Developing a Healthy Gut Flora in Children

Science and nature in balance

Claire Barnes

Probiotics International,

Lopen Head, Somerset

Protexin®

Agenda

- About myself
- How the microbiome develops from birth
  - What factors alter its development
- How the immune system develops and the interactions between the microbiome and immune system
- How the interactions of the microbiome and the immune system could have an affect on developing childhood conditions, such as:
  - Immune imbalances
  - Autism
  - Obesity/Type 2 diabetes
  - Fussy eaters
- Improving the developing microbiome in children – how probiotics could help

Science and nature in balance

Protexin®

Claire Barnes BA(hons),DipNT,mBANT,CNHC
Technical Advisor,

Science and nature in balance

Natural & Organic Products Europe LONDON
The Natural Food Show
Natural Beauty & Spa
Natural Living
Natural Health

Integrative Healthcare SYMPOSIUM

camexpo

Mail Online HELLO! True Health EXPRESS prima

Protexin®

How the microflora develops from birth

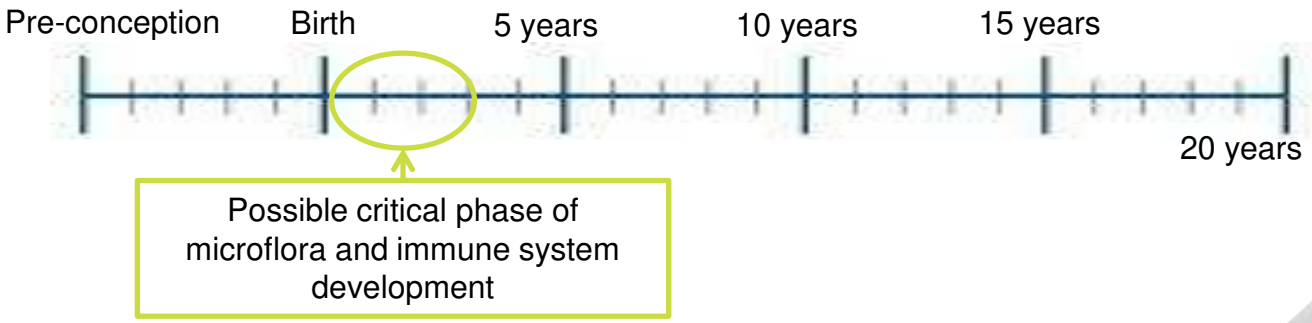
- Mode of birth
- Feeding method
- Gestational time
- Antibiotics
- Environment
- Weaning

Science and nature in balance

Protexin®

Is there a Critical Phase of Infant Development?

- Recent studies have suggested that early microbiota imbalances are not reflected in adults, (Falony *et al,* 2016).
- Birth cohort studies have shown that alterations to an infants microbiome can have an affect on the immune system which may impact conditions later in childhood, (Hoskin-Parr *et al*, 2013, Sjögren *et al*, 2009).
- If the microbiome is altered within a critical phase, could it potentially have an affect on later immune conditions developing?

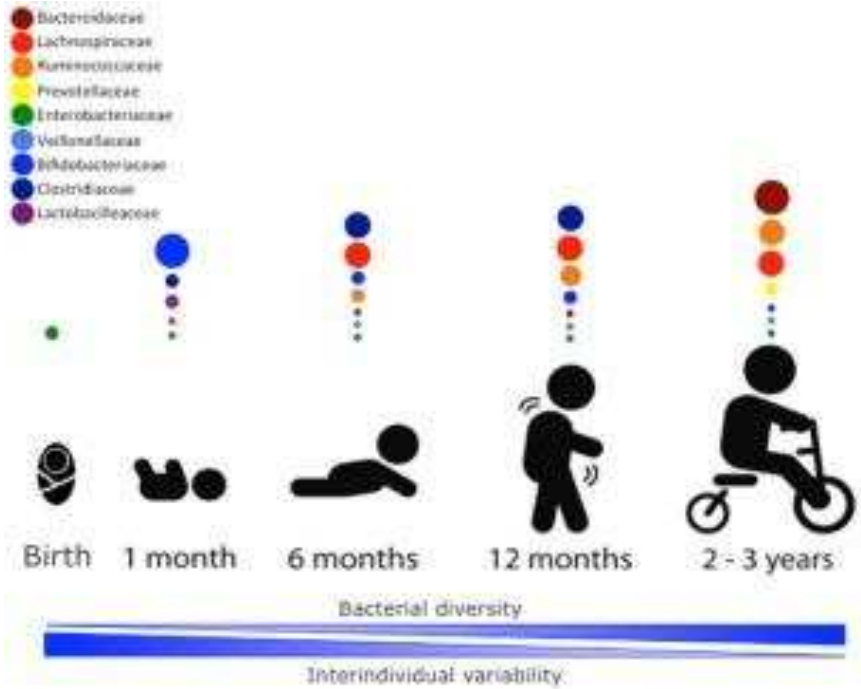


Science and nature in balance

Protexin®

Seeding the Infant Microbiome

- The reproductive tract was previously believed to be sterile, however recently experts have speculated that seeding of the infants microbiome starts with the placenta.
- Studies have shown that newborns have complex microbial communities in the gut within the first few weeks, which then fluctuate in bacterial composition until a relatively mature diversity is reached around 1-3 years, (Biasucci et al, 2008).
- The first bacteria to establish in the newborn gut are usually aerobic, which then consume oxygen and change the environment of the intestines making it more suitable for anaerobic bacteria to thrive, (Alderberth, 2008).



http://journal.frontiersin.org/article/10.3389/fimmu.2014.00427/full

Science and nature in balance

Protexin®

How the microflora develops from birth

- Mode of birth
- Feeding method
- Gestational time
- Antibiotics
- Environment
- Weaning

Science and nature in balance

Protexin®

Mode of Birth

- Infants born vaginally compared to caesarean show increased diversity in their intestinal microbiome.
- Biasucci *et al*, (2008) discovered an absence of Bifidobacterium in the intestinal microbiome of C-section infants on day 3 of life. Hill *et al*, (2017) suggest that caesarean infants are more often colonised with C difficile, compared to vaginal births.
    - Vaginal birth microbiomes = mothers vaginal microbiome
    - Caesarean birth microbiomes = skin microbiome
        - (Dominguez-Bello *et al*, 2010)
- Emergency C-section were found to have the highest species richness and diversity rather than those born by elective caesarean or vaginally, (Azad *et al*, 2013).

Science and nature in balance

Protexin®

Mode of Birth

- C-section infants gradually progressed to harbouring a microbiota closely resembling vaginal delivery by week 8 of life, which was maintained at week 24, (Hill *et al*, 2017).
- Is the immune development of infants born by caesarean is altered within this early window of dysbioisis?
- Vaginal swabs have been shown to partially restore the microbiome of c-section infants, (Dominguez-Bello et al, 2016)

Science and nature in balance

Protexin®

Poll Question

How many births in the UK were by caesarean section for the year 2013-2014?

a) 16%

b) 26%

c) 36%

Science and nature in balance

https://www.nct.org.uk/professional/research/maternity%20statistics/maternity-statistics-england

http://www.birthchoiceuk.com/Professionals/BirthChoiceUKFrame.htm?http://www.birthchoiceuk.com/Professionals/statistics.htm

Protexin®

Feeding Method

- Bifidobacteria dominated the microbiota of breast-fed infants, whereas formula-fed babies had significantly higher proportions of Bacteroides and members of the *Clostridium coccoides* and Lactobacillus groups, (Fallani *et al*, 2010).
- Exclusively formula-fed infants were more often colonised with *E coli, C difficile, Bacteroides, and lactobacilli*, compared with breastfed infants, (Penders *et al*, 2006).

Science and nature in balance

Protexin®

Feeding Method

- Breastfed infants have a lower bacterial richness and diversity. The unique oligosaccharides found in breast milk, serve as prebiotics for a limited number of gut microbes, (Azad *et al*, 2013)
- Five genera of bacteria were significantly more abundant in infants that were breastfed for longer than four months and four genera were more abundant in infants that were breastfed for a shorter duration, (Hill *et al,* 2017).
- The introduction of formula milk or solid food perturbs bacterial colonisation and the development of the neonatal immune system, (Hill *et al,* 2017).

Science and nature in balance

Protexin®

Gestational Time

- The gut microbiota of preterm infants displays a significantly greater abundance of *Proteobacteria* compared to full term infants at week 1, (Hill, et al, 2017).
- Hospitalisation and prematurity were associated with higher prevalence and counts of *C difficile,* (Penders *et al*, 2006).
- The sterile environment of the neonatal intensive care unit (NICU) may alter the natural pattern of acquisition of microbiota, (Hill, et al, 2017).
- The duration of gestation impacts the mother's breast milk microbiome. The abundance of *Bifidobacterium* species is higher in breast milk from mothers who delivered at full term as compared with mothers of preterm infants, (Khodayar-Pardo *et al,* 2014).

Science and nature in balance

Protexin®

Antibiotics

- Antibiotic use by the infant is associated with decreased numbers of bifidobacteria and Bacteroides, (Penders *et al*, 2006).
- Hussey *et al*, (2011) detected bifidobacteria in all control infants at both four and eight weeks, however only six out of nine antibiotic-treated infants had detectable bifidobacteria at four weeks.
- Greater diversity of *Bifidobacterium* spp. in the control group compared with antibiotic-treated infants, (Hussey *et al*, 2011)

Science and nature in balance

Protexin®

Environment

- Many differing factors in the environment surrounding the newborn and even whilst in utero may have an effect on their developing microflora. The Old Friends Theory of interaction of the host with microbes is more relevant than the hygiene hypothesis, (Bloomfield *et al*, 2016).
- Infants with older siblings have shown to have slightly higher numbers of bifidobacteria, compared with infants without siblings, (Penders *et al*, 2006).
- Exposure to pets increases the abundance of two bacteria, *Ruminococcus* and *Oscillospira*, which have been associated with reduced atopic conditions and obesity, (Tun et al, 2017).

Science and nature in balance

Protexin®

Environment

- Children living on farms were exposed to a wider range of microbes and this exposure explains the inverse relationship between asthma and growing up on a farm, (Ege *et al*, 2011).
- Traditional farming methods compared to industrialised farms are exposed to an environment rich in microbes, and show exceedingly low rates of asthma (Stein *et al*, 2016).
- Hand dishwashing = less allergic diseases in children, (Hesselmar *et al*, 2015).

Science and nature in balance

Protexin®

Weaning

- Hill *et al,* (2017) suggests that the introduction of formula milk or solid food perturbs bacterial colonisation and the development of the neonatal immune system.
- Diet composition and nutritional status are the most critical modifiable factors regulating the gut microbiota at different time points across the lifespan and under various health conditions, (Sandhu *et al*, 2017).

Science and nature in balance

Protexin®

The Developing Microbiome of the Infant

Natural childbirth, breast feeding, increased social exposure, less time spent indoors, diet and appropriate antibiotic use, may help restore the microbiome and perhaps reduce risks of allergic disease. Preventive efforts must focus on early life, (Bloomfield et al, 2016).

If the establishment of the stable adult microbiota is programmed in infancy, it may lead to a lifelong signature with significant effects on health, (Hill *et al*, 2017)

Science and nature in balance

Protexin®

Poll question

Which of these statements do you believe is a good description of a newborns immune system?

a) A newborns immune system is fully developed from birth

b) A newborns immune system does not exist at birth

c) A newborns immune system requires microbial contact in order to develop

Science and nature in balance

Protexin®

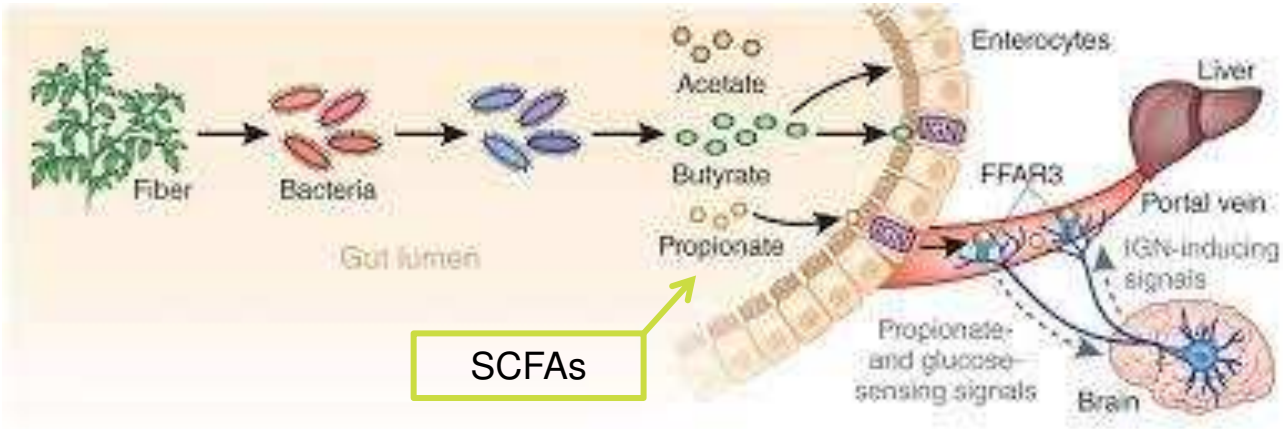
Immune System Development

- The neonatal immune system is not fully developed at birth; newborns have adequate lymphocyte counts but these cells lack function, (Aquilano *et al*, 2016).
- The immune system is a learning device, and at birth it resembles a computer with hardware and software but few data. Additional data must be supplied during the first years of life, through contact with microorganisms from other humans and the natural environment. (Bloomfield et al, 2016).
- IgA is found in breastmilk and can prevent immune activation in infants by binding microbial antigens, (Tomkovich and Jobin, 2016).

Protexin®

How does the Microbiota and Immune System Interact?

- The immune system and microbiota develop and mature together, beginning at birth, or even potentially in the womb, (Aagaard *et al*, 2014).
- Germ-free mice have an underdeveloped immune system, (Tomkovich and Jobin, 2016).
- The microbiota impacts host immunity by limiting pathogen colonisation through niche occupation and resource use, (Tomkovich and Jobin, 2016).
- Components and metabolites of the microbiome affect immunity in the intestine. SCFAs increase serotonin production, which has an impact on host immunity. SCFAs also directly impact innate immune cells in the brain and central nervous system, (Tomkovich and Jobin, 2016).

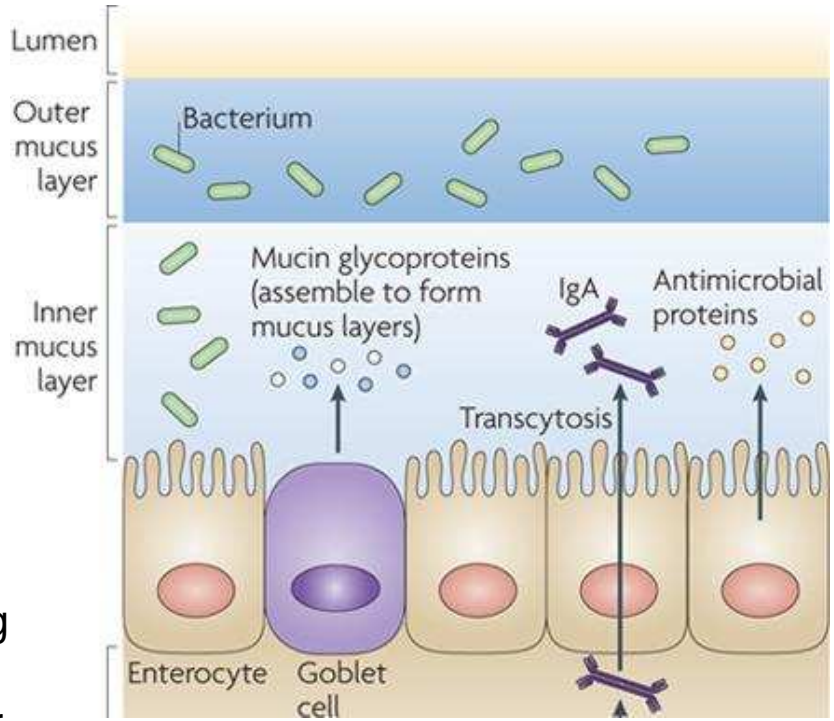


Science and nature in balance

Protexin®

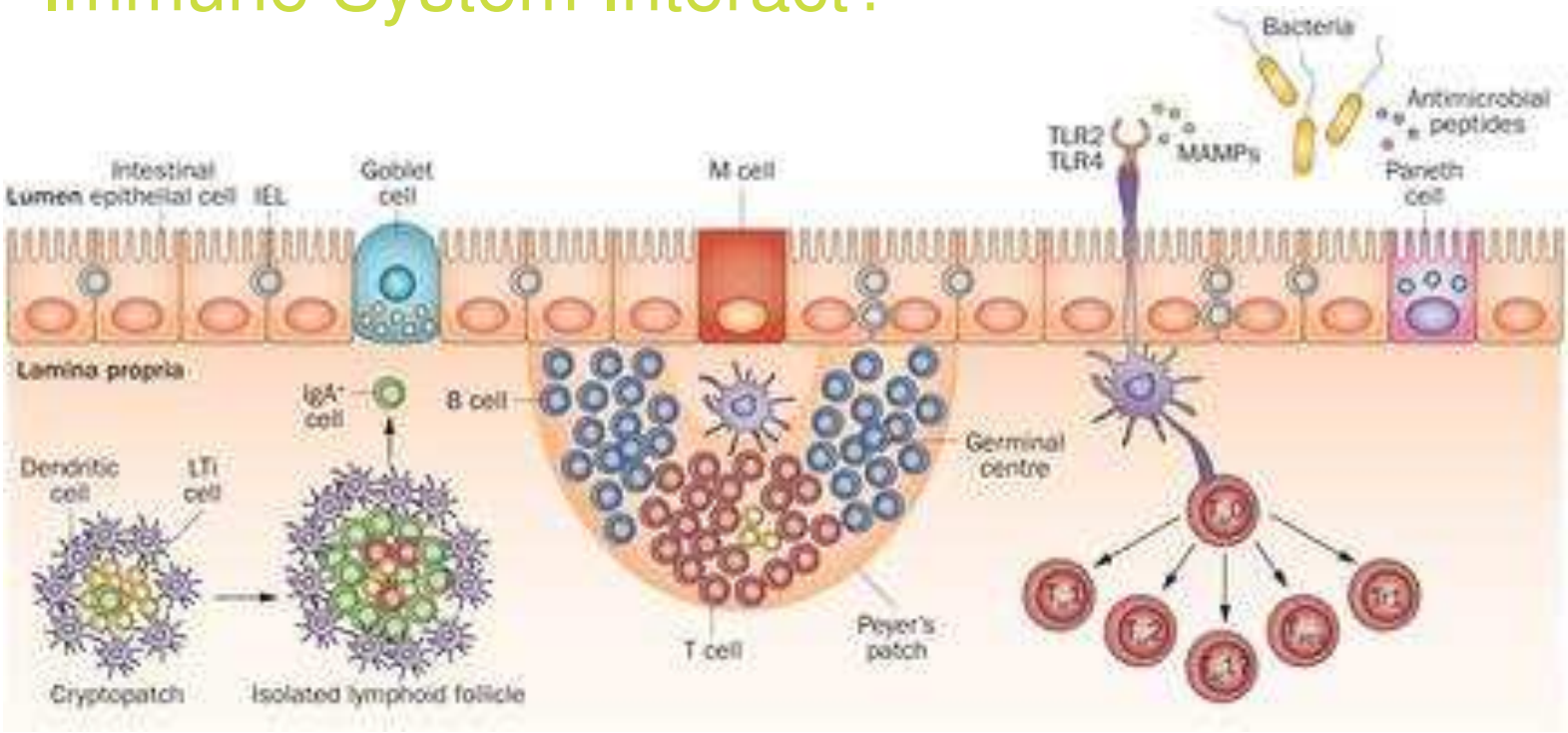
How does the Microbiota and Immune System Interact?

- Three way interaction between mucosal immune cells, the intestinal epithelium and the microbial communities (Powell and MacDonald, 2017).
- An important function of the intestinal immune system is to control the exposure of bacteria to host tissues, thereby lessening the potential for pathological outcomes, (Hooper et al, 2012).
- Intestinal goblet cells secrete mucin glycoproteins that create a thick viscous coating at the intestinal epithelial cell surface.
  - Colon: two distinct mucus layers, the outer layer contains large numbers of bacteria whilst the inner mucus layer is resistant to bacterial penetration.
  - Small intestine: lacks a clearly distinct inner and outer mucus layer.
    - (Hooper et al, 2012).



Protexin®

How does the Microbiota and Immune System Interact?

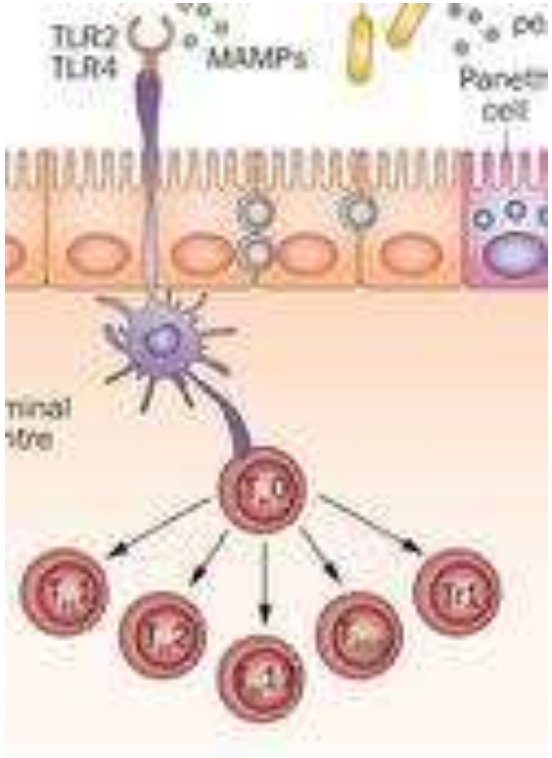


http://www.nature.com/nrgastro/journal/v12/n1/full/nrgastro.2014.153.html

Protexin®

Immune Development Th1/Th2 Balance

- Homeostasis in the gut mucosa is maintained by a system of checks and balances between Th1, Th2, Th17 and Treg cells, (Hooper, 2012).
- A naïve T cell (Th0) becomes a Th1, Th2 or a Th17 depending on the cytokines in the environment, which is influenced by antigen.
- Newborn's tend to be biased towards Th2 dominance, which can be switched off quickly after birth through microbial exposure, (Berger, 2000).



Science and nature in balance

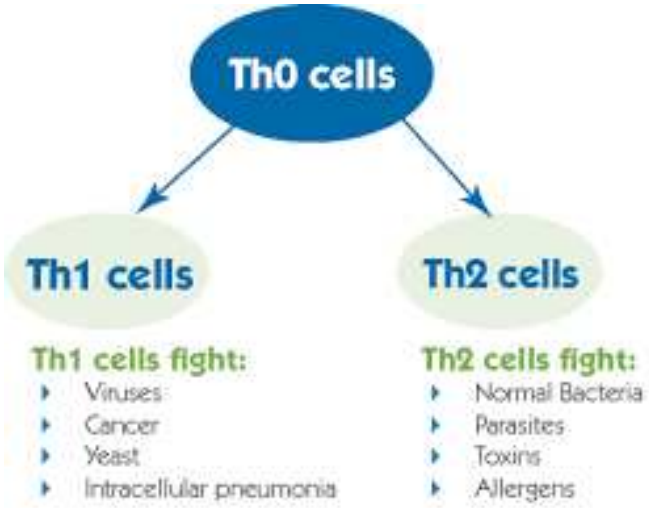
Protexin®

Immune Development Th1/Th2 Balance

- Th1-type cytokines: produce the pro-inflammatory response. Responsible for killing intracellular parasites and for perpetuating autoimmune responses.
- Th2-type cytokines: more of an anti-inflammatory response. Promotion of IgE and eosinophilic responses in atopic conditions.
    - The optimal scenario would therefore seem to be that humans should produce a well balanced Th1 and Th2 response, suited to the immune challenge,

(Berger, 2000).

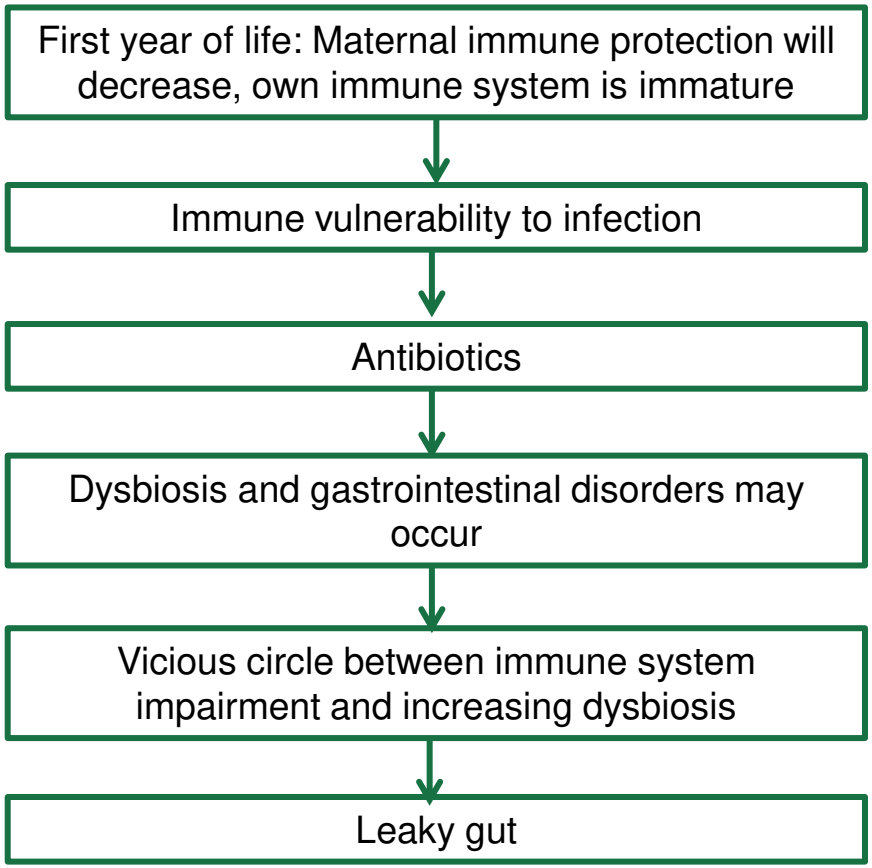
- Over-activation of either pattern can cause disease, and either pathway can down-regulate the other, (Kidd, 2003).



Science and nature in balance

Protexin®

Inadequate Colonisation and Inappropriate Immune Programming



Mezzelani et al, (2015)

Science and nature in balance

Protexin®

How the interactions of the microbiome and the immune system could have an affect on developing childhood conditions

Science and nature in balance

Protexin®

Microbiota, Immune Development and Allergy

- A more diverse gut microbiota early in life might prevent allergy development**,** (Sjögren et al, 2009).
- The epidemic of allergy and asthma results from reduced exposure to natural environments with rich microbiota, changed diet and sedentary lifestyle, (Haahtela *et al*, 2015).
- Studies have identified mode of birth, pet exposure, and having older siblings as being significant risk modifying factors in the development of food allergy, (Blázquez and Berin, 2017).
- Children reported to have taken antibiotics during infancy were more likely to have asthma at 7.5 years, (Hoskin-Parr *et al,* 2013).
- Younger gestational age at birth was associated with childhood asthma outcomes, (Sonnenschein-van der Voort *et al*, 2014).

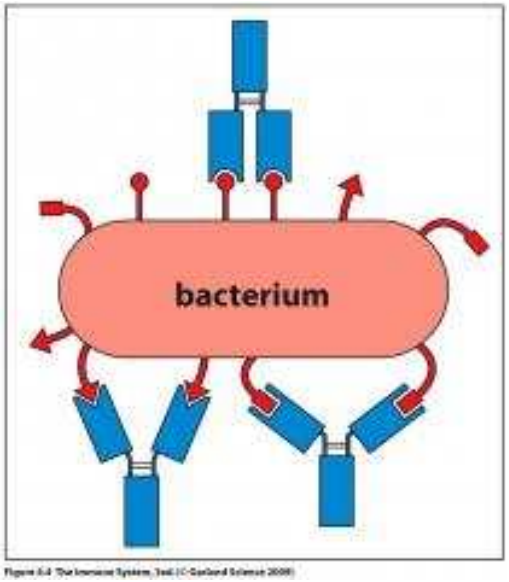
Science and nature in balance

Protexin®

Microbiota, Immune Development and Allergy

- Secretory IgA produced by resident B cells in GALT bind allergens in the gut and prevent their uptake
- Microbial colonisation has been shown to be important in the development of Th1 and regulatory T cells, which are necessary to maintain immunologic balance and promote tolerance
- The gut microbiota plays a significant role in the development and maintenance of barrier function and it is thought that a breakdown of this epithelial barrier may lead to allergic sensitisation,

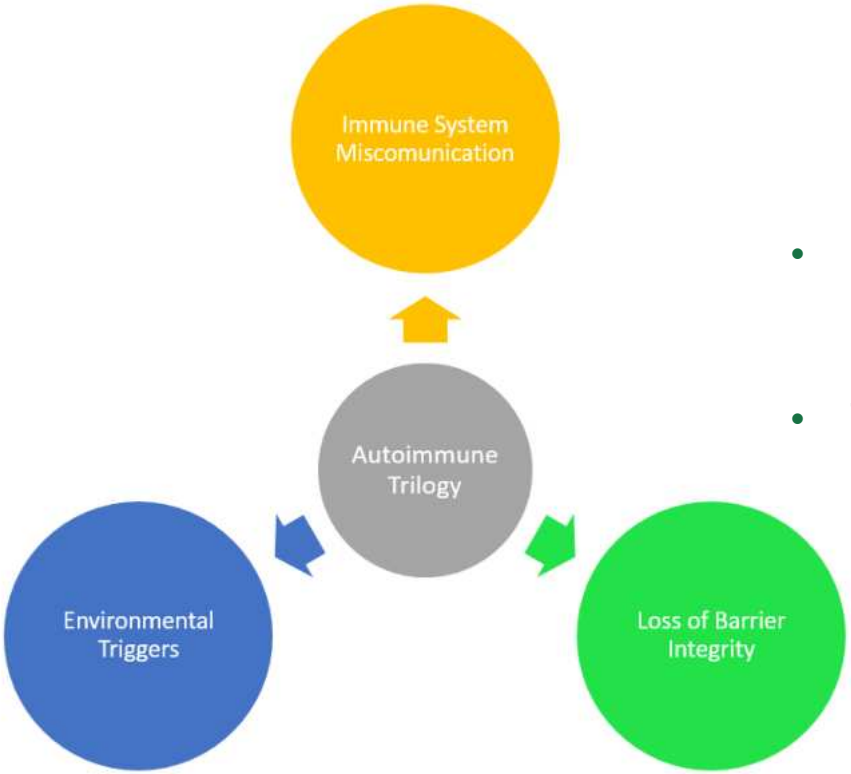
(Prince *et al*, 2015).



Science and nature in balance

Protexin®

Microbiota, Immune Development and Auto-Immunity



- Abnormalities in gut permeability have been linked to the development of type 1 diabetes mellitus. A larger proportion of the phylum Bacteroidetes has been observed in children with T1DM, (Uusitalo *et al,* 2016).
- Microbes can be protective, neutral or provocative for the development of autoimmunity.
- The diversity of microbiota was reduced in diabetic patients.

(Yurkovetskiy *et al*, 2015).

Science and nature in balance

Protexin®

Microbiota, Immune Development and Autism

- Recent studies have made links between particular bacteria from the indigenous gut microbiota and phenotypes relevant to Autism Spectrum Disorder (ASD) raise the important question of whether microbial dysbiosis plays a role in the development or presentation of ASD symptoms, (Vuong and Hsiao, 2017).
- Disturbances of microbiome composition coupled with the influence of host genetics can result in long-term effects on physiology and behaviour, (Dinan and Cryan, 2017).

Science and nature in balance

Protexin®

Microbiota, Immune Development and Obesity

- Germ-free mice colonised with faecal microbes obtained from an obese human exhibited excessive weight and fat mass gain whereas mice whose gut microbiome originated from a lean individual remained lean. Ridaura *et al* (2013)
- Cassidy-Bushrow *et al*, (2015) reported a twofold higher risk of obesity at the age of 2 in caesarean delivered infants with no household pets compared to those born vaginally.

Science and nature in balance

Protexin®

Microbiota, Immune Development and Fussy Eaters

- Diet has profound effects on microbiota composition and metabolite production, both of which influence host immunity, (Tomkovich and Jobin, 2016).
- Dietary iron depletion at weaning imprints low diversity in the microbiota that is not easily recovered, (Pereira *et al,* 2015).
- SCFA production depends on two interdependent factors: dietary fibre and microbiota composition.
- The addition of GOS/FOS to solid foods increases the faecal proportion of bifidobacteria in the intestinal microbiota of fully formula-fed infants in the weaning period, (Scholtens *et al*, 2006).

Science and nature in balance

Protexin®

Improving the developing microflora in children – how probiotics could help

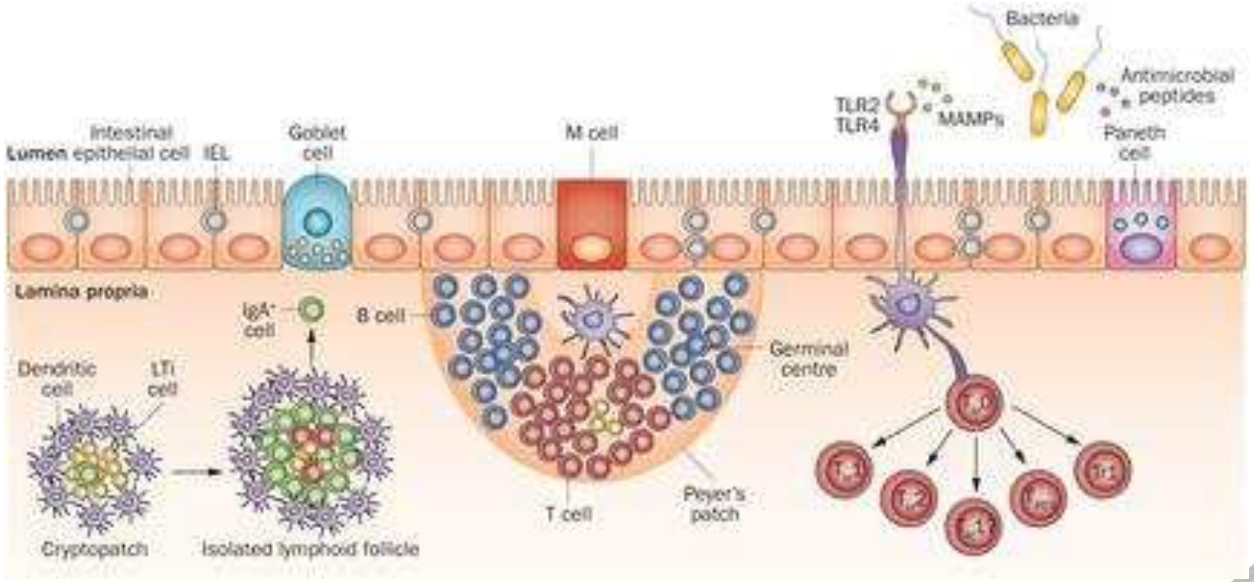
- The aim of the probiotic approach is to repair the deficiencies in the gut flora and restore the protective effect, (Bezirtzoglou and Stavropoulou, 2011).
- Supplementation of probiotic organisms in infancy could help prevent immune-mediated diseases in childhood, (Ashraf and Shah, 2014).
- Certain probiotic strains or multi strain mixtures have potent immunomodulatory activity in diverse disorders including allergic asthma, atopic dermatitis and rheumatoid arthritis, (Kang and Im 2015).

Science and nature in balance

Protexin®

Improving the developing microflora in children – how probiotics could help

- Probiotics have a strain-dependent capability to endow T cells with regulatory properties (Tregs), (Farid, *et al* 2011).
- The influence of commensal bacteria on the balance of T cell subsets is now known to extend well beyond the intestines, (Hooper, 2012).
- Live probiotics or their metabolites could interact with B and T cells and confer them to have immunoregulatory functions. Through this interaction, probiotics could contribute to maintaining immune homeostasis by balancing pro-inflammatory and anti-inflammatory immune responses, (Kang and Im 2015).

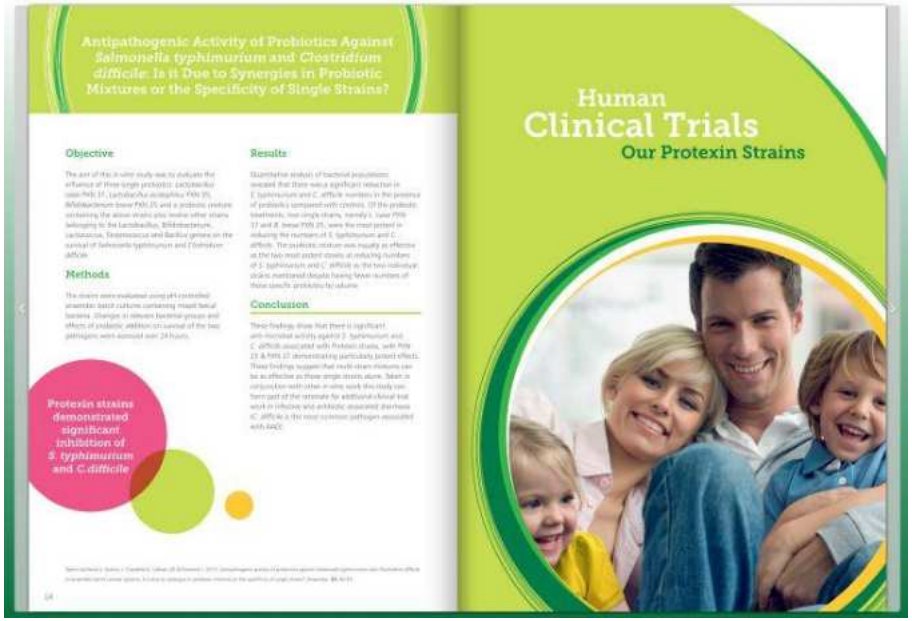


Science and nature in balance

Protexin®

Improving the developing microflora in children – how probiotics could help

- Our own Protexin study provides evidence that a mixture of seven strains of probiotics and Fructooligosaccharide can clinically improve the severity of Atopic Dermatitis in young children, (Farid *et al*, 2011).
- Early probiotic supplementation (at the age of 0-27 days) was associated with a decreased risk of islet autoimmunity when compared with probiotic supplementation after 27 days or no probiotic supplementation, (Uusitalo *et al*, 2016).



http://www.protexin.com/research

Science and nature in balance

Protexin®

Improving the developing microflora in children – how probiotics could help

‘**Protecting and repairing the developmental processes of the healthy infant microbiome is the modern medical frontier**’,

(Meropol and Edwards, 2015).

Science and nature in balance

Protexin®

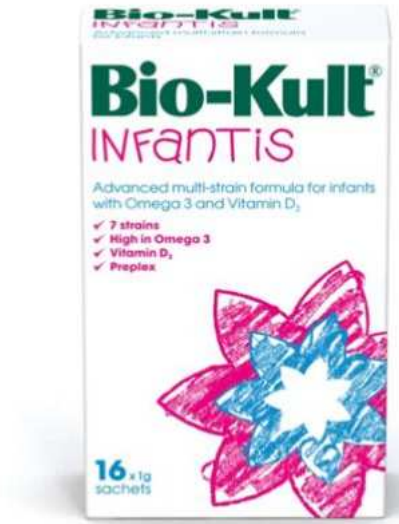
Bio-Kult

Science and nature in balance

Protexin®

Bio-Kult Infantis

- **7** different strains
- 1 billion CFU/sachet
- Omega 3
- Vitamin D
- Preplex
- Sachets



Science and nature in balance

Protexin®

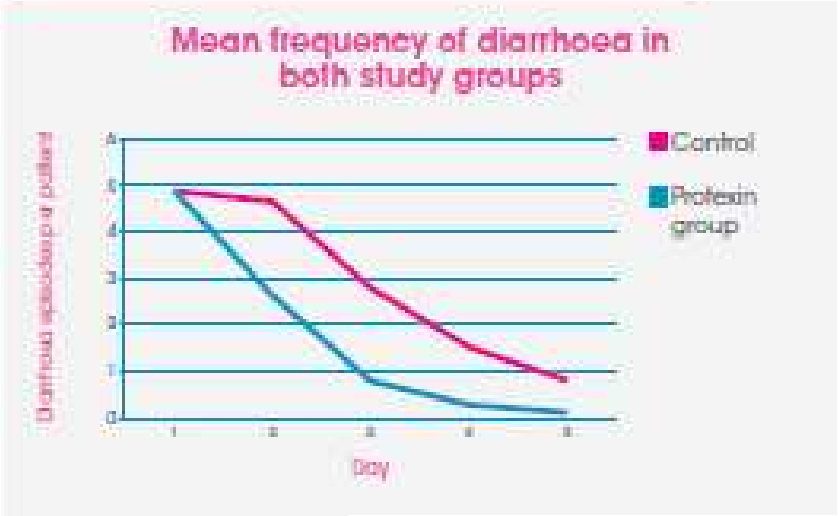
Bio-Kult Infantis Studies

- Studies using 7 strains of live probiotic bacteria with the prebiotics
  - reduced diarrhoea
  - improved constipation
  - improved eczema
  - improved colic

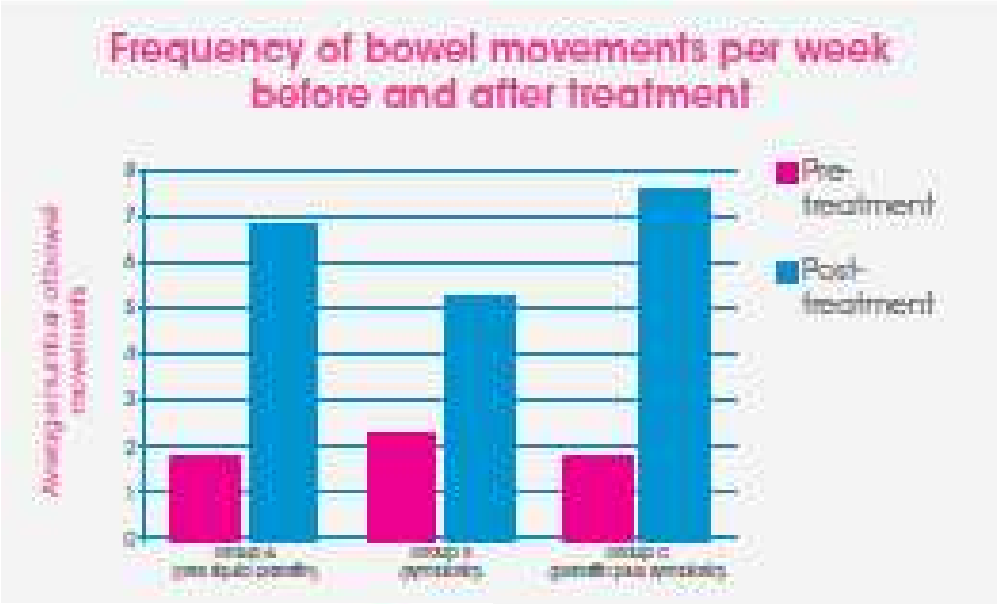
Science and nature in balance

Protexin®

REDUCED DIARRHOEA, IMPROVED STOOL CONSISTENCY AND SHORTENED HOSPITAL STAY IN INFANTS 2 MONTHS TO 2 YEARS OLD WITH ACUTE GASTROENTERITIS [17]



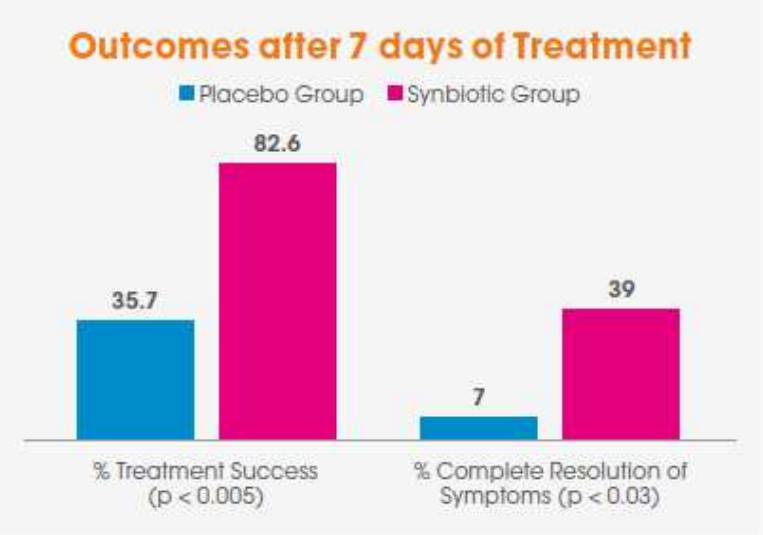
IMPROVED SYMPTOMS OF CONSTIPATION IN 97 CHILDREN AGED 4-12 YEARS [18]

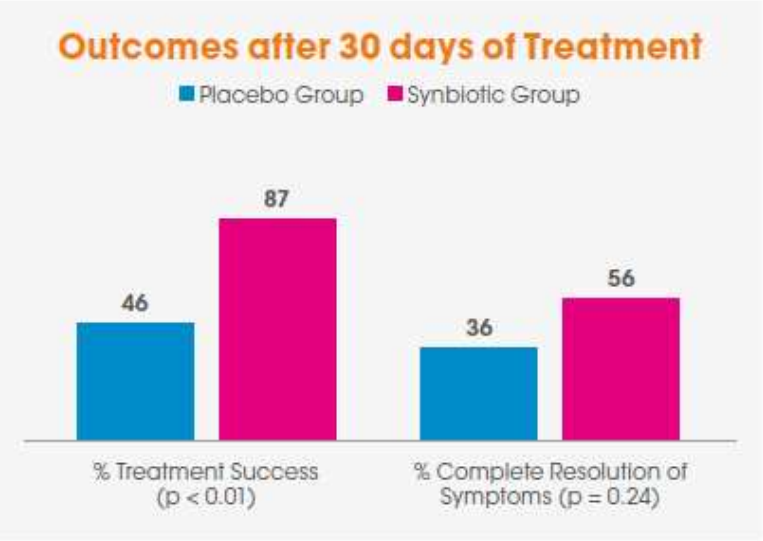


These specific 7 probiotic strains used in this trial can be found in Bio-Kult Infantis.

Protexin®

Colic Study





IMPROVED THE SEVERITY OF ATOPIC DERMATITIS (ECZEMA) IN 40 INFANTS AND CHILDREN AGED 3 MONTHS TO 7 YEARS[19]

Mean Reduction in SCORAD Index (The Severity Scoring of Atopic Dermatitis)

	Control group	Study group
visit 1 and 2	-11.06	-29.51
visit 1 and 3	-20.1	-39.2
visit 2 and 3	-7.66	-9.4

These specific 7 probiotic strains used in this trial can be found in Bio-Kult Infantis.

Protexin®

References

Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., & Versalovic, J. (2014). The placenta harbors a unique microbiome. *Science Translational Medicine*, *6*(237), 237ra65. https://doi.org/10.1126/scitranslmed.3008599

Adlerberth, I. (2008). Factors Influencing the Establishment of the Intestinal Microbiota in Infancy. In *Personalized Nutrition for the Diverse Needs of Infants and Children* (Vol. 62, pp. 13–33). Basel: KARGER. https://doi.org/10.1159/000146245

Aquilano G, Capretti MG, Nanni F, *et al.* Altered Intracellular ATP Production by Activated CD4+ T-Cells in Very Preterm Infants. *J Immunol Res* 2016; **2016**: 1–8.

Ashraf R, Shah NP. Immune System Stimulation by Probiotic Microorganisms. *Crit Rev Food Sci Nutr* 2014; **54**: 938–56.

Azad MB, Konya T, Maughan H, *et al.* Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *Can Med Assoc J* 2013; **185**: 385–94.

Berger, A. (2000). Th1 and Th2 responses: what are they? *BMJ (Clinical Research Ed.)*, *321*(7258), 424. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10938051

Bezirtzoglou E, Stavropoulou E. Immunology and probiotic impact of the newborn and young children intestinal microflora. *Anaerobe* 2011; **17**: 369–74.

Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. *J Nutr* 2008; **138**: 1796S – 1800S.

Science and nature in balance

Protexin®

References

Bloomfield SF, Rook GA, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspect Public Health* 2016; **136**: 213–24.

Cassidy-Bushrow, A. E., Wegienka, G., Havstad, S., Levin, A. M., Lynch, S. V, Ownby, D. R., … Johnson, C. C. (2015). Does pet-keeping modify the association of delivery mode with offspring body size? *Maternal and Child Health Journal*, *19*(6), 1426–33. https://doi.org/10.1007/s10995-014-1649-y

Dinan, T. G., & Cryan, J. F. (2017). Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *The Journal of Physiology*, *595*(2), 489–503. https://doi.org/10.1113/JP273106

Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, *et al.* Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016; published online Feb 1. DOI:10.1038/nm.4039.

Ege MJ, Mayer M, Normand A-C, *et al.* Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011; **364**: 701–9.

Fallani M, Young D, Scott J, *et al.* Intestinal Microbiota of 6-week-old Infants Across Europe: Geographic Influence Beyond Delivery Mode, Breast-feeding, and Antibiotics. *J Pediatr Gastroenterol Nutr* 2010; **51**: 77–84.

Falony G, Joossens M, Vieira-Silva S, *et al.* Population-level analysis of gut microbiome variation. *Science* 2016; **352**: 560–4.

Science and nature in balance

Protexin®

References

Farid R, Ahanchian H, Jabbari F, Moghiman T. Effect of a new synbiotic mixture on atopic dermatitis in children: a randomized-controlled trial. *Iran J Pediatr* 2011; **21**: 225–30.

Haahtela T, Laatikainen T, Alenius H, *et al.* Hunt for the origin of allergy - comparing the Finnish and Russian Karelia. *Clin Exp Allergy* 2015; **45**: 891–901.
Blázquez AB, Berin MC. Microbiome and food allergy. *Transl Res* 2017; **179**: 199–203.

Hesselmar B, Hicke-Roberts A, Wennergren G. Allergy in children in hand versus machine dishwashing. *Pediatrics* 2015; **135**: e590–7.

Hill CJ, Lynch DB, Murphy K, *et al.* Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET Cohort. *Microbiome* 2017; **5**: 4.

Hooper L V, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**: 1268–73.

Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJW. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. *Pediatr Allergy Immunol* 2013; **24**: 762–71.

Hussey S, Wall R, Gruffman E, *et al.* Parenteral antibiotics reduce bifidobacteria colonization and diversity in neonates. *Int J Microbiol* 2011; **2011**. DOI:10.1155/2011/130574.

Science and nature in balance

Protexin®

References

KANG, H.-J., & IM, S.-H. (2015). Probiotics as an Immune Modulator. *Journal of Nutritional Science and Vitaminology*, *61*(Supplement), S103–S105. https://doi.org/10.3177/jnsv.61.S103

Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. *Altern Med Rev* 2003; **8**: 223–46.

Khodayar-Pardo P, Mira-Pascual L, Collado MC, Martínez-Costa C. Impact of lactation stage, gestational age and mode of delivery on breast milk microbiota. *J Perinatol* 2014; **34**: 599–605.

Meropol SB, Edwards A. Development of the infant intestinal microbiome: A bird's eye view of a complex process. *Birth Defects Res Part C Embryo Today Rev* 2015; **105**: 228–39.

Mezzelani, A., Landini, M., Facchiano, F., Raggi, M. E., Villa, L., Molteni, M., … Marabotti, A. (2015). Environment, dysbiosis, immunity and sex-specific susceptibility: a translational hypothesis for regressive autism pathogenesis. *Nutritional Neuroscience*, *18*(4), 145–61. https://doi.org/10.1179/1476830513Y.0000000108

Penders J, Thijs C, Vink C, *et al.* Factors Influencing the Composition of the Intestinal Microbiota in Early Infancy. *Pediatrics* 2006; **118**: 511–21.

Pereira DIA, Aslam MF, Frazer DM, *et al.* Dietary iron depletion at weaning imprints low microbiome diversity and this is not recovered with oral nano Fe(III). *Microbiologyopen* 2015; **4**: 12–27.

Powell N, MacDonald TT. Recent advances in gut immunology. *Parasite Immunol* 2017; : e12430.

Science and nature in balance

Protexin®

References

Prince BT, Mandel MJ, Nadeau K, Singh AM. Gut Microbiome and the Development of Food Allergy and Allergic Disease. *Pediatr Clin North Am* 2015; **62**: 1479–92.

Ridaura VK, Faith JJ, Rey FE, *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; **341**: 1241214.

Sandhu, K. V., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T. G., & Cryan, J. F. (2017). Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. *Translational Research*, *179*, 223–244. https://doi.org/10.1016/j.trsl.2016.10.002

Scholtens PAMJ, Alles MS, Bindels JG, van der Linde EGM, Tolboom JJM, Knol J. Bifidogenic Effects of Solid Weaning Foods With Added Prebiotic Oligosaccharides. *J Pediatr Gastroenterol Nutr* 2006; **42**: 553–9.

Sjögren YM, Jenmalm MC, Böttcher MF, Björkstén B, Sverremark-Ekström E. Altered early infant gut microbiota in children developing allergy up to 5 years of age. *Clin Exp Allergy* 2009; **39**: 518–26.

Sonnenschein-van der Voort AMM, Arends LR, de Jongste JC, *et al.* Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children. *J Allergy Clin Immunol* 2014; **133**: 1317–29. 1

Stein MM, Hrusch CL, Gozdz J, *et al.* Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med* 2016; **375**: 411–21.

Science and nature in balance

Protexin®

References

Tomkovich S, Jobin C. Microbiota and host immune responses: a love-hate relationship. *Immunology* 2016; **147**: 1–10.

Tun, H. M., Konya, T., Takaro, T. K., Brook, J. R., Chari, R., Field, C. J., … CHILD Study Investigators. (2017). Exposure to household furry pets influences the gut microbiota of infants at 3–4 months following various birth scenarios. *Microbiome*, *5*(1), 40. https://doi.org/10.1186/s40168-017-0254-x

Uusitalo U, Liu X, Yang J, *et al.* Association of Early Exposure of Probiotics and Islet Autoimmunity in the TEDDY Study. *JAMA Pediatr* 2016; **170**: 20–8.

Vuong HE, Hsiao EY. Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. *Biol Psychiatry* 2017; **81**: 411–23.

Yurkovetskiy, L. A., Pickard, J. M., & Chervonsky, A. V. (2015). Microbiota and autoimmunity: exploring new avenues. *Cell Host & Microbe*, *17*(5), 548–52. https://doi.org/10.1016/j.chom.2015.04.010

Science and nature in balance

Protexin®

Any questions?

Science
and nature
in balance

Protexin®

Any further queries?

claire.barnes@protexin.com

01460 243230

Thank you for your attention

Protexin®