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Trial of probiotic to prevent necrotising enterocolitis and infection

Early *Bifidobacterium breve* BBG-001 to prevent Necrotising Enterocolitis, late onset sepsis and death: The PiPS Trial.

K Costeloe, M Wilks, P Hardy, C Nelis, MR Millar for
The Probiotics in Neonates Study Group

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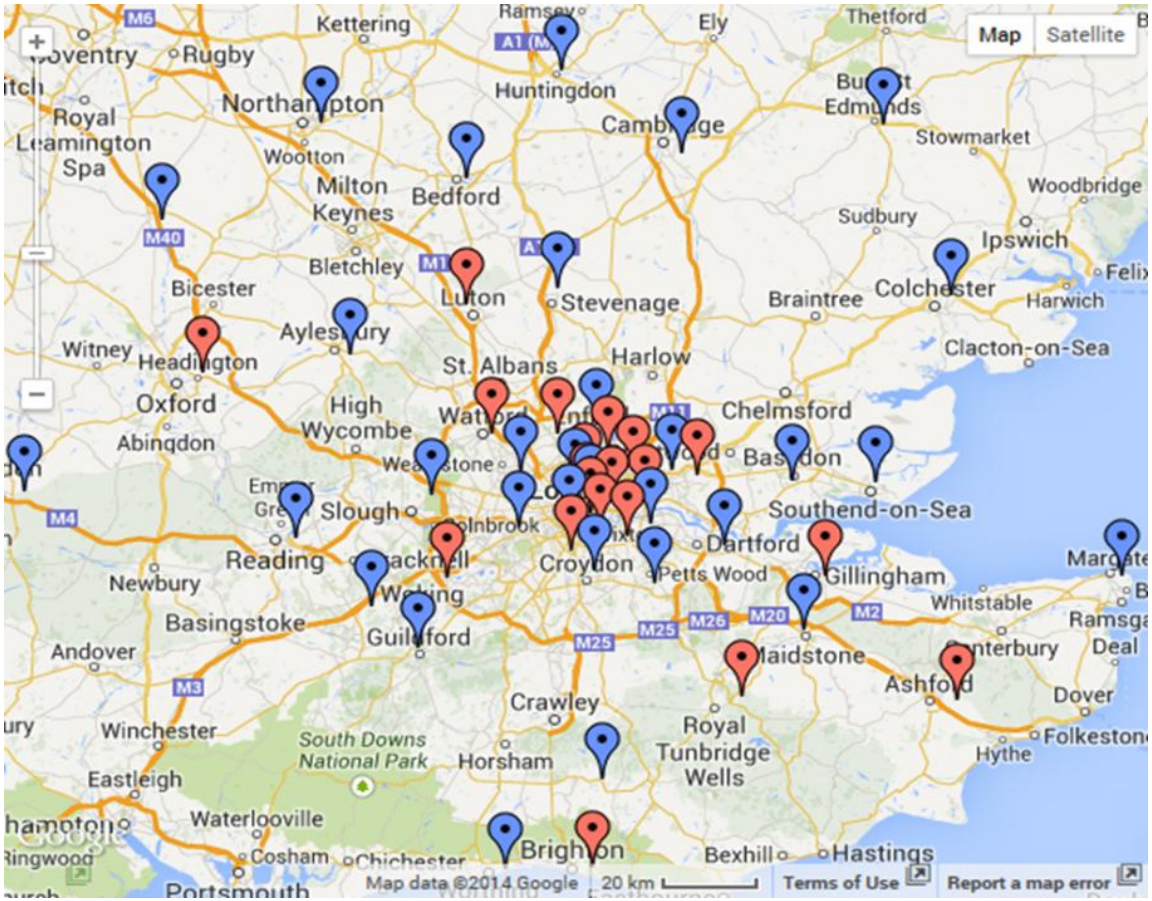

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Background

- Despite >20 trials involving >5,000 babies[1] routine use of probiotics is limited
- A wide range of issues have been raised about some published trials[2]; many on-going questions remain:
  - use of placebo / 'blinding'/ lack of intention to treat analyses
  - Heterogeneity of populations / range of interventions
  - Paucity of efficacy data < 28w GA & <1000g BWt

1. AlFaleh & Anabrees, Cochrane Library, 2014. 2. Mihatsch WA et al. Clin Nutrition, 2012

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We aimed to:

- Recruit an unselected population
- Start the intervention early
- Use a single bacterial strain
- Monitor colonisation

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The product:

- Kitajima H. et al. 1997, evidence of nutritional advantage with *Bifidobacterium breve* BBG-001
- Quality and stability sufficient to support application to MHRA for Clinical Trials Certificate
- Trial complied with ICH-GCP
- Could be reliably identified in stools so making monitoring of colonisation feasible

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The primary outcomes

- Positive blood culture on a sample drawn after 72 hours and before 46w pma with an organism other than a recognised skin commensal: 'Sepsis'
- Necrotising enterocolitis, ≥Bell stage II: 'NEC'
- Death before discharge from hospital: 'Death'

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The population

- 23w+0d to 30w+6d
- Randomised within 48h of birth
- Exclusions:
  - known lethal congenital anomaly or any gastro-intestinal anomaly
  - no realistic chance of survival
- Minimised for site, gestational age, randomisation within 24h of birth

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Trial design

- Multi-centre Double Blind Randomised Placebo controlled trial
- Active intervention: 1 ml *Bifidobacterium breve* BBG-001 (2.1 to 5.3 x 10^8 CFU) suspended in 1/8^{th} strength 'Neocate'
- Placebo: 1 ml 1/8 strength Neocate
- Intervention started ASAP after randomisation, continued to 36w postmenstrual age
- Clinical care at the discretion of local clinicians
- Stools 'colonisation' monitored at 2w pna & 36w pma
- All primary and subgroup analyses by Intention to Treat

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Sample size[1]

- A trial of 1,300 babies will have 90% power to detect a 40% relative risk reduction from 15% to 9.1%
- If the incidence is closer to 12%, a trial of this size will still have 90% power to be able to detect a 44% relative risk reduction from 12% to 6.7%
- …..and a 44% reduction from 10% to 5.6%.

1. PiPS trial protocol at www.npeu.ox.ac.uk/pips

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Analysis

- The primary analyses were by intention to treat (ITT)
- All comparative analyses were adjusted for sex, gestational age at birth, randomisation within 24h of birth and multiple birth
- Subgroup analyses for primary outcomes by ITT were performed for birth at or above vs below 28w and for stool colonisation status at 2w postnatal age
- A secondary analysis of primary outcomes was performed by stool colonisation status at 2w
- Logistic regression analysis was performed to study determinants of colonisation at 2w in those administered probiotic

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Results

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Total Randomised, 24 hospitals, 37months
n=1315

Allocation: *B breve*
n=654
649 received *B breve* BBG
5 received no intervention

- Withdrawal of parental consent to use data: n=4
- **ANALYSED: n=650**

Allocation: Placebo
n=661
656 received placebo
3 received no intervention

- Withdrawal of parental consent to use data: n=1
- **ANALYSED: n=660**

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Baseline characteristics

- A wide range of maternal and perinatal characteristics were well balanced between the groups
- The median gestational age was 28.0 weeks and birthweight 1010g; 48% were below 28w GA
- Over 90% had been exposed to ante-natal corticosteroid

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Early post-randomisation characteristics

- The groups were well balanced:
- The first dose of intervention was given at median age 44 hours
- The median age at the first enteral feed was 3 days
- 94% were exposed to some maternal breast milk in the first 14 days

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Primary outcomes by Intention to Treat

- The rates of the primary outcomes in the placebo group were:
  - NEC ≥stage 2: 10.0%
  - late onset sepsis: 11.7%
  - Death: 8.5%.

- There was no evidence of efficacy to prevent these outcomes

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Subgroup analyses of primary outcomes by Intention to Treat

The subgroup analyses did not provide evidence that efficacy was impacted either by gestational age or by stool colonisation by *B breve* BBG at 2 weeks postnatal age

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Secondary outcomes by Intention to Treat

There was no evidence of efficacy to reduce a range of adverse outcomes including the severity and age of onset of NEC≥ stage 2

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Stool colonisation with *B breve* by ITT

- Of those babies still alive, stools were received from 94% at 2w pna and 84% at 36w pma
- Stool colonisation was monitored by strain specific culture and by PCR at 2w and by culture alone at 36w
- At 2w 85% of the probiotic group and 37% of the placebo group and at 36w 84% of the probiotic and 49% of the placebo group tested positive for *B breve* BBG

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Secondary analysis of the primary outcomes by colonisation with *B breve* at 2w pna

- Of those babies from whom stools were received there were trends towards lower rates of NEC, sepsis and death for those colonised with *B breve* BBG (n=724) vs those who were not colonised (n=462); these did not reach statistical significance
- These groups are not random and this is not an intention to treat analysis

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Determinants of successful 'colonisation' at 2w in those given probiotic (n=649)

- Using logistic regression analysis the only maternal items or neonatal characteristics known in the first 14 days statistically significantly associated with stool colonisation were:
  - Increasing gestation in weeks: OR 1.36
  - Continued antibiotics after day 5: OR 0.26
- Decreasing gestation at birth and prolonged antibiotic use are recognised risk factors for NEC

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Summary

- We found no evidence that *Bifidobacterium breve* BBG-001 given early to babies born before 31 weeks prevents sepsis, NEC or death
- Cross colonisation of the placebo group was high but we did not find evidence that it impacted the results
- Stool colonisation at 2w with the administered probiotic in this population appears to be more common in those who may be at lower risk of NEC

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Summary

- These results are at variance with the published meta-analyses that conclude that probiotics reduce NEC and death in preterm babies
- The only recently published large trial[1] (n=1099), which used a different product[2] shows no evidence of protection from death or from NEC in the subgroup <28w GA

1. Jacobs SE et al. Pediatrics 2013;132:1055
2. Bifidobacterium lactis, Bifidobacterium infantis & Strep thermophilus.

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Implications

- These results do not support the routine use of probiotics at the present time

- The extent of cross colonisation must be taken into consideration when designing future trials of live microbial interventions

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Thank you