

Effects of metformin on the equine gut microbiome



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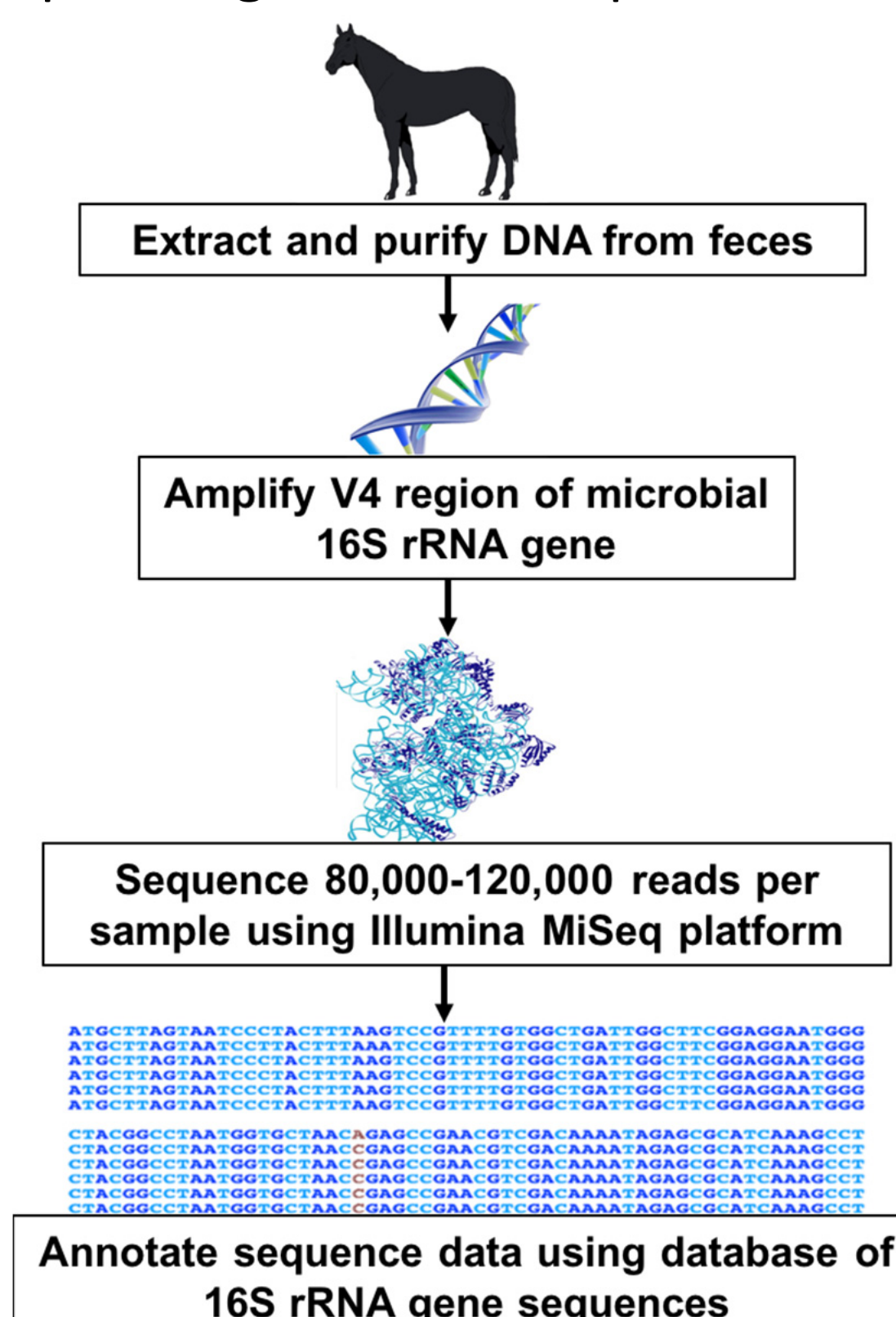
Background

- Equine metabolic syndrome (EMS) is the most common cause of endocrinopathic laminitis. Laminitis resulting from EMS has been attributed to dysregulated circulating plasma insulin (hyperinsulinemia).
- Preventive measures for EMS and laminitis should include strategies intended to reduce hyperinsulinemia.
- Metformin has been shown to ameliorate post-prandial glucose absorption and insulin-spiking in horses and is commonly employed for the management of EMS.
- Unlike the situation for people, the oral bioavailability of metformin in horses is poor and its beneficial effect appears to be occurring locally at the epithelial lining of the small intestine.
- Metformin-induced changes in the gut microbiota of mice and humans include increased abundance of *Akkermansia*, bacteria in the *Verrucomicrobia* phylum, associated with increased metabolic rate, decreased obesity, and increased insulin sensitivity.

The principle objective of this study was to ascertain whether treatment of horses with metformin would cause an increase in *Verrucomicrobia* bacteria in the fecal microbiota and a concomitant reduction in plasma insulin concentrations during and oral sugar test (OST).

Methods

- Six horses were moved from MU Middlebush farm to the MU VHC, switched from pasture to an all hay diet, and acclimated for five days before the study started.
- Four horses were treated with metformin twice daily for seven days (30 mg/kg of body weight); two horses were controls.
- Insulin status of horses was assessed by an OST on the first and last days of the study.
- Gut microbiome characterizations were done using Next Generation Sequencing on fecal samples collected daily.



Results

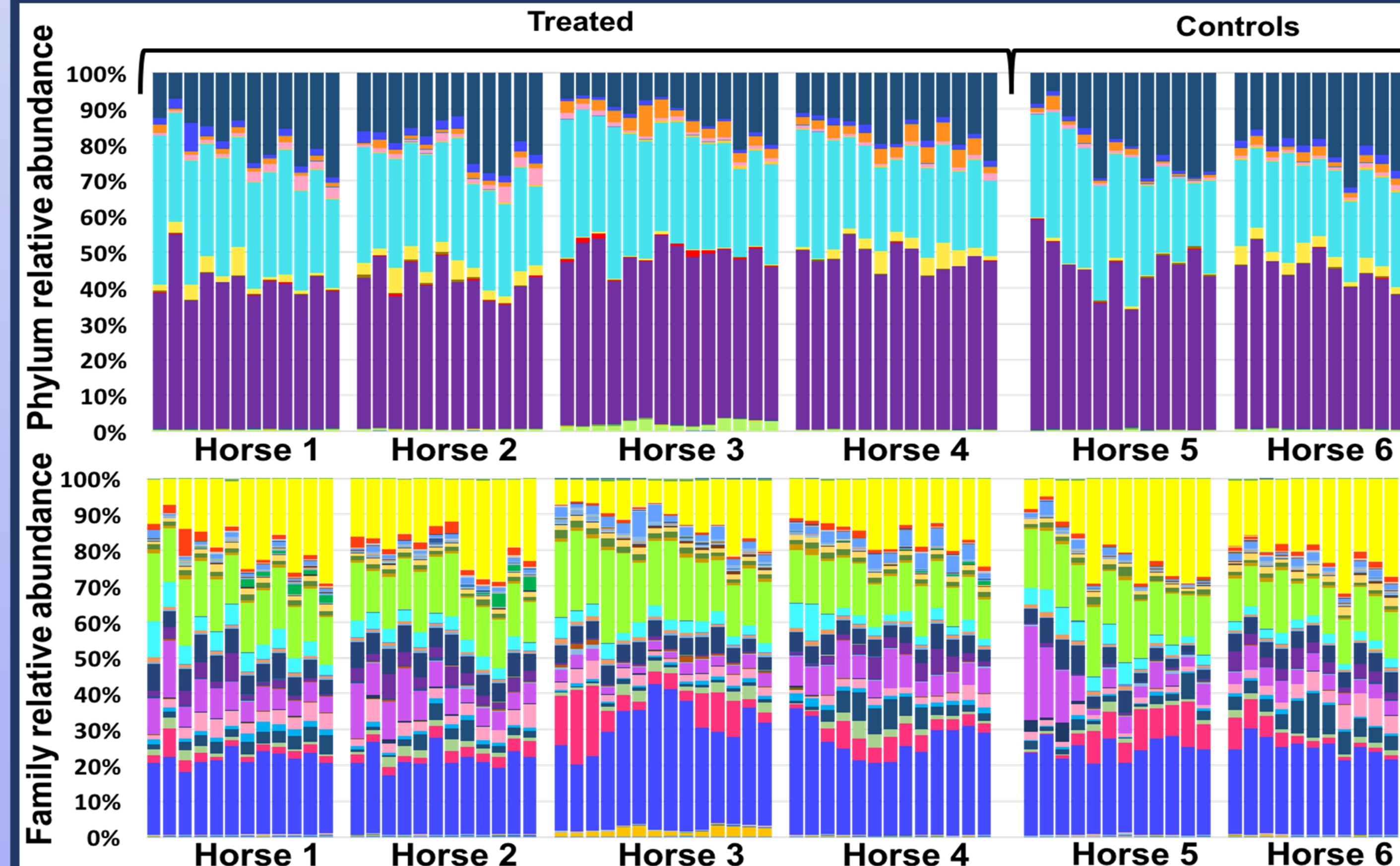


Figure 1: Stacked bar charts showing the relative taxonomic abundance at phylum (upper) and family (lower) levels in the fecal microbiota.

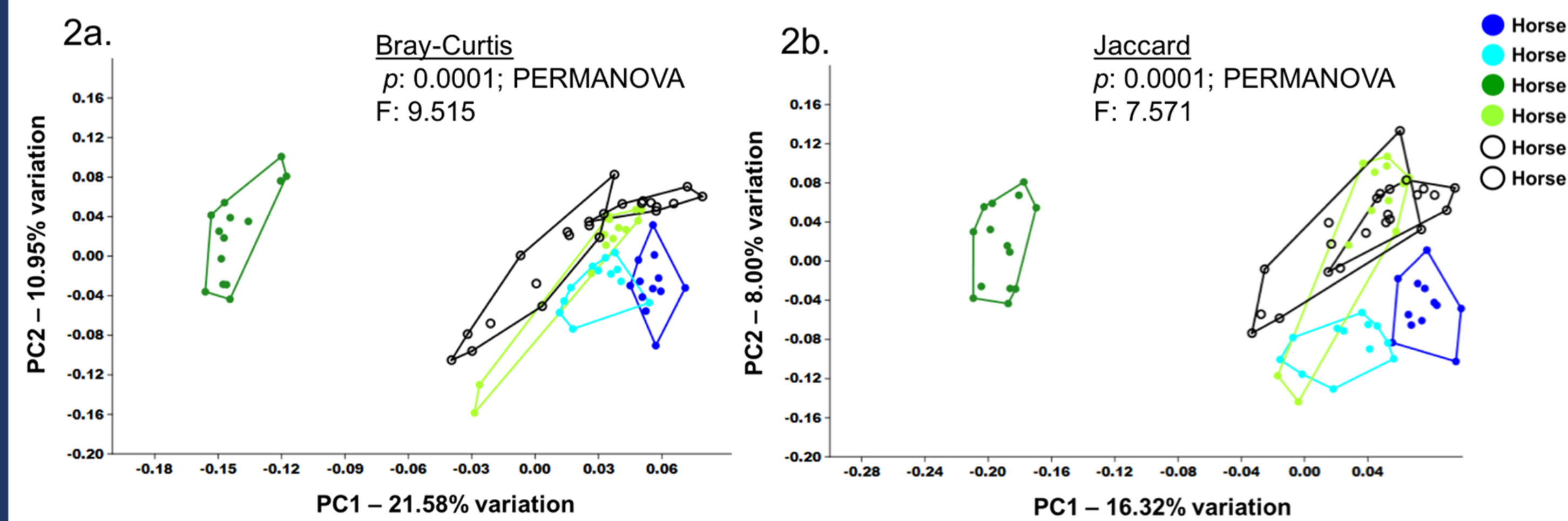


Figure 2: Principal coordinate analysis of the samples shown using Bray-Curtis (a) and Jaccard (b) distances. Control samples shown in black and white.

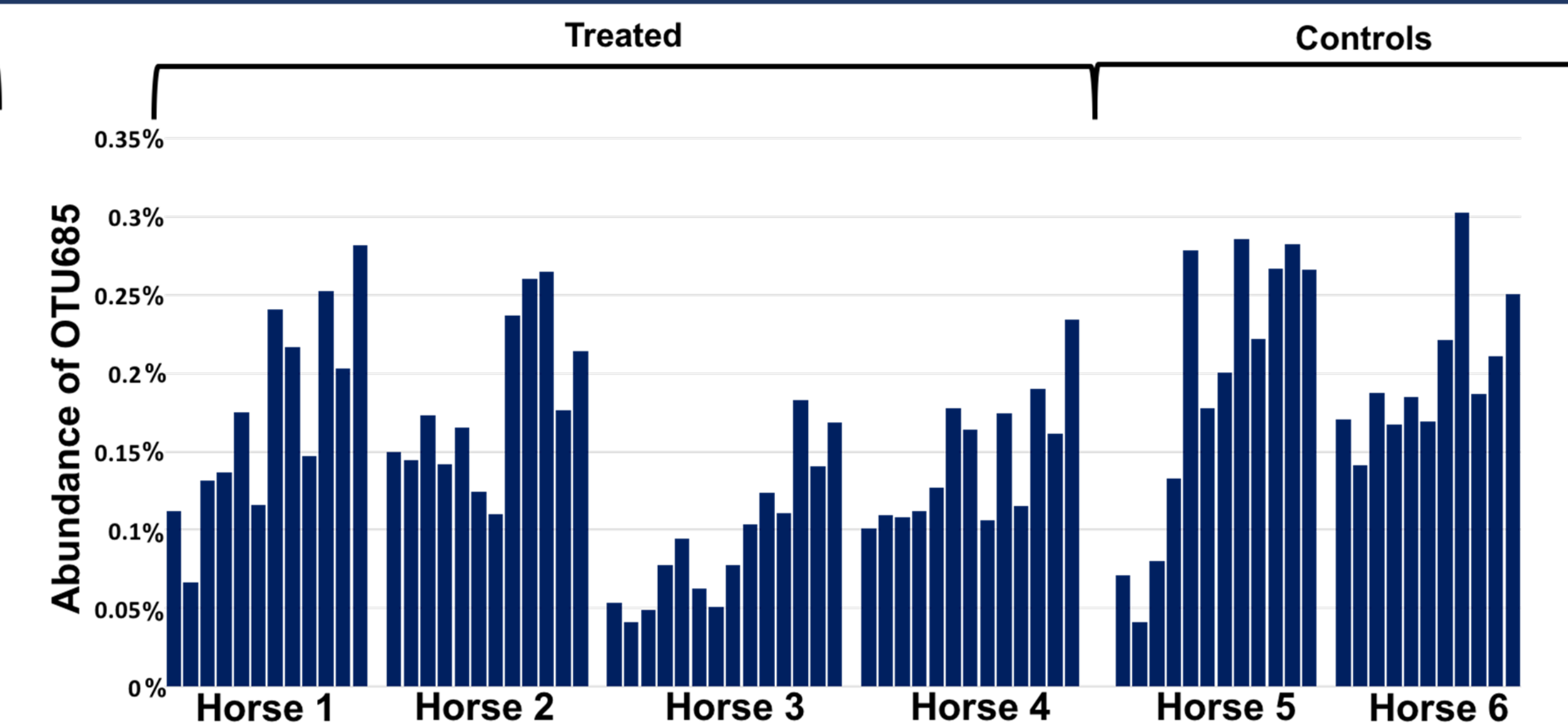


Figure 3: Relative abundance of OTU685 in *Verrucomicrobia* phylum in each sample.

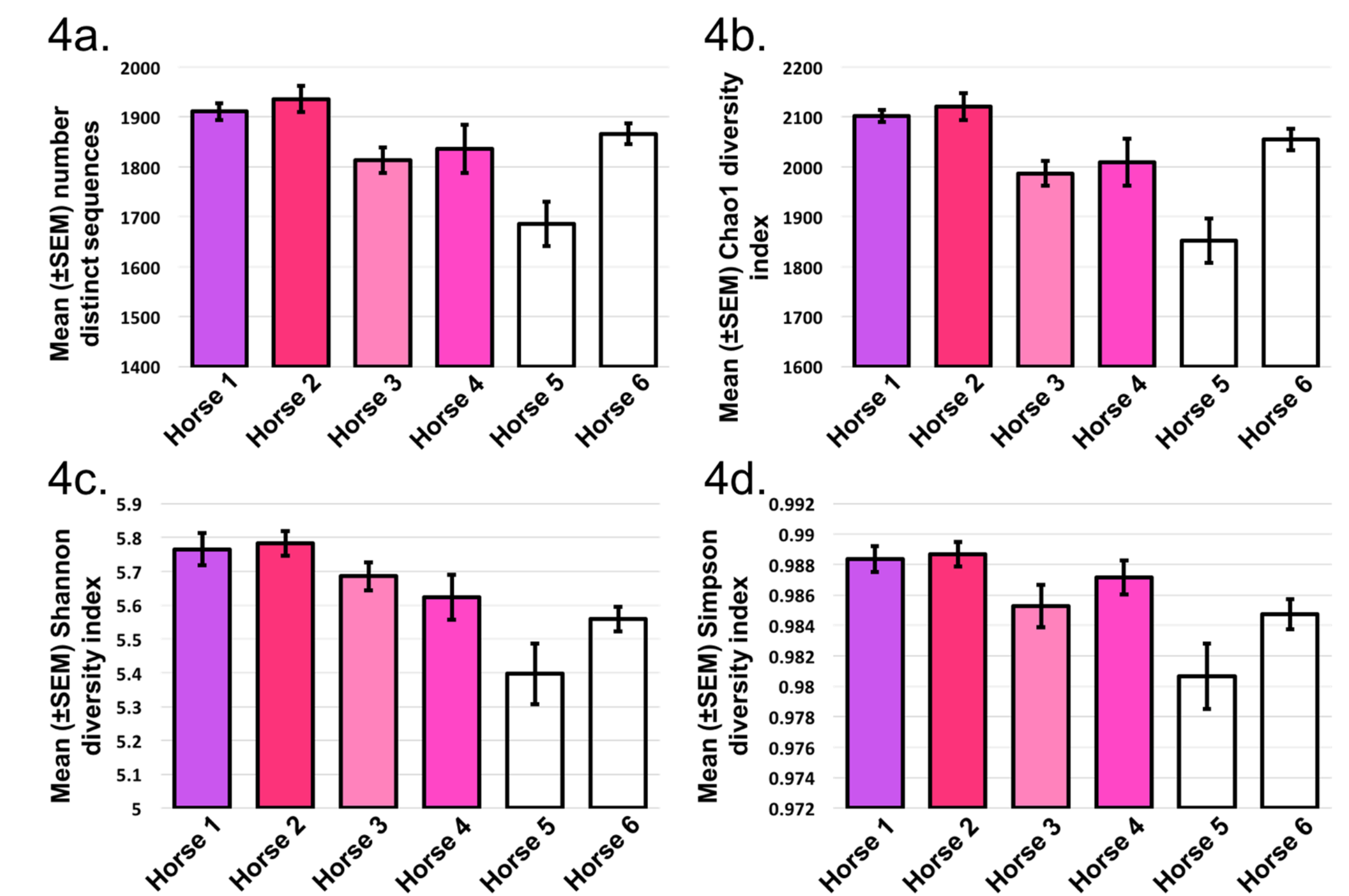


Figure 4: Bar charts showing microbiota richness (a,b) and alpha-diversity (c,d) in treated and control fecal samples. Control samples shown in black and white.

Conclusions

- Each horse retained a unique and idiosyncratic gut (fecal) microbiome signature throughout the study period
- Abundance of *Verrucomicrobia* increased in all horses while the proportion of the dominant groups (*Firmicutes* and *Bacteroidetes*) decreased
- Treatment with metformin did not result in a significant difference in the gut microbiome between treated and untreated horses
- Observed changes in the gut microbiome could have resulted from adjusted husbandry (stall accommodation, diet, etc.)
- An effect of metformin on basal, resting (fasted) insulin levels and OST outcomes was not detected (data not shown)

Study Limitations

- Small number of unrelated horses, one of which was affected with equine metabolic syndrome
- Short study period only lasting 7 days
- Fecal microbiome may not reflect the effects of orally administered metformin on the small intestine microbiome
- Compounded, rather than medical-grade, metformin was used in this study

Acknowledgements

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