

Supplement – Bergen *et al.*, Clinically relevant plasma concentrations of colistin in combination with imipenem enhance PD activity against MDR *P. aeruginosa* at multiple inocula

Table S1: Log changes at 6, 24 or 48 h at two inocula with colistin (Col) and imipenem (Imi) against 3 isolates of *P. aeruginosa* susceptible to both antibiotics. Gray background indicates activity (a reduction of $\geq 1\text{-log}_{10}$ cfu/mL below the initial inoculum); green background indicates synergy (a $\geq 2\text{-log}_{10}$ decrease in the number of cfu/mL between the combination and its most active component); red background indicates additivity (a 1.0 to $< 2\text{-log}_{10}$ decrease in the number of cfu/mL between the combination and its most active component). Data presented here represents additional data not included in Table 2 of the main manuscript.

Isolate	Inoculum (cfu/mL)	Time (h)	Log change (= $\log_{10}(\text{CFU}_t) - \log_{10}(\text{CFU}_0)$)			
			Col 16× MIC *	Col 16× MIC * + Imi 0.5× MIC	Col 16× MIC * + Imi 4× MIC	Col 16× MIC * + Imi 16× MIC
ATCC 27853	~10 ⁶	6	-6.03	-5.98	-5.97	-6.01
		24	-1.23	-0.35	-1.65	-6.01
		48	+0.39	+0.90	-0.98	-6.01
	~10 ⁸	6	-7.68	-7.76	-7.78	-7.81
		24	-3.34	-2.83	-7.78	-7.81
		48	-1.97	-1.46	-7.78	-7.81
19056 muc	~10 ⁶	6	-5.16	-5.82	-5.89	-5.88
		24	-5.16	-5.82	-5.89	-5.88
		48	-0.37	-5.82	-5.89	-5.88
	~10 ⁸	6	-7.94	-7.94	-7.91	-7.76
		24	-7.94	-7.94	-7.91	-7.76
		48	-5.03	-4.00	-4.45	-7.76
20509 n/m	~10 ⁶	6	-5.89	-5.95	-6.05	-6.05
		24	-0.94	-3.35	-6.05	-6.05
		48	+0.81	-1.80	-4.27	-3.58
	~10 ⁸	6	-3.41	-3.50	-4.94	-7.94
		24	-0.28	-1.58	-3.71	-4.49
		48	+1.89	+1.03	-1.42	-3.22

*For ATCC 27853, Col 8× MIC used at the 10⁶ cfu/mL inoculum only.

Table S2: Log changes at 6, 24, or 48 h at two inocula with colistin (Col) and imipenem (Imi) against a colistin-resistant, imipenem-susceptible isolate and two colistin-susceptible, imipenem-resistant isolates of *P. aeruginosa*. Gray background indicates activity (a reduction of ≥ 1 -log₁₀ cfu/mL below the initial inoculum); green background indicates synergy (a ≥ 2 -log₁₀ decrease in the number of cfu/mL between the combination and its most active component); red background indicates additivity (a 1.0 to < 2 -log₁₀ decrease in the number of cfu/mL between the combination and its most active component). For colistin-resistant isolate 19147 n/m, synergy or additivity were compared with imipenem monotherapy only. Data presented here represents additional data not included in Table 3 of the main manuscript.

Isolate	Inoculum (cfu/mL)	Time (h)	Log change (= log ₁₀ (CFU _t) - log ₁₀ (CFU ₀))		
			Col 32 mg/L + Imi 0.5× MIC	Col 32 mg/L + Imi 4× MIC	Col 32 mg/L + Imi 16× MIC
Col resistant, Imi susceptible	~10 ⁶	6	-2.81	-2.79	-3.15
		24	-1.95	-3.95	-4.26
		48	+1.58	-3.72	-4.21
	~10 ⁸	6	-2.54	-2.65	-2.79
		24	-1.02	-5.90	-6.11
		48	-0.02	-3.09	-7.71

Table S2 (Continued):

Isolate	Inoculum (cfu/mL)	Time (h)	Log change (= $\log_{10}(\text{CFU}_t) - \log_{10}(\text{CFU}_0)$)				
			Col 16× MIC	Col 16× MIC + Imi 1.0 mg/L	Col 16× MIC + Imi 8.0 mg/L	Col 16× MIC + Imi 32 mg/L	
Col susceptible, Imi resistant	~10 ⁶	6	-3.88	-5.70	-5.77	-5.75	
		24	-3.68	-3.92	-5.77	-5.75	
		48	-1.29	-2.89	-5.77	-5.75	
	~10 ⁸	6	-3.18	-4.81	-4.97	-5.36	
		24	-2.95	-2.52	-3.66	-6.22	
		48	-0.46	-0.01	-3.14	-4.24	
	20891 n/m	~10 ⁶	6	-5.97	-5.92	-5.96	-5.98
			24	-4.57	-5.92	-5.96	-5.98
			48	-3.20	-3.77	-5.96	-5.98
~10 ⁸		6	-5.50	-5.97	-7.35	-7.52	
		24	-2.65	-4.60	-5.35	-4.83	
		48	-2.61	-3.65	-3.92	-3.58	

Time-kill plots:

Figure S1: Time-kill curves for ATCC 27853 at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

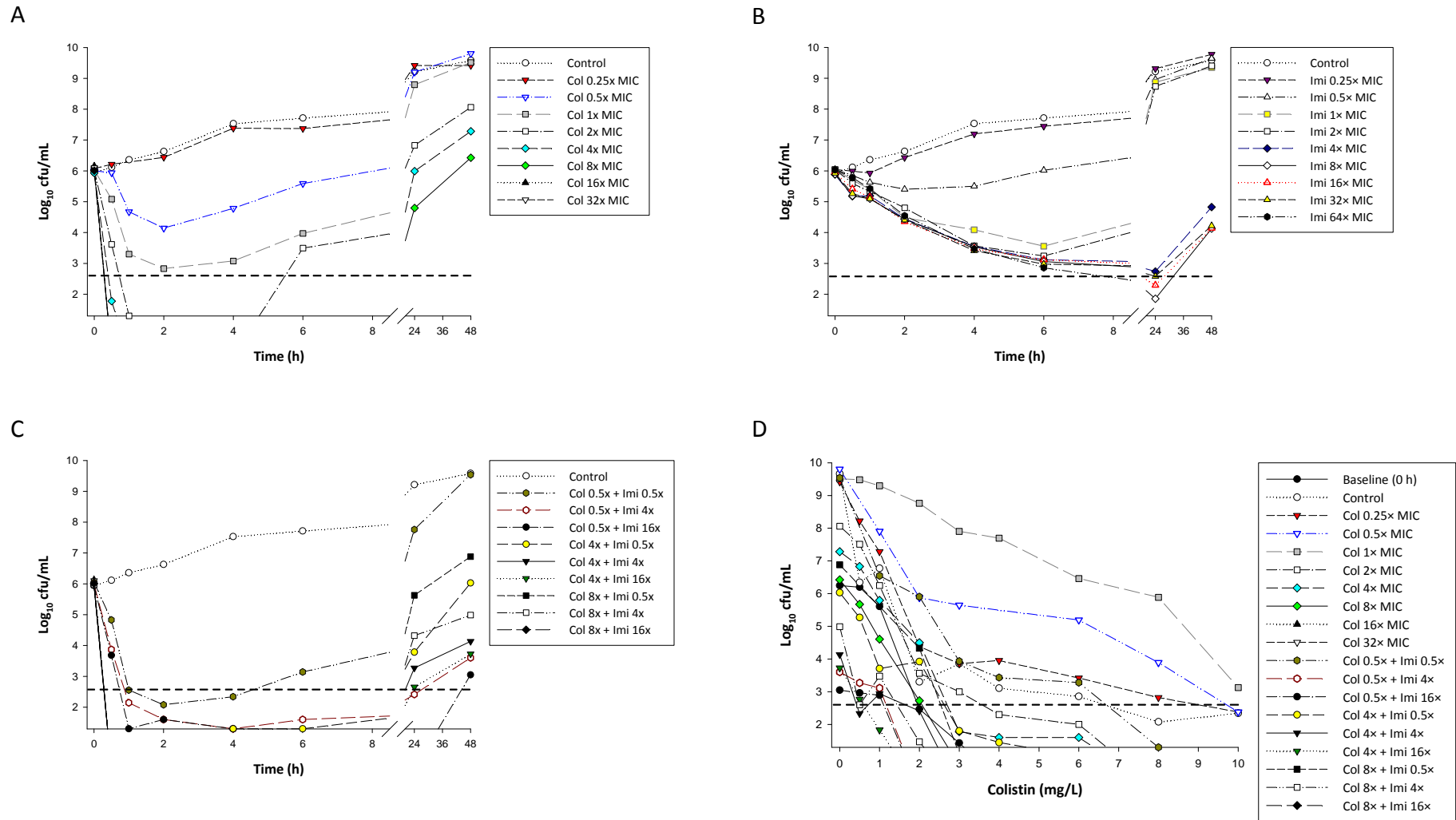


Figure S2: Time-kill curves for ATCC 27853 at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

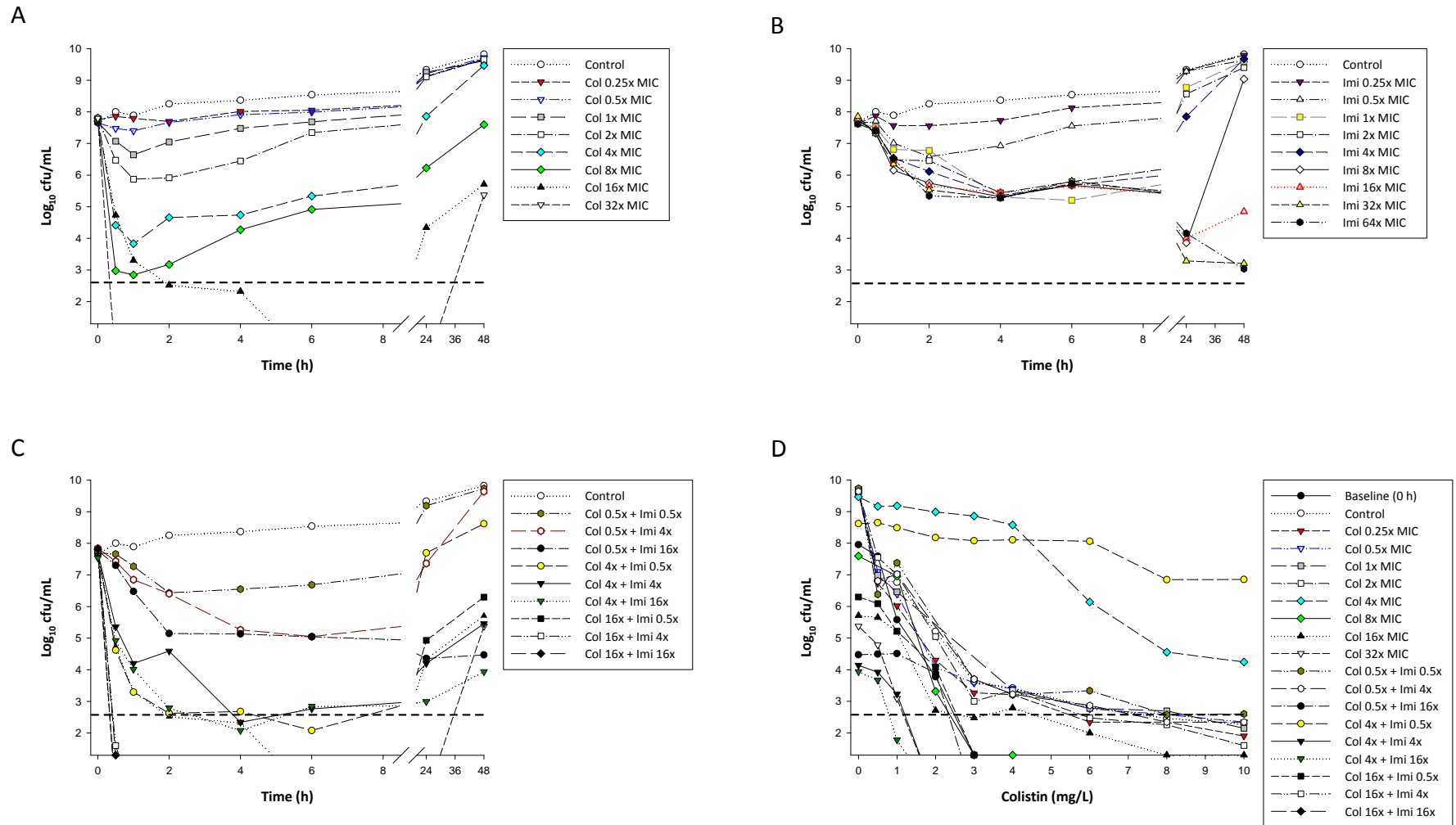


Figure S3: Time-kill curves for 19147 n/m at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

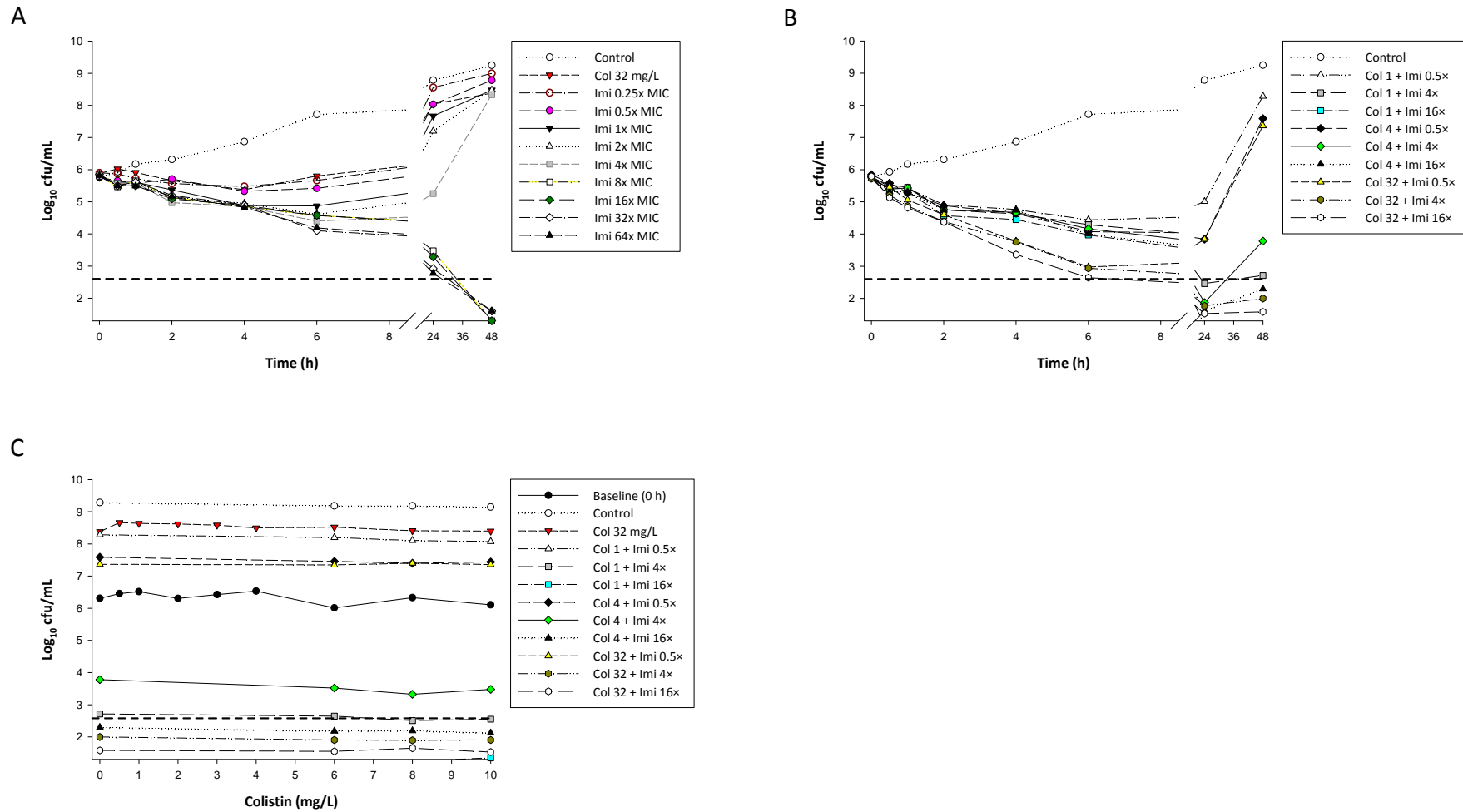


Figure S4: Time-kill curves for 19147 n/m at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

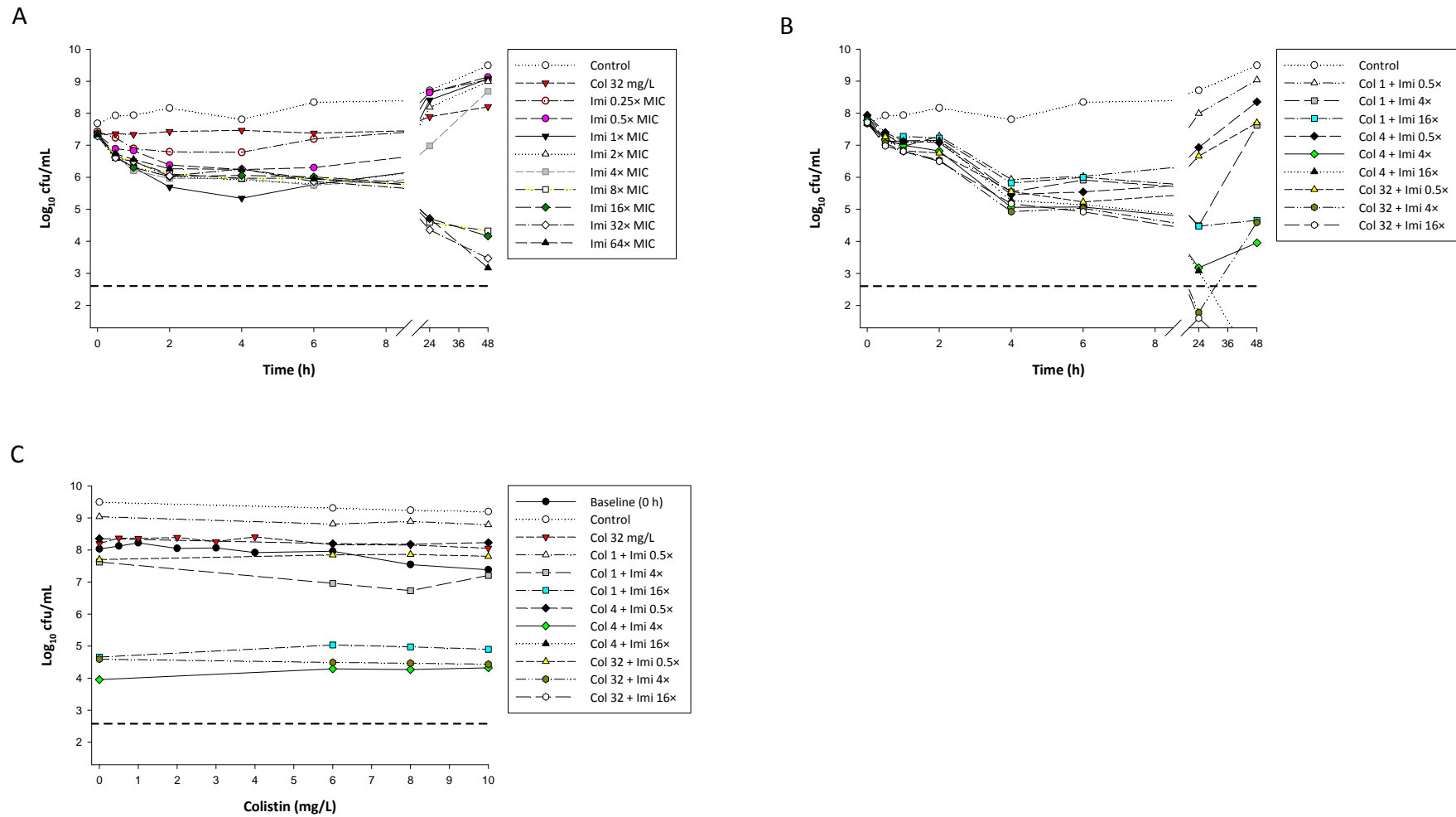


Figure S5: Time-kill curves for 19056 muc at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

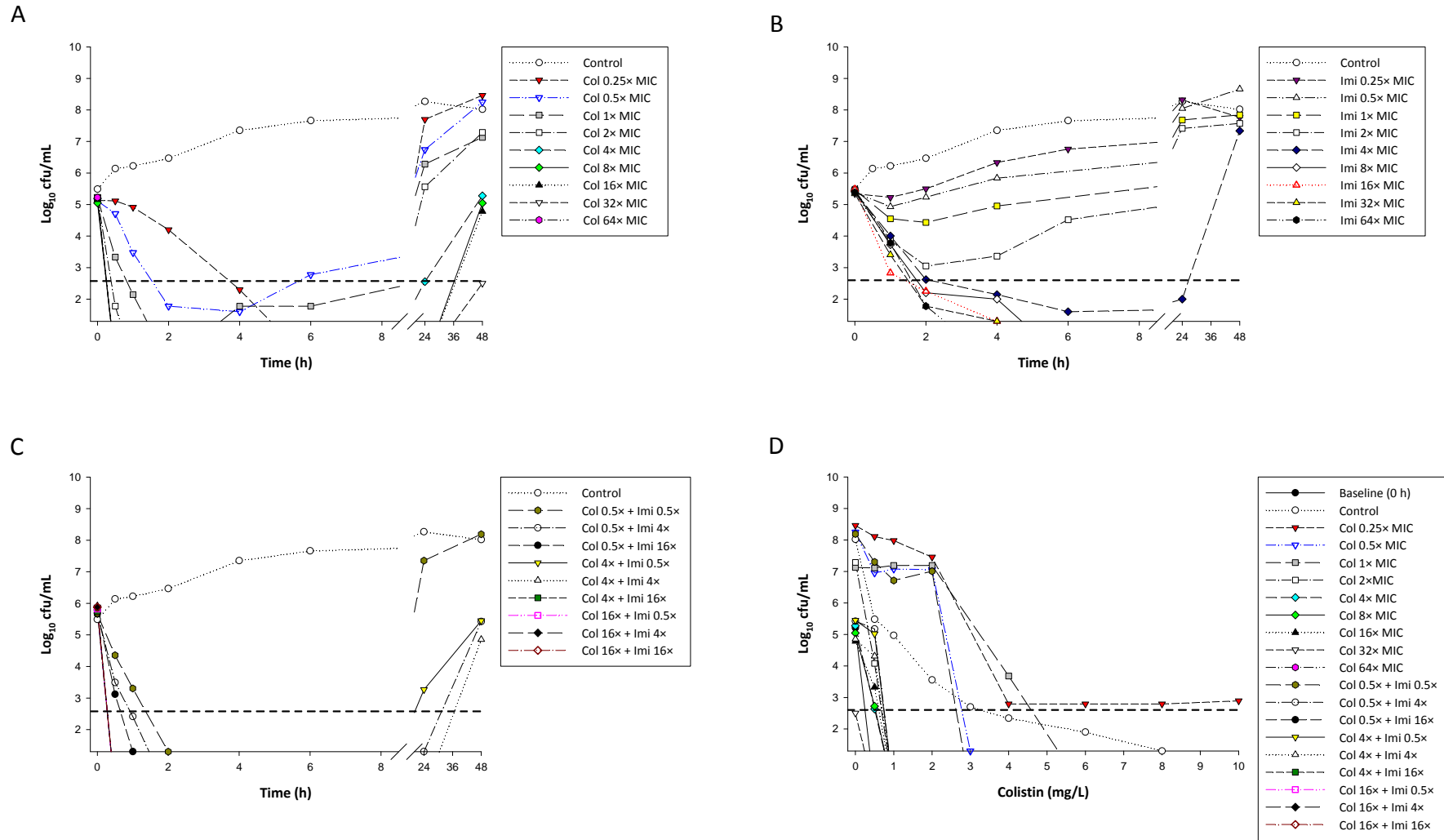


Figure S6: Time-kill curves for 19056 muc at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

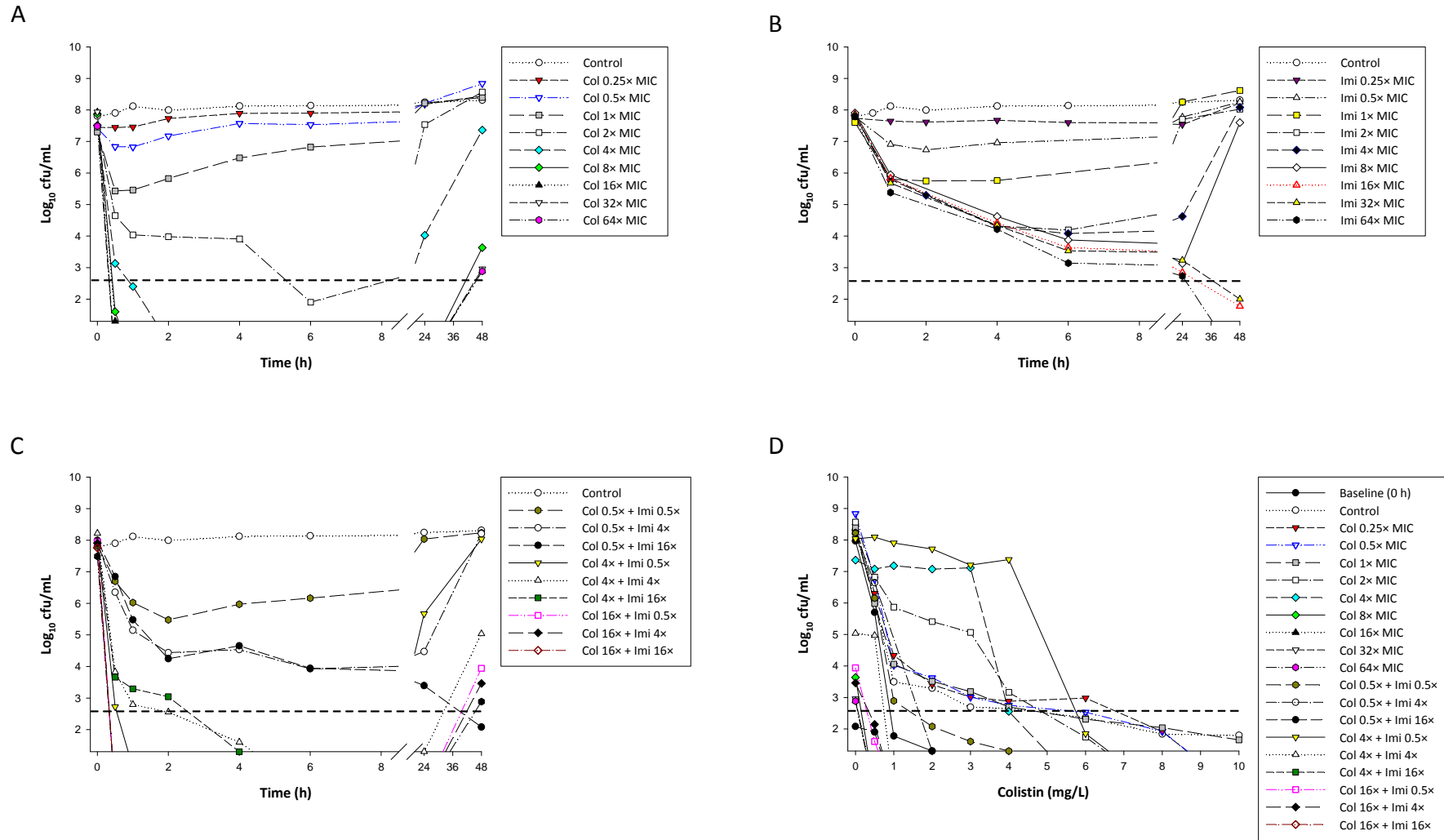


Figure S7: Time-kill curves for 20509 n/m at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

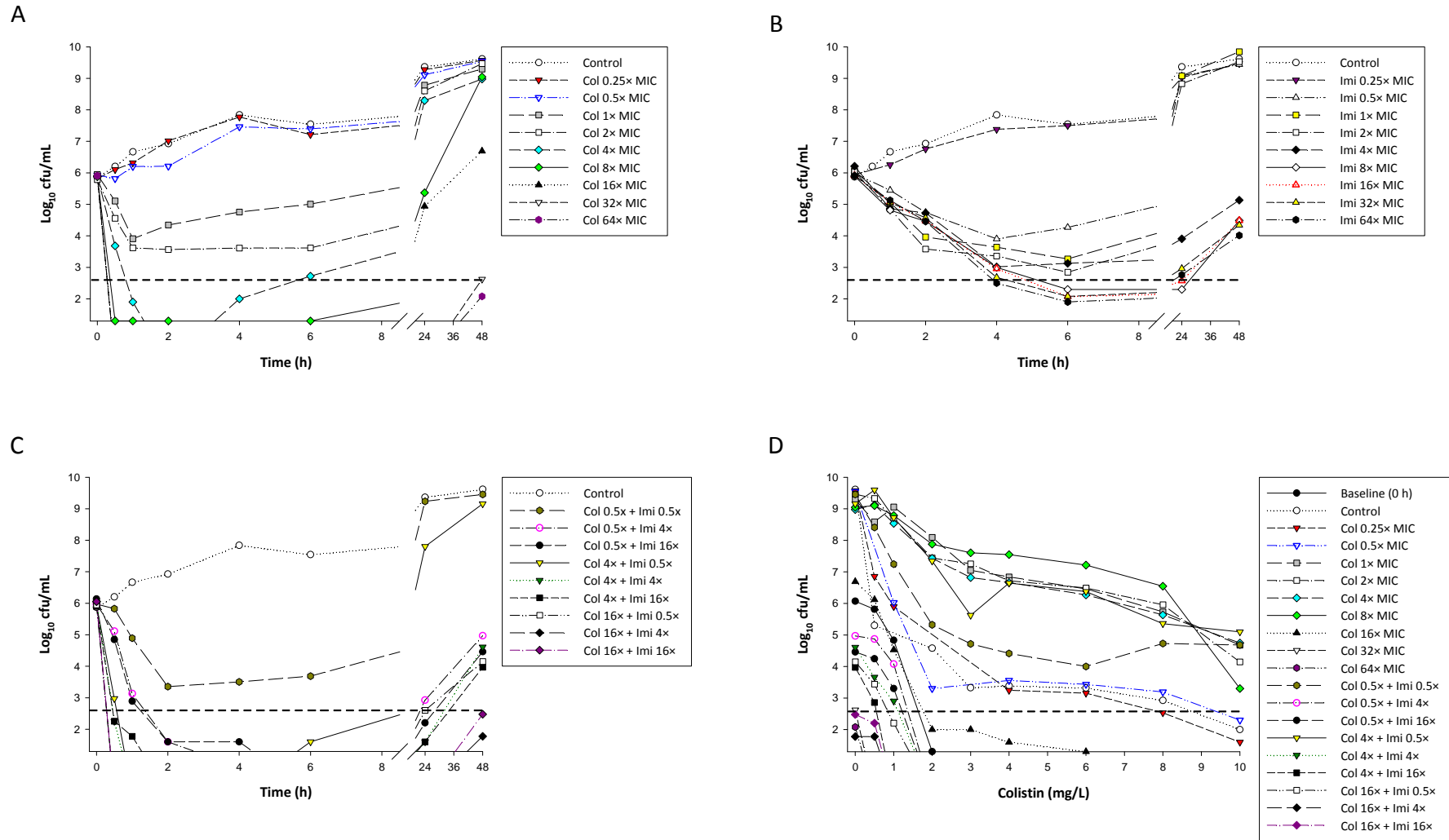


Figure S8: Time-kill curves for 20509 n/m at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin alone, (B) imipenem alone, and (C) in combination. Panel (D) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

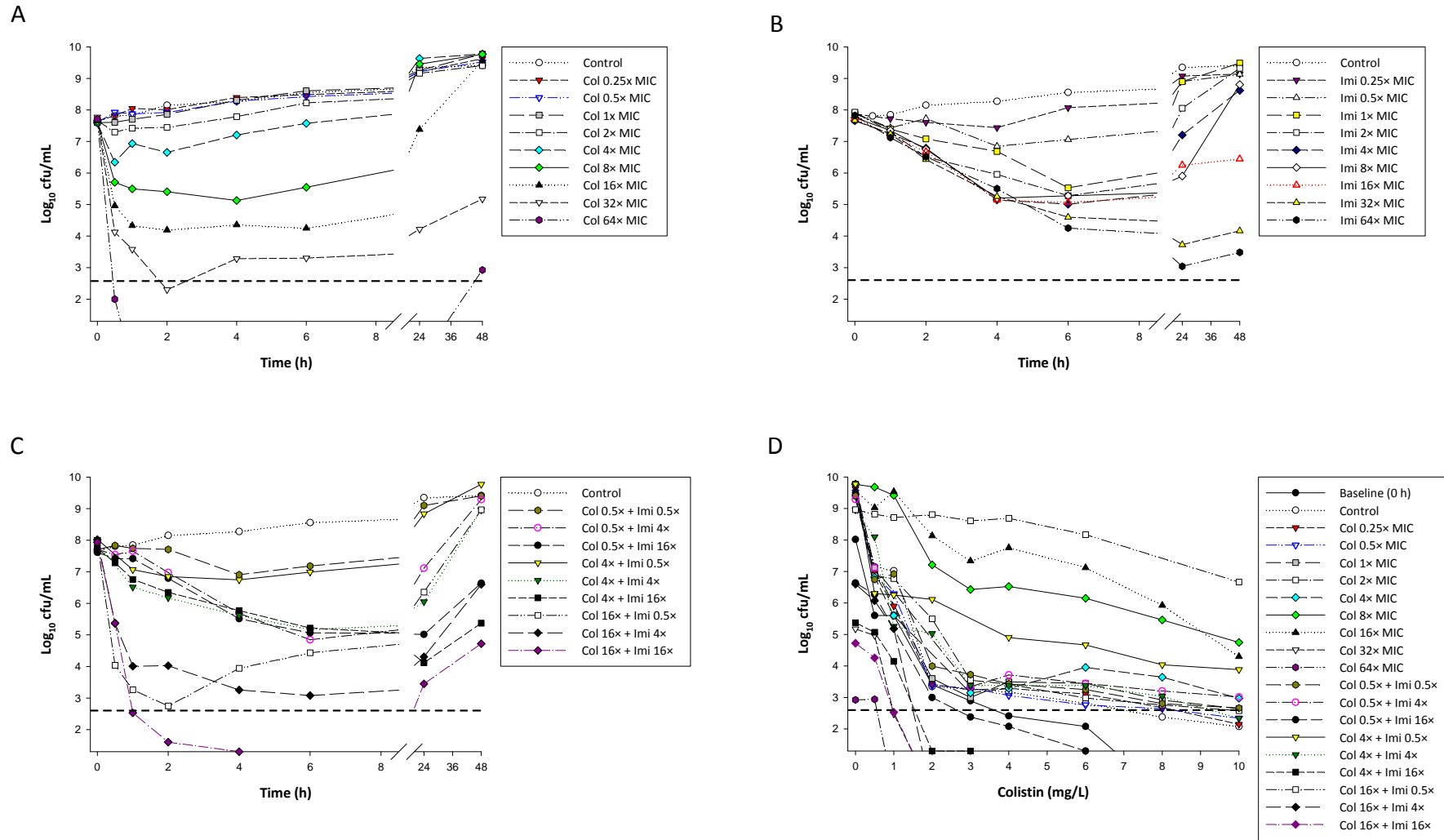


Figure S9: Time-kill curves for 19271 n/m at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

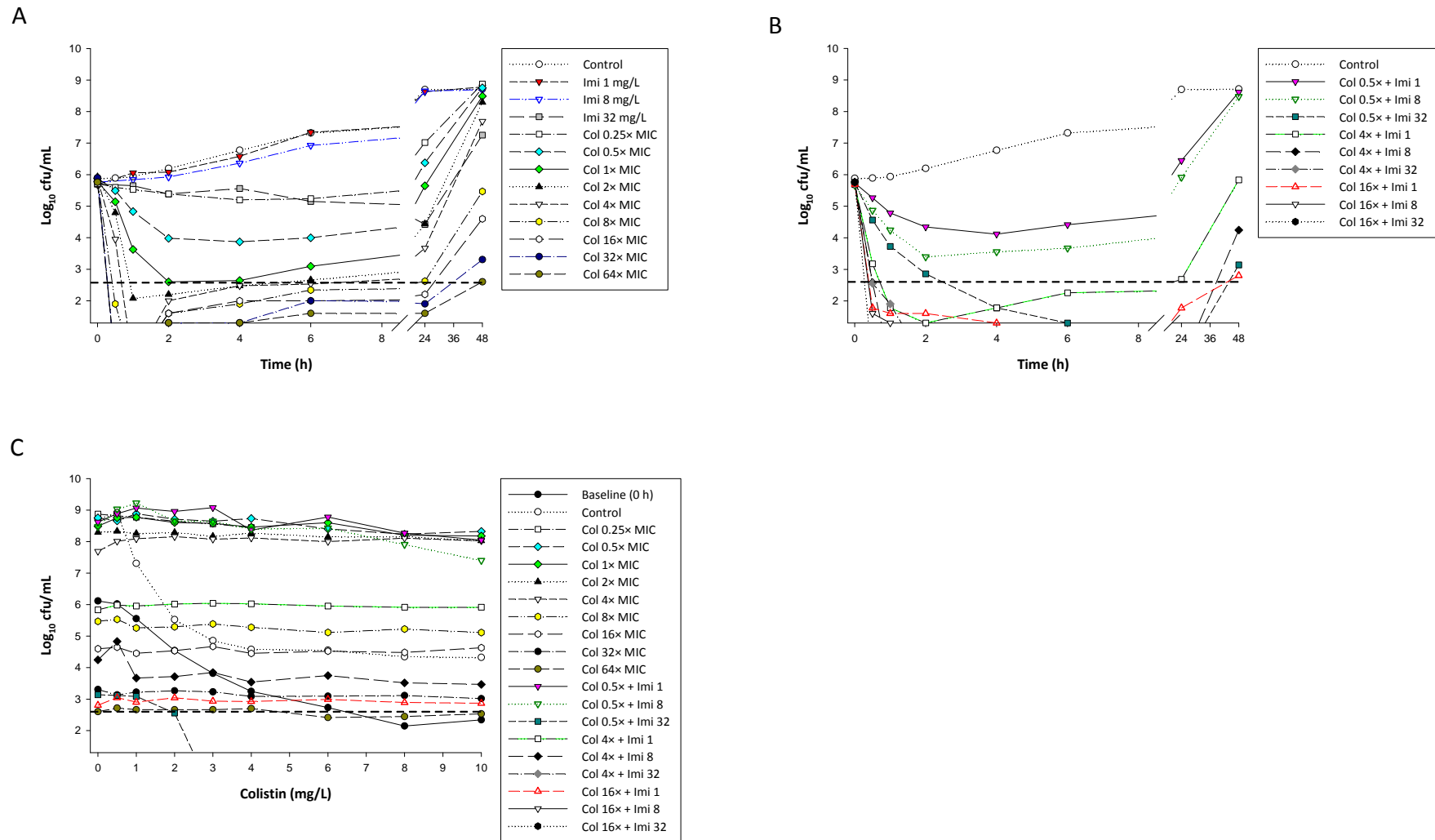


Figure S10: Time-kill curves for 19271 n/m at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

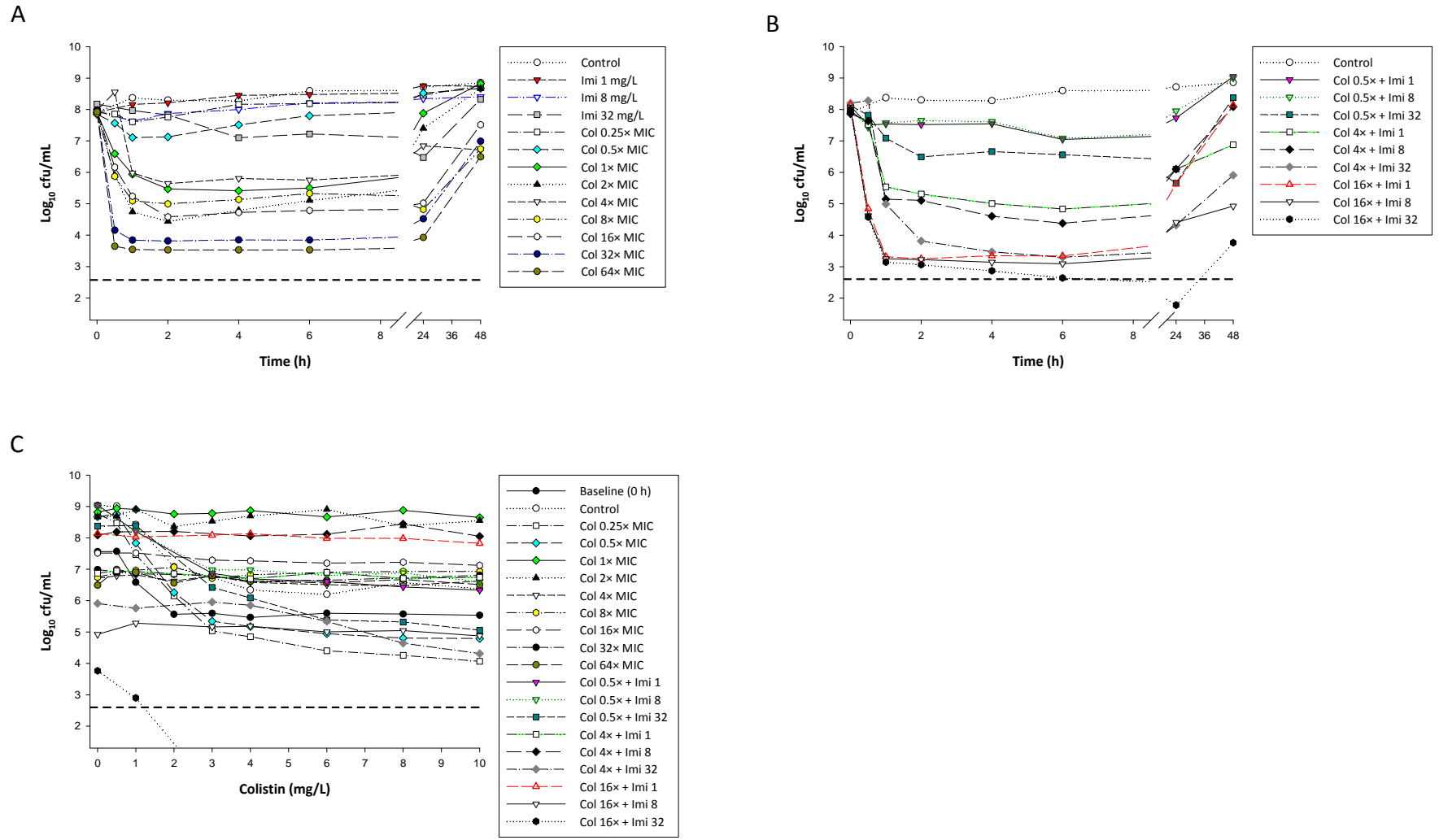


Figure S11: Time-kill curves for 20891 n/m at an inoculum of $\sim 10^6$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

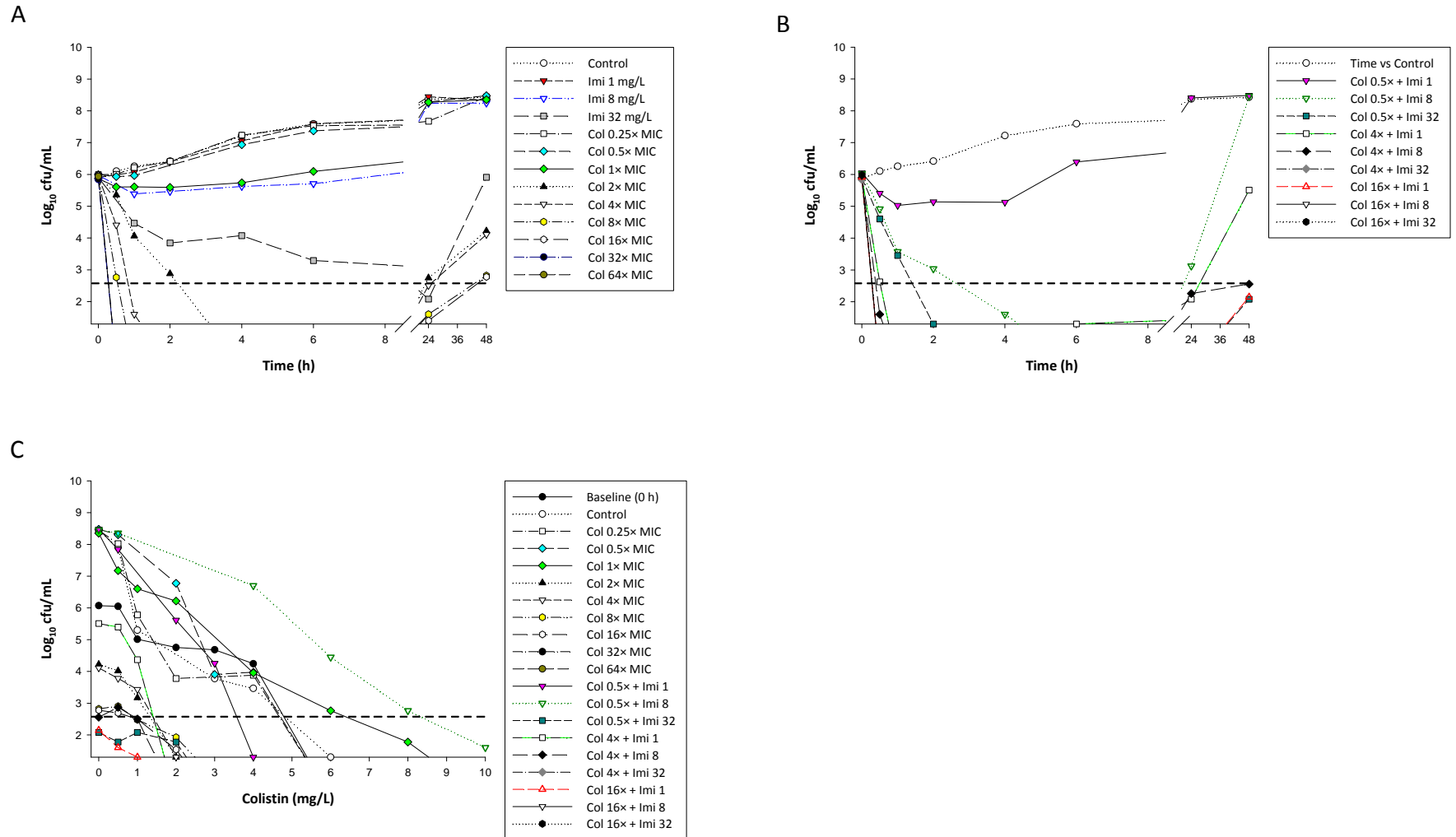


Figure S12: Time-kill curves for 20891 n/m at an inoculum of $\sim 10^8$ cfu/mL with (A) colistin and imipenem alone, and (B) in combination. Panel (C) shows the PAPs at baseline (0 h) and after 48 h exposure to colistin monotherapy, colistin/imipenem combination therapy, or neither antibiotic (control). The Y-axis starts from the limit of detection and the limit of quantification (LOQ) is indicated by the horizontal broken line.

