Accelerating model-informed decisions for COVID-19 vaccine candidates using a model-based meta-analysis approach

Bhargava Kandala,[a,*,1] Nele Plock,[b,1] Akshita Chawla,[a,1] Anna Largajolli,[b,1] Seth Robey,[a,1] Kenny Watson,[b] Raj Thatavarti,[b] Sheri A. Dubey,[a] S.Y. Amy Cheung,[b] Rik de Greef,[b] Julie Stone,[a] and Jeffrey R. Sachs[a]

[a]Merck & Co., Inc.; Rahway, NJ, USA
[b]Certara; Princeton, NJ, USA

eBioMedicine 2022;84: 104264
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104264

Summary

Background The COVID-19 pandemic has increased the need for innovative quantitative decision tools to support rapid development of safe and efficacious vaccines against SARS-CoV-2. To meet that need, we developed and applied a model-based meta-analysis (MBMA) approach integrating non-clinical and clinical immunogenicity and protection data.

Methods A systematic literature review identified studies of vaccines against SARS-CoV-2 in rhesus macaques (RM) and humans. Summary-level data of 13 RM and 8 clinical trials were used in the analysis. A RM MBMA model was developed to quantify the relationship between serum neutralizing (SN) titres after vaccination and peak viral load (VL) post-challenge in RM. The translation of the RM MBMA model to a clinical protection model was then carried out to predict clinical efficacies based on RM data alone. Subsequently, clinical SN and efficacy data were integrated to develop three predictive models of efficacy – a calibrated RM MBMA, a joint (RM-Clinical) MBMA, and the clinical MBMA model. The three models were leveraged to predict efficacies of vaccine candidates not included in the model and efficacies against newer strains of SARS-CoV-2.

Findings Clinical efficacies predicted based on RM data alone were in reasonable agreement with the reported data. The SN titre predicted to provide 50% efficacy was estimated to be about 21% of the mean human convalescent titre level, and that value was consistent across the three models. Clinical efficacies predicted from the MBMA models agreed with reported efficacies for two vaccine candidates (BBV152 and CoronaVac) not included in the modelling and for efficacies against delta variant.

Interpretation The three MBMA models are predictive of protection against SARS-CoV-2 and provide a translational framework to enable early Go/No-Go and study design decisions using non-clinical and/or limited clinical immunogenicity data in the development of novel SARS-CoV-2 vaccines.

Funding This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Keywords: COVID-19; Vaccines; SARS-CoV-2; Systematic literature search; Model-based meta-analysis (MBMA); Modelling; Modelling and simulation

Introduction

The COVID-19 pandemic has caused significant morbidity and mortality across the world and is unlikely to end until effective vaccines are administered globally to reduce transmission, prevent hospitalization, severe disease, and death.[9] Several COVID-19 vaccines have currently been authorized, and/or approved. However, with the emergence of newer variants of concern and waning immunity[10] in the currently vaccinated population, there is still a need for newer vaccines to be developed, and for optimization of existing vaccines. Conduct of efficacy trials is lengthy and challenging to perform in a progressively more immunized population, necessitating reliable methods for prioritizing

*Corresponding author.
E-mail address: bhargava.kandala@merck.com (B. Kandala).
[1] These authors contributed equally to this work.

Research in context

Evidence before this study

With the emergence of newer strains of SARS-CoV-2, there is a need for booster shots of existing vaccines and/or newer vaccines to be developed rapidly while maintaining adequate safety and efficacy. Establishing immune correlates of protection (CoP) and the availability of quantitative models predictive of clinical efficacy could substantially help address that need. A (non-systematic) literature review of PubMed (LitCovid), and preprint servers (MedRxiv, BioRxiv) between June, 2020 and October, 2021 revealed 3 publications[1-3] that establish neutralizing titres as potential CoP in RM, and 4 publications[4-7] that propose neutralizing titres as a CoP in humans, with two establishing a 50% protective titre against SARS-CoV-2 through quantitative models of immune protection.[4,7] However, the RM publications to date do not integrate available vaccine protection data across different platforms, and none of the publications describe the translation of non-clinical vaccine data and its integration with early clinical immunogenicity data to inform early Go/No-Go and study design decisions for novel vaccine development.

Added value of this study

We leverage a model-based meta-analysis (MBMA) approach using emerging non-clinical and clinical data; this enables decisions to be made based on the totality of evidence[8] through the integration of prior information across different vaccine mechanisms, dose-levels, regimens, endpoints, assay methods, and study designs. We demonstrate that neutralizing titres are a potential CoP in RMs through the MBMA model developed with aggregate level RM protection data (protection for RM is defined here as reduction in viral load). Further, via translation of the RM MBMA to a clinical protection model we demonstrate the successful prediction of clinical efficacy of novel vaccine candidates against SARS-CoV-2 using only RM immunogenicity data (SN titres). Subsequently, we illustrate how clinical efficacy predictions can be improved with the additional integration of early clinical data via the calibration approach and with a joint MBMA model. Thereafter, once clinical efficacy data from additional candidates became available, we developed a clinical MBMA model that allowed for clinical efficacy predictions based on clinical data alone. We corroborate previous findings with the estimation of a 50% protective titre in humans using all three MBMA models. Finally, we demonstrate the predictive ability and the future application of these models through efficacy predictions of BBV152 and CoronaVac, whose data weren't used in the development of the models, and with predictions of vaccine efficacies against delta and omicron variants of SARS-CoV-2.

Implications of all the available evidence

To effectively control the COVID-19 pandemic and to meet the unprecedented global need for vaccines, there is a need for newer vaccines and/or optimization of existing vaccines (expanding indication to other age groups, booster shots for waning immunity, increased efficacy against newer variants, etc.). Vaccine efficacy trials are lengthy and expensive, and therefore quantitative tools that can be leveraged to inform early Go/No-Go decisions are invaluable. The MBMA models presented here are predictive of protection against SARS-CoV-2 and provide a powerful translational framework to enable early Go/No-Go decisions and to accelerate study design decisions using only non-clinical and/or limited clinical immunogenicity data in the development of novel vaccines.

candidates as rapidly (and with as little data) as possible. Hence, establishing correlates of protection and developing quantitative tools that use the existing body of non-clinical and clinical data and that are predictive of clinical efficacy are paramount to addressing rapid vaccine development. Protection against SARS-CoV-2 (viral load reduction) for several vaccine candidates[11–13] [Reference 12 is a preprint/non peer reviewed article] has been demonstrated using the Rhesus Macaque (RM; non-human primate) model. Serum neutralizing (SN) titre has been established as a potential correlate of protection (CoP) in RM.[1,2] Similarly, SN titre has been established as potential CoP clinically,[5] and predictive models[4] have been reported based on aggregate-level clinical data. However, a quantitative framework that translates protection in RM to humans and integrates RM and clinical data to predict clinical efficacy has been lacking. Here, we present a model-based meta-analysis (MBMA) approach[8] to quantify the relationship between immunogenicity ("immunogenicity" refers only to SN titres throughout our analysis) and protection through the integration of prior information across different species (RM & humans), vaccine mechanisms, dose-levels, regimens, endpoints, assay methods, and study designs. We also demonstrate the application of the MBMA models in predicting (using RM data alone and in combination with clinical immunogenicity data) the clinical efficacies of newer vaccine candidates and of vaccines against delta variant of SARS-CoV-2. Efficacies against the omicron variant are also predicted using the MBMA based on clinical data.

Methods

We provide a framework to use animal (non-clinical) data available early in vaccine development to predict vaccine efficacy, to improve vaccine efficacy predictions by enabling incorporation of clinical (and non-clinical) immunogenicity data when available, and, thus, to support model-informed decision making in vaccine development. To enable development of such a framework rapidly enough to support vaccine discovery and

development efforts, we started by conducting systematic literature searches to identify challenge studies demonstrating vaccine protection against SARS-CoV-2 in RM (no clinical data were available). We then developed a RM MBMA model using these data to quantify the relationship between immunogenicity (SN titres) and protection data in RM (protection for RM is defined here as reduction in viral load). Translation of the RM MBMA model enabled prediction of clinical efficacy based on RM data alone. As clinical SN titre and efficacy data of vaccine candidates became available, we could improve predictions by integrating those data with the RM data through calibration and (separately) joint RM-clinical modelling. As additional clinical data became available, a clinical MBMA model could be developed based solely on clinical data. We demonstrate the predictive ability of the models by predicting the efficacies of two vaccine candidates whose data were not used in the development of the models. Efficacies against the delta and omicron variants of SARS-CoV-2 were also predicted as an application of the models. A schematic with the timeline of RM and clinical literature searches and the development of MBMA models is shown in Figure S1. The methodology behind the systematic literature search, development of the MBMA models, and the efficacy predictions from those models are described below.

Development of a predictive model-based meta-analysis (MBMA) in rhesus macaques (RM)

Systematic literature search. A systematic search was performed to identify non-clinical trials of vaccines against SARS-CoV-2 and of prior infection with SARS-CoV-2 (vaccine and re-challenge) in rhesus macaque (RM). It included searches in PubMed (LitCovid), BioRxiv, and MedRxiv. Through an automated screening approach, titles and abstracts of all references related to SARS-CoV-2 were screened for a defined list of lexicon terms (a description of systematic search is in Supplementary Material, including Table S1). This resulted in approximately 1429 references of potential interest from screening of 104472 references with data cut-off of 25 Jan 2021. Out of these, 111 references contained words related to RM, and were reviewed to check if the reference was reporting challenge study results after vaccination, monoclonal antibody administration or initial virus challenge, and provided information on

1) SN titre data following vaccine administration, monoclonal antibody administration, or initial challenge (for rechallenge studies), and
2) Viral load (VL) data post challenge in relevant tissue matrices.

The details of these studies were reviewed, and an exploratory analysis was conducted to assess information provided on vaccine type (mechanism), dose-level, regimen, challenge dose, time of challenge, SN assay description, SN titres, units of SN, and viral load in tissue matrices. 13 of the publications provided information enabling them to be used for the MBMA analysis.

Software. Data preparation and visualization was performed using Excel 2016 and R version 3.5.0 or higher. MBMA model development was done using the nlme package in R, and efficacy predictions were carried out using R version 3.5.0 or higher.

Immunogenicity and viral load data derivation rules. Summary level $\log_2$ SN titres and geometric mean $\log_{10}$ peak VL data were of interest. SN titre data from live virus assays were preferred over pseudo-virus assay results if both were reported in the same reference at the time point of interest (time point closest to and prior to the time of challenge). Geometric means were derived from individual data, if available from the source. If only median data were available and individual data were not reported, the median values were retained in the analysis dataset. SN titre and VL data were log-transformed using base two and base 10 (respectively) prior to analysis to align with the standard units used in the literature.

Data were either directly reported or derived from reported values. If the SN titres for control arms were clearly reported at (or at half of) the lower limit of quantification/detection (LLOQ/LLOD), or, if no LLOQ/LLOD values were reported, $\log_2$ SN data for control arms were set to zero. Alternate imputation rules for SN titres (e.g., fixing to half LLOD/LLOQ) were tested during model development, however no substantial impact on model parameters was identified. If peak $\log_{10}$ VL was reported at LLOQ/LLOD, it was set to half this threshold level, and if no LLOQ/LLOD was available, $\log_{10}$ VL was set to zero. This approach ensures that, for sufficiently high titres, we can predict viral load corresponding to the maximum possible protection (as measured in each experiment and specimen type). The high efficacies in the clinic and low VLs in RM suggest that it is reasonable to assume that viral load can be reduced to zero. To minimize any possible impact of VL imputation on model parameters and to ensure consistency between measured and modelled minimum response, we matched the appropriate model parameter value (VL_{min} defined below) to the corresponding imputed VL value (for a given experiment and specimen type). To avoid numerical problems during model fitting, a constant with a value small enough to not impact results (determined through a sensitivity analysis, $<<$ 0.1) was added to VL values.

MBMA of serum neutralizing titres vs peak viral load. Non-linear mixed-effects modelling was implemented

to characterize the relationship between geometric mean SN titres and VL data from vaccine studies against SARS-CoV-2 conducted in RM. During modelling, study-level parameters could either be shared across specimens or be estimated separately. The model relationship is of the form

$$VL_{i,j,k,l} = VL_{max_{i,k,l}} * e^{\ln\left(\frac{VL_{min_{i,k}}}{VL_{max_{i,k,l}}}\right) * suppr} + \varepsilon_{ijkl} \quad (1)$$

where $VL_{i,j,k,l}$ is the post-challenge log_{10} peak viral load for study i, arm j, specimen type k, and challenge inoculum dose l with SARS-CoV-2. This functional form was originally developed to describe Poisson distribution data such as respiratory syncytial virus (RSV) incidence rates (IR) and was subsequently shown to also describe nonclinical RSV viral load data successfully.[13]

$VL_{max_{i,k,l}}$, is the maximum log_{10} peak viral load for study i, specimen type k, and challenge (inoculum) dose l (which had more than one value in at least one study). $VL_{max_{i,k,l}}$ was estimated in the MBMA model using a study-specific exponential random effect on VL_{max} to account for the variability in peak viral load because of different experimental conditions between and within studies:

$$VL_{max_{i,k,l}} = VL_{max_k} * \exp(\eta_{i,l}) \quad (2)$$

Here $\eta_{i,l} \sim N(0, \omega^2)$ is normally distributed with a mean 0 and variance ω^2. $VL_{min_{i,k}}$ is the minimum log_{10} peak viral load for study i and specimen type k and was fixed to half of the respective reported LLOQ/LLOD values; and $suppr$ represents the suppression of the peak viral load with increasing SN titre values and is described by

$$suppr = \frac{(log_2[SN_{i,j}])^{\gamma}}{(log_2[SN_{i,j}])^{\gamma} + (log_2[IT_{50}]_k)^{\gamma}} \quad (3)$$

Here $log_2[SN_{i,j}]$ is the log_2 serum neutralizing titre closest and prior to the time of SARS-CoV-2 virus challenge in study i, arm j; $(log_2[IT_{50}]_k)$ is the SN titre for each specimen type k at which log VL has been reduced by 50% of the difference between VL_{min} and VL_{max}. At this log_2 SN, VL is the geometric mean of VL_{min} and VL_{max}. While study-specific differences between $log_2[IT_{50}]$ may be present (e.g., due to assay differences), no study-specific exponential random effect was included on the $log_2[IT_{50}]$ parameter to not overparameterize the model. It was assumed that this would not introduce substantial bias into the estimated typical value parameter, $log_2[IT_{50}]$, i.e., that there are sufficient data and that they are appropriately representative of assays used. The parameter γ is the Hill coefficient that describes the slope of the curve, and ε_{ijkl} is the within-arm residual variability estimated with an additive normal distribution. The residual error was weighted by the inverse of the sample size in each trial arm. In this model, the predictor variable (SN titer), covariate effect (tissue type on IT_{50}; see Results), and the random effect on VL_{max}, together with the residual variability, account for any heterogeneity between studies.

Covariate analysis. A visual inspection of the covariate relationships was carried out before testing covariate effects in the model. If no clear trend was observable, then no formal model testing was performed. If a trend was observable from visual inspection, the covariate was evaluated in terms of model fit and statistical significance using the criteria described in the following section. The list of covariates deemed potentially impactful on the SN titre vs. peak VL relationship and explored during the MBMA model development and their relevance are shown in Table S2.

Model assessments and qualification. Nested models (e.g., covariate models) were compared through the likelihood ratio test that assumes that minus twice the difference of the log-likelihood (-2LL) values of the nested models is approximately chi-square distributed with the number of degrees of freedom (dof) equal to the number of new parameters. A drop of 3.84 (p-value=0.05, likelihood ratio test) caused by an introduction of one dof was considered a significant improvement and retained in the model. Non-nested models were compared by means of the Akaike Information Criterion (AIC), which is the likelihood of the model corrected for the number of parameters estimated; the lower the AIC values, the better the model fit. In addition, the precision of the parameter estimates was assessed by the confidence intervals (CIs) calculated using a normal approximation to the distribution of maximum likelihood estimators: the narrower the CIs, the lesser the uncertainty on model parameters. Furthermore, Pearson residual plots and V^{2}ACHER[14] plots were produced to evaluate goodness-of-fit. (V^{2}ACHER is a method that enables intuitive visualization of data overlayed on the covariate-containing models fit to them).

Translation of RM MBMA to a clinical protection model

The translation of the RM MBMA model to a clinical protection model was carried out in two steps. First, the peak VL vs. log_2 SN titre relationship in RM (Eq. (1)) was transformed to obtain a % IR of clinical disease vs log_2 SN titre relationship in humans. Clinical disease was defined as symptomatic disease of any severity with PCR-confirmed SARS-COV-2. This transformation was made using the assumption that VL in RM is a translational surrogate for the IR of clinical disease and assuming that the shape of these two relationships is the same (Figure S2A-B). The equation for the transformation is a simple linear scaling as shown below:

$$\frac{IR_i - IR_{min}}{IR_{max} - IR_{min}} = \frac{VL_i - VL_{min}}{VL_{max} - VL_{min}} \quad (4)$$

VL_i is the $\log_{10}$ peak post-challenge viral loads measured for vaccine i; VL_{min} is the mean of minimum log_{10} peak viral loads across all studies in the RM-MBMA; VL_{max} is the estimated maximum log_{10} peak viral load from the RM MBMA model; IR_i is the predicted incidence rate of clinical disease for vaccine i; IR_{min} and IR_{max} are the minimum and maximum attainable incidence rates of clinical disease. IR_{min} was prospectively assumed to be 0, based on findings from RM data that robust neutralizing titres resulted in complete protection against detectable viral load (qPCR copy number). When IR_{min} is set to 0 IR scales proportionally with IR_{max}, and therefore IR_{max} can be arbitrarily fixed to 1. This assumption resulted in the following simplification of Eq. (4) above:

$$IR_i = \frac{VL_i - VL_{min}}{VL_{max} - VL_{min}} \quad (5)$$

Next, the % vaccine efficacy vs. $\log_2$ SN titre relationship in humans was derived from the predicted % incidence rate vs $\log_2$ SN relationship (Figure S2C) using:

- $IR_{vaccine}$ – incidence rate of clinical disease for vaccinated subjects, predicted using the reported Phase 1 or 2 geometric mean (GM) SN, and
- $IR_{placebo}$ – incidence rate of clinical disease for placebo subjects. We are predicting the efficacy of a vaccine in COVID-19 naïve individuals with baseline SN titres assumed to be near the LLOD, corresponding to an incidence rate approaching IR_{max}, here fixed to 1.

The % *Vaccine Efficacy* is defined as the relative reduction in incidence rate of the vaccine compared to placebo arm in each trial:

$$\%\ Vaccine\ Efficacy = 100 \cdot \left(1 - \frac{IR_{\ vaccine}}{IR_{\ placebo}}\right) \quad (6)$$

Curation of clinical immunogenicity and efficacy data of COVID- 19 vaccine candidates. A systematic literature review was performed to identify clinical data for those vaccine candidates with reported Phase 1/2 immunogenicity data and Phase 3 efficacy data (a cut-off date of July 2021 was employed, at which a total of 71 references were selected for curation based on criteria outlined in the Supplementary Material, including Table S1). Additional data which were available after this date were included on an *ad hoc* basis if deemed to add sufficient value to the analysis (e.g., preliminary efficacy data from CoronaVac and BBV152 vaccines to facilitate external model validation). Summary level data from eight vaccines that met the criteria were curated and were included in the clinical database. Consistent with curation of the RM data, SN titre data obtained from live virus assays were preferred over pseudo-virus assay data. When available at more than one timepoint, SN titres obtained closest to (but after) the start of the efficacy assessment period (after the last dose) were selected. If not reported along with the published vaccine efficacy, SN titre values were obtained from alternative publications (e.g., Phase 1 safety and immunogenicity reports). However, SN titres were always matched with estimates of vaccine efficacy obtained from identical dosing regimens. SN titres from population strata (e.g., age) were selected to be from strata commensurate with the population in which efficacy was measured. Geometric mean Human Convalescent Serum (HCS) titres using the same assay were also included to quantitatively account for assay differences across trials. The respective definitions in each trial of efficacy endpoints and of HCS are described in Table S3. Data from 6 vaccine candidates (BNT162b2, mRNA-1273, Ad26.COV2.S, 2019nCoV, Gam-COVID-Vac, ChAdOx1 nCoV-19) were leveraged in the development of the MBMA models. The efficacy measure employed was the relative reduction of COVID-19 IR of all disease severities, confirmed by PCR, relative to control. Efficacy selected for inclusion was that assessed at the time defined as the primary endpoint, at least 7 days after the final dose. The data from CoronaVac and BBV152, which became available after the models were built, were used as part of the external validation by comparing their published efficacies to the VE predicted using their respective SN GMT data as input to the three MBMA models. Additional SN titre data were also collected from a non-systematic *ad hoc* literature search to inform simulations to predict vaccine efficacy against the delta and omicron variants.

Estimation of SN calibration factor

The clinical SN titres were normalized using the geometric mean HCS titres from their respective assays to account for the assay differences across trials. The same approach was not carried out for the RM SN titre data, as convalescent titres using the corresponding assays were either not reported or the definition of convalescence was not clearly stated in these RM studies.

Generalized least squares (GNLS) was used to estimate a calibration factor to align the RM MBMA (scaled to 0-100% efficacy range) with the HCS-normalized clinical SN. The calibration factor, F_c, was estimated by minimizing the sum of squared residuals between the reported point estimates for clinical efficacy and the corresponding HCS-normalized titre with the RM-MBMA curve predicted from the maximum likelihood estimates of the MBMA using the following equation:

$$\log(SN_{cal_i}) = \log\left(\frac{SN_{human_i}}{HCS_{human_i}}\right) + \log(F_c) \quad (7)$$

where SN_{human_i} is the observed SN titre of the i^{th} vaccine candidate at timepoint closest to (but after) the start of

the efficacy assessment (after the last dose), HCS_{human_i} is the observed HCS titre using the same assay and the same trial as the i^{th} vaccine, and SN_{cal_i} is the SN titre of the i^{th} vaccine candidate when it is used for prediction of clinical results from the RM MBMA. F_c was then used for calibration to enable prediction of clinical efficacy from clinical immunogenicity data and the non-clinical MBMA.

Development of joint MBMA model

A joint MBMA using RM data and clinical data was conducted to establish the relationship between SN titres and protection in both species. To model the non-clinical and clinical data jointly, the following steps were taken:

Step 1. Transformation of the NHP data

The viral load data in RM was transformed to an efficacy scale (0, 1) using Eqs. (8)-(9) so the response variables were the same for both species

$$Scaled\ VL_{i,j,k,l} = \frac{VL_{i,j,k,l}}{VL_{i,j=control,k,l}} \quad (8)$$

where $VL_{i,j,k,l}$ is the log_{10} peak viral load for study i, arm j, specimen type k, and challenge inoculum dose l post challenge with SARS-CoV-2. $Scaled\ VL_{i,j,k,l}$ was set to 0 if $VL_{i,j,k,l}$ was equal to reported LLOQ or LLOD, corresponding to an assumed full response. $VL_{i,j=control,k,l}$ refers to the log_{10} peak viral load corresponding to the placebo/control arm in study i, specimen type k, and challenge inoculum dose l post challenge with SARS-CoV-2.

Efficacy (Scaled response) was calculated as

$$Scaled\ response_{i,j,k,l} = 1 - Scaled\ VL_{i,j,k,l} \quad (9)$$

Step 2. Collate the efficacy and immunogenicity data from both species (RM and humans(h))

$$VE = (Scaled\ response_{i,j,k,l},\ Clinical\ Efficacy_m)\ \forall\ i,j,k,l,m \quad (10)$$

$$Imm = (\log_2[SN_{RM}])_{i,j},\left[\frac{SN_{h,m}}{HCS_{h,m}}\right])\ \forall\ i,j,k,l,m$$

Here, for the m^{th} clinical vaccine candidate, Clinical Efficacy$_m$ is the reported efficacy, $SN_{h,m}$ is the human serum neutralizing titre obtained at time closest to (but after) the start of efficacy assessment (after last dose), and $HCS_{h,m}$ is the corresponding human convalescent serum titre reported. $(log_2[SN_{RM}])_{i,j}$ is the log_2 serum neutralizing titre closest prior to the time of SARS-CoV-2 virus challenge in study i, arm j, in the RM experiments.

Step 3. Build the joint MBMA model (with data indexes (i, j, k, l, and m) omitted for readability):

$$VE \sim VE_{max} * \frac{(log_2[SN_{RM}])^{\gamma_{RM}}}{(log_2[SN_{RM}])^{\gamma_{RM}} + (log_2[IT_{50}])^{\gamma_{RM}}} I[Species = RM] + \frac{\frac{SN_h}{HCS}^{\gamma clin}}{\frac{SN_h}{HCS}^{\gamma clin} + [\frac{SN}{HCS}]_{50}^{\gamma clin}} I[Species = Human] \quad (11)$$

VE_{max} is the maximum efficacy estimated in the MBMA model. SN_h is the serum neutralizing titre obtained at time closest to start of efficacy assessment (after last dose), and HCS is the human convalescent serum titre reported for the corresponding clinical vaccine candidates. $log_2[SN_{RM}]$ is the log_2 serum neutralizing titre closest to and prior to the time of SARS-CoV-2 virus challenge in the RM experiments. $log_2[IT_{50}]$ is the log_2SN titre required to obtain 50% protection in RMs for specimen type k = BAL (& lung tissue), and nasal; $[\frac{SN}{HCS}]_{50}$ is the ratio of vaccine SN titre to HCS titres required to obtain 50% efficacy in humans, γ_{RM} and γ_{clin} are the Hill coefficients that control the slope of the curve for the RM and human data, respectively. (The log of the hill coefficient was modelled to ensure non-negative parameter values.) $I[Species = RM]$ is an indicator variable that takes a value of 1 for RM data, and is otherwise 0, and analogously for $I[Species = Human]$. A GNLS approach was used for model building. When fitting the model parameters, the vaccine efficacy observations were weighted by the number of participants in each trial, and the RM studies were, separately, weighted by the number of animals. The weights for the clinical data ranged from 0.129-1, and for RM data from 0.1-1. A normally distributed residual error term was used in the joint MBMA model. A species-specific random effect was also tested: its variance was estimated to be close to zero, and it resulted in a worse model fit based on AIC criteria.

Development of clinical MBMA model

A clinical MBMA was conducted to establish the relationship between HCS-normalized SN titres (SN/HCS ratio) and clinical efficacy. The clinical SN titres were normalized to the geometric mean HCS titres as described above. A sigmoidal relationship was used:

$$VE_{i,j}(\%) = \frac{VE_{max} * \left(\frac{SN_{i,j}}{HCS_i}\right)^{\gamma}}{\left(\frac{SN_{i,j}}{HCS_i}\right)^{\gamma} + (ET_{50,\ human})^{\gamma}} + \varepsilon_{i,j} \quad (12)$$

Here, VE_{max} is the maximum vaccine efficacy (%), $\frac{SN_{i,j}}{HCS_i}$ is the HCS-normalized SN titre of the i^{th} vaccine candidate and j^{th} age group, $ET_{50,human}$ is the SN/HCS titre ratio corresponding to 50% vaccine efficacy in humans, γ is the Hill coefficient that controls the slope of the curve,

and $\varepsilon_{i,j}$ is the additive residual variability estimated with a normal distribution. When fitting the model parameters, the vaccine efficacy observations were weighted by the number of participants in each trial.

Methods for prediction/simulation

Efficacy predictions were generated from each model using available clinical or non-clinical immunogenicity data. First, sets of 1,000 model parameters were sampled from the multi-variate normal variance-covariance matrix to account for parameter uncertainty. To account for uncertainty in the reported GMT in vaccinated and convalescent samples, each set of model parameters was paired with a set of GMTs from vaccinated or convalescent samples drawn from the log-normally distributed uncertainty (standard error). For predictions of efficacy against the newer variants (delta, omicron), we also accounted for uncertainty in the reported ratio of SN for WT vs. newer variant when available. While predicting from the RM-MBMA model using clinical calibration factor F_C, each parameter set was also paired with a calibration factor sampled from the uncertainty in the mean estimate for F_C. Clinical efficacy was predicted using each model for each sampled parameter set, calibration factor (where appropriate), and clinical GMT. Predicted efficacies were summarized as the median and 95% confidence interval. Root mean squared prediction error (RMSPE) was used to compare the predictive power of different modelling approaches.

Role of the funders

The authors from Merck & Co., Inc., Rahway, NJ, USA participated in study design, data collection, analysis, interpretation, and writing of the report. The funders reviewed the penultimate draft of the manuscript. All authors had full access to the data in the study and approved the decision to submit for publication.

Results

Analogously to the Methods section, we first describe the RM dataset obtained from the systematic literature search, and the resulting relationship between SN titres and protection data in RM quantified by the RM MBMA model. We then show the predictions of vaccine clinical efficacies with RM data alone through the translation of the RM MBMA to a clinical protection model. Subsequently, we illustrate how clinical efficacy predictions can be made with the integration of early clinical data and RM data via the calibration approach, and also with the joint MBMA model. Thereafter, we describe the relationship between HCS-normalized SN titres and clinical efficacy via the clinical MBMA model. Finally, to illustrate the predictive ability of the three MBMA models, we show efficacy predictions of 2 vaccine candidates whose data were not used in the development of the models. In addition, predictions of vaccine efficacies against the delta and omicron variants of SARS-CoV-2 are predicted as this is an important application of the models.

Exploratory analysis suggests SN titres predictive of protection in RM

In total, summary level data from 13 studies including 21 SARS-CoV-2 vaccine candidates across various platforms were included in the RM MBMA analysis dataset (Table 1). To evaluate the potential of SN titres as an immune correlate of protection in the RM model, post-challenge peak VL in BAL, lung and nasal tissue were used as protection endpoints to indicate severity of infection, interpreting them as potential translational surrogates for clinical disease. Sub-genomic RNA (sgRNA) was assumed to best represent replicating virus.[16] Therefore, only sgRNA peak VL was included an "efficacy" (protection) endpoint in the MBMA model. The SN level closest to and prior to the time of challenge was assumed to be predictive of efficacy and hence included as the predictor. Exploratory visual analysis indicated a potential decrease in peak VL (increasing protection) with increase in SN in BAL, lung, and nasal tissues (Figure S3), supporting the evaluation of SN as a potential immune correlate of protection and the development of an MBMA model.

RM MBMA characterizes protective SN levels in rhesus macaques

A model-based meta-analysis (MBMA) enables decisions to be made based on the totality of evidence[8] through the integration of prior information across different vaccine mechanisms, dose-levels, regimens, endpoints, and study designs. A non-linear mixed effect modelling approach was used to build an MBMA model (as described in Methods) to characterize the sigmoidal relationship between SN titres after vaccination and peak VL post-challenge in RM. The post-challenge peak sgRNA VL data in BAL, lung, and nasal tissue were modelled jointly. For IT_{50} (defined to be the $\log_2$ SN titre at which $\ln(VL_{max})$ has been reduced by 50% of the difference between $\ln(VL_{min})$ and $\ln(VL_{max})$), model development indicated that estimating this parameter for BAL and lung tissue, and, separately, for nasal tissue ($IT_{50,nasal}$), was statistically superior to using a single IT_{50} value across all tissue matrices. The final model therefore contained two IT_{50} estimates (i.e., having tissue type as a covariate, as expected), while all other parameters were shared across all tissue matrices.

Challenge studies varied in terms of the type of neutralization assays used (plaque reduction neutralization test (PRNT), microneutralization (MN), and cytopathic effect (CPE) assays), and type of virus (live vs. pseudo)

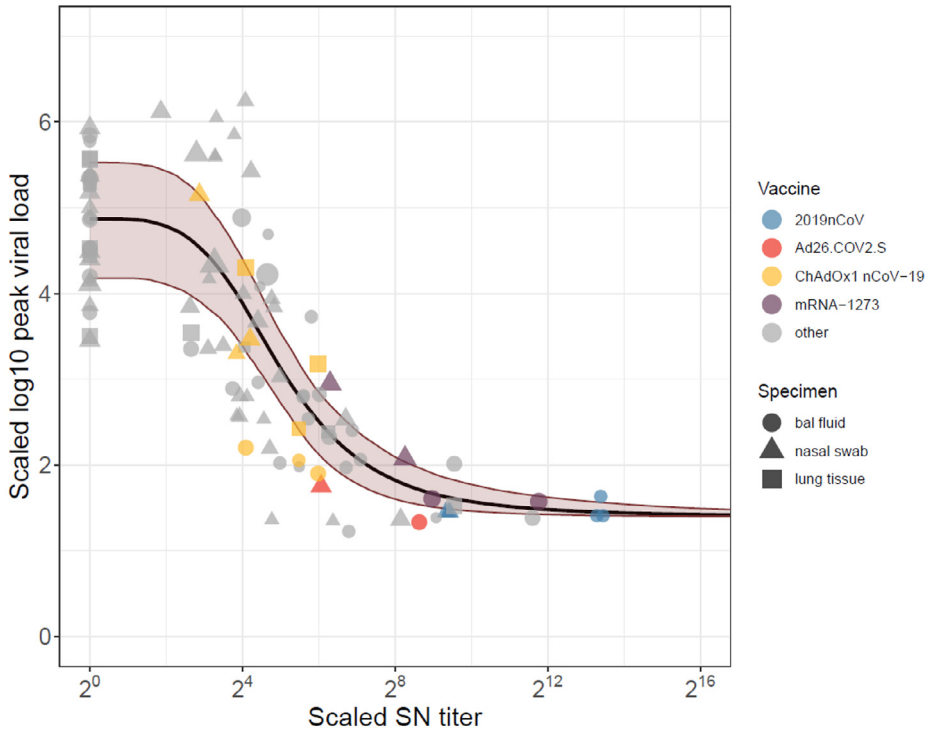
Study	Study type	Number of arms	Mechanism of vaccine	Interventions	Dose and regimen	Adjuvant	Live/ Pseudo	SN assay (% Inhibition)	Specimen	Reported efficacy in clinic
Chandrashekar 2020 [17]	Challenge	3	NA	Control, none	NA	No	lvnt	50	Nasal/naso-pharyngeal	NA
Corbett 2020 [11]	Vaccine	3	RNA	mRNA-1273, placebo	IM, week 0 and 4, 10 or 100 μg	No	lvnt	50	Bal fluid, nasal/naso-pharyngeal	Yes
Yang 2020 [18]	Vaccine	4	Subunit	SARS-CoV-2 vaccine, control	IM, day 0 and 7, 20 or 40 μg	Yes	lvnt	unknown	lung tissue	No
Mercado 2020 [12]	Vaccine	8	Adenovirus-vectored	Placebo, S.PP, tPA.S, tPA.S.PP, S, S.dCT, tPA.WT.S, S.dTM.PP	IM, day 0, 10^{11} viral particles	No	Psvnt[a]	50	Bal fluid, nasal/naso-pharyngeal	Yes
Guebre 2020 [19]	Vaccine	4	Subunit	NVX-CoV2373, placebo	IM, day 0 and 21, 5 or 25 μg	Yes	lvnt	100	Bal fluid, nasal/naso-pharyngeal	Yes
Patel 2020 [20,b]	Vaccine	2	DNA	INO-4800, control	ID-EP, week 0 and 4, 1 mg	No	Psvnt	50	Bal fluid, nasal/naso-pharyngeal	No
Yu 2020 [21]	Vaccine	7	DNA	Placebo, S, S.dCT, S.dTM, S1, RBD peptide, S.dTM.PP	IM, week 0 and 3, 5 mg	No	lvnt	50	Bal fluid, nasal/naso-pharyngeal	No
van Doremalen 2020 [22]	Vaccine	3	Adenovirus-vectored	ChAdOx1 GFP, ChAdOx1 nCoV-19	IM, -56 and/or only -28 dpi. 2.5×10^{10} VP/animal	No	lvnt	100	Bal fluid, nasal/naso-pharyngeal, lung tissue	Yes
Rauch 2020 [23,b]	Vaccine	3	RNA	Control, CVnCoV	IM, day 0 and 28, 0.5 µg or 8 µg	No	lvnt	50	lung tissue, bal fluid, nasal/naso-pharyngeal	Yes
Furuyama W 2021 [24,b]	Vaccine	3	Vesicular stomatitis virus recombinant	VSV-EBOV, VSV-SARS2-EBOV	IM or IN, day10, 1×10^{7} PFU	No	lvnt	100	Nasal/naso-pharyn-geal, bal fluid, lung tissue	No
Brouwer 2020 [25,b]	Vaccine	2	subunit	Control, SARS-CoV-2 S-I53-50NP	IM, week 0, 4 and 10, 50 ug	Yes	lvnt	50	Bal fluid, nasal/naso-pharyngeal	No
McMahan 2020 [1]	Antibody	4	NA	Sham, igg	IV, day 0, 250 mg kg^{-1}, 25 mg kg^{-1}, 2.5 mg kg^{-1}	No	Psvnt	50	Bal fluid, nasal/naso-pharyngeal	NA
van Doremalen 2021 [13,b]	Vaccine	2	Adenovirus-vectored	ChAdOx1 GFP, ChAdOx1 nCoV-19	IN, -56 and -28 DPI, 1 ml	No	lvnt	100	Nasal/naso-pharyn-geal, bal fluid, lung tissue	Yes

***Table 1*: Characteristics of studies in the RM database used in the MBMA of SN vs VL.**

Bal=Bronchoalveolar lavage; IN=intranasal; IM=intramuscular; IV=intravenous; Lvnt=live-virus neutralization titres; Psnvt=Pseudo-virus neutralization titres.

[a] Mercado et al.: pseudo-virus SN titres were preferred to the live-virus SN titres as only the pseudo-virus titres were available at the time of challenge.

[b] References 13, 20, 23, 24 and 25 are preprint/non peer reviewed articles.



Efficacy endpoint	*BAL*	*Lung tissue*	*Nasal*	*Total*
sgRNA	41	15	47	103

Figure 1. Relationship between SN titres and peak Viral Load in RM across all specimens quantified via the RM MBMA model. The table provides the count of data points for each specimen-type included in the MBMA model. Each point represents a study arm in the literature, showing its $\log_{10}$ peak VL (via sgRNA) and the corresponding $\log_2$ SN titre. Data points corresponding to vaccines with reported efficacy in humans are labelled and the others are shown in grey, and all points are sized by number of animals in respective study arm. All viral load data points and model predictions are scaled to viral load originating from a curve with typical VL_{max} and a single selected VL_{min} (IIV correction), and nasal SN titres are scaled to their BAL fluid/lung tissue equivalents (adjustment for covariate effects on independent variable), using the V^2ACHER scaling approach.[15] The solid line and the shaded region correspond to the median and 95% Confidence Interval of RM MBMA prediction, calculated from 1000 model simulation replicates. The width of the confidence interval decreases at higher titres because minimum viral load was fixed in the model.

used in those assays. Unlike clinical trials, convalescent titres using the corresponding assays were either not reported or the definition of (clinical) convalescence was not clearly stated in these RM studies. Hence the approach to normalize the SN titres to their corresponding convalescent titres was not carried out for the RM data. Therefore, after developing the base MBMA model, an exploratory analysis was conducted to assess the potential impact of these assay differences on the relationship between SN titres and peak VL. This visual assessment (Figure S4) showed notable consistency in the data from different assays, with no apparent trends suggesting systematic differences between the assays. As a result, no covariates on assay type were included in the final model. (In general, a covariate was considered unlikely to be important if the CIs of two V^2ACHER plot curves corresponding to different values of that covariate overlap).

The goodness of fit plots (Figure S5) and the V^2ACHER plot (Figure 1) revealed that the final model provided a robust fit to the VL and SN titre data across all specimens and for all vaccine platforms. The model-estimated parameters are provided in Table 2. The IT_{50} estimate for BAL and lung tissue of 5.84 (5.2 – 6.5) [mean (95% CI)] $\log_2$ units is lower than the $IT_{50,nasal}$ for nasal tissue which was 8.3 (7.1 – 9.5) [mean (95% CI)] $\log_2$ units, suggesting higher SN levels required for protection in the nasal tissue compared to the lower

Parameter	Estimate	95% confidence interval
VL_{max}	4.86	4.13 – 5.60
γ	4.14	2.83 – 5.45
IT_{50}	5.84	5.21 – 6.47
$IT_{50,nasal}$	8.32	7.11 – 9.53
IIV on VL_{max}	0.24	0.15 – 0.39
Residual standard error	1.91	1.65 – 2.22

***Table 2*: Parameter estimates of RM MBMA model.**
VL_{max} is the maximum log_{10} peak viral load; IT_{50} is the log2 SN titre at which ln(VL_{max}) has been reduced by 50% of the difference between ln(VL_{min}) and ln(VL_{max}) in BAL and lung tissue, $IT_{50,nasal}$ is defined analogously for nasal tissue; γ is the Hill coefficient that controls the slope of the curve; IIV is the inter-study/challenge inoculum dose variability expressed in standard deviation units.

respiratory tract. Data from 4 vaccine candidates whose Phase 3 clinical efficacy is reported (2019nCoV, Ad26.COV2.S, ChAdOx1 nCoV-19, and mRNA-1273) are coloured (non-gray) in Figure 1. It is apparent that the relative order of model-predicted and observed vaccine protection for these four vaccines is similar to that of their Phase 3 clinical efficacies (Table 3). Overall, higher SN titres resulted in lower peak viral loads across all specimens in RM.

Immunogenicity in RMs is broadly predictive of clinical vaccine efficacy

The translation of the RM MBMA model enabled prediction of VE in humans using only immunogenicity data in RM. This translation required scaling viral load to clinical incidence rate using the assumption that relative changes in RM VL vs SN titre relationship correspond to the same relative changes in incidence rate vs SN titre relationship (same shape) as described under Methods above. The translated RM MBMA model was then leveraged to predict clinical vaccine efficacy using RM SN titres as input. Five vaccine candidates were included in the predictions. (These are the only ones with reported clinical efficacy and corresponding SN titres in RM. Although the clinical efficacy was reported for BNT162b2, a suitable VL endpoint in RM was not available. Hence those data were used in efficacy predictions but not in the estimation of RM MBMA.) Predictions were made using the RM MBMA model for protection measured in BAL fluid/lung (i.e., with IT_{50}) and then for the nasal swab (i.e., using $IT_{50,nasal}$) parameters (Table 2). The predictions using the BAL/lung tissue model parameters performed better than the predictions from nasal swab model parameters (root mean squared prediction error (RMSPE) = 12% vs 21%). The VE predictions with the nasal swab model parameters were lower than the those predicted with the BAL/lung model parameters given the higher estimated protective titres in nasal swab ($IT_{50,nasal} > IT_{50}$) as shown in Table S4. Figure 2 shows that the predicted vaccine efficacies were generally consistent with the observed clinical efficacies.

Calibration enables prediction of clinical vaccine efficacy using clinical SN titres and the RM MBMA

As phase 1 clinical immunogenicity data of COVID-19 vaccine candidates became available, the data were

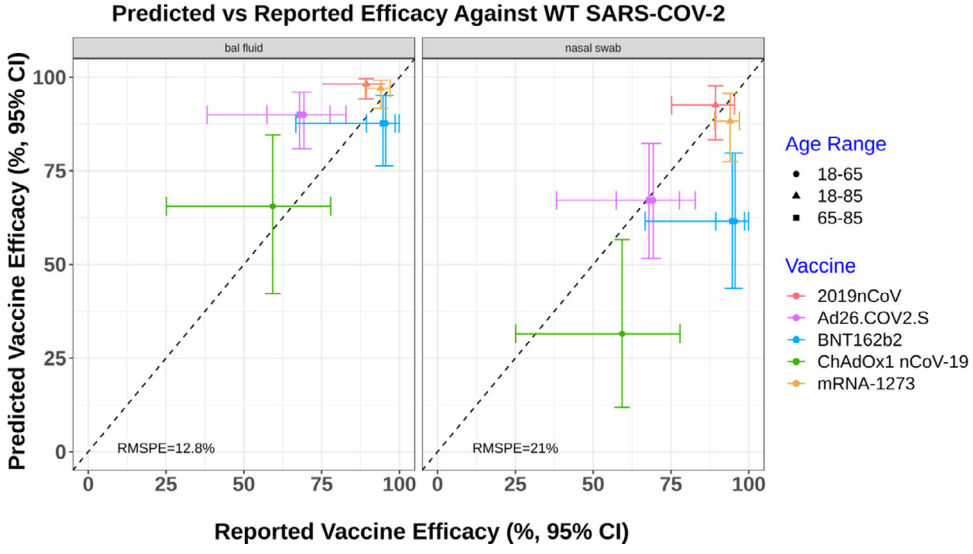


Figure 2. Clinical vaccine efficacy predictions via translation of the RM MBMA Model. Each point represents the predicted vaccine efficacy using the RM MBMA translation versus the corresponding reported clinical vaccine efficacy. The error bars represent the 95% confidence intervals for the vaccine efficacy. The black dotted line is a reference (the line of identity along which predicted VE = observed VE). RMSPE – root mean square prediction error.

Sponsor	Vaccine	Dosage	Regimen	Second Dose Day	SN Titre Day	SN Assay	Age Strata	SN Titre (GM)	SN Titre 95% CI low	SN Titre 95% CI high	SN Data Source	HCS (GM)	HCS 95% CI low	HCS 95% CI High	HCS Data Source	Efficacy	Efficacy 95% CI low	Efficacy 95% CI high
Pfizer [26-28]	BNT162b2	30 µg	2 Dose	21	28	LVNT-MN50	Younger adults [a]	360.9	237.3	544.4	Fig 6	93.7	61.8	143.1	Figure 4B	95.6	89.4	98.6
Pfizer [26-28]	BNT162b2	30 µg	2 Dose	21	28	LVNT-MN50	Older adults [b]	155.7	80.5	307.1	Fig 7	93.7	61.8	143.1	Figure 4B	94.7	66.7	99.9
Moderna [29,30]	mRNA-1273	100 µg	2 Dose	28	42	LVNT-MN50	Adults [c]	1179.4	1130.5	1230.5	Table 15	321	237.1	440.3	Figure 3B	94.1	89.3	96.8
Janssen [31,32]	Ad26.COV2.S	0.5*10^11 virus particles	1 Dose	-	28	LVNT-MN50	Younger adults [d]	224	158	318	Figure 3	522	301.3	911	Figure 2B	69.3	57.4	77.7
Janssen [31,32]	Ad26.COV2.S	0.5*10^11 virus particles	1 Dose	-	28	LVNT-MN50	Older adults [e]	258	154.6	387.4	Figure 3	522	301.3	911	Figure 2B	67.9	38.2	82.8
Novavax [33,i,34]	2019nCoV	5 µg 50 µg Matrix-M	2 Dose	21	35	LVNT-MN50	Adults [f]	1433	978.2	2099.4	Table S8	453	259	790	Figure 3B	89.3	75.2	95.4
Gamaleya [35,36]	Gam-COVID-Vac	1*10^11 virus particles	2 Dose	21	42	LVNT-MN100	Adults [c]	44.5	31.8	62.2	Table S2	33.0	31.5	34.5	Table S6	91.1	83.8	95.1
Astra-Zeneca [37,38]	ChAdOx1 nCoV-19	5|3.5-6.5 *10^10 virus particles	2 Dose	28	35	PSVNT-CPE50	Younger adults [g]	347.4	94.8	599.9	Figure 5	509.6	386.3	672.3	Figure 5	59.3	25.1	77.9
Sinovac [39,40]	CoronaVac	3 µg	2 Dose	14	42	LVNT-CPE100	Adults [h]	23.8	20.5	27.7	Table S6-1	163.7	128.5	208.6	Fig S6-3	50.7	35.7	62.2
Bharat Biotech [41,i,42]	Bbv152	6 µg	2 Dose	28	56	LVNT-MN50	Adults [c]	125.6	111.2	141.8	Table 4	170.2	113.2	255.9	Figure 2C	77.8	65.2	86.4

***Table 3*: Clinical Immunogenicity and Efficacy Data used in calibration, validation, and modelling.**

[a] 18-55 years & 16-55 years for SN titre and efficacy data, respectively.
[b] 65-85 years & ≥65 years for SN titre and efficacy data, respectively.
[c] ≥18 years.
[d] 18-55 years & 18-59 years for SN titre and efficacy data, respectively.
[e] ≥ 65 years & ≥ 60 years for SN titre and efficacy data, respectively.
[f] 18-84 years & ≥ 18 years for SN titre and efficacy data, respectively.
[g] 18-55 years.
[h] 18-59 years & ≥ 18 years for SN titre and efficacy data, respectively.
[i] References 33 and 41 are preprint/non peer reviewed articles.

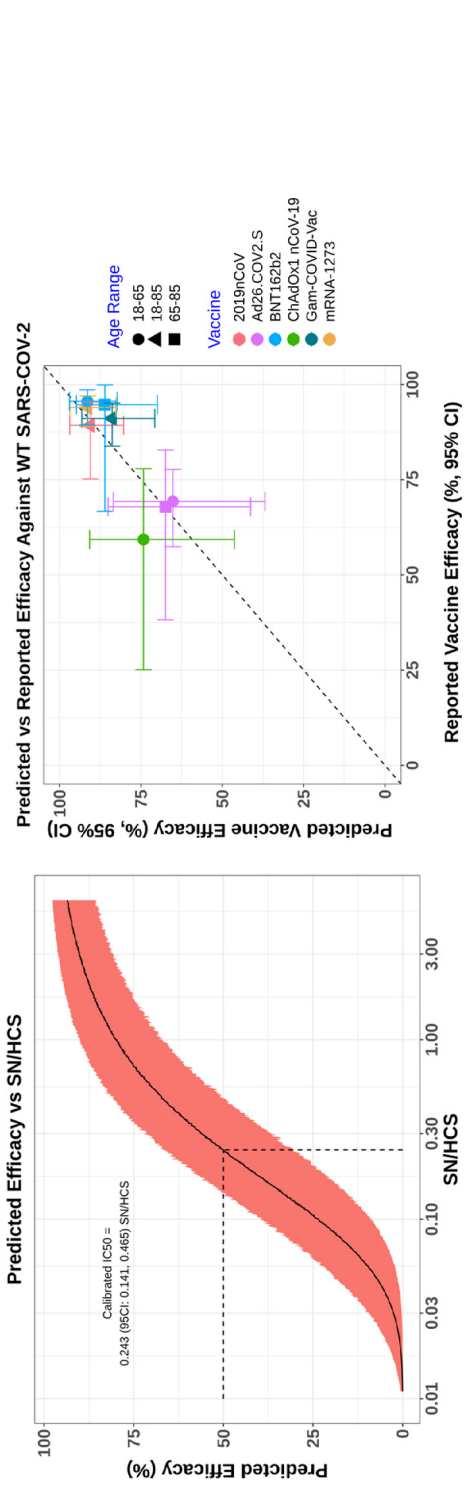


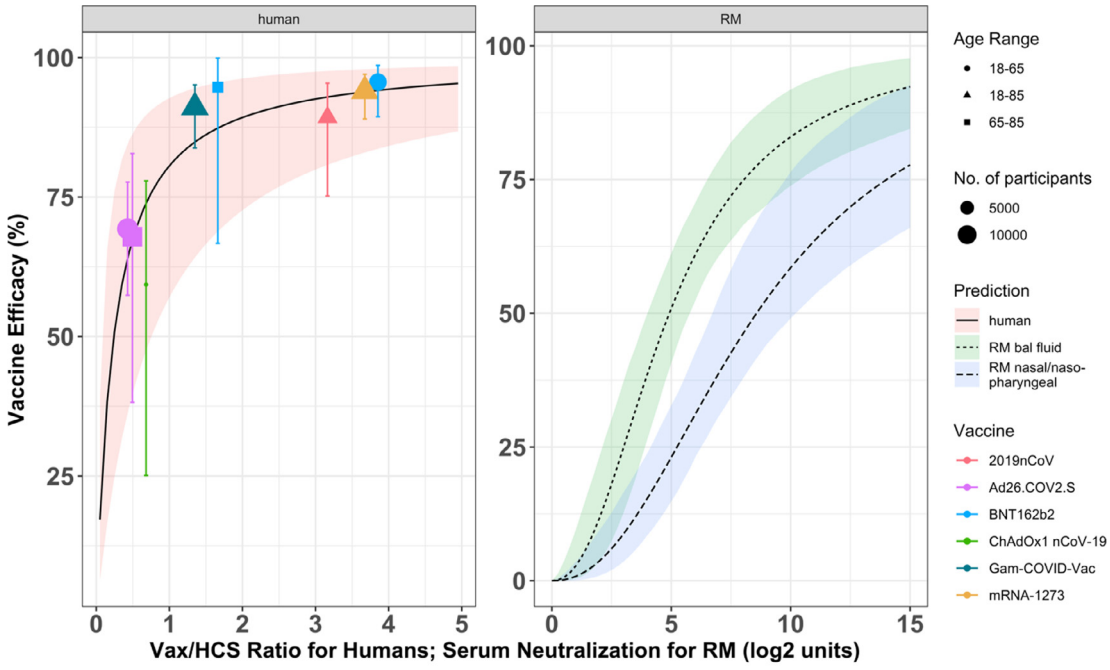
Figure 3. RM-MBMA calibrated to clinical HCS-normalized SN titre and efficacy data. Left: Calibrated clinical efficacy vs HCS-normalized SN titre. The black curve describes the median relationship with the ribbon showing the 95% confidence interval (noisy due to being determined via stochastic simulation). Right: Each point displays the efficacy predicted from the calibrated RM-MBMA versus the point estimate for the reported clinical efficacy. Vertical error bars represent the 95% confidence interval for the prediction, and the horizontal error bars represent the reported 95% confidence interval for the Phase 3 clinical efficacy.

integrated with the RM MBMA translation to predict their clinical efficacy. The immunogenicity data from phase 1 and 2 trials and the corresponding phase 3 clinical efficacies (Table 3) of six vaccine candidates (BNT162b2, mRNA-1273, Ad26.COV2.S, 2019nCoV, Gam-COVID-Vac, ChAdOx1 nCoV-19) were available at the time of model development and included in the analysis. (This analysis was originally done when only data from mRNA-1273 and BNT162b2 were available, and the resulting calibration (result not shown) was similar). The vaccine SN titres (all obtained from live virus assays, except for ChAdOx1 nCoV-19 for which only pseudo virus data were available) were normalized to their respective GMT HCS titres, as described in Methods, to account for inter-assay differences. The GNLS approach (see Methods) was used to estimate a calibration factor to align the RM-MBMA curve (using the BAL/lung model parameters) with the clinical immunogenicity and efficacy data of the six vaccine candidates. The calibration factor, F_c, was estimated to be 143.9 (95% CI: 90.9, 196.9): this number can be interpreted as the average SN titre (across these assays and their corresponding HCS data sets) of a typical HCS sample. An example of calibration with specific numbers can be found below Fig S6. The calibration shows good alignment between the clinical data and RM-MBMA prediction. (Figure S6)

Simulations from the calibrated RM-MBMA model were conducted to predict the HCS-normalized SN titre level expected to provide 50% vaccine clinical efficacy. As shown in Figure 3, the 50% protective titre was predicted to be 24.3% (95%CI: 14.1%, 46.5%) of HCS. To assess the predictive power of this approach, the calibrated RM-MBMA was used to predict (retrospectively) the clinical efficacy of each of the six vaccine candidates based on their respective Phase 1 or 2 HCS-normalized SN titres. Figure 3 shows reasonable agreement between the predicted and observed clinical efficacies for all the vaccine candidates. Predictions from the calibrated RM-MBMA model had a RMSPE of 7% (n=8 data points: 6 vaccines – Ad26.COV2.S and BNT162b2 each had separate efficacies for subjects aged 18-65 and 65-85 years).

Joint MBMA allows simultaneous estimation of protective titres in RM and humans

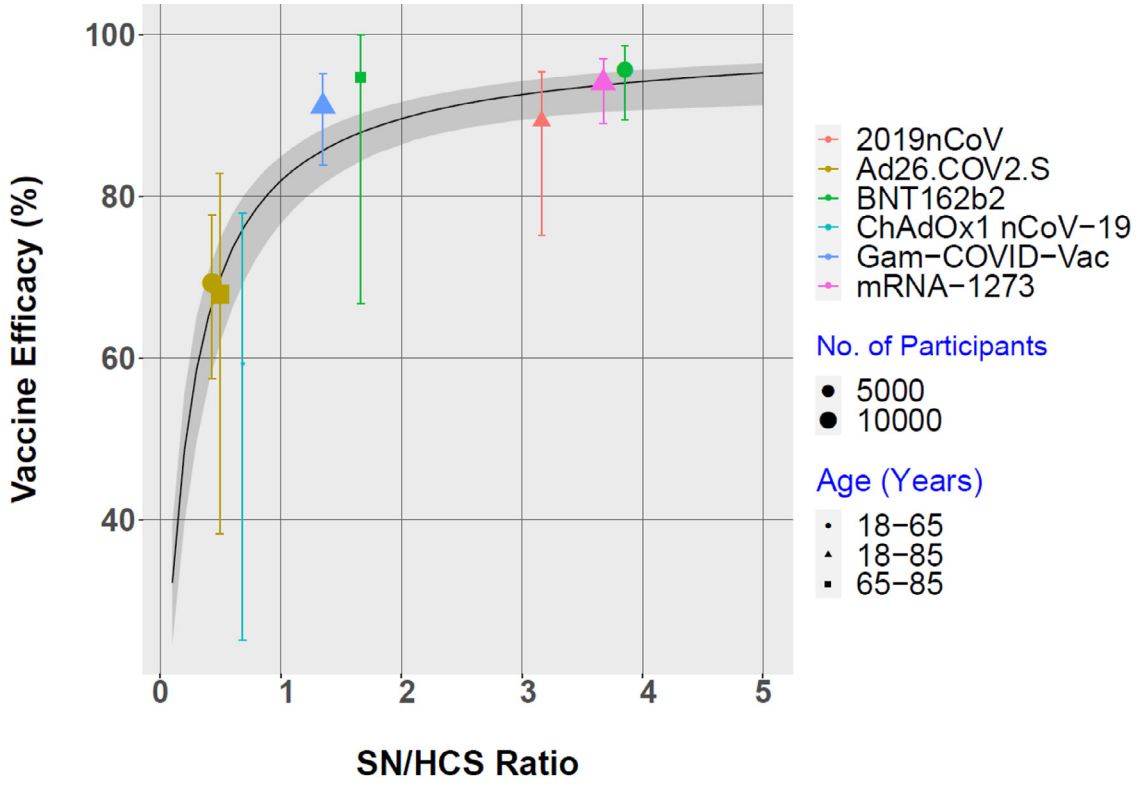
A joint MBMA model (i.e., one using both RM and clinical data, with species as a covariate) was developed to explore an alternative approach to integrating clinical and RM data in developing a quantitative model predictive of clinical vaccine efficacy. The joint model uses clinical SN titres scaled by HCS GMT titres (see Methods) and assumes that the form of the sigmoidal function describing the efficacy vs. SN titre relationship in humans is the same as that for protection (VL reduction) versus titre in RM, leveraging all the data



Parameter	Estimate (95% CI)
VE_{max}	1 (fixed)
γ_{RM}	2.23 (1.50, 3.33)
γ_{clin}	1 (fixed)
$log_2[IT_{50}]_{RM,BAL}$	4.92(4.06, 5.78)
$log_2[IT_{50}]_{RM,nasal}$	8.57 (6.86, 10.30)
$\left[\frac{SN}{HCS}\right]_{50}$	0.24 (0.07,0.77)

Figure 4. Joint MBMA of vaccine efficacy vs. SN titres in humans and RM informs the 50% efficacious titre levels in both species. The vaccine SN titres in humans are normalized to the mean HCS titre (SN/HCS) using the corresponding assay to account for the assay differences across trials. The vaccine SN titres in RM are reported in log2 units. Vaccine efficacy is expressed as a % on the y-axis. The solid line and the pink shaded region correspond to the predicted median and 95% Confidence Interval in humans from the joint model. The points are the reported SN/HCS titre ratio and the corresponding vaccine efficacy in humans. The error bars represent the 95% confidence interval of vaccine efficacy. The dashed line with the green shaded region and the double dashed line with the blue shaded region correspond, respectively, to the predicted median and 95% Confidence Interval in BAL fluid and nasal swab specimens in RM.

VE_{max} is the maximum vaccine efficacy (parameter shared across species); γ is the Hill coefficient that describes the slope of the curve (either for RM or human); $log_2[IT_{50}]_{RM,BAL}$ is the log_2 SN titre corresponding to 50% VE in BAL and lung tissue; $log_2[IT_{50}]_{RM,nasal}$ is the log_2 SN titre corresponding to 50% VE in nasal tissue; $\left[\frac{SN_b}{HCS}\right]_{50}$ is the SN/HCS titre ratio corresponding to 50% VE in humans.



Parameter	Estimate (95% CI)
VE_{max}	1.00 (0.94, 1.07)
$ET_{50,human}$	0.21 (0.15, 0.30)

Figure 5. Clinical MBMA reveals a strong relationship between HCS-normalized titres and VE in humans. The vaccine SN titres for each trial are normalized to (divided by) their assay's respective mean HCS titre (SN/HCS) to account for the assay differences across trials. The solid line and the shaded region correspond to the predicted median and 95% Confidence Interval of clinical MBMA prediction. The points are the reported SN/HCS titre ratio and the corresponding vaccine efficacy in humans. The error bars represent the 95% confidence interval of vaccine efficacy. The vaccine efficacy observations are weighted by the number of participants in each trial. VE_{max} is the maximum vaccine efficacy (%). $ET_{50,human}$ is the SN/HCS titre ratio corresponding to 50% vaccine efficacy in humans.

simultaneously and enabling simultaneous estimation of (human and RM) model parameters. As described in Methods, the viral load data in RM was transformed to an efficacy scale, so that the response variables were the same for both species. Summary level data from 13 RM studies and clinical data corresponding to six vaccine candidates (BNT162b2, mRNA-1273, Ad26.COV2.S, 2019nCoV, Gam-COVID-Vac, ChAdOx1 nCoV-19) were used in the development of the joint model.

Using the same model function for both species allowed flexibility in the number of shared parameters between them. During model development, initially all the model parameters were shared between the two species except for the 50% protective titres ($log_2[IT_{50}]_{RM,BAL}$, $log_2[IT_{50}]_{RM,nasal}$, $\left[\frac{SN_h}{HCS}\right]_{50}$) in RM and humans. While this model was able to describe the data used for model building reasonably well, it did not perform well in predicting additional clinical efficacy data used for model validation (results not shown). Therefore, additional species-specific Hill coefficients (γ) were identified. Human γ ($\gamma clin$) was estimated close to 1, but was imprecise, and was therefore fixed to a value of 1 (AIC reduced by 2 units). A similar approach of fixing VE_{max} to a value of 1 further reduced AIC by 2 units. The Hill

Vaccine	Reported Phase 3 VE, % (95% CI)	Calibration Method VE, % (95% CI)	Joint MBMA VE, % (95% CI)	Clinical MBMA VE, % (95% CI)
BBV152	77.8 (65.2 - 86.4) [41]	75.3 (60.3 - 87.9)	76.2 (48.2 – 91.3)	77.2 (67.1 - 84.0)
CoronaVac	50.7 (35.7-62.2) [39, 40]	34.3 (15.5 - 51.8)	38.0 (15.6 – 67.7)	40.9 (30.6 - 51.3)

***Table 4*: Comparison of vaccine efficacy predictions using clinical SN data.**

Vaccine	Fold Decrease in SN Titre (Delta relative to WT) GM (SE)	Calibrated RM-MBMA VE, % (95% CI)	Joint MBMA VE, % (95% CI)	Clinical MBMA VE, % (95% CI)	Reported efficacy VE, %
ChAdOx1 nCoV-19	4.29 (1.15) [(a) 43]	57.0 (18.2, 88.9)	41.1 (11.6, 78.0)	43.0 (18.8, 67.7)	59.8, 60 [44,b]
BNT162b2	2.49 (1.13) [(a) 43]	85.3 (67.8, 96.3)	87.4 (58.8, 98.0)	87.4 (75.2, 96.5)	79, 87.9 [44,b]

***Table 5*: Predictions of vaccine efficacy against the delta variant.**
[(a)] Geometric mean: calculated as exp(mean(ln(x))) where x indicates 25 values obtained from Table S4 of the original publication.
Geometric SE: calculated as exp(SE) where SE=SD(ln(x))/25 and x indicates 25 values obtained from Table S4 of the original publication.
SN titres for the age group 18 – 65 years were used for efficacy predictions.
[b] Reference 44 is a preprint/non peer reviewed article.

coefficient for RM data was estimated to be (2.23, 95% CI [1.50 – 3.33]). The joint MBMA model has a shared error structure and parameters between the two species.

The overlay of the observed vaccine efficacy with the prediction from the joint MBMA (Figure 4, Figure S7) reveals that the final model fit the vaccine efficacy and titre data for all vaccine candidates. The $ET_{50,human}$ parameter estimate (Figure 4) revealed the 50% protective SN titre level to be 24% (95% CI (7%, 77%)) of the geometric mean human convalescent titre level. The 50% protective SN titres in RM were consistent with those estimated in the RM MBMA model.

Clinical MBMA informs protective SN titre levels in humans

While the RM MBMA model could be used for VE predictions with RM data alone, and the calibrated-RM MBMA model enables predictions with the integration of clinical data from one or two vaccine candidates, a stand-alone clinical MBMA required more clinical data. As soon as sufficient phase 3 clinical efficacy (and immunogenicity) data were reported, a clinical MBMA was conducted. This quantified the relationship between HCS-normalized SN titres (SN/HCS ratio) and clinical efficacy using only clinical data. The observed SN titre data from phase 1 and 2 trials and the corresponding phase 3 clinical efficacies (Table 3) of six vaccine candidates against SARS-CoV-2 (BNT162b2, mRNA-1273, Ad26.COV2.S, 2019nCoV, Gam-COVID-Vac, ChAdOx1 nCoV-19) were used in the model development. The sigmoidal relationship form described in Eq. (12) was used to quantify the relationship. The 95% CI of the log of the Hill coefficient estimate contained 0 (0.29; 95% CI (-0.88, 1.48)), and hence was fixed to 0 in the final model.

The overlay of the observed vaccine efficacy with the prediction from the clinical MBMA (Figure 5) revealed that the final model fit the % vaccine efficacy and SN/HCS titre data for all vaccine candidates. The model-estimated parameters are also provided in Figure 5 and the $ET_{50,human}$ parameter estimate revealed the 50% protective SN titre level to be 21% (95% CI – (15%, 30%)) of the geometric mean human convalescent titre level.

Independent validation of vaccine efficacy predictions

An independent validation of the three MBMA models – RM MBMA and its translation via the calibration method, the Joint MBMA, and the Clinical MBMA – was carried out to assess their predictive ability. The SN/HCS titre data of 2 vaccine candidates, BBV152 and CoronaVac, were used as input for the three models to predict the corresponding clinical efficacies. Table 4 reveals that the predicted vaccine efficacies for the two vaccine candidates using the three approaches are consistent with the reported efficacies.

Prediction of vaccine efficacy against newer strains of SARS-CoV-2. To further validate and to investigate the relevance of MBMA-based efficacy predictions to emerging variants of concern, clinical efficacies against the delta variant were predicted from reported fold change in SN titre against the delta variant relative to wild-type. The three MBMA models provided reasonable efficacy predictions when compared with the reported efficacies as shown in Table 5.

Discussion

Quantitative models that use only nonclinical and or Phase I immunogenicity data to predict clinical vaccine efficacy against SARS-CoV-2 provide a powerful translational framework to inform critical vaccine development decisions. These decisions include informing dose selection, target population, early Go/No Go (preventing execution of Phase 3 efficacy trials where success is unlikely), efficacy against newer strains, and expected efficacy with booster vaccinations. Here, we present this translational framework through the development of MBMA models by integrating prior information across different vaccine mechanisms, species, doses/regimens, endpoints, assay methods, and study designs. This modelling was used to help inform decisions on vaccine candidates, as reported elsewhere.[45,46]

Early in the pandemic, as challenge studies demonstrating vaccine protection against SARS-CoV-2 in RM were published (and no clinical data were available), we developed a RM MBMA model using data from 13 vaccine studies that quantified the robust relationship between SN titres post vaccination and peak VL post challenge in RM. The estimated 50% protective titre in RM in the BAL/lung tissue and nasal swab tissues were 5.84 (5.2 − 6.5) [mean (95% CI)] log2 units, and 8.3 (7.1 − 9.5) [mean (95% CI)] log2 units respectively, suggesting higher SN levels required for protection (defined as reduction in peak VL relative to sham-treated animals) in the nasal tissue compared to the lower respiratory tract. Similar findings were reported by Corbett et.al. [2]; while evaluating immune correlates of protection after mRNA-1273 vaccination they concluded that, in RM, protection in the lower respiratory tract was achieved at lower serum antibody concentrations than in the upper respiratory tract. This outcome was also supported by the data from challenge studies in RM which were used as input to the RM MBMA model, wherein only a few vaccine candidates eliciting the strongest immune responses demonstrated protection in the upper airways in addition to the lower airways.[11,12,19] This trend has also been seen in other respiratory viruses such as respiratory syncytial virus.[47] A potential explanation for the higher infectivity in nasal tissue may be the skewed receptor distribution towards the upper airways, which has been reported for SARS-CoV-2.[48] This may lead to differences in reproductive ratio between tissues, warranting higher titres and thus higher IT_{50} in nasal specimen to achieve the same level of virus inhibition.[49]

Results further demonstrate that non-clinical immunogenicity data alone can be predictive of clinical efficacy through the translation of the RM MBMA protection model to a clinical efficacy model. The clinical efficacy predictions from the translational model using the BAL/lung tissue model parameters performed better than the predictions from nasal swab model parameters (RMSPE of 12% vs 21% respectively). While reduction of viral load in the lower airways is relevant clinically in reducing moderate to severe disease, reduction in both upper and lower airways could be relevant clinically in preventing mild disease and reducing risk of transmission.[2] This potentially explains why the BAL/lung tissue model was more accurate in predicting clinical vaccine efficacies, given that the definition of the efficacy endpoint across vaccine trials is symptomatic disease of any severity confirmed by PCR. Therefore, the BAL/lung tissue parameters are more relevant to the definition of efficacy in the clinical trials, and hence were used for clinical efficacy predictions in the calibration and the joint MBMA models.

As phase 1/2 clinical immunogenicity and efficacy data of COVID-19 vaccine candidates became available, we integrated the data into the RM MBMA translation through the calibration method or combined them with the RM data to develop a joint MBMA model. These two approaches provide quantitative frameworks to predict clinical efficacy of vaccine candidates when there are insufficient clinical data to develop a standalone clinical MBMA model. In the calibration method, a calibration factor was estimated to align the RM-MBMA curve with the clinical immunogenicity and efficacy data. The leave-one-out cross validation approach[50] (Figure S8) showed that the calibration factor was relatively insensitive to any trial data being excluded during estimation. Integration of phase 1/2 clinical immunogenicity data improved the predictions of VE compared to predictions from RM data alone (RMSPE 7% vs 12%). Using species as a covariate in a joint MBMA model provides an alternative approach to integrating clinical and RM data for predicting (quantitatively) clinical vaccine efficacy. The joint model assumes the same curve (titres appropriately normalized) for both humans and RM, thereby enabling simultaneous modelling of all the data while providing flexibility in the number of shared parameters between the two species during estimation. The joint MBMA model also reasonably predicted VE (RMSPE 6.6%).

Once sufficient phase 3 clinical data were reported, clinical data alone enabled an MBMA to quantify the relationship between HCS-normalized SN titres (SN/HCS ratio) and clinical efficacy. The 50% protective titres predicted from the calibrated RM MBMA model, joint MBMA model, and the clinical MBMA model were consistent across the three approaches (24.3% (95%CI: 14.1%-46.5%), 24.1% (95%CI: 7.0%, 77.0%), and 21.0% (95%CI: 15.0%, 30.0%), respectively, of HCS). The consistency in the point estimate provides additional confidence in leveraging these approaches for VE predictions based on the data available at a given stage of development for a new vaccine candidate. The larger CI obtained with the joint MBMA model is perhaps due to the model describing the protection data in both species simultaneously.

We also assessed the predictive ability of these three models through the prediction of clinical efficacies of BBV152 and Coronovac, whose data were not included in the development of the models. The predictions were carried out using only their clinical SN/HCS ratio as the input to the MBMA models. All three models accurately predict the efficacy of BBV152 and the 95% CI. While the predicted 95% CI of CoronaVac encompasses the observed efficacy point estimate, the point estimate is not accurately predicted. CoronaVac has a reported clinical efficacy of 50% and therefore occurs in the most sensitive region of the efficacy vs. titre relationship. We attribute the lack of accuracy in the efficacy predictions of CoronaVac to the limited data and the large uncertainty in normalized SN titres corresponding to a ~ 50% vaccine efficacy in the available clinical dataset. ChAdOx1 nCoV-19, for which data were included in model building, had 5-fold higher normalized SN titres than CoronaVac and reported efficacy similar to CoronaVac's. When CoronaVac was included in the clinical MBMA model estimation as a sensitivity analysis, model parameters changed only marginally: the IT50 estimate was slightly lower, 0.186 (95% C.I.: 0.131-0.265) as compared to 0.21 when CoronaVac was not included in the model estimation. In addition, when the model was refit including BBV152 and CoronaVac in the clinical MBMA model and excluded ChAdOx1 nCoV-19, and BNT162b2, the RMSPE for the new model was lower (3.6%) compared to the original model (6.9%), indicating an improvement in fit. However, the model parameters changed only marginally (about 15% for IT50), therefore suggesting the model is relatively robust to the difference in data sets. To highlight another important application, we predicted the efficacies of two vaccines (BNT162b2, and ChAdOx1 nCoV-19) against the delta variant using the reported drop in in-vitro SN titres for that variant compared to the original strain. Although the efficacy predictions of BNT162b2 are more accurate than those for ChAdOx1 nCoV-19, the data suggest that, overall, the three models have demonstrated reasonable predictive power, especially given that only the *in vitro* data of the fold decrease in SN titre of the variant relative to WT was leveraged in predicting clinical efficacies for the corresponding variant. The wider 95% CIs are due to the wider variability of the titre ratios that needed to be incorporated in the predictions. Therefore, the VE predictions consistent with the reported efficacies of these vaccines against the delta variant demonstrate the utility of these models to predict vaccine efficacies against variants. In addition, these results demonstrate SN titres could be predictive of efficacy regardless of vaccine mechanism or variant, and therefore suggesting that this approach may also be predictive of vaccine efficacy after a booster dose. Recently, the fold change decrease in SN titres against the omicron variant after three doses (relative to SN titres against the WT strain after two doses of the vaccine) have been reported for a few vaccines (Table S5).[51–53] Based on these reports, the model-predicted VE for BNT162b2, mRNA-1273, and 2019nCoV vaccines against the omicron variant would be 83.4% (95% CI: 72.5% -90.4%), 89.8% (95% CI: 85.5% -93.0%), and 92.7% (95% CI: 86.7% -96.3%) respectively. (No quantitative estimate of efficacy against omicron was available currently.) Recent literature based on nonclinical species[3] as well as human data support that SN titre time-course seems predictive of efficacy at a given time (i.e., it is the SN titre at the time of exposure that determines efficacy, not just the peak titre after vaccination), and efficacy after vaccine booster shots has been predicted elsewhere.[54] [Reference 54 is a preprint/non peer reviewed article]

The quantitative relationship the model provides between clinical efficacy and titres enables dose selection using only a clinical dose-immunogenicity relationship (for a given vaccine candidate). The presented model relates immunogenicity to protection in RM and to relative incidence rate observed in clinical trials. Therefore, an initial prediction based on nonclinical data requires the assumption that the immunogenicity in RM of the dose used in RM represents the (calibrated) clinical immunogenicity in a manner consistent with the other vaccines tested. In the examples used here, the fit and prediction results generally seem to indicate that the assumption is supported when the RM and clinical doses are the same. If dose-ranging is performed in RM, then a dose which provides a "plateau" response would, based on the model, be assumed to provide maximal possible clinical efficacy for that vaccine. Translation of the dose-response itself requires a different kind of modelling than that used here, and this becomes substantially more complex when multiple doses are required so that inter-dose timing becomes an additional (and important) factor. As suggested above, using dose-immunogenicity modelling on clinical data can provide more direct evidence of a plateau in immune response (caveats about multi-dose regimens are similarly applicable). The framework presented here illustrates how such emerging clinical immunogenicity data can be used to predict efficacy and, once corresponding efficacy data are available, and how to refine predictions based on a learn-and-confirm paradigm.

There are limitations to our analysis. Different neutralization assays were used across studies. Therefore, normalization of SN titres with the corresponding convalescent serum titre using the same assay was carried out (even though the definition of convalescence was not uniform across studies), as has been established by other groups[4,5] as a reasonable approach to harmonize SN titres across studies. Vaccine studies in RM also used different types of neutralization assays (PRNT, MN, and CPE assays), and the type of virus (live vs. pseudo) used in those assays also differed. Unlike clinical trials, convalescent titres using the corresponding

assays were either not reported or the definition of convalescence was not clearly stated in most of these RM studies. Hence the approach to normalize the SN titres to their corresponding convalescent titres was not carried out for the RM data. The RM MBMA analysis established a strong relationship between SN titres and viral load without normalizing the SN titres, probably because of the relatively large number of vaccine studies (data points) included in the RM MBMA model (essentially enabling the model to average out the impact of assay differences), a different circumstance than that for the relatively sparse clinical data. We found a notable consistency in the data that used different assays and no systematic impact of the assay differences was found on the relationship between SN titres and VL in RM. This seems supported by literature, indicating substantial variability in assay results, but no clear systematic differences between live and pseudo virus assay results.[55–57] The translation of the RM MBMA model assumed that the relationship of log(viral load) to log (SN) has the same shape as that of incidence rate (IR) to log (SN) (an assumption about the mapping of viral load in RM to clinical incidence rate). The assumption was made based on previous investigations in RSV[14] which successfully used the same type of mapping. The efficacy predictions resulting from the mapping were in reasonable agreement with the observed data. However, a reasonable fit does not constitute an independent validation of the translational assumption, and therefore this assumption is a limitation of the translational approach requiring support by additional (future) data. Another limitation of our approach is that we have only looked at neutralizing antibody data as predictor of efficacy given the strong evidence of its role in protection. Cellular responses (T and B cell memory) and non-neutralizing Fc effector functions could also potentially contribute to protection, and as additional evidence on their role in protection becomes available that could also be modelled.

In summary, the MBMA models presented here are predictive of vaccine-induced efficacy against SARS-CoV-2. Although there are reports in the literature demonstrating neutralizing antibodies as a CoP in RM,[1–3] this study adds the translation of protection in RM to clinical efficacy based on SN titres. This translation provides a powerful quantitative framework, enabling early prioritization of (and Go/No Go decisions for) vaccine candidates in discovery before substantial time and resources are invested in the clinical development of those candidates. The predicted 50% protective titres from the MBMA models also corroborate previous findings by Khoury et al.,[4] and are consistent with more recent work by Padmanabhan et al.,[58] increasing the confidence in that number. The models also can predict VE against variants of concern (including delta and omicron variants). Overall, the correlates-of-protection models relating SN titre to clinical outcome presented here are also generalizable to vaccines beyond SARS-CoV-2, as recently shown by Maas et al. for RSV.[14] The work shown here serves as an important example of a framework to predict VE using only protection data in animal models, and thereafter a framework to incorporate early clinical immunogenicity data to improve VE predictions driving model-informed decision-making during vaccine development.

Contributors

BK, NP, AC, AL, SR, SYAC, RDG, RJS, and JRS were involved in conceptualization of this study. BK, NP, AC, AL, KW, RT, SYAC, and JRS managed data curation for this study. Formal data analysis was performed by BK, NP, AC, AL, SR, SAD, SYAC, and JRS. Funding for this study was acquired by JRS. Investigation was performed by BK, AC, SR, SYAC, and JRS. BK, NP, AC, AL, SR, SYAC, JS, and JRS developed or designed methodology for this study. BK, SYAC, RDG, and JRS served as project administrators. AC, AL, SR, and SYAC provided software assistance. BK, KW, SYAC, RDG, JS, and JRS played a supervisory role. Validation of research outputs and verification of underlying data was provided by BK, NP, AC, AL, SR, SYAC, and JRS. BK, NP, AC, AL, SR, RDG, and JRS prepared or created visualization/ data presentations for this study. BK, NP, AC, AL, KW, SYAC, and JRS wrote the original draft and all authors participated in reviewing and editing the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is available at http://engagezone.msd.com/ds_documentation.php through the EngageZone site or via email to dataaccess@merck.com. (For the purposes of this manuscript, this also applies to code).

Declaration of interests

Certara received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, for modelling work. BK, AC, SR, SAD, JS, and JRS are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA, and have received support for attending meetings and/or travel. NP, AL, KW, RT, and RDG are employees of Certara, Princeton, NJ, USA and hold stock or stock options. SYAC is an employee of Certara, Princeton, NJ, USA and holds Certara and AstraZeneca stock or stock options.

Acknowledgements

We thank Maheswar Ganta, Marianne van Vugt, Nina Tsuneda, Niharika Gandhapuneti, and Neelima

Kankanampati from Certara Data Science Group for literature search and review, digitization of literature data, database development, curation, augmentation, and QC. We also thank (both of Certara, Princeton, NJ) Jos Lommerse for valuable scientific input on MBMA model development, and Amy Porter for medical writing support. We thank (all of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of this analysis): Amy Espeseth, Kalpit Vora, Andrew Bett, Antonios Aliprantis, Kevin Russell and many others from Vaccine Discovery, Clinical, Translational Medicine, Bioanalytical, and Quantitative Pharmacology and Pharmacometrics for careful review of the abstracts, for valuable input on assays and model assumptions, and for critical review of the manuscript. This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104264.

References

1 McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature*. 2021;590:630–634.
2 Corbett KS, Nason MC, Flach B, et al. Immune correlates of protection by mRNA-1273 vaccine against sars-cov-2 in nonhuman primates. *Science*. 2021;373:eabj0299.
3 Roozendaal R, Solforosi L, Stieh DJ, et al. SARS-CoV-2 binding and neutralizing antibody levels after Ad26.COV2.S vaccination predict durable protection in rhesus macaques. *Nat Commun*. 2021;12:5877.
4 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205–1211.
5 Earle KA, Ambrosino DM, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine*. 2021;39:4423–4428.
6 Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:2032–2040.
7 Padmanabhan P, Desikan R, and Dixit NM. 2021. Modelling the population-level protection conferred by covid-19 vaccination. medRxiv. 2021.2003.2016.21253742. https://doi.org/10.1101/2021.03.16.21253742.
8 Upreti VV, Venkatakrishnan K. Model-based meta-analysis: optimizing research, development, and utilization of therapeutics using the totality of evidence. *Clin Pharmacol Ther*. 2019;106:981–992.
9 Wouters OJ, Shadlen KC, Salcher-Konrad M, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *Lancet*. 2021;397:1023–1034.
10 Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among us veterans during 2021. *Science*. 2021:375:331–336.
11 Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *N Engl J Med*. 2020;383:1544–1555.
12 Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature*. 2020;586:583–588.
13 van Doremalen N, Purushotham JN, Schulz JE, et al. Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces shedding of SARS-CoV-2 D614G in rhesus macaques. *bioRxiv*. 2021:2021.2001.2009.426058. https://doi.org/10.1101/2021.01.09.426058.
14 Maas BM, Lommerse J, Plock N, et al. Forward and reverse translational approaches to predict efficacy of neutralizing respiratory syncytial virus (RSV) antibody prophylaxis. *EBioMedicine*. 2021;73:103651.
15 Lommerse J, Plock N, Cheung SYA, Sachs JR. V²ACHER: visualization of complex trial data in pharmacometric analyses with covariates. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:1092–1106.
16 Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020;581:465–469.
17 Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science*. 2020;369:812–817.
18 Yang J, Wang W, Chen Z, et al. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. *Nature*. 2020;586:572–577.
19 Guebre-Xabier M, Patel N, Tian JH, et al. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. *Vaccine*. 2020;38:7892–7896.
20 Patel A, Walters J, Reuschel EL, et al. Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model. *bioRxiv*. 2020:2020.2007.2028.225649. https://doi.org/10.1101/2020.07.28.225649.
21 Yu J, Tostanoski LH, Peter L, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science*. 2020;369:806–811.
22 van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature*. 2020;586:578–582.
23 Rauch S, Gooch K, Hall Y, et al. mRNA vaccine CVnCoV protects non-human primates from SARS-CoV-2 challenge infection. *bioRxiv*. 2020:2020.2012.2023.424138. https://doi.org/10.1101/2020.12.23.424138.
24 Furuyama W, Shifflett K, Pinski AN, et al. Rapid protection from COVID-19 in nonhuman primates vaccinated intramuscularly but not intranasally with a single dose of a recombinant vaccine. *bioRxiv* 2021.01.19.426885. https://doi.org/10.1101/2021.01.19.426885.
25 Brouwer PJM, Brinkkemper M, Maisonnasse P, et al. Two-component spike nanoparticle vaccine protects macaques from SARS-CoV-2infection. *bioRxiv*. 2020:2020.2011.2007.365726. https://doi.org/10.1101/2020.11.07.365726.
26 Pfizer. *Pfizer-BioNTech COVID-19 Vaccine (BNT162, PF-07302048) Vaccines and Related Biological Products Advisory Committe Briefing Document*. 2020. Available at; https://www.fda.gov/media/144246/download. Accessed 7 November 2021.
27 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383:2603–2615.
28 Walsh EE, Frenck Jr. RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med*. 2020;383:2439–2450.
29 Moderna. *mRNA-1273 Sponsor Briefing Document Vaccines and Related Biological Products Advisory Committee*. 2020. Available at; https://www.fda.gov/media/144452/download. Accessed 7 November 2021.
30 Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. 2021;39:2791–2799.
31 Janssen Biotech Inc. *COVID-19 Vaccine Ad26.COV2.S VAC31518 (JNJ-78436735) Sponsor Briefing Document Vaccines and Related Biological Products Advisory Committee*. 2021. Available at; https://www.fda.gov/media/146219/download. Accessed 7 November 2021.
32 Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine. *N Engl J Med*. 2021;384:1824–1835.
33 Formica N, Mallory R, Albert G, et al. Evaluation of a SARS-CoV-2 Vaccine NVX-CoV2373in younger and older adults. *medRxiv*. 2021:2021.2002.2026.21252482. https://doi.org/10.1101/2021.02.26.21252482.
34 Novavax. *Efficacy Data Updates from Novavax' Protein-Based Vaccine Candidate*. 2021. Available at; https://www.novavax.com/sites/default/files/2021-02/20210202-NYAS-Novavax-Final.pdf. Accessed 7 November 2021.
35 Logunov DY, Dolzhikova IV, Shcheblyakov DV, 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;397:671–681.
36 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;396:887–897.
37 Folegatti PM, Ewer KJ, Aley PK, 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;396:467–478.
38 Voysey M, Clemens SAC, Madhi SA, 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*. 2021;397:99–111.
39 Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21:181–192.
40 Sinovac. *Summary of Clinical Trial Data of Sinovac's COVID-19 Vaccine (CoronaVac®)*. 2021. Available at; http://www.sinovacbio.com/news/shownews.php?id=1154&lang=en. Accessed 7 November 2021.
41 Ella R, Reddy S, Blackwelder W, et al. Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial. *medRxiv*. 2021:2021.2006.2030.21259439. https://doi.org/10.1101/2021.06.30.21259439.
42 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;21:950–961.
43 Liu C, Ginn HM, Dejnirattisai W, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell*. 2021;184. 4220–4236.e4213.
44 Cromer D, Steain M, Reynaldi A, et al. SARS-CoV-2 variants: levels of neutralisation required for protective immunity. *medRxiv*2021:2021.2008.2011.21261876. https://doi.org/10.1101/2021.08.11.21261876.
45 Robbins JA, Tait D, Huang Q, et al. Safety and immunogenicity of intramuscular, single-dose V590 (rVSV-SARS-CoV-2 Vaccine) in healthy adults: results from a phase 1 randomised, double-blind, placebo-controlled, dose-ranging trial. *EBioMedicine*. 2022;82:104138. https://doi.org/10.1016/j.ebiom.2022.104138.
46 Vanhoutte F, Liu W, Wiedmann RT, et al. Safety and immunogenicity of measles vector-based SARS-CoV-2 vaccine candidate, V591, in adults: results from a phase 1/2 randomized, double-blind, placebo-controlled, dose ranging trial. *EBioMedicine*. 2022;75:103811.
47 Lommerse J. (lost in) translation: Rodent modeling and validation with mbma. American Conference of Pharmacometrics (ACoP). *Virtual*. 2021. Available at; https://www.go-acop.org/default.asp?id=44&keuze=meeting&mid=8. Accessed 15 February 2022.
48 Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26:681–687. https://doi.org/10.1038/s41591-020-0868-6.
49 Jacqmin P, McFadyen L, Wade JR. Basic PK/PD principles of drug effects in circular/proliferative systems for disease modelling. *J Pharmacokinet Pharmacodyn*. 2010;37:157–177. https://doi.org/10.1007/s10928-010-9151-7.
50 Celisse A. Optimal cross-validation in density estimation with the *L*2-loss. *Ann Stat*. 2014;42:1879–1910.
51 Muik A, Lui BG, Wallisch AK, et al. Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-elicited human sera. *Science*. 2022;375:678–680. https://doi.org/10.1126/science.abn7591.
52 Pajon R, Doria-Rose NA, Shen X, et al. SARS-CoV-2 omicron variant neutralization after mRNA-1273 booster vaccination. *N Engl J Med*. 2022;386:1088–1091. https://doi.org/10.1056/NEJMc2119912.
53 Novavax. Novavax announces initial Omicron cross-reactivity data from COVID-19 vaccine booster and adolescent studies. 2021. Available at: https://ir.novavax.com/2021-12-22-Novavax-Announces-Initial-Omicron-Cross-Reactivity-Data-from-COVID-19-Vaccine-Booster-and-Adolescent-Studies. Accessed 2 February 2022.
54 Chen X, Wang W, Chen X, et al. Prediction of long-term kinetics of vaccine-elicited neutralizing antibody and time-varying vaccine-specific efficacy against the SARS-CoV-2 delta variant by clinical endpoint. *medRxiv*. 2021:2021.09.23.21263715 https://doi.org/10.1101/2021.09.23.21263715.
55 Sholukh AM, Fiore-Gartland A, Ford ES, et al. Evaluation of cell-based and surrogate SARS-CoV-2 neutralization assays. *J Clin Microbiol*. 2021;59:e0052721.
56 Mattiuzzo G, Bentley EM, Hassall M, et al. *Establishment of the WHO International Standard and Reference Panel for Anti-SARS-CoV-2 Antibody*. World Health Organization; 2020. Available at; https://cdn.who.int/media/docs/default-source/biologicals/ecbs/bs-2020-2403-sars-cov-2-ab-ik-17-nov-2020_4ef4fdae-e1ce-4ba7-b21a-d725c68b152b.pdf. Accessed 15 February 2022.
57 COVAX. COVID-19: correlates of protection. *Clinical Development & Operations and Enabling Sciences SWAT Teams*. 2020. Available at; https://media.tghn.org/medialibrary/2020/11/201119_COVAX_CoP_Workshop_Complete_Materials_vF.pdf. Accessed 15 February 2022.
58 Padmanabhan P, Desikan R, Dixit NM. Modeling how antibody responses may determine the efficacy of covid-19 vaccines. *Nat Comput Sci*. 2022;2:123–131.