Supplementation of Infant Formula With Probiotics and/or Prebiotics: A Systematic Review and Comment by the ESPGHAN Committee on Nutrition

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ABSTRACT

Infant formulae are increasingly supplemented with probiotics, prebiotics, or synbiotics despite uncertainties regarding their efficacy. The present article, developed by the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition, systematically reviews published evidence related to the safety and health effects of the administration of formulae supplemented with probiotics and/or prebiotics compared with unsupplemented formulae. Studies in which probiotics/prebiotics were not administered during the manufacturing process, but thereafter, for example in capsules, the contents of which were supplemented to infant formula or feeds, were excluded. On the basis of this review, available scientific data suggest that the administration of currently evaluated probiotic- and/or prebiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects. The safety and clinical effects of 1 product should not be extrapolated to other products. At present, there is insufficient data to recommend the routine use of probiotic- and/or prebiotic-supplemented formulae. The Committee considers that the supplementation of formula with probiotics and/or prebiotics is an important field of research. There is a need in this field for well-designed and carefully conducted randomised controlled trials, with relevant inclusion/exclusion criteria and adequate sample sizes. These studies should use validated clinical outcome measures to assess the effects of probiotic and/or prebiotic supplementation of formulae. Such trials should also define the optimal doses and intake durations, as well as provide more information about the long-term safety of probiotics and/or prebiotics. Because most of the trials were company funded, independent trials, preferentially financed jointly by national/governmental/European Union bodies and other international organisations, would be desirable.

Key Words: feeding, microbiota, modification, paediatric nutrition

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INTRODUCTION

Infant formulae are increasingly being supplemented with probiotics, prebiotics, or synbiotics despite uncertainties regarding their efficacy (1–4). Previously, 2 position papers related to this issue were published by the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. The first one, published in 2004, commented on probiotic bacteria (5). On the basis of the evidence obtained in a search up to July 2003, the Committee concluded that clinical trials have provided only limited data on the safety and clinical effects of adding probiotic preparations to infant formulae, follow-on formulae, and special medical foods. The Committee also concluded that there is no published evidence of any long-term clinical benefits of infant formula supplementation with probiotic bacteria. The second position paper, also published in 2004, commented on the addition of prebiotic oligosaccharides to infant and follow-on formulae (6). On the basis of evidence obtained in a search up to January 2004, the Committee concluded that only limited studies have evaluated the effects of the addition of prebiotic substances to dietetic products for infants. The Committee stated that although the administration of prebiotic oligosaccharides has the potential to increase the total number of bifidobacteria in faeces and may also soften stools, there is no published evidence of any clinical benefits of adding prebiotic oligosaccharides to dietetic products for infants. Of note, according to the Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae, fructooligosaccharides (FOS) and galactooligosaccharides (GOS) may be voluntarily added to infant formulae if their content does not exceed 0.8 g/100 mL of a combination of 90% oligogalactosyl-lactose and 10% high-molecular-weight oligofructosyl-saccharose. Other combinations and maximum levels of FOS and GOS may be used provided their suitability has been demonstrated through a systematic review of the available data related to the expected benefits and safety considerations (7).

A number of studies related to the use of probiotic-/prebiotic-supplemented products for infants have been published in recent years. Given this, and in conjunction with the interest on the part

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of caregivers, health care professionals, and regulatory bodies regarding the benefits and risks related to such supplementation, particularly in very young infants, the Committee decided to update and review the published evidence related to the safety and health effects of the administration of formulae supplemented with probiotics and/or prebiotics compared with unsupplemented formulae. The Committee considers that there are some major issues related to the addition of probiotic bacteria and/or prebiotics to dietetic products for infants. First, timing, that is, the administration often begins in early infancy, sometimes at birth when the gut microbiota is not fully established, and factors that influence microbiota may permanently affect the development of the ecosystem. Second, duration, that is, the daily administration of such products is often prolonged (several weeks or months). Last but not least, delivery is in the form of a specific matrix (infant formula) that could be the only source of feeding of an infant.

This document is intended for practitioners, researchers, and regulatory bodies. It also aims to identify needs for future research. This document replaces the earlier 2 position papers related to probiotics and prebiotics published in 2004 by the Committee.

MATERIALS AND METHODS

The Committee carried out a systematic review of randomised controlled trials (RCT) according to the guidelines from the Cochrane Collaboration. Only studies that compared use of infant formula or follow-on formula supplemented with probiotics and/or prebiotics during the manufacturing process were included. Studies in which probiotics/prebiotics were not administered during the manufacturing process, but thereafter, for example in capsules, the contents of which were supplemented to infant formula or feeds, were excluded. For full details, as well as definitions of probiotics and prebiotics, see additional Methods information at *http://links.lww.com/MPG/A33*.

PROBIOTICS

Description of Studies Included in the Review

Twenty publications met the inclusion criteria for this systematic review (8–27). See Table 1 at *http://links.lww.com/MPG/A33*, which summarises characteristics of the included trials, and Table 2 *http://links.lww.com/MPG/A33*, which summarises characteristics of the excluded trials, including the reasons for exclusion. The quality of the included RCT varied (Table 3 at *http://links.lww.com/MPG/A33*). Almost all of the included trials had a number of methodological limitations. The most common problems were a lack of description of randomisation procedures and/or allocation concealment.

All of the studies were carried out in healthy term infants. Two RCT (23,24) were performed in healthy infants born to HIV-infected mothers. In most of the included trials, the investigators used a standard infant or follow-on formula. In 1 RCT (23), an acidified formula was used. In another RCT (24), both a chemically acidified formula and a biologically acidified formula were used. The studies varied in the types of probiotics used. The most commonly studied probiotic was *Bifidobacterium animalis* ssp *lactis* CNCMI-3446 (previously known as *B bifidum* or *B lactis* Bb12 but subjected to reclassification (28 [hereafter referred to as *B lactis*]); this probiotic was administered either alone (8,9,18,19,23,24,26,27), in combination with *Streptococcus thermophilus* (13,18–21), or in combination with *S thermophilus* and *Lactobacillus helveticus* (11,15). Other probiotics studied are as follows: *L acidophilus johnsonii* La1 (10,14); *B longum* BL999 (BL999) and *L rhamnosus* LPR (LPR) (12), *L rhamnosus* GG (LGG) (25), *L reuteri* ATCC 55730 (26,27), and *L salivarius* CECT5713 (17). Only some RCT reported characterisation of probiotics provided in infant formulae by referring to the culture collections and strain number. The doses of probiotics varied considerably. Doses ranged from 1×10^7 colony-forming units (CFU)/g (25–27) to 10^8 CFU/g (14,39) to 6×10^9 CFU/100 mL (8,9) for single probiotics; the dose was 10^6 CFU/g (11,15) for a combination of probiotics. The supplementation periods varied from 15 days (13) to 8 months (19). A number of RCT described the same study population but reported different outcome measures (eg, 8 and 9; 16 and 22; 18 and 19). One study reported in 2 publications was a cluster RCT (18,19). Another study (20) had 3 arms comparing 2 doses of *B lactis* and *S thermophilus* with placebo. A number of studies had >2 arms comparing different probiotics (18,19,26,27).

Summary of Reported Results

ADMINISTRATION OF PROBIOTIC-SUPPLEMENTED FORMULA STARTED IN INFANTS ≤4 MONTHS OF AGE (OR ≤6 MONTHS OF AGE PROVIDED THAT THEY HAVE NOT STARTED COMPLEMENTARY FEEDING) AND CONTINUED FOR AT LEAST 2 WEEKS (Table 4 at *http://links.lww.com/MPG/A33*)

Growth

B lactis

The impact of *B lactis* administration on weight and growth was studied in 3 trials (23,24,27). Two of those trials (23,24) were carried out in healthy infants of HIV-positive mothers and assessed growth parameters in infants fed with formula supplemented with *B lactis* since birth. Urban et al (23) reported that healthy infants of HIV-positive mothers who received the acidified formula with *B lactis* compared with the controls who received the acidified formula without probiotics had more rapid head growth (mean difference 0.05 ± 0.03 mm/day; $P = 0.04$); however, there was no significant difference in weight gain and length gain between groups ($P = 0.06$ and $P = 0.24$, respectively) during the first 4 months of life. In addition, no differences between groups were found for weight for age, length for age, or head circumference, suggesting that the changes in head circumference during the intervention did not have a real significance. In a similar population of infants born to HIV-positive mothers, Velaphi et al (24) reported that there was an increase in *z* scores for all of the studied formulae (including the chemically acidified probiotic-supplemented formula); there were no differences in weight for age ($P = 0.22$), length for age ($P = 0.56$), head circumference for age ($P = 0.66$), or weight for length ($P = 0.13$) among groups who received the different study formulae. The third study that evaluated the effect of *B lactis* supplementation of formula on growth revealed no significant differences between the *B lactis*–supplemented formula group and the unsupplemented formula group with regard to growth parameters (27). However, the Committee noted a small number of participants, a short follow-up period, and inappropriate statistical methodology in the present study.

B bifidum and S thermophilus and L helveticus

The impact of *B bifidum* + *S thermophilus* + *L helveticus* administration on weight was studied in 1 RCT (15). In the present study, *B bifidum* was added to an infant formula that had been biologically acidified by *S thermophilus* and *L helveticus*. Anthropometric data consisting of weight, length, and head circumference were recorded at birth, 1 month, and 2 months; however, no data on growth were presented in the study. The authors reported normal

growth during the first 2 months of life without any significant differences in growth between infants in the probiotic-supplemented formula and unsupplemented formula groups. However, there was no information on how this conclusion was reached. The Committee noted that the study was too small with insufficient power to identify relevant effects on growth.

B longum BL999 and L rhamnosus LPR

One RCT (12) evaluated the effects and tolerance (assessed as weight gain) of several formulae containing probiotics and prebiotics, including 1 formula that contained BL999 and LPR. The authors reported equivalent weight gain in the study and control groups in both the intention-to-treat and per-protocol analyses.

LGG

One study (25) demonstrated that infants who received an LGG-supplemented formula for 6 months grew better. Changes in length and weight standard deviation scores (ΔSDS) at the end of the study were significantly higher in the supplemented group compared with infants who received regular formula (0.44 ± 0.37 vs 0.07 ± 0.06, $P < 0.01$ and 0.44 ± 0.19 vs 0.07 ± 0.06, $P < 0.005$, respectively).

L reuteri ATCC 55730

Weizman and Alsheikh (27) revealed no significant differences in growth parameters between the infants who received *L reuteri*–supplemented formula compared with unsupplemented formula. However, the Committee noted a small number of participants, a short follow-up period, and inappropriate statistical methodology in this study.

Summary and interpretation of data on growth
The Committee notes that interpreting studies on the effects of probiotic supplementation of infant formula on growth is difficult due to the limited number of studies that analysed the effects of a given probiotic strain; the studies were often too small with insufficient power to identify relevant effects on growth, and the follow-up periods in the trials were short. In general, for a few probiotic strains that were used to supplement infant formula, it can be concluded that these strains support normal growth in healthy term infants.

Gastrointestinal Infections

B lactis

One RCT (24) reported no significant difference in the frequency of gastroenteritis between infants fed with chemically acidified formula supplemented with *B lactis* CNCM I-3446 and infants fed with the standard formula. However, there were only 4 infants who developed gastroenteritis. In addition, the study was not powered to assess this effect.

B longum BL999 and L rhamnosus LPR

One RCT (12) demonstrated that infants who received a formula supplemented with BL999 and LPR compared with a control formula had similar incidences of diarrhoea during the intervention period (4/64 vs 3/59, respectively; relative risk [RR] 1.2, 95% confidence interval [CI] 0.3–4.8). However, the incidence of diarrhoea was lower in the probiotics group than in the control group during the postintervention observational period [5/37 vs 13/30, respectively; RR 0.3, 95% CI 0.12–0.7]. It must be noted that the latter observation was made in a subgroup (67/123, ie, 54.5%) of the originally randomised subjects.

Summary and interpretation of data on gastrointestinal infections
Limited available evidence shows that formula supplementation with the probiotics studied (ie, *B lactis*; BL999 and LPR) does not reduce the risk of gastrointestinal infections. However, the Committee considers that there is too much uncertainty to draw reliable conclusions from the available data.

Respiratory Symptoms

B lactis

One RCT (24) found no significant difference in the rate of bronchopneumonia between infants fed with chemically acidified formula supplemented with *B lactis* CNCM I-3446 and infants fed with standard formula (3/18 vs 4/18, respectively; RR 0.75, 95% CI 0.2–2.6).

Summary and interpretation of data on respiratory infections
Limited available evidence shows that formula supplementation with *B lactis* does not reduce the risk of respiratory infections. However, the Committee considers that there is too much uncertainty to draw reliable conclusions from the available data.

Antibiotic Use

B longum BL999 and L rhamnosus LPR

One RCT (12) found no difference in the rate of antibiotic use between 37 infants whose formula was supplemented with BL999 and LPR and 30 infants who received the control formula (RR 0.8, 95% CI 0.05–12).

Summary and interpretation of data on antibiotic use
Limited available evidence suggests that probiotic supplementation of formula with BL999 and LPR is not associated with a reduced use of antibiotics. However, the Committee considers that there is still too much uncertainty to draw reliable conclusions from the results.

Colic, Crying, Irritability

B lactis

One RCT (27) found no significant difference between the *B lactis*–supplemented formula group and the control formula group in either the daily crying score on a 1 to 4 scale ($P = 0.58$) or the number of daily crying episodes ($P = 0.62$).

B longum BL999 and L rhamnosus LPR

One RCT (12) reported no significant difference in the frequency of colic between the probiotics-supplemented formula group and the control formula group ($P > 0.1$; data not shown).

L reuteri ATCC 55730

One RCT (27) found no significant difference between the *L reuteri*–supplemented formula group and the control formula group in either the daily crying score on a 1 to 4 scale ($P = 0.58$) or the number of daily crying episodes ($P = 0.62$).

LGG

One RCT (25) found no significant difference between the LGG-supplemented formula group and the placebo group in crying behaviour (sum of hours in study period 6.2 ± 1.8 vs 6.1 ± 1.4, respectively).

Summary and interpretation of data on colic/irritability
The administration of *B lactis*, BL999 and LPR, *L reuteri,* or LGG was not associated with a lower frequency of colic, crying, or irritability. However, the Committee considers that there is too much uncertainty to draw reliable conclusions from the available data.

Allergy

B longum BL999 and L rhamnosus LPR

One RCT (22) found no difference in the rates of eczema and allergen sensitisation (positive skin-prick test against food and inhalant allergens) between the BL999 and LPR-supplemented formula group and the control formula group (RR 0.9, 95% CI 0.55–1.4, and RR 1.2, 95% CI 0.8–2.1, respectively).

Summary and interpretation of data on allergy
Limited data available suggest no effect of the probiotics studied (BL999 and LPR) on allergy. However, the Committee considers that there is too much uncertainty to draw reliable conclusions from the available data.

Stool Frequency

LGG

One RCT (25) found that the LGG-supplemented formula group had a significantly higher defecation frequency than the control formula group (9.1 ± 2.6 vs 8.0 ± 2.8, respectively; $P < 0.05$).

B lactis

The administration of *B lactis* was not associated with a change in stool frequency (8,24).

B longum BL999 and L rhamnosus LPR

The administration of BL999 and LPR was not associated with a change in stool frequency (12).

Summary and interpretation of data on stool frequency
Limited available data suggest that LGG, but not *B lactis* or BL999 and LPR, administration had a modest, statistically significant effect on stool frequency. However, the clinical significance of this effect is unclear.

Stool Consistency

LGG

One RCT (25) found that the LGG-supplemented formula group had significantly greater summative indexes of loose stools than the control formula group (9.5 ± 1.2 vs 10.2 ± 1.7, respectively; $P < 0.05$).

B lactis or L reuteri ATCC 55730

The administration of *B lactis* or *L reuteri* was not associated with a change in stool consistency (27).

B longum BL999 and L rhamnosus LPR

The administration of BL999 and LPR was not associated with a change in stool consistency (13).

Summary and interpretation of data on stool consistency
Limited available data suggest that LGG, but not *B lactis* or *L reuteri* ATCC 55730 or BL999 and LPR, administration had a modest, statistically significant effect on stool consistency. However, the clinical significance of this effect is unclear.

Nonclinical Outcomes

See Table 4 at *http://links.lww.com/MPG/A33*.

Summary and interpretation of data on nonclinical outcomes
Probiotic supplementation of infant formula has the potential to affect a number of nonclinical outcomes, such as gut microbiota composition and activity. However, the Committee notes that interpretation of these findings is difficult. Whether a change in any of these parameters per se is of benefit to the infants is currently not established.

ADMINISTRATION OF PROBIOTIC-SUPPLEMENTED INFANT OR FOLLOW-ON FORMULA AT ANY OTHER AGE BEYOND EARLY INFANCY AND REGARDLESS OF THE DURATION OF THE INTERVENTION (Table 5 at *http://links.lww.com/MPG/A33*)

Growth

A number of studies have analysed the effects of administering probiotic-supplemented infant or follow-on formula on growth. The probiotics studied were *B lactis* (18,26), *B lactis* and *S thermophilus* (18,20,21), *B lactis* and *S thermophilus* and *L helveticus* (11), *L johnsonii* La1 (10), *L reuteri* ATCC 55730 (26), and *L salivarius* CECT5713 (17). Except for 1 RCT (18), all of the trials reported adequate growth with no significant differences between the probiotic and control groups. The only RCT (18) with different results reported that the 2 groups that received probiotics (*B lactis* and *B lactis* and *S thermophilus*) had a significantly greater length velocity towards the end of the intervention than did the control group ($P < 0.05$). The difference was equal to about 0.5 SD. However, the Committee noted important deficiencies in the quality of evidence, with a large age range from 6 to 36 months. Because growth velocity and regulation of growth are different in young infants and toddlers, it is impossible to conclude that probiotics induced better growth.

Summary and interpretation of data on growth
Limited available evidence suggests that the probiotic supplementation of formula beyond early infancy is associated with adequate growth.

Gastrointestinal Infections

B lactis

Two studies provided data regarding the frequency of gastrointestinal infections (19,26). One cluster RCT (19) reported a statistically significant increase in the incidence of diarrhoea in the probiotic-supplemented formula group compared with the unsupplemented formula group (RR 2.6, 95% CI 1.6–4.4). Weizman et al (26) reported a significant reduction in the number of days with diarrhoea during the study period in the *B lactis*–supplemented formula group compared with the control formula group (0.37, 95% CI 0.08–0.66 vs 0.59, 95% CI 0.34–0.84, respectively; $P < 0.001$), as well as a significant reduction in the number of episodes of diarrhoea (0.13, 95% CI 0.05–0.21 vs 0.31, 95% CI 0.22–0.4; $P < 0.001$).

B lactis and S thermophilus

Four studies compared the effects of formula supplemented with *B lactis and S thermophilus* with unsupplemented formula on gastrointestinal infections (13,19–21). Two of these studies (13,20) reported a significant reduction in the risk of gastrointestinal infections in the *B lactis and S thermophilus*–supplemented formula group compared with the control formula group, whereas 1 cluster RCT of questionable methodological quality (19) reported a contradictory result.

One RCT (21) reported no significant difference between the probiotic and control groups in the number of episodes of loose or watery stools and in the number of episodes of emesis or fever with loose or watery stools.

B lactis and S thermophilus and L helveticus

One RCT (11) found no significant differences between the probiotics-supplemented and -nonsupplemented groups in the percentage of children with diarrhoea (RR 0.73, 95% CI 0.4–1.32), the number of episodes of diarrhoea per infant lasting not >7 days (0.4 ± 0.9 vs 0.5 ± 0.8, respectively; NS), the mean number of stools per day (4 ± 1.6 vs 3.9 ± 1.3, respectively; NS), and the mean cumulative duration of episodes of diarrhoea (5.1 ± 3.3 days vs 7 ± 5.5 days, respectively; NS). However, the authors of this trial reported that administration of the probiotics-supplemented formula compared with the control formula resulted in a significant reduction in the mean number of days with diarrhoea (1.15 ± 2.5 vs 2.3 ± 4.5 days, respectively; $P = 0.0002$), the daily probability of diarrhoea (0.84 vs 1.55, respectively; $P = 0.0014$), and the number of days with diarrhoea per child-year (3.06 vs 5.67, respectively; $P = 0.0002$).

The pooled results of 4 RCT (11,13,19,20) involving the administration of infant formula supplemented with *B lactis* and *S thermophilus* (single or in combination) revealed no significant difference in the rate of diarrhoea between the probiotic and control groups (4 RCT, n = 477; RR 0.76, 95% CI 0.31–1.89; random effect model). However, significant heterogeneity was found ($\chi^2 = 22.2$, $P < 0.0001$; $I^2 = 86\%$). Inspection of the results indicated that the source of heterogeneity was likely to be caused by 1 cluster RCT of questionable methodological quality (19). When this study was excluded from analysis, the reduction in the risk of gastrointestinal infections was significant and no heterogeneity was found (3 RCT, n = 302, RR 0.54, 95% CI 0.36–0.81; $\chi^2 = 2.40$, $P = 0.30$; $I^2 = 17\%$) (Figure 1 at *http://links.lww.com/MPG/A33*).

L johnsonii La1

One study (10) revealed no difference in the number of diarrhoeal episodes between the group of infants who received formula supplemented with *L johnsonii* La1 and the control formula group.

L reuteri ATCC 55730

One RCT (26) reported a significant reduction in the number of days with diarrhoea in the *L reuteri*–supplemented formula group compared with the control formula group (0.15, 95% CI 0.12–0.18 vs 0.59, 95% CI 0.34–0.84, respectively; $P < 0.001$), as well as a significant reduction in the number of episodes of diarrhoea (0.02, 95% CI 0.01–0.05 vs 0.31, 95% CI 0.22–0.4; $P < 0.001$).

L salivarius CECT5713

One RCT (17) reported a significant reduction in the rate of diarrhoea in the *L salivarius*–supplemented formula group compared with the control formula group (7/40 vs 26/40, $P < 0.05$).

Summary and interpretation of data on gastrointestinal infections
There is some evidence from the pooled trials to suggest that supplementation of infant formula with *B lactis* (single or in combination) is associated with a reduction in the risk of nonspecific gastrointestinal infections in children. Data related to other probiotics studied (ie, *L reuteri* ATCC 55730, *L johnsonii* La1, *L salivarius* CECT5713), whether positive or negative, are too limited to allow conclusions to be drawn.

Respiratory Symptoms

B lactis

One RCT (26) reported no significant difference in the number of days with respiratory illness in the *B lactis*–supplemented formula group compared with the control formula group (0.68, 95% CI 0.17–1.19 vs 0.60, 95% CI 0.31–0.89, respectively; $P = 0.169$), as well as no significant difference between groups in the number of respiratory illness episodes (0.25, 95% CI 0.15–0.35 vs 0.24, 95% CI 0.13–0.35; $P = 0.457$).

L reuteri ATCC 55730

One RCT (26) reported no significant difference in the number of days with respiratory illness in the *L reuteri*–supplemented formula group compared with the control formula group (0.38, 95% CI 0.10–0.66 vs 0.60, 95% CI 0.31–0.89, respectively; $P = 0.169$), as well as no significant difference between groups in the number of respiratory illness episodes (0.17, 95% CI 0.08–0.26 vs 0.24, 95% CI 0.13–0.35; $P = 0.457$).

L johnsonii La1

One RCT (10) reported no significant difference between the *L johnsonii* La1–supplemented formula group and the control formula group in the number of upper and lower respiratory infections (data not shown; $P > 0.05$).

L salivarius CECT5713

One RCT (17) reported a significant reduction in the number of episodes of respiratory infections in the *L salivarius*–supplemented formula group compared with the control formula group (36 vs 53, $P < 0.05$).

Summary and interpretation of data on respiratory infections
Limited available evidence from RCT showed that formula supplementation with the probiotics studied (ie, *B lactis*, *L reuteri* ATCC 55730, *L johnsonii* La1) is not associated with a reduction in the risk of respiratory infections. Data related to *L salivarius* are too limited to allow conclusions to be drawn.

Antibiotic Use

This outcome was evaluated in 2 RCT (21,26). One RCT (21) reported that compared with placebo, the administration of *B lactis* and *S thermophilus* significantly reduced the use of antibiotics. On the basis of the results of 1 RCT (26), the use of *L reuteri* ATCC 55730, but not *B lactis*, resulted in a significant decrease in the number of antibiotic prescriptions ($P = 0.037$).

Summary and interpretation of data on antibiotic use
Limited available evidence from RCT suggests that probiotic supplementation of formula with *B lactis* and *S thermophilus* or *L reuteri* ATCC 55730, but not with *B lactis*, is associated with a reduced use of antibiotics. The Committee considers that data are too limited to draw reliable conclusions from the results.

Colic, Crying, Irritability

B lactis

One RCT (27) found no significant difference between the *B lactis*–supplemented formula group and the control formula group in either the daily crying score on a 1 to 4 scale ($P = 0.58$) or the number of daily crying episodes ($P = 0.62$).

B lactis and S thermophilus

One RCT (21) reported that compared with placebo, *B lactis* and *S thermophilus* supplementation of formula, regardless of the studied dose, was associated with a lower frequency ($P < 0.001$) of colic or irritability (definition not given for either of them).

L reuteri ATCC 55730

One RCT (27) found no significant difference between the *L reuteri*–supplemented formula group and the control formula group in either the daily crying score on a 1 to 4 scale ($P = 0.58$) or the number of daily crying episodes ($P = 0.62$).

L salivarius CECT5713

One RCT (17) found no significant difference between the *L salivarius*–supplemented formula group and the control formula group in outcomes such as spitting up, night awakening, irritability, and severe crying.

Summary and interpretation of data on colic/irritability
One RCT found that the administration of *B lactis* and *S thermophilus,* regardless of the studied dose, was associated with a lower frequency of colic or irritability. No such effect was observed when *B lactis* alone or *L reuteri* ATCC 55730 or *L salivarius* were used. The Committee considers that data are too limited to draw reliable conclusions from the results.

Stool Consistency

Only 1 RCT (27) reported data related to stool consistency. The authors found no significant difference between the 2 groups that received the probiotics studied (*B lactis* or *L reuteri* ATCC 55730) and the control group in the stool consistency score.

Summary and interpretation of data on stool consistency
Limited available evidence suggests that the studied probiotics (ie, *B lactis, L reuteri* ATCC 55730) do not have an effect on stool consistency.

Nonclinical Outcomes

See Table 5 at *http://links.lww.com/MPG/A33*.

Summary and interpretation of data on nonclinical outcomes
Compared with controls, probiotic supplementation of formula beyond early infancy has the potential to affect a number of nonclinical outcomes. However, the Committee notes that interpretation of these findings is difficult. Whether a change in any of these parameters per se is of benefit to the infants is currently not established.

Adverse Events

Of the 20 trials included in this review, information on adverse effects was provided in only 10 trials (11–13,20–24,26,27). In those trials, probiotic supplementation with *B lactis* (single or in combination), BL999 and LPR, *L reuteri* ATCC 55730, and *L johnsonii* La1 was well tolerated, and no significant differences between the intervention and control groups were observed in regard to adverse effects. However, certain aspects of safety, such as D-lactic acidosis, have been only rarely studied. As stated earlier, studies in which probiotics were not administered during the manufacturing process but thereafter were excluded from the present review. However, in the context of this comment, observations made by some investigators in studies with probiotic administration during early life, such as higher rates of various airways symptoms in the probiotic-supplemented group (29–31), merit attention.

Summary and interpretation of data on adverse events
Limited available evidence from RCT shows that formula supplementation with the probiotics studied (ie, *B lactis* single or in combination, BL999 and LPR, *L reuteri* ATCC 55730, *L johnsonii* La1) was not associated with adverse outcomes.

HYDROLYSED FORMULA SUPPLEMENTED WITH PROBIOTICS

Only 1 RCT addressing this intervention was found (32). This study had 3 arms that compared the effects of an extensively hydrolysed casein formula, the same formula supplemented with LGG, and a partially hydrolysed 60% whey/40% casein formula supplemented with LGG on growth and tolerance in healthy term infants. No significant differences were found between the study groups with regard to growth rates from day 14 to day 30, 120, or 150. No relevant differences in formula tolerance, adverse events, or allergic and immune markers were demonstrated between groups.

Summary and interpretation of data on hydrolysed formula supplemented with probiotics
Limited available evidence suggests that the extensively and partially hydrolysed formulae supplemented with LGG support normal growth in healthy, term infants and are well tolerated and safe. However, the Committee considers that there is too much uncertainty to draw reliable conclusions from these results.

PREBIOTICS

Description of Studies Included in the Review

Twenty-three publications met our inclusion criteria (8–10,33–52). See Table 6 at *http://links.lww.com/MPG/A33*, which summarises characteristics of the included trials, and Table 7 (*http://links.lww.com/MPG/A33*), which summarises characteristics of the excluded trials, including the reasons for exclusion. The quality of the identified RCT varied (Table 3 at *http://links.lww.com/MPG/A33*). Almost all of the included trials had methodological limitations. The most common problems were a lack of description of randomisation procedures and/or allocation concealment.

All of the studies were carried out in healthy term infants. The studies varied in the types of prebiotics used. The most commonly studied prebiotic was a 9:1 mixture of short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) (8,9,33,40,41,43–48,50). Other prebiotics studied were GOS (10,36–38), acidic oligosaccharides (AOS) (42), GOS/FOS/AOS (42), oligofructose plus inulin (39), and polydextrose (PDX) plus GOS (with or without lactulose) (49,52). The doses of prebiotics ranged from 0.15 to 0.8 g/100 mL, and the duration of the intervention ranged from 2 weeks to 6 months. All but 2 RCT (10,39) reported the prebiotic supplementation of a standard infant formula. In these trials, prebiotics were used to supplement follow-on formula.

Some of these RCT were included in 2 published well-conducted systematic reviews of RCT (53,54). The first systematic review of RCT and quasi-RCT evaluated the effectiveness of prebiotic supplementation in full-term infants (53). The Cochrane Library, MEDLINE, EMBASE, and CINAHL databases were searched in January 2010, as well as proceedings of relevant conferences. No language restrictions were applied. To be included in the review, the supplementation should have started at or before 28 days of age and be continued for at least 2 weeks. At least 1 of the following outcome measures had to be evaluated: stool colony counts (bifidobacteria, lactobacilli, and pathogens), pH, consistency, frequency, anthropometry, and symptoms of intolerance. This systematic review included 11 trials involving 1459 infants, which were reported in 13 publications, 1 of which was an abstract (8,9,33,36,38,40–42,46–48,52,55). The second systematic review, the Cochrane Review (56) published in 2007 (search date February 2007), was aimed at determining the effect of different prebiotics (GOS/FOS, only FOS, GOS together with PDX and lactulose) on the prevention of allergic disease or food hypersensitivity in infants. This systematic review included 7 trials (10,36,42,48,52,57,58). Two of the included RCT reported on allergic outcomes for 432 infants.

Summary of Reported Results

For outcomes of interest that have been reviewed systematically in 1 of the identified systematic reviews, the Committee has summarised the findings from those reviews. If other data exist, then the Committee has also updated those systematic reviews with data from additional RCT published subsequent to those reviews or from RCT not included for other reasons. For outcomes that have not been evaluated systematically, the Committee has reviewed those RCT that met its inclusion criteria. A summary of reported results from the systematic reviews and from studies identified after the published systematic reviews is provided in Tables 8 to 10 at *http://links.lww.com/MPG/A33*.

ADMINISTRATION OF PREBIOTIC-SUPPLEMENTED FORMULA STARTED IN INFANTS ≤4 MONTHS OF AGE

(OR ≤6 MONTHS OF AGE PROVIDED THEY HAVE NOT STARTED COMPLEMENTARY FEEDING) AND CONTINUED FOR AT LEAST 2 WEEKS

Growth

Previously Published Systematic Review: Various Prebiotics

For growth, the systematic review by Rao et al (53) identified 10 publications (33,36,38,40–42,46–48,52) that evaluated the effect of prebiotic supplementation on physical growth during the first year of life. None of these RCT individually showed a difference in physical growth between the experimental and control groups. Meta-analysis of 4 RCT (n = 436) reported in 5 publications (40,42,46–48) showed that compared with placebo, administration of a formula supplemented with prebiotics (various) had a significant effect on weight gain during the trial period (weighted mean difference [WMD] 1.07 g/day, 95% CI 0.14–1.99). The Committee notes that this meta-analysis pooled data on different prebiotics supplemented either in infant formula or in extensively hydrolysed whey formula.

In the Cochrane Review, meta-analysis of 3 RCT reporting data on growth parameters in term infants (42,48,52) revealed a significant increase in weight gain (WMD 0.93 g/day, 95% CI 0.02–1.84) in infants fed a prebiotic formula. Meta-analysis of 2 studies (42,48) revealed no significant difference in length gain between the prebiotic-supplemented formula and control formula groups (WMD 0.01 cm/week, 95% CI −0.02 to 0.04). One RCT (48) revealed no significant difference in head circumference gain between the prebiotic-supplemented formula and control formula groups (MD −0.01, 95% CI −0.02 to 0.00). The authors concluded that no consistent effects of prebiotic supplementation of infant formula were found on infant growth (Table 8 at *http://links.lww.com/MPG/A33*).

Studies Identified After the Previously Published Systematic Review

Among studies that were not included in the systematic review, only Nakamura et al (49) reported small but statistically significant differences in mean weight- and length-for-age *z* scores at enrollment and study day 28 between the groups fed formula supplemented with prebiotics (PDX and GOS with/without lactulose) and the unsupplemented group. However, this RCT was not designed to evaluate growth as a primary clinical outcome.

Summary and interpretation of data on growth
The Committee notes that interpreting studies on the effects of prebiotic supplementation of infant formula on growth can be difficult. This is because only a limited number of studies have analysed the effects of a given prebiotic, the studies were often too small with insufficient power to identify relevant effects on growth, and the follow-up periods in the trials were short. The Committee concludes that prebiotic supplementation of infant formula, primarily with a mixture of GOS/FOS, has no adverse effects on growth in healthy term infants, but the effect on improved growth is modest at best.

Tolerance

Previously Published Systematic Review: Various Prebiotics

In regard to tolerance, the systematic review by Rao et al (53) identified 7 RCT that reported in 8 publications (36,38,40–42,46–48) information related to this outcome. No significant differences were found between the prebiotic (various)-supplemented formula groups and the control formula groups in the incidences of symptoms such as excessive irritability, crying, regurgitation, and vomiting. Only 1 RCT (52) reported that infants in the prebiotic (PDX and GOS with/without lactulose)-supplemented formula groups compared with the control formula group had a higher risk of diarrhoea (18% vs 4%; $P = 0.008$), irritability (16% vs 4%, $P = 0.027$), and eczema (18% vs 7%; $P = 0.046$).

Stool pH

Previously Published Systematic Review: Various Prebiotics

Rao et al (53) pooled the results of 6 RCT (33,36,41,42,46,55) and demonstrated a significant reduction in stool pH in infants who received prebiotic supplementation (WMD −0.65; 95% CI −0.76 to −0.54).

Summary and interpretation of data on stool pH
Compared with controls, prebiotic supplementation of infant formula has the potential to reduce faecal pH. The Committee notes that whether this reduction in faecal pH per se is of benefit to the infants is currently not established.

Stool Frequency

Previously Published Systematic Review: Various Prebiotics

Four RCT (40,46–48) identified in the systematic review by Rao et al (53) consistently showed that infants in the prebiotic-supplemented formula groups had a significantly higher frequency of stools (similar to the frequency in breast-fed infants) than infants in the control formula groups.

Studies Identified After the Previously Published Systematic Review

One RCT (44) found that the administration of a GOS/FOS–supplemented formula was not associated with a change in stool frequency.

Summary and interpretation of data on stool frequency
Limited available data suggest that prebiotic supplementation of infant formula has the potential to increase stool frequency. However, the clinical significance of this finding is unclear.

Stool Consistency

Previously Published Systematic Review: Various Prebiotics

Six RCT (40,42,52,46–48) identified in the systematic review by Rao et al (53) reported data on the effects of prebiotic supplementation of infant formula on stool consistency. All of the trials revealed a significantly softer stool consistency in the prebiotic-supplemented formula group compared with the control formula group.

Studies Identified After the Previously Published Systematic Review

One RCT (44) found that the median stool consistency for infants in both the GOS/FOS–supplemented formula group and the control formula group was mushy/soft, and this remained constant in both study groups throughout the study.

Summary and interpretation of data on stool consistency

Limited available data suggest that prebiotic supplementation of infant formula has the potential to soften stools. However, the clinical significance of this finding is unclear.

Nonclinical Outcomes

See Table 8 at *http://links.lww.com/MPG/A33*.

Summary and interpretation of data on nonclinical outcomes

Administration of infant formula supplemented with prebiotic oligosaccharides resulted in significantly higher stool colony counts of bifidobacteria, as assessed by appropriate microbiological analyses. Such administration also has the potential to increase faecal lactobacilli counts. The clinical significance of these changes is unclear. The effect of supplementation of infant formula with prebiotics on the reduction of pathogenic bacteria is limited.

ADMINISTRATION OF PREBIOTIC-SUPPLEMENTED INFANT OR FOLLOW-ON FORMULA AT ANY OTHER AGE BEYOND EARLY INFANCY AND REGARDLESS OF THE DURATION OF THE INTERVENTION

The impact of prebiotic supplementation of follow-on formula was reported in 2 RCT (10,39). The prebiotics studied were FOS (10) and oligofructose plus inulin (39). Administration of follow-on formula supplemented with the studied prebiotics resulted in significantly higher stool colony counts of bifidobacteria. Limited available evidence from 1 RCT suggests that supplementation with FOS, but not with oligofructose plus inulin, is associated with softer stools. No significant differences were observed between the groups for any other outcome studied (Table 9 at *http://links.lww.com/MPG/A33*).

Summary and interpretation of data on the administration of prebiotic-supplemented follow-on formula

Prebiotic supplementation of follow-on formula with FOS, GOS, or oligofructose plus inulin has the potential to increase faecal bifidobacteria counts. FOS supplementation has the potential to soften stools. The clinical significance of these findings is unclear.

EXTENSIVELY HYDROLYSED FORMULA SUPPLEMENTED WITH PREBIOTICS

Three publications (34,35,48) reported data from an RCT that investigated the effects of the administration of an extensively hydrolysed whey formula supplemented with a prebiotic mixture (90% short-chain GOS, 10% long-chain FOS; dosage 0.8 g/100 mL) (Table 10 at *http://links.lww.com/MPG/A33*) during the first 6 months of life in infants at risk for allergy (with at least 1 parent with documented allergic disease confirmed by a physician). Two hundred fifty-nine infants were randomly assigned to receive extensively hydrolysed whey formula supplemented either with 0.8 g/100 mL of scGOS/lcFOS (experimental group; n = 129) or 0.8 g/100 mL of maltodextrin as placebo (control group; n = 130) (48).

Growth

No significant difference was found in any of the anthropometric parameters assessed between the experimental and control groups (35,48).

Clinical Outcomes

At 6 months of age, 206 (79.5%) infants were included in the per-protocol analysis. Infants who received formula supplemented with GOS/FOS (n = 102) compared with the control formula group (n = 104) (48) had a significantly reduced frequency of atopic dermatitis (9.8% vs 23.1%; RR 0.42, 95% CI 0.2–0.8), similar severity of atopic dermatitis as scored by the scoring atopic dermatitis index, higher defecation frequency (1.75 ± 0.6 vs 1.50 ± 0.6 episodes per day; $P = 0.006$), greater loose consistency of stools as shown by the stool consistency score (2.44 ± 0.7 vs 3.22 ± 0.9 points on a scale of 1 [watery] to 5 [hard] points; $P < 0.0001$), less frequent episodes of regurgitation ($P = 0.0027$) and crying ($P = 0.0057$), and a similar frequency of vomiting episodes. Additionally, infants who received formula supplemented with GOS/FOS compared with the control formula group (34) had a reduced number of overall infectious episodes (21/102 vs 47/104; RR 0.5, 95% CI 0.3–0.7), reduced risk of upper respiratory tract infections (14/102 vs 30/104; RR 0.5, 95% CI 0.3–0.8), similar risk of otitis media (4/102 vs 6/102; RR 0.7, 95% CI 0.2–2.2), reduced risk of recurrent respiratory tract infections (3% vs 10%; RR 0.3, 95% CI 0.09–0.99), similar risk of gastrointestinal infections (1/102 vs 4/104; RR 0.25, 95% CI 0.04–1.7), similar risk of urinary tract infections (2/102 vs 7/104; RR 0.3, 95% CI 0.07–1.2), and a

similar number of infections requiring antibiotic treatment ($P = 0.10$).

At 24 months of age, 134 of 259 (52%) of the initially randomised infants were included in the per-protocol analysis. Infants who received formula supplemented with scGOS/lcFOS (n = 66) compared with the control formula group (n = 68) had (35) a reduced cumulative incidence of atopic dermatitis (14% vs 28%; $P < 0.05$), a reduced cumulative incidence of recurrent wheezing (8% vs 21%; $P < 0.05$), a reduced cumulative incidence of allergic urticaria (1.5% vs 10.3%; $P < 0.05$), fewer episodes of any kind of physician-diagnosed infections (4.1 ± 3.1 vs 5.9 ± 4.1; $P = 0.01$), fewer episodes of upper respiratory tract infections (2.1 ± 1.8 vs 3.2 ± 2.2; $P < 0.01$), fewer episodes of infections requiring antibiotic prescriptions (1.8 ± 2.3 vs 2.7 ± 2.4; $P < 0.05$), fewer fever episodes recorded by the parents (2.2 ± 1.9 vs.3.9 ± 2.5; $P < 0.0001$), a similar number of episodes of lower respiratory tract infections (0.9 ± 1.1 vs 1.3 ± 0.8; NS), a similar number of episodes of otitis media (0.5 ± 1.0 vs 0.7 ± 1.2; NS), a similar number of episodes of gastrointestinal infections (0.4 ± 0.7 vs 0.6 ± 0.9; NS), and a similar number of episodes of urinary tract infections (0.0 ± 0.0 vs 0.1 ± 0.5; NS).

Stool Bifidobacteria and Lactobacilli

In a subgroup of 98 infants, the parents provided fresh stool samples for microbiological analysis using plating techniques; the faecal counts of bifidobacteria were significantly higher in the group fed with the scGOS/lcFOS–supplemented formula compared with the control group (35). No significant difference was found in the lactobacilli count between groups.

Summary and interpretation of data on extensively hydrolysed formula supplemented with prebiotics

The Committee notes that interpreting these findings can be difficult. First, intention-to-treat analysis was not performed. Second, the dropout rate was high, particularly at 24 months. Third, both the definition and diagnosis of outcomes were not always clearly described. Fourth, the prevalence of eczema in the placebo group was relatively high. Limited available evidence from a single trial suggests that administration of an extensively hydrolysed whey formula supplemented with GOS/FOS resulted in significantly higher stool colony counts of bifidobacteria; it also had a modest, statistically significant effect on stool consistency and frequency. The administration of GOS/FOS was associated with a number of beneficial health outcomes, particularly a reduced risk of some allergic reactions and some types of infections. The Committee considers that these results should not influence practice until confirmed by additional studies.

SYNBIOTICS

Description of Studies Included in the Review

Three RCT met the inclusion criteria for the review (12,59,60). The characteristics of the included trials are presented in Table 11 at *http://links.lww.com/MPG/A33*, and the methodological quality of the studies is presented in Table 3 (*http://links.lww.com/MPG/A33*). The synbiotics studied were as follows: BL999 + GOS/FOS (59), BL999 + LPR + GOS/FOS (12), BL999 + *Lactobacillus paracasei* ST11 + GOS/FOS (12), and *L paracasei* ssp *paracasei* + *B animalis* ssp *lactis* + GOS (60).

Summary of Reported Results

Data regarding synbiotics are limited. The first RCT to address this issue was performed by Puccio et al (59). The aim of the study was to assess the safety and tolerability of the combined administration of probiotics and prebiotics in infant formula. In this trial, 138 infants who were not breast-fed after day 14 received an experimental formula containing a probiotic (*B longum* BL999 at a dose of 2×10^7 CFU) and prebiotics (90% GOS and 10% FOS) or standard infant formula. Both study formulae were administered until the infants were 112 days of age. The investigators reported that weight gain did not differ between the groups. Moreover, no statistically significant difference in recumbent length, head circumference, or the incidence of adverse events was found between the 2 groups. Compared with the control group, infants in the experimental group had a significantly higher stool frequency (2.2 ± 0.7 vs 1.8 ± 0.9 occur-occurrences/day, $P = 0.018$), a lower risk of constipation ($P = 0.03$), and a reduced risk of respiratory tract infections, although the latter was of borderline statistical significance (RR 0.6, 95% CI 0.37–1.03).

Another RCT (12) involving 284 infants evaluated the safety and tolerability of infant formulae containing probiotics only or synbiotics. In this trial, healthy full-term infants were exclusively fed with either a control formula or 1 of 3 experimental formulae containing the following: BL999 + LPR, BL999 + LPR + 4 g/L of 90% GOS/10% scFOS, or BL999 + *L paracasei* ST11 + 4 g/L of GOS/scFOS. The study products were administered from ≤2 to 16 weeks of age. Infants fed with formulae containing either probiotics or synbiotics showed weight gain similar to those fed with a control formula. There was no significant difference between the study groups regarding any of the secondary outcomes (including recumbent length, head circumference, digestive tolerance, and frequency of adverse events), which were evaluated at 2, 4, 8, 12, 16, and 52 weeks of age. The only difference between groups was related to stool frequency, which was significantly higher in infants in the BL999 + LPR + GOS/scFOS group compared with the control group (2.1 d vs 1.6 d, $P = 0.03$).

The most recent RCT (60), conducted in the Netherlands, randomised a total of 126 newborn infants into 2 treatment groups. One arm received an infant formula containing the prebiotic GOS (0.24 g/100 mL) supplemented with the probiotics *L paracasei* ssp *paracasei* and *B animalis* ssp *lactis* (synbiotic group); another arm received the same prebiotic formula with no probiotic supplementation (prebiotic only group). The intervention lasted for 3 months. Eighty of the 126 infants continued the study formulae until 6 months of age. No significant differences were observed in SD change scores for weight, length, and head circumference between the study groups during the first 3 and 6 months. Compared with the control (prebiotic only) group, the synbiotic group had a higher stool frequency during the first 3 months (1.29 vs 1.52 times/day, respectively; $P = 0.04$). Similarly, the synbiotic group had a higher stool consistency score than the control group during the first 3 months (2.57 vs 2.36, respectively, $P = 0.05$). For both parameters, no difference was seen between groups later during the observation period. There were no significant differences between groups in crying and sleeping hours, number of parent-diagnosed infections, antibiotic use, visits to the general practitioner, and number of adverse events.

Summary and interpretation of data on synbiotics
Only a limited number of synbiotic preparations administered in infant formulae have been studied in the context of a formal RCT. The Committee considers that although the available data suggest that the products are safe, the limited data call for caution in overinterpretation of these results. In the future, the efficacy and safety of each synbiotic product should be established.

EVIDENCE SUMMARY AND RECOMMENDATIONS

The Committee considers that recommendations for using probiotic- and/or prebiotic-supplemented formulae are determined by their nutritional adequacy, potential short- and long-term benefits, and safety related to the continued administration of such formulae. In reaching conclusions, the Committee took into consideration primarily evidence from studies included in the systematic reviews. However, consideration was also given to documents developed by other organisations (1–4). On the basis of the evidence available, the Committee has reached the following conclusions.

Probiotics

1. For healthy infants, the available scientific data suggest that the administration of currently evaluated probiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects.
2. The administration of probiotic-supplemented infant formula during early life (≤4 months of age) does not result in any consistent clinical effects.
3. The administration of a few probiotics (single or in combination) supplemented to infant or follow-on formulae and given beyond early infancy may be associated with some clinical benefits, such as a reduction in the risk of nonspecific gastrointestinal infections, a reduced risk of antibiotic use, and a lower frequency of colic and/or irritability. However, the available studies varied in methodological quality, the specific probiotics studied, the durations of the interventions, and the doses used. The Committee considers there is still too much uncertainty to draw reliable conclusions from the available data.
4. The safety and clinical effects of 1 probiotic microorganism should not be extrapolated to other probiotic microorganisms.
5. In general, there is a lack of data on the long-term effects of the administration of formula supplemented with probiotics. Such data would be of particular importance if the effects persisted after the administration of the probiotic(s) has ceased.
6. Considering the above, the Committee does not recommend the routine use of probiotic-supplemented formula in infants.

Prebiotics

1. For healthy infants, the available scientific data suggest that the administration of currently evaluated prebiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects.
2. The clinical effects and safety of 1 prebiotic product should not be extrapolated to other prebiotics.
3. There is evidence demonstrating that the administration of formula supplemented with some prebiotics is associated with some clinical effects, such as increased stool frequency and stool softening, the clinical relevance of which remains questionable.
4. There is evidence from only 1 RCT with methodological limitations demonstrating that the administration of extensively hydrolysed formula supplemented with GOS/FOS is associated with a reduced risk of some allergic reactions and some types of infections. However, the Committee considers there is still too much uncertainty to draw reliable conclusions from the available data.
5. There is a lack of data on the long-term effects of the administration of formula supplemented with prebiotics. Such data would be of particular importance if the effects persisted after the administration of the prebiotic(s) has ceased.
6. Considering the above, the Committee does not recommend the routine use of formula supplemented with prebiotics in infants.

Synbiotics

1. Only a limited number of synbiotic preparations administered in infant formulae have been studied in the context of a formal RCT. The available data suggest that infant formulae supplemented with synbiotics are not associated with adverse effects. However, the paucity of data calls for caution in overinterpretation of these results. In the future, the efficacy and safety of each synbiotic-containing infant formula should be established.
2. Considering the above, the Committee does not recommend the routine use of formula supplemented with synbiotics in infants.

Future Research

1. The Committee considers that the supplementation of formula with probiotics and/or prebiotics is an important field of further research. In the future, validated clinical outcome measures assessing the effects of probiotic and/or prebiotic supplementation of formulae should be used in well-designed and carefully conducted RCT, with relevant inclusion/exclusion criteria and adequate sample sizes. Such trials should also define the optimal doses and intake durations, as well as the safety of the probiotics and prebiotics.
2. Because most of the trials were company funded, independent trials, preferentially financed jointly by national/governmental/European Union bodies and international organisations, would be desirable.

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