Letter to Editor:

CURRENT USE OF PROBIOTICS TO PREVENT NECROTISING ENTEROCOLITIS

Samuel Duffield[1], Paul Clarke[1,2]

[1] Neonatal Unit, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK.
[2] Norwich Medical School, University of East Anglia, Norwich, UK

Correspondence to: Dr P Clarke, paul.clarke@nnuh.nhs.uk Consultant Neonatologist, Neonatal Intensive Care Unit, Norfolk & Norwich University Hospital NHS Foundation Trust, Norwich, NR4 7UY, UK.

Each year in England ~230 babies born at <32 weeks gestation develop severe necrotising enterocolitis (NEC), with approximately half of them dying.[1] Successive meta-analyses indicate that dual-strain probiotics - specifically the combination of *Bifidobacterium* and *Lactobacillus* species - significantly reduce the incidence of NEC in very low birth weight infants (VLBWI; <1500g) and halve mortality.[2-4] A 2014 national UK survey[4] done prior to publication of the Probiotic in Preterm babies Study (PiPS) trial,[5] showed that only 12% (7/58) UK tertiary NICUs were using probiotics, while more than half were awaiting the PiPS results. We aimed to determine if the prevalence of probiotic use has changed since publication of the PiPS study in 2015.

During June-July 2018, we telephone surveyed all 58 UK tertiary-level NICUs. We asked a senior member of the medical team (registrar/ANNP/consultant) if their NICU was currently using probiotics for prophylaxis of NEC.

All 58 (100%) units responded. Only 10 (17%) currently used probiotics routinely, all used multi-strain formulations (*Lactobacillus acidophilus* plus ≥1 *Bifidobacterium)*: n=7 Labinic Drops® (Biofloratech, UK); n=3 Infloran® (Desma Healthcare, Switzerland). There has been no significant increase in probiotics use in UK NICUs since 2014 (10/58 versus 7/58, p-value =0.6, χ^2).

Notwithstanding the strong evidence of benefit from using dual-strain probiotics shown by meta-analyses,[2,3] the large PiPS trial which used a single-strain *Bifidobacterium breve* and had a null result has likely influenced the wider adoption of probiotics in the UK. If current meta-analyses are misleading then several hundred high-risk babies receive probiotics annually in the UK for no benefit, albeit at a small monetary cost to the NHS but negligible risk otherwise. However, if the meta-analyses *are not* misleading then thousands of high-risk UK babies (and their families) are being denied an important treatment that, with a risk reduction of ~0.5[2,3], would be preventing severe NEC in at least 100 babies born in England per year and saving the lives of at least 50 annually.

How to negotiate the impasse? Is a new large RCT of dual-strain prophylaxis required to finally adjudicate? It seems unlikely that such a trial will be done. Based on the 3% incidence of severe NEC in babies <32 weeks gestation,[1] to show a halving of severe NEC incidence with a prophylactic dual-strain *Lactobacillus-Bifidobacterium* probiotic combination, a theoretical future RCT would require ~n=3500 babies.

Meanwhile there is mounting supportive evidence from many countries that have already introduced dual-strain probiotics. In Germany most centres routinely offer probiotics below 32 weeks' gestation and 70% of German VLBWI receive dual-strain probiotics,[6] a stark contrast to UK practice. A large observational time-series analysis comparing n=5818 dual-strain probiotic treated (Infloran®) versus n=5072 untreated VLBWI from 44 German NICUs showed that probiotics were associated with markedly reduced NEC incidence (hazard ratio 0.48, 95% CI: 0.38-0.62), reduced overall mortality (hazard ratio 0.60, 95% CI: 0.44-0.83) and post-NEC mortality (hazard ratio 0.51, 95% CI: 0.26-0.99).[7] These impressive findings mirror those of the meta-analyses.

One valid conclusion from the cumulated mass of current evidence is that widespread UK adoption of dual-strain probiotics for VLBWI would save the lives of >50 babies each year, not to mention the huge morbidity/cost burden to the NHS and families of surviving NEC babies. With such high stakes, a NICE (National Institute for Health and Care Excellence) guideline making evidence-based recommendations on the clinical and cost effectiveness of probiotics to prevent NEC in preterm infants is urgently needed and would be universally welcomed.

Reliable up-to-date data on NEC incidence are needed from all UK NICUs, but there is a particular onus on probiotics-using centres to present their data. NEC rates may possibly have reduced generally in recent years in line with increased breast-milk feeding. However, until a standardised, strict NEC working definition is agreed, any comparisons may remain confounded.

Acknowledgements: The authors thank all colleagues who kindly responded to the survey by providing data regarding their units.
Competing interests: None
Contributions: PC devised the study. SD collected all data. SD and PC together drafted the manuscript and approve the final version.
Ethics approval: Not required.

REFERENCES:

1. Battersby C, Longford N, Mandalia S, et al. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012-13: a whole-population surveillance study. *Lancet Gastroenterol Hepatol* 2017;2:43-51. doi: 10.1016/S2468-1253(16)30117-0. Epub 2016 Nov 8.
2. Chang HY, Chen JH, Chang JH, et al. Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: An updated meta-analysis. *PLoS One* 2017;12:e0171579. doi: 10.1371/journal.pone.0171579. eCollection 2017.
3. Thomas JP, Raine T, Reddy S, at al. Probiotics for the prevention of necrotising enterocolitis in very low-birth-weight infants: a meta-analysis and systematic review. *Acta Paediatr* 2017;106:1729-41. doi: 10.1111/apa.13902. Epub 2017 Jun 9.
4. Sesham R, Oddie S, Embleton ND, et al. Probiotics for preterm neonates: parents' perspectives and present prevalence. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F345.
5. Costeloe K, Hardy P, Juszczak E, et al. Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. *Lancet* 2016;387(10019):649-60. doi: 10.1016/S0140-6736(15)01027-2. Epub 2015 Nov 28.
6. Härtel C, Pagel J, Rupp J, et al. Prophylactic use of Lactobacillus acidophilus/Bifidobacterium infantis probiotics and outcome in very low birth weight infants. *J Pediatr* 2014;165:285-289.e1. doi: 10.1016/j.jpeds.2014.04.029. Epub 2014 May 29.
7. Denkel LA, Schwab F, Garten L, et al. Protective Effect of Dual-Strain Probiotics in Preterm Infants: A Multi-Center Time Series Analysis. *PLoS One* 2016;11:e0158136. doi: 10.1371/journal.pone.0158136. eCollection 2016.