

Omadacycline was Shown to Preserve the Microbiome in a Murine Model of Post-Influenza MRSA Pneumonia

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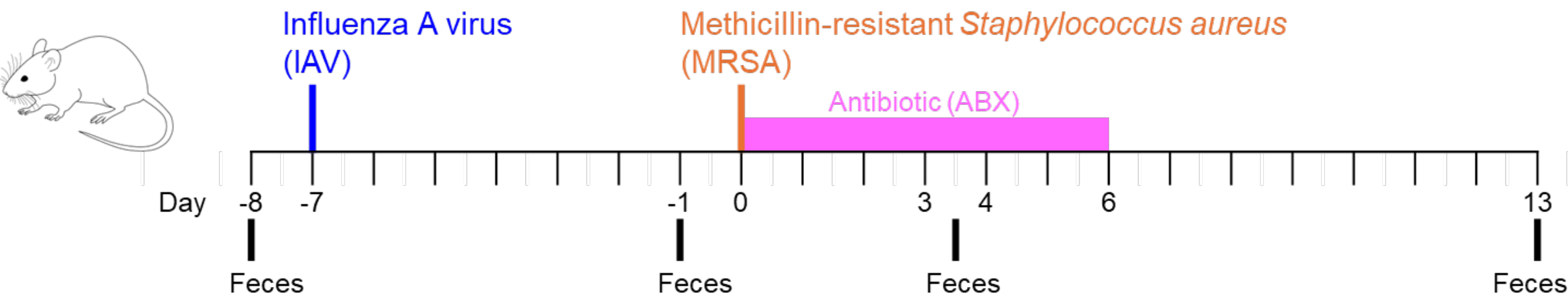
Background

- Secondary bacterial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of death following influenza A virus (IAV) infection
- Gut dysbiosis is a major contributor to bacterial superinfection due to changes in pulmonary immunity from decreased short-chain fatty acid (SCFA) production¹
- Omadacycline (OMC) is a US FDA-approved antibiotic for the treatment of adult community-acquired bacterial pneumonia²
- Linezolid (LZD) is commonly used for the treatment of post-influenza (PI)-MRSA pneumonia³
- Omadacycline improved survival in a murine model of PI-MRSA³

Methods

- Healthy uninfected mice or mice infected with IAV/MRSA were treated with OMC or LZD (Fig. 1)
- Fecal samples were collected for 16S rRNA sequencing, and SCFAs were quantified by LC-MS
- Survival and weight were monitored
- Statistical analysis was conducted using GraphPad Prism software
 - Two-way ANOVA was used with the Geisser-Greenhouse correction and Tukey's multiple comparison test post hoc
 - Kaplan-Meier survival curves were evaluated by pairwise comparison to vehicle by the log-rank (Mantel-Cox) test. **P*<0.05, ***P*<0.01, ****P*<0.001, and *****P*<0.0001
 - Linear discriminant analysis Effect Size (LEfSe) was used to determine significantly enriched taxa and associated biomarkers

Figure 1. Study Design

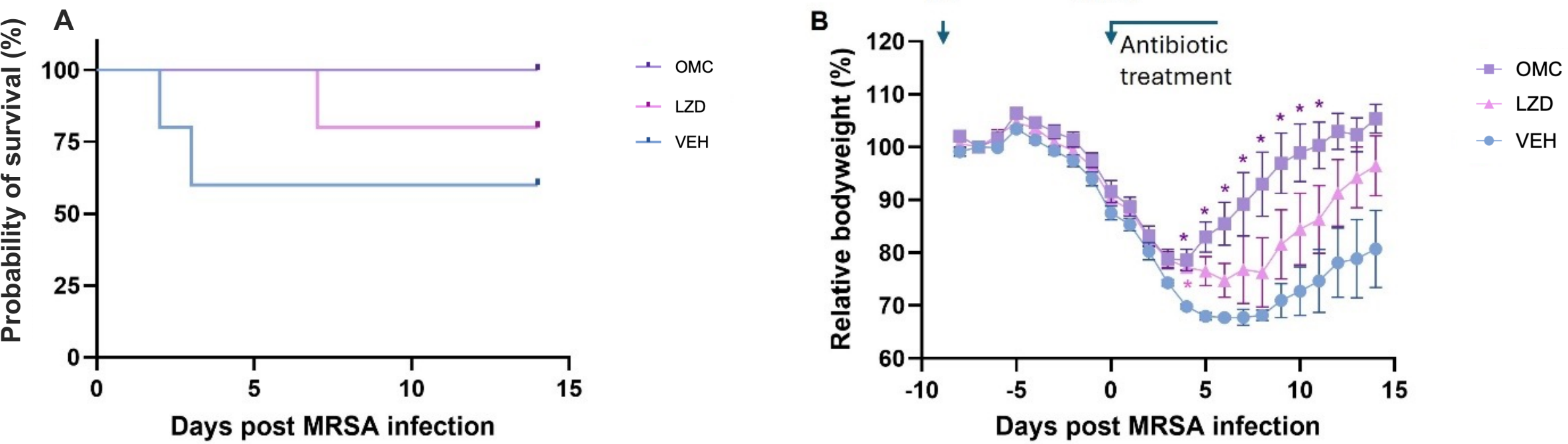


Female BALB/c mice were infected intranasally with influenza A/Puerto Rico/8/34 (H1N1) virus, and 7 days post-infection with CA-MRSA USA300. OMC (5 mg/kg IP), LZD (120 mg/kg PO) or vehicle (sterile water IP) were administered twice daily for six days. Feces were collected on the appropriate days for 16S rRNA gene profiling and SCFA quantification.

Results

Figure 2. OMC Improved Survival and Recovery in a Murine Model of PI-MRSA

(A) Survival. (B) Body weights. N= 5 mice/group. **P*<0.05 for OMC and LZD on Day 4 vs. VEH and OMC vs. VEH on all other days.



Objective

Determine the effect of omadacycline on the gut microbiome in a murine model of PI-MRSA in comparison to linezolid

Conclusion

Omadacycline treatment maintained a higher level of diversity in murine gut microbiota along with increased levels of SCFAs compared to linezolid, and warrants further investigation

Results

- OMC treatment resulted in improved recovery, i.e., faster increase in body weight post infection, and survival compared to LZD (100% vs 80%) in IAV-MRSA infected mice (Fig. 2)
- Microbiome diversity was significantly higher in the OMC-treated group than LZD-treated group in both PI-MRSA-infected mice (Fig. 3) and uninfected mice (Fig. 4)
- In both models, treatment with OMC enriched taxa known to produce SCFAs:
 - Day 4 (PI-MRSA): Increased *Lactobacillaceae*, *Enterobacteriaceae* (*Proteus*), *Bacteroidaceae*
 - Day 13 (PI-MRSA): Increased *Lachnospiraceae*, *Ruminococcaceae*, *Anaeroplasmataceae*, *Porphyromonadaceae*, *Clostridiales*, and *Erysipelotrichaceae*
- Treatment with LZD resulted in expansion of *Enterobacteriaceae*, specifically the enteropathogen *Citrobacter*, in PI-MRSA-infected mice (Fig. 3) and uninfected mice (Fig. 4)
- Total SCFA levels, especially acetate and propionate, were less affected by OMC treatment than LZD treatment (Figs. 3 and 4).

Funding and Disclosures: This study was funded by Paratek Pharmaceuticals, Inc. J.V.P. is an employee and shareholder of Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by AIM Biomedical LLC (Clayton, MO).

References: 1. Sencio V, et al. *Mucosal Immunol.* 2021;14:296-304. 2. NUZYRA [package insert]. 2025. King of Prussia, PA: Paratek Pharmaceuticals, Inc. 3. Gomi S, et al. *Antimicrob Agents Chemother.* 2025;69:e00469-25.

Abbreviations: CA, community-acquired; IAV, influenza A virus; IP, intraperitoneally; LZD, linezolid; MRSA, methicillin-resistant *Staphylococcus aureus*; OMC, omadacycline; PI, post-influenza; PO, orally; SCFA, short-chain fatty acid;



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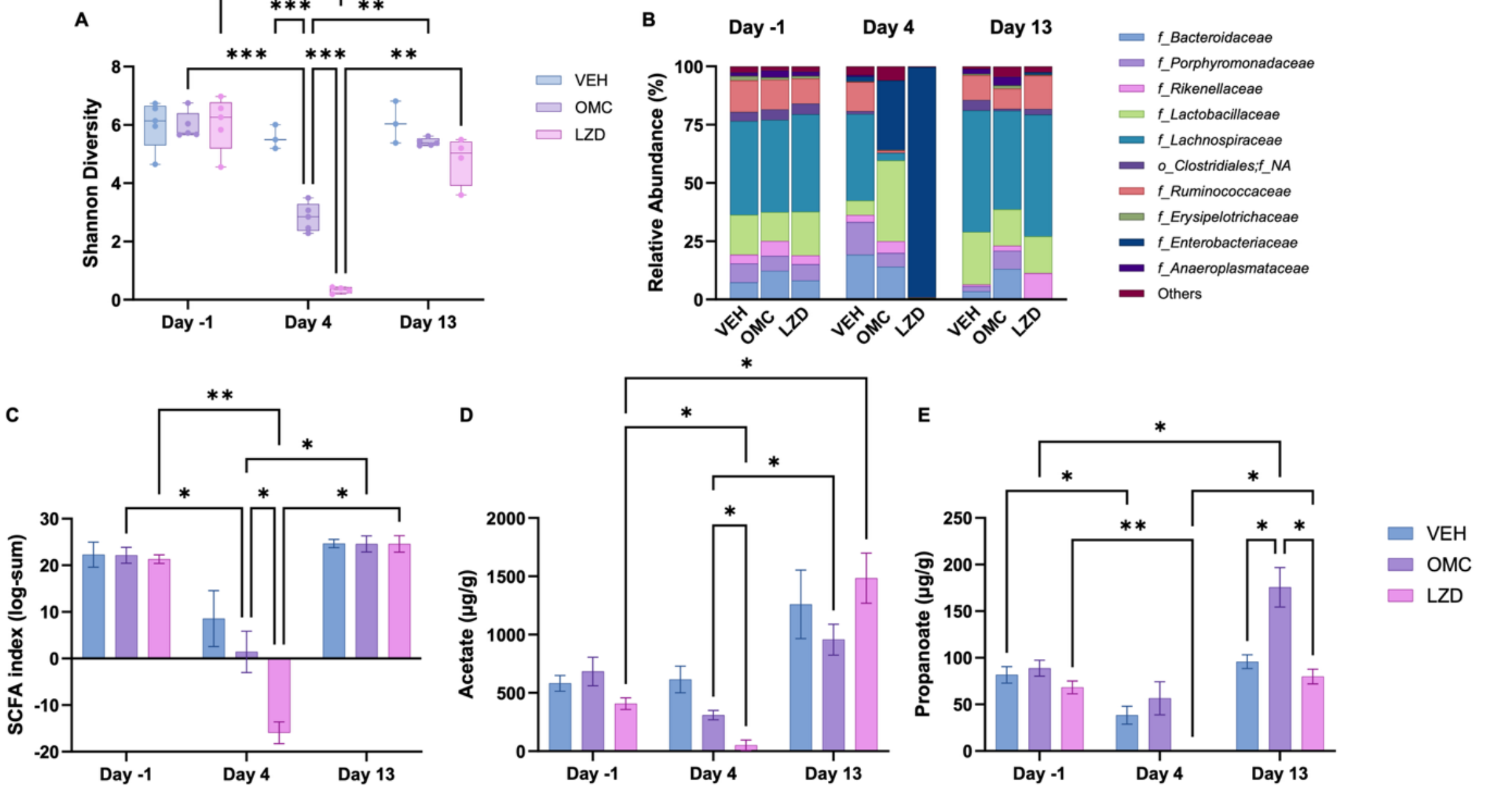
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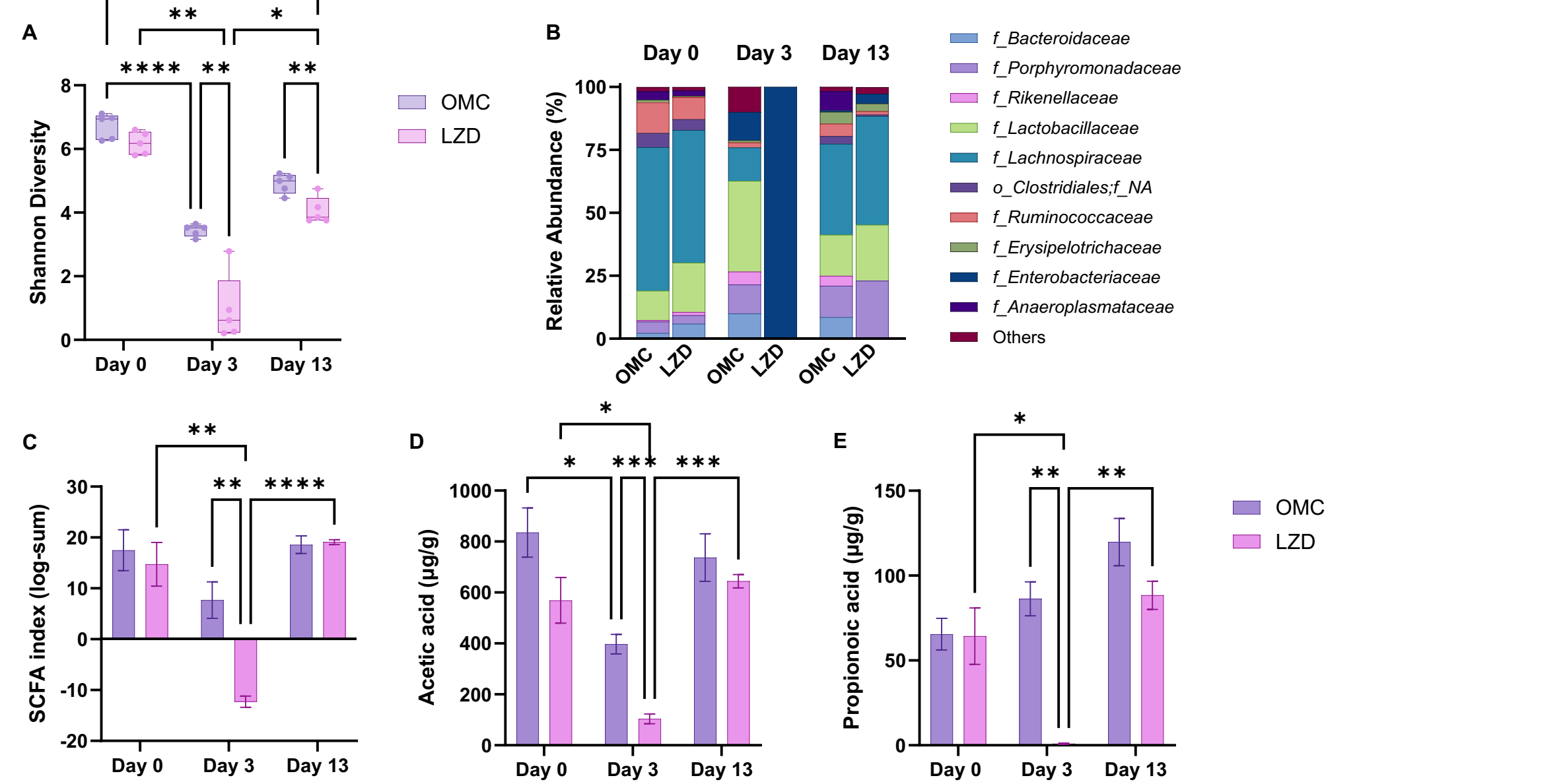
Results

Figure 3. OMC Preserved Alpha Diversity and Composition in the Gut Microbiota in PI-MRSA-Infected Mice Compared to LZD



(A) Alpha diversity of fecal microbiota. (B) Mean relative abundance (n=5) of bacterial taxa at the family level. (C,D,E) SCFA quantification. Day 3 and 4 are during antibiotic treatment, Day 13 is 1 week following end of treatment. **P*<0.05, ***P*<0.01, ****P*<0.001, and *****P*<0.0001

Figure 4. OMC Preserved Alpha Diversity and Composition in the Gut Microbiota of Healthy, Uninfected Mice Compared to LZD



(A) Alpha diversity of fecal microbiota. (B) Mean relative abundance (n=5) of bacterial taxa at the family level. (C,D,E) SCFA quantification. Day 3 and 4 are during antibiotic treatment, Day 13 is 1 week following end of treatment. **P*<0.05, ***P*<0.01, ****P*<0.001, and *****P*<0.0001