INPLASY PROTOCOL

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None declared.

Differential probiotics for the prevention of traveler's diarrhea: study protocol of a network meta-analysis

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Review question / Objective: **We aim to perform a systematic review and meta-analysis to examine the comparative effectiveness of differential probiotics in the prevention of TD.**
Condition being studied: **Probiotics might be beneficial for the prevention of traveler's diarrhea (TD). Owing to the diversity in probiotic strains, it is difficult for clinicians to recommend specific probiotic treatments; and previous systematic review and meta-analyses have not assessed the comparative effectiveness of differential probiotics in the prevention of TD.**
Information sources: **We will search Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinical registries from the inception of the databases to November 30, 2021, and the search will be performed without any language restriction.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2021 and was last updated on 28 July 2021 (registration number INPLASY202170089).

INTRODUCTION

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Condition being studied: **Probiotics might be beneficial for the prevention of traveler's diarrhea (TD). Owing to the diversity in probiotic strains, it is difficult for clinicians to recommend specific probiotic treatments; and previous systematic review and meta-analyses have not assessed the comparative effectiveness of differential probiotics in the prevention of TD.**

METHODS

Participant or population: **Healthy adults (aged over 18 years) who plan to travel to**

countries in the continents of Africa, central and south America, and Asia, which are considered as high-risk areas for TD.

Intervention: RCTs that assess the efficacy of probiotics, synbiotics, and prebiotics for the prevention of TD will be included.

Comparator: The controls will be no treatment, placebo, active control recommended by guidelines or suggested effective by previously published systematic reviews.

Study designs to be included: Randomized controlled trials (RCTs) that examine the effect of probiotics on prevention of TD will be included.

Eligibility criteria: RCTs with parallel design will be preferentially selected; RCTs with crossover design will be included if the results of the first phase (before crossover) are separately reported.

Information sources: We will search Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinical registries from the inception of the databases to November 30, 2021, and the search will be performed without any language restriction.

Main outcome(s): The primary efficacy outcome will be the incidence of TD. With consideration of the ACG clinical guideline5 and a previous systematic review6, TD is defined as the passage of at least three unformed stools within a 24-hour period accompanied with at least one of the following conditions: abdominal pain or cramps, nausea, vomiting, fever (≥37.8°C), fecal urgency, the passage of gross blood or mucus in stool, tenesmus, or moderate to a severe increase in intestinal gas. The safety outcome will be treatment-related adverse events. RCTs that report any of the two outcomes will be included.

Quality assessment / Risk of bias analysis: The risk of bias (RoB) of the included trials will be assessed by using the revised Cochrane risk of bias tool (RoB 2).9 A trial will be evaluated in five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and each domain will be rated into low RoB, high RoB, or some concerns according to the response to signaling questions for each domain. RCTs with all the five domains rated as low RoB will be judged with overall low RoB.

Strategy of data synthesis: The comparative effectiveness of differential probiotics in the incidence of TD will be calculated through a frequentist-approach network meta-analysis. Placebo will be treated as a common comparator, and the effect size of each probiotic product will be computed by comparison with placebo. The results of the included RCTs will be pooled through a random-effects model, and the relative ratio (RR) and corresponding 95% confidence interval (95%CI) will be estimated for each probiotic in comparison with placebo. The comparative effectiveness of the probiotics will be ranked by using a P-score, which is a measure of the mean probability of a treatment being the most effective in all the included treatments.

Subgroup analysis: We will also perform subgroup analyses. First, we will classify the destination of the travel, and re-run the analysis in RCTs with the same travel destination. Second, we will categorize interventions into monotherapy and adjunctive therapy and re-run the analysis separately.

Sensitivity analysis: Several sensitivity analyses will be performed. First, we will exclude RCTs with high RoB or some concerns and re-perform the analysis, to check whether the results are consistent with the main analysis. Second, we will exclude RCTs with financial support from private companies or RCTs without any financial support and re-perform the analysis. Third, we will exclude RCTs with potentially underpowered designs and re-perform the analysis. The comparative effectiveness of differential probiotics in the incidence of TD will be calculated

through a frequentist-approach network meta-analysis. Placebo will be treated as a common comparator, and the effect size of each probiotic product will be computed by comparison with placebo. The results of the included RCTs will be pooled through a random-effects model, and the relative ratio (RR) and corresponding 95% confidence interval (95%CI) will be estimated for each probiotic in comparison with placebo. The comparative effectiveness of the probiotics will be ranked by using a P-score, which is a measure of the mean probability of a treatment being the most effective in all the included treatments.

Country(ies) involved: China.

Keywords: Differential probiotics; traveler's diarrhea; network meta-analysis.

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