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ARTICLE
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On the safety and effectiveness of COVID-19 vaccines, certainties and uncertainties

Sobre a segurança e efetividade das vacinas para COVID-19, certezas e incertezas

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ABSTRACT

Introduction: The COVID-19 vaccines in use (inactivaded virus, encapsulated m-RNA, non-replicating adenovirus-vectored DNA) were clinically tested in randomized placebo-controlled phase-3 studies. **Objective:** To address certainties and uncertainties about safety and effectiveness of COVID-19 vaccines that were approved for use in various countries. **Method:** The evidence provided by clinical studies on the efficacy and safety of COVID-19 vaccines was critically appraised. **Results:** COVID-19 vaccines proved to be efficacious and safe in clinical trials. Adverse events were mostly those of minor severity commonly noted with other vaccines such as injection site pain, mild flu-like symptoms, headache and asthenia. Although being very rare, anaphylaxis-like reactions were noted with mRNA vaccines. Uncertainties regarding vaccine effectiveness refer mainly to the (long-term) duration of immunity provided by vaccination, the degree of protection conferred to elderly people, and how effective vaccines are against emerging SARS-CoV-2 variants. There are few uncertainties about vaccine safety including the absence of clinical trial data in pregnant women (and the impact on the unborn child), children and adolescents. **Conclusions:** Notwithstanding the knowledge gaps about effectiveness and safety of COVID-19 vaccines (to be further addressed by observational studies), there is overwhelming evidence that public health benefits of vaccination by far outweigh any foreseeable risk.

KEYWORDS: COVID-19; Vaccines; Adverse Events; Randomized Placebo-controlled Trials

RESUMO

Introdução: As vacinas contra COVID-19 (vírus inativado, m-RNA encapsulado, vetor adenovírus não replicante) foram testadas em ensaios clínicos randomizados (fase-3) controlados com placebo. **Objetivo:** Abordar as certezas e incertezas sobre segurança e efetividade das vacinas para COVID-19 já aprovadas para uso em vários países. **Método:** A evidência clínica de eficácia e segurança das vacinas contra COVID-19 foram examinadas criticamente. **Resultados:** As vacinas (COVID-19) mostraram ser eficazes e seguras nos ensaios clínicos. Os eventos adversos foram predominantemente os de menor gravidade comumente observados com outras vacinas, tais como dor no local da injeção, sintomas gripais leves, cefaleia e fraqueza. Embora sejam raras, reações do tipo anafilático foram registradas com vacinas mRNA. As incertezas sobre efetividade referem-se à duração da imunidade conferida pela vacina, o grau de proteção de idosos, e a efetividade das vacinas contra as novas variantes do SARS-CoV-2. As incertezas sobre segurança são poucas e incluem a ausência de estudos clínicos em grávidas (e sobre o bebê no útero), em crianças e adolescentes. **Conclusões:** Não obstante as poucas lacunas acerca da efetividade e segurança das vacinas contra COVID-19 (a serem abordadas por estudos observacionais), os previsíveis benefícios da vacinação para a saúde pública excedem de longe quaisquer riscos antecipáveis.

PALAVRAS-CHAVE: COVID-19; Vacinas; Eventos Adversos; Ensaios Aleatorizados Controlados com Placebo

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INTRODUCTION

Early this year (January 11th, 2021), World Health Organization (WHO) listed 172 or so candidate COVID-19 vaccines in pre-clinical testing, and 63 in different stages of clinical development[1,2]. Some vaccines of the latter group, developed with traditional (virus inactivated) or innovative biotechnological platforms (encapsulated m-RNA, and adenovirus-vectored DNA), proved to be safe and efficacious in randomized placebo-controlled trials (RCTs). In Brazil, two vaccines, CoronaVac (inactivated virus) and Covishield/ChAdOx1nCoV-19 (adenovirus-vectored) were approved for emergency use (EU) by the regulatory authority (*Agência Nacional de Vigilância Sanitária* – Anvisa) on January 17th[3,4]. Hopefully, authorization for use during the public health emergency will be ensued by a countrywide mass immunization campaign that is our best bet to change the game in this struggle against steadily rising death tolls, looming threatens of local emergency healthcare collapse, and an enduring ruin of economic activities.

To have various efficacious vaccines ready to use, one year or so after the COVID-19 pandemic arose in Wuhan, is an outstanding achievement of mankind's Scientific endeavour that – at the outset – many believed not to be feasible in such a short time. Some hurdles, however, still need to be overcome before we can cross the arrival line. Production of vaccines in the amounts needed to global immunization, optimization of product supply and logistics, and complying with the moral obligation to make immunization equally accessible to underprivileged populations and developing countries, are among the greatest challenges still lying ahead.

In Brazil, at least of the same importance has been the misinformation about vaccine risks and efficacy in preventing SARS-CoV-2 infection and morbi-mortality. This article adresses major issues about evaluation of vaccine safety and efficacy, the robusteness of the evidence examined by regulatory agencies and the potential public health benefits of these immunizing products.

METHOD

This article is based on a narrative review of the literature, whose focus was placed on the clinical evidence about the safety and efficacy of vaccines developed for COVID-19 since December 2019/January 2020 when the SARS-CoV-2 virus emerged in Wuhan-China and rapidly spread worldwide. Only COVID-19 vaccines whose phase-3 trial results have been published in peer-reviewed journals (up to January 2021) were examined. Full texts of these published studies were recovered and critically appraised by the authors. The only exception to this rule were the data on the phase-3 trial of CoronaVac vaccine performed in Brazil and unpublished so far. For discussing CoronaVac, the authors relied on the detailed report published by Anvisa (GGMED) on its website, and also by Butantan Institute on the occasion of CoronaVac and Covishield vaccines approval for EU in Brazil (January 17th, 2021).

Articles and documents relevant for the topic addressed in this paper were searched for in electronic databases and websites as follows: Pubmed, World Health Organization, Anvisa, US Food and Drug Admnistration (US-FDA), US Center for Disease Control (US CDC), US National Institutes of Health (US-NIH), and European Medicines Agencies (EMA). All literature/document searches were conducted between December 2020 and February 7th, 2021. The searching terms (keywords) using Boolean connectors "AND" and/or "OR" were as follows: "SARS-CoV-2" OR "COVID-19", "vaccine", "emergency use authorization", "approval for use", "efficacy", "effectiveness", "phase-3", "phase-2", "phase 1", "phase 2/3", "global efficacy", "clinical trial", "clinical study", "safety", "adverse effects", "immunogenicity", "immune response", "neutralizing antibodies". The inclusion criterion was original clinical studies on the safety or efficacy of COVID-19 vaccines published by peer-reviewed journals and/or reports submitted to (and approved by) regulatory authorities with special reference to those approved for use in Brazil. There was no restriction regarding the language of the article or document recovered by the search.

RESULTS AND DISCUSSION

Vaccine candidates testing for safety and efficacy

As any other new medication, vaccine candidates go through rigorous preclinical and clinical stages of testing before being approved for use. The clinical stage of vaccine development is a three-tier testing approach. In the phase-1 trial, the vaccine is given to a small number of healthy volunteers to obtain preliminary data on product safety at increasing doses, and to evaluate how it works to induce immune responses in humans. If phase-1 raises no safety concerns and gives rise to promising immunogenic responses, it is ensued by randomized and controlled phase-2 trials in which hundreds of people (with diversity of demographic features and health status) receive different dosages. This second phase of clinical testing provides additional and robust safety information and assesses relationships between administered doses and immunogenic responses, a surrogate endpoint (*i.e.*, a marker that may correlate with real clinical efficacy, but does not have a guaranteed relationship) for vaccine efficacy. The phase-3 is a randomized placebo-controlled (double- or triple-blinded) study, typically involving thousands of people. It is designed to generate straigthforward clinical information on the vaccine efficacy (VE) and safety. The primary efficacy endpoint in phase-3 clinical trials is the degree to which the immunizing product reduces the disease incidence in vaccinated participants compared to the incidence recorded in the unvaccinated (placebo-recipient) control group. It also provides information about the immune response elicited by vaccination and the occurrence of product-related adverse events.

Determination of VE and effectiveness

Phase-3 trial data are used to calculate the so-called global efficacy, an estimator of the vaccine effectiveness. In clinical trials as those performed for COVID-19 vaccines, or in field studies, the

vaccine global efficacy (phase-3 trials) or effectiveness (observational epidemiological studies) is determined by calculating disease incidences (attack rates) among all vaccinated and unvaccinated people, who, in the case of phase-3 trials, are those participants who received a placebo[5].

The calculated incidence rates (IR) are used to determine VE, or the percentage (%) reduction among the vaccinated people compared to that in the unvaccinated ones, the basic formula of which is: VE % = [(IRU – IRV)/IRU] x 100; where IRU (or ARU) is IR (or attack rates, AR) among unvaccinated people and IRV (or ARV) is the rate among those who have received the vaccine. For example, VE = 100% indicates that full protection was achieved under the trial conditions, or, in other words, that no disease occurred in the vaccinated population within the follow-up time period, VE = 100%, or [(IRU-0)/IRU] x100. In contrast, VE = 0% indicates that the tested immunizing product conferred no protection at all, or that the disease incidence did not differ between vaccinated and unvaccinated populations. Any statistically significant VE (*i.e.*, lower bound of 95% CI greater than 0, and $p < 0.05$) in-between 0% and 100% corresponds to the estimated proportion of a vaccinated healthy population that are likely to be protected from becoming a case[5].

In clinical trials of therapeutic interventions (*e.g.*, with drugs), participants with a previously diagnosed disease or condition (inclusion criterion) are assigned at random to each of the different study arms and the effect of treatment is then prospectively assessed according to predefined primary and secondary efficacy endpoints. When prophylatic products are tested, however, the intervention (vaccination) precedes this time point when participants do/do not become infected as the epidemic evolves. All participants are thus "healthy" at the outset, and therafter they are prospectively assessed as to whether they do or do not get sick (in this case, COVID-19). This implies that phase-3 trials have to be conducted when and where SARS-CoV-2 virus spreads with, preferably, an elevated reproduction number (R number, or basic reproductive rate). A target number of participants who get sick during the trial (*i.e.*, a statistically estimated minimum number of infected people) has to be attained or exceeded before a meaningful VE can be determined. Up to this point in time, the study was double- (or triple-) blinded and then masking is broken to calculate VE. To attain this target number of infected participants in a suitable time, it may be advantageous to selectively enroll people at a higher risk of getting infected during the study. Healthcare professionals (physicians, nurses and others) in direct and daily contact with COVID-19 patients, for instance, are people running such a high occupational risk of getting infected. At least two (CoronaVac and ChAdOx1nCoV-19) phase-3 trials conducted in Brazil[3,4] enrolled mostly healthcare professionals thereby ensuring that the target number of infected participants required to calculate VE would be reached in a relatively short time interval. Obviously, this selective group of people does not represent (*i.e.*, it is not a random sample of) the general population that is expected to be vaccinated after regulatory approval. The participants of another phase-3 trial (Pfizer-BioNTech COVID-19 mRNA vaccine) conducted in Brazil were from the general population.

It is noteworthy that VE is a measure of how well a test product succeeded in achieving its prophylatic aims (*i.e.*, to confer protection) under the strictly controlled conditions of a clinical trial (RCT), whereas vaccine effectiveness refers to how well it succeeded in preventing the disease when a larger and more diverse population is vaccinated.

The vaccine effectiveness and safety is assessed by large observational field studies conducted on large vaccinated and unvaccinated populations, after vaccine approval for use. Effectiveness refers to the immunization performance of a vaccine in a real-world scenario of use.

Efficacy (VE) cut-off values for approval of COVID-19 vaccines

Although not setting *a priori* a minimum level of efficacy or cut-off efficacy rate for approving COVID-19 vaccines, the European Medicines Agency (EMA) informed that demonstration of an efficacy of at least 50% is expected[6]. The WHO also recommends that "[...] the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is > 30%"[7]. WHO also remarks that, regarding the 95% CI for a secondary efficacy endpoint, "a lower bound ≤ 30% but > 0% may be acceptable as a statistical success criterion...., provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint"[7]. Along the same line, US FDA requires a point estimate VE for a placebo-controlled efficacy trial of at least 50%, with a lower bound of 95% CI of > 30%[8].

A common misunderstanding of the reason why the agencies set such a tentative cut-off for COVID-19 vaccines is to think that candidate vaccines with VEs lower than this point estimate are ineffective or useless. Actually, various vaccines with lower VEs proved to be effective and extremely useful to prevent infection-associated morbidity and mortality, and to contain and eventually stop the spread of several contagious diseases. We should be aware that a minimum VE of 50% for COVID-19 vaccines is an arbitrary cut-off point that tentatively takes into account variables such as cost-effectiveness issues, logistics, risk to benefit balance, available alternatives, and foreseeable public health impacts of vaccines intended to be deployed to millions of people worldwide. In other words, agencies' experts believe that a minimum efficacy rate of 50% is enough to make a difference in the management of this public health emergency. Moreover, as EMA[6] stressed, not only high efficacy rates, but also other advantages such as better safety profiles (fewer and less severe side effects), an easier storage and delivery, and a good performance for a specific age group or subpopulation, eventually contribute to the public health success of COVID-19 vaccines.

Vaccines with nearly 50% or even lower point estimates of efficacy were repeatedly demonstrated to be useful to reduce the incidence of other infections and to attenuate their morbidity and toll rates. Effectiveness of influenza (flu) vaccines, for instance, varies a lot and recent studies demonstrated that they

decrease the risk of flu illness by between 30% and 60% among the general population[9]. These studies also showed the influenza vaccines reduce the risk of flu-associated hospitalizations among older people on average by about 40%, or even more[9]. It has been generally agreed that annual vaccination of the older population against influenza brings undeniable public health benefits.

Certainties and uncertainties regarding COVID-19 vaccines

Effectiveness

VE determined in phase-3 trials may differ from the product performance (or effectiveness) when it is used to immunize a large population outside the pre-established conditions of a clinical study. The reasons for this uncertainty are manifold and involve issues related to external and internal validities of clinical studies.

The study external validity refers to the extent to which its conclusions can be applied to the general population, or whether the study findings are generalizable to a distinct context. Internal validity, on the other hand, refers to the extent to which conclusions drawn within the context of a particular study are reliable and valid.

In phase-3 trials enrolling (exclusively or predominantly) healthcare professionals, who are not only daily exposed but also in close contact with high viral (SARS-CoV-2) loads, the product-conferred immunization is strongly challenged compared to the general population under real-world scenarios of exposure. It is therefore plausible to think that VE determined for this high-risk group of people tend to underestimate the real performance (effectiveness) when the product is used in mass vaccination campaigns.

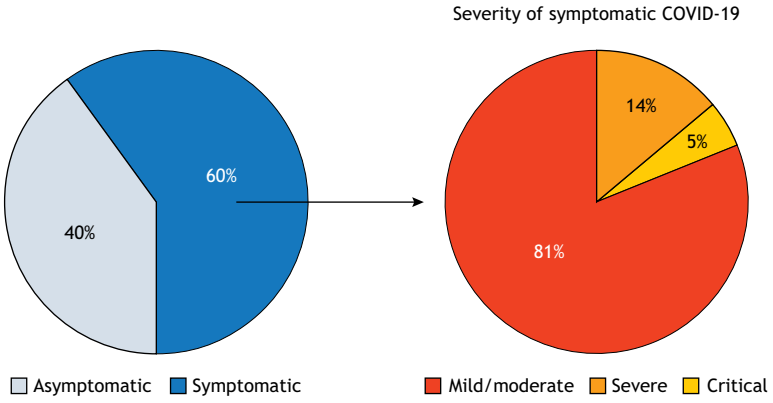
Another uncertainty about COVID-19 vaccines that remained after phase-3 results came to light is the extent to which vaccination impacts on the occurrence of asymptomatic infections. The primary efficacy endpoint of vaccine phase-3 trials refers to symptomatic infections, regardless of how severe they are. Asymptomatic infections are not detected by laboratory testing during the clinical trial. That is, VE determination takes into account only diagnosed cases or participants who showed infection symptoms with a laboratory confirmation (PCR) of COVID-19.

According to US NIH's and CDC's classification of illness severity of patients with COVID-19 (Table 1), the spectrum of disease severity ranges from asymptomatic and mild cases to severe and critical illness[10]. The exact proportion of asymptomatic COVID-19 is uncertain. Based on data from three large cohorts that identified cases by population-based testing, it was estimated that infections may progress asymptomatically in 33 to 40% of all people infected with SARS-CoV-2 (Figure)[11,12].

Table 1. Range of illness severity of patients infected with SARS-CoV-2 (COVID-19).[#]

Severity	Criteria for classification into the category
Asymptomatic or presymptomatic infection	Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.
Mild Illness	Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
Moderate Illness	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on room air at sea level
Severe Illness	Individuals who have SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%.
Critical Illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Source: # CDC – US National Institutes of Health (US NIH); www.covid19treatmentguidelines.nih.gov and https://www.covid19treatmentguidelines.nih.gov/overview/ clinical-spectrum/, 2021.
[#] CDC – US National Institutes of Health (US NIH) www.covid19treatmentguidelines.nih.gov
US-NIH: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/



Source: Elaborated by the authors, 2021.

Figure. According to recent studies 33.0% to 40.0% COVID-19 infections are asymptomatic[11,12]. Among the patients with a confirmed SARS-CoV-2 infection (symptomatic infections), 81.0% have a mild to moderate illness, 14.0% a severe disease, while 5.0% progress to respiratory failure, septic shock, and/or multiple organ dysfunction (critical illness)[10,33]. Overall death rate was 2.3%; all deaths were recorded among the critical cases[33].

The effect of vaccination on the transmissibility of SARS-CoV-2 infection is another knowledge gap. This issue was not directly addressed by phase-3 trials.

It is believed that a sizeable portion of community COVID-19 transmission events are from asymptomatic transmissions[13,14]. Notwithstanding being plausible, public heath impact of asymptomatic transmission remains uncertain. Findings from a recent Singapore's study indicated that although asymptomatic COVID-19 cases are infectious, they might be much less infectious than symptomatic cases thereby representing lower transmission risks[13,14]. It is of note that, in addition to bearing lower viral loads, asymptomatic people do not cough and/or sneeze, symptoms that considerably enhance virus spread and infectivity.

The type of protection conferred by vaccines widely used for preventing different diseases, range from those that block infection progress to severe illness and death, but do not prevent infection (most immunizing products do so), to those (few ones) that avert infections, producing the so-called "sterilizing immunity". In this latter case, the immune system of vaccinated persons blocks virus entry into cells and thus viral replication. Of course this is highly advantageous because the vaccinated person is protected and virus community transmission is promptly blocked. As far as the second type of protection (non sterilizing) is concerned, vaccinated people may continue to transmit the disease if viral loads are high enough to allow infection of their contacts. Rotavirus vaccines are typical examples of immunizing products that although not stopping infection and transmission, have a powerful beneficial effect in reducing severe diarrhea and infant mortality, and so are strongly recommended by pediatricians[15,16].

At any rate, although phase-3 trials of COVID-19 vaccines did not fully elucidate their impact on transmissibility, one can assume that all approved vaccines shall confer individual protection and, additionally, if mass vaccination takes place, shall decisively contribute to stop community transmission, particularly if combined to a good adherence to nonpharmacological protective measures.

Protection against severe illness requiring hospitalization

All vaccines tested in phase-3 trials were claimed to strongly protect against severe COVID-19 illness. Actually, clinical trial results showed that whereas a number of cases of severe COVID-19, including those leading to hospital admission, occurred among placebo-controls, severe disease and hospitalization was not recorded in vaccinated participants. Although this finding was consistently observed with different COVID-19 vaccines in various multicenter trials, the total number of severe cases in the placebo arm was relatively small so that a robust statistical demonstration of this protective effect was not always feasible. This is not surprising because phase-3 studies were primarily designed to demonstrate global efficacy, the primary efficacy endpoint. Therefore, the estimated (target) minimum number of COVID-19 cases for calculating VE includes only symptomatic cases among which largely predominate those of mild illness (Figure). At any rate, phase-3 trial results were fairly consistent with the hypothesis that a great deal of protection against severe COVID-19 illness is provided by all vaccines. This type of protection against severe disease has been repeatedly observed and demonstrated by large field observational studies of other vaccines as, for instance, those of influenza vaccines[17,18].

Protection of elderly people, children and pregnant women

Owing to the senescence of immune system responses[19,20], a reasonable doubt may exist as to whether, and the extent to which, COVID-19 vaccines would protect elderly people, a population age stratum at considerably higher risks of developing severe illness. Although phase-3 results suggested that all tested COVID-19 vaccines are also beneficial to old people, the number of infected participants at this age stratum in some trials was not sufficient for a statistically robust demonstration of efficacy. This knowledge gap should be addressed by further observational studies in large cohorts of vaccinated and unvaccinated people. It is of note that, since several existing vaccines proved to be effective, further placebo-controlled trials become unethical, particularly if people at high-risk of severe disease and infection-associated deaths are left unprotected. Further studies to address this issue, therefore, should be observational investigations or clinical trials using active comparators (*i.e.*, a vaccine of proven efficacy).

For ethical reasons, phase-3 studies did not enroll pregnant women and thus efficacy and safety of COVID-19 vaccines in pregnancy remains undemonstrated by clinical trials. There is no *a priori* reason to think, however, that these vaccines, particularly those products based on inactivated viruses or non-replicating adenovirus vectors, might be less effective in pregnant women or pose health risks to unborn children.

A recent large study analyzed maternal and cord blood sera from 1471 mother-newborn pairs for IgG and IgM antibodies against receptor-binding domain of the SARS-CoV-2 spike protein[21,22]. Results showed that 83 women (6% of the study population) had detectable IgG and/or IgM antibodies at delivery and that their infants (72 of 83 or 87%) also had detectable IgG at birth suggesting active IgG transplacental transfer at transfer ratios > 1.0[21]. Based on these findings, one may expect that maternal immunization during pregnancy shall protect not only the mother but also her unborn child.

Since vaccine phase-3 studies involved only participants aged ≥18 years, safety and efficacy of COVID-19 vaccines in children and adolescents were not tested so far. Clinical trials of vaccines and medications in children and adolescents (vulnerable groups), however, generally ensue the initial demonstration that these products are safe and effective in adults. Clinical studies of COVID-19 vaccines in the pediatric population are necessary and expected to begin soon.

Duration of immunity provided by vaccination

In phase-3 clinical trials, the protection after vaccination is assessed when a minimum (target) number of infected participants is obtained or exceeded. For the interim analysis of

efficacy and safey, masking is broken and, depending on the study design, an open follow up continues up to 12 months or so after vaccination. How long immunity lasts beyond the time interval evaluated in the clinical studies remains undetermined. The estimated duration of vaccine-conferred protection after one or two-doses vaccination schemes shall be further clarified by observational investigations and/or post-approval follow up studies. It is of note that post-approval (phase-4) studies may lead to optimization of vaccination schemes by adjusting doses and time-interval between doses, and by administration of booster doses.

Efficacy against emerging SARS-CoV-2 variants

It is known that virus genome constantly changes through mutations and, therefore, it is not surprising that new variants of a virus occur over time. The emergence of variants can be tracked by systematically sequencing the genome of a virus that circulates in a population. Some viral variants emerge and disappear whereas others tend to persist and may become predominant. In this regard, SARS-CoV-2 is not an exception. Some variants of COVID-19 virus are of concern because they affect the S (spike) glycoprotein that allows the virus to penetrate host cells and cause infection. Epidemiologists and public health managers are deeply worried with the emergence of SARS-CoV-2 variants affecting the spikelike S-protein in the UK (B.1.1.7), South Africa (B.1.351) and in the Amazonian region of Brazil (P.1). These emerging variants are apparently more contagious than the wild-type virus[23,24].

The question arises as to whether currently available COVID-19 vaccines also protect – and the extent to which they do it – against infections by these new variants.

In *in vitro* neutralizing capabilities of mRNA vaccines BNT162b2 (Pfizer-BionTech) and mRNA-1273 (Moderna) were tested against these SARS-CoV-2 variants. No significant effect on neutralization against the B.1.1.7 variant was noted in either case, while m-RNA-1273 produced a weaker, but still significant neutralization of the B.1.351 variant[23,24].

A recent multicenter clinical trial (ENSEMBLE) of a single-dose adenovirus-vectored immunization product (Ad26.COV2.s produced by Johnson & Johnson) showed that at post-vaccination day 28 it was 72% effective (moderate-to-severe COVID-19 cases) in the US, 66% in Latin America, and 57% in South Africa. Since in South Africa 95% of all cases of COVID-19 were due to infections with B.1.351 this finding might indicate that the Ad26.COV2.s vaccine is less effective against this variant[25].

The bright side of this worrying situation is that mRNA and adenovirus vectored vaccines can be easily re-designed and rapidly adjusted to effectively face these SARS-CoV-2 variants, the genome of which has been sequenced. Virus variants can also be replicated in cell culture and used to produce new inactivated virus immunizing products containing antigens of one or more variants of interest.

Safety issues

Results from large phase-2 and phase-3 trials clearly indicated that the different vaccines so far developed against COVID-19 are rather safe products inducing only minor (grade 1) and transient adverse events such as pain in the injection site, mild flu-like illness symptoms, headache and asthenia. This safety profile has been confirmed in the ongoing large-scale vaccination with these immunizing products. The most serious vaccine adverse events were hypersentivity (anaphylaxis-like) reactions observed with the mRNA vaccines. Although being rare, these events are serious and life-threatening and thus patients with a history of severe allergy should be preferably vaccinated with other products. Moreover, vaccination rooms using mRNA immunizing products should be equipped with drugs (epinephrine, glucucorticoids, antihistamines and beta-agonists, e.g., albuterol), supplemental oxygen, and a trained staff to prompt act when facing such an emergency.

An aspect of the safety profile of vaccines not evaluated in phase-3 trials is the risk of adverse events of COVID-19 vaccines on people who had previously had a symptomatic illness. In principle, enhancement of immune responses by vaccines might trigger auto-immune vascular damage if SARS-CoV-2 antigens are still present in the endothelial lining of blood vessels. Since studies indicated that convalescent patients acquired some immunity against COVID-19, for precaution, a reasonable time interval between the symptomatic illness and vaccination should be observed[26,27,28].

Obviously, the evidence that COVID-19 vaccines are safe is overwhelmig. It is limited, however, the evaluation of short- and medium-term adverse events in phase-2, phase-3 and post-vaccination monitoring. The long-term safety assessment depends on observational epidemiological studies that certainly will be performed in the vaccinated population in the coming years. Based on what is known about other widely used vaccines, however, there is no reason to think that long-term adverse events might occur with COVID-19 vaccines.

CONCLUSIONS

A set of COVID-19 vaccines using different technologies (platforms) were developed in a relatively short time since the emergence of the pandemic (Table 2). Abundant and robust clinical data (phases 1-3 trials) are available on their safety profile and efficacy against COVID-19. All vaccines approved for EU proved to be safe and efficacious – particularly regarding the prevention of moderate to severe disease – and are expected to strongly impact on the course of the pandemic and its death toll, if a massive vaccination campaign is promptly undertaken (Table 2). A few uncertainties, however, remain to be further elucidated by observational studies (Table 3). The knowledge gaps on vaccine effectiveness include the effects on transmissibility, efficacy in preventing asymptomatic infections, and how long immunity provided by vaccination endures. It is unclear how new SARS-CoV-2 variants will challenge the immunity provided by these vaccines

Table 2. Efficacy and safety outcomes of randomized placebo-controlled (phase-3) trials of some COVID-19 vaccines.

Vaccine	Study population	Efficacy	Adverse events	Remarks	Ref.
Adenovirus (non-replicating) vectored DNA *(spike glycoprotein gene)*					
Gam-COVID-Vac (Sputnik V); two vector components, rAd26-S and rAd5-S (Gamaleya Research Institute).	≥ 18 y; healthy volunteers with no COVID-19 (PCR and IgM and IgG titers); and no contact with anyone with COVID-19 in the preceding 14d. Rand. participants, N = 21,977; High, medium or general risk of infection.	21-d after first dose; Total cases = 78. Overall efficacy (95% CI): 91·6% (85·6-95·2); Moderate or severe cases N = 20 Efficacy 100% (94.4-100.0).	AE: flu-like illness, injection site reactions, headache, and asthenia. AE (7485 [94·0%] of 7966) were grade 1; 451 were grade 2 (5·66%) and 30 were grade 3 (0·38%).	Randomised (3:1 vaccine/placebo), double blinded, placebo (buffer) controlled, multicentre study. Two doses 21 d apart.	29
ChAdOx1 nCoV-19, chimpanzee adenoviral vector - Covishield® (AstraZeneca-Oxford).	≥ 18 y; healthy volunteers with no COVID-19; Interim efficacy analysis: Rand. participants, N = 11636 (7548 in the UK, 4088 in Brazil among which healthcare workers).	Symptomatic COVID-19: N = 98, Placebo N = 71, Vaccinated N = 27 Overall efficacy (95% CI): 62.1% (41.0-75.7). 21 d after 1st dose 10 cases of hospitalized patients, with 01 severe and 01 death, all in the placebo group.	AE: Three cases of transverse myelitis in participants considered unrelated to vaccination possibly due to idiopathic demyelination, one case of high fever who recovered, four deaths unrelated to vaccine (accidents).	Randomised (1:1 vaccine/placebo), single blinded, placebo (meningococcal group A, C, W, and Y conjugate vaccine or saline). Two doses 8-12 weeks apart.	4,31
Inactivated SARS-CoV-2 virus					
CoronaVac Sinovac Life Sciences Co #	≥18 y; healthcare workers (at a risk of infection) with no COVID-19. Rand. participants, N=12270 (Brazil) 6129 received vaccine, 6141 received placebo.	Symptomatic COVID-19: N=244, Placebo N=166, Vaccinated N=85 Overall efficacy (95% CI): 50.39% (35.26-61.98). Moderate and/or severe cases N=7 (all in the placebo group).	AE: pain, erythema, swelling or pruritus in the site of injection (3.02%). Systemic > 1%, mostly grade ½, fever, fatigue, headache No severe adverse event.	Data from Brazilian (multicentre) phase 3 only. Ramdomized (1:1), double-blinded placebo-controlled. (Placebo: Aluminium hydroxide, Sodium chloride, disodium hydrogen phosphate).	3
m-RNA of SARS-CoV-2 S protein fragment (encapsulated in lipid-nanoparticles)					
BNT162b2 (Pfizer-BioNTech)	≥ 16 y; healthy volunteers with no COVID-19; Rand. participants, N = 43448 of whom 21720 received BNT162b2 and 21,728 placebo.	Symptomatic COVID-19; 7-d after second dose: N = 170 cases, 162 among placebo, 8 among vaccine recipient participants. Overal efficacy (95% CI): 95% (90.3-97.6). Severe COVID-19 after first dose (N = 10): 09 in placebo and 01 in vaccine group.	AE: mild-to-moderate pain at the injection site, fatigue (59%), and headache (52%). Fever (≥ 38°C) after the 2nd dose (16%). Lymphadenopathy (0.3%). Early safety monitoring detected 21 cases of anaphylaxis after reported administration of 1,893,360 first doses.	Ramdomized (1:1); single (observer) blinded, placebo-controlled, multicentre (US, Argentina, Brazil, South Africa, Germany, Turkey). Two doses 21d apart.	32,34
mRNA-1273 (Moderna)	≥ 18 y; healthy volunteers with no COVID-19 at appreciable and/or high risk of infection. Rand. participants, N = 30,420,	Symptomatic COVID-19: N = 196, Placebo N = 185, Vaccinated N = 11 Overall efficacy (95% CI): 95.1% (89.3-96.8). Severe COVID-19 N = 30 (including one death), all in the placebo group,	AE: Pain and erythema in injection site, fatigue, headache. Possible Bell's palsy and hypersensitivy reactions, yet rare, need further monitoring. Anaphylaxis-like reactions,	Randomized (1:1), single (observer) blinded, placebo (saline) controlled, multicentre, 99 US cities. Two-doses 28d apart.	30,34

Source: Elaborated by the authors, 2021.
AE: adverse events. #Data were from the phase-3 trial conducted in Brazil that was designed and headed by Butantan Institute clinical research staff. Phase 3 trial of CoronaVac in Turkey and Indonesia reported (interim results) overall efficacies of 91.25% and 65.3%, respectively. These results, however, have not been published so far.

Table 3. Certainties and uncertainties about safety and effectiveness of COVID-19 vaccines evaluated in randomized placebo-controlled trials and approved for emergency use in Brazil and other countries.

Confidence	Certainties	Uncertainties
Effectiveness	All vaccines proved to be efficacious in phase-3 trials with estimated global efficacy ≥ 50%.	Effectiveness (general population) may be different from the global efficacy estimated in phase-3 studies. It may be even greater than the efficacy measured under the phase-3 study conditions.
	Vaccines proved to be effective in preventing COVID-19 moderate to severe illness and hospitalization.	Sterilizing immunity is unlikely and protection against asymptomatic infection and overall impact on transmissibility were not assessed
	Clinical studies indicated that vaccines protect elderly people compared to unvaccinated persons of their age.	It is uncertain whether or not vaccines are less effective in elderly people, and if so, the extent to which protection provided by vaccines decreases with age.
	Preliminary tests (mostly in vitro) suggests that vaccines also protect against so far identified variants.	Emergence of potentially more contagious new virus variants may occur and poses permanent challenges to existing vaccines. Re-design/adaptation is feasible and may be needed.
	Vaccines immunize against COVID-19 and effective protection lasts for at least several months, certainly for a time longer than the phase-3 trial duration.	The exact duration of protection provided by vaccines remains undetermined.
Safety	All COVID-19 vaccines proved to be safe in phase 2/3 studies. Only minor adverse events, commonly observed with other vaccines (site of injection pain, headache and mild flu-like symptoms), were recorded. Although being rare, serious anaphylaxis-like reactions occurred with mRNA vaccines.	Safety in pregnancy (for the unborn child) and in children and adolescents was not evaluated in clinical trials. Safety of vaccination of people who had a previous symptomatic COVID-19 remains undetermined. Long-term safety of vaccines depend on further follow up monitoring studies and observational investigations in vaccinated populations.

Source: Elaborated by the authors, 2021.

and whether it would be needed to change the vaccines to improve neutralization of highly contagious variants. The degree to which vaccines circumvent the problem of immune system senescence and protect older age people is another question that remains open for several immunizing products. The real effectiveness of vaccines in immunization campaigns may differ from the global efficacy determined in phase-3 trials and, in the case of some vaccines, the real world use effectiveness might be even greater than the efficacy estimated in phase 3 studies. As far as safety is concerned, uncertainties refer mainly to effects on the unborn child health when pregnant women are vaccinated, and the incidence and severity of adverse events in children and adolescents. Safety of COVID-19 vaccines for people who recently had a symptomatic illness also remains to be evaluated.

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Authors' Contribution

Oliveira ACAX, Paumgartten FJR - Conception, planning (study design), acquisition, analysis, interpretation of results and writing of the work. Delgado IF - Conception, planning (study design) and writing of the work. All authors approved the final version of the work.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.