Identifying COVID-19 optimal vaccine dose using mathematical Immunostimulation/Immunodynamic Modelling

Abstract

Introduction: Identifying optimal COVID-19 vaccine dose is essential for maximizing their impact. However, COVID-19 vaccine dose-finding has been an empirical process, limited by short development timeframes, and therefore potentially not thoroughly investigated. Mathematical IS/ID modelling is a novel method for predicting optimal vaccine dose which could inform future COVID-19 vaccine dose decision making.

Methods: Published clinical data on COVID-19 vaccine dose-response was identified and extracted. Mathematical models were calibrated to the dose-response data stratified by subpopulation, where possible to predict optimal dose. Predicted optimal doses were summarised across vaccine type and compared to chosen dose for the primary series of COVID-19 vaccines to identify vaccine doses that may benefit from re-evaluation.

Results: 30 clinical dose-response datasets in adults and elderly population were extracted for four vaccine types and optimal doses predicted using the models. Results suggest that, if re-assessed for dose, COVID-19 vaccines Ad26.cov, ChadOx1 n-Cov19, BNT162b2, Coronavac, and NVX-CoV2373 could benefit from increased dose in adults and mRNA-1273 and Coronavac, could benefit from increased and decreased dose for the elderly population, respectively.

Discussion: Future iterations of COVID-19 vaccines could benefit from re-evaluating dose to ensure most effective use of the vaccine and mathematical modelling can support this.

Introduction

COVID-19 is one of the largest global public health challenges ever and has had a devastating effect, societally and economically (1). The push to develop COVID-19 vaccines is unparalleled with over 20 vaccines now currently being rolled out globally and approximately 300 candidate vaccines still in development (2). These vaccines are a promising step toward ending the current pandemic.

Essential to achieving maximal vaccine efficacy against COVID-19, or any disease, is identifying optimal vaccination dose amount (hereafter 'dose'). However, as COVID-19 vaccines have been developed at a rapid pace compared to conventional vaccine development (3), it is likely that this has led to less evaluation of optimal dose. This is evident in the development of ChAdOx1 nCoV-19 vaccine, whereby a mistake in the dosing administration interval led to unexpected efficacy results, which could have provided potentially better protection (4). It is clear that not fully investigating COVID-19 vaccine dose-response curves to identify optimal dose could result in potential suboptimal protection and potentially wasted vaccine resources.

Currently, dose finding in vaccine product development studies is primarily an empirical and essentially qualitative approach (5). Evaluation of a wide range of vaccine doses is time-

consuming and costly and therefore not rigorously conducted, even under normal circumstances (5). Unfortunately, this means sub-optimal doses may be progressing to the latter stages of development (examples of this can be seen in yellow fever (6, 7), meningitis (8) and malaria (9) vaccines). It is clear that a more effective method is urgently needed to find optimal vaccine dose.

Historically, the development of new drugs has encountered similar issues with dose identification, but today benefits from systematic, extensive use of mathematical models that describe within-host drug dynamics (10). Model-Based Drug Development (MBDD) is recognized as an efficient tool to accelerate and streamline drug development, by minimizing developmental time and resources (11). MBDD has been established for decades in the pharmaceutical industry (12) and is often required by regulatory agencies in all stages of drug development. As such, MBDD is regularly used to establish optimal drug dose (13).

In contrast, until our recent work, there has been very few vaccine dose-finding studies using similar quantitative modelling methods. To address this, we have launched the novel field of vaccine 'Immunostimulation/Immunodynamic' (IS/ID) modelling, an adaptation of methods used in drug development to systematically and quantitatively identify 'best' dose. We have shown its potential in a novel TB vaccine (14, 15) and Adenoviral-based vaccines (16-18) and IS/ID modelling has been recognised by vaccine developers and modellers as the future methodology to optimise vaccine development (19-23).

Applying IS/ID models to COVID-19 vaccine dose-response data should allow us to identify optimal dose which may ultimately lead to more effective COVID-19 vaccines in terms of

protection and efficient use of product (18, 21, 22). As there are multiple COVID-19 vaccines within a vaccine type (e.g. Adenoviral, mRNA, etc.) it is possible to aggregate IS/ID dose-response and optimal dose predictions across vaccine type. Further to this, many COVID-19 vaccine dose-escalation trials have stratified the vaccination population by potential high-risk factors for COVID-19 disease (e.g. age), allowing for optimal dose predictions for each risk-factor groups. Finally, by using IS/ID models to predict optimal dose, we can identify if dose-sparing is possible for vaccines that have progressed into the latter stages of development and therefore a dose has been selected. As many COVID-19 vaccines are now fully rolled out and some in the process of being administered as follow-up boosts, any potential for dose-sparing will be key in bringing down cost of development and spreading the vaccines further.

We aimed to predict, using IS/ID models, the optimal dose of COVID-19 vaccines in humans using antibody dose-response data from existing published COVID-19 vaccines. We did this by (i) extracting published clinical antibody dose-response data for COVID-19 vaccines, (ii) calibrating IS/ID models to the dose-response data and predicting optimal dose across vaccine type by subpopulation and (iii) identifying, for the primary series of COVID-19 vaccines, vaccines where chosen dose may be sub-optimal, by vaccine type.

Methods

Objective 1: Extraction of clinical dose-response data for COVID-19 vaccines

Our aim in Objective 1 was to identify publications that contained COVID-19 neutralizing antibody (NAb) dose-response data. NAb were chosen as they are currently believed to be

important for protection against COVID-19 (24-26). We conducted a literature review of the online databases Medline, using the search themes relating to “Covid-19 or SARS-CoV-2” and “vaccine dose”. The literature was searched using these search terms between January 2020 and December 2021. The resulting publications were screened, first, by abstract, followed by full text. Inclusion criteria included the administration of multiple (2+) dose-levels of the vaccine in the study and assessment of the NAb following vaccination. If multiple publications were found on the same vaccine dataset (e.g. as an update to a preliminary dataset), the latest publication was taken. NAb data presented in the paper were extracted by eye if in a table and using WebPlotDigitzer (27) if in graphical form.

Objective 2: Calibration of IS/ID models to clinical dose-response data for COVID-19 vaccines to predict optimal dose across vaccine type by subpopulation

Simple IS/ID models were used to describe the NAb dose-response curve at the latest time point available in the data. We chose IS/ID models that represented either a saturated or peaked curve shape to account for the possibility that the dose-response could saturate or decrease (as seen in TB vaccines (14)) at higher dose levels. We chose a sigmoidal equation as the saturating curve defined as

$$Response = \frac{R_{max}}{1 + \left(\frac{R_{50}}{Dose}\right)^{p}}$$

Where Rmax is the saturation maximum, R50 is the value where the response is 50% of the saturation maximum. The sigmoidal equation is able to capture when there is a range of small

doses with zero response (p>1) (Figure 1A) or when the response increases immediately after zero dose (p>=1) (Figure 1B).

We chose a combined exponential curve to represent a peaked curve defined as,

$$Response = \mathrm{a} * (e^{-b*Dose} - e^{-c*Dose})$$

where a is a scalar and b<c. The combined exponential curve provides flexibility in the degree in which the dose-response curve decreases after the peak which other peaked curve equations cannot (Figure 1C). However, in the case where there is a small range of doses with zero response, which the combined exponential curve cannot capture, the following gamma probability density function (pdf) was chosen,

$$Response = \left(S * \frac{r^{shape}}{\Gamma(shape)} * Dose^{(shape-1)} * e^{-rate*Dose} \right)$$

where S is a scalar multiplying the gamma pdf, rate is the gamma rate parameter, and shape, the gamma shape parameter (Figure 1D).

The three curves were calibrated to the log Geometric Mean Titre (GMT) and 95% CI NAb data using nonlinear regression, by the function nlsLM, in the software R (28). To establish which of the shapes best described the dose-response curves the goodness-of-fit measure, the Akaike information criteria (AIC) was compared, where a lower AIC indicates a better fit (29). The 'best fit' model, with the lowest AIC was then used to make the optimal dose prediction.

In the case where only two dose levels were available in the study, placebo data (if available) or 'zero response' data at dose zero, were added to enable calibration of the models. This was necessary as all the models have three parameters, so require, at a minimum, three data points to calibrate.

For a saturating dose-response curve, optimal dose is defined as the smallest dose after which the curve plateaus, i.e. there is negligible increase in response if dose is increased beyond this optimal value. For a peaked curve, optimal dose is defined as the dose where an increase in dose leads to a decrease in response. For a saturating curve, we used an 'acceptance threshold', which defined what constituted a negligible increase in response. Optimal dose is then the smallest dose at which further increasing dose will lead to a negligible increase in response, i.e. below the acceptance threshold. Figure 2 below illustrates how optimal dose is identified using an Acceptance Threshold (AT). Doses are increased by increments of δDose and the resulting increase in response is assessed against the AT. The optimal dose (indicated by a red line in Figure 2) is the minimum dose at which an increase in dose of δDose results in an increase in response less than the AT (boxed in Figure 2).

For vaccines measured in ug, δDose was 10% of the maximum dose administered and the acceptance threshold was a less than 0.1% increase in response. For example, if the maximum administered dose was 10ug, δDose would be 1ug and optimal dose would be the smallest dose for when an increase of δDose leads to a less than 0.1% increase in response. For a vaccine measured in Viral Particles (VP) or Plaque Forming Units (PFU), δDose was 0.5log10 dose. For a peaked curve, the same acceptance threshold was applied with the expectation that for further increasing dose beyond the optimal dose would not only lead to a negligible increase in response, but eventually, a decrease in response.

NAb dose-response curve and optimal dose were predicted separately for each subpopulation where data on subpopulation responses were available. Subpopulation was defined as where the population was stratified into sub-groups, for example, by age. The median and IQR of the predicted optimal doses were calculated across vaccine type (overall and by subpopulation).

Objective 3. Identify, for the primary series of COVID-19 vaccines, vaccines where chosen dose may be sub-optimal, by vaccine type

To identify, for the primary series of COVID-19 vaccines, vaccines where chosen dose may be sub-optimal, we assessed if the chosen dose lay within the IQR of the optimal doses predicted in Objective 2 for each vaccine type and subpopulation. If the chosen dose was above the IQR then future iterations of the vaccine could benefit from decreased dose (dose-sparing), conversely, if the dose was above the IQR, dose should be increased.

Results

Objective 1: Extraction of clinical dose-response data for COVID-19 vaccines

A total of 20 publications were identified (search conducted 11th June 2021) to be included in the analysis (Figure 3) and from those, a total of 30 datasets were extracted. A summary of the dose-response data, grouped by vaccine type, can be found in Table 1. Publications were available on adenoviral (n=4) (30-33), RNA/DNA (n=6) (34-39), Inactivated (n=6) (40-45), Subunit (n=3) (46-48) and nanoparticle (n=1) (49) vaccines. For each vaccine type (except for

the nanoparticle vaccine), dose-response data were available for both adult (ages 18-55 year) and elderly populations (56-85 years, across all publications). For RNA/DNA, Inactivated and subunit vaccines, data on 8 dose levels were available. There was available data on four dose levels for adenoviral vaccines and two for the nanoparticle vaccine. A detailed summary of the search results, including the methods used to measure NAb titres, can be found in Table S1.

Objective 2: Calibration of IS/ID models to clinical dose-response data for COVID-19 vaccines to predict optimal dose across vaccine type by subpopulation

Figure 4 shows the results of the model calibration and prediction of optimal dose for the adenoviral COVID-19 vaccines. All the Adenoviral curve shapes were best described using the saturating model, except for data from (30, 31) (Figure4.1 and 4.2). The predicted optimal doses ranged between 4 $x10^{10}$ to $7x10^{16}$ vp which overlapped the higher end of the administered dose range of $2.2x10^{10}$ to $1.5x10^{11}$vp. The median predicted optimal dose across all datasets is 6.1 $x10^{10}$ vp (IQR: 5 $x10^{10}$ – 6.1 $x10^{11}$ vp). In adults, the median predicted optimal dose was 4.3 $x10^{11}$ vp (IQR: 6.5 $x10^{10}$ – 1.8 $x10^{16}$ vp). In the elderly population it was 4.5 $x10^{10}$vp (IQR: 4.2 $x10^{10}$- 4.8 $x10^{10}$vp).

Figure 5 shows the results of the model calibration and prediction of optimal dose for the RNA and DNA COVID-19 vaccines. The RNA vaccines dose-response curves were described by both the saturating and peaked curve shapes. Although it is worth noting that the mRNA-1273 vaccine datasets (34, 35, 38) were exclusively best described by the saturating curve shape. The predicted optimal doses ranged between 21ug to 225ug which overlapped with

administered dose range of 1 to 250ug. The median predicted optimal dose across all datasets is 75ug (IQR: 21-90ug). The median predicted optimal dose for adults and the elderly population is 63ug (IQR: 43-113ug) and 80ug (IQR: 21-90ug), respectively. The DNA vaccine dose-response curve was best described by peaked curve shape and the predicted optimal dose was 1.4ug.

Figure 6 shows the results of the model calibration and prediction of optimal dose for the Inactivated COVID-19 vaccines. The majority of inactivated vaccines dose-response curves were best described by the saturating curve shape with the exception of data for the Inactivated whole-virus vaccine in adults (41) and CoronaVac in 70+ year adults (44) which were best described using a peaked curve (Figure 6.2 and 6.9). For those vaccine measured in ug, the predicted optimal doses ranged between 2 – 36ug which overlapped the administered dose range 2.5 – 10 ug. The median predicted optimal dose across all datasets is 7ug (IQR: 5-18ug). The median predicted optimal dose for adults and the elderly population is 7ug (IQR: 5-14ug) and 9ug (IQR: 5-19ug), respectively. For the Inactivated vaccine measured in EU (43), the predicted optimal dose of 690 EU was above the maximum dose administered (150 EU).

Figure 7 shows the results of the model calibration and prediction of optimal dose for the subunit and nanoparticle COVID-19 vaccines. All Subunit vaccines dose-response curves were best described by the peaked curve shape with the exception of SCB-2019 datasets (48) in adults which were best described by a saturating curve shape (Figure 7.3). The predicted optimal doses ranged between 4.5ug – 290ug which overlapped the administered dose range of 3 – 50 ug. The median predicted optimal dose across all datasets is 21ug (IQR: 11-95ug). The median predicted optimal dose for adults and the elderly population is 30ug (IQR: 20-

161ug) and 12ug (IQR: 12-12ug), respectively. The nanoparticle vaccine dose-response curve was best described by peaked curve shape. The predicted optimal dose was 12ug.

The model calibration results for each dataset can be found in table S2.

Objective 3. Identify, for the primary series of COVID-19 vaccines, vaccines where chosen dose may be sub-optimal, by vaccine type

The chosen dose for the primary series of COVID-19 vaccines, (where this data was available) were compared to the aggregate predicted optimal dose for the overall, adult and elderly populations from Objective 2 (Table 2).

For the Adenoviral vaccines, Ad26.cov (Janssen vaccine) and ChadOx1 n-Cov19 (Astra Zeneca vaccine), the chosen dose, $5x10^{10}$ vp (50) (51), was within the IQR of the predicted optimal doses found in Objective 2 for the overall population. However, the modelling suggests this dose may be too low in adults, with the median optimal predicted Adenoviral dose in adults approximately a log higher ($4.3\ x10^{11}$ vp). The median optimal predicted dose in the elderly population was smaller than the chosen dose, but only by 0.5log ($4.5\ x10^{10}$vp). The modelling suggests, the dose of both vaccines could be increased for adults, if safety permits.

For the RNA vaccine, BNT162b2 (Pfizer vaccine), the chosen dose, 30ug (52), was within the IQR of the predicted RNA optimal doses found in Objective 2 for the overall population and the elderly population. However, the modelling suggests the dose was too low in adults, with

the optimal predicted RNA dose in adults 33ug higher (63ug). The modelling suggests the dose could be increased for adults and maintained for the elderly population.

For the RNA vaccine, mRNA-1273 (Moderna vaccine) the chosen dose, 100ug (53), was above the IQR of the predicted RNA optimal doses found in objective 2 for the overall population. Modelling suggests this dose was too high in the elderly population, with the median optimal predicted RNA dose in the elderly population 20ug lower (80ug). The modelling suggests the dose could be decreased in the elderly population and maintained for adults.

For the Inactivated vaccine, Coronavac, the chosen dose, 3ug (40, 53), was below the IQR of the predicted optimal doses found in Objective 2 for the overall population, adult and the elderly population. The modelling suggests the dose should be increased for all age groups.

For the Inactivated vaccine, BBV152, the chosen dose, 6ug (53), was within the IQR of the predicted optimal doses found in objective 2 for the overall population, adult and the elderly population. The modelling suggests the dose could be maintained for all age groups.

For the nanoparticle vaccine, NVX-CoV2373 the chosen dose, 5ug (53), was below the median predicted optimal doses found in Objective 2 for adults. The modelling suggests the dose could be increased.

Discussion

Given the urgent need for COVID-19 vaccines to end the current pandemic, it is vital that these vaccines are optimised to reach the population in the most efficient and effective way possible. Immunostimulation/Immunodynamic (IS/ID) modelling is a novel method which,

when applied to antibody dose-response data, can aid in optimising dose selection for COVID-19 vaccines. We used modelling to predict optimal dose for published COVID-19 in adults and the elderly population summarised over vaccine type. We predicted that to provide optimal immunogenicity in adults, adenoviral vaccines Ad26.cov, and ChadOx1 n-cov19, mRNA vaccine, BNT162b2, inactivated vaccine, Coronavac and nanoparticle vaccine, nvx-cov2373 may desire to be increased in dose in future iterations of development. In order to provide optimal immunogenicity in the elderly population, mRNA vaccine, mrna-1273 may need to increase dose and inactivated vaccine, Coronavac, may need to decrease dose.

There are key strengths to this work. The application of the simple IS/ID models to COVID-19 vaccine dose-response data can provide valuable insight into the shape of the COVID-19 vaccine dose-response curve, which is conventionally, only empirically investigated (21). Quantitative analysis of the dose-response curve shape allows us to interpolate between empirical dose-response data and can be used to inform dosing decisions on similar or emerging vaccines not only for COVID-19 but related pathogens.

By using simple IS/ID models that do not take into account the biological mechanism as a result of vaccination, we could predict optimal dose regardless of the NAb measure chosen in the study (e.g. PRNT, microneutralization (MN) assay). Our method of predicting optimal dose using a pre-specified acceptance threshold which was assessed against proportion of the dosing range in the study meant each optimal dose prediction was standardised for each dataset. This meant that the differences in NAb measure across studies did not impact the prediction of optimal dose and allowed us to aggregate optimal dose predictions across vaccines developed by different groups, regardless of any difference in laboratory methods.

There were weaknesses to our work. To best predict optimal dose by vaccine type and subpopulation, our aggregated optimal dose predictions were based on limited studies and datasets in most cases. It would not have been appropriate to ignore vaccine type to increase power for subpopulation prediction, given the difference in COVID-19 vaccine types currently in development. Similarly, the limited range of dose-levels and sample sizes per study meant the 95% confidence interval of the model parameters was wide or not predictable. This means the uncertainty in the estimated model parameters is high and that the optimal dose prediction is based only on the GMT of the data. However, we believe that the dose-response trend this represents can still be a valuable guide to identifying optimal dose. Unfortunately, this is a challenge not just for IS/ID modelling, but for current empirically-based vaccine development in general, as usually only a very limited number of doses are investigated in clinical trials. Despite this, vaccine dosing decisions are still empirically made based on this same limited data.

We choose to use only Neutralising Antibodies (NAb) to represent the immune response to COVID-19 which have been suggested as important for protection against COVID-19 (24-26). However, a correlate of protection for COVID-19, which is likely to be more complex than only NAb, not yet been identified. As an example, T cells were not considered in this work even though they have been shown to contribute to the COVID-19 immune response (54). This means that by only considering the NAb dose-response curves we are unlikely to have found the true 'optimal immunogenic dose'. However, given NAb are a strong indication of response and have been, so far, a routine and more abundant measure of COVID-19 vaccine immunogenicity, we believe we our methods have predicted a reasonable estimate of optimal

dose. A more complex QSP or immune response 'network model' could provide better understanding of optimal immunogenic dose for multiple immune response readouts, but with limited data, this was not possible for this work.

We used the latest timepoint available in the published dataset to make optimal dose predictions on the most mature immune response possible. However, the latest time point was variable across the studies, ranging from 28 to 70 days resulting in aggregated optimal dose predictions based on different levels of response maturation. NAb responses taken at early and late time points may not be comparable, as affinity maturation may lead to delayed increases. To overcome this issue, we could have predicted optimal dose at the timepoint common to all datasets, 28 days. However, under this condition we would not have been able to capture the effect of the boost immunization (administered at day 28 for most of the vaccines), which has been critical to increase protection in real world trials.

The acceptance threshold was arbitrarily chosen and changing this value will change the prediction of optimal dose. However, this value was considered conservative and ensured the plateau of the saturating dose-response curve was sufficiently flat, resulting in a robust optimal dose prediction.

To our knowledge, there are few published studies using mathematical models to predict COVID-19 vaccine dose and none that have used all available published dose-response datasets for COVID-19 vaccine dose prediction.

Giorgi et. al. use a Quantitative Systems Pharmacology (QSP) model to predict the percentage COVID-19 responders over time by dose after vaccination with mRNA vaccine, mRNA-1273. Their results show that, early on, there is little difference in the percentage of those who responded (using median convalescent serum concentration as a threshold measure) between the 30ug and 100ug dose of the vaccine regardless of age. However after approximately a year, responders decreases (22). Empirical data support this as lower doses mRNA-1273 of 25µg had as high antibody immune responses as those who were given the dose chosen Phase III dose, 100ug (54). This suggests mRNA-1273 doses could be equally as effective at a lower dose, a finding our predictions support.

Empirical data for mRNA vaccine BNT162b2 show that antibody responses appear to wane six months after second vaccination, especially in adult men (55) which could be a result of under-dosing. Although we did not stratify our analysis by gender, our predictions support this by suggesting a higher dose of BNT162b2 in adults could be more immunogenic.

In our previous work, we have used mechanistic models in a PK/PD style framework to characterise the immune response over time, the effect of vaccine dose on the response dynamics as well as the variation in vaccine response across a population (15, 56). Mechanistic models can provide valuable understanding of the underlying biology of immune responses to vaccination. Applications of mechanistic models to vaccine data could potentially be shared to inform model-predicted dose-response for similar or emerging vaccines, reducing the need for empirical data (21). We were not able to apply these methods in this work as only data on early responses were available. Mechanistic modelling in a pharmacometric framework of

COVID-19 vaccine dose-responses could be conducted when more longitudinal data is available.

There are other areas for future research. Most importantly, the modelling predictions in this work should be validated and strengthened with further data. This should be done in a clinical setting to show that our predictions are reflective of reality. It is likely that since the initial literature search was conducted, more datasets have become available given the pace at which COVID-19 vaccines have been developed. More optimal dose predictions from emerging COVID-19 vaccine data will strengthen the predictions made in this analysis.

There are many other applications of IS/ID modelling that can accelerate development for vaccines not only against COVID-19 but other pathogens. These could include; cross-species and cross-disease dose translation (e.g. 'borrowing' dose-response information for similar diseases like MERS or SARS to make further predictions for COVID-19 vaccines); further work on the optimal COVID-19 vaccine dosing regimen (timing of vaccination)(22) and the effect of a third or fourth boost; and how we can use model-based adaptively designed vaccine trials to reduce the time taken to explore the full range of doses. These applications are common in drug-development and should be explored further in vaccines.

In general, IS/ID modelling offers a promising solution to accelerate how we develop all vaccines (23). This is especially true of vaccines developed under urgent circumstances, like in the case of COVID-19 where the timely application of IS/ID modelling can vastly improve our ability to protect the global population, saving lives.

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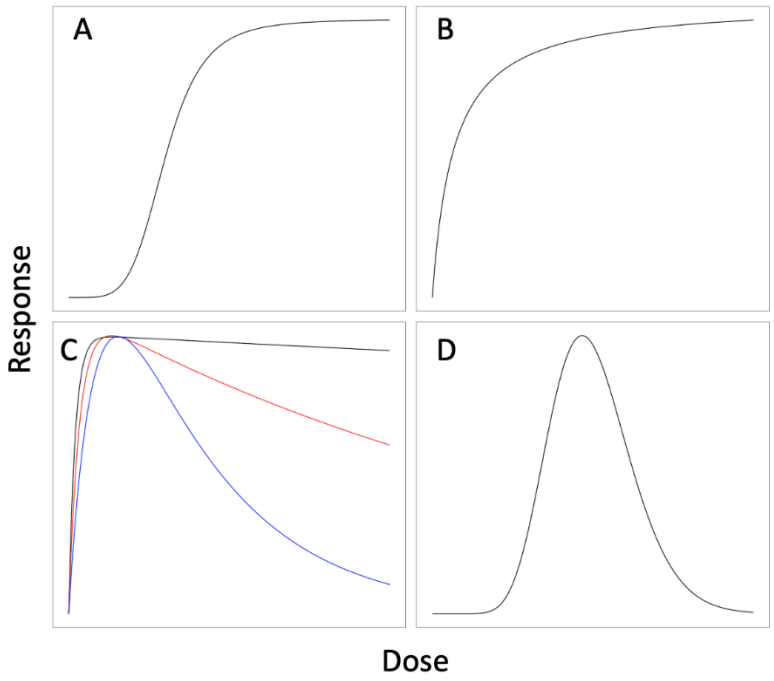

Figure 1. Representation of the saturating and peaked curves. A. Sigmoidal curve equation (p>1), B. Sigmoidal curve equation (p<1), C. Combined exponential curve equation, D. Gamma PDF curve equation.

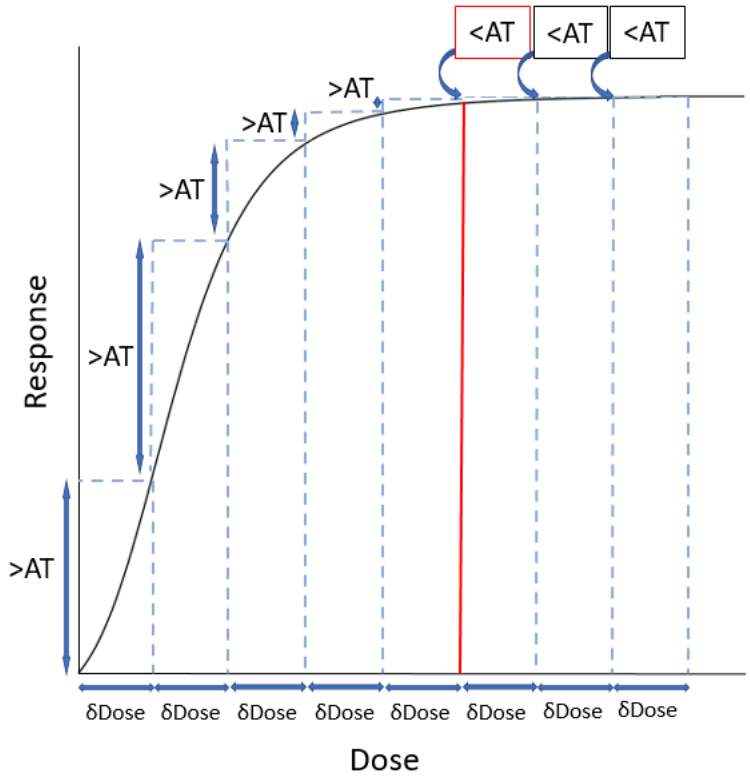

Figure 2. Illustration and example saturating dose-response curve and identification of optimal dose using the acceptance threshold. The red line indicates the smallest dose at which the increase in response is below the acceptance threshold for an increase of δDose. AT= Acceptance Threshold, δDose = Incremental increase in dose.

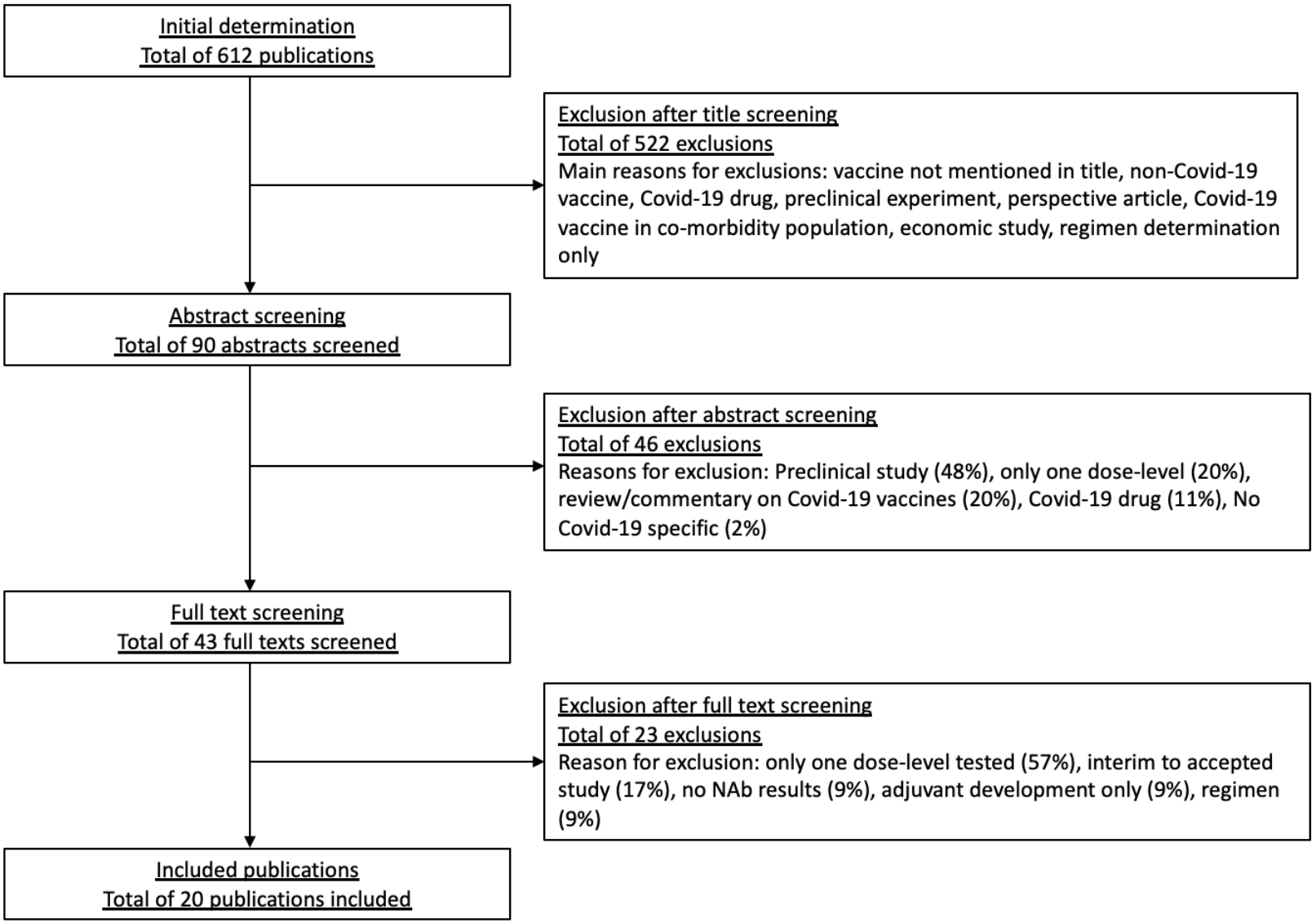

Figure 3. Flowchart of data extraction and screening

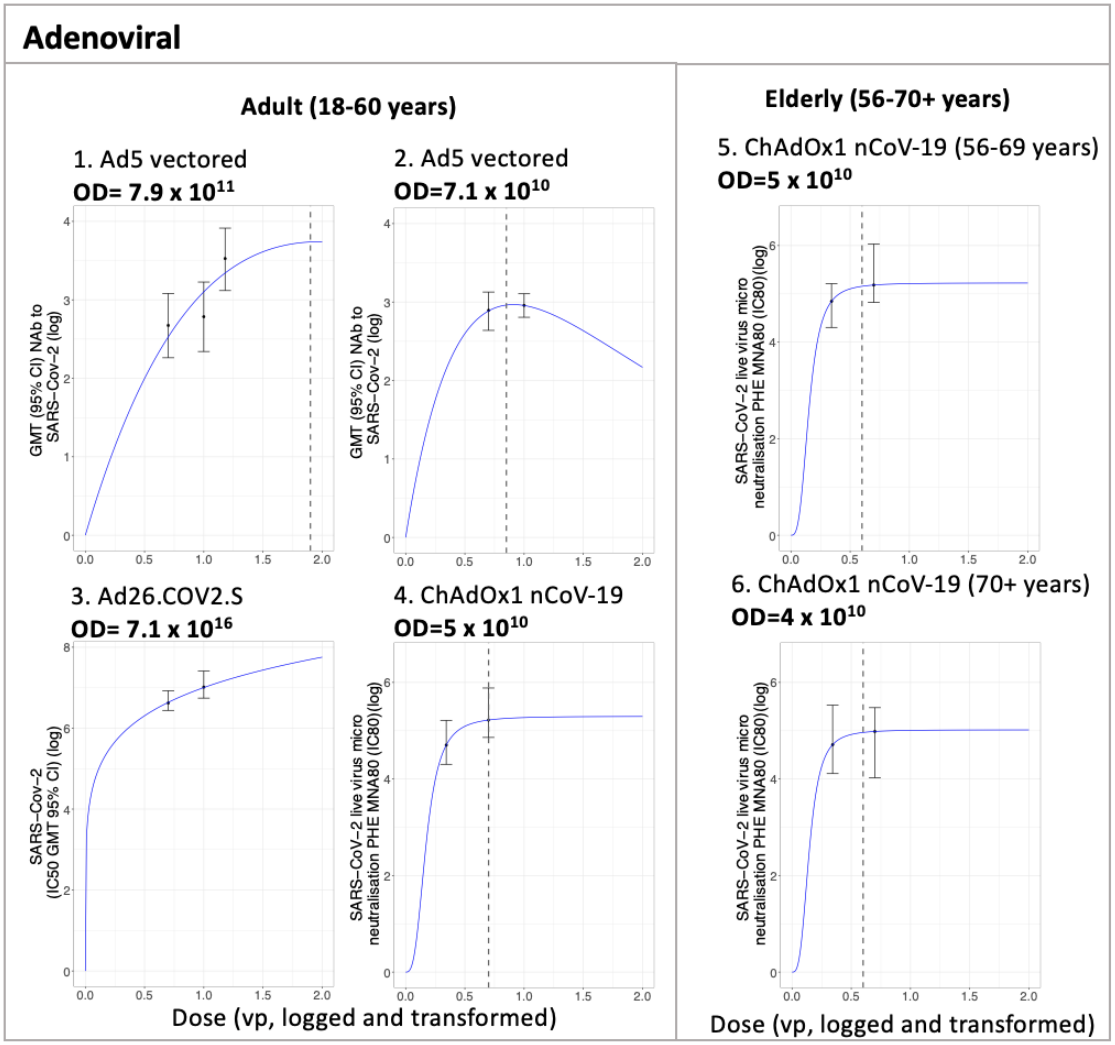

Figure 4. Predicted optimal dose for Adenoviral COVID-19 vaccines.

Figure numbers correspond to datasets from publications as follows: 1. (30), 2. (31), 3. (33), 4-6, (32). The black points and error bars correspond to the NAb Geometric Mean Titre and 95% CI of the data. The blue line is the model-predicted NAb dose-response curve and the vertical dashed line is the predicted optimal dose using the acceptance threshold. Dose on the x-axis is logged and transformed for ease of model calibration, but optimal doses are transformed back to the original scale in figure. OD= Optimal Dose, vp=Viral Particle.

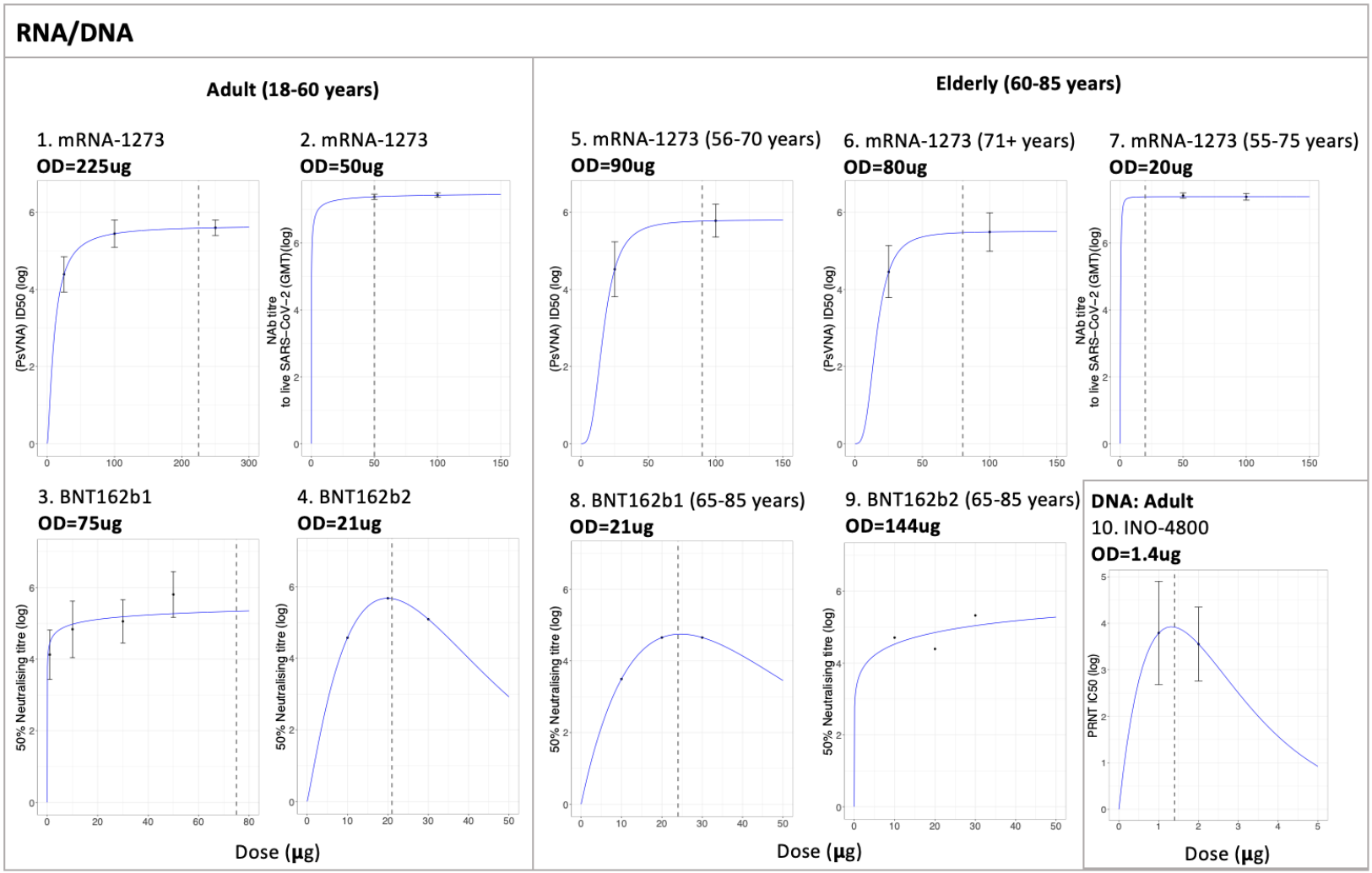

Figure 5. Predicted optimal dose for RNA/DNA COVID-19 vaccines. Figure numbers correspond to datasets from publications as follows: 1. (34), 2. (35), 3. (36, 37), 4. (37), 5-6. (38), 7. (35), 8-9, (37), 10. (39). The black points and error bars correspond to the NAb Geometric Mean Titre and 95% CI of the data. The blue line is the model-predicted NAb dose-response curve and the vertical dashed line is the predicted optimal dose using the acceptance threshold. OD= Optimal Dose.

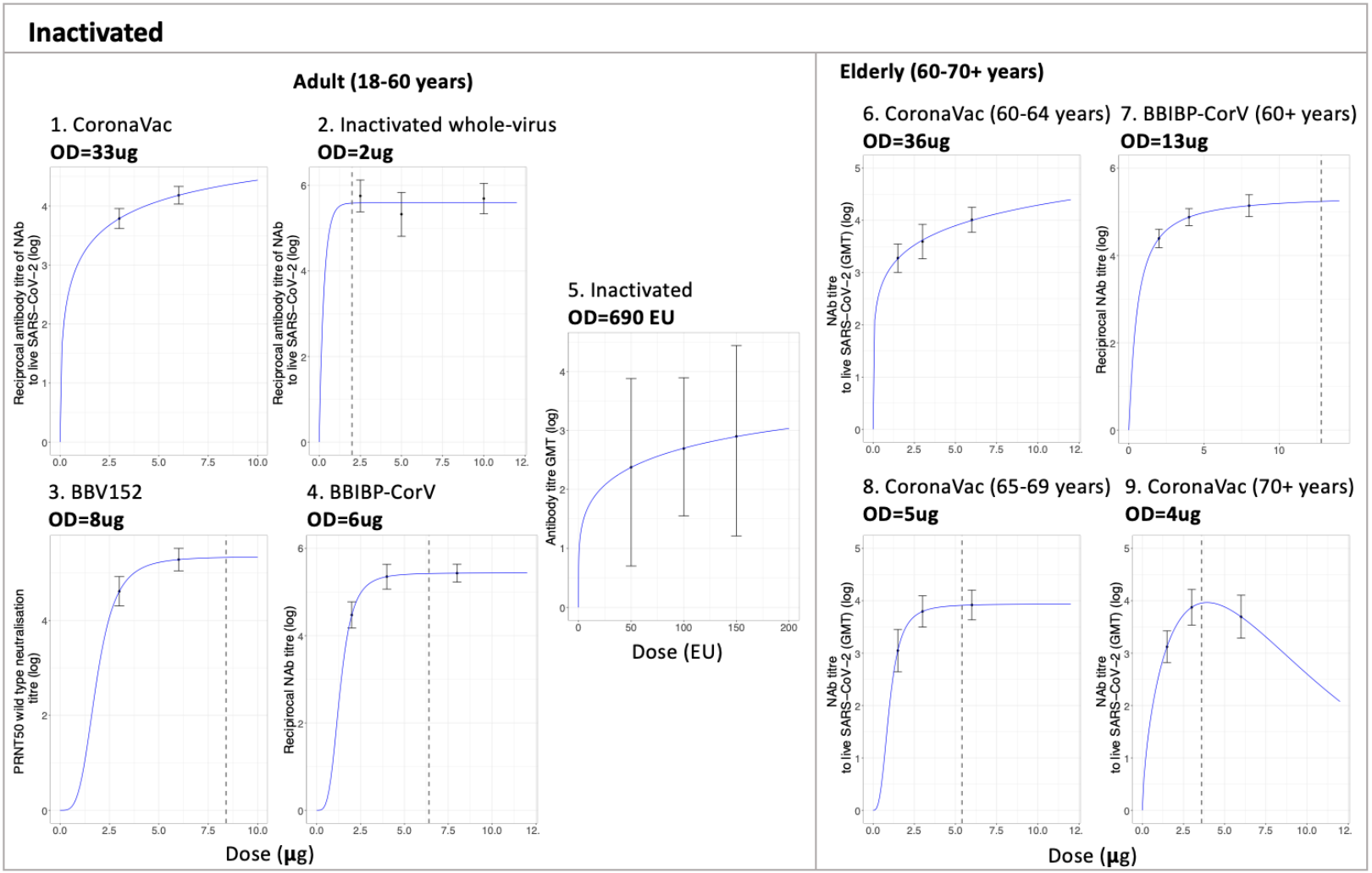

Figure 6. Predicted optimal dose for Inactivated COVID-19 vaccines. Figure numbers correspond to datasets from publications as follows: 1. (40), 2. (41), 3. (45), 4. (42), 5. (43), 6. (44) 7. (42), 8-9. (44). The black points and error bars correspond to the NAb Geometric Mean Titre and 95% CI of the data. The blue line is the model-predicted NAb dose-response curve and the vertical dashed line is the predicted optimal dose using the acceptance threshold. OD=Optimal Dose, EU=European Units

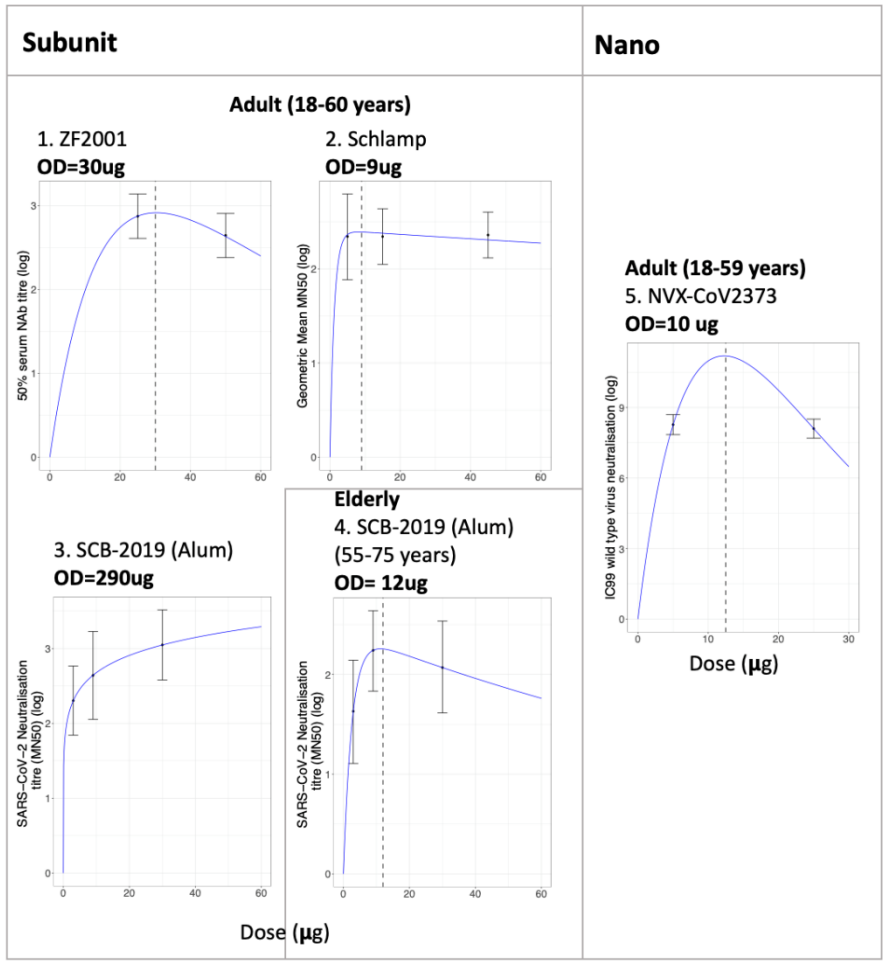

Figure 7. Predicted optimal dose for Subunit and Nano COVID-19 vaccines. Figure numbers correspond to datasets from publications as follows: 1. (46), 2. (47), 3-4. (48), 5. (49). The black points and error bars correspond to the NAb Geometric Mean Titre and 95% CI of the data. The blue line is the model-predicted NAb dose-response curve and the vertical dashed line is the predicted optimal dose using the acceptance threshold. OD=Optimal Dose.

Vaccine Type	**No. of publications /datasets**	**No. of total participants***	**Population stratification (N_s =No. of datasets, N_t=No. of total participants*)**	**Distinct dose levels given***	**References**
Adenoviral	4/6	800	Adults (18-55 years) (N_s = 4, N_t= 640) Elderly (56-69 years) (N_s = 1, N_t= 60) Elderly (70+ years) (N_s = 1, N_t= 100)	2.2×10^{10}, 5×10^{10}, 1×10^{11} or $1{\cdot}5\times10^{11}$ vp	(30-33)
RNA/DNA	6/10	917	Adults (18-55 years) (N_s = 5, N_t=505) Elderly (56-70 years) (N_s = 2, N_t= 320) Elderly (71+ years) (N_s = 1, N_t= 20) Elderly (65-85 years) (N_s = 2, N_t= 72)	1, 10, 20, 25, 30, 50, 100 or 250 µg	(34-39)
Inactivated	6/9	1205	Adult (18-59 years) (N_s = 5, N_t=836) Elderly (60-64 years) (N_s = 1, N_t=99) Elderly (65-69 years) (N_s = 1, N_t=99) Elderly (70+ years) (N_s = 1, N_t=99) Elderly (60+ years) (N_s = 1, N_t=72)	1.5, 2, 2.5, 3, 4, 5, 6, 8 or 10 µg 50,100 or 150 EU	(40-45)
Subunit	3/4	786	Adult (18-55 years) (N_s = 3, N_t=726) Elderly (55-75 years) (N_s = 1, N_t=60)	3, 5, 9, 15, 25, 30, 45 or 50 µg	(46-48)
Nanoparticle	1/1	50	Adult (18-59 years) (N_s = 1, N_t=50)	5 or 25 µg	(49)

Table 1. Summary of the dose-response data, grouped by vaccine type. *Across all publications

Vaccine Type	Vaccine name (alias)	Current phase of development	Chosen dose	Comparison of chosen dose to aggregate predictions of optimal dose in objective 2		
				Overall	Adult	Elderly
Adenoviral	Ad26.cov (Janssen vaccine)	In use in the UK	$5x10^{10}$ vp (50)	Within IQR	Below IQR	Above IQR
	ChadOx1 n-Cov19 (Astra Zeneca vaccine)	In use in the UK	$5x10^{10}$ vp (51)			
RNA/DNA	BNT162b2 (Pfizer vaccine)	In use in the UK	30ug (52)	Within IQR	Below IQR	Within IQR
	mRNA-1273 (Moderna vaccine)	In use in the UK	100ug (53)	Above IQR	Within IQR	Above IQR
Inactivated	Coronavac	In Phase III	3ug (40, 53)	Below IQR	Below IQR	Below IQR
	BBV152	In Phase III	6ug (53)	Within IQR	Within IQR	Within IQR
Nano	NVX-CoV2373	In Phase III	5ug (53)	Below IQR	*NA*	*NA*

Table 2. Chosen dose for the vaccines that are currently in phase III or above, comparison to the aggregate predicted optimal dose for the overall, adult and elderly populations and recommendations for further testing of doses for these vaccines.