

# Appendix: Modeling the CD8+ T cell immune response to influenza infection in adult and aged mice

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## Appendix A

### A.1 Model Equations

Model	Expressions
MA1	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - d_T^{\text{half life}} T$
MA2	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T^{\text{half life}} T$
MA3	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MA4	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MB1	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - d_T^{\text{half life}} T$
MB2	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T^{\text{half life}} T$
MB3	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MB4	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MC1	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - d_T^{\text{half life}} T$
MC2	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T^{\text{half life}} T$
MC3	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MC4	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - c_T/(1 + V^2)T - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MD1	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - d_T^{\text{half life}} T$
MD2	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T^{\text{half life}} T$
MD3	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$
MD4	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - c_T/(1 + V^2)T - (d_T^{\text{half life}} + d_T^{\text{downregulation}})T$

**Table A.1.1.** Mathematical form of the 16 models considered.

MA1		MA2		MA3		MA4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
$k_T$	✓			$s_T$	✓	$d_T$	✓
$c_V$	✓	$k_T$	✓	$k_V$	✓	$c_T$	✓
		$c_V$	✓	$T(t)$	✓	$c_V$	✓
$k_V$	✓	$p$	✓	$r$	✓	$k_V$	✓
$p$	✓	$r$	✓	$c_V$	✓	$p$	✓
$T(t)$	✓	$s_T$	✓	$d_T$	✓	$T(t)$	✓
$V(t)$	✓	$k_V$	✓	$V(t)$	✓	$V(t)$	✓
$r$	✓	$T(t)$	✓	$p$	✓	$r$	✓
$s_T$	✓	$V(t)$	✓	$k_T$	✓	$s_T$	✓
		$c_T$	✓			$k_T$	✓

**Table A.2.1.** Model group A structural identifiabilities. Model group A uses a logistic form for viral dynamics and Michaelis-Menten form for CD8+ T cell proliferation.

MB1		MB2		MB3		MB4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
$d_I$	✓	$c_T$	✓	$s_T$	✓	$c_T$	✓
$V(t)$	✓	$p$		$c$	✓	$V(t)$	✓
$r$	✓	$T(t)$	✓	$I(t)$		$r$	✓
		$k_T$	✓	$T(t)$	✓	$d_I$	✓
$c$	✓	$\beta$	✓	$\beta$	✓	$c$	✓
$k_T$	✓	$V(t)$	✓	$d_I$	✓	$d_T$	✓
$U(t)$		$d_I$	✓	$U(t)$		$U(t)$	
$\beta$	✓	$r$	✓	$r$	✓	$\beta$	✓
$T(t)$	✓	$s_T$	✓	$V(t)$	✓	$T(t)$	✓
$p$		$U(t)$		$p$		$p$	
$s_T$	✓	$c$	✓	$d_T$	✓	$s_T$	✓
$I(t)$				$k_T$	✓	$I(t)$	
		$I(t)$				$k_T$	✓

**Table A.2.2.** Group B structural identifiabilities. Model group B uses a target cell limited model for viral dynamics and Michaelis-Menten form for CD8+ T cell proliferation.

MC1		MC2		MC3		MC4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
$c_V$	✓			$s_T$	✓	$d_T$	✓
				$k_V$	✓	$c_T$	✓
$k_V$	✓	$c_V$	✓	$T(t)$	✓	$c_V$	✓
$p$	✓	$p$	✓	$r$	✓	$k_V$	✓
$T(t)$	✓	$r$	✓	$c_V$	✓	$p$	✓
$V(t)$	✓	$s_T$	✓	$d_T$	✓	$T(t)$	✓
$r$	✓	$k_V$	✓	$V(t)$	✓	$V(t)$	✓
$s_T$	✓	$T(t)$	✓	$p$	✓	$r$	✓
		$V(t)$	✓			$s_T$	✓
		$c_T$	✓				

**Table A.2.3.** Group C structural identifiabilities. Model group C uses a logistic form for viral dynamics and bilinear form for CD8+ T cell proliferation.

MD1		MD2		MD3		MD4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
$d_I$	✓	$c_T$	✓	$s_T$	✓	$c_T$	✓
$V(t)$	✓	$p$		$c$	✓	$V(t)$	✓
$r$	✓	$T(t)$	✓	$I(t)$		$r$	✓
				$T(t)$	✓	$d_I$	✓
$c$	✓	$\beta$	✓	$\beta$	✓	$c$	✓
		$V(t)$	✓	$d_I$	✓	$d_T$	✓
$U(t)$		$d_I$	✓	$U(t)$		$U(t)$	
$\beta$	✓	$r$	✓	$r$	✓	$\beta$	✓
$T(t)$	✓	$s_T$	✓	$V(t)$	✓	$T(t)$	✓
$p$		$U(t)$		$p$		$p$	
$s_T$	✓	$c$	✓	$d_T$	✓	$s_T$	✓
$I(t)$						$I(t)$	
		$I(t)$					

**Table A.2.4.** Group D structural identifiabilities. Model group D uses a target cell limited model for viral dynamics and bilinear form for CD8+ T cell proliferation.

### 14 A.3 All Model Parameter Fits

#### 15 A.3.1 Model Group A

Model MA1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	6.05	2.57	[1e-2, 1e2]	1	-
$k_V$	Carrying capacity of virus	(PFU/ml)	1.2	1.2	-	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} cell^{-1}$	2.84e-6	1.78e-6	[1e-8, 1e-4]	2	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}$	2.21e-1	99.9	[1e-4, 1e2]	1,3	
$k_T$	CD8+ T cell half saturation constant	(PFU/ml)	5.11e+3	2.35e+7	[1e1, 1e8]	4	
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	0.011	0.012	-	6	

**Table A.3.1.** Summary of MA1 parameters. The mathematical expression for MA1 is presented in A.1.1.

Model MA2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	5.93	3.07	[1e-2,1e2]	1	-
$k_V$	Carrying capacity of virus	(PFU/ml)	1.2	1.2	-	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} cell^{-1}$	2.61e-6	1.98e-6	[1e-8,1e-4]	2	-
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}$	2.05e-1	1.68e-1	[1e-4,1e2]	1,3	-
$k_T$	CD8+ T cell half saturation constant	(PFU/ml)	3.77e+3	1e1	[1e1, 1e8]	4	-
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	0.011	0.012	-	6	-
$c_T$	nonlinear CD8+ T cell downregulation rate	$(PFU/ml)d^{-1}$	2.49e-2	4.89e-2	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.2.** Summary of MA2 parameters. The mathematical expression for MA2 is presented in [A.1.1](#).

Model MA3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$[d^{-1}]$	5.07 (4.52,5.68)	2.57	[1e-2,1e2]	1	-
$k_V$	Carrying capacity of virus	[PFU/ml][10 <sup>6</sup> ]	1.2	1.2	-	1	Determined from data
$c_V$	Viral clearance rate	$[d^{-1} cell^{-1}][10^{-6}]$	2.21 (1.92,2.62)	1.78	[1e-2,1e2]	2	-
$s_T$	Homeostatic CD8+ T cell proliferation rate	$[cell \cdot d^{-1}]$	$d_T T(0)$	-	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$[d^{-1}]$	2.74e-1 (2.36e-1,3.16e-1)	99.9	[1e-4,1e2]	1,3	-
$k_T$	CD8+ T cell half saturation constant	[PFU/ml][10 <sup>3</sup> ]	2.48e3 (1.58e3,3.98e3)	2.35e7	[1e1, 1e7]	4	-
$d_T^{half\ life}$	CD8+ T cell half life	$[d^{-1}]$	1.1e-2	1.2e-2	-	6	-
$d_T^{downregulation}$	CD8+ T linear downregulation	$[d^{-1}]$	6.65e-2 (4.43e-2,8.50e-2)	1.0e-4	[1e-4,1e0]	4,5	-

**Table A.3.3.** Parameters for MA3, the selected adult model. The mathematical expression for MA3 is presented in [A.1.1](#).

Model MA4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$[d^{-1}]$	5.45	3.07	[1e-2,1e2]	1	-
$k_V$	Carrying capacity of virus	[PFU/ml][10 <sup>6</sup> ]	1.2	1.2	-	1	Determined from data
$c_V$	Viral clearance rate	$[d^{-1} cell^{-1}][10^{-6}]$	2.16	1.97	[1e-2,1e2]	2	-
$s_T$	Homeostatic CD8+ T cell proliferation rate	$[cell \cdot d^{-1}]$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$[d^{-1}]$	2.73e-1	1.69e-1	[1e-4,1e2]	1,3	-
$k_T$	CD8+ T cell half saturation constant	[PFU/ml][10 <sup>3</sup> ]	2.20e3	1e1	[1e1, 1e7]	4	-
$d_T^{half\ life}$	CD8+ T cell half life	$[d^{-1}]$	1.1e-2	1.2e-2	-	6	-
$d_T^{downregulation}$	CD8+ T linear downregulation	$[d^{-1}]$	6.47e-2	1.0e-4	[1e-4,1e0]	4,5	-
$c_T$	nonlinear CD8+ T cell downregulation rate	$(PFU/ml)d^{-1}$	2.32e-9	4.86e-2	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.4.** Parameters for MA4, the selected adult model. The mathematical expression for MA4 is presented in [A.1.1](#).

## 16 A.3.2 Model Group B

Model MB1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$[PFU/ml]^{-1}[d^{-1}][10^{-5}]$	2.23	4.63 (1.69,6.80)	[1e-3,1e1]	2	-
$d_I$	Clearance rate of infected cells	$[cells^{-2}][10^{-7}]$	6.81	4.68 (3.85,5.32)	[1e-1,1e3]	2	-
$p$	Production rate of virus	$[d^{-1}]$	1	1	-	2	Fixed for structural identifiability.
$c$	Clearance rate of virus	$[d^{-1}][10^1]$	2.13e-1	1.23 (1.33e-1,1.88)	[1e-3,1e1]	2	-
$s_T$	Homeostatic CD8+ T cell proliferation rate	$[cell d^{-1}]$	$d_T T(0)$	-	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$[d^{-1}][10^{-1}]$	4.45	2.15 (1.70, 2.71)	[1e-3,1e3]	1,3	-
$k_T$	CD8+ T cell half saturation constant	[PFU/ml][10 <sup>1</sup> ]	4.45e3	1.15 (1.0,13.1)	[1e0, 1e7]	4	-
$d_T^{half\ life}$	CD8+ T half life	$[d^{-1}][10^{-2}]$	1.1	1.2	-	6	-

**Table A.3.5.** Parameters for model MB1, the selected aged model. The mathematical expression for MB1 is presented in [A.1.1](#).

Model MB2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$[\text{PFU/ml}]^{-1} [d^{-1}] [10^{-5}]$	2.23	4.63	[1e-3,1e1]	2	-
$d_I$	Clearance rate of infected cells	$[\text{cells}^{-2}] [10^{-7}]$	6.79	4.68	[1e-1,1e3]	2	Fixed for structural identifiability.
$p$	Production rate of virus	$[d^{-1}]$	1	1	-	2	
$c$	Clearance rate of virus	$[d^{-1}] [10^1]$	2.14e-1	1.23	[1e-3,1e1]	2	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$[\text{cell} d^{-1}]$		$d_T T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$[d^{-1}] [10^{-1}]$	4.38	2.14	[1e-3,1e3]	1,3	
$k_T$	CD8+ T cell half saturation constant	$[\text{PFU/ml}] [10^1]$	4.34e3	1.16	[1e0, 1e7]	4	
$d_T^{\text{half life}}$	CD8+ T half life	$[d^{-1}] [10^{-2}]$	1.1	1.2	-	6	Assumed similar to $d_T$
$c_T$	CD8+ T cell nonlinear downregulation rate	$(\text{PFU}/\text{ml}) d^{-1}$	2.99e-3	2.08e-9	[0,1e0]	-	

**Table A.3.6.** Parameters for model MB2. The mathematical expression for MB2 is presented in A.1.1.

Model MB3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(\text{PFU}/\text{ml})^{-1} d^{-1}$	2.21e-5	1.77e-5	[1e-8,1e-4]	2	-
$d_I$	Clearance rate of infected cells	$\text{cells}^{-2}$	5.55e-7	4.33e-6	[1e-8,1e-4]	2	Fixed for structural identifiability.
$p$	Production rate of virus	$d^{-1}$			1e0	2	
$c$	Clearance rate of virus	$d^{-1}$	2.19	1.42	[1e-2,1e2]	2	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}$	4.18e-1	2.03e-1	[1e-4,1e2]	1,3	
$k_T$	CD8+ T cell half saturation constant	$(\text{PFU}/\text{ml})$	1.05e4	1e1	[1e1, 1e8]	4	
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	-	6	
$d_T^{\text{downregulation}}$	CD8+ T cell linear downregulation rate	$d^{-1}$	8.37e-2	1.00e-4	[1e-4,1e0]	4,5	

**Table A.3.7.** Summary of MB3 parameters. The mathematical expression for MB3 is presented in A.1.1.

Model MB4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(\text{PFU}/\text{ml})^{-1} d^{-1}$	2.21e-5	4.63e-5	[1e-8,1e-4]	2	-
$d_I$	Clearance rate of infected cells	$\text{cells}^{-2}$	5.55e-7	4.68e-7	[1e-8,1e-4]	2	Fixed for structural identifiability.
$p$	Production rate of virus	$d^{-1}$			1e0	2	
$c$	Clearance rate of virus	$d^{-1}$	2.19	12.3	[1e-2,1e2]	2	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}$	4.18e-1	2.15e-1	[1e-4,1e2]	1,3	
$k_T$	CD8+ T cell half saturation constant	$(\text{PFU}/\text{ml})$	1.05e4	1.14e1	[1e1, 1e8]	4	
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	[1e-4,1e0]	6	
$d_T^{\text{downregulation}}$	CD8+ T cell linear downregulation rate	$d^{-1}$	8.37e-2	1.00e-4	[1e-4,1e0]	4,5	
$c_T$	CD8+ T cell nonlinear downregulation rate	$(\text{PFU}/\text{ml}) d^{-1}$	5.98e-14	3.65e-8	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.8.** Summary of MB4 parameters. The mathematical expression for MB4 is presented in A.1.1.

### 17 A.3.3 Model Group C

Model MC1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	4.61	2.71	[1e-2,1e2]	1	-
$k_V$	Carrying capacity of virus	$(\text{PFU}/\text{ml})$			1.2e6 (fixed)	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} \text{cell}^{-1}$	1.84e-6	2.06e-6	[1e-8,1e-4]	2	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state Bounds are scaled.
$r$	CD8+ T cell proliferation rate	$d^{-1} (\text{PFU}/\text{ml})^{-1}$	2.08e-6	4.22e-6	[1e-4/ $k_V$ , 1e2/ $k_V$ ]	1,3	
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	0.011	0.012	-	6	

**Table A.3.9.** Summary of MC1 parameters. The mathematical expression for MC1 is presented in A.1.1.

Model MC2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	5.42	3.16	[1e-2,1e2]	<sup>1</sup>	-
$k_V$	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} cell^{-1}$	2.13e-6	2.08e-6	[1e-8,1e-4]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(PFU/ml)^{-1}$	1.31e-6	3.84e-6	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	-	<sup>6</sup>	
$c_T$	CD8+ T cell nonlinear downregulation rate	$(PFU/ml)d^{-1}$	1.30e-1	2.27e-1	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.10.** Summary of MC2 parameters. The mathematical expression for MC2 is presented in A.1.1.

Model MC3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	4.60	2.71	[1e-2,1e2]	<sup>1</sup>	-
$k_V$	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} cell^{-1}$	1.84e-6	2.06e-6	[1e-8,1e-4]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(PFU/ml)^{-1}$	2.08e-6	4.28e-6	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	0.011	0.012	-	<sup>6</sup>	
$d_T^{downregulation}$	CD8+ T cell linear downregulation rate	$d^{-1}$	1e-4	3.4e-3	[1e-4,0]	<sup>4,5</sup>	

**Table A.3.11.** Summary of MC3 parameters. The mathematical expression for MC3 is presented in A.1.1.

Model MC4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$p$	Viral replication rate	$d^{-1}$	5.42	3.16	[1e-2,1e2]	<sup>1</sup>	-
$k_V$	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
$c_V$	Viral clearance rate	$d^{-1} cell^{-1}$	2.13e-6	2.08e-6	[1e-8,1e-4]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(PFU/ml)^{-1}$	1.31e-6	3.84e-6	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	-	<sup>6</sup>	
$d_T^{downregulation}$	CD8+ T cell linear downregulation rate	$d^{-1}$	1e-4	1e-4	[1e-4,0]	<sup>4,5</sup>	
$c_T$	CD8+ T cell nonlinear downregulation rate	$(PFU/ml)d^{-1}$	1.30e-1	2.27e-1	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.12.** Summary of MC4 parameters. The mathematical expression for MC4 is presented in A.1.1.

#### 18 A.3.4 Model Group D

Model MD1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(PFU/ml)^{-1}d^{-1}$	2.15e-5	4.07e-5	[1e-8,1e-4]	<sup>2</sup>	-
$d_I$	Clearance rate of infected cells	$cells^{-2}$	6.72e-7	4.28e-7	[1e-8,1e-4]	<sup>2</sup>	
$p$	Production rate of virus	$d^{-1}$			1e0	<sup>2</sup>	Fixed for structural identifiability.
$c$	Clearance rate of virus	$d^{-1}$	2.06	11.3	[1e-2,1e2]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(PFU/ml)^{-1}$	2.61e-6	1.17e-5	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{half\ life}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	-	<sup>6</sup>	

**Table A.3.13.** Summary of MD1 parameters. The mathematical expression for MD1 is presented in A.1.1.

Model MD2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1}d^{-1}$	2.15e-5	1.67e-5	[1e-8,1e-4]	<sup>2</sup>	-
$d_I$	Clearance rate of infected cells	$\text{cells}^{-2}$	6.72e-7	4.43e-7	[1e-8,1e-4]	<sup>2</sup>	Fixed for structural identifiability.
$p$	Production rate of virus	$d^{-1}$			1e0	<sup>2</sup>	
$c$	Clearance rate of virus	$d^{-1}$	2.06	13.1	[1e-2,1e2]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(\text{PFU/ml})^{-1}$	2.61e-6	7.78e-6	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	0.0648	1.00e-4	[1e-4,1e0]	<sup>6</sup>	
$c_T$	CD8+ T cell nonlinear downregulation rate	$(\text{PFU/ml})d^{-1}$	4.28e-12	1.72e-1	[0,1e0]	-	Assumed similar to $d_T$

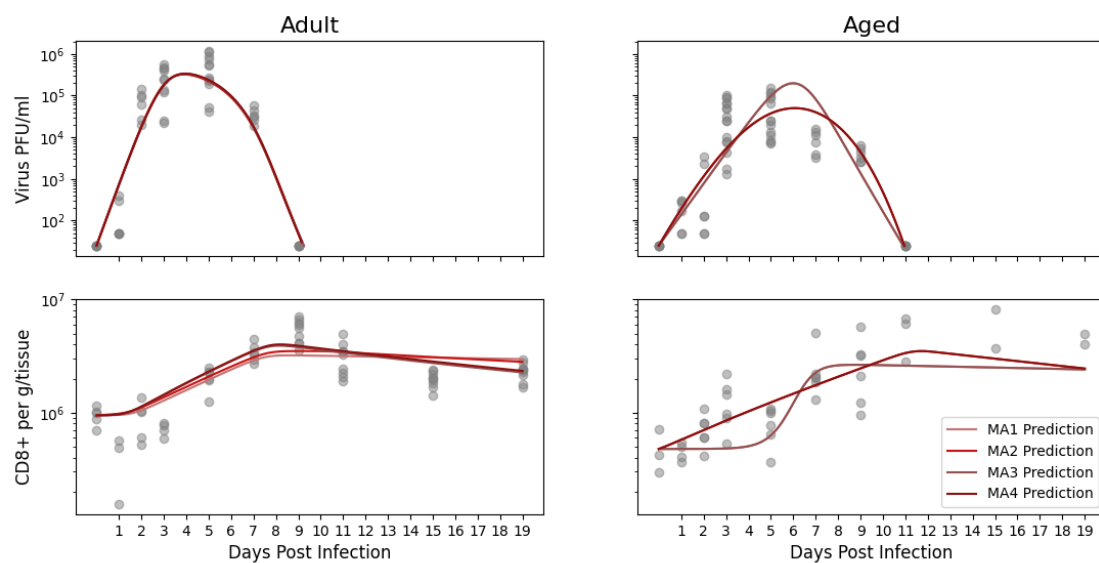
**Table A.3.14.** Summary of MD2 parameters. The mathematical expression for MD2 is presented in [A.1.1](#).

Model MD3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1}d^{-1}$	2.08e-5	1.71e-5	[1e-8,1e-4]	<sup>2</sup>	-
$d_I$	Clearance rate of infected cells	$\text{cells}^{-2}$	5.76e-7	6.00e-6	[1e-8,1e-4]	<sup>2</sup>	Fixed for structural identifiability.
$p$	Production rate of virus	$d^{-1}$			1e0	<sup>2</sup>	
$c$	Clearance rate of virus	$d^{-1}$	2.05	1.25	[1e-2,1e2]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(\text{PFU/ml})^{-1}$	3.13e-6	1.24e-5	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	[1e-4,1e0]	<sup>6</sup>	
$d_T^{\text{downregulation}}$	CD8+ T cell linear downregulation rate	$d^{-1}$	5.42e-2	1.00e-4	[1e-4,1e0]	<sup>4,5</sup>	

**Table A.3.15.** Summary of MD3 parameters. The mathematical expression for MD3 is presented in [A.1.1](#).

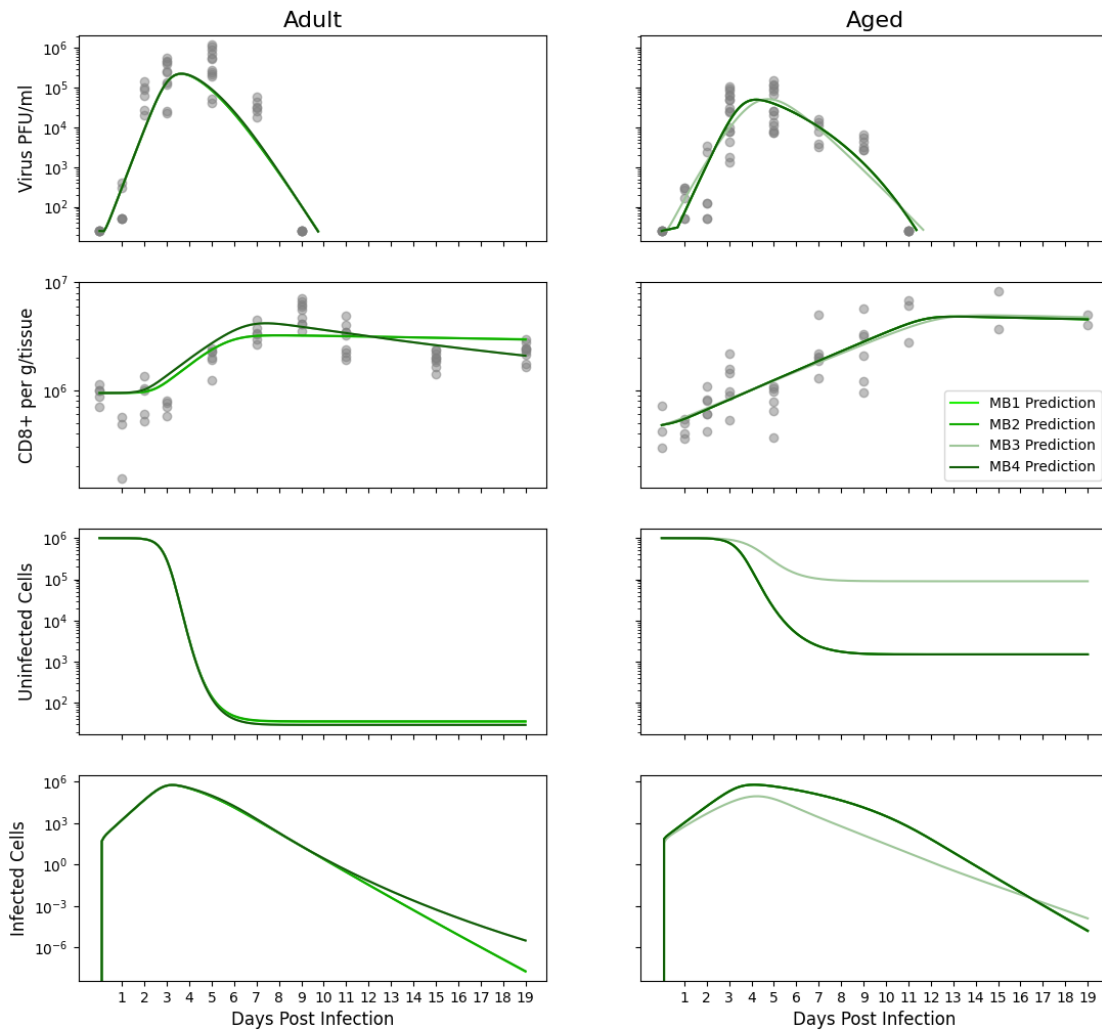
Model MD4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
$\beta$	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1}d^{-1}$	2.08e-5	1.67e-5	[1e-8,1e-4]	<sup>2</sup>	-
$d_I$	Clearance rate of infected cells	$\text{cells}^{-2}$	5.76e-7	4.43e-6	[1e-8,1e-4]	<sup>2</sup>	Fixed for structural identifiability.
$p$	Production rate of virus	$d^{-1}$			1e0	<sup>2</sup>	
$c$	Clearance rate of virus	$d^{-1}$	2.05	1.31	[1e-2,1e2]	<sup>2</sup>	
$s_T$	Homeostatic CD8+ T cell proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
$r$	CD8+ T cell proliferation rate	$d^{-1}(\text{PFU/ml})^{-1}$	3.13e-6	7.78e-6	[1e-4/ $k_V$ ,1e2/ $k_V$ ]	<sup>1,3</sup>	Bounds are scaled.
$d_T^{\text{half life}}$	CD8+ T cell half life	$d^{-1}$	1.1e-2	1.2e-2	[1e-4,1e0]	<sup>6</sup>	
$d_T^{\text{downregulation}}$	CD8+ T cell linear downregulation rate	$d^{-1}$	5.42e-2	1.00e-4	[1e-4,1e0]	<sup>4,5</sup>	
$c_T$	CD8+ T cell nonlinear downregulation rate	$(\text{PFU/ml})d^{-1}$	1.02e-11	1.72e-1	[0,1e0]	-	Assumed similar to $d_T$

**Table A.3.16.** Summary of MD4 parameters. The mathematical expression for MD4 is presented in [A.1.1](#).

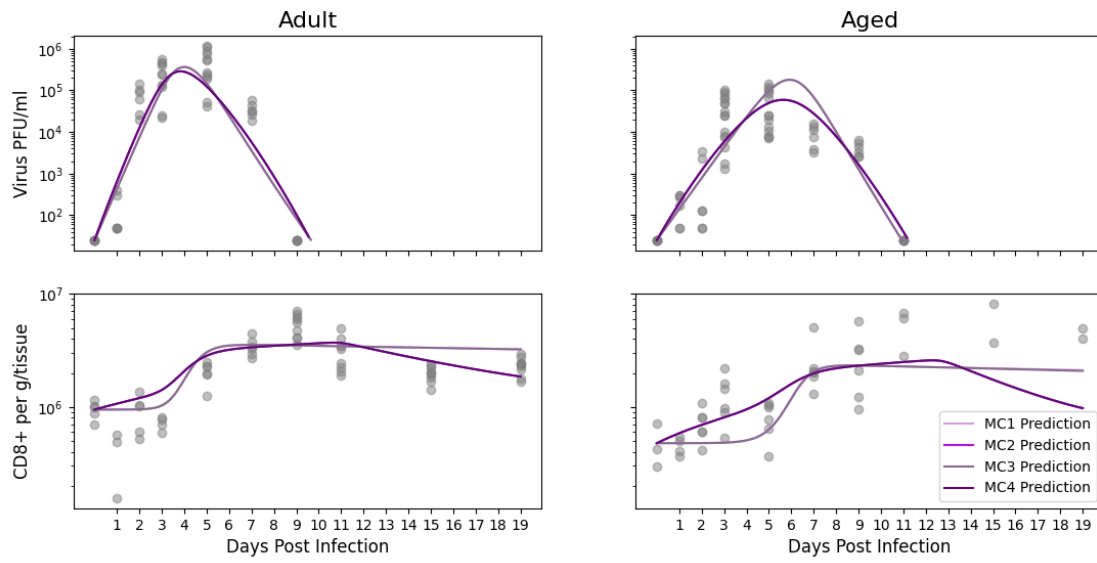


**Figure A.4.1.** Group A fitted model trajectories alongside the data from Toapanta et al.<sup>7</sup>.

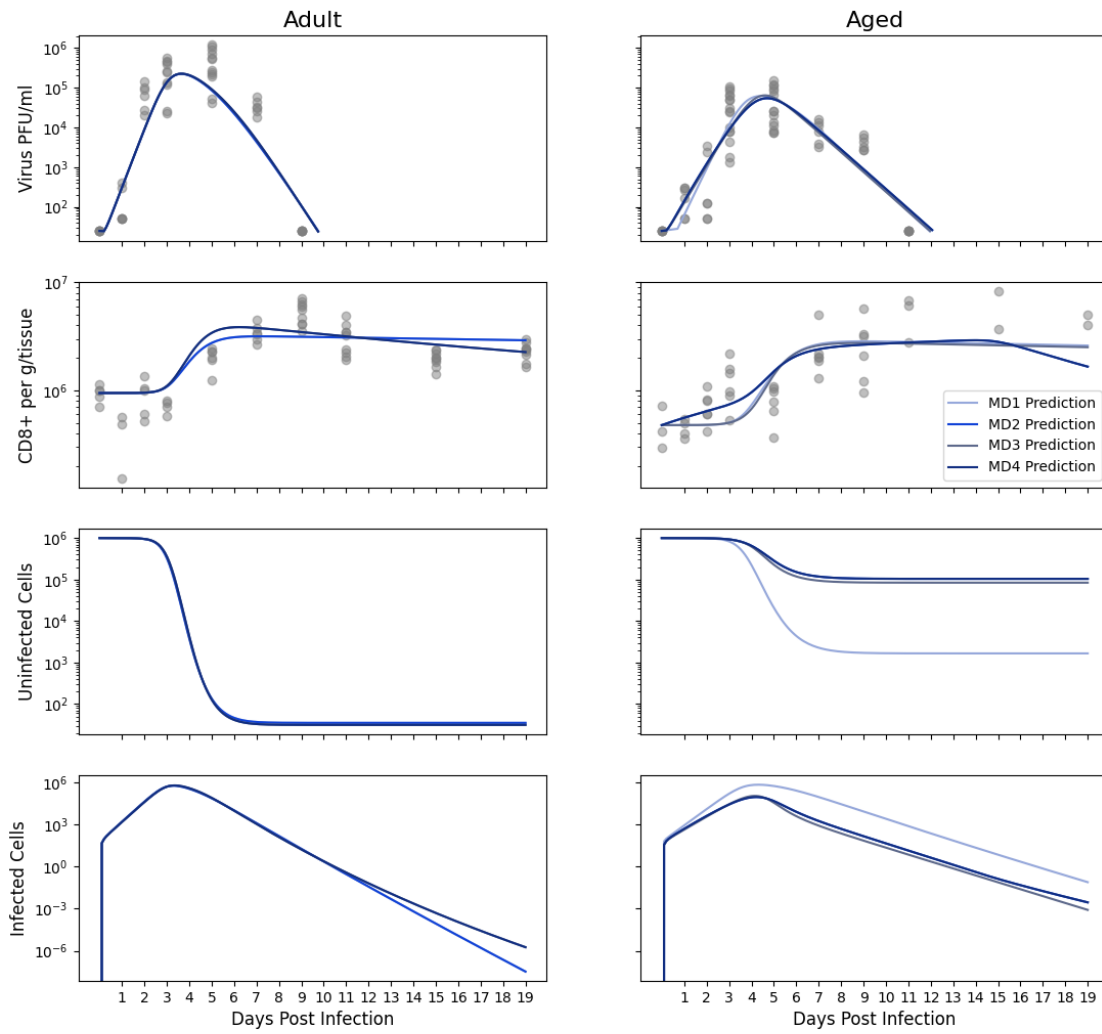




**Figure A.4.2.** Group B fitted model trajectories alongside the data from Toapanta et al.<sup>7</sup>.

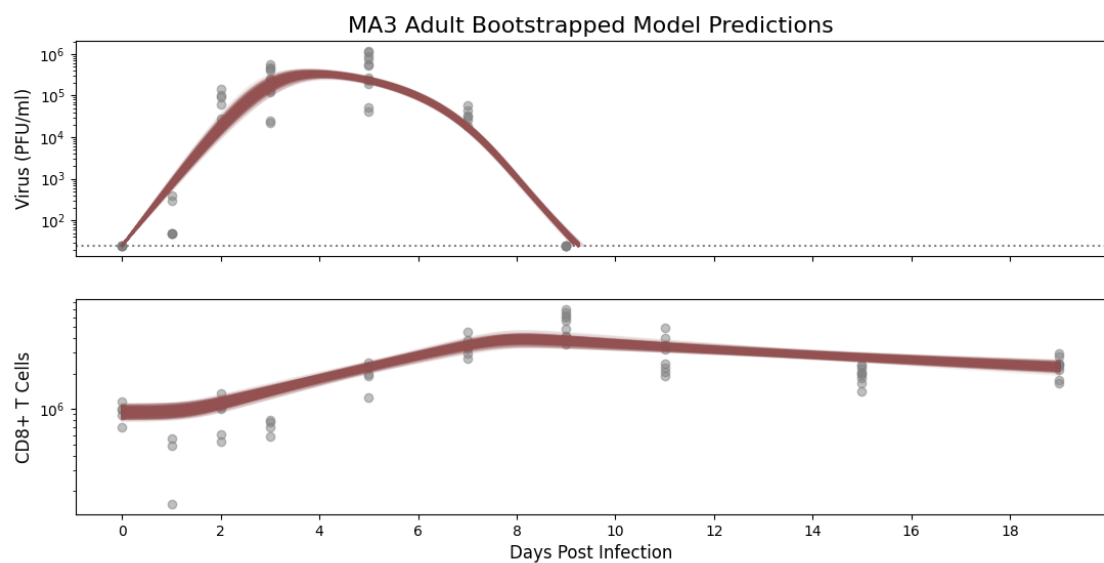


**Figure A.4.3.** Group C fitted model trajectories alongside the data from Toapanta et al.<sup>7</sup>.

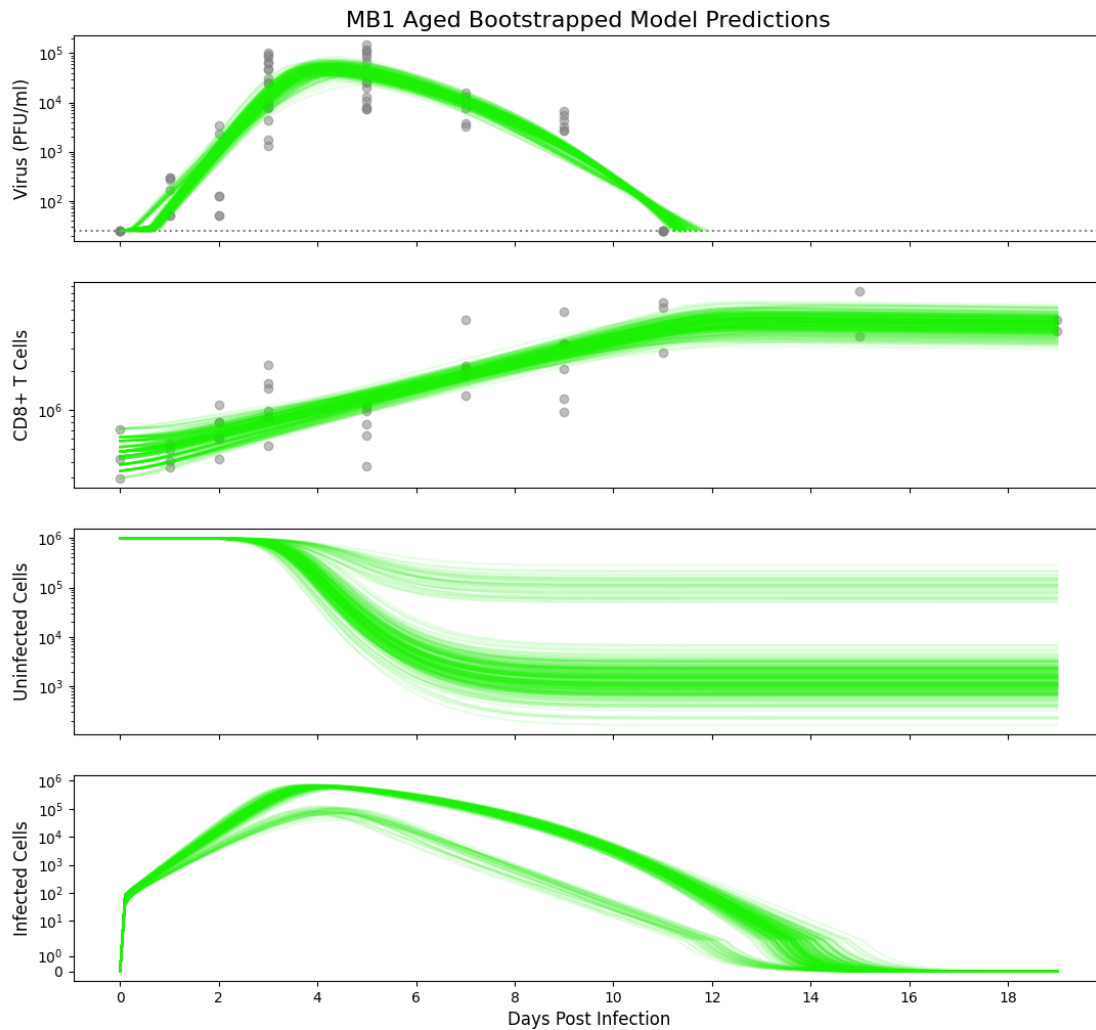


**Figure A.4.4.** Group D fitted model trajectories alongside the data from Toapanta et al.<sup>7</sup>.

20 **A.5 Bootstrapped Predictions for the Selected Models**



**Figure A.5.1.** Adult model (MA3) bootstrapped trajectories alongside the data from Toapanta et al.<sup>7</sup>.



**Figure A.5.2.** Aged model (MB1) bootstrapped trajectories alongside the data from Toapanta et al.<sup>7</sup>.

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