Letter to the Editor:

Probiotics for preterm infants and the recent FDA alert in the US

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The US Food and Drug Administration (FDA) recently issued a warning regarding probiotic use in preterm infants[1] leading to the withdrawal of at least two products in the USA. Product withdrawal may extend to Europe, if companies become unwilling to risk legal challenges for products that may not generate significant profits. The FDA alert highlighted the risk of 'invasive, potentially fatal' sepsis with probiotics, and the unregulated nature of the market. Product marketing may have implied probiotics reduce necrotising enterocolitis (NEC), when such a claim can only be made with high-quality randomised controlled trial (RCT) evidence. Despite a plethora of RCTs and meta-analyses (MAs), no RCT with NEC as a primary outcome has shown benefit, nor has any RCT been powered with NEC as the primary outcome. This is disappointing as NEC is responsible for more than 1:20 child deaths before age 10 years.[2] Nevertheless, most neonatal medicine practice is based on MAs, observational studies and clinician experience rather than definitive RCTs.

Probiotics for the prevention of NEC have been studied for over 20 years, yet there remains substantial uncertainty around efficacy partly because of the wide range of strains and combinations tested. However, current MAs suggest a significant reduction in NEC (one-third) and all-cause mortality (one-fifth).[3,4] Furthermore, there is no report of probiotic sepsis within any RCT despite >10 000 treated, although other case reports exist, and overall rates of bacterial sepsis are lower with

probiotics. Infection with probiotic species is rare but important and the true incidence may be under-reported; however, data from our own hospitals suggest the risk is <1:500 treated infants.

Clinicians should practise based on best available evidence. Support from professional bodies would assist clinicians balancing potential benefits of probiotic administration against potential risks and mitigate any caution which may be accentuated by the FDA alert.

Parents and families should be adequately informed and involved in decision-making for their baby. Specifically, parents of babies in all neonatal units should be informed about the data on potential probiotic benefits and risks, and remaining uncertainties.[5] Information sharing should not be limited to parents in units currently using probiotics.

We believe the current data from MAs on risks versus benefits do not demand signed informed consent, but parents have the right to written information and an opportunity to decline probiotics for their baby. We call upon professional organisations such as the British Association of Perinatal Medicine, to work in partnership with parents and advocacy organisations to co-produce evidence-based information leaflets. We recognise the need for further research and share concerns about these unregulated bioactive products available as dietary supplements to augment gut health, but which are unlicensed to prevent the diseases for which they are being given. Meanwhile, balancing benefits versus risks, we believe it is right to continue to offer high-quality probiotics that are quality controlled and produced to Good Manufacturing Practice standards, and in the rights of all parents to be informed of the evidence.

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Ethics approval: Not applicable.

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