The relevance of probiotics in Caesarean-born neonates

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Abstract. There is growing interest in the use of probiotics in neonates. In particular, *Lactobacillus rhamnosus*, *L. acidophilus*, *Bifidobacterium breve* and *B. longum* have been well studied. Caesarean-section (CS)-born infants often lack *Lactobacillus* spp. and *Bifidobacterium* spp., which showed increasing evidence in establishing the neonatal immune system. Furthermore, CS increases the difficulties for mothers in initiating and sustaining breastfeeding. Increasing evidence shows CS-born infants are more susceptible to allergy, infections and chronic inflammatory diseases later in life. The number of CS births has increased continuously, now accounting for 35% of all deliveries Australia wide. In this context, probiotics may have a role in establishing a healthy neonatal gut microbiome.

Introduction

'An ounce of prevention is worth a pound of cure' is an axiom by Benjamin Franklin, one that is relevant especially in the current COVID-19 pandemic. In Australia, rates of delivery by Caesarean-section (CS) have increased and reached 35% in 2017[1]. Antibiotics are used regularly for both prophylaxis and treatment of infections in mothers who deliver babies through CS[2]. This excess use is important for its potential role in driving antimicrobial resistance worldwide[3] and also has an impact on the establishment of the neonatal gut microbiome.

CS is associated with significant difficulties in initiating breastfeeding when compared with vaginal birth[4]. The microbiome of breast milk contains bacteria, including lactic-acid bacteria (LAB), and is

important in establishing the gut microbiome of neonates[5]. Breast-feeding helps to establish healthy gut microbiome. LAB were first described by Pasteur as part of fermentation to prevent spoilage approximately 70 years before the discovery of penicillin in 1928[6] (Figure 1).

CS-born infants generally lack LAB, i.e. *Lactobacillus* spp. and *Bifidobacterium* spp., which appear important in establishing the neonatal immune system[7]. Recent data support the theory that probiotic administration to CS-born infants may prevent allergy in children and young people[8]. Certain species of *Bifidobacterium* spp. may only be isolated from human breast milk within a few days after birth[9]. Early intervention through probiotic administration in neonates, especially in neonates born via CS may improve general health, given their susceptibility to various chronic diseases[7] as well as potential prevention of chronic inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, coeliac disease and diabetes mellitus later in life[10].

Probiotics, in particular *Lactobacillus* spp. and *Bifidobacterium* spp., are considered normal flora and part of human gut microbiota[7]. *Lactobacillus* spp. and *Bifidobacterium* spp. are considered generally regarded as safe, especially for oral administration[11]. In international guidelines such as the FAO/WHO guideline, probiotics are recognised as having a role in maintaining gut health and may modulate host immunity[11]. In this article, the genomes of *Lactobacillus* spp. and *Bifidobacterium* spp. are described along with the mechanisms of action of LAB in interfering against pathogenic bacteria.

Very recently the taxonomy within genus *Lactobacillus* spp. was re-classified into 25 genera[12]. As the changes were very recent, and these new genera have not been adopted to the WHO/FAO guideline for probiotics, genus *Lactobacillus* will be used for this article.

It is proposed that genus *Lactobacillus* of *L. casei*, *L. paracasei* and *L. rhamnosus* as genus *Lacticaseibacillus*[12]. *L. salivarius* and *L. fermentum* have been named as *Ligilactobacillus salivarius* and *Limosilactobacillus fermentum*, respectively[12]. Genus *Lactobacillus* of *L. acidophilus* and *L. gasseri* have not changed[12].

Probiotic use in neonates

There have been extensive studies of the use of probiotics in neonates including preterm infants[13–16]. In particular, these studies have focussed on the role of probiotics in reducing the incidence of necrotising enterocolitis (NEC) and sepsis. Most significantly, a randomised controlled trial of a symbiotic preparation including *L. plantarum* in 4500 term neonates in the community resulted in a 42% reduction in neonatal sepsis[17].

In addition to its impact on neonatal sepsis, probiotics may reduce gastrointestinal complications in neonates though the evidence is mixed[18]. The large Probiotics in Preterm Infants Study (PiPS) Trial randomised 1310 pre-term babies to treatment with *Bifidobacterium breve* BBG-001 or placebo and showed no reduction in rates of sepsis, NEC or death[16]. In contrast, the ProPrems trial, a randomised-controlled trial that included 1099 preterm infants from Australia and New Zealand demonstrated a reduction of NEC of approximately 50%[19]. The strains being used in the ProPrems trial were *B. infantis*, *S. thermophilus* and *B. lactis*. A metagenomic approach to characterise the gut microbiota was also used in a sub-study of ProPrems trial, which showed abundance of *Bifidobacterium* spp. in the infants administered with probiotic[15]. In neonates, while considered generally safe, cases of *Lactobacillus* bacteraemia have been reported including in a <1000 g weight pre-term infant following a laparotomy[20].

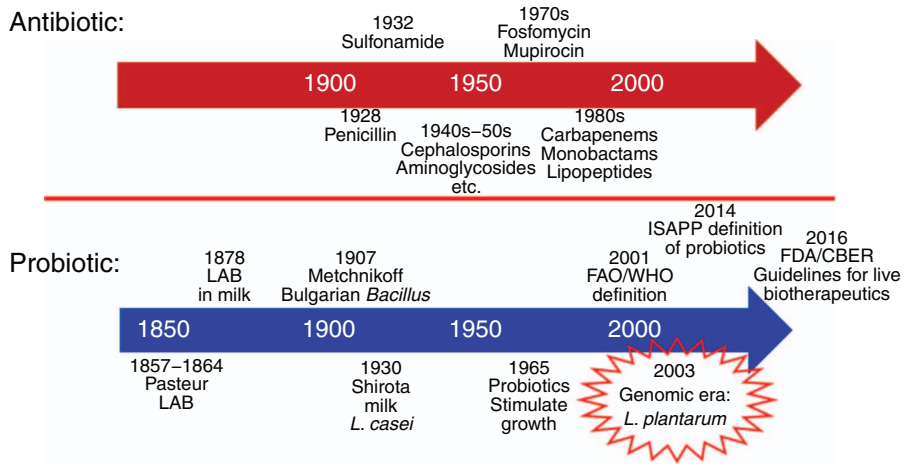

Figure 1. Timeline of probiotic development in comparison to the antibiotic development.

L. plantarum, *L. gasseri* and *L. salivarius* have been isolated from infants' oral and faecal samples[21–23]. Therefore, these three genera are considered normal infants' microbiota and warrant further research. Thus far, there is no published research study of using *L. gasseri* and *L. salivarius* in neonates. Further, these strains are not commercially available for infants or neonates yet. Research is required to include species not typically in the current formulation of probiotics for neonates. As *L. plantarum* may reduce atopic dermatitis[24], and *L. gasseri* and *L. salivarius* may have immunomodulatory effects[21,22], these should be considered for inclusion in probiotic formula for neonates. In the potential formulation of the probiotics, *Bifidobacterium* spp. have been reported as predominant genus in breastmilk microbiome[7]. Therefore, to add another strain to the formula would need to consider the species proportion in the breastmilk, i.e. with lower CFU than *Bifidobacterium* spp. Of note, *L. plantarum*, *L. gasseri* and *L. salivarius* are in the commercial formula available for adults.

Probiotic administration has also significantly reduced the length of stay in pre-term infants[23]. A cost-saving analysis in pre-term infants supplemented with probiotics showed a saving of €2000 per infant[25]. The clinical impact and cost effectiveness of probiotic administration require further well designed laboratory, clinical and cost analysis research.

Mechanisms of probiotics in interfering with pathogens and immune modulation

Probiotics interfere with pathogens through acid production, hydrogen peroxide production and bacteriocin activity[26]. Production of bacteriocins, small peptides with anti-bacterial activity of *Lactobacillus* spp. has been reported to inhibit pathogen growth[26]. Specific short-chain fatty acids (SCFA) have been studied to understand their beneficial properties, such as butyrate for the antagonistic activity against cancer cells and anti-inflammatory property[27]. SCFA production by *Bifidobacterium* spp. in the gastrointestinal tract results in a lower pH and inhibition of potentially pathogenic bacteria[28].

Bacterial exopolysaccharide has been known to possess immunostimulatory properties[29,30]. Extracellular vesicles (EV) in Gram-negative bacteria have been studied for their pathogenicity, host-pathogen interaction and potential targets in vaccine development[31]. Very recently, studies on EV were performed in probiotic strains and revealed potential delivery of bacteriocins and other beneficial properties through the EV[32,33]. Advancing research on EV of probiotics is highly recommended as it will provide further understanding on molecular mechanisms of probiotic bactericidal properties against pathogens and immune modulation. Evidence of *Bifidobacterium* spp. in boosting immune systems has been demonstrated mostly in the mouse model, marked by the stimulation of IL-6 and IL-10 in the ileal Peyer's patches and in weaned pig model, marked by the increase of IgA against the parasite and IgG[34,35].

Genomes of LAB

Genome data provides comprehensive data that might also help to determine the beneficial properties and the potential virulence determinants in the strains. Genome data enable the comparison of the strains with publicly available genome data. We limit the discussion of the genomes to the strains being used commercially in humans. The recent genus *Lactobacillus* name changes have not impacted the species and genomes, as we abbreviate the genera.

L. rhamnosus GG (LGG) has been the most commercially popular probiotic strain. More than 1100 studies on *L. rhamnosus* GG were found in NCBI (accessed 22 April 2020). *L. plantarum* 299v has shown beneficial properties such as effectiveness to treat irritable bowel syndrome[36]; regardless, only 112 studies on *L. plantarum* 299v versus 204 studies on *L. plantarum* WCFS1 were in NCBI. Very few studies were on *L. salivarius* with 39 studies of *L. salivarius* UCC118 found from NCBI. As previously described, the *L. plantarum* WCFS1 genome was first sequenced in the early 2000s and has been well described with its genome of 3 308 273 bp (GenBank accession number NC_004567.2) and a total of nearly 1200 identified proteins. The beneficial properties of *L. plantarum* WCFS1 include the ability of this strain to survive in a wide range of environments with temperature and pH changes[37]. The parental strain of *L. plantarum* WCFS1 is *L. plantarum* NCIMB 8826, which was isolated from human saliva[38]. *L. plantarum* NCIMB 8826 colonises the oral cavity well but not the human intestine, although it has been demonstrated to survive in the gastrointestinal tract, including faeces[39]. *L. gasseri* ATCC33323 (Accession Number of NC_008530.1) was the complete reference *L. gasseri* genome in the NCBI database with its genome of 1 894 360 bp. *L. gasseri* ATCC33323 is an autochthonous microbe in the gastrointestinal system[40]. Therefore, oral application of the *L. gasseri* ATCC33323 for intestinal colonisation may be well tolerated. For a comprehensive genome description of *L. salivarius* UCC118, the reference strain being used here is available through the study by Claesson and colleagues[41]. The size of the chromosomal genome of *L. salivarius* UCC118 was 1 827 111 bp (GenBank accession number: NC_007929.1). General probiotic properties of *L. salivarius* were the ability to eliminate pathogens and the adaptation to the

gastrointestinal niche[42]. *L. salivarius* UCC118 has broad spectrum activity versus Gram-positive bacteria[43]. Therefore, *L. salivarius* UCC118 has very strong probiotic properties and is autochthonous to the gastrointestinal tract.

Genomes of *Bifidobacterium* spp. have also been described, i.e. *B. longum* (n = 349), *B. breve* (n = 109), *B. bifidum* (n = 104) and *B. animalis* (n = 83) (from NCBI, accessed 2 March 2020). *B. longum* NCC2705, *B. breve* DSM 20213, *B. bifidum* PRL2010 and *B. animalis* subsp. *lactis* DSM 10140 are the reference genomes in NCBI with genome sizes of 2.257, 2.257, 2.215 and 1.938 Mb, respectively (GenBank Accession Numbers: NC_004307.2, NZ_JDUD000000000.1, NC_014638.1 and CP001606.1, respectively).

Current evidence

Probiotic supplementation in neonates has been frequently studied. In an era of interventional birth leading to high rates of CS, probiotics may have a role in establishing a healthy gut microbiome. The impact of probiotics in this setting may include a reduction in important acute complications such as neonatal sepsis, and NEC and longer-term impacts relating to the development of mucosal immunity and atopy. The heterogeneity of trial results may relate to the differing strains used. Genomic and metagenomics approaches to analysing the gut microbiome may improve understanding of gut dysbiosis and its role in these complications.

L. rhamnosus, *L. casei*, *L. acidophilus*, *L. plantarum*, *L. gasseri* and *L. salivarius* are listed in the three main regulatory bodies in

Table 1. Commercially available probiotics for infants including neonates.

Product (company)	Composition	Administration	Countries
Infloran (Laboratorio Farmaceutico)	*L. acidophilus* NCDO1748 and *Bifidobacterium bifidum* NCDO 2203	Neonates including premature infants up to 6 years	Product of Italy Available in Australia Widely used in neonatal units in Australia
Infant Probio (Health Aid)	*L. reuteri* NCIMB 30351 (200 million CFU per dose)	Drops (5 drops, 1/day), infants up to 3 years	Product of UK
Upspring Probiotic + colostrum (Upspring)	Six probiotic strains (*B. lactis*, *B. longum*, *B. breve*, *L. rhamnosus*, *L. acidophilus*, *L. reuteri*), 3 billion for Bifidobacterium and 2 billion for *Lactobacillus* spp. + colostrum	0–4 months (half pack per day) 4–12 months (one full pack daily)	Product of USA Available in Australia
Probiotic Baby (Jamieson)	*B. animalis* subs. lactis or BB-12 (1 billion CFU in 6 drops)	Drops 1–36 months	Product of Canada
Protectis baby drop (Biogaia)	*L. reuteri* DSM 17938 (100 million CFU in 5 drops)	Drops do not specify the age bracket, but for baby	Product of Sweden Available in Australia
Inner Health Baby Probiotic (Inner Health Plus)	*B. breve* (BR03 and B632) (2 million CFU in 5 drops)	6–36 months	Product of Australia
MetaKids Baby probiotics (Metagenics)	*L. rhamnosus* GG and *B. animalis* subs. *lactis* (BB12) (1 billion CFU in 6 drops)	0–12 months	Product of USA Available in Australia
Probiotics Baby Drops (Radiance)	*B. lactis* (BB12), 6 drops (1 billion CFU in 6 drops)	Pregnancy and baby including newborn	Product of New Zealand
Kids Smart Drops Probiotic (Nature's Way)	*B. animalis* subsp *lactis* BB12 (1 billion CFU per mL)	0–12 months – 0.5 mL daily (12–24 months – 1 mL)	Product of Australia
Baby probiotic colic drops (Renew Life)	*Pediococcus pentosaceus* and *B. longum* strains (1 billion CFU in 5 drops)	0–36 months	Product of USA Available in Australia
Flora Baby (Renew Life)	*B. breve* (600 million CFU), *L. rhamnosus* (500 million CFU), *B. bifidum* (400 million CFU), *B. longum* subp *infantis* (300 million CFU) and subp. *longum* (200 million CFU) in 500 mg	0–12 months (500 mg) >12 months (1 g)	Product of USA Available in Australia
Probiotic Powder for Infant (Life-Space)	Two types of probiotics that are naturally found in breastmilk	1–6 months	Product of Australia

European Food Safety Authority (EFSA), Canada and China as strains can be added in food[44], which may broaden the use of these strains as human food supplement in countries outside Europe, e.g. China and Canada. Europe has been the epicentre for probiotic development and generation so far. EFSA allowed 37 different *Lactobacillus* spp. for consumption through food[44]. Therefore, supplementation of *Lactobacillus* spp. and *Bifidobacterium* spp. to infants and neonates can be categorised as natural administration of beneficial microbes or probiotics to maintain gut microbiota and immune systems[45].

Infloran containing *Bifidobacterium bifidum* and *Lactobacillus acidophilus* is a commercial probiotic widely used in neonatal units in Australia. Other probiotics available in pharmacies are listed in Table 1. Many commercial preparations are not included in the table due to a lack of published data on the strain identity and CFU counts. Guidelines in choosing the right probiotics are available from International Scientific Association for Probiotics and Prebiotics website (https://isappscience.org/). Industry-related probiotic information can be found from the International Probiotic Association website (http://internationalprobiotics.org/). As probiotic administration is now becoming broader than oral administration, the use of the food-medicine interface guidance tool within Therapeutic Goods Australia (https://www.tga.gov.au/) is highly recommended in translating probiotic research to industry.

In summary, with the increasing evidence of CS births in Australia and worldwide, and antibiotic prophylaxis administration in CS births, as well as the potential delay of the breastfeeding initiation, it would be highly recommended to provide probiotics those commonly isolated from breastmilk, to CS born neonates. Probiotic administration mimicking the LAB of breastmilk will be likely a better option than inoculation of swabs originated from vagina, often called seeding. Future studies that include microbiome analysis, neurocognitive development as well as economic analysis of probiotic administrations are highly recommended.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

Dr Hanna E Sidjabat is a molecular microbiologist with a strong industry link in translating her probiotic research to manufacturing. In addition to her probiotic expertise, she has a solid background in antibiotic resistance mechanisms including genome and proteome due to 15 years of research experience. She has strong research focus in the bacterial genome, proteome of pathogens and probiotics. To date, Dr Sidjabat has published 87 peer-reviewed articles in international journals. Dr Sidjabat has supervised and mentored 35 PhD students, Postdoctoral Research Fellows, Master and Honours students, Microbiology Registrars, local and international Infectious Diseases Visiting Academics following the completion of her PhD in 2007.

Alaa Mohammed Ali Alsaggaf is a Master graduate in molecular microbiology from the University of Queensland, School of Chemistry and Molecular Biosciences. Alaa has worked extensively on the genome of *Lactobacillus* spp. within Sidjabat's team at the University of Queensland Centre for Clinical Research (UQCCR). She has clinical microbiology role in Saudi Arabia within Ministry of Health. She received the UQ SCMB Dean's award for her project in the second semester of 2018.

Akshatha Gopalakrishna has a Masters degree in molecular biology research and is equipped with extensive microbiology and biochemistry laboratory skills from the University of Queensland, School of Chemistry and Molecular Biosciences. She has worked extensively on *Lactobacillus* spp. for screening of probiotic strains within Sidjabat's team at the UQCCR. She has further extended her skills on histology, immunohistochemistry staining, various microscopic skills and sample preparation for MRI at the UQ Centre for Advanced Imaging.

Evelyn Nadar is a graduate of Master's in molecular biology research extensive with extensive laboratory skills from the University of Queensland, School of Chemistry and Molecular Biosciences. She has worked extensively on *Lactobacillus* spp. proteomic analysis of probiotic research within Sidjabat's team at the UQCCR. She has also expanded her animal handling skills and histology including microscopy skills.

Dr Adam Irwin is a conjoint Senior Lecturer and academic lead for Paediatric Infectious Disease at Children's Health Queensland and the University of Queensland. His research focuses on diagnostic evaluations to optimise the use of antimicrobials in children. Specifically, he is interested in healthcare-associated infections and infections resistant to antimicrobial therapy. He is also interested in the clinical and molecular epidemiology of invasive Gram-negative infections. Dr Irwin studied at the University of Birmingham Medical School and completed training in Paediatric Infectious Disease and Immunology in London. He was awarded his PhD by the University of Liverpool Institute of Infection and Global Health in 2016.

Dr Pieter Koorts is the Director of Neonatology Royal Brisbane and Women's Hospital since 2016, Acting Director of Neonatology RBWH (2015–2016), Deputy Director of Neonatology RBWH (2009–2015), Staff Specialist Neonatologist RBWH (2007–2009). Dr Koorts has affiliation as a Senior Lecturer with School of Medicine, University of Queensland since 2007. Dr Koorts started his career in paediatrics in 1998 and into neonatology as a Senior Lecturer and Senior Staff Neonatologist (2005–2006) at Pretoria University, South Africa. Dr Koorts was a neonatal fellow at Mercy Hospital for Women, Melbourne, in 2002–2005.

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