**Supplementary File 1**

**Model 1: Effect of daptomycin on proportion of daptomycin-resistant VR *E. faecium***

**Input data:** Figure 2 – source data 1 (Fig2AB\_VRESusceptibility.csv on Dryad)

**Model structure in R:**

glmmTMB(CFU\_DAP ~ Antibiotic + Day + offset(log(CFU\_noDAP)) + (1|Mouse), data = na.omit(data), ziformula = ~1, family = nbinom1)

summary()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Estimate  | Std. Error  | z value  | Pr(>|z|)  |
| (Intercept)  | -4.581731  | 0.365351  | -12.541  | < 2e-16  |
| Antibioticdaptomycin  | 4.645379  | 0.365523  | 12.709  | < 2e-16  |
| Day  | -0.032638  | 0.008015  | -4.072  | 4.66e-05 |

**Model 2: Effect of daptomycin on total shedding of VR *E. faecium***

**Input data:** SuppFig1\_VREDensity.csv (available on Dryad)

**Model structure in R:**

glmmTMB(VRE.CFU.per.10mgFeces ~ Antibiotic + Day + (1|Mouse), data = data[data$Day>1,], ziformula=~1, family=nbinom1)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Estimate  | Std. Error  | z value  | Pr(>|z|)  |
| (Intercept)  | 13.117624  | 0.441897 | 29.685 | <2e-16 |
| Antibioticdaptomycin  | 0.001027 | 0.403890 | 0.003 | 0.9980 |
| Day  | 0.045302 | 0.022206 | 2.040 | 0.0413 |

**Model 3: Effect of cholestyramine on proportion of daptomycin-resistant VR *E. faecium***

**Input data:** Figure 5 - source data 1 (Fig5\_VREDensity.csv on Dryad)

**Data processing:**

1. Create a version of Day variable structured as a factor with levels 1:14 (Day.factor).

2. Drop entries where noDAP.VRE.CFU.per.10mgFeces < 20 (detection limit).

3. Create a variable for proportion resistant colonies (DAP.VRE.CFU.per.10mgFeces /noDAP.VRE.CFU.per.10mgFeces)

4. Normalize proportions to be bounded by 0 and 1. Divide all proportions by maximum proportion value, to create variable PropNorm.

**Model structure in R:**

glmmTMB(PropNorm ~ Diet\*Antibiotic + Day + Experiment + (1|Mouse) + ar1(Day.factor + 0 | Mouse), data = data[data$Day>1,]), family = binomial, weights= noDAP.VRE.CFU.per.10mgFeces, control = glmmTMBControl(optimizer = optim, optArgs = list(method="BFGS")))

**Output:**

summary()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Estimate  | Std. Error | z value | Pr(>|z|)  |
| (Intercept) | -6.21957 | 0.50384 | -12.344 | < 2e-16 |
| Dietcholestyramine | 0.31196 | 0.55510 | 0.562 | 0.57413 |
| Antibioticdaptomycin | 4.24574 | 0.46674 | 9.097 | < 2e-16 |
| Day | 0.01062 | 0.02381 | 0.446 | 0.65556 |
| ExperimentB | 0.66805 | 0.44487 | 1.502 | 0.13319 |
| ExperimentC  | -3.53285 | 0.40434 | -8.737 | < 2e-16 |
| ExperimentD | -1.79728 | 0.45953 | -3.911 | 9.19e-05 |
| Dietcholestyramine:Antibioticdaptomycin | -2.16041 | 0.65702 | -3.288 | 0.00101 |

Random effects:

Groups Name Variance Std.Dev. Corr

Mouse (Intercept) 4.130e-07 0.0006427

Mouse.1 Day.factor2 6.434e+00 2.5366239 0.54 (ar1)

Note: We also ran this model including only data with a higher total number of bacterial colonies counted (noDAP.VRE.CFU.per.10mgFeces > 150). This was a check to see if the results were affected by samples with low total counts, which might give inaccurate proportions. The key result from this model, a significant effect of Diet\*Antibiotic, remains true with the higher cutoff (p = 0.0004).

**Model 4: Effect of cholestyramine on proportion of daptomycin-resistant VR *E. faecium*, Days 8 & 14**

**Input data:** Fig5\_VRESusceptibility.csv (available on Dryad)

**Data processing:**

1. Create a variable for proportion resistant colonies (CFU\_DAP/CFU\_noDAP).

3. Normalize proportions to be bounded by 0 and 1. Divide all proportions by maximum proportion value, to create variable PropNorm.

**Model structure in R:**

glmmTMB(PropNorm ~ Diet\*Antibiotic + Day + Experiment + (1|Mouse), data = na.omit(data), family = binomial, weights = CFU\_noDAP)

summary()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Estimate  | Std. Error | z value | Pr(>|z|)  |
| (Intercept) | -7.20705 | 0.70739 | -10.188 | < 2e-16 |
| Dietcholestyramine | 1.22512 | 0.84030 | 1.458 | 0.145 |
| Antibioticdaptomycin | 6.46804 | 0.72579 | 8.912 | < 2e-16 |
| Day14 | 0.12750 | 0.02077 | 6.140 | 8.27e-10 |
| ExperimentB | 0.78377 | 0.57735 | 1.358 | 0.175 |
| ExperimentC  | -4.12226 | 0.60214 | -6.846 | 7.59e-12 |
| ExperimentD | -0.13626 | 0.61947 | -0.220 | 0.826 |
| Dietcholestyramine:Antibioticdaptomycin | -4.06349 | 0.97461 | -4.169 | 3.05e-05 |

Random effects:

Groups Name Variance Std.Dev.

Mouse (Intercept) 4.7 2.168

**Model 5: Effect of cholestyramine on shedding of daptomycin-resistant VR *E. faecium***

**Input data:** Figure 5 - source data 1 (Fig5\_VREDensity.csv on Dryad)

**Data processing:** Added 1 to density variables DAP.VRE.CFU.per.10mgFeces and noDAP.VRE.CFU.per.10mgFeces so that data could be logged.

**Model structure in R:**

lme(data=data[data$Day >1,],

log10(DAP.VRE.CFU.per.10mgFeces) ~ Antibiotic\*Diet\* Day + Experiment, random=~1|Mouse, correlation = corAR1(form = ~Day|Mouse))

**Output:**

anova()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | numDF | denDF |  F-value | p-value |
| (Intercept) | 1 | 556 | 1189.4014 | <.0001 |
| Antibiotic | 1 | 133 | 3.4018 | 0.0674 |
| Diet | 1 | 133 | 1.0057 | 0.3178 |
| Day | 1 | 556 | 27.6576 | <.0001 |
| Experiment | 3 | 133 | 32.1013 | <.0001 |
| Antibiotic:Diet | 1 | 133 | 0.0993 | 0.7532 |
| Antibiotic:Day | 1 | 556 | 25.4397 | <.0001 |
| Diet:Day | 1 | 556 | 8.1842 | 0.0044 |
| Antibiotic:Diet:Day | 1 | 556 | 23.2725 | <.0001 |

summary()

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | Value  | Std. Error  | DF  | t-value  | p-value |
| (Intercept)  | 5.697248  | 0.4507439  | 556  | 12.639655  | 0.0000 |
| Antibioticdaptomycin  | -1.241995  | 0.4711206  | 133  | -2.636257  | 0.0094 |
| Dietcholestyramine  | -0.989360  | 0.5613877  | 133  | -1.762348  | 0.0803 |
| Day  | -0.249036  | 0.0370298  | 556  | -6.725290  | 0.0000 |
| ExperimentB  | 1.019619  | 0.3543514  | 133  | 2.877423  | 0.0047 |
| ExperimentC  | -1.884019  | 0.3188225  | 133  | -5.909305  | 0.0000 |
| ExperimentD  | -1.058643  | 0.3543514  | 133  | -2.987552  | 0.0033 |
| Antibioticdaptomycin:Dietcholestyramine  | 1.841121  | 0.6642429  | 133  | 2.771759  | 0.0064 |
| Antibioticdaptomycin:Day  | 0.304636  | 0.0438142  | 556  | 6.952911  | 0.0000 |
| Dietcholestyramine:Day  | 0.129620  | 0.0523680  | 556  | 2.475173  | 0.0136 |
| Antibioticdaptomycin:Dietcholestyramine:Day  | -0.293358  | 0.0619626  | 556  | -4.734433  | 0.0000 |

Random effects:

Formula: ~1 | Mouse

 (Intercept) Residual

StdDev: 1.19095 1.524979

**Model 6: Effect of cholestyramine on total VR *E. faecium* shedding**

**Input data:** Figure 5 - source data 1 (Fig5\_VREDensity.csv on Dryad)

**Data processing:** Added 1 to density variables DAP.VRE.CFU.per.10mgFeces and noDAP.VRE.CFU.per.10mgFeces so that data could be logged.

**Model structure in R:**

lme(data=data[data$Day >1,],

log10(noDAP.VRE.CFU.per.10mgFeces) ~ Antibiotic\*Diet\* Day + Experiment, random=~1|Mouse, correlation = corAR1(form = ~Day|Mouse))

**Output:**

anova()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | numDF  | denDF  | F-value  | p-value |
| (Intercept)  | 1  | 556  | 1893.8435  | <.0001 |
| Antibiotic  | 1  | 133  | 6.5129  | 0.0118 |
| Diet  | 1  | 133  | 1.1657  | 0.2822 |
| Day  | 1  | 556  | 26.5513  | <.0001 |
| Experiment  | 3  | 133  | 5.9143  | 0.0008 |
| Antibiotic:Diet  | 1  | 133  | 1.5648  | 0.2132 |
| Antibiotic:Day  | 1  | 556  | 2.7475  | 0.0980 |
| Diet:Day  | 1  | 556  | 16.0355  | 0.0001 |
| Antibiotic:Diet:Day  | 1  | 556  | 14.3794  | 0.0002 |

summary()

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | Value  | Std. Error  | DF  | t-value  | p-value |
| (Intercept)  | 7.144392  | 0.4763063  | 556  | 14.999573  | 0.0000 |
| Antibioticdaptomycin  | -2.095335  | 0.4937631  | 133  | -4.243604  | 0.0000 |
| Dietcholestyramine  | -0.600540  | 0.5882331  | 133  | -1.020921  | 0.3091 |
| Day  | -0.134885  | 0.0365464  | 556  | -3.690774  | 0.0002 |
| ExperimentB  | 0.722889  | 0.3851389  | 133  | 1.876956  | 0.0627 |
| ExperimentC  | -0.614066  | 0.3465231  | 133  | -1.772078  | 0.0787 |
| ExperimentD  | -0.585066  | 0.3851389  | 133  | -1.519103  | 0.1311 |
| Antibioticdaptomycin:Dietcholestyramine  | 2.275048  | 0.6960068  | 133  | 3.268715  | 0.0014 |
| Antibioticdaptomycin:Day  | 0.166631  | 0.0432423  | 556  | 3.853423  | 0.0001 |
| Dietcholestyramine:Day  | 0.055012  | 0.0516845  | 556  | 1.064374  | 0.2876 |
| Antibioticdaptomycin:Dietcholestyramine:Day  | -0.231896  | 0.0611539  | 556  | -3.792015  | 0.0002 |

Random effects:

Formula: ~1 | Mouse

 (Intercept) Residual

StdDev: 1.331139 1.505074

**Model 7. Effect of cholestyramine on total VR *E. faecium* shedding in control mice (no daptomycin)**

**Input data:** Figure 5 - source data 1 (Fig5\_VREDensity.csv on Dryad)

**Data processing:** Added 1 to density variables DAP.VRE.CFU.per.10mgFeces and noDAP.VRE.CFU.per.10mgFeces so that data could be logged.

**Model structure in R:**

lme(data= data[data$Day>1 & data$Antibiotic=="control",],

log10(noDAP.VRE.CFU.per.10mgFeces) ~ Diet\*Day + Experiment, random=~1|Mouse, correlation = corAR1(form = ~Day|Mouse))

**Output:**

anova()

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | numDF  | denDF  | F-value  | p-value |
| (Intercept)  | 1  | 158  | 668.8815  | <.0001 |
| Diet  | 1  | 35  | 0.2386  | 0.6282 |
| Day  | 1  | 158  | 28.0471  | <.0001 |
| Experiment  | 3  | 35  | 1.5892  | 0.2094 |
| Diet:Day  | 1  | 158  | 1.8403  | 0.1768 |

summary()

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | Value  | Std. Error  | DF  | t-value  | p-value |
| (Intercept)  | 7.120770  | 0.5537743  | 158  | 12.858614  | 0.0000 |
| Dietcholestyramine  | -0.600540  | 0.5394026  | 35  | -1.113342  | 0.2731 |
| Day  | -0.134885  | 0.0286741  | 158  | -4.704063  | 0.0000 |
| ExperimentB  | 0.615201  | 0.6556186  | 35  | 0.938353  | 0.3545 |
| ExperimentC  | -0.803163  | 0.6556186  | 35  | -1.225047  | 0.2287 |
| ExperimentD  | -0.193794  | 0.6556186  | 35  | -0.295590  | 0.7693 |
| Dietcholestyramine:Day  | 0.055012  | 0.0405513  | 158  | 1.356595  | 0.1768 |

Random effects:

Formula: ~1 | Mouse

 (Intercept) Residual

StdDev: 1.367585 1.180871