

# Bacillus clausii for the treatment of acute diarrhea in children: a systematic review and meta-analysis of randomized controlled trials

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## INTRODUCTION

Acute diarrhea is a burdensome disease with potentially harmful consequences, especially in childhood. Acute diarrhea is defined as an abnormally frequent discharge of semi-solid or fluid fecal matter from the bowel, lasting less than 14 days.

Currently, the World Health Organization (WHO) recommends treatment of acute childhood diarrhea with oral rehydration salts (ORS) and continued feeding for the prevention and treatment of dehydration, as well as zinc supplementation to shorten the duration and severity of the diarrheal episode.

*Bacillus clausii* is a rod-shaped, non-pathogenic, spore-forming, aerobic, Gram-positive bacterium that is able to survive transit through the acidic environment of the stomach and colonize the intestine even in the presence of antibiotics.

Despite its large use in clinical practice, the efficacy of the probiotic *Bacillus clausii* in treating acute childhood diarrhea remains unclear.

## OBJECTIVE

The aim of this paper is to systematically review randomized controlled trials that assessed the efficacy and safety of *Bacillus clausii* in the treatment of acute childhood diarrhea.

## METHODS

### Criteria for considering studies for this review

Randomized controlled trials conducted among children under 18 years of age with acute diarrhea. The experimental group had to receive *Bacillus clausii* at any dose and in the following bacterial strains: O/C, SIN, N/R and T. The control groups had to receive either a placebo, an appropriate standard of care or no treatment.

The primary outcome measures were duration of diarrhea, stool frequency after intervention and hospitalization duration. The secondary outcome measures were vomiting episodes, quality of life and adverse events.

### Search strategy for identification of studies

The following electronic databases were systematically searched up to October 2017: MEDLINE (via PubMed/OVID), EMBASE (via OVID), Cochrane Central Database of Controlled Trials (via CENTRAL), Google Scholar, and ClinicalTrials.gov

### Statistical methods

Overall effect for each meta-analysis was derived by using a random effects model. Statistical heterogeneity between studies was assessed by Cochran's Q test and I squared. Statistical assessment of funnel plot asymmetry was done using Egger's regression asymmetry test and Bett's adjusted rank correlation test. All statistical analyses were conducted by using the metaphor package (Maastricht University). p-values < 0.05 were considered statistically significant.

## RESULTS

### Characteristics of included studies

From 2165 potential relevant citations, 11 full papers were reviewed and finally 6 citations were included in the final meta-analysis. In total 919 patients were included in the meta-analysis (467 in the experimental group and 452 in the control group). The age of the patients ranged from 3 months to 12 years.

One study, administrated  $1 \times 10^9$  colony-forming units (CFU) of *Bacillus clausii* twice daily, four other studies administrated  $2 \times 10^9$  twice daily and another study administered either  $2 \times 10^9$  or  $4 \times 10^9$  CFU depending on the age. Duration of the interventions was five days in all clinical trials with the exception of the Urtula and Dacula trial which treated for three days.

### Primary findings

- Significant reduction in the duration of diarrhea (mean difference = -9.12 h, 95% CI: -16.49 -1.75)  $p = 0.015$ .
- Reduction in stool frequency (mean difference = -0.19 diarrheal motions, 95% CI: -0.43 to 0.06)  $p = 0.14$ .
- Significant reduction in the duration of hospitalization (mean difference = -0.85 days, 95% CI: -1.56 to 0.15)  $p = 0.017$ .significant.

### Secondary findings

- Vomiting episodes were similar in the group treated with *Bacillus clausii* and in the control group.
- *Bacillus clausii* was well tolerated and no adverse events were observed. Outcomes related to quality of life were not reported.

Figure 1: Forest plot showing effect of *Bacillus clausii* on mean duration of diarrhea. CI, confidence Interval, RE, random effects.

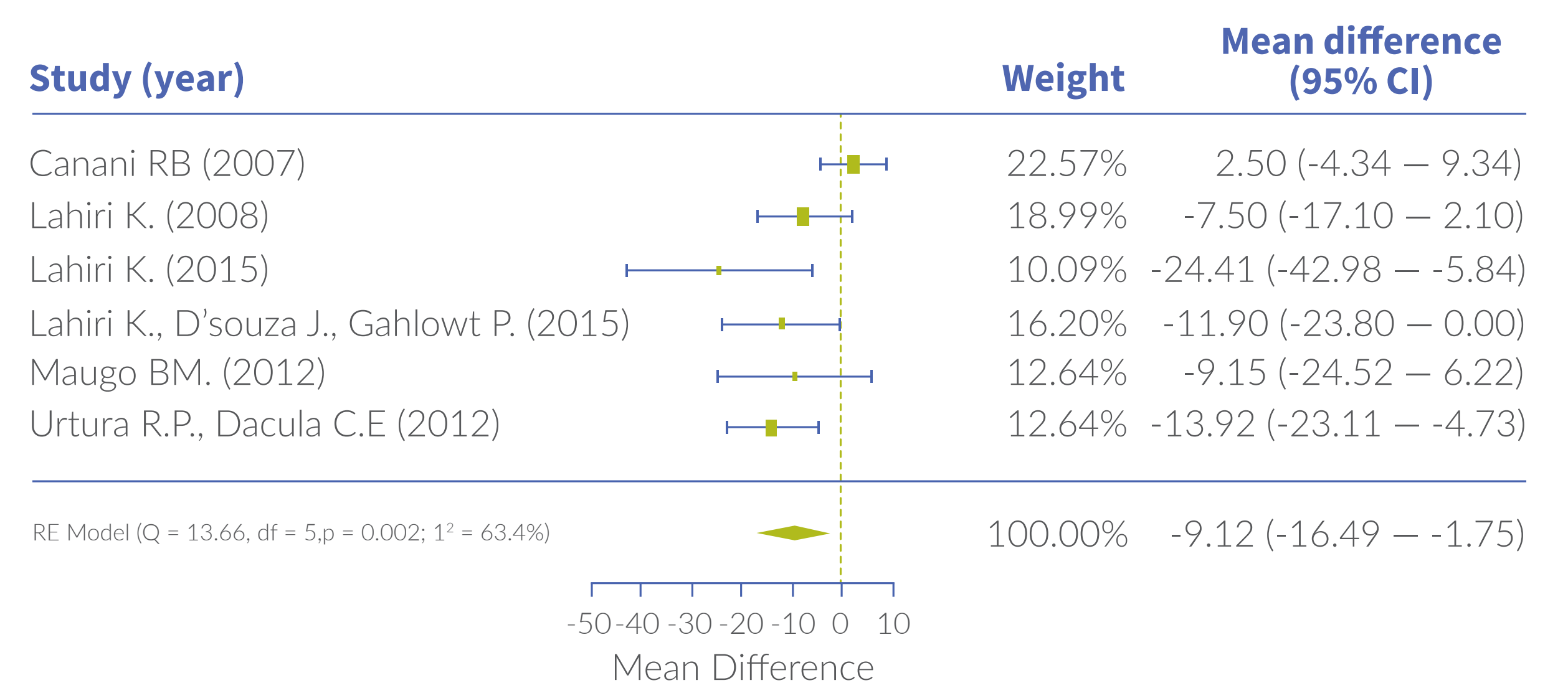


Figure 2: Forest plot showing effect of *Bacillus clausii* on mean stool frequency. CI, confidence Interval, RE, random effects.

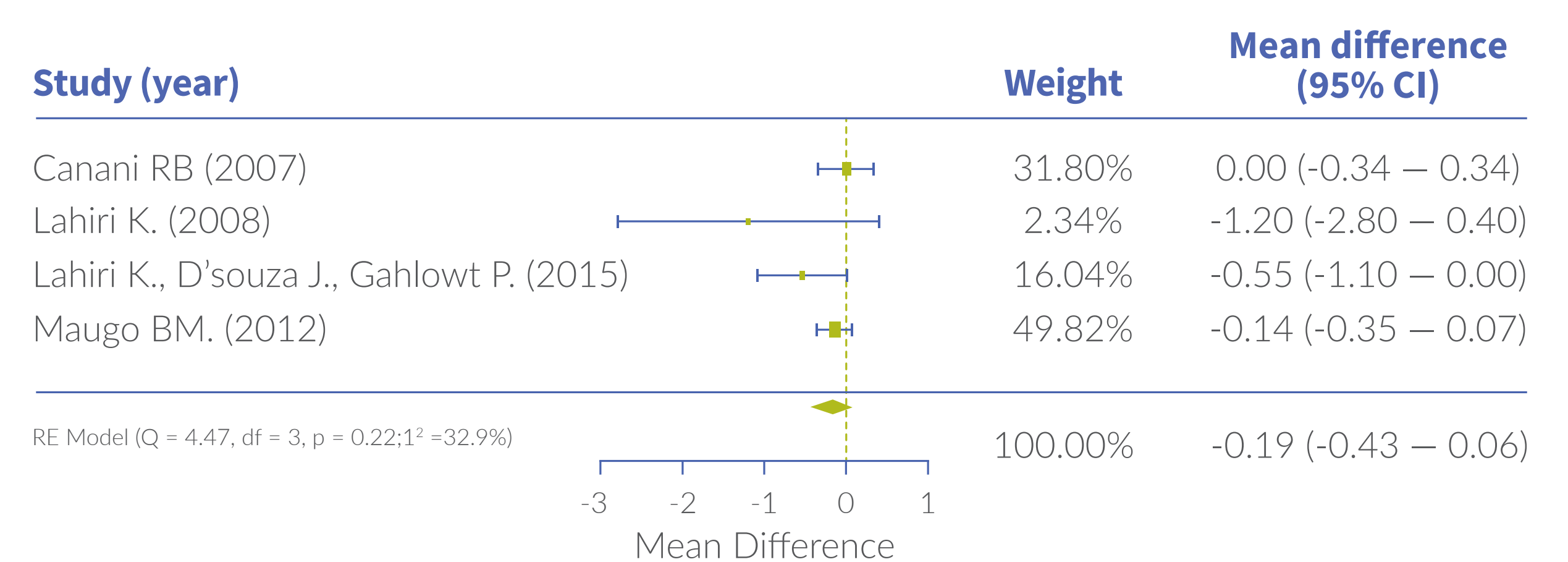
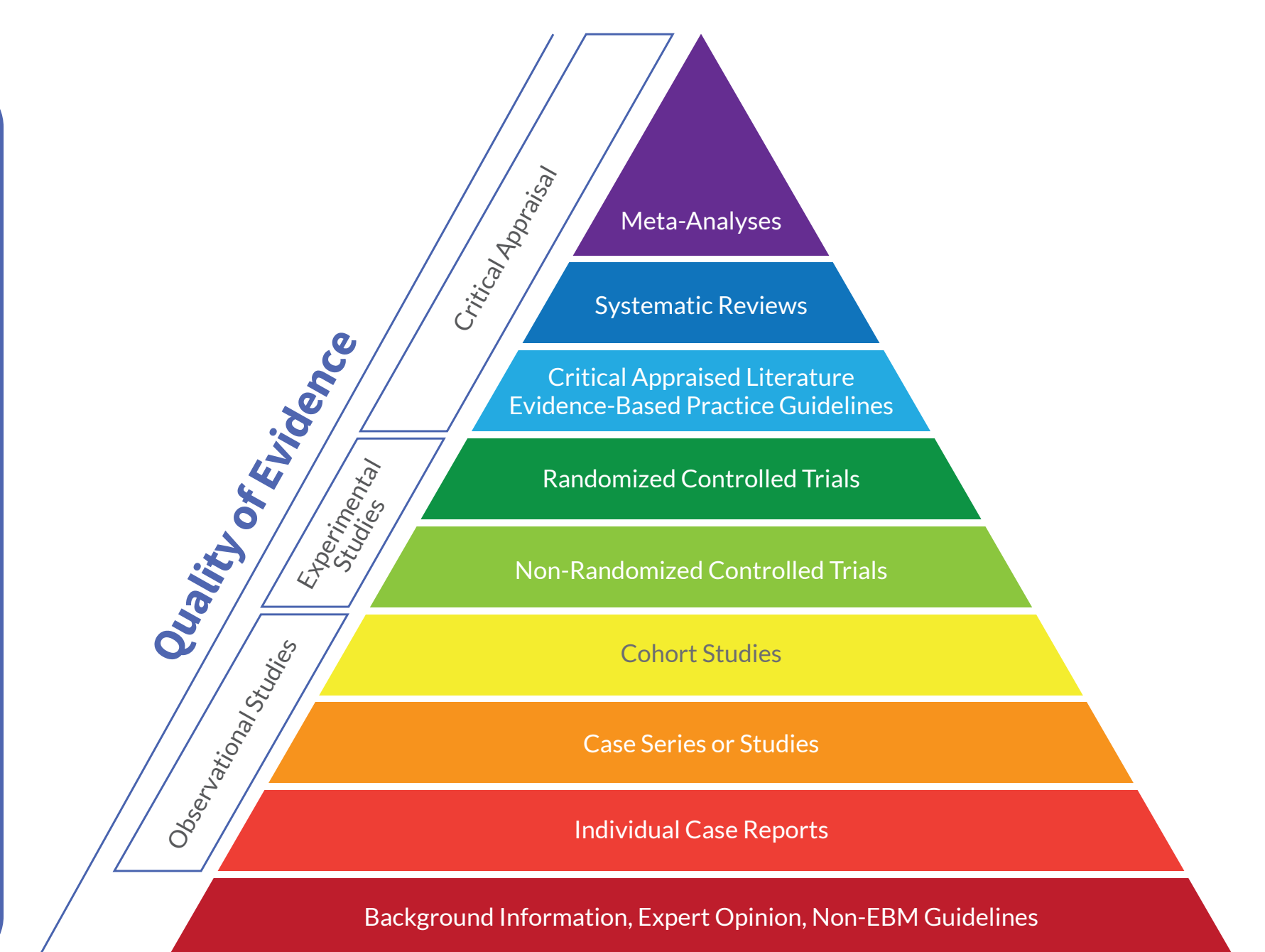
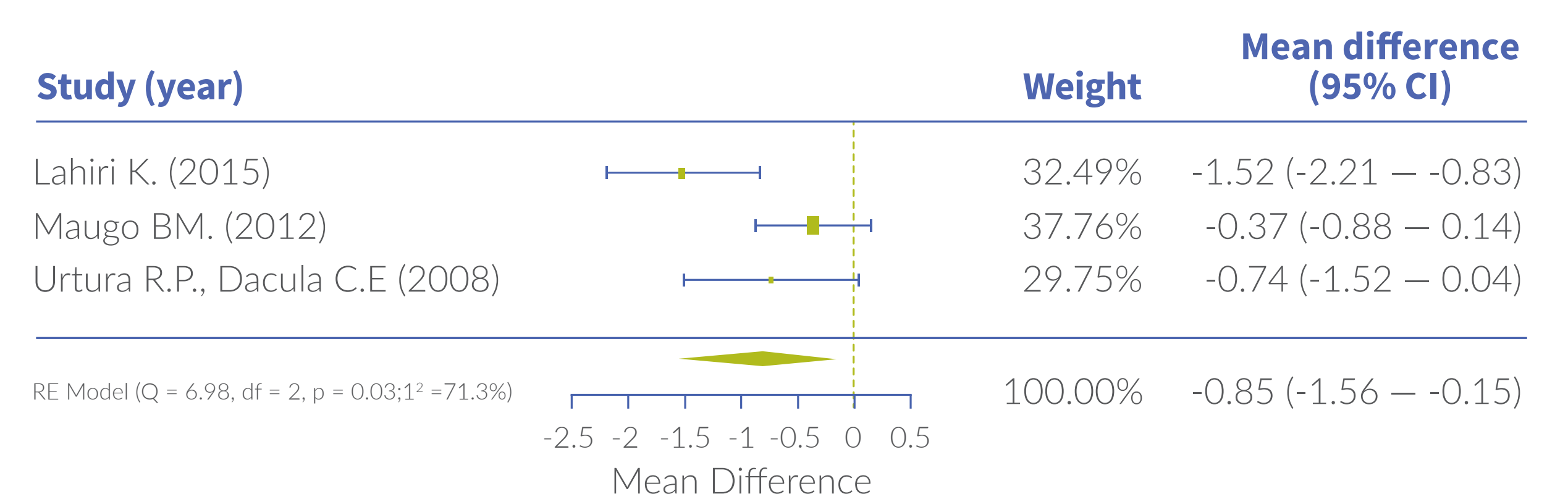


Figure 3: Forest plot showing effect of *Bacillus clausii* on mean duration of hospitalization. CI, confidence Interval, RE, random effects.



## CONCLUSIONS

- Results indicate that *Bacillus clausii* combined with ORS might significantly reduce the duration of acute childhood diarrhea and the duration of hospital stay compared to ORS alone.
- Our systematic review suggested that treatment with *Bacillus clausii* is well tolerated, without causing serious adverse events.
- Our results indicate that *Bacillus clausii* might represent an effective therapeutic option in acute childhood diarrhea, with a good safety profile.
- One limitation of this meta-analysis is represented by the heterogeneity among the studies, that prevent us from drawing definitive conclusions.