

Table S1. PK, Granuloma, PD, and Inhaled Carrier Model Parameters

<i>Pharmacokinetic Parameters</i> ⁽¹⁾				
Parameter	Description	INH	RIF	Reference
K_a	Absorption Rate Constant (h^{-1})	[0.75 – 1.35]	[0.1 – 0.5]	Fit to ^{1,2}
CL_A	Clearance Rate Constant – 2 nd Abs Comp. (L/h*kg)	[9.5 – 16]	[0.01 – 0.075]	Fit to ^{1,2}
CL_{PE}	Clearance Rate Constant – Peripheral Comp. (L/h*kg)	[0.025 – 0.1]	[0.1 – 1.0]	Fit to ^{1,2}
CL_M	Clearance Rate Constant – Macrophage Comp. (L/h*kg)	0.005	0.0053	Fit to ^{1,2}
Q_P	Transfer Rate Constant – Plasma to Peripheral (h^{-1})	0.25	0.25	Fit to ^{1,2}
Q_L	Transfer Rate Constant – Plasma to Non-Infected Lung (h^{-1})	0.25	0.25	Fit to ^{1,2}
V_{PL}	Apparent Volume Distribution – Plasma (L/kg)	0.06	0.06	Fit to ^{1,2}
V_{PE}	Apparent Volume Distribution – Periphery (L/kg)	[0.01 – 0.1]	[0.5 – 5]	Fit to ^{1,2}
V_L	Apparent Volume Distribution – Non-Infected Lung (L/kg)	0.00875	0.00875	Fit to ^{1,2}
PC_L	Partition Coefficient – Non-Infected Lung/Granuloma	0.25	3.3	Fit to ^{1,2}
L_L	Total Lung Volume (L)	0.04375	0.04375	³⁻⁷
L_P	Total Plasma Volume (L)	0.42	0.42	³⁻⁷
N_M	Number of Macrophages in Non-Infected Lung	2.26×10^8	2.26×10^8	Estimated
<i>Granuloma and Non-Infected Lung Related Parameters</i>				
Parameter	Description	INH	RIF	
δ_{ext}	Extracellular Degradation Rate Constant (s^{-1})	5.52×10^{-9}	7.5×10^{-8}	Supp. Paper
δ_{int}	Intracellular Degradation Rate Constant (s^{-1})	6.4×10^{-3}	6.7×10^{-3}	Supp. Paper
D	Apparent Diffusivity in Lung Tissue (cm^2/s)	1.11×10^{-7}	6.96×10^{-7}	Supp. Paper
E_M	Equilibrium Partition Coefficient	0.35	17.8	Supp. Paper
p	Vascular Permeability (cm/s)	8.42×10^{-6}	8.42×10^{-6}	Supp. Paper
L_M	Macrophage Volume (L)	4.85×10^{-12}	4.85×10^{-12}	Supp. Paper
L_{Grid}	Micro-Compartment Volume (L)	8×10^{-12}	8×10^{-12}	Supp. Paper
<i>Pharmacodynamic Parameters</i>				
Parameter	Description	INH	RIF	
$C_{50,BI}$	Intracellular <i>Mtb</i> – C50 (mg/L)	0.02	10	Supp. Paper
$C_{50,BE}$	Extracellular Replicating <i>Mtb</i> – C50 (mg/L)	0.04	1.23	Supp. Paper
$C_{50,BN}$	Extracellular Non-Replicating <i>Mtb</i> – C50 (mg/L)	0.5	5	Supp. Paper
H_{BI}	Intracellular <i>Mtb</i> – Hill Constant	1	0.48	Supp. Paper
H_{BE}	Extracellular Replicating <i>Mtb</i> – Hill Constant	1	0.7	Supp. Paper
H_{BN}	Extracellular Non-Replicating <i>Mtb</i> – Hill Constant	1	0.7	Supp. Paper
$E_{max,BI}$	Intracellular <i>Mtb</i> – Max Activity (timestep ⁻¹)	0.046	0.069	Supp. Paper
$E_{max,BE}$	Extracellular <i>Mtb</i> – Max Activity (timestep ⁻¹)	0.155	0.296	Supp. Paper
<i>Inhaled Carrier Parameters</i> ⁽²⁾				
Parameter	Description	INH	RIF	
T_{Dose}	Total Carrier Dose to Lungs (# of carriers)	1.2×10^9	1.2×10^9	Fit to ²
f_D	Dose Fraction to Granuloma Compartment	1.18×10^{-6}	1.18×10^{-6}	Estimated
P_{load}	Inhaled Carrier Drug Loading (mg/carrier)	$[1 \times 10^{-8} - 5 \times 10^{-7}]$	$[1 \times 10^{-9} - 5 \times 10^{-8}]$	⁸⁻¹⁸
P_{size}	Diameter of Carrier (μm)	[2.0 – 8.0]	[2.0 – 8.0]	¹⁹⁻²²
$P_{sizeDev}$	Range of Diameter of Carrier (μm)	1.0	1.0	¹⁹⁻²²

$P_{drugDiff}$	Diffusivity of Drug in Carrier ($\mu\text{m}^2/\text{s}$)	$[1 \times 10^{-8} - 5 \times 10^{-6}]$	$[1 \times 10^{-8} - 5 \times 10^{-6}]$	8–18
P_{intDeg}	Carrier Intracellular Degradation Rate (s^{-1})	$[5 \times 10^{-6} - 5 \times 10^{-5}]$	$[5 \times 10^{-6} - 5 \times 10^{-5}]$	8–18
P_{extDeg}	Carrier Extracellular Degradation Rate (s^{-1})	$[5 \times 10^{-6} - 5 \times 10^{-5}]$	$[5 \times 10^{-6} - 5 \times 10^{-5}]$	8–18
P_{zeta}	Carrier Zeta Potential (mV)	$[-40.0 - 0]$	$[-40.0 - 0]$	19–22
P_{diff}	Carrier Apparent Diffusivity in Lung Tissue (cm^2/s)	$[2 \times 10^{-10} - 1.95 \times 10^{-9}]$	$[2 \times 10^{-10} - 1.95 \times 10^{-9}]$	23
M_{uptake}	Macrophage Maximum Carrier Uptake Probability	$[0.01 - 0.95]$	$[0.01 - 0.95]$	Estimated
P_{TL}	Density of Targeting Ligand on Carrier (#/carrier)	$[1 \times 10^1 - 1 \times 10^4]$	$[1 \times 10^1 - 1 \times 10^4]$	24–27
M_{TR}	Density of Targeting Receptor on Macrophages (#/cell)	$[1 \times 10^1 - 1 \times 10^4]$	$[1 \times 10^1 - 1 \times 10^4]$	24–27
K_{D-TLR}	Ligand-Receptor Equilibrium Rate Constant (M)	$[1 \times 10^{-9} - 1 \times 10^{-7}]$	$[1 \times 10^{-9} - 1 \times 10^{-7}]$	24–27
k_{TLR}	Poisson – Ligand-Receptor Carrier Uptake Rate (#/cell*s)	$[5 \times 10^{-4} - 5 \times 10^{-3}]$	$[5 \times 10^{-4} - 5 \times 10^{-3}]$	Estimated
W_{Shape}	Weibull – Carrier Size Uptake Rate – Shape Parameter	1.9	1.9	19–22
W_{Scale}	Weibull – Carrier Size Uptake Rate – Scale Parameter	3.5	3.5	19–22
W_{Max}	Weibull – Carrier Size Uptake Rate – Max Parameter	0.2372	0.2372	19–22
C_{Scale}	Parabolic – Carrier Zeta-Potential Uptake Rate – Scale Parameter	400	400	19–22

(1) Ranges given to account for inter-individual variability. These ranges are also used in sensitivity analysis.

(2) Ranges given are used in sensitivity analysis

Table S2. Agent-Based Model Parameters – From ^{28,29} (Supplemental Paper)

Parameter Description	Value(s)
Bacterial carrying capacity of each grid compartment (#)	114.5
Intracellular bacterial growth rate (timestep ⁻¹)	1.0045
Extracellular bacterial growth rate (timestep ⁻¹)	1.0025
Rate of death of bacteria trapped in caseated compartments (timestep ⁻¹)	0.85
Number of host cell deaths causing caseation (#)	9
Time to heal caseation (timesteps)	1467
TNF threshold for causing apoptosis (# of molecules)	1147
Rate of TNF induced apoptosis (s^{-1})	1.7×10^{-6}
Minimum chemokine concentration allowing chemotaxis (# of molecules)	0.47
Maximum chemokine concentration allowing chemotaxis (# of molecules)	476
Initial macrophage density (fraction of grid)	0.04
Time steps before a resting macrophage can move (timesteps)	3
Time steps before an activated macrophage can move (timesteps)	19
Time steps before an infected macrophage can move (timesteps)	170
TNF threshold for activating NFkB (# of molecules)	73
Rate of TNF induced NFkB activation (s^{-1})	1.06×10^{-5}
Number of bacteria resting macrophage can phagocytose (#)	1
Probability of resting macrophage killing bacteria	0.12
Adjustment for killing probability of resting macrophages with NFkB activated	0.2
Number of extracellular bacteria that can activate NFkB (#)	253
Threshold for intracellular bacteria causing chronically infected macrophages (#)	12
Threshold for intracellular bacteria causing macrophage to burst (#)	23
Number of bacteria activated macrophage can phagocytose (#)	5
Probability of an activated macrophage healing a caseated compartment in its Moore neighborhood	0.0055
Probability of a T-cell moving to the same compartment as a macrophage	0.046

IFN- γ -producing T-cell probability of inducing Fas/FasL mediated apoptosis	0.035
IFN- γ -producing T-cell probability of producing TNF	0.045
IFN- γ -producing T-cell probability of producing IFN	0.35
Cytotoxic T-cell probability of killing a macrophage	0.009
Cytotoxic T-cell probability of killing a macrophage and all of its intracellular bacteria	0.71
Cytotoxic T-cell probability of producing TNF	0.047
Regulatory T-cell probability of deactivating activated macrophage	0.008
Time before maximum recruitment rates are reached (timesteps)	982
Macrophage maximal recruitment probability	0.32
Macrophage chemokine recruitment threshold (# of molecules)	0.86
Macrophage TNF recruitment threshold (# of molecules)	0.011
Macrophage half sat for TNF recruitment (# of molecules)	1.63
Macrophage half sat for chemokine recruitment (# of molecules)	2.16
IFN- γ -producing T-cell maximal recruitment probability	0.15
IFN- γ -producing T-cell chemokine recruitment threshold (# of molecules)	0.072
IFN- γ -producing T-cell TNF recruitment threshold (# of molecules)	1.27
IFN- γ -producing T-cell half sat for TNF recruitment (# of molecules)	1.34
IFN- γ -producing T-cell half sat for chemokine recruitment (# of molecules)	1.87
Cytotoxic T-cell maximal recruitment probability	0.12
Cytotoxic T-cell chemokine recruitment threshold (# of molecules)	4.48
Cytotoxic T-cell TNF recruitment threshold (# of molecules)	1.27
Cytotoxic T-cell half sat for TNF recruitment (# of molecules)	1.19
Cytotoxic T-cell half sat for chemokine recruitment (# of molecules)	8.62
Regulatory T-cell maximal recruitment probability	0.029
Regulatory T-cell chemokine recruitment threshold (# of molecules)	2.05
Regulatory T-cell TNF recruitment threshold (# of molecules)	1.63
Regulatory T-cell half sat for TNF recruitment (# of molecules)	2.23
Regulatory T-cell half sat for chemokine recruitment (# of molecules)	1.5

Tunable Resolution Related Parameters

Parameter Description	Value(s)
Apparent TNF consumption rate (s^{-1})	0.00077
Apparent IL-10 consumption rate (s^{-1})	0.0004
Partition factor for estimating internalized bound receptors	11.3
Threshold for IL-10 inhibition of TNF secretion	-1.93
Shape parameter for IL-10 inhibition of TNF secretion	0.181
Apparent TNF secretion rate by macrophages (# of molecules/s)	1.5
Apparent IL-10 secretion rate by activated macrophages (# of molecules/s)	0.3
Apparent IL-10 secretion rate by infected macrophages (# of molecules/s)	0.02
Apparent TNF secretion rate by IFN γ producing T-cells (# of molecules/s)	0.15
Apparent TNF secretion rate by cytotoxic T-cells (# of molecules/s)	0.015
Apparent IL-10 secretion rate by regulatory T-cells (# of molecules/s)	0.739
Affinity of TNF for TNFR1 (M)	1.9×10^{-11}
Affinity of IL-10 for IL-10R (M)	4.56×10^{-10}

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