharm-Wuhan/Beijing), mRNA-1273 (Moderna), Sputnik V (Gamaleya). It is estimated that 21.5% of the world population was vaccinated with at least the first dose against Covid-19. 2.6 billion doses were administered globally.
In this context, the vaccine development against the coronavirus is occurring very rapidly when compared with other vaccines that take several years\textsuperscript{9,10}.

This accelerated process has brought suspicion about the safety and efficacy of these vaccines\textsuperscript{5,6}. Some studies, such as Kreps et al. and Sherman et al. showed that the efficacy of vaccines is one of the strongest arguments for people to trust and get vaccinated willingly\textsuperscript{11,12}. However, comparison of results directly from clinical trials can be deceiving as the numbers do not take into consideration different variables between each study\textsuperscript{9,13,14}.

Since the Ebola outbreak in the last decade, the WHO created new guidelines that propose the use of technologies that assist in the development of research in the non-clinical phase, in order to provide safety and efficacy for vaccines to be used in a public health emergency context\textsuperscript{6}. Based on past learning of viruses from similar strains to Sars-Cov-2, such as MERS, different action platforms for vaccines have been developed, such as: adenovirus vectors, DNA, mRNA, and recombinant protein, to ensure greater variability in the induction of body immunization against the etiological agent\textsuperscript{6,7}. This process was facilitated by the development of the entire genetic code of Sars-Cov-2. Several pharmaceutical companies use this data as a basis for the preparation of vaccines that act by different mechanisms\textsuperscript{5,6,7}.

Global governments and public health officials need to work together and elaborate effective mass vaccination petitions, which includes building public trust and following a strategy that prioritizes the administration of doses in a way that reduces morbidity and mortality from the infectious disease\textsuperscript{9,10}.

Additionally, it is also important to consider that many new vaccines are being tested against the same disease and will be marketed in the near future. It is necessary to compare different vaccines and show whether the interventions already available are more beneficial or not, so that the introduction of a new immunizer may be reconsidered\textsuperscript{15}. By gathering such information in this research in an organized manner, we are also able to contribute in this aspect\textsuperscript{14,15}. Differences such as study population (age group, ethnicity, gender), period of testing (different pandemic stages), study protocols, among other variables, should be considered when comparing data across trials, so that people do not perceive in a false manner that one vaccine works better than the other, reducing vaccine hesitancy\textsuperscript{9,14}. 
Thus, the aim of the study was to carry out a review of vaccine clinical trials in phase III against Covid-19, comparing their characteristics, so that the information is systematized and analyzed.

2 METHODS

This is an original research to identify studies that investigated vaccines against COVID-19 in phase III clinical trials.

Eligibility criteria

The inclusion criteria were phase III clinical trials of COVID-19 vaccines, covering the period from June 06, 2020 to June 06, 2021.

Search strategy

We searched the electronic database Clinical Trials (Clinical Trials.gov), using the following filters:

- Condition or disease: CoronaVirus Infection;
- Other terms: Vaccine;
- Study type: Interventional Studies (Clinical Trials);
- Study results: All studies;
- Recruitment status: Not yet recruiting, recruiting, enrolling by invitation, terminated, completed;
- Additional Criteria: Phase 3;
- Study start: From 06-06-2020 to 06-06-2021.

Thus, 182 studies were found. Two independent authors carried out the search for clinical trials and excluded all studies that investigated drug therapy or vaccines that were not exclusive to Covid-19. Any disagreement was solved by a third author. At the end of the screening 56 studies were selected and evaluated. We extracted and summarized data from the fully reviewed studies using a form to list study characteristics, including: type of vaccine, storage, number of doses, interval, route of administration, tested age range, estimated total of participants, tested countries, seroconversion interval after last dose. Additional information about general efficacy and pharmacodynamics was obtained from literature, and the vaccines country distribution was obtained in datasets with recent official numbers, such as The New York Times (https://nyti.ms/2Selnmx) and Our World in Data (https://ourworldindata.org/) websites on June 08, 2021.
Data analysis

All studies retained for review were described in qualitative synthesis. The selected variables were used as criteria for comparing the different Covid-19 vaccines characteristics. From the selected variables, absolute and relative frequencies were calculated, maps and graphs were included in this study, to facilitate the visualization and understanding of the collected data. The graphics and maps were created in software R 3.6.3 (R Development Core Team, 2020, a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna) and QGIS 3.16.7 (www.qgis.org), respectively. For the graphics, the package ggplot2 was used and the shapefiles of maps were extracted from www.gadm.org.

3 RESULTS

In this research, we found 56 clinical trials related to 28 different new vaccines in phase III clinical trials, produced to bring the Covid-19 pandemic under control.

Regarding vaccine general efficacy, approximately 50% of the vaccines did not present these values until the writing of this manuscript. The percentages, among the vaccines that had this data, were, in decreasing order: EpiVacCorona (100%), VAT00008 (97.50%), BNT162b2 (95%), mRNA-1273 (94.10%), Sputnik V (91.60%), NVX-CoV2373 (89.30%), BBIBP-CorV (86.00%), ChAdOx1 nCoV-19 (82.40%), Covaxin (80.00%), VLA2001 (79.40%), Ad26.COV2.S (66.00%), Ad5-nCoV (65.70%), Coronavac (50.38%). The percentages found exceeded the 50% mark (Fig 1B).

Within the selected studies, vaccines such as AG0302-COVID19 and West China Hospital COVID-19 Vaccine had the lowest estimated total of participants, corresponding to 500 and 140 people, respectively. The highest number of participants tested was in the study of the Ad26.COV2.S vaccine, with a result of 575,675 individuals. As for other vaccines, 2 (7.14%) had a total estimate within 50,000-100,000 volunteers, 15 (53.57%) were in the 25,000-50,000, another 8 (28.57%) between 1,000-25,000, and 2 (7.14%) in the range of under 1,000 participants (Figure 1C).

As for vaccine testing countries, 35 were used as a testing site. The distribution was: 9 (SBC-2019 and Ad26.COV2.S), 8 (BNT162b2), 6 (ChAdOx1 nCoV-19), 5 (CoronaVac, and Ad5-nCoV), 4 (NVX-CoV2373, BBIBP-CorV and Sputnik V), 3 (mRNA-1273 and CVnCoV), 2 (VLA2001, CoVLP, VPM1002, UB-612 and Chinese Academy of Medical Sciences Vaccine), and 1 country (Sputnik Light, VAT00008,
Walvax mRNA, West China Hospital Vaccine, GRAd-CoV2, Minhai Vaccine, ZF2001, Covaxin, AG032-COVID19, INO-4800, EpiVacCorona and QazCovid-in). Figure 2 shows that the Americas, Asia and Europe were the continents with the most countries tested for vaccines in phase III against Covid-19, corresponding to 91.42%, while in Africa only 3 countries (8.58%) tested vaccines, and none were tested in Oceania. (Figure 2).

The age group delimited as >=18 years represented most of the selected clinical trials, shown in 41 studies, corresponding to 73.21% of the 56 studies. The following age groups were tested in only one study each: 6 months-11 years (mRNA-1273), 12-17 years (mRNA-1273), >=12 (BNT162b2), 18-26 (mRNA-1273), 18-45 (CVnCoV), 18-84 (NVX-CoV 2372), >=60 years (VPM1002) and >=65 (CVnCoV). Two studies tested 18-59 years (CoronaVac) and 18-85 years (BBIBP-CorV and Ad5-nCoV). Three other studies tested: 18-55 years (Ad26.COV2.S and BNT162b2) and 18-60 years (EpiVacCorona, Sputnik V, BBIBP-CorV). Among the studies evaluated, 11 vaccines (39.28%) were tested in more than one age group in different studies.

It was identified that 20 (80.00%) of the 25 vaccines had their storage temperatures between 2-8 °C. VLA2001 requires storage at -18°C, mRNA-1273 requires storage at -20°C, and BNT162b2 at -70°C. The AG0302-COVID19 and INO-4800 vaccines, on the other hand, need refrigeration at room temperature (approximately 20°C). This information was not found for the Chinese Academy of Medical Sciences Vaccine, the recombinant West China Hospital Vaccine and Minhai Vaccine.

Concerning the route of administration, only the VPM1002 and INO-4800 vaccines are intradermal (7.14%), while the others are administered intramuscularly (92.86%). Most of the vaccines studied (23 immunizers or 82.14%) are administered in two doses, with varying intervals. Of these, 10 vaccines (43.47% of 23) are administered 21 days apart, while 9 vaccines (39.13% of 23) are administered only after 28 days, and 4 (17.39% of 23) after 14 days. Differently, 4 vaccines (14.29% of 28), Ad26.COY2.S, Ad5-nCoV, Sputnik Light and VPM1002 immunization are applied in a single dose and ZF2001 (3.57% of 28) is applied in 3 doses, with an interval of 28 days between the application of each one (Fig1F).

As for seroconversion interval, it was identified that 15 vaccines (53.60%) had a period of seroconversion equal to 14 days. 8 (28.60%) has a period equal to 21 days, 2 (7.14%) with seroconversion > 15 days, 1 (3.57%) with 28 days, 1 (3.57%) with 30 days, 1 (3.57%) with 10 days (Fig. 1D).
Vaccines formed with recombinant viral vectors, mostly with adenovirus, constituted 50% of the total, while those made of inactivated viruses made up 25%. Complementing the list, 14.28% were RNA, 7.15% were DNA, and finally, 3.57% were attenuated viruses (Fig. 1A). Pharmacodynamics has particularities that depend on each type of vaccine (table 2). For vaccines composed of inactivated viruses (25%), the process takes place through the internalization of the virus by the antigen-presenting cell that will culminate in the activation of other defense cells responsible for directing the attack on Sars-CoV-2. Vaccines formed by recombinant viral (46.43%) vectors are composed of nanoparticles that will be internalized by the cells of the defense systems, resulting in the immunization process. RNA vaccines (7.14%) use lipid nanoparticles that surround messenger RNA, which will be internalized by target cells, resulting in the formation of memory immunity. Attenuated immunizers (3.57%) use double-stranded DNA to express antigens on the surface of their membrane promoting the maturation and activation of different immune cells.

Approximately 50% of the vaccines in phase III against covid-19 did not have their approval status for use confirmed until the deadline of this research. 7.14% vaccines were distributed to over 100 countries, including ChAdOx1 nCoV-19 (174 countries) and BNT162b2 (104 countries). In contrast, 14.29% of the vaccines were distributed to only 1 country each, namely GRAd-CoV2 (Italy), ZF2001 (Uzbekistan), Minhai Vaccine (Chine) and QazCovid-in (Kazakhstan). Other vaccines, such as BIBP-CorV, Sputnik V, CoronaVac, Ad26.COV2.S, Covaxin, EpiVacCorona were approved for use in 56, 43, 30, 20, 6 and 2 countries, respectively (Fig. 1E).

Both the continents of North America and South America had a percentage of 100% of their territories (4 in North America and 13 in South America) approving the distribution of at least one vaccine. The other continents had the following percentages, in approximate values, which were established considering the total territories contained in each: Europe with approximately 99% (50 nations), Asia also with approximately 99% (49 nations), Central America and the Caribbean with 62.16% (37 nations), Oceania with 36.11% (36 nations) and Africa with 90.74% (54 nations). (Figure 3).

4 DISCUSSION

Public health experts highlight that all Covid-19 vaccines being applied on the population are effective, particularly at preventing serious disease\textsuperscript{16,17}. All immunizers in phase III trials cross the 50% mark, as shown in this study\textsuperscript{18}. However, because trials
were conducted with different methodological settings and at different periods at the pandemic scenario, only direct comparison of efficacy can be misleading, essentially when comparing trials that were tested for different outcomes\textsuperscript{19,20}. It is important to highlight that the outcome of an infection depends on many variables, such as age, sex, ethnicity, comorbidities and population heterogeneity\textsuperscript{21,22}. 

For example, Pfizer (BNT162B2) and Moderna (mRNA-1273), both tested for symptomatic disease, but they started counting cases in different periods of time after the last dose: 1 week and 2 weeks respectively\textsuperscript{20}. On the other hand, the J&J (AD26.COV2.S) vaccine tested to determine whether one dose was able to protect against moderate to severe infection, beginning from 2 or 4 weeks after the shot\textsuperscript{20}.

The mRNA-1273 vaccine for an example had a decrease in numbers when tested on the population above 65 years old, going from an efficacy of 95.1\% to 85\%\textsuperscript{22}. The Food and Drug Administration (FDA) committee explained that the trial result could have been influenced by the fact there were few cases in that age range\textsuperscript{19}. The Ad26.COV2.S vaccine, whose efficacy against moderate to severe coronavirus infections varied based on geographic locations, ranging from 57\% to 66\% and 72\% when tested in South Africa, South America and United States (US), respectively, although differences across age groups among trial participants were not found\textsuperscript{23}. When tested for a different outcome, however, to prevent severe and critical Covid-19 cases, the efficacy was raised to 85.9\% in the US and to 81.7\% in South Africa, also hospitalization numbers were decreased and no deaths due to Covid-19 occurred in the vaccine group\textsuperscript{24,25}.

The number of the participants in the phase III clinical trials is another important characteristic that should be taken into consideration, as it interferes with precision, which leads to increased power of study to detect an effect of a certain magnitude and also interfere with the efficacy result\textsuperscript{13}. Different factors can be contributed to the number of participants: inclusion criteria, size sample, funding support and others. Perhaps, these aspects explain the different number of participants between vaccines. Although, we have found that vaccines were approved in at least 20 countries had at least more than 30,000 participants and were tested in at least 3 countries.

During the development of vaccines that are in phase III, these immunizing agents begin to be applied in specific population groups, selected according to certain age groups or due to the presence of comorbidities or special conditions\textsuperscript{26}. Most of the vaccines present in the study in question carried out their trials with individuals present in the age group greater than or equal to 18 years of age\textsuperscript{26}. This is because this age encompasses the
adult and elderly population, the main ones aggravated by the Covid-19 pandemic, and more susceptible to tests because their immune system already has its capacity for seroconversion altered\textsuperscript{27}. Added to this, the infant age group is unaffected in a serious way by the viral action of Sars-Cov-2, which denotes the little predilection of studies in phase III for this audience\textsuperscript{27}.

The Food and Drug Administration (FDA) establishes that, in the scale of progression of clinical trials of a vaccine, doses of the immunizing agent must first be applied to adults, and only in the future they can be tested in children and adolescents\textsuperscript{28,29}. Thus, priority groups are better analyzed, such as individuals with comorbidities and specific conditions, and the vaccine may have its efficacy better established\textsuperscript{28,29,30}. Vaccines at a higher stage of advancement in studies, such as BNT162B2, have already had the opportunity to be tested in children, more specifically within the age group of 12 to 16 years\textsuperscript{29,30}. This fact, in addition to ensuring greater safety for the immunizing agent, can be used as a basis to better establish its effectiveness in different population groups\textsuperscript{30}.

The Covid-19 vaccines have different specifications for storage temperature as shown in this study, varying between 2 °C to 8 °C, -20 °C, and -70 °C\textsuperscript{31}. Exposure to any inadequate condition between the time of manufacture and vaccination can cause potency loss\textsuperscript{32,33}. These conditions include exposure to heat or cold at temperatures outside of the recommended domain and also exposure to light at any stage within the cold chain, which involves manufacturing, transport, delivery, storage at the provider facility and administration\textsuperscript{31,32}. Once potency is lost it cannot be restored, leading to public health concerns, such as limited protection, possible reactions at the site of administration, necessity of revaccination of the population, loss of patient confidence, and significant waste of money\textsuperscript{31,32,33}.

The equipment available in most countries for vaccine storage ranges from 2 °C to 8 °C, yet some of the Covid-19 vaccines require storage at ultralow temperature, to slow down the molecular movements and prevent damages, especially the mRNA-1273 and BNT1622, which are mRNA vaccines\textsuperscript{34}. This type of vaccine is intrinsically unstable and susceptible to degradation due to the RNAses in the blood\textsuperscript{35}. Protein-based vaccines, such as the ChAdOx1 nCoV-19, can be transported and stored in less rigorous conditions\textsuperscript{36}. Inactivated vaccines must also be kept at refrigerater temperature, between 2°C and 8°C and must not be exposed to frozen temperatures, especially if associated with an adjuvant, because they may lose their potency permanently\textsuperscript{31,32}. Once thawed, the mRNA Covid-19 vaccines cannot be refrozen\textsuperscript{31,36}.
The Pfizer-BioNTech unpunctured vials may be kept between 2°C and 8°C up to 31 days at room temperature (25°C) for 2 hours maximum, while the Moderna unpunctured vials may be kept in a refrigerator up to 30 days or between 8°C and 25°C for 24 hours\textsuperscript{36,37}. The AstraZeneca vaccine, on the other hand, may have unpunctured vials stored at the same refrigerator temperature until the product expiration date\textsuperscript{36}. Thus, vaccines with an ultralow temperature requirement can lead to economic and logistical challenges, especially for countries with low-income or low-middle-income economies and located in remote warm regions\textsuperscript{38}. Ultra-cold chain equipment is usually limited to higher-level facilities or to countries that conducted Ebola epidemic immunization\textsuperscript{31}. For the last year, the manufacturers were in a hurry to get the vaccines to the population, now however, they are focusing on updating the immunizers to facilitate the process of storage and distribution\textsuperscript{39}. Nevertheless, with the lipid nanoparticle technologies, the mRNA vaccine has increased stability, thus can be maintained at more flexible conditions\textsuperscript{40}.

It has come to the attention that, besides being a mRNA type vaccine, the CVnCoV (CureVac) had stability evaluated at both ultralow temperature (-60°C) and refrigerated temperature (5°C), for at least 3 months, and can also be stable at room temperature up to 24 hours\textsuperscript{39,41}. This immunizer has been tested on approximately 40,000 people, in three countries from Central America and Europe, as shown in this study, but is not yet available for distribution. If the results of the trials involving this vaccine turn out to be successful in the near future, it could be a potential alternative for low and middle-income countries, as it will have a beneficial effect on distribution, cost and wastage\textsuperscript{41}.

Other vaccines, such as the DNA based INO-1400 immunizer, that is currently being tested, does not require frozen temperature for transport and has proven to be stable at room temperature for over a year\textsuperscript{42}. Immunizers with better safety and tolerability could help in the implementation of mass immunization, by eliminating vaccine hesitancy, crucial in the pandemic battle\textsuperscript{43}. Moreover, the improvement of vaccine stability at refrigerator or room temperatures can contribute in a positive manner with the distribution logistic to countries that lack capacity for storage at lower temperatures\textsuperscript{44}.

Our results showed that over 90% of the Covid-19 vaccines in phase III clinical trials are administered as an intramuscular injection on the deltoid muscle. The preference of this site is due to immunogenicity optimization and minimal related adverse reactions\textsuperscript{45}. The muscle is rich in vascularity, contrary to other sites such as subcutaneous fat for example, which leads to faster antigen mobilization and processing, and higher
seroconversion rates as well. The deltoid is usually the preferential muscle because it is located close to lymph nodes clusters from under the armpits, facilitating the immunological process. Once injected into the muscle tissue, important defense cells present at this site can recognize the vaccine, alert other cells and carry the antigen into the lymph nodes, where there are more immune cells that recognize the antigen and start the antibody production.

Only 2 of the 28 immunizers shown in this study are being tested intradermally. The VPM-1002 is a BCG based vaccine, thus being administered intradermally due to the better delayed type of hypersensitivity response and minimization of adverse events. The INO-4000 vaccine, which is still being tested, is the other Covid-19 immunizer injected intradermally, but is associated with electroporation to encourage DNA uptake by the immune cells. DNA based vaccines in general can be administered intramuscularly, like the AG0302-COVID19 vaccine, or intradermally, like the INO-4000, where defense cells take up the nucleic acid to encode and synthesize the antigen that will originate the immunological response.

Moreover, our results have also shown that over 80% of the vaccines require 2 shots, with varying intervals between them. The British Society of Immunology refers to the second dose as a “prime-boosting” shot, used to maximize immune memory and protection. This method has been tested in most of the Covid-19 vaccines clinical trials. When the BNT162B2 and mRNA-1273 vaccines, for example, were first being tested, it was found that the first dose caused a weak immune response compared to a highly effective response, with higher amount of antibodies, after the second dose was administered. A recent study, published in June 2021, ratifies that the immune response after the second dose of the BNT162B2 increases significantly, providing immune protection also from concerning new Sars-Cov-2 variants, such as the Alpha (B.1.1.7) and Delta (B.1.617.2). The ChAdOx1 nCoV-19 immunizer has also shown to be more protective against symptomatic coronavirus infection after the “prime-boosting”, going from an efficacy of 76% on the first dose to 81% after the second dose was administered with an interval of 3 months.

Some other vaccines present on the phase III trials, may have less or more doses applied to develop a good and prolonged immune response, as shown in our result table. The J&J’s Ad26.COVID2.S vaccine has shown to be very effective with one dose, reaching 85% in preventing severe infection and 100% against mortality, beginning 28 days after vaccination, as discussed earlier in this study. There is another one-dose vaccine in
phase III trials (NCT04741061), that has not yet been approved for emergency use by the
World Health Organization nor by the European Medicines Agency, which is the Sputnik
Light vaccine. This immunizer consists of the components of the Sputnik V (Gam-
COVID-Vac) first dose (adenovirus rAd26), which has been said to have a 79.4% efficacy
by itself, according to the Russian’s vaccination program that authorized its use in the
country. If this vaccine turns out to be approved for world distribution it may help
positively those countries with low-income economies. The Ad5-nCoV (CanSino
Biologics) is another single-dose vaccine, currently approved in 4 countries, that is
composed of the human adenovirus type 5 as well as the Sputnik V’s second dose.
Contrarily, the ZF2001 vaccine is a 3-dose vaccine present in the current clinical trials,
that even if proven to have a successful efficacy result, may not be a practical solution on
the ongoing pandemic.

About the variable interval between doses, the period may vary according to the
initial testing of the vaccines associated with effectiveness evaluation overtime.
Regarding the emergency situation experienced globally during the last year, the clinical
trials had to be done in a quicker way and so most manufacturers chose an interval
between 14 and 28 days, corresponding to the seroconversion interval, to reach a minimal
number of Covid-19 infection cases and finish the studies rapidly. In the real world,
however, the vaccine doses have been applied with longer gaps from those established in
the trials, as a strategy from many countries to accelerate the population's immunization,
since evidence suggests that the first dose of the available Covid-19 immunizers can
decrease, by itself, significantly the risk of passing the infection from one person to the
other. It is important to highlight that there is no maximal interval between doses
because the organism has an inherent immunological memory and many vaccines in fact,
create a longer lasting immune response when administered after an extended interval.
The only actual issue is that, during the extended interval the individual remains without
the fullest protection and prone to getting the disease.

Seroconversion interval can be defined as the time required for an individual,
vaccinated or not, to develop antibodies (seroconversion) against the etiologic agent of
the disease. Our study identified variations in the values of this phenomenon for
different vaccines, such as ad26.cov2.s, which presented a 14-day seroconversion period,
qazcovid-in, with 21 days, and mrna-1273, with 21 days. One of the factors directly
related to seroconversion, and which may explain the different periods found to produce
antibodies, is the type of immunizing agent. Vaccines composed of attenuated antigens
can induce a more basal immune response, when compared to immunizing with adenovirus Sars-Cov-2 and the other types, in addition to having protein subunits that can induce faster immune responses. For this reason, such vaccines can generate protection in a shorter period, compared to other immunizing agents.

In the same way that it can be related to vaccination, seroconversion can be obtained naturally from the production of antibodies after the initial contact with the virus. The knowledge of seroconversion rate allows the recognition of people with strong immune responses against the pathogen and the identification of which antibody is related to the defense against the coronavirus. Although IgM is known to increase and decrease before the IgG rates start going up and stay present, Long, QX., Liu, BZ., Deng, HJ. et al’s study regarding the seroconversion of people infected with Sars-CoV-2 has shown that the IgM can increase anytime, before or after IgG levels rise, or may not even rise at all.

The health industry has developed vaccines of different types, which mechanisms of action are different from each other. Although there are five basic types of vaccines (inactivated, viral vector, based on proteins, RNA and DNA and adenovirus), composed of different approaches to viral action, the objective is the same: induce the body's immune response to develop antibodies against Sars-Cov-2. The high mutagenic capacity of the virus associated with the need to have different “attack” points throughout the stages of viral infection and multiplication in the human body, have motivated the development of different types of vaccine. Added to this, the fact that there are many vaccines in development increases the chances that there will be one or more of the immunizers that will be successful, and will prove to be safe and effective for the study population group. The type of technology used in the composition of the vaccine will also influence the appearance of post-dose application reactions. An example is the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine, which, as it is a viral vector, induces greater stimulation of the immune system of the vaccinated, which consequently generates more side effects. Perhaps the reason that recombinant vaccines are accompanied by a greater immune response is because these immunizers have vectors. The vector, which can be liposomal in the case of BNT162B2 or adenovirus in the case of ChAdOx1 nCoV-19 or mRNA-1273, for example, carries part of the viral protein or genetic material directly to the antigen-presenting cells. This direct delivery to these immune cells through vectors may explain the greater immune response that these new vaccines trigger. However, the fact that all vaccines generated an effective immune
response must be reinforced. Thus, the differences that occurred can be by the development platform of these vaccines, as explained above.

Understanding the pharmacodynamics of each type of immunizing agent is extremely important not only for vaccine developers, but also for the target audience of our study, since this process defines the understanding of the biochemical effects that each immunizing agent will generate in the human body\textsuperscript{76}. This also complements the study about the side effects that each vaccine generates.

Vaccines developed with inactivated antigens can lead the immune system to a strong immunization inducing a response to the entire virus, but this response can occur more slowly\textsuperscript{19,76}. For this reason, the results of the global efficacy of approximately 51\% of CoronaVac in the first dose, for example, can be explained\textsuperscript{19}. On the other hand, mRNA and adenovirus vaccines can trigger a stronger and faster immune response, which can justify an immunization of approximately 75\% in the first dose, as shown in Table 1A\textsuperscript{75}. Although there is no systematic study that classifies these different vaccines into groups, it is possible to suggest a simple classification between the new vaccines (with viral vectors, nucleic acids, and protein subunits) such as Pfizer, AstraZeneca, Moderna, Sputnik, with classic vaccines such as coronavac\textsuperscript{76}. For this reason, the difference between vaccines can lead to distinctions in the profile and kinetics of the immune response\textsuperscript{19,75}.

Based on the results shown in this study it is possible to observe that there is a significant vaccine inequity regarding global distribution, with high-income-countries, such as the US, UK and Canada, being more privileged than low and middle-income economy regions. Our maps show that countries from the African continent were the ones that least tested and approved vaccines, reinforcing economic and technological discrepancies. The manufacturers of Covid-19 vaccines approved for emergency use, especially those that are already more spread around the world (mRNA-1273, BNT162b2 and ChAdOx1 nCoV-19), have estimated that it is possible to offer sufficient doses for more than 30\% of the population worldwide by the end of this year\textsuperscript{78}. However, richer countries tend to secure more doses for their own population, with sizable pre-purchasing agreements, as well as the local manufacturers\textsuperscript{78,79}. So, it is possible that low-income regions may have to wait a longer period for its population to be fully vaccinated\textsuperscript{79}. Another obstacle for these countries is the high cost regarding the doses, distribution, and storage process, which can cause a domino effect and compromise other necessary routine vaccination and health services, risking the spike of other diseases previously
controlled\textsuperscript{80}. So far only the Oxford-AstraZeneca has in solidarity committed to be distributed on a non-profit manner as long as the pandemic takes place\textsuperscript{81}. If this lack of vaccination equity takes place, the world will be prevented from the end and recovery from the coronavirus pandemic\textsuperscript{80,82}.

5 CONCLUSION

Although different types of immunizers are being developed to combat Sars-Cov-2, each country should consider the different variables regarding these vaccines to choose those that best suit them and their population. This research displayed the variables in an organized manner and facilitated their understanding using graphs and maps. The analysis and understanding of this data can contribute to reducing the general population's hesitation about choosing the “best vaccine” for use. It is up to the nations, through their National Immunization Programs, as well as the World Health Organization, to define the best use for each immunizing agent, considering the needs imposed on each country by the pandemic.

Thus, global governments and public health officials need to work together and elaborate effective mass vaccination petitions, which includes building public trust and following a strategy that prioritizes the administration of doses in a way that reduces morbidity and mortality from the infectious disease.
REFERENCES


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**Author Contributions Statement**

All authors contributed to the study conception and design. Material preparation and data collection was performed by C.D.F., F.A.R.S.N., and Y.J.M. Data analysis, and construction of figures was performed by C.D.F., F.A.R.S.N., Y.J.M. and R.A.S.S. The first draft of the manuscript was written by all authors. All authors provided critical feedback and helped shape the manuscript. All authors read and approved the final manuscript.

**Figures and Tables**
Figure 1 - Characteristics of Covid-19 vaccines in phase III clinical trials
Figure 2- Number of vaccines tested in countries

Number of vaccines tested in countries

Legend
- 0 vaccine
- 1 vaccine
- 2 vaccines
- 3 vaccines
- 4 vaccines
- 5 vaccines
- 6 vaccines
- 8 vaccines

0 10 20 km

Figure 3- Number of vaccines tested in each country

Number of vaccines approved in each country

Legend
- 0 vaccine
- 1 vaccine
- 2 vaccines
- 3 vaccines
- 4 vaccines
- 5 vaccines
- 6 vaccines

0 10 20 km
Table 1. Summary of ongoing clinical trials for Covid-19 vaccines in phase III

<table>
<thead>
<tr>
<th>vaccines</th>
<th>NCT numbers</th>
<th>general efficacy</th>
<th>estimated total of participants</th>
<th>tested countries</th>
<th>tested age range (years)</th>
<th>type</th>
<th>storage (°C)</th>
<th>route of administration</th>
<th>number of doses</th>
<th>interval (days)</th>
<th>serum conversion interval (days)</th>
<th>country destination</th>
</tr>
</thead>
<tbody>
<tr>
<td>ad26cov2.s</td>
<td>NCT04614948; NCT04838795; NCT04505722; NCT04908722</td>
<td>66%</td>
<td>575675</td>
<td>be, br, co, de, ne, pa, ph, pl, za</td>
<td>≥ 18, 18-55</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>ad5-ncoV</td>
<td>NCT045262090; NCT045340419.</td>
<td>65.70%</td>
<td>40500</td>
<td>as, cl, mx, pk, ru, jp</td>
<td>≥ 18, 18-85</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>ag0302-cov19</td>
<td>NCT04655625</td>
<td>...</td>
<td>500</td>
<td></td>
<td>≥ 18</td>
<td>recombinant</td>
<td>20</td>
<td>intramuscular</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>bbibp-cov1</td>
<td>NCT04510207; NCT04612972; NCT04560881; NCT04885764</td>
<td>86.00%</td>
<td>58000</td>
<td>cn, pe, ar, eg</td>
<td>≥ 18, 18-60-80-85</td>
<td>inactivated</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>21</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>bat162b2</td>
<td>NCT04368728; NCT04713553; NCT04816669; NCT04805125; NCT04754594</td>
<td>95%</td>
<td>46968</td>
<td>us, ar, br, de, za, tr, es, ch</td>
<td>≥ 12, ≥ 18, 18 to 55</td>
<td>ma</td>
<td>-70</td>
<td>intramuscular</td>
<td>2</td>
<td>21</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>chadox1 ncoV-19</td>
<td>NCT04516746; NCT04664561.</td>
<td>82.40%</td>
<td>34019</td>
<td>ar, cl, co, pr, us, uk</td>
<td>≥ 18</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>28</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>chinese academy of medical sciences covid-19 vaccine</td>
<td>NCT045659239</td>
<td>...</td>
<td>34020</td>
<td>br, my</td>
<td>≥ 18</td>
<td>inactivated</td>
<td>...</td>
<td>intramuscular</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>coronavac</td>
<td>NCT04582334; NCT0456595; NCT04651790; NCT04674833; NCT04580775</td>
<td>50.38%</td>
<td>31020</td>
<td>tr, br, cl, cn, id</td>
<td>≥ 18, 18-59</td>
<td>inactivated</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>covaxin</td>
<td>NCT04654184; NCT04636697</td>
<td>80.60%</td>
<td>25800</td>
<td>in</td>
<td>≥ 18</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>14</td>
<td>&gt;15</td>
<td>NA</td>
</tr>
<tr>
<td>covlp</td>
<td>NCT04674189; NCT04652310; NCT04686258; NCT04838447</td>
<td>...</td>
<td>30918</td>
<td>us, ca</td>
<td>≥ 18</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>21</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>cvnccov</td>
<td>NCT04527575; NCT047800035.</td>
<td>100%</td>
<td>3100</td>
<td>ru</td>
<td>≥ 18, 18-60</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>21</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>epi-vac-covrana</td>
<td>NCT04791423</td>
<td>...</td>
<td>10300</td>
<td>it</td>
<td>≥ 18</td>
<td>recombinant</td>
<td>2 - 8</td>
<td>intramuscular</td>
<td>2</td>
<td>21</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>grad-cov2</td>
<td>NCT04642638</td>
<td>...</td>
<td>6578</td>
<td>us</td>
<td>≥ 18</td>
<td>dna</td>
<td>20</td>
<td>intradermal</td>
<td>2</td>
<td>28</td>
<td>14</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes: Inactivated: 27163
### Table: Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>minhai covid-19 vaccine</td>
<td>NCT04852705…</td>
</tr>
<tr>
<td>minha-1273</td>
<td>NCT04649151; NCT04470427; NCT04860297; NCT04798696; NCT04811664; NCT04804613; NCT03805125.</td>
</tr>
<tr>
<td>msv-cov2373</td>
<td>NCT04553995; NCT04611802.</td>
</tr>
<tr>
<td>qazcovid-in</td>
<td>NCT04691908.</td>
</tr>
<tr>
<td>sputnik v</td>
<td>NCT04640233; NCT04658613; NCT0454303896; NCT04642339.</td>
</tr>
<tr>
<td>sputnik light</td>
<td>NCT04741061</td>
</tr>
<tr>
<td>ut-612</td>
<td>NCT046833224.</td>
</tr>
<tr>
<td>var0008</td>
<td>NCT04904549</td>
</tr>
<tr>
<td>vlac2001</td>
<td>NCT04864561</td>
</tr>
<tr>
<td>vpm1002</td>
<td>NCT04439045; NCT04435379.</td>
</tr>
<tr>
<td>walvac mrna</td>
<td>NCT04847102.</td>
</tr>
<tr>
<td>westchina hospital covid-19 vaccine</td>
<td>NCT04756271.</td>
</tr>
<tr>
<td>xd2001</td>
<td>NCT04646090.</td>
</tr>
</tbody>
</table>

Note: Acronyms of countries according to the ISO 3.166 model, following the alpha-2 code, available at the electronic address: https://www.iso.org/obp/ui/#search (country codes option). Countries whose acronyms were not found adopted the following pattern: bses-Bonaire Sint Eustatius and Saba; cur - Curacao; eng - England; kv - Kosovo; tmc - Northern Cyprus; nir - Northern Ireland; sco - Scotland; uk - United Kingdom. Missing information indicated by an ellipsis (...) and not applicable data indicated by "NA".
Table 2. Types of vaccines x Pharmacodynamics

<table>
<thead>
<tr>
<th>Type</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Spike protein gene present in plasmid -&gt; Crosses the cell membrane after electroporation -&gt; Cell captures DNA -&gt; Transcription and translation -&gt; Vaccinated cell express spike proteins (S) and fragments on their surface -&gt; Recognized by the immune system -&gt; B cells can lock on to the spikes on the surface and if they are activated by Th cells, they will proliferate and produce antibodies that target the S protein. When a vaccinated cell dies, the S proteins and fragments can be taken by an antigen-presenting cell -&gt; Presents a S protein fragmente do Th cell (raise the alarm and help recruit other immune cells to fight the infection) or Nk cell (destroys any infected cells that display S protein fragments).</td>
</tr>
<tr>
<td>RNA</td>
<td>Lipid nanoparticles surrounding mRNA -&gt; Fuse to cells releasing mRNA -&gt; Translating and Transcription -&gt; Vaccinated cell express spike proteins (S) and fragments on their surface -&gt; Recognized by the immune system -&gt; B cells can lock on to the spikes on the surface and if they are activated by Th cells, they will proliferate and produce antibodies that target the S protein. When a vaccinated cell dies, the S proteins and fragments can be taken by an antigen-presenting cell -&gt; Presents a S protein fragmente do Th cell or Nk cell.</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Double-stranded DNA for S protein inserted into the adenovirus -&gt; Adenovirus attaches itself to proteins on the surface of cells -&gt; The cell wraps the virus in a bubble and pulls it in -&gt; Virus escapes from bubble and injects its DNA into the nucleus -&gt; The gene can be read and copied into an mRNA -&gt; Translating and Transcription -&gt; Vaccinated cell express S proteins and fragments on their surface -&gt; Recognized by the immune system -&gt; B cells can lock on to the spikes on the surface and if they are activated by Th cells, they will proliferate and produce antibodies that target the S protein. When a vaccinated cell dies, the S proteins and fragments can be taken by an antigen-presenting cell -&gt; Presents a S protein fragmente do Th cell or Nk cell.</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Inactivated viruses are internalized by the antigen presenting cell that will express some of its fragments on its surface -&gt; Activates Th cells -&gt; Activated Th cells can bind to B cells that express coronavirus S proteins on their surface, activating them -&gt; B cell proliferation and formation of antibodies against S proteins.</td>
</tr>
<tr>
<td>Attenuated</td>
<td>Double-stranded DNA for S protein inserted into the adenovirus -&gt; Adenovirus attaches itself to proteins on the surface of cells -&gt; The cell wraps the virus in a bubble and pulls it in -&gt; Virus escapes from bubble and injects its DNA into the nucleus -&gt; The gene can be read and copied into an mRNA -&gt; Translating and Transcription -&gt; Vaccinated cell express S proteins and fragments on their surface -&gt; Recognized by the immune system -&gt; B cells can lock on to the spikes on the surface and if they are activated by Th cells, they will proliferate and produce antibodies that target the S protein. When a vaccinated cell dies, the S proteins and fragments can be taken by an antigen-presenting cell -&gt; Presents a S protein fragmente do Th cell or Nk cell.</td>
</tr>
</tbody>
</table>