



# PROBIOTIC SUPPLEMENTATION DURING ANTIBIOTIC THERAPY MODULATES THE DIVERSITY OF GUT MICROBIOME

a systematic review and meta-analysis of randomized controlled trials



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## INTRODUCTION

Antibiotics are among the main causes of **low-diversity dysbiosis**. Probiotics are used to prevent dysbiosis, however the effects of concurrent **probiotic supplementation** on fecal microbiota diversity and taxonomical composition during antibiotic therapy has not been well established. The use of many **different indices** and the **lack of standard values** make it even more difficult to interpret and compare results.

## CONCLUSION

The summarized results of the included articles are **not convincing enough** for promoting probiotic supplementation during antibiotic therapy to maintain microbial diversity. Although the **meta-analysis of Shannon diversity index showed a significant effect of probiotics** modulating diversity, a single index is insufficient to describe the richness and the evenness of bacterial communities. Changes in the taxonomic composition tend to be similar and a **tendency of restoration** can be observed during a follow-up of 2-8 weeks in both groups. **Standardization of methods** for microbiome  **$\alpha$ - and  $\beta$ -diversity** measurement, definition of its optimal value, and standard follow-up periods will allow future studies generating more homogenous data with increased clinical relevance.  $\tau$

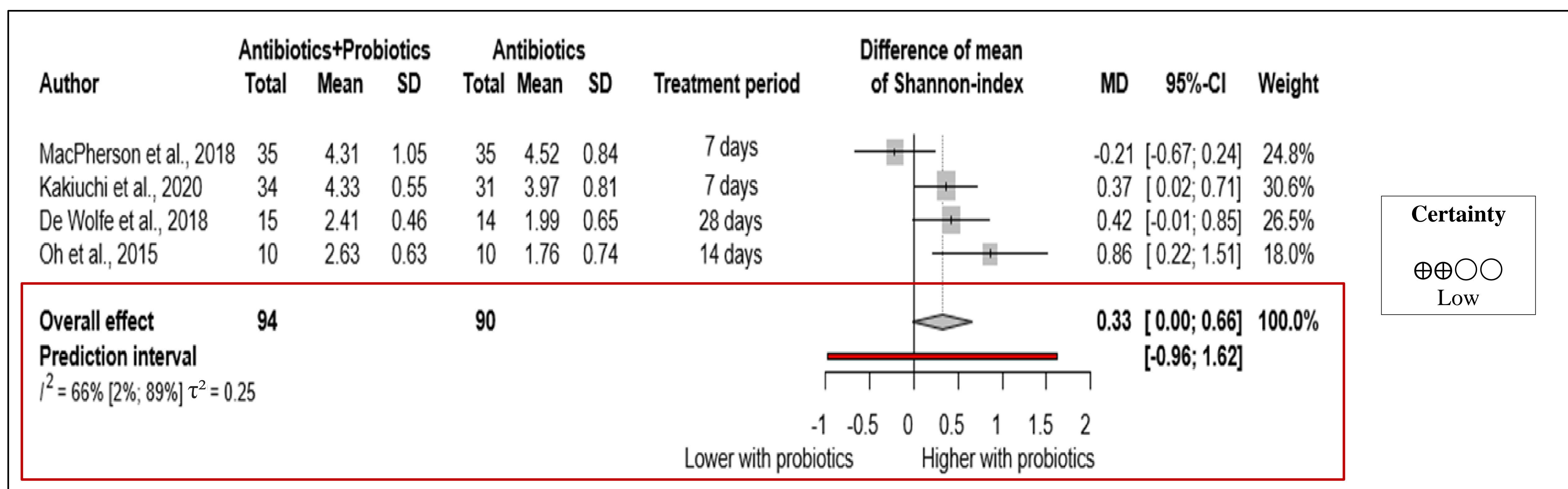


Figure 1. Shannon diversity index is significantly higher in the simultaneously probiotic supplemented group at the cessation of antibiotic therapy CI: confidence interval

Table 1. Systematic review of the microbiome  $\alpha$ -diversity indices as measured immediately after the end of the simultaneous antibiotic and probiotic treatment

Study	Shannon diversity index	Chao1 index	Observed OTUs	Pielous evenness	Strong index	Sobs index	ACE index	Faiths Phylogenetic Diversity
Cárdenas et al. (2020)								
Chen et al. (2018)								
De Wolfe et al. (2018)								
Kabbani et al. (2017)								
Kakiuchi et al. (2020)								
MacPherson et al. (2018)								
Oh et al. (2016)								
Tang et al. (2021)								
Zhong et al. (2021)								

Legend:   
no significant difference between groups   
favors intervention group   
favors control group   
not applicable

Table 2. Systematic review of the microbiome  $\beta$ -diversity indices as measured immediately after the end of the simultaneous antibiotic and probiotic treatment

Study	Bray-Curtis dissimilarity index	Euclidean distance	Jaccard similarity coefficient	Canberra distance	Weighted UniFrac distance	Unweighted UniFrac distance
Cárdenas et al. (2020)						
Engelbrekton et al. (2009)						
De Wolfe et al. (2018)						
Kakiuci et al. (2020)						
MacPherson et al. (2018)						
Tang et al. (2021)						

## RESULTS

Our systematic search provided a total of 11.769 duplicate-free records, from which **15 articles were eligible for qualitative synthesis** with total number of **877 patients**. **4 studies** were suitable for **quantitative synthesis of Shannon diversity index**, with the total number of **184 patients**.

The Shannon diversity index, which reflects on both the number of species and the inequality between species abundances, was **significantly higher in the intervention group** by comparison with the control group when assessed immediately after antibiotherapy (MD=0.33, 95%CI [0.00; 0.66], I<sup>2</sup>=66% [2%; 89%]). Penury of data prevented us from meta-analyzing other diversity indices. According to our systematic review,  **$\alpha$ - and  $\beta$ -diversity indices are however reported not significantly different** between the groups in most of the cases. The affected phyla and genera tend to be similar after the antibiotic treatment in the two groups, but the **level of changes might be larger in the control** than in the intervention group. However, these changes are **restored to levels similar to baseline in both groups after 2-8 weeks of follow-up**, and differences between the groups also disappears.

## MATERIALS AND METHODS

We submitted our study protocol previously to the International prospective register of systematic reviews (CRD42021282983). The systematic search was performed without filters on the 15th of October 2021 in three medical databases – **MEDLINE (via PubMed)**, **Embase**, and **Cochrane Central Register of Controlled Trials (CENTRAL)**. We included all the studies that met the following eligibility criteria: population (P)— people treated with **antibiotics**; Intervention (I) — **simultaneous probiotic** supplementation; comparison group (C) — **no probiotic** supplementation / placebo. The assessed outcomes (O) were **gut microbial diversity (and composition)** (at the end of intervention, after follow-up). Only randomized controlled trials (**RCTs**) were included. For continuous variables we calculated **mean differences with 95% confidence intervals (CIs)**. We followed the recommendation of the "Grades of Recommendation, Assessment, Development, and Evaluation (**GRADE**)" workgroup to evaluate the quality of evidence.