

Is it time for routine probiotic use in UK neonatal units?

Paul Fleming ^{1,2}

Probiotics have been evaluated extensively in preterm babies for more than 30 years. Early studies in the 1990s sought to ascertain whether or not these live microorganisms could colonise the preterm intestinal tract, while others evaluated their potential to improve nutritional outcomes. From the late 1990s, a series of small studies (including randomised controlled trials (RCTs)) reported outcomes of reduced necrotising enterocolitis (NEC) in babies receiving probiotics and interest in their use as a preventative strategy for NEC accelerated from the early 2000s.¹ In 2010, a meta-analysis concluded that probiotics were effective at reducing stage II NEC and all-cause mortality and recommended no more placebo controlled trials *if* a suitable product was available.²

Some neonatal centres in the UK were pioneers in the early adoption of probiotic use. Granger and colleagues report the findings from a pre-implementation and post-implementation study of probiotic use at a large tertiary neonatal unit in the north of England.³ A total of 1061 infants born <32 weeks' gestation were included; 509 in the pre-probiotic period and 552 in the post-probiotic period. Two different probiotic products were used during the implementation period including one containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* and the other containing *L. acidophilus*, *B. bifidum* and *B. longum* spp *infantis*. Between the two periods (pre-implementation and post-implementation), the overall unadjusted risk of NEC was 9.2% vs 10.6% ($p=0.48$), late-onset sepsis 16.3% vs 14.1% ($p=0.37$) and mortality 9.2% vs 9.7% ($p=0.76$). In a subgroup analysis of 645 infants >28 weeks, the adjusted OR for NEC in the probiotic cohort was 0.42 (95% CI 0.2 to 0.99, $p=0.047$) suggesting some evidence of benefit in this subgroup.

These results differ to previous pre-implementation and post-implementation

studies⁴ but concur with the observed inconsistencies seen in large randomised trials. Among the two largest RCTs, the ProPrams trial reported a significant reduction in NEC among babies randomised to a probiotic combination containing *B. infantis*, *Streptococcus thermophilus* and *B. lactis*⁵; for participants in the PiPS trial, there was no evidence of NEC reduction among babies randomised to *B. breve* BBG-001.⁶ Neither trial reported significant reductions in late-onset sepsis or mortality.

That these opposing results might occur should not come as a surprise. Different probiotics are very likely to have different mechanisms of action and not all confer similar health benefits. This difference in efficacy between probiotics has led to some uncertainty around which probiotic (or combination thereof) might exert the greatest benefit in preterm babies. A large network meta-analysis evaluated efficacy of different probiotic strains and found that some may be more beneficial than others.⁷ The same review cautions that without clear evidence of efficacy for some probiotics, 'clinicians may be left using inadequately tested, potentially unsafe and possibly ineffective treatments'. The importance of optimum strain selection is highlighted in Granger and colleagues' paper.³ More recently, conditional recommendations from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) for certain probiotic strains have been made⁸ though the American Academy of Pediatrics does not support routine universal probiotic administration, especially to babies <1000 g.⁹ The latter recommendation cites lack of evidence of benefit in modern trials, together with lack of availability of pharmaceutical grade probiotics (in the USA) informing this recommendation.

The most recent Cochrane meta-analysis showed that probiotics may reduce the risk of NEC (RR 0.54, 95% CI 0.45 to 0.65 (54 trials, 10 604 infants; $I^2=17%$); RD -0.03, 95% CI -0.04 to -0.02) [RR=risk ratio; RD=risk difference; CI=confidence interval]. However, due to limitations in trial design and funnel plot asymmetry consistent with publication bias, the evidence was assessed as low certainty. A sensitivity meta-analysis of

trials at low risk of bias showed a reduced risk of NEC (RR 0.70, 95% CI 0.55 to 0.89 (16 trials, 4597 infants; $I^2=25%$); RD -0.02, 95% CI -0.03 to -0.01). The review also showed that probiotics probably reduce mortality (RR 0.76, 95% CI 0.65 to 0.89; (51 trials, 10 170 infants; $I^2=0%$); RD -0.02, 95% CI -0.02 to -0.01) and late-onset invasive infection (RR 0.89, 95% CI 0.82 to 0.97 (47 trials, 9762 infants; $I^2=19%$); RD -0.02, 95% CI -0.03 to -0.01). The evidence for mortality and late-onset invasive infection was assessed as moderate certainty for both these outcomes because of the limitations in trial design. A sensitivity meta-analysis of 16 trials (4597 infants) at low risk of bias did not show an effect on mortality or infection.¹⁰ This review recommended further assessment of probiotics in RCTs but added a caveat that investigators should establish whether families and caregivers would support such a trial.

Similar to the findings by Granger and colleagues,³ the Cochrane review also reported that babies >1000 g appear to benefit more from probiotic supplementation.¹⁰ The factors that underpin why more immature babies may not benefit from probiotic interventions are unclear. It may perhaps relate to increased use of antibiotics in this group, delayed probiotic administration, delayed feeding or indeed, some intrinsic factors within the preterm intestine that prohibit adequate bacterial adherence. While there are many mechanisms by which probiotics might exert benefit, these mechanisms are understudied in preterm babies, partly because the targets on which to base probiotic mechanistic evaluations in this specific patient group are difficult to adequately define and evaluate.¹¹

Uncertainties around optimum probiotic strains selection for use in preterm babies and of probiotics safety have likely contributed to a lower than expected uptake of their use in the UK. A survey of neonatal units conducted in England in 2018 reported 17% of neonatal units using probiotics.¹² The number of neonatal units using probiotics has probably increased since then and will likely continue to do so in light of ESPGHAN recommendations.⁸ Recent reviews have reported that ongoing large randomised trials would not change the findings of NEC reduction in probiotic-treated babies.¹³ However, whichever view one holds, the evidence of benefit for the highest risk preterm babies is less clear.

Large RCTs are essential in order to properly evaluate interventions. In recent times, this has become particularly

¹Neonatal Unit, Homerton University Hospital, London, UK

²Centre for Genomics and Child Health, Queen Mary University of London, London, UK

Correspondence to Dr Paul Fleming, Neonatal Unit, Homerton University Hospital, London E9 6SR, UK; paulfleming1@nhs.net

relevant in evaluating effective treatments for severe disease with SARS-CoV-2. Through clinical networks and collaboration, many treatments for which plausible scientific evidence of benefit existed were subsequently discounted, while other lifesaving interventions were identified (<https://www.recoverytrial.net/results>) using adaptive clinical trial models. As a neonatal community, we should evaluate regulated probiotic interventions with the same degree of enthusiasm and by using similar trial models to find the most effective interventions to reduce NEC in the highest risk preterm babies. Uncertainties around probiotic efficacy will likely remain until such evaluations are undertaken.

Acknowledgements Sincerest thanks to Dr C Howarth, Professor N Aladangady and Mr A Darwin for their assistance with reviewing this manuscript.

Contributors PF is the sole author of this paper and was responsible for writing, editing and reviewing the content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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To cite Fleming P. *Arch Dis Child Fetal Neonatal Ed* 2022;**107**:F344–F345.

Received 25 October 2021

Accepted 7 February 2022

Published Online First 21 February 2022



► <http://dx.doi.org/10.1136/fetalneonatal-2021-322252>

Arch Dis Child Fetal Neonatal Ed 2022;**107**:F344–F345. doi:10.1136/fetalneonatal-2021-323091

ORCID iD

Paul Fleming <http://orcid.org/0000-0001-6027-4212>

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