Table S1. Estimated pharmacodynamic parameters based on *in vitro* static time-kill data.

Parameter	Abbreviation	ATCC 27853		PAO1		FADDI-PA022	
		Estimated value	SE (%)	Estimated value	SE (%)	Estimated value	SE (%)
		2-Subpopulation model		3-Subpopulation model		3-Subpopulation model	
Colistin concentration causing 50% E_{max} for susceptible-subpopulation (mg/L)	**EC_{50S}**	2.19	8.05	0.872	10.8	1.06	4.52
Colistin concentration causing 50% E_{max} for intermediate-subpopulation (mg/L)	**EC_{50I}**	NA	NA	2.8	1.32	2.26	4.14
Colistin concentration causing 50% E_{max} for resistant-subpopulation (mg/L)	**EC_{50R}**	6.26	0.44	57.6	141	36.1	180

Maximum colistin-induced killing rate constant (1/h)	$\mathbf{E_{max}}$	436	1.54	41.4	3.67	152	9.94
Natural bacterial death rate (1/h)	$\mathbf{K_d}$	0.229	30.2	0.236	4.15	0.187	5.19
Bacterial density at which growth rate is half-maximal (CFU/Lung)	$\mathbf{Log_{10}CFU_m}$	7.78	2.38	8.45	0.458	8.48	0.453
Maximum bacterial population (CFU/Lung)	$\mathbf{Log_{10}CFU_{max}}$	8.96	0.624	9.12	0.154	8.99	0.618
Log_{10} Initial inoculum for total bacterial population (CFU/Lung)	$\mathbf{Log_{10}CFU_0}$	5.95	2.68	7.03	0.526	6.86	1.77
Log_{10} initial inoculum for intermediate-subpopulation	$\mathbf{Log_{10}I}$	NA	NA	-3.81	1.9	-3.18	2.65
Log_{10} initial inoculum for resistant-subpopulation	$\mathbf{Log_{10}R}$	-6.64	21.9	-9.47	4.63	-5.8	1.67

NA, Not applicable

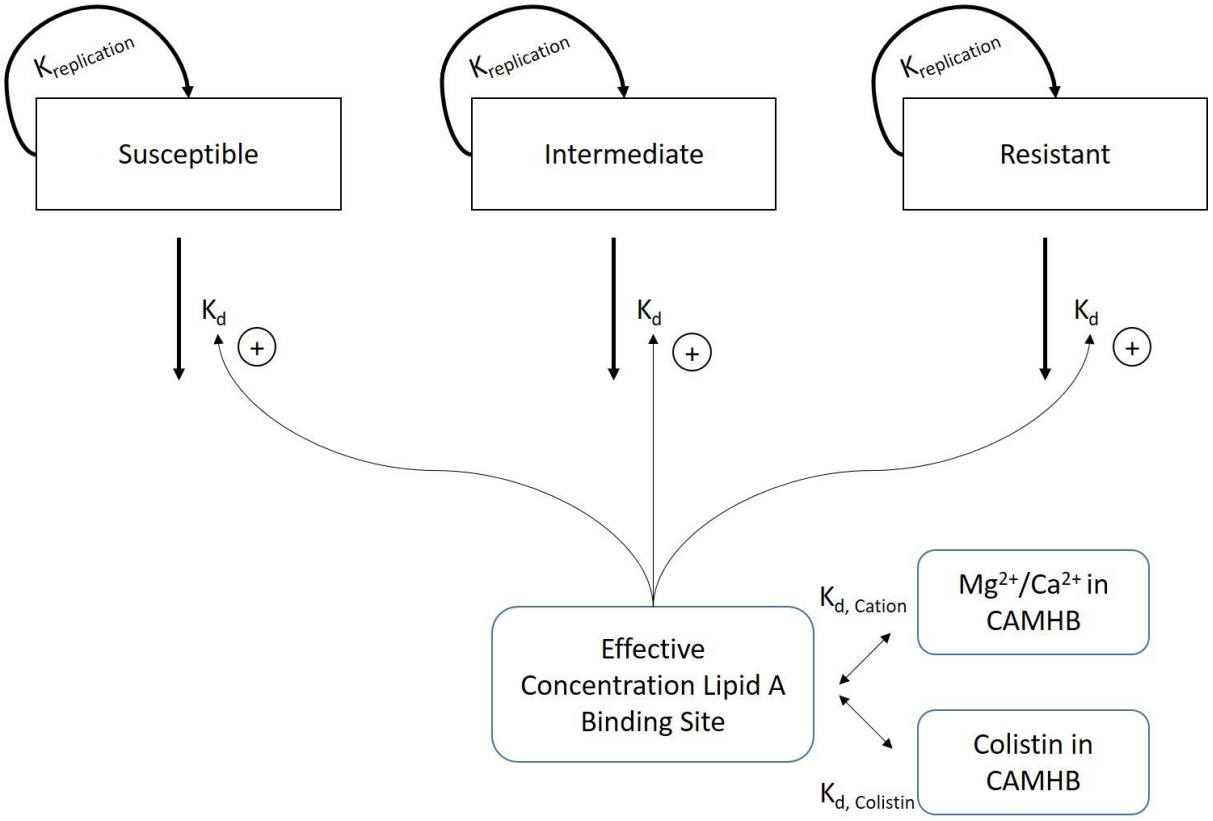

Figure S1. Schematic diagram of the mechanism-based pharmacodynamic model based on *in vitro* static concentration time-kill data.

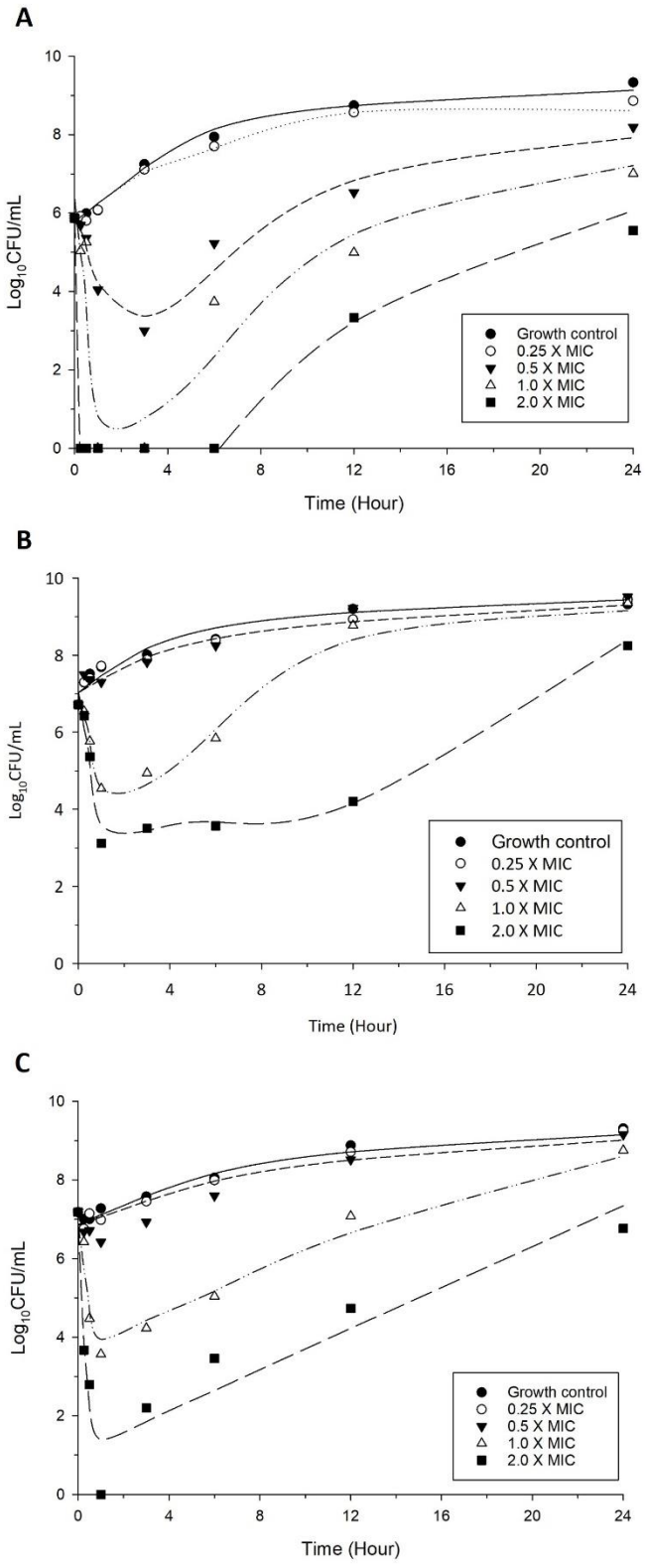

Figure S2. *In vitro* static time-kill profiles for **(A)** *P. aeruginosa* ATCC 27853, **(B)** PAO1 and **(C)** FADDI-PA022 after exposure to colistin at concentrations ranging from 0 to 2 x MIC. The solid and broken lines are model-predicted bacterial load.

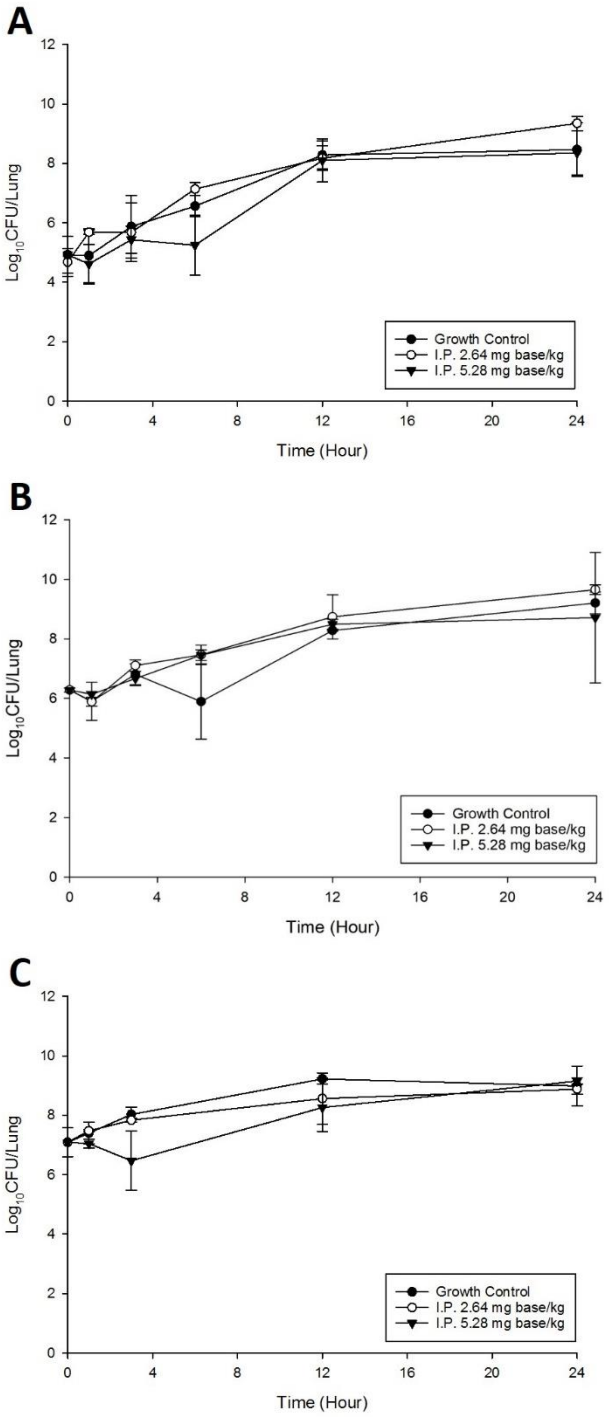

Figure S3. Killing kinetics in mouse lungs against *P. aeruginosa* **(A)** ATCC 27853, **(B)** PAO1, and **(C)** FADDI-PA022 following intraperitoneal administration (I.P.) of 2.64 and 5.28 mg base/kg colistin. The limit of detection is 164 CFU/Lung (one colony per plate). Data represent mean ± standard deviation (n = 3 or more per time point).

Methods for *in vitro* static time-kill

Static time-kill experiments were performed with an initial inoculum of ~10^6 CFU/mL. All experiments were conducted in 50-mL pyrogen-free and sterile polypropylene tubes with 20 mL of cation-adjusted Mueller-Hinton broth (CAMHB). Colistin concentrations were 0.25, 0.5, 1 and 2 mg/L, and a growth control (without colistin treatment) was also included. Serial samples (50 µL) were taken at 0, 15, 30 min and 1, 3, 6, 12, and 24 h for viable counting with nutrient agar plates and the limit of detection was 110 CFU/mL (equivalent to one colony per plate).

Results for MBM for *in vitro* static time-kill data

The static time-kill experiments showed an initial rapid killing followed by regrowth at all colistin concentrations tested. The developed MBM described well the kinetics of bacterial killing and regrowth (Figures S1 and S2). PAO1 and FADDI-PA022 were described by a three-subpopulation model, whereas ATCC 27853 was described by a two-subpopulation model (Table S1). Rates of natural bacterial growth and death were assumed to be the same for all subpopulations within each isolate. Subpopulations within each isolate were assumed to have different initial inocula and EC_{50} values. The parameter estimates of the final model are shown in Table S1. Deterministic simulation with mouse PK data resulted in poor prediction of the *in vivo* efficacy of aerosolized colistin observed in the mouse lung infection model (data not shown).