Neuraminidase inhibitor treatment of seasonal and severe influenza

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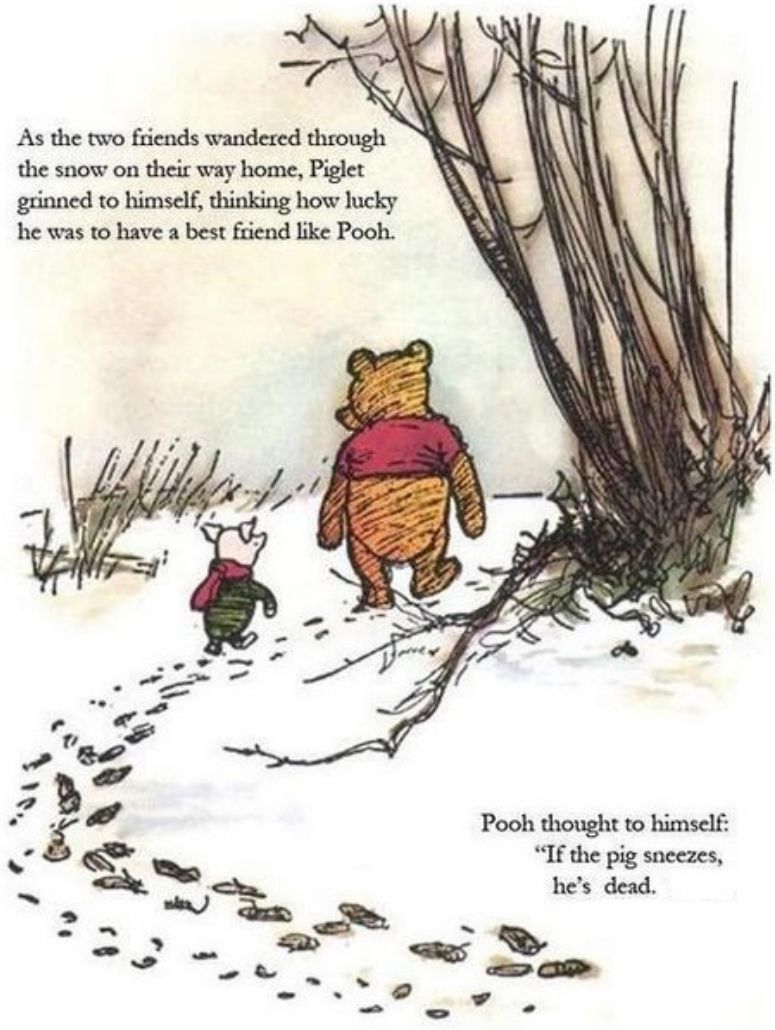
Disclaimer

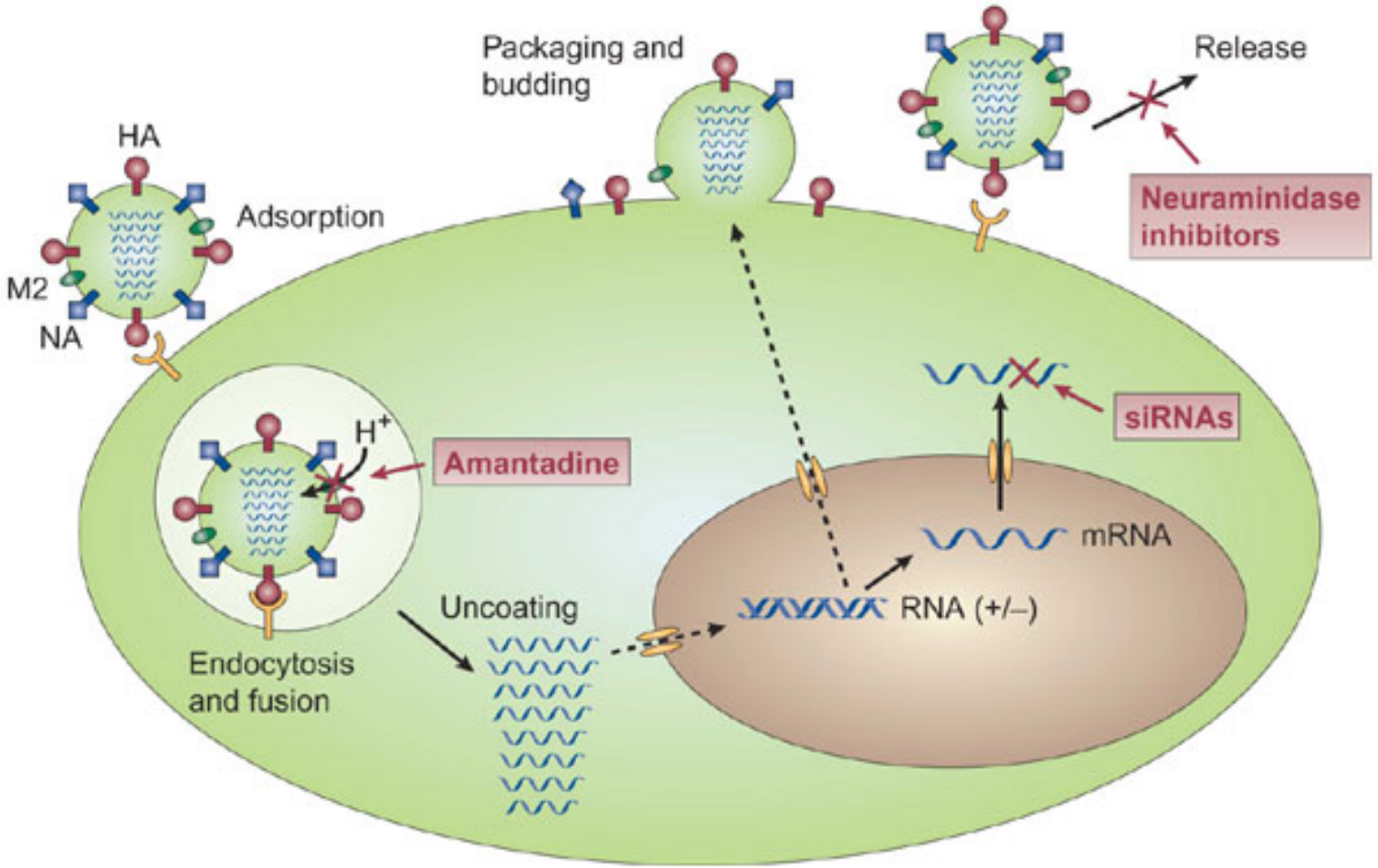
This work was performed under contract for F. Hoffmann-LaRoche.

Influenza Infection

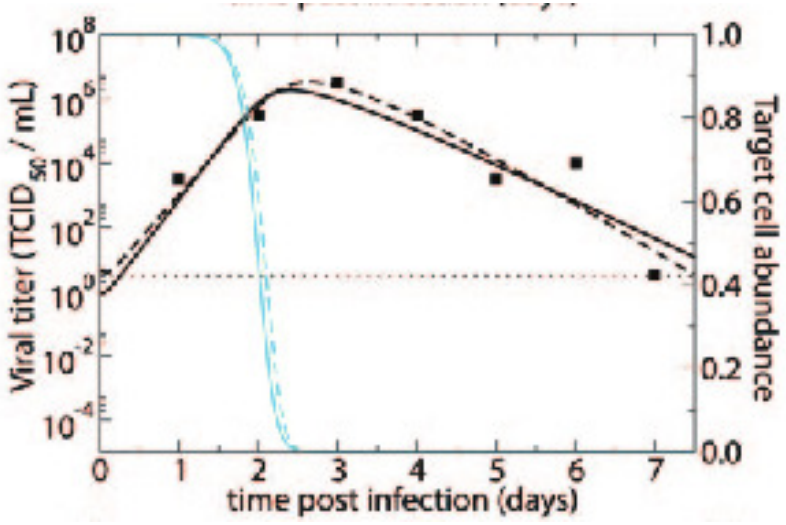
- Influenza is a viral infection that annually causes $\sim$5 million cases of severe illness and 250,000-500,000 deaths world-wide.
- In Canada, 700-2500 deaths annually are caused by influenza
- Occasional pandemic outbreaks cause even more illness and death



Influenza Virus



Seasonal Influenza

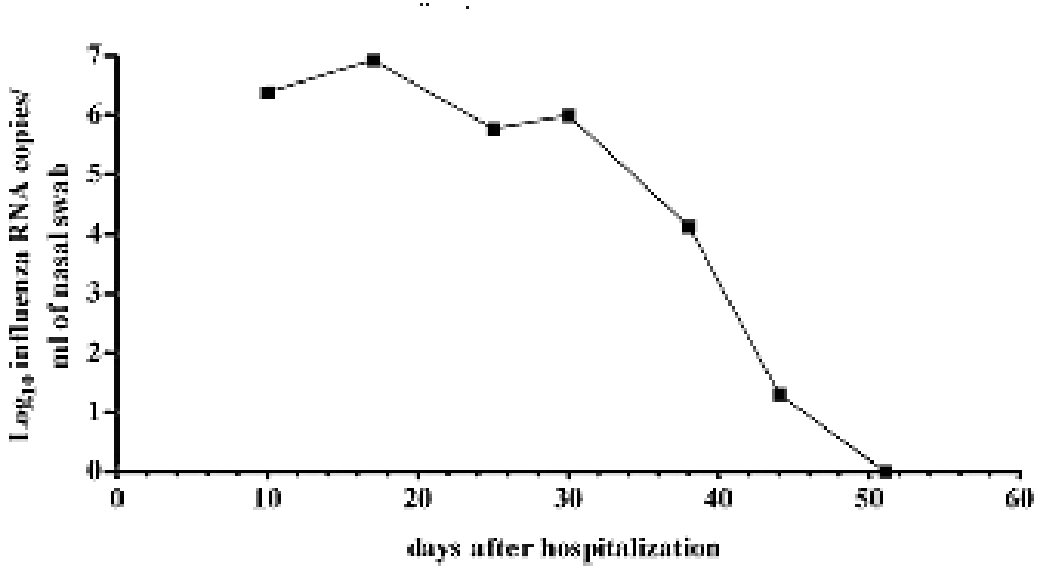


Baccam et al. J. Virol (2006)

$$\begin{aligned}
\frac{dT}{dt} &= -\beta TV \\
\frac{dE}{dt} &= \beta TV - kE \\
\frac{dI}{dt} &= kE - \delta I \\
\frac{dV}{dt} &= pI - cV \ ,
\end{aligned}$$

- Seasonal influenza typically lasts a few days and resolves without intervention
- Seasonal influenza dynamics are captured by a simple infection model

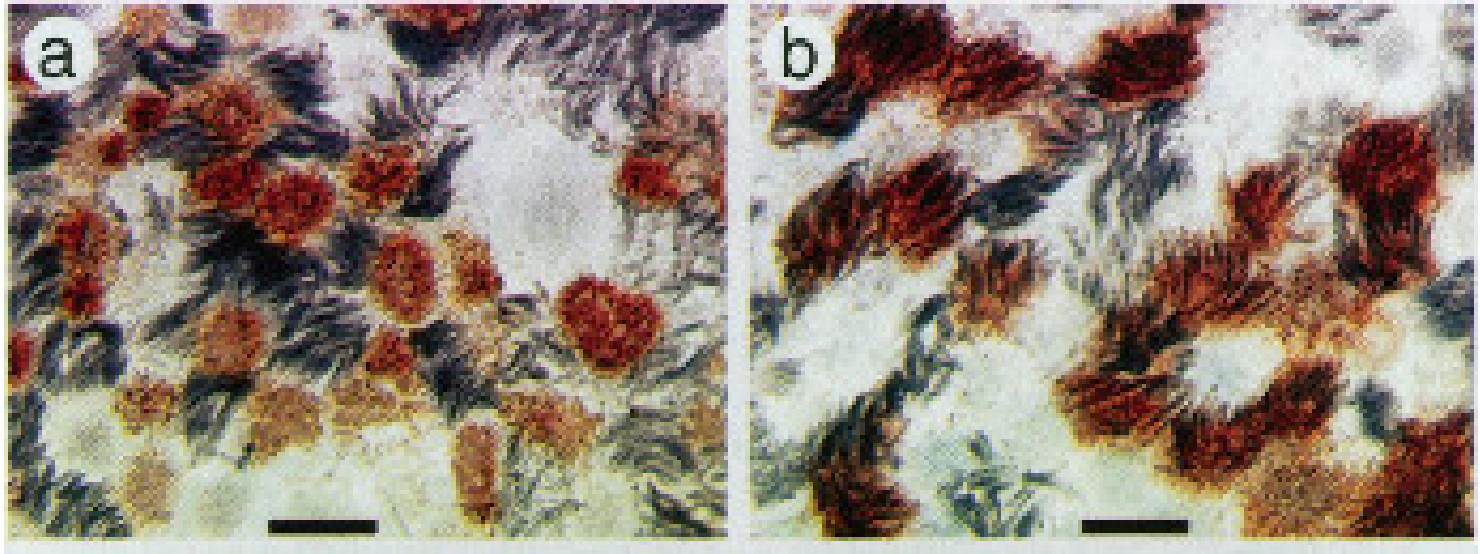
Severe Influenza



Campanini et al. J. Clin. Virol. (2010)

- Severe influenza is typically caused by new influenza strains, can last for weeks and has a higher mortality rate
- The simple infection model cannot capture these viral dynamics well

Cell tropism



Matrosovich et al. PNAS (2004)

- Human flu strains have adapted to the cell receptors that dominate in the human respiratory tract
- Novel flu strains may still prefer to bind to cell receptors that dominate in other animals
- Cell tropism has been observed in avian flu (H5N1) and swine flu (H1N1)

Two target cell model

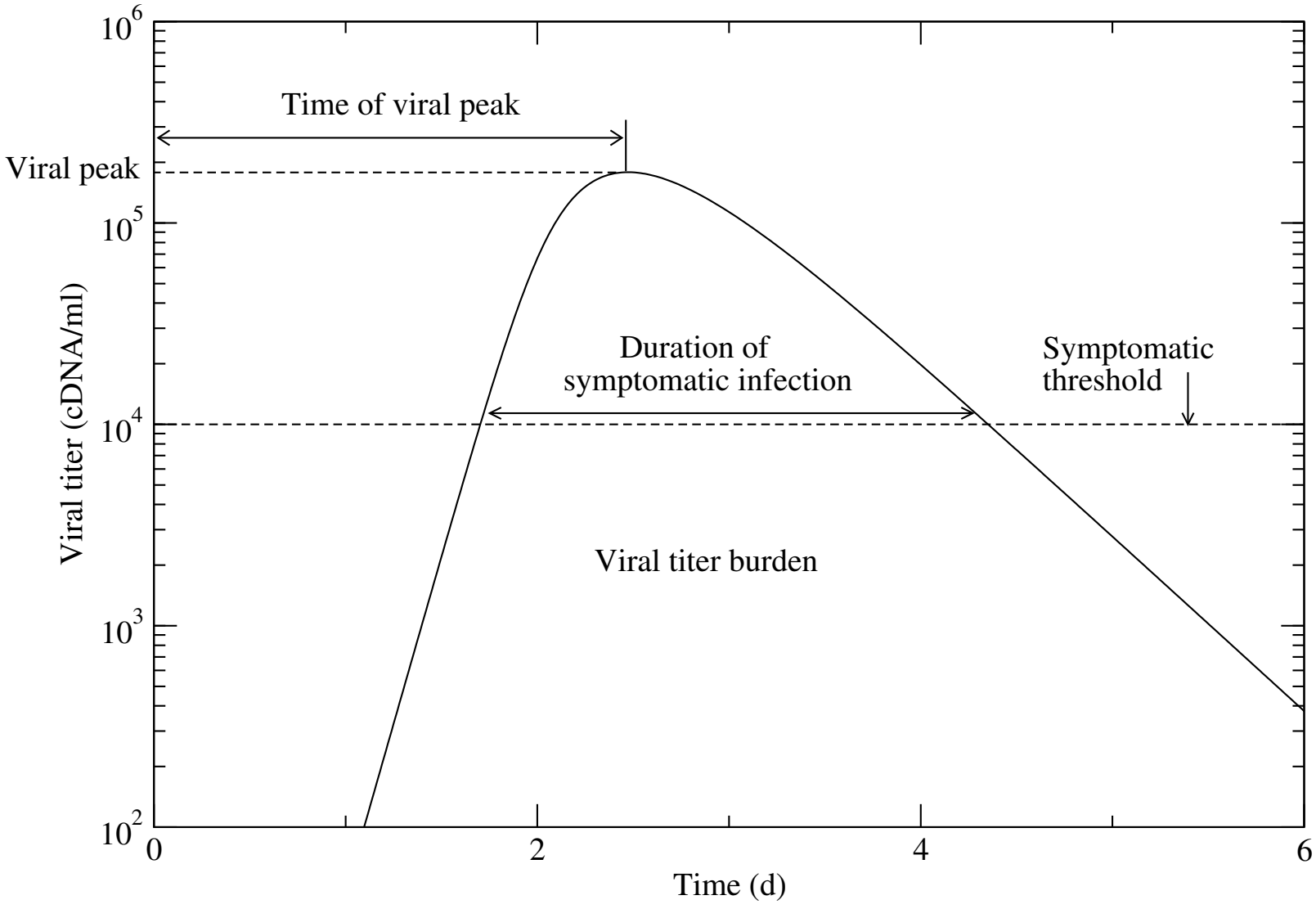
- Model is an extension of the simple infection model by including two target cell populations
- Viruses “prefer” one cell population over the other – one cell type is easier to infect than the other
- Once infected, cells of different types can produce different amounts of virus

Equations

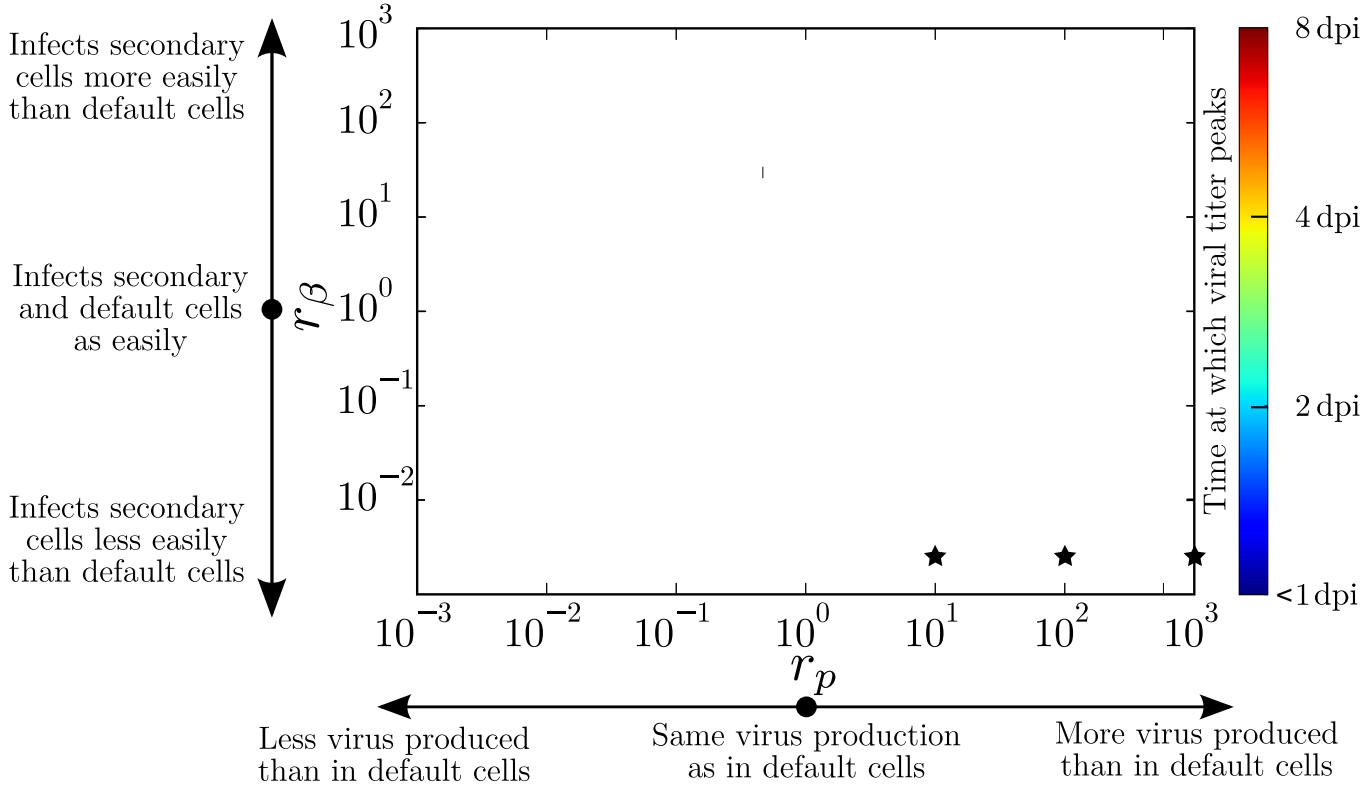
$$
\begin{aligned}
\text{Target cells}: \quad & \frac{\mathrm{d}T_d}{\mathrm{d}t} = -\beta T_d V && \frac{\mathrm{d}T_s}{\mathrm{d}t} = -r_\beta \beta T_s V \\
\text{Eclipse cells}: \quad & \frac{\mathrm{d}E_d}{\mathrm{d}t} = \beta T_d V - kE_d && \frac{\mathrm{d}E_s}{\mathrm{d}t} = r_\beta \beta T_s V - kE_s \\
\text{Infected cells}: \quad & \frac{\mathrm{d}I_d}{\mathrm{d}t} = kE_d - \delta I_d && \frac{\mathrm{d}I_s}{\mathrm{d}t} = kE_s - \delta I_s \\
\text{Virus}: \quad & \frac{\mathrm{d}V}{\mathrm{d}t} = pI_d + r_p pI_s - cV \ . &&
\end{aligned}
$$

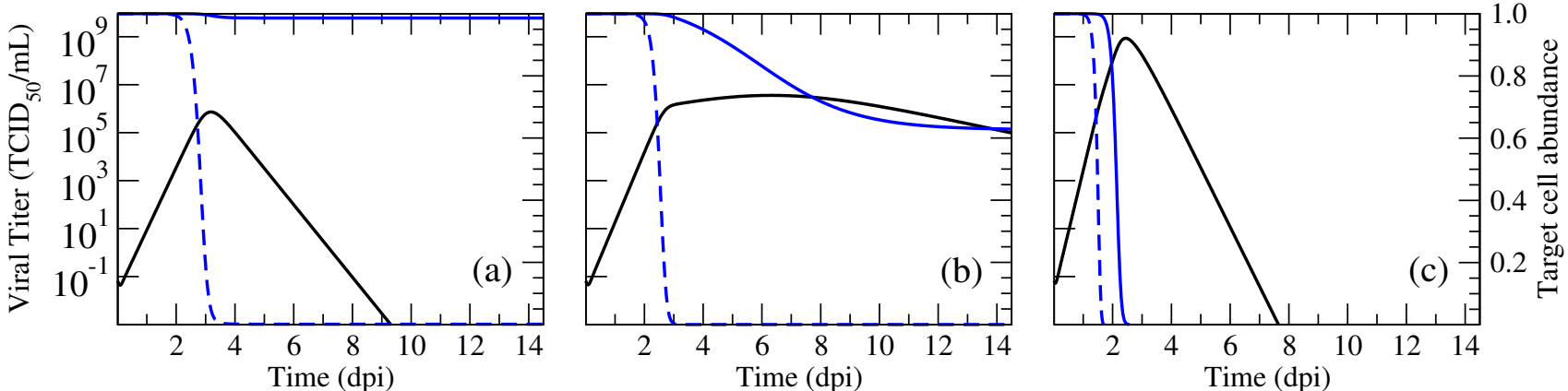
- Base parameters are from Baccam et al. for seasonal influenza
- Initial cell population is divided into r_T default cells and $(1 - r_T)$ secondary cells

Characterizing viral titer

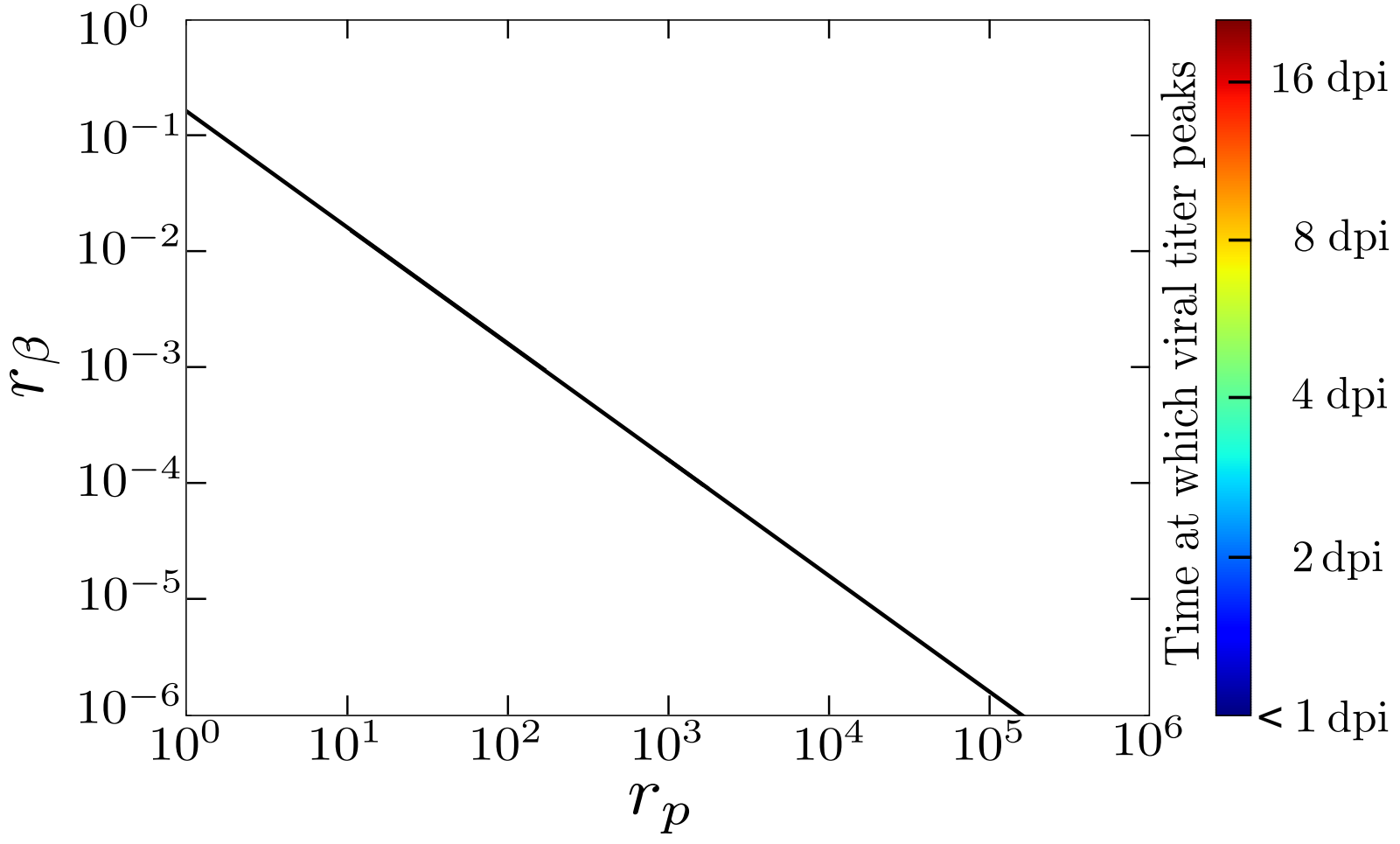


Viral peak

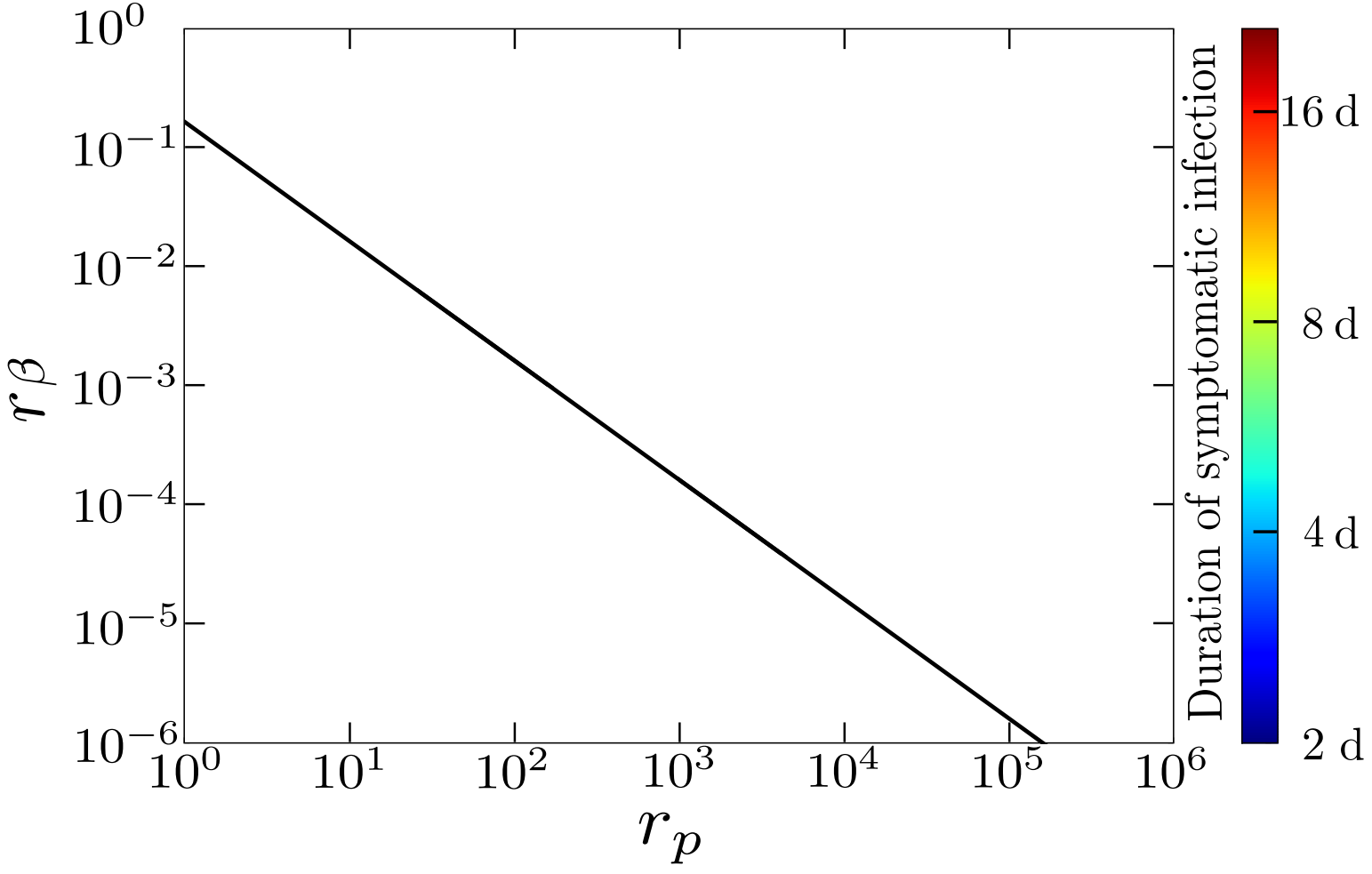

Infects secondary cells more easily than default cells
Infects secondary and default cells as easily
Infects secondary cells less easily than default cells
r_β
10^3
10^2
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-2}
10^{-1}
10^0
10^1
10^2
10^3
r_p
Time at which viral titer peaks
8 dpi
4 dpi
2 dpi
<1 dpi
Less virus produced than in default cells
Same virus production as in default cells
More virus produced than in default cells


Viral Titer (TCID$_{50}$/mL)
10^9
10^7
10^5
10^3
10^1
10^{-1}
(a)
(b)
(c)
2 4 6 8 10 12 14
Time (dpi)
Target cell abundance
1.0
0.8
0.6
0.4
0.2

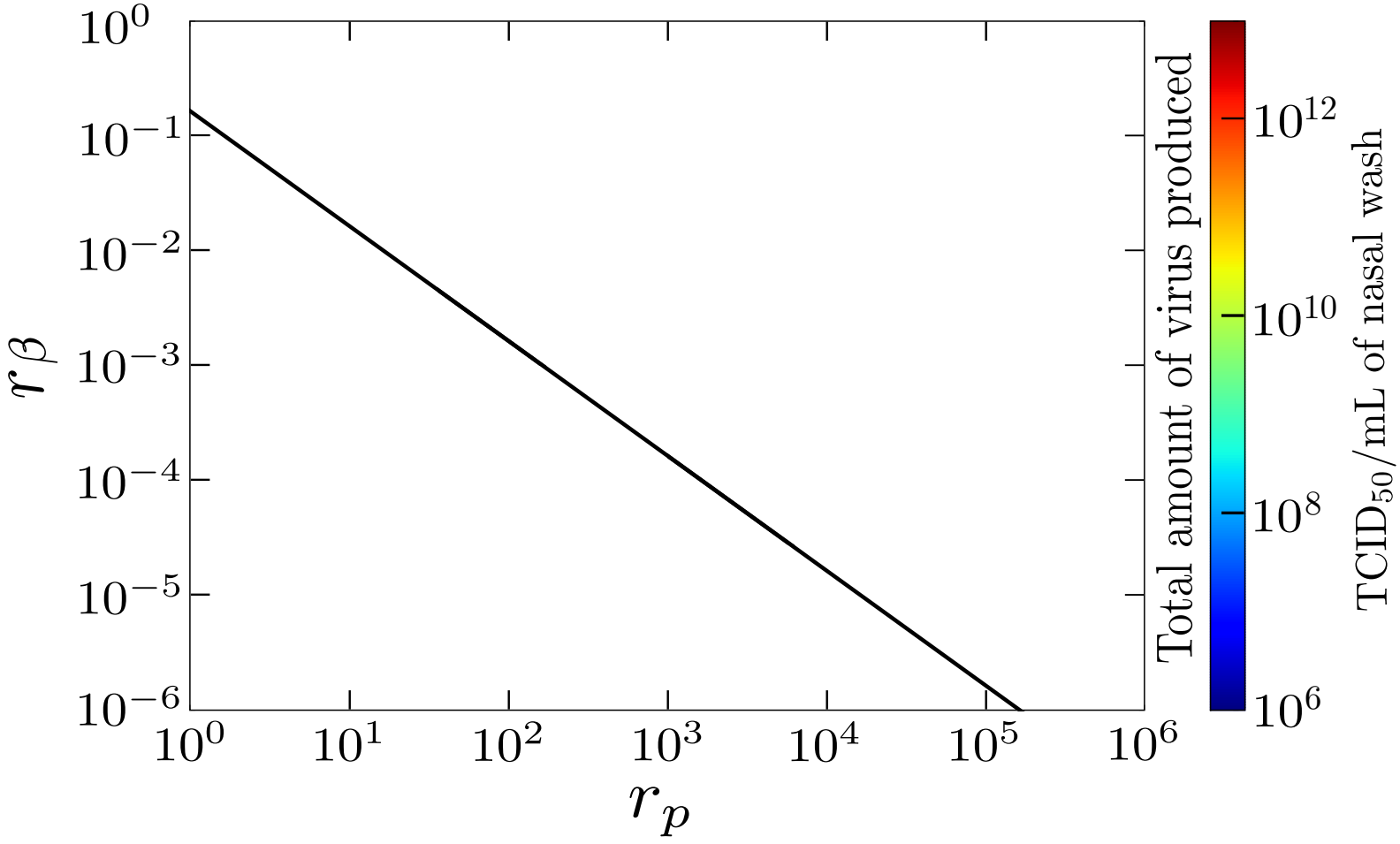
Time of viral peak



Infection duration



Total virus produced



Sustained viral production

- For our base parameters, sustained production occurs when T_s is harder to infect but produces more virus than T_d
- Changing the ratio of default to secondary cells changes production rates, but not infection rates:

$$\text{Target cells}: \quad T_d' = \frac{r_T'}{r_T} T_d \quad T_s' = \frac{(1 - r_T')}{(1 - r_T)} T_s$$

$$\text{Viral production rate}: \quad p_d' = \frac{r_T}{r_T'} p_d \quad p_s' = \frac{(1 - r_T)}{(1 - r_T')} p_s \ .$$

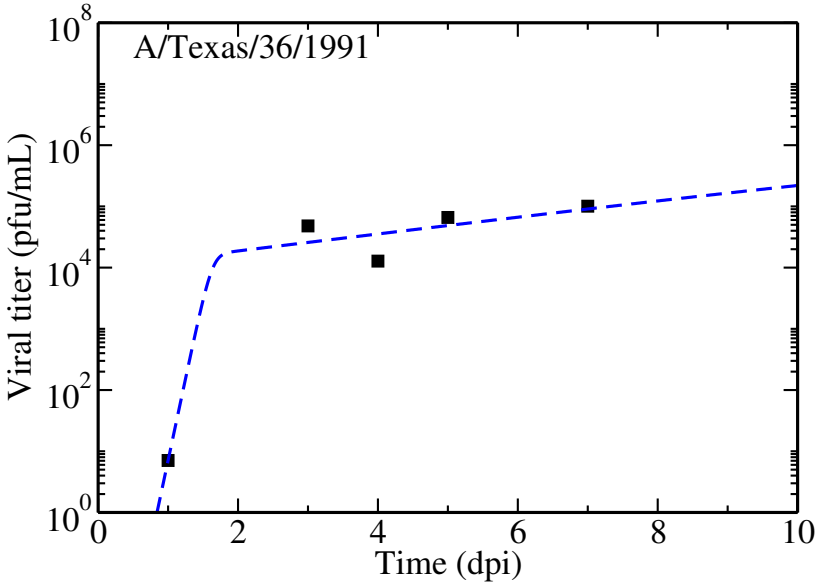
- Allows for production rate of T_s to be smaller than T_d if the initial number of secondary cells is large

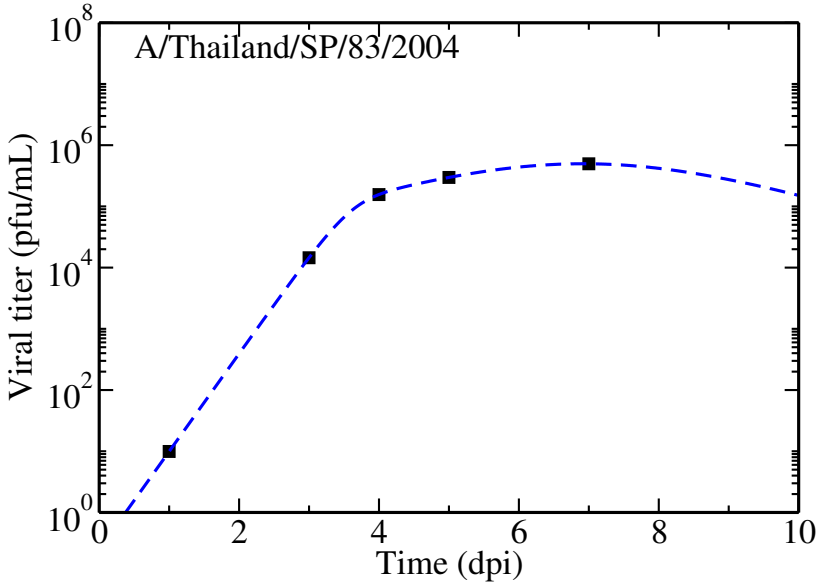
Basic Reproductive number

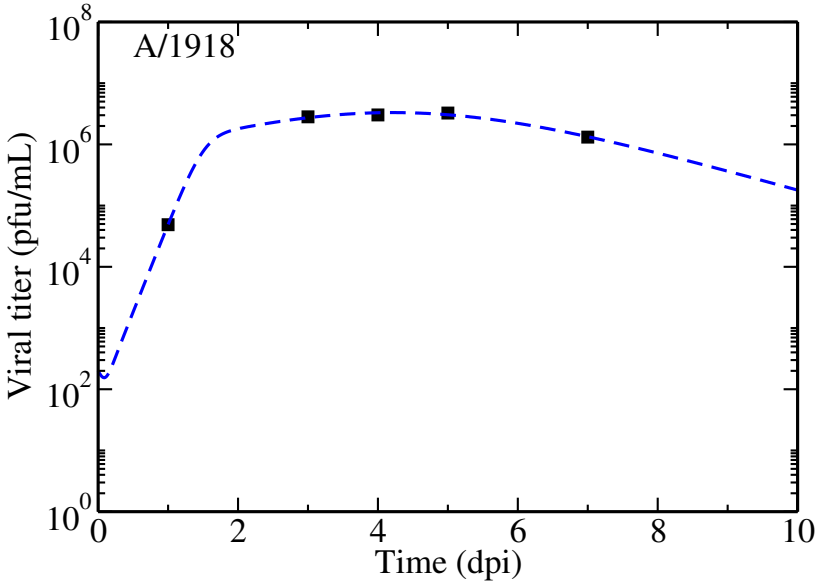
$$R_d = \frac{\beta p r_T T_0}{\delta c} \qquad R_s = \frac{(r_\beta \beta)(r_p p)((1 - r_T) T_0)}{\delta c} \; .$$

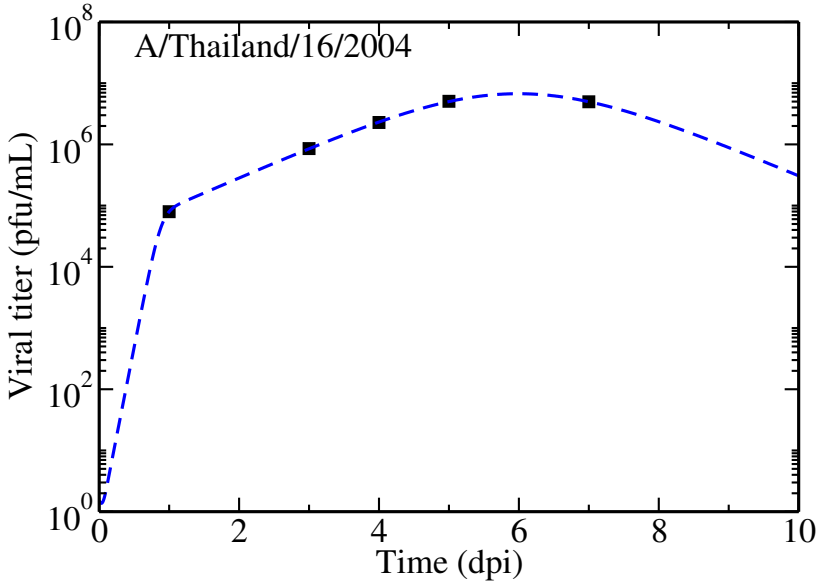
- Basic reproductive number gives number of secondary infections resulting from a single infected cell placed in a homogeneous susceptible population
- Sustained titer occurs when $R_s > 1$, but is still small
- Secondary cell population participates in the infection, but is consumed very slowly

Fitting the model to data









Summary

- Two target cell model based on virus preference for certain cells
- Cell populations have different infection rates and production rates
- Model exhibits sustained viral production when secondary cell population is consumed slowly
- Model can reproduce experimental data of severe influenza infection

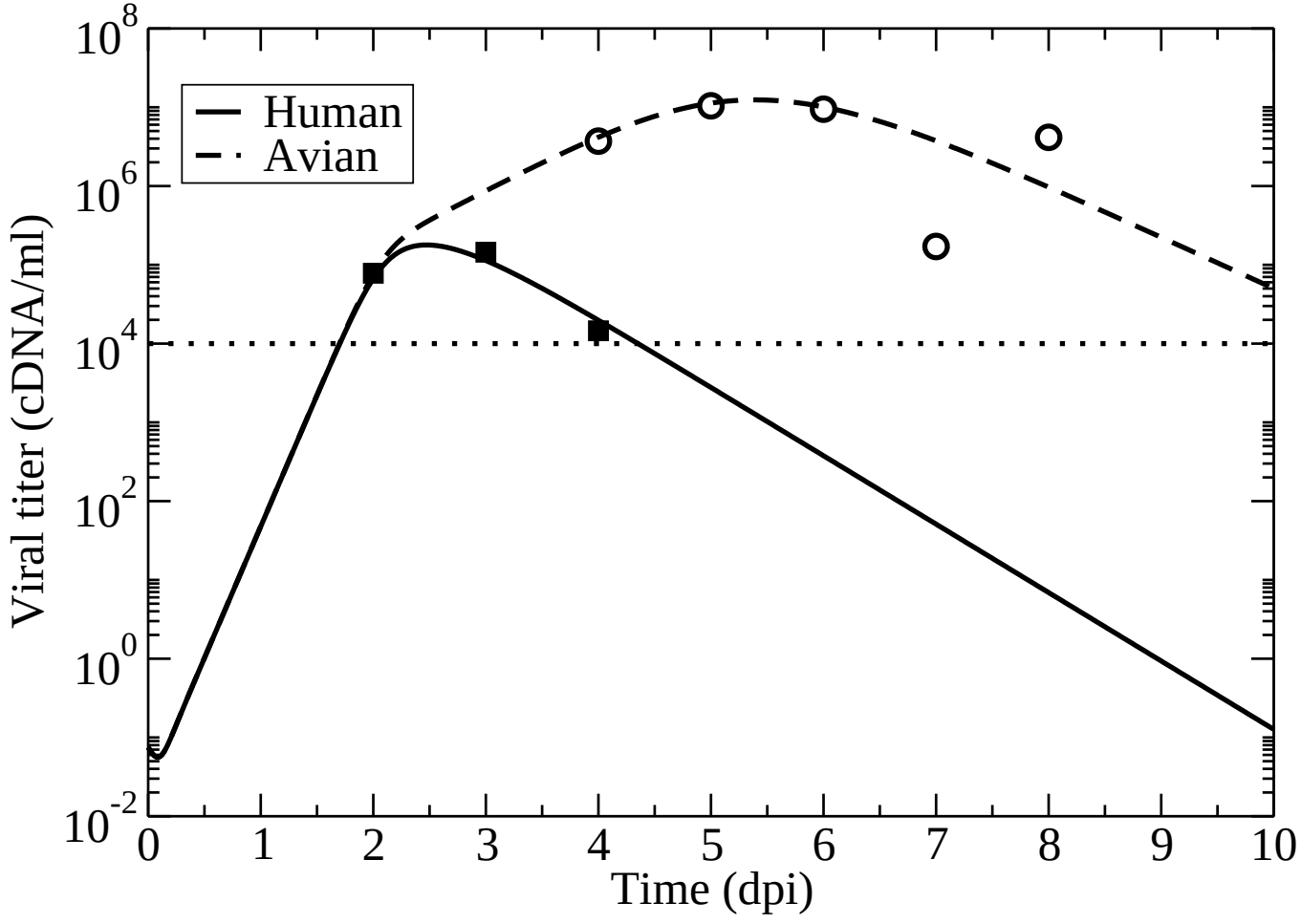
Modelling of NAIs

- Neuraminidase inhibitors (NAIs) block activity of NA protein which hinders the ability of the virus particles to free themselves from the bounds of the producing cells
- NAI treatment is modelled as blocking production of the virus

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (1-\varepsilon)p_d I_d + (1-\varepsilon)p_s I_s - cV,$$

- For simplicity, we assume the drug effect is the same on both target cell populations and that it remains constant once it is applied

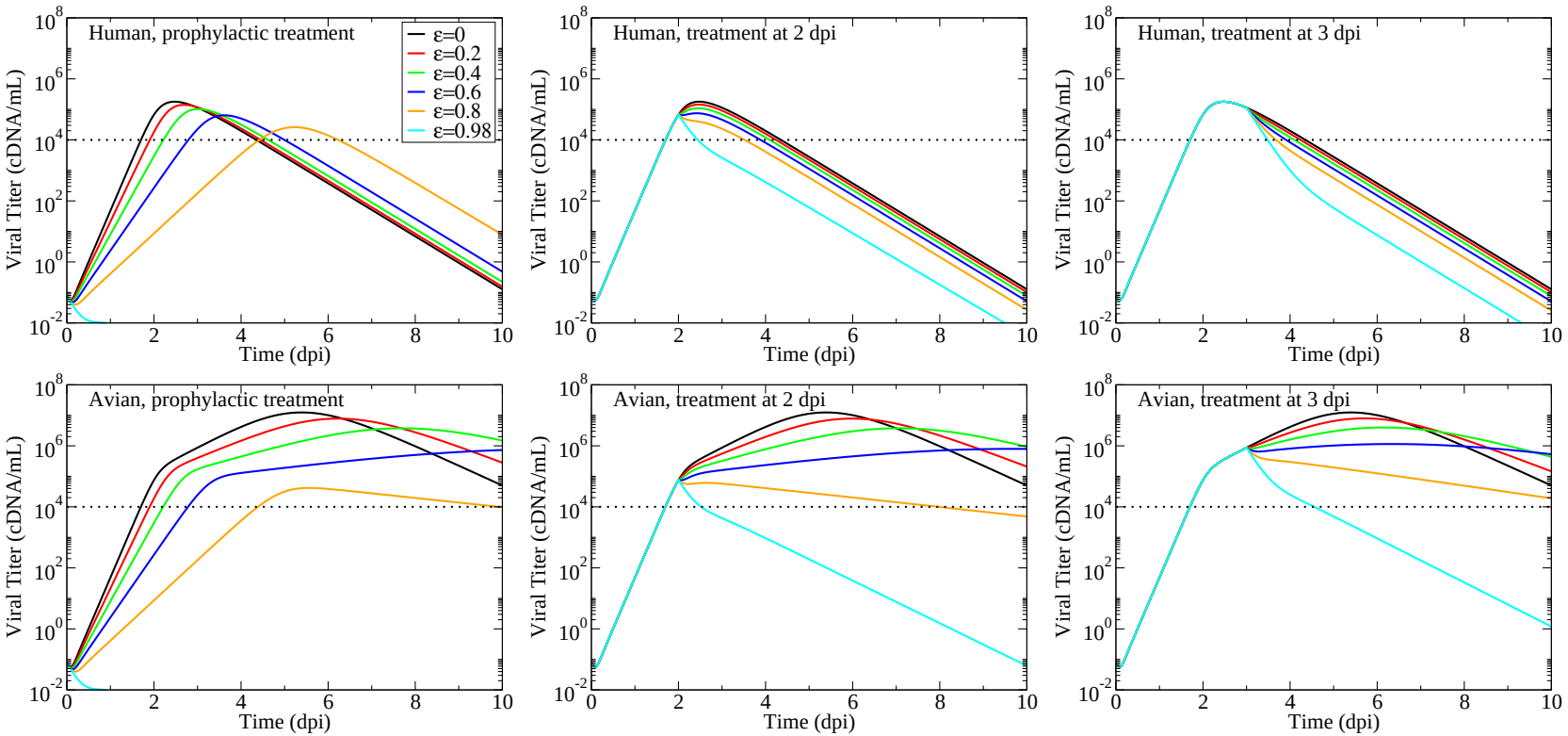
Finding parameters for seasonal and severe influenza



de Jong et al. Nat. Med. (2006)

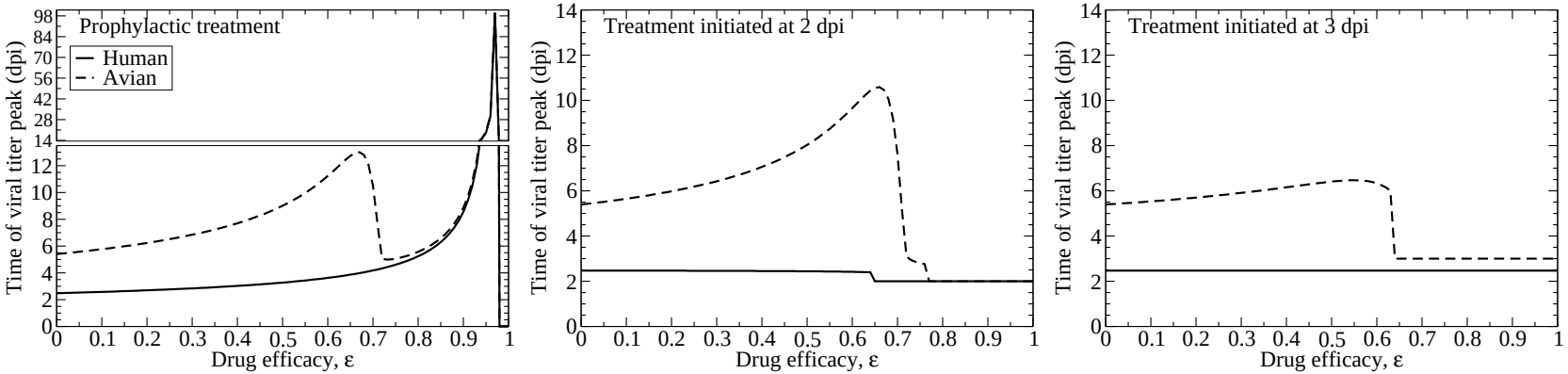
Use data from humans infected with seasonal (H1N1 or H3N2) or avian (H5N1) flu

Effect of NAIs

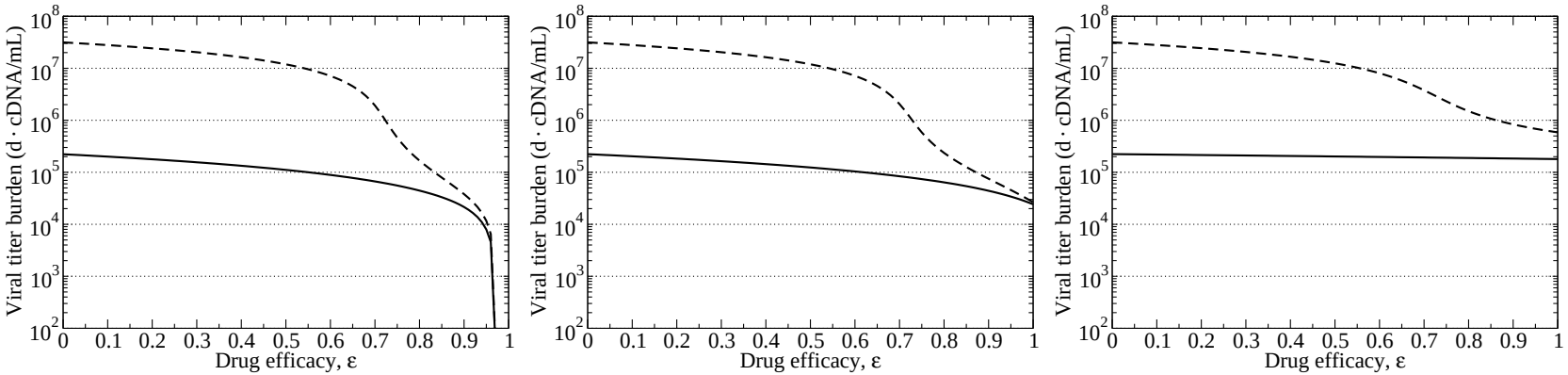


Viral titer characteristics

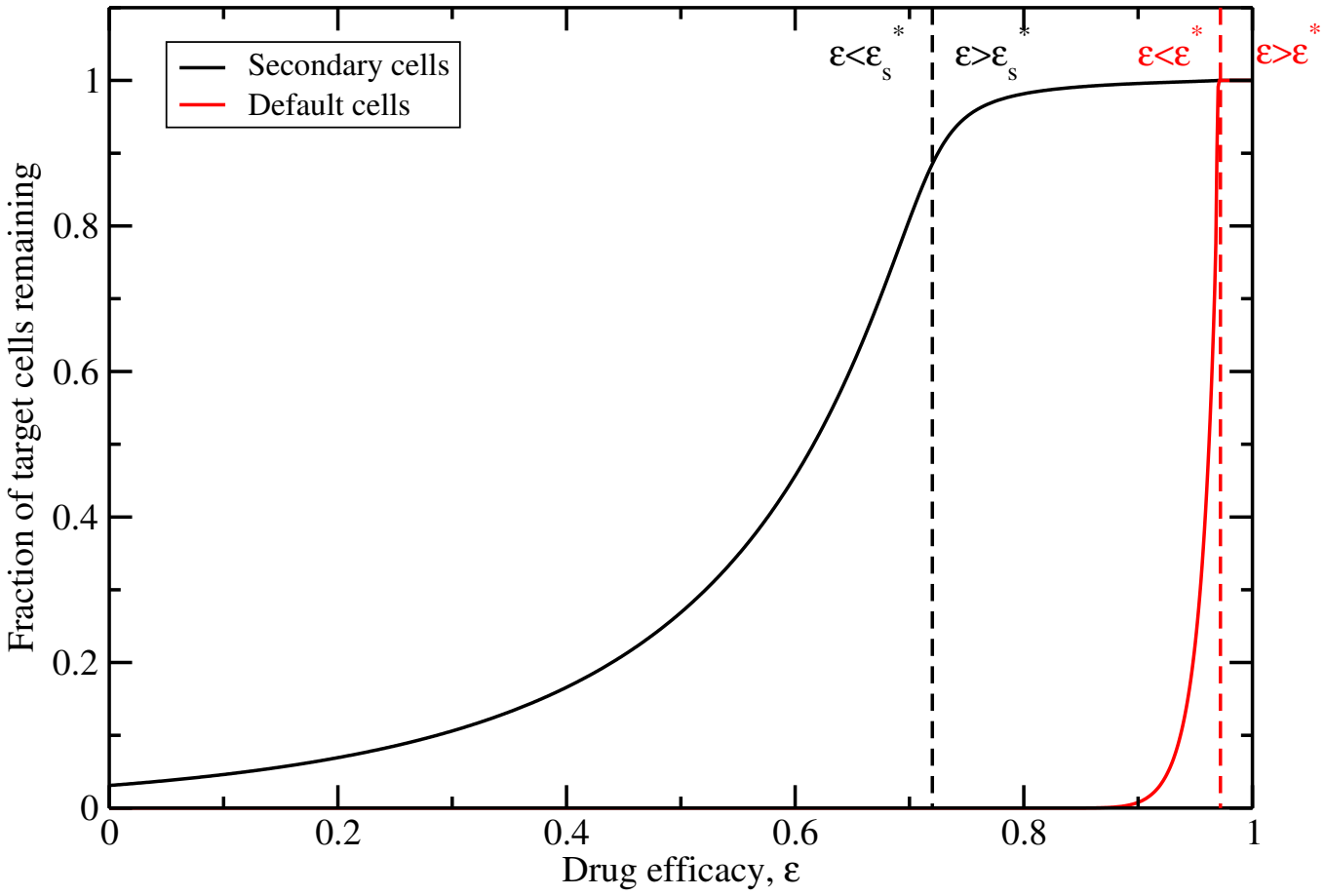
Time of viral peak



Viral titer burden



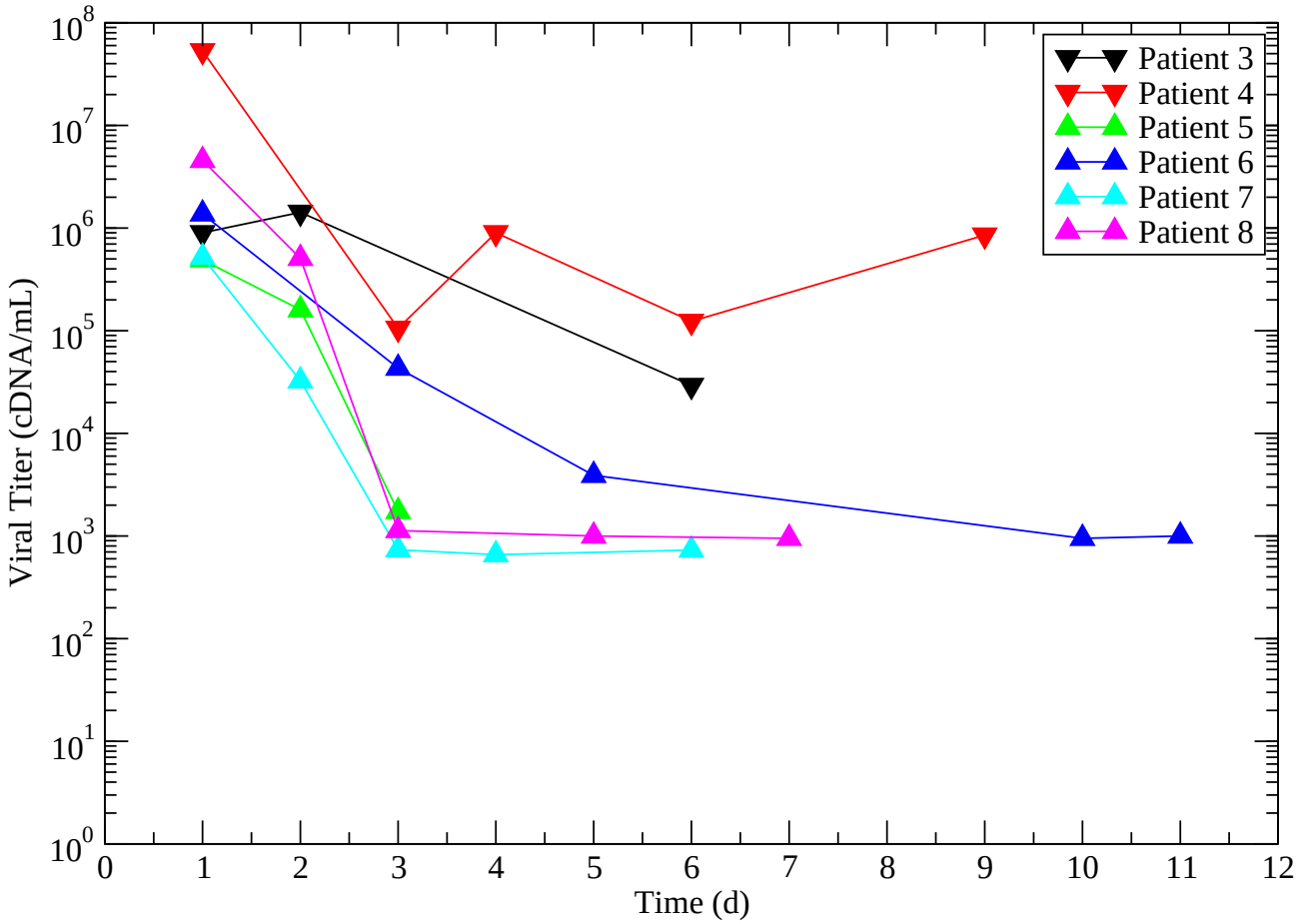
Critical drug efficacy



Infection is suppressed in:

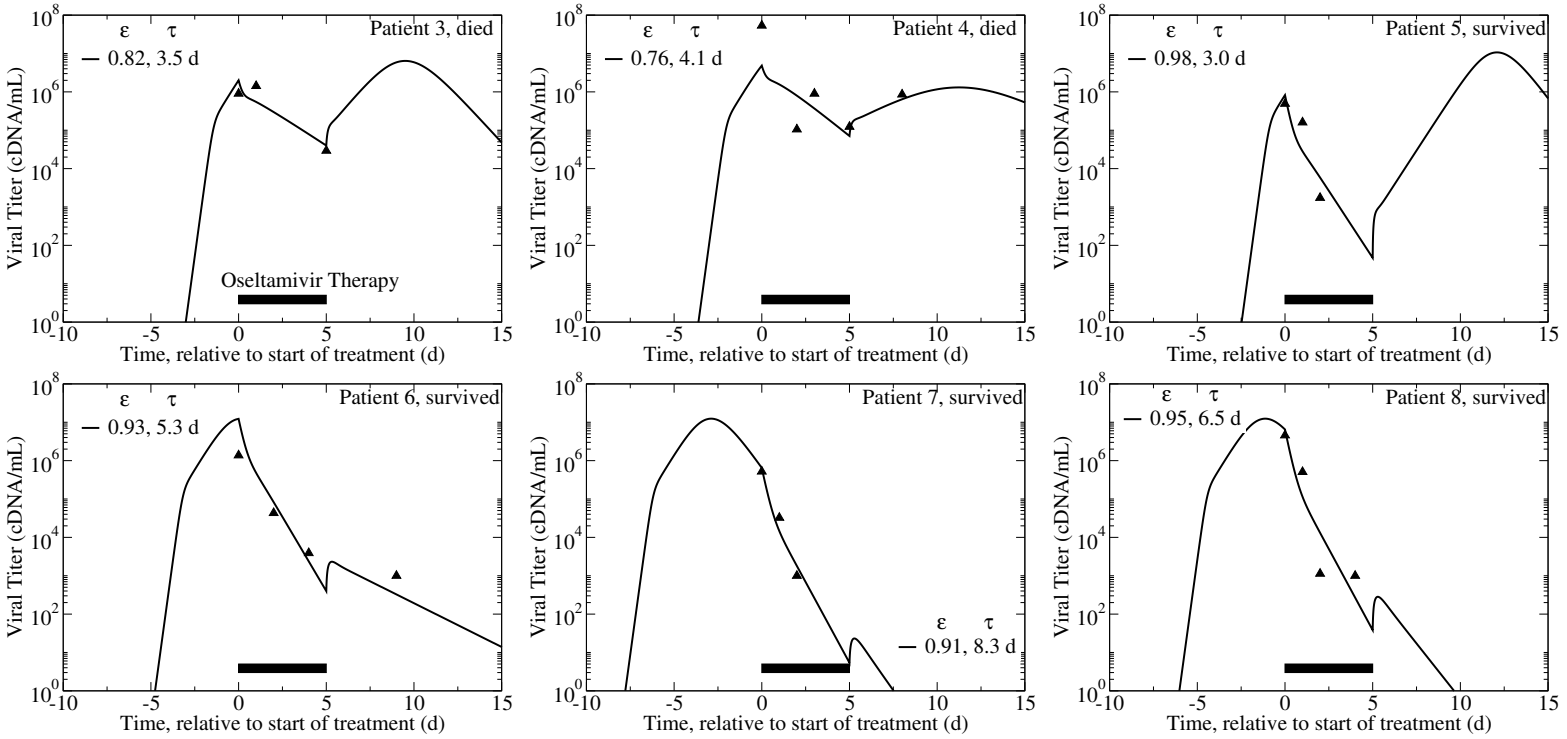
- both populations when $\varepsilon > 1 - 1/(R_s + R_d)$
- secondary population only when $\varepsilon > 1 - 1/R_s$

Fitting patient data



de Jong et al. NEJM (2005)

Model fits



- Patients who died have lower drug efficacies than those who survived
- Treatment delays are in line with onset of infection reported by patients

Conclusions

- There is an increased window of opportunity for treatment during sustained viral production
- If treatment with sufficient efficacy is applied before the peak of the viral titer curve, we see:
  - reduction of the viral load
  - decrease in the duration of the infection
- If treatment is at low efficacy, the duration of the infection can be increased which increases the opportunity for drug resistance to arise

Future Directions

- Determine the effect of sustained viral production on the emergence of drug resistance
- Incorporate immune system into the model
- Incorporate pharmacokinetics into the treatment model

Acknowledgements

Phymbie group:

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- Marc Baron

Collaborators:

- Nelson Jumbe
- Brian Davies
- Ronald Gieschke

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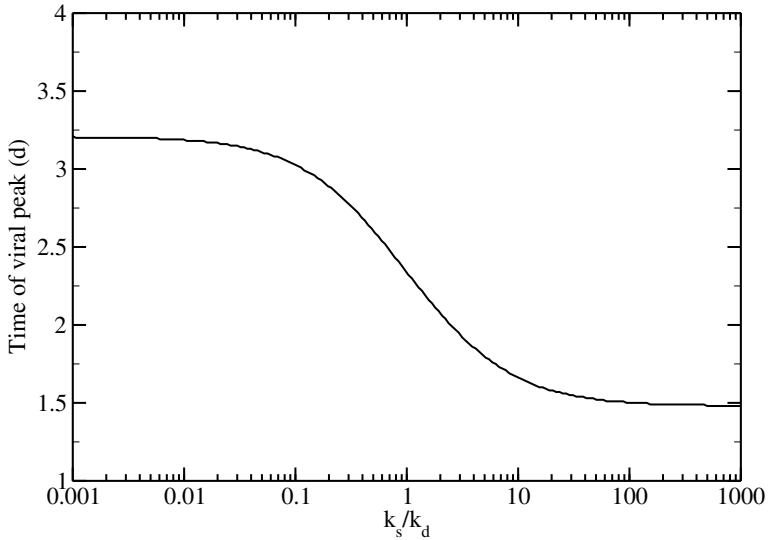
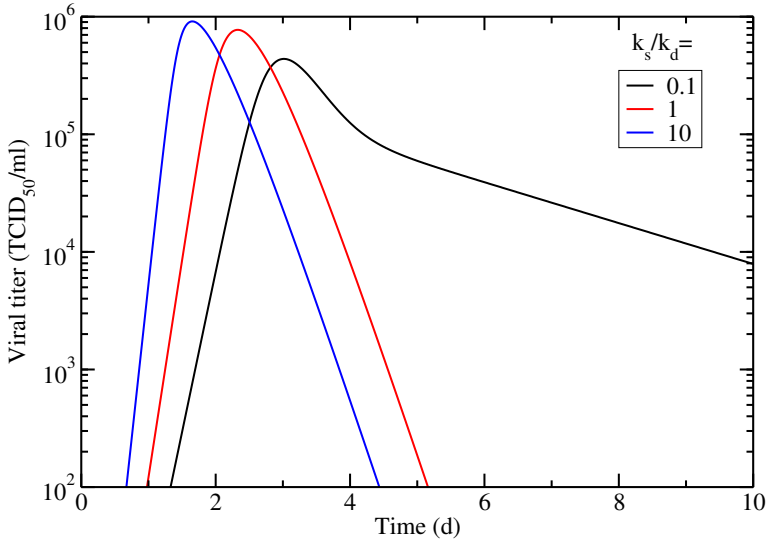
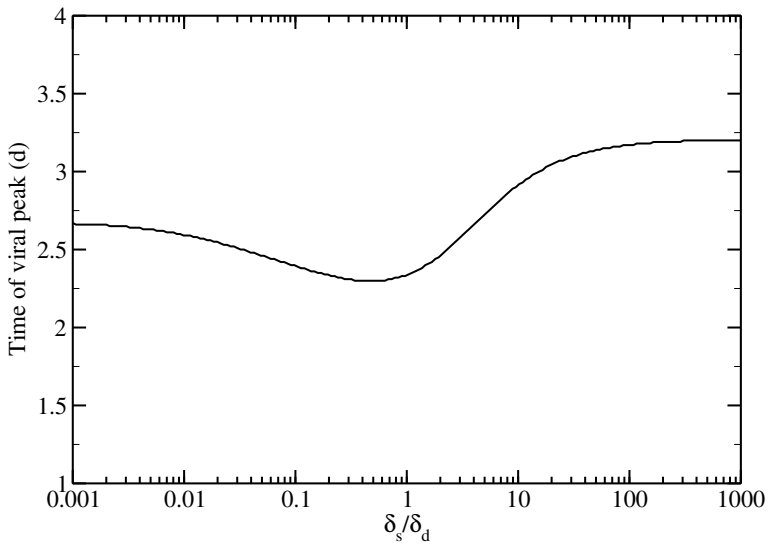
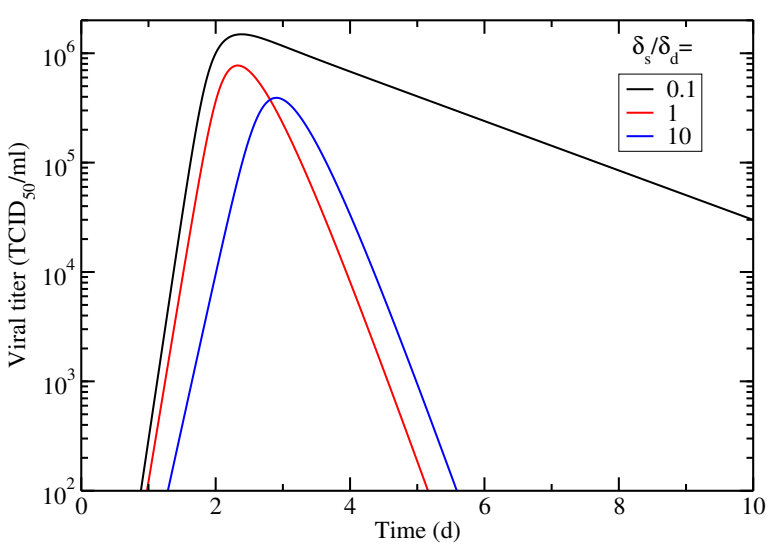
k and δ


Time of viral peak (d)
4
3.5
3
2.5
2
1.5
1
0.001
0.01
0.1
1
10
100
1000
k_s/k_d


Viral titer ($TCID_{50}$/ml)
10^6
10^5
10^4
10^3
10^2
0
2
4
6
8
10
Time (d)
k_s/k_d=
0.1
1
10

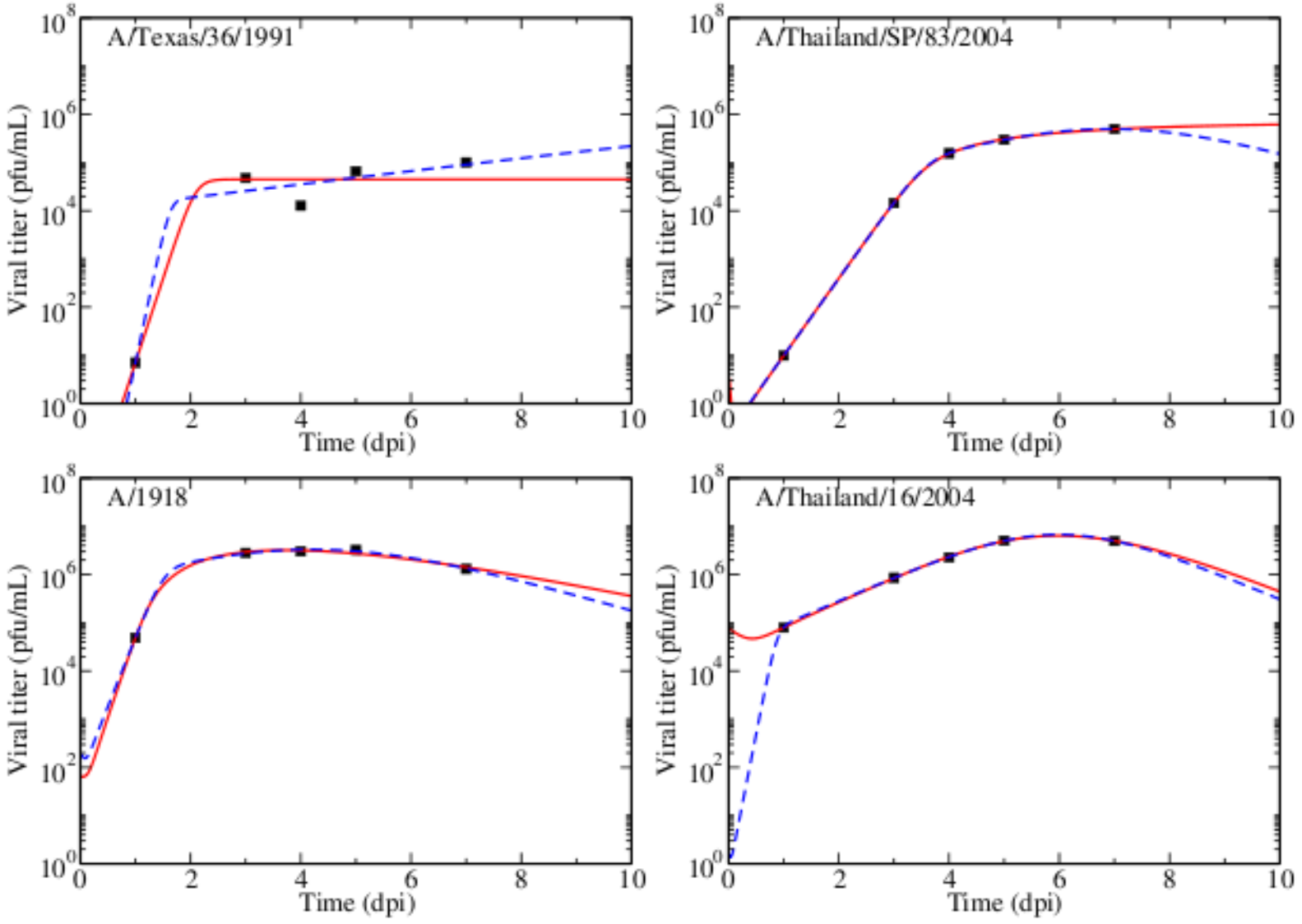

Time of viral peak (d)
4
3.5
3
2.5
2
1.5
1
0.001
0.01
0.1
1
10
100
1000
δ_s/δ_d


Viral titer ($TCID_{50}$/ml)
10^6
10^5
10^4
10^3
10^2
0
2
4
6
8
10
Time (d)
δ_s/δ_d=
0.1
1
10

Causes of severe influenza

- Cell tropism – Human flu strains have adapted to the cell receptors that dominate in the human respiratory tract. Novel flu strains may still prefer to bind to cell receptors that dominate in other animals.
- Hypercytokinemia – Because of the novelty of the flu strain, the immune system over-reacts.
- Infection of lower respiratory tract – Seasonal influenza is typically limited to the upper respiratory tract; severe influenza can infect the lower respiratory tract
- Lack of pre-existing immunity – Seasonal influenza changes slowly from year to year, so the immune system recognizes part of the virus and can get a head start on eliminating the virus; a novel strain is not recognized at all, so the immune system takes longer to respond.

Mouse fits


A/Texas/36/1991
A/Thailand/SP/83/2004
A/1918
A/Thailand/16/2004
Viral titer (pfu/mL)
Time (dpi)

Mouse fits

Table 2: Model parameter fits for experimental influenza infection in mice.

	V_0 ([V])	$1/k$ (h)	$1/\delta$ (h)	$1/c$ (h)	$\beta_{2,6}/\beta_{2,3}$ ($[V]^{-1}\cdot d^{-1}$)	$p_{2,6}/p_{2,3}$ ($[V]\cdot d^{-1}$)	$R_{2,6}/R_{2,3}$	SSR	AIC_C
Single target cell model									
LH	5.9×10^{-3}	4.4×10^{5}	7.3	1.2	1.1×10^{-3}/–	7.7/–	8.8×10^{5}/–	0.45	-35
LA	8.2	240	130	0.41	6.9×10^{-5}/–	0.019/–	810/–	2.8×10^{-4}	-72
HH	65	33	32	34	9.8×10^{-5}/–	0.0012/–	1600/–	7.8×10^{-3}	-56
HA	1.5×10^{5}	16	∞	7.1	5.9×10^{-7}/–	0.0027/–	∞/–	3.3×10^{-4}	-71
Two target cell model ($r_{2,6}=0.1$)									
LH	4.1×10^{-3}	24	0.74	0.80	$2.4\times10^{-8}/8.2\times10^{-4}$	77/0.0030	1.3/16	0.29	-32
LA	1.4	9.2	1.1	1.3	$2.7\times10^{-7}/3.3\times10^{-5}$	2.9/0.0039	1.3/2.0	2.1×10^{-19}	-240
HH	19	4.9	5.0	5.0	$5.2\times10^{-8}/2.4\times10^{-5}$	0.90/0.0033	1.4/22	2.3×10^{-3}	-56
HA	4.8×10^{3}	2.9	3.5	3.8	$4.1\times10^{-8}/9.4\times10^{-5}$	$2.4/2.2\times10^{-4}$	1.6/3.0	7.4×10^{-5}	-74

LH: Low-pathogenic human A/Texas/36/91 (H1N1). HH: High-pathogenic human A/1918 (H1N1).
LA: Low-pathogenic avian A/Thai/SP/83/2004 (H5N1). HA: High-pathogenic avian A/Thai/16/2004 (H5N1).

de Jong fit

Infections with human strains	
β_d	$1.6 \times 10^{-4}\ (\mathrm{cDNA/mL})^{-1} \cdot \mathrm{d}^{-1}$
p_d	$3.3 \times 10^{6}\ \mathrm{cDNA/mL} \cdot \mathrm{d}^{-1}$
Infections with avian strains	
β_d	$1.1 \times 10^{-7}\ (\mathrm{cDNA/mL})^{-1} \cdot \mathrm{d}^{-1}$
p_d	$4.8 \times 10^{8}\ \mathrm{cDNA/mL} \cdot \mathrm{d}^{-1}$
β_s	$1.3 \times 10^{-4}\ (\mathrm{cDNA/mL})^{-1} \cdot \mathrm{d}^{-1}$
p_s	$8.6 \times 10^{6}\ \mathrm{cDNA/mL} \cdot \mathrm{d}^{-1}$
Shared initial conditions	
V_0	$7.5 \times 10^{-2}\ \mathrm{cDNA/mL}$
E_0, I_0	0

Oseltamivir fits