Supporting information for the article "Superinfection and cell regeneration can lead to chronic viral coinfections"

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1 Detailed steady states of model 1

Here we show all the possible chronic coinfection equilibria of the model where superinfection with cell regeneration and death are considered (model 1, according to main text).

1.1 Steady states of model 1

In model 1 or the most general case of superinfection model that includes target cell regeneration along with natural cell death, we found five different equilibria. Among them one is the infection free equilibrium (Q_1^*)

$$Q_1^* = (T^*, 0, 0, 0, 0, 0, 0, 0, 0), \text{ where } T^* \in \mathbb{R}_{\geq} \text{ or } \{T^* \in \mathbb{R} \mid T^* \geq 0\}.$$

The rest four are the chronic coinfection equilibria ($Q_2^{*'}$, $Q_2^{*''}$, $Q_2^{*'''}$, $Q_2^{*''''}$). Following are the four possible chronic coinfection equilibria with their respective parameter constraints.

Chronic coinfection equilibrium, $Q_2^{*'}$

$$
\begin{aligned}
T^{*'} =& \frac{r}{\beta_1 V_1^{*'} + \beta_2 V_2^{*'} + a},\ E_1^{*'} = \frac{\beta_1 T^{*'} V_1^{*'}}{k_1 + \beta_{21} V_2^{*'}},\ E_2^{*'} = \frac{\beta_2 T^{*'} V_2^{*'}}{k_2 + \beta_{12} V_1^{*'}},\\
E_3^{*} =& \frac{1}{k_3}(\beta_{12} E_2^{*'} V_1^{*'} + \beta_{21} E_1^{*'} V_2^{*'}),\ I_1^{*} = \frac{k_1}{\delta_1} E_1^{*'},\ I_2^{*'} = \frac{k_2}{\delta_2} E_2^{*'},\ I_3^{*'} = \frac{k_3}{\delta_3} E_3^{*'},\\
V_1^{*'} =& \frac{1}{2\beta_1\beta_{12} c_1 \delta_1 \delta_3 (k_1 + \beta_{21} V_2^{*'})} \Bigg[\Big\{ r\beta_1\beta_{12}(p_1 k_1 \delta_3 + p_{12}\delta_1 V_2^{*'}) - c_1\delta_1\delta_3(k_1 + \beta_{21} V_2^{*'})\\
& (\beta_1 k_2 + \beta_2 \beta_{12} V_2^{*'} + a\beta_{12}) \Big\} + \sqrt{\Bigg[\Big\{ c_1\delta_1\delta_3(k_1 + \beta_{21} V_2^{*'})(\beta_1 k_2 + \beta_2\beta_{12} V_2^{*'} + a\beta_{12}) \Big\}^2}\\
& + \Big\{ r\beta_1\beta_{12}(p_1 k_1 \delta_3 + p_{12}\delta_1 V_2^{*'}) \Big\}^2 + 4r\beta_2 V_2^{*'} p_{12} \beta_1 \beta_{12}^2 c_1 \delta_1^2 \delta_3 (k_1 + \beta_{21} V_2^{*'})^2\\
& + 4r\beta_1^2 k_2 \beta_{12} c_1 \delta_1 \delta_3 (k_1 + \beta_{21} V_2^{*'})(p_1 k_1 \delta_3 + p_{12}\beta_{21}\delta_1 V_2^{*'})\\
& - \Bigg(4\beta_1\beta_{12} c_1^2 \delta_1^2 \delta_3^2 (k_1 + \beta_{21} V_2^{*'})^2 (\beta_2 k_2 V_2^{*'} + a k_2)\\
& + 2 r c_1 \delta_1 \delta_3 \beta_1 \beta_{12} (k_1 + \beta_{21} V_2^{*'})(\beta_1 k_2 + \beta_2 \beta_{12} V_2^{*'} + a\beta_{12})(p_1 k_1 \delta_3 + p_{12}\delta_1 V_2^{*'}) \Bigg) \Bigg] \Bigg],\\
V_2^{*'} =& \frac{1}{2\beta_2\beta_{21} c_2 \delta_2 \delta_3 (k_2 + \beta_{12} V_1^{*'})} \Bigg[\Big\{ r\beta_2\beta_{21}(p_2 k_2 \delta_3 + p_{21}\delta_2 V_1^{*'}) - c_2\delta_2\delta_3(k_2 + \beta_{12} V_1^{*'})\\
& (\beta_2 k_1 + \beta_1 \beta_{21} V_1^{*'} + a\beta_{21}) \Big\} + \sqrt{\Bigg[\Big\{ c_2\delta_2\delta_3(k_2 + \beta_{12} V_1^{*'})(\beta_2 k_1 + \beta_1\beta_{21} V_1^{*'} + a\beta_{21}) \Big\}^2}\\
& + \Big\{ r\beta_2\beta_{21}(p_2 k_2 \delta_3 + p_{21}\delta_2 V_1^{*'}) \Big\}^2 + 4r\beta_1 V_1^{*'} p_{21} \beta_2 \beta_{21}^2 c_2 \delta_2^2 \delta_3 (k_2 + \beta_{12} V_1^{*'})^2\\
& + 4r\beta_2^2 k_1 \beta_{21} c_2 \delta_2 \delta_3 (k_2 + \beta_{12} V_1^{*'})(p_2 k_2 \delta_3 + p_{21}\beta_{12}\delta_2 V_1^{*'})\\
& - \Bigg(4\beta_2\beta_{21} c_2^2 \delta_2^2 \delta_3^2 (k_2 + \beta_{12} V_1^{*'})^2 (\beta_1 k_1 V_1^{*'} + a k_1)\\
& + 2 r c_2 \delta_2 \delta_3 \beta_2 \beta_{21} (k_2 + \beta_{12} V_1^{*'})(\beta_2 k_1 + \beta_1 \beta_{21} V_1^{*'} + a\beta_{21})(p_2 k_2 \delta_3 + p_{21}\delta_2 V_1^{*'}) \Bigg) \Bigg] \Bigg].
\end{aligned}
$$

Given the term inside the square root generates real positive number with the parameters, this chronic coinfection equilibrium exists if the following conditions are satisfied.

The conditions for V_1 and V_2 are respectively

$$r\beta_1\beta_{12}\frac{(p_1k_1\delta_3+p_{12}\delta_1V_2^{*'})}{(k_1+\beta_{21}V_2^{*'})}\geq c_1\delta_1\delta_3(\beta_1k_2+\beta_2\beta_{12}V_2^{*'}+a\beta_{12}),\ \text{and}$$
$$r\beta_2\beta_{21}\frac{(p_2k_2\delta_3+p_{21}\delta_2V_1^{*'})}{(k_2+\beta_{12}V_1^{*'})}\geq c_2\delta_2\delta_3(\beta_2k_1+\beta_1\beta_{21}V_1^{*'}+a\beta_{21}).$$

Chronic coinfection equilibrium, $Q_2^{*''}$

$$\begin{aligned}
T^{*''}=&\frac{r}{\beta_1V_1^{*''}+\beta_2V_2^{*''}+a},\ E_1^{*''}=\frac{\beta_1T^{*''}V_1^{*''}}{k_1+\beta_{21}V_2^{*''}},\ E_2^{*}=\frac{\beta_2T^{*''}V_2^{*''}}{k_2+\beta_{12}V_1^{*''}},\\
E_3^{*''}=&\frac{1}{k_3}(\beta_{12}E_2^{*''}V_1^{*''}+\beta_{21}E_1^{*''}V_2^{*''}),\ I_1^{*''}=\frac{k_1}{\delta_1}E_1^{*''},\ I_2^{*}=\frac{k_2}{\delta_2}E_2^{*''},\ I_3^{*''}=\frac{k_3}{\delta_3}E_3^{*''},\\
V_1^{*''}=&\frac{1}{2\beta_1\beta_{12}c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''})}\Bigg[\bigg\{r\beta_1\beta_{12}(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''})-c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''})\\
&(\beta_1k_2+\beta_2\beta_{12}V_2^{*''}+a\beta_{12})\bigg\}-\sqrt{\Bigg[\bigg\{c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''})(\beta_1k_2+\beta_2\beta_{12}V_2^{*''}+a\beta_{12})\bigg\}^2}\\
&+\bigg\{r\beta_1\beta_{12}(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''})\bigg\}^2+4r\beta_2V_2^{*''}p_{12}\beta_1\beta_{12}^2c_1\delta_1^2\delta_3(k_1+\beta_{21}V_2^{*''})^2\\
&+4r\beta_1^2k_2\beta_{12}c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''})(p_1k_1\delta_3+p_{12}\beta_{21}\delta_1V_2^{*''})\\
&-\bigg(4\beta_1\beta_{12}c_1^2\delta_1^2\delta_3^2(k_1+\beta_{21}V_2^{*''})^2(\beta_2k_2V_2^{*''}+ak_2)\\
&+2rc_1\delta_1\delta_3\beta_1\beta_{12}(k_1+\beta_{21}V_2^{*''})(\beta_1k_2+\beta_2\beta_{12}V_2^{*''}+a\beta_{12})(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''})\bigg)\Bigg]\Bigg],\\
V_2^{*''}=&\frac{1}{2\beta_2\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''})}\Bigg[\bigg\{r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''})-c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''})\\
&(\beta_2k_1+\beta_1\beta_{21}V_1^{*''}+a\beta_{21})\bigg\}-\sqrt{\Bigg[\bigg\{c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''})(\beta_2k_1+\beta_1\beta_{21}V_1^{*''}+a\beta_{21})\bigg\}^2}\\
&+\bigg\{r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''})\bigg\}^2+4r\beta_1V_1^{*''}p_{21}\beta_2\beta_{21}^2c_2\delta_2^2\delta_3(k_2+\beta_{12}V_1^{*''})^2\\
&+4r\beta_2^2k_1\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''})(p_2k_2\delta_3+p_{21}\beta_{12}\delta_2V_1^{*''})
\end{aligned}$$

$$- \Bigg(4\beta_2\beta_{21}c_2^2\delta_2^2\delta_3^2(k_2 + \beta_{12}V_1^{*''})^2(\beta_1 k_1 V_1^* + ak_1)$$
$$+ 2rc_2\delta_2\delta_3\beta_2\beta_{21}(k_2 + \beta_{12}V_1^{*''})(\beta_2 k_1 + \beta_1\beta_{21}V_1^{*''} + a\beta_{21})(p_2k_2\delta_3 + p_{21}\delta_2 V_1^{*''})\Bigg)\Bigg]\Bigg].$$

Similarly, this chronic coinfection equilibrium exists if the following conditions are satisfied. The conditions for V_1 and V_2 are respectively

$$r\beta_1\beta_{12}\frac{(p_1k_1\delta_3 + p_{12}\delta_1 V_2^{*''})}{(k_1 + \beta_{21}V_2^{*''})} \geq c_1\delta_1\delta_3(\beta_1 k_2 + \beta_2\beta_{12}V_2^{*''} + a\beta_{12}), \text{ and}$$
$$r\beta_2\beta_{21}\frac{(p_2k_2\delta_3 + p_{21}\delta_2 V_1^{*''})}{(k_2 + \beta_{12}V_1^{*''})} \geq c_2\delta_2\delta_3(\beta_2 k_1 + \beta_1\beta_{21}V_1^{*''} + a\beta_{21}).$$

Chronic coinfection equilibrium, $Q_2^{*'''}$

$$T^{*'''} = \frac{r}{\beta_1 V_1^{*'''} + \beta_2 V_2^{*'''} + a}, \ E_1^{*'''} = \frac{\beta_1 T^* V_1^{*'''}}{k_1 + \beta_{21}V_2^{*'''}}, \ E_2^{*'''} = \frac{\beta_2 T^* V_2^{*'''}}{k_2 + \beta_{12}V_1^{*'''}},$$
$$E_3^{*'''} = \frac{1}{k_3}(\beta_{12}E_2^{*'''}V_1^{*'''} + \beta_{21}E_1^{*'''}V_2^{*'''}), \ I_1^{*'''} = \frac{k_1}{\delta_1}E_1^{*'''}, \ I_2^{*'''} = \frac{k_2}{\delta_2}E_2^{*'''}, \ I_3^{*'''} = \frac{k_3}{\delta_3}E_3^{*'''},$$
$$V_1^{*'''} = \frac{1}{2\beta_1\beta_{12}c_1\delta_1\delta_3(k_1 + \beta_{21}V_2^{*'''})}\Bigg[\Bigg\{ - r\beta_1\beta_{12}(p_1k_1\delta_3 + p_{12}\delta_1 V_2^{*'''}) + c_1\delta_1\delta_3(k_1 + \beta_{21}V_2^{*'''})$$
$$(\beta_1 k_2 + \beta_2\beta_{12}V_2^{*'''} + a\beta_{12})\Bigg\} + \sqrt{\Bigg[\Bigg\{c_1\delta_1\delta_3(k_1 + \beta_{21}V_2^{*'''})(\beta_1 k_2 + \beta_2\beta_{12}V_2^{*'''} + a\beta_{12})\Bigg\}^2}$$
$$+ \Bigg\{r\beta_1\beta_{12}(p_1k_1\delta_3 + p_{12}\delta_1 V_2^{*'''})\Bigg\}^2 + 4r\beta_2 V_2^{*'''}p_{12}\beta_1\beta_{12}^2c_1\delta_1^2\delta_3(k_1 + \beta_{21}V_2^{*'''})^2$$
$$+ 4r\beta_1^2 k_2\beta_{12}c_1\delta_1\delta_3(k_1 + \beta_{21}V_2^{*'''})(p_1k_1\delta_3 + p_{12}\beta_{21}\delta_1 V_2^{*'''})$$
$$- \Bigg(4\beta_1\beta_{12}c_1^2\delta_1^2\delta_3^2(k_1 + \beta_{21}V_2^{*'''})^2(\beta_2 k_2 V_2^{*'''} + ak_2)$$
$$+ 2rc_1\delta_1\delta_3\beta_1\beta_{12}(k_1 + \beta_{21}V_2^{*'''})(\beta_1 k_2 + \beta_2\beta_{12}V_2^{*'''} + a\beta_{12})(p_1k_1\delta_3 + p_{12}\delta_1 V_2^{*'''})\Bigg)\Bigg]\Bigg],$$

$$
\begin{aligned}
V_2^{*'''} =& \frac{1}{2\beta_2\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*'''})}\Bigg[\Bigg\{-r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*'''})+c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*'''}) \\
&(\beta_2k_1+\beta_1\beta_{21}V_1^{*'''}+a\beta_{21})\Bigg\}+\sqrt{\Bigg[\Bigg\{c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*'''})(\beta_2k_1+\beta_1\beta_{21}V_1^{*'''}+a\beta_{21})\Bigg\}^2} \\
&+\Big\{r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*'''})\Big\}^2+4r\beta_1V_1^{*'''}p_{21}\beta_2\beta_{21}^2c_2\delta_2^2\delta_3(k_2+\beta_{12}V_1^{*'''})^2 \\
&+4r\beta_2^2k_1\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*'''})(p_2k_2\delta_3+p_{21}\beta_{12}\delta_2V_1^{*'''}) \\
&-\Bigg(4\beta_2\beta_{21}c_2^2\delta_2^2\delta_3^2(k_2+\beta_{12}V_1^{*'''})^2(\beta_1k_1V_1^{*'''}+ak_1) \\
&+2rc_2\delta_2\delta_3\beta_2\beta_{21}(k_2+\beta_{12}V_1^{*'''})(\beta_2k_1+\beta_1\beta_{21}V_1^{*'''}+a\beta_{21})(p_2k_2\delta_3+p_{21}\delta_2V_1^{*'''})\Bigg)\Bigg]\Bigg].
\end{aligned}
$$

Similarly, this chronic coinfection equilibrium exists if the following conditions are satisfied. The conditions for V_1 and V_2 are respectively

$$
\begin{aligned}
r\beta_1\beta_{12}\frac{(p_1k_1\delta_3+p_{12}\delta_1V_2^{*'''})}{(k_1+\beta_{21}V_2^{*'''})} &\le c_1\delta_1\delta_3(\beta_1k_2+\beta_2\beta_{12}V_2^{*'''}+a\beta_{12}),\ \text{and} \\
r\beta_2\beta_{21}\frac{(p_2k_2\delta_3+p_{21}\delta_2V_1^{*'''})}{(k_2+\beta_{12}V_1^{*'''})} &\le c_2\delta_2\delta_3(\beta_2k_1+\beta_1\beta_{21}V_1^{*'''}+a\beta_{21}).
\end{aligned}
$$

Chronic coinfection equilibrium, $Q_2^{*''''}$

$$
\begin{aligned}
T^{*''''} =& \frac{r}{\beta_1V_1^{*''''}+\beta_2V_2^{*''''}+a},\ E_1^{*''''}=\frac{\beta_1T^{*''''}V_1^{*''''}}{k_1+\beta_{21}V_2^{*''''}},\ E_2^{*''''}=\frac{\beta_2T^{*''''}V_2^{*''''}}{k_2+\beta_{12}V_1^{*''''}}, \\
E_3^{*''''} =& \frac{1}{k_3}(\beta_{12}E_2^{*''''}V_1^{*''''}+\beta_{21}E_1^{*''''}V_2^{*''''}),\ I_1^{*''''}=\frac{k_1}{\delta_1}E_1^{*''''},\ I_2^{*''''}=\frac{k_2}{\delta_2}E_2^{*''''},\ I_3^{*''''}=\frac{k_3}{\delta_3}E_3^{*''''},
\end{aligned}
$$

$$
\begin{aligned}
V_1^{*''''} =& \frac{1}{2\beta_1\beta_{12}c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''''})}\Bigg[\Bigg\{-r\beta_1\beta_{12}(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''''})+c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''''})\\
&(\beta_1k_2+\beta_2\beta_{12}V_2^{*''''}+a\beta_{12})\Bigg\}-\sqrt{\Bigg[\Bigg\{c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''''})(\beta_1k_2+\beta_2\beta_{12}V_2^{*''''}+a\beta_{12})\Bigg\}^2}\\
&+\Bigg\{r\beta_1\beta_{12}(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''''})\Bigg\}^2+4r\beta_2V_2^{*''''}p_{12}\beta_1\beta_{12}^2c_1\delta_1^2\delta_3(k_1+\beta_{21}V_2^{*''''})^2\\
&+4r\beta_1^2k_2\beta_{12}c_1\delta_1\delta_3(k_1+\beta_{21}V_2^{*''''})(p_1k_1\delta_3+p_{12}\beta_{21}\delta_1V_2^{*''''})\\
&-\Bigg(4\beta_1\beta_{12}c_1^2\delta_1^2\delta_3^2(k_1+\beta_{21}V_2^{*''''})^2(\beta_2k_2V_2^{*''''}+ak_2)\\
&+2rc_1\delta_1\delta_3\beta_1\beta_{12}(k_1+\beta_{21}V_2^{*''''})(\beta_1k_2+\beta_2\beta_{12}V_2^{*''''}+a\beta_{12})(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''''})\Bigg)\Bigg]\Bigg],\\
V_2^{*''''} =& \frac{1}{2\beta_2\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''''})}\Bigg[\Bigg\{-r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''''})+c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''''})\\
&(\beta_2k_1+\beta_1\beta_{21}V_1^{*''''}+a\beta_{21})\Bigg\}-\sqrt{\Bigg[\Bigg\{c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''''})(\beta_2k_1+\beta_1\beta_{21}V_1^{*''''}+a\beta_{21})\Bigg\}^2}\\
&+\Bigg\{r\beta_2\beta_{21}(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''''})\Bigg\}^2+4r\beta_1V_1^{*''''}p_{21}\beta_2\beta_{21}^2c_2\delta_2^2\delta_3(k_2+\beta_{12}V_1^{*''''})^2\\
&+4r\beta_2^2k_1\beta_{21}c_2\delta_2\delta_3(k_2+\beta_{12}V_1^{*''''})(p_2k_2\delta_3+p_{21}\beta_{12}\delta_2V_1^{*''''})\\
&-\Bigg(4\beta_2\beta_{21}c_2^2\delta_2^2\delta_3^2(k_2+\beta_{12}V_1^{*''''})^2(\beta_1k_1V_1^{*''''}+ak_1)\\
&+2rc_2\delta_2\delta_3\beta_2\beta_{21}(k_2+\beta_{12}V_1^{*''''})(\beta_2k_1+\beta_1\beta_{21}V_1^{*''''}+a\beta_{21})(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''''})\Bigg)\Bigg]\Bigg].
\end{aligned}
$$

Similarly, this chronic coinfection equilibrium exists if the following conditions are satisfied. The conditions for V_1 and V_2 are respectively

$$
\begin{aligned}
r\beta_1\beta_{12}\frac{(p_1k_1\delta_3+p_{12}\delta_1V_2^{*''''})}{(k_1+\beta_{21}V_2^{*''''})} &\leq c_1\delta_1\delta_3(\beta_1k_2+\beta_2\beta_{12}V_2^{*''''}+a\beta_{12}), \text{ and}\\
r\beta_2\beta_{21}\frac{(p_2k_2\delta_3+p_{21}\delta_2V_1^{*''''})}{(k_2+\beta_{12}V_1^{*''''})} &\leq c_2\delta_2\delta_3(\beta_2k_1+\beta_1\beta_{21}V_1^{*''''}+a\beta_{21}).
\end{aligned}
$$

1.2 Simulation results

Numerical simulations of infected cell populations from model 1 and 2 (according to main text) are compared in figure 1. Figure 1 shows that chronic infection with both virus is maintained by the superinfected cells in the presence of cell regeneration (green solid lines in the plots).

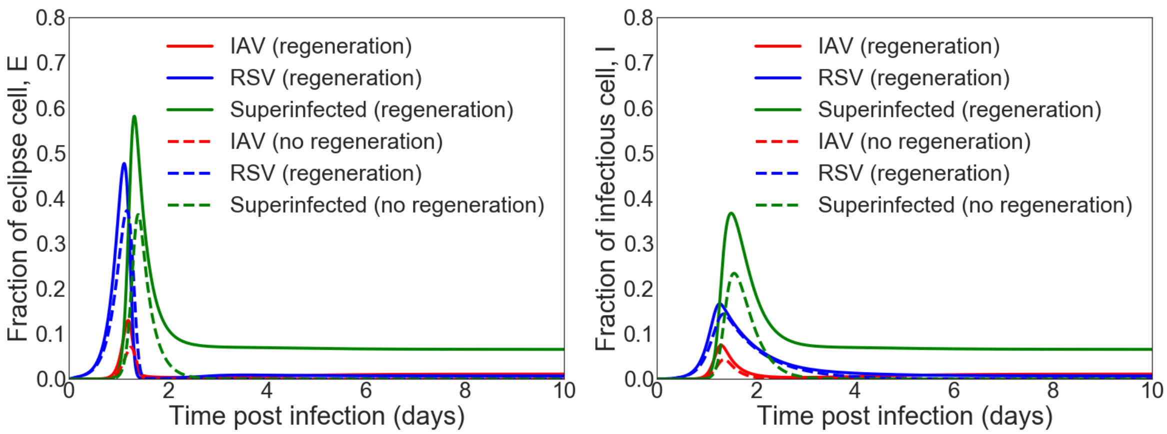

Figure 1: **Comparison of infected cell dynamics during superinfection with (model 1) and without (model 2) target cell regeneration.**

2 Sensitivity analysis

For sensitivity simulations, we calculated percentage change in model dynamics, i.e. viral peaks and infection durations for each superinfection scenario for models 1 (subsection 2.2) and 2 (subsection 2.1) by varying model parameters individually 10% higher and lower than their baseline values given in table 1 and used in figures 2, 3 and 6 in the main text. The effects that each parameter has on the viral dynamics are shown in figures 2, 3, 4, 5, 6 and 7. These analysis show that small changes in the production rates, p_1, p_{12}, p_2 and p_{21}, result in intermediate to small level changes in viral peak loads, while infection durations are mostly influenced by the viral clearance rates, c_1 and c_2, for each scenario.

2.1 Superinfection with no cell regeneration and death (model 2)

Viral peak load Model 2 solutions in figures 2 and 3 show percentage increase and decrease in viral peaks for 10% increase and decrease in model parameters, respectively. With 10% increase in the baseline value of IAV production rate, p_1, the model produces 0.9% higher peak load for influenza virus (figure 2, top row) while 10% decrease in the production rate leads to decline in the peak level (figure 3, top row). IAV peak increases and decreases by almost 0.6% higher than the normal value due to 10% increase and decrease in the ability of superinfected cells to produce IAV (p_{12}). Increases in IAV eclipse transition rate (k_1) leads to higher IAV peak level while increases in the rate of IAV clearance (c_1) and superinfected infectious cell death (δ_3) lower the IAV peak level. This model has no effect in response to change in superinfection rate, β_{21} and production rate, p_{21}, of RSV. Other parameters of IAV such as the infection rates (β_1 and β_{12}), infectious cell death rate (δ_1) and superinfected eclipse transition rate (k_3) slightly influence the IAV peak level. All RSV infection parameters such as β_2, k_2, p_2, c_2, δ_2 have negligible impacts on IAV peak load. Perturbation in the RSV production rate (p_2) elevates the RSV peak load by 2% higher than the normal level. However, the RSV peak load also increases for increase in the other RSV parameters such as β_2, k_2, p_{21}, it declines in response to increase in the RSV clearance rate (c_2). In addition, if the infection rate of IAV is increased, the peak level of RSV decreases by 1%. All other parameters cause slight change in the model dynamics.

Coinfection duration Model 2 solutions in figures 4 and 5 show percentage change in infection durations for 10% increase and decrease in model parameters, respectively.

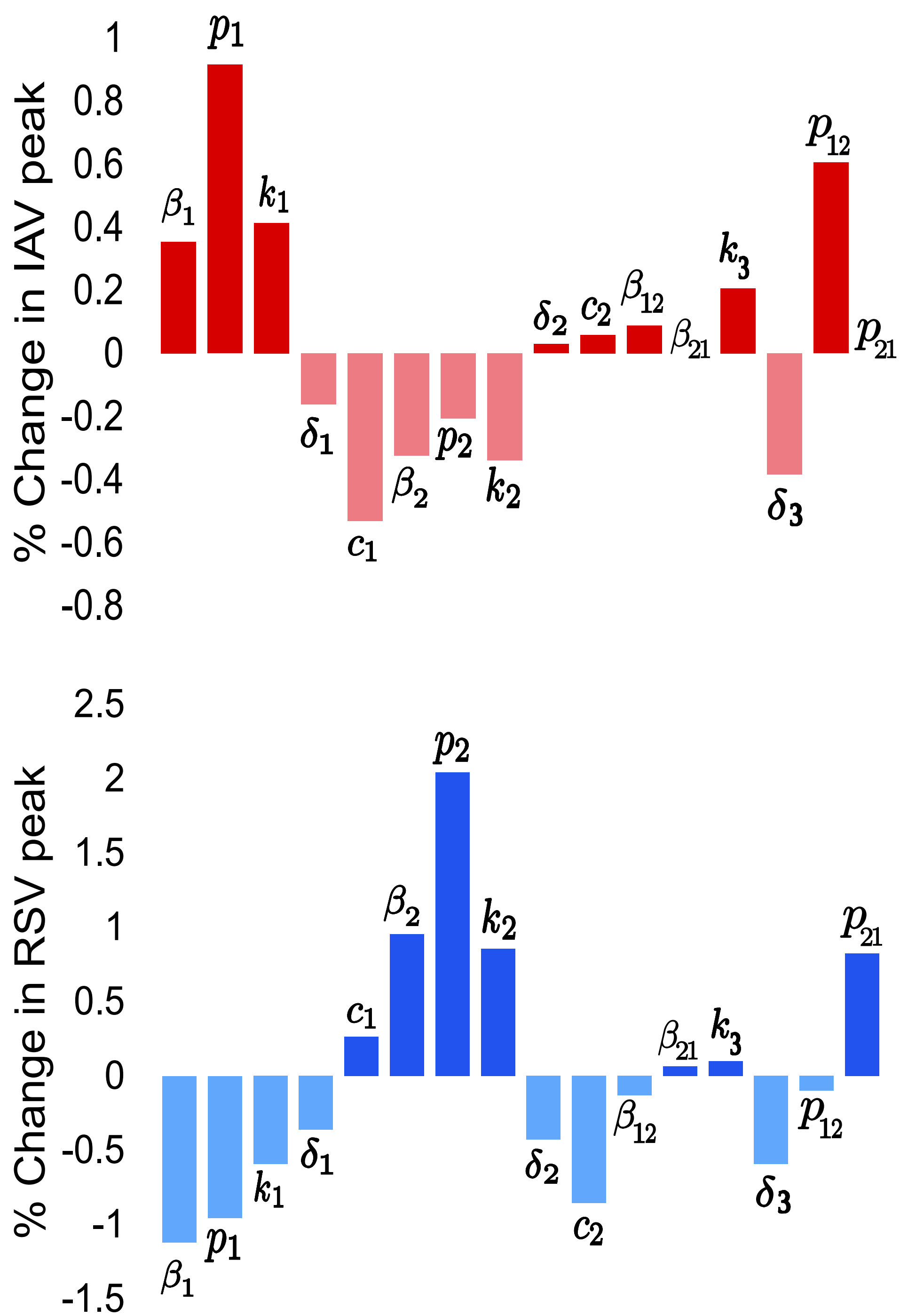

Figure 2: **Sensitivity analysis of superinfection model with no cell regeneration and death for viral peak load; model 2, main text.** Percentage increase in IAV and RSV peak load is calculated for 10% increased parameter values from the baseline values.

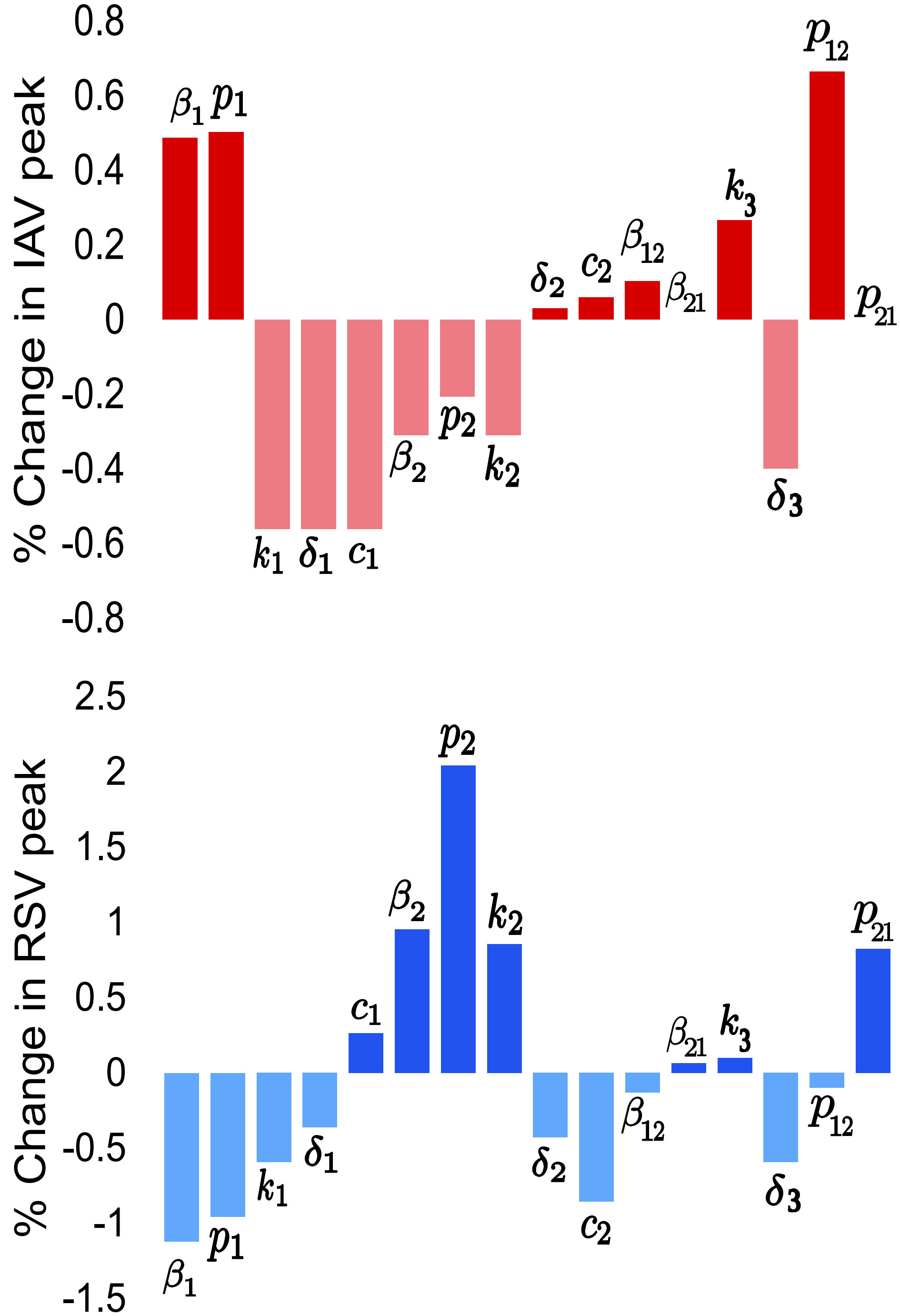

Figure 3: **Sensitivity analysis of superinfection model with no cell regeneration and death for viral peak load; model 2, main text.** Percentage decrease in IAV and RSV peak load is calculated for 10% decreased parameter values from the baseline values.

Decreases in the viral clearances rates (c_1 and c_2) lead to prolong the single and coinfection durations (figures 5) while increasing the clearance rates decrease the durations with less amount (figure 4). Only increase in the superinfection production rate, p_{12}, results in longer coinfection duration. Among the parameters that characterize superinfection, the slower eclipse transition rate (k_3) and superinfection infectious cell death (δ_3) change the infection durations. In this model the coinfection duration is mostly dominated by the IAV dynamics.

2.2 Superinfection with cell regeneration and cell death (model 1)

Model 1 solutions in figures 6 and 7 show percentage change in viral peaks for 10% increase and decrease in model parameters, respectively. The viral peaks are similarly influenced by the model parameters as were found in the previous model analysis (model 2, main text). In this model (model 1, main text) changes in the model parameters have no effect on the infection durations.

3 Octave code for generating solutions to Figure 2, 3 and 6

```
#!/usr/bin/octave
global par;

function xdot = superinfection(x,t)

global par;
```

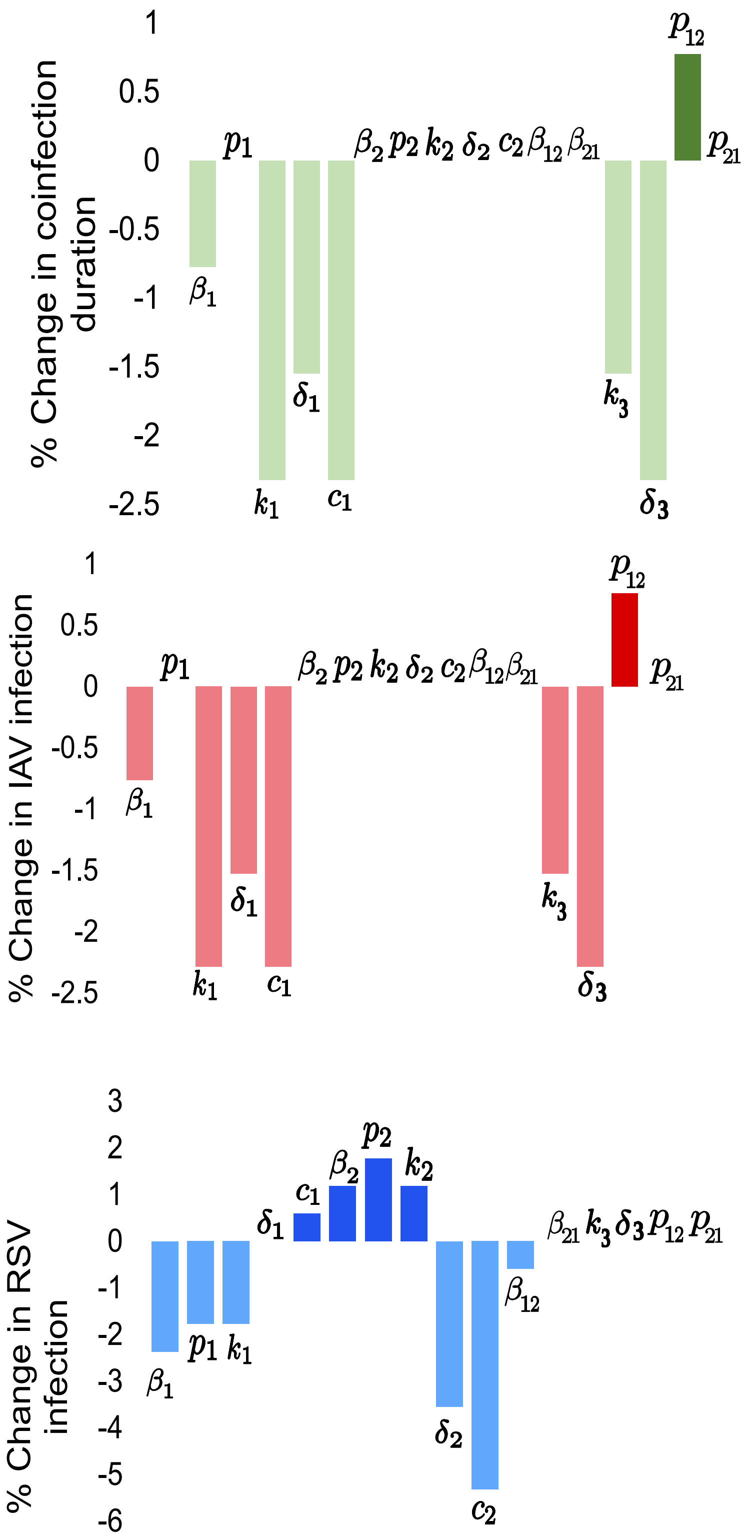

Figure 4: **Sensitivity analysis of superinfection model with no cell regeneration and death for coinfection and single infection durations; model 2, main text.** Percentage increase in IAV and RSV single viral infection duration and coinfection are calculated for 10% increased parameter values from the baseline values.

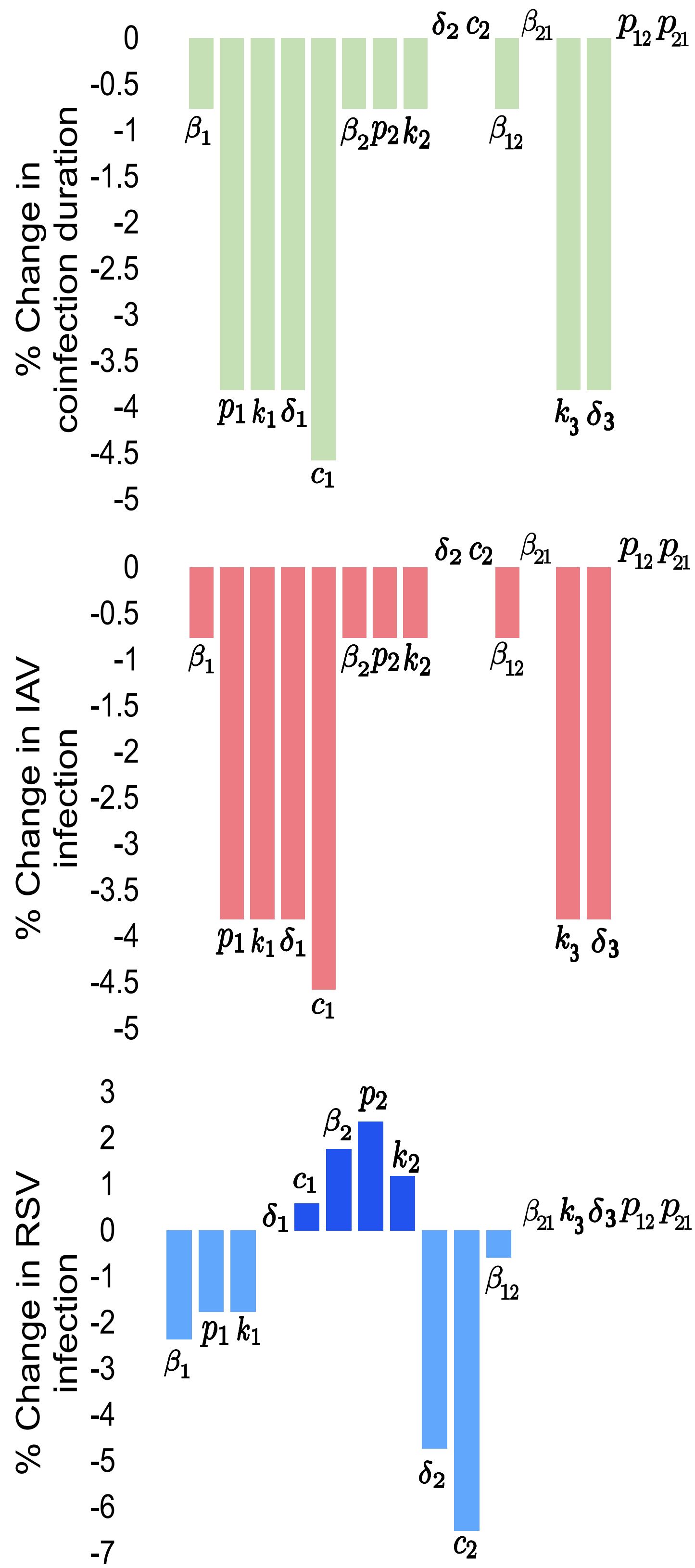

Figure 5: **Sensitivity analysis of superinfection model with no cell regeneration and death for coinfection and single infection duration; model 2, main text.** Percentage decrease in IAV and RSV single viral infection duration and coinfection are calculated for 10% decreased parameter values from the baseline values.

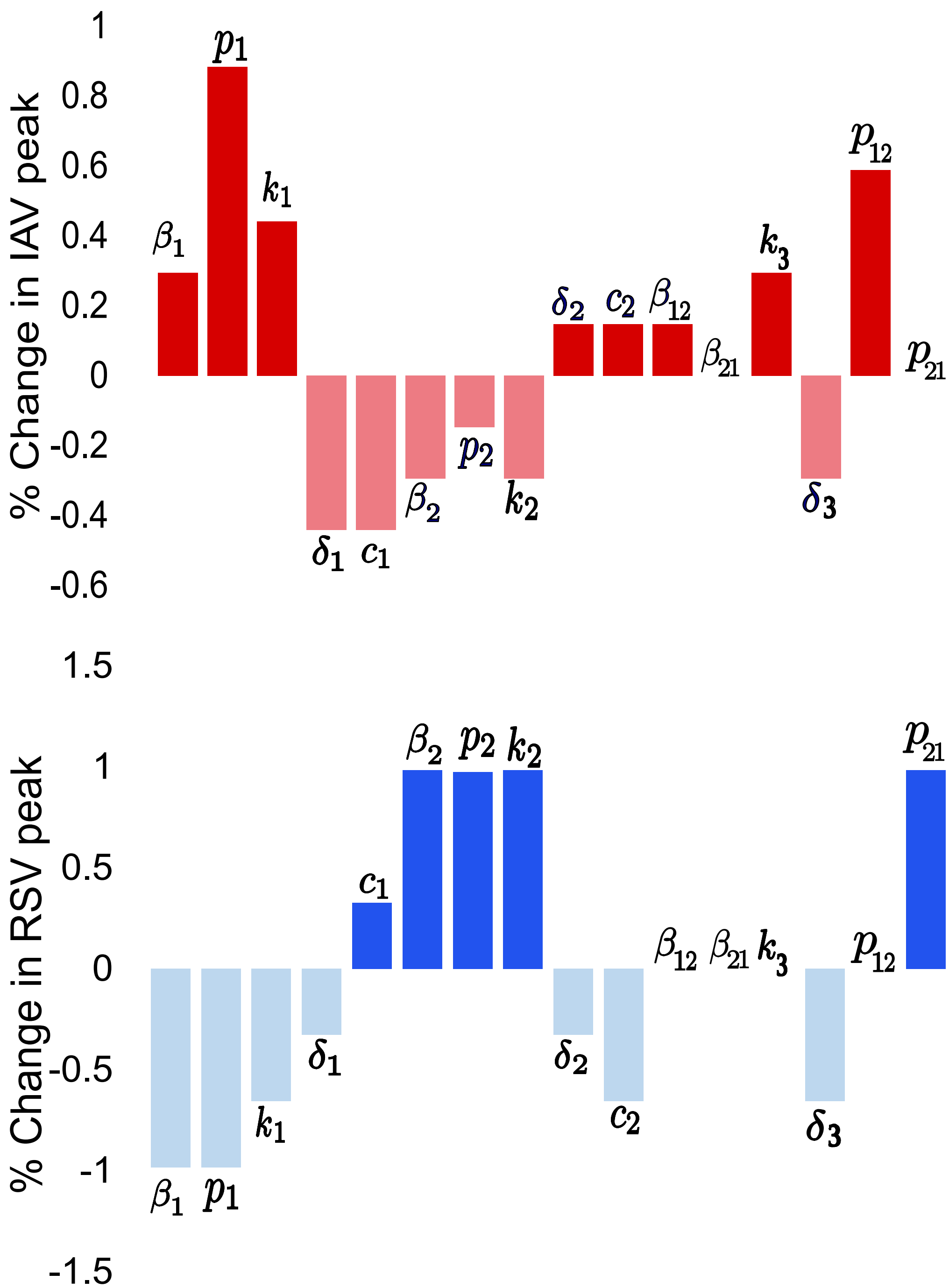

Figure 6: **Sensitivity analysis of superinfection model with cell regeneration and cell death for peak viral load; model 1, main text.** Percentage increase in IAV and RSV peak load is calculated for 10% increased parameter values from the baseline values.

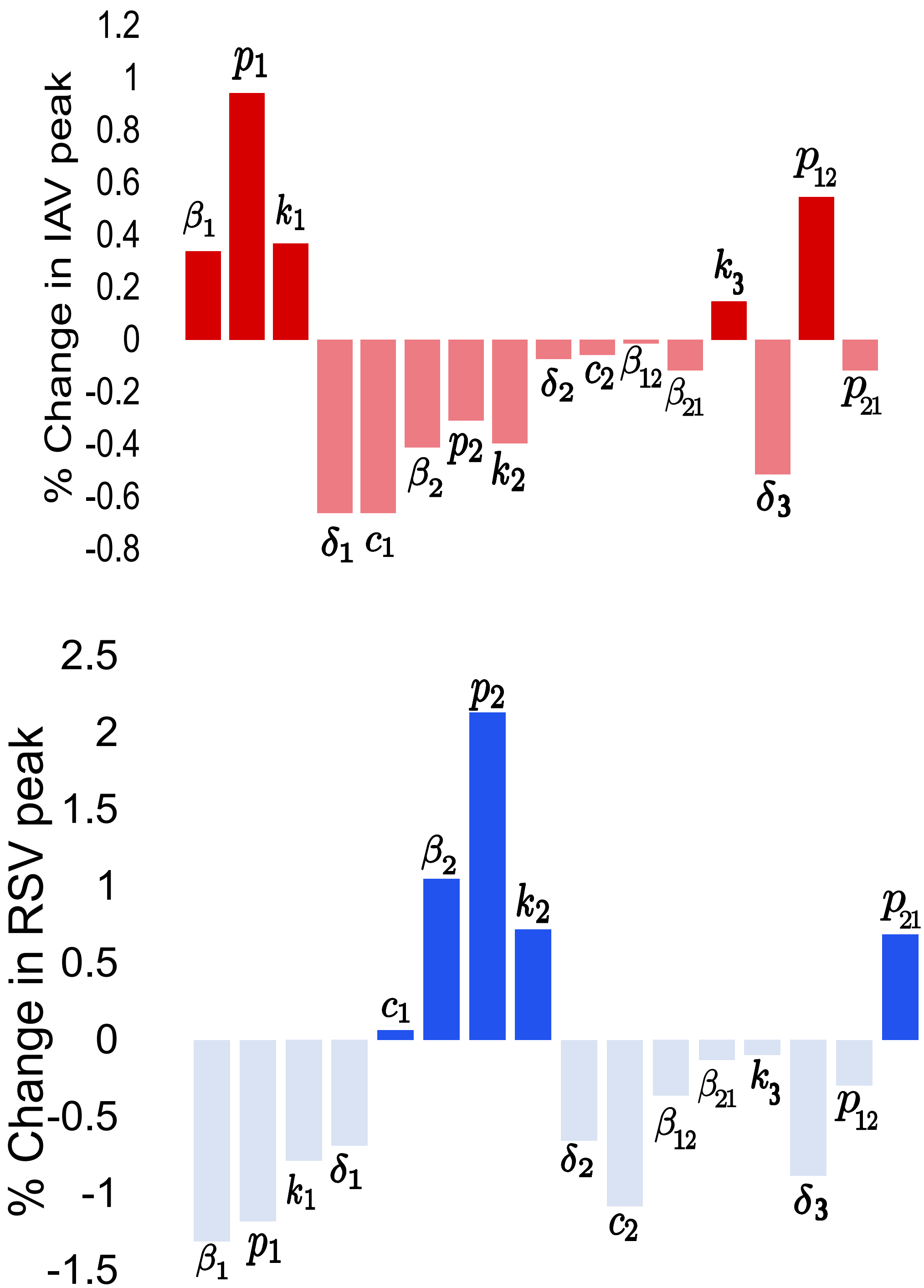

Figure 7: **Sensitivity analysis of superinfection model with cell regeneration and cell death for viral peak load; model 1, main text.** Percentage decrease in IAV and RSV peak load is calculated for 10% decreased parameter values from the baseline values.

```
b_1=par(1); k_1=par(2); d_1=par(3); p_1=par(4); c_1=par(5);
b_2=par(6); k_2=par(7); d_2=par(8); p_2=par(9); c_2=par(10);
k_3=par(11); d_3 =par(12); p_12=par(13); p_21=par(14); r=par(15);

    T = 1; E_1 = 2; E_2 = 3; E_3 = 4; I_1 = 5; I_2 = 6; I_3 = 7;
    D_1 = 8; D_2 = 9; D_3 = 10; V_1 = 11; V_2 = 12;

     xdot = zeros(12,1);
     xdot(T) = -(b_1)*x(V_1)*x(T)-(b_2)*x(V_2)*x(T)+r;
     xdot(E_1) = (b_1)*x(V_1)*x(T)-(k_1)*x(E_1)-(b_2)*x(E_1)*x(V_2);
     xdot(E_2) = (b_2)*x(V_2)*x(T)-(k_2)*x(E_2)-(b_1)*x(E_2)*x(V_1);
     xdot(E_3) = (b_2)*x(E_1)*x(V_2)+(b_1)*x(E_2)*x(V_1)-(k_3)*x(E_3);
     xdot(I_1) = (k_1)*x(E_1) - (d_1)*x(I_1);
     xdot(I_2) = (k_2)*x(E_2) - (d_2)*x(I_2);
     xdot(I_3) = (k_3)*x(E_3) - (d_3)*x(I_3);
     xdot(D_1) = (d_1)*x(I_1);
     xdot(D_2) = (d_2)*x(I_2);
     xdot(D_3) = (d_3)*x(I_3);
     xdot(V_1) = (p_1)*x(I_1)+(p_12)*x(I_3)- (c_1)*x(V_1);
     xdot(V_2) = (p_2)*x(I_2)+(p_21)*x(I_3)- (c_2)*x(V_2);

endfunction

# Open a file for superinfection model solution
fd = fopen("Vtiter_IAVRSV.dat","w");
# Open a file for superinfection with cell regeneration model solution
```

```
#fdr = fopen("Vtiter_IAVRSV_r.dat","w");

# Model parameters
#b1  k1  d1 p1  c1
#Flu :82.73e-7 4.2 4.2 0.12e9 4.03
#b2  k2  d2   p2   c2
#rsv : 0.0308 1.272 1.272 7645.649 1.272

# Model parameters for superinfection model
#b1  k1  d1 p1  c1  b2  k2  d2   p2   c2 k3=k1 d3=d1 p12=p1 p21=p2
par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272
7645.649 1.272 4.2 4.2 0.12e9 7645.649];

# Model parameters for superinfection model with cell regeneration model
#par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272
7645.649 1.272 4.2 4.2 0.12e9 7645.649 0.033];

# Initial conditions
x0 = [1 zeros(1,9) 1.0 1.0];

# Solve model for untreated case
t = [0:0.01:100]';
y= lsode("superinfection",x0',t);

fprintf(fd,"%g %g %g %g\n",[t y(:,1) y(:,2) y(:,3) y(:,4) y(:,5)
                                     y(:,6) y(:,7) y(:,11) y(:,12)]');
```

```
#fprintf(fdr,"%g %g %g %g\n",[t y(:,1) y(:,2) y(:,3) y(:,4) y(:,5)
                     y(:,6) y(:,7) y(:,11) y(:,12)]');

fclose(fd);
#fclose(fdr);
```

4 Octave code for generating solutions to Figure 4 and 7

```
#!/usr/bin/octave
global par;
# Set of differential equations
function xdot = superinfection(x,t)

global par;
b_1=par(1); k_1=par(2); d_1=par(3); p_1=par(4); c_1=par(5);
b_2=par(6); k_2=par(7);  d_2=par(8); p_2=par(9); c_2=par(10);
k_3=par(11); d_3 =par(12);  p_12=par(13); p_21=par(14);#r=par(15);

    T = 1; E_1 = 2; E_2 = 3; E_3 = 4; I_1 = 5; I_2 = 6; I_3 = 7;
    D_1 = 8; D_2 = 9; D_3 = 10; V_1 = 11; V_2 = 12;

     xdot = zeros(12,1);
     xdot(T) = -(b_1)*x(V_1)*x(T)-(b_2)*x(V_2)*x(T);#+r;
     xdot(E_1) = (b_1)*x(V_1)*x(T)-(k_1)*x(E_1)-(b_2)*x(E_1)*x(V_2);
     xdot(E_2) = (b_2)*x(V_2)*x(T)-(k_2)*x(E_2)-(b_1)*x(E_2)*x(V_1);
```

```
    xdot(E_3) = (b_2)*x(E_1)*x(V_2)+(b_1)*x(E_2)*x(V_1)-(k_3)*x(E_3);
    xdot(I_1) = (k_1)*x(E_1) - (d_1)*x(I_1);
    xdot(I_2) = (k_2)*x(E_2) - (d_2)*x(I_2);
    xdot(I_3) = (k_3)*x(E_3) - (d_3)*x(I_3);
    xdot(D_1) = (d_1)*x(I_1);
    xdot(D_2) = (d_2)*x(I_2);
    xdot(D_3) = (d_3)*x(I_3);
    xdot(V_1) = (p_1)*x(I_1)+(p_12)*x(I_3)- (c_1)*x(V_1);
    xdot(V_2) = (p_2)*x(I_2)+(p_21)*x(I_3)- (c_2)*x(V_2);

endfunction

# Open a file
fd = fopen("tcoin_rp_IAVRSV.dat","w");

# Model parameters
#Flu :82.73e-7 4.2 4.2 0.12e9 4.03
#rsv : 0.0308 1.272 1.272 7645.649 1.272

rP12=logspace(0,10,100);
rP21=logspace(0,10,100);

for i=1:length(rP12)
for j=1:length(rP21)

#b1   k1  d1   p1   c1    b2   k2   d2   p2  c2 k3 d3 p12 p21
```

```
par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272
7645.649 1.272 4.2 4.2 rP12(i) rP21(j)];#0.033];

# Initial conditions
x0 = [1.0 zeros(1,9) 1.0 1.0];

# Solve model for untreated case
t = [0:0.01:100]';
y= lsode("superinfection",x0',t);

#Find coinfection time for both viruses
V1=find(y(:,11)>1.0);
V2=find(y(:,12)>1.0);

if isempty(V1) | isempty(V2)
 tcoin(i,j) = 0;
else
 tcoin(i,j) = (min([V1(end),V2(end)])- max([V1(1),V2(1)]))/100;
end
fprintf(fd,"%g %g %g\n",[rP12(i) rP21(j) tcoin(i,j)]');
endfor;
endfor;

#Draw Contour plot of the coinfection duration
pcolor(tcoin)
colorbar(tcoin)
```

```
drawnow
pause(10)
fclose(fd);
```

5 Octave code for generating solutions to Figure 5

```
#!/usr/bin/octave
global par;
function xdot = superinfection(x,t)
global par;
b_1=par(1); k_1=par(2); d_1=par(3); p_1=par(4); c_1=par(5);
b_2=par(6); k_2=par(7);  d_2=par(8); p_2=par(9); c_2=par(10);
k_3=par(11); d_3 =par(12);  p_12=par(13); p_21=par(14);

   T = 1; E_1 = 2; E_2 = 3; E_3 = 4; I_1 = 5; I_2 = 6; I_3 = 7;
   D_1 = 8; D_2 = 9; D_3 = 10; V_1 = 11; V_2 = 12;

     xdot = zeros(12,1);
     xdot(T) = -(b_1)*x(V_1)*x(T)-(b_2)*x(V_2)*x(T);
     xdot(E_1) = (b_1)*x(V_1)*x(T)-(k_1)*x(E_1)-(b_2)*x(E_1)*x(V_2);
     xdot(E_2) = (b_2)*x(V_2)*x(T)-(k_2)*x(E_2)-(b_1)*x(E_2)*x(V_1);
     xdot(E_3) = (b_2)*x(E_1)*x(V_2)+(b_1)*x(E_2)*x(V_1)-(k_3)*x(E_3);
     xdot(I_1) = (k_1)*x(E_1) - (d_1)*x(I_1);
     xdot(I_2) = (k_2)*x(E_2) - (d_2)*x(I_2);
     xdot(I_3) = (k_3)*x(E_3) - (d_3)*x(I_3);
     xdot(D_1) = (d_1)*x(I_1);
```

```
     xdot(D_2) = (d_2)*x(I_2);
     xdot(D_3) = (d_3)*x(I_3);
     xdot(V_1) = (p_1)*x(I_1)+(p_1)*x(I_3)- (c_1)*x(V_1);
     xdot(V_2) = (p_2)*x(I_2)+(p_2)*x(I_3)- (c_2)*x(V_2);

endfunction

# Open a file
fd1 = fopen("V1max_rkd_IAVRSV.dat","w");
fd2 = fopen("V2max_rkd_IAVRSV.dat","w");
#fd3 = fopen("VmaxRatio_rkd_IAVRSV.dat","w");

rk=linspace(0,10,100);
rd=linspace(0,10,100);

for i=1:length(rk)
for j=1:length(rd)

# Model parameters
# b1 k1 d1 p1 c1 b2 k2 d2   p2c2 k3 d3 #p12 p21

par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272
7645.649 1.272 rk(i) rd(j) 0.12e9 7645.649];

# Initial conditions
# T E I D V
```

```
x0 = [1.0 zeros(1,9) 1.0 1.0];

# Solve model for untreated case
t = [0:0.01:100]’;
y= lsode("superinfection",x0’,t);

V1max(i,j)=max(y(:,11));
V2max(i,j)=max(y(:,12));
#VmaxRatio(i,j)=max(y(:,12))/max(y(:,11));

fprintf(fd1,"%g %g %g\n",[rk(i) rd(j) V1max(i,j)]’);
fprintf(fd2,"%g %g %g\n",[rk(i) rd(j) V2max(i,j)]’);
#fprintf(fd3,"%g %g %g\n",[rk(i) rd(j) VmaxRatio(i,j)]’);

endfor;
endfor;

fclose(fd1);
fclose(fd2);
#fclose(fd3);
```

6 Octave code for generating solutions to Figure 8

```
#!/usr/bin/octave
global par;
# Set of differential equations
```

```
function xdot = superinfection_r(x,t)

global par;
b_1=par(1); k_1=par(2); d_1=par(3); p_1=par(4); c_1=par(5);
b_2=par(6); k_2=par(7); d_2=par(8); p_2=par(9); c_2=par(10);
k_3=par(11); d_3 =par(12); p_12=par(13); p_21=par(14); r=par(15);


T = 1; E_1 = 2; E_2 = 3; E_3 = 4; I_1 = 5; I_2 = 6; I_3 = 7;
D_1 = 8; D_2 = 9; D_3 = 10; V_1 = 11; V_2 = 12;

     xdot = zeros(12,1);
     xdot(T) = -(b_1)*x(V_1)*x(T)-(b_2)*x(V_2)*x(T)+r;
     xdot(E_1) = (b_1)*x(V_1)*x(T)-(k_1)*x(E_1)-(b_2)*x(E_1)*x(V_2);
     xdot(E_2) = (b_2)*x(V_2)*x(T)-(k_2)*x(E_2)-(b_1)*x(E_2)*x(V_1);
     xdot(E_3) = (b_2)*x(E_1)*x(V_2)+(b_1)*x(E_2)*x(V_1)-(k_3)*x(E_3);
     xdot(I_1) = (k_1)*x(E_1) - (d_1)*x(I_1);
     xdot(I_2) = (k_2)*x(E_2) - (d_2)*x(I_2);
     xdot(I_3) = (k_3)*x(E_3) - (d_3)*x(I_3);
     xdot(D_1) = (d_1)*x(I_1);
     xdot(D_2) = (d_2)*x(I_2);
     xdot(D_3) = (d_3)*x(I_3);
     xdot(V_1) = (p_1)*x(I_1)+(p_12)*x(I_3)- (c_1)*x(V_1);
     xdot(V_2) = (p_2)*x(I_2)+(p_21)*x(I_3)- (c_2)*x(V_2);

endfunction
```

```
# Open a file
fd = fopen("r_IAVRSV.dat","w");

# Model parameters
#Flu :82.73e-7 4.2 4.2 0.12e9 4.03
#rsv : 0.0308 1.272 1.272 7645.649 1.272

rpoints=linspace(0,0.1,1000);
for i=1:length(rpoints)

#b1   k1  d1   p1   c1    b2   k2   d2   p2  c2 k3 d3 p12 p21
par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272 7645.649
1.272 4.2 4.2 0.12e9 7645.649 rpoints(i)];

# Initial conditions
# T E I D V
x0 = [1.0 zeros(1,9) 1.0 1.0];

# Solve model for untreated case
t = [20:21:1000]’;
y= lsode("superinfection_r",x0’,t);
endfor;

#Find viral load as a fucntion of cell regeneration
fprintf(fd,"%g %g %g\n",[rpoints(i) y(:,11) y(:,12)]’);
```

```
fclose(fd);
```

7 Octave code for generating solutions to Figure 9

```
#!/usr/bin/octave
global par;
# Set of differential equations
function xdot = superinfection(x,t)

global par;

b_1=par(1); k_1=par(2); d_1=par(3); p_1=par(4); c_1=par(5);
b_2=par(6); k_2=par(7); d_2=par(8); p_2=par(9); c_2=par(10);
k_3=par(11); d_3 =par(12); p_12=par(13); p_21=par(14); r=par(15);

T = 1; E_1 = 2; E_2 = 3; E_3 = 4; I_1 = 5; I_2 = 6; I_3 = 7;
D_1 = 8; D_2 = 9; D_3 = 10; V_1 = 11; V_2 = 12;

     xdot = zeros(12,1);
     xdot(T) = -(b_1)*x(V_1)*x(T)-(b_2)*x(V_2)*x(T)+r;
     xdot(E_1) = (b_1)*x(V_1)*x(T)-(k_1)*x(E_1)-(b_2)*x(E_1)*x(V_2);
     xdot(E_2) = (b_2)*x(V_2)*x(T)-(k_2)*x(E_2)-(b_1)*x(E_2)*x(V_1);
     xdot(E_3) = (b_2)*x(E_1)*x(V_2)+(b_1)*x(E_2)*x(V_1)-(k_3)*x(E_3);
     xdot(I_1) = (k_1)*x(E_1) - (d_1)*x(I_1);
     xdot(I_2) = (k_2)*x(E_2) - (d_2)*x(I_2);
     xdot(I_3) = (k_3)*x(E_3) - (d_3)*x(I_3);
```

```
    xdot(D_1) = (d_1)*x(I_1);
    xdot(D_2) = (d_2)*x(I_2);
    xdot(D_3) = (d_3)*x(I_3);
    xdot(V_1) = (p_1)*x(I_1)+(p_12)*x(I_3)- (c_1)*x(V_1);
    xdot(V_2) = (p_2)*x(I_2)+(p_21)*x(I_3)- (c_2)*x(V_2);

endfunction


# Open a file
fd = fopen("data/FluFirstRSV24hoursDelay.dat","w");

# Model parameters
#b1   k1  d1   p1   c1    b2   k2   d2   p2  c2 k3 d3 p12 p21
par= [82.73e-7 4.2 4.2 0.12e9 4.03 0.0308 1.272 1.272 7645.649
1.272 4.2 4.2 0.12e9 7645.649 0.033];

# Initial conditions
x0 = [1.0 zeros(1,9) 1.0 0];

# Solve model for untreated case
t = [ 0:0.01:1.0 ]';
y1 = lsode("Superinfection",x0',t);

x0 = y1(end,:);
x0(12) = 1.0;
```

```
t = [ 1.0:0.01:100 ]';
y2= lsode("Superinfection",x0',t);
t = [0:0.01:100]';
y=[y1(1:end-1,:);y2];

fprintf(fd,"%g %g %g\n",[t y(:,11) y(:,12)]');
fclose(fd);
```