INFECTIOUS DISEASES

Correlates of protection via modeling

A recent study proposes a mathematical model of SARS-CoV-2 to help identify mechanistic correlates of protection, which can be used to assist in determining vaccine efficacy.

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Establishing correlates of protection (COP) for vaccine preventable infections is an important public health priority. COP are specific, measurable components of a pathogen-specific immune response that are statistically proven to surpass a quantitative threshold required for protection[1], and they may be identified after natural infection or vaccination. COP are typically validated with symptomatic illness as an endpoint, but they can also be applied to other outcomes, such as asymptomatic infection, severe disease or transmissibility. Validated COP are used as surrogate endpoints in vaccine trials;[2] such surrogate endpoints are useful because they allow rapid ascertainment of vaccine efficacy without having to rely on clinical infection endpoints, which occur in only a fraction of participants. All participants contribute an endpoint in trials with pre-assigned surrogate endpoints, and such trials can be adequately powered with fewer people and completed in a shorter time at less expense. Identifying COP is, however, a challenging task. An even greater challenge is to define mechanistic correlates of protection (mCOP) for a pathogen. mCOP are COP that are necessary and sufficient for protection against infection-related outcomes. mCOP remain poorly characterized for most human infections. For severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previous work in non-human primates suggests that high neutralizing antibody levels prevent infection, whereas adequate numbers of functional cytolytic T cells limit severity once viral replication is established in the airways[3]. However, these mCOP have yet to be established in humans. Writing in *Nature Computational Science*, Pranesh Padmanabhan and colleagues report that they have developed a mathematical framework to interpret complex multidimensional data to help identify mCOP for SARS-CoV-2[4].

Establishing COP requires diligent trial planning with strategically timed immunologic measurements, skilled biostatistical analysis and some luck, in the sense that the trial data employed for analysis must demonstrate vaccine efficacy but with sufficient numbers of breakthrough infections to power the analysis. COP were established for SARS-CoV-2 using trial outcomes as the measurement unit. Fortunately, trials of nine vaccines showed efficacy varying from 50% to 95% (ref. [5]). Vaccine efficacy correlated with average levels of neutralizing antibody among participants in the intervention arms of each study. In addition, analysis of a phase III clinical trial of the mRNA-1273 vaccine showed that an individual's post-vaccination neutralizing antibody titer can be used as a correlate of efficacy[2]. Because of a wide range of observed antibody titers, neutralizing antibody levels are now available as a practical surrogate endpoint and were used to help justify the Food and Drug Administration's Emergency Use Authorization for third doses of coronavirus disease 2019 (COVID-19) vaccines, which, in turn, allowed rapid and widespread access to booster shots. Neutralizing antibodies are less expensive and more convenient to measure than B- and T-cell responses against specific viral peptides. There is also plausibility that they can prevent infection at mucosal barriers of entry[6]. Yet, it remains uncertain whether neutralizing antibodies are true standalone mCOP.

Identification of mCOP requires a multidisciplinary approach (Fig. 1). Animal infection models allow systematic knockout of different arms of the immune response to isolate the impact of multiple humoral or cell-mediated specific responses on prevention or mitigation of infection. However, animal models fail to recapitulate all features of human infection and must be corroborated with relevant human

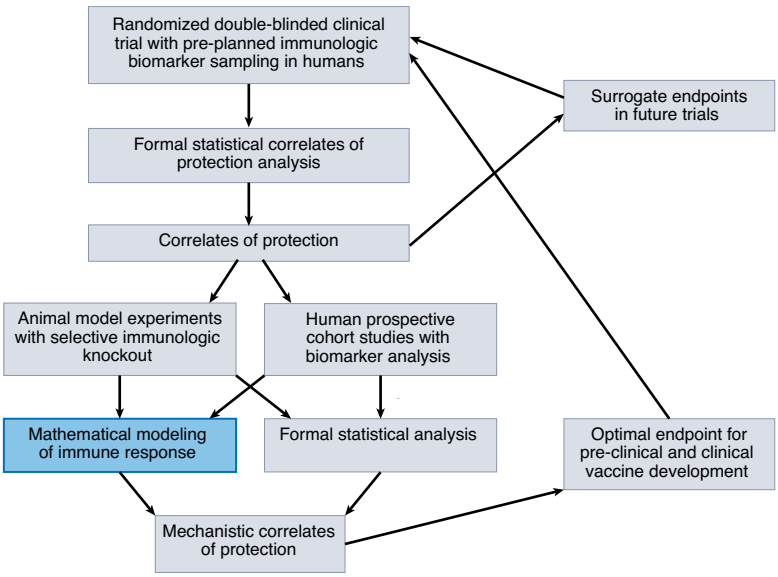

Fig. 1 | A new role of mathematical modeling in establishing mechanistic correlates of protection. The pathway to identification of mechanistic correlates of protection is shown. While statistical analysis of appropriate vaccine clinical trial data is necessary and sufficient for identification of correlates of protection, animal models of infection coupled with confirmatory human cohort studies, as well as statistical analysis and mathematical modeling are also needed to identify mechanistic correlates of protection.

cohorts. Moreover, certain crucial effector populations such as tissue-resident T cells are not measured in most COP studies due to technical challenges of sampling in deep tissues[7]. Another complication is that humoral and cellular immune responses are often mechanistically intertwined and temporally colinear[8]. An optimal mCOP might include a composite score capturing several arms of pathogen-specific immunity. Finally, immune responses are spatially dynamic within tissue and nonlinear over time, which necessitates mathematical modeling for complete interpretation of serial longitudinal immune data. While neutralizing antibodies may be a valid COP early after vaccination, conditions may change at later time points if cellular and humoral immunity decay at different rates[9]. Tissue-resident cellular populations theoretically could become more important as antibody levels decrease. Moreover, multiple clones of virus-specific antibodies and T cells are generated post infection, and their cumulative benefit is often ignored[10,11].

To this end, the work by Padmanabhan and colleagues represents a promising initial framework for analyzing mCOP[4]. The authors constructed a shape space that fuses dose–response curves of multiple neutralizing antibodies into a single graph linking plasma dilution with degree of viral inhibition. This approach allows an estimation of the cumulative potency of the entire humoral immune response rather than just the dominant antibody. The authors coupled this estimation of antiviral potency with a within-host mathematical model to estimate threshold levels of antibody combinations at which infection is predicted to extinguish. Model output is compatible with studies linking viral inhibition of sampled plasma with vaccine efficacy[5].

By considering the impact of all circulating antibodies as well as the nonlinearity of endogenous immune pressure against SARS-CoV-2, the proposed approach partially accounts for the true complexity of a protective response against SARS-CoV-2. A current limitation is the exclusion of all cellular components of immunity. The model also does not consider immune waning following vaccination or keep pace with loss of antibody protection against new variants of concern. Its future utility will be increased with validation against viral and immune dynamic data from breakthrough infections in vaccinated people.

While it is currently beyond the scope of mathematical modeling to define mCOP for SARS-CoV-2, Padmanabhan and colleagues establish a useful and logical theoretical framework for linking high dimensional, nonlinear virologic and immunologic data following vaccination. Nonlinear mixed-effects approaches are now commonly used to compare dozens of complex models (each representing a mutually exclusive set of scientific hypotheses) against multiple streams of contemporaneously gathered virologic and immune data. These models are ranked based on their likelihood of explaining the data according to data fit and parsimony. Given appropriate datasets in the future, further iterations of models will be invaluable for helping delineate how vaccines induce various levels of protection. ❐

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Competing interests

The author declares no competing interests.