Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

SARS-CoV-2 vaccines: Clinical endpoints and psychological perspectives: A literature review

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ABSTRACT

Background: About 270 million cases have been confirmed, and 5.3 million fatalities Worldwide due to SARS-CoV-2. Several vaccine candidates have entered phase 3 of the clinical trial and are being investigated to provide immunity to the maximum percentage of people. A safe and effective vaccine is required to tackle the current COVID-19 waves. There have been reports that clinical endpoints and psychological parameters are necessary to consider vaccine efficacy. This review examines the clinical endpoints required for a successful SARS-CoV-2 vaccine and the influences of psychological parameters on its efficacy.

Methods: The main research question was to find out the clinical endpoints that determine the vaccine efficacy? And what kind of psychological parameters affect the vaccine efficacy? The information was taken from several journals, databases, and scientific search engines like Googe scholar, Pubmed, Scopus, Web of Science, Science direct, WHO website, and other various sites. The research studies were searched using keywords; SAR-CoV-2 vaccine efficacy, psychological effect on SARS-CoV-2 vaccine, SARS-CoV-2 vaccine endpoints.

Results: This review has highlighted various clinical endpoints that are the main determinants of clinical vaccine efficacy. Currently, vaccinations are being carried out throughout the world; it is important to investigate the main determinants affecting vaccine efficacy. We have focused on the clinical endpoints and the influence of psychological parameters that affect the vaccine efficacy in clinical settings. The primary endpoints include the risk of infection, symptoms, and severity of COVID-19, while hospitalization length, supplemental oxygen requirement, and mechanical ventilation are secondary endpoints in the clinical endpoints. Some tangential endpoints were also considered, including organ dysfunction, stroke, and MI. Many psychological associated things have influenced the vaccine efficacy, like the lower antibody titers in

Abbreviations: AE, Adverse Events; AD, Alzheimer's Disease; Ad, Adjuvant; ADCD, Antibody-Dependent Complement Deposition; ADM, Adaptive Defence Mechanisms; ADNP, Antibody-Dependent Neutrophil Phagocytosis; AIRD, Autoimmune Rheumatic Disease; AIS, Adaptive immune system; AR, Adverse Reaction; ASFA, Antigen-specific functional antibodies; BAH, Bilateral Adrenal Haemorrhage; BOD, Burden of Disease; C-C, Critical Care; CEPI, Coalition for Epidemic Preparedness Innovations; CGP, Chinese General Public; CMI, Cell-mediated immunity; CS, cross-sectional; CVST, Cerebral Venous Sinus Thrombosis; CVT, Cerebral Venous Thrombosis; DVT, Deep Vein Thrombosis; HCP, Health Care Professionals; HCS, Health Care Systems; HFQT, high-flow oxygen therapy; IS, Immune System; ISt, Ischemic Stroke; IV, Invasive Ventilation; LT, Long term; LTS, Long Term Stressors; MV, Mechanical Ventilation; MHPs, Moscow Hospitals and Polyclinics; MI, Myocardial infarction; NIV, Non Invasive Ventilation; n-MV, non-Mechanical Ventilation; NRP, Non-Randomized Phase; NSIIR, non-specific innate immune response; PC, Placebo controlled; PE, Pulmonary Embolism; PP, Pneumococcal Polysaccharides; PV, Placebo Vaccine; PVT, Portal Vein Thrombosis; RC, Replication component; RDRP, RNA dependent RNA polymerase; RS, Reactogenicity Subset; SCFA, Short Chain Fatty Acids; SCLDC, Shangqiu City Liangynan District Center; SCW, Singaporean Chinese Women; SIA, Shoulder Injury Adenopathy; SN, seronegative; SOI, Site of Injection; SP, seropositive; SS, serostatus; ST, Short term; STS, Short Term Stressors; SV, structural ventilation; SVT, Splanchnic vein thrombosis; TTP, Thrombotic Thrombocytopenic Purpura; TTS, Thrombosis with Thrombocytopenia Syndrome; TV, Typhoid Vaccine; UAd, Unadjuvanted; VITT, Vaccine Induced Thrombocytopenia; VSC, Vaccine Success Criteria; VTE, Venous Thromboembolism; VZ, Varicella Zoster

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the vaccinated people. In addition to that, Short- and long-term stress and sleep deprivation were also found to affect the vaccine efficacy.

Conclusion: The review summarizes the important clinical endpoints required for a successful vaccine candidate. In addition to primary and secondary endpoints, auxiliary endpoints and the disease burden also play an important role in modulating vaccine efficacy. Moreover, the psychological perspective also influences vaccine efficacy. Effective follow-up of participants should follow to examine the clinical endpoints to reach any conclusion about vaccine efficacy.

Contents

Introduction

Although SARS-CoV-2 has affected more than 270 million people Globally, many pathogenesis aspects of SARS-CoV-2, including the connection among viral replication points, are unknown [1-6]. Earlier, nasopharynx viral load was linked to enhanced disease severity and mortality in the SARS-CoV-1 outbreak [7]. Moreover, SARS-CoV-1 and 2 have considerable differences in the timing of viral shedding [8], infectivity, epidemiology, and clinical symptoms [9]. SARS-CoV-2 viral tests are required not just for respiratory specimens but also for blood samples [10]. COVID-19 patients primarily died from respiratory failure, while hyperactive immunological response and vascular impairment are observed in the respiratory and extrapulmonary systems [6,11]. Although findings have been limited to the absence of quantifiable viral load [12], plasma viremia load might also be associated with disease seriousness, which can act as a biomarker for viral exposure. In this review, we have discussed the primary and secondary endpoints to assess the efficacy of vaccine candidates, endpoints comparison profiles for approved vaccines, and the possible correlation of psychological variables on the efficacy of COVID-19 vaccines.

SARS-CoV-2 linked with disease seriousness

Detectable plasma viremia was linked to higher illness among hospitalized subjects, with 44% of individuals on oxygen gas masks having measurable viremia compared to 19% of those accepting supplementary oxygen via nasal cannula [13]. Raised D-dimer levels indicate massive thrombin formation and fibrinolysis. They are affiliated with a poor prognosis in COVID-19, prompting health care professionals to hypothesize that raised D-dimer concentration levels suggest co-existing venous thromboembolism, which may contribute to ventilation-perfusion disparity [14]. A study was conducted on 343 COVID-19 patients suggested that patients with D-dimer levels of more than 2.0 μg/mL have high mortality (12/67) rate when compared to patients with less than 2.0 μg/mL D-dimer level (1/267) [15]. In another study, D-dimer levels of ≥ 1.0 μg/mL were linked to increased-hospital mortality [16]. These studies suggest that D-dimer could be an early biomarker for COVID-19 patients. Cardiac dysfunction blood markers are also linked to the severity of COVID-19. A retrospective cohort analysis of 138 patients revealed that ICU patients were more prone to rapid cardiac damage than non-ICU patients. However, the precipitating events were not specified [17]. Furthermore, underlying cardiovascular diseases (CVDs) increases the likelihood of severe COVID-19-related consequences [16]. Multiple investigations have found that individuals with severe COVID-19 have lower granulocyte counts than those with mild COVID-19 [14]. In a survey of 81 participants, those with a greater neutrophil-to-lymphocyte ratio (> 9.8) had a greater prevalence of ARDS (P = 0.005) and greater rates of n-MV and MV (P = 0.002 and P = 0.048, respectively) [18]. An additional survey of 329 SARS-CoV-2 contaminated patients found that those with impaired liver enzyme evaluations at the time of hospitalization had a greater admittance rate to the ICU (20% vs. 8%; P = 0.001), the need for MV (14% vs. 6%; P = 0.005), acute renal failure (22% vs. 13%, P = 0.009), and mortality (21% vs. 11%, P = 0.009) [19]. Another study revealed that 2 out of 16 COVID-19 confirmed outpatients (13%) exhibited measurable SARS-CoV-2 plasma viremia, in contrast to no one of the 74 subjects with negative clinical nasopharyngeal screening SARS-CoV-2 RNA and no one of the 53 cured COVID-19 patients. There was no detectable plasma SARS-CoV-2 RNA in 18 plasma trials from intensive care unit subjects before the COVID-19 period. Detectable SARS-CoV-2 RNA in the respiratory tract was prevalent, regardless of disease severity [13].

SARS-CoV-2 related through transmission risk

SARS-CoV-2, like other coronaviruses, is primarily transferred via contaminated pulmonary droplets. The epithelium of the human respiratory structure, comprising the oropharynx and upper airway, incorporates the majority of target host receptors. Contamination can similarly reach through the conjunctiva and GIT, acting as communication gateways [20]. Transmission risk is determined by surroundings, the infectiousness of the host, and socioeconomic

influences. Nearby series interaction (such as 15 min face to face and within 2 m) [21] accounts for the majority of transmission. Propagation is most efficient within families, relatives, and helpers, whereas community subordinate outbreak rates range from 4% to 35%. Infection risk increases by staying in the same room or being married to an affected person while reduced by isolating the sick person from the rest of the family [22]. Eating in nearby areas to a diseased individual, distributing meals, and participating in assembly events are highly dangerous. Compared to outside settings, the risk of contamination significantly increases in bounded surroundings [23]. According to a comprehensive review of transmission clusters, most super spreading episodes happened indoors [24].

The aerosol transmitter can still be an issue during a long stay in a busy, imperfectly aerated interior environment (where the transmission can happen at a closeness of more than 2 m) [25]. The importance of fecal shedding in SARS-CoV-2 transmission, besides the degree of fomite (through inanimate surfaces) communication, is indefinite. Even on surfaces (stainless steel, plastic, glass) with lower temperatures and humidity, both SARS-CoV-2 and SARS-CoV-1 stay sustained for longer periods (e.g., air-conditioned atmospheres) [26].

Therefore, the disease can be transmitted from contaminated surfaces to the eyes, nasal, and oral mucosa via unwashed hands. This means of spread might take part, predominantly in organizations with public areas, where the atmospheric contamination risk is greater. Both SARS-CoV-1 and SARS-CoV-2 are denatured by conventional antiseptics, highlighting the significance of cleanliness and handwashing. SARS-CoV-2 RNA has been identified in feces samples which last much longer than respiratory samples [27]. There are no documented shreds of evidence for fecal-oral transfer. In the SARS-CoV-1 epidemic, studies suggest that the virus is aerosolized and transmitted throughout an apartment building due to a malfunctioning sewage system [28]. It's unclear whether SARS-CoV-2 will transmit in the same way.

Clinical endpoints to access SARS-CoV-2 vaccine efficacy in clinical trials

Vaccine efficacy is measured using a range of outcomes that differ based on the pathogens, infection repercussion, and kinetics of transference [29]. ADMs against viral infections are the foundation of traditional vaccine development. Endpoints are very crucial for determining the efficacy of vaccine candidates. Optimal endpoints should incorporate the rate of change of vaccinated populations and better expression of antiviral protective immunity [30]. Since immunogenicity is an important consideration when developing a vaccine, the intensity of the immune response necessary to safeguard against SARS-CoV-2 infection is unpredictable [31].

The US FDA proposed that laboratory-confirmed COVID-19 or SARS-CoV-2 infection be adopted as the primary endpoint in vaccine effectiveness studies, with a 50% endpoint estimation for placebo-controlled effectiveness trials [29]. Infection, severity, or transmission might be prevented with an effective vaccine. Individuals' responses to SARS-CoV-2 infection vary and depend on various factors, including age, comorbidities, ethnicity, and sex. Individually, the effects of infection might range from asymptomatic states to hospitalization, the need for breathing support, and even death [29]. Two important endpoints, symptomatic SARS-CoV-2 infection without severe symptoms and virologically authenticated SARS-CoV-2 infection with severe symptoms are employed as specific endpoints throughout all vaccine trials. The FDA emphasizes that definitions based on symptoms must be adjusted for pediatric patients and those with respiratory comorbidities [32]. Therefore, 1) SARS-CoV-2 infection, 2) symptomatic COVID-19, and 3) severe COVID-19 are used as the trio primary endpoints. Hence, statistical power can be boosted and eventually raise the possibility of satisfying VSC, resulting in faster vaccine discovery and approval [33].

A collection of clinical endpoints for modulated vaccine efficacy analysis and comparison

a) COVID-19 (symptomatic infection) and asymptomatic infection
In many people, SARS-CoV-2 infection causes relatively moderate, non-specific symptoms that might not end up in contact with HCP, which are difficult to detect [34]. Serial vaccination sampling, such as once-weekly diagnostic testing, could ensure that infected individuals are recognized, irrespective of having symptoms, eventually providing an indicator for infection duration [35]. The antibodies are generated against nucleoprotein and spike protein, with an increased antibody response that starts from 14 to 21 days after the appearance of symptoms [36].
Most vaccine candidates for the SARS-CoV-2 aim to generate neutralizing anti-spike protein antibodies [37,38]. In vaccine efficacy trials, seroconversion of vaccines could be used as a surrogate for infection and rule out individuals who appear as being seropositive for SARS-CoV-2, keeping in mind that the antibody test is a unique infection and consequently not being produced by the vaccine [39]. When paired with quantitative RT-PCR testing, seroconversion may access disclosure of current or recovered infection with vaccines with limited symptoms that typically do not appear via quantitative RT-PCR and may escalate the chances of diagnosis [29]. Because seropositivity lasts longer than it takes to detect RNA, serological testing has a significant practical benefit over quantitative RT-PCR, providing a greater time frame to apprehend the endpoint [38].
Remdesivir was compared to placebo in a double-blind, randomized controlled trial in COVID-19 participants who were hospitalized. The primary endpoint considered was the period of recovery, which was described as the first time throughout follow-up that the patient achieved a grade of 1, 2, or 3. Perhaps these patients were no longer hospitalized but no more required supplementary oxygen or careful hospital care. The lengths of hospitalization, supplementary oxygen, and mechanical ventilation were among the important secondary endpoints covered in the research protocol [40].

b) The severity of COVID-19 disease and mortality
A COVID-19 vaccination could effectively help to minimize the degree of sickness caused by SARS-CoV-2 infection. To evaluate this possibility, rigorous collection of data and evaluation of markers of severe disease are required. Testing to diagnose and determine the causal pathogen is critical since not all individuals satisfy the criteria required for clinical assessment. A variety of factors like viral load, sample type, and most importantly, time gets impacted and is typically imprecise in context to the specificity of quantitative RT-PCR, unfortunately, the only current assay for diagnosing the virus [41]. A significant proportion of patients are still treated as presumed COVID-19 patients in clinical settings, even after constantly getting negative tests for the virus, possibly due to the constraints in diagnostic assays and a rapidly increasing information of the clinical demonstration and period of SARS-CoV-2 Infection [32].
Conventional indicators of disease severity, such as hospitalization, the need for pulmonary assistance, or admittance to ICU, are significant endpoints because they constitute the phenotypes for the clinical setup that exert the most strain on HCS [29]. However, these phenotypes may only reflect a small percentage of persons afflicted [42]. A virological confirmation has been recommended as the chief endpoint for evaluating the efficacy by the CEPI group since the insights of COVID-19 expand awareness of the wide symptoms range and indications affiliated with the overgrowing infection [34,42].
The clinical criteria used to trigger diagnostic testing must balance sensitivity and specificity to recognize all instances. Because this medical assessment is based on spontaneous onset of

symptoms and involves extensive commitment and determination on the participant's part, indications that would elicit communication with the scientific research personnel must be disclosed to trial participants effectively. As more information becomes available, recognizing additional particular symptoms may necessitate a revision in the diagnostic criteria [29].

A three-arm, multi-center, experimental, parallel-group, randomized study was conducted in which the mortality at day 28 was considered the primary endpoint. Tangential endpoints included VFDs, rescue delivery of steroids with high doses of medications that modulate the immune system, switching from non-invasive to invasive respiratory support during a stay in the ICU system, the delay between the initiation of NIV and the transition to IV, all of these reasons caused mortality during the ICU stay and hospital release, as well as ICU free days (IFDs) on day 28, the new infections that occurred from the randomization to stay till day 28, the eventuality of dysfunction of the new organ, and the severity of the deterioration during the ICU. Period, a VTE, a stroke, or a MI that has been clinically established. Also, safety endpoints included hematoma and significant bleeding, recognized as the infusion of two or multiple volumes of packaged RBCs in one day [43,44].

Because severe COVID-19 accounts for a reasonably small proportion of COVID-19 cases, an efficacy assessment for severe COVID-19 is likely inadequate in investigations. A longer-term follow-up would therefore improve the specificity of detecting vaccination impacts on severe COVID-19 infection [45–47]. When a potential vaccine is confirmed to be safe and efficacious against one or more clinical endpoints, efficient preparation of mass immunization programs and tactics will necessitate information about the duration of such protection [48]. Several vaccines, including the RTS S/AS01 malaria vaccine, have shown declining efficacy against a clinical endpoint in randomized controlled studies [49] and comparable killed whole-cell oral cholera vaccines [32]. Observational case-control studies of numerous vaccinations, including influenza, have demonstrated decreased vaccination efficacy against a clinical endpoint [32]. In particular, to improve understanding of the duration of effects, extending follow-up gives critical information on if a vaccine could make COVID-19 more dangerous, a concept known as disease enhancement [32].

McCaw et al. considered the length of hospitalization endpoint as the virtual endpoint for the number of time patients spent in the hospital undergoing appropriate medical treatment to establish adequate event-free mortality statistical analysis [50]. A multicenter, randomized, double-blinded experiment controlled by placebo at ten facilities in Hubei, China. The chief outcome was the time taken for clinical betterment till day 28, which was delineated as the timeline (preferably in days) from randomization to the 2-point decline on a 6-point rating scale (which considered one as discharged to 6 as death) or being released as survived from the institution, whatever is earlier. The 6-point measurement indicated: death= 6, hospital admittance for oxygen or SV= 5, NIV or HFOT= 4, admittance to hospital for O_2 therapy= 3, hospital admittance, however not needing O_2 therapy= 2, released or having met released criteria= 1. Secondary endpoints included the ratios of patients in each six-point scale category on days 7,14, and 28 after randomization; mortality of all possible causes on day 28; the amplitude of obtrusive mechanical respiration; the period of O_2 therapy; the period of hospitalization; and the fraction of patients with hospital-acquired infection [51].

c) Transmission of SARS-CoV-2

SARS-CoV-2 is easily escalated between people, primarily via the transfer of droplets (airborne) [52]. However, there has been no conclusive evidence on newborn infections (mother to child) [53]. Individuals have been known to escalate the virus by being in asymptomatic and pre-symptomatic stages of the disease [35]. Exuviation of viral RNA from patients can take several weeks during recovery and even longer if severely immunocompromised [54,55]. However, there is no obvious link between RNA detection by quantitative RT-PCR and the capability to cultivate the virus in vitro [56].

It is plausible that a SARS-CoV-2 vaccination would lessen the severity of the sickness but result in prolonged viral shedding, which may have serious implications on the public's health if the exuviation increases the transmittance rate. As a result, researchers must consider not just the period of RNA positive in routine samples, but also whether such samples contain RC virus being alive or not. A marker of active SARS-CoV-2 proliferation has been proposed: quantitative RT-PCR identifying sub-genomic RNA containing homologous proteins in structure [56]. Because the transcription of these RNAs is dependent on the host cell's translation of the ORF1 gene and the concomitant assemblage of an RDRP, the recognition of sub-genomic RNAs can contribute to the identification of RC and thereby transmittable virus [57]. However, new evidence reveals that sub-genomic RNAs may be more durable than previously thought and may be detectable for longer than previously thought, even after the actively reproducing virus has vanished [58].

Auxiliary Immunological endpoints

A plausible auxiliary outcome for a SARS-CoV-2 vaccine might presumably be determined by vaccination properties such as the structure of antigen, route of delivery, antigen processing, and presentation. Because SARS-CoV-2 is a new infection, primary antibodies are scarce. Furthermore, if SARS-CoV-2 infection in humans successfully guards towards re-exposure is debatable. Although assuming such antibodies are adequate but do not know the exact titer needed for prevention or the diverse spectrum of innate immune effector actions on which antibody activity can be relied, such as ADCD and ADNP [59,60]. The cellular immune accord has been documented in response to infection, which constitutes a significant defensive adaptable immune response [61]. An effective SARS-CoV-2 vaccine may confer protection via a mechanism different from the one induced by natural infection. It is difficult to distinguish immunological indicators of infection from molecular determinants of protection, but it is necessary for rational vaccine design [29].

If the vaccine for SARS-CoV-2 proves to be effective, establishing an in-vitro correlation or additional endpoint of safety might be the first effective task. Subsequently, candidates for other vaccinees might be judged as beneficial, potent, effective, and licensed if they elicited comparable immune system response scores in a non-inferiority test. Post-licensure studies would be required to demonstrate disease effectiveness; however, this technique could significantly fasten the development and progress of several vaccinees for the SARS-CoV-2 [32]. The creation of ASFA, which primarily includes neutralizing antibodies, averts infection by impeding the entry of viruses into the host target cells; via this way, most efficacious vaccines work. Also, for the construction of the majority of the experimental vaccines, the antigenic target is the spike protein of the SARS-CoV-2, which has an important role in interactions with host cells, and an immune response is also generated against spike protein. As a result, the induction of neutralizing antibodies to the spike proteins is the fundamental purpose of the candidate vaccine [62]. In the scarcity of human datasets, animal research can assist in identifying plausible determinants of protection [51]. In rhesus monkeys, development of NtAbs after the first manifestation of the infection, a minimal NtAbs titer is postulated. Hence, immunity in opposition to repeated infections with SARS-CoV-2 was seen [59,63]. However, since SARS-CoV-2 is preferably a newer virus, any auxiliary objective established in pre-clinical experimentation should ideally be

validated in clinical trials to determine whether they accurately anticipate effectiveness in people [29].

Suppose the human efficacy data is not gathered. In that case, the licensure for the vaccination for the SARS-CoV-2 might be based on the animal rule, using data on vaccination efficacy acquired after vaccine distribution. However, researchers will pick up the threads to seek the proof clinically for the vaccine effectiveness in human trials in case the lack of acknowledged auxiliary endpoint in people or pre-clinical studies substantially expected to anticipate the therapeutic advantage of a SARS-CoV-2 vaccination [29]. A methodology for rapid exploratory evaluation of immunization efficacy and the prompt rejection of vaccine prospects has been implemented: providing a predetermined dose of the virus in a carefully regulated setting [64].

The in-hospital study, multicentred, RC, open-label, parallel-group, superiority, two arms considered epistaxis, often known as gingival bleeding as the secondary endpoint and the already considered endpoints [65]. A two-arm, prospective, randomized (ratio1:1) controlled trial with parallel groups was carried out in a single center. Mechanical ventilation is started at random and continues until ICU admittance or hospital clearance; whichever comes first was taken as the primary endpoint. AEs/Serious Adverse Events Safety Assessment, cytokine storm death and the necessity for Critical Care admission, O2 saturation levels, and the demand for supplementary oxygen were considered secondary endpoints [66].

A critical factor to consider is the timing of the endpoint assessment. A therapy benefit that appears promptly but fades with time might not be medically substantial. If the analysis is completed quickly, a therapeutic impact may be overlooked before the arbitration has already had time. Scheduling assessment is critical, and it can be especially difficult in a newer condition with significant variability. Endpoints are appraised based on their ease of implementation, repeatability, clinical relevance, and potentiality to manipulate numerous clinical circumstances and disease progression over time [67]. Table 1 depicts several outcomes for COVID-19, primarily from the standpoint of a conclusive clinical trial.

Advantages and Disadvantages of different endpoints for use as primary endpoints

Prevention of a severe COVID-19 is likely the most important therapeutic benefit expected from a successful vaccine, both from a community health and an individual standpoint. Hence, many immunizations are more effective against severe disease than milder cases [32]. Moreover, severe COVID-19 accounts for a small proportion of cases involving COVID-19, and incidence varies greatly by age, underlying risk, and ethnicity [45-47], inferring that the statistical power to showcase satisfactory vaccine effectiveness against the severe COVID-19 endpoint could be significantly smaller than that for an endpoint that incorporates decrement in non-severe COVID-19. Given the evidence that immunizations can raise the risk of severe disease in specific populations, the evaluation of the severe COVID-19 endpoint is particularly intriguing [32] in complement to the usual analysis, which includes all randomly allocated volunteers and therefore offers a sensible argument with strong certainty, supplementary analyses that contrast rates of the severe COVID-19 endpoint cases between vaccine and placebo COVID-19 endpoint cases are also suggested. As a result, the data collection should account for baseline prognostic factors of severe COVID-19 and incorporate sensitivity analyses to examine the results' resilience to significant post-randomization bias [32,67].

The BOD endpoint (an extensive endpoint encompassing all COVID-19 cases and subjectively distinguishes severe from non-severe COVID-19) encrypts severe disease as uglier than non-severe disease perceived as more enlightening than the COVID-19 endpoint [77]. Furthermore, statistical power can be enhanced if the vaccine provides stronger prevention towards severe COVID-19 over non-severe COVID-19.

The BOD endpoint complies with regulatory standards for the primary or major secondary endpoint in phase III trials, incorporating clinical significance in weighting serious disease endpoints and susceptibility to detect a substantial intervention impact properly measured using the randomization principle [78]. There are three potential drawbacks to using the BOD endpoint. To begin with, unlike the COVID-19 endpoint, vaccination efficacy towards BOD cannot be stated as a proportion decline in the risk of establishing an endpoint "case," which can be difficult to interpret for some. Second, there is no consensus on the appropriate technique to rating the severity of COVID-19 occurrences. A third significant constraint, similar to the catastrophic COVID-19 endpoint, is that some severe COVID-19 endpoints require follow-up following diagnosis, whereas non- severe COVID-19 can be assessed more quickly and readily [32].

Diversely, the transfer characteristics of the virus are unknown; the capacity of contaminated individual people to propagate infection while asymptomatic or pre-symptomatic means that contagion control initiatives rely primarily on mitigating transference from the symptomatic individuals will be inadequate to stop SARS-CoV-2 from spreading [68]. Blacks, people of old age, nationality, gender, age, Asians, other minorities are conditions by which intensity and death rates vary, leading to greater chances of hospitalization, C-C admittance, and deaths.

If 20–29 years old were to be engaged in a phase III efficacy trial, this age group's intended modest death toll would necessitate an unfathomably huge sample size to satisfactorily potentiate the survey to analyze the endpoints particularly the mortality one. Nonetheless, the survey would rely on the high incidence of transmittance to reach additional endpoints for efficacy. Participants above the age of 80 were chosen because they had a high death rate. However, recruiting older people for vaccine studies has been difficult [34].

Analytical evaluation is necessary to determine the causal infectious agent since not all individuals satisfying the clinical standard would be contaminated by the SARS-CoV-2. Present brilliant benchmark evaluation for diagnosing the SARS-CoV-2, i.e., qRT-PCR reliability, is, unfortunately, imprecise and impacted by factors of type of sample, time, and a load of the sample [29,41]. Conventional measures of illness severity, such as hospitalization, the need for breathing assistance, or admittance to intensive care, are significant endpoints because they constitute the clinical characteristics, exerting the utmost strain on HCS. However, these phenotypes may only reflect a small percentage of afflicted persons [79]. Table 2 depicts the endpoint with its advantages and disadvantages.

Table 1
Outcomes for COVID-19, primarily from the standpoint of a conclusive trial (Phase III).

Endpoints	*Comments*	*References*
Primary endpoints	Period of recovery, Day 28: all-cause mortality, length of hospitalization, virologically confirmed COVID-19	[68-72]
Secondary endpoints	Supplementary oxygen, ventilation by mechanical means, period of oxygen therapies, FDs, rescue delivery of a high dose of steroids/immuno-modulatory medications, new infections, organ dysfunctions, and the severity of dysfunctions, venous thromboembolism, MI, gingival bleeding.	[70,73,72,74,75]
Safety endpoints	Hematoma	[70,73]
Auxiliary endpoints	Structure of antigen, route of delivery, antigen processing, and presentation in vaccinations	[76]

Vaccine efficacy predictors based on psychological and behavioral factors

The immediate and delayed vaccine response

Inflammatory indicators increase after immunization, owing to its early and NSIIR, which can cause symptoms such as tiredness, lethargy, headache, and agitation. An initial prong of an immune reaction and Inflammatory reaction normally takes several days. However, it can be protracted in some people, like people suffering from depression. The adaptive immune system is in charge of mounting the latter phase of the immune reaction. Because it focuses on certain vaccine elements, it takes much slower to deliver. Immunizations are intended to imprint the AIS with a long remembrance of bacterial or viral elements, allowing it to respond promptly and successfully whenever presented with authentic microorganisms [80].

Vaccinology focuses on the humoral immune system, a component of the AIS. The AIS has a memory and soaring level of specificity. This system comprises the cell-mediated immune system and the humoral immune system. Immune reactions, including antibodies produced by B cells, are called humoral immune responses. On the other hand, cell-mediated immunity refers to responses obtained from T cells and occurs in the absence of antibodies. At the same time, humoral immunity might be passed on to other persons by utilizing antibody-containing serum [81]. There isn't much knowledge on how these antibodies and various other immune cells in the bodyguard are at odds with the invasion of SARS-CoV-2, considering it as new, and research about it is still ongoing. CMI, i.e., T-cell immunity, should be essential in avoiding concurrent infections from COVID-19 because antibody levels decline months after being infected [82]. The titer for the antibody is considered a clinically important indicator from the protection of SARS-CoV-2. However, it is not the only one. COVID-19 individuals exhibit a very heterogeneous antibody reaction, higher infection intensity correlated to higher antibody, indicating medical prognosis [69,83]. Level of antibodies stand belated substantially divergent for weeks: A study found a variance of 200-fold in antibody levels of SARS-CoV-2 after the exposure to virus till 6 months, indicating significant changeability that might be related to attribution and features of a formerly infected person [80].

If certain concentrations are proven to be beneficial (such as being established in doing the particular test in a proper laboratory), the immune reaction, in that case, is acceptable, and therefore no additional testing is necessary. Based on the vaccination and that of the patient's age, either alone shot (e.g., adult PP vaccinee) or a set of shots (e.g., primary diphtheria) might be required to maintain appropriate concentrations to converse protection [84]. It is critical to understand that only IgG is useful for assessing vaccine response when measuring titers. Both diseases and vaccinations elicit the response to the antibody by those of IgA, IgG, and IgM. On the other hand, only IgG antibodies provide long-term protection and are regarded as indicators of immunity. To avoid low post-vaccination titers, pre-and post-vaccine titers should be at least one month apart [81].

Important psychological factors including stress, anxiety, and depression

There is evidence that stress affects numerous elements of immune functioning, although the medical significance is unknown. Immunization is not just advantageous to individuals and rightly pertinent to medical situations, but additionally a useful model for assessing the potentiality of the immune system to respond to infections, understanding that everybody obtains an equal standardized dose, but responses to them differ greatly. According to research among healthy young adults, the level of stress rated by oneself in 10 days following immunization might be significantly more effective to antibody reaction than that of the stress in earlier two days, and according to research, insomnia due to stress may be a key explanation [80]. Socio-psychological stress, defined as both anticipated stress and prominence to distressing experiences in life, has been linked to lower antibody levels following many vaccinations [85]. The consequences of stress in the young population that received influenza vaccination have received little investigation.

Furthermore, significantly elevated risk or/and experienced distress in students who do not have a specific long-term source of stress has been linked to lower antibody prestige after previous immunizations. A study conducted by Burns et al. showed five weeks following immunization, 94% of the young, healthy subjects had a sufficient antibody response, compared to 16–66% of senior groups [85]. Moynihan et al. recently showed that increased stress levels and despair had been related to a wider subsequent rise in antibody

Table 2
Advantages and disadvantages of different clinically established endpoints.

End points	*Advantages*	*Disadvantages*
Mortality/ admittance to ICU	Extremely important in severe/critical disease, good reproducibility, easily measurable	Other significant improvements in patient status might be overlooked, causes multiple disease states, recruiting older patients is difficult, the requirement of huge sample size, differ by age, gender, and nationality and with older people
Recovery	Clinically meaningful, easily measurable	Big sample size is required; longer observation times may be required in greater severity groups
Respiratory failure/ breathing assistance	Measurable easily, clinically meaningful	Depending on resources, the requirement of special considerations in case of deaths,
Hospitalization	Measurable easily, clinically meaningful	Depends on resources, does not incorporate improvements, can cause multiple disease states
Time to intubation or death	Time element plays an important role	Possibility of "relapse," a slew of problems that increase mortality and morbidity
Viral load	The severity of the disease might be predicted	Difficult to quantify consistently, relationship to clinical outcomes is not well established
Oxygen/SpO_2	Good reproducibility	SpO_2 has not been fully established, not easily measurable, differ by age, gender, and nationality, and with older people
COVID-19 (symptomatic infection)	Assessed more quickly and readily	The reliability of quantitative RT-PCR is imprecise
Asymptomatic infection	No requirement of huge sample size, the timing of sampling plays an important role	The reliability of quantitative RT-PCR is imprecise
The burden of disease (BOD)	Compiles with regulatory standards, incorporates clinical significance, susceptibility to detect a substantial intervention impact properly measured encompasses all COVID-19 cases and subjectively distinguishes severe from non-severe COVID-19	Vaccination efficacy towards BOD cannot be stated, no consensus on the appropriate technique to rating the severity of COVID-19 occurrences, severe COVID-19 endpoints require follow-up following diagnosis

concentration in the case of flu vaccination in undergraduates two weeks after immunization [70].

In the absence of external stressors, humans' propensity to produce and feel long-term psychological stress can manifest in extended amplification of the cognitive stress reaction, which can have detrimental ramifications. Hormones such as glucocorticoids and catecholamines might major impact the functionality and deployment of immune cells if stress induces elevations in such hormones [73]. It is commonly established that psychological stress is related to inadequate antibody responses and greater inflammatory markers in older persons. Caregiving has been analogous with decreased response to antibody and greater IL-6 levels following vaccination in research of dementia caregivers, suggesting that it may impede the longevity of the IgG antibody response to the PP vaccine. There is evidence that anxiety and other forms of vulnerability, such as age, a higher BMI, and a lack of physical activity, have synergistic effects [86]. The elderly suffer the most from stress-related immunological dysregulation. To keep a slew of infectious agents at bay that has developed through time suggests that the weakened immune system is already distrait and less sensitive to new immunological trials such as vaccinations [87,88]. Depression is correlated with proinflammatory cytokine activation and can decrease innate and adaptive CMI [86].

Glaser et al. colleagues. discovered that caregiver stress weakened the early vaccination antibody response, potentially making caretakers more vulnerable to infection. Comparable observations in younger adults suggest that cognitive elements like distress and psychosocial aid influence immunological reactions to bacterial vaccinations [71,89]. Psychological anxiety and destructive thinking patterns in caregivers may influence vaccination response. Children and family members of AD patients in retirement communities with higher purported anxiety and stress and the symptoms of depression had less increase in antibody concentration followed by a tetanus vaccination than the majority of the caregivers [72].

Similarly, depressive recurrent thought suggested considerable sadness after vaccination and lesser antibody concentrations in caretakers after accounting for baseline titers [90]. Both LTS (such as caregivers) and STS (such as examinations in academia) might decrease immunization response—preferably the antibody response, which is considered a prime endpoint in several analyses. However, reaction to CMI is lower according to some information [91,92]. It is worth noting. However, relatively short (such as 600 s) stressors that have a defined aim occurring post-immunization might eventually boost reaction to antibody [80] but may cause side effects. When compared to non-care-givers, the response to primary antibody in caretakers did not drop immediately one week or four weeks after receiving PP vaccination; however, it later dropped 3 and 6 months after vaccination [71] which might be important in context to the vaccination for SARS-CoV-2 since they 1) demonstrated that prime responses of the immune system could be impacted by stress and 2) Additionally, production of antibiotics might be degraded over a certain period due to chronic stress. In the case of a considerable proportion of a particular community, the initial reaction of the immune system will be important because of the introductory exposure in SARS-CoV-2 vaccination with that of the antigen. Furthermore, unspecified how far the SARS-CoV-2 vaccine candidate will keep recipients safe from infections. Even though current top vaccine candidates have typically demonstrated great efficacy, persistent stress in vaccine recipients will probably reduce this response with time, prompting more frequent immunization to maintain immunity [80].

A double-blinded, randomized trial was conducted. Individuals were allocated to any of the following categories: TV/rest, PV/rest, TV/stress, and PV/stress provided convincing scientific evidence about acute stress [93]. Like the pneumococcal pneumonia vaccine, the typhoid vaccination induces a basic immune reaction irrespective of the previous subjection. After a vaccine shot, candidates slept or conducted intellectually demanding ten minutes, including a Stroop challenge and language challenge. Perhaps those, as mentioned earlier, relatively short stress-inducing periods enhanced the inflammation-causing reaction after the vaccination. Contestants also experienced a greater enhancement in detrimental emotion following the stressor if they obtained the vaccination for typhoid in place of placebo [93], exhibiting that stress and immunization can have a synergism impact. Later, these effects were mitigated in people with significant levels of disposition optimism [93]. As a result, the interaction of state and trait psychological characteristics may have a role in post-vaccination adverse effects.

Natural defenses are usually downregulated in case most people face depression closely before receiving a vaccination, as demonstrated by increased inflammation [94]. This prolonged inflammation may impair vaccination response [95]. Untreated patients with depression, all of whom had previously been exposed to VZ, reduced cell-mediated reaction to a VZ virus vaccination when compared to people with clinical depression on anti-depressant medications and people who were not facing depression, implying that they might be at a higher chance of VZ recurrence [96]. Unsurprisingly, distress being a component of the global COVID-19 virus; in a test conducted by the US, dread of COVID-19 alone, dubbed "corona phobia," induced melancholy along with generalized anxiety, regardless of controlling for social demographic characteristics and further cognitive sensitivity aspects like psychoticism [76]. In an additional large comprehensive sample conducted in the United States, individuals with heightened COVID-19 dreadfulness had a significantly higher chance of clinically severe depression symptoms [97]. Paradoxically, apprehension of COVID-19 alone might reduce the potential of vaccines to protect the pathogen.

One factor influencing adults' readiness to be immunized for SARS-CoV-2 in the US is the likelihood of vaccine-related adverse effects [98]. Minimizing stress exposures across the time of vaccination, to the full extent practicable, may reduce the chance of unpleasant side effects [93]. Grief and sadness, similar to stress, might decrease immune system functioning, also influencing vaccine response in youthful and healthier individuals. The examination discovered that deserted and isolated university-going candidates in their initial year's coursework possessed reduced concentrations of antibodies 4 and 16 weeks following their 1st seasonal flu shot. Limited civil connectivity (around 4–12 individuals) exacerbated the insufficient responses [99]. When the social connection was substantial (19–20 participants), lonelier persons did not have a weaker antibody response, implying that interaction with numerous people may give some security even if it is not individually fulfilling [99].

Other health behaviors include altered diet, disturbed sleep, and cigarette smoking

According to a recent meta-analysis, individuals who were not smokers have contrasted to heavy smokers showed a 1.53 times chance of not responding towards a Hepatitis B vaccination [90]. Smoking may be linked to a weaker vaccine response due to chronic inflammation [100]. Additionally, a sole food or shortage of specific nutrients might show a negligible effect on vaccine reaction; altogether, nutrition might be an essential factor [101]. For example, the Mediterranean diet, which has a pinnacle of calories, strained carbohydrates, and food that is being filtered and processed causes an outbreak of long-term inflammatory cascade and metabolic syndrome [74]. Furthermore, nutrition strongly influences gut microbiota [75], which also influences vaccine reactions [102]. As an analogy, dietary fiber consumption encourages the growth of good microbes (probiotics) that create SCFA, which can increase response to antibodies [103,104].

Sleep has a significant impact on immunological function. Individuals who are sleepless and barred on day-to-day norms typically are at higher incidence of unresponsive towards vaccination and severe sickness. Both cross-sectional studies [105] and investigations involving artificially imposed sleep deprivation have linked sleep disruption and decreased antibody responses [106]. Healthy young males who regularly slept between 7 and 8 h per night were limited to only four hours of sleep every night for six consecutive nights, which was afterward increased to twelve hours every night for the next seven nights to recoup from the deprivation. They were given an influenza virus vaccine the morning following their 4th night. Amidst the sleep recuperation interval, these people exhibited poorer antibody generation than colleagues who took rest regularly for two weeks approximately following immunization, when basal concentrations of antibodies were considered. The significant variations in contrast to participants and each group revealed that reactions in conjunction with the antibody production are not affected by consistently losing sleeping patterns [98]. Sleep length is also important for vaccination efficacy in middle-aged adults. In one trial, participants with zero serologic proof of antecedent Hep B infection revealed poorer sleeping patterns—particularly the two nights preceding a Hepatitis B vaccinee—revealed reduced concentrations for antibodies 1 and 4 months belatedly [107]. Together, this research demonstrates that decreased sleeping durations reduce response to antibodies [106] and promotes longer-term impairments in CMI along with a range of vaccinees and irrespective of past exposures [106,107].

Activity tracker data gathered from geriatric SCW revealed a data where all individuals who marched (greater than 18,509 footsteps per day) for 15 days after being given a flu shot seemed to have higher innate immune initiation two days later, relatively large immune response one week later, and increased antibody responses forward to a next immunization to their lower engaged peer group (10,927 footsteps every day) [108].

The COVID-19 epidemic is eroding healthcare practices. A recent article emphasized the entrenched alcoholic behaviors and stress, implying global spread of the virus leads to an increase in drug addiction, putting an additional burden on care and treatment programs [109]. Regarding sleep quality, survey information from the CGP collected in February 2020 while COVID-19 eruption revealed 20% satisfied diagnosed sleep disruption thresholds, also similar percentage passed longer than one hour to sleep [110]. Furthermore, throughout the crisis, women, younger persons, and those with higher infection incidence SARS-CoV-2 front-line health facility employees) experienced more acute sleeplessness [110]. Before the outbreak, those with psychiatric illnesses had a much higher incidence of heightened depression, anxiety, and sleeplessness during the stringent lockdown restrictions [111]. Obese people gained an average of 3.3 pounds after 30 days in Italy. People were put under quarantine, which was connected with inadequate food intake, heightened boredom, elevated anxiety and depressive symptoms, and lesser activity [112]. Also, there are concerns that pandemic-related educational institute disruptions will encourage children's poor eating habits and weight growth [113]. Furthermore, undernourishment, widespread in the elderly, may compromise the elderly's immunization response.

Combined collectively, the COVID-19 outbreak and associated stress enhance suboptimal health habits, which impair mental and physical health in a vicious spiral, eventually leading to weight increase. In an eerie coincidence, the pandemic lifestyle may reduce the efficiency of a SARS-CoV-2 vaccination. According to the findings, psychological and behavioral therapies may improve immunological reactions to immunizations. Interpositions differ in nature, dosage, period and can eventually be chosen based on personal requirements [80].

Bodywork, relaxation, creative writing, and stress reduction are examples of psychological therapies that could be used as vaccine adjuvants [114]. However, the results are inconclusive, mostly because of changes in sample age, immunization category, treatment category, and different durations among immunization and interpositions. Behavioral approaches have yielded encouraging effects. A systematic assessment of exercise interventions discovered pretty strong confirmation that both ST and LT workout programs might increase immunological reactions to immunization, particularly those predisposed to poor responses [115]. In one randomized, controlled research, aged people who got a comprehensive fluid dietary supplement encompassing anti-oxidants showed great antibodies 30 days after receiving the flu shot than those who achieved a placebo [116]. A further randomized, double-blinded experiment amongst geriatric retirement home citizens found that Zn fortification raised serum Zn concentrations in serum and enhanced T-cell proliferation [117], which could portend well for vaccination response.

Conclusion

As of the end of February 2021, ten of the twelve vaccines covered in this article got approval for global usage. Vaccination has begun on a large scale in Israel, United Arab Emirates, and United States, although slow progress has been noted in Africa, Europe, Canada, and other developing countries. It is critical to provide a standard COVID-19 endpoint that might be employed systematically throughout trials, both for interpreting data and facilitating trial meta-analysis. Collaborative and regulated methodologies for measuring efficacy endpoints will be required to enable credible comparability and determine that the most successful applicants are implemented. Excellent drug safety studies should be undertaken to assure continuing vaccine safety evaluation. Apart from that, physiological and behavioral factors play an important role in our immune system's response during vaccination. Also, follow-ups are more important in evaluating these vaccines, and recipients should be advised to get along with these follow-ups. Hence, more attention should be laid down on all of these parameters during the clinical trials of vaccine candidates to evaluate efficacy profiles.

CRediT authorship contribution statement

Jonaid Ahmad Malik: Conceptualization and Writing orginal draft; **Mir Aroosa** and **Sakeel Ahmed**: Writing; **Mrunal Shinde**: Literature search; **Saleh Alghamdi** and **Khaled Almansour**: Critical review; **Turki Al Hagbani** and **Muteb Sultan Alanazi**: Editing and Review; **Sirajudheen Anwar**: Supervision, Editing and Finalizing. Finalizing.

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