Prebiotics and sepsis in infants: An updated systematic review and meta-analysis

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Abstract

Background. Sepsis is a critical situation, and its treatment and reduction are important clinical issues. Antibiotics are a routine treatment option, but their adverse effects are a concern in pediatric patients, especially infants. Prebiotics might be an alternative option.

Objectives. The aim of this study was to provide an updated systemic review and meta-analysis of randomized controlled trials (RCTs) on the use of prebiotics for sepsis in infants, which could assist clinicians in deciding whether to use this treatment.

Methods. The study included RCTs related to prebiotics and sepsis in infants. A random effects model and the odds ratio (OR) were applied to estimate the effect of prebiotic use and the incidence of sepsis in infants. The analysis included 16 studies with a total of 6,438 infants. The primary outcome was the OR of sepsis for infants who received prebiotics.

Results. The results of the meta-analysis demonstrated that the pooled OR of sepsis was significantly lower for infants who used prebiotics. However, the results indicated a medium level of heterogeneity.

Conclusions. The results showed that the use of prebiotics might be associated with a reduction of sepsis in infants. The standardized application of this treatment might be an intriguing topic for future clinical research.

Key words: sepsis, meta-analysis, odds ratio, infant, prebiotic

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Introduction

Infants are prone to sepsis, especially those with lower birth weight, lower gestational age, asphyxia, and those administered antibiotics.[1–3] In addition, infants can easily contract infections, such as necrotizing enterocolitis, which can lead to sepsis and alterations in laboratory parameters.[4] Changes in non-cytotoxic T lymphocytes could also occur after the onset of sepsis due to the suppression of immune function in infants.[5] Furthermore, sepsis in infants may result in warm shock physiology accompanied by vasodilation, which could contribute to septic shock and increase the mortality rate.[6] Therefore, understanding the relationship between infants and sepsis is critical.

The therapeutic options for treating sepsis in infants are limited. Mechanical ventilation and empirical antibiotics have been reported to be associated with higher sepsis frequency in infants.[1–3] Thus, clinicians may need to establish other therapeutic options for such patients, and one possible alternative is prebiotics. The current evidence on the mechanisms of prebiotics in immune function mostly comes from animal studies, which provide clues about how to relieve sepsis in infants through immunomodulatory actions.

Prebiotics could promote the growth of beneficial bacteria, enhance immune-stimulatory processes, and increase the expression of immunomodulatory functions with antioxidant characteristics.[7–9] Furthermore, they may enhance intestinal trophic effects and immune system maturation.[10]

Oligosaccharides from human breast milk are prebiotics that have been shown to modulate immune responses,[11] which is consistent with the latest studies on the mechanisms of prebiotic effects on immunomodulatory function. In addition, prebiotics seem to have no significant side effects,[12] and may help to avoid mechanical ventilation use in infants. Therefore, they have the potential to decrease sepsis risk in such patients.[13]

Objectives

Sepsis is a critical situation in clinical practice for which antibiotic therapy is a routine option. However, adverse effects of antibiotics have to be considered in pediatric patients. This meta-analysis aimed to provide an update on the effects of prebiotic use in sepsis events in infants. Based on the literature, we hypothesized that prebiotics would decrease the risk of sepsis. We included randomized controlled trials (RCTs) with placebo controls (no administration of prebiotics) due to the lower risk of bias in such studies. The results could provide valuable information on how to manage infants.

Methods

Literature database and enrollment criteria

We searched the literature using the following keywords: "prebiotic," "versus," "placebo," "comparison," "short-chain galacto-oligosaccharides," "long-chain fructo-oligosaccharides," "pectin-derived acidic oligosaccharides," "acidic oligosaccharides," "sepsis," "neonate," "infant," "septic," "oligosaccharides," "fructans," "oligofructose," "inulin," "randomized," "clinical," "controlled," "trials," "treatment," "therapy," "efficacy," and "outcome." We searched the ScienceDirect, PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials databases for relevant prospective RCT studies published before October 2022. The inclusion criteria were: 1. Studies comparing prebiotics with placebo in infants; 2. Those with information on the sepsis characteristics, including the occurrence and rates; 3. Reports published in journals in the Science Citation Index Database written in English; and 4. RCTs with a placebo-controlled design.

Assessment of study quality and data collection

We conducted the meta-analysis in accordance with the Cochrane Handbook for Systematic Reviews and Interventions[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] Data collected from the studies included sepsis events, the number of infants who experienced such events after receiving prebiotics or a placebo, the odds ratio (OR), and the standard error (SE).

Data collection and assessment

Two reviewers screened abstracts and collections of articles and extracted data on sepsis outcomes from the texts, tables and figures. The risk of bias was then assessed according to the following criteria: 1. Bias arising from the randomization process; 2. Bias due to deviations from intended interventions; 3. Bias due to missing outcome data; 4. Bias in the measurement of the outcomes, and 5. Bias in the selection of the reported results. The reviewers showed strong agreement in their assessments (kappa = 0.9). Ultimately, the final results were reviewed by all authors.

Meta-analysis and statistical analysis

We generated pooled estimates of the relative risks (RRs) and ORs for sepsis events and prebiotic treatments and used the Cochrane Collaboration Review Manager Software Package RevMan v. 5.4 (Cochrane Collaboration, Copenhagen, Denmark) to perform the meta-analyses.

The Mantel–Haenszel method was used to calculate RR, with DerSimonian and Laird's random effects models and summary statistics also produced. The risk estimates of individual studies were combined using the variance-weighted averages in the random effects model.

The group that received prebiotic treatments and the control group were compared to determine whether prebiotics decreased the rate of sepsis events. The χ^2 tests were performed, and the I^2 statistic was used to examine the heterogeneity between studies.[15] According to the Cochrane Handbook for Systematic Reviews and Interventions,[14] the choice between a fixed-effect and a random-effects meta-analysis should not solely be made according to the statistical test for heterogeneity. Methodological or conceptual heterogeneity is unavoidable in a meta-analysis, so a random effects model may be more reasonable. Therefore, a random effects model was applied in this study. Two-sided p-values were obtained from the statistical analyses, and a funnel plot was used to assess publication bias.

Results

Study screening and enrollment

After the initial search, 112 articles were selected, with no additional records found from other sources. These articles included 59 duplicates, which were removed. After evaluating the relevance of the abstracts and titles of the remaining 53 articles, 19 were excluded. The full texts of the remaining 34 articles were screened, and 18 more were discarded.

Ultimately, 16 articles were included in the meta-analysis.[16–31] The PRISMA flow diagram of this study is shown in Fig. 1. The prebiotics group included 3,211 infants, with 3,227 infants in the control group (the total population size was 6,438). Table 1 summarizes the demographic data and characteristics of the 16 studies. Figure 2 shows the assessment of risk bias of the included 16 studies.

Risk ratio and odds ratio of sepsis events between groups

The prebiotics group had a significantly lower RR of sepsis events according to the random effects model (Z = 3.70 and p = 0.001 for overall effect). Low heterogeneity was obtained, with an I^2 value of 32% (Fig. 3). The prebiotics group also had a significantly lower OR of sepsis events according to the model (Z = 3.31 and p = 0.001 for overall effect), and the heterogeneity was low, with an I^2 value of 38% (Fig. 4).

Discussion

The results suggest that prebiotic treatment could be beneficial for reducing the rate of sepsis events in this large sample of infants, which was supported by the RR, OR and 95% confidence intervals (95% CIs). One strength of this

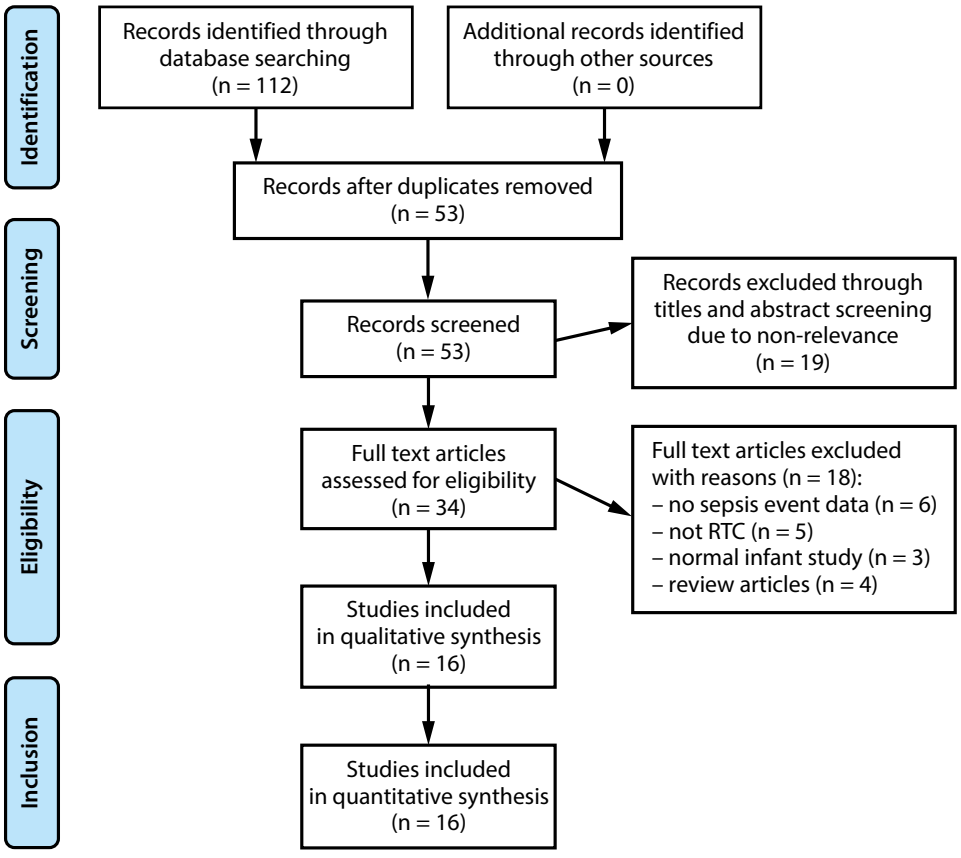

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. The identification and selection of potentially relevant literature, through abstract and title screening, adhered to the PRISMA guidelines. The full texts of eligible studies were screened, and suitable articles were enrolled into the final meta-analysis

Table 1. Summary of enrolled studies

Studies	Subjects (prebiotic compared to control)	Prebiotic content compared to control	Blinded and treatment duration	Outcome of interest
Armanian et al., 2016 (Iran)[16]	25 (30.48 ±2.31 weeks old) compared to 50 (29.80 ±2.16 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides 1.5 g/kg/day compared to distilled water	double-blinded 21 days	growth of beneficial *Lactobacillus* colonies, sepsis, fecal microbiota pattern, duration of dependency to oxygen, hospitalization, and death
Campeotto et al., 2011 (France)[17]	24 (15 M, 9 F, 33.5 ±1.3 weeks old) compared to 34 (16 M, 18 F, 33.4 ±1.4 weeks old)	fermentation-induced non-digestible oligosaccharides compared to formula	double-blinded 30 days	benefits on inflammatory and immune markers, sepsis, inflammatory and immune markers
Dasopoulou et al., 2015 (Greece)[18]	85 (34 ±0.33 weeks old) compared to 82 (34 ±0.33 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides 1.2 g/kg/day compared to formula	double-blinded 16 days	increase motilin, reduce gastric residue, motilin, necrotizing enterocolitis, mortality, sepsis, and feeding intolerance
Dilli et al., 2015 (Turkey)[19]	100 (52 M, 48 F, 29 ±1.7 weeks old) compared to 100 (58 M, 42 F, 28.2 ±2.2 weeks old)	inulin 1.35 g/kg/day compared to maltodextrin	double-blinded 56 days	inulin could not decrease necrotizing enterocolitis sepsis, mortality, duration of hospital stay
Guney-Varal et al., 2017 (Turkey)[20]	70 (29.7 ± 1.9 weeks old compared to 40 (29.3 ± 1.7 weeks old	383 mg of fructooligosaccharides and 100 mg of galactooligosaccharides compared to formula	double-blinded 36.5 ±12.6 days	≥stage 2 necrotizing enterocolitis and mortality, culture-proven sepsis and days to reach full enteral feeding
LeCouffe et al., 2014 (the Netherlands)[21]	48 (26 M, 22 F, 30.2 ±1.6 weeks old) compared to 45 (26 M, 19 F, 29.5 ±2.0 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides, pectin-derived acidic oligosaccharides 1.5 g/kg/day compared to maltodextrin	single-blinded 28 days	neurodevelopmental outcome, sepsis
Luoto et al., 2014 (Finland)[22]	23 (11 M, 12 F) compared to 24 (19 M, 5 F) 32–35 weeks old	short chain galactooligosaccharides/ polydextrose 1.2 g/kg/day compared to microcrystalline cellulose and dextrose anhydrate	double-blinded 57 days	respiratory tract infections and its duration, sepsis
Modi et al., 2010 (UK)[23]	73 (48 M, 25 F, 30 ±0.5 weeks old) compared to 81 (50 M, 31 F, 31 ±0.5 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides 1.2 g/kg/day compared to formula	double-blinded 28 days	necrotizing enterocolitis, mortality, sepsis, feeding intolerance
Nandhini et al., 2016 (India)[24]	108 compared to 110	100 mg of fructooligosaccharide compared to no intervention	open-label 7 days	necrotizing enterocolitis, mortality, sepsis, hospitalization duration, number of days to reach full enteral feeding and colony counts in stool culture
Niele et al., 2013 (the Netherlands)[25]	48 (30.1 ±1.6 weeks old) compared to 46 (29.5. ±2 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides, pectin-derived acidic oligosaccharides 1.5 g/kg/day compared to maltodextrin	double-blinded 28 days	allergic and infectious diseases, sepsis
Panigrahi et al., 2017 (India)[26]	2278 compared to 2278 (2314 M, 2242 F)	150 mg of fructooligosaccharide with 100 mg maltodextrin as excipient compared to 250 mg of maltodextrin	double-blinded	a composite of sepsis or death, the former composed of septicemia, meningitis, culture-negative sepsis other infections (including diarrhea, omphalitis, local infections, abscess, and otitis media) and weight gain
Riskin et al., 2010 (Israel)[27]	15 (10 M, 5 F, 30.3 ±2.8 weeks old) compared to 13 (5 M, 8 F, 128.7 ±2.9 weeks old)	digestible oligosaccharides lactulose 1.5 g/kg/day compared to dextrose	double-blinded 35 days	necrotizing enterocolitis, mortality, sepsis, feeding intolerance, and days to reach full enteral feeding
Serce et al., 2020 (Turkey)[28]	104 (61 M, 43 F 29 ±1.9 weeks old) compared to 104 (52 M, 52 F 28 ±2.2 weeks old)	383 mg of fructooligosaccharide, 100 mg of galactooligosaccharide, 2 mg of bovine lactoferrin compared to distilled water	double-blinded 21 days	necrotizing enterocolitis severity, mortality, sepsis, hospitalization duration, time to reach 100 mL/kg/day of oral feeding
Torres et al., 2020 (Peru)[29]	99 compared to 100	oligosaccharides compared to mature breast milk	single-blinded	late-onset sepsis, neonatal sepsis
van den Berg et al., 2013 (the Netherlands)[30]	38 (21 M, 17 F, 29.9 ±1.7 weeks old) compared to 39 (24 M, 15 F, 29.6 ±2.1 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides, pectin-derived acidic oligosaccharides 1.5 g/kg/day compared to maltodextrin	single-blinded 28 days	neurodevelopment, cytokines, infections, sepsis
Westerbeek et al., 2011 (the Netherlands)[31]	73 (29.9 ±1.9 weeks old) compared to 81 (29.3 ±2.1 weeks old)	short chain galactooligosaccharides/ long chain fructooligosaccharides, pectin-derived acidic oligosaccharides 1.5 g/kg/day compared to maltodextrin	double-blinded 28 days	stool viscosity, stool frequency, stool pH, sepsis

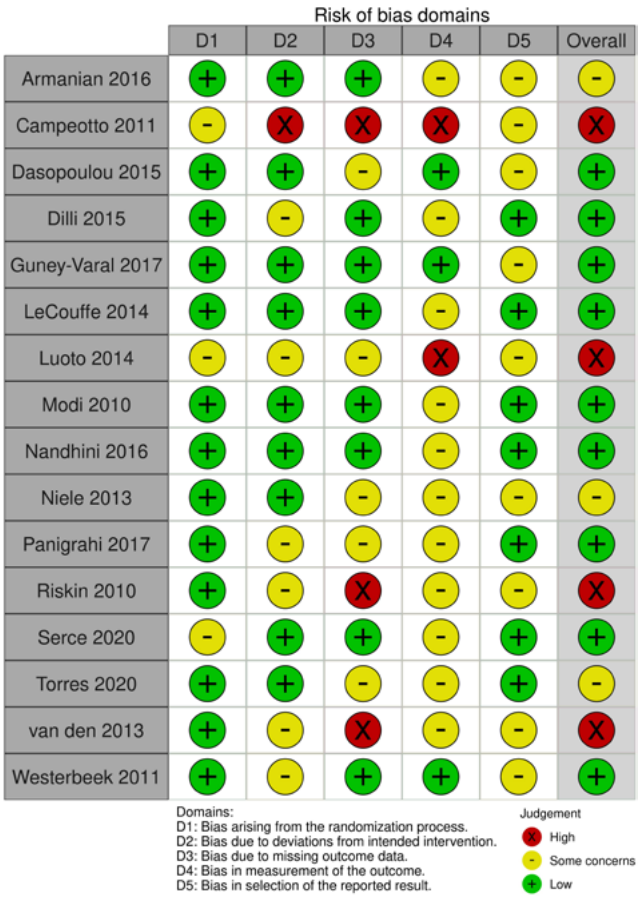

Fig. 2. Risk of bias assessment visualization. The risk of bias assessment updated version (ROB v2) was used to assess the risk of bias for the randomized controlled trials (RCTs)

meta-analysis is that the studies were RCTs, and most only used prebiotics for the treatment groups. The results indicate that this treatment could be an option for infant patients.

Prebiotics may decrease the colonization and growth of pathogenic bacteria and other pathogens, which could help decrease the risk of sepsis and mortality.[32] In the intestines, they may also reduce pathogen cytotoxicity and adhesion,[33] improve motility and permeability, and improve the integrity of the epithelial surface.[34] Furthermore, strengthening of the intestinal barrier by prebiotics may prevent sepsis and infection by inhibiting the migration of pathogens and toxins across the intestinal mucosa and promoting their removal. In addition, prebiotics could enhance immune responses and modulate the responses to pathogens or toxins.[35–38]

Oligosaccharides are prebiotics reported to significantly enhance the growth of probiotic bacteria, such as *Bifidobacteria* and *Lactobacilli*. In addition, oligosaccharides may reduce pathogen adhesion.[39] A study on the long-term safety and effects of prebiotics in pediatric patients found that they can decrease the amount of antibiotics required, which suggests that this treatment is associated with a lower rate of infection.[40] Another study also supports the protective role of prebiotics in suppressing the germination of spores, inhibiting growth into toxin-producing cells, and reducing the colonization of pathogens in the gut.[41] These mechanisms could explain the decreased rate of sepsis events among infants that received prebiotics.

The effects of prebiotics are comparable to those of breast milk in several ways, such as increased body weight, lower fever rates, modulatory effects on diarrhea, decreased constipation,

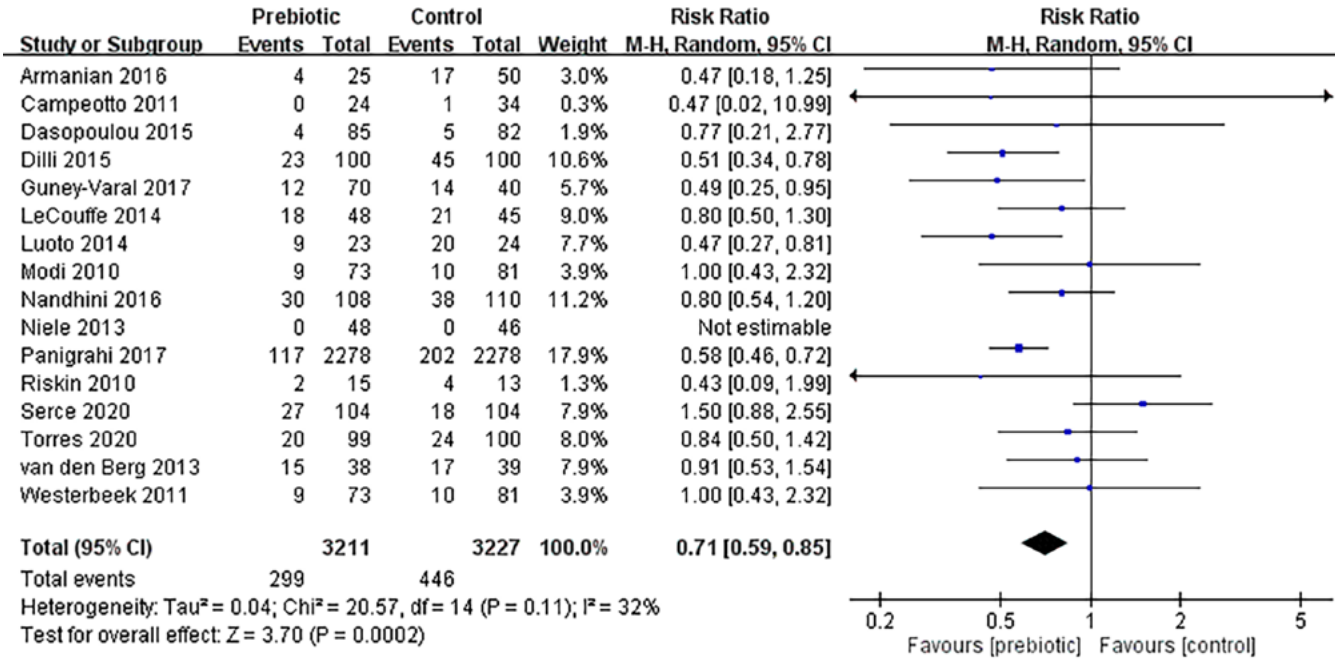

Fig. 3. Forest plot of risk ratio (RR) for sepsis events in infants (prebiotic compared to control). The prebiotic group of preterm infants had a significantly lower RR of sepsis events than the control group

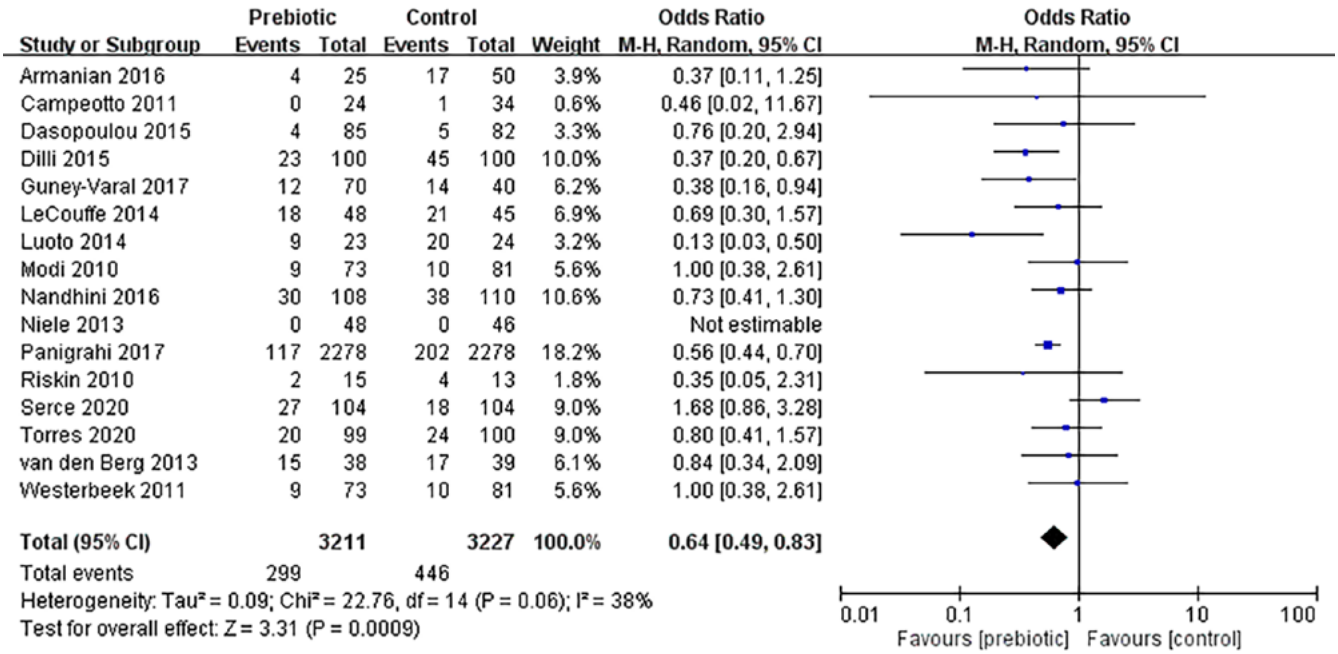

Fig. 4. Forest plot of odds ratio (OR) for sepsis events in infants (prebiotic compared to control). The prebiotic group of preterm infants had a significantly lower OR of sepsis events than the control group

and inhibitory effects on respiratory tract infections in infancy.[42] Prebiotic supplementation has also been recommended if breast milk is unavailable. Therefore, treatment with prebiotics could be an economical choice for infants.

Limitations

This study had several limitations. First, some RCTs had small sample sizes, while others had appropriate sample sizes, and this imbalance could be a concern. Even though a weighting method was applied to decrease the bias, the impact of this issue should not be ignored.

There was also an imbalance in the sexes of the infants examined, which could influence the interpretation of the results. Similarly, there were variations in age, prebiotic content, doses, placebo used, and treatment duration, which are also potential sources of bias. The lack of patient-level data may be another concern and prevented us from fully evaluating patient-level covariates. Thus, possible subgroup effects could not be investigated.

Another limitation is that the definition and severity of sepsis in the included RCTs differed. Also, some RCTs were double-blinded, while some were single-blinded, and the timing of sepsis was variable between studies, which could affect the results. This issue required consideration when we reported such a significant result of lower sepsis (OR or RR) in this group of pediatric patients.

Conclusions

The results of this meta-analysis showed that prebiotic use could be associated with a reduction in sepsis rates in infants, and prebiotics significantly lowered the sepsis risk in preterm infants. Therefore, they should be considered as an option in clinical practice. Fewer sepsis events under the use of prebiotics might potentially suggest that prebiotics might decrease the mortality and the damage to vulnerable organs. In addition, prebiotics might decrease the sequelae of infection, and the need for antibiotic use among preterm infants. Future clinical research should examine the standardized application of prebiotics in infant patients.

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