Novel Polymyxin Combination with Antiretroviral Zidovudine Exerts Synergistic Killing against NDM-producing MDR *Klebsiella pneumoniae*

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Figure S1. Observed bacterial counts *versus* individual **(upper panel)** and population **(lower panel)** fitted bacterial counts for polymyxin B and zidovudine alone or in combination against NDM-producing *Klebsiella pneumoniae* isolates. The solid red lines represent the line of identity. The values below the limit of detection are plotted as zero.

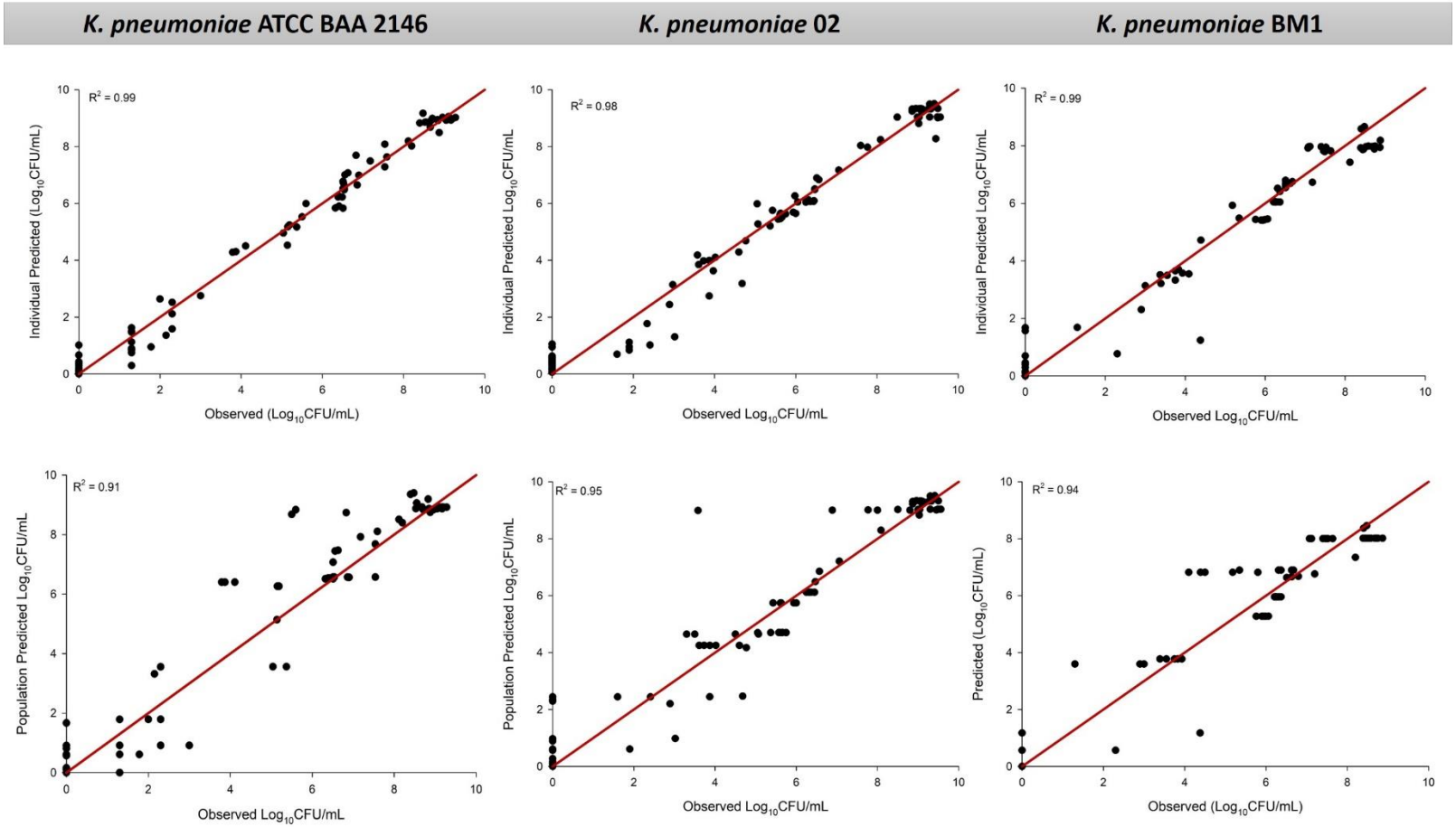

Figure S2. Fractional inhibitory concentrations for polymyxin B and zidovudine against NDM-producing *K. pneumoniae* ATCC BAA 2146. Grey indicates no visual bacterial growth.

		Zidovudine (mg/L)										
		0	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Polymyxin B (mg/L)	**0**											
	0.0625											
	0.125											
	0.25											
	0.5											
	1											
	2											
	4											

Figure S3. Fractional inhibitory concentrations for polymyxin B and zidovudine against NDM-producing *K. pneumoniae* 02. Grey indicates no visual bacterial growth.

		Zidovudine (mg/L)										
		0	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Polymyxin B (mg/L)	**0**											
	0.0625											
	0.125											
	0.25											
	0.5											
	1											
	2											
	4											

Figure S4. Fractional inhibitory concentrations for polymyxin B and zidovudine against NDM-producing *K. pneumoniae* BM1. Grey indicates no visual bacterial growth.

		Zidovudine (mg/L)										
		0	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
Polymyxin B (mg/L)	**0**											
	0.0625											
	0.125											
	0.25											
	0.5											
	1											
	2											
	4											

Table S1. Population mean parameter estimates for the synergic combination of polymyxin B and zidovudine against three NDM-producing *K. pneumoniae* strains. Values in parentheses are standard errors.

Parameter	Symbol	Unit	Population mean (SE [%]) for each strain and treatment		
			***K. pneumoniae* ATCC BAA 2146**	***K. pneumoniae* 02**	***K. pneumoniae* BM1**
Initial inoculum for total bacterial population	$Log_{10}CFU_O$	CFU/mL	6.57 (1.01%)	6.49 (0.735%)	6.64 (1.12%)
Maximum population size	$Log_{10}CFU_{max}$	CFU/mL	8.92 (0.998%)	9.03 (0.356%)	8.02 (1.97%)
Mutation frequency					
Subpopulation 2	$Log_{10}(MUT,S2)$	CFU/mL	-4.99 (2.56%)	-6.26 (1.29%)	-6.53 (5.49%)
Subpopulation 3	$Log_{10}(MUT,S3)$	CFU/mL	-6.55 (1.61%)	-8.62 (1.77%)	-6.68 (0.775%)
First order bacterial death rate constant	K_d	1/h	0.224 (fixed)	0.434 (fixed)	0.209 (fixed)
Bacterial density at which VG_{max} is half-maximal					
Subpopulation 1	$Log_{10}CFU_m$	CFU/mL	7.5 (1.3%)	8.44 (0.515%)	8.32 (1.53%)

Subpopulations 2 & 3	$Log_{10}CFU_m$	CFU/mL	8.14 (1.2%)	8.44 (0.515%)	6.89 (2.53%)
Maximum fold-enhancement of K_d due to polymyxin B	$K_{max,PMB}$	1/h	145 (4.57%)	1320 (4.92%)	602 (7.23%)
Polymyxin concentration resulting in 50% of $K_{max,PMB}$					
Susceptible	$KC_{50,PMB}$	mg/L	0.178 (35.8%)	0.345 (10.6%)	0.144 (10.6%)
Intermediate			-	21.7 (4.98%)	-
Resistant		mg/L	23.6 (7.9%)	180 (10.2%)	137 (5.16%)
Maximum fold-reduction of VG_{max} due to Zidovudine	$K_{max,ZID}$	1/h	0.983 (5.37%)	1.6 (7.86%)	10.3 (4.52%)
Zidovudine concentration resulting in 50% of $K_{max,ZID}$					
Susceptible	$KC_{50,ZID}$	mg/L	0.999 (9.39%)	0.314 (15.6%)	0.355 (30.3%)
Intermediate		mg/L	-	3.48 (7.67%)	-
Resistant		mg/L	754 (10.1%)	251 (5.58%)	155 (13.3%)
Hill coefficient for polymyxin effect	Log_{10}(Hill, PMB)	-	0.733 (10.5%)	0.522 (5.81%)	0.835 (15.8%)

Hill coefficient for zidovudine effect	Log_{10}(Hill, ZID)	-	0.729 (17%)	0.793 (20.2%)	0.785 (14.9%)
Polymyxin B concentration resulting in 50% of $IMAX_{ii}$	$IC_{50,SYN,PMB}$	mg/L	10.8 (6.42%)	0.502 (18.7%)	0.471 (16.5%)
Maximum fractional decrease of $IC_{50,Synergy,Polymyxin}$ by polymyxin B	$IMAX_{ii}$	1/h	7.72 (1.48%)	5.86 (1.98%)	1.97 (4.24%)

The between-curve variability was set to a coefficient of variation of 15% for all parameters.