Supplementary Material

Antibody Dynamics of Severe and Non-Severe Patients with COVID-19

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A. Bifurcation analysis

We seek an equilibrium point with virus, denoted E^*. To obtain a working expression for E^*, we introduce

$$\overline{w_M} = \frac{\overline{r_M}}{\overline{q} + \overline{\delta_M}}, \qquad \overline{w_G} = \frac{\overline{r_q}\,\overline{w_M}^2}{\overline{\delta_G}}.$$

Let us introduce the function

$$f(x,\lambda) = \left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\left[x^2 - \left(\widehat{y} + x_G^*\right)x\right] + \left(\frac{\lambda + \overline{c_T}}{\overline{c_T}}\right), \tag{25}$$

$$\mathcal{H}_0(x,\lambda) = 1 - \frac{1}{f(x,\lambda)} = \frac{f(x,\lambda) - 1}{f(x,\lambda)}, \tag{26}$$

where

$$x_G^* = (\overline{w_M})^{-1} + (\overline{w_G})^{-1}, \qquad \widehat{y} = \frac{\overline{c_M}\,\overline{w_M} + 1}{\overline{c_G}\,\overline{w_G}}.$$

Writing $E^* = (x^*, y^*, z^*, w_M^*, w_G^*)$ where $x^* > 0$, we establish that E^* is a function of x^*.

Theorem 2. *A necessary condition for E^* to exist is $\lambda + \overline{c_T} > 0$. Under this condition, E^* takes the form*

$$E^* = (x^*,\ f(x^*,\lambda),\ x^*,\ \overline{w_M}x^*,\ \overline{w_G}x^*(x_G^* - x^*)) \tag{27}$$

where x^* satisfies

$$\mathcal{H}(x^*, \overline{K_T}) = \mu\, \mathcal{H}_0(x^*, \lambda), \qquad \mu := \overline{\delta_T}/\overline{r_T}. \tag{28}$$

Proof. Eqs. (16)-(20) provide the following equations:

$$0 = \lambda + \overline{c_T} - x^* - \overline{c_T} y^* - \overline{c_M} w_M^* - \overline{c_G} w_G^*, \tag{29}$$

$$0 = \overline{\delta_T} + \overline{r_T} y^*\, \mathcal{H}(x^*, \overline{K_T}) - \overline{\delta_T} y^*, \tag{30}$$

$$0 = (\overline{\tau_B})^{-1}(x^* - z^*), \tag{31}$$

$$0 = \overline{r_M} z^* - (\overline{q} + \overline{\delta_M}) w_M^*, \tag{32}$$

$$0 = \overline{r_q} w_M^*(1 - w_M^*) + \overline{\delta_G}(z^* - w_G^*), \tag{33}$$

with $\lambda + \overline{c_T} = 1 - \overline{c}$. If E^* exists, then we get

$$0 = \lambda + \overline{c_T} - x^* - \overline{c_T} y^* - \overline{c_M} w_M^* - \overline{c_G} w_G^* < \lambda + \overline{c_T}$$

from Eq. 29. Therefore, it is necessary that $\lambda + \overline{c_T} > 0$ for E^* to exist.

Proceeding with the condition $\lambda + \overline{c_T} > 0$, we get $z^* = x^*$ from Eq (31). Now, we can rewrite Eqs. (32) and (33) as

$$0 = \overline{w_M}(\overline{q} + \overline{\delta_M}) x^* - (\overline{q} + \overline{\delta_M}) w_M^*, \tag{34}$$

$$0 = \overline{w_G}\,\overline{\delta_G} w_M^*(1 - w_M^*) + \overline{w_M}^2 \overline{\delta_G}(z^* - w_G^*). \tag{35}$$

Eq. (34) yields

$$w_M^* = \overline{w_M} x^*. \tag{36}$$

Substituting this result into Eq. (35), we obtain

$$0 = \overline{w_G}\,\overline{\delta_G}\,\overline{w_M} x^*(1 - \overline{w_M} x^*) + \overline{w_M}^2 \overline{\delta_G}(x^* - w_G^*),$$

$$0 = \overline{w_G}\, x^*(1 - \overline{w_M} x^*) + \overline{w_M}(x^* - w_G^*),$$

$$w_G^* = \overline{w_G}\, x^*((\overline{w_M})^{-1} - x^*) + x^*,$$

$$w_G^* = \overline{w_G}\, x^*((\overline{w_M})^{-1} + (\overline{w_G})^{-1} - x^*),$$
$$w_G^* = \overline{w_G}\, x^*(x_G^* - x^*). \tag{37}$$

From Eq. (29) we have

$$\overline{c_T}\, y^* = \lambda + \overline{c_T} - x^* - \overline{c_M} w_M^* - \overline{c_G} w_G^*. \tag{38}$$

Substituting Eqs. (37) and (36) into Eq. (38), we get

$$\overline{c_T}\, y^* = \lambda + \overline{c_T} - x^* - \overline{c_M}\,\overline{w_M} x^* - \overline{c_G}\,\overline{w_G}\, x^*(x_G^* - x^*),$$
$$\overline{c_T}\, y^* = \overline{c_G}\,\overline{w_G}(x^*)^2 - (1 + \overline{c_M}\,\overline{w_M} + \overline{c_G}\,\overline{w_G}\, x_G^*)(x^*) + \lambda + \overline{c_T},$$
$$\overline{c_T}\, y^* = \overline{c_G}\,\overline{w_G}[(x^*)^2 - (\widehat{y} + x_G^*)(x^*)] + \lambda + \overline{c_T}.$$

The last equation is equivalent to $y^* = f(x^*, \lambda)$. Therefore, E^* takes the form in Eq. (27). Moreover, taking $y^* = f(x^*, \lambda)$ in Eq. (30) yields:

$$0 = \overline{\delta_T} + \overline{r_T} f(x^*, \lambda)\, \mathcal{H}(x^*, \overline{K_T}) - \overline{\delta_T} f(x^*, \lambda),$$
$$\mathcal{H}(x^*, \overline{K_T}) = \frac{\overline{\delta_T} f(x^*, \lambda) - \overline{\delta_T}}{\overline{r_T} f(x^*, \lambda)},$$

which is Eq. (28). □

Theorem 3. *Assume that $\lambda + \overline{c_T} > 0$ and let $\mathcal{H}_G^* := \mathcal{H}(x_G^*, \overline{K_T})$. Let $\mathcal{I}$ be the set of all x such that*

- $0 < x \le x_G^*$,
- $f(x, \lambda) > 1$, *and*
- *either $\mu \le \mathcal{H}_G^*$ or $f(x, \lambda) \le \frac{\mu}{\mu - \mathcal{H}_G^*}$.*

Then every virus-positive equilibrium point E^* has the viral load $x^* \in \mathcal{I}$.

Proof. Eq. (27) in Theorem 2 requires that $f(x^*, \lambda) > 0$ and $0 < x^* \le x_G^*$. Since $\mathcal{H}(x, \lambda)$ increases over positive values of x, we have

$$0 < \mathcal{H}(x^*, \lambda) \le \mathcal{H}_G^*$$
$$\iff 0 < \mathcal{H}_0(x^*, \lambda) \le \frac{\mathcal{H}_G^*}{\mu} \qquad \text{by Eq. (28)}$$

$$\iff 0 < \frac{f(x^*,\lambda)-1}{f(x^*,\lambda)} \le \frac{\mathcal{H}_G^*}{\mu} \qquad \text{by Eq. (26)}$$
$$\iff 1 < f(x^*,\lambda) \le 1 + \frac{\mathcal{H}_G^*}{\mu} f(x^*,\lambda)$$

The last inequality is equivalent to

$$f(x^*,\lambda)\left[1 - \frac{\mathcal{H}_G^*}{\mu}\right] \le 1 < f(x^*,\lambda),$$

or

$$f(x^*,\lambda) > 1, \text{ and either } \mu \le \mathcal{H}_G^* \text{ or } f(x^*,\lambda) \le \frac{\mu}{\mu - \mathcal{H}_G^*}.$$

Therefore, $x \in \mathcal{I}$. □

The set $\mathcal{I}$ in Theorem 3 locates all possible values of the positive viral load x^* at E^*. Note that this set may take different forms according to λ and μ. Both quantities put bound restrictions on $f(x,\lambda)$ as follows:

- The parameter λ restricts $f(x,\lambda)$ with $f(x,\lambda) > 1$, which is needed for both $y^* > 0$ and $\mathcal{H}_0(x^*) > 0$.
- If $\mu > \mathcal{H}_G^*$, then μ puts an additional restriction: $f(x,\lambda) \le \mu/(\mu - \mathcal{H}_G^*)$.

To determine these forms, we collect some properties of f as a quadratic function in x restricted to the interval $(0, x_G^*]$.

1. We have $f(\hat{y},\lambda) = f(x_G^*,\lambda) < f(0,\lambda)$ due to
$$f(0,\lambda) = \left(\frac{\lambda + \overline{c_T}}{\overline{c_T}}\right),$$
$$f(x_G^*,\lambda) = -\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\left(\hat{y}\,x_G^*\right) + \left(\frac{\lambda + \overline{c_T}}{\overline{c_T}}\right).$$
2. The graph of $y = f(x,\lambda)$ in the xy-plane is concave up, due to the leading coefficient $(\overline{c_G}\,\overline{w_G}/\overline{c_T})$.
3. The same graph also has its vertex point $(\hat{x}_0, f_{\min})$, where
$$\hat{x}_0 := \frac{\hat{y} + x_G^*}{2}, \qquad f_{\min} := f(\hat{x}_0,\lambda) = f(0,\lambda) - \left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\hat{x}_0^2.$$
Thus, $f(x,\lambda)$ decreases with negative $\frac{\partial f}{\partial x}$ for $x < \hat{x}_0$ and increases with positive $\frac{\partial f}{\partial x}$ for $x > \hat{x}_0$.
4. We have $2(\hat{x}_0 - x_G^*) = \hat{y} - x_G^*$, hence $\operatorname{sgn}(\hat{x}_0 - x_G^*) = \operatorname{sgn}(\hat{y} - x_G^*)$. Moreover, $\hat{x}_0 \le x_G^*$ if $\hat{y} \le x_G^*$.

5. Finally, the quadratic formula gives the following roots of $f(\cdot\,, \lambda) - 1$:

$$\widehat{x}_1 := \widehat{x}_0 - \sqrt{\widehat{x}_0^2 - \frac{\overline{c_T}}{\overline{c_G}\,\overline{w_G}}\,[f(0,\lambda) - 1]},$$
$$\widehat{x}_2 := \widehat{x}_0 + \sqrt{\widehat{x}_0^2 - \frac{\overline{c_T}}{\overline{c_G}\,\overline{w_G}}\,[f(0,\lambda) - 1]}.$$

Note that $\widehat{x}_1 \le \widehat{x}_2$.

For a simpler analytical approach, we may consider the following set

$$\mathcal{I}_0 := \{x \mid 0 < x \le x_G^* \text{ and } f(x,\lambda) > 1\},$$
$$\implies \mathcal{I} = \mathcal{I}_0 \cap \left\{ x \mid \mu \le \mathcal{H}_G^* \text{ or } f(x,\lambda) \le \frac{\mu}{\mu - \mathcal{H}_G^*} \right\}.$$

Then Theorem 3 implies that $E^* \in \mathcal{I}_0$. That is, $\mathcal{I}_0$ provides regions to locate E^*, while $\mathcal{I}$ provides additional restriction.

To determine the possible sets that $\mathcal{I}_0$ takes, we appeal to the monotone and concave properties of $f(\cdot\,, \lambda)$, particularly that $f(x, \lambda)$ decreases for $x < \widehat{x}_0$ and increases for $x > \widehat{x}_0$. Consider partitioning the parameter space into the following cases.

- Case 1: $f(0, \lambda) \le 1$.

  If $\widehat{x}_0 > x_G^*$, then $f(x, \lambda)$ decreases with x over $(0, x_G^*]$. Otherwise, the image of $(0, x_G^*]$ under $f(\cdot\,, \lambda)$ is $[f_{\min}, f(0, \lambda)) \subset (-\infty, 1)$. Therefore, $\mathcal{I}_0$ is empty.

- Case 2: $f(x_G^*, \lambda) \le 1 < f(0, \lambda)$.

  Restricting $f(x, \lambda)$ for $0 < x < x_G^*$ and following the same cases for $\widehat{x}_0$, we see that $f(x, \lambda) = 1$ uniquely at $x = \widehat{x}_1$. Moreover, $\mathcal{I}_0 = (0, \widehat{x}_1)$, with $f(x, \lambda) > 1$ for $0 < x < \widehat{x}_1$, and $f(x, \lambda) < 1$ for $\widehat{x}_1 < x \le x_G^*$.

- Case 3: $f(x_G^*, \lambda) > 1$, and either $\widehat{y} \ge x_G^*$ or $f_{\min} > 1$.

  Note in this case that $f(0, \lambda) > f(x_G^*, \lambda) > 1$. If $\widehat{y} \ge x_G^*$ (equivalently, $\widehat{x}_0 \ge x_G^*$), then as x increases from zero to x_G^*, the value of f decreases from $f(0, \lambda)$ to $f(x_G^*, \lambda) > 1$. Otherwise, with $f_{\min} > 1$, the image of $(0, x_G^*]$ under $f(\cdot\,, \lambda)$ is $[f_{\min}, f(0, \lambda)) \supset (1, \infty)$. Therefore, $\mathcal{I}_0 = (0, x_G^*]$.

- Case 4: $f(x_G^*, \lambda) > 1$, $\widehat{y} < x_G^*$ (equivalently $\widehat{x}_0 < x_G^*$), and $f_{\min} \le 1$.

  Here, both $f(0, \lambda)$ and $f(x_G^*, \lambda)$ are above one, but $f_{\min} \le 1$. Thus, the roots $\widehat{x}_1$ and $\widehat{x}_2$ of $f(\cdot\,, \lambda)$ exist, with $\widehat{x}_1 \le \widehat{x}_0 \le \widehat{x}_2$. Since $f(x, \lambda)$ decreases for $x < \widehat{x}_0$ and increases for $x > \widehat{x}_0$, we conclude that $\mathcal{I}_0 = (0, \widehat{x}_1) \cup (\widehat{x}_2, x_G^*]$.

Table S1
Different cases for the set $\mathcal{I}_0$. All cases assume that $\lambda > -\overline{c_T}$, which is necessary for E^* to exist (Theorem 2).

Case	Conditions	Set $\mathcal{I}_0$
1	$-\overline{c_T} < \lambda \leq 0$	Empty
2	$0 < \lambda \leq \Lambda_1$	$(0, \hat{x}_1)$
3	$\lambda > \Lambda_1$, and either $\hat{x}_0 \geq x_G^*$ or $\lambda > \Lambda_2$	$(0, x_G^*]$
4	$\hat{x}_0 < x_G^*$ and $\Lambda_1 < \lambda \leq \Lambda_2$	$(0, \hat{x}_1) \cup (\hat{x}_2, x_G^*]$

We may express the conditions of the four cases in λ by writing

$$
\begin{aligned}
f(0, \lambda) - 1 &= \lambda(\overline{c_T})^{-1}, \\
f(x_G^*, \lambda) - 1 &= \frac{\lambda - \Lambda_1}{\overline{c_T}}, \\
f_{\min} - 1 &= \frac{\lambda - \Lambda_2}{\overline{c_T}},
\end{aligned}
$$

where

$$
\begin{aligned}
\Lambda_1 &:= (\overline{c_G}\,\overline{w_G})(2\hat{x}_0 - x_G^*)\, x_G^* = (\overline{c_G}\,\overline{w_G})\,\hat{y}\, x_G^*, \\
\Lambda_2 &:= (\overline{c_G}\,\overline{w_G})\,\hat{x}_0^2.
\end{aligned}
$$

These yield the following sign equations

$$
\begin{aligned}
\operatorname{sgn}[f(0, \lambda) - 1] &= \operatorname{sgn} \lambda, \\
\operatorname{sgn}[f(x_G^*, \lambda) - 1] &= \operatorname{sgn}(\lambda - \Lambda_1), \\
\operatorname{sgn}(f_{\min} - 1) &= \operatorname{sgn}(\lambda - \Lambda_2),
\end{aligned}
$$

in addition to $\operatorname{sgn}(\hat{x}_0 - x_G^*) = \operatorname{sgn}(\hat{y} - x_G^*)$. Table S1 summarizes our analysis on the different intervals (or union of intervals) that $\mathcal{I}_0$ takes.

We now investigate the equation

$$
\mathcal{H}(\,\cdot\,, \overline{K_T}) = \mu\, \mathcal{H}_0(\,\cdot\,, \lambda) \text{ on } \mathcal{I}_0 \tag{39}
$$

from Eq. (28), where the root(s) determine the viral load size(s) x^* at E^*. We have

$$
\frac{\partial \mathcal{H}}{\partial x} = \frac{m\overline{K_T}^m \cdot x^{m-1}}{(x^m + \overline{K_T}^m)^2} > 0 \qquad \text{for } x > 0, \tag{40}
$$

so $\mathcal{H}(\cdot, \overline{K_T})$ increases over $(0, x_G^*]$ and particularly over $\mathcal{I}_0$. On the other hand, we can determine the monotone properties of $\mathcal{H}_0(\cdot, \lambda)$ by applying Eqs. (25) and (26), assuming that $f > 0$. Now,

$$\begin{aligned}\frac{\partial f}{\partial x} &= \left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\left[2x - (\hat{y} + x_G^*)\right] \\ &= 2\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)(x - \hat{x}_0).\end{aligned} \tag{41}$$

Then

$$\begin{aligned}\frac{\partial \mathcal{H}_0}{\partial x} &= \frac{\partial}{\partial x}\left(1 - \frac{1}{f}\right) = \frac{1}{f^2}\frac{\partial f}{\partial x} \\ &= \frac{2}{[f(x,\lambda)]^2}\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)(x - \hat{x}_0).\end{aligned} \tag{42}$$

For concavity, we may compute the following second partial derivative:

$$\begin{aligned}\frac{\partial^2 \mathcal{H}_0}{\partial x^2} &= \frac{2}{[f(x,\lambda)]^3}\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\left[2(\hat{x}_0 - x)\,\frac{\partial f}{\partial x} + f\right] \\ &= \frac{2}{[f(x,\lambda)]^3}\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)\left[f(x,\lambda) - 4\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)(x - \hat{x}_0)^2\right] \\ &= \frac{8}{[f(x,\lambda)]^3}\left(\frac{\overline{c_G}\,\overline{w_G}}{\overline{c_T}}\right)^2\left[\frac{1}{4}\left(\frac{\overline{c_T}}{\overline{c_G}\,\overline{w_G}}\right)f(x,\lambda) - (x - \hat{x}_0)^2\right].\end{aligned} \tag{43}$$

Since $f(\cdot, \lambda) > 1 > 0$ on $\mathcal{I}_0$, Eqs. (41)-(43) yield the following sign equations for all $x \in \mathcal{I}_0$:

$$\operatorname{sgn}\frac{\partial \mathcal{H}_0}{\partial x} = \operatorname{sgn}(x - \hat{x}_0) = \operatorname{sgn}\frac{\partial f}{\partial x}, \tag{44}$$

$$\operatorname{sgn}\frac{\partial^2 \mathcal{H}_0}{\partial x^2} = \operatorname{sgn}\left[\frac{1}{4}\left(\frac{\overline{c_T}}{\overline{c_G}\,\overline{w_G}}\right)f(x,\lambda) - (x - \hat{x}_0)^2\right]. \tag{45}$$

In particular, both $\mathcal{H}_0(\cdot, \lambda)$ and $f(\cdot, \lambda)$ share the same monotone properties over $\mathcal{I}_0$. We also note that

$$\operatorname{sgn}\mathcal{H}_0(0, \lambda) = \operatorname{sgn}[f(0, \lambda) - 1]$$

Armed with these observations, we revisit Cases 2-4 in Table S1. We skip Case 1 because $\mathcal{I}_0$ is empty and thus E^* does not exist. For Cases 2-4, $f(0, \lambda) > 1$ and $\mathcal{H}_0(0, \lambda) > 0$. Recalling $\mu = \overline{\delta_T}/\overline{r_T}$, the signs of $\mathcal{H}_0$, $\mu\,\mathcal{H}_0$ and their partial derivatives are equal. Eq. (28), we also have

- Under Case 2, we have $\mathcal{I}_0 = (0, \hat{x}_1) \subseteq (0, \hat{x}_0)$. Hence by eq. (42), $\mathcal{H}_0(\cdot, \lambda)$ decreases over $\mathcal{I}_0$. Considering

eq. (40) and that

$$\mu\,\mathcal{H}_0(\widehat{x}_1,\lambda) = 0 < \mu\,\mathcal{H}_0(0,\lambda),$$

Eq. (39) admits exactly one solution x^*.

- Under Case 3, we now have $\mathcal{I}_0 = (0, x_G^*]$ so that $\mathcal{H}_0(x,\lambda) > 0$ for $0 < x \leq x_G^*$. We proceed with the following subcases:

  - Subcase 3a. If $\widehat{x}_0 \geq x_G^*$, then according to Eq. (44) we have $\frac{\partial \mathcal{H}_0}{\partial x} < 0$ and $\mathcal{H}_0(\,\cdot\,,\lambda)$ decreases over $\mathcal{I}_0$. Furthermore, eq. (39) admits a solution if and only if

    $$\mu\,\mathcal{H}_0(x_G^*,\lambda) \leq \mathcal{H}(x_G^*,\overline{K_T}) = \mathcal{H}_G^*.$$

    This solution is unique due to the decreasing property of $\mathcal{H}_0(\,\cdot\,,\lambda)$.

  - Subcase 3b. If $0 < \widehat{x} < x_G^*$, then $\mathcal{H}_0(\,\cdot\,,\lambda)$ decreases over $(0,\widehat{x}_0)$ and increases over $(\widehat{x}_0, x_G^*)$. Similar to the Subcase 3a, we conclude that Eq. (39) *restricted to* $(0,\widehat{x}_0)$ has a solution (which is unique) if and only if

    $$\mu\,\mathcal{H}_0(\widehat{x},\lambda) \leq \mathcal{H}(\widehat{x},\overline{K_T}).$$

    Over $(\widehat{x}_0, x_G^*]$, the behavior of Eq. (39) may be intricate due to the changing convexities of both functions $\mathcal{H}(\,\cdot\,,\overline{K_T})$ and $\mu\,\mathcal{H}_0(\,\cdot\,,\lambda)$. Future work may need to determine possible numbers of roots of Eq. eq. (39) over $(\widehat{x}_0, x_G^*]$.

- Finally, we have $\mathcal{I}_0 = (0,\widehat{x}_1) \cup (\widehat{x}_2, x_G^*]$ (disjoint union of intervals) in Case 4. Similar to Case 1, we find that Eq. (39) attains a unique solution over $(0,\widehat{x}_1)$. Similar to Case 3b, we might expect the same kind of intricate behavior of Eq. (39) over $(\widehat{x}_2, x_G^*]$ depending on μ and the concave properties of $\mathcal{H}$ and $\mathcal{H}_0$.

We are ready to consolidate our analysis on the existence of virus-positive equilibria. Anticipating the possibility of more than one virus-positive equilibrium points, we may write $\mathcal{H} - \mu\,\mathcal{H}_0$ as a rational function in x, where both the numerator and the denominator are polynomials in x of degree $m+2$. Hence, we deduce that the equation $\mathcal{H}(\,\cdot\,,\overline{K_T}) = \mu\,\mathcal{H}_0(\,\cdot\,,\lambda)$ admits at most $m+2$ distinct roots in $\mathcal{I}_0$. We will denote these roots as x_1^*, x_2^*, ..., x_ℓ^*, where $\ell \leq m+2$ an $x_j < x_k$ for $j < k$ (provided both x_j and x_k exist). These roots correspond to the existence of the virus-positive

equilibrium points

$$E_k^* = (x_k^*, f(x_k^*, \lambda), x_k^*, \overline{w_M} x_k^*, \overline{w_G} x_k^* (x_G^* - x_k^*)), \qquad k = 1, 2, \ldots, \ell.$$

The number ℓ determines how many virus-positive equilibrium points exist, so that $\ell = 0$ means that the only equilibrium point is virus-free (i.e., E_0). In the simplest case where $m = 2$, we can expect up to four virus-positive equilibrium points ($\ell \leq 4$).

We consolidate our preceding analysis, especially Table S1 and Theorems 2 and 3, into the following summary.

Theorem 4. *Dimensionless Model 6, Eqs.* (16)-(20)*, admits virus-positive equilibrium points only if* $\lambda > 0$*. Under this condition, we have the following cases:*

(a) If $0 < \lambda \leq \Lambda_1$*, then* $\ell = 1$ *and* E_1^* *is the unique virus-positive equilibrium point. Furthermore,* $x_1^* \in (0, \widehat{x}_1)$*.*

(b) If $\lambda > \Lambda_1$ *and* $\widehat{x}_0 \geq x_G^*$*, then* $\ell = 1$ *and the virus-positive equilibrium point* E_1^* *exists with* $x_1^* \in (0, x_G^*]$*.*

(c) Suppose that $\lambda > \Lambda_1$ *but* $\widehat{x}_0 < x_G^*$*, and* $\lambda > \Lambda_2$*. Then* E_k^* *exists with* $x_k^* \in (\widehat{x}_0, x_G^*]$ *for* $k = 2, \ldots, \ell$*. Moreover:*

- *If* $\mu\, \mathcal{H}_0(\widehat{x}, \lambda) \leq \mathcal{H}(\widehat{x}, \overline{K_T})$*, then* $x_1^* \in (0, \widehat{x}_0)$ *and* $\ell \geq 1$*.*
- *Otherwise,* $x_1^* \in (\widehat{x}_0, x_G^*]$ *and we can only conclude that* $\ell \geq 0$*. Here, the value of* ℓ *may depend on the concavity of* $\mathcal{H}$ *and* $\mu\, \mathcal{H}_0$*.*

(d) Suppose that $\widehat{x}_0 < x_G^*$ *and* $\Lambda_1 < \lambda \leq \Lambda_2$*. Then* $\ell \geq 1$ *and* E_1^* *exists with* $x_1^* \in (0, \widehat{x}_1)$*. Moreover,* E_k^* *exists with* $x_k^* \in (\widehat{x}_2, x_G^*]$ *for* $k = 2, \ldots, \ell$*.*

Remark. Further analysis, either through numerical exploration or advanced mathematical tools, is needed in the following cases:

- $\lambda > \max(\Lambda_1, \Lambda_2)$ and $\widehat{x}_0 < x_G^*$.
- $\widehat{x}_0 < x_G^*$ and $\Lambda_1 < \lambda \leq \Lambda_2$, only for the equilibrium points E_2^*, ..., E_ℓ^*.

B. Math Modelling

B.1. Model 2

$$\frac{dV}{dt} = pV\left(1-\frac{V}{K_V}\right) - c_tVT - \varepsilon MV - \eta GV - cV, \tag{46}$$

$$\frac{dT}{dt} = \delta_t T(0) + rT\left(\frac{V^m}{V^m + k_t^m}\right) - \delta_t T, \tag{47}$$

$$\frac{dM}{dt} = \alpha V(t-\tau_1) - (\gamma+\beta)M, \tag{48}$$

$$\frac{dG}{dt} = \gamma M + \lambda V(t-\tau_2) - \rho G. \tag{49}$$

B.2. Model 4

$$\frac{dV}{dt} = pV\left(1-\frac{V}{K_V}\right) - c_tVT - \varepsilon MV - \eta GV - cV, \tag{50}$$

$$\frac{dT}{dt} = \delta_t T(0) + rT\left(\frac{V^m}{V^m + k_t^m}\right) - \delta_t T, \tag{51}$$

$$\frac{dB}{dt} = r_b\left(\frac{1}{1+l_vV}\right)\left(\frac{1}{1+l_tT}\right)(1-B), \tag{52}$$

$$\frac{dM}{dt} = r_mB - (q+\delta_m)M, \tag{53}$$

$$\frac{dG}{dt} = qM + r_gB - \delta_gG. \tag{54}$$

B.3. Model 5

$$\frac{dV}{dt} = pV\left(1-\frac{V}{K_V}\right) - c_tVT - \varepsilon MV - \eta GV - cV, \tag{55}$$

$$\frac{dT}{dt} = \delta_t T(0) + rT\left(\frac{V^m}{V^m + k_t^m}\right) - \delta_t T, \tag{56}$$

$$\frac{dB}{dt} = \frac{\delta_vV - B}{\tau_b}, \tag{57}$$

$$\frac{dM}{dt} = r_mB - (q+\delta_m)M, \tag{58}$$

$$\frac{dG}{dt} = q\left(\frac{M^n}{M^n + k_q^n}\right) + r_gB - \delta_gG. \tag{59}$$

C. AIC scores for each severe patients

Table S2
AIC scores for severe patients

Patient	AIC Model 1	AIC Model 2	AIC Model 3	AIC Model 4	AIC Model 5	AIC Model 6
2	7.32	-5.74	-13.24	-42.57	-57.92	-63.02
3	35.86	12.52	23.75	-12.63	-36.84	-15.46
5	21.08	-6.24	1.32	-32.61	-11.72	-28.25
12	14.63	-1.02	-32.70	-30.84	-20.93	-18.76
15	27.37	-4.27	-14.59	-19.52	-5.96	-19.13
20	42.60	4.85	4.85	-31.08	-29.41	-9.26
34	16.93	7.29	-1.19	-28.85	-25.74	-34.49
Media	23.68	1.05	-4.54	-28.30	-26.93	-26.91

D. AIC scores for each non-severe patients

Table S3
AIC scores for each non-severe patients

Patient	AIC Model 1	AIC Model 2	AIC Model 3	AIC Model 4	AIC Model 5	AIC Model 6
1	32.57	25.76	6.23	4.84	-36.1	-13.65
4	4.56	13.57	-20.36	-59.27	-24.82	-166.21
7	57.34	34.08	5.25	-8.29	-3.73	-13.32
8	25.78	11.41	-16.39	-2.04	-14.42	-24.88
9	9.47	-2.69	-18.87	4.06	-25.38	-29.18
13	-5.12	7.63	-48.31	-7.49	-16.11	-61.75
14	12.45	19.54	3.48	-8.16	-17.93	-36.27
16	41.63	23.97	4.72	-2.93	11.03	-9.49
17	6.28	25.06	-1.38	-17.26	-6.49	-19.32
18	-3.93	17.42	-19.65	-11.42	-28.53	-25.86
19	5.84	19.70	-3.27	-2.98	-26.77	-14.09
21	34.72	2.86	-25.93	-36.07	-21.53	-48.30
22	23.67	-4.84	-2.21	-12.30	-9.64	-7.38
24	11.63	10.65	-23.74	-2.04	-35.23	-27.10
25	-7.32	38.32	-43.91	-55.72	-85.41	-173.52
26	17.48	3.05	-16.01	-28.04	-21.63	-37.16
27	9.37	23.94	-2.72	2.63	-37.50	-18.56
29	17.82	-7.13	12.54	-28.42	-26.94	-30.22
31	16.21	4.21	3.90	-12.63	-33.71	-45.27
35	8.84	-12.74	11.34	-27.75	-52.02	-63.34
36	19.36	-18.95	2.45	-9.03	-5.94	-12.89
37	26.21	11.62	-47.25	-2.49	-16.83	-6.81
38	21.45	4.29	-15.68	-24.23	-26.56	-30.18
39	12.87	-2.16	-14.63	-9.62	-8.34	-24.02
40	35.97	-3.59	2.03	-2.73	3.65	-7.93
42	23.92	-1.08	4.78	-8.38	-36.7	-6.71
53	31.37	-8.60	-2.47	-23.52	-21.26	-24.92
57	48.93	-2.57	11.19	-2.96	-7.40	-9.70
59	27.80	4.89	1.53	-13.06	-2.87	-19.18
61	15.04	3.86	-23.64	-5.14	-27.81	-31.70
63	48.52	-4.43	-9.05	2.85	-42.43	-20.56
64	4.63	-10.86	-14.32	-20.45	-8.92	-17.33
Media	19.85	7.06	-9.38	-13.43	-22.32	-33.65

E. Estimated parameters of Model 6 for each severe patients

Table S4
Estimated parameters for each severe patients

Patients	c_M	c_G	τ_b	r_M	q	r_G	K_q	r_q	r_B
2	1.24E-04	1.20E-04	2.95E+00	5.00E-06	1.00E-01	7.00E-06	2.35E+01	1.05E-01	2.33E-01
3	6.06E-03	2.93E-01	1.96E+01	1.92E-04	5.27E-02	4.77E-04	9.19E+00	7.76E+00	2.34E-01
5	2.13E-03	1.77E-01	3.23E+01	1.00E-06	7.88E-04	1.00E-06	2.13E+02	1.71E-01	1.42E-01
12	1.53E-03	1.82E-02	4.72E+00	6.64E-07	9.97E-02	1.00E-09	3.68E+02	1.76E-01	1.93E-01
15	3.35E-03	2.78E-02	3.99E+01	4.00E-06	1.35E-03	1.00E-09	3.88E+02	6.88E-02	2.17E-01
20	7.81E-03	2.40E-02	3.98E+01	2.00E-06	9.79E-04	1.00E-09	3.90E+02	1.60E-01	2.36E-01
34	8.98E-03	2.81E-01	1.50E+00	3.37E-04	7.32E-02	8.07E-03	3.74E+02	2.31E+01	1.34E-01

F. Estimated parameters of Model 6 for each non-severe patients

Table S5
Estimated parameters for each non-severe patients

Patients	c_M	c_G	τ_b	r_M	q	r_G	K_q	r_q	r_B
1	6.04E-03	4.08E-02	6.48E+00	1.25E-03	3.34E-03	3.03E-04	3.66E+02	9.19E-03	1.05E-01
4	9.39E-03	2.71E-04	2.56E+00	1.00E-09	8.57E-02	8.79E-07	1.02E+02	1.96E-02	1.19E-01
7	7.43E-03	2.09E-03	1.09E+01	4.75E-08	1.20E-04	4.07E-07	8.20E+01	1.04E-02	2.90E-01
8	5.11E-03	2.45E-01	3.97E+01	9.79E-09	4.01E-02	6.53E-07	9.39E+01	1.37E+00	1.10E-01
9	6.68E-03	1.47E-01	3.15E+01	2.86E-08	1.11E-03	3.00E-06	1.75E+02	2.74E-01	1.53E-01
13	9.46E-03	1.77E-02	6.68E+00	6.78E-07	4.62E-02	1.00E-09	3.82E+02	6.13E-01	1.55E-01
14	2.85E-03	7.11E-02	1.52E+01	1.00E-06	1.70E-03	1.00E-09	3.32E+02	1.55E-01	2.02E-01
16	4.92E-04	8.09E-03	3.97E+01	5.00E-06	2.78E-03	1.00E-09	3.96E+02	1.14E-01	2.19E-01
17	2.63E-04	1.45E-02	6.34E+00	7.25E-07	7.06E-02	1.00E-09	2.51E+02	5.64E-01	1.60E-01
18	4.30E-03	8.19E-02	3.97E+01	8.08E-07	4.04E-03	1.00E-09	3.80E+02	9.63E-02	9.18E-01
19	3.43E-04	2.16E-01	3.98E+01	8.57E-07	9.20E-04	1.00E-09	3.87E+02	3.91E-02	5.83E-01
21	7.83E-04	2.90E-01	2.18E+01	1.00E-06	3.86E-03	1.00E-09	3.95E+02	2.37E-02	3.15E-01
22	5.56E-03	2.87E-01	3.88E+01	6.79E-07	2.68E-03	1.00E-09	3.97E+02	1.78E-02	7.56E-01
24	6.00E-03	7.21E-02	8.25E+00	9.00E-07	5.80E-02	1.00E-09	3.29E+02	1.11E-01	1.60E-01
25	7.20E-03	2.66E-01	3.70E+01	6.32E-08	9.93E-02	1.06E-09	3.89E+02	1.34E+00	1.03E-01
26	8.18E-03	2.51E-01	3.99E+01	1.32E-07	7.82E-04	1.29E-09	2.79E+02	3.02E-01	1.02E-01
27	2.44E-03	4.75E-03	1.07E+01	4.69E-07	3.28E-02	1.05E-09	3.96E+02	7.59E-02	4.62E-01
29	3.05E-03	1.50E-01	3.49E+01	2.24E-09	4.85E-02	8.73E-08	9.60E+01	1.38E+00	1.27E-01
31	6.38E-03	2.88E-01	2.37E+00	1.63E-09	2.31E-02	2.31E-07	1.66E+02	5.10E+00	1.09E-01
35	8.11E-03	5.70E-04	2.21E+00	4.79E-08	1.15E-02	3.00E-06	3.33E+02	2.34E+00	1.16E-01
36	4.48E-03	3.00E-01	1.00E+00	1.00E-09	1.00E-01	1.00E-02	3.03E+02	2.27E+01	7.82E-01
37	1.92E-03	3.95E-04	3.16E+01	4.10E-05	6.75E-03	9.37E-08	9.19E+01	1.10E+00	1.42E-01
38	2.21E-03	1.55E-01	3.35E+01	8.76E-08	2.56E-02	3.23E-08	2.05E+02	5.64E-01	3.62E-01
39	7.75E-03	1.93E-01	3.18E+01	2.00E-06	9.60E-02	2.00E-06	1.66E+02	1.68E+00	1.15E-01
40	3.09E-03	1.56E-01	1.00E+00	2.00E-05	1.00E-01	2.60E-05	3.69E+02	1.12E+01	1.06E-01
42	4.11E-04	5.19E-04	3.99E+01	8.00E-06	2.14E-03	1.00E-09	3.99E+02	5.09E-01	1.85E-01
53	9.56E-03	1.09E-01	3.81E+01	5.77E-09	9.99E-02	1.55E-09	3.76E+02	1.75E+00	1.15E-01
57	1.00E-02	3.00E-01	1.00E+00	6.50E-03	1.00E-01	1.00E-02	1.78E+02	4.00E+01	1.00E-01
59	8.97E-03	2.04E-01	1.12E+00	1.00E-09	1.00E-01	7.93E-04	3.23E+02	3.08E+01	1.12E-01
61	7.89E-03	2.70E-01	3.04E+01	3.94E-08	5.35E-02	4.97E-07	3.39E+02	3.49E+00	1.05E-01
63	4.09E-03	5.71E-03	3.18E+00	1.00E-06	1.94E-03	6.21E-07	1.80E+02	5.04E-01	1.24E-01
64	8.80E-03	2.95E-01	4.08E+00	1.14E-03	3.14E-02	7.29E-04	4.81E+00	9.86E+00	1.48E-01

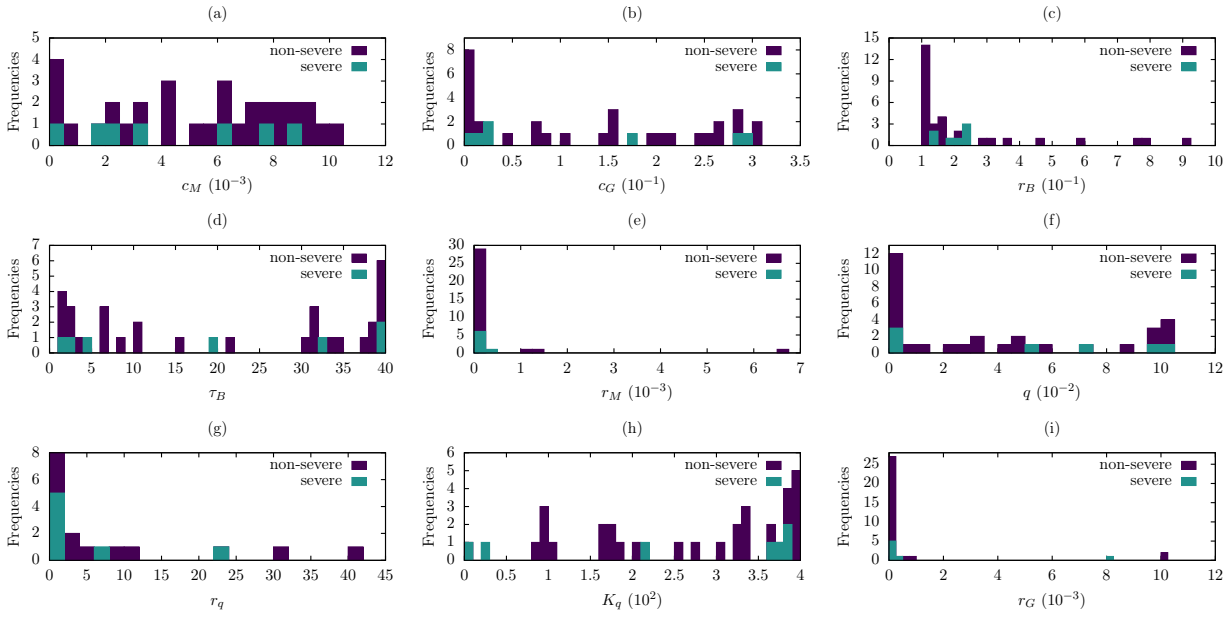

Figure S1: Parameter distributions for 7 severe patients (green) and 32 non-severe patients (purple).

G. Dynamics of Model 6 for each patient

Dynamics of viral load and immune response for each patient using the Model 6 and the parameter estimated from IgG antibody data of each patient reported in [21]. Severe D patients are presented in yellow color, severe E patients are presented in green color, and non-severe patients are presented in purple color. In each figure: (a) Viral load, (b) T cell level, (c) B cell level, (d) IgM antibody level, (e) IgG antibody level; solid line is the model output and the dots are the data.

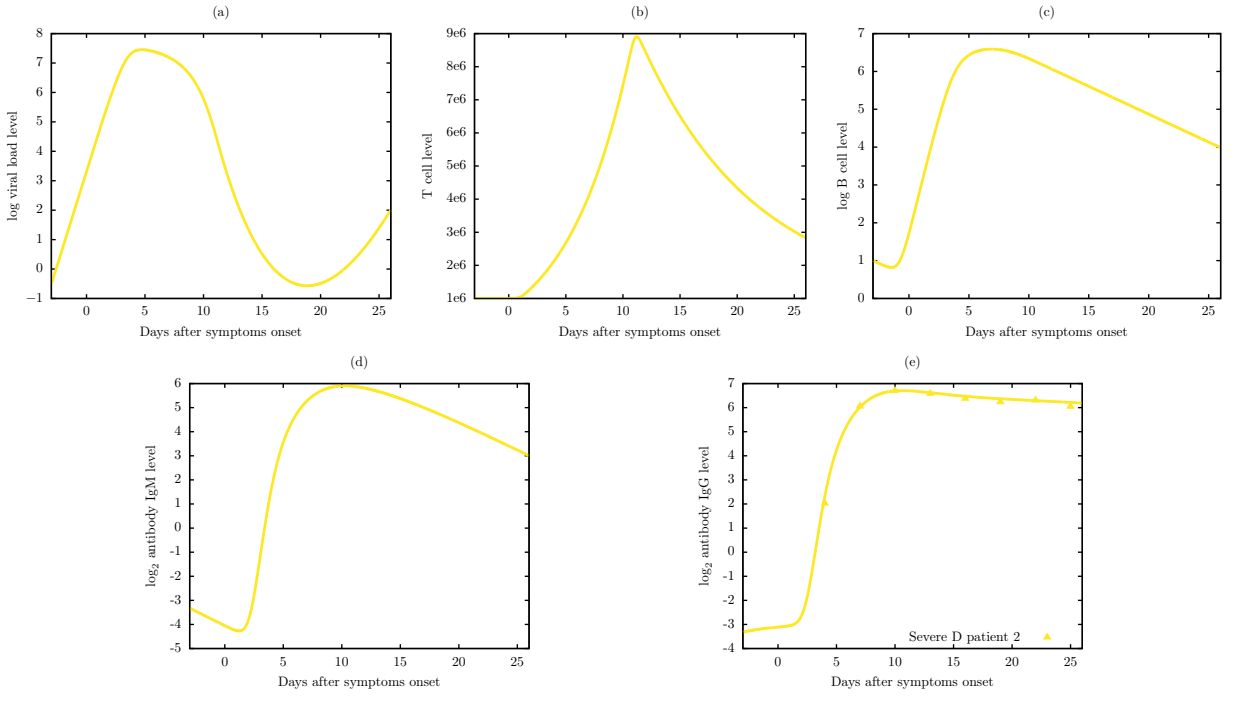

Figure S2: Viral dynamic and immune response of Model 6 for severe D patient 2.

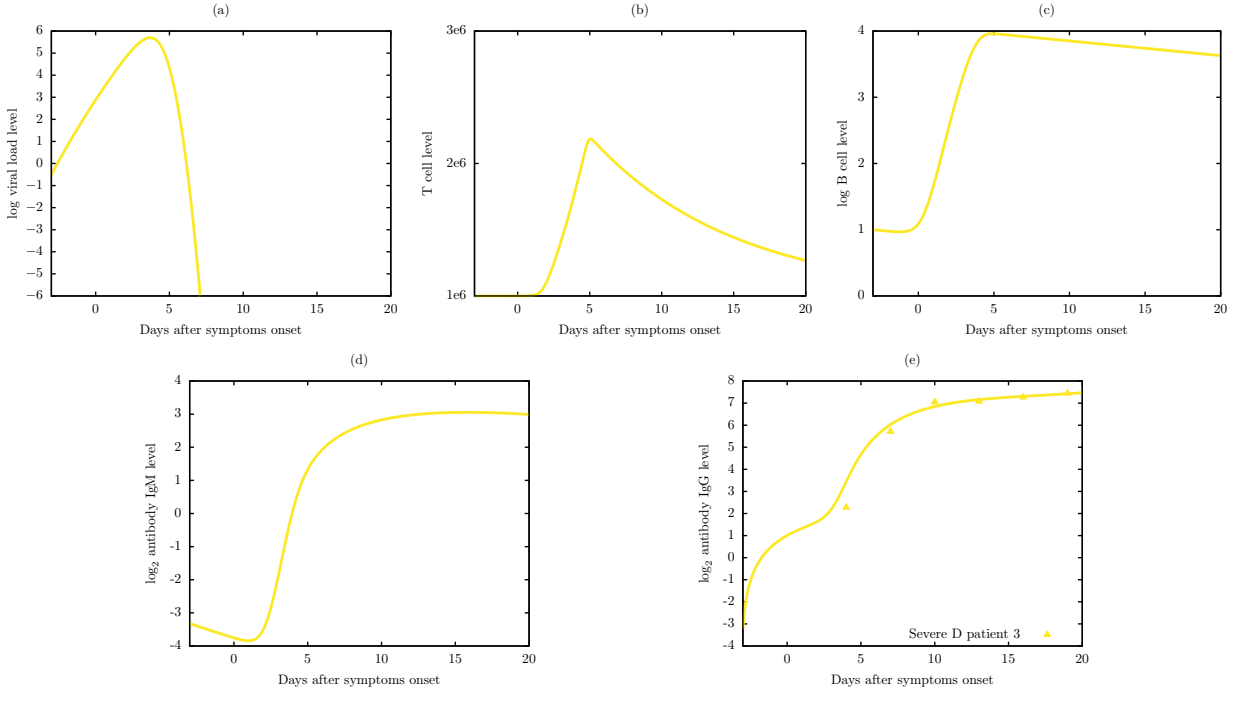

Figure S3: Viral dynamic and immune response of Model 6 for severe D patient 3.

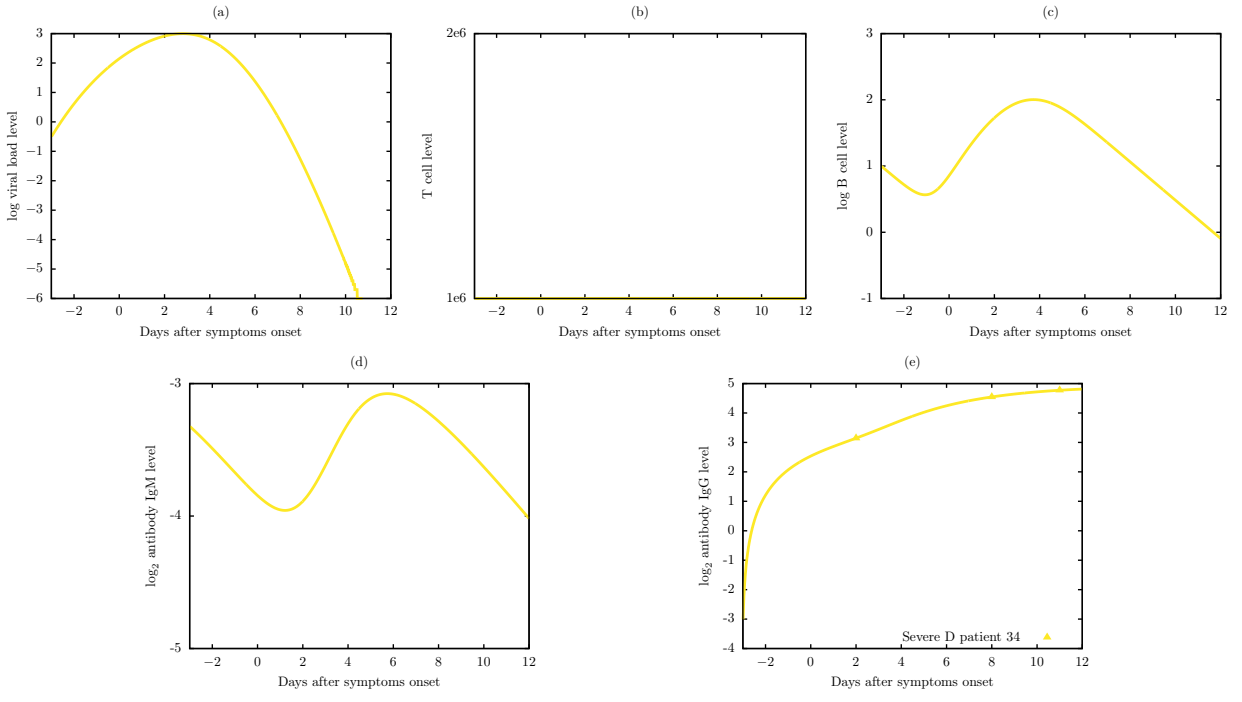

Figure S4: Viral dynamic and immune response of Model 6 for severe D patient 34.

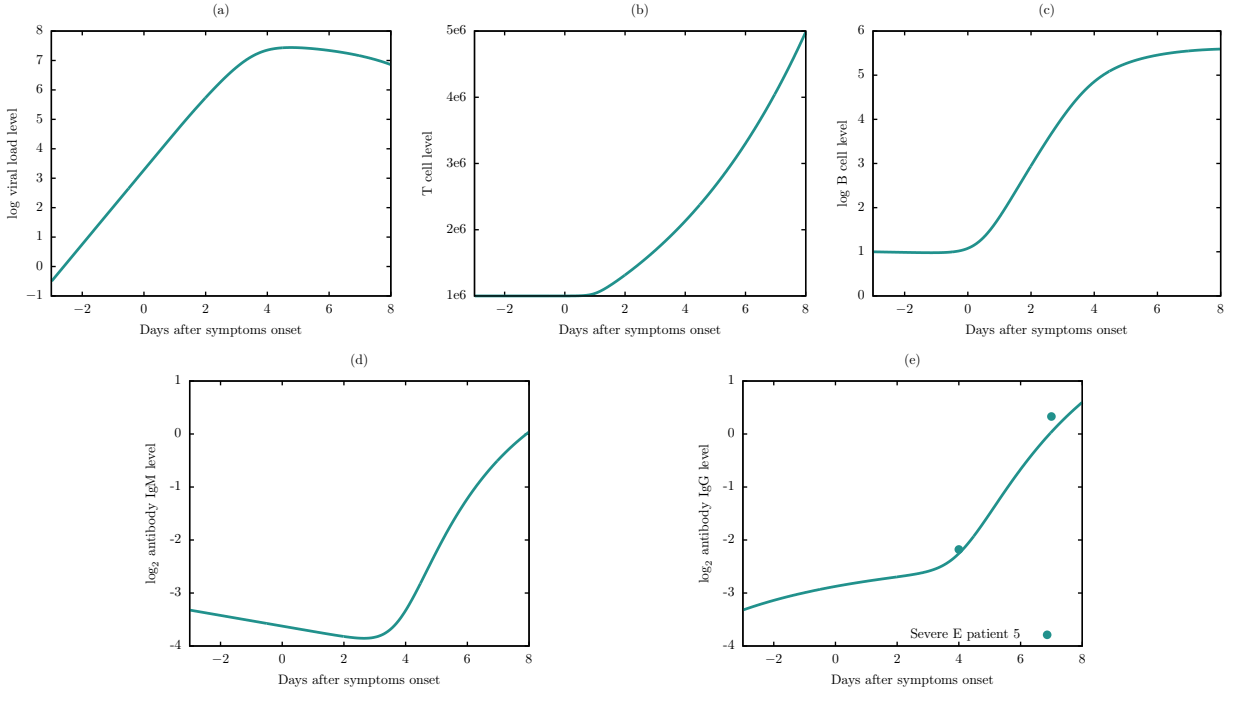

Figure S5: Viral dynamic and immune response of Model 6 for severe E patient 5.

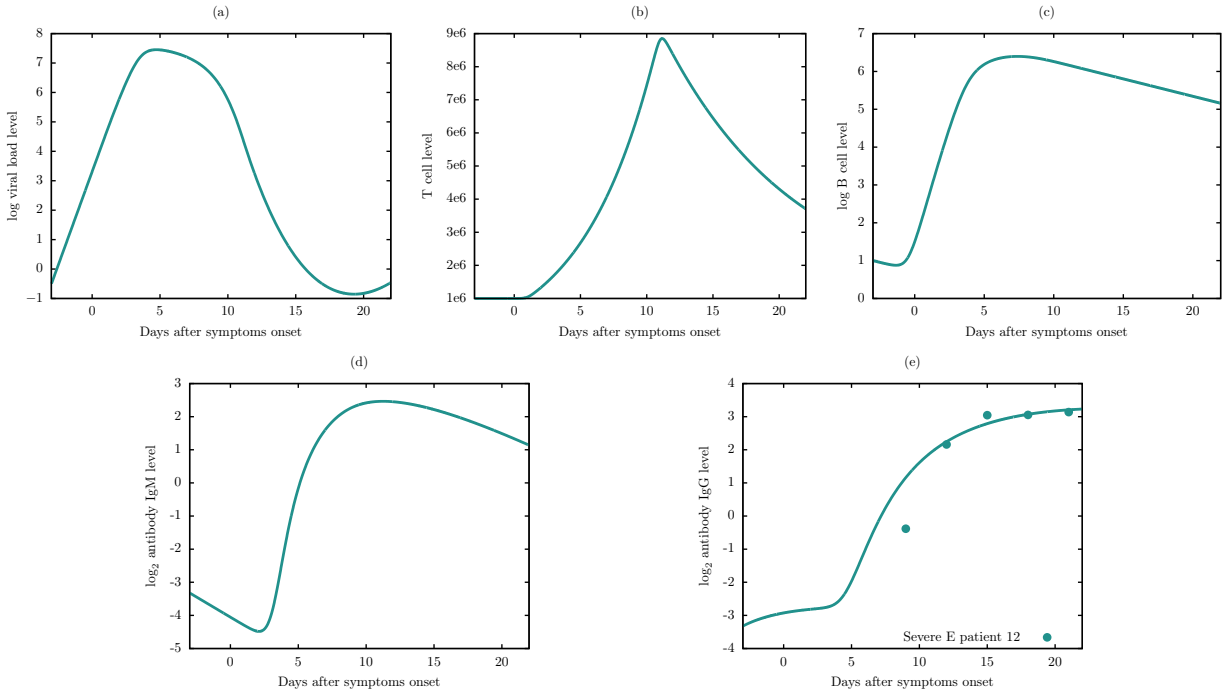

Figure S6: Viral dynamic and immune response of Model 6 for severe E patient 12.

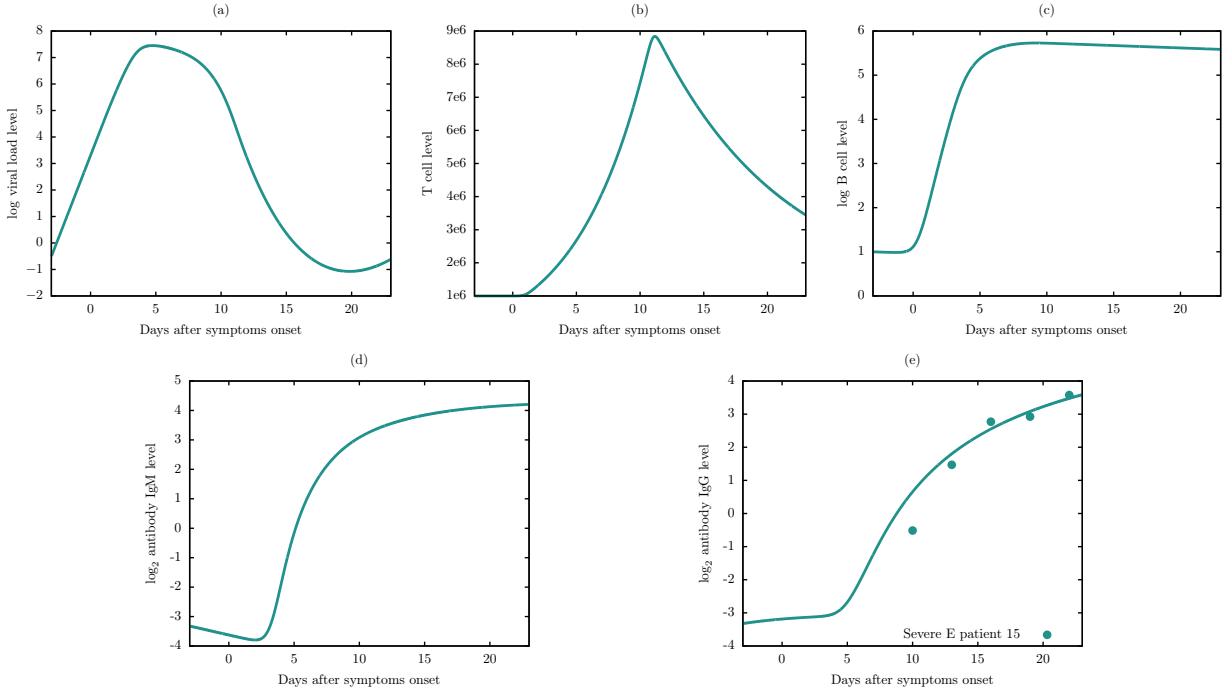

Figure S7: Viral dynamic and immune response of Model 6 for severe E patient 15.

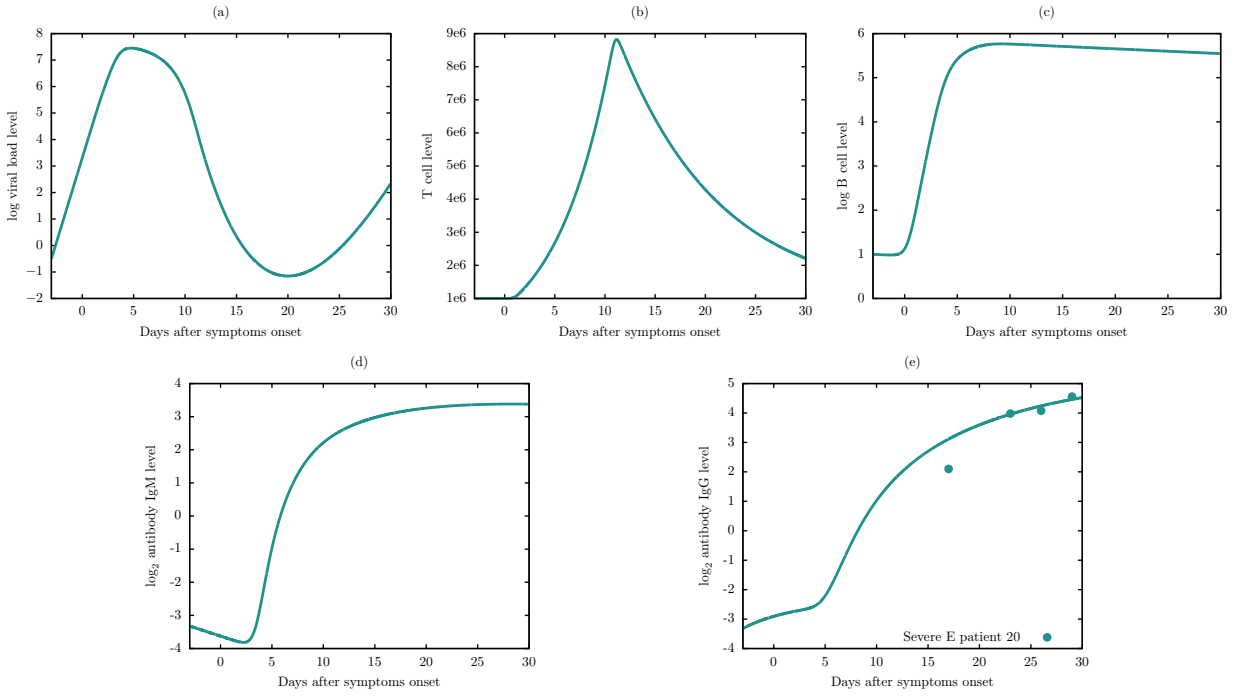

Figure S8: Viral dynamic and immune response of Model 6 for severe E patient 20.

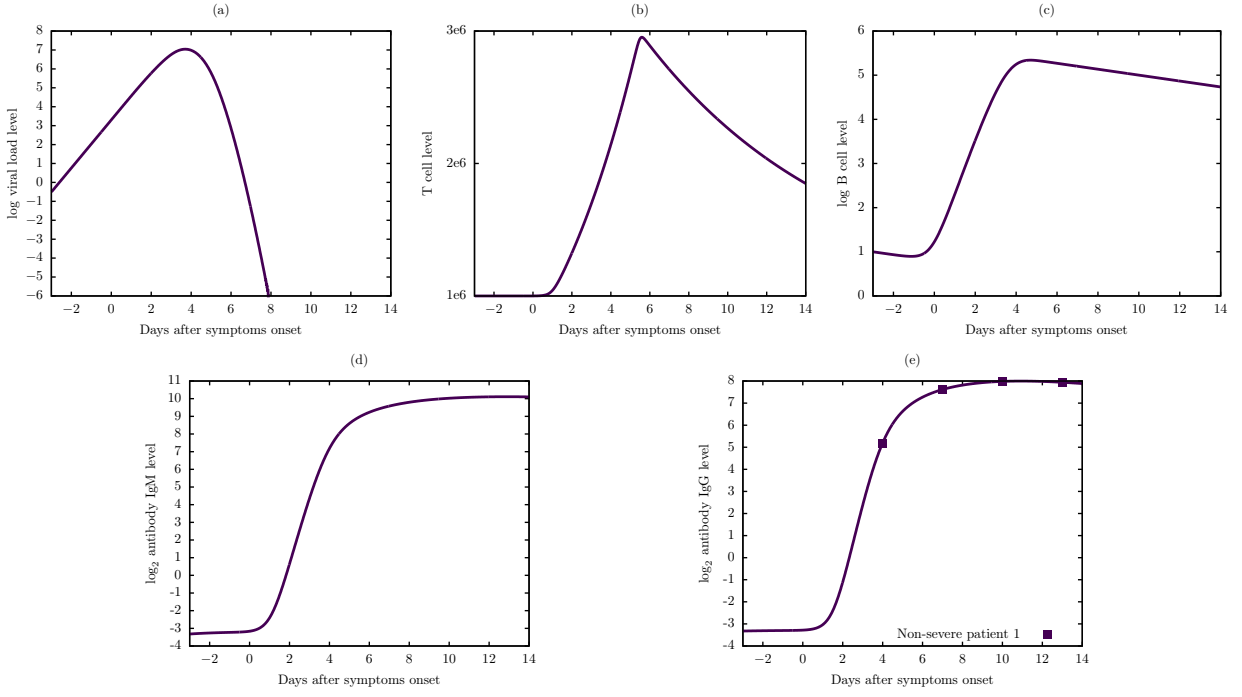

Figure S9: Viral dynamic and immune response of Model 6 for non-severe patient 1.

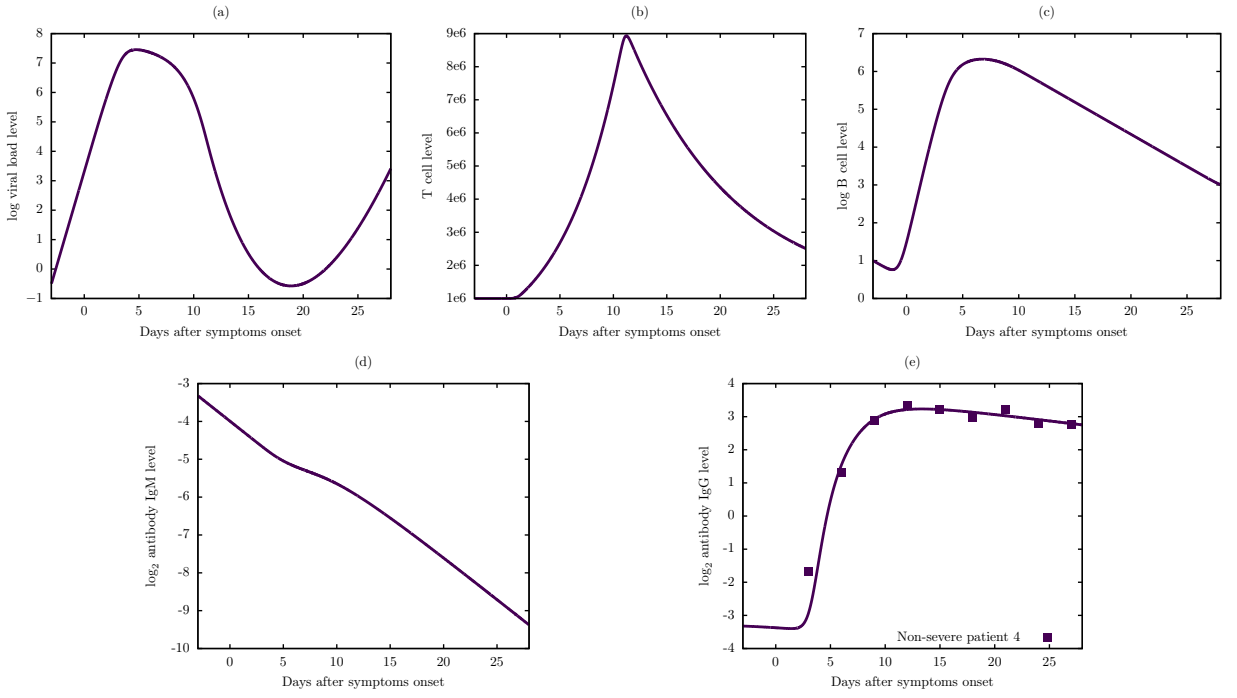

Figure S10: Viral dynamic and immune response of Model 6 for non-severe patient 4.

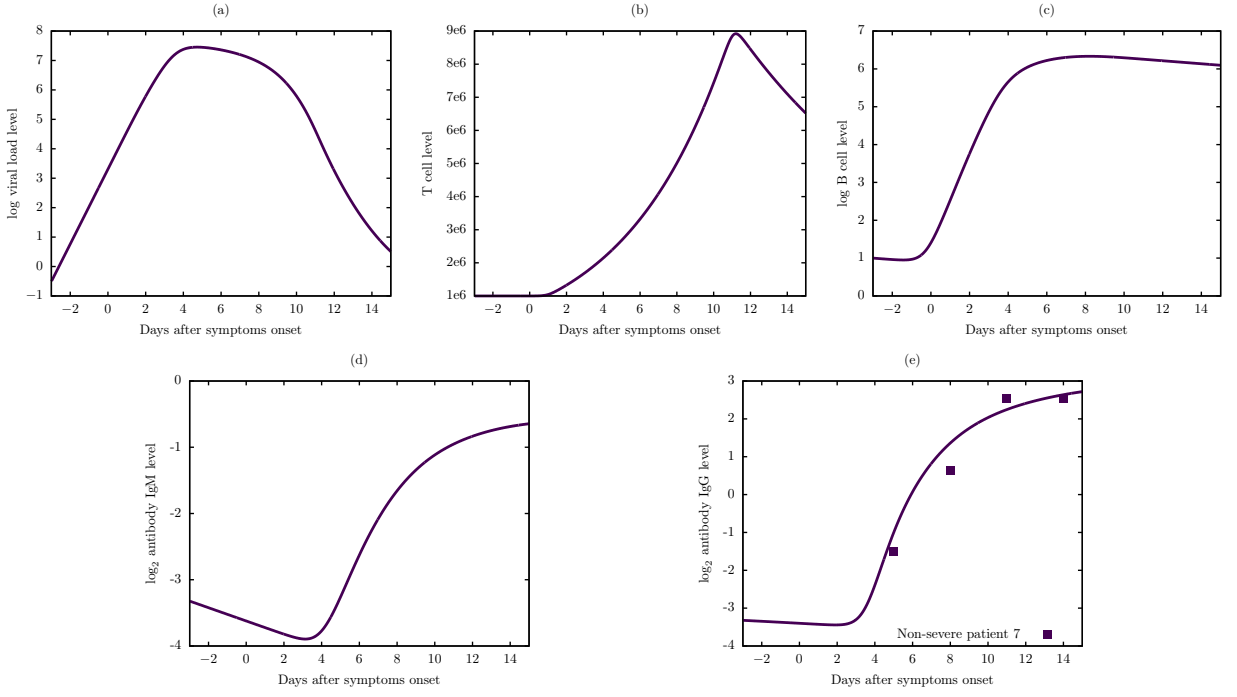

Figure S11: Viral dynamic and immune response of Model 6 for non-severe patient 7.

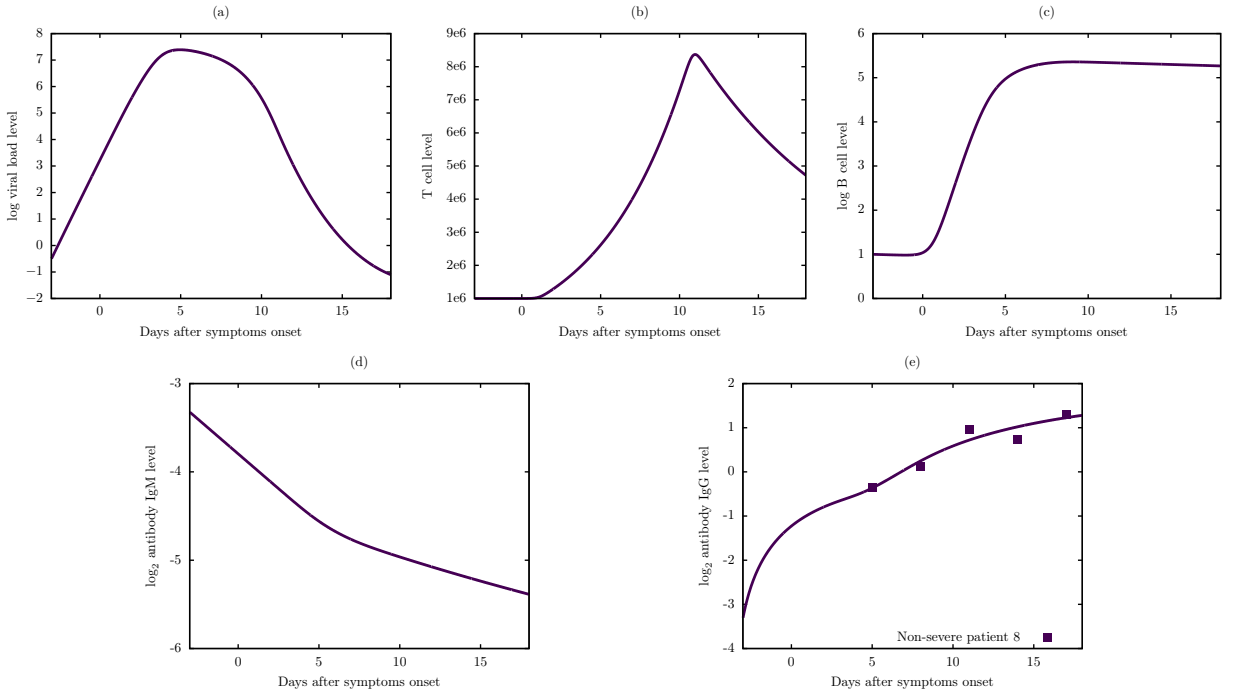

Figure S12: Viral dynamic and immune response of Model 6 for non-severe patient 8.

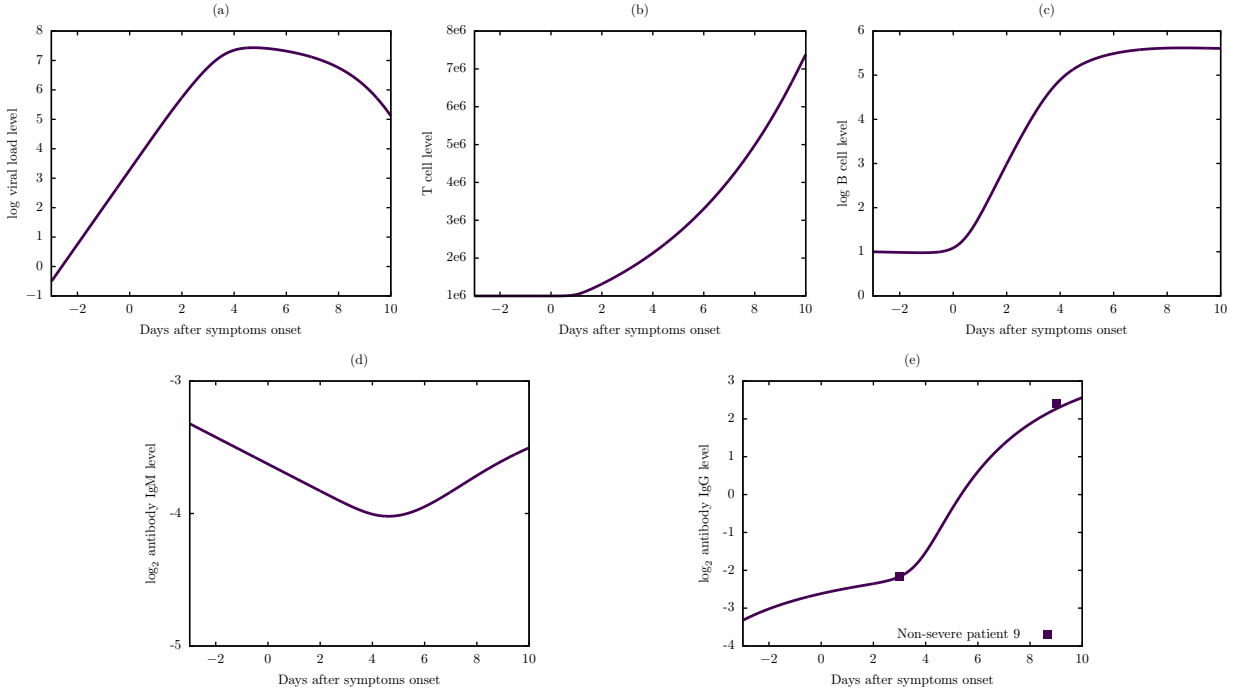

Figure S13: Viral dynamic and immune response of Model 6 for non-severe patient 9.

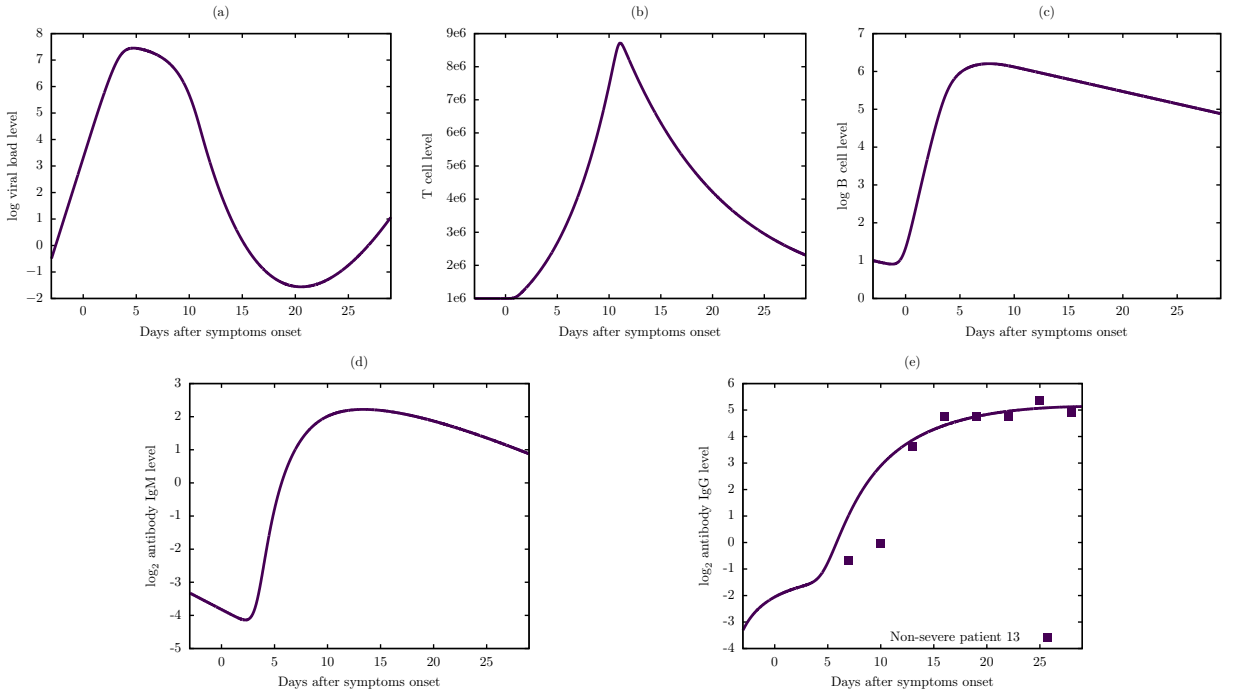

Figure S14: Viral dynamic and immune response of Model 6 for non-severe patient 13.

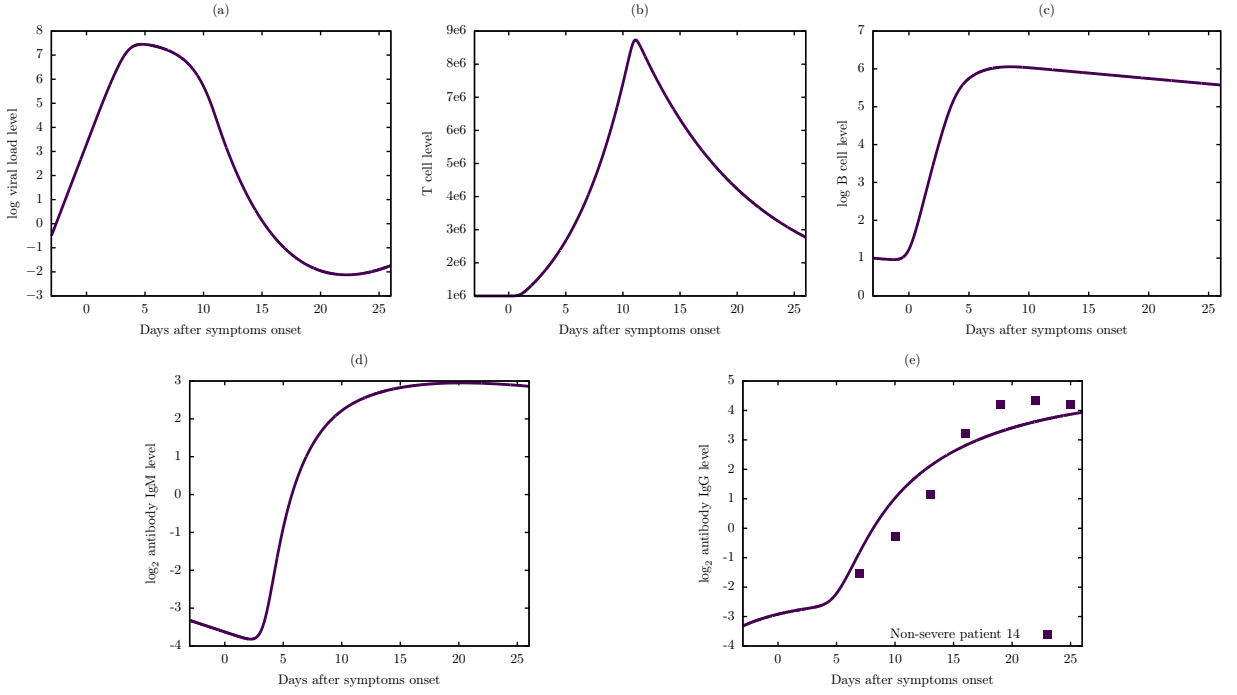

Figure S15: Viral dynamic and immune response of Model 6 for non-severe patient 14.

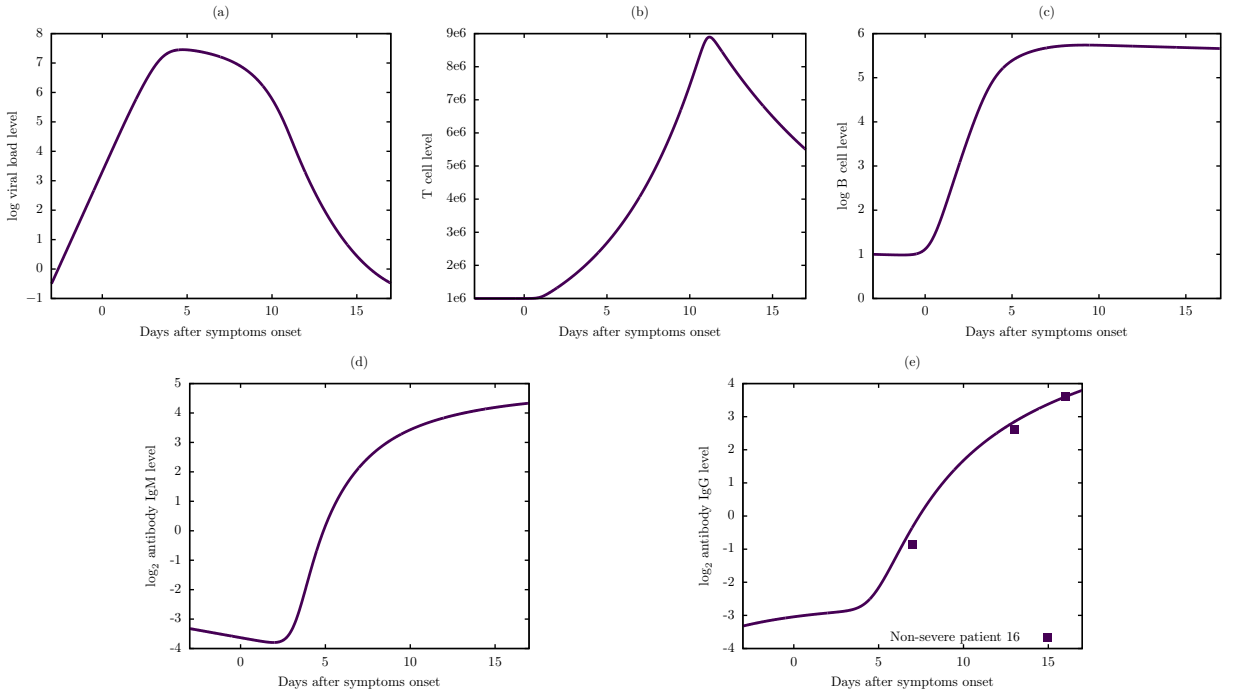

Figure S16: Viral dynamic and immune response of Model 6 for non-severe patient 16.

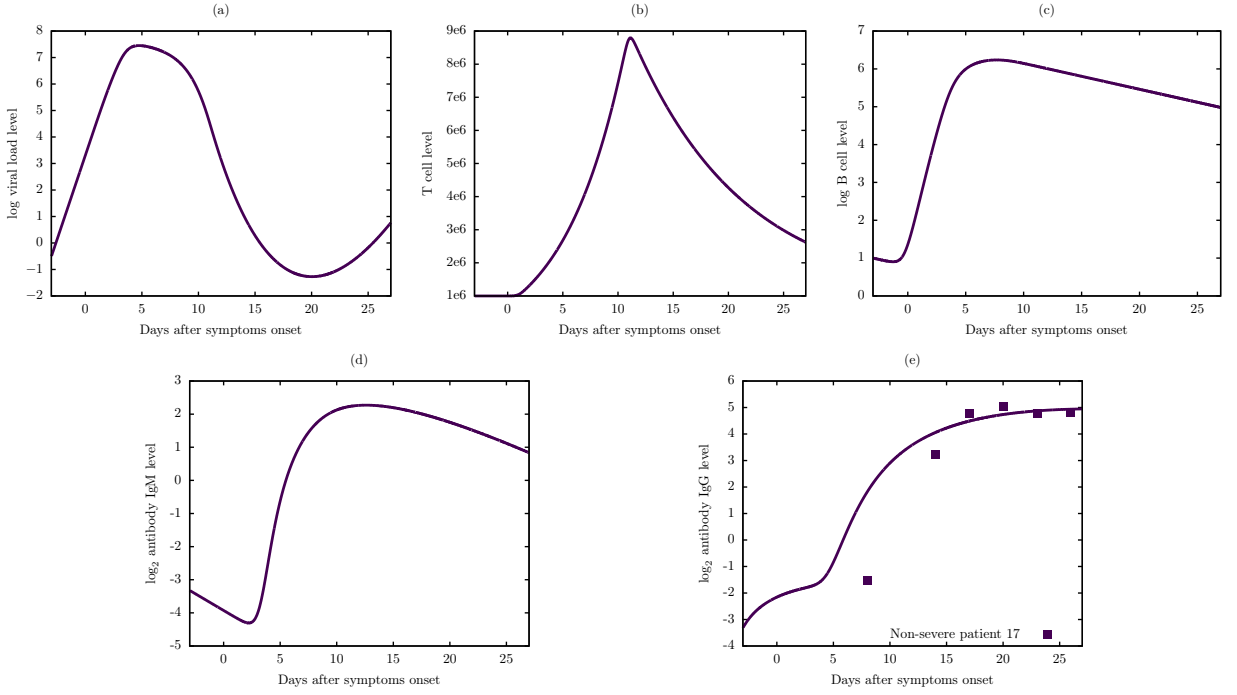

Figure S17: Viral dynamic and immune response of Model 6 for non-severe patient 17.

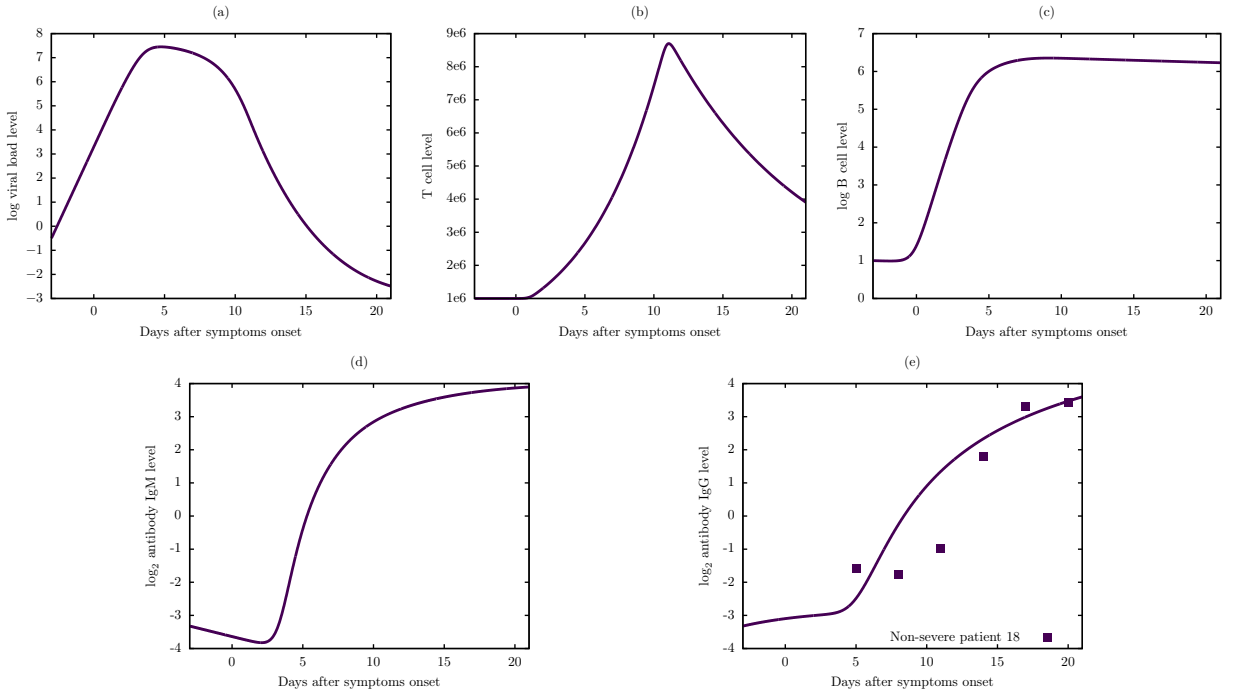

Figure S18: Viral dynamic and immune response of Model 6 for non-severe patient 18.

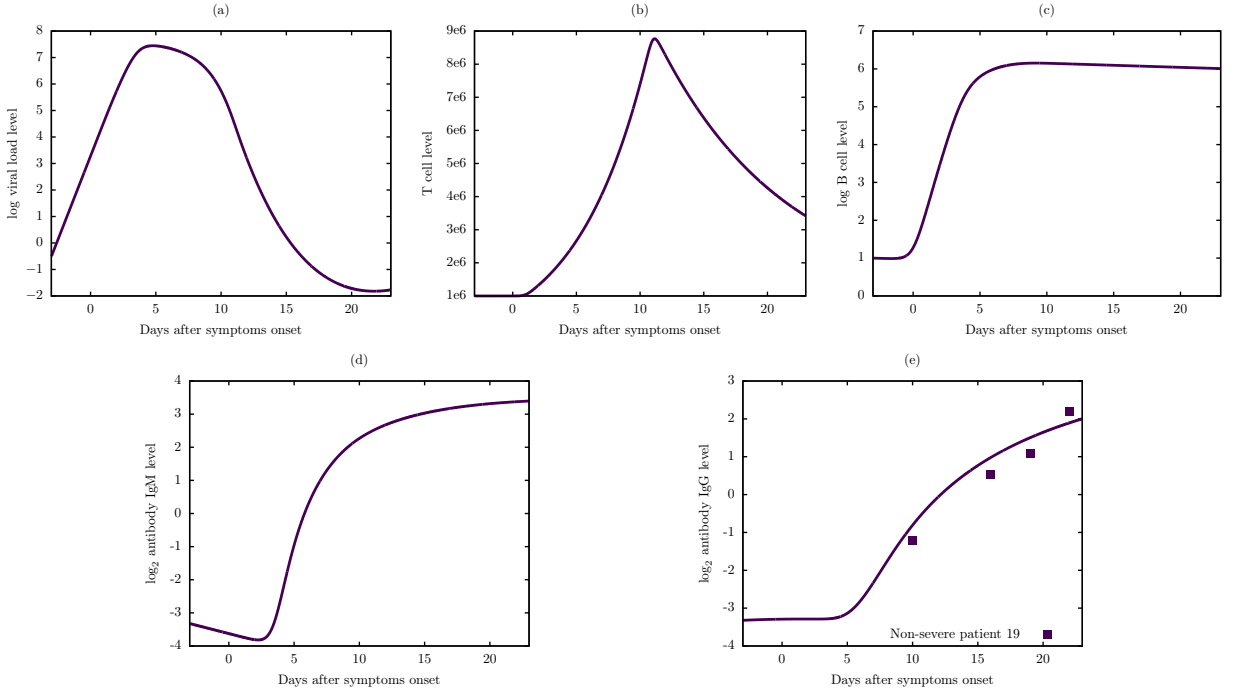

Figure S19: Viral dynamic and immune response of Model 6 for non-severe patient 19.

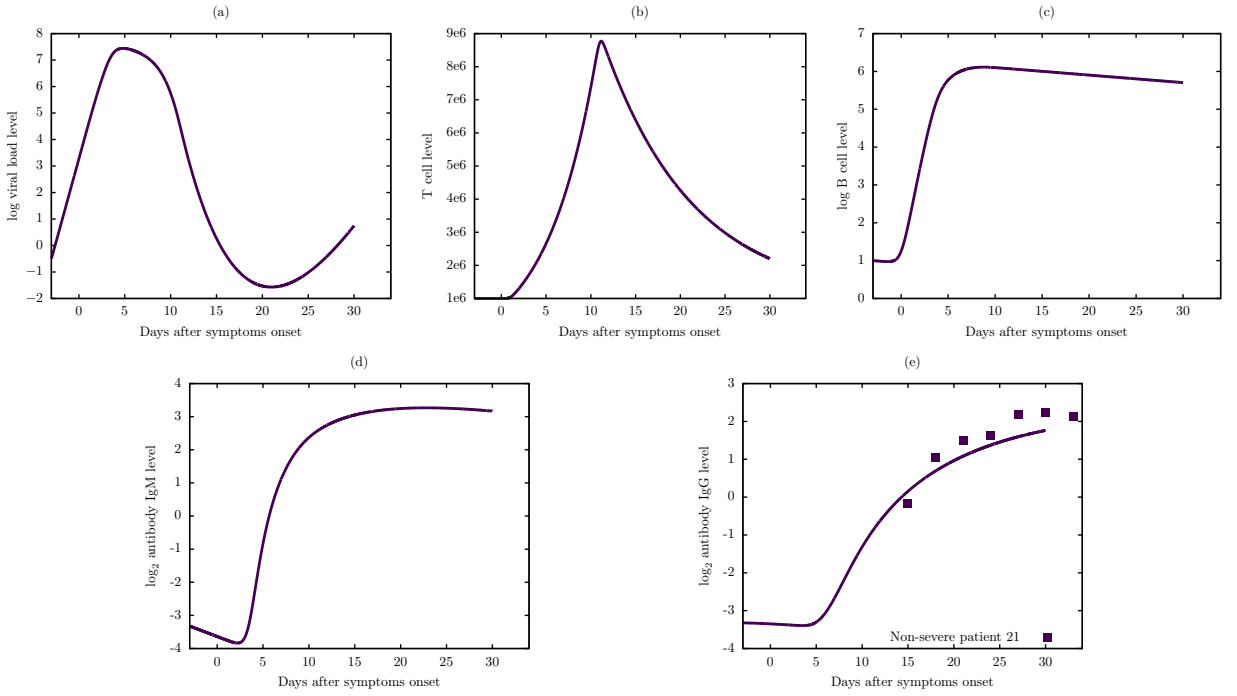

Figure S20: Viral dynamic and immune response of Model 6 for non-severe patient 21.

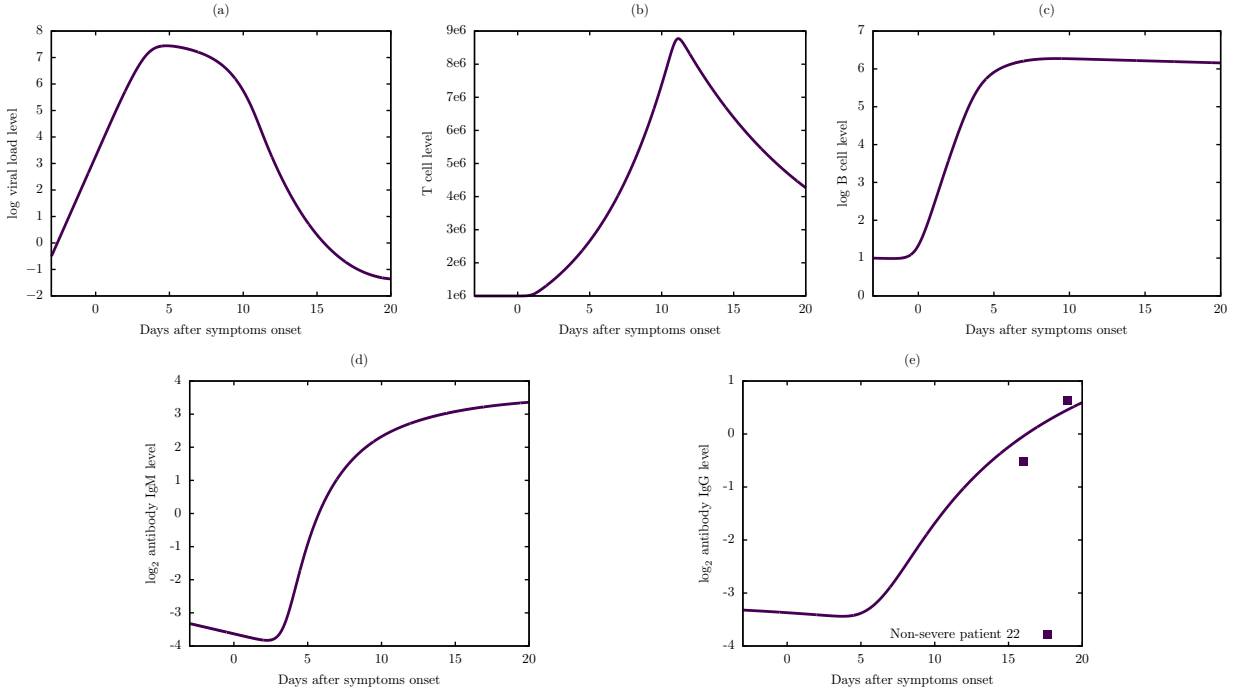

Figure S21: Viral dynamic and immune response of Model 6 for non-severe patient 22.

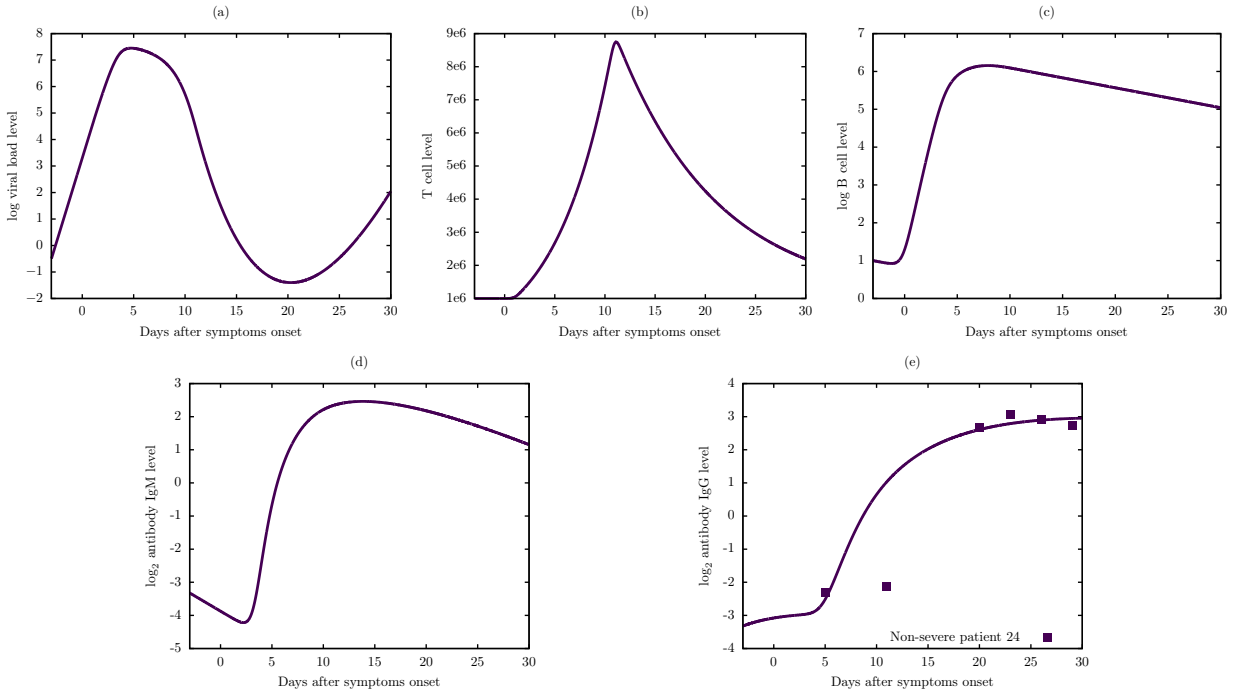

Figure S22: Viral dynamic and immune response of Model 6 for non-severe patient 24.

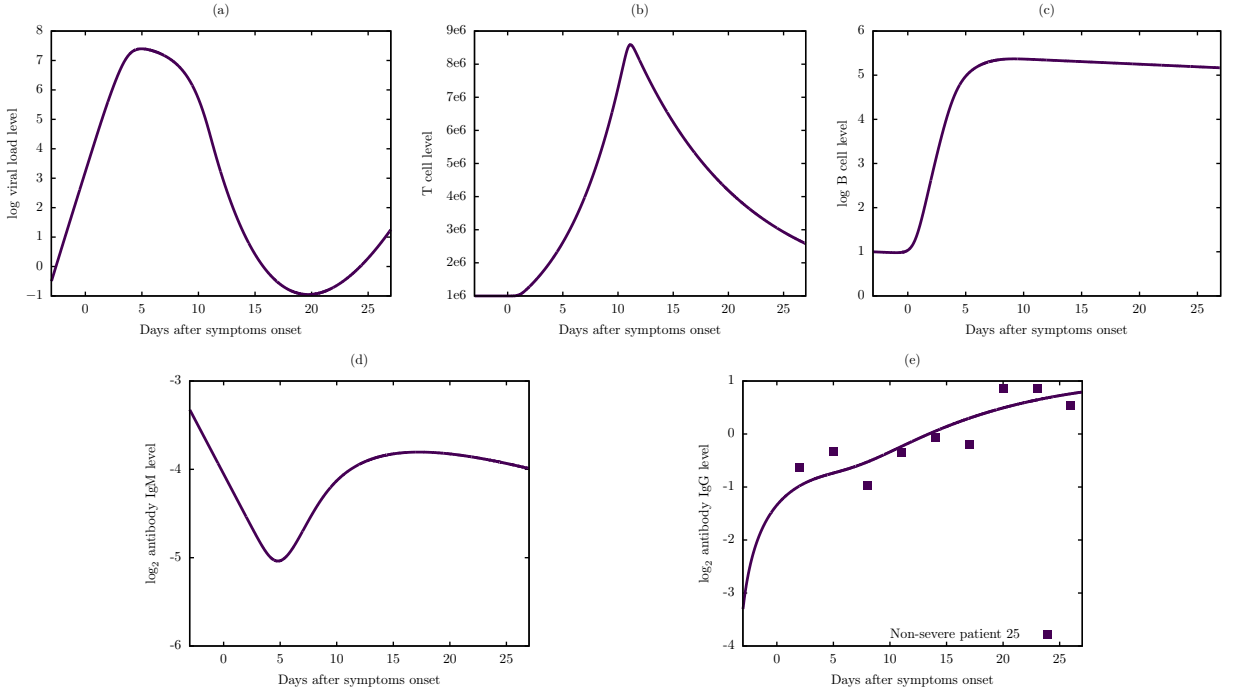

Figure S23: Viral dynamic and immune response of Model 6 for non-severe patient 25.

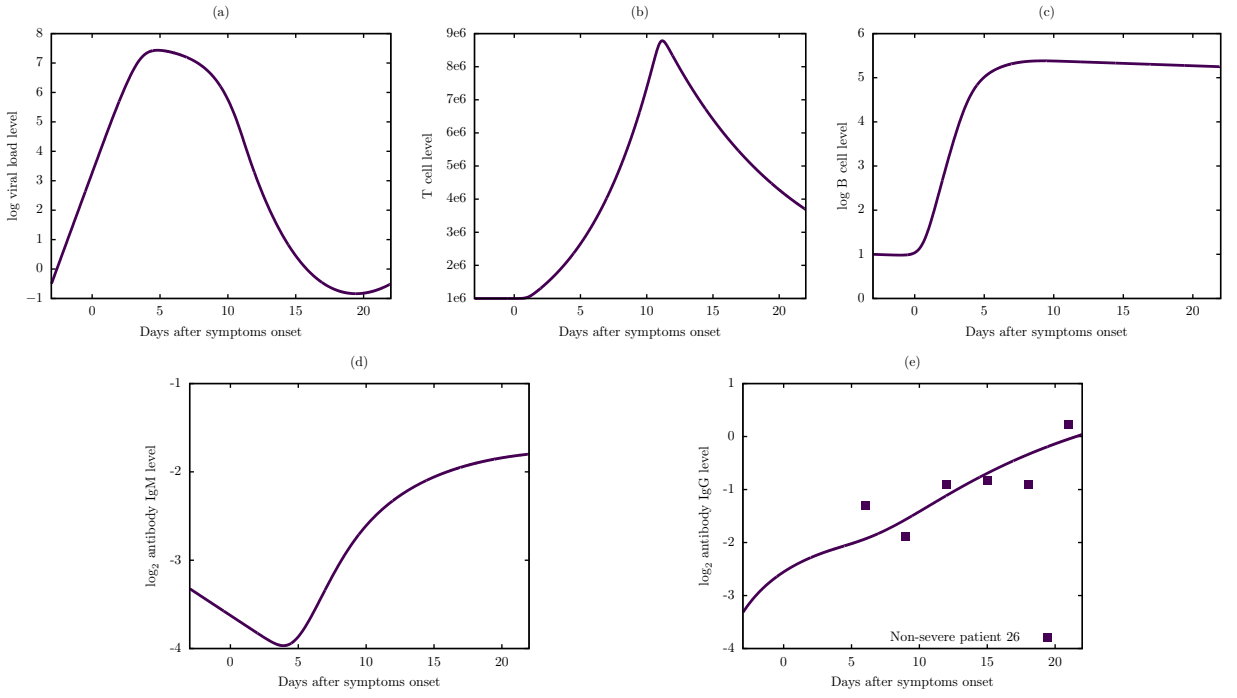

Figure S24: Viral dynamic and immune response of Model 6 for non-severe patient 26.

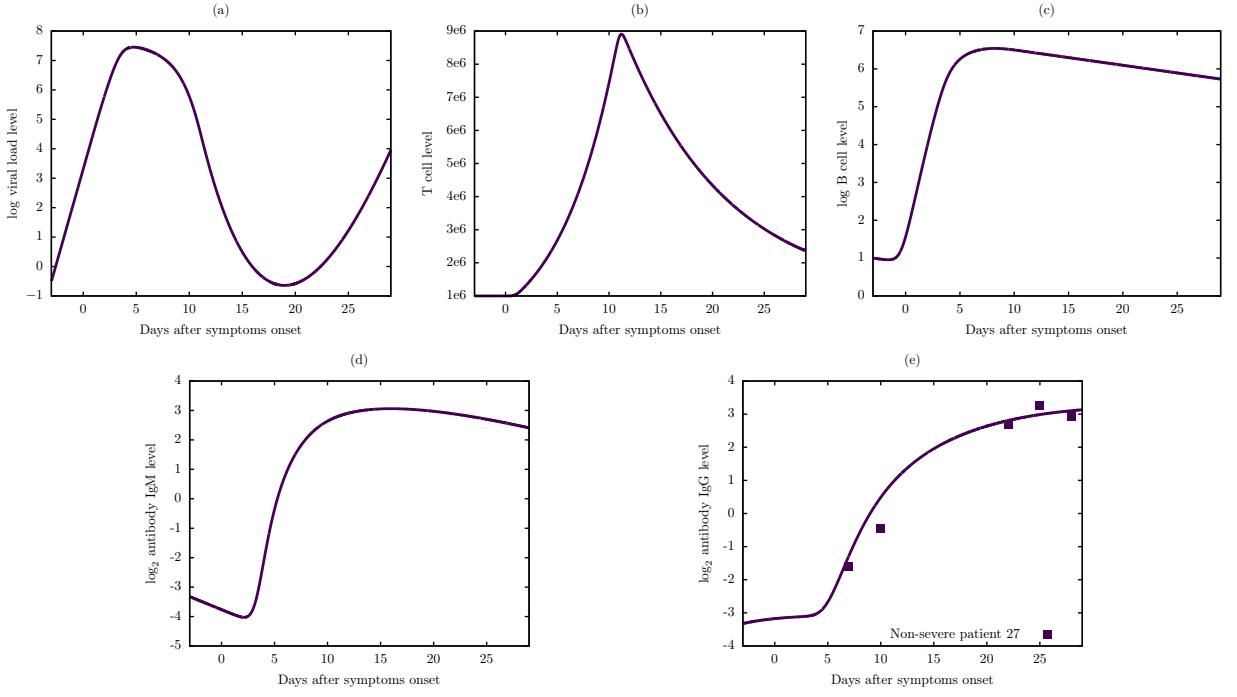

Figure S25: Viral dynamic and immune response of Model 6 for non-severe patient 27.

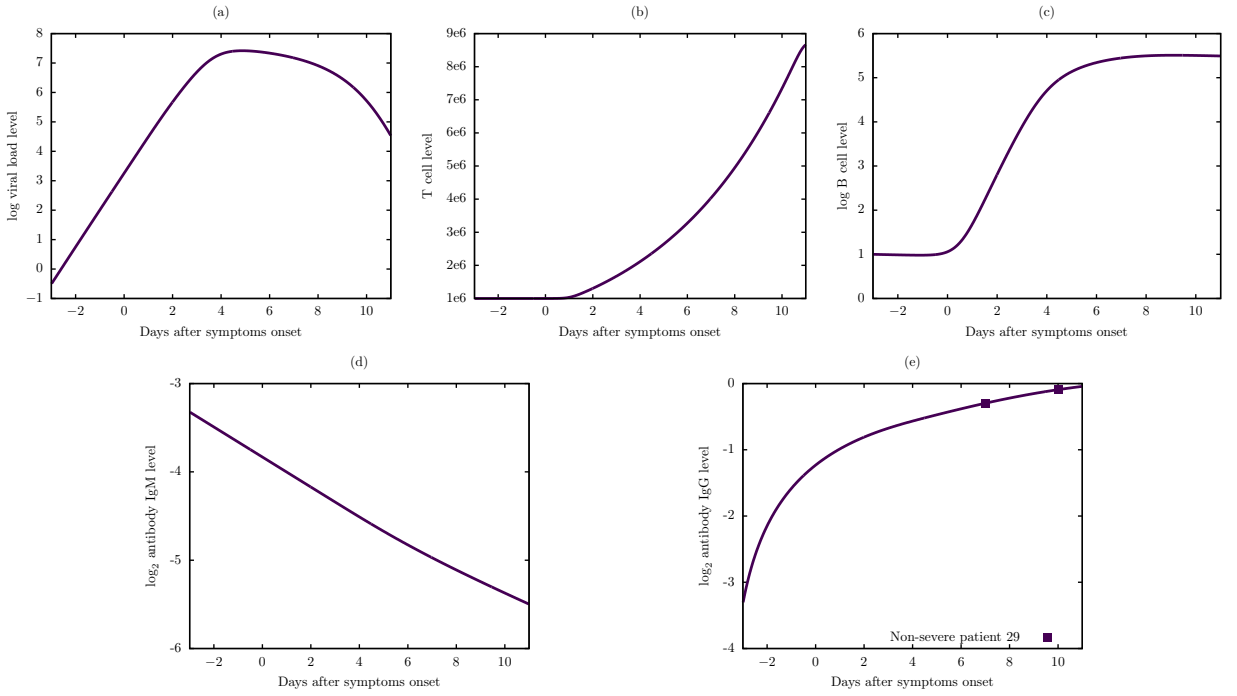

Figure S26: Viral dynamic and immune response of Model 6 for non-severe patient 29.

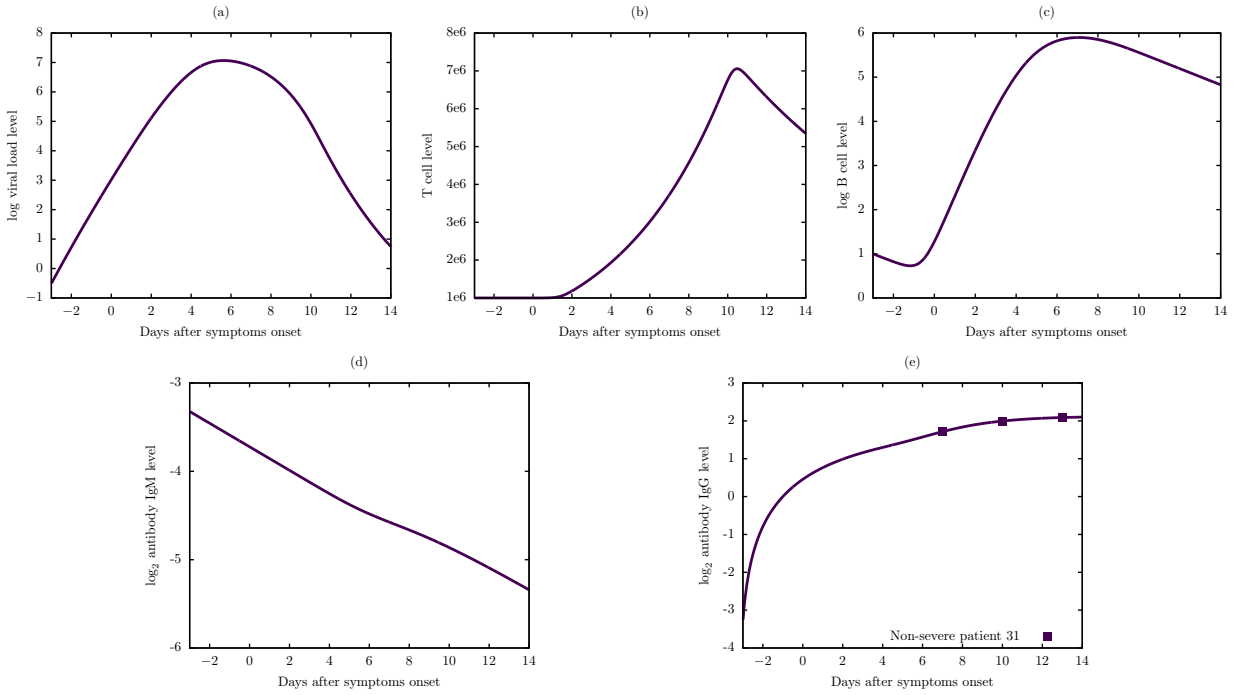

Figure S27: Viral dynamic and immune response of Model 6 for non-severe patient 31.

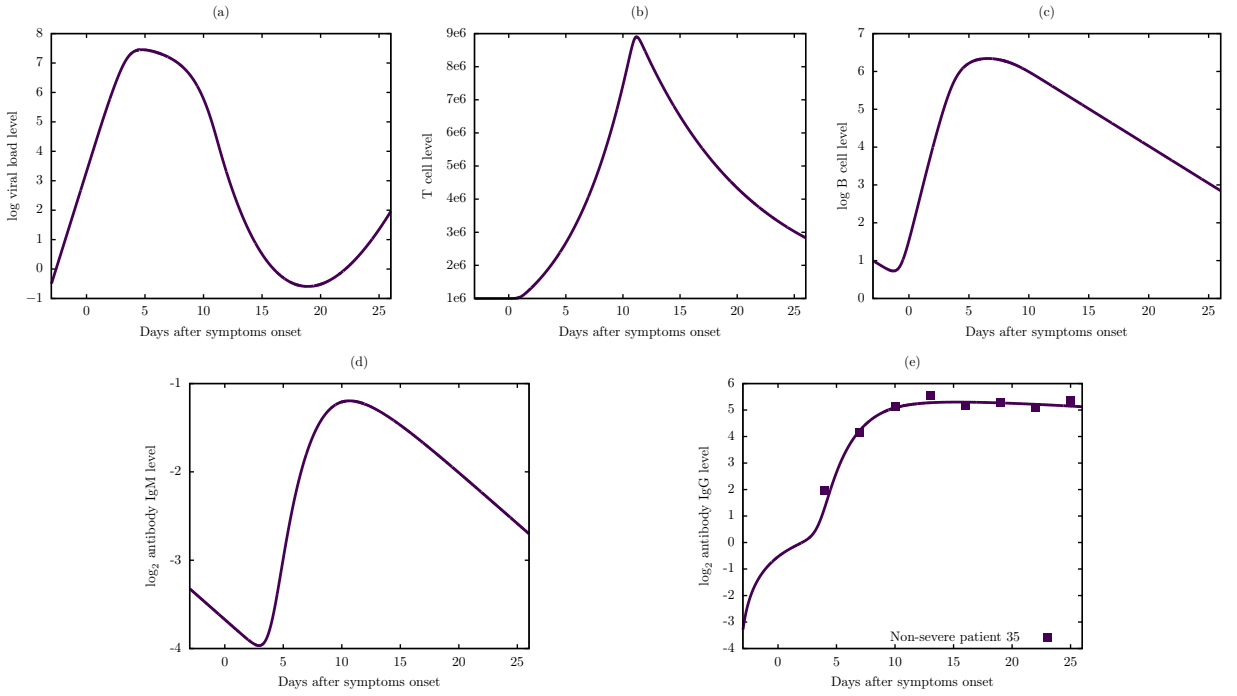

Figure S28: Viral dynamic and immune response of Model 6 for non-severe patient 35.

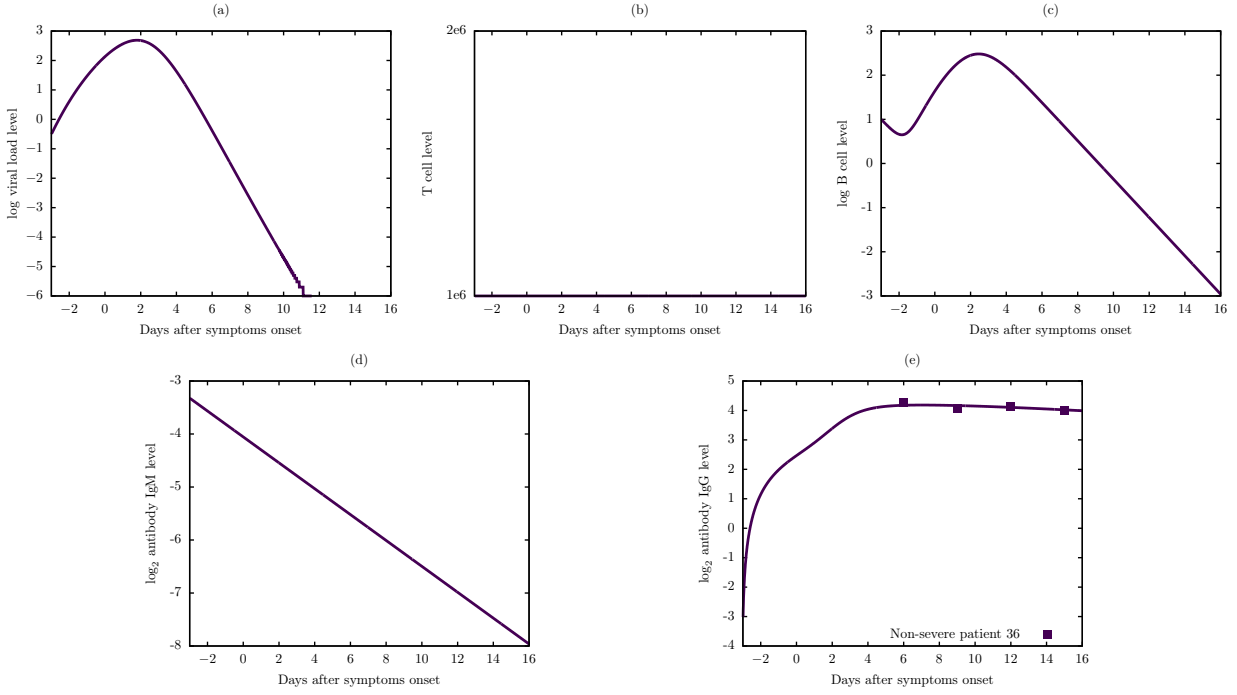

Figure S29: Viral dynamic and immune response of Model 6 for non-severe patient 36.

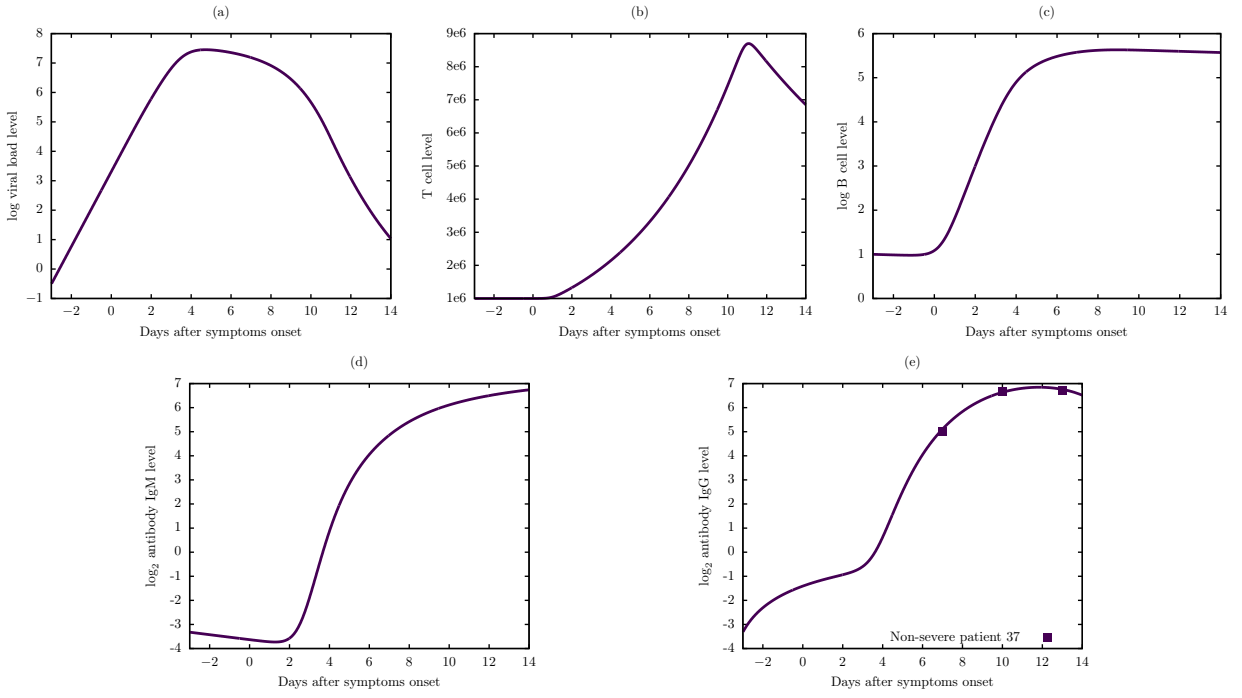

Figure S30: Viral dynamic and immune response of Model 6 for non-severe patient 37.

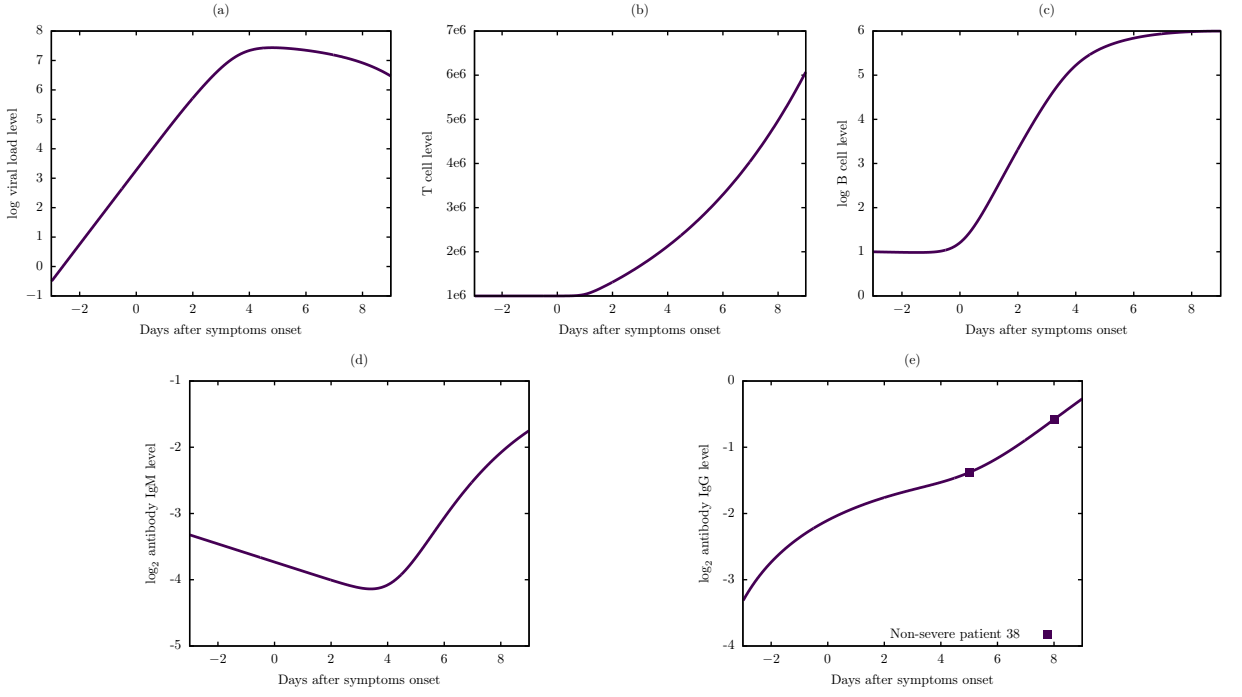

Figure S31: Viral dynamic and immune response of Model 6 for non-severe patient 38.

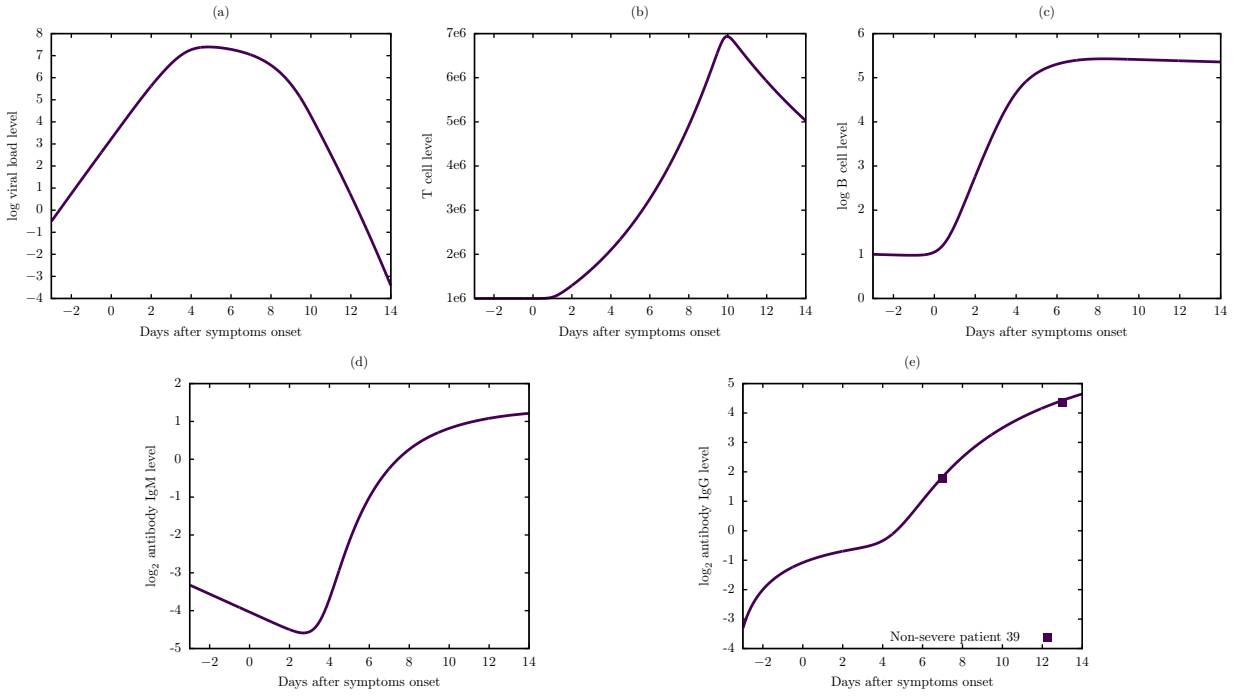

Figure S32: Viral dynamic and immune response of Model 6 for non-severe patient 39.

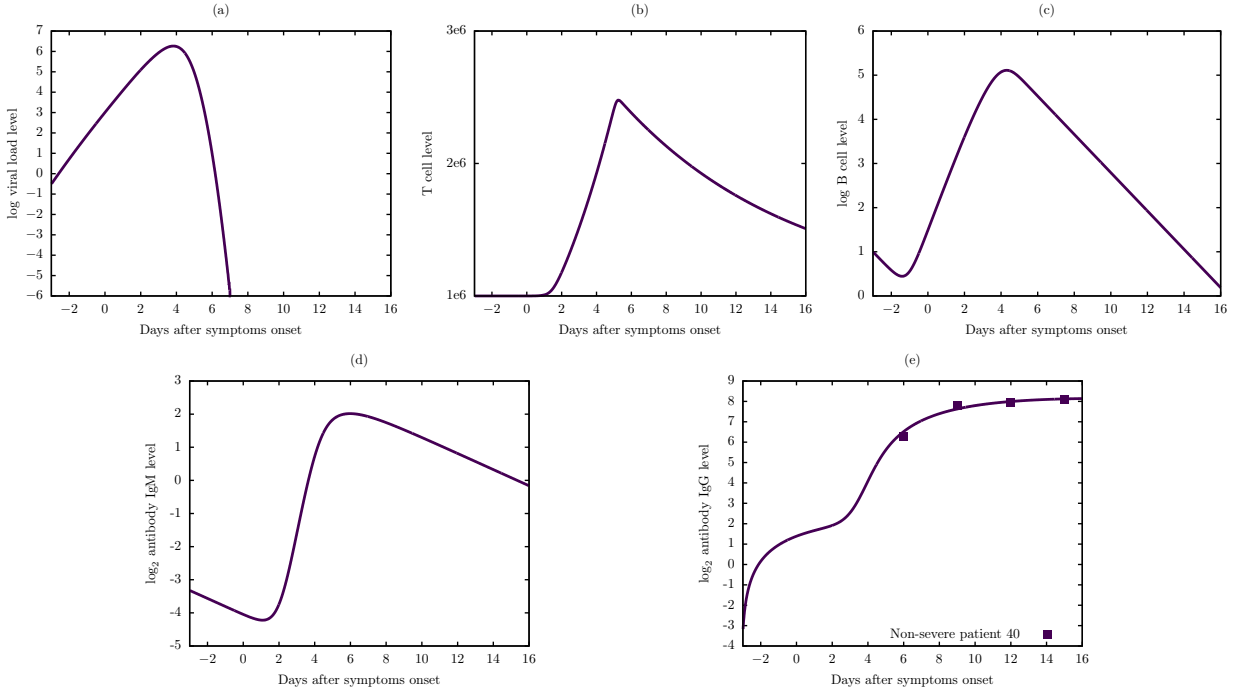

Figure S33: Viral dynamic and immune response of Model 6 for non-severe patient 40.

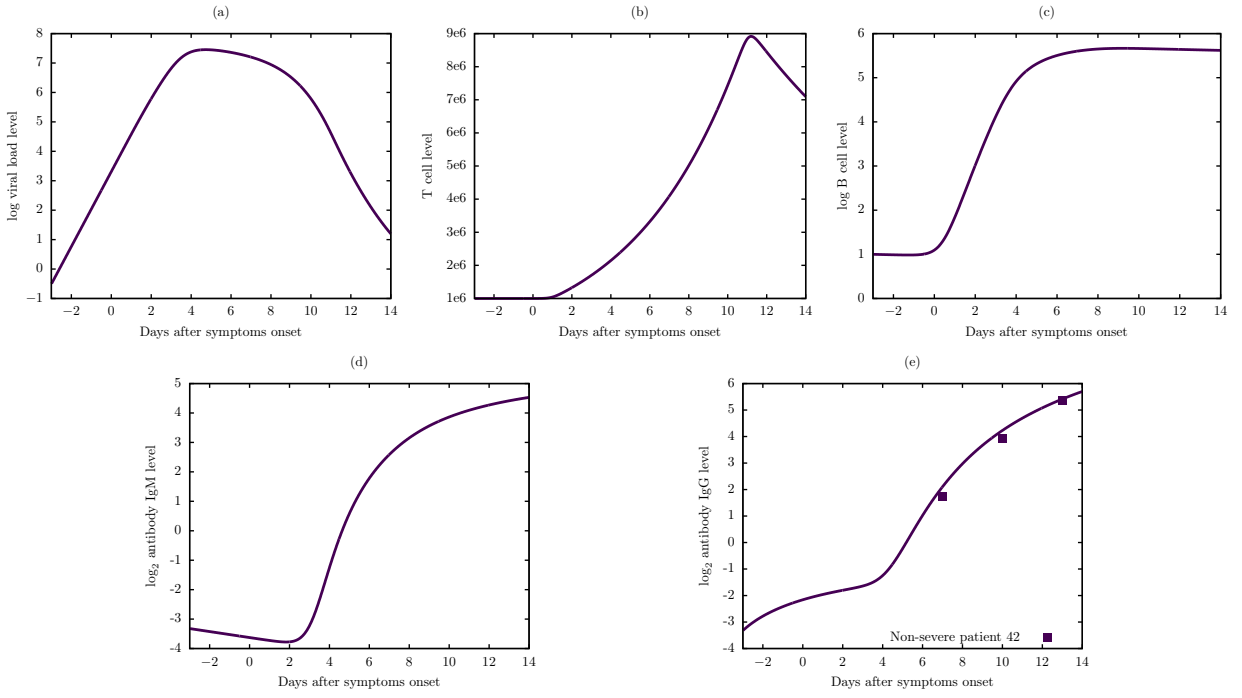

Figure S34: Viral dynamic and immune response of Model 6 for non-severe patient 42.

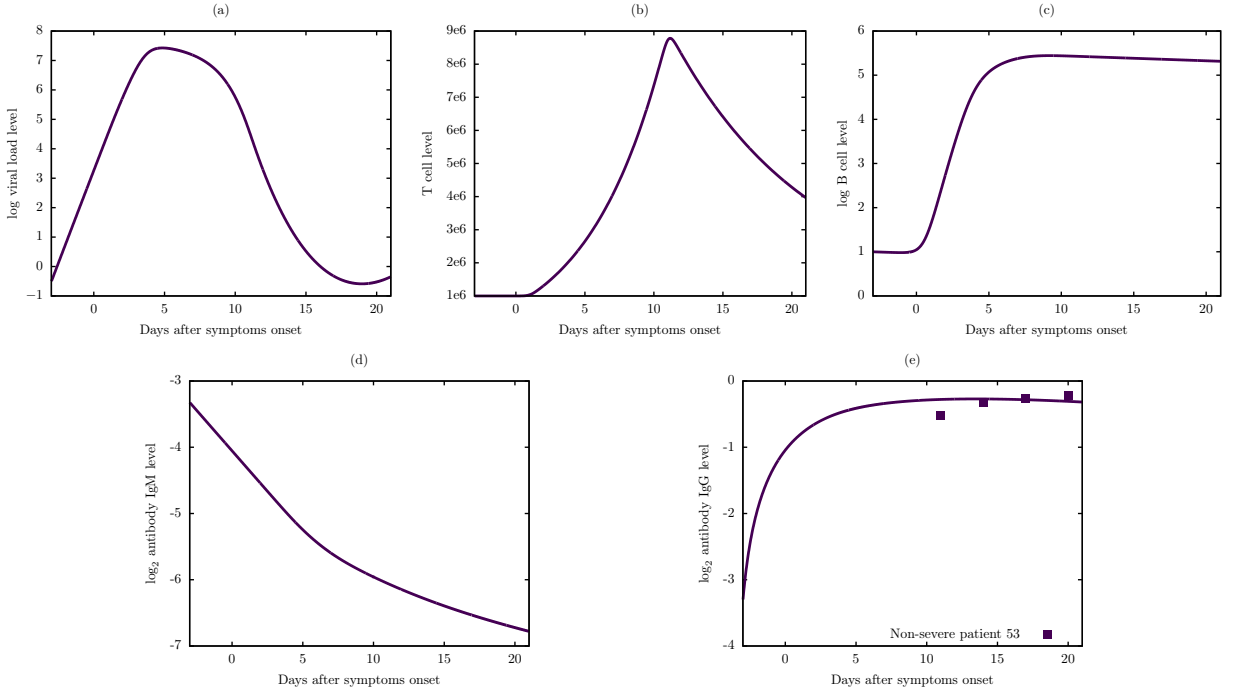

Figure S35: Viral dynamic and immune response of Model 6 for non-severe patient 53.

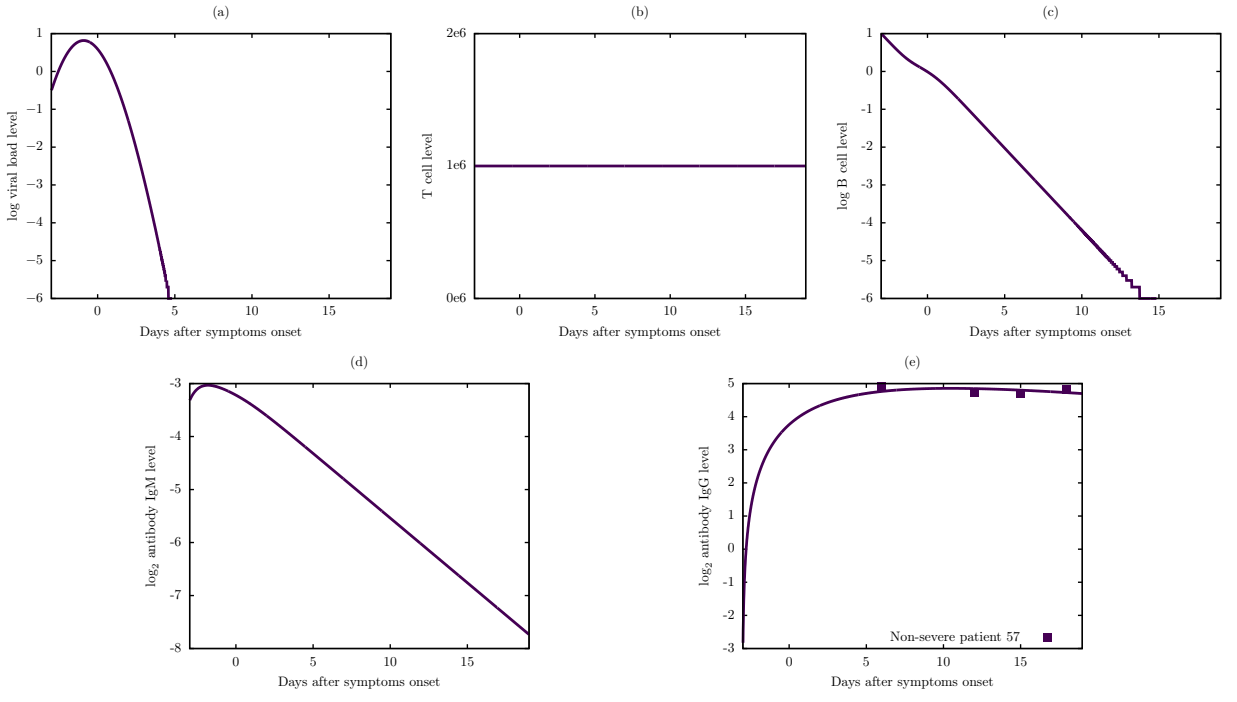

Figure S36: Viral dynamic and immune response of Model 6 for non-severe patient 57.

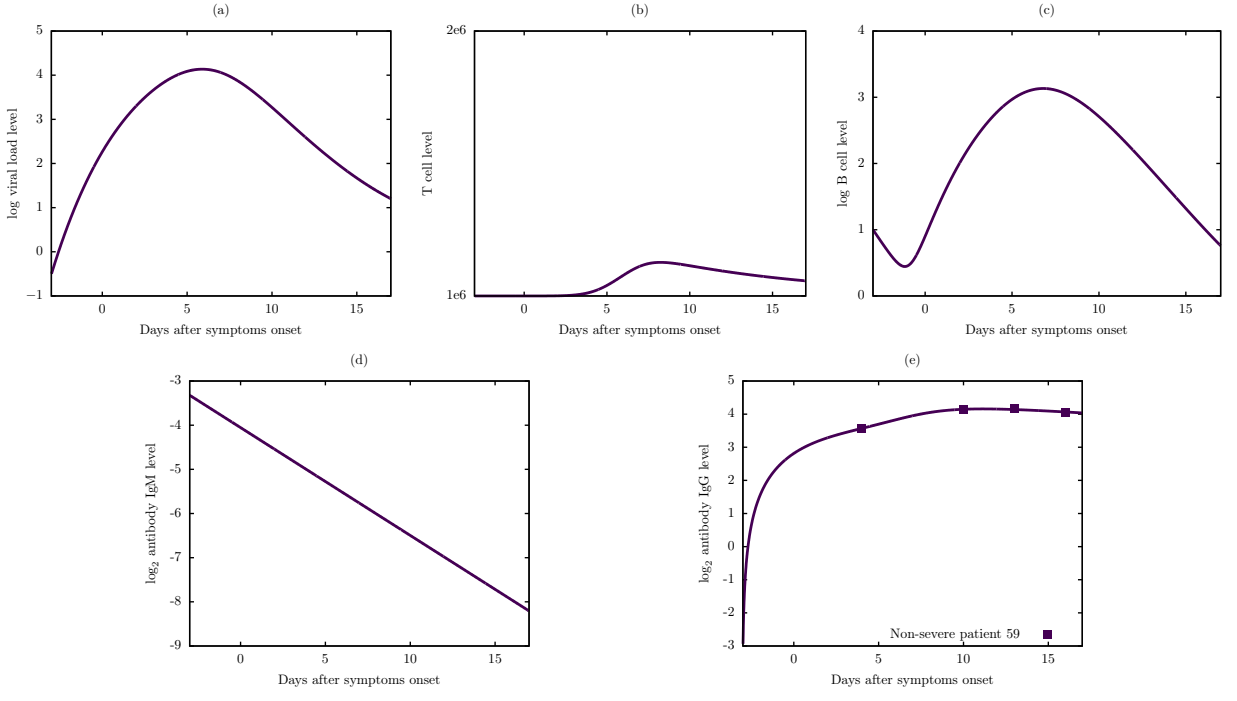

Figure S37: Viral dynamic and immune response of Model 6 for non-severe patient 59.

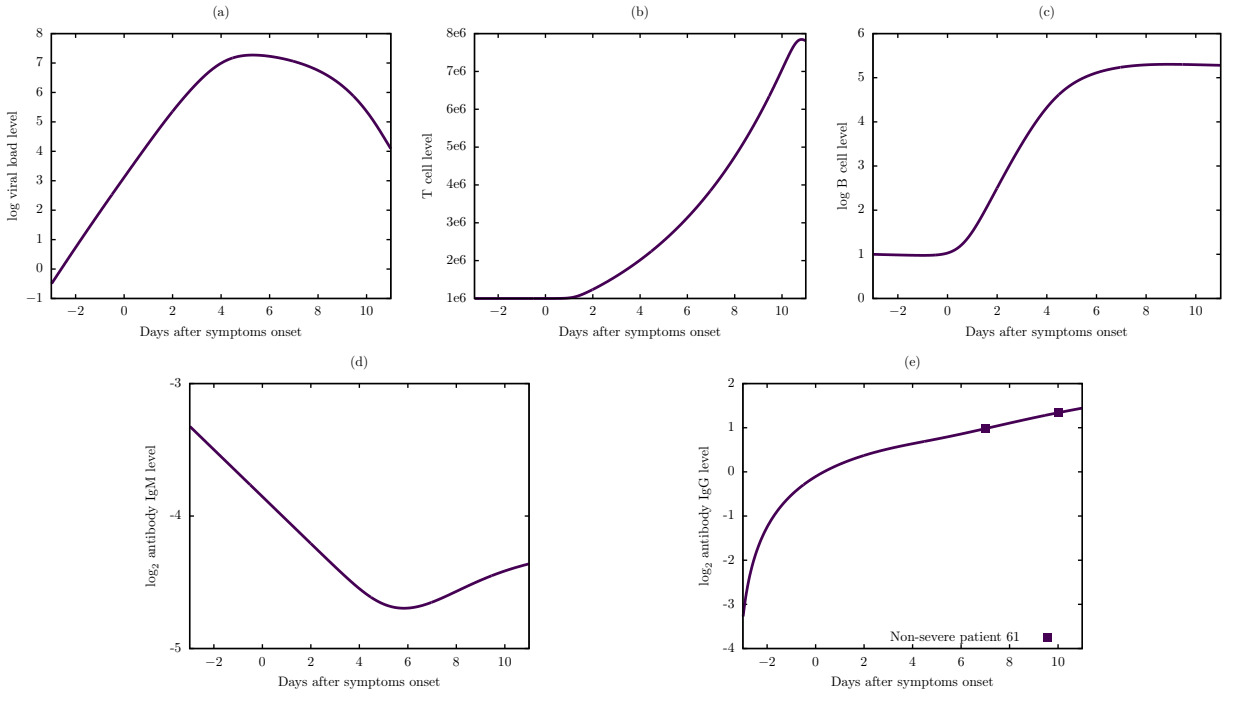

Figure S38: Viral dynamic and immune response of Model 6 for non-severe patient 61.

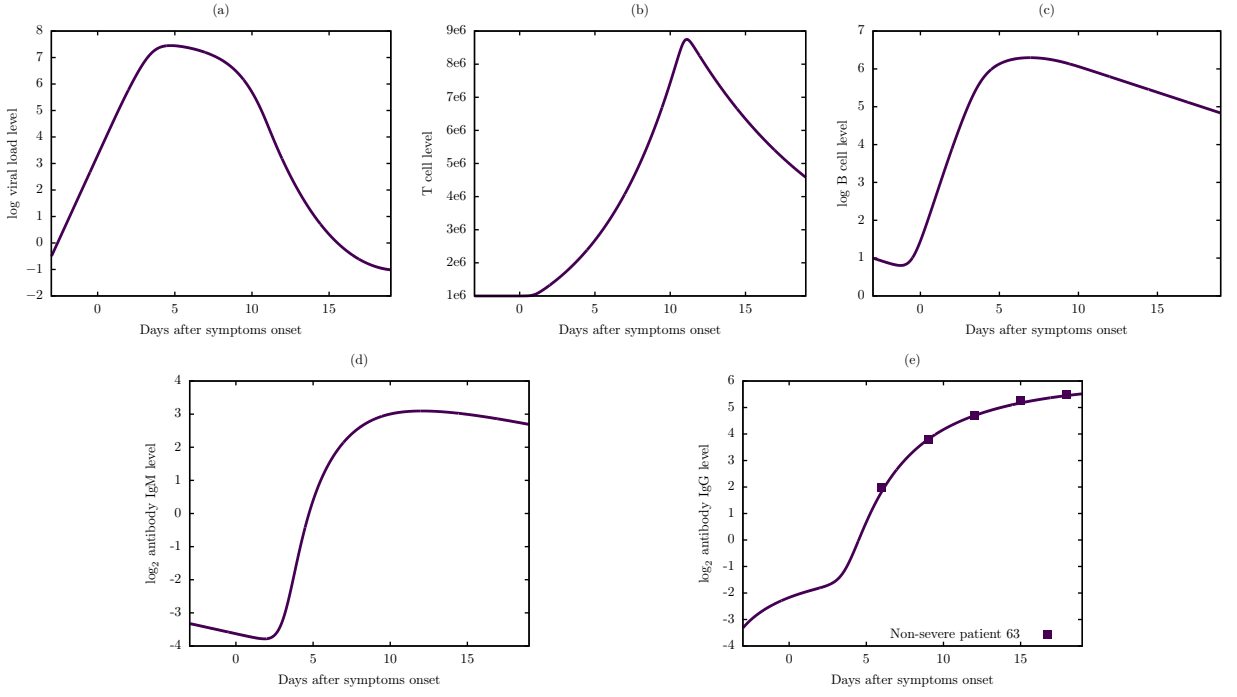

Figure S39: Viral dynamic and immune response of Model 6 for non-severe patient 63.

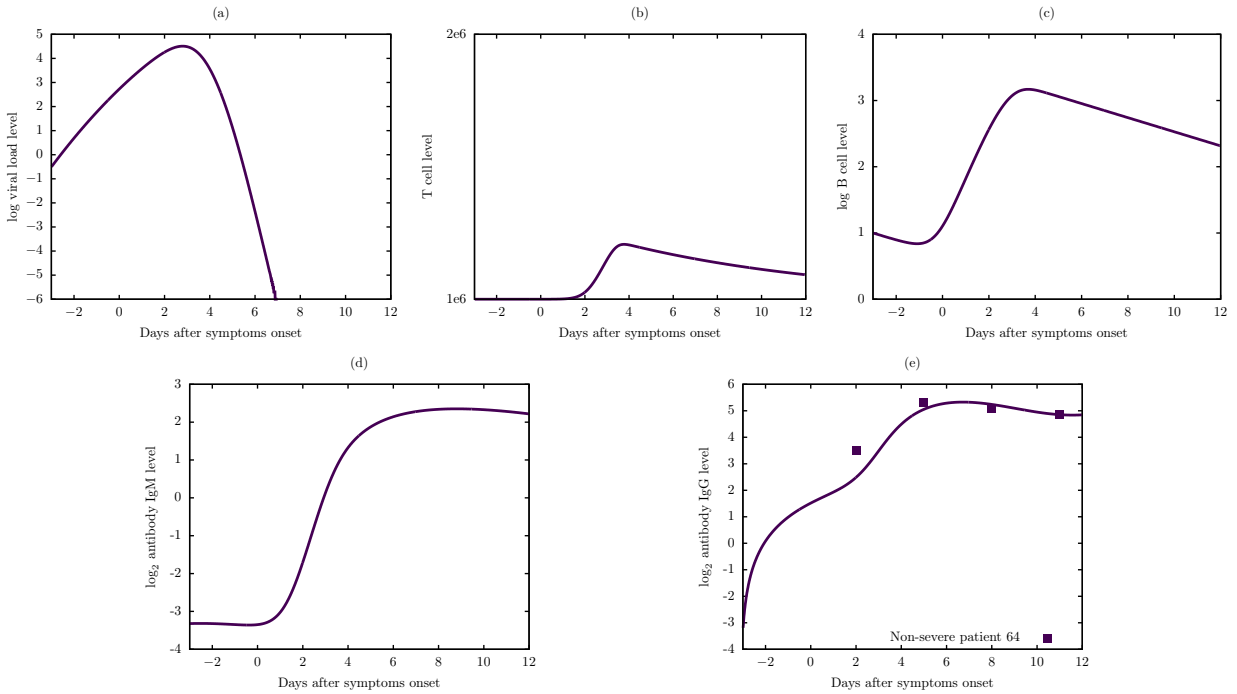

Figure S40: Viral dynamic and immune response of Model 6 for non-severe patient 64.