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NATURAL PROBIOTIC DISCOVERED IN UK NEWBORNS MICROBIOMES

Subtitle: In the largest genomic analysis of UK infant microbiomes to date, researchers have uncovered a type of bacterium that helps digest breast milk and protects a baby's gut from pathogens.

Newborn babies have one of three pioneer bacteria in their gut shortly after birth, one of which could be used to develop new personalised infant therapeutic probiotics, researchers show.

In the largest study of UK baby microbiomes to date, researchers from the Wellcome Sanger Institute, University College London (UCL), and the University of Birmingham, used whole genome sequencing to analyse stool samples from 1,288 healthy infants, all under one month old from the UK Baby Biome Study[1].

This research, published today (6 September) in *Nature Microbiology*, found that one of these beneficial bacterial pioneers was genetically adapted to make full use of the nutrients in breast milk, suggesting that it is the most suited to thrive in a baby's microbiome. The team uncovered that this bacterium can also block pathogens from colonising the babies' gut, highlighting its significant potential as a natural probiotic.

The findings could support the development of infant formulas and therapeutic probiotics containing the most effective natural strains for the baby's gut. Currently, most commercial infant probiotics contain a different bacterial strain not found in the early microbiomes of infants in industrialised societies like the UK and the US[2,3].

In addition to the two beneficial pioneer bacteria, researchers highlighted a third bacterium that is considered risky as it can lead to the colonisation of antibiotic-resistant bacteria. This can interfere with the development of the infant microbiome and increase the risk of pathogens colonising the gut.

In the future, it could be possible to predict how a baby's gut will develop by mapping their gut microbiome profile right after birth to assess which pioneer bacteria they have. If needed, a personalised probiotic could be provided to help promote healthy microbiome development and protect against potentially pathogenic infections.

Further research such as the Microbes, Milk, Mental Health and Me (4M) project is needed to understand the impact of pioneer bacteria on health.[4] This project, co-led by the Wellcome Sanger Institute, is part of the Children Growing Up in Liverpool study involving 10,000 mothers and infants. This extensive research seeks to explore how factors such as the infant gut microbiome and early life feeding affect brain development, behaviour, emotions and mental health later in life.

The gut microbiome is a complex ecosystem of millions of microbes that are vital for human health and important in immune system development. As it begins to form immediately at birth, the first month is the earliest window for intervention with probiotics that could be used to restore or boost the microbiome. However, before this study, there was a lack of high-resolution data showing how the microbiome develops in this period of life, and which bacteria would be the most useful in healthy newborns.

Building on a previous UK Baby Biome Study that showed babies born by vaginal birth had a different microbiome compared to those born via caesarean[5], this new research analysed an expanded dataset of 2,387 stool samples from 1,288 UK infants born in hospitals and some of their mothers. The team from the Wellcome Sanger Institute, UCL, and the University of Birmingham, found that all

newborns fell into one of three microbiome profiles, each characterised by a different dominant pioneer bacterium.

Out of these pioneer bacteria, *Bifidobacterium longum subsp. longum* (*B. longum*) and *Bifidobacterium breve* (*B. breve*) are considered beneficial as they promote the stable colonisation of other beneficial microbes, and *Enterococcus faecalis* (*E. faecalis*) is considered risky.

B. longum was found to come from the mother's gut during childbirth, however, the team found that *B. breve* was not transmitted in this way[6]. The team also uncovered that *B. breve* was genetically adapted to fully utilise the nutrients found in breast milk and can block potentially damaging pathogens from colonising the babies' guts.

Around 85 per cent of the babies studied were breastfed in the first few weeks of life. Researchers found that breastfeeding versus formula feeding did not seem to influence the type of pioneer bacteria in the baby's gut, however the use of antibiotics did[7]. Researchers highlight that other factors such as maternal age and how many times someone has given birth may also play a role, but further research is needed to investigate this and the impact on long-term health outcomes.

They also showed that a bacterium commonly found in commercial infant probiotics known as *Bifidobacterium longum subsp. infantis (B. infantis)* was not a pioneer bacterium, and is rare in UK infants. This finding is aligned with research from other Western industrialised countries that also shows a lack of naturally occurring *B. infantis* in early infant microbiomes[2,3] and suggests that *B. breve* could be a more effective natural probiotic.

Dr Yan Shao, first author from the Wellcome Sanger Institute, said: "If we think of a newborn baby's gut as an ecosystem that starts to establish right from birth, there was very little known about which and how microbes plant the very first seeds to establish themselves before the findings of the UK Baby Biome Study. By analysing the high-resolution genomic information from over 1,200 babies, we have identified three pioneer bacteria that drive the development of the gut microbiota, allowing us to group them into infant microbiome profiles. Being able to see the make-up of these ecosystems and how they differ is the first step in developing effective personalised interventions to help support a healthy microbiome."

Professor Louise Kenny, Lead Investigator of the Children Growing up in Liverpool study from the University of Liverpool, said: "Decisions around mode of childbirth and breastfeeding are complex and personal, and it's important to note that there is no one size fits all approach when it comes to what the best options are for you and your baby. It is also important to note that we still have an incomplete understanding of how the role of mode of birth and different methods of infant feeding influence microbiome development and how this impacts later health. That's why this research is vital. We must continue to find new ways to ensure that all children are supported to have the best possible start in life."

Professor Nigel Field, study co-author from UCL, said: "While our study has shortlisted three pioneer bacteria as important for babies' microbiome development, it remains to be determined if and how different pioneer bacteria affect health and diseases, both in childhood and later in life. The UK Baby Biome Study is actively following up participants to give clues about this, and now even bigger cohorts are needed to investigate the role of the infant microbiome on health."

Dr Trevor Lawley, senior author from the Wellcome Sanger Institute, said: "The development of the microbiome at the beginning of a person's life could have huge implications for them later on. It is also a time when the use of infant probiotics could be highly effective, if we know what bacteria are both important and relevant to the target populations. Our study highlights a hugely beneficial pioneer bacterium that can fully digest breast milk and protect the newborn against harmful microbes. This has the potential to be a highly effective natural probiotic as it can already establish itself in the child's gut, and I hope that our open-access study encourages the rational selection of

probiotic strains and development of novel microbiome-based therapeutics built on genomic research."

ENDS

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Notes to Editors:

The researchers would like to thank the participating families for their time and contribution to the Baby Biome Study and the research midwives at the recruiting hospitals.

1. The UK Baby Biome study is a large-scale UK birth cohort study and biobank, with longitudinal follow-up through electronic health data linkage. It aims to understand how interactions between microorganisms, the immune system, and clinical, social, and behavioural factors during pregnancy and early life influence later health and disease. Stool samples were collected from newborns and mothers, along with vaginal swabs from the mothers and umbilical cord blood. Funded by Wellcome, it was a collaboration between the Wellcome Sanger Institute, UCL, the University of Birmingham and collaborating hospitals.
2. Ennis, D., Shmorak, S., Jantscher-Krenn, E. Yassour, M. (2024) Longitudinal quantification of Bifidobacterium longum subsp. infantis reveals late colonization in the infant gut independent of maternal milk HMO composition. *Nature Communications*. DOI: 10.1038/s41467-024-45209-y
3. Casaburi, G. *et al*. (2021) Metagenomic insights of the infant microbiome community structure and function across multiple sites in the United States. *Scientific Reports*. DOI: 10.1038/s41598-020-80583-9
4. Sanger Institute researchers and collaborators are building the most detailed dataset on microbiome development in the world to unlock new insights into human health, specifically focusing on how the microbiome impacts mental health. This project, called 'Microbes, Milk, Mental Health and Me' is part of the new Children Growing Up in Liverpool (C-GULL) study. Funded by Wellcome, this study will track the health of 10,000 babies and their families, from early pregnancy to childhood. It aims to unravel the complex interactions between genetics, environment and early life exposures on long-term health outcomes and seeks to explore how factors such as the infant gut microbiome and early life feeding affect brain development, behaviour, emotions and mental health later in life. Volunteer registration is currently live, for more information, please visit: https://www.cgullstudy.com/taking-part/
5. The previous study analysed 1,679 samples of gut bacteria from nearly 600 healthy babies and 175 mothers. It found that babies born vaginally have different gut bacteria than those delivered by caesarean. It showed that vaginally born babies got most of their gut bacteria from their mother's gut, not their vagina as previously thought. Babies born via caesarean did not acquire the bacteria from their mothers and instead had more bacteria associated with hospital environments. The researchers found that the differences in gut bacteria between vaginally born and caesarean-delivered babies largely evened out by 1 year old. The full release can be found: https://www.sanger.ac.uk/news_item/babies-gut-bacteria-affected-delivery-method-baby-biome-project-shows/
6. While *B. longum* was found to come from the mother's gut during childbirth, *B. breve* was not transmitted in this way. This study did not identify the exact source of transmission for

this bacterium, however, researchers suggest that it could have been from another area of the mother, for example, the skin microbiome. It was also found to be more common in children whose mothers identified as Asian.

7. This study suggests that the use of antibiotics increases the chance of *E. faecalis* colonising infant guts, however, it is not clear if this has any long-term health impact. Profiling a newborn microbiome and developing personalised probiotic treatment could benefit infants with this microbiome profile.

Author interests:

Dr Trevor Lawley is also a co-founder and Chief Scientific Officer of Microbiotica, a clinic-ready biopharmaceutical company specialising in the development of precision live biotherapeutic products with lead products in immuno-oncology and inflammatory bowel disease**.**

Publication:

Y. Shao, C. Garcia-Mauriño, S. Clare, *et al*. (2024) Primary succession of Bifidobacteria drives pathogen resistance in neonatal microbiota assembly. *Nature Microbiology*. DOI: 10.1038/s41564-024-01804-9

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Selected websites:

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