Supplement for *Postexposure Prophylaxis and Treatment of* Bacillus anthracis *Infections in Animals Models: Systematic Review*

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Table of Contents

Supplementary Figure 1. Search String for Systematic Review of In Vivo Data for Postexposure Prophylaxis and Treatment of *Bacillus Anthracis* Infections

Anthrax OR Anthracis

AND

antibiotic* OR antiinfective* OR anti-infective* OR antibacterial* OR anti-bacterial* OR antimicrobial* OR anti-microbial* OR Ciprofloxacin OR Moxifloxacin OR Levofloxacin OR Gentamicin OR Erythromycin OR Azithromycin OR Clarithromycin OR Penicillin* OR Amoxicillin OR Ampicillin OR Amoxi?clav OR Piperacillin OR Imipenem OR Meropenem OR Ceftriaxone OR Cefotaxime OR Cefoxitin OR Vancomycin OR Dalbavancin OR Telavancin OR Oritavancin OR Tetracycline OR Doxycycline OR Minocycline OR Linezolid OR Tedizolid OR Clindamycin OR Quinupristin OR dalfopristin OR Rifampin OR Streptomycin OR Chloramphenicol

AND

Trial* OR RCT OR study OR studies OR in vitro OR in vivo

Supplementary Text 1. Methods for Quality Score Assessment

Study quality was assessed on a 24-point scale comprising 4 main topics (Supplementary Figure 2). Points were allotted for 1) animal descriptions mentioning the species or strain, nonhuman primates (NHPs), sample size, age, weight, presence of a control group, presence of a positive control group (ie, ciprofloxacin or doxycycline), study conditions, and blinding; 2) exposures specifying the *B. anthracis* strain, challenge dose, inoculation dose measurement overall and for specific arms, spores being used rather than vegetative cells, inoculation route, and exposure group randomization; 3) antimicrobial descriptions mentioning pharmacokinetic data or humanization of the dose (ie, animal drug exposures are matched human exposures) [1], route of administration, and MICs; and 4) outcomes specifying all causes of death, immunological parameters such as antibody levels, pathology (eg, brain, lung), and results for all variables. Quality scores were categorized as low (0-5 points), fair (6-13 points), good (14-17 points), and high (18-24 points) based on natural breaks in a histogram of the scores and discussions with an internal CDC steering committee.

References for Quality Score Assessment

Bulitta JB, Hope WW, Eakin AE, et al. Generating Robust and Informative Nonclinical In Vitro and In Vivo Bacterial Infection Model Efficacy Data To Support Translation to Humans. Antimicrob Agents Chemother 2019; 63(5).

Supplementary Figure 2. Quality Assessment Tool for In Vivo Studies

Animals: Did the authors report/describe the…

	Y	N	
1	☐	☐	specific strain/breed of animal?
2	☐	☐	NHP?
3	☐	☐	sample size of each arm clearly?
4	☐	☐	the ages of animals?
5	☐	☐	the weights of animals?
6	☐	☐	the control groups adequately (e.g., were they treated with vehicle / saline [same dosing regimen])?
7	☐	☐	using a positive control (e.g., ciprofloxacin)?
8	☐	☐	study conditions (i.e., good laboratory practices [GLP])?
9	☐	☐	whether the people assessing outcomes were blinded?

Exposure: Did the authors report…

	Y	N	
10	☐	☐	the *Bacillus anthracis* strain?
11	☐	☐	the *B. anthracis* challenge dose (1 for overall range, 2 for specific exposure for each arm)?
12	☐	☐	how the *B. anthracis* inoculation dose was measured?
13	☐	☐	if *B. anthracis* spores (as opposed to vegetative cells) were used?
14	☐	☐	the specific route through which the animals were inoculated with *B. anthracis* (e.g., whole-body aerosol)?
15	☐	☐	whether animals were randomized by exposure group if not all exposed at once?

Antibiotics: Did the authors report…

	Y	N	
16	☐	☐	PK data for relevant antibiotics (or was dose that was used justified (i.e., reference to other article)?
17	☐	☐	whether the antibiotic doses were humanized?
18	☐	☐	how the antibiotics were administered (route, dose, frequency, duration)?
19	☐	☐	relevant MICs (for challenge strain)?

Outcomes: Did the authors report…

	Y	N	
20	☐	☐	specific causes of all deaths?
21	☐	☐	immunity (anti-PA, response to rechallenge)
22	☐	☐	pathology (e.g., tissue CFUs)?
23	☐	☐	results of all outcome variables assessed completely?
24	☐	☐	MICs done on isolates from animals that died?

Supplementary Table 1. Line List of In Vivo Postexposure Prophylaxis and Treatment Studies by Study Arm

			Bacillus anthracis challenge						Antimicrobial										
					Multiples of LD50	Spores/animals					(hours)								
Publication	Species	Subjects	Strain	Resistant to Abx	Mean (range)	Median (range)	Mean (range)	Route	Name	Start Time or Trigger	PEP/Rx	Route	mg/kg/day	units/kg/day	Repetition	Duration, Days	Follow Up Days	Fatalities
Barnes, 1947 [1]	R	5	Monroe	N		50000		IV	penicillin	bact	Rx	IV		1440	4	2	2	5
Barnes, 1947 [1]	R	10	Monroe	N		100000		IV	control								6	10
Barnes, 1947 [1]	R	10	Monroe	N		100000		IV	penicillin	48	Rx	IV		1440	4	6	6	10
Barnes, 1947 [1]	R	4	Monroe	N		100000		IV	control						4		8	4
Henderson, 1956 [2]	NHP	10		N			214000	A	control			IM			24	5	49	9
Henderson, 1956 [2]	NHP	10		N			214000	A	penicillin	24	PEP	IM		34803	24	5	49	8
Henderson, 1956 [2]	NHP	10		N			390000	A	control			IM			24		59	10
Henderson, 1956 [2]	NHP	9		N			390000	A	penicillin	24	PEP	IM		38412	24	5	59	9
Henderson, 1956 [2]	NHP	9		N			390000	A	penicillin	24	PEP	IM		38412	24	10	59	9
Henderson, 1956 [2]	NHP	6		N			390000	A	penicillin	24	PEP	IM		38412	24	20	44	2
Henderson, 1956 [2]	NHP	10		N			200000	A	control								50	9
Henderson, 1956 [2]	NHP	10		N			750000	A	control								50	10
Gochenour, 1962 [3]	NHP	6	Vollum	N		783000 (345000-1200000)		A	control								31	6
Gochenour, 1962 [3]	NHP	5	Vollum	N		783000 (345000-1200000)		A	procaine penicillin	24	PEP	IM		63830	24	5	31	4
Gochenour, 1962 [3]	NHP	5	Vollum	N		783000 (345000-1200000)		A	procaine penicillin	48	Rx	IM		63830	24	5	31	1
Gochenour, 1962 [3]	NHP	4	Vollum	N		783000 (345000-1200000)		A	procaine penicillin	72	Rx	IM		63830	24	5	31	2
NA, 1971[c]	NHP	6	Vollum	N			783000 (345000-1200000)	HOA	control								31	6
NA, 1971[c]	NHP	5	Vollum	N			783000 (345000-1200000)	HOA	penicillin	24	PEP	IM		63830	24	5	31	4
NA, 1971[c]	NHP	5	Vollum	N			783000 (345000-1200000)	HOA	penicillin	48	Rx	IM		63830	24	5	31	1
NA, 1971[c]	NHP	4	Vollum	N			783000 (345000-1200000)	HOA	penicillin	72	Rx	IM		63830	24	5	31	2
Pomerantsev, 1992 [4]	M	10	H-7	N		10		SC	control									6
Pomerantsev, 1992 [4]	M	10	H-7	N		10		SC	tetracycline	3	PEP	IM	32		24	5		0
Pomerantsev, 1992 [4]	M	10	H-7	N		10		SC	tetracycline	20	PEP	IM	32		24	7		0
Pomerantsev, 1992 [4]	M	10	H-7	N		100		SC	control									8
Pomerantsev, 1992 [4]	M	10	H-7	N		100		SC	tetracycline	3	PEP	IM	32		24	5		0
Pomerantsev, 1992 [4]	M	10	H-7	N		100		SC	tetracycline	20	PEP	IM	32		24	7		0
Pomerantsev, 1992 [4]	M	10	H-7	N		1000		SC	control									10
Pomerantsev, 1992 [4]	M	10	H-7	N		1000		SC	tetracycline	3	PEP	IM	32		24	5		0
Pomerantsev, 1992 [4]	M	10	H-7	N		1000		SC	tetracycline	20	PEP	IM	32		24	7		0

Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	control								8
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	tetracycline	20	PEP	IM	4	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	tetracycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	tetracycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	doxycycline	20	PEP	IM	4	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	doxycycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	doxycycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	minocycline	20	PEP	IM	2	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	minocycline	20	PEP	IM	4	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	minocycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		10	SC	minocycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	control								10
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	tetracycline	20	PEP	IM	4	24	7		10
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	tetracycline	20	PEP	IM	8	24	7		4
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	tetracycline	20	PEP	IM	16	24	7		2
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	doxycycline	20	PEP	IM	4	24	7		4
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	doxycycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	doxycycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	minocycline	20	PEP	IM	2	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		100	SC	minocycline	20	PEP	IM	4	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N			SC	minocycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N			SC	minocycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N	100		SC	control								10
Pomerantsev, 1992 [4]	H	10	H-7	N	100		SC	tetracycline	20	PEP	IM	4	24	7		10
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	tetracycline	20	PEP	IM	8	24	7		10
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	tetracycline	20	PEP	IM	16	24	7		4
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	doxycycline	20	PEP	IM	4	24	7		8
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	doxycycline	20	PEP	IM	8	24	7		8
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	doxycycline	20	PEP	IM	16	24	7		6
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	minocycline	20	PEP	IM	2	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	minocycline	20	PEP	IM	4	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	minocycline	20	PEP	IM	8	24	7		0
Pomerantsev, 1992 [4]	H	10	H-7	N		1000	SC	minocycline	20	PEP	IM	16	24	7		0
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		10	SC	control								1
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		10	SC	tetracycline	3	PEP	IM	32	24	5		3
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		10	SC	tetracycline	20	PEP	IM	32	24	7		4
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		100	SC	control								6
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		100	SC	tetracycline	3	PEP	IM	32	24	5		8
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		100	SC	tetracycline	20	PEP	IM	32	24	7		7
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		1000	SC	control								10
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		1000	SC	tetracycline	3	PEP	IM	32	24	5		9
Pomerantsev, 1992 [4]	M	10	H-7 (pBC16)	Y		1000	SC	tetracycline	20	PEP	IM	32	24	7		9
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10	SC	control								8
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10	SC	tetracycline	20	PEP	IM	4	24	7		9
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10	SC	tetracycline	20	PEP	IM	8	24	7		9
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10	SC	tetracycline	20	PEP	IM	16	24	7		8

Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	doxycycline	20	PEP	IM	4		24	7		8
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	doxycycline	20	PEP	IM	8		24	7		9
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	doxycycline	20	PEP	IM	16		24	7		9
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	minocycline	20	PEP	IM	2		24	7		2
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	minocycline	20	PEP	IM	4		24	7		2
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	minocycline	20	PEP	IM	8		24	7		0
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		10		SC	minocycline	20	PEP	IM	16		24	7		0
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	control									10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	tetracycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	tetracycline	20	PEP	IM	8		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	tetracycline	20	PEP	IM	16		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	doxycycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	doxycycline	20	PEP	IM	8		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	doxycycline	20	PEP	IM	16		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	minocycline	20	PEP	IM	2		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	minocycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	minocycline	20	PEP	IM	8		24	7		0
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		100		SC	minocycline	20	PEP	IM	16		24	7		0
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	control									10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	tetracycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	tetracycline	20	PEP	IM	8		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	tetracycline	20	PEP	IM	16		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	doxycycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	doxycycline	20	PEP	IM	8		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	doxycycline	20	PEP	IM	16		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	minocycline	20	PEP	IM	2		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	minocycline	20	PEP	IM	4		24	7		10
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	minocycline	20	PEP	IM	8		24	7		8
Pomerantsev, 1992 [4]	H	10	H-7 (pBC16)	Y		1000		SC	minocycline	20	PEP	IM	16		24	7		0
Friedlander, 1993 [5]	NHP	10	Vollum 1B	N	8		400000	HOA	control			IM			12	30	70	9
Friedlander, 1993 [5]	NHP	10	Vollum 1B	N	8		400000	HOA	procaine penicillin G	24	PEP	IM		38298	12	30	70	3
Friedlander, 1993 [5]	NHP	9	Vollum 1B	N	8		400000	HOA	ciprofloxacin	24	PEP	PO	27		12	30	70	1
Friedlander, 1993 [5]	NHP	10	Vollum 1B	N	8		400000	HOA	doxycycline	24	PEP	PO	6		12	30	70	1
Kalns, 2002 [6]	M	10	Sterne	N		5000000		SC	control			IP			24	1	14	8
Kalns, 2002 [6]	M	10	Sterne	N		5000000		SC	doxycycline	48	Rx	IP	1.5		24	1	14	9
Heine, 2006 [7]	M	10	Ames	N	(50-100)			WBA	ciprofloxacin	24	PEP	IP	60		12	21	45	1
Heine, 2006 [7]	M	10	Ames	N	(50-100)			WBA	control								45	9
Kao, 2006 [8]	NHP	10	Ames	N	44			HOA	control								100	9
Kao, 2006 [8]	NHP	10	Ames	N	49			HOA	ciprofloxacin	24	PEP	PO	32		12	30	100	2
Kao, 2006 [8]	NHP	10	Ames	N	56			HOA	levofloxacin	24	PEP	PO	19		24	30	100	1
Heine, 2007 [9]	M	10	Ames	N	50			WBA	ciprofloxacin	24	PEP	IP	60		12	14	60	2
Heine, 2007 [9]	M	10	Ames	N	50			WBA	doxycycline	24	PEP	IP	160		6	14	60	1
Heine, 2007 [9]	M	10	Ames	N	50			WBA	ciprofloxacin	24	PEP	IP	60		12	21	60	0
Heine, 2007 [9]	M	10	Ames	N	50			WBA	doxycycline	24	PEP	IP	160		6	21	60	3
Heine, 2007 [9]	M	10	Ames	N	50			WBA	ciprofloxacin	36	Rx	IP	60		12	21	60	2
Heine, 2007 [9]	M	10	Ames	N	50			WBA	ciprofloxacin	48	Rx	IP	60		12	21	60	1

Heine, 2007 [9]	M	10	Ames	N	50		WBA	control					12	21	60	9
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	ciprofloxacin	24	PEP	IP	60	12	14	30	1
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	15	48	14	35	0
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	control							30	10
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	0.05	48	14	30	10
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	0.15	48	14	30	7
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	0.5	48	14	30	5
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	1.5	48	14	30	0
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	5	48	14	30	0
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IV	5	24	1	30	6
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IV	15	24	1	30	3
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IV	50	24	1	30	0
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	36	Rx	IP	5	48	14	35	1
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	48	Rx	IP	5	48	14	35	5
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	oritavancin	24	PEP	IP	15	48	14	35	0
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	ciprofloxacin	36	Rx	IP	60	12	14	35	3
Heine, 2008 [10]	M	10	Ames	N	(50-75)		A	ciprofloxacin	48	Rx	IP	60	12	14	35	2
Heine, 2008 [10]	M	9	Ames	N	(50-75)		A	oritavancin	42	Rx	IV	50	24	1	35	4
Gill, 2010 [11]	M	10	Ames bla1/bla2	N	100		A	control			IP		12	14	27	10
Gill, 2010 [11]	M	10	Ames bla1/bla2	N	100		A	ciprofloxacin	24	PEP	IP	60	12	14	27	1
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	control			IP		12	14	42	10
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	ciprofloxacin	24	PEP	IP	60	12	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	10	36	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	20	36	14	42	2
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	40	36	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	80	36	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	10	72	14	42	1
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	20	72	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	40	72	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	24	PEP	IP	80	72	14	42	2
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	36	Rx	IP	40	36	14	42	1
Heine, 2010 [12]	M	7	Ames	N	(50-100)		A	dalbavancin	36	Rx	IP	40	72	14	42	2
Heine, 2010 [12]	M	4	Ames	N	(50-100)		A	ciprofloxacin	48	Rx	IP	60	12	14	42	0
Heine, 2010 [12]	M	10	Ames	N	(50-100)		A	dalbavancin	48	Rx	IP	40	36	14	42	0
Heine, 2010 [12]	M	6	Ames	N	(50-100)		A	dalbavancin	48	Rx	IP	40	72	14	42	1
Heine, 2010 [13]	M	10	Ames	N	(75-100)		A	ciprofloxacin	24	PEP	IP	60	12	14	43	2
Heine, 2010 [13]	M	10	Ames	N	(75-100)		A	control			SC		12	14	43	9
Heine, 2010 [13]	M	10	Ames	N	(75-100)		A	ciprofloxacin	24	PEP	IP	60	12	21	43	1
Heine, 2010 [13]	M	10	Ames	N	(75-100)		A	daptomycin	24	PEP	SC	100	12	21	43	1
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	control			IM		12	6	13	5
Peterson, 2010 [14]	R	7	Ames	N	100	10000000	IN	control			IM		24	6	25	6
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	control			IM		24	6	22	5
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	levofloxacin	48	Rx	IM	14	24	6	22	3
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	levofloxacin	57	Rx	IM	14	24	6	22	5
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	levofloxacin	72	Rx	IM	14	24	6	22	5
Peterson, 2010 [14]	R	5	Ames	N	100	10000000	IN	levofloxacin	96	Rx	IM	14	24	6	22	5

Yee, 2010 [15]	R	8	Ames	N	143		HOA	control	PA		IV		12	5	28	8
Yee, 2010 [15]	R	7	Ames	N	101		HOA	levofloxacin	PA	Rx	IV	13	12	5	28	2
Yee, 2010 [15]	R	8	Ames	N	136		HOA	levofloxacin	PA	Rx	IV	25	12	5	28	1
Nelson, 2011 [16]	NHP	6	Ames	N	5	126000	HOA	ciprofloxacin	9	PEP		35	12	10	31	2
Nelson, 2011 [16]	NHP	2	Ames	N	5	140000	HOA	control							31	2
Weiss, 2011 [17]	GP	9	Vollum ATCC 14578	N	75	3000000	IN	control	24							9
Weiss, 2011 [17]	GP	70	Vollum ATCC 14578	N	75	3000000	IN	doxycycline	30	Rx		20	12	21	50	24
Weiss, 2011 [17]	GP	59	Vollum ATCC 14578	N	75	3000000	IN	ciprofloxacin	30	Rx		20	12	21	50	26
Weiss, 2011 [17]	R	26	Vollum ATCC 14578	N	10	(2000000-6000000)	IN	doxycycline	bact	Rx	PO	30	12	14	44	15
Weiss, 2011 [17]	R	48	Vollum ATCC 14578	N	10		IN	ciprofloxacin	bact	Rx	PO	60	12	14	44	30
Leffel, 2012 [18]	R	18	Ames	N	256		NOA	levofloxacin	9	PEP	PO	50	24	7	30	8
Leffel, 2012 [18]	R	10	Ames	N	256		NOA	control			PO		24	7		10
Watkins, 2013 [c]	NHP	6	Ames	N	159 (135-252)		HOA	clarithromycin	24	PEP	PO	60	12	30	75	2
Watkins, 2013 [c]	NHP	6	Ames	N	109 (86-135)		HOA	azithromycin	24	PEP	PO	3.8	24	29	75	3
Watkins, 2013 [c]	NHP	4	Ames	N	124 (90-158)		HOA	levofloxacin	24	PEP	PO	4	24	30	75	2
Watkins, 2013[c]	NHP	4	Ames	N	234 (135-327)		HOA	control			PO		12	30	75	4
Batelle, 2014[c]	R	4	Ames	N	200		HOA	control							5	4
Batelle, 2014 [c]	R	10	Ames	N	200		HOA	eravacycline	fever	Rx	IV	0.8	24	28	56	0
Batelle, 2014 [c]	R	10	Ames	N	200		HOA	eravacycline	fever	Rx	IV	1.6	24	28	56	0
Kammanadiminti, 2014 [19]	R	8	Ames	N	178		A	control							30	8
Kammanadiminti, 2014 [19]	R	8	Ames	N	178		A	levofloxacin	30	Rx	PO	50	24	3	30	0
Kammanadiminti, 2014 [19]	R	8	Ames	N	178		A	levofloxacin	36	Rx	PO	50	24	3	30	0
Kammanadiminti, 2014 [19]	R	8	Ames	N	178		A	levofloxacin	48	Rx	PO	50	24	3	30	0
Kammanadiminti, 2014 [19]	R	8	Ames	N	178		A	levofloxacin	60	Rx	PO	50	24	3	30	1
Kammanadiminti, 2014 [19]	R	18	Ames	N	282		A	control			PO				32	18
Kammanadiminti, 2014 [19]	R	10	Ames	N	282		A	levofloxacin	60	Rx	PO	50	24	3	32	1
Kammanadiminti, 2014 [19]	R	20	Ames	N	282		A	levofloxacin	72	Rx	PO	50	24	3	32	9
Kammanadiminti, 2014 [19]	R	9	Ames	N	282		A	levofloxacin	84	Rx	PO	50	24	3	32	6
Kammanadiminti, 2014 [19]	R	8	Ames	N	282		A	levofloxacin	96	Rx	PO	50	24	3	32	6
Public Health England, 2014 [c]	NHP	4	Ames	N	413 (356-485)		A	amoxicillin-clavulanate	24	PEP	PO	27	12	28	88	0
Public Health England, 2014 [c]	NHP	2	Ames	N	421 (307-534)		A	control			PO		12	28	10	2
Migone, 2015 [20]	R	104	Ames	N	189 (86-305)		A	control							35	104
Migone, 2015 [20]	R	37	Ames	N	174 (83-277)		A	levofloxacin	84	Rx	PO	50	24	3	35	13
Public Health England, 2015 [c]	NHP	4	Ames ANT/121/11	N	(194-324)		A	control			PO		12	28	8	4
Public Health England, 2015 [c]	NHP	5	Ames ANT/121/11	N	(291-647)		A	amoxicillin-clavulanate	24	PEP	PO	27	12	28	88	0
Public Health England, 2015 [c]	NHP	2	Ames ANT/121/11	N	(259-409)		A	amoxicillin	24	PEP	PO	27	12	28	88	0
Public Health England, 2015 [c]	NHP	4	Ames ANT/121/11	N	(210-388)		A	control			PO		12	28	8	4
Public Health England, 2015 [c]	NHP	8	Ames ANT/121/11	N	(210-372)		A	amoxicillin	24	PEP	PO	27	12	28	88	0
Weiss, 2015 [21]	R	4	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	control							30	4

Weiss, 2015 [21]	R	16	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	amoxicillin-clavulanate	32	Rx	SC	200	12	14	30	4
Weiss, 2015 [21]	R	23	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	vancomycin	32	Rx	SC	80	12	14	30	3
Weiss, 2015 [21]	R	19	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	imipenem	32	Rx	SC	40	12	14	30	2
Weiss, 2015 [21]	R	19	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	rifampin	32	Rx	PO	100	12	14	30	14
Weiss, 2015 [21]	R	32	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	clarithromycin	32	Rx	PO	160	12	14	30	20
Weiss, 2015 [21]	R	15	Vollum ATCC 14578	N	100	(2000000-6000000)	IN	linezolid	32	Rx	PO	100	12	14	30	5
Weiss, 2015 [21]	R	16	Vollum ATCC 14578	N	(100-200)		IN	ciprofloxacin	32	Rx	PO	120	12	14	30	11
Grossman, 2017 [22]	M	9	Ames	N	18		NOA	control					24	21	60	7
Grossman, 2017 [22]	M	13	Ames	N	18		NOA	doxycycline	24	PEP	IP	80	12	21	60	9
Grossman, 2017 [22]	M	10	Ames	N	88		NOA	control							62	9
Grossman, 2017 [22]	M	13	Ames	N	88		NOA	doxycycline	48	Rx	IP	80	12	21	62	5
Heine, 2017 [23]	M	10	Cip-R Ames	Y	(7-32)		WBA	control			IP		12	14	28	9
Heine, 2017 [23]	M	10	Cip-R Ames	Y	(7-32)		WBA	ciprofloxacin	36	Rx	IP	60	12	14	28	7
Slay, 2017[a]	M	32	Ames	N	200		A	levofloxacin	24	PEP	PO	80	6	14	30	15
Slay, 2017[a]	M	32	Ames	N	200		A	azithromycin	24	PEP	PO	6	6	13	30	32
Slay, 2017[a]	M	32	Ames	N	200		A	clarithromycin	24	PEP	PO	30	12	14	30	32
Slay, 2017[a]	M	32	Ames	N	200		A	amoxicillin	24	PEP	PO	30	8	14		7
Slay, 2017[a]	M	32	Ames	N	200		A	amoxicillin-clavulanate	24	PEP	PO	30	8	14	30	6
Slay, 2017[a]	M	80	Ames	N	200		A	control							30	80
Slay, 2017[a]	M	15	Ames	N	200		A	control							30	15
Slay, 2017[a]	M	15	Ames	N	200		A	levofloxacin			PO	160	12	30	30	0
Slay, 2017[a]	M	15	Ames	N	200		A	azithromycin			PO	12	12	29	30	14
Slay, 2017[a]	M	15	Ames	N	200		A	clarithromycin			PO	60	12	30	30	15
Slay, 2017[a]	M	15	Ames	N	200		A	amoxicillin			PO	60	12	30	30	1
Slay, 2017[a]	M	15	Ames	N	200		A	amoxicillin-clavulanate			PO	60	12	30	30	2
Slay, 2017[a]	NHP	10	Ames	N	200		A	amoxicillin-clavulanate	24	PEP	PO	27	12	28	60	0
Slay, 2017[a]	NHP	10	Ames	N	200		A	control							60	10
Slay, 2017[a]	NHP	10	Ames	N	200		A	amoxicillin	24	PEP	PO	27	12	28	60	0
Slay, 2017[a]	NHP	10	Ames	N	200		A	amoxicillin-clavulanate			PO	27	12	28	60	0
Slay, 2017[a]	NHP	10	Ames	N	200		A	control							60	10
Steenbergen, 2017 [24]	M	10	Ames	N	9.8 (7.6-12)		WBA	control							38	6
Steenbergen, 2017 [24]	M	9	Ames	N	9.8 (7.6-12)		WBA	ciprofloxacin	24	PEP	IP	60	12	14	38	0
Steenbergen, 2017 [24]	M	10	Ames	N	9.8 (7.6-12)		WBA	doxycycline	24	PEP	IP	20	12	14	38	0
Steenbergen, 2017 [24]	M	10	Ames	N	9.8 (7.6-12)		WBA	omadacycline	24	PEP	IP	10	12	14	38	0
Steenbergen, 2017 [24]	M	10	Ames	N	9.8 (7.6-12)		WBA	omadacycline	24	PEP	IP	20	12	14	38	0
Steenbergen, 2017 [24]	M	10	Ames	N	9.8 (7.6-12)		WBA	omadacycline	24	PEP	IP	40	12	14	38	0
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)		WBA	doxycycline	24	PEP	IP	1.5	12	14	40	8
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)		WBA	doxycycline	24	PEP	IP	5	12	14	40	3

Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	doxycycline	24	PEP	IP	15	12	14	40	0
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	doxycycline	24	PEP	IP	30	12	14	40	0
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	omadacycline	24	PEP	IP	1.5	12	14	40	6
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	omadacycline	24	PEP	IP	5	12	14	40	2
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	omadacycline	24	PEP	IP	15	12	14	40	0
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	omadacycline	24	PEP	IP	30	12	14	40	0
Steenbergen, 2017 [24]	M	9	Ames	N	30.53 (27.3-37.2)	WBA	ciprofloxacin	24	PEP	IP	60	12	14	40	0
Steenbergen, 2017 [24]	M	10	Ames	N	30.53 (27.3-37.2)	WBA	control			IP		12	14	40	10
Steenbergen, 2017 [24]	M	10	Ames	N	30.5	WBA	control			IP		12	14	40	10
Steenbergen, 2017 [24]	M	10	Ames	N	30.5	WBA	doxycycline	48	Rx	IP	30	12	14	40	3
Steenbergen, 2017 [24]	M	10	Ames	N	30.5	WBA	omadacycline	48	Rx	IP	30	12	14	40	4
Steenbergen, 2017 [24]	M	9	Ames	N	30.5	WBA	ciprofloxacin	48	Rx	IP	60	12	14	40	2
Vietri, 2020 [25]	NHP	4	Ames	N	172 (35-463)	A	control	bact						60	4
Vietri, 2020 [25]	NHP	11	Ames	N	172 (35-463)	A	ciprofloxacin	bact	Rx	IV	33	12	10	60	0
Vietri, 2020 [25]	NHP	12	Ames	N	172 (35-463)	A	clindamycin	bact	Rx	IM	60	8	10	60	3

Abbreviations: A, aerosol; bact, bacteremia; GP, guinea pig; H, hamster; HOA, head-only aerosol; IN, intranasal IN; IP, intraperitoneal; intravenous; M, mouse; N, No; NHP, nonhuman primate; PA, protective antigen; PEP, postexposure prophylaxis; R, rabbit; Rx, treatment; SC, subcutaneous; WBA, whole-body aerosol

[a] Unpublished data

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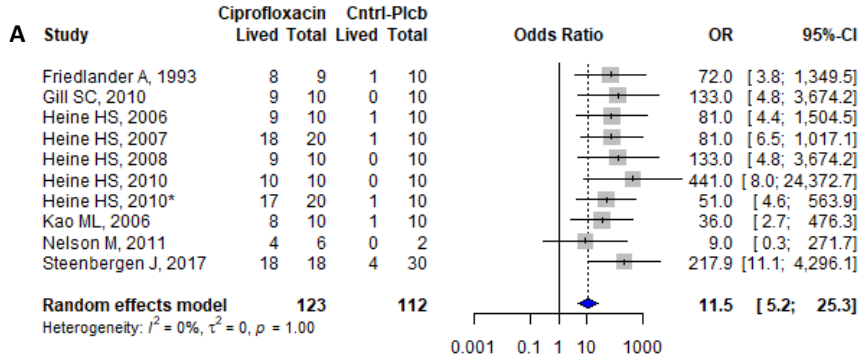
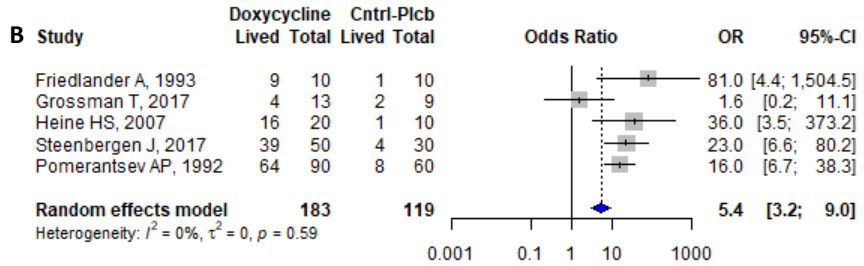
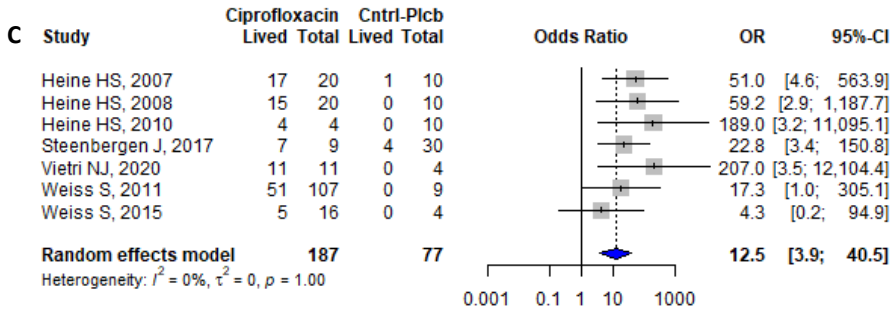
Supplementary Figure 3. Forest Plots for Monotherapy Studies

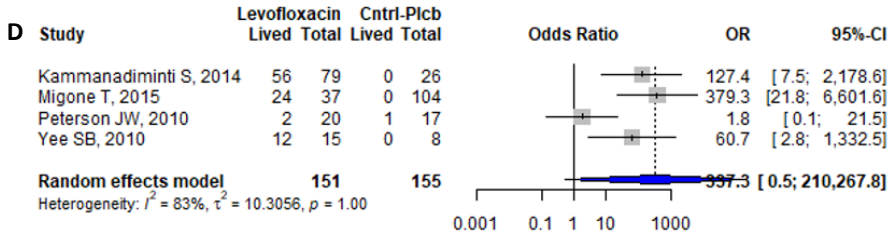
Postexposure Prophylaxis

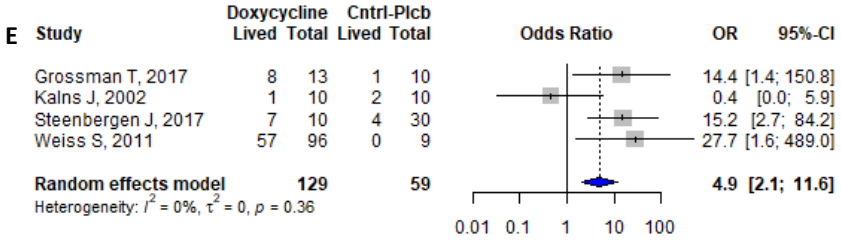




Treatment Studies







Supplementary Text 2. Information on Monte Carlo Simulations

The purpose of these simulations was to determine drug exposures and target attainment probabilities for various antimicrobials for the treatment and postexposure prophylaxis of anthrax. The main manuscript provides an overview of the general methods employed to determine the drug exposures from published pharmacokinetic (PK) datasets as well as to predict the probabilities of attaining pharmacokinetic / pharmacodynamic (PK/PD) targets associated with survival in animal studies. While commonly employed techniques were used for these PK predictions and Monte Carlo simulations, this supplement provides additional details on the approach and results.

METHODS

Published animal PK data from studies evaluating postexposure prophylaxis (PEPAbx) or treatment of anthrax were used to predict the average unbound drug exposures and subsequently establish exposure-response relationships. We systematically obtained the doses, dosing intervals, and routes of administration for published anthrax studies in mice, rabbits, and nonhuman primates (NHPs) [1].
Simulations were performed to predict the overall free (ie, non-protein-bound) drug exposures in plasma (i.e., the area under the unbound plasma concentration time curve, fAUC) for the dosage regimens studied in animals. Plasma protein binding was assumed to be similar in mice and humans for levofloxacin and ciprofloxacin (~30% bound), as well as for doxycycline (~80 to 90% bound) [2]. Known differences in protein binding between species were incorporated for dalbavancin (93% bound in humans vs. 98.4% in mice) [3, 4] and oritavancin (85% bound in humans vs. 93.6% in mouse serum) [5, 6].

As no PK data in anthrax-infected animals were available for β-lactam antibiotics, quantitative PK/PD relationships could not be established for this class of antimicrobials. For non-β-lactam antibiotics (and especially for drugs with long half-lives), the fAUC/MIC is usually the most predictive PK/PD index for bacterial killing in mice at 24 h and for beneficial outcomes in patients [7]. To obtain the fAUC/MIC, the predicted fAUC was divided by the MIC of the *B. anthracis* strain used in the respective animal experiment [8, 9]. When determining the PK/PD targets of oritavancin, we used the reported MIC of the *B. anthracis* Ames strain (0.015 mg/L) in the presence of 0.002% polysorbate 80 [6]. Then, each fAUC/MIC was plotted against the observed mortality to identify PK/PD exposure targets associated with a high level of survival (eg, ≥80%). Ciprofloxacin and dalbavancin achieved near-maximal survival at the lowest studied doses for treatment and PEPAbx. Thus, the PK/PD targets for ciprofloxacin and dalbavancin were conservative (i.e., high). The exposure-response relationship data for levofloxacin was more heterogeneous than that for ciprofloxacin. Given the similar mechanisms of action between these fluoroquinolones, the PK/PD targets from ciprofloxacin were borrowed for levofloxacin. Additionally, a more conservative AUC0-24h/MIC target of 226 (equivalent to a fAUC0-24h/MIC of 158) was considered for levofloxacin.

The exposure response data for doxycycline were sparser than those for ciprofloxacin. Thus, a range of 3 PK/PD targets was employed.

The PK/PD targets for ciprofloxacin, levofloxacin, and doxycycline are based on the AUC from 0 to 24 h (AUC0-24h). Because dalbavancin has a weekly dosing interval in humans, we calculated the AUC from 0 to 7 days (AUC0-7days) and used this drug exposure metric for PK/PD target evaluations. Likewise, due to the long half-life of oritavancin, the AUC from 0 to 14 days (AUC0-14days) was used for PK/PD target assessment. Given the sparse and heterogeneous nature of these PK/PD datasets arising from different animal species in various studies, we did not perform formal logistic regression analyses and instead considered a variety of potential PK/PD target values as described above.

To predict drug exposures (AUCs) in humans, Monte Carlo simulations with 10,000 virtual subjects for each dosage regimen were performed. Due to their long half-lives, we calculated the fAUC over weekly intervals (fAUC0-7days and fAUC7-14days) for dalbavancin in both humans and mice. For oritavancin, the fAUC from time zero to infinity (fAUC0-infinity) in humans was compared to the AUC over the entire 14-day treatment duration in mice (fAUC0-14days).

Total clearance (CL) or, for oral dosing, apparent total clearance (CL/F) is the main PK parameter determining the drug exposures (AUC), along with the administered dose. Thus, between-subject variability (ie, the coefficient of variation [CV] of CL or CL/F) was obtained from studies of healthy volunteers and patient populations, with a preference for studies employing population PK modeling. Monte Carlo simulations were performed using the smaller variability from healthy volunteers to reflect PEPAbx or the moderate variability from non-critically ill patients to reflect the early stages of anthrax infections.
The simulated fAUC/MIC ratios in humans over a wide range of MICs were then compared to the PK/PD targets associated with high survival in PEPAbx or treatment studies. The fraction of virtual subjects achieving the respective PK/PD target was used to approximate the probability of target attainment (PTA) (ie, efficacy). We defined the PK/PD breakpoint for PEPAbx and treatment of anthrax patients as the highest MIC with a PTA of at least 98%. This conservative cutoff was chosen due to the life-threatening nature of systemic anthrax. The PTA vs. MIC profiles were provided, and thus PK/PD breakpoints for other cutoff values can be readily obtained from these plots.

RESULTS

In our PK/PD analyses, ciprofloxacin AUC0-24h/MIC targets were derived from several mouse infection model studies [4, 6, 10-13]. A target of 44 (unpublished data, Henry Heine) to 68 was identified in these PEPAbx studies to yield 80% to 100% survival at all studied drug exposures, suggesting near-maximal efficacy at the lowest dose. Survival was 67% to 89% in 3 NHP studies [14-16] at AUC0-24h/MIC of 158 to 200. For treatment studies, survival rates in mice and NHPs were 70% to 100% at AUC0-24h/MIC of 68 to 564, with no apparent exposure-response relationship. Therefore, an AUC0-24h/MIC target of 44 was used for PEPAbx and an AUC0-24h/MIC target of 68 for treatment by ciprofloxacin. After accounting for 30% protein binding, these ciprofloxacin targets are equivalent to fAUC0-24h/MIC of 31 for PEPAbx and of 48 for treatment.

Monte Carlo simulations for oral ciprofloxacin used an average CL/F of 34.2 L/h [17-19]. We simulated daily ciprofloxacin doses of 1000 or 1500 mg (ie, 500 mg ciprofloxacin orally every 8 or 12 h). When using the 20% CV in CL/F, the 1000 mg daily dose of ciprofloxacin achieved robust (>98%) PTAs up to MICs of 0.25 mg/L for the AUC0-24h/MIC targets of 44 and 68. At the higher dose (1500 mg per day), robust PTAs were achieved up to 0.5 mg/L at the AUC/MIC target of 44, and up to 0.25 mg/L at the AUC0-24h/MIC target of 68. These PK/PD breakpoints were similar or slightly lower (0.125 to 0.5 mg/L) when simulating with a moderately large CV of 30% for between-subject variability in CL/F.

For levofloxacin, the achieved AUC0-24h/MIC in rabbits and NHPs ranged from 113 to 487 [15, 20-24]. Survival rates were considerably lower when treatment was initiated at 48 h or longer post infection. Thus, these late treatment onset arms were excluded from the PK/PD analysis. Survival rates for PEPAbx ranged from 50% to 90% with no obvious exposure-response relationship. One study with 90% survival in NHPs had an AUC0-24h/MIC of 233 [15]. For treatment studies in rabbits, survival was 87.5% or 100% at AUC0-24h/MIC of 218 or higher. Therefore, we used the average AUC0-24h/MIC target of 226 for levofloxacin (equivalent to a fAUC0-24h/MIC of 158), in addition to the ciprofloxacin AUC0-24h/MIC targets of 44 and 68. These ciprofloxacin and levofloxacin targets were within the range of quinolone targets for other bacterial pathogens in mice and man [7].

We simulated a once-daily dose of 750 mg oral levofloxacin with an average population mean clearance of 10 L/h and a CV of 20% or 30% [19, 25]. For the scenario with smaller variability, levofloxacin achieved robust PTAs up to an MIC of 1 mg/L at the AUC0-24h/MIC target of 44, up to an MIC of 0.5 mg/L at the AUC0-24h/MIC target of 68, and up to an MIC of 0.125 mg/L for the AUC0-24h/MIC target of 226. These PK/PD breakpoints were similar or slightly lower (0.125 to 0.5 mg/L) when we used a CL/F with a 30% CV.

For doxycycline, near-maximal efficacy in mice was observed for PEPAbx at AUC/MIC of 274 and higher [11, 13, 26]. Three studies [13, 26, 27] were available to determine PK/PD relationships for doxycycline treatment. Survival rates were 62% to 70% at AUC0-24h/MIC of 548 and 1525, whereas an AUC0-24h/MIC of 27 yielded only 10% survival. Thus, we used the AUC0-24h/MIC target of 274 for PEPAbx and of 538 and 1525 for treatment. Assuming an 85% plasma protein binding of doxycycline (i.e., unbound fraction of 0.15), these targets are equivalent to a fAUC0-24h/MIC of 41 for PEPAbx as well as of 81 and 229 for treatment.

Doxycycline clearance was simulated in two scenarios: one recent population PK analysis showed a mean CL/F of 4.63 L/h (19.3% CV) [28]; in the second scenario, we pooled several studies and obtained an average CL/F of 3.27 L/h (33.4% CV) [29, 30]. At a daily dose of 200 mg oral doxycycline, robust PTAs were achieved up to an MIC of 0.0625 mg/L for the AUC0-24h/MIC target of 274 and up to 0.031 mg/L for the AUC0-24h/MIC target of 548 in both clearance scenarios. For the more conservative treatment target of AUC0-24h/MIC of 1525, the breakpoint was 0.0156 mg/L.

For oritavancin, a clear exposure-response relationship [6] was observed for PEPAbx with near-maximal survival achieved at a fAUC0-14days/MIC of 2,363 in mice. The same study found a 90% survival at a fAUC0-14days/MIC of 7,875, when treatment was started at 36 h. When treatment was initiated later, survival was 50% to 56% (at fAUC0-14days/MIC of 6,354 or 7,875). Therefore, we used a fAUC0-14days/MIC target of 2,363 for PEPAbx. As only a narrow range of oritavancin exposures was studied for treatment by oritavancin, we used the highest studied drug exposure as a conservative target for treatment (fAUC0-14days/MIC of 7,875). For Monte Carlo simulations, we used a population mean clearance of 0.45 L/h with either a 20% or 30% CV [31-35]. A single IV dose of 1200 mg oritavancin achieved robust PTAs up to an MIC of 0.0625 mg/L for the PEPAbx target and up to an MIC of 0.031 mg/L or 0.0156 mg/L (depending on the variability in CL) for the treatment target. Of note, the *B. anthracis* Ames strain MIC of 0.015 mg/L was reported in the presence of 0.002% polysorbate 80 [6] and this MICs was used for PK/PD evaluation. Therefore, the predicted PTA vs. MIC profiles for oritavancin refer to MICs in the presence of 0.002% polysorbate 80.

One mouse study assessed the PK/PD for dalbavancin [4] and showed near maximal efficacy (survival ≥80%) at all studied fAUC0-7days/MIC, ranging from 850 to 6,800 when assessing PEPAbx. All treatment arms of the same study evaluated a fAUC0-7days/MIC of 3400 which led to survival rates of 71% to 100%. As a conservative approach, we used the fAUC0-7days/MIC target of 850 for PEPAbx and the target of 3400 for treatment. Monte Carlo simulations used an IV dose of 1000 mg dalbavancin at day 0 and of 500 mg at day 7. The fAUC from days 0 to 7 and from days 7 to 14 were calculated based on PK data from Scoble et al. [36]. The variability in CL and thus in AUC was set to 23% based on two population PK analyses [37, 38]. Additionally, we simulated a scenario with 30% CV in CL. Under both scenarios, robust PTAs were achieved up to MICs of 0.0625 mg/L for the PEPAbx target and up to 0.0156 mg/L for the conservative treatment target.

References for Supplementary Text 2

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