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The Administration of Probiotics in Extremely Low-Birth-Weight Infants and the Incidence of Necrotizing Enterocolitis and Mortality: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Encouraging findings were previously demonstrated in a previous meta-analysis that analyzed the results of randomized controlled trials (RCTs) that investigated the potential favorable effects of probiotics administration in preterm infants to prevent necrotizing enterocolitis (NEC) and feeding intolerance. This evidence has only been linked to low birth-weight infants (<1000 g), while evidence regarding the impact of administration of these modalities for Extremely Low-Birth-Weight

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Infants (ELBW) infants is still controversial among the different studies in the literature. A systematic review was conducted to retrieve all the relevant randomized controlled trials in the literature that investigated the impact of probiotics administration on the different outcomes in ELBW infants, including the incidence of mortality and NEC. A thorough search was then conducted through the different databases to find the relevant articles.A total of 11 RCTs were included in the present systematic review. All articles were published between 2007 and 2021, with a total of 3225 ELBW infants were included in both the intervention and control groups across the different included trials. Our results indicate that the administration of these modalities does not have a significant impact on these outcomes. However, it has been reported that they enhance the growth rate, especially head growth circumference, which has been reported to be superior to the placebo effect. Further investigations for ELBW should be encouraged to furtherly validate these modalities, although no adverse events have been reported for their administration among trials in the current systematic review.

Keywords: Preterm; low-birth-weight; ELBW; probiotics; development; infants; pediatrics; NEC; nectotizing enterocolitis; neurodevelopment; mortality.

1. INTRODUCTION

In extremely low birth-weight (ELBW) infants (<1000 g), it is logical that nutrition is important for these infants to enhance the neurodevelopmental and general growth outcomes [1]. Feeding intolerance has been demonstrated to be the commonest cause for delayed or insufficient nutrition in this population because they cannot usually be fed by the enteral route. Furthermore, it has been demonstrated that feeding intolerance is usually associated with different gastrointestinal tract manifestations, including abdominal pain and distension, and in many cases, intravenous catheters are inserted. Encouraging findings were previously demonstrated in a previous meta-analysis that analyzed the results of randomized controlled trials (RCTs) that investigated the potential favorable effects of probiotics administration in preterm infants to prevent necrotizing enterocolitis (NEC) and feeding intolerance [2, 3].

Growth and development within the 1st weeks after birth in ELBW have been reported to be extremely low, which is not even equal to intrauterine growth [4]. Length growth and head circumference are not usually enhanced at the same rate that general growth and development occur within these infants'last period of hospitalization [5]. At pre-school follow-up, previous investigations have furtherly demonstrated that neurodevelopmental outcomes usually deteriorate in these children due to poor growth parameters, especially the head circumference, and development [1, 6]. Furthermore, evidence indicates that gut microbiota is important for brain development and growth as previously demonstrated in the microbiota-gut-brain axis hypothesis [7]. In fact, some previous investigations demonstrated that ameliorated autism-like symptoms, altered microbial composition, and corrected gut permeability were all significantly associated with the administration of probiotics in animal models [8-10]. Further human trials indicated that favorable neurodevelopmental outcomes were reported for preterm infants in low socioeconomic countries following the administration of probiotics [11].

Although the current evidence supports that probiotics administration can significantly enhance NEC and feeding intolerance among preterm infants, this evidence has only been linked to low birth-weight infants (<1000 g) while evidence regarding the impact of administration of these modalities for ELBW infants is still controversial among the different studies in the literature [12]. Among these trials, different probiotics were proposed in the literature with favorable effects that were validated in animal investigations. For instance, reduced food intolerance increased gastric emptying, and increased intestinal peristalsis were previously reported as favorable events following the administration of these modalities in animals and humans [13, 14]. In the present systematic review, we aim to discuss the impact of probiotics administration in ELBW infants on the incidence of mortality and NEC, and other outcomes. We will discuss the different sets of probiotics that were reported among the different RCTs that aimed to validate them among their ELBW population.

2. METHODS

2.1 Study Design and Intended Outcomes

This systematic reviewis done according tothe Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) recommendations [15]. The main outcome of the present investigation is to assess the effect of probiotics administration on NEC and bacterial colonization. The other outcome of this study would also include the effect of these modalities on the incidence of mortality among the included population and whether these outcomes are comparable or different from the placebo groups among the different investigations.

2.2 Search Strategy

The PICO question was formulated as follows: population; Extremely low preterm infants, intervention: different types and formulas of probiotics, comparator: placebo, primary outcome: impact on NEC rate, secondary outcome: impact on mortality rate. Accordingly, a preliminary screening was done to the relevant articles to possibly identify the relevant keywords from these investigations to build up a solid search strategy and identify all the relevant articles that would meet our inclusion criteria [16, 17]. The included keywords were: (Probiotics [Mesh] OR probiotic* OR Bifidobacterium [Mesh] OR bifidobacterium* OR Lactobacillus [Mesh] OR lactobacill* OR Saccharomyces boulardii [Mesh] OR Saccharomyces OR Prebiotics [Mesh] OR Prebiotic* OR Oligosaccharides [Mesh] OR Oligosaccharide* OR Inulin [Mesh] OR Inulin* OR Fructooligosaccharide* ORFructo- oligosaccharide* OR FOS OR FOSs OR galacto- oligosaccharide* OR galactooligosaccharide* OR Lactoferrin [Mesh] OR Lactoferrin* OR Lactulose* OR Lactulose [Mesh] OR Synbiotics [Mesh] OR Synbiotic*) AND (prematurity OR premature OR preterms OR preterm OR "very low birth" OR "Infant, Low Birth Weight"[Mesh] OR "Infant, Extremely Premature"[Mesh] OR "low birth weight" OR "Infant, Premature"[Mesh]).

The electronic search strategy was conducted via these databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), the System for Information on Grey Literature in Europe (SIGLE), International Standard Randomised Controlled Trial Number (ISRCTN), Virtual Health Library, Web of Science, Google Scholar, and Scopus. The above-mentioned search terms were adjusted based on the terms and conditions of each database to look for and include all the relevant and published investigations only.

2.3 Criteria and Screening

We aimed to include the following articles: 1) randomized controlled trials (RCTs), 2) that included extremely low preterm infants, 3) that were published in English, 4) investigated the effect of probiotics administration in this population and reported the incidence of NEC and/or mortality, and 5) were published any time. Accordingly, we excluded other articles that were: 1) observational or non-RCTs generally 2) investigated preterm infants in general and did not specify their ELBW population and outcomes, 3) the intended outcomes and relevant data were overlapping, 4) were not published in English, 5) were protocols, thesis, abstract-only articles, and other non-suitable designs.

Based on these criteria, we included the relevant investigations through a comprehensive screening strategy that was composed of both title and abstract, and full-text screening. Before this, all the search results through the electronic databases were exported into a single library in Endnote to exclude the potential duplicates among the different search portals. Finally, all of the identified unique studies were exported into an Excel sheet and each was given a numerical ID for enhanced identification and to prevent any potential overlap between the different investigations. Finally, at least two reviewers were involved in the screening process and a discussion was conducted whenever needed to decide whether an article should be included or not. This was furtherly performed under the supervision of the senior author who was continuously consulted whenever needed.

2.4 Data Extraction and Quality Assessment

This was the following step after we were finished with the screening strategy. Our strategy for this step was also systematic, where at least two authors were involved in the process of extracting data from the relevant articles that were finally included. This took place in a well-performed extraction sheet by an experienced author (which was also modified whenever needed based on the nature of the extract data as the sheet was preliminary designed on some, and not all, included articles). The sheet mainly included three parts: I- for baseline characteristics and referencing, II- for outcome measures and study population characteristics, and III- for the risk of bias assessment. All of these data were then used to formulate evidence and draw our results.

The setup of quality assessment was conducted via the Cochrane risk of bias tool for randomized controlled trials will be used to achieve this purpose for the included studies [18]. At least three authors were involved in this step, and as usual, a final decision should be reached before making a conclusion about their decisions either by a thorough discussion between the authors or with the senior member.

3. RESULTS

3.1 Search Results

All the results of the search strategy are presented in the PRISMA flow diagram **Fig. 1**. Totally, 7454 citations were identified and exported from these databases and relevant articles, and the number was sharply shortened to 75 only after duplicate removal and title and abstract screening. Finally, only nine articles were identified, in addition to the other two articles that were manually retrieved when we searched the references of the included articles.

3.2 Risk of Bias

Regarding quality assessment of the included trials, overall, most of the included studies had an overall low risk of bias, except for three trials, as two had unclear risk while only one had a high risk of bias **(Fig. 2A, 2B)**. Reporting and attrition bias domains had the lowest rate of bias across the different included trials, and the risk of bias among other domains was also mostly low but unclear and high in a few investigations as exhibited in the relevant figures.

3.3 Characteristics of Studies

A total of 11 RCTs were included in the present systematic review. **Table 1** shows the detailed characteristics and summary outcomes of the included investigations. Briefly, all articles were published between 2007 and 2021, 2 RCTs were conducted in the USA, Sweden, and India, while one was conducted in Japan, another in Turkey, and the final one was conducted in the UK. A total of 3225 ELBW infants were included in both the intervention and control groups across the different included trials. The used interventions and related regimens, and characteristics of the included populations are present in **Table 1**. A detailed discussion of the result and intended outcomes are presented in the following section.

4. DISCUSSION

In the present section, we will discuss the outcomes of the included trials. We aimed to conduct a systematic review to discuss the use of probiotics for ELBW infants to reduce the incidence and mortality of NEC among this population based on evidence from the relevant investigations in the literature.

The study by Al-Hosni et al. [19]demonstrated that the growth velocity was significantly higher in the probiotics group that received both Bifidobacterium spp. and Lactobacillus spp. supplementation than in the control group. Furthermore, it has been reported that the incidence of enterocolitis (Probiotics: 2/50, Control: 2/51) and mortality (Probiotics: 3/50, Control: 4/50) was similar between the two groups. In another investigation by Costeloe et al. [20], the authors demonstrated that no significant differences were noticed between the two included groups, indicating no evidence for the administration of Bifidobacterium breve BBG-001 in ELBW infants. It has been demonstrated that the rates of NEC (Probiotics: 9%, Control: 10%), sepsis (Probiotics: 11%, Control: 12%), and deaths (Probiotics: 8%, Control: 9%) were similar between the two groups, and no significant side effects were reported secondary to the administration of probiotics.In another trial, Havranek et al. [21] reported that the administration of Lactobacillus rhamnosus and Bifidobacteriuminfantis was significantly associated with an increase in the postprandial intestinal blood flow, which can potentially help against formulating better interventions against ELBW infants. However, no significant differences were noticed between the probiotics and control groups, in terms of NEC (Probiotics: 0/15, Control: 1/16), sepsis (Probiotics: 0/15, Control: 3/16), and deaths (Probiotics: 3/15, Control: 6/16).

Jacobs et al. [22] also reported that no significant differences were noticed between their population of ELBW infants in terms of NEC (Probiotics: 10/235, Control: 14/239), or mortality

Table 1. A summary of the characteristics, findings, and main conclusions of the included trials in this review

Reference	Year	Country	Settings	Data colle-ction	Study design	Population	Sample size	Male (n)	Interventions: Probiotic group					Control group					Author conclusion
									n	Gestational age (weeks)	Birth weight (g)	Used probiotic (s)	Routine	n	Gestational age (weeks)	Birth weight (g)	Intervention	Routine	
Al-Hosni et al.[19]	2012	USA	Multi-center	Pros-pective	RCT	ELBW	101	50	50	25.7 (1.4)	778 (138)	Bifidobacterium spp. and Lactobacillus spp.	once/day; 1st milk feed-34 weeks' postmenstrual age	51	25.7 (1.4)	779 (126)	Placebo	once/day; 1st milk feed-34 weeks' postmenstrual age	Growth velocity was higher in the probiotic group, however, the incidence of NEC and mortality was similar between the two groups
Costeloe et al.[20]	2015	UK	Multi-center	Pros-pective	RCT	ELBW	1310	744	650	28 (26.1-29.4)	1039 (312)	Bifidobacterium breve BBG-001	once/day; 1st milk feed-36 weeks' postmenstrual age	660	28 (26.1-29.6)	1043 (317)	Placebo	once/day; 1st milk feed-36 weeks' postmenstrual age	No significant events were noticed following the administration of the probiotic
Havranek et al.[21]	2013	USA	Multi-center	Pros-pective	RCT	ELBW	31		15	25.9 (1.3)	856 (105)	Lactobacillus rhamnosus and Bifidobacterium infantis	once/day; 1st milk feed-34 weeks' postmenstrual age	16	25.9 (1.5)	789 (129)	Placebo	once/day; 1st milk feed-34 weeks' postmenstrual age	Probiotics significantly increase the postprandial intestinal blood flow. No significant differences were noticed in NEC, mortality, or sepsis.
Jacobs et al.[22]	2013	Australia	Multi-center	Pros-pective	RCT	ELBW	1099	572	548	27.9 (2)	1063 (259)	Bifidobacterium spp. and Streptococcus spp.	once/day; 1st milk feed-dischrage	551	27.8 (2)	1048 (260)	Placebo	once/day; 1st milk feed-discharge	In ELBW infants, no significant differences were noticed in terms of NEC and mortality
Spreckels et al.[28]	2021	Sweden	Single center	Pros-pective	RCT	ELBW	56	24	48	25.4 (1.3)	728 (130)	Lactobacillus reuteri	once/day; 1st milk feed-36 weeks' postmenstrual age	8	25.8 (1.1)	702 (142)	Placebo	once/day; 1st milk feed-36 weeks' postmenstrual age	Higher rates of bacterial colonization and better head growth were noticed in the probiotics group more than the placebo one with no significant differences in terms of severe morbidities.
Oncel et al.[23]	2013	Turkey	Single-center	Pros-pective	RCT	ELBW	196	-	93	-	-	Lactobacillus reuteri	once/day; 1st milk feed-discharge	103	-	-	Placebo	once/day; 1st milk feed-discharge	No significant differences were noticed in terms of mortality or NEC, while sepsis was significantly more in the placebo group
Martí et al.[29]	2021	Sweden	Multi-center	Pros-pective	RCT	ELBW	134	58	54	25.5 (1.3)	727.5 (172.2)	Lactobacillus reuteri	once/day; 1st milk feed-36 weeks' postmenstrual age	54	25.5 (1.3)	763 (197.8)	Placebo	once/day; 1st milk feed-36 weeks' postmenstrual age	No significant differences were noticed in terms of mortality or NEC, while head growth was significantly better in the probiotics group

Reference	Year	Country	Settings	Data colle-ction	Study design	Popul ation	Sample size	Male (n)	Interventions										Author conclusion
									Probiotic group					Control group					
									n	**Gestational age** (weeks)	**Birth weight** (g)	**Used probiotic (s)**	**Routine**	**n**	**Gestational age** (weeks)	**Birth weight** (g)	**Intervention**	**Routine**	
Roy et al.[24]	2014	India	Single-center	Prospective	RCT	ELBW	22	-	11	-	-	Lactobacillus acidophilus, B. longum, B. bifidum, and B. lactis	From 72 hours after birth until 6 weeks or until discharge	11			Placebo	From 72 hours after birth until 6 weeks or until discharge	No significant differences were noticed in terms of NEC, but the duration of hospitalization was longer in the control group
Tewari et al.[25]	2015	India	Single center	Prospective	RCT	ELBW	120	63	61	-	-	Bacillus clausii	3 times/day, From 72 hours after birth until 6 weeks or until discharge or death	59	-	-	Placebo	3 times/day, From 72 hours after birth until 6 weeks or until discharge or death	No significant differences were noticed in terms of NEC, and late-onset sepsis
Wang et al.[26]	2007	Japan	Single center	Prospective	RCT	ELBW	22	12	11	28.4 (2.4)	788 (125)	Bifidobacterium breve	2 times/day, since birth until hospital discharge	11	26.2 (3.6)	717 (149)	Placebo	2 times/day, from birth until hospital discharge	No NEC events were noticed in both groups
Wejryd et al.[27]	2018	Sweden	Single center	Prospective	RCT	ELBW	134	74	68	25.2 (1.2)	731 (129)	Lactobacillus reuteri	once/day; 1st milk feed-36 weeks' postmenstrual age	66	25.5 (1.3)	740 (148)	Placebo	once/day; 1st milk feed-36 weeks' postmenstrual age	Better head growth was significant in the probiotics group and no significant difference was noticed in the rate of NEC between the two groups.

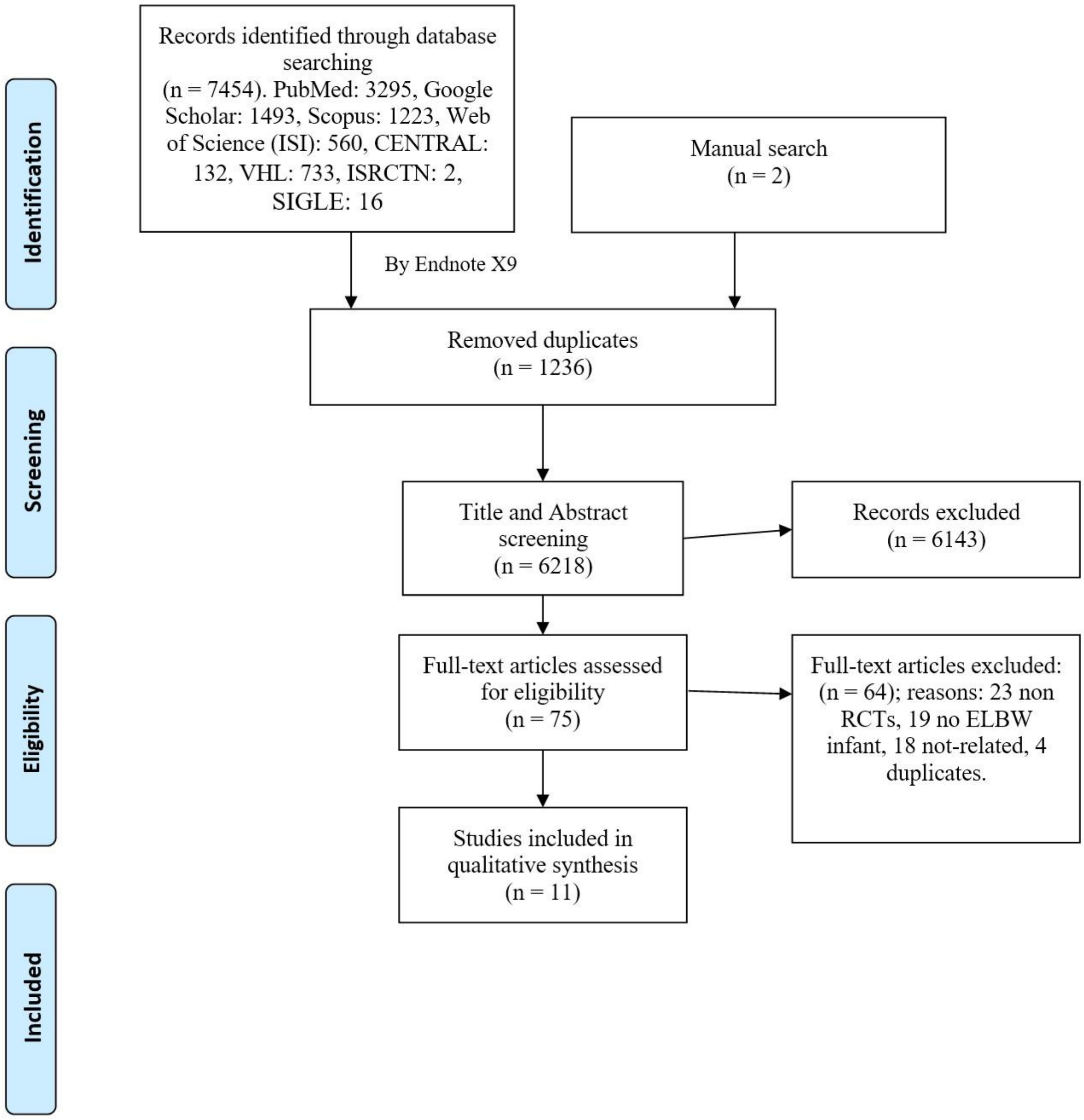

Fig. 1. Our PRISMA flow chart for the search strategy

(Probiotics: 27/235, Control: 28/239) after the administration of Bifidobacterium spp. And Streptococcus spp. However, it should be noted that the authors reported that the incidence of NEC was significantly lower in the probiotics group than in the control group in their overall population of VLBW infants. However, the differences between the two groups in the rates of sepsis and mortality were also non-significant.The previous single-center investigation by Oncel et al. [23] reported that no significant differences were noticed between the group that received the Lactobacillus reuteri and the placebo group in terms of mortality (Probiotics: 16.1%, Control: 23.3%, p-value= 0.14) and NEC (Probiotics: 5.4%, Control: 8.7%, p-value= 0.26). On the other hand, the authors reported that the incidence of proven sepsis was significantly higher in the placebo group in their population of ELBW infants (Probiotics: 16.5%, Control: 18.4%, p-value= 0.01). In India, Roy et al. [24]also indicated that the NEC rates among the placebo and control groups in ELBW infants were similar (Probiotics: 1/11, Control: 1/11). On the other hand, it has been demonstrated that the duration of hospitalization was significantly longer in the control than in the probiotics group (Probiotics: 28.78±9.16, Control: 34.21±11.68 days, p-value= 0.004). The other investigation that was also conducted in India by Tewari et al. [25], that investigated the impact of the administration of Bacillus clausii probiotic, also reported that no significant differences were noticed between the two groups in terms of mortality (Probiotics: 8/61, Control: 9/59) and developing NEC (Probiotics: 0/61, Control: 0/59). Furthermore, no significant differences were noticed in terms of preventing or reducing the incidence of late-onset sepsis between the two groups.

Fig. 2. Risk of bias graph (A) Overall summary (B) for the individual studies

A previous trial in Japan was also conducted by Wang et al. [26]that investigated the effect of using Bifidobacterium breve on the frequency and rates of fatty acids and their impact on the intervention of some colon-related diseases, including NEC. It has been demonstrated that among the two groups of ELBW infants, no events of NEC were noticed between the two groups. However, significantly favorable effects of short-chain fatty acids and lactic acid were noticed in the probiotics group. The previous trial that was conducted in Sweden by Wejryd et al. [27] also demonstrated that the differences between the group that administered Lactobacillus reuteri as their intervention and the placebo group were not significant in terms of NEC rates (Probiotics: 7/68, Control: 8/66). On the other hand, it has been reported that the favorable effect of using probiotics for the included ELBW infants was significant in terms of better head growth than the placebo group. The most recent Cochrane meta-analysis that analyzed the findings of investigations that compared the rates of NEC and mortality between the probiotics and the placebo groups including only ELBW infants, showed that the pooled analysis indicated that no significant differences were noticed between the two groups in terms of NEC and mortality for ELBW infants. Furthermore, the authors also indicated that no significant differences were noticed between the two groups in terms of the rates of developing invasive infections [3]. Accordingly, it has been concluded that probiotics administration did not have a significant association between the NEC development and mortality.

In 2021, another investigation in Sweden was also conducted by Spreckels et al. [28] reported that the administration of Lactobacillus reuteri was associated with higher rates of bacterial colonization and better head growth in their ELBW infantile population as compared to the placebo group. Thus, this can potentially reduce the incidence of NEC. It should be noted that the rates of severe morbidities and the length and weight growth rates were similar between the two groups, with no significant differences were reported. Another trial in 2021 was also reported by Martí et al. [29] where the authors indicated that no significant differences were noticed between the probiotics and placebo groups in terms of NEC (Probiotics: 7/54, Control: 8/54) and sepsis (Probiotics: 25/54, Control: 23/54). However, it should be noted that better head growth rates were more significant in the probiotics than in the control groups.

Our study is limited by the small number of the included trials, which might not be adequate to compare between the different probiotics and included populations in this systematic review and adds to significant heterogeneity in the reported outcomes. Accordingly, the current findings should be interpreted with caution until further evidence with proper sampling and study designs have been provided in the literature.

5. CONCLUSION

The results of this systematic review discuss the impact of probiotics administration in ELBW infants and the effect on the incidence of NEC and mortality. Our results indicate that the administration of these modalities does not have a significant impact on these outcomes. However, it has been reported that they enhance the growth rate, especially head growth circumference, which has been reported to be superior to the placebo effect. Therefore, further investigations for ELBW should be encouraged to furtherly validate these modalities, although no adverse events have been reported for their administration among trials in the current systematic review. Further studies exploring the efficiacy of probiotics should be persuaded on a national level by the Ministry of Health to determine the impact of it on the targeted group.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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