



**Background and Transparency:** This newsletter was commissioned by Biofloratech Ltd, who manufacture Labinic® drops, which contain *Lactobacillus Acidophilus*, *Bifidobacterium infantis* and *Bifidobacterium bifidum*. Information intended for healthcare professionals.

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## **Labanic use in moderately preterm babies leads to significantly greater bacterial diversity in Day 10 stool samples**

**Chong CYL, Vatanen T, Alexander T, Bloomfield FH, O'Sullivan JM. Factors Associated With the Microbiome in Moderate-Late Preterm Babies: A Cohort Study From the DIAMOND Randomized Controlled Trial. Front Cell Infect Microbiol. 2021 Mar 1;11:595323.**

The use of Labanic in moderately preterm babies is described as part of the DIAMOND study from New Zealand which included 221 moderate to late-preterm infants. Nearly 64% of babies in the cohort were delivered by Caesarean section. 325 stool samples were examined by 16s rRNA at day 10 and at 4 months of age and various factors examined to determine the extent of microbial diversity in the stool. The later samples showed that bacterial diversity improved over time. A combination of prematurity and delivery by Caesarean section particularly reduced the abundance of Bifidobacteria.

Babies who received probiotics had significantly ( $p=0.01$ ) greater diversity in the day 10 stool samples compared to infants who had not, and in particular Lactobacillus was more abundant. Over time, the differences between the groups became less significant, and other factors such as hospital of birth, socio-economic status as well as feeding practices had effects on the infant microbiome in this work which require further study.

There was also an association between the gut composition and the growth velocity in female infants.

### **Comment:**

The use of prophylactic antibiotics at Caesarean section is recommended by the WHO to reduce risks of maternal wound infection. However it appears to have an immediate but also persisting negative effect on the baby's gut microbial diversity. In this paper, low levels of Bifidobacteria were thought to be due to Caesarean section compounded by slightly slower establishment of breast feeding due to prematurity.

**The positive effects noted on bacterial diversity in the probiotic-treated babies is welcome evidence of colonisation of the gut with probiotic bacteria as a simple and safe way to counteract negative effects from mode of delivery and hospital environmental effects on the gut microbiome.**

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## Caesarean Delivery negatively affects Lactobacillus species

Pan K, Zhang C, Tian J. The Effects of Different Modes of Delivery on the Structure and Predicted Function of Intestinal Microbiota in Neonates and Early Infants. Pol J Microbiol. 2021 Mar;70(1):45-55.

The authors used 16s RNA analysis of term newborn stool samples at 3 and 30-42 days to determine the bacterial diversity. Lactobacillus, Bifidobacteria and Bacteroides predominated in the vaginally delivered infants; those born by Caesarean section showed predominance of Staph, Strep and Corynebacteria, and these differences were significant in the 3-day samples.

In the 30-42 day samples there were similar populations (Bifidobacteria, Bacteroides, Escherichia-Shigella) but Lactobacillus was abundant in only the vaginally-delivered babies.

### Comment:

This study from China adds to the existing evidence of the negative impact on the newborn microbiota due to delivery by Caesarean section. What was interesting however is that, in this work, the recovery of the probiotic population during the first month meant that the main difference that persisted between the groups was a delayed increase in both Bifidobacteria but also Lactobacilli species in the Caesarean section babies.

Lactobacilli are important probiotic bacteria which have a regulatory effect in the microbiome, and also have direct effects on cholesterol, gut function and improved immunity to potentially harmful bacteria, and work cooperatively with Bifidobacteria species.

**Regardless of ethnicity, the presence of Lactbacilli and Bifidobacteria in the gut of healthy newborn babies is associated with short and long term health.**

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## Neonatal antibiotic-related dysbiosis can affect growth (in boys) for years

**Uzan-Yulzari A et al. Neonatal antibiotic exposure impairs child growth during the first six years of life by perturbing intestinal microbial colonization  
Nature Communications volume 12, Article number: 443 (2021)**

This was a large cohort study from Finland, including 12,422 children, of whom just under 10% had received antibiotics in the neonatal period. In the majority, this was Benzylpenicillin and Gentamicin. Just under half received antibiotics for risk of infection, the others for treatment of confirmed/clinical infection. Boys exposed to antibiotics showed significant reductions in weight and height gain in the first 6 years, regardless of indication for antibiotics. Findings were not replicated in girls. However later antibiotic treatment after the neonatal period resulted, in another database interrogation, in higher weight gains in boys, but again not in girls

In a small embedded microbiome study, the authors showed that neonatal antibiotic exposure decreased the ‘richness’ of the lower GI microbiome, but this had recovered by 6 months of age.

Bifidobacteria were most affected by antibiotic exposure, and this effect persisted for 2 years.

### Comment:

Given that previous reports have associated neonatal antibiotic exposure with obesity later on in childhood, this is an interesting finding regarding the timing of effects, which was correlated by examining additional datasets. These were “real-world” cohorts, and were adjusted for confounding factors. The persistence of the abnormality in Bifidobacterial abundance for 2 years post-exposure is interesting, and important given the evidence that the microbial profile tends to reach a settled and persistent equilibrium in the first few years (see next article reviewed). Also interesting is that later exposure to antibiotics resulted in an opposite effect with excessive weight gain.

**The limitation of antibiotics (such as through the use of risk-based approaches e.g. the Kaiser Permanente calculator) would appear to be an intervention which might have long lasting benefits.**

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## Development of the gut microbiota over the first 5 years of life

**Roswall J et al. Developmental trajectory of the healthy human gut microbiota during the first 5 years of life. *Cell Host & Microbe* (2021); doi.org/10.1016/j.chom.2021.02.021**

471 Swedish children underwent surveillance from birth to the age of 5 years, with stool samples collected at the ages of 4 months and 1,3 and 5 years with comparison to an adult population. Even by the age of 5, the microbiota was not completely the same as the adult profile, but there were clear developmental changes in the profiles at the time points measured. Weaning appeared to be a critical time-point. This data also showed that babies born by Caesarean section (and therefore maternal antibiotic treatment perioperatively) had different profiles (the diversity was lower at 4 months but higher at 5 years). *Ruminococcus gnavus* was a marker for an immature profile. High proportions of *R. gnavus* have previously been linked to obesity and metabolic syndrome, cardiovascular and inflammatory bowel disease.

### Comment:

The association between the mode of birth (and thus exposure to antibiotics) with the development of allergies and obesity is becoming clearer and clearer, and there are now specific gut bacteria which can be used as biomarkers of risk.

This is potentially exciting, given that access to these biomarkers (in stool) is easy, and analysis might be possible early enough for treatment (in the form of appropriate probiotics) to be given to reduce the risks of the disease in the future.

The questions will then be whether screening programmes should evaluate candidates for probiotic treatment, or whether the routine use of age-appropriate probiotics could be considered to be a cost-effective and safe intervention for all.

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## Mapping the Human Milk Microbiome

**McGuire MK and McGuire MA. Mapping the Human Milk Microbiome: Impetus for a Long-Awaited Renaissance in Maternal and Infant Nutrition Research? *The Journal of Nutrition*, Volume 151, Issue 2, February 2021, 278–280**

The recognition of the conserved evolutionary complexity and health benefits of human milk continues to grow. In this commentary, the authors consider two papers in the February edition of *The Journal of Nutrition* which describe the impact of infant feeding, mode of delivery and maternal antibiotic treatment on the human milk microbiome. The work raises more questions than answers, but clearly indicates the potential for manipulation of the

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maternal milk microbiome and to consider maternal diet as a potential risk or advantage factor to an optimal milk microbiome.

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**Do the findings of probiotic RCTs in premature babies translate across to real-world practices?**

**Deshmukh M and Patole S. Prophylactic Probiotic Supplementation for Preterm Neonates—A Systematic Review and Meta-Analysis of Nonrandomized Studies, Advances in Nutrition, 2021**

This review of non-RCT publications of the use of probiotics in preterm babies graded the evidence used, and set out to evaluate effects of probiotic supplementation on NEC, sepsis and mortality. 30 studies were included, with data from over 77,000 babies.

The analysis showed that routine use of probiotics resulted in significant reductions in NEC (OR 0.6), late-onset sepsis (OR 0.85) and mortality (OR 0.77). In babies <1000g, NEC was significantly reduced but not sepsis or mortality.

The analysis also showed that multistrain probiotics were more effective than single strain ones.

**Comment:**

This is yet more evidence from real world use, in a huge number of premature babies, that multi-strain probiotics are safe and effective for important outcomes.

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**Labinic is a multi-strain probiotic manufactured to extremely high-quality control standards. Labinic has an excellent safety profile and is widely used in NHS and overseas neonatal units.**

**We are pleased to see further evidence of its use emerging in clinical papers and we are happy to confirm that we have had no influence over any publications describing its use.**

Thank you for reading this update, we hope you found it interesting. Please feel free to share with healthcare-professional colleagues.

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