INTRODUCTION

Preterm neonates are a fragile patient group [1]. A population-based survey in the UK showed that the predominant causes of mortality among them gradually changed between 1988 and 2008 [2]. The overall survival improved with time and mortality from respiratory etiologies decreased. However, the proportion of deaths due to necrotizing enterocolitis (NEC) increased [2]. NEC incidence in very low birth weight preterm neonates is about 16% [3]. The mortality rates due to NEC in this patient group has been reported to be between 21.9% and 50% [4-7]. Studies in developed countries showed that the incidence of NEC was higher in infants, born before 32 weeks’ gestation (7%, compared to 2% for term neonates) and infants with a birth weight, lower than 1000 g (22%, compared to normal weight neonates). However, among all NEC patients, there is a minority of about 15% neonates that are full-term [8]. It is difficult to predict and identify early on the onset of NEC due to high interindividual variability [9].

Pathogenesis

In the first hours after the birth of preterm infants, respiratory diseases predominate, but after the first
few days, NEC and late onset sepsis take the lead, becoming the prevalent emergency situations. The pathogenesis is not fully understood, but gut immaturity or “leaky gut”, dysbiosis and inflammation are believed to be the key factors [10]. NEC is associated with excessive, immature inflammatory response to pathogenic and commensal bacteria, bleeding, intestinal permeability to bacteria, accompanied by hypoxia-ischemia, necrosis, perforation and late onset sepsis. In comparison to term infants, very low birth weight preterm infants, have a delayed and abnormal bacterial colonization with a deficiency of normal enteric species as *Bifidobacteria* [11, 12]. Ma et al. [6] suggested that shorter antibiotic duration, breastfeeding and the colonization of the gut with commensal *Clostridiales* [13] species helps the gut to mature faster. NEC severity depends on the degree of dysbiosis, ischemia, oxidative stress, mucosal injury, and the use of formula feeds [9, 14].

**The Role of microbiota**

The gut-associated microbial ecosystem (bacteria, archaea and eukaryotes) not only participates in food digestion, but also constantly interacts with human physiological processes as immune system modulation and formation of epithelial barrier components [15, 16]. Moreover, gut microbiota can influence processes in remote organs as the liver [17] and brain [18]. Its composition and pertinent nutrition-related factors are linked to degenerative pathologies as immune and metabolic diseases. Although often underestimated, gut microbiota-host synergy is recognized as a significant factor in overall health or disease [19].

In neonates, the cross-talk between the at-first-sterile gut and the first colonizing bacteria leads to the development of host defenses against infection and the prevention of allergy and autoimmunity [20]. Commensal bacteria can create a balanced T helper development and a self-limited immune response [16]. It has been hypothesized that neutrophils and neutrophil-released neutrophil extracellular traps are important contributors to pathological hyperinflammation and tissue damage in NEC [21]. In normal conditions, breast milk is the predominant postnatal source of microbiota, colonizing the infant’s gut [22]. Human milk normally contains predominantly *Streptococci* and *Staphylococci*, followed by *Bifidobacteria, Lactobacilli, Propionibacteria, Enterococci* and species from *Enterobacteriaceae* family [23]. The microbial composition of breast milk can be affected by factors such as mode of delivery and lactation stage [24]. It is generally accepted that the specific bacterial components (DNA, peptidoglycan constituents, bacterial capsular polysaccharide A, exopolysaccharides, lipoteichoic acid, lipopolysaccharides, etc.) are affecting physiology upon recognition by human cells’ primitive pattern recognition receptors [25]. However, it remains to be elucidated whether dead bacteria debris may be equally effective as whole, live bacteria and in case there are such probiotic effects of dead bacteria, whether they are strain-specific [26]. Bacterial metabolic processes as part of trophic networks influence the physicochemical conditions in the gut (acidity), the composition of microbiota and host defenses (production of mucin, sIgA, antimicrobial peptides) [15]. Metabolic products as short chain fatty acids (SCFA) are important not only by enhancing the proportion of non-pathogenic microbes [27]. Butyrate is a food source for gut epithelial cells, stimulates tight junction formation and repair [28] and exerts antiproliferative activity [29]. Yet, Suhas et al. suggested that in conditions as immature states of mucosal defenses, SCFA may also cause injury [30].

A difference between full-term and preterm infants is that as a consequence of the application of conventional broad-spectrum antibiotics in preterm infants, the predominant source of microbial colonization of the gastro-intestinal tract (GIT) may be the surrounding surfaces, touched by humans in the room [31]. For example, the source of bacteria, which causes sepsis may well be the parents [32]. Hand hygiene and nonsterile glove use in Neonatal Intensive Care Units (NICUs) reduces gram-positive bloodstream infections in preterm infants by 53% and central line-associated bloodstream infections by 64% [33]. However, applying even more stringent hygiene policies in NICUs during the COVID-19 pandemic didn’t decrease the probability of NEC development, although late-onset sepsis (LOS) occurrence in baseline LOS high-risk rooms was reported to be decreased [34].

**Prophylaxis and management strategies**

Although early diagnosis and treatment are critical for the outcome of NEC, the most common diagnostic sign, feeding intolerance is unspecific and more often seen in patients, who won’t develop NEC [35]. In their highly influential paper, Bell et al. [36] suggested a scoring system for differentiating between three general stages of disease – suspicious (I), definitive (II) and advanced (III), according to systemic, abdominal and radiographic signs. The disease stage influences the treatment approach and is still the standard for decision-making [37, 38].

As the topic of this work is focused on probiotic use in preterm neonates, a detailed description of the strategies for early diagnosis, prevention and treatment of NEC has been omitted and only an outline has been provided [35, 39]. Research on the optimal strategies for NEC prevention is still ongoing. Up
to this moment, common approaches are the use of glucocorticoids and antibiotics antenatally [39], early introduction of breast milk in the diet, enteral feeding regimens, standardized feeding protocols, restricted water intake, probiotics, attempts at early diagnosis and prevention [40]. The promotion of using mother’s own milk or donor’s milk has been strongly encouraged [41]. Despite the uncertainties regarding prophylactic probiotic intake, which this study aims to address, probiotics have been broadly implemented in many NICUs [42]. Probiotic alternatives, aiming to lower the risk of bacteremia, while retaining the positive effects on preterm infants’ microbiome and inflammatory system maturation are prebiotics and lactoferrin [43-45].

Regarding NEC management, high standard of care is paramount for its outcome as early identification and management of metabolic derangement and sepsis are strong predictors of survival [46]. Blood products transfusion, abdominal decompression, empirical antibiotic use with anaerobic coverage in case perforation is suspected, primary peritoneal drainage or laparotomy with bowel resection are common strategies for handling NEC [40].

**Prophylactic probiotic use**

Due to the high mortality rates, effective prevention strategy implementation is paramount in NICUs. Probiotics are a popular option, despite there is a knowledge gap on their choice and therapeutic scheme [47]. Probiotics are products, containing sufficient numbers of live microorganisms, which, usually after ingestion, can alter a host’s microbiota composition. Usually probiotic products only claim to confer unspecified health benefits due to their legal regulation [26]. Doubt has been casted on meta-analyses, comparing clinical studies on different strains of probiotic organisms [48]. Despite the availability of mechanistic data on probiotic health effects, there is a missing link between this data and clinically relevant endpoints [49].

**RESULTS**

**Publication history and citation scores**

The chronological analysis of yearly publications showed the development of research interest on the topic. The first scientific publication describing the use of probiotics in preterm infants, intended to prevent NEC was published in 1993 by Millar et al. [54] (Figure 1A). It shows that in a small group of neonates of gestational age 33 weeks or less, Lactobacillus GG probiotic intake did not decrease the amount of potential pathogens in the gut. Although this study failed to demonstrate beneficial effects, the following publication on the topic in 1997 by Kitajima et al. did [55]. It was a randomized clinical trial with a size about three times the one used in the first publication, and it showed that the use of a *Bifidobacterium breve* -containing probiotic successfully colonized the gut and lead to improved weight gains and reduced the volume of air, aspirated from the stomach [55]. In another study, published the same year, the use of *Lactobacillus rhamnosus* strain GG failed to reduce the colonization with *Klebsiella oxytoca*, related to severe NEC cases in preterm neonates [56]. The next two articles in chronological order are among the most influential up to now. In 2002, Dani et al. [57] conducted the first double-blind multicenter study on the use of *Lactobacillus GG* in 12 Italian NICUs. It showed that 7 days’ treatment with this probiotic didn’t reduce the incidence bacterial sepsis, NEC or urinary tract infections in preterm infants [57]. The local citation score of this publication has been the second highest up to this moment (Table 1). The local citation score shows how many times a document has been cited by other documents on the specific topic, i.e. the collection of 82 selected records. It is an important metric as it shows the relevance of the publication among researchers, focused particularly
on the same area of research. The historical direct citation graph (Fig. 1B) further supports the suggestion that the study of Dani et al. [57] has had a major influence as it has been directly cited by half of the most influential articles on the topic.

This is visible from the number of prospectively outgoing connection lines. The next study by chronological order is also one of high local and general citation scores. However, it isn’t that popular among the top-cited articles on the historical direct citation graph (Fig. 1B). Probably, the reason for this is that it differs by studying the effects of *Saccharomyces boulardii* on infants’ microbiomes and the therapeutic applicability of the conclusions is rather vague [58]. The most influential publication according to all studied metrics is the article of Lin et al. [59], published in 2005 in the journal Pediatrics (Table 1, Fig. 1B). It showed a reduction of NEC incidence and severity in preterm infants, treated with a combination of *Lactobacillus acidophilus* and *Bifidobacterium infantis*. Both the publications by Dani et al. [57] and by Lin et al. [59] have the leading citation scores (Table 1) and influenced the most top-cited publications on the topic (Fig. 1B). The importance of those articles seems to be confirmed by a trend in the annual production graph (Fig. 1A), which shows that soon after 2005, a clear exponential increase of publication numbers on the topic started. This trend peaked at the year 2016 and then rapidly plummeted. In order to understand the events, which might be related to this abrupt decrease in interest on the topic, we examined the articles, published several years before the peak, which are the most influential. Among the publications after 2010, the highest local and global citation scores are those of the articles of Jacobs et al. (2013) [60] and Costeloe et al. (2016) [61] (Table 1). They described two multicentre blinded randomised controlled trials. Jacobs et al. showed that the probiotic combination *Bifidobacterium infantis*, *Streptococcus thermophilius*, and *Bifidobacterium lactis* reduced NEC of Bell stage 2, but did not affect LOS or mortality. Costeloe et al. on the other hand, showed that *Bifidobacterium breve* BBG-001 did not affect the incidence of necrotising enterocolitis and LOS. The historical graph (Fig. 1B) shows that Costeloe et al. cited the publication by Jacobs et al., as well as a case series by Zbinden et al. (2015) [62], describing *Bifidobacterium longum* bacteriemia in three preterm neonates. Based on these associations between the most cited articles,

![Fig. 1.](image)

*Fig. 1.* Graphic representations of bibliometric data, generated by the bibliometrix package [52]. A. Density plot of annual publication counts, B. Historical direct citation network of the top 15 articles with highest local citation scores, C. Author keyword co-occurrence map
it seems plausible that the reason for the decline in publication on the topic after 2016 (Fig. 1A) might be the contradicting results on efficacy of a promising \textit{Bifidobacterium strain} and the proof that bacteremia can result from the prophylactic use of a promising probiotic \textit{Bifidobacterium strain}. Yet, despite the valid safety concerns, comparing the effects of different therapeutic regimens with probiotic products with different contents and making conclusions on their benefit/risk ratio could be a misleading oversimplification [47, 63].

\textbf{Keyword co-occurrence}

The author keyword co-occurrence analysis showed that there was one predominating, well defined cluster, colored in red and two clusters of more loosely-related keywords, colored in blue and green (Figure 1C).

The red cluster is dominated by the co-occurring keywords “neonatal necrotizing enterocolitis”, “preterm infants”, “birth weight”, “probiotics”, “microbiota” and “bacterial colonization”. This cluster is related to some keywords with secondary importance, but separated from the rest of clusters. These keywords are “\textit{Bifidobacterium breve}”, “\textit{formula}”, “\textit{Lactobacillus GG}”, “\textit{Lactobacillus reuteri}” and “late-onset sepsis” (Figure 1C). This cluster contains the majority of papers on clinical trials and case studies, focusing on the effects of different probiotics on the endpoints NEC and weight gain. It shows that the probiotic strains, most common in the biggest major body of publications, focused specifically on our topic of interest are \textit{Bifidobacterium breve}, \textit{Lactobacillus rhamnosus} GG and \textit{Lactobacillus reuteri}.

In the second biggest cluster, colored in blue, the predominating keywords are “double-blind”, “meta-analysis”, “supplementation” and “infection”. The secondary keywords, typical only for this cluster are “risk”, “efficacy”, “infection” and “\textit{Bifidobacterium lactis}” (Figure 1C). This cluster seems to be related to specific studies, providing high-quality evidence as randomized double-blind clinical trials and meta-analyses of risk and efficacy. It seems that a higher proportion on the studies of the strain \textit{Bifidobacterium lactis} are of this type.

The smallest cluster, colored in green contains only a few, loosely related keywords, which are less specific for the outcomes, relevant to NEC prevention in preterm infants and may be related to studies, focusing on endpoints of secondary clinical importance: “prevention”, “gastro-intestinal”, “diarrhoea”, “bifidobacterium” and “children” (Figure 1C).

\begin{table}
\centering
\caption{List of the most cited articles on probiotic use in preterm infants. LCS – local citation score, GSC – global citation score} \label{tab:1}
\begin{tabular}{|l|p{8cm}|c|}
\hline
\textbf{Author, Year} & \textbf{Title} & \textbf{LCS} & \textbf{GCS} \\
\hline
Lin H, 2005 [59] & Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants & 29 & 437 \\
Costalos C, 2003 [58] & Enteral feeding of premature infants with \textit{Saccharomyces boulardii} & 15 & 121 \\
Jacobs S, 2013 [60] & Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial & 12 & 176 \\
Manzoni P, 2006 [64] & Oral supplementation with \textit{Lactobacillus casei} subspecies rhamnosus prevents enteric colonization by \textit{Candida} species in preterm neonates: a randomized study & 11 & 199 \\
Mihatsch W, 2010 [66] & Effect of \textit{Bifidobacterium lactis} on the incidence of nosocomial infections in very-low-birth-weight infants: a randomized controlled trial & 9 & 85 \\
Costeloe K, 2016 [61] & \textit{Bifidobacterium breve} BBG-001 in very preterm infants: a randomised controlled phase 3 trial & 9 & 213 \\
Stratiki Z, 2007 [67] & The effect of a bifidobacter supplemented bovine milk on intestinal permeability of preterm infants & 8 & 132 \\
Braga T, 2011 [70] & \textit{Efficacy of Bifidobacterium breve} and \textit{Lactobacillus casei} oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial & 8 & 128 \\
Rojas M, 2011 [71] & Prophylactic probiotics to prevent death and nosocomial infection in preterm infants & 6 & 91 \\
Rojas M, 2015 [72] & \textit{Bifidobacterium longum} bacteremia in preterm infants receiving probiotics & 6 & 78 \\
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DISCUSSION

Challenges in probiotic use

Besides efficacy, the safety of the most common probiotics is well established in healthy people [73]. However, there could be a significant variability in the response between different strains of a species. For example, *Escherichia coli* Nissle 1917 is considered to be a probiotic, while *Escherichia coli* O157:H7 may induce haemolytic uremic syndrome [74].

However, in immunocompromised patients such as preterm neonates, bacteremia is a possible complication that may be difficult to recognize. There have been such reports of bacteremia cases with different strains identified, particularly *Bifidobacterium infantis* and *Lactobacillus rhamnosus* GG [72, 75, 76]. They may originate from intestinal permeability, but contaminated intravenous lines after probiotic powder spills in the NICU cannot be excluded [63]. As the keyword co-occurrence shows, the aforementioned reports of bacteremia may have been quite concerning to the probiotic research community as the both *Bifidobacterium infantis* and *Lactobacillus rhamnosus* GG are among the strains, associated with the major body research and belonging to the predominant, red-colored keyword cluster (Fig. 1C).

Bacterial metabolism could also potentially cause side effects in preterm neonates, which tend to be acidic. As D-lactate’s total body clearance is slower than that of the endogenous L-lactate, a D-lactic acidosis may occur when D-lactic acid-producing probiotics are used. D-lactic acidosis may especially affect infants with kidney failure and short bowel syndrome [63]. Mack (2004) suggested that properly labeling such probiotics, would provide clinicians in NICUs with valuable information [77].

Bacteria-induced immune hyperactivity by mechanisms, related to modulation of cytokines, T-cell activity, macrophage and natural killer function is theoretically possible, but there is still not enough information, related to such outcomes due to probiotic strains [78]. Another theoretical consideration is that short-chain fatty acids, produced by probiotics may cause mild oxidative stress, which conditions the expression of gut antioxidant enzymes and is beneficial as prevention, but can be detrimental in an acute oxidative stress situation, such as NEC [79].

Saccharomyces boulardii is not a probiotic of choice as the European Medicine Agency concluded that there could be “possible complications of sepsis related to *Saccharomyces boulardii* systemic fungaemia in fragilized patients, i.e. immunocompromised, with a central venous catheter or being severely ill” [80]. As preterm infants are immunocompromised and severely ill, the use of Saccharomyces is not recommended. This could be related to the lower influence of Saccharomyces boulardii studies (Fig. 1 B, C)

Recommendations on the use of probiotics in preterm neonates

Some authors assume that data from clinical trials is enough to support the routine use of probiotics in enteral feedings as it may not be safe not to use probiotics in preterm infants within a determined weight limit [4, 81-83]. Based on limited evidence, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published an up-to-date position paper, encouraging the use of specific probiotic strains and discouraging the use of others, which has been summarized in Fig. 2 [63]. The position paper builds upon a network meta-analysis approach, identifying the strains with strongest evidence base for preventing the leading gastrointestinal pathologies in preterm infants [84]. However, the recommendations are cautiously presented in light of the lack of conclusive data about efficacy and safety.

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**Fig. 2.** An outline of the recommendations on probiotic use in preterm infants, provided in the position paper by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [63]
A recent report from the American Academy of Pediatrics also takes a conservative stance and “does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of < 1000 g” [85]. Furthermore, authors warn about the risk of altering the flora of facilities, where diverse pathologies may be treated. However, they don’t reject the efficacy of combined, multistrain probiotics, but accentuate on the lack of FDA-regulated pharmaceutical-grade products, which would be a guarantee for its quality, safety, and efficacy [85]. According to Neu [48], statements about the efficacy of probiotics in suppressing growth and translocation of potential pathogens, preventing excessive inflammation and reducing the incidence of NEC should be proven unambiguously before changes in guidelines are made. A retrospective study done in The Stead Family Children’s Hospital at the University of Iowa confirms this position by concluding that six years after the introduction of routine multispecies probiotic containing *Bifidobacterium breve*, *bifidum*, *infantis*, and *longum* and *Lactobacillus rhamnosus* GG for all infants < 33 weeks, no reduction in overall mortality or NEC incidence was observed [86]. In a comparison between the probiotic combinations, used in the double-blind, randomized trial by Jacobs et al. [60], which showed a reduction of NEC of Bell stage 2 or more, and the retrospective chart review by Juber et al. [86], it appears that the major difference was that unlike Juber et al. [86], Jacobs et al. [60] had used a combination, including *Streptococcus thermophilus* and *Lactobacillus lactis*, which according to the keyword co-occurrence map is predominantly associated to the body of high quality research on the topic (Fig. 1C).

**Regulation of probiotic products**

Probiotics are currently sold as part of traditionally used fermented foods or dietary supplements with market share, which is rapidly increasing [87]. They have been recommended mostly in self-limiting conditions, associated with diarrhea, gastro-intestinal tract inflammation and irritable bowel syndrome [88]. In a meta-analysis of eight diseases, each accompanied by some of the mentioned three major conditions, Ritchie and Romanuk [88] came to the conclusions that overall, probiotic use is most efficacious in pouchitis, and that the choice of probiotic strain is important.

If the species and strain of a microorganism do not raise safety concerns or, if safety concerns can be defined and excluded, it is granted a “Qualified Presumption of Safety” (QPS) status in the European Union and exempted from the obligation of further safety assessment. If a microorganism can be categorically identified to belong to a QPS group (*Lactobacillus, Bifidobacterium, Streptococcus thermophilus, Saccharomyces cerevisiae* etc.), it is only tested for antibiotic resistance. Microorganisms not qualifying for QPS undergo a full safety assessment [89, 90].

A study of 16 commercial probiotics, some of which marketed for use by infants and children, revealed that the information on the label corresponded to the actual contents in one out of sixteen probiotic products [91]. As probiotics are food supplements, there may be unannounced changes in the production process and contents. A case of a fatal gastrointestinal mucormycosis was caused by mould-contaminated combined probiotic [92]. These cases exemplify that the unregulated market is a major limitation for establishing the successful use of probiotics. The comparison of results on the efficacy of incorrectly labelled probiotics could result in totally misleading conclusions. Potentially, the use of unannounced on the label strains with transferable antibiotic resistance plasmids could result in antibiotic resistance and superinfections. In accordance to the position paper of ESPGHAN [84], the extensive use of products, manufactured by implementing effective quality control methods [93], according to the Current Good Manufacturing Practice (cGMP) would be a step in the right direction.

**Probiotic marketing and health claims**

Caselli et al. [26] suggested that the knowledge gap on probiotic efficacy and the lack of pharmaceutical-grade products might be due to market strategies, ‘based on “easy” trade of live microorganisms’ which dampen producers to undertake the risk and investments, necessary for the development of “pharmacobiotic” products with unambiguously clear mode of action, toxicology, pharmacokinetics, tolerability and effectiveness. Although the promotion of health and the prevention of disease are practically indivisible, under European law, a “beneficial physiological effect” or a “health claim” of a food constituent should be approved by the European Food Safety Authority (EFSA) according to the Nutrition and Health Claims Regulation (1924/2006). However, there is a ban on “medical claims” which otherwise should be authenticated with loads of detailed evidence for efficacy and safety and approved by European Medicines Agency regardless whether it is a new drug or a yoghurt. For example if a probiotic does prevent pouchitis (a medical claim), it is illegal to state that to consumers. Thus, a probiotics manufacturer would rationally choose to market the products as bolstering “defenses” and “healthy intestines” and to avoid further expensive studies with an uncertain outcome. Yet, fortunately,
there is no ban on publication of scientific proof of probiotic products [49].

Resolving contradictions

There is currently a lot of data, showing efficacy or the opposite – lack of efficacy of probiotic regimens in specific subgroups of preterm infants at high risk of developing NEC. Among the tested probiotic treatment regimens, there are some patterns, which could be associated with favorable outcomes and have been taken into consideration by the ESPGHAN position paper (Fig. 2). There are several problematic areas, which fuel contradictions, regarding the use of probiotics in preterm infants. The efficacy of NEC prevention in preterm infants has been shown to be strain-specific and combination-specific so unifying strains with different biochemical and microbiological properties under the umbrella term “probiotics” is a drawback from finding the most effective probiotic protocols. Athalye-Jape and Patole [47] suggest that the overall picture convincingly shows that there is no superior intervention than probiotic use for preventing NEC and its complications and the aforementioned controversies are a result of the irrational process of comparing different strains. A solution for this problem could be collecting more data from uniform and convergent trials and focusing on the effects of specific strains, combinations, dosage regimens and other specific details as relevant patient stratification before therapeutic protocol selection and elucidation on the effects of confounding factors [47]. However, in order to achieve this goal, clinical data needs to be based on medical-grade probiotic products. The lack of stringent control and standardization of food supplements is a prerequisite for not only misleading results, but contamination with pathogens and potential harm [85].

CONCLUSION

Specific probiotic strains and combinations have been found to be effective in NEC prevention in preterm neonates. However, the risk of bacteremia due to probiotic use in NICUs and the lack of efficacy in some clinical trials have discouraged the research on probiotic use in this fragile patient group. However, for more than a decade probiotic use has been routinely implemented in the protocols of neonatal nurseries in Finland, Italy and Japan [81]. In order to advance knowledge on the topic and adopt safe and effective probiotic use, drawbacks such as lack of stringent legal requirements for cGMP application, inconsistencies between contents and labelling and lack of convergence of clinical trial design. Until these issues are solved, it is advisable to adhere to available guidelines for their introduction in enteral feeds [82, 83] and the latest recommendations [63].

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