

What level of neutralising antibody protects from COVID-19?

5 David S Khoury^{1*}, Deborah Cromer^{1*}, Arnold Reynaldi¹, Timothy E Schlub^{1,2}, Adam K Wheatley³, Jennifer A Juno³, Kanta Subbarao^{3, 4}, Stephen J Kent^{3, 5, 6}, James A Triccas^{7*}, Miles P Davenport^{1*#}.

- 10 1. Kirby Institute, University of New South Wales, Sydney, Australia
 2. Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia
 3. Department of Microbiology and Immunology, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
 15 4. WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
 5. Australian Research Council Centre for Excellence in Convergent Bio-Nano Science and Technology, University of Melbourne, Melbourne, Victoria, Australia
 6. Melbourne Sexual Health Centre and Department of Infectious Diseases, Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia.
 20 7. School of Medical Sciences and Marie Bashir Institute, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW, Australia.

25 * These authors contributed equally to the work.
 # Corresponding author: m.davenport@unsw.edu.au

Abstract:

Both previous infection and vaccination have been shown to provide potent protection from COVID-19. However, there are concerns that waning immunity and viral variation may lead to a loss of protection over time. Predictive models of immune protection are urgently needed to identify immune correlates of protection to assist in the future deployment of vaccines. To address this, we modelled the relationship between in vitro neutralisation levels and observed protection from SARS-CoV-2 infection using data from seven current vaccines as well as convalescent cohorts. Here we show that neutralisation level is highly predictive of immune protection. The 50% protective neutralisation level was estimated to be approximately 20% of the average convalescent level (95% CI = 14-28%). The estimated neutralisation level required for 50% protection from severe infection was significantly lower (3% of the mean convalescent level (CI = 0.7-13%, $p = 0.0004$). Given the relationship between in vitro neutralization titer and protection, we then used this to investigate how waning immunity and antigenic variation might affect vaccine efficacy. We found that the decay of neutralising titre in vaccinated subjects over the first 3-4 months after vaccination was at least as rapid as the decay observed in convalescent subjects. Modelling the decay of neutralisation titre over the first 250 days after immunisation predicts a significant loss in protection from SARS-CoV-2 infection will occur, although protection from severe disease should be largely retained. Neutralisation titres against some SARS-CoV-2 variants of concern are reduced compared to the vaccine strain and our model predicts the relationship between neutralisation and efficacy against viral variants. Our analyses provide an evidence-based prediction of SARS-CoV-2 immune protection that will assist in developing vaccine strategies to control the future trajectory of the pandemic.

Main text:

SARS-CoV-2 has spread globally over the last year, infecting an immunologically naïve population and causing significant morbidity and mortality. Immunity to SARS-CoV-2 induced either through natural infection or vaccination has been shown to afford a degree of protection and/or reduce the risk of clinically significant outcomes. For example, seropositive recovered subjects have been estimated to have 89% protection from reinfection ¹, and vaccine efficacies from 50 to 95% have been reported ². However, the duration of protective immunity is unclear, with primary immune responses inevitably waning ³⁻⁵, and ongoing transmission of increasingly concerning viral variants that escape immune control ⁶.

A critical question at present is to identify the immune correlate(s) of protection from SARS-CoV-2 infection and therefore predict how changes in immunity will be reflected in clinical outcomes. A defined correlate of protection will permit both confidence in opening up economies and facilitate rapid improvements in vaccines and immunotherapies. In influenza infection, for example, a hemagglutination inhibition (HAI) titre of 1:40 is thought to provide 50% protection from influenza infection ⁷ (although estimates range from 1:17 – 1:110 ^{8,9}). This level was established over many years using data from a standardised HAI assay¹⁰ applied to serological samples from human challenge and cohort studies. At present, however, there are few standardised assays for assessing SARS-CoV-2 immunity, little data comparing immune levels in susceptible versus resistant individuals, and no human challenge model ¹¹.

The data currently available for SARS-CoV-2 infection includes immunogenicity data from phase 1 / 2 studies of vaccines and data on protection from preliminary reports from phase 3 studies and in seropositive convalescent individuals (see Supplementary Tables 1 and 2). While antiviral T and B cell memory certainly contribute some degree of protection, strong evidence of a protective role for neutralising serum antibodies exists. For example, passive transfer of neutralising antibodies can prevent severe SARS-CoV-2 infection in multiple animal models ^{12,13} and Regeneron has recently reported similar data in humans ¹⁴. We therefore focus our studies on *in vitro* virus neutralisation titres reported in studies of vaccinated and convalescent cohorts. Unfortunately, the phase 1 / 2 studies all use different assays for measuring neutralisation. Normalisation of responses against a convalescent serum standard has been suggested to provide greater comparability between the results from

different assays¹⁵. Although all studies compare immune responses after vaccination against the responses in convalescent individuals, the definition of convalescence is not standardised across studies. Similarly, in phase 3 studies the timeframes of study and case-definitions of infection also vary amongst studies (see Supplementary Table 2). Recognising these limitations, we aimed to investigate the relationship between vaccine immunogenicity and protection.

To compare neutralisation titres across studies we determined the mean and standard deviation (on log-scale) of the neutralisation titre in each study. These were normalised to the mean convalescent titre using the same assay in the same study (noting that the definition of convalescence was also not standardised across studies and a variable number of convalescent samples are studied). We then compared this normalised neutralisation level in each study against the corresponding protective efficacy reported from the phase 3 clinical trials. Despite the known inconsistencies between studies, comparison of normalised neutralisation levels and vaccine efficacy demonstrates a remarkably strong non-linear relationship between average neutralization level and reported protection across different vaccines (Spearman $r=0.905$; $p=0.0046$, Figure 1A).

To further dissect the relationship between immunogenicity and protection in SARS-CoV-2 we considered the parallels with previous approaches to estimating a ‘50% protective titre’ in influenza infection. These historic studies in influenza involved comparison of HAI titres in infected versus uninfected subjects (in either natural infection or human challenge studies), and used logistic or receiver-operating characteristics (ROC) approaches to identify an HAI titre that provided protection^{7-9,16,17}). We adapted these approaches to analyse the existing data on ‘average neutralisation level’ in different studies and the observed level of protection from infection (details of statistical methods are provided in the Supplementary material).

We first fitted a logistic model to estimate the ‘50% protective neutralisation level’ (across all studies) that best predicted the protective effect observed in each study (consistent with the use of a logistic function to model protection in influenza serological studies^{16,17}). We estimate from this model a 50% protective neutralisation level of 19.9% (95% CI = 14.1% – 28.1%) of the mean convalescent level (Figures 1A and 1B), and that this model provided a good explanation of the relationship between average neutralisation level and protection across the studies. Since the model is dependent on the mean and distribution of

neutralisation levels, we also estimated these using different approaches, leading to similar estimates (Fig. S2 and Supplementary Methods).

To relax the assumption that neutralisation levels are normally distributed in the above model, we also estimated the protective level using a distribution-free approach applied to the raw data for individual neutralisation levels reported in the studies. This method finds a protective neutralisation threshold that maximises the chances of classifying individuals as protected or not protected based on their neutralisation level being above or below the threshold and on the observed protective efficacy in Phase 3 trials (i.e.: it does not rely on neutralisation levels being normally distributed). We refer to this as the ‘protective neutralisation classification model’. Using this classification approach the estimated protective threshold was 28.6% (CI= 19.2% – 29.2%) of the average convalescent level. As expected, the estimated protective level using the classification method was slightly higher than the 50% protective level estimated using the logistic method, as the classification method essentially estimates a level of 100% protection instead of 50% protection.

This analysis suggests that the 50% neutralisation level for SARS-CoV-2 is approximately 20% of the average convalescent titre. This analysis shows that the relationship between the average protective levels and the observed protective efficacy across different vaccines can be predicted based on consideration of the level and distribution of neutralisation titres. To test the potential utility of this in predicting the protective efficacy of an unknown vaccine, we repeated our analysis with a ‘leave-one-out’ approach. That is, we fitted all possible groups of seven vaccine or convalescent studies and used this to predict the efficacy of the 8th. Figure 1C shows the results of using the logistic model of protection to predict the efficacy of each vaccine from the results of the other seven. In addition, after fitting the model to the data for eight vaccine / convalescent studies, the phase 3 results of another vaccine were released in a press release on 3 March 2021. Using the observed neutralisation level (a mean of 79.2% of the convalescent titre in that study (See Supplementary Table 1) the predicted efficacy of the new vaccine was 79.4%, (95% Predictive Interval: 76.0%-82.8%), which is in very close agreement with the reported efficacy of 80.6%¹⁸, and suggests good predictive value of the model (Figure 1A).

As discussed above, a major caveat of our estimate of the relative protective level of antibodies in SARS-CoV-2 infection is that it includes aggregation of data collected from

diverse neutralisation assays and clinical trial designs. Clearly, a more standardised approach to assays and trials design would allow refinement of these analyses¹¹, although this has not occurred so far. In addition, the association of neutralisation with protection across these studies does not prove that neutralising antibodies are mechanistic in mediating protection. It is possible that neutralisation is correlated with other immune responses, leading to an apparent association (as has been suggested for the use of HAI titre in influenza ¹⁹⁻²¹). Another important refinement of this approach would be to have standardised measures of other serological and cellular responses to infection to identify if any of these provide a better predictive value than neutralisation. However, despite these limitations it is tempting to consider the implications of this protective titre for immunity to SARS-CoV-2 infection.

Recent studies have identified a decline in neutralisation titre with time after both natural infection and vaccination^{3,4}. An average half-life of 90 days over the first 8 months of infection has been reported⁵ although our analysis suggests that an early rapid decline slows with time³. A major question is whether vaccine-induced responses may be more durable than those following infection. Limited studies have analysed the trajectory of neutralisation titre after vaccination²². To compare decay in neutralisation titre we fitted a model of exponential decay over equivalent time periods in data from either convalescent³ or mRNA vaccination²² cohorts. Comparing neutralisation titres measured between 26 and 115 days after either mRNA-based vaccination²² or symptom onset for post-infection sera ³, we found similar half-lives (65 days vs 58 days, respectively, $p = 0.88$, likelihood ratio test. See supplementary Figure S3). Although this comparison relies on limited data, it suggests that decay of vaccine-induced neutralisation is similar to that observed after natural infection.

If the relationship between neutralisation level and protection that we observe cross-sectionally between different vaccines is maintained over time, we can use our model to predict how the observed waning of neutralisation titres might affect vaccine effectiveness. Important caveats to such an extrapolation are that (i) it assumes that neutralisation is a major mechanism of protection (or that the mechanism of protection remains correlated with neutralisation), although B cell memory and T cell responses may be more durable ^{3-5,23} (and indeed B cell responses have been shown to increase following infection ³), (ii) it applies the decay of neutralisation observed in convalescence to the vaccine data, and (iii) it assumes that the decay in titre is the same regardless of the initial starting titre (whereas others have suggested faster decay for higher initial levels ²⁴). These limitations notwithstanding, we used

the estimated half-life of neutralisation titre of 90 days derived from a study of convalescent individuals⁵ and modelled the decay of neutralisation and protection over the first 250 days after vaccination (Figure 2A). Our model predicts that waning neutralisation titre will have non-linear effects on protection from SARS-CoV-2 infection, depending on initial vaccine efficacy. For example, a vaccine starting with an initial efficacy of 95% would be expected to maintain 58% efficacy by 250 days. However, a response starting with an initial efficacy of 70% would be predicted to drop to 18% efficacy after 250 days. This analysis can also be used to estimate how long it would take a response of a given initial efficacy to drop to 50% (or 70%) efficacy, which may be useful in predicting the time until boosting is required to maintain a minimal level of efficacy (Figure 2B). Clearly data generated from standardised assays are needed to track the long-term decay of post-vaccination immune responses and their relationship to clinical protection. However, this model provides a framework that can be adapted to predict outcomes as further immune and protection data becomes available. Indeed, if a disconnect between the decay of neutralisation titre and protection is observed, this may be a direct pointer to the role of non-neutralising responses in protection.

In addition to the effect of declining neutralisation titre over time, reduced neutralisation titres and reduced vaccine efficacy to different viral variants have also been observed^{6,25-28}. For example, it has been reported that the neutralisation titre against the B.1.351 variant in vaccinated individuals is between 7.6-fold and 9-fold lower compared to the early Victoria variant²⁹. Our model predicts that a lower neutralisation titre against a variant of concern will have a larger effect on vaccines for which protective efficacy against the wild-type virus was lower (Figure 2C). For example, a five-fold lower neutralisation titre is predicted to reduce efficacy from 95% to 67% in a high efficacy vaccine, but from 70% to 25% for a vaccine with lower initial efficacy.

The analysis above investigates vaccine (and convalescent) protection against detectable SARS-CoV-2 infection (using the definitions provided in the different phase 3 and convalescent studies, see Supplementary Table 2). However, it is thought that the immune response may provide greater protection from severe infection than from mild infection. To investigate this, we also analysed data on the observed level of protection from severe infection where this was available (Supplementary Table 3, noting that the definition of severe infection was not consistent across studies). As there have been under 100 severe infections reported across all the phase 3 trials combined, the confidence intervals on the

level of protection from severe infection are broad. The neutralisation level for 50% protection from severe infection was 3.1% of the average convalescent level (CI= 0.75% - 12.7%), which was significantly lower than the 20% level required for protection from any infection ($p = 0.0004$, likelihood ratio test, Supplementary Table 4). An important caveat to this analysis is the implicit assumption that neutralisation titre itself confers protection from severe infection, while cellular responses may also be important³⁰⁻³².

The estimated neutralisation level for protection from severe infection is approximately 6 times lower than the level required to protect from any infection. Thus, a higher level of protection against severe infection is expected for any given level of vaccine efficacy against mild (any) SARS-CoV-2 infection. Assuming that this relationship remains constant over time, it appears likely that immunity to severe infection may be much more durable than overall immunity to any infection. Long-term studies of antibody responses to other vaccines suggest that these responses generally stabilise with half-lives >10 years^{33,34}. Therefore we projected beyond the reported decay of SARS-CoV-2 responses (out to 8 months post-infection⁵) assuming that after 8 months post-infection the decay rate decreases exponentially (at rate $0.01d^{-1}$) until a 10-year half-life is achieved (details in Supplementary Methods). This analysis predicts that even without immune boosting a significant proportion of individuals may maintain protection from severe infection with an antigenically similar strain over the long term, even though they may become susceptible to mild infection (Figure 3B,C).

Understanding the relationship between measured immunity and clinical protection from SARS-CoV-2 infection is urgently needed for planning the next steps in the COVID-19 vaccine program. Placebo controlled vaccine studies are unlikely to be possible in the development of next generation vaccines, and therefore correlates of immunity will become increasingly important in planning booster doses of vaccine, prioritising next-generation vaccine development and powering efficacy studies³⁵. Our work uses available data on immune responses and protection to model both the protective titre and long-term behaviour of SARS-CoV-2 immunity. It suggests that neutralisation titre will be an important predictor of vaccine efficacy in future as new vaccines emerge. The model also predicts that immune protection from infection may wane with time as neutralisation levels decline and that booster immunisation may be required within a year. However, protection from severe infection may be considerably more durable, as lower levels of response may be required or alternative responses (such as cellular immune responses) may play a more prominent role. Our results

are consistent with studies of both influenza and seasonal coronavirus infection, where
260 reinfection is possible a year after initial infection, although usually resulting in mild
infection^{36,37}. Similarly, after influenza virus vaccination, protective efficacy is thought to
decline by around 7% per month³⁸. Our modelling and predictions are based on a number of
assumptions on the mechanisms and rate of loss of immunity. Important priorities for the
field are the development of standardised assays to measure neutralisation and other immune
265 responses, as well as standardised clinical trial protocols. These data will allow further testing
and validation of other potential immune correlates of protection. However, our study
develops a modelling framework for integrating available, if imperfect, data from vaccination
and convalescent studies to provide a tool for predicting the uncertain future of SARS-CoV-2
immunity.

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Ethics statement:

This work was approved under the UNSW Sydney Human Research Ethics Committee (approval HC200242).

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Figures:

Figure 1: Understanding the relationship between neutralisation and protection.

- A) Relationship between neutralisation level and protection from SARS-CoV-2 infection. The reported mean neutralisation level (x-axis) from phase 1 / 2 trials and protective efficacy from phase 3 trials (y-axis) for seven vaccines, as well as the protection observed in a seropositive convalescent cohort are shown (details of data sources in Supplementary Tables 1 and 2). Mean / point estimates are indicated by dots (95% confidence intervals are indicated as whiskers). Red solid line indicates the best fit of the logistic model and shaded red indicates the 95% predictive interval of the model. The mean neutralisation level and protective efficacy of the Covaxin vaccine is indicated as a green circle (data from this study was only available after modelling was complete and did not contribute to fitting).
- B) Schematic illustration of the logistic approach to identifying the protective neutralisation level. The data for each study includes the mean and distribution of the in vitro neutralisation titre against SARS-CoV-2 in vaccinated or convalescent subjects (as a proportion of the titre in convalescent subjects)(green/red bell curve), accompanied by a level of protective efficacy for the same regimen. The efficacy is illustrated by the proportion of bell curve 'protected' (green) versus 'susceptible (red) for individual studies (shaded areas in between reflect the changing risk). The modelling fits the optimal 50% protective neutralisation level (blue dashed line, shaded areas indicate 95% confidence limits) that best estimates the correct levels of protection observed across the different studies.
- C) Predictions of the 'leave one out' analysis. Modelling was repeated multiple times using all potential sets of seven vaccination / convalescent studies to predict the efficacy of the eighth study. Dots indicate point estimates and whiskers indicate 95% confidence / predictive intervals.

Figure 2: The effects of waning neutralisation titre on protection.

- A) Predicting the effects of declining neutralisation titre. Assuming the observed relationship between neutralisation level and protection is consistent over time, we estimate the decline in efficacy for vaccines starting with different levels of early protection. The model assumes a half-life of neutralisation titre of 90 days over the first 250 days (as observed in a convalescent cohort⁵). Coloured lines indicate the predicted trajectory for groups starting with different initial efficacy.
- B) Modelling the time for efficacy to drop to 70% (red line) or 50% (blue line) for scenarios with different initial efficacy (indicated on the y-axis). For example, for a group starting with an initial protective efficacy of 90% the model predicts that 70% efficacy will be reached after 131 days, and 50% efficacy after 221 days.
- C) Estimating the impact of viral antigenic variation on vaccine efficacy. *In vitro* studies have shown that neutralisation titres against some SARS-CoV-2 variants are reduced compared to titres against wild-type virus. If the relationship between neutralisation and protection remains constant, we can predict the difference in protective efficacy against wild-type and variant viruses from the difference in neutralisation level. For cohorts with a given initial protective efficacy measured against wild-type (vaccine strain) virus (x-axis), we model the impact of a two-fold (red), 5-fold (green) or 10-fold (blue) reduction in neutralisation titre to a variant virus. The y-axis indicates the

predicted new efficacy against the variant strain. Dashed line indicates equal protection against wild-type and variant strains.

Details of the data and modelling are provided in the Supplementary Material.

Figure 3: Protection from severe infection.

- A) The predicted relationship between efficacy against mild (any) SARS-CoV-2 infection (x-axis) versus efficacy against severe infection (y-axis). The black line indicates the best fit model for the relationship between protection against any versus severe SARS-CoV-2 infection. Shaded areas indicate 95% confidence intervals. Efficacy against severe infection was calculated by using a severe threshold that was a factor of 0.16 smaller than mild infection (CI = 0.039 to 0.66).
- B) Extrapolating the decay of neutralisation titres over time. This model assumes a half-life of SARS-CoV-2 neutralisation titre of 90 days over the first 250 days⁵, after which the decay decreases (at rate $0.01d^{-1}$) until a 10-year half-life is achieved^{33,34}. For different initial starting levels the model projects the decay in level over the subsequent 1000 days. The green line indicates the predicted 50% protective titre from mild SARS-CoV-2 infection, and the purple line indicates the 50% protective titre from severe SARS-CoV-2 infection. The model illustrates that, depending on the initial neutralisation level, individuals may maintain protection from severe infection whilst becoming susceptible to mild infection (ie: with neutralisation levels remaining in the green shaded region).
- C) Extrapolating the trajectory of protection for groups with different starting levels of protection. The model uses the same assumptions on the rate of immune decay discussed in panel B.

Note: The projections beyond 250 days rely on an assumption of how the decay in SARS-CoV-2 neutralisation titre will slow over time. In addition, the modelling only projects how decay in neutralisation is predicted to affect protection. Other mechanisms of immune protection may play important roles in providing long-term protection that are not captured in this simulation.

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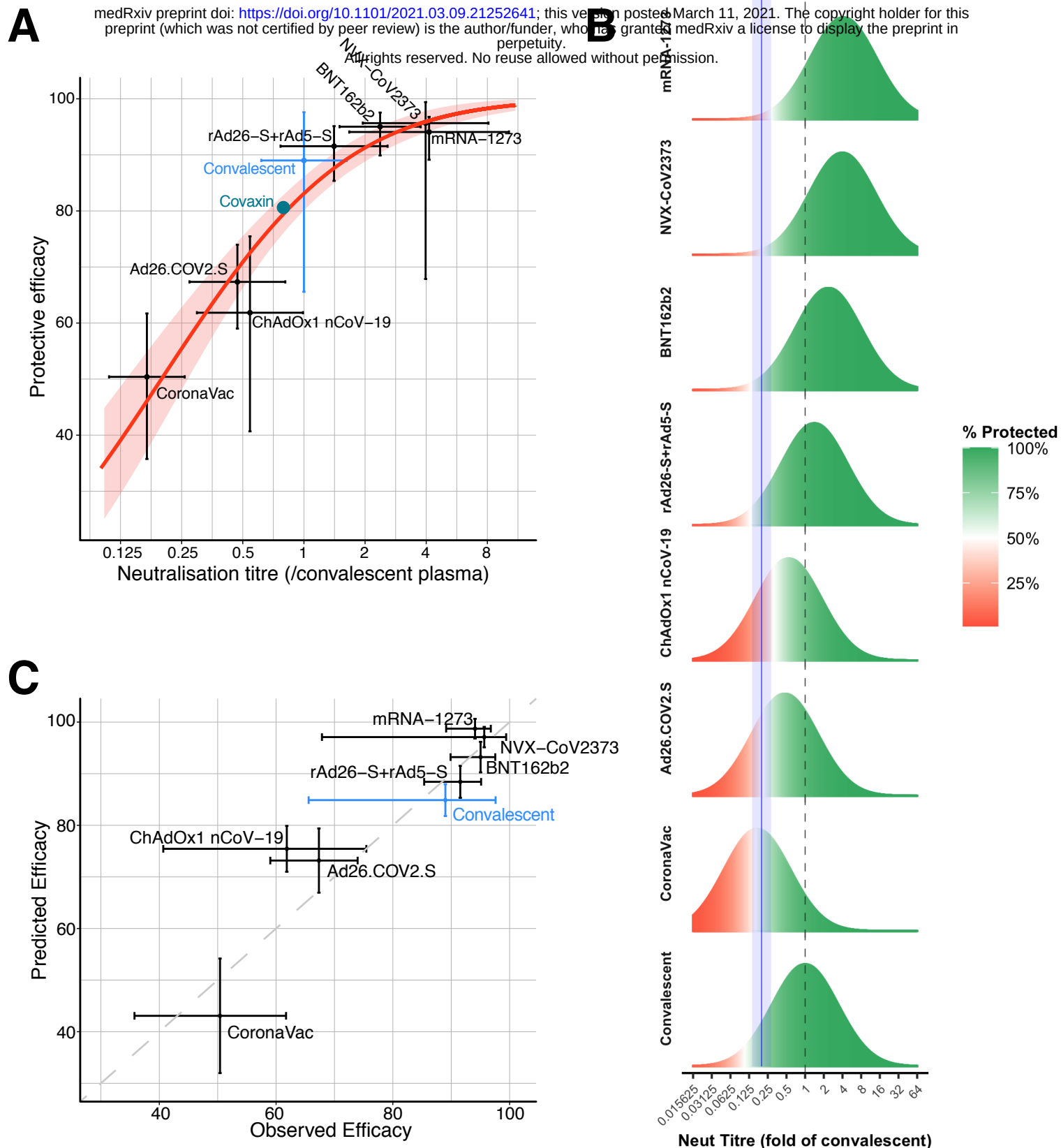


Figure 1: Understanding the relationship between neutralisation and protection. (A) Relationship between neutralisation level and protection from SARS-CoV-2 infection. The reported mean neutralisation level (x-axis) from phase 1 / 2 trials and protective efficacy from phase 3 trials (y-axis) for seven vaccines, as well as the protection observed in a seropositive convalescent cohort are shown (details of data sources in Supplementary Tables 1 and 2). Mean / point estimates are indicated by dots (95% confidence intervals are indicated as whiskers). Red solid line indicates the best fit of the logistic model and shaded red indicates the 95% predictive interval of the model. The mean neutralisation level and protective efficacy of the Covaxin vaccine is indicated as a green circle (data from this study was only available after modelling was complete and did not contribute to fitting). (B) Schematic illustration of the logistic approach to identifying the protective neutralisation level. The data for each study includes the mean and distribution of the in vitro neutralisation titre against SARS-CoV-2 in vaccinated or convalescent subjects (as a proportion of the titre in convalescent subjects)(green/red bell curve), accompanied by a level of protective efficacy for the same regimen. The efficacy is illustrated by the proportion of bell curve 'protected' (green) versus 'susceptible' (red) for individual studies (shaded areas in between reflect the changing risk). The modelling fits the optimal 50% protective neutralisation level (blue dashed line, shaded areas indicate 95% confidence limits) that best estimates the correct levels of protection observed across the different studies. (C) Predictions of the 'leave one out' analysis. Modelling was repeated multiple times using all potential sets of seven vaccination / convalescent studies to predict the efficacy of the eighth study.

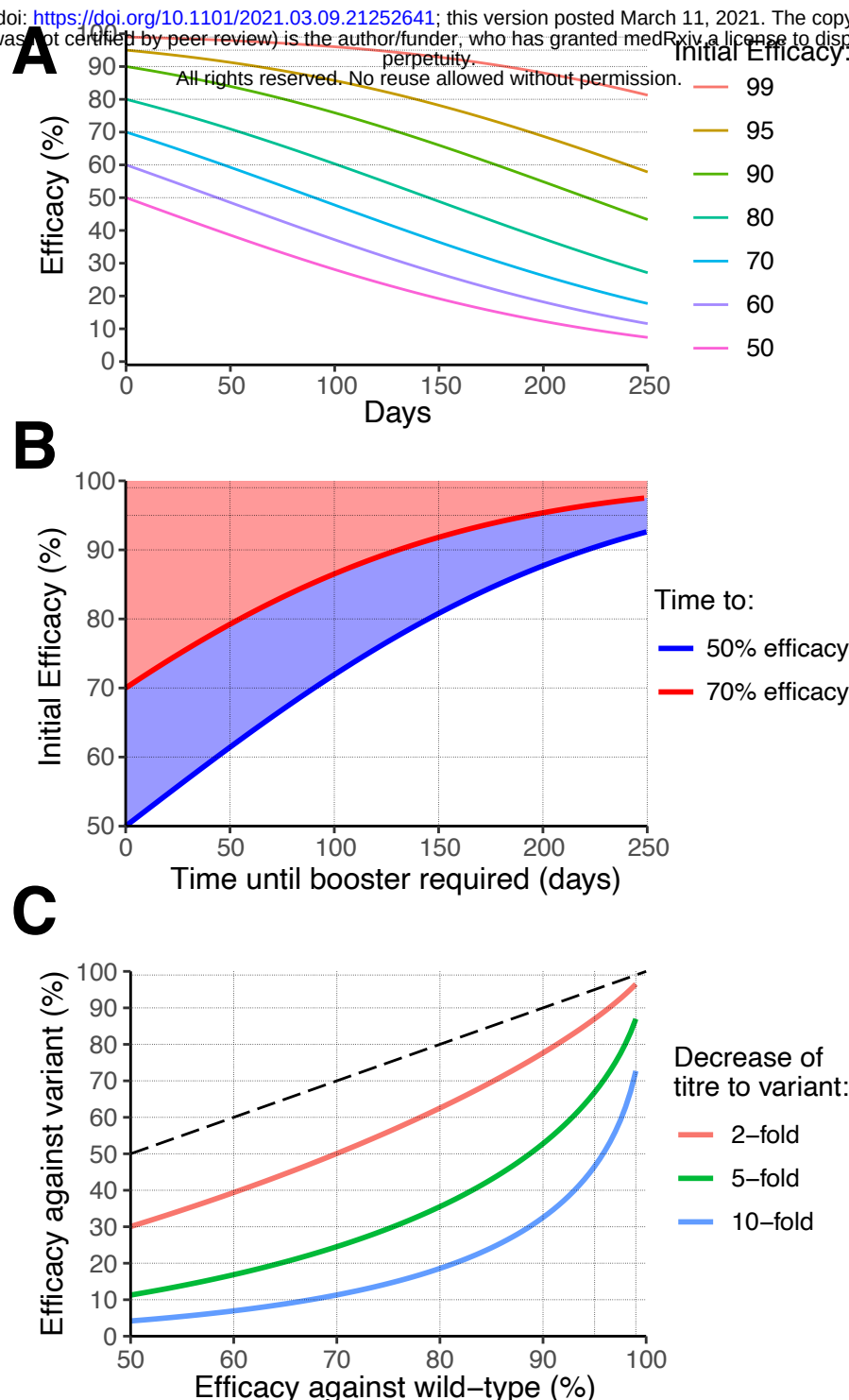


Figure 2: The effects of waning neutralisation titre on protection. (A) Predicting the effects of declining neutralisation titre. Assuming the observed relationship between neutralisation level and protection is consistent over time, we estimate the decline in efficacy for vaccines starting with different levels of early protection. The model assumes a half-life of neutralisation titre of 90 days over the first 250 days (as observed in a convalescent cohort⁵). Coloured lines indicate the predicted trajectory for groups starting with different initial efficacy. (B) Modelling the time for efficacy to drop to 70% (red line) or 50% (blue line) for scenarios with different initial efficacy (indicated on the y-axis). For example, for a group starting with an initial protective efficacy of 90% the model predicts that 70% efficacy will be reached after 131 days, and 50% efficacy after 221 days. (C) Estimating the impact of viral antigenic variation on vaccine efficacy. In vitro studies have shown that neutralisation titres against some SARS-CoV-2 variants are reduced compared to titres against wild-type virus. If the relationship between neutralisation and protection remains constant, we can predict the difference in protective efficacy against wild-type and variant viruses from the difference in neutralisation level. For cohorts with a given initial protective efficacy measured against wild-type (vaccine strain) virus (x-axis), we model the impact of a two-fold (red), 5-fold (green) or 10-fold (blue) reduction in neutralisation titre to a variant virus. The y-axis indicates the predicted new efficacy against the variant strain. Dashed line indicates equal protection against wild-type and variant strains. Details of the data and modelling are provided in the Supplementary Material.

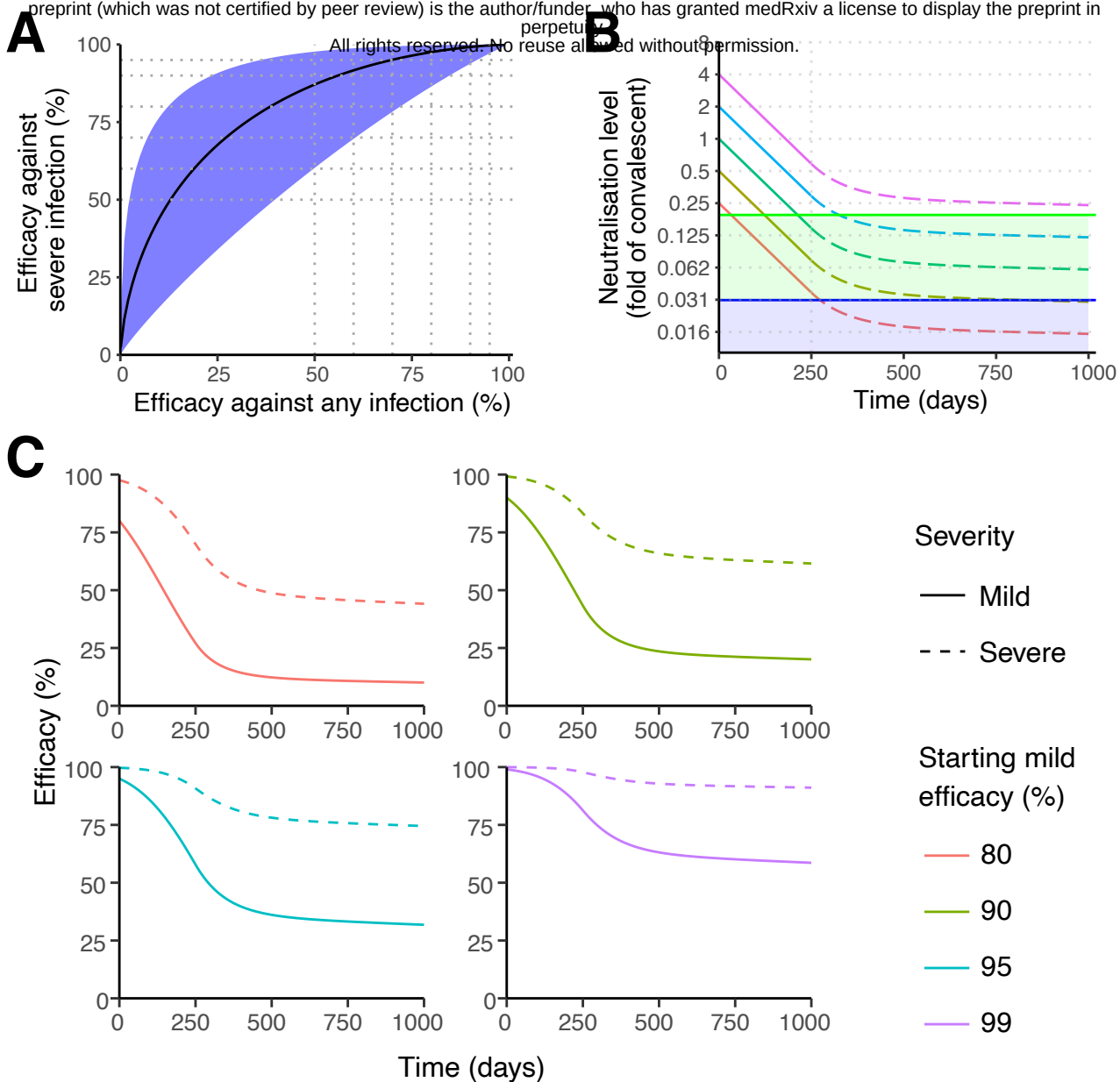


Figure 3: Protection from severe infection. (A) The predicted relationship between efficacy against mild (any) SARS-CoV-2 infection (x-axis) versus efficacy against severe infection (y-axis). The black line indicates the best fit model for the relationship between protection against any versus severe SARS-CoV-2 infection. Shaded areas indicate 95% confidence intervals. Efficacy against severe infection was calculated by using a severe threshold that was a factor of 0.16 smaller than mild infection (CI = 0.039 to 0.66). (B) Extrapolating the decay of neutralisation titres over time. This model assumes a half-life of SARS-CoV-2 neutralisation titre of 90 days over the first 250 days, after which the decay decreases (at rate 0.01d⁻¹) until a 10-year half-life is achieved 33,34. For different initial starting levels the model projects the decay in level over the subsequent 1000 days. The green line indicates the predicted 50% protective titre from mild SARS-CoV-2 infection, and the purple line indicates the 50% protective titre from severe SARS-CoV-2 infection. The model illustrates that, depending on the initial neutralisation level, individuals may maintain protection from severe infection whilst becoming susceptible to mild infection (ie: with neutralisation levels remaining in the green shaded region). (C) Extrapolating the trajectory of protection for groups with different starting levels of protection. The model uses the same assumptions on the rate of immune decay discussed in panel B. Note: The projections beyond 250 days rely on an assumption of how the decay in SARS-CoV-2 neutralisation titre will slow over time. In addition, the modelling only projects how decay in neutralisation is predicted to affect protection. Other mechanisms of immune protection may play important roles in providing long-term protection that are not captured in this simulation.

Supplementary material for:

What level of neutralising antibody protects from COVID-19?

David S Khoury^{1*}, Deborah Cromer^{1*}, Arnold Reynaldi¹, Timothy E Schlub^{1,2}, Adam K Wheatley³, Jennifer A Juno³, Kanta Subbarao^{3, 4}, Stephen J Kent^{3, 5, 6}, James A Triccas^{7*}, Miles P Davenport^{1*#}.

1. Kirby Institute, University of New South Wales, Sydney, Australia
2. Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia
3. Department of Microbiology and Immunology, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
4. WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
5. Australian Research Council Centre for Excellence in Convergent Bio-Nano Science and Technology, University of Melbourne, Melbourne, Victoria, Australia
6. Melbourne Sexual Health Centre and Department of Infectious Diseases, Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia.
7. School of Medical Sciences and Marie Bashir Institute, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW, Australia.

* These authors contributed equally to the work.

Corresponding author: m.davenport@unsw.edu.au

Supplementary Methods and Results

Data extraction

Where possible, data values were used as directly stated in publications. In addition, where necessary, raw data was directly extracted from the original publications using an online digitizer tool (<https://automeris.io/WebPlotDigitizer/>).

Methods for Modelling and Data Analysis

Estimating the standard deviation of neutralisation titres

Neutralisation titres were extracted for each study (as above) and used to determine the standard deviation of the log-transformed neutralisation titres for each study. The standard deviation for each study had to consider that some measurements of neutralisation titre fell below the limit of detection (LOD) of that study assay (LOD varied for each study, table S1). To remove the effect of LOD censoring on estimates of the standard deviation of neutralisation titres we used a censored regression model to fit the distribution of the neutralisation titres for each study. The likelihood function is given by,

$$\mathcal{L}(\mathbf{D}_s | \mu_{cens}, \sigma_{cens}, L_s) = \prod_{n_i \in \mathbf{D}_s} f(n_i | \mu_{cens}, \sigma_{cens})^{1-I_i} F(L_s | \mu_{cens}, \sigma_{cens})^{I_i} \quad (1)$$

where, $\mathbf{D}_s$ is a vector of all the log-neutralisation titres, n_i , study s . The function f is the probability function of a normal distribution with mean μ_{cens} and standard deviation σ_{cens} , and F is the cumulative density function of the same distribution. The limit of detection of the assay for study s is given by L_s and when the index variable I_i is 1 when $n_i \leq L_s$ and 0 otherwise. The negative log of this likelihood function was minimised in R using the built-in optimiser “nlm” to estimate the mean and standard deviation of the log transformed neutralisation titres after factoring in the LOD. When no limit of detection was reported or all values were above the LOD, the L_s was set to $-\text{Inf}$.

Pooled standard deviation

Given the differing sample size of the neutralisation data for each study, the accuracy of estimations of the standard deviation for each study varied considerably. Therefore, despite finding some limited evidence of a differences in the standard deviation between each study ($P=0.049$, Fligner-Killeen test), we combined all extracted data and calculated a standard deviation of the pooled data. To do this we first centred the neutralisation data for each study at the reported mean of the neutralisation titres for that study. The limit of detection associated for each study was also adjusted in the same way. This provided a combined dataset of neutralisation titres from all studies, which was fitted using the likelihood model in equation 1 to the pooled data to produce an estimate of the standard deviation of the pooled data.

Modelling the relationship between neutralisation and protection.

In the above we used neutralisation titre information from each vaccine and convalescent individuals to estimate a distribution in neutralisation titres for each study. However, as discussed in the main text, given the diversity of assays used to assess neutralisation in each study (Table S1), from this point forward we normalise the neutralisation titres in each study by the mean of the neutralisation titre in the corresponding convalescent individuals contained within each study. Also, in all the analysis below we take the log-transform of the

normalised neutralization titres. For simplicity, in the remainder of this document, we refer to these log-transformed normalised neutralisation titres as the **neutralisation levels**.

Logistic method.

To model the relationship between neutralisation level of antibodies collected from individuals after vaccination (or during convalescence) and protection from COVID-19 we assumed we assumed a logistic relationship between neutralisation level and protective efficacy, such that,

$$E_I(n | n_{50}, k) = \frac{1}{1 + e^{-k(n-n_{50})}} \quad (2)$$

where E_I is the protective efficacy of an individual given the neutralisation level of n (note the definition of neutralisation level above). The parameter n_{50} is the neutralisation level at which an individual will have a 50% protective efficacy (i.e. half the chance of being infected compared with an unvaccinated person). The steepness of this relationship between protective efficacy and neutralisation level is determined by the parameter k .

We assume that a vaccine (or prior exposure) will induce a (normal) distribution of neutralisation levels (n) in a population with some mean μ_s and standard deviation σ_s . The mean neutralisation level for each study (μ_s), is the difference between the log-transformed mean neutralisation titres for vaccinated and convalescent individuals within that study. The standard deviation (σ_s) is the standard deviation for vaccinated individuals in that study only. (Note that the distribution of neutralisation level for convalescent individuals has a mean of zero by definition (i.e. the log of the mean of neutralisation titres for convalescent individuals normalised by itself)). Therefore, the proportion of the vaccinated population for a study, s , that will be protected will be given by,

$$P(n_{50}, k, \mu_s, \sigma_s) = \int_{-\infty}^{\infty} E_I(n | n_{50}, k) f(n | \mu_s, \sigma_s) dn \quad (3)$$

where, f is the probability density function of a normal distribution, and E is the logistic function in equation (2). The above integral is the so-called logistic-normal integral and the mean of the logit-normal distribution, which has no analytical solution¹. Therefore, we use a simple numerical approximation (left Riemann sum).

Fitting the logistic model and confidence intervals

The above model of protection was fit to data on the protective efficacy of vaccines from Phase III (and another large cohort study of convalescent individuals). For each vaccine and convalescence study the number of: (1) control (unvaccinated/placebo/naïve) individuals enrolled (N_s^c), (2) control individuals infected (I_s^c), (3) vaccinated (previously exposed) individuals enrolled (N_s^v) and (4) vaccinated individuals infected (I_s^v) were used in fitting the model. The likelihood of observing the number of infected individuals in the control and vaccinated groups for each study, given some parameters, is,

$$\begin{aligned} \mathcal{L}_s(N_s^c, I_s^c, N_s^v, I_s^v, \mu_s, \sigma_s | n_{50}, k, b_s) \\ = Bi(N_s^c, I_s^c, b_s) Bi(N_s^v, I_s^v, b_s(1 - P(n_{50}, k, \mu_s, \sigma_s))) \end{aligned} \quad (4)$$

where b_s is the probability of an unvaccinated control individual becoming infected in study s (baseline risk), $b_s(1 - P(n_{50}, k, \mu_s, \sigma_s))$ is the probability of infection in the vaccination

group (see eq. 3) and $Bi(N, K, p)$ is the binomial probability mass function of probability of K events from a sample size of N , where each event has a probability p of occurring. However, we wish to fit all studies simultaneously, and so the total likelihood of observing the data in all studies, given some parameters, is,

$$\begin{aligned} \mathcal{L}(\mathbf{N}^c, \mathbf{I}^c, \mathbf{N}^v, \mathbf{I}^v, \boldsymbol{\mu}, \boldsymbol{\sigma} \mid n_{50}, k, \mathbf{b}) \\ = \prod_{\forall s} Bi(N_s^c, I_s^c, b_s) Bi(N_s^v, I_s^v, b_s(1 - P(n_{50}, k, \mu_s, \sigma_s))) \end{aligned} \quad (5)$$

where $\mathbf{N}^c, \mathbf{I}^c, \mathbf{N}^v, \mathbf{I}^v, \boldsymbol{\mu}, \boldsymbol{\sigma}$ are vectors containing the data $N_s^c, I_s^c, N_s^v, I_s^v, \mu_s, \sigma_s$ for each study s , and $\mathbf{b}$ is a vector of the baseline risk parameters b_s for each study. Best fitting parameters n_{50}, k and $\mathbf{b}$ were found using the “nlm” optimiser in R by minimising $-\log(\mathcal{L})$. The standard error (SE) of these estimates were estimated using the hessian H output from this function, and the formula $SE = \sqrt{\text{diag}(H^{-1})}$. The 95% confidence intervals were taken as $\pm 1.95 \times SE$ of the estimated parameters.

The variable μ_s is the mean neutralisation level, which can be calculated in two ways, firstly taking the geometric mean of neutralisation titres in vaccinated individuals over the geometric mean of the neutralisation titre in convalescent individuals in the same study. This is, in most cases, the ratio of two values directly reported in the immunogenicity studies. However, this approach does not account for situations in which the neutralisation assay had neutralisation titres below the limit of detection, so we also estimated this value by extracting the neutralisation titres from figures within each immunogenicity study (table S1), and computing the mean neutralisation titre for vaccinated and convalescent individuals in each study using censoring regression (equation (1)). Additionally, although it was in principle possible to compute the standard deviation of neutralisation levels for each study (as above), these appeared somewhat confounded by varying numbers of individuals between studies, hence we fit the above model using: 1) the standard deviation estimates for each study, 2) one standard deviation from one larger study to which we had direct access to raw data² (i.e. no manual data extraction required) and 3) an estimate of the standard deviation for all studies pooled together. The two different methods for estimating μ_s for each study, and the three methods for estimating σ_s gives rise to 6 versions of the above model. All of these versions of the model were fitted, and the estimated protective levels were very similar (fig. S1).

Protective Neutralisation Classification Model (PNC Model)

The above modelling approach assumed neutralisation levels were normally distributed. Here we present a method for determining the protective threshold that is free of assumptions regarding the distribution of neutralisation levels. This model assumes that there is protective neutralisation level, T , above which individuals will be protected from infection and below which individuals will be susceptible. Using the protective efficacy observed in Phase III clinical trials of vaccinated individuals (and another large cohort study of convalescent individuals,³) (table S2), E_s , represents the proportion of individuals in each study who should possess a neutralisation level above the protective threshold. It follows then the number of individuals above the protective threshold in study s is a function of T , which we denote $K_s(T)$. Therefore, the probability of observing $K_s(T)$ individuals above the protective threshold, given that there were N_s individuals in the immunogenicity study (which are much smaller studies than the Phase III studies), is given by,

$$P(K_s(T) \mid N_s, T) = Bi(K_s(T), N_s, E_s) \quad (6)$$

where, Bi is a binomial distribution. Note that,

$$K_s(T) = \sum_{n_i \in \mathbf{D}_s} H(n_i - T) \quad (7)$$

and $N_s = |\mathbf{D}_s|$, such that H is the heavy-side step function taking the value 1 when $n_i - T > 0$, or 0 otherwise, and $|\mathbf{D}_s|$ denotes the size of set $\mathbf{D}_s$ (i.e. number of neutralisation levels measured). To determine one protective threshold using the results of all efficacy studies in this paper, we construct a likelihood function,

$$\mathcal{L}(\mathbf{D} | T) = \prod_{\mathbf{D}_s \in \mathbf{D}} Bi(K_s(T), N_s, E_s) \quad (8)$$

where $\mathbf{D}$ is the set of vectors of the neutralisation levels from each study. Note that this likelihood function is discontinuous as the threshold T is varied. Therefore, we evaluate this likelihood function with the threshold T set equal to all observed neutralisation levels n_i across all studies, and find the T value that maximises this likelihood (fig. S1). This method is determining a protective level at which the proportion of individuals with neutralisation levels above the threshold is in greatest agreement with the observed protective efficacy of that vaccine.

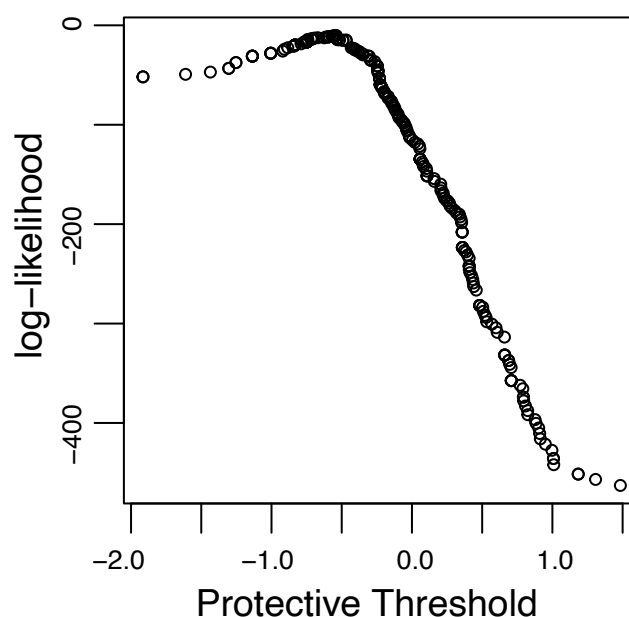


Figure S1: Fitting the PNC Model.

This figure shows the estimated log-likelihood (log of equation 9) as a function of protective neutralisation threshold. To estimate the protective neutralisation threshold that is most consistent with the reported efficacy of each vaccine (and convalescence), the log-likelihood function (log of equation 9) was evaluated at all neutralisation levels observed in any of the studies listed in Supp Table 1, and the best fitting protective level was determined as the neutralisation level that maximised the likelihood function.

Equation (8) is the likelihood function that should be adopted when neutralisation measurements are not impacted by a limit of detection. In the case that some neutralisation levels are measured below the limit of detection the likelihood function is adjusted as below,

$$\mathcal{L}(\mathbf{D}|T) = \prod_{D_s \in \mathbf{D}} Bi(K_s(T), N_s, E_s)^{1-J_s} \times Q(C_s, N_s, 1 - E_s)^{J_s} \quad (9)$$

where, J_s is an index taking the value 1 when the LOD of study s is above the threshold T and at least one value is censored, or 0 otherwise. C_s is the number of censored values in study s and Q is the cumulative binomial distribution function. This later term considers the probability that as many as all of the censored values were below the threshold T given the protective efficacy of the study E_s .

To determine the 95% confidence intervals for estimated protective neutralisation level a bootstrapping approach was used, in which the neutralisation levels were resampled 1000 times at random with replacement. Resampling was performed so as to preserve the total number of neutralisation levels in each study. These randomly generated samples of the original data were then fitted in the same way as described above, which generated 1000 corresponding estimates of the protective neutralisation level. The 95% confidence interval was calculated as the 2.5% and 97.5% percentiles of these 1000 estimates of the protective neutralisation level.

Assessing predictive ability of model with a “Leave-one-out” analysis

To determine the ability of the model to predict a vaccine's efficacy, we performed a “leave one out” analysis, where we systematically excluded one of the vaccine (or convalescent) studies and performed the same model fitting procedure described above. Using the model fitted on the subset of the studies we estimated the efficacy of the vaccine that was “left out” from the fitted model. This “leave one out” analysis was performed with all versions of the logistic model (i.e. the 6 methods of estimating the mean neutralisation level and standard deviation outlined above were all considered). The predicted efficacy for each vaccine and convalescence obtained while leaving the study out are plotted against the reported efficacy in figure 1C. Also, the 50% protective level estimates each time a study was left out of the analysis provides a metric of the sensitivity of the model to the inclusion of each study. Note that excluding any of the studies did not greatly influence the estimate of the 50% protective level (fig. S2).

Error bars and regions in efficacy and neutralisation

In figure 1B there are both horizontal and vertical error bars as well a 95% predictive interval shown (shaded red) presented for the fitted model. The vertical error bars indicate the 95% confidence intervals on the efficacy estimates for each study, these were calculated using the Katz-log method specified in Table 1 of⁴. The horizontal error bars indicate 95% confidence intervals in the difference of the mean of the ($\log_{10}$) neutralisation titres for vaccinated and convalescent individuals in each study. That is, these represent,

$$\pm 1.96 \times \sqrt{\frac{\sigma_v^2}{n_v} + \frac{\sigma_c^2}{n_c}}$$

where σ_v and σ_c are the standard deviation in the $\log_{10}$ of the neutralisation titres for vaccinated and convalescent individuals, respectively, and were estimated as described in section “*Estimating the standard deviation of neutralisation titres*” above. n_v and n_c are the number of vaccinated and convalescent individuals that were included for each study. The

95% predictive interval in figure 1 (shaded red region) was calculated using the delta method⁵.

Comparing the protective level in mild vs severe infection

We also tested if the protective neutralisation level was different between mild and severe infection by fitting the combined dataset with two different mathematical models. The simplest model assumes we could use the same protective level in both severe and mild infection (ie, shared steepness parameter (k) and 50% protective level (n_{50}) in the logistic model (above)); and the alternative model uses different protective level parameters while we constrained the model to have the same k in severe and mild infection (equation (3)). We used both the Akaike Information Criterion (AIC) and a likelihood ratio test to determine which model provided the best fit of the dataset for severe and all COVID-19 cases reported (Table S4).

Modelling the decay of neutralisation and effects of antigenic variation.

Comparing decay in convalescence vs. vaccination.

A number of studies have analysed the decay in neutralisation titre in convalescent subjects. These have generally shown a rapid early decay that slow with time^{2,6-9}. We identified one study by Widge et. al.¹⁰ where a time-course of neutralisation titre after mRNA vaccination was able to be analysed. This study measured decay of neutralisation titre out to 115 days. To compare the half-life of decay of neutralisation titre in vaccinated versus convalescent cohorts we analysed decay in this vaccination study compared with a previously published study of convalescent neutralisation titre², restricting the convalescent data over the same time intervals (fig. S3).

The Widge et al data¹⁰ provided a timecourse of individual titres (as did the convalescent data), therefore we compared decay rates using linear mixed effects, by treating vaccination group as a binary variable. Statistical significance was determined based on the value of this covariate (if it was significantly different from zero), which was calculated by using the likelihood ratio test.

Predicting the loss of efficacy as neutralisation wanes and due to variants

The decay in efficacy with time (Figure 2A, B) was modelled by reducing the neutralisation levels at a rate corresponding to a half-life of 90 days and recalculating efficacy given this new distribution in neutralisation levels using equation (3). The efficacy against a SARS-CoV-2 variant, given an associated decrease in neutralisation (Figure 2C), was calculated by reducing the mean neutralisation level by a factor of 2, 5 or 10 and using equation (3). Efficacy against severe infection was similarly calculated using the same approach as above, but using the 50% protective level associated with the severe threshold (Table S4) that was a factor of 0.16 smaller than mild infection (CI = 0.039 to 0.66) (Figure 3C,E). We also extrapolated the decay of neutralisation level beyond the current data, assuming that neutralisation levels decay with a half-life of 90 days up until day 250, after which the decay decreases exponentially (at rate $0.01d^{-1}$) until a 10-year half-life is achieved (Figure 3D, E).

Results of Modelling

Fitting with different models give similar estimates of protective neutralisation level

Due to the limitations of reconciling data across the 7 vaccines (and studies of convalescent individuals) a number of approaches (described above) were employed to estimate the 50% protective neutralisation level. Additionally, variation in estimates of the 50% protective neutralisation level was explored when studies were excluded as a sensitivity analysis (“leave one out analysis”). All of the approaches applied produced similar estimates of the 50% protective level (fig. S2).

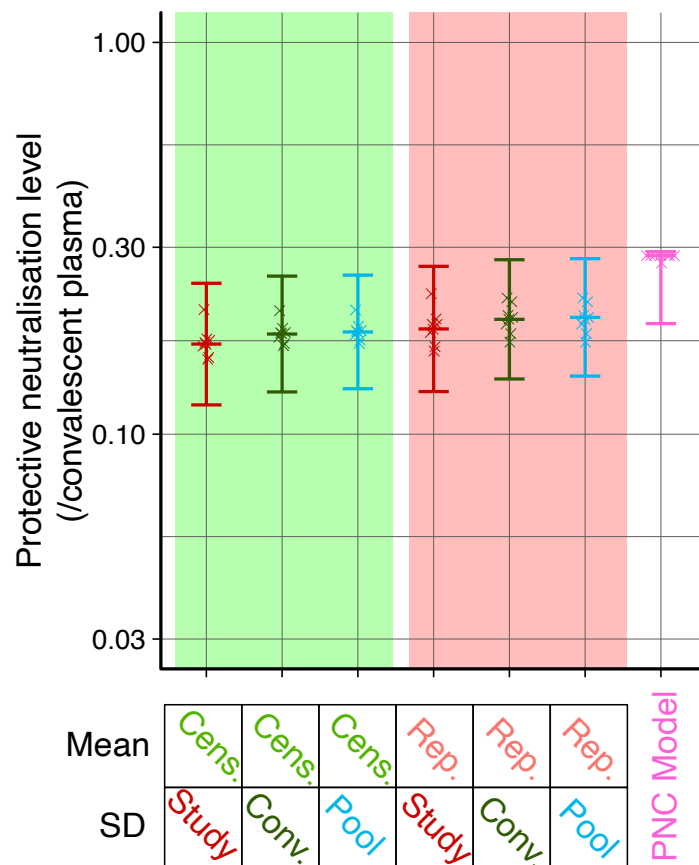


Figure S2: Estimates of the 50% protective neutralisation level with different models.

Two models, the logistic model (green and red shaded regions) and the protective neutralisation classification model (PNC Model, purple), were fit to the data on neutralisation levels in each study and protective efficacy of vaccination (and convalescence) from 8 studies. The logistic model was fit 6 times using a mean and standard deviation of the distribution in neutralisation levels for each study that was estimated under different methods described above. Central horizontal bars indicate the estimated 50% protective neutralisation level (for the logistic model), or protective threshold (for the PNC model) from each model. The error bars indicate the 95% confidence interval on these estimates. The 8 crosses overlayed on each model indicate the estimates of the protective level obtained when the same model is fit to only 7 of the 8 studies (i.e. excluding one study), and highlights that no single study strongly influences the estimate of protective neutralisation level.

*Note that in this figure we present non-log transformed protective neutralisation levels to maintain consistency with the main text.

Estimated decay rates of neutralisation titres in vaccination and convalescence

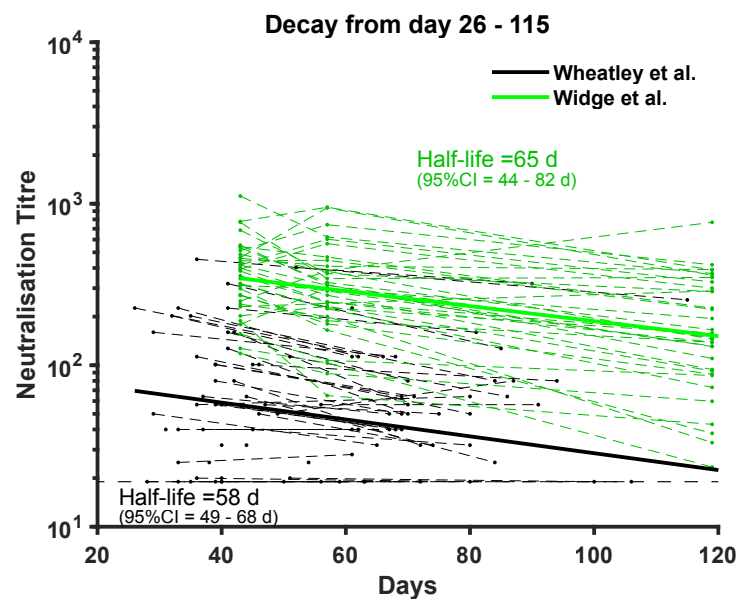


Figure S3: Neutralisation titres reported in vaccinated and convalescent individuals over time.

The decay half-lives estimated for a linear mixed effects model were not significantly different between vaccinated and convalescent individuals ($P=0.88$, likelihood ratio test).

Data sources

Manufacturer	Technical Name	Dosage	Dose 2 (Day)	Measured on Day	Assay*	Reference	Data derived from?
Moderna	mRNA-1273	100 µg	29	42	Live WT virus PRNT ₈₀ ¹	¹¹	Table 2
Novavax	NVX-CoV2373	5 µg + 50 µg Matrix-M1 adjuvant	21	35	Live WT MN IC _{>99} ²	¹²	Figure 3, Panel B
Pfizer	BNT162b2	30 µg	21	28	Live fluorescent WT virus PRNT IC ₅₀ ³	¹³	Figure 4, Panel B, combining data from all age groups
Sputnik	rAd26-S+rAd5-S	10 ¹¹ viral particles	21	42	Live WT virus MN IC ₅₀ ⁴	¹⁴	Figure 2, Panel D and Supp Figure 6-3
Astrazeneca	ChAdOx1 nCoV-19	5x10 ¹⁰ viral particles (SD)	28	42	Live WT virus MN IC ₅₀ ⁵	¹⁵	Figure 4, Panel B
Johnson & Johnson	Ad26.COV2.S	5x10 ¹⁰ viral particles	N/A	29	Live WT virus PRNT IC ₅₀ ⁶	¹⁶	Figure 2, Panel B, combining data from all age groups
Sinovac	CoronaVac	3 µg	14	28	Live WT virus MN IC ₅₀ ⁷	¹⁷	Figure 3, Panel C and supp fig 6-3

¹ Reduction in infectivity by at least 80% after 20 minutes incubation of serum dilution and SARS-CoV-2/human/USA/USA-WA1/2020 on Vero E6 cells, plaques counted at 3 days.

² WT virus microneutralisation assay using USA-WA1/2020 isolate on Vero E6 cells, counting vCPE at 72 hours. Inhibitory concentration of >99% deemed to be first sample dilution showing vCPE.

³ Concentration yielding 50% reduction in fluorescent viral foci of genetically modified fluorescent virus (USA_WA1/2020 with mNeonGreen inserted into ORF7 of viral genome) on Vero CCL81 cells at 16-24 hours.

⁴ WT Microneutralization assay with TCID₅₀ of 100 (hCoV-19/Russia/Moscow_PMVL-1/2020). Cells and counting method not clear.

⁵ Concentration giving absence of cytopathic effect (CPE) with 100 TCID₅₀ of BavPat1/2020 isolate on Vero E6 cells, read at 4 days (described as ‘Marburg virus neutralisation assay’).

⁶ 50% inhibitory concentration of 100 PFU Victoria/1/2020 strain virus on Vero E6 cells, serum incubated for 60-90 minutes, assay read at 24 hours.

⁷ Microneutralisation assay – 100 CCID₅₀ of the CHN/CN1/2020 strain incubated with serum dilution for 2 hours, vCPE read at 5 days (bespoke method for assigning inhibitory concentration from vCPE in duplicates, cell line not clear).

Bharat Biotech	BBV152	6 µg with Algel-IMDG	28	42	Live WT virus PRNT ₅₀ ⁸	¹⁸	Figure 2, Panel A
N/A	Convalescent Plasma	N/A	N/A	N/A	Live WT virus MN IC ₅₀ ⁹	²	Figure 1, Panel B

Table S1: Data sources for Immunogenicity Data

**WT = wild type, MN = micro-neutralisation, PRNT = plaque reduction neutralization test, MN = microneutralisation, IC = inhibitory concentration, numerical subscript = percentage neutralisation that is claimed in the assay.*

⁸ Assay details in Supplementary Appendix, not yet available online.

⁹ Microneutralisation using 100 TCID₅₀ of CoV/Australia/VIC01/2020 incubated with serum dilution for one hour before placing on Vero cells. The neutralising antibody titre (IC₅₀) was calculated 5 days post-inoculation using the Reed/Muench method.

Manufacturer	Technical Name	Dosage	Dose 2 (Day)	Trial Started (Day)	Measure of effectiveness	Reference	Data derived from?
Moderna	mRNA-1273	100 µg	29	42	Prevention of primary symptomatic COVID-19 illness. ¹⁰	¹⁹	Figure 4
Novavax	NVX-CoV2373	5 µg + 50 µg Matrix-M1 adjuvant	21	35	Prevention of PCR-positive symptomatic mild, moderate, or severe COVID-19 illness ¹¹ .	²⁰	Text from press release
Pfizer	BNT162b2	30 µg	21	28	Prevention of primary covid-19 illness ¹²	²¹	Table 2
Sputnik	rAd26-S+rAd5-S	10 ¹¹ viral particles	21	21	Prevention of PCR confirmed COVID-19	²²	Table 2
Astrazeneca	ChAdOx1 nCoV-19	5x10 ¹⁰ viral particles (SD)	28	42	Prevention of primary symptomatic COVID-19 ¹³	²³	Table 2 (SD/SD only)
Johnson & Johnson	Ad26.COV2.S	5x10 ¹⁰ viral particles	N/A	29	Prevention of primary molecularly confirmed	²⁴	Text from press release

¹⁰ Definition of symptomatic illness was: “Covid-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature $\geq 38^{\circ}\text{C}$), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test.”

¹¹ Symptomatic disease defined as a minimum of either (i) fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications), (ii) New onset cough or (iii) ≥ 2 of the following: (a) New onset or worsening of shortness of breath or difficulty breathing compared to baseline, (b) New onset fatigue, (c) New onset generalised muscle or body aches, (d) New onset headache lasting ≥ 48 hours, (e) New loss of taste or smell, (f) Acute onset of sore throat, congestion, and runny nose, (g) New onset nausea, vomiting, or diarrhea lasting ≥ 48 hours.

¹² Efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

¹³ Primary symptomatic covid-19 was defined as “virologically confirmed, symptomatic COVID-19, defined as a NAAT- positive swab combined with at least one qualifying symptom (fever $\geq 37.8^{\circ}\text{C}$, cough, shortness of breath, or anosmia or ageusia).”

					moderate to severe/critical COVID-19 illness ¹⁴		
Sinovac	CoronaVac	3 µg	14	Not reported	Prevention of COVID-19	^{25,26}	News / Media Articles
N/A	Convalescence	N/A	N/A	N/A	Prevention of PCR-Positive COVID-19	³	Table 1

Table S2: Data sources for Efficacy Data

¹⁴ Moderate defined as any one of the following new or worsening signs or symptoms (a) Respiratory rate ≥ 20 breaths/minute, (b) Abnormal saturation of oxygen (SpO₂) but still $>93\%$ on room air at sea level, (c) Clinical or radiologic evidence of pneumonia, (d) Radiologic evidence of deep vein thrombosis (DVT), (e) Shortness of breath or difficulty breathing, or any two of the following new or worsening signs or symptoms: (i) Fever ($\geq 38.0^\circ\text{C}$ or $\geq 100.4^\circ\text{F}$), (ii) Heart rate ≥ 90 bpm, (iii) Shaking chills or rigors, (iv) Sore throat, (v) Cough, (vi) Malaise as evidenced by 1 or more of the following: Loss of appetite, Generally unwell, Fatigue, Physical weakness, (vii) Headache, (viii) Muscle pain (myalgia), (ix) Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain) (x) New or changing olfactory or taste disorders, (xi) Red or bruised looking feet or toes.

Manufacturer	Technical Name	Definition of Severe disease	Reference	Data derived from?
Moderna	mRNA-1273	One of a list of severe criteria ¹⁵	19	Text and Supplementary Table S16
Novavax	NVX-CoV2373	Participants meeting at least one of a list of endpoint criteria ¹⁶ .	20	Text from press release
Pfizer	BNT162b2	Severe disease, occurring after the day of the first dose ¹⁷	21	Supplementary Table S5
Sputnik	rAd26-S+rAd5-S	Included moderate of severe disease (no further definition provided).	22	Table 2
Astrazeneca	ChAdOx1 nCoV-19	Includes both hospitalised and severe cases ¹⁸ .	23	Table 5 (all dose regimens)
Johnson & Johnson	Ad26.COV2.S	Prevention of primary molecularly confirmed moderate to severe/critical COVID-19 illness ¹⁹	24	Text from press release, severe case numbers inferred to be the minimum numbers that could generate this efficacy.

Table S3: Data sources for data showing Efficacy against Severe Disease

¹⁵ Severe Covid-19 was defined as “one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; acute respiratory distress syndrome; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death.

¹⁶ Endpoint criteria for severe disease were listed as: (a) Tachypnea: ≥ 30 breaths per minute at rest, (b) Resting heart rate ≥ 125 beats per minute, (c) SpO₂: $\leq 93\%$ on room air or PAO₂/FiO₂ < 300, (d) High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP), (e) Mechanical ventilation or ECMO, (f) One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: i. ARDS, ii. Acute renal failure, iii. Acute hepatic failure, iv. Acute right or left heart failure, v. Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg, vi. Acute stroke (ischemic or hemorrhagic), vii. Acute thrombotic event: AMI, DVT, PE, viii. Requirement for: vasopressors, systemic corticosteroids, or hemodialysis, (g) Admission to an ICU, (h) Death

¹⁷ Severe Covid-19 is defined as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an in- tensive care unit; or death.

¹⁸ Hospitalised cases have WHO clinical progression score ≥ 4 . Severe cases were defined as those with WHO clinical progression score ≥ 6 .

¹⁹ Severe disease defined as one or more of the following: (a) Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths/minute, heart rate ≥ 125 beats/minute, oxygen saturation (SpO₂) $\leq 93\%$ on room air at sea level, or partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) <300 mmHg), (b) Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), (c) Evidence of shock (defined as systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors), (d) Significant acute renal, hepatic, or neurologic dysfunction, (e) Admission to the ICU, (f) Death

Model Structure	LL	AIC	Slope (k)	Severe n_{50}	Mild n_{50}	p-value
Different n_{50}	-66.22	138.44	3.31(2.22 – 4.95)	0.03 (0.0075 – 0.13)	0.19 (0.14 – 0.27)	0.0004
Same n_{50}	-72.48	148.96	3.64 (2.4 – 5.5)	0.19 (0.14 – 0.26)	0.19 (0.14 – 0.26)	

Table S4: Model comparison of the protective level in mild and severe infection

Table shows log-likelihood, AIC and parameter estimates (95% CI), for a logistic model having either the same (top row) or different (bottom row) 50% protective level (n_{50}) for severe and mild infection. p-value was obtained from a likelihood ratio test comparing the two models.

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