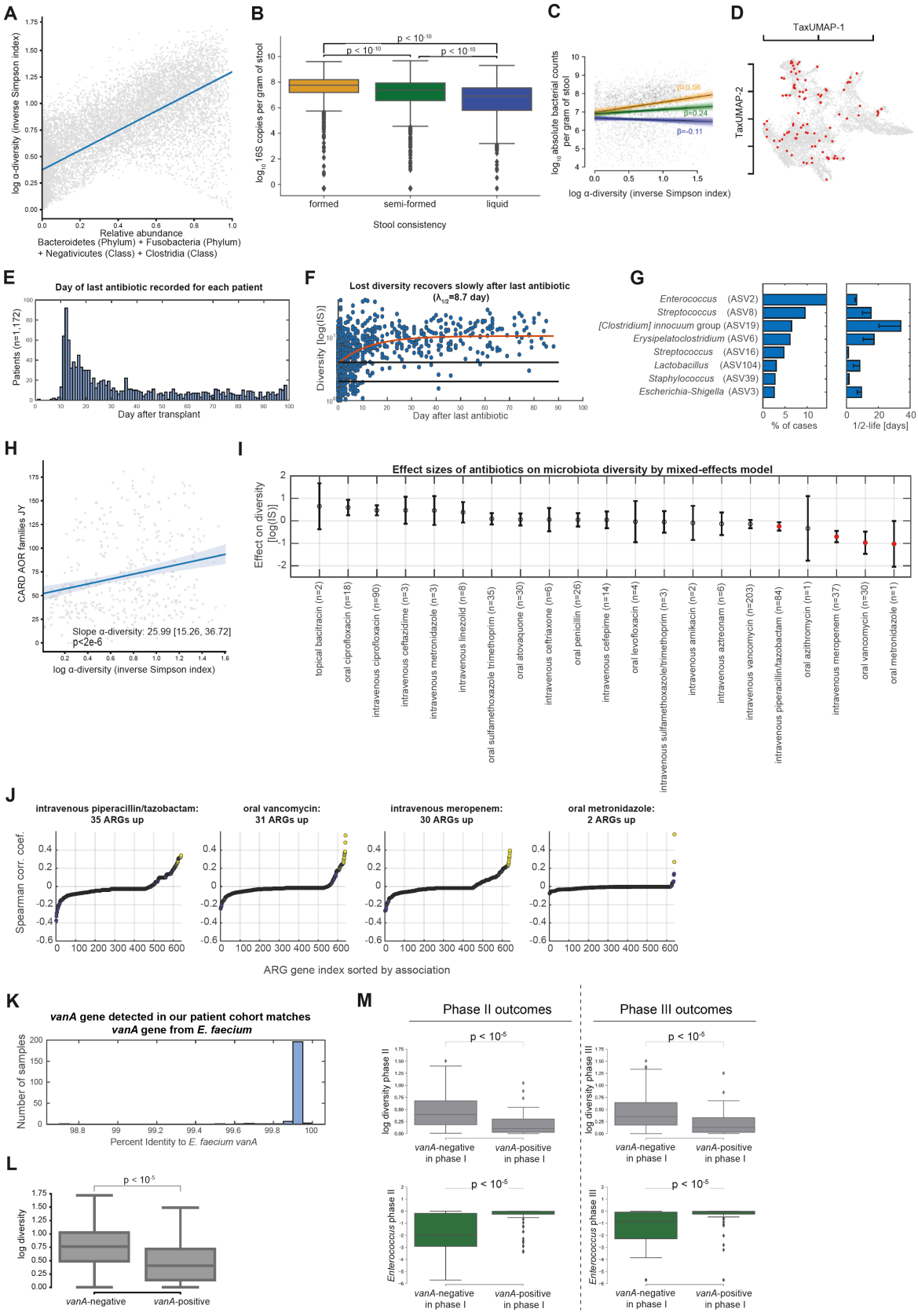
A
log α-diversity (inverse Simpson index)
Relative abundance
Bacteroidetes (Phylum) + Fusobacteria (Phylum)
+ Negativicutes (Class) + Clostridia (Class)
B
p < 10-10
p < 10-10
p < 10-10
log10 16S copies per gram of stool
formed
semi-formed
liquid
Stool consistency
C
log10 absolute bacterial counts per gram of stool
β=0.56
β=0.24
β=-0.11
log α-diversity (inverse Simpson index)
D
TaxUMAP-1
TaxUMAP-2
E
Day of last antibiotic recorded for each patient
Patients (n=1,172)
Day after transplant
F
Lost diversity recovers slowly after last antibiotic
(λ1/2=8.7 day)
Diversity [log(IS)]
Day after last antibiotic
G
Enterococcus (ASV2)
Streptococcus (ASV8)
[Clostridium] innocuum group (ASV19)
Erysipelatoclostridium (ASV6)
Streptococcus (ASV16)
Lactobacillus (ASV104)
Staphylococcus (ASV39)
Escherichia-Shigella (ASV3)
% of cases
1/2-life [days]
H
CARD AOR families JY
Slope α-diversity: 25.99 [15.26, 36.72]
p<2e-6
log α-diversity (inverse Simpson index)
I
Effect sizes of antibiotics on microbiota diversity by mixed-effects model
Effect on diversity [log(IS)]
topical bacitracin (n=2)
oral ciprofloxacin (n=18)
intravenous ciprofloxacin (n=90)
intravenous ceftazidime (n=3)
intravenous metronidazole (n=3)
intravenous linezolid (n=8)
oral sulfamethoxazole trimethoprim (n=35)
oral atovaquone (n=30)
intravenous ceftriaxone (n=6)
oral penicillin (n=26)
intravenous cefepime (n=14)
oral levofloxacin (n=4)
intravenous sulfamethoxazole/trimethoprim (n=3)
intravenous amikacin (n=2)
intravenous aztreonam (n=6)
intravenous vancomycin (n=203)
intravenous piperacillin/tazobactam (n=84)
oral azithromycin (n=1)
intravenous meropenem (n=37)
oral vancomycin (n=30)
oral metronidazole (n=1)
J
intravenous piperacillin/tazobactam:
35 ARGs up
oral vancomycin:
31 ARGs up
intravenous meropenem:
30 ARGs up
oral metronidazole:
2 ARGs up
Spearman corr. coef.
ARG gene index sorted by association
K
vanA gene detected in our patient cohort matches
vanA gene from E. faecium
Number of samples
Percent Identity to E. faecium vanA
L
p < 10-5
log diversity
vanA-negative
vanA-positive
M
Phase II outcomes
Phase III outcomes
p < 10-5
log diversity phase II
log diversity phase III
vanA-negative in phase I
vanA-positive in phase I
Enterococcus phase II
Enterococcus phase III

Figure S1. The effect of antibiotics on persistence of dominations and relationship between bacterial diversity, density, stool consistency and presence of antimicrobial resistance genes. Related to Figure 2. A) Log-diversity of the bacterial microbiota is positively correlated with the summed relative abundances of obligate anaerobe taxa. Blue: regression line with 95% CI from a linear model, slope: 0.92, $p<10^{-4}$. B) Liquid and semi-formed stool samples have significantly lower bacterial densities than found in formed stool ($p<10^{-10}$; two-sided t-tests). C) Formed and semi-formed stool samples show a positive relationship between diversity and total bacterial counts, whereas a negative relationship is found in liquid stool samples; 1,000 regression lines sampled from the joint posterior for formed (orange), semi-formed (green) and liquid (blue) stool samples, and corresponding posterior regression line means (black lines, beta: slope values) from a Bayesian mixed effects model with random intercepts and slopes per consistency category. D) Start locations of volatile switches (volatility >= 0.9) are found across the TaxUMAP. E) Percentage of patients that received their last antibiotic on the specific day relative to the day of transplant indicated on the x-axis; N=1,172 patients. F) The microbiome diversity ($\log_{10}$ of the inverse Simpson index) tends to stay low even after the last antibiotic administration. An exponential decay model (orange line, N=853 samples) reveals the average diversity recovers slowly, towards a plateau at approximately 10 (95% CI between 9.7 and 11.2). This model also determines that the half-life for diversity recovery is 9 days (with a 95% confidence interval of 6 to 14 days). G) Half-life for each of the eight most prevalent dominating states varies highly. The plot on the left represents the percentage of cases with one of the top eight domination states. The plot on the right represents domination half-life calculated by a linear mixed-effects model, and its lower bounds. IS: inverse Simpson index; ASV: amplicon sequence variant. H) More diverse samples harbor more unique antimicrobial resistance phenotypes (blue: regression line from a linear model with 95% CI, $p<10^{-5}$). I) The association coefficients between antibiotic treatments on bacterial diversity ($\log_{10}$ of the inverse Simpson index) as estimated by a linear mixed-effects model; circles: maximum likelihood estimate, error bars: 95% CI. The analysis revealed four antibiotics as significantly associated with the loss of bacterial diversity (marked in red intravenous piperacillin/tazobactam, intravenous meropenem, oral vancomycin and oral metronidazole). (Sample size N for each treatment stated in

parenthesis next to the name of the antibiotic, $p<0.05$, linear mixed-effects model). J) Administration of these four antibiotics associated with the loss of bacterial diversity leads to an increase in a subset of the total range of ARGs. X axis represents ARG gene index sorted by the association strength and y axis represents Spearman correlation coefficient between ARG and diversity. Marked in yellow are the ARG genes whose number rises upon administration of each of the four antibiotics. (N=640 ARG genes, $p<0.05$ after multiple hypothesis testing, Spearman correlation). IS: inverse Simpson index; ARG: antibiotic resistance gene; CI: confidence interval. K) *vanA* gene detected in our patient cohort matches the *vanA* gene from *E. faecium*. L) Diversity in samples corresponding to positive *vanA* detection in PCRs from rectal swabs is significantly lower ($p<10^{-5}$, Wilcoxon rank sum test, first sample per *vanA* status and per patient if multiple samples available, *vanA* negative: n=508, *vanA* positive: n=195). M) Positive *vanA* rectal swabs during phase I predict more severe loss of diversity in phases II and III, and higher *Enterococcus* abundances in phases II and III; if multiple samples per patient and clinical phase were available, the minimum observed diversity and maximum observed *Enterococcus* abundances were chosen in patients of either *vanA* group. P values from Wilcoxon rank sum tests; *vanA* negative in phase I: n=644, *vanA* positive in Phase I: N=85.

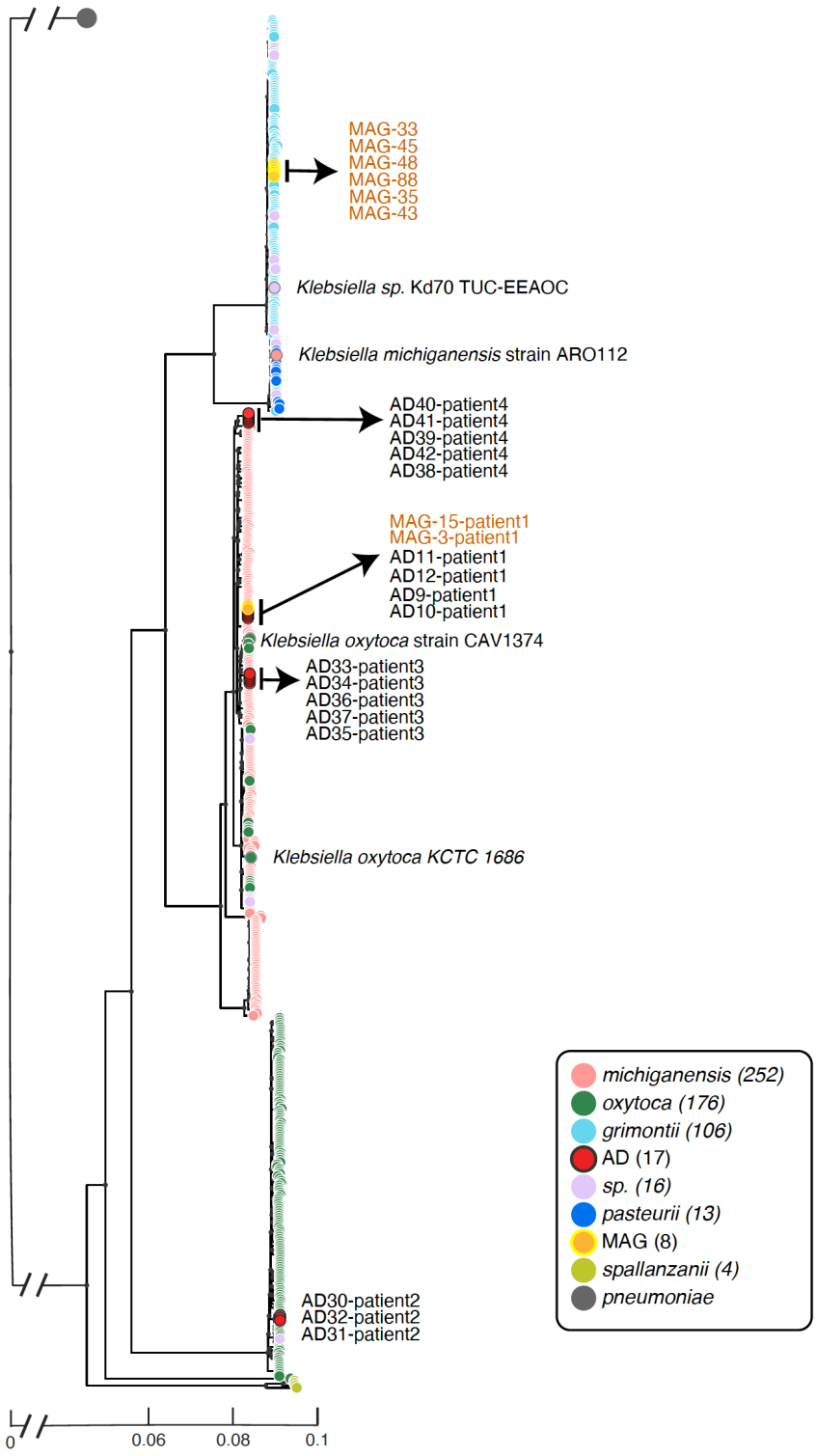

Figure S2. Phylogenetic tree representing the relationship between ASV-36-*Klebsiella* isolates and other publicly available *Klebsiella* genomes. Related to Figure 4. The tree was built using genomes deposited at NCBI database whose 16S rRNA gene matched the

16S sequence of ASV-36-*Klebsiella* exactly, 8 MAGs constructed from our patients' samples and the genomes of ASV-36 closest neighbors (*i.e. K. oxytoca* CAV1374 and *K. oxytoca* KCTC1686) and the genome of *K. michiganensis* ARO112. The tree was rooted with a genome of the pathobiont *K. pneumoniae subsp. pneumoniae* HS1128 strain. Colors correspond to taxonomic classification at the level of species.

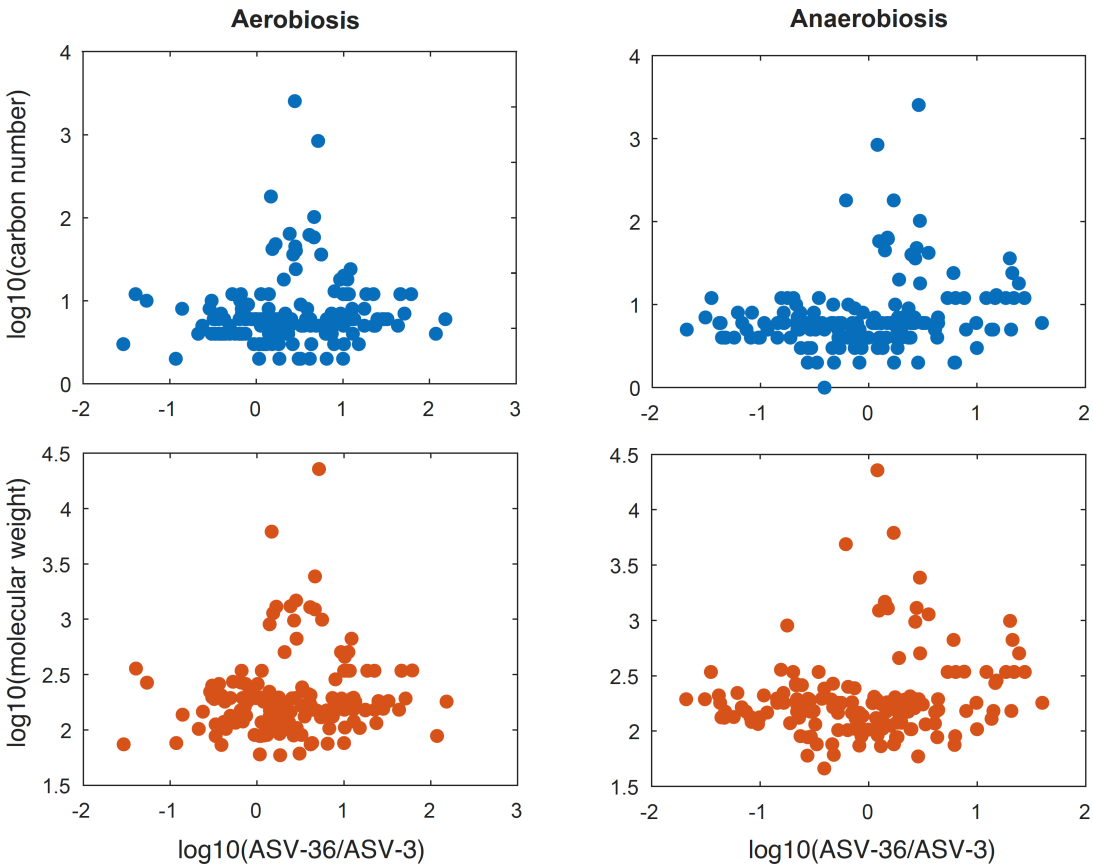

Figure S3. Correlation between ASV-36 to ASV-3 ratio, obtained after growth in anaerobic and aerobic conditions, and molecular weight and carbon numbers of carbon sources from BIOLOG PM1 and PM2A plates. Related to Figure 5.

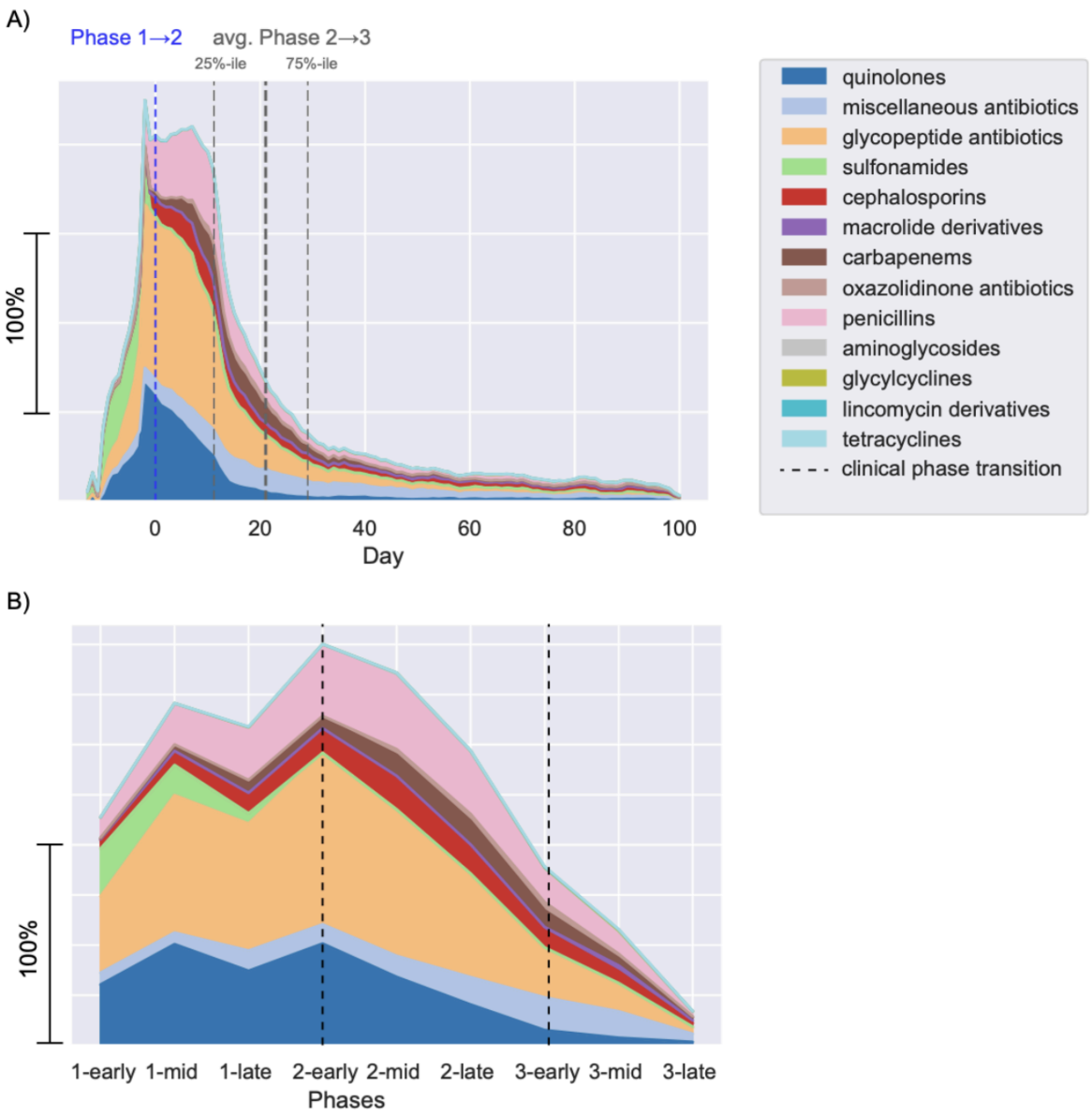

Figure S4. Antibiotic administration exposures. Related to Methods. Over time (A) and in the time bins representing distinct therapy phases as pseudotime (B); dashed vertical lines represent the transition timepoints between clinical phases in days relative to stem cell transplantation (A) and in pseudotime (B).

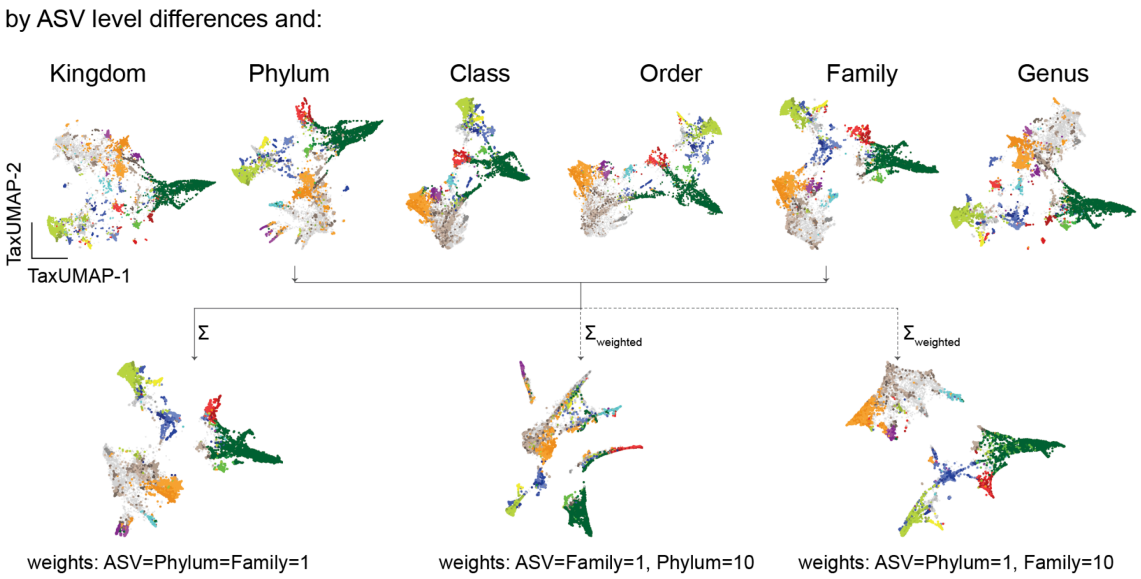

Figure S5. Different TaxUMAP parameter choices. Related to Methods. In addition to sample-by-sample distances based upon ASV level differences (naïve UMAP), the indicated taxonomic level was included in the sample-by-sample distance estimation (top row). Multiple levels may be combined; in the main text, we combined Phylum and Family with equal weights (bottom row, left). Increased weights for Phylum (middle) or Family (right) accentuate corresponding compositional features of the measured microbial compositions in a sample.

Isolate ID (as in Figure 4 and Figure S2)	ASV	Sample ID	Patient ID	BioProject	Accession Isolate
AD9	ASV-36-*Klebsiella*	FMT.0009U	FMT.0009	PRJNA545312	SRR14131380
AD10	ASV-36-*Klebsiella*	FMT.0009U	FMT.0009	PRJNA545312	SRR14131379
AD11	ASV-36-*Klebsiella*	FMT.0009U	FMT.0009	PRJNA545312	SRR14131378
AD12	ASV-36-*Klebsiella*	FMT.0009U	FMT.0009	PRJNA545312	SRR14131376
AD24	ASV-3-*E. coli*	745A	745	PRJNA606262	SRR14131383
AD25	ASV-3-*E. coli*	745A	745	PRJNA606262	SRR14131382
AD26	ASV-3-*E. coli*	745A	745	PRJNA606262	SRR14131381
AD30	ASV-36-*Klebsiella*	149D	149	PRJNA545312	SRR14131374
AD31	ASV-36-*Klebsiella*	149D	149	PRJNA545312	SRR14131373
AD32	ASV-36-*Klebsiella*	149D	149	PRJNA545312	SRR14131372
AD33	ASV-36-*Klebsiella*	729E	729	PRJNA545312	SRR14131389
AD34	ASV-36-*Klebsiella*	729E	729	PRJNA545312	SRR14131387
AD35	ASV-36-*Klebsiella*	729E	729	PRJNA545312	SRR14131386
AD36	ASV-36-*Klebsiella*	729E	729	PRJNA545312	SRR14131385
AD37	ASV-36-*Klebsiella*	729E	729	PRJNA545312	SRR14131384
AD38	ASV-36-*Klebsiella*	1392M	1392	PRJNA545312	SRR14131400
AD39	ASV-36-*Klebsiella*	1392M	1392	PRJNA545312	SRR14131399
AD40	ASV-36-*Klebsiella*	1392M	1392	PRJNA545312	SRR14131388
AD41	ASV-36-*Klebsiella*	1392M	1392	PRJNA545312	SRR14131377
AD42	ASV-36-*Klebsiella*	1392M	1392	PRJNA545312	SRR14131375
AD48	ASV-3-*E. coli*	1814W	1814	PRJNA607574	SRR16077561
AD49	ASV-3-*E. coli*	1814W	1814	PRJNA607574	SRR16077560

Table S1. The list of all ASV-3-*E. coli* and ASV-36-*Klebsiella* isolates used in this study and their NCBI accession numbers ("Accession Isolate" column). Related to Figure 4 and Figure S2.

	Coef.	Std.Err.	z	P>|z|	[0.025	0.975]
Intercept	8.264	0.205	40.388	0	7.863	8.665
mix==True	-0.744	0.289	-2.572	0.01	-1.311	-0.177
ASV==ASV3	0.48	0.289	1.658	0.097	-0.087	1.047
mix==True:ASV==ASV3	0.462	0.372	1.241	0.214	-0.267	1.19
Time	-0.045	0.01	-4.535	0	-0.064	-0.026
mix==True:Time	0.041	0.014	2.961	0.003	0.014	0.069
Time:ASV==ASV3	-0.033	0.014	-2.383	0.017	-0.061	-0.006
mix==True:Time:ASV==ASV3	-0.037	0.02	-1.879	0.06	-0.076	0.002
Group Var	0.073	0.104				

Table S4. Model summary results of *in vivo* experiment analyses. Related to Methods.

		Phase		
antibiotic category	days administered per patient	1	2	3
aminoglycosides	mean	0.050524	0.108803	0.028634
	std	0.597643	0.803477	0.246822
carbapenems	mean	0.876072	2.115727	1.572687
	std	3.312291	4.971947	4.643664
cephalosporins	mean	1.177312	2.143422	1.829295
	std	3.236395	4.415567	4.722806
glycopeptide antibiotics	mean	7.711153	10.69535	4.044053
	std	6.305629	7.476178	6.725049
glycylcyclines	mean	0.026692	0.038576	0.024229
	std	0.501194	0.522272	0.524449
lincomycin derivatives	mean	0.055291	0.016815	0.085903
	std	1.3123	0.260833	1.393519
macrolide derivatives	mean	0.171592	0.271019	1.068282
	std	1.319667	2.046427	4.616705
miscellaneous antibiotics	mean	1.734986	2.6182	4.394273
	std	4.631901	5.221493	8.721392
oxazolidinone antibiotics	mean	0.222116	0.723046	0.632159
	std	1.385326	2.749699	2.432131
penicillins	mean	3.062917	5.443126	3.114537
	std	4.952816	6.662997	6.33397
quinolones	mean	4.125834	4.757666	1.39207
	std	4.220699	6.005907	3.378123
sulfonamides	mean	1.35939	0.09001	0.375551
	std	2.539292	1.028702	2.250796
tetracyclines	mean	0.019066	0.007913	0.035242
	std	0.407022	0.160249	0.410545

Table S5. Antibiotic administration exposure in three clinical phases. Related to Methods.