

# Long-term durability of immune responses to the BNT162b2 and mRNA-1273 vaccines based on dosage, age and sex

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## 1 Supporting Text

| Variable | Definition          | Units | Initial condition |
|----------|---------------------|-------|-------------------|
| $L$      | Lipid nano particle | A.U.  | 1                 |
| $V$      | Vaccinated cell     | A.U.  | 0                 |
| $T$      | CD4+ T cell         | A.U.  | 0                 |
| $B$      | Plasma B cell       | A.U.  | 0                 |
| $A$      | Antibodies          | A.U   | $A_0$             |
| $C$      | CD8+ T cell         | A.U.  | 0                 |
| $F$      | IFN- $\gamma$       | pg/ml | 0                 |
| $I$      | Interleukin         | pg/ml | $I_0$             |

Table S1: Model variables and initial conditions for individual and population fits used throughout this work. We simultaneously fit to multiple IgG data sets, where the data sets come from different labs and have arbitrary units (a.u.). We therefore fit an initial condition A given by  $A_0$ . We furthermore simultaneously fit to 4 different interleukin data sets, each having varying responses through time and initial dynamics. We therefore fit the initial condition  $I_0$ . The initial conditions in this table represent the *population* initial condition from our fits; every individually-fitted data set may have slightly varying initial dynamics.

## 2 Population fit values for two standard doses

The population fit values are determined through a fit to all individual data data sets use for each vaccine dosage regimen. Values and figures for every individual fit for each data set are shown in the following sections.

## 3 Two standard doses mRNA vaccination of BNT162b2 or mRNA-1273

All individual fits shown in this section were fit simultaneously in Monolix.

|               |                                                        | Population fit values      |                           |              |
|---------------|--------------------------------------------------------|----------------------------|---------------------------|--------------|
| Parameter     | Definition                                             | Two standard doses (RSE %) | SD Random Effects (RSE %) | Comment      |
| $\mu_{LV}$    | LNP absorption rate with antigen presenting cells      | 0.91 (NaN)                 | 1.41 (71)                 | Fit          |
| $\gamma_L$    | LNP degradation rate                                   | 0.00013 (NaN)              | 2.87 (260)                | Fit          |
| $\gamma_V$    | Antigen presenting cell death rate                     | 0.07 (83.3)                | 0.5 (40)                  | Fit          |
| $\mu_{TV}$    | CD4+ activation rate by vaccinated cells               | 4.98 (228)                 | 1.31 (26)                 | Fit          |
| $\gamma_T$    | CD4+ natural death rate                                | 0.055 (NA)                 | 0.54 (NA)                 | Ref. [1]     |
| $\mu_{TB}$    | Plasma B cell activation rate by CD4+ cells            | 0.098 (29)                 | 0.8 (NaN)                 | Fit          |
| $\alpha_{BI}$ | Plasma B cell stimulation by Interleukin               | 2.4 (21)                   | 0.45                      | Fit          |
| $S_I$         | Plasma B cell duplication threshold due to Interleukin | 1000 (NA)                  | (NA)                      | Fixed        |
| $\gamma_B$    | Plasma B cell natural death rate                       | 0.071 (49)                 | 0.91 (107)                | Fit          |
| $\mu_{BA}$    | Released antibody rate by plasma B cells               | 0.51 (26.9)                | 0.98                      | Fit          |
| $\gamma_A$    | Antibody natural degradation rate                      | 0.042 (27.2)               | 0.37 (40.2)               | Fit          |
| $\mu_{CV}$    | CD8+ activation rate by vaccinated cells               | 0.000022 (65)              | 3.93 (300)                | Fit          |
| $\alpha_{CF}$ | CD8+ stimulation by IFN- $\gamma$                      | 0.0000014 (NaN)            | NA                        | Fit (no REs) |
| $S_F$         | CD8+ duplication threshold due to IFN- $\gamma$        | 600 (NA)                   | NA                        | Fixed        |
| $\gamma_C$    | CD8+ natural death rate                                | 0.01 (NA)                  | 5.1 (NA)                  | Ref. [2]     |
| $\mu_{TF}$    | IFN- $\gamma$ stimulation rate by Thelper cells        | 194.79 (191)               | 0.6 (NaN)                 | Fit          |
| $\alpha_{FC}$ | IFN- $\gamma$ clearance by cytotoxic Tcells            | 0.0000013 (NaN)            | NA                        | Fit (no REs) |
| $\gamma_F$    | IFN- $\gamma$ natural degradation rate                 | 201.24 (179)               | 1.78 (NaN)                | Fit          |
| $\mu_{TI}$    | Interleukin secretion by CD4+ cells                    | 2.07 (102)                 | 1.7 (NaN)                 | Fit          |
| $\alpha_{IB}$ | Interleukin clearance by Plasma B cells                | 0.0019 (222)               | 0.64 (NaN)                | Fit          |
| $\gamma_I$    | Natural interleukin degradation rate                   | 0.027 (179)                | 0.76 (NaN)                | Fit          |
| $A_0$         | Antibody initial condition                             | 22.5 (75)                  | 1.2 (21)                  | Fit          |
| $I_0$         | Interleukin initial condition                          | 5.18 (41)                  | 1.9 (68)                  | Fit          |
| BIC           | Bayesian Information Criteria                          |                            | 3468                      | Fit          |
| AIC           | Akaike Information Criteria                            |                            | 3421                      | Fit          |

Table S2: Model parameters definition and population fitted values for two standard doses of BNT162b2 or mRNA-1273. The dosing times are separated by 21 and 28 days for BNT162b2 and mRNA-1273, respectively. A value of “NA” refers to “Not Applicable”, whereby the random effects were turned off for said parameter because it was fixed for all individual study fits or the parameter was fit but due to clear identifiability issues (explored in the Model complexity reduction section below) random effects were turned off. A value of “NaN” means our algorithm was unable to estimate the Relative Standard Error (RSE) for that parameter.

### 3.1 Individual data set fitted values

| Data set ID            | Figure reference, quantity used   | Vaccine                 | $\mu_{LV}$ | $\gamma_L$ | $\gamma_V$ | $\mu_{TV}$ | $\gamma_T$ | $\mu_{TB}$ | $\alpha_{BI}$ | $S_I$ | $\gamma_B$ | $\mu_{BA}$ | $\gamma_A$ |
|------------------------|-----------------------------------|-------------------------|------------|------------|------------|------------|------------|------------|---------------|-------|------------|------------|------------|
| Goel et al. [3]        | Fig. 1b, RBD IgG                  | BNT162b2<br>& mRNA-1273 | 0.77       | 0.00012    | 0.07       | 0.75       | 0.054      | 0.07       | 2.67          | 1000  | 0.18       | 0.27       | 0.042      |
| Goel et al. [3]        | Fig. 1b, Spike IgG                | BNT162b2<br>& mRNA-1273 | 1.08       | 0.00012    | 0.07       | 1.34       | 0.055      | 0.077      | 2.42          | 1000  | 0.12       | 0.5        | 0.043      |
| Stankov et al. [4]     | Fig. 1a, Spike IgG                | BNT162b2                | 0.86       | 0.0001     | 0.081      | 9.42       | 0.068      | 0.092      | 2.84          | 1000  | 0.31       | 0.07       | 0.048      |
| Bergamaschi et al. [5] | Fig. 1a, Spike-RBD IgG,           | BNT162b2                | 1.08       | 0.00013    | 0.079      | 1.97       | 0.065      | 0.078      | 2.32          | 1000  | 0.21       | 0.91       | 0.047      |
| Camara et al. [6]      | Fig. 1b, Spike IgG,               | BNT162b2                | 0.94       | 0.00013    | 0.083      | 4.05       | 0.067      | 0.082      | 2.63          | 1000  | 0.21       | 0.22       | 0.048      |
| Bergamaschi et al. [5] | Fig. 2A, IFN- $\gamma$            | BNT162b2                | 3.88       | 0.00012    | 0.067      | 4.02       | 0.051      | 0.098      | 2.41          | 1000  | 0.071      | 0.51       | 0.042      |
| Camara et al. [6]      | Fig. 1a, IFN- $\gamma$ ,          | BNT162b2                | 1.14       | 0.00012    | 0.057      | 8.21       | 0.044      | 0.098      | 2.39          | 1000  | 0.071      | 0.5        | 0.042      |
| Bergamaschi et al. [5] | Fig. 2c, IL-6                     | BNT162b2                | 0.36       | 0.00011    | 0.071      | 0.81       | 0.059      | 0.094      | 2.39          | 1000  | 0.073      | 0.53       | 0.042      |
| Bergamaschi et al. [5] | Fig. 2b, IL-8                     | BNT162b2                | 1.04       | 0.00012    | 0.13       | 7.16       | 0.11       | 0.088      | 4.44          | 1000  | 0.026      | 0.45       | 0.042      |
| Bergamaschi et al. [5] | Fig. 2a, IL-15                    | BNT162b2                | 0.45       | 0.00012    | 0.068      | 0.78       | 0.054      | 0.096      | 2.39          | 1000  | 0.074      | 0.53       | 0.042      |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 18-55 yrs) | mRNA-1273               | 0.9        | 0.00012    | 0.06       | 12.44      | 0.048      | 0.096      | 2.43          | 1000  | 0.044      | 0.74       | 0.04       |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 56-70 yrs) | mRNA-1273               | 0.17       | 0.00011    | 0.066      | 14.55      | 0.057      | 0.083      | 2.13          | 1000  | 0.062      | 0.94       | 0.045      |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 70+ yrs)   | mRNA-1273               | 0.17       | 0.00013    | 0.066      | 12.73      | 0.056      | 0.1        | 2.25          | 1000  | 0.061      | 0.87       | 0.045      |
| Bergamaschi et al. [5] | Fig. 2b (IL-16)                   | BNT162b2                | 1.64       | 0.00012    | 0.067      | 26.84      | 0.053      | 0.11       | 2.2           | 1000  | 0.54       | 0.54       | 0.042      |
| Wang et al. [8]        | Fig. 1e (RBD IgG)                 | mRNA-1273               | 0.97       | 0.00012    | 0.064      | 6.36       | 0.049      | 0.098      | 2.45          | 1000  | 0.044      | 0.56       | 0.039      |
| Wang et al. [8]        | Fig. 1f (Spike IgG)               | mRNA-1273               | 0.95       | 0.00012    | 0.064      | 6.57       | 0.048      | 0.099      | 2.45          | 1000  | 0.043      | 0.57       | 0.039      |
| Wang et al. [8]        | Fig. 1e (RBD IgG)                 | BNT162b2                | 0.93       | 0.00012    | 0.066      | 7.25       | 0.052      | 0.099      | 2.47          | 1000  | 0.057      | 0.59       | 0.04       |
| Wang et al. [8]        | Fig. 1f (Spike IgG)               | BNT162b2                | 1.05       | 0.00012    | 0.065      | 7.2        | 0.05       | 0.098      | 2.47          | 1000  | 0.053      | 0.6        | 0.04       |
| Suthar et al. [9]      | Fig. 1a (Spike IgG, Male)         | BNT162b2                | 1.2        | 0.00012    | 0.068      | 6.57       | 0.051      | 0.11       | 2.36          | 1000  | 0.03       | 0.38       | 0.039      |
| Suthar et al. [9]      | Fig. 1a (Spike IgG, Female)       | BNT162b2                | 0.99       | 0.00012    | 0.072      | 5.23       | 0.054      | 0.13       | 2.2           | 1000  | 0.026      | 0.42       | 0.039      |

Table S3: Individual fit values for to the various data sets used in this work. This table contains all fitted parameters from equations 9a, 9b, 9c, 9d, and 9e.

| Data set ID            | Paper Fig. reference, quantity used | Vaccine                 | $\mu_{CV}$ | $\alpha_{CF}$ | $S_F$ | $\gamma_C$ | $\mu_{TF}$ | $\alpha_{FC}$ | $\gamma_F$ | $\mu_{TI}$ | $\alpha_{IB}$ | $\gamma_I$ | $A_0$  | $I_0$  |
|------------------------|-------------------------------------|-------------------------|------------|---------------|-------|------------|------------|---------------|------------|------------|---------------|------------|--------|--------|
| Goel et al. [3]        | Fig. 1b, RBD IgG                    | BNT162b2<br>& mRNA-1273 | 0.000021   | 1.4E-06       | 600   | 0.0078     | 194.83     | 1.3E-06       | 202.39     | 2.97       | 0.0019        | 0.022      | 0.58   | 2.14   |
| Goel et al. [3]        | Fig. 1b, Spike IgG                  | BNT162b2<br>& mRNA-1273 | 0.000022   | 1.4E-06       | 600   | 0.014      | 195.27     | 1.3E-06       | 199.53     | 1.14       | 0.0016        | 0.024      | 0.52   | 3.74   |
| Stankov et al. [4]     | Fig. 1a, Spike IgG                  | BNT162b2                | 0.000024   | 1.4E-06       | 600   | 0.018      | 185.85     | 1.3E-06       | 196.98     | 1.33       | 0.0035        | 0.026      | 1.12   | 3.23   |
| Bergamaschi et al. [5] | Fig. 1a, Spike-RBD IgG              | BNT162b2                | 0.00002    | 1.4E-06       | 600   | 0.0083     | 193.89     | 1.3E-06       | 207.77     | 2.34       | 0.0013        | 0.024      | 3.69   | 3.54   |
| Camara et al. [6]      | Fig. 1b, Spike IgG                  | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.0028     | 195.21     | 1.3E-06       | 202.22     | 1.35       | 0.0023        | 0.026      | 2.88   | 3.52   |
| Bergamaschi et al. [5] | Fig. 2A, IFN- $\gamma$              | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.0094     | 189.29     | 1.3E-06       | 266.97     | 2.27       | 0.0019        | 0.027      | 22.85  | 5.34   |
| Camara et al. [6]      | Fig. 1a, IFN- $\gamma$              | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.01       | 207.17     | 1.3E-06       | 124.78     | 2.07       | 0.0019        | 0.027      | 23.4   | 4.96   |
| Bergamaschi et al. [5] | Fig. 2c, IL-6                       | BNT162b2                | 0.000024   | 1.4E-06       | 600   | 0.0093     | 191.21     | 1.3E-06       | 230.1      | 0.035      | 0.0018        | 0.05       | 18.39  | 0.89   |
| Bergamaschi et al. [5] | Fig. 2b, IL-8                       | BNT162b2                | 0.00002    | 1.4E-06       | 600   | 0.011      | 193.87     | 1.3E-06       | 212.17     | 12.28      | 0.0017        | 0.027      | 26.26  | 0.65   |
| Bergamaschi et al. [5] | Fig. 2a, IL-15                      | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.011      | 192.95     | 1.3E-06       | 200.71     | 0.049      | 0.0018        | 0.035      | 23.43  | 2.06   |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 18-55 yrs)   | mRNA-1273               | 0.000022   | 1.4E-06       | 600   | 0.01       | 195.09     | 1.3E-06       | 200.28     | 15.79      | 0.0016        | 0.028      | 404.79 | 4.95   |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 56-70 yrs)   | mRNA-1273               | 0.000021   | 1.4E-06       | 600   | 0.004      | 194.37     | 1.3E-06       | 224.13     | 25.77      | 0.0014        | 0.028      | 440.37 | 5.18   |
| Widge et al. [7]       | Fig. 1a (RBD antibody, 70+ yrs)     | mRNA-1273               | 0.000026   | 1.4E-06       | 600   | 0.02       | 192.49     | 1.3E-06       | 195.36     | 22.97      | 0.0015        | 0.028      | 515.75 | 3.44   |
| Bergamaschi et al. [5] | Fig. 2b (IL-16)                     | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.0089     | 195.54     | 1.3E-06       | 203.12     | 13.22      | 0.0021        | 0.027      | 21.99  | 235.56 |
| Wang et al. [8]        | Fig. 1e (RBD IgG)                   | mRNA-1273               | 0.000022   | 1.4E-06       | 600   | 0.009      | 194.74     | 1.3E-06       | 201.76     | 3.52       | 0.0018        | 0.027      | 50.9   | 5.21   |
| Wang et al. [8]        | Fig. 1f (Spike IgG)                 | mRNA-1273               | 0.000022   | 1.4E-06       | 600   | 0.01       | 195        | 1.3E-06       | 200.52     | 3.45       | 0.0018        | 0.027      | 50.82  | 5.13   |
| Wang et al. [8]        | Fig. 1e (RBD IgG)                   | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.01       | 194.79     | 1.3E-06       | 201.13     | 4.09       | 0.0018        | 0.027      | 50.87  | 5.16   |
| Wang et al. [8]        | Fig. 1f (spike IgG)                 | BNT162b2                | 0.000021   | 1.4E-06       | 600   | 0.01       | 195.24     | 1.3E-06       | 199.48     | 4.1        | 0.0018        | 0.027      | 51.08  | 5.33   |
| Suthar et al. [9]      | Fig. 1a (Spike IgG, Male)           | BNT162b2                | 0.000021   | 1.4E-06       | 600   | 0.012      | 195.2      | 1.3E-06       | 200.65     | 0.43       | 0.0022        | 0.028      | 104.2  | 6.21   |
| Suthar et al. [9]      | Fig. 1a (Spike IgG, Female)         | BNT162b2                | 0.000022   | 1.4E-06       | 600   | 0.012      | 195.21     | 1.3E-06       | 201.71     | 0.43       | 0.0025        | 0.028      | 118.33 | 7.31   |

Table S4: Individual fit values for to the various data sets used in this work. This table contains all fitted parameters from equations 9f, 9g and 9h.

### 3.2 Individual fits to IgG data sets

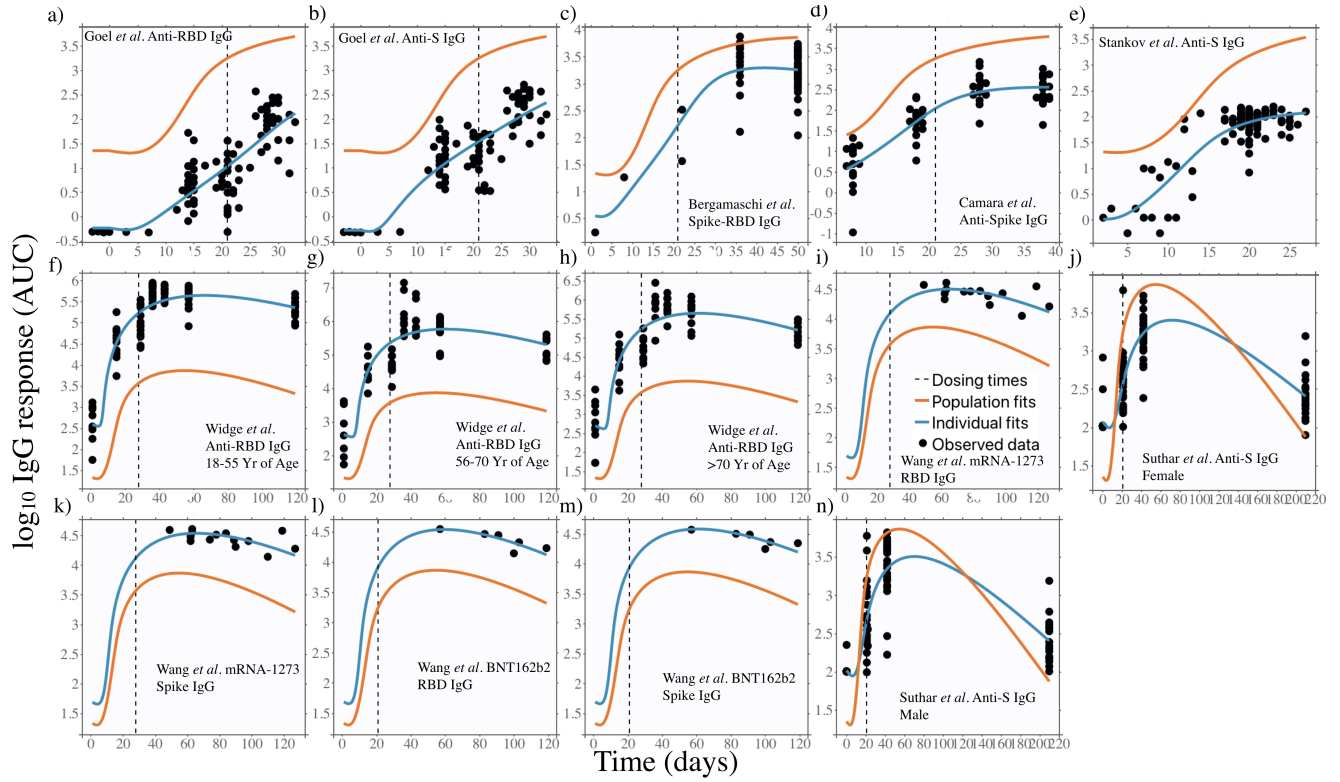


Figure S1: Individual fits to all standard dose IgG data sets used in this work. References for the data set sources can be found in Table 1 of the main text, all individual fitted parameters for each fit can be found in Tables S3 and S4.

### 3.3 Individual fits to IFN- $\gamma$ data sets

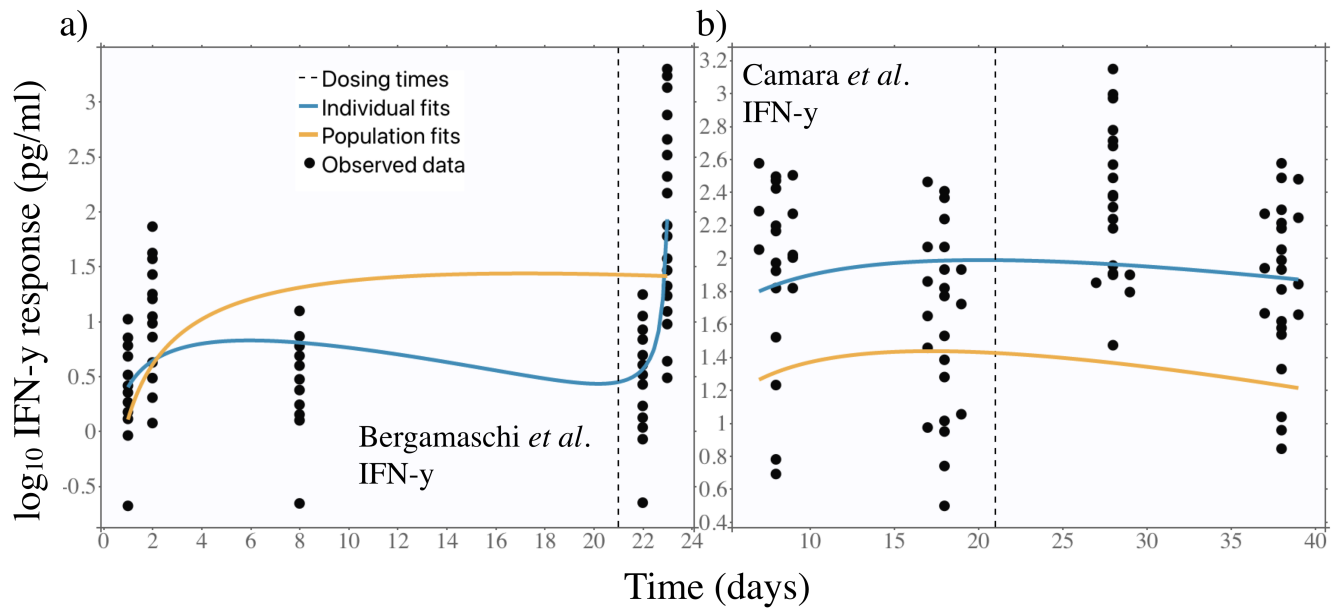


Figure S2: Individual fits to various IFN- $\gamma$  data sets. References for the data set sources can be found in Table 1 of the main text, all individual fitted parameters for each fit can be found in Tables S3 and S4.

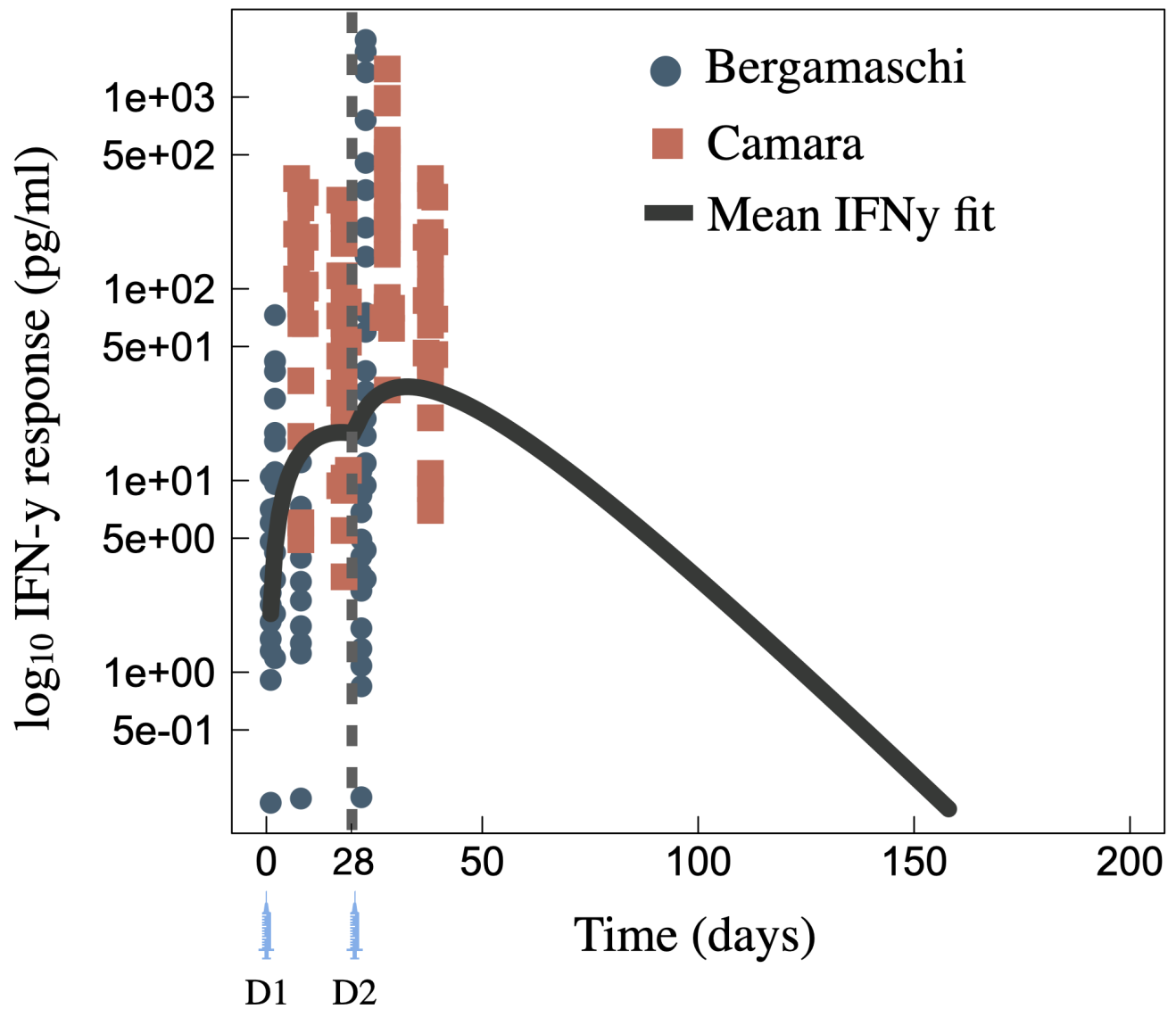


Figure S3: Mean IFN $\gamma$  fit response to the Bergamaschi and Camara data sets.

### 3.4 Individual fits to Interleukin data sets

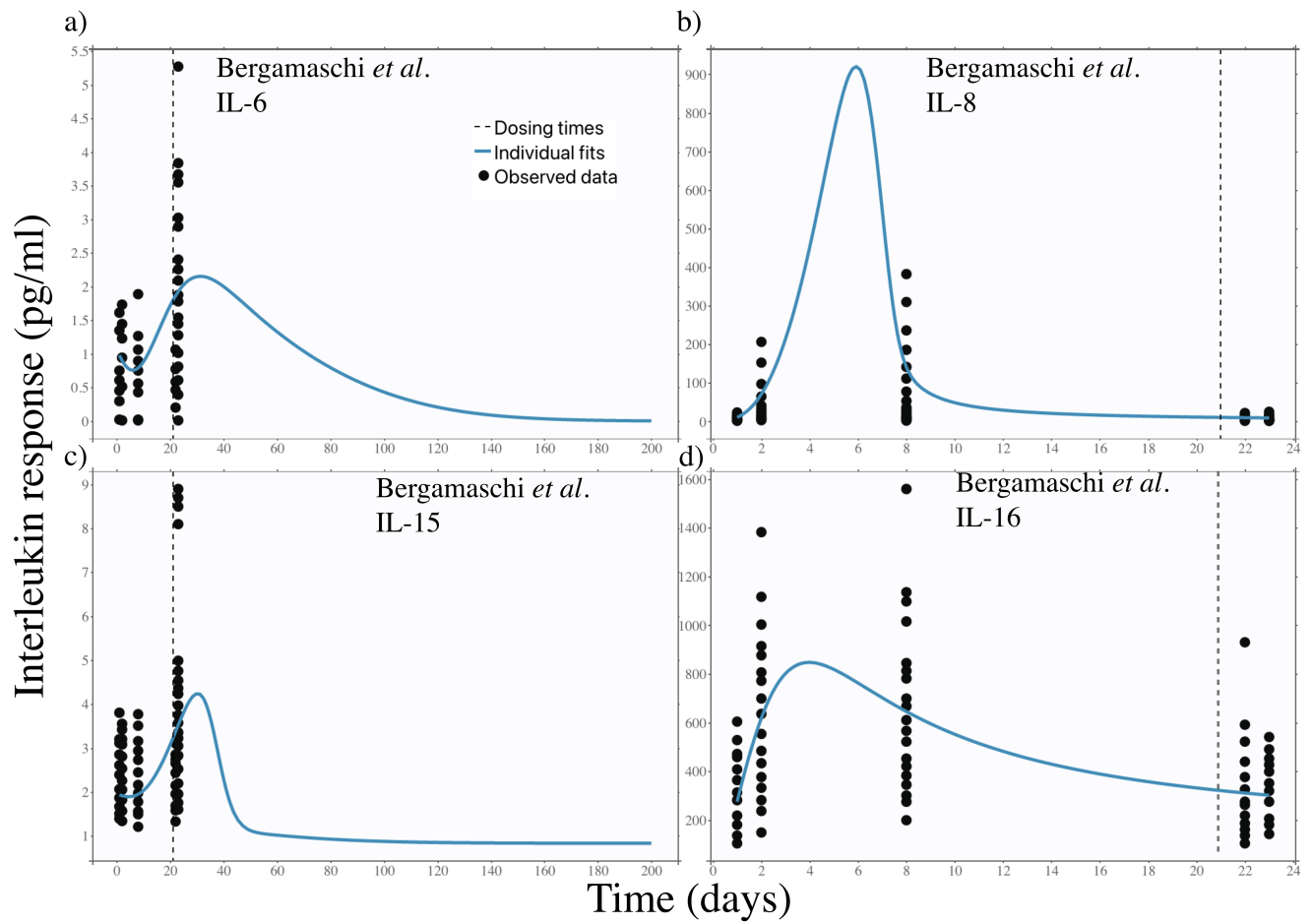


Figure S4: Individual fits to various interleukin data sets. References for the data set sources can be found in Table 1 of the main text, all individual fitted parameters for each fit can be found in Tables S3 and S4.

### 3.5 Goodness of fit predictive checks and parameter distributions

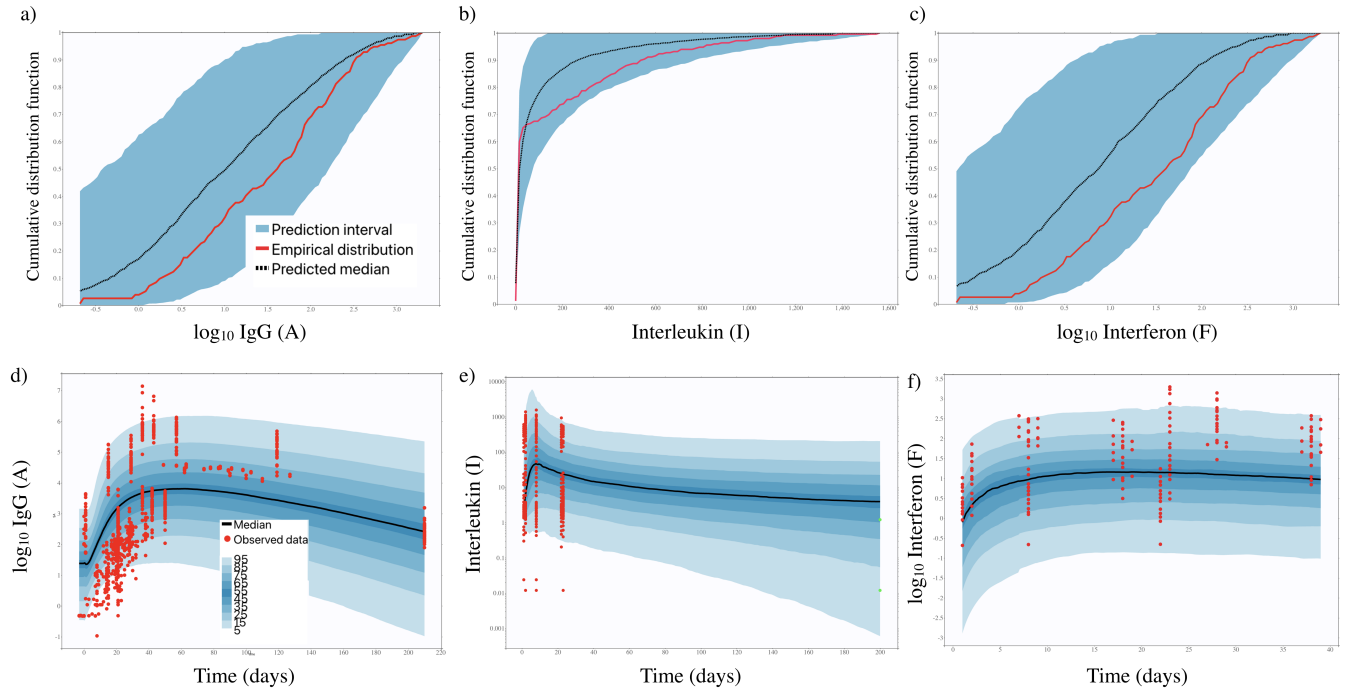


Figure S5: Predictive checks for two-dose mRNA results. a)-c) Numerical predictive checks for IgG, Interleukin, and Interferon, corresponding to fits to equations 9e, 9g, and 9h, respectively. d)-f) Prediction distributions for IgG, Interleukin, and Interferon as a function of time.

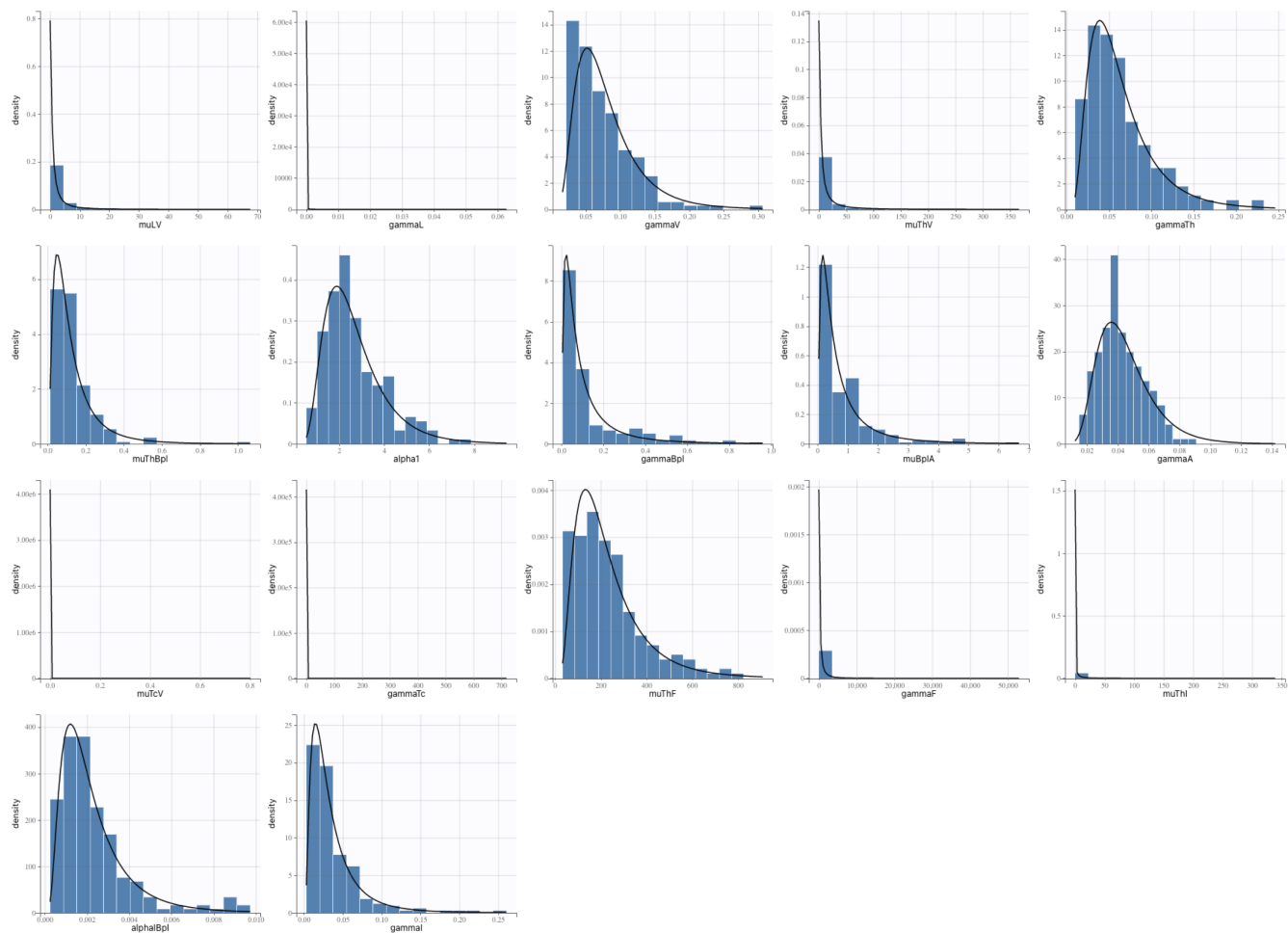


Figure S6: Monolix-determined fitted parameter distributions for all two standard dose fitted parameters.

### 3.6 Standardized random effects

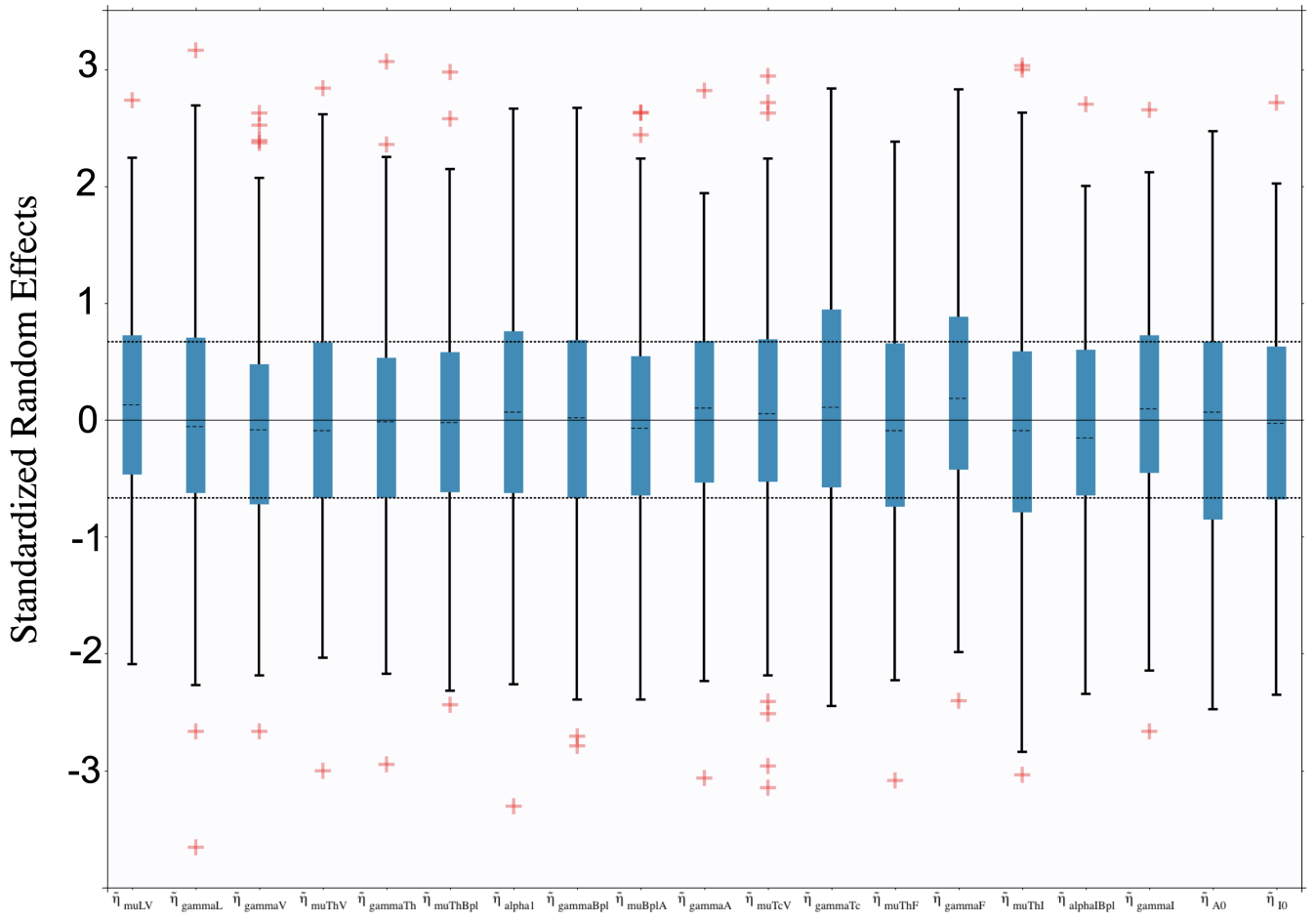


Figure S7: Boxplots of standardized random effects for all fitted model parameters for the two-dose mRNA data. The dashed line represents the median, the blue boxes represent the 25th and 75th percentiles, whiskers extend to extreme data points. Outliers are shown as red crosses.

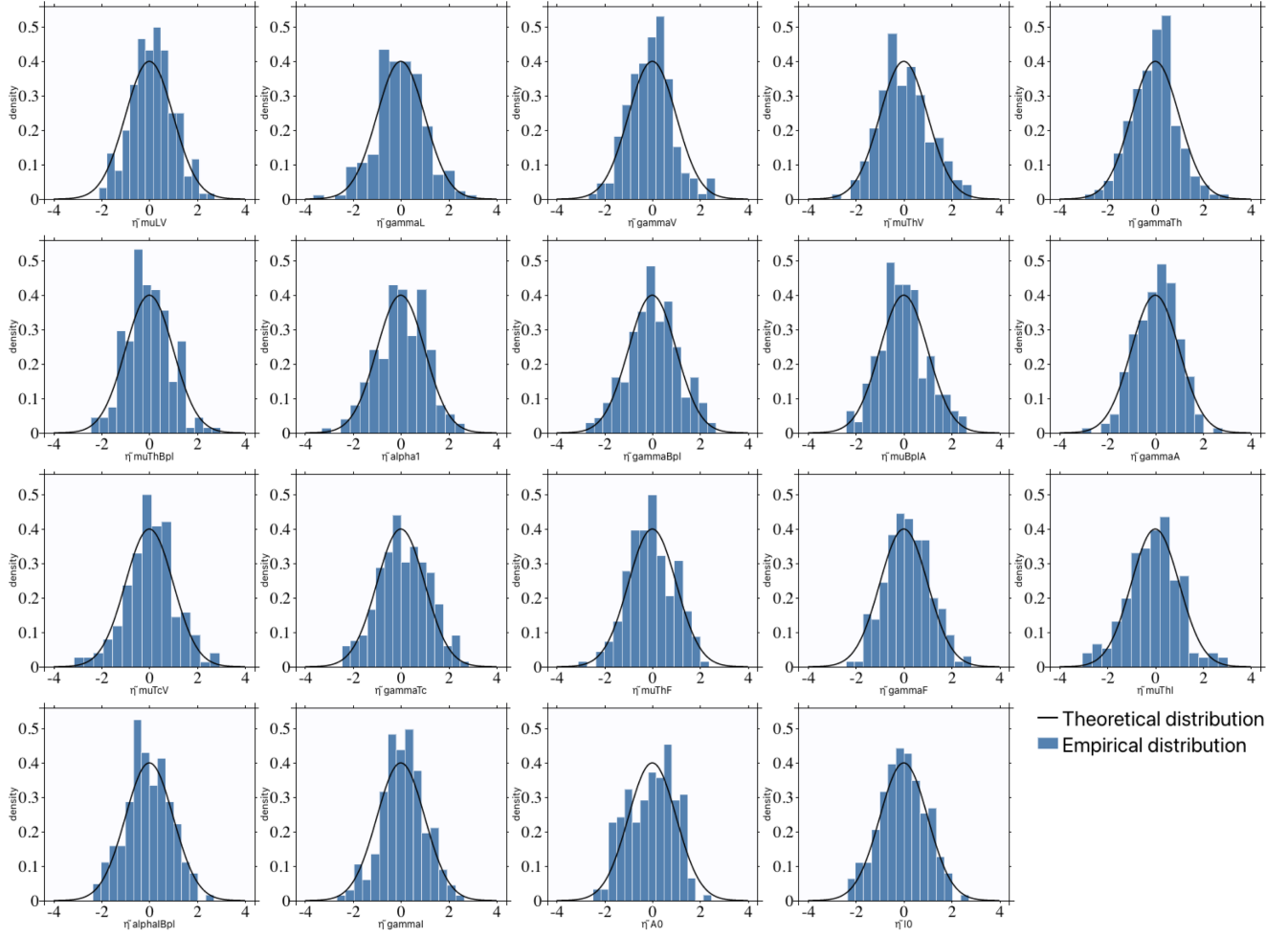


Figure S8: distributions of standardized random effects for all fitted model parameters for the two-dose mRNA data. The solid black line is an overlaid Guassian distribution.

## 4 Two low doses of mRNA-1273 vaccination

Two-low-dose mRNA-1273 data used in this work is sourced from Ref. [10]. This section contains tables summarizing the individual data set fitted parameters.

| Parameter     | Definition                                             | Population fit values |                   | Comment      |
|---------------|--------------------------------------------------------|-----------------------|-------------------|--------------|
|               |                                                        | Two standard doses    | SD Random Effects |              |
| $\mu_{LV}$    | LNP absorption rate with antigen presenting cells      | 0.023                 | 0.01              | Fit          |
| $\gamma_L$    | LNP degradation rate                                   | 0.00026               | 2.52              | Fit          |
| $\gamma_V$    | Antigen presenting cell death rate                     | 0.098                 | 0.056             | Fit          |
| $\mu_{TV}$    | CD4+ activation rate by vaccinated cells               | 3.86                  | 0.027             | Fit          |
| $\gamma_T$    | CD4+ natural death rate                                | 0.055                 | N/A               | Ref. [1]     |
| $\mu_{TB}$    | Plasma B cell activation rate by CD4+ cells            | 2.48                  | 0.02              | Fit          |
| $\alpha_{BI}$ | Plasma B cell stimulation by Interleukin               | 0.019                 | 3.1               | Fit          |
| $S_I$         | Plasma B cell duplication threshold due to Interleukin | 1000                  | N/A               | Fixed        |
| $\gamma_B$    | Plasma B cell natural death rate                       | 0.072                 | 0.034             | Fit          |
| $\mu_{BA}$    | Released antibody rate by plasma B cells               | 0.48                  | 0.022             | Fit          |
| $\gamma_A$    | Antibody natural degradation rate                      | 0.067                 | 0.05              | Fit          |
| $\mu_{CV}$    | CD8+ activation rate by vaccinated cells               | 0.00033               | 17.5              | Fit          |
| $\alpha_{CF}$ | CD8+ stimulation by IFN- $\gamma$                      | 0.00096               | N/A               | Fit (no REs) |
| $S_F$         | CD8+ duplication threshold due to IFN- $\gamma$        | 600                   | N/A               | Fixed        |
| $\gamma_C$    | CD8+ natural death rate                                | 0.01                  | 9.29              | Ref. [2]     |
| $\mu_{TF}$    | IFN- $\gamma$ stimulation rate by Thelper cells        | 0.22                  | 27.7              | Fit          |
| $\alpha_{FC}$ | IFN- $\gamma$ clearance by cytotoxic Tcells            | 0.000004              | N/A               | Fit (no REs) |
| $\gamma_F$    | IFN- $\gamma$ natural degradation rate                 | 64.82                 | 5.06              | Fit          |
| $\mu_{TI}$    | Interleukin secretion by CD4+ cells                    | 0.000057              | 9.10              | Fit          |
| $\alpha_{IB}$ | Interleukin clearance by Plasma B cells                | 1.07                  | 5.0               | Fit          |
| $\gamma_I$    | Natural interleukin degradation rate                   | 0.00001               | 36                | Fit          |
| $A_0$         | Antibody initial condition                             | 3.8                   | 0.018             | Fit          |
| $I_0$         | Interleukin initial condition                          | 1.0                   | 37.53             | Fit          |
| BIC           | Bayesian Information Criteria                          |                       | 315               | Fit          |
| AIC           | Akaike Information Criteria                            |                       | 252               | Fit          |

Table S5: Model parameters definition and population fitted values for two low doses of mRNA-1273. The dosing times are separated by 28 days for mRNA-1273.

## 4.1 Model parameter population fits and individual data set fitted values

| Data set ID               | Figure from paper   | $\mu_{LV}$ | $\gamma_L$ | $\gamma_V$ | $\mu_{TV}$ | $\gamma_T$ | $\mu_{TB}$ | $\alpha_{BI}$ | $s_I$   | $\gamma_B$ | $\mu_{BA}$ | $\gamma_A$ |
|---------------------------|---------------------|------------|------------|------------|------------|------------|------------|---------------|---------|------------|------------|------------|
| Mateus <i>et al.</i> [10] | Fig. 1a (Spike IgG) | 0.023      | 0.00027    | 0.099      | 3.85       | 0.056      | 2.48       | 0.019         | 1003.37 | 0.073      | 0.48       | 0.068      |
| Mateus <i>et al.</i> [10] | Fig. 1b (RBD IgG)   | 0.023      | 0.00025    | 0.097      | 3.87       | 0.054      | 2.49       | 0.019         | 1002.3  | 0.071      | 0.48       | 0.066      |

Table S6: Individual fit values for to the two low doses of mRNA-1273. This table contains all fitted parameters from equations 9a, 9b, 9c, 9d, and 9e.

| Data set ID               | $\mu_{CV}$ | $\alpha_{CF}$ | $S_F$  | $\gamma_C$ | $\mu_{TF}$ | $\alpha_{FC}$ | $\gamma_F$ | $\mu_{TI}$ | $\alpha_{IB}$ | $\gamma_I$ |
|---------------------------|------------|---------------|--------|------------|------------|---------------|------------|------------|---------------|------------|
| Mateus <i>et al.</i> [10] | 0.00033    | 0.00096       | 608.69 | 0.0099     | 0.21       | 0.000004      | 64.94      | 0.000057   | 1.07          | 0.0000074  |
| Mateus <i>et al.</i> [10] | 0.00033    | 0.00096       | 604.89 | 0.0099     | 0.2        | 0.000004      | 64.94      | 0.000056   | 1.07          | 0.0000074  |

Table S7: Individual fit values for to the two low doses of mRNA-1273. This table contains all fitted parameters from equations 9f, 9g and 9h.

## 4.2 Individual fits to IgG data sets

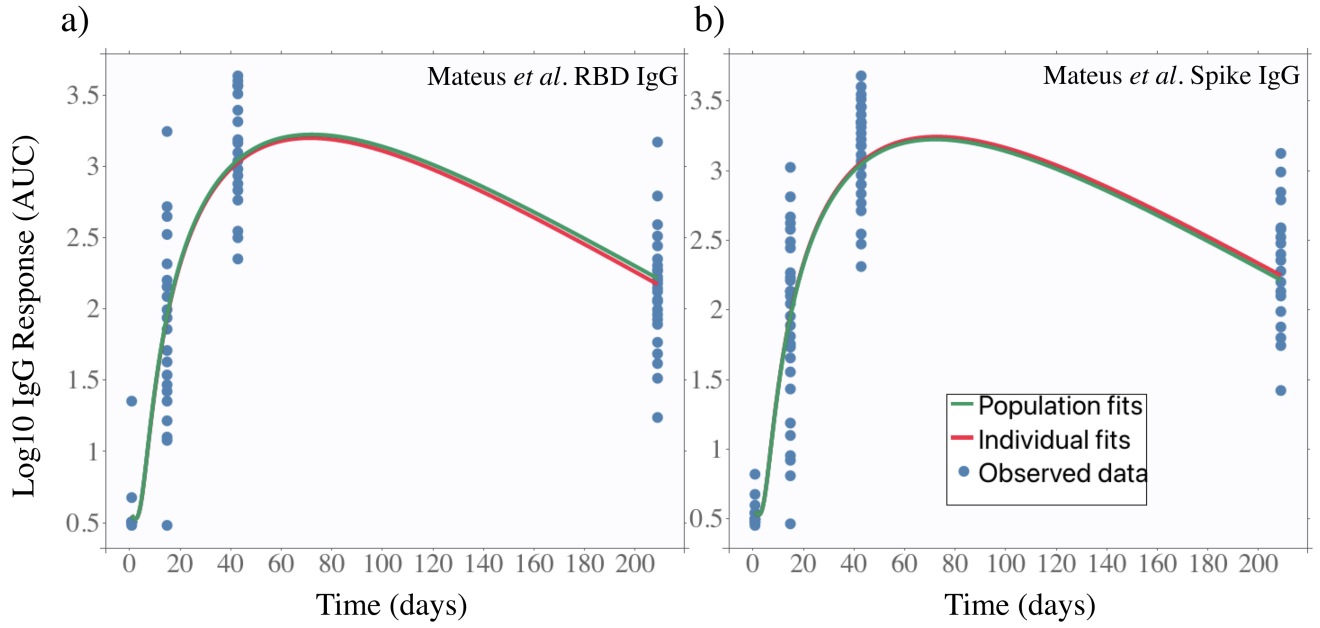


Figure S9: Individual fits to the two low doses of mRNA-1273. All individual fitted parameter values can be found in Tables S6 and S7.

### 4.3 Goodness of fit predictive checks

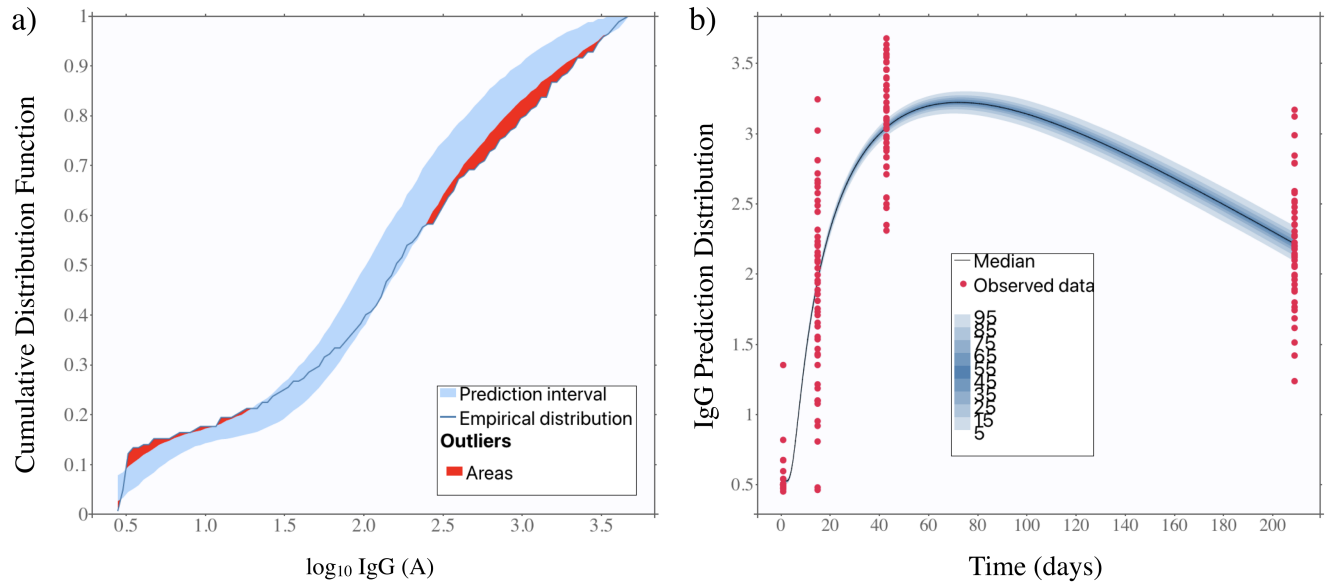


Figure S10: Predictive checks for fits to two low doses of mRNA-1273. a) Numerical predictive checks for the IgG data sets. b) Prediction distributions for the IgG fits as a function of time.

#### 4.4 Standardized random effects

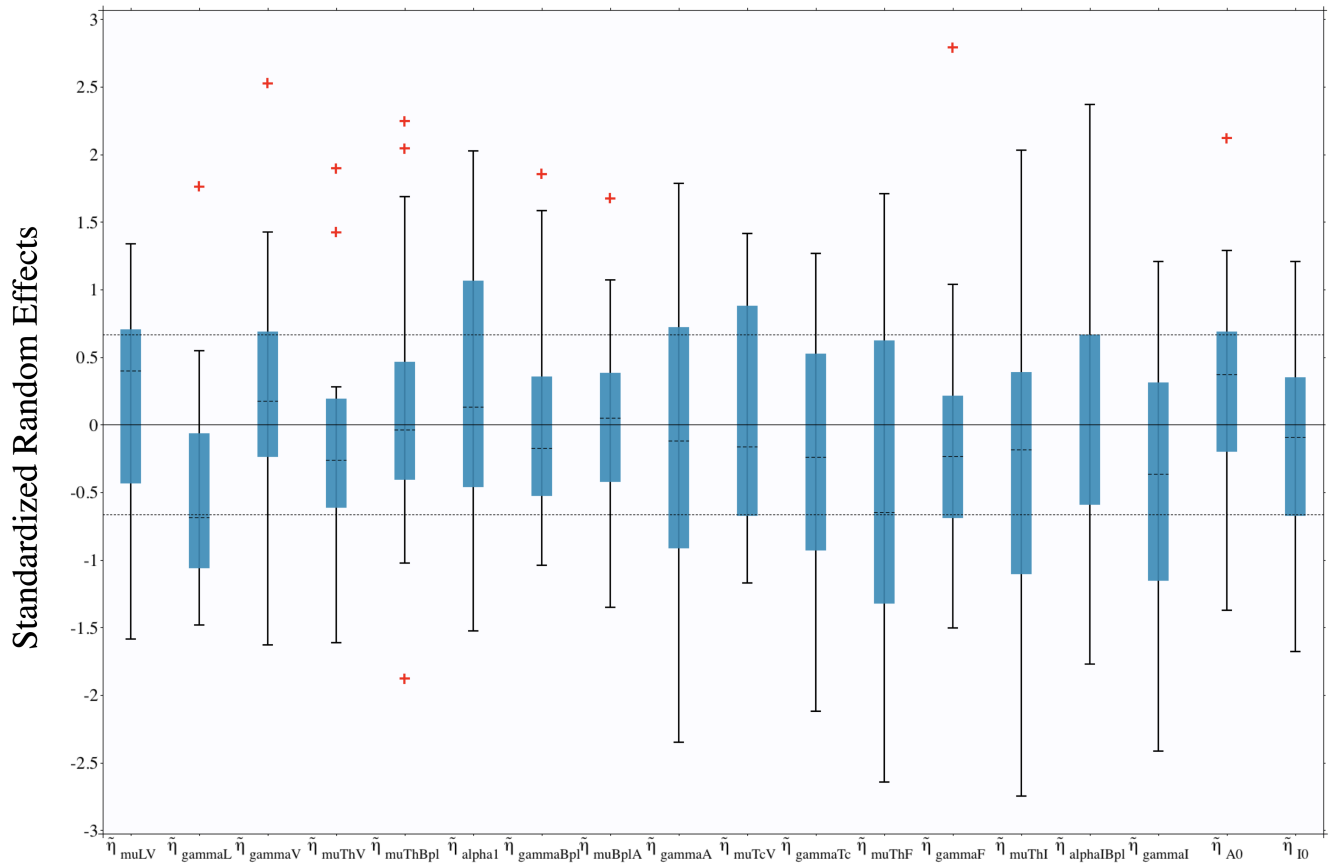


Figure S11: Boxplots of standardized random effects for all fitted model parameters for the low dose mRNA data. The dashed line represents the median, the blue boxes represent the 25th and 75th percentiles, whiskers extend to extreme data points. Outliers are shown as red crosses.

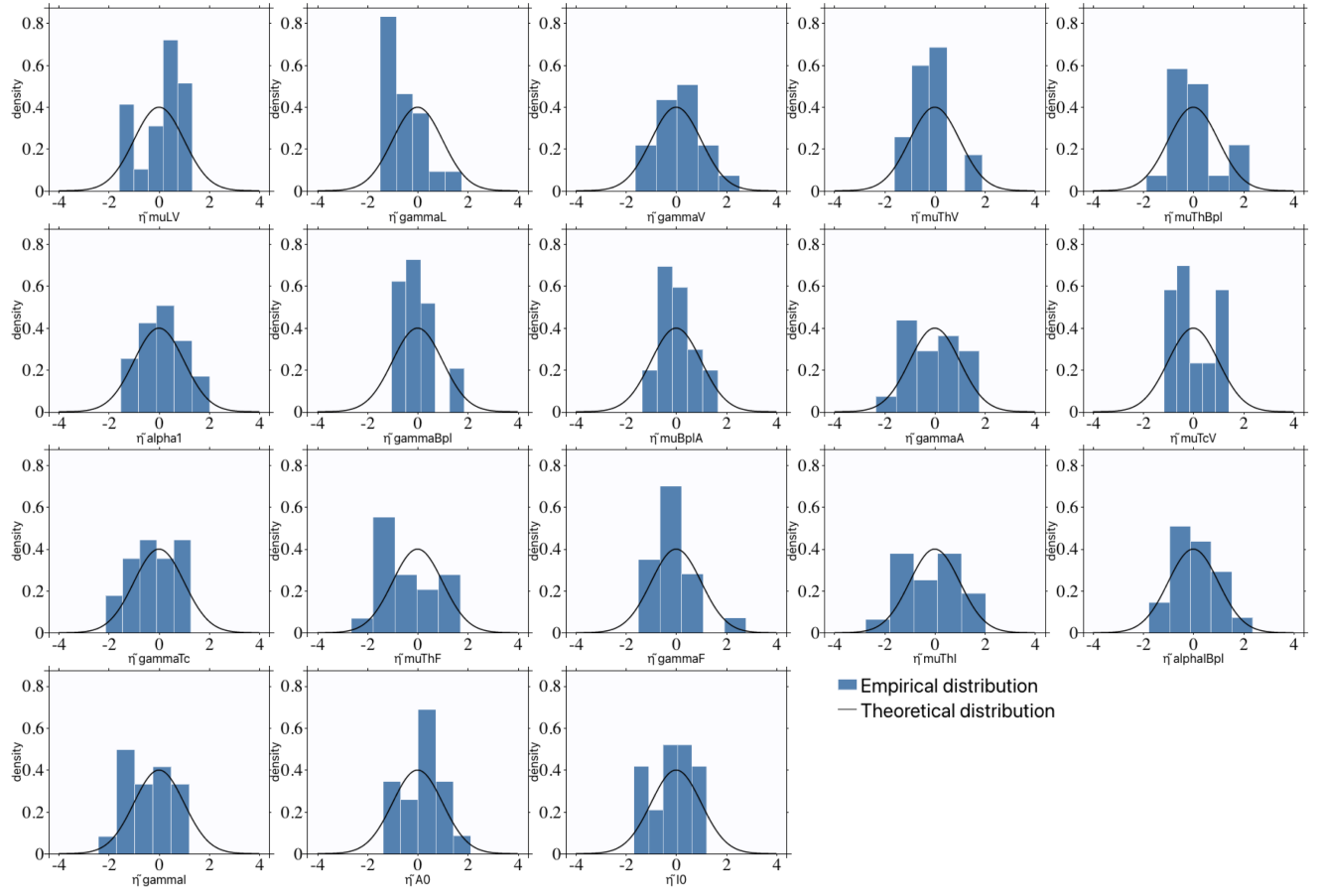


Figure S12: distributions of standardized random effects for all fitted model parameters for the low dose mRNA data. The solid black line is an overlaid Guassian distribution.

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## 5 Sensitivity Analysis

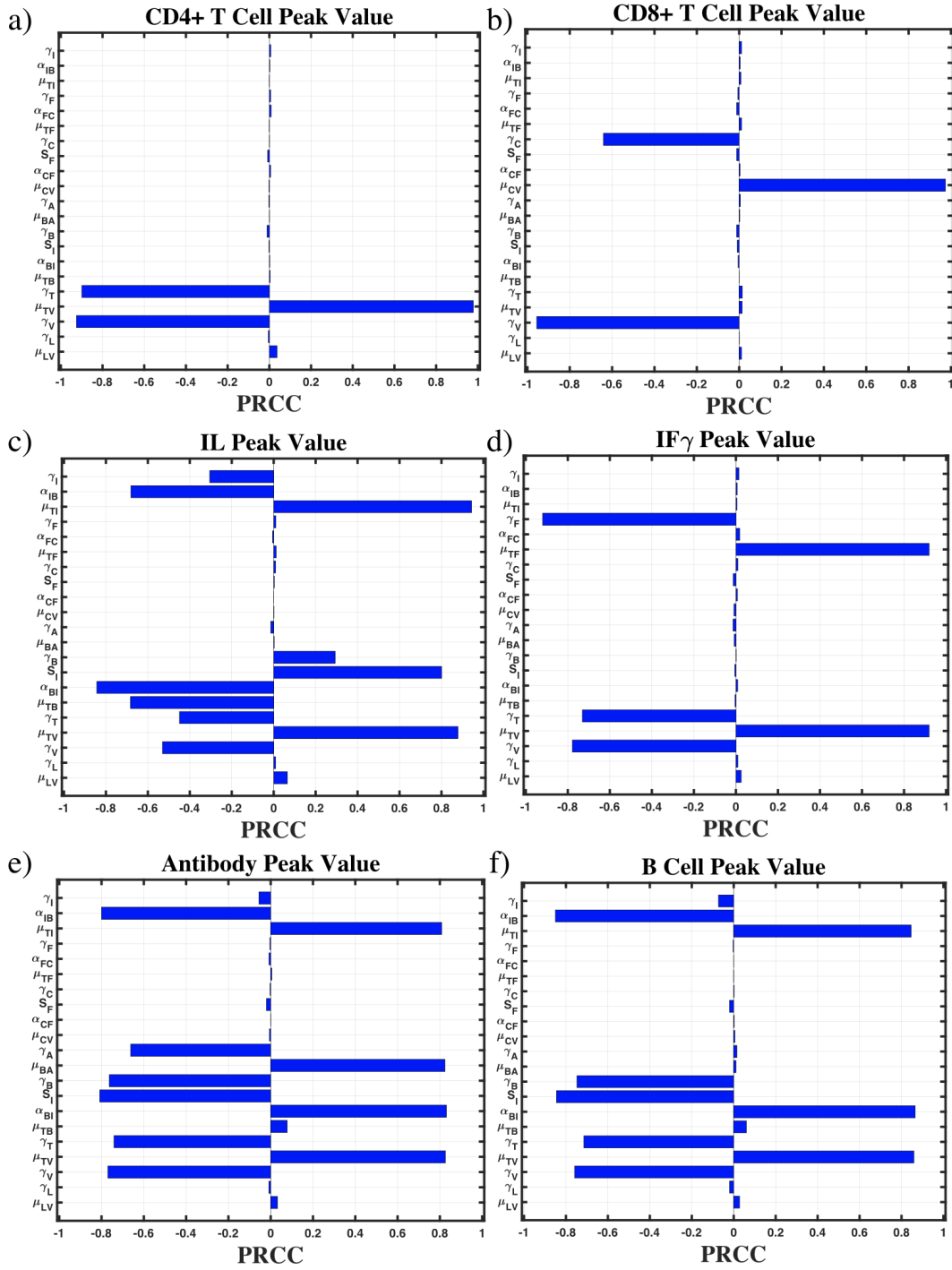


Figure S13: PRCC sensitivity analysis. PRCC analysis is performed on model parameters where the peak value of each state variable is selected as the model output. Panels a-f show the sensitivity analysis for CD4+ T cells ( $T$ ), CD8+ T cells ( $C$ ), Interleukin ( $I$ ), IFN $\gamma$  ( $F$ ), Antibody ( $A$ ), and Plasma B cells ( $B$ ), respectively.

## 6 Model complexity reduction

The full model (Eq.9) was derived following a biologically consistent approach to the immune response upon receiving an LNP mRNA based vaccine. On the surface it appears to be a complex 8 equation coupled model and thus parameter estimation would lead to coupled overfitting complications. However, the model is actually only weakly coupled through an effective activation-inhibition mechanism between plasma B-cells and interleukin.

We first note the immediate decoupling in the model. The first equations, Eq.9a-c, for  $L$ ,  $V$ , and  $T$  are a cascade of linear equations which can be solved in sequence (and analytically). Furthermore, the equation for  $A$  depends on, but is decoupled from,  $B$  and thus can be solved once the solution for  $B$  is independently known,

$$A = \mu_{BA} e^{-\gamma_A t} \int_0^t B(s) e^{\gamma_A s} ds. \quad (1)$$

Thus, there are two sets of equations remaining, a coupled system for  $B$  and  $I$  and a coupled system for  $C$  and  $F$ . The parameter fitting in Table S4 demonstrates that the  $CD8^+$  cell-mediated removal of  $IFN-\gamma$  is eclipsed by its natural decay rate. This suggests that the term associated to  $\alpha_{FC}$  can be ignored. Furthermore, the production of  $IFN-\gamma$ ,  $\mu_{TF}$  is comparable to the decay rate  $\gamma_F$  which are both very quick. This suggests a quasi-steady balance of production and decay and that

$$F = \frac{\mu_{TF}}{\gamma_F} T. \quad (2)$$

If the  $CD8^+$  cell-mediated removal of  $IFN-\gamma$  is small then it is reasonable to suggest that the  $IFN-\gamma$  mediated production of  $CD8^+$  cells is also negligible which is supported by the small value of  $\alpha_{CF}$  compared to  $\gamma_C$  and  $\mu_{CV}$  in Table S4. This means that the equation for  $C$  also decouples and follows a similar solution to that of the  $CD4^+$  T-cells,

$$\frac{dC}{dt} = \mu_{CV} V - \gamma_C C. \quad (3)$$

Therefore, with these assumptions our eight equation model really becomes a two equation non-linear coupled system for plasma B-cells and interleukin. However, if we anticipate that the response of the vaccine is mostly transient then we are likely not near the threshold required for saturation effects. This suggests that the parameter  $s_I$  is not needed for model consistency. This parameter was arbitrarily chosen and its value being unimportant demonstrate strong model robustness. Overall, we then expect the reduced eight equation model is equivalent to solving

$$\frac{dB}{dt} = \mu_{TB} T + \alpha_{BI} IB - \gamma_B B \quad (4a)$$

$$\frac{dI}{dt} = \mu_{TI} T - \alpha_{IB} IB - \gamma_I I. \quad (4b)$$

Fig.S14 shows the full solution (solid blue) to the full model (Eq.9) and the reductions (dashed red) Eq.1 for  $A$ , Eq.2 for  $F$ , and Eq.3 for  $C$  as well as the analytically obtained decoupled solutions for  $L$ ,  $V$ , and  $T$ . We also

demonstrate in Figure Fig.S14h that indeed the saturation parameter being removed does not change the Interleukin response with the red dashed curve having the parameter excluded from the model.

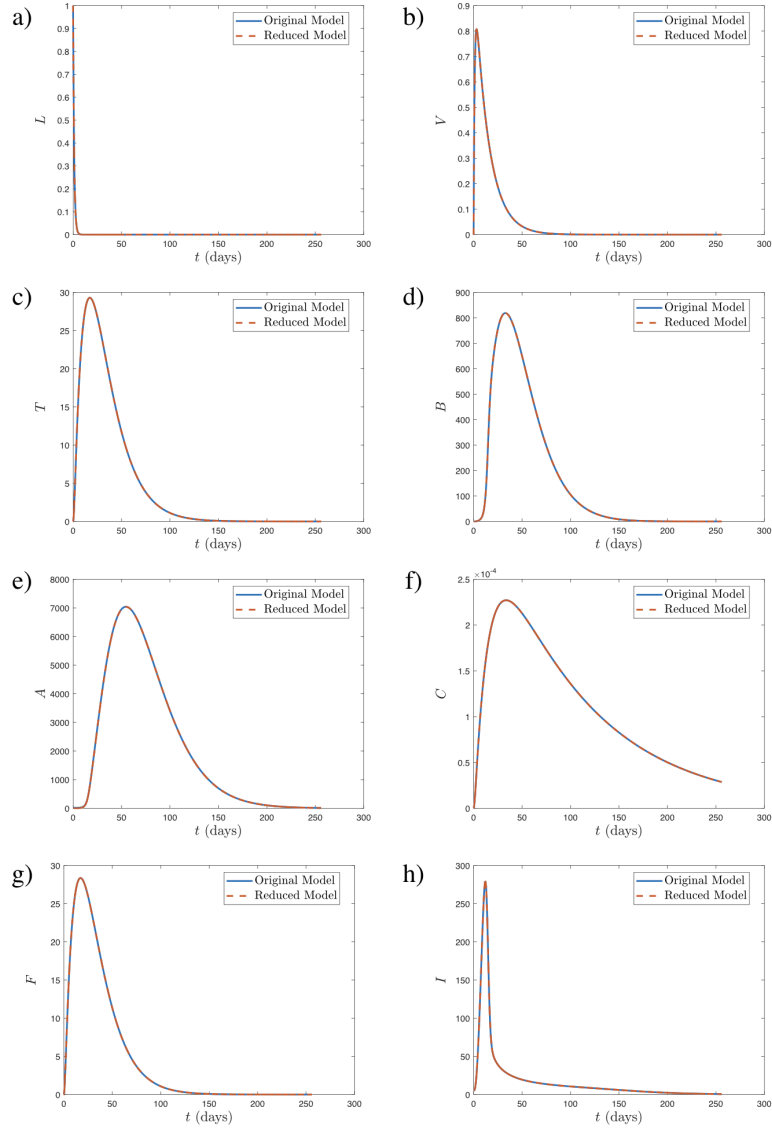


Figure S14: Comparison of the full model (Eq.9) (in solid blue) and the various reduction assumptions (1), (3), (2), and (4) as well as the analytic reductions for  $L$ ,  $V$ , and  $T$  (in dashed red). The parameter sets chosen were the population fits in Table S2.

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