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Vaccine-Induced Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Response and the Path to Accelerating Development (Determining a Correlate of Protection)

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KEYWORDS

• SARS-CoV-2 • Vaccines • Serologic diagnostics

KEY POINTS

- A marker of immunity that describes clinical efficacy for SARS-CoV-2 vaccines would be a valuable clinical and epidemiological tool.
- A "correlate" or "surrogate" of SARS-CoV-2 vaccine-induced protection needs to be well-defined, including clear endpoints (e.g., hospitalization, severe disease, transmission).
- Different statistical models and methodologies can be used to determine a correlate or surrogate of protection.
- Many factors including host characteristics, vaccine platform, and immunologic parameters may impact the correlate or surrogate of protection.

INTRODUCTION

Less than 18 months after the identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its genome, 13 authorized or approved COVID-19 vaccines are being deployed around the world,[1] and many more candidates are currently undergoing evaluation in clinical trials. In the United States, 3 vaccines have been granted an Emergency Use Authorization (EUA) by the Food and Drug

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Clin Lab Med 42 (2022) 111–128
https://doi.org/10.1016/j.cll.2021.10.008
labmed.theclinics.com

Administration: BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and Ad26.CoV2.S (Janssen Biotech, Inc). Although the phase 3 clinical trials have demonstrated clinical efficacy in preventing moderate to severe COVID-19 disease, the underlying immune mechanisms that confer protection are still not known. Furthermore, determining protection against SARS-CoV-2 infection in vaccinated people using laboratory markers would be extremely useful. Efficacy studies, such as randomized controlled trials (RCTs), depend on large and expensive clinical trials, whereas large population studies during vaccine rollout often have confounding variables. Using a "surrogate" or "correlate" of protection allows for easier monitoring and surveillance of a particular vaccine's effectiveness, which can aid in both vaccine development and licensure.[2] Markers of immune responses can also be applied to determine a population response for new variants or strains of a virus, across unique characteristics of a population (eg, elderly, immunocompromised), and across different manufacturing or lots. Furthermore, COVID-19 vaccine boosters may be necessary, and a correlate of protection (CoP) would allow for efficient measurement of persistent protection. To date, there is no accepted CoP for COVID-19 vaccine-induced immunity.

The current knowledge regarding antibody-induced responses to SARS-CoV-2 vaccines, the definition of a CoP, proposed CoP for SARS-CoV-2, and special considerations for defining an SARS-CoV-2 vaccine-induced CoP are discussed.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINES AND ANTIBODY RESPONSES

The varied COVID-19 vaccines that have been approved for emergency use or are still undergoing clinical evaluation use different technologies, administration schedules, and antigen targets (**Table 1**), which may result in different cellular and humoral responses following immunization. The available data on the dynamics, duration, and magnitude of the antibody responses following COVID-19 immunization are discussed in relation to different vaccine platforms.

Antibody responses to COVID-19 vaccines are commonly reported using 2 different assays: immunoassays to detect binding antibodies (bAb) and neutralization assays to detect neutralizing antibodies (nAb).[3] Immunoassays, such as enzyme-linked immunosorbent assays (ELISA), detect and quantify antibodies that have the capacity to bind a specific antigen in vitro. Except for inactivated vaccines, all available COVID-19 vaccines target the SARS-CoV-2 spike protein or one of its components (eg, receptor binding domain or RBD, S1, S2). Thus, it is expected that these vaccines will lead to the production of bAb against the spike protein, but not against the nucleocapsid protein. This antibody response signature is different from what is seen after natural infection or vaccination with inactivated vaccines, where detection of both spike and other antigens (such as nucleocapsid) bAb is expected. Neutralization assays are used to quantify functional antibodies that have the capacity to inhibit the replication of SARS-CoV-2 in vitro. Alternatively, a pseudovirus expressing SARS-CoV-2 spike protein can be used instead of wild-type SARS-CoV-2, providing significant safety and versatility advantages. In most phase 1/2 trials, a strong correlation was seen between bAb and nAb elicited postvaccination.[4–7]

Dynamics of Antibody Responses Postvaccination

In participants without previous SARS-CoV-2 infection, bAb, such as immunoglobulin G (IgG) against the full spike, S1, S2, or RBD, are usually detectable 14 days after the initial dose and tend to further increase on days 21 to 28, when the second dose is

Table 1
Vaccine platforms, dose and schedule, and antigen targets

Vaccine Platform	Vaccine Name	Approved/ Authorized	Vaccine Dose and Schedule	Antigen Target
mRNA-based vaccines	BNT162b2 (Pfizer/BioNTech)	≥85 countries US EUA 12/11/2020	30 μg 2 doses, 21 d apart[9]	Prefusion-stabilized full-length S protein
	mRNA-1273 (Moderna)	≥46 countries US EUA 12/18/2020	100 μg 2 doses, 28 d apart[5,11,85]	Prefusion-stabilized full-length S protein
Vector vaccines	AZD1222 (Astra-Zeneca) Vector: ChAdeno	≥139 countries Not in the US	5×10^{10} VP 2 doses, 4–12 wk apart[8,86]	Full-length S protein
	Ad26.CoV2.S (Janssen) Vector: Ad26	≥41 countries USA EUA 2/27/2021	5×10^{10} VP, 1 dose[4]	Prefusion-stabilized full-length S protein
	Sputnik V (Gamaleya Center) Vector: rAd26/rAd5	≥65 countries Not in the US	10^{11} VP, 2 doses 21 d apart[6]	Full-length S protein
	Convidicea (CanSino) Vector: rAd5	≥5 countries Not in the US	5×10^{10} VP, 1 dose[7]	Full-length S protein
Inactivated vaccines	CoronaVac (Sinovac)	≥24 countries Not in the US	3 μg, 2 doses 14–28 d apart[10,87]	Inactivated SARS-CoV-2 (CN02 strain)
	BBIBP-CorV (Sinopharm)	≥40 countries Not in the US	4 μg, 2 doses 21–28 d apart[63]	Inactivated SARS-CoV-2 (HB02 strain)
	Covaxin (Bharat Biotech)	≥9 countries Not in the US	6 μg, 2 doses 28 d apart[15,88]	Inactivated SARS-CoV-2 (NIV-2020-770 strain)
	WIBP-CorV (Sinopharm)	2 countries Not in the US	5 μg, 2 doses 21 d apart[89]	Inactivated SARS-CoV-2 (WIV04 strain)
	CoviVac (Chumakov Center)	1 country Not in the US	N/A, 2 doses, 14 d apart	Inactivated SARS-CoV-2 (strain N/A)
Subunit vaccine	EpiVacCorona (Vector Institute)	2 countries Not in the US	N/A, 2 doses 21–28 d apart (NCT04780035)	Synthesized peptide antigens of SARS-CoV-2
	ZF2001 (Anhui Zhifei Longcom Biopharmaceutical)	2 countries Not in the US	25 μg, 3 doses, 0–30–60 d[16]	Receptor-binding domain

administered.[5,8] All the 2-dose schedule vaccines show a *prime-boost* effect, with further significant increase of bAb peaking around 7 to 14 days after the second dose.[5,9,10]

In general, nAb are detected at a low level starting at day 14 and significantly increase after the second dose.[5,6,8] nAb tend to increase at a rate slower than bAb, however, like bAb, tend to peak 7 to 14 days postdosing schedule. The single-dose vaccines Ad26.CoV2.S (Janssen Biotech, Inc), a nonreplicating adenovirus serotype 26 (Ad26) vector vaccine, and Convidicea (CanSino), a nonreplicating adenovirus serotype 5 vector vaccine, produce bAb and nAb by day 28, that tend to further increase by day 56 for Ad26.CoV2.S.[4,7]

Limited data are available regarding the duration of antibody responses post-COVID-19 vaccines. Data generated from the phase 1 and phase 3 clinical trials are critical to better understand the duration of protection, as participants in these trials were vaccinated as early as March 2020 and July 2020, respectively. This prolonged follow-up period provides early understanding of the kinetics of antibody response and vaccine efficacy over time and may guide the need for future booster dose. In the mRNA-173 phase 1 study, in which 33 participants received 2 doses of vaccine 28 days apart, bAb and nAb titers decreased but persisted through 6 months after the second dose as assessed by 3 different assays.[11] There is also growing evidence from the phase 3 trials that vaccination with messenger RNA (mRNA) vaccines remains clinically effective to prevent confirmed symptomatic cases of COVID-19 for at least 6 months.[12,13]

Magnitude of Antibody Responses

The magnitude of postvaccination bAb and nAb published to date is difficult to compare between COVID-19 vaccine types, because researchers use different assays and methods to quantitate antibody levels. Furthermore, for bAb, assays target different antigens, such as the full spike protein or one of its fragments (S1, S2, RBD).[14] For this reason, some groups have included a panel of control convalescent serum specimen from individuals with prior COVID-19 to compare the vaccine-induced responses with the natural infection. mRNA and vector vaccines were shown to induce bAb and nAb titers similar to or higher than what is detected in convalescent sera.[4,5,8,9] For inactivated vaccines, only CoronaVac and Covaxin trials reported comparison with convalescent sera and showed respectively lower or similar nAb titers in sera from vaccinated participants compared with convalescents sera.[15] The recombinant vaccine ZF2001 showed significantly higher nAb titers in vaccinated participants than in convalescent sera.[16] However, these data must be cautiously interpreted because the serum panels differ among the different studies. Antibody titers after natural infection can vary significantly in convalescent individuals, based on host's characteristics, severity of disease, and timing from symptom onset.[3,17]

Impact of Previous Infection on Antibody Responses to Vaccines

In individuals with previous SARS-CoV-2 infection, postvaccination humoral responses differ significantly in terms of dynamics and magnitude. In those who received BNT162b2 (Pfizer, Inc) or mRNA-1273 (ModernaTx, Inc), a rapid increase of bAb is seen after the first dose, starting as early as 5 to 8 days.[18] The titers quickly peak at high levels between days 9 and 12 and do not significantly increase after the second dose. In comparison with those without preexisting immunity, the titers were 10 to 45 times higher after the first dose and remained 6 times higher after the second dose. Another study showed that 2 doses of BNT162b2 (Pfizer, Inc) in previously uninfected individuals induced lower nAb titers than a single dose in those with previous infection.

COVID-19 Vaccines Humoral Responses and Variants

In the early phase 1/2 COVID-19 vaccine trials, vaccine-induced neutralizing activity was assessed by neutralization assays using pseudovirus expressing the wild-type Spike protein or using wild-type SARS-CoV-2. However, since January 2021, many different genetic variants of SARS-CoV-2 have emerged around the world. These variants have various substitutions, insertions, and/or deletions in the spike protein gene that may lead to increased transmissibility or disease severity, and may also reduce vaccine-induced protection.[19] Current variants of concern according to the Centers for Disease Control and Prevention include B.1.1.7 (first identified in United Kingdom), P1 (first identified in Brazil), B1.351 (first identified in South Africa), and B.1.427 and B.1.429 (first identified in California, USA). Emerging data have shown reduced, but variable neutralizing activity of postvaccination sera on these variants, with a small to moderate reduction in activity on the B.1.1.7, P1, B.1.427, and B.1.429,[20,21] and more significant reduction of neutralization was shown on the B1.351 variant, particularly with AZD1222, where complete virus escape has been described.[22] In patients with previous SARS-CoV-2 infection, a single dose of BNT162b2 substantially increased the serum neutralizing activity against B.1.1.7, P1, and B.1.351, with similar titers across patients for each variant.[23]

DEFINITION AND HISTORICAL EXAMPLES OF CORRELATES OF PROTECTION AND RISKS

There are several definitions of the terms “correlate of protection” and “correlates of risk.” Plotkin and Plotkin[24] define a CoP as “a specific immune response to a vaccine that is closely related to protection against infection, disease, or other defined end point.” A CoP is typically a measurable immune marker, and preferably one that is relatively easy to obtain by standard laboratory techniques, for facile scalability and reproducibility. Importantly, Plotkin and Plotkin argue that the correlate itself confers protection, which they distinguish from a “surrogate,” which is not itself protective but is an appropriate substitute for a different immune response that does offer protection. When defining a CoP, it is equally important to define the endpoint being described. For example, does the immunologic parameter provide protection against infection, transmission, hospitalization, or death? Depending on the outcome measure, the threshold value of a CoP may vary. The term “correlates of risk” was described by Qin and colleagues[25,26] as the statistical assessment of a CoP in the context of a clinical trial. In this assessment, the clinical endpoint is the outcome measure of efficacy as predetermined in the clinical trial.

The humoral immune response is an essential feature of protection for many vaccine-preventable diseases. Antibodies have been described as good correlates of protection for several different types of pathogens, including tetanus, pneumococcus, hepatitis A, hepatitis B, diphtheria, and *Haemophilus influenzae* b.[27–29] Passive immunity from transfer of antibodies can be shown to be protective. For example, antibodies transferred from maternal transmission to the fetus or antibodies provided clinically by injection can confer protection, which demonstrates a direct protective effect of the immune marker in question. Often, a discrete and quantitative antibody threshold value for protection can be described. However, it should be noted that antibody quality rather than quantity may also be important, and thus, a potential limitation in identifying a simplistic quantity of antibody as being protective for a given pathogen.

The immune system is complex and redundant. Thus, some have proposed that a CoP for a given vaccine is not reflective in a single immune marker, but rather could

be a series of immune markers in an immune cascade, or numerous independent immune markers. For example, a clear correlate for measles protection has been identified, with an antibody level of plaque reduction neutralization greater than 120 mIU/mL, as demonstrated by successful protection with maternal-fetal transmission of antibodies.[30] However, individuals who are unable to produce antibodies because of humoral deficiencies can clear measles infection, demonstrating an alternative pathway of T-cell–induced immunity that confers protection.[31,32] Therefore, multiple immune pathways may be important for generating protection depending on the pathogen and characteristics of the host, with several unique correlates of protection.

Methods to Evaluate Immune Correlates

Much controversy exists in the literature regarding the meaning and utilization of immune-based correlates. A vaccine can be shown to induce a specific immune response; however, this does not necessarily translate to clinical efficacy. A vaccine may also have an immune response that is statistically associated with an assessment of efficacy; however, this value does not directly translate into a causal relationship between the immune marker and protection. To further refine how correlates should be described and thereby applied, several investigators have suggested validation models using a combination of statistical and clinical data.

Prentice[33] developed 4 criteria to evaluate endpoints for RCTs. These criteria have been adapted in the context of vaccine trials, as listed below[34]:

1. Protection against the clinical endpoint is significantly related to having received the vaccine.
2. The substitute endpoint is significantly related to the vaccination status.
3. The substitute endpoint is significantly related to protection against the clinical endpoint.
4. The full effect of the vaccine on the frequency of the clinical endpoint is explained by the substitute endpoint, as it lies on the sole causal pathway.

Although described specifically for RCTs, others have demonstrated that the Prentice criteria can also be applied for observational studies, although this was elucidated in relation to cancer research and not vaccinology research.[35]

Qin and colleagues[25] proposed a framework to statistically describe 3 different levels of correlates of protection and defined the data requirements needed to systematically validate the immune marker for each level. The 3 levels are defined as follows: (1) “correlate of risk,” which is most closely associated with protection against a clinical outcome as determined in a clinical trial; followed by (2) “level 1 specific surrogate of protection” (further split between statistical and principal surrogates); and (3) “level 2 general surrogate of protection.” Although “correlate of risk” was initially described in the context of a clinical trial, Qin’s methods have been adapted for use in the setting of outbreak investigations, as with Ebola vaccinations in the Democratic Republic of the Congo.[36] Qin’s “level 1” statistical category must adhere to the Prentice criteria, and “level 2” can be determined only through a large-scale phase 3 trial or large post-licensure studies that have the statistical power to calculate vaccine efficacy across populations.

The threshold method has also been described, in which a specific level of the immune marker is identified. Individuals who have values above the threshold are considered protected against the clinical endpoint, whereas those with levels below the threshold are susceptible.[29,37] Different statistical tests can estimate the threshold by either (1) comparing preexposure immune marker levels to disease incidence

immune marker levels in observational/cohort studies or (2) examining the proportion of vaccinated and unvaccinated individuals below the threshold and calculating the immune marker-derived vaccine efficacy.[38,39] The threshold method and variations have been used to describe specific antibody-associated levels of protection for several vaccines, including the pneumococcal conjugate vaccine,[29] meningococcal C conjugate vaccine,[40] and rubella vaccine.[39]

Although the methodologies described by Prentice, Qin, and others can be valuable to statistically validate a CoP, the foundation rests on the measurement of the immunologic marker. Assays that have a wide degree of variability and measurement error will impact the subsequent statistical calculations used in these models. Measurement errors should be carefully considered for the SARS-CoV-2 antibody assays, which have shown varying degrees of sensitivity and specificity, with no gold standard, and with various types of assays used for different COVID-19 vaccine trials and post-EUA analyses.[41,42]

THE PATH TO DEFINING CORRELATE OF PROTECTION FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 VACCINES

Determining a CoP for SARS-CoV-2 is essential to determine both individual and population level immunity, and to describe protection both after natural infection and after vaccination. Furthermore, as new variants emerge and current vaccines are adapted, a defined CoP will be useful to efficiently generate and implement vaccination programs and identify novel vaccines for use in specific populations. As described above, an important factor in describing a CoP is defining and harmonizing the clinical or efficacy endpoint. A uniform endpoint for SARS-CoV-2 has not been clearly defined, with heterogeneous outcome measures described across clinical trials and other COVID-19 studies.[43] The current literature describes the insights gained from passive immunization of monoclonal antibodies in humans as well as possible correlates of protection as shown in animal models and cohort studies (summarized in **Table 2**). RCTs, large population observational studies, and challenge trials may also aid in identifying CoPs for SARS-CoV-2. Furthermore, as new SARS-CoV-2 variants emerge, sieve analyses may be used to better understand the mechanism behind vaccine protection by using genetic and statistical approaches to measure dissimilarity between virus strains in vaccinated individuals as compared with virus strains in placebo recipients.[44] Similar approaches have been used in the field of HIV-1 vaccines and prevention.[45]

Passive Immunity

described earlier, a true CoP is an immune component that is responsible for protection against a disease endpoint and can be demonstrated by passive transfer from an immune individual to a naïve individual. For SARS-CoV-2, monoclonal antibodies (mAb) have been developed that validate the role of neutralization antibodies as a mechanism of protection against disease.[46] A double-blind, phase 1 to 3 trial investigated the use of an antibody cocktail (REGN-COV2) in nonhospitalized, symptomatic patients.[47] The cocktail is composed of 2 neutralizing human IgG1 antibodies that target the RBD of SARS-CoV-2. The interim analysis demonstrated reduction of the SARS-CoV-2 viral load in participants who received the REGN-COV2 antibody cocktail, with a more pronounced effect in individuals who had not yet produced endogenous antibody. Another randomized, placebo-controlled phase 2 study (BLAZE-1) evaluated the role of LY-CoV555, an anti-spike neutralizing mAb that binds with high affinity to the RBD region of SARS-CoV-2 in patients with mild to moderate COVID-19 disease in the outpatient setting.[48] For one of the 3 dose levels tested, there

Table 2
Proposed correlates of protection

Study Design	Authors	Natural Infection or Postimmunization	Endpoint	Correlates of Protection Identified
Passive immunity	Weinreich et al,[47] 2021 Chen et al,[48] 2021	Passive antibody transfer	SARS-CoV-2 viral load	nAb, no specific threshold determined
Animal model	McMahan et al,[50] 2021	Natural infection	SARS-CoV-2 PCR detection in BAL	50 for pseudovirus nAb titers; 100 for RBD ELISA titers; 400 for S ELISA titers
Animal model	Corbett et al,[52] 2020	Postimmunization	SARS-CoV-2 PCR detection in BAL	nAb, no specific threshold determined
Animal model	Mercado et al,[51] 2020	Postimmunization	SARS-CoV-2 PCR detection in BAL	nAb 100–250
Cohort study	Addetia et al,[58] 2020	Natural infection	SARS-CoV-2 PCR (nasopharyngeal) and clinical symptoms	nAb were protective in 3 crew members with levels of 1:174, 1:161, and 1:3082

was a significant decline in viral load by day 11 as compared with the placebo group as well as a trend toward fewer hospitalizations and lower symptom burden in patients who received LY-CoV555. These data suggest a direct beneficial role of nAb in COVID-19. Studies are ongoing to better understand if mAb would also be beneficial in preventing SARS-CoV-2 infection in close contacts of infected individuals (eg, NCT04452318), which would provide additional insight into the role of humoral immunity in protection.

Animal Models

An animal model with rhesus macaques was developed and demonstrated SARS-CoV-2 infection and replication in pneumocytes and bronchial epithelial cells.[49] All macaques produced SARS-CoV-2 anti-spike bAb and nAb responses as well as SARS-CoV-2–specific cellular immune responses. After 35 days from the initial viral infection, the macaques were rechallenged with the same dose of SARS-CoV-2. Limited levels to no levels of viral RNA were detected from bronchoalveolar lavage (BAL) or nasal swabs in the rechallenged animals, which exhibited asymptomatic or mild clinical disease. These data suggest immunologic control upon rechallenge. However, because of the small sample size and near complete protection of the animals after rechallenge, no immune correlates of protection were identified. Given the positive responses of bAb, nAb, and cellular immune activation, the relative dominance of any one of these immune markers could not be determined.

The investigators next investigated the use of IgG transfer from convalescent macaque sera to naïve macaques who were subsequently challenged with SARS-CoV-2 as well as depletion of $CD8^+$ T cells in convalescent macaques to identify a CoP.[50] The macaques who received the purified IgG were protected against the challenge infection in a dose-dependent manner. Using logistic regression models, antibody thresholds greater than 50 for pseudovirus nAb titers, 100 for RBD ELISA titers, and 400 for S ELISA titers were demonstrated to be protective. In the $CD8^+$ T-cell–depleted group, some breakthrough infections occurred, suggesting that protection is not independently related to T-cell function, but that cellular immunity likely plays a role, especially in the setting of low antibody titers.

The same macaque model was then used to assess for vaccine-induced protection with DNA vaccine candidates and Ad26 vector vaccines.[51] Viral replication in BAL fluid and nasal secretions was measured for the endpoint analyses. Because of variability in the outcomes based on the different vaccine constructs administered, the investigators were able to evaluate for immune CoPs. An inverse correlation was described between nAb (both pseudovirus and live virus nAb titers) and RNA levels from BAL and nasal secretions, suggesting nAb as an immune CoP, with nAb titers between 100 and 250 offering complete protection.

Nonhuman primate challenge models have also been used to evaluate immune responses and determine CoP after vaccination. To evaluate CoP in the context of mRNA-1273 administration, nonhuman primates were challenged with intratracheal and intranasal SARS-CoV-2 four weeks after the second vaccination with mRNA-1273.[52] The endpoint assessment was quantification of SARS-CoV-2 RNA in BAL fluid and nasal secretions. mRNA-1273–induced serum neutralization activity was then correlated with RNA from BAL and nasal secretions and was found to be negatively correlated. Given this finding, in combination with the rapid reduction in viral replication 24 to 48 hours after challenge, the investigators speculated that antibodies do serve as the primary mechanism of protection. However, a specific threshold could not be determined, because the vaccine-induced immune response offered high protection with limited variation in viral replication.

A limitation of animal models is the inability to entirely recapitulate human pathogenesis and disease. The concentration and inoculation of virus for the challenge in animals may not reflect true transmission dynamics in humans.

Cohort and Observational Studies

Cohort and observational studies can provide information about CoP through epidemiologic analyses. Several cohort studies have examined rates of reinfection within distinct populations, which can also provide clues regarding CoP.[53–55] For example, a large, prospective cohort study in the United Kingdom, the SIREN (SARS-CoV-2 Immunity and Reinfection Evaluation) study, enrolled more than 30,000 health care workers and documented SARS-CoV-2 polymerase chain reaction (PCR) and antibody testing every 2 to 4 weeks.[56] The investigators describe that the seropositive participants (those with a prior history of SARS-CoV-2 infection) had an 84% lower risk of reinfection (adjusted incidence rate ratio 0.159; 95% CI 0.13–0.19). The data provide evidence that antibodies are protective against reinfection, although the investigators did not correlate specific antibody thresholds with protection.[57]

The outbreak that occurred on a fishery boat departing from Seattle was essential in determining that nAb were protective against SARS-CoV-2. One hundred three out of 117 individuals were seronegative before departure and were subsequently infected. Three members of the crew were seropositive with high nAb (1:174, 1:161, and 1:3082) before departure and did not develop infection as evidenced by negative SARS-CoV-2 PCR from nasopharyngeal swabs and lack of clinical symptoms.[58] Thus, high nAb were associated with protection, but no exact threshold could be determined from this observational study.

Challenge Studies

Human challenge studies involve the direct and controlled infection of healthy human volunteers and have been used to investigate novel vaccine candidates. Unlike RCTs or large population-based studies, controlled human challenge studies are faster and require fewer participants to measure efficacy and immune responses. These designs have been used to study other respiratory viral pathogens like influenza[59] and HCoV-229E and have been proposed to evaluate SARS-CoV-2.[60,61] Challenge models are attractive designs to determine immune CoP, because the exact timing of natural infection and/or immunization and dose can be tightly controlled, allowing for high-resolution assessment of correlations between immune markers and efficacy endpoints.

COVID-19 human challenge studies have begun in the United Kingdom.[62] The trials are currently ongoing; no data have been released yet regarding early findings. Later stages may offer insight to discerning CoP.

Randomized Controlled Trials

RCTs are well suited to define CoP, because clear clinical endpoints are established and measures of both vaccine efficacy and immune markers are documented at defined intervals. Using the threshold method and other statistical calculations, the vaccine efficacy can be correlated with an immune marker level to determine a CoP. Current evaluation of the phase 3 data is ongoing to determine a CoP, which may vary for different vaccine constructs.

OTHER CONSIDERATIONS RELATING TO CORRELATES OF PROTECTION

Based on correlates of protection for other infectious diseases, other important factors must be considered when defining immunologic markers of protection after COVID-19

vaccination. This section reviews some of these considerations, such as host factors, the vaccine platform and target antigen, and other important immunologic aspects of the immune response to vaccination.

Host Factors

Host factors, such as age, chronic medical conditions, and the use of immunosuppressive therapies, have been shown to impact the antibody responses to COVID-19 vaccines. These factors may also impact definitions of COVID-19 postvaccination correlates or surrogates of protection.

Age is an important factor influencing humoral vaccine responses. Most of the COVID-19 vaccine phase 1/2 trials showed that the magnitude of the vaccine-induced antibody responses in older individuals is generally lower than the antibody magnitude produced by younger individuals. For example, mRNA vaccines were shown to produce lower titers of bAb and lower or similar titers of nAb in participants older than 55 to 65 years of age.[5,9] The same tendency was shown with vector vaccines, except for AZD1222, which showed similar bAb and nAb titers in all age groups.[4,8,10] BBIP-CorV, an inactivated vaccine, led to lower nAb production in those aged 60 and older.[63]

The components of the immune response postvaccination that best correlate with protection may differ quantitively and qualitatively because of immunosenescence.[64] For example, in adults up to 50 years old, serum influenza hemagglutination inhibition levels of about 1:40 correlate well with protection.[24] However, higher postvaccination titers $\geq$1:40 are common among older individuals who develop influenza, suggesting that this threshold is not protective for older individuals.[65] In older individuals, T-cell responses may be a better correlate of vaccine protection against influenza.[66]

The effect of age on COVID-19 vaccine immune correlates is currently unknown. The correlation of bAb and nAb titers after Ad26.CoV2.S was stronger in younger individuals than in those 65 years and older.[4] This suggests a variation in the immune response phenotype in older individuals, which could influence the definition of immune correlates in this population.

Data are emerging regarding other host factors that are associated with lower humoral responses to COVID-19 vaccines, such as chronic comorbidities and immunocompromised states. For example, patients undergoing maintenance hemodialysis showed significant lower bAb than controls after 2 doses of BNT162b2.[67] Individuals with chronic inflammatory disease treated with immunosuppressive therapies, in particular those receiving B-cell depletion therapy of corticosteroids, exhibit significantly lower bAb and nAb titers after mRNA vaccines.[68] Solid organ transplant recipients were shown to have poor humoral responses after mRNA vaccines,[69,70] with older individuals and those receiving antimetabolite therapy having some of the poorest humoral responses.

Immunocompromised individuals have a significantly reduced humoral response to COVID-19 vaccines. CoP in this population may be different than in the general population. For example, patients treated with B-cell depletion therapy (anti-CD20) are usually unable to mount strong humoral immune responses to COVID-19 vaccines or SARS-CoV-2 infection.[71,72] However, infected individuals on such therapy still have the ability to clear the virus, which suggest that the cellular immune response or other arms of the immune system may have an important role.

Socioeconomic status, usually closely related to other factors, such as nutritional status, risk, and frequency of exposure, has been shown to impact immune correlates for other diseases. For example, the antibody titers associated with protection against pneumococcal infection has been shown to be higher among infants who live in low-

resource settings.[29,73] The impact of socioeconomic status of environmental factors on correlates of protection from SARS-CoV-2 vaccination is unknown. However, because lower socioeconomic status has been already recognized as a risk factor for disease incidence and mortality,[74,75] it may be an important factor to consider as well when defining immune correlates after vaccination.

Vaccine Platform and Vaccine Antigens

Vaccines using different technological platforms and antigen targets may induce different qualitative and quantitative antibodies, which is another important factor to consider when establishing immune correlates for COVID-19 vaccines. This concept has been well described with other vaccines, such as those against *H influenzae* type b (polysaccharide vs conjugated vaccine) and *Bordetella pertussis* (whole cell vs acellular vaccine),[76,77] where different platforms were shown to yield different immune repertoire. COVID-19 vaccines use different technologies (mRNA, vector, subunit, inactivated) and different antigen targets (full spike, prefusion stabilized spike protein, RBD, inactivated virus), which may lead to different immune response quality and repertoire. Inactivated vaccines have the unique characteristic of presenting the whole virus to the immune system, which leads to the production of antibodies other than anti-spike, such as antinucleocapsid.[15] Even if the main target of nAb against SARS-CoV-2 appears to be the spike protein,[78] the antibody repertoire and diversity produced by inactivated vaccines may have immunologic significance against SARS-CoV-2 and the circulating variants that possess critical spike protein mutations.[79,80]

Immunologic Factors

The immune mechanisms leading to protection are complex and usually involve a combination of both humoral and cellular responses.[81] The impact of the relative importance of these 2 branches of the adaptive immune system for protection against SARS-CoV-2 is still unknown. Many studies have shown that antibodies are associated with protection against reinfection,[56] but few have evaluated the implication of cellular immune response on reinfection. COVID-19 vaccines have been shown to induce strong humoral immunity, but T-cell responses were also elicited after vaccination.[4,5] In a nonhumate primate study using an adenovirus-based vaccine (Ad26-S.PP), T-cell responses did not seem to correlate with protection.[51] It is still unknown if the cellular response contributes to protection in humans; however, there are clues that cellular responses are important. For example, the clinical protection from BNT162 against COVID-19 may start as soon as 12 days after the first dose.[82] However, nAb titers within the first 21 days after vaccination are low or undetectable.[9] Researchers showed that 3 weeks after the first BNT162b2 dose, nAb were not detected, but strong responses of RBD and spike antibodies with Fc-mediated effector functions and cellular responses largely by $CD4^+$ T-cell responses were seen.[83]

Mucosal immunity is another possible key component of COVID-19 protection, as SARS-CoV-2 initially infects the respiratory mucosal surfaces.[84] However, the mucosal immunity that results from COVID-19 natural infection and vaccination and its implication in defining COVID-19 correlates of protection remain largely unknown.

SUMMARY

The vaccine-induced CoP for SARS-CoV-2 has yet to be defined. When establishing a CoP, it will be essential not only to identify the appropriate immune marker but also to properly define the endpoint measure (eg, clinical disease, especially severe illness; transmission, SARS-CoV-2 PCR positivity) and understand the nuances of CoP in

terms of host and antigen characteristics. Furthermore, standardized assays for the chosen immune marker or markers must be established in order to ensure comparability between disparate vaccine platforms and conditions of use. Ideally, these assays should be a test that is relatively easy to perform and does not require specialized equipment or reagents to promote easy scalability across the globe. Much of the focus has been to determine a humoral CoP, in part because of the ease of collection and evaluation, although cellular responses are also likely to be important.

As new public health challenges relating to COVID-19 emerge, such as variant strains, waning vaccine efficacy over time, and decreased vaccine efficacy for special populations (such as immunocompromised hosts), it is important to determine a CoP to allow accurate bridging studies for special populations and against variants of concern. In the context of a global pandemic with dynamic threats to public health, large-scale phase 3 clinical trials are inefficient to rapidly assess novel vaccine candidates for variant strains or for special populations, because these trials are slow and costly. Defining a practical CoP will aid in efficiently conducting future assessments to further describe protection for individuals and on a population level for surveillance.

CLINICS CARE POINTS

- The clinical utility of a correlate or surrogate of vaccine-induced immunity would be useful to assess individual and population-level protection, and allow for new vaccine candidates to be tested without costly and large efficacy trials.
- Further standardization of laboratory SARS-CoV-2 serologic tests are an equally important step to be able to use a correlate of protection in clinical practice.
- Clinicians and laboratorians must acknowledge that different vaccine platforms, circulating variants, and host factors may impact the correlate of the protection, and that a single marker of immunity may not be able specifically predict protection for all scenarios.

REFERENCES

1. COVID-19 vaccine tracker. Available at: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Accessed April 25, 2021.
2. Plotkin SA. Immunologic correlates of protection induced by vaccination. Pediatr Infect Dis J 2001;20:63–75.
3. Immunogenicity of clinically relevant SARS-CoV-2 vaccines in nonhuman primates and humans | Science Advances. Available at: https://advances.sciencemag.org/content/7/12/eabe8065. Accessed April 25, 2021.
4. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. New Engl J Med 2021;0. https://doi.org/10.1056/NEJMoa2034201.
5. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. New Engl J Med 2020;0. https://doi.org/10.1056/NEJMoa2022483.
6. Logunov DY, Dolzhikova IV, Zubkova OV, 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.
7. Zhu F-C, Guan X-H, Li Y-H, 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.
8. Folegatti PM, Ewer KJ, Aley PK. 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;396:467–78.
9. Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. New Engl J Med 2020;383:2439–50.
10. Zhang Y, Zeng G, Pan H, 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.
11. Doria-Rose N, Suthar MS, Makowski M, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. New England Journal of Medicine 2021. https://doi.org/10.1056/NEJMc2103916.
12. Pfizer and BioNTech confirm high efficacy and no serious safety concerns through up to six months following second dose in updated topline analysis of landmark COVID-19 vaccine study. 2021. Available at: https://www.businesswire.com/news/home/20210401005365/en/Pfizer-and-BioNTech-Confirm-High-Efficacy-and-No-Serious-Safety-Concerns-Through-Up-to-Six-Months-Following-Second-Dose-in-Updated-Topline-Analysis-of-Landmark-COVID-19-Vaccine-Study. Accessed May 3, 2021.
13. Moderna provides clinical and supply updates on COVID-19 vaccine program ahead of 2nd annual vaccines day | Moderna, Inc., (n.d.). Available at: https://investors.modernatx.com/news-releases/news-release-details/moderna-provides-clinical-and-supply-updates-covid-19-vaccine/. Accessed May 20, 2021.
14. Klasse PJ, Nixon DF, Moore JP. Immunogenicity of clinically relevant SARS-CoV-2 vaccines in nonhuman primates and humans. Sci Adv 2021;7:eabe8065.
15. Ella R, Reddy S, Jogdand H, 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. https://doi.org/10.1016/S1473-3099(21)00070-0.
16. Yang S, Li Y, Dai L, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis 2021. https://doi.org/10.1016/S1473-3099(21)00127-4.
17. Seow J, Graham C, Merrick B, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat Microbiol 2020;5:1598–607.
18. Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. New Engl J Med 2021;384:1372–4.
19. CDC. Cases, Data, and surveillance. Centers for Disease Control and Prevention; 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html. Accessed April 30, 2021.
20. Shen X, Tang H, Pajon R, et al. Neutralization of SARS-CoV-2 variants B.1.429 and B.1.351. New Engl J Med 2021;0. https://doi.org/10.1056/NEJMc2103740.
21. Wu K, Werner AP, Koch M, et al. Serum neutralizing activity elicited by mRNA-1273 vaccine. New Engl J Med 2021;384:1468–70.

22. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. New Engl J Med 2021;0. https://doi.org/10.1056/NEJMoa2102214.
23. Lustig Y, Nemet I, Kliker L, et al. Neutralizing response against variants after SARS-CoV-2 infection and one dose of BNT162b2. New Engl J Med 2021;0. https://doi.org/10.1056/NEJMc2104036.
24. Plotkin SA, Plotkin SA. Correlates of vaccine-induced immunity. Clin Infect Dis 2008;47:401–9. https://doi.org/10.1086/589862.
25. Qin L, Gilbert PB, Corey L, et al. A framework for assessing immunological correlates of protection in vaccine trials. J Infect Dis 2007;196:1304–12.
26. Plotkin SA, Gilbert PB. Nomenclature for immune correlates of protection after vaccination. Clin Infect Dis 2012;54:1615–7.
27. Denoël PA, Goldblatt D, de Vleeschauwer I, et al. Quality of the Haemophilus influenzae type b (Hib) antibody response induced by diphtheria-tetanus-acellular pertussis/Hib combination vaccines. Clin Vaccin Immunol 2007;14:1362–9.
28. Jack AD, Hall AJ, Maine N, et al. What level of hepatitis B antibody is protective? J Infect Dis 1999;179:489–92.
29. Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of antipneumococcal capsular polysaccharide antibodies. Vaccine 2007;25:3816–26.
30. Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reevaluation of protective titers. J Infect Dis 1990;162:1036–42.
31. Plebani A, Fischer MB, Meini A, et al. T cell activity and cytokine production in X-linked agammaglobulinemia: implications for vaccination strategies. Int Arch Allergy Immunol 1997;114:90–3.
32. Gans HA. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 Months. JAMA 1998;280:527.
33. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8:431–40.
34. World Health Organization. Correlates of vaccine-induced protection: methods and implications. 2013. Available at: https://apps.who.int/iris/bitstream/handle/10665/84288/WHO_IVB_13.01_eng.pdf. Accessed April 13, 2021.
35. Schatzkin A, Freedman LS, Dorgan J, et al. Using and interpreting surrogate endpoints in cancer research. IARC Sci Publ.; 1997. p. 265–71.
36. Halloran ME, Longini IM, Gilbert PB. Designing a study of correlates of risk for Ebola vaccination. Am J Epidemiol 2020;189:747–54.
37. Chen X, Bailleux F, Desai K, et al. A threshold method for immunological correlates of protection. BMC Med Res Methodol 2013;13:29.
38. Siber GR. Methods for estimating serological correlates of protection. Dev Biol Stand 1997;89:283–96.
39. Skendzel LP. Rubella immunity. Defining the level of protective antibody. Am J Clin Pathol 1996;106:170–4.
40. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England, (n.d.). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC193909/. Accessed April 15, 2021.
41. Galipeau Y, Greig M, Liu G, et al. Humoral responses and serological assays in SARS-CoV-2 infections. Front Immunol 2020;11. https://doi.org/10.3389/fimmu.2020.610688.
42. Whitman JD, Hiatt J, Mowery CT, et al. Evaluation of SARS-CoV-2 serology assays reveals a range of test performance. Nat Biotechnol 2020;38:1174–83.

43. Mehrotra DV, Janes HE, Fleming TR, et al. Clinical endpoints for evaluating efficacy in COVID-19 vaccine trials. Ann Intern Med 2020;174:221–8.
44. Rolland M, Gilbert PB. Sieve analysis to understand how SARS-CoV-2 diversity can impact vaccine protection. PLOS Pathog 2021;17:e1009406.
45. Corey L, Gilbert PB, Juraska M, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. New Engl J Med 2021;384:1003–14.
46. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol 2021;1–12.
47. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. New Engl J Med 2021;384:238–51.
48. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. New Engl J Med 2021;384:229–37.
49. Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science 2020;369:812–7.
50. McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature 2021;590:630–4.
51. Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020;586:583–8.
52. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. New Engl J Med 2020;383:1544–55.
53. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. New Engl J Med 2021;384:533–40.
54. Hansen CH, Michlmayr D, Gubbels SM, et al. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. The Lancet 2021;397:1204–12.
55. Harvey RA, Rassen JA, Kabelac CA, et al. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 2021. https://doi.org/10.1001/jamainternmed.2021.0366.
56. Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet 2021;397:1459–69.
57. Krammer F. Correlates of protection from SARS-CoV-2 infection. Lancet 2021;397:1421–3.
58. Addetia A, Crawford KHD, Dingens A, et al. Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with a high attack rate. J Clin Microbiol 2020;58. https://doi.org/10.1128/JCM.02107-20.
59. Sherman AC, Mehta A, Dickert NW, et al. The future of flu: a review of the human challenge model and systems biology for advancement of influenza vaccinology. Front Cell. Infect. Microbiol. 2019;9. https://doi.org/10.3389/fcimb.2019.00107. Available at:.
60. Deming ME, Michael NL, Robb M, et al. Accelerating development of SARS-CoV-2 vaccines — the role for controlled human infection models. New Engl J Med 2020;383:e63.
61. Callow KA, Parry HF, Sergeant M, et al. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect 1990;105:435–46.
62. Kirby T. COVID-19 human challenge studies in the UK. Lancet Respir Med 2020;8:e96.
63. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. The Lancet Infect Dis 2021;21:39–51.

64. Grubeck-Loebenstein B, Della Bella S, Iorio AM, et al. Immunosenescence and vaccine failure in the elderly. Aging Clin Exp Res 2009;21:201–9.
65. Gravenstein S, Drinka P, Duthie EH, et al. Efficacy of an influenza hemagglutinin-diphtheria toxoid conjugate vaccine in elderly nursing home subjects during an influenza outbreak. J Am Geriatr Soc 1994;42:245–51.
66. McElhaney JE, Xie D, Hager WD, et al. T cell responses are better correlates of vaccine protection in the elderly. J Immunol 2006;176:6333–9.
67. Grupper A, Sharon N, Finn T, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis,. CJASN 2021. https://doi.org/10.2215/CJN.03500321.
68. Glucocorticoids and B Cell depleting agents substantially impair immunogenicity of mRNA vaccines to SARS-CoV-2 | medRxiv. Available at: https://www.medrxiv.org/content/10.1101/2021.04.05.21254656v2. Accessed April 30, 2021.
69. A. Grupper, L. Rabinowich, D. Schwartz, et al, Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus, Am J Transplant. Available at: 10.1111/ajt.16615.
70. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA 2021. https://doi.org/10.1001/jama.2021.4385.
71. Fallet B, Kyburz D, Walker UA. Mild course of COVID-19 and spontaneous virus clearance in a patient with depleted peripheral blood b cells due to rituximab treatment. Arthritis Rheumatol 2020;72:1581–2.
72. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021. https://doi.org/10.1182/blood.2021011568.
73. Jódar L, Butler J, Carlone G, et al. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine 2003;21:3265–72.
74. Karmakar M, Lantz PM, Tipirneni R. Association of social and demographic factors with COVID-19 incidence and death rates in the US. JAMA Netw Open 2021;4:e2036462.
75. Clouston SAP, Natale G, Link BG. Socioeconomic inequalities in the spread of coronavirus-19 in the United States: a examination of the emergence of social inequalities. Soc Sci Med 2021;268:113554.
76. Edwards KM, Meade BD, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. Pediatrics 1995;96:548–57.
77. Jelonek MT, Chang SJ, Chiu CY, et al. Comparison of naturally acquired and vaccine-induced antibodies to Haemophilus influenzae type b capsular polysaccharide. Infect Immun 1993;61:5345–50.
78. Barnes CO, Jette CA, Abernathy ME, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature 2020;588:682–7.
79. Huang B, Dai L, Wang H, et al. Serum sample neutralisation of BBIBP-CorV and ZF2001 vaccines to SARS-CoV-2 501Y.V2. Lancet Microbe 2021;0. https://doi.org/10.1016/S2666-5247(21)00082-3.
80. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 variants — clinical, public health, and vaccine implications. New Engl J Med 2021;0. https://doi.org/10.1056/NEJMc2100362.
81. Amanna IJ, Slifka MK. Contributions of humoral and cellular immunity to vaccine-induced protection in humans. Virology 2011;411:206–15.
82. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New Engl J Med 2020;383:2603–15.

83. Tauzin A, Nayrac M, Benlarbi M, et al. A single BNT162b2 mRNA dose elicits antibodies with Fc-mediated effector functions and boost pre-existing humoral and T cell responses. BioRxiv 2021;2021. https://doi.org/10.1101/2021.03.18.435972.
84. Russell MW, Moldoveanu Z, Ogra PL, et al. Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. Front Immunol 2020;11. https://doi.org/10.3389/fimmu.2020.611337.
85. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. New Engl J Med 2020. https://doi.org/10.1056/NEJMoa2028436.
86. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020;396:1979–93.
87. Wu Z, Hu Y, Xu M, 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;0. https://doi.org/10.1016/S1473-3099(20)30987-7.
88. Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report | medRxiv. Available at: https://www.medrxiv.org/content/10.1101/2020.12.21.20248643v1. Accessed April 30, 2021.
89. Xia S, Duan K, Zhang Y, 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.