is also an exception for cases in which exchange is "technically infeasible." In addition, the HHS Office of Inspector General (OIG), which has been tasked with investigating information blocking and enforcing compliance with information-blocking policies, has yet to issue its final rule on this topic. Since it can take 18 months for the OIG to issue regulations, the industry will effectively be granted all or part of the delay it's requesting. Furthermore, if penalties for violations are challenged in court, regulators may have difficulty proving that specific actions by providers constituted information blocking.

*An audio interview with Dr. Blumenthal is available at NEJM.org*

These exceptions and regulatory delays raise legitimate concerns about whether the new rule will have sufficient punch to overcome market disincentives to information exchange. Beyond this issue, the ONC's Cures Act rule, by providing an exception for perceived threats to the privacy of patient data, highlights again the need for a comprehensive reworking of U.S. health information privacy laws. Requirements to share personal health data raise threats to privacy that weren't foreseeable when HIPAA was passed, given our rapidly evolving digital world. Nevertheless, if implemented effectively, the October 6 regulation has the potential to move the country closer to the HITECH Act's ultimate vision: a national capability for health information exchange. Such an outcome would most likely be welcomed by patients and clinicians alike and could both improve the quality of health care and reduce its cost.

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# A Covid-19 Milestone Attained — A Correlate of Protection for Vaccines

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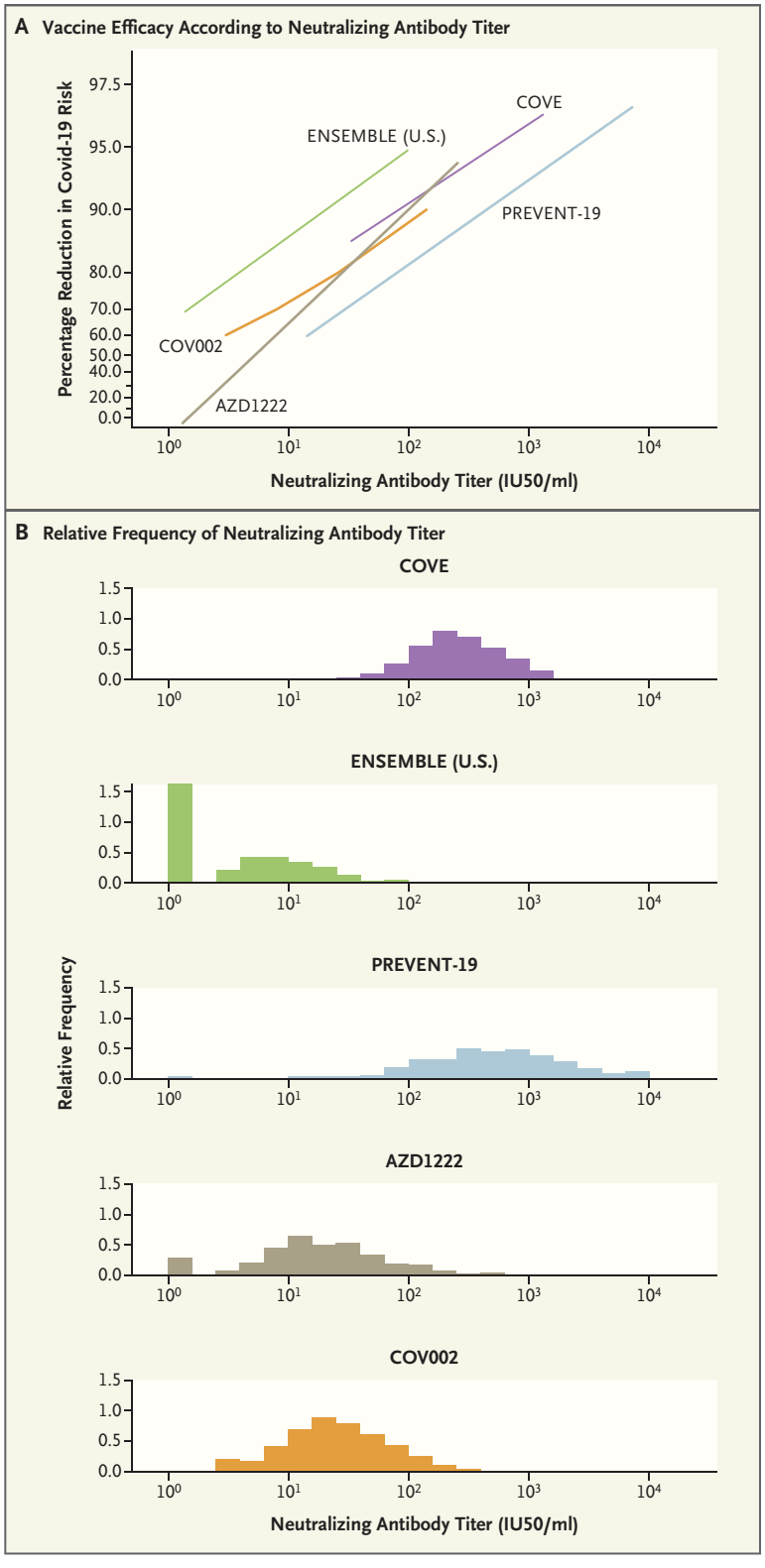
The rapid identification of a correlate of protection (CoP) for Covid-19 vaccines — on the basis of several harmonized randomized phase 3 trials using common validated assays — constitutes an important success in vaccinology. A CoP is an immune marker that can be used to reliably predict a vaccine's level of efficacy in preventing a clinically relevant outcome. The level of this marker is measured shortly (2 to 4 weeks) after completion of the vaccination regimen and provides an actionable basis for decisions such as regulatory approval of an efficacious vaccine for a new population that was not included in the pivotal randomized phase 3 trials, or approval of a refined version of a vaccine that was previously shown to be efficacious.

Once established, a CoP can be used as the primary end point for provisional or full approval of a vaccine for a specific use, if a clinical immunobridging study confirms that high enough levels of the CoP are achieved. For example, the Food and Drug Administration (FDA) extended approval of the mRNA-1273 (Moderna) and BNT162b2 (Pfizer–BioNTech) Covid vaccines from older to younger age groups on the basis of a comparison of neutralizing antibody titers. Moreover, FDA guidance and a European Medicines Agency declaration from the International Coalition of Medicines Regulatory Authorities recommended that approval of new vaccine strains and booster doses




**Correlation between Covid-19 Vaccine Efficacy and Neutralizing Antibody Titers.**

Panel A shows the vaccine efficacy observed among participants in five randomized, controlled trials of Covid-19 vaccines who tested negative for SARS-CoV-2 at baseline, according to the postvaccination neutralizing antibody titers of the trial participants. Vaccine efficacy was defined as the percentage reduction in the average risk of Covid-19 among vaccine recipients, as compared with the risk among placebo recipients, and was estimated with the use of a marginalized Cox proportional-hazards model.[1] The data are from trials of four vaccines: COVE for mRNA-1273,[1] ENSEMBLE for Ad26.COV2.S (U.S. study sites only),[2] PREVENT-19 for NVX-CoV2373,[3] AZD1222 for ChAdOx1 nCoV-19, and COV002 also for ChAdOx1 nCoV-19.[4] Pseudovirus 50% neutralizing antibody titers were measured on day 57 after the first vaccine dose in COVE, AZD1222, and COV002; on day 29 in ENSEMBLE (U.S.); and on day 35 in PREVENT-19. Follow-up periods for the assessment of vaccine efficacy ranged from 2 months to 5 months after vaccination. Curves are plotted over the 2.5th percentile to the 97.5th percentile of antibody titer for COVE, ENSEMBLE (U.S.), PREVENT-19, and AZD1222, and over 3 to 140 International Units 50% inhibitory dose (IU50) per milliliter for COV002. All analyses were adjusted for the baseline risk score; COVE also adjusted for coexisting conditions and racial or ethnic background, and AZD1222 adjusted for age. Panel B shows histograms (relative frequencies) of neutralizing antibody titers in these trials.

be based on clinical immunobridging studies showing noninferiority or superiority with respect to a CoP end point. Other applications of a CoP include ensuring vaccine consistency from lot to lot, supporting recommendations for coadministration with other vaccines, and determination of appropriate expiration dates.

Confusion about CoPs is understandable, given the myriad complicated issues involved in identi-

fying them and the fact that different uses for CoPs require different validation measures. Evidence that a marker is a CoP is generally derived from five main sources: natural history studies that correlate infection-induced immune responses with outcomes; vaccine-challenge studies in animals or humans; studies that experimentally manipulate the immune marker to directly assess mechanistic causation (e.g., by administering various vaccine doses or using passive antibody transfer); efficacy trials that quantify the relationship between vaccine efficacy and the level of the immune marker in individual vaccine recipients; and meta-analyses of series of efficacy trials that correlate vaccine efficacy with the mean immune-marker level.

Strong evidence has been generated from all five of these sources for both serum anti-spike IgG concentration and anti–SARS-CoV-2 neutralizing antibody titer as CoPs for vaccines against symptomatic Covid-19; for brevity, we focus here on the neutralizing antibody titer. Meta-analyses have established high correlations between the standardized mean titer and vaccine efficacy, and the neutralizing antibody titer has consistently been shown to be a mechanistic CoP in challenge studies in nonhuman primates. The U.S. government's COVID-19 Vaccine Correlates of Protection Program assessed CoPs in phase 3 trials of four vaccines: COVE for mRNA-1273,[1] ENSEMBLE for Ad26.COV2.S,[2] PREVENT-19 for NVX-CoV2373,[3] AZD1222 (United States/Chile/Peru) for ChAdOx1 nCoV-19, and COV002 (United Kingdom) also for ChAdOx1 nCoV-19.[4] Vaccine efficacy always markedly increased with the titer (see graphs).

Though we believe the evidence strongly supports the designation of the neutralizing antibody titer as a CoP, at recent meetings, key opinion leaders stressed the lack of a CoP. Why does their interpretation of the evidence differ from ours? One reason may be the use of different definitions for a deployable CoP. Often, an immune marker can be used as a CoP because a threshold level can be identified that convincingly discriminates between vaccine recipients with breakthrough Covid-19 illness and those without SARS-CoV-2 infection. For infections in which viremia is key to pathogenesis (e.g., polio), we can identify such a threshold because sufficient levels of antibody can prevent dissemination of the pathogen through the bloodstream. The same does not hold for Covid-19, however, since it is caused by a mucosal infection that can be invasive.

***Although a threshold CoP is ideal because it can provide an absolute benchmark for approving a vaccine without the need for a comparator vaccine, this goal is probably unattainable for Covid-19.***

Although a threshold CoP is ideal because it can provide an absolute benchmark for approving a vaccine without the need for a comparator vaccine, this goal is probably unattainable for Covid-19, because the amount of virus to which trial participants are exposed varies widely and because CoPs must be capable of predicting vaccine efficacy over a period of postvaccination follow-up during which antibody levels decline. These factors insert uncontrollable variability into the analysis such that even if neutralizing antibodies were a perfect mechanistic CoP, the titer values among people with Covid-19 would overlap with those among people without SARS-CoV-2 infection, as has been observed in all trials. Yet these partial separations, combined with evidence from all five types of sources defined above, can validate a nonthreshold CoP. And such a CoP can be used to predict vaccine efficacy by averaging the estimated vaccine efficacy-by-titer curve (see graphs) over the distribution of titers.

In the phase 3 correlates analyses, investigators studied the titer of neutralizing antibodies against the original vaccine strain as a CoP against Covid-19 caused by circulating strains, which were from the original or variant lineages before the emergence of delta (B.1.617.2) and omicron (B.1.1.529). Going forward, defining and validating the antibody-titer CoP for omicron and for fu-

ture lineages will be critical. In ongoing correlates studies of long-term follow-up from the phase 3 trials, researchers are measuring titers against circulating lineages before and after booster doses, enabling these analyses, including the determination of whether higher antibody levels are needed for protection against omicron subvariants than for protection against pre-delta viruses. This validation is important given that decisions such as booster recommendations depend on an omicron-specific titer CoP: in its June 28, 2022, meeting, the FDA vaccine advisory board used these titers as the key end point for comparing vaccine constructs.

The correlates analyses focused on a single clinical outcome in the phase 3 trials: symptomatic Covid-19. This clinical end point is appropriate as a basis for decisions. However, CoPs may vary with the outcome of interest and so should be assessed specifically for distinct end points. Ongoing U.S. government-supported correlates research for the phase 3 trials addresses the most important outcome: severe Covid-19. If relatively few antibodies are needed to prevent severe disease, these analyses could define lower bars for approvals based on clinical immunobridging findings. Whereas neutralizing antibodies are the mechanistic CoP against infection, other immune responses, including production of Fc-effector antibody functions and T-cell functions, play a role in controlling infection if it occurs, and researchers should pursue correlates that depend on other immunologic functions.

In addition, mucosal anti-spike IgA was a correlate for prevention of acquisition of omicron infection as determined by positive results on polymerase-chain-reaction testing for viral RNA in triple-vaccinated health care workers,[5] raising the question of whether mucosal markers are the mechanistic CoP and serum titers a nonmechanistic (noncausal) CoP. But though the serum titer may not be a mechanistic CoP against initial acquisition of infection, it is probably such a CoP for end points reflecting the presence of invasive disease. In future research, various time points for measuring antibodies and T cells should also be studied.

Both binding and neutralizing antibodies have been accepted as CoPs by regulators and have provided very high value for vaccine research, development, and use for more than a dozen vaccines against diverse viral or bacterial diseases. Large studies have generated robust evidence that these antibody markers are CoPs for Covid-19 vaccines — indeed, more evidence than is available for many CoPs for other types of vaccines. The FDA has accepted the titer of neutralizing antibodies against likely circulating strains as a CoP for multiple Covid-19 vaccines. Many open questions remain, given that this CoP was identified in trials involving people who had not previously been infected with SARS-CoV-2 and who received intramuscular, spike-only vaccines and were then exposed to pre-delta viruses. Nevertheless, while pursuing the next milestones — identifying CoPs for new viral variants, for new populations including previously infected people, for new vaccine classes, and for various aspects of Covid-19 disease (e.g., symptom types, durations, and severities) — we should acknowledge that neutralizing antibodies are the current CoP for vaccine efficacy, which merits use for near-term decisions about vaccines.

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