Supplemental Material:

Mechanism-based modeling methods

The final model included three subpopulations that represented susceptible bacteria (CFU_{SS}), intermediate bacteria (CFU_{IR}, meropenem intermediate, tobramycin resistant) and resistant bacteria (CFU_{RI}, meropenem resistant, tobramycin intermediate). The proportions of intermediate and resistant bacteria present in the initial inoculum were estimated (Log_{10} proportion of resistant $bacteria_{IR}$ [$LogPRB_{IR}$], and Log_{10} proportion of resistant $bacteria_{RI}$ [$LogPRB_{RI}$]). These model-estimated less-susceptible subpopulations did not directly reflect the observed bacterial counts on agar containing 2.5× and 10× the meropenem and tobramycin MIC. For each subpopulation, a life-cycle growth model described bacterial growth and replication. The model included bacteria that are preparing for replication (state 1) and bacteria immediately before the replication step (state 2). The first-order growth rate constant k_{12} described transition from state 1 to state 2, where k_{12} = 60/MGT and MGT was mean generation time. The replication constant k_{21} was assumed to be fast. The total concentration of all viable bacteria (CFU_{ALL}) was described as:

$$CFU_{ALL} = CFU_{SS1} + CFU_{SS2} + CFU_{IR1} + CFU_{IR2} + CFU_{RI1} + CFU_{RI2} \quad (1)$$

A direct bacterial killing process with a Hill function was used to describe the killing by each antibiotic as the rates of bacterial killing by high concentrations of meropenem and tobramycin or by their synergistic combinations were faster than the bacterial growth rate. The differential equation for the concentration of bacteria in state 1 of the susceptible population (CFU_{SS1}) incorporated killing by meropenem (C_{MEM}) and tobramycin (C_{TOB}):

$$\frac{d(CFU_{SS1})}{dt} = REP \cdot k_{21} \cdot CFU_{SS2} - k_{12SS} \cdot CFU_{SS1} - \left(\frac{K_{max,MEM,SS} \cdot C_{MEM}^{Hill_{MEM}}}{C_{MEM}^{Hill_{MEM}} + (OM\_effect \cdot KC_{50,MEM,SS})^{Hill_{MEM}}} + \frac{K_{max,TOB,SS} \cdot C_{TOB}^{Hill_{TOB}}}{C_{TOB}^{Hill_{TOB}} + KC_{50,TOB,SS}^{Hill_{TOB}}} \right) \cdot CFU_{SS1} \quad (2)$$

where REP is the replication factor which ensures that CFU_{ALL} cannot exceed the maximum population size CFU_{max}:

$$REP = 2 \cdot \left(1 - \frac{CFU_{ALL}}{CFU_{max} + CFU_{ALL}}\right) \quad (3)$$

At low CFU_{ALL}, REP approaches 2 which represents a 100% probability of successful replication. As CFU_{ALL} approaches CFU_{max}, REP approaches 1. This represents a 50% probability of successful replication where bacteria continue to transition between states 1 and 2 but the total viable count remains constant. The maximum killing rate constant for meropenem ($K_{max,MEM,SS}$), the meropenem concentration causing 50% of K_{max} for the susceptible population ($KC_{50,MEM,SS}$), and the Hill coefficient for meropenem ($Hill_{MEM}$) affected both states 1 and 2 of the population. The maximum killing rate constant for tobramycin was $K_{max,TOB,SS}$ and the tobramycin concentration causing 50% of K_{max} was $KC_{50,TOB,SS}$. The ability of tobramycin to permeabilize the outer membrane (OM_effect; *i.e.* the synergy term) is described in equation 5 below. State 2 of population 1 (CFU_{SS2}) was described as:

$$\frac{d\left(CFU_{SS2}\right)}{dt} = -k_{21} \cdot CFU_{SS2} + k_{12SS} \cdot CFU_{SS1} - \left(\frac{K_{max,MEM,SS} \cdot C_{MEM}^{Hill_{MEM}}}{C_{MEM}^{Hill_{MEM}} + \left(OM\_effect \cdot KC_{50,MEM,SS}\right)^{Hill_{MEM}}} + \frac{K_{max,TOB,SS} \cdot C_{TOB}^{Hill_{TOB}}}{C_{TOB}^{Hill_{TOB}} + KC_{50,TOB,SS}^{Hill_{TOB}}}\right) \cdot CFU_{SS2} \quad (4)$$

The differential equations for the CFU_{IR} and CFU_{RI} populations had the same structure as for CFU_{SS}, but different parameters for k_{12}, $K_{max,MEM}$, $KC_{50,MEM}$, $K_{max,TOB}$ and $KC_{50,TOB}$ as described previously.

Mechanism-based modeling of synergy: Mechanistic synergy (*i.e.* one antibiotic enhancing the killing by the other antibiotic against one or multiple bacterial populations) was incorporated by assuming that disruption of the bacterial outer membrane by tobramycin increases the target site penetration of meropenem. The term OM_effect described the effect of tobramycin on decreasing the $KC_{50,MEM}$:

$$OM\_effect = 1 - \left(\frac{I_{max,OM} \cdot C_{TOB}^{Hill_{OM}}}{C_{TOB}^{Hill_{OM}} + IC_{50,OM}^{Hill_{OM}}}\right) \quad (5)$$

The $\log_{10}$ bacterial counts were fitted using an additive residual error model on $\log_{10}$ scale. For counts below 100 CFU/mL (<10 colonies/plate), a previously developed residual error model was utilized to fit the number of colonies per plate.

TABLE S1 Log_{10} mutation frequencies at 2.5 mg/liter meropenem (2.5× MIC) and 5 mg/liter tobramycin (10× MIC) at various time points for each concentration (monotherapy and combinations) in the SCTK.[a]

		Time (h)	Control	TOB 1 (mg/liter)	TOB 4 (mg/liter)	TOB 8 (mg/liter)	MEM 2 (mg/liter)	MEM 8 (mg/liter)	MEM 16 (mg/liter)	TOB 1 + MEM 2 (mg/liter)	TOB 1 + MEM 8 (mg/liter)	TOB 1 + MEM 16 (mg/liter)	TOB 4 + MEM 2 (mg/liter)	TOB 4 + MEM 8 (mg/liter)	TOB 4 + MEM 16 (mg/liter)	TOB 8 + MEM 2 (mg/liter)	TOB 8 + MEM 8 (mg/liter)	TOB 8 + MEM 16 (mg/liter)
PAO1 WT	MEM 2.5 mg/liter	24	-7.04	-	-	-	-1.78	<-2.58	<-2.61	<-4.34	<-1.51	<-1.41	<-3.16	<-1.53	<-1.38	<-2.59	<-1.20	<0.70
		48	-6.55	-	-	-	-0.31	<-1.56	<-1.38	<-2.46	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70
		96	-6.64	-	-	-	-0.26	-2.07	<0.70	-2.39	<-1.40	<-1.55	-0.46	<0.70	<-0.12	<0.70	<0.70	<-2.62
	TOB 5 mg/liter	24	<-9.29	-4.89	-1.10	-0.63	-	-	-	<-4.34	<-1.51	<-1.41	<-3.16	<-1.53	<-1.38	<-2.59	<-1.20	<0.70
		48	<-9.08	-5.49	-4.14	-2.61	-	-	-	<-2.46	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70	<0.70
		96	-7.10	-6.34	-4.72	-1.33	-	-	-	<-1.73	-2.06	-2.20	-2.31	<0.70	<-0.12	<0.70	<0.70	<-2.62
PAOΔ*mutS*	MEM 2.5 mg/liter	24	-4.96	-	-	-	-0.05	-0.89	<-2.56	-1.88	<-2.02	<-1.97	-3.76	<-3.72	<-1.53	-3.89	<2.37	<-1.34
		48	-5.45	-	-	-	-0.12	-0.52	<-1.82	-0.33	<0.70	<-0.30	-1.92	<-1.26	<0.70	<-1.75	<-0.30	<0.70
		96	-6.82	-	-	-	-0.14	-0.01	-2.57	-0.07	<-1.92	-3.78	-1.63	<-1.77	<-3.92	<-1.94	<0.70	<0.70
	TOB 5 mg/liter	24	-6.68	-5.05	-2.95	-2.85	-	-	-	<-4.23	<-2.02	<-1.97	<-4.54	<-3.72	<-1.53	<-3.89	<-2.37	<-1.34
		48	-6.18	-4.93	-1.20	-1.20	-	-	-	-2.47	<0.70	<-0.30	-0.41	<-1.26	<0.70	-1.27	<-0.30	<0.70
		96	-8.82	-5.46	-2.30	-4.14	-	-	-	-4.68	<-1.92	-2.44	0.04	<-1.77	<-3.92	-0.05	<0.70	<0.70

TOB, tobramycin; MEM, meropenem.

[a] When no colonies were present on antibiotic-containing plates, mutation frequencies reported represent an upper limit based on the total viable count.

TABLE S2 Log_{10} changes in viable counts at various time points for each concentration (monotherapy and combinations) in the SCTK. TOB, tobramycin; MEM, meropenem. A grey background indicates synergy (a ≥2-log_{10} decrease in the number of CFU/ml with the combination compared to its most active component).

	Time (h)	Control	TOB 1 (mg/ liter)	TOB 4 (mg/ liter)	TOB 8 (mg/ liter)	MEM 2 (mg/ liter)	MEM 8 (mg/ liter)	MEM 16 (mg/ liter)	TOB 1 + MEM 2 (mg/ liter)	TOB 1 + MEM 8 (mg/ liter)	TOB 1 + MEM 16 (mg/ liter)	TOB 4 + MEM 2 (mg/ liter)	TOB 4 + MEM 8 (mg/ liter)	TOB 4 + MEM 16 (mg/ liter)	TOB 8 + MEM 2 (mg/ liter)	TOB 8 + MEM 8 (mg/ liter)	TOB 8 + MEM 16 (mg/ liter)
PAO1 WT	1	0.35	-0.56	-2.53	-2.93	-0.11	-0.81	-1.08	-1.19	-1.27	-1.32	-2.81	-2.85	-2.67	-3.00	-3.09	-3.30
	3	1.16	-2.04	-3.11	-3.30	-1.17	-2.52	-2.67	-2.86	-2.88	-3.25	-3.16	-3.11	-3.08	-3.82	-3.74	-4.58
	6	1.39	-2.19	-3.73	-4.08	-2.58	-2.76	-2.86	-3.14	-3.71	-3.93	-4.00	-4.63	-4.13	-4.95	-4.96	-5.26
	24	2.20	1.17	-1.85	-3.09	-3.29	-4.52	-4.49	-2.75	-5.59	-5.68	-3.93	-5.56	-5.71	-4.50	-5.89	-7.79
	29	1.35	1.29	-1.67	-2.63	-4.04	-4.87	-4.87	-3.86	-6.32	-7.79	-5.45	-7.79	-7.79	-6.79	-7.79	-7.79
	48	1.99	1.92	1.41	-1.22	-3.56	-5.54	-5.71	-4.63	-7.79	-7.79	-7.79	-7.79	-7.79	-7.79	-7.79	-7.79
	72	2.30	2.22	2.10	1.32	-2.52	-6.32	-7.79	-6.79	-7.79	-7.79	-6.49	-7.79	-7.79	-7.79	-7.79	-7.79
	96	2.11	2.03	1.44	0.96	0.64	-7.79	-7.79	-7.79	-6.79	-7.79	-7.79	-7.79	-7.79	-7.79	-7.79	-7.79
PAOΔ*mutS*	1	0.51	-0.06	-1.71	-2.54	-0.01	-0.66	-0.70	-0.62	-0.89	-1.17	-2.13	-2.54	-2.45	-2.91	-2.66	-2.70
	3	1.31	-0.67	-2.45	-2.82	-0.61	-1.58	-0.54	-2.06	-2.18	-2.73	-2.66	-2.60	-2.71	-3.49	-3.09	-3.54
	6	1.45	-0.75	-2.77	-3.64	-1.53	-2.61	-2.64	-2.87	-3.77	-3.80	-3.35	-3.38	-3.64	-3.85	-3.91	-4.84
	24	2.18	1.78	1.45	1.19	1.35	-3.18	-4.41	-2.74	-4.95	-4.99	-2.43	-3.25	-5.43	-3.07	-4.60	-5.62
	29	1.36	1.42	0.88	1.18	1.35	-4.53	-4.58	-3.65	-5.71	-5.82	-4.49	-4.72	-6.66	-4.85	-6.18	-7.66
	48	2.43	2.18	2.24	2.15	2.17	-0.85	-5.14	-3.54	-7.66	-6.66	-4.34	-5.71	-7.66	-5.21	-6.66	-7.66
	72	2.39	2.43	1.54	1.58	1.62	0.77	-5.96	-1.73	-7.66	-5.58	-4.34	-6.66	-7.66	-5.76	-7.66	-7.66
	96	2.10	2.09	2.01	1.64	2.12	1.03	-5.32	1.27	-7.66	-5.28	-4.04	-7.66	-7.66	-5.25	-7.66	-7.66

TABLE S3 Population parameter estimates for meropenem and tobramycin in SCTK against PAO1 and PAO*ΔmutS*

Parameter	Symbol (unit)	Population mean (SE [%])
Bacterial growth and subpopulations		
Log_{10} CFU initial inoculum	$Log_{10}CFU_0$	7.72 (1.0)
Mean generation time		
susceptible population	MGT_{SS} (min)	57.3 (11.2)
intermediate population	MGT_{RI} (min)	2341 (10.5)
resistant population	MGT_{IR} (min)	78.4 (4.7)
Log_{10} CFU maximum population size	$Log_{10}CFU_{max}$	9.57 (1.4)
Log_{10} (proportion of resistant bacteria)		
intermediate population	$Log_{10}PRB_{RI}$	-8.53 (3.3)[a], -7.63 (2.2)[b]
resistant population	$Log_{10}PRB_{IR}$	-3.08 (3.6)[a], -2.99 (4.3)[b]
Bacterial killing by meropenem		
Maximum killing rate constant		
susceptible population	$K_{max,MEM,SS}$ (h^{-1})	3.77 (18.6)[a], 2.81 (17.9)[b]
intermediate population[c]	$K_{max,MEM,RI}$ (h^{-1})	0.652 (14.9)[a], 0.458 (9.5)[b]
resistant population[d]	$K_{max,MEM,IR}$ (h^{-1})	3.92 (17.2)[a], 1.69 (12.4)[b]
Meropenem concentration causing 50% of K_{max}		
susceptible population	$KC_{50,MEM,SS}$ (mg/liter)	2.07 (16)
intermediate population	$KC_{50,MEM,RI}$ (mg/liter)	81.2 (17.2)

resistant population	$KC_{50,MEM,IR}$ (mg/liter)	61.5 (15.5)[a], 40.0 (13.9)[b]
Hill coefficient	$Hill_{MEM}$	0.563 (18.9)
Bacterial killing by tobramycin		
Maximum killing rate constant		
susceptible population	$K_{max,TOB,SS}$ (h^{-1})	7.03 (16.7)[a], 5.73 (12.3)[b]
intermediate population	$K_{max,TOB,RI}$ (h^{-1})	0.624 (26.8)[a], 0.182 (23.4)[b]
resistant population	$K_{max,TOB,IR}$ (h^{-1})	0.156 (21.8)
Tobramycin concentration causing 50% of K_{max}		
susceptible population	$KC_{50,TOB,SS}$ (mg/liter)	1.62 (20.2)
intermediate population	$KC_{50,TOB,RI}$ (mg/liter)	31.0 (14.8)
resistant population	$KC_{50,TOB,IR}$ (mg/liter)	92.8 (7.4)
Hill coefficient	$Hill_{TOB}$	3.03 (12.9)
Synergistic bacterial killing		
Maximum fractional decrease of $KC_{50,MER}$ by tobramycin *via* outer membrane disruption	$I_{max.OM}$	1.0[e]
Tobramycin concentration causing 50% of $I_{max,OM}$	$IC_{50,OM}$ (mg/liter)	0.587 (19.5)
Residual variability		
SD of additive residual error on log_{10} scale	SD_{CFU}	0.41 (5.6)

[a] parameter estimates for strain PAO1, [b] parameter estimates for strain PAO*ΔmutS*, [c] TOB^{I} / MEM^{R}, [d] TOB^{R} / MEM^{I}, [e] fixed.

TABLE S4 Log_{10} mutation frequencies at 2.5 and 5 mg/liter meropenem (2.5× and 5× MIC) and 2.5 mg/liter tobramycin (5× MIC) at various time points for each dosage regimen (monotherapy and combinations) for PAO1 in the HFIM. [a] MEM, meropenem; TOB, tobramycin.

	Time (h)	Control	MEM 1 g 8-hourly	MEM 3 g/day CI	TOB 10 mg/kg 24-hourly	MEM 1 g 8-hourly + TOB	MEM 3 g/day CI + TOB
MEM 2.5 mg/liter (2.5× MIC)	0	-5.95	-5.95	-5.95	-	-5.95	-5.95
	5	-7.62	< -5.57	< -6.16	-	< -1.64	< -1.45
	23	-7.07	< -3.94	< -3.58	-	< -2.08	< -1.26
	47	-7.61	< -2.98	< -3.09	-	< -0.60	< 0.70
	71	-7.20	< -2.28	< -2.00	-	< -0.30	< 0.70
	95	-8.58	< -2.51	< -3.09	-	< -1.64	< 0.70
	119	-7.03	< -2.66	< -1.85	-	< 0.70	< 0.70
	143	-	-	-	-	< 0.70	< 0.70
	167	-6.58	-1.07	< -1.26	-	< -0.48	< 0.70
	191	-	-	-	-	< -1.00	< 0.70
	215	-7.17	1.58	< -1.08	-	< 0.70	< 0.70
	239	-7.13	-0.23	< -4.01	-	< 0.70	< 0.70
MEM 5 mg/liter (5× MIC)	0	< -7.71	< -7.71	< -7.71	-	< -7.71	< -7.71
	5	< -9.08	< -5.57	< -6.16	-	< -1.64	< -1.45
	23	-8.36	< -3.94	< -3.58	-	< -2.08	< -1.26
	47	-6.40	< -2.98	< -3.09	-	< -0.60	< 0.70
	71	< -9.65	< -8.04	< -2.28	-	< -0.30	< 0.70
	95	-6.29	< -2.51	< -3.09	-	< -1.64	< 0.70
	119	-7.55	< -2.66	< -1.85	-	< 0.70	< 0.70
	143	-	-	-	-	< 0.70	< 0.70
	167	-6.62	-0.84	< -1.26	-	< -0.48	< 0.70
	191	-	-	-	-	< -0.48	< 0.70
	215	-7.02	1.57	< -1.08	-	< 0.70	< 0.70
	239	-6.95	-0.30	< -4.01	-	< 0.70	< 0.70
TOB 2.5 mg/liter (5× MIC)	0	-7.11	-	-	-7.11	-7.11	-7.11
	5	-7.70	-	-	< -2.72	< -1.64	< -1.45
	23	-8.27	-	-	< -1.08	< -2.08	< -1.26
	47	-7.74	-	-	-0.52	< -0.60	< 0.70
	71	-7.19	-	-	-1.81	< -0.30	< 0.70
	95	-7.19	-	-	-2.42	< -1.64	1.60
	119	-7.37	-	-	-2.16	< 0.70	< 0.70
	143	-	-	-	-	< 0.70	< 0.70
	167	-7.05	-	-	-2.95	< -0.48	< 0.70
	191	-	-	-	-	< -1.00	< 0.70
	215	-7.52	-	-	-2.03	< 0.70	< 0.70
	239	-7.57	-	-	-2.51	< 0.70	1.00

[a] When no colonies were present on antibiotic-containing plates, mutation frequencies reported represent an upper limit based on the total viable count.

TABLE S5 Log_{10} mutation frequencies at 2.5 and 5 mg/liter meropenem (2.5× and 5× MIC) and 2.5 mg/liter tobramycin (5× MIC) at various time points for each dosage regimen (monotherapy and combinations) for PAOΔ*mutS* in the HFIM. [a] MEM, meropenem; TOB, tobramycin.

	Time (h)	Control	MEM 1 g 8-hourly	MEM 3 g/day CI	TOB 10 mg/kg 24-hourly	MEM 1 g 8-hourly + TOB	MEM 3 g/day CI + TOB
MEM 2.5 mg/liter (2.5× MIC)	0	-3.38	-3.38	-3.38	-	-3.38	-3.38
	5	-4.14	-4.20	-3.91	-	-3.05	-2.91
	23	-4.12	-0.53	-0.23	-	-2.78	< -2.42
	47	-3.43	-0.95	-0.71	-	< -2.12	-2.06
	71	-3.73	-0.61	-0.85	-	1.08	0.48
	95	-3.59	-0.64	-0.91	-	-0.91	< -1.65
	119	-3.16	-0.96	-0.40	-	-0.65	< -0.7
	143	-	-	-	-	-0.055	< -0.6
	167	-2.77	-0.56	-0.52	-	-0.87	< 0.7
	191	-	-	-	-	0.014	< -0.7
	215	-3.18	-0.03	0.02	-	-0.52	-0.48
	239	-3.222	-0.225	0.161	-	-0.092	< 0.7
MEM 5 mg/liter (5× MIC)	0	-5.95	-5.95	-5.95	-	-5.95	-5.95
	5	-6.24	-5.46	-5.46	-	< -3.89	< -3.95
	23	-6.55	-1.10	-0.24	-	< -2.78	< -2.42
	47	-6.24	-1.53	-0.69	-	-1.82	-2.06
	71	-6.71	-0.89	-1.18	-	< 0	< -0.6
	95	-6.89	-0.88	-1.26	-	-2.74	< -1.65
	119	-6.93	-0.97	-1.22	-	-2.00	< -0.7
	143	-	-	-	-	-1.75	< -0.6
	167	-5.73	-0.79	-0.61	-	-1.75	< 0.7
	191	-	-	-	-	-1.06	< -0.7
	215	-6.11	-0.87	-0.84	-	-1.29	-0.48
	239	-6.28	-0.06	0.43	-	-1.04	< 0.7
TOB 2.5 mg/liter (5× MIC)	0	-6.51	-	-	-6.51	-6.51	-6.51
	5	-6.12	-	-	< -3.38	< -3.89	< -3.95
	23	-6.22	-	-	-2.12	< -2.78	< -2.42
	47	-5.93	-	-	-0.14	< -2.12	-2.37
	71	-6.32	-	-	-0.95	< 0	< -0.6
	95	-6.58	-	-	-1.21	-2.68	-1.18
	119	-7.07	-	-	-1.26	-2.85	< -0.7
	143	-	-	-	-	-2.95	< -0.6
	167	-6.36	-	-	-1.33	-2.61	< 0.7
	191	-	-	-	-	-2.57	< -0.7
	215	-7.73	-	-	-1.72	-2.28	< -0.48
	239	-7.24	-	-	-1.43	-2.52	< 0.7

[a] When no colonies were present on antibiotic-containing plates, mutation frequencies reported represent an upper limit based on the total viable count.

TABLE S6 MIC values from colonies obtained from drug-containing agar plates (meropenem at 2.5 and 5 mg/liter, equivalent to 2.5× and 5× MIC; tobramycin at 2.5 mg/liter, equivalent to 5× MIC) before treatment (0 h) and at various times for each dosage regimen and bacterial strain simulated in the HFIM.

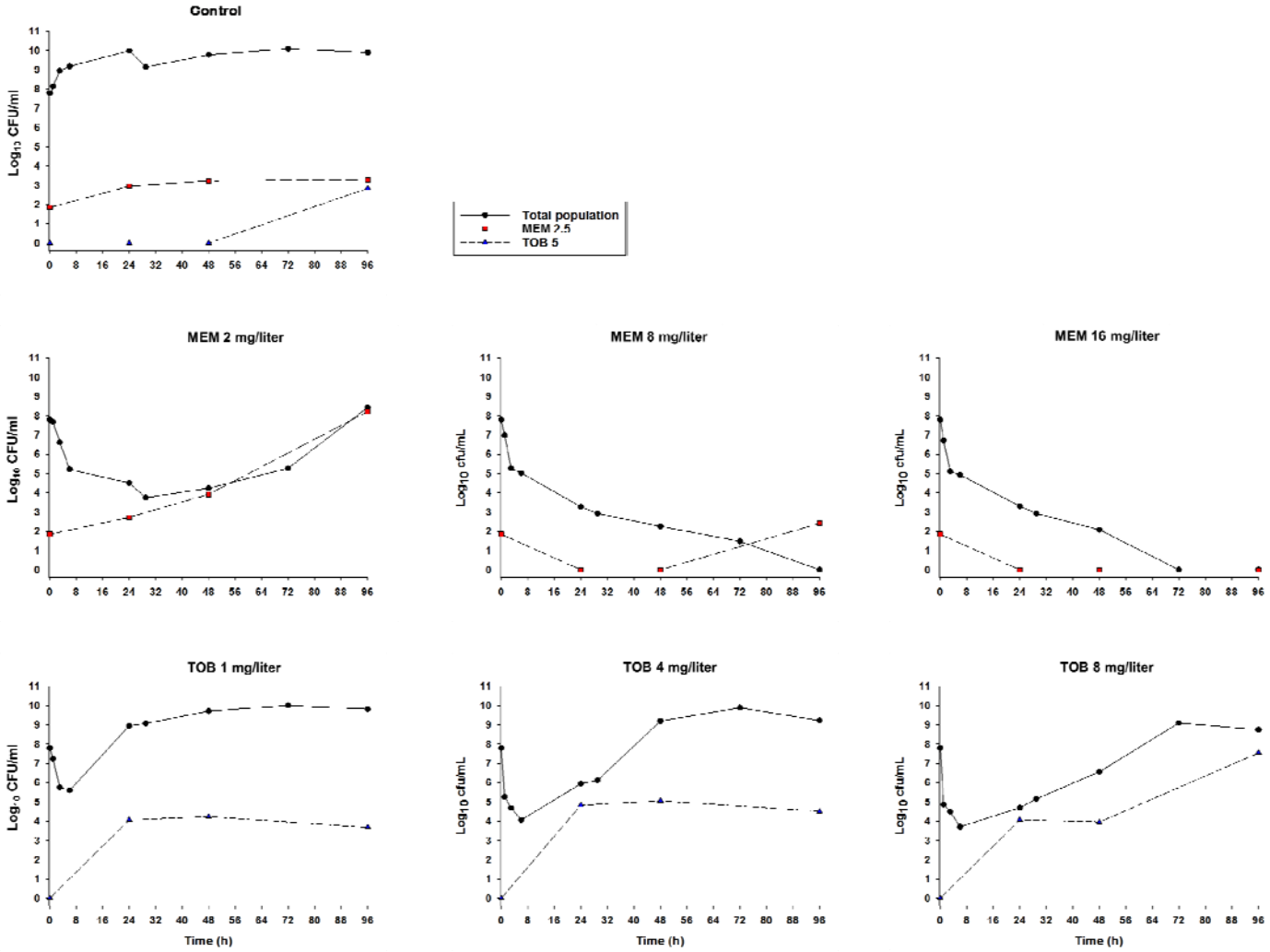
		Meropenem			Tobramycin	
		5 mg/liter	2.5 mg/liter		2.5 mg/liter	
Treatment	Time (h)	PAOΔ*mutS*	PAO1	Time (h)	PAOΔ*mutS*	PAO1
	0	8	4	0	4	8
Control	95	32	-	95	8	4
	215	16	4[a]	239	8	1
MEM 1 g 8-hourly	95	32	-	.	.	.
	215	32	32[b]	.	.	.
MEM 3 g CI	95	64	-	.	.	.
	215	64	-	.	.	.
TOB 10 mg/kg 24-hourly	.	.	.	95	16	8
	.	.	.	239	32	8
MEM 1 g 8-hourly + TOB 10 mg/kg 24-hourly	95	32	-	95	8	-
	215	32	-	239	8	-
MEM 3 g CI + TOB 10 mg/kg 24-hourly	95	-	-	95	32	8
	215	32	-	239	-	-

- , no colonies on antibiotic-containing plates.

[a] The MIC was determined at 167 h.

[b] The MIC was 32 mg/liter at both 167 h and 239 h. MEM, meropenem; TOB, tobramycin

FIG S1 Time-course of the total and less susceptible bacterial populations (*i.e.* able to grow in the presence of meropenem 2.5 mg/liter or tobramycin 5 mg/liter) of PAO1 for each concentration (monotherapy and combinations) in the SCTK. MEM, meropenem. TOB, tobramycin.



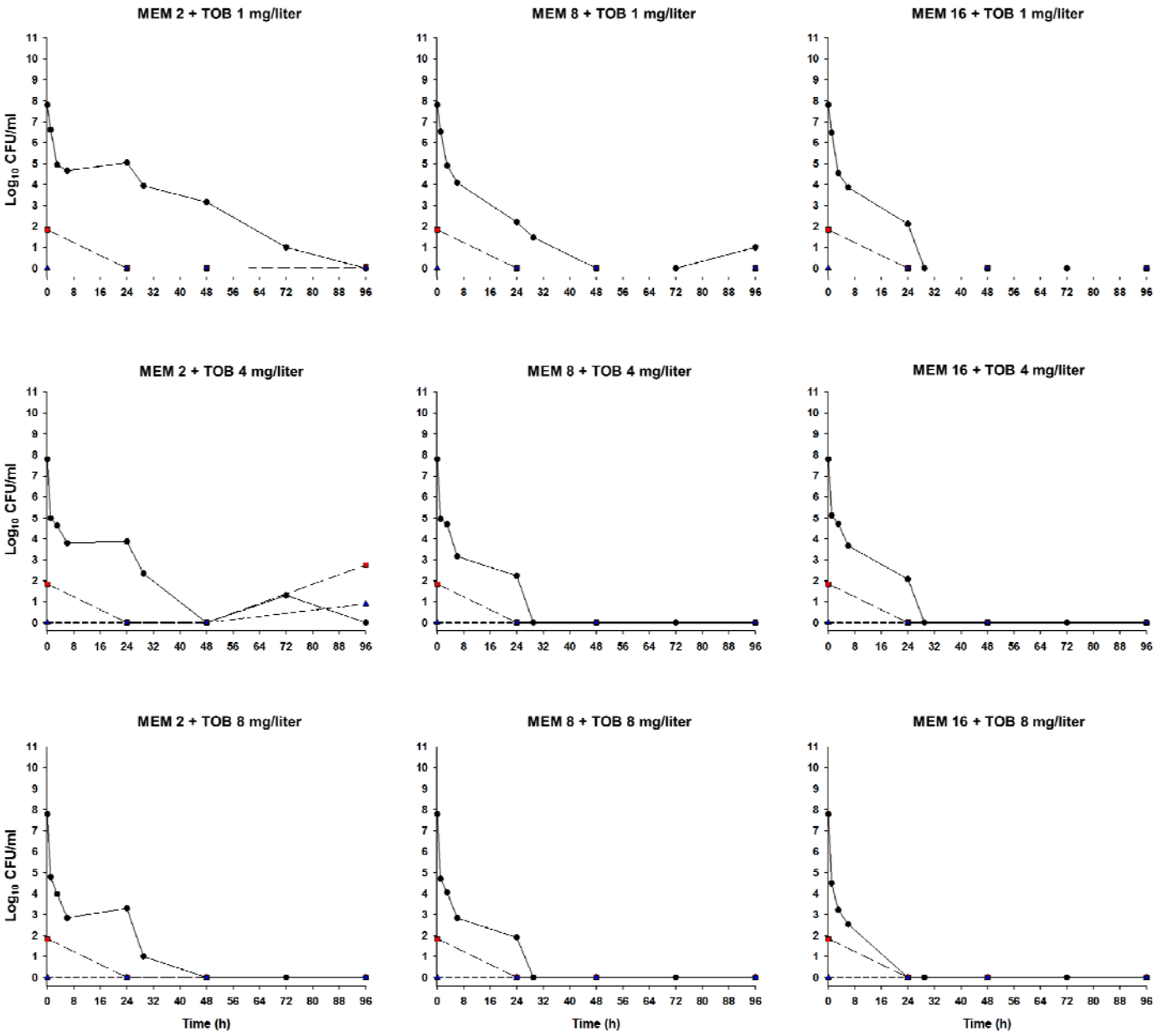
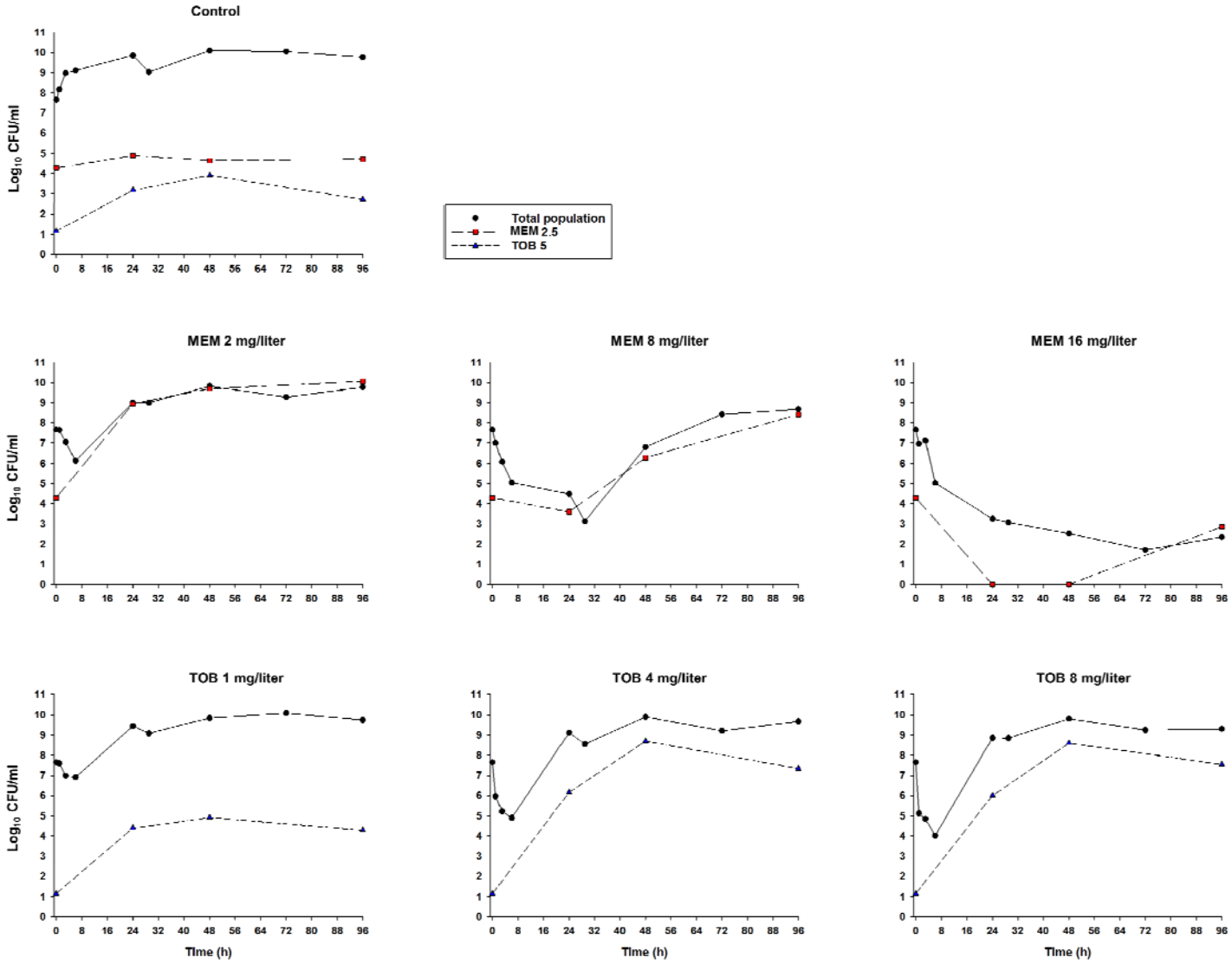

MEM 2 + TOB 1 mg/liter
MEM 8 + TOB 1 mg/liter
MEM 16 + TOB 1 mg/liter
MEM 2 + TOB 4 mg/liter
MEM 8 + TOB 4 mg/liter
MEM 16 + TOB 4 mg/liter
MEM 2 + TOB 8 mg/liter
MEM 8 + TOB 8 mg/liter
MEM 16 + TOB 8 mg/liter
Log10 CFU/ml
Time (h)
0 8 16 24 32 40 48 56 64 72 80 88 96
0 1 2 3 4 5 6 7 8 9 10 11

FIG S2 Time-course of the total and less susceptible bacterial populations (*i.e.* able to grow in the presence of meropenem 2.5 mg/liter or tobramycin 5 mg/liter) of PAOΔ*mutS* for each concentration (monotherapy and combinations) in the SCTK. MEM, meropenem. TOB, tobramycin.



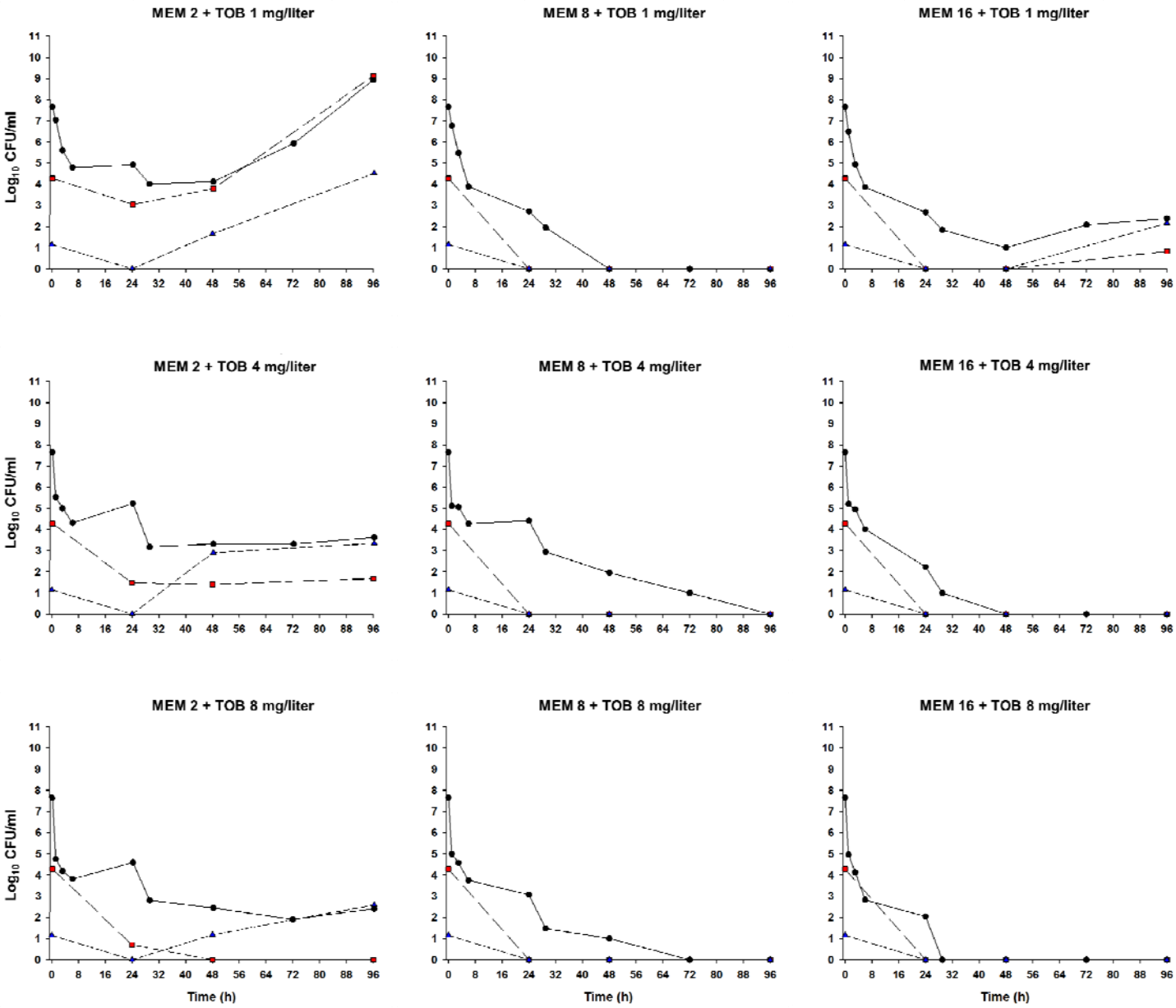
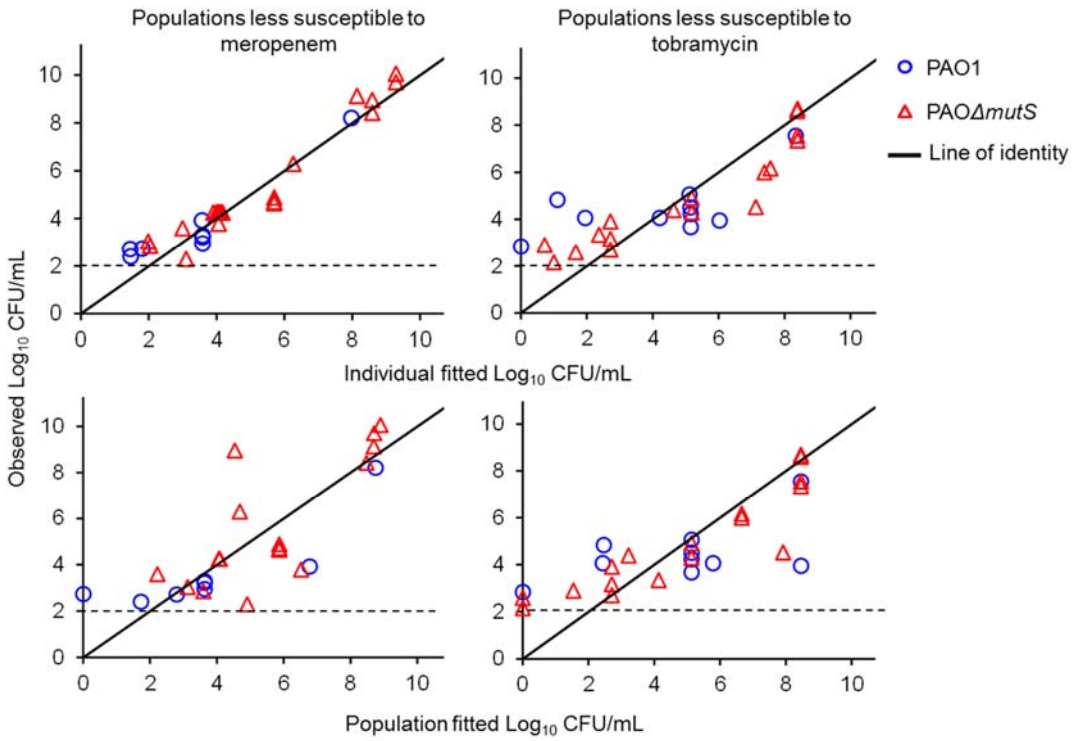

MEM 2 + TOB 1 mg/liter
MEM 8 + TOB 1 mg/liter
MEM 16 + TOB 1 mg/liter
MEM 2 + TOB 4 mg/liter
MEM 8 + TOB 4 mg/liter
MEM 16 + TOB 4 mg/liter
MEM 2 + TOB 8 mg/liter
MEM 8 + TOB 8 mg/liter
MEM 16 + TOB 8 mg/liter
Log10 CFU/ml
Time (h)
0 8 16 24 32 40 48 56 64 72 80 88 96
0 1 2 3 4 5 6 7 8 9 10 11

FIG S3 Observed *vs.* individual (top) and population fitted (bottom) viable counts of populations that were less susceptible to meropenem and tobramycin. The MBM fitted all viable counts for PAO1 and PAO*ΔmutS* simultaneously.



Dashed line: Counts below 100 CFU/mL (<20 colonies/antibiotic-containing plate) are subject to random error due to observing only an integer number of colonies and described by a Poisson error in the observation model.