Review / Derleme

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The Rationale Behind the Effectiveness of COVID-19 Vaccines and Associated Immunological Mechanisms

COVID-19 Aşılarının Etkililiğinin ve İlişkili İmmünolojik Mekanizmaların Arkasındaki Gerekçe

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Abstract

The basic concept of vaccination has been based on engendering an adaptive immune response armed with effective immune cells, memory cells, and cytokines. These elements cooperate to mount either a humoral or a cell-mediated response. Coronavirus disease-2019 vaccines, although diversified, adapted the same objective with the previous vaccines prepared since Edward Jenner's work. The spike surface protein (S) and the receptor binding domain constituted the main antigenic determinants for which the binding antibodies as well as the neutralizing antibodies were secreted. The unprecedented use of mRNA vaccines represented an unmatched breakthrough, which paved the road for a new era of vaccine generation. They showed a substantial ability to elicit antibody secretion with a moderate helper T cell response just after inoculation of the first dose. Besides, the adenoviruses-shuttled vaccines were able to engender a spectrum of polyclonal antibodies including neutralizing antibodies apt to drive a multitude of antibodies-mediated functions and activate T cell immune responses. In either case, the antibody titers as well as lymphocytes-mediated responses were significantly intensified. Deciphering the mechanisms of immune response activation by the inoculated vaccines in addition to the elaboration of innate elements involvement should open the door for a better decryption of the induced immune protection and pave the road for the formulation of a more effective vaccine that surmounts the incessant mutational variation of the viral antigenic attributes.

Keywords: SARS-CoV-2 vaccines, mRNA vaccines, adenovirus-shuttled vaccine, whole-virion inactivated vaccine, protein subunit vaccine, spike protein, receptor binding protein

Öz

Aşılamanın temel konsepti, etkili bağışıklık hücreleri, bellek hücreleri ve sitokinlerle donanmış adaptif bir bağışıklık tepkisi oluşturmaya dayanmaktadır. Bu ögeler, bir hümoral ya da hücre aracılı bir tepki oluşturmak için iş birliği yaparlar. Koronavirüs hastalığı-2019 aşılarında, çeşitlendirilmiş olmasına rağmen, Edwards Jenner'ın çalışmasından bu yana hazırlanan önceki aşılarla aynı amaç benimsenmiştir. Spike yüzey proteini (S) ve reseptör bağlanma alanı, nötralize edici antikorların yanı sıra bağlayıcı antikorların salgılandığı ana antijenik belirleyicileri oluşturmuşlardır. mRNA aşılarının benzeri görülmemiş kullanımı, yeni bir aşı üretimi çağının yolunu açan eşsiz bir başlangıcı temsil etmiştir. İlk dozun uygulanmasından hemen sonra orta derecede yardımcı T hücre yanıtı ile antikor sekresyon yeteneği gözlenmiştir. Ayrıca, adenovirüs-shuttle aşılar, çok sayıda antikor aracılı işlevi yürütmeye ve T hücrelerinin bağışıklık tepkilerini aktive etmeye uygun nötralize edici antikorlar da dahil olmak üzere bir poliklonal antikor spektrumu oluşturabilmiştir. Her iki durumda da lenfositlerin aracılık ettiği tepkilerin yanı sıra antikor titreleri de önemli ölçüde yoğunlaşmıştır. Doğuştan gelen unsurların ayrıntılandırılmasına ek olarak inoküle aşılar tarafından bağışıklık tepkilerinin aktivasyon mekanizmalarının deşifre edilmesi, indüklenen bağışıklık korumasının daha iyi bir şekilde çözülmesinin ve viral antijenik özelliklerin sürekli mutasyonel varyasyonunun üstesinden gelen daha etkili bir aşı formülasyonunun yolunu açmalıdır.

Anahtar Kelimeler: SARS-CoV-2 aşıları, mRNA aşıları, adenovirüs-shuttle aşı, whole-virion inaktive aşı, protein altbirim aşısı, spike proteini, reseptör bağlayıcı protein

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Introduction

The dawning of the year 2020 was full of unprecedented challenges. The International Community as well as the World Health Organization (WHO) were not very well prepared for the most challenging confrontations with an emerging pandemic that would stand behind the loss of more than three million lives around the world (1,2). According to Johns Hopkins University, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) turned into a pandemic within weeks, sickened more than three hundred people within a period of 25 months, and have claimed the lives of more than 3.5 million around the world (3). One of the most life-threatening diseases, the highly contagious and rapidly transmissible coronavirus disease-2019 (COVID-19), has been shown to cause more fatalities than its predecessor, SARS, emerging in 2002 and lasting for one year and the Middle East respiratory syndrome (MERS), which appeared in 2012 in the Middle Eastern Region (4). Since ever, a large number of scientific works have been conducted aiming at the elaboration of the SARS-CoV-2 molecular attributes where highly budgeted researches were extensively devoted worldwide for that purpose (5). The genetic sequencing of the viral genome raised up a great suspicion of a zoonotic disease as the aligned sequences showed a high similarity rate with other viruses derived from bats. The concomitant understanding of the genetic map promoted further efforts to develop the reverse transcriptase-polymerase chain reaction diagnostic kits and launched the global race for the development of effective and safe vaccine(s) to reduce the fatality of the virus and hinder its overwhelming transmission that caused the failure of health systems in different countries (6). The previous experience in SARS and MERS-based vaccine projects has incited an exponential increase in vaccine progress and an average of 270-280 candidates, more than 90 of which were introduced in pre-clinical and/or clinical phases, are currently under meticulous development (7,8). The most promising varieties include the nucleic acid-based vaccines (either DNA or RNA) (9-12), human replication-deficient or simian replication-deficient vaccines (13,14), replication-competent adenovirus particles shuttled vaccines (15), wholly inactivated viruses (16), subunit-protein based vaccines, and putative virus-like based particles (17). Around mid-April 2021, many of the mentioned vaccines acquired their emergency authorization where industrial pharmaceutical companies fueled the global market with billions of shots delivered by the order of priority adopted by the ministries of health around the world (18).

The launching of vaccination campaigns represented a quantum leap in the fight against COVID-19 where a majority of the countries witnessed a decrease in hospitalization rate of the infected population with a remarkable alleviation of severe cases compared to the overwhelming first wave's outcomes. Despite the promising impact of the authorized vaccines, most of the formulations are believed to entail repetitive doses at relatively short intervals to reach the optimal immunity, which involves the landing of a logistic taskforces at different levels including the cold and ultra-cold preservation chains required for mRNA-based vaccines which are barely available in the majority of the low-middle income's countries (19). Besides, the continuous and perpetual evolution of the causative agent introduces a large number of mutations resulting in the emergence of novel strains, and does not last the highly contagious Omicron variant which appeared on December 2021 (20). Although evidence for antigenic drift has not been revealed till now, these concomitant mutations risk to further enhance the transmissibility of the virus and the severity of the disease leading to the appearance of novel strains that escape the vaccine-induced protection which impose an enduring effort to optimize and improve the vaccines formula (21,22). In this review, we elaborate the mechanisms of the immune response to the so-called SARS-CoV-2 with an emphasis on the process of immune-protection engendered by the main licensed vaccines for which the results of the Phase III clinical trials are published. A correlation of vaccine-induced protection with the gained insights generated in the immunized population will be elaborated to offer a guide for the incessant efforts to improve the vaccine candidates and favor the production of neutralizing antibodies directed against viral proteins.

Humoral & Cell Mediated Immunological Responses to COVID-19

Studies conducted on samples provided by recovering patients on the issue of their infection with SARS-CoV-2 have shown that humoral and cell-mediated attributes are involved in the responses of the human body (23-25). The biochemical analysis of the serum from hospitalized patients has shown a primary production of anti-spike (S) functional antibodies which have been correlated with patients' survival in addition to neutralizing antibodies (NAbs) (similarly directed against the spike viral protein) in the majority of the infected people samples (26). Many factors were attributed to the magnitude of these NAbs, which correlates with the patients' age (higher in elderly compared to younger age), the severity of the illness (more prone in severe hospitalized cases compared to moderate ones), and essentially viral load (proportionally correlated) (27-30). Pre-clinical studies in a Rhesus Macaque model have shown that the level of neutralizing antibodies directed against the viral surface protein (S), known to mediate the binding of viral particles to the cellular membrane, seems to strongly correlate with an efficient immune protection against SARS-CoV-2 (12,31). These findings stimulated

the mandatory release of NAbs after inoculation with any of the candidate vaccines. Other biological functions of the Nabs would also confer a considerable role to these proteins in the development of a strong protection throughout the stimulatory signals transduced via their Fc-regions activating a spectrum of Fc-mediated responses including antibody-dependent cell-mediated toxicity, mediated phagocytosis (where the antibodies play the role of opsonin), and natural killer cells activation (32,33). Besides, only those antibodies that incite an inflammatory response leading to a storm of cytokines secretion elicit a severe illness associated with a high rate of intensive care admission and clinical complications (34,35).

In vertebrates, the prevention of the human body's infection is reinforced by the so-called mucosal immunity, where amounts of the secretory form of the IgA antibodies are released by plasma cells generated in the germinal centers of the mucosa associated lymphoid tissues just beneath the respiratory tract's epithelium. These antibodies are shown to provide an effective protective barrier against many infectious agents as they contribute to the neutralization of these pathogens, preventing their adherence and attachment to the surface of the epithelial cells (36,37). Samples of nasal cavity washes or salivary samples from SARS-CoV-2 convalescent patients have shown an increased level of sIgA. This increase has been correlated with a reduced transmissibility of the virus mediated by viral neutralization and other effective Fc-mediated functions. Since the virus is able to easily undertake an intercellular spread outside the context of the extracellular environment, the antibodies that impede the out-warding viral receptors have a limited impact on the spread of intracellular particles (38).

Besides the B-cell activation and maturation, engendered by viral infection, T-cells are shown to be a matchless adjunct in the human body response to COVID-19 infection. T lymphocytes promote the activation of resting B-cells, enhance the production of antibodies, and moderate the vaccine-associated disease (39). Helper T-cells and cytotoxic T-cell responses have been perceived at the issue of viral infection (40,41). A moderate illness with mild to minor clinical symptoms has been associated with enriched expansion of $CD8^+$ clones of T-cells, particularly in the blood circulation and the lungs (42-44). Specialized clones of $CD8^+$ and $CD4^+$ T lymphocytes comprising $CD8^+$ memory cells were revealed in the blood and tissues of recovering patients, although their plausible role in the immune protection against any subsequent infection still remains under investigation (45-47). A T helper cell subtype (Th1) producing considerable amounts of Interferon-gamma (IFN-γ) has been detected in the cases of acute infection where highly effective immune responses mostly skewed towards Th1 are more likely to be associated with moderate illness (23,48).

Seemingly, there are a number of evidence and many serum indicators showing that patients producing a higher level of IFN-γ secreting lymphocytes develop a milder disease and the benefit from an enhanced immune protection (49). The studies of biopsies collected from patients with mild symptoms have shown an enriched follicular T helper response engendered in the germinal centers, which promotes the activation and maturation of plasma cells and increases the production of effectively functional antibodies (50). Immuno-deficient mice transfused with antigen-specific T-cells were able to develop an effective immune response after being challenged with SARS and MERS coronaviruses, whereas the withdraw of $CD8^+$ T lymphocytes was shown to be detrimental for mice models leading to an impaired response while passively transfused neutralizing antibodies were shown to provide an effective protection (51). These indications suggest that $CD4^+$ Th1 cell-biased responses enhanced with a high amount of Nabs, and associated with a strong cytotoxic T-cell response, are the ingredients of a protective immune response against viral infection with COVID-19 (52,53).

Similar to other respiratory illnesses causing agents, SARS-CoV-2 virus is able to evade the mechanisms of fundamental host protection prompted via innate immunity (54,55). The molecular studies of the cellular interactions with viral particles uncovered a range of schemes utilized by SARS-CoV-2 viruses to antagonize immune cellular processes leading to suppression of the host defenses (56). A multitude of evasion strategies have been recently revealed, including the inhibition of the response engendered by type I interferon (IFN-I) leading to the impairment of viral RNA molecules recognition (56-61), the impairment of the nuclear pro-inflammatory transcription factor translocation in addition to the failure of the cytoplasmic domain phosphorylation of the Interferon key mediators (STAT1 and STAT2). Moreover, the inadequate production of IFN-I or even the lack of adequate response to interferons (I, II, & III) is likely to be associated with increased risk of severe illness (62-64). These immune mediators appear to induce a protective state when secreted at the early stage of the response, while a reduced effectiveness has been correlated with increased immune pathology occurring at later time (65-67).

The Potential of Spike Surface Protein as a Candidate of Coronavirus Vaccine

Despite the great diversity of the COVID-19 vaccine candidates, the majority of the formulas are intended to generate effective immune responses mediated by a sufficient amount of neutralizing antibodies directed

towards the trimeric spike surface glycoprotein (S) in the form of S1 and S2. The subunit S1 bears a specific receptor binding domain (RBD), which adheres to a specific receptor called angiotensin converting enzyme 2 (ACE2) commonly expressed at the surface of the respiratory tract's tissue including the epithelial cells of the nasal cavity, the bronchial ciliated cells, the alveolar cells, and the pneumocytic cells (Type I & Type II) (68-70). A metastable status of the trimeric protein characterizes the S protein, which undergoes a significant conformational change at the moment of viral fusion with the host cell. Certain strains bear a number of identified mutations causing the stabilization of the spike protein in its pre-conformed structure prior to their cell fusion (71,72). A number of current vaccine formulations that are taken into consideration these mutated sequences that would induce protective immune responses potentially effective in declining the rate of viral transmission. Studies dedicated to depict the structure of the S protein have shown the presence of an amino-terminal end formed by the S1 subunit and a carboxyl-terminal end including the S2 subunit (73). The RBD positioned within the S1 subunit constantly undergoes a series of conformational restructuring which alternatively exposes or hides the key dominions of receptor binding. In the context of "sterilizing immunity" intended to offer a complete protection against infection, enormous efforts have been devoted to manipulate the vaccine formulations in such a way that they become able to elicit an immune response generating antibodies that bind and block the RBD assuming that this blockage hinders the viral entry into the host cells which supports the herd immunity of affected communities (74-76). The broader ability of the vaccine to target diverse antigenic determinants might alleviate the ability of the virus to evade the immune response (77).

The Place of Antibodies in the Vaccine Induced Enhanced Disease

The development of immune reactions following viral infection might stand behind the raising of certain concerns on the issue of administration of vaccines, especially in those individuals who were virally infected prior to immunization. These later are at risk of developing vaccine enhanced disease mediated by the so-called antibody-dependent enhancement (ADE) mechanism (78). In such cases, the SARS-CoV-2 viruses are internalized inside of the epithelial cells lacking ACE2 receptor by a process involving Fc mediated adherence and that in the presence of non-neutralizing antibodies (Non-NAbs), immune complex deposition, or/and inadequate lymphocytes responses leading to the development of vaccine associated enhanced respiratory disease (VAERD) in the respiratory tract of the immunized patients (79). Previous preclinical experiences with inactivated vaccines designed against respiratory syncytial virus and measles virus or other coronaviruses lead to the development of Th2 cell, $CD4^+$ biased T-cell responses, accompanied with a significant increase of interleukin (IL)-4, IL-5, and IL-13 (14,79-88). Contrarily, in case a Th1 cell, $CD4^+$ biased T-cell responses are stimulated in an IFN-γ enriched environment and containing IL-2 and tumor necrosis factor (TNF), VAERD failed to develop. Most of the projected vaccines are intended to favor a cell-biased Th1 reaction or an evenly balanced Th1 and Th2 cell response (44,47,48,89). The absence of VAERD and ADE in the case of SARS-CoV-2 has been related to the viral inability to infect macrophages and the ineffective enhancement of the virulence (90,91). The spectrum of diverse antibodies with a multitude of functions generated by the issue of the process of vaccination would be very significant in limiting the risk of ADE. This has been associated with the IgG immunoglobulins bearing a reduced fucosylation of the Fc fragment but improved binding ability to FcγRIII (32,35). As the antibody titer declines in the post-vaccination period following the engenderment of the adaptive response, the vulnerability of the immune system to ADE is heightened despite the fact that viral recurrence has been associated with mild to moderate illness (92).

Perceptions of SARS-CoV-2 Vaccine Induced Immunity

Data collected from preclinical studies on developed formulations followed by urged Phase I & Phase II clinical trials offered a concrete base over which mass immunization campaigns were launched worldwide. Insights gained from these studies were fundamental to depict the mechanisms of vaccine-induced immune responses (93,94). Worth to say that the majority of the insights were collected from early clinical studies based on the large spectrum of formulations used to develop the vaccines. Despite the great diversity of vaccine formulations and the miscellaneous dosing regimens applied during the clinical trials, the vaccines engendered antibodies and T-cell pathways (Th1 or Th2) in addition to the associated cytokines profile were defined in the samples of serum collected from immunized patients or those who were in a convalescent period following SARS-CoV-2 infection. The collected data offered a reliable reference based on which the comparative analysis has been conducted (95-98).

mRNA-Based Vaccines

The two different versions of the mRNA vaccines developed, respectively, by BioNTech/Pfizer and Moderna (BNT162b2 and mRNA-1273) (Table 1) have proven to be highly effective based on the Phase III conducted clinical trials (99-101). These vaccines were able to elicit

a resilient immune protection (Figure 1), reducing the rate of symptomatic illness in more than 90% of infected cases just after the first dose, while neutralizing antibodies still at their lowest (<5%) following the peak reached after the second dose (102-107). Moderna's vaccine (mRNA1273) incited the immune system to mount Th1 mediated response as a primary outcome of the first inoculation where 0.05% of circulating lymphocytes were revealed to be $CD4^+$ T-cells producing a substantial amount of TNF and IL-2 at the issue of the challenge with peptides derived from S protein (108,109). Moreover, both BNT162b2 and mRNA-1273 vaccines engendered binding antibodies directed against the Spike protein and the RBD and that just after the first inoculation (69,110). The measured titers of these antibodies parallelized or even exceeded those detected in convalescent patients. Contrarily, the activation of $CD8^+$ mediated cellular responses seems to be relatively limited even after inoculating the 2^{nd} dose of the vaccine (84,111). These findings suggest that the acquired immune protection following immunization is directed by either high level of binding antibodies, or by low levels of neutralizing antibodies and low frequency of T-cells. Alternatively, the innate immune system might also play a crucial role in the mounting of an unspecific but protective responses mediated by cytokines (INF-I or INF-III) and that in the context of the so-called "trained immunity" previously described for the BCG based vaccines (112). The concerned mRNA vaccines (BNT162b2 & mRNA-1273) in addition to the adenovirus-shuttled vaccine (ChAdOx1, nCoV-19) were proven apt to elicit IFN-I secretion leading to the prospective pathogen-agnostic protection essentially based on a process of viral evasion from pathogen-induced immuno-suppressive mechanisms and enhanced efficacy of the innate trained immunity (113,114). Given the worldwide critical health state related to the life-threatening illness, the urged clinical trials of licensed vaccines did not include a control group containing the shuttle vector alone (lacking the

Table 1. Categorization of developed vaccine formulations based on their attributes and associated dosing regimens

Vaccine's name & developer	Immunogenic inducing factor	Vaccine formulation	Dosing regimen	Number of doses	Interval days
BNT162b2 BioNTech/Pfizer (94,100,144)	mRNA	Full length S protein (2 proline mutations)	30 µg mRNA	2	21
mRNA-1273 Moderna (84)	mRNA	Full length S protein (2 proline mutations)	100 µg mRNA	2	28
ChAdOx1 nCoV-19 Astra-Zeneca (98,145)	Viral vector	Full length S protein (tPA leader sequence)	$2.5\text{-}5x10^{10}$ particles	2	≥28
Gam-COVID-Vac Gamaleya (124,146)	Viral vector	Full length S protein (recombinant protein)	10^{11} particles	2	21
Ad26.COV2.S Janssen (147-149)	Viral vector	Full length S protein (2 proline mutations) (modified cleavage site)	$5x10^{10}$ particles	1	-
Ad5-nCoV CanSino Biologics (14,122)	Viral vector	Full length S protein (tPA leader sequence)	$5x10^{10}$ particles	1	-
NVX-CoV2373 Novavax (150)	Protein subunit	Full length S protein (2 proline mutations) (modified cleavage site)	5 µg protein	2	21
CoronaVac Sinovac Biotech (127,130)	Inactivated virus	Adsorbed whole SARS-CoV-2 Propiolactone inactivated virus	3 µg protein	2	14-28
BBIBP-CorV Sinopharm (129)	Inactivated virus	Adsorbed whole SARS-CoV-2 Propiolactone inactivated virus	4 µg protein	2	21
WIBP-CorV Sinopharm (128)	Inactivated virus	Adsorbed whole SARS-CoV-2 propiolactone inactivated virus	5 µg protein	2	21
BBV152 Bharat Biotech (126)	Inactivated virus	Adsorbed whole SARS-CoV-2 Propiolactone inactivated virus	5 µg protein	2	28

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

immunogenic S protein or the RBD subunit) among their batches, which prevents the assessment of pathogen-agnostic immunity-based on the collected data. Purposes of pathogen unspecific stimulation of the Interferon pathways are based on preclinical insights gained from different vaccine formulations inoculated in animal models (114-116). Along with such conditions, it is worth mentioning that the assumed mechanisms of immune protection would readily differ between individuals inoculated with either one or two consecutive doses. The neutralizing antibodies are presumed to be the main actor playing a central role in developing protective responses to the issue of the consecutive doses of the vaccine (117). Analysis of the already collected data suggests that humoral responses are able to persist for a longer period, whereas cell-mediated responses are prone to faster decay and waning over time. Consequently, in case of a tangible miscellany in the amplitude and/or pathways of immune protection after the first and the second inoculation, the decryption of the differences might pave the road to adopt a definite decision regarding the intervals that should be adopted between consecutive doses or any upcoming booster dose as the current standards differ between various continents and countries with a range of 21-28 days in clinical trials whilst a period of six weeks has been recommended by the WHO or the equivalent of 12-16 weeks by the United Kingdom and Canada respectively (93,118). Moreover,

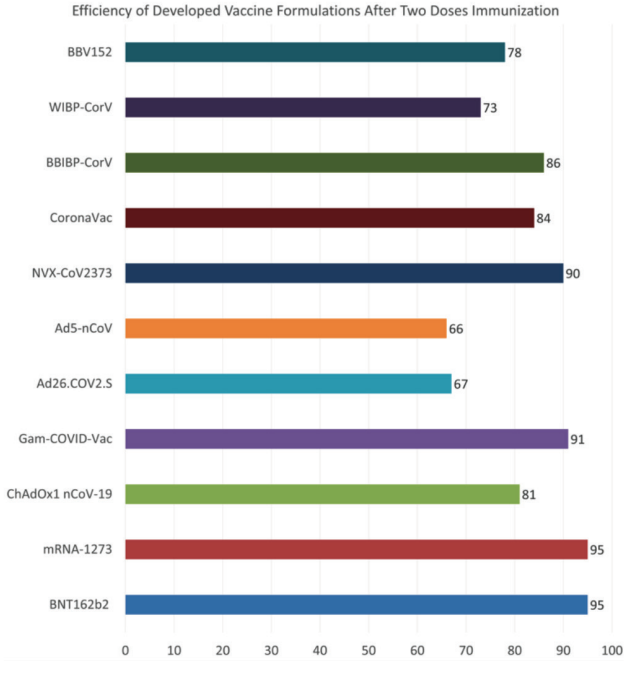

Figure 1. Comparative scheme of vaccine efficacy based on data collected from Phase III clinical trials represented as a percentage of vaccinated individuals who developed binding and neutralizing antibodies to SARS-CoV-2 virus following inoculation with different categories of vaccines

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

the effectiveness of humoral components shed light on the presumed role of memory B-cells in the mounting of immune responses. The comparison of healthy uninfected individuals to those recovering from a SARS-CoV-2 infection has shown that the viral infection stands behind the priming of memory cells development on the issue of the challenging of the immune system with either a viral infection or even a vaccine shot. In this way, a subsequent encounter with the same viral strain (later infection or second dose of the vaccine) will lead to an improvement of the adaptive memory B-cell responses (Table 2, Table 3) (119,120). mRNA vaccines offer a more advantageous and valuable formulation compared to the alternative virally shuttled vaccines, which might engender the synthesis of antibodies directed against the vector surface and a structure that hinders the immune responses at each booster shot (121,122).

Adenoviruses-based Vector Vaccines

The comparison of the collected data from both mRNA and adenoviruses-based vaccines show alternates between similarities in some issues and discrepancies in others. Regarding the efficacy of the vaccines (Figure 1), the studies showed that mRNA vaccines were able to reduce the severity and alleviate the clinical symptoms in 90% of the cases inoculated with two consecutive doses (93,94). With regard to adenoviruses-based vaccines (Table 1), the findings are miscellaneous. The records of the clinical trials reported a significant impact on symptomatic patients in 70% of the cases inoculated with ChAdOx-1 nCoV-19 (after 1st and/or 2nd dose) or Ad26.COV2.S (after 1st dose) (98,123). The promising impact has been to improve in the case of Gam-COVID-Vac after being inoculated with the 2nd dose (124). This improvement has been potentially correlated with the use of two different adenoviral vectors for each of the planned doses' formulations (adenoviral vector 26 for the first dose and adenoviral vector 5 for the second dose) which contribute to the decrease of the potential risk to develop an antivector immune response which might interfere and hinder the production of anti-Spike's antibodies as it has been shown in the case of Ad5-nCoV or other vaccines (121,122). It is worth mentioning that significant vaccine's efficacy in more than 80% of the cases has been revealed in the cases of both BNT162b2 and ChAdOx1 nCoV-19 (97). For both types of vaccines (mRNA & adenovirus vectored), they have shown a great potential to elicit a substantial level of neutralizing antibodies proclaimed to be more heightened than those measured in the serum of convalescent individuals with an emphasis on the levels induced by mRNA formulations. The inoculation of the first ChAdOx1 nCov-19 dose has been shown to induce the synthesis of a spectrum of polyclonal antibodies with a multitude of biological activities including viral

neutralization, surface binding, and opsonization. These antibody-dependent processes are expected to promote the immune response and reduce the severity of the illness (125). Explicitly, the diverse clones of antibodies engendered by the ChAdOx1, nCov-19 were shown to efficiently contribute to monocyte-mediated phagocytosis, neutrophil-mediated phagocytosis, and antibody-dependent complement activation, induced just after the reception of the first dose and remarkably enhanced after the second dose (97,125). Beside the effective humoral response(s) induced by the adenovirus vectored vaccines, evidence for the cell-mediated response has been also established. Just after the inoculation of the first dose, T-cell mediated responses culminated at 2 weeks in well-association with the secretion of significant amounts of TNF and IFN-γ cytokines by $CD4^+$ T lymphocytes challenged with the viral antigen *in vitro*. Paradoxically, individuals inoculated with only one dose or even two sequential doses of ChAdOx1 nCov-19 vaccine showed comparable responses despite a highly active antibody-mediated humoral response and a restraint T lymphocyte cell-mediated reaction (123). This inconsistency would suggest the contribution of a number of different concomitant factors interfering after the first and the second doses (Tables 2, 3). Besides, the immunogenicity and the vaccine's efficiency are more prone to increase with the adoption of longer intervals between consecutive doses, leading to more effective protection and enhanced immunity. In a long run, the so-called 'homologous prime-boosting, using the same adenovirus shuttled vaccines might be hindered by the potential antivector immunity.

Heterologous based approaches such as the one adopted for Gam-COVID-Vac or those implementing strategies including hybrid formulations might be a suitable alternative to overcome the risk (14,121,122).

Table 2. Effectiveness of the developed vaccine formulation as assessed following immunization

Vaccine's name and developer	Immunogenic inducing factor	Efficacy in case of symptomatic cases (Phase III clinical trials)	Post immunization efficacy
BNT162b2 BioNTech/Pfizer (104,107,121,151,152)	mRNA	52% after first dose	Asymptomatic 90% (2 doses)
		95% after second dose	Symptomatic 94-96% (2 doses)
		91% six months after 2nd dose	Hospitalization 71-85% (2 doses)
mRNA-1273 Moderna (107,108)	mRNA	92% after first dose	80% after first dose
		95% after second dose	90% after second dose
ChAdOx1 nCoV-19 Astra-Zeneca (97,98,101,123)	Viral vector	76% after one dose	80-94% after first dose in hospitalized patients
		76-81% after two doses	
		90% low followed by high dose	
		36-69 days median dose interval	
Gam-COVID-Vac Gamaleya (124,146)	Viral vector	74% after first dose	NA
		91% after second dose	
Ad26.COV2.S Janssen (148,153)	Viral vector	67% after the first dose	NA
Ad5-nCoV CanSino Biologics (154,155)	Viral vector	66% after first dose	NA
		50% six months post immunization	
NVX-CoV2373 Novavax (156)	Protein subunit	90% one week after the 2nd dose	NA
CoronaVac Sinovac Biotech (157,158)	Inactivated virus	50-84% after two doses inoculation	NA
BBIBP-CorV Sinopharm (159)	Inactivated virus	86% after two doses inoculation	NA
WIBP-CorV Sinopharm (160)	Inactivated virus	73% after two doses inoculation	NA
BBV152 Bharat Biotech (161)	Inactivated virus	78% after two doses inoculation	NA

NA: Not assessed

Table 3. Humoral and cell-mediated responses generated by the different vaccine formulations

Vaccine's name	Humoral response attributes	Cell mediated attributes
BNT162b2 BioNTech/Pfizer (111,162)	Anti-S1 antibodies generated after 1st dose	$CD4^+$, $CD8^+$ responses perceived after 2nd dose
	Anti-S1 Abs titer increased after 2nd dose	Highlighted in Ag-specific IFN-γ responses
	Neutralizing Abs perceived after 2nd dose	Predominant secretion of IFN-γ compared to IL-4
	Binding and NAbs were detected	Th1 mediated cellular polarization
mRNA-1273 Moderna (84)	Anti-S Abs detected 14 days after 1st dose	Substantial increase of $CD4^+$ T-cells
	Moderately increased after 28 days	Significant release of Th1 cytokines (TNF, IL-2)
	Insignificant Nabs after 1st dose	Cytokines titers peak after 2nd dose
	Peak of Nabs 2 weeks after 2nd dose	Minor activation of Th2 responses, Low $CD8^+$
ChAdOx1 nCoV-19 Astra-Zeneca (145,163)	Anti-S antibodies secreted 14 days after 1st dose	T lymphocytes activation peaks after 1st dose
	Substantial increase after 2nd dose	Slightly higher outcomes 28 days after 2nd dose
	Peak at 2 weeks after 2nd dose	Increase in TNF and IFN-γ secretion by $CD4^+$ T-cells
	IgG1 & IgG3 predominance in the serum	Cytokines peak at day 14
	Neutralizing Abs detected after 1st dose	
	Nabs titers increased at 2 weeks after 2nd dose	
	IgG avidity enhanced 28-56 days post 1st dose	
	IgM and IgA peaks reached at 14 & 28 days	
Gam-COVID-Vac Gamaleya (124,146)	Anti-S antibodies perceived in 85-89% of the cases	$CD4^+$, $CD8^+$ responses perceived 14 days after 1st dose
	Neutralizing Abs detected in 61% of individuals	All tested samples contained Ag-specific IFN-γ
	NAbs peaks detected 14 days after 1st dose	The majority had S-specific IFN-γ 7 days after 1st dose
	Nabs boosted after inoculation with 2nd dose	
Ad26.COV2.S Janssen (148,153)	Anti-S Abs are secreted one week after 1st dose	$CD4^+$, $CD8^+$ responses perceived 14 & 28 days post-vacination
	Both, binding & neutralizing Abs were perceived	Substantial secretion of IFN-γ compared to IL-2
	Anti-S Abs perceived in 99% 28 days post-vacination	Th1 mediated cellular phenotypic polarization
	Abs level were sustained 84 days post-vacination	
Ad5-nCoV CanSino Biologics (14,122,154)	44% of individuals produce anti-RBD antibodies	78-88% prompted T-cell mediated responses
	Anti-RBD antibodies are produced 14 days post-vacination	T-cell mediated responses perceived 28 days post-vacination
	28 days post-vac, 97% produced anti-RBD Abs	T-cell responses reached a peak 14 days post-vacination
	Only 47-50% generated neutralizing antibodies	
NVX-CoV2373 Novavax (150,164)	Spike binding Abs detected 21 days after 1st dose	$CD4^+$ mediated response incited 7 days after second dose
	Substantial increase of Abs titer after 2nd dose	S protein directed cytokines IFN-γ, TNF, and IL-2
	Low amount of NAbs were detected after 1st dose	strongly biased Th1 response phenotype
	NAbs significantly increased 7 days after 2nd dose	Predominance of IL-5 and IL-13 associated Th2 cells
CoronaVac Sinovac Biotech (127,130,132)	Anti-RBD Abs perceived in 88-97% of the cases	Data not available
	Peak at 28 days after 2nd dose (14 days interval)	
	Raise to 100% in case of 28 days interval	
	NAbs present in 94-100% at 28 days post-vacination	
BBIBP-CorV Sinopharm (16,129)	Binding Abs present in 46-87% of the cases	Data not available
	Significant titer present 14 days after 2nd dose	
	Titers increase by 28 days in 92-100% of cases	
	NAbs were perceived 21 days after 2nd dose	
WIBP-CorV Sinopharm (128)	100% of cases secreted binding Abs	Data not available
	Binding Abs detected 14 days after second dose	
	Abs are directed against whole inactivated virus	
	98% of the cases produced NAbs	
BBV152 Bharat Biotech (126,165)	65% of participants showed anti-S binding Abs	Resilient evidence of Th1 biased cellular phenotype
	Anti-S binding Abs detected after 1st dose	Th1 biased responses mediated by IFN-γ and TNF
	At 14 days after 2nd dose 98% produce anti-S Abs	Minimal activation of Th2 as mediated by IL-5 and IL-13
	48% of the cases synthesized NAbs after 1st dose	Memory $CD4^+$, $CD45RO^+$ T-cells were identified
	97% showed high NAbs titers 14 days after 2nd dose	Memory T-cells were perceived 76 days after 2nd dose
	Mean Abs titers significantly increased after 2nd dose	

RBD: Receptor binding domain, TNF: Tumor necrosis factor, IL: Interleukin, Ig: Immunoglobulin, Nab: Neutralizing antibodies

Inactivated and Protein Subunit Vaccines

This set includes weakened or inactivated particles unable to infect human cells or to replicate in the host cells to produce novel active viruses or/and those prepared with selected subunits composed of proteinaceous antigenic determinants or even polysaccharides. NVX-CoV2373 developed by Novavax has a significant efficacy (89-91%) against most of the traditional variants of interest (Alpha and Beta). BBIBP-CorV (Sinopharm), CoronaVac (Sinovac), WIBP-CorV (Sinopharm), and BBV152 (Bharat Biotech) (Table 1) were able to induce a protection at a rate varying between 50% and 90% (without a specification of the concerned strains) as they have been shown to incite the secretion of neutralizing and binding antibodies (Figure 1) (126-130).

Prospective Outlooks on SARS-CoV-2 Vaccines and Potential Enhancement Strategies

Despite the fact that the efforts devoted for the urgent development and validation of formulations' safety and efficacy have accomplished a substantial milestone in the context of vaccines' development, a number of promising outcomes are starting to loom raising the hope to surmount the pandemic which ravaged millions of susceptible individuals worldwide (131,132). For that purpose, health organizations and medical centers are required to categorize the innate and adaptive immune responses and to decrypt the mechanisms of protection engendered by different components of the immune system including the humoral path, cell-mediated path, and the complement system involvement and that should be based on a resilient, representative, and continuously updated data. Previous records and documentation collected at the issue of the emergency authorization have offered a capital resource that will help in the complete decryption of the immune response enigma. Preliminary analysis of the collected data on the basis of clinical trials launched for a set of seven different vaccine formulations shows that antibodies directed towards the spike protein are considered as one of the main pillars of immune protection. A strong correlation has been found between the high titers of neutralizing antibodies and the efficacy of the inoculated vaccine (r=0.79). Similarly, a strong correlation has also been reported between antibodies directed towards S protein and the assessed efficiency (r=0.93) at the end of the vaccination timeline (133). Unfortunately, the aforementioned outcomes are based on a short period of two to three months after inoculation. Long term follow-up cannot be escaped to draw a comprehensive scheme without neglecting any of the potential components of the immune system outside the context of bias towards neutralizing antibodies or adaptive immune responses without ignoring the role of innate immunity and associated barriers or components. The prospective findings that are to be collected from large cohort studies should be launched in different target populations and subjected to a systematic analysis to draw the conclusive results (134). In line with the continuous emergence of SARS-CoV-2 mutant strains with a multitude of mutations accumulating in the genetic sequence encoding the spike protein, it turns out to be an issue of utmost necessity to focus on the stimulation of the main immunological pathways represented by humoral and cell-mediated responses as well as the elaboration of the role assumed by the innate immune components (19). Despite preliminary observations reporting a reduced protection against mutant variants (i.e., beta variant of concern named B.1.351), emergent clinical data recently confirm the resilience of strong protection against severe illness and high rate of hospitalization. Conceptually, it is highly recommended to consider various SARS-CoV-2 epitopes, and antigenic structures (other than spike protein) that are less prone to genetic variation in the formulations of the upcoming generations of vaccines, which enhance the efficacy of the vaccines against the different nascent variants (135). In this context, it has been reported that antibodies provoked by Omicron variant (B.1.1.529) are expected to neutralize the viral particles of the Delta variant of concern (B.1.617.2). Convalescent patients with post-Omicron infection are subsequently less likely to experience repetitive infection with Delta variants (136,137). Ella and his colleagues, in a study aiming at the assessment of the immunogenicity and the safety of BBV152, a whole-virion inactivated form of SARS-CoV-2 vaccine, showed that anti-nucleocapsid and anti-spike binding immunoglobulins were profusely secreted in the serum of the inoculated individuals (126). The understanding of the role of these two types of antibodies will help to elaborate the mechanism of mediated protection. For that purpose, prompt efforts and analytical plans should be launched to achieve the decryption of the biological mechanisms that govern the normal functioning of the human immune system to secure the protection against viral infection, in addition to the monitoring of the proteomic changes and the genomic mapping of the factors involved in the mounting of an effective response (138,139). The mode of action which directs the involvement of the B and T memory cells is a key factor that conducts the correlation between the risk of infection with the viral spread and the severity of the disease in the framework of a long-termed follow-up. Simulated models that take the aforementioned factors into consideration may be of central significance in the search for the most appropriate vaccination regimen using either different vaccines or a combination of vaccine formulations to be inoculated only

once, or boosted with repetitive doses. This also applies to the assessment of recidivism and the impact of vaccines on the rate of reinfection in concordance with neutralizing antibodies and the mucosal immunity (140). Besides, analytical studies should be conducted to evaluate the impact of amended vaccination programmes, including the lowering of the inoculated dose, the adoption of a unique single dose, the use of multiple spaced doses, or mixed vaccine formulations. In parallel, data referring vulnerable populations (i.e., pregnant women, immuno-deficient patients, immuno-compromised patients, auto-immune carriers, or cancer patients and survival…) should also be collected and immediately subjected to a critical analysis by scientific experts and medical specialists to reach a set of standardized protocols based on comprehensive guidelines to be authenticated by the WHO representing the worldwide ultimate health authority and applied to the licensure of the currently developed or upcoming vaccines projects (141,142).

Conclusions and Perspectives

With the subsequent release of emergency use authorization for vaccines, billions of doses were deployed for immediate distribution in the developed countries of the first world, while the populations of underdeveloped countries might need to spend months or even long years before sufficient amounts of well-stored and well-transported vaccines are made accessible for concerned populations and clinical trials on novel formulations should keep running in parallel. In this context, the inequity of vaccines' dispatching and distribution, the ethical concerns in the framework of controlled clinical trials, the reduced incidence of severe cases, and the variable transmissibility besides the virulence of the different emergent variants of concerns complicate the devoted efforts of data collection and analysis. Based on the aforementioned attributes, the authentication of future vaccines should take into consideration the validation of the different variables affecting the effectiveness of the developed formulations at the molecular, cellular, and physiological levels without neglecting the global impact at the societal and communal scale (96,99,142). Although designed to fundamentally shield the most vulnerable symptomatic cases predisposed to hospitalization and intensive medical care, uncertainties continue to endure around asymptomatic cases and those at risk of recidivism what place the efficacy of the vaccines under a critical state of ambivalence and inconsistency. Preliminary records following the implementation of the authorized mRNA vaccines showed that despite being vaccinated, SARS-CoV-2 recidivist experienced certain clinical symptoms but with reduced viral load in the nasopharyngeal cavity, which would be related to the incessant emergence of novel mutant's strains. This enforces current vaccines to induce the synthesis of polyclonal antibodies able to adhere to a wide spectrum of antigenic determinants and epitopes on the surface spike protein. However, insights on viral transmissibility are not available yet (141). Hindering viral transmission is expected to ensure the protection of susceptible individuals where rigorous evaluation of the attributes of communal herd immunity in the framework of mass vaccination campaigns becomes a prerequisite for certified surveillance authorities in charge of implementing reliable recommendations to monitor the consecutive waves of the pandemic (5). A key step forward in the complete understanding of the SARS-CoV-2 virulence and pathogenicity is represented by the instant full genome sequencing of the virus and all of its emergent strains biopsied from symptomatic, non-symptomatic, vaccinated, and recidivist ones followed by its correlation with the immune interactions and outcomes. Each individual develops a variety of adaptive immune responses armed with memory cells and cytokines secreting lymphocytes, engendered by similar but previous coronaviruses strains (143). Significant insights in vaccine development correlated with the understanding of the COVID-19 pandemic attributes have been gained along the last two years (96). Further strategic efforts must be invested to secure unconditional, unrestricted, and affordable access to authenticated vaccines worldwide without any discrimination.

Ethics

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References

1. Callaway E, Cyranoski D, Mallapaty S, Stoye E, Tollefson J. The coronavirus pandemic in five powerful charts. Nature. 2020;579;482-3.
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91:157-60.
3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20:533-4.
4. Diamond MS, Pierson TC. The challenges of vaccine development against a new virus during a pandemic. Cell Host Microbe. 2020;27:699-703.
5. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol. 2021;21:475-84.
6. Thanh Le T. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020;19;305-6.
7. Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity. 2020;52;583-9.
8. El Khatib S. COVID-19 Vaccines, a Global Marathon Between Methodical Heritages and Future Challenges. Molecular Biotechnology & Genomic Editing. 2021;4.

9. Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020;586;567-71.

10. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586;589-93.

11. Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun. 2020;11:2601.

12. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science. 2020;369:806-11.

13. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. Preprint at. bioRxiv. 2020;2020:2020.05.13.093195. [Preprint].

14. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet. 2020;395:1845-54.

15. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020;369:77-81.

16. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell. 2020;182:713-21.e9.

17. Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep. 2020;7:61-4.

18. Kashte S, Gulbake A, El-Amin Iii SF, Gupta A. COVID-19 vaccines: rapid development, implications, challenges and future prospects. Hum Cell. 2021;34:711-33.

19. Abdool Karim SS, Oliveira T. New SARS-CoV-2 variants - clinical, public health, and vaccine implications. N Engl J Med. 2021;384:1866-8.

20. Kannan S, Shaik Syed Ali P, Sheeza A. Omicron (B.1.1.529) - variant of concern - molecular profile and epidemiology: a mini review. Eur Rev Med Pharmacol Sci. 2021;25:8019-22.

21. Ganusov VV, Antia R. Imperfect vaccines and the evolution of pathogens causing acute infections in vertebrates. Evolution. 2006;60:957-69.

22. Weigand MR, Peng Y, Cassiday PK, Loparev VN, Johnson T, Juieng P, et al. Complete genome sequences of Bordetella pertussis isolates with novel pertactin-deficient deletions. Genome Announc. 2017;5:e00973-17.

23. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620-9.

24. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med. 2020;383:1727-34.

25. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26:1636-43.

26. Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C, et al. Distinct early serological signatures track with SARS-CoV-2 survival. Immunity. 2020;53:524-32.e4.

27. Lee WT, Girardin RC, Dupuis AP, Kulas KE, Payne AF, Wong SJ, et al. Neutralizing antibody responses in COVID-19 convalescent sera. J Infect Dis. 2020;223:47-55.

28. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol. 2020;35:1123-38.

29. Robbiani DF, Gaebler C, Muecksch F, Lorenzi JCC, Wang Z, Cho A, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature. 2020;584:437-42.

30. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.

31. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science. 2020;369:812-7.

32. Chakraborty S, Gonzalez J, Edwards K, Mallajosyula V, Buzzanco AS, Sherwood R, et al. Proinflammatory IgG Fc structures in patients with severe COVID-19. Nat Immunol. 2021;22:67-73.

33. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature. 2020;586:583-8.

34. Jennewein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelette FJ, Krykbaeva M, et al. Fc glycan-mediated regulation of placental antibody transfer. Cell. 2019;178:202-15.e14.

35. Larsen MD, de Graaf EL, Sonneveld ME, Plomp HR, Nouta J, Hoepel W, et al. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science. 2020;371:eabc8378.

36. Callow KA. Effect of specific humoral immunity and some non-specific factors on resistance of volunteers to respiratory coronavirus infection. J Hyg (Lond). 1985;95:173-89.

37. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect. 1990;105:435-46.

38. Butler SE, Crowley AR, Natarajan H, Xu S, Weiner JA, Lee J, et al. Features and functions of systemic and mucosal humoral immunity among SARS-CoV-2 convalescent individuals. Preprint at. medRxiv. 2020;2020.08.05.20168971.

39. Fenrich M, Mrdenovic S, Balog M, Tomic S, Zjalic M, Roncevic A, et al. SARS-CoV-2 dissemination through peripheral nerves explains multiple organ injury. Front Cell Neurosci. 2020;14:229.

40. DiLillo DJ, Tan GS, Palese P, Ravetch JV. Broadly neutralizing hemagglutinin stalk-specific antibodies require FcγR interactions for protection against influenza virus in vivo. Nat Med. 2014;20:143-51.

41. Excler JL, Ake J, Robb ML, Kim JH, Plotkin SA. Nonneutralizing functional antibodies: a new "old" paradigm for HIV vaccines. Clin Vaccine Immunol. 2014;21:1023-36.

42. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020;26:842-4.

43. Wen W, Su W, Tang H, Le W, Zhang X, Zheng Y, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov. 2020;6:31.

44. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell. 2020;181:1489-501.e15.

45. Neidleman J, Luo X, Frouard J, Xie G, Gill G, Stein ES, et al. SARS-CoV-2-specific T cells exhibit unique features characterized by robust helper function, lack of terminal differentiation, and high proliferative potential. bioRxiv. 2020;2020.06.08.138826.

46. Ni L, Ye F, Cheng ML, Feng Y, Deng YQ, Zhao H, et al. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity. 2020;52:971-7.e3.

47. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell. 2020;183:158-68.e14.

48. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NMA, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020;5:eabd2071.

49. Wyllie D, Jones HE, Mulchandani R, Tricket A, Taylor-Philips S, Brooks T, et al. SARS-CoV-2 responsive T cell numbers are associated with protection from COVID-19: a prospective cohort study in keyworkers. medRxiv. 2020.

50. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol. 2020;5:eabd7114.

51. Zhao J, Zhao J, Mangalam AK, Channappanavar R, Fett C, Meyerholz DK, et al. Airway memory CD4+ T cells mediate protective immunity against emerging respiratory coronaviruses. Immunity. 2016;44:1379-91.

52. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol. 2020;20:615-32.

53. McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature. 2021;590:630-4.

54. Kikkert M. Innate immune evasion by human respiratory RNA viruses. J Innate Immun. 2020;12:4-20.

55. Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell. 2021;184:1671-92.

56. Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol. 2020;20:585-6.

57. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. Nat Rev Immunol. 2020;20:397-8.

58. Banerjee AK, Blanco MR, Bruce EA, Honson DD, Chen LM, Chow A, et al. SARS-CoV-2 disrupts splicing, translation, and protein trafficking to suppress host defenses. Cell. 2020;183:1325-39.

59. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181:1036-45.e9.

60. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020;583:459-68.

61. Sa Ribero M, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoS Pathog. 2020;16:e1008737.

62. Konno Y, Kimura I, Uriu K, Fukushi M, Irie T, Koyanagi Y, et al. SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant. Cell Rep. 2020;32:108185.

63. Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat Commun. 2020;11:3810.

64. Xia H, Cao Z, Xie X, Zhang X, Chen JY, Wang H, et al. Evasion of type I interferon by SARS-CoV-2. Cell Rep. 2020;33:108234.

65. Ahmed-Hassan H, Sisson B, Shukla RK, Wijewantha Y, Funderburg NT, Li Z, et al. Innate immune responses to highly pathogenic coronaviruses and other significant respiratory viral infections. Front Immunol. 2020;11:1979.

66. Higgins PG, Phillpotts RJ, Scott GM, Wallace J, Bernhardt LL, Tyrrell DA. Intranasal interferon as protection against experimental respiratory coronavirus infection in volunteers. Antimicrob Agents Chemother. 1983;24:713-5.

67. Park A, Iwasaki A. Type I and type III interferons - induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe. 2020;27:870-8.

68. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271-80.e8.

69. Pardi N, Tuyishime S, Muramatsu H, Kariko K, Mui BL, Tam YK, et al. Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. J Control Release. 2015;217:345-51.

70. Rauch S, Jasny E, Schmidt KE, Petsch B. New vaccine technologies to combat outbreak situations. Front Immunol. 2018;9:1963.

71. Bosch BJ, Zee R, Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. 2003;77:8801-11.

72. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3:237-61.

73. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol. 2020;41:355-9.

74. Coughlin M, Lou G, Martinez O, Masterman SK, Olsen OA, Moksa AA, et al. Generation and characterization of human monoclonal neutralizing antibodies with distinct binding and sequence features against SARS coronavirus using XenoMouse. Virology. 2007;36:93-102.

75. Duan J, Yan X, Guo X, Cao W, Han W, Qi C, et al. A human SARS-CoV neutralizing antibody against epitope on S2 protein. Biochem Biophys Res Commun. 2005;333:186-93.

76. Lipsitch M, Grad YH, Sette A, Crotty S. Cross-reactive memory T cells and herd immunity to SARS-CoV-2. Nat Rev Immunol. 2020;20:709-13.

77. Wang L, Shi W, Chappell JD, Joyce MG, Zhang Y, Kanekiyo M, et al. Importance of neutralizing monoclonal antibodies targeting multiple antigenic sites on the Middle East respiratory syndrome coronavirus spike glycoprotein to avoid neutralization escape. J Virol. 2018;92:e02002-17.

78. Graham BS. Rapid COVID-19 vaccine development. Science. 2020;368:945-6.

79. Wang F, Flanagan J, Su N, Wang LC, Bui S, Nielson A, et al. RNAscope: a novel in situ RNA analysis platform for formalin-fixed, paraffin-embedded tissues. JMD. 2012;14:22-9.

80. Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, et al. A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85:12201-15.

81. Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. Vaccine. 2005;23:2273-9.

82. Fulginiti VA, Eller JJ, Downie AW, Kempe CH. Altered reactivity to measles virus. Atypical measles in children previously immunized with inactivated measles virus vaccines. JAMA. 1967;202:1075-80.

83. Hou YJ, Okuda K, Edwards CE, Martinez DR, Asakura T, Dinnon KH 3rd, et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. Cell. 2020;182:429-46. e14.

84. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020;383:1920-31.

85. Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89:422-34.

86. Lambert PH, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 2020;38:4783-91.

87. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586:594-9.

88. Scobey T, Yount BL, Sims AC, Donaldson EF, Agnihothram SS, Menachery VD, et al. Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. Proc Natl Acad Sci U S A. 2013;110:16157-62.

89. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol. 2020;21:1336-45.

90. Arvin AM, Fink K, Schmid MA, Cathcart A, Spreafico R, Havenar-Daughton C, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020;584:353-63.

91. Halstead SB, Katzelnick L. COVID-19 vaccines: should we fear ADE? J Infect Dis. 2020;222:1946-50.

92. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018;379:327-40.

93. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2020;384:403-16.

94. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603-15.

95. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384:1412-23.

96. Huang AT, Garcia-Carreras B, Hitchings MDT, Yang B, Katzelnick LC, Rattigan SM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun. 2020;11:4704.

97. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Assessing the effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 vaccination in prevention of hospitalisations in elderly and frail adults: a single centre test negative case–control study. SSRN. 2021.

98. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2020;397:99-111.

99. Izda V, Jeffries MA, Sawalha AH. COVID-19: A review of therapeutic strategies and vaccine candidates. Clin Immunol. 2021;222:108634.

100. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines-a new era in vaccinology. Nat Rev Drug Discov. 2018;17:261-79.

101. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. Preprint at. SSRN. 2021;397:1646-57.

102. Andrejko K, Pry JM, Myers JF, Jewell NP, Openshaw J, Watt J, et al. Early evidence of COVID-19 vaccine effectiveness within the general population of California. medRxiv. 2021.

103. Bernal JL, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv, 2021.

104. Chodick G, Tene L, Patalon T, Gazit S, Tov AB, Cohen D, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection: real-world evidence. SSRN. 2021.

105. Regev-Yochay G, Amit S, Bergwerk M, Lipsitch M, Leshem E, Kahn R, et al. Decreased infectivity following BNT162b2 vaccination. SSRN. 2021;7.

106. Tande AJ, Pollock BD, Shah ND, Farrugia G, Virk A, Swift M, et al. Impact of the COVID-19 vaccine on asymptomatic infection among patients undergoing pre-procedural COVID-19 molecular screening. Clin Infect Dis. 2022;74:59-65.

107. Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. MMWR. 2021;70:495-500.

108. Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. 2020;384:80-2.

109. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383:2427-38.

110. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med. 2020;383:2439-50.

111. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol. 2020;20:335-7.

112. Collignon C, Bol V, Chalon A, Surendran N, Morel S, van den Berg RA, et al. Innate immune responses to chimpanzee adenovirus vector 155 vaccination in mice and monkeys. Front Immunol. 2020;11:579872.

113. Hensley SE, Cun AS, Giles-Davis W, Li Y, Xiang Z, Lasaro MO, et al. Type I interferon inhibits antibody responses induced by a chimpanzee adenovirus vector. Mol Ther. 2007;15:393-403.

114. Devoldere J, Dewitte H, Smedt SC, Remaut K. Evading innate immunity in nonviral mRNA delivery: don't shoot the messenger. Drug Discov Today. 2016;21:11-25.

115. Hartman ZC, Appledorn DM, Amalfitano A. Adenovirus vector induced innate immune responses: impact upon efficacy and toxicity in gene therapy and vaccine applications. Virus Res. 2008;132:1-14.

116. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371:eabf4063.

117. Ledford H. How can countries stretch COVID vaccine supplies? Scientists are divided over dosing strategies. Nature. 2021;589;182.

118. Quach C, Deeks S. COVID-19 vaccination: why extend the interval between doses? J Assoc Med Microbiol Infect Dis Can. 2021;6:73-8.

119. Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, et al. Distinct antibody and memory B cell responses in SARS-CoV-2 naive and recovered individuals following mRNA vaccination. Sci Immunol. 2021;6:eabi6950.

120. Li M, Wang H, Tian L, Pang Z, Yang Q, Huang T, et al. COVID-19 vaccine development: milestones, lessons and prospects. Signal Transduct Target Ther. 2022;7:146.

121. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008;372:1881-93.

122. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020;396:479-88.

123. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397:881-91.

124. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021;397:671-81.

125. Barrett JR, Belij-Rammerstorfer S, Dold C, Ewer KJ, Folegatti PM, Gilbride C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. 2020;27:279-88.

126. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis. 2021;21:637-46.

127. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:803-12.

128. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. JAMA. 2020;324-951-60.

129. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21:39-51.

130. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:181-92.

131. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int J Infect Dis. 2022;114:252-60.

132. Sampath V, Rabinowitz G, Shah M, Jain S, Diamant Z, Jesenak M, et al. Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives. Allergy. 2021;76:1640-60.

133. Kristen AE, Donna MA, Andrew FG, David G, Peter BG. Evidence for antibody as a protective correlate for COVID-19 vaccines. medRxiv. 2021.

134. Shannon CP, Blimkie TM, Ben-Othman R, Gladish N, Amenyogbe N, Drissler S, et al. Multi-omic data integration allows baseline immune signatures to predict hepatitis B vaccine response in a small cohort. Front Immunol. 2020;11:578801.

135. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 COVID-19 vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021;385:187-9.

136. Ren SY, Wang WB, Gao RD, Zhou AM. Omicron variant (B.1.1.529) of SARS-CoV-2: Mutation, infectivity, transmission, and vaccine resistance. World J Clin Cases. 2022;10:1-11.

137. Singhal T. The Emergence of Omicron: Challenging Times Are Here Again! Indian J Pediatr. 2022;89:490-6.

138. Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD, et al. Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. Cell. 2016;166:1512-25.e12.

139. Wang A, Luan HH, Medzhitov R. An evolutionary perspective on immunometabolism. Science. 2019;363:eaar3932.

140. Kirby T. COVID-19 human challenge studies in the UK. Lancet Respir Med. 2020;8:e96.

141. Levine-Tiefenbrum M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Decreased SARS-CoV-2 viral load following vaccination.. medRxiv. 2021.

142. Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. Science. 2020;370:1277-9.

143. Gilbert P, Self S, Rao M, Naficy A, Clemens J. Sieve analysis: methods for assessing from vaccine trial data how vaccine efficacy varies with genotypic and phenotypic pathogen variation. J Clin Epidemiol. 2001;54:68-85.

144. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367:1260-3.

145. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020;396:467-8.

146. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. 2020;396:887-97.

147. Sadoff J, Gars ML, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Safety and immunogenicity of the Ad26. COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. medRxiv. 2020.

148. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim results of a phase 1-2a trial of Ad26. COV2.S COVID-19 vaccine. N Engl J Med. 2021;384:1824-35.

149. Bos R, Rutten L, van der Lubbe JEM, Bakkers MJG, Hardenberg G, Wegmann F, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines. 2020;5:91.

150. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. N Engl J Med. 2020;383:2320-32.

151. Skowronski DM, Serres G. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2021;384:1576-7.

152. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN Study). SSRN. 2021.

153. Janssen Biotech. COVID-19 Vaccine Ad26.COV2.S. Sponsor Briefing Document (Vaccines and Related Biological Products Advisory Committee, 2021).

154. Reuters. CanSinoBIO's COVID-19 vaccine 65.7% effective in global trials, Pakistan official says. Reutershttps://www.reuters.com/article/us-health-coronavirus-vaccine-pakistan/cansinobios-covid-19-vaccine-65-7-effective-in-global-trials-pakistan-official-says-idUSKBN2A81N0 (2021). Available on URL: https://www.reuters.com/article/us-health-coronavirus-vaccine-pakistan/cansinobios-covid-19-vaccine-65-7-effective-in-global-trials-pakistan-official-says-idUSKBN2A81N0

155. Reuters. CanSinoBIO says COVID-19 shot may be less effective over time, booster shot promising. Reutershttps://www.reuters.com/article/us-health-coronavirus-vaccine-cansinobio-idUSKBN2BO4CG (2021). Available on URL: https://www.reuters.com/article/us-health-coronavirus-vaccine-cansinobio-idUSKBN2BO4CG

156. Novavax. Novavax confirms high levels of efficacy against original and variant COVID-19 strains in United Kingdom and South Africa trials. Novavaxhttps://ir.novavax.com/news-releases/news-release-details/novavax-confirms-high-levels-efficacy-against-original-and-0 (2021). Available on URL: https://ir.novavax.com/news-releases/news-release-details/novavax-confirms-high-levels-efficacy-against-original-and-0

157. BBC. Sinovac: Brazil results show Chinese vaccine 50.4% effective. BBC Newshttps://www.bbc.com/news/world-latin-america-55642648 (2021). Available on URL: https://www.bbc.com/news/world-latin-america-55642648

158. Reuters. Turkish study revises down Sinovac COVID-19 vaccine efficacy to 83.5%. Reutershttps://www.reuters.com/article/us-health-coronavirus-turkey-sinovac/turkish-study-revises-down-sinovac-covid-19-vaccine-efficacy-to-83-5-idUSKBN2AV13A (2021). Available on URL: https://www.reuters.com/article/us-health-coronavirus-turkey-sinovac/turkish-study-revises-down-sinovac-covid-19-vaccine-efficacy-to-83-5-idUSKBN2AV13A

159. Reuters. UAE says Sinopharm vaccine has 86% efficacy against COVID-19. Reutershttps://www.reuters.com/business/healthcare-pharmaceuticals/uae-says-sinopharm-vaccine-has-86-efficacy-against-covid-19-2020-12-11/ (2020). Available on URL: https://www.reuters.com/business/healthcare-pharmaceuticals/uae-says-sinopharm-vaccine-has-86-efficacy-against-covid-19-2020-12-11/

160. Reuters. Sinopharm's Wuhan unit reports 72.5% efficacy for COVID shot, seeks approval in China. Reutershttps://www.reuters.com/business/healthcare-pharmaceuticals/sinopharms-wuhan-unit-reports-725-efficacy-covid-shot-seeks-approval-china-2021-02-24/ (2021). Available on URL: https://www.reuters.com/business/healthcare-pharmaceuticals/sinopharms-wuhan-unit-reports-725-efficacy-covid-shot-seeks-approval-china-2021-02-24/

161. Bharat Biotech. Bharat Biotech and ICMR Announce Interim Results from Phase 3 trials of COVAXIN®; Demonstrates overall Interim Clinical Efficacy of 78% and 100% efficacy against Severe COVID-19 diseasehttps://www.bharatbiotech.com/images/press/covaxin-phase3-clinical-trials-interim-results.pdf (2021). Available on URL: https://www.bharatbiotech.com/images/press/covaxin-phase3-clinical-trials-interim-results.pdf

162. Pfizer. Pfizer-Biontech COVID-19 Vaccine (BNT162, PF-07302048) Vaccines and Related Biological Products Advisory Committee Briefing Document (Pfizer Inc, 2020).

163. Ewer KJ. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med. 2020;27. Available on URL: https://doi.org/10.1038/s41591-020-01194-5

164. Dunkle LM, Kotloff KL, Gay CL, Áñez G, Adelglass JM, Barrat Hernández AQ, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2022;386:531-43.

165. Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis. 2021;21:950-61.