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

Mohammed Khalid Harasani¹, Sarah Abdulrahman Almosaiteer², Faisal Saleh Aloraini³, Saleh Khalid Aldakhil³, Jamilah Sulaiman Alsaiairi⁴, Abdulrahman Muhaidib Almuhaidib³, Omar Muhaidib Almuhaidib³, Mohammed Alia Alisi³, Othman Majed Alothman³, Thamer Saleh Alanazi³ and Asalah Tariq Alsigh⁵

¹Department of Pediatrics, Al Aziziyah Children Hospital, Jeddah, Saudi Arabia.
²College of Medicine, Qassim University, Qassim, Saudi Arabia.
³College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.
⁴College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia.
⁵College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia.

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...
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; necrotizing 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 review is done according to the 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* OR Fructo- oligosaccharide* OR FOS OR FOSs OR galacto- oligosaccharide* OR lactooligosaccharide* OR Lactoferrin [Mesh] OR Lactoferrin* OR Lactulose* OR Lactulose [Mesh] OR Synbiotics [Mesh] OR Synbiotic*) AND (prematurity OR premature 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]).

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 (Probio: 9%, Control: 10%), sepsis (Probio: 11%, Control: 12%), and deaths (Probio: 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 Bifidobacterium infantis 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 (Probio: 0/15, Control: 1/16), sepsis (Probio: 0/15, Control: 3/16), and deaths (Probio: 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 (Probio: 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 collection | Study design | Population | Sample size | Male (n) | Probiotic group | Interventions | Control group | Intervention | Routine | Author conclusion |
|--------------------|------|---------|--------------|----------------|--------------|------------|------------|----------|-----------------|---------------|---------------|--------------|---------|-------------------|
| Al-Hosri et al.    | 2012 | USA     | Multi-center | Prospective    | RCT          | ELBW       | 101        | 50       | 50              | 25.7 (1.4)     | 778 (138)    | Placebo     | once/day; 1st milk-feed 34 weeks' postmenstrual age | n | Gestational age (weeks) | Birth weight (g) | Used probiotic (s) | Routine | n | Gestational age (weeks) | Birth weight (g) | Interventions | Route |
| Costeloe et al.    | 2015 | UK      | Multi-center | Prospective    | RCT          | ELBW       | 1310       | 744      | 650              | 28 (26.1-29.4) | 1039 (312)   | Placebo     | once/day; 1st milk-feed 36 weeks' postmenstrual age | 51 | 25.7 (1.4)     | 779 (126)    | Lactobacillus spp. and Bifidobacterium spp. | Random | 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.    | 2013 | USA     | Multi-center | Prospective    | RCT          | ELBW       | 31         | 15       | 15              | 25.9 (1.3)     | 856 (105)    | Placebo     | once/day; 1st milk-feed 34 weeks' postmenstrual age | 16 | 25.9 (1.5)     | 789 (129)    | Lactobacillus rhamnosus and Bifidobacterium infantis | Random | 25.8 (1.1)     | 702 (142)    | 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.      | 2013 | Australia | Multi-center | Prospective    | RCT          | ELBW       | 1099       | 572      | 548              | 27.9 (2)       | 1063 (259)   | Placebo     | once/day; 1st milk-feed 34 weeks' postmenstrual age | 551 | 27.8 (2)       | 1048 (260)   | Lactobacillus spp. and Streptococcus spp. | Random | 25.8 (1.1)     | 702 (142)    | Placebo | once/day; 1st milk-feed discharge | In ELBW infants, no significant differences were noticed in terms of NEC and mortality |
| Spreckels et al.   | 2021 | Sweden  | Single-center | Prospective    | RCT          | ELBW       | 56         | 24       | 48              | 25.4 (1.3)     | 728 (130)    | Placebo     | once/day; 1st milk-feed discharge | 8  | 25.8 (1.1)     | 702 (142)    | Lactobacillus reuteri | Random | 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.       | 2013 | Turkey  | Single-center | Prospective    | RCT          | ELBW       | 196        | -        | 93              | -             | -             | Placebo     | once/day; 1st milk-feed discharge | 103 | -             | -             | Lactobacillus reuteri | Random | -           | -             | 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 |
| Mati et al.        | 2021 | Sweden  | Multi-center | Prospective    | RCT          | ELBW       | 194        | 58       | 54              | 25.5 (1.3)     | 727.5 (172.2)| Placebo     | once/day; 1st milk-feed 36 weeks' postmenstrual age | 54 | 25.6 (1.3)     | 763 (197, 8) | Lactobacillus reuteri | Random | 25.6 (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 | Study design | Popul ation | Sample size | Male (n) | Probiotic group | Interventions | Control group | Routine | Male (n) | Gestational age (weeks) | Birth weight (g) | Birth weight (g) | Intervention | Placebo | Routine | Routine |
|------------|------|---------|----------|--------------|-------------|-------------|----------|----------------|--------------|--------------|---------|----------|-----------------------|----------------|----------------|-------------|---------|---------|---------|
| Roy et al. [24] | 2014 | India   | Single-center | Prospective RCT | ELBW | 22 | - | 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 | 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 | Bifidobacterium breve | 2 times/day, since birth until hospital discharge | 11 | 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 | Lactobacillus reuteri | once/day; 1st milk feed 36 weeks' postmenstrual age | 66 | 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 efficacy 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.

REFERENCES

1. Ehrenkranz RA, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics, 2006;117(4): 1253-61.
2. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014;(4):Cd005496.
3. Sharif S, et al. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2020; 10(10):Cd005496.

4. Stoltz Sjöström E, et al. Nutrient intakes independently affect growth in extremely preterm infants: results from a population-based study. Acta Paediatr. 2013; 102(11):1067-74.

5. Hansen-Pupp I, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatr Res. 2011;69(5 Pt 1):448-53.

6. Franz AR, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics. 2009;123(1):e101-9.

7. De Angelis M, et al. The food-gut-human axis: The effects of diet on gut microbiota and metabolome. Curr Med Chem. 2019;26(19):3567-3583.

8. Heijtz RD, et al. Normal gut microbiota modulates brain development and behavior. Proceedings of the National Academy of Sciences. 2011;108(7):3047-3052.

9. Buffington SA, et al. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell. 2016;165(7):1762-1775.

10. Hsiao EY, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013;155(7):1451-1463.

11. Khurshid M, et al. Bacterial munch for infants: Potential pediatric therapeutic interventions of probiotics. Future Microbiology. 2015;10.

12. Abrahamsson TR, et al. The time for a confirmative necrotic enterocolitis prophylactic intervention trial in the extremely low birth weight infant in North America is now! J Pediatr. 2014; 165(2):389-94.

13. Wu RY, et al. Spatiotemporal maps reveal regional differences in the effects on gut motility for Lactobacillus reuteri and rhamnosus strains. Neurogastroenterol Motil. 2013;25(3):e205-14.

14. Indrio F, et al. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. J Pediatr. 2008;152(6):801-6.

15. Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Plos Medicine. 2009;6(7):28.

16. Mahmoud AR, et al. Association between sarcoidosis and cardiovascular comorbidity: A systematic review and meta-analysis. Heart Lung. 2020; 49(5):512-517.

17. El-Qushayri AE, et al. The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: A systematic review and meta-analysis. Rev Med Virol. 2021;e2278.

18. Higgins JP, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343.

19. Al-Hosni M, et al. Probiotics-supplemented feeding in extremely low-birth-weight infants. Journal of Perinatology. 2012; 32(4):253-259.

20. Costeloe K, et al. Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. The Lancet. 2016;387(10019):649-660.

21. Havranek T, Al-Hosni M, Armbrecht E. Probiotics supplementation increases intestinal blood flow velocity in extremely low birth weight preterm infants. Journal of Perinatology. 2013;33(1): 40-44.

22. Jacobs SE, et al. Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. Pediatrics. 2013;132(6):1055-1062.

23. Oncel MY, et al. Lactobacillus reuteri for the prevention of necrotising enterocolitis in very low birthweight infants: a randomised controlled trial. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2014;99(2):F110-F115.

24. Roy A, et al. Role of enteric supplementation of probiotics on late-onset sepsis by Candida species in preterm low birth weight neonates: a randomized, double blind, placebo-controlled trial. North American Journal of Medical Sciences. 2014;6(1):50.

25. Tewari VV, Dubey SK, Gupta G. Bacillus clausii for prevention of late-onset sepsis in preterm infants: a randomized controlled trial. Journal of Tropical Pediatrics. 2015;61(5):377-385.

26. Wang C, et al. Effects of oral administration of Bifidobacterium breve on fecal lactic acid and short-chain fatty acids in low birth weight infants. Journal of
27. Wejryd E, et al. Probiotics promoted head growth in extremely low birthweight infants in a double-blind placebo-controlled trial. Acta Paediatrica. 2019;108(1):62-69.

28. Spreckels JE, et al. Lactobacillus reuteri Colonisation of Extremely Preterm Infants in a Randomised Placebo-Controlled Trial. Microorganisms. 2021;9(5).

29. Martí M, et al. Effects of Lactobacillus reuteri supplementation on the gut microbiota in extremely preterm infants in a randomized placebo-controlled trial. Cell Rep Med. 2021;2(3):100206.