



Florajen[®]
Probiotics

**Healthful
Aspects of
Probiotic
Regimens**

SEPTEMBER 2018

Introduction

The Florajen® Probiotics line of products contains unique blends of well studied probiotic cultures which have a significant body of literature supporting their use by the medical community in restoring and maintaining gastrointestinal and vaginal health. The use of probiotic products has demonstrated real health benefits in managing a variety of medical conditions, with some of the strongest supportive data in the area of digestive health. There is also evidence that these probiotic species modulate the immune system and exert antimicrobial action.

Florajen, like other probiotics, is labeled as a nutritional supplement and is not intended to diagnose, treat or mitigate disease. Nonetheless, Florajen is specifically formulated to provide nutrients which support healthy, normal microbial balance in patients from age 6 months and up.

This White Paper explores the evidence in the literature supporting the use of probiotics in patients, particularly multi-culture probiotic strains, and to provide the clinician with the framework to recommend these products for their patients.

The Human Microbiome and Health

The human microbiota consists of 10-100 trillion symbiotic microbial cells. These microbes (bacteria, fungi and parasites) live on or within the human body and outnumber our own cells 10:1. The delicate balance of the human microbiome is essential to good health. Disruption of this balance may negatively affect the immune system, vaginal and respiratory health and most particularly, the gut. It is estimated that the GI tract hosts more than 500 species of bacteria and that the bacterial genome outnumbers the human genome by a factor of 100:1. [Ciorba 2012] Disturbance of the gut microbiome has been implicated in diarrhea, functional constipation, irritable bowel syndrome and inflammatory conditions of the GI tract such as inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis.

Use – and overuse – of antibiotics has been recognized as a serious healthcare issue affecting all age groups and demographics. Despite the establishment of antibiotic stewardship programs by the Joint Commission to reduce inappropriate antimicrobial use, widespread antibiotic use continues. [JC 2016] The CDC estimates that at least 50% of antibiotic prescriptions outside the hospital for acute respiratory conditions are unnecessary.

These excess prescriptions each year put patients at needless risk for reactions to drugs or side effects. Rampant antibiotic use is recognized as a major disrupter of the gut microbiome. These agents do not discriminate between inhibiting harmful bacteria and those bacteria essential in maintaining good gastrointestinal health.

Not surprisingly, the incidence of side effects associated with antibiotics has seen a major increase. For example, antibiotic-associated diarrhea (AAD) ranges from 13-60%, primarily in the hospital setting [McFarland 2006]. Up to 35% of adults get antibiotic-associated diarrhea when taking an antibiotic, [McFarland 1998] and up to 40% of children get antibiotic-associated diarrhea. [Vanderhoof 1999] Nearly any antibiotic can cause AAD, but AAD is more likely to occur due to antibiotics called cephalosporins and penicillins. [Mayo Clinic 2017]

According to the Cleveland Clinic, the most reliable way to hinder AAD is to take a probiotic. [Cleveland Clinic 2017] Probiotics can also assist with other antibiotic side effects like cramping and gas. [Cleveland Clinic 2017]

Percent of Antibiotic Prescriptions That Were Unnecessary

	All Conditions*	Acute Respiratory Conditions**
0-19 year olds	29%	34%
20-64 year olds	35%	70%
≥65 year olds	18%	54%
All ages	30%	50%

*All conditions included acute respiratory conditions, urinary tract infections, miscellaneous bacterial infections, and other conditions.

**Acute respiratory conditions included ear infections, sinus infections, sore throats, pneumonia, acute bronchitis, upper respiratory infections (i.e. common colds), influenza, asthma, allergy, and viral pneumonia.

Antibiotic Class	Antibiotic Class Members	Most Common Side Effects
Penicillins	Penicillin, amoxicillin, amoxicillin-clavulanate, ampicillin, piperacillin-tazobactam, nafcillin, oxacillin	Rash, diarrhea, abdominal pain, nausea/vomiting, drug fever, hypersensitivity reactions
Cephalosporins	Cephalexin, cefaclor, cefuroxime, ceftibuten, cefdinir, cefixime, ceftriaxone	Rash, diarrhea, nausea/vomiting (rare), hypersensitivity (allergic) reactions, serum sickness, vaginal candidiasis
Aminoglycosides	Gentamicin, tobramycin, amikacin	Renal (kidney) toxicity, ototoxicity (hearing loss), dizziness, nausea/vomiting, nystagmus
Carbapenems	Meropenem, ertapenem, doripenem, imipenem-cilastatin	Diarrhea, nausea/vomiting, headache, rash, liver toxicity, eosinophilia (elevated white blood cells)
Glycopeptides	Vancomycin, telavancin	Vancomycin: red man syndrome (flushing, hypotension, itching); phlebitis; telavancin: taste alteration, nausea/vomiting, headache, dizziness
Macrolides	Erythromycin, azithromycin (Z Pak), clarithromycin	Abdominal pain, diarrhea, anorexia, nausea/vomiting, taste alterations (clarithromycin)
Sulfonamides	Trimethoprim-sulfamethoxazole, erythromycin-sulfisoxazole, sulfadiazine	Nausea/vomiting, diarrhea, anorexia, abdominal pain, rash, photosensitivity, headache, dizziness
Tetracyclines	Tetracycline, doxycycline, minocycline	Nausea/vomiting, diarrhea, anorexia, abdominal pain, tooth discoloration in children < 8 years, liver toxicity
Quinolones	Ciprofloxacin (Cipro), levofloxacin (Levaquin), moxifloxacin (Avelox), ofloxacin (Floxin)	Nausea/vomiting, diarrhea, abdominal pain, headache, lethargy, insomnia, photosensitivity (can be severe)
Lincomycin derivatives	Clindamycin, lincomycin	Pseudomembranous colitis (may be severe), diarrhea, nausea/vomiting, rash, hypersensitivity, jaundice (clindamycin)
Miscellaneous	Metronidazole (oral)	Nausea/vomiting, dizziness, headache, vaginal candidiasis, metallic taste

Source: Anderson 2017 www.drugs.com/article/antibiotic-sideeffects-allergies-reactions.html Accessed April 19, 2018

There is ample evidence that probiotics help maintain the health of the human microbiome, particularly with respect to GI health. Credible organizations recommending probiotic use range from the National Institutes of Health and the International Scientific Association for Probiotics and Prebiotics, to the guidelines and recommendations of third party medical organizations such as American Academy of Pediatrics, Infectious Disease Society of America and the American College of Gastroenterology.

What are Probiotics?

The word probiotic was coined in 1965 meaning “for life” in Latin. The most common definition from the World Health Organization (WHO), describes probiotics as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. This requires that the probiotic strains ingested remain viable after they pass the GI tract, resisting both acid and bile. High colony count is also linked to efficacy, with an effective probiotic delivering both the right cell strains and the right cell count. A probiotic with billions of cells is recommended to help maintain “good” bacteria in patients. Dosing and administration of probiotics are variable but the consensus is that the minimum number of viable cells to provide activity is 1×10^9 CFU, with many commercially available probiotics such as Florajen exceeding that. [Hill 2014]

The beneficial effects of fermented foods have been known since antiquity. Biblical accounts attribute Abraham’s longevity to drinking sour milk and Roman accounts dating back to 76 BC recount fermented milk as a treatment for gastric upset. In 1907, the Nobel winning Russian scientist E. Metchnikoff recognized and linked consumption of lactic acid bacteria in fermented dairy foods with health benefits.

Literature over the past 100 years has documented that nonpathogenic species of live bacteria have demonstrated health benefits to the people who consume them. [Islam 2016].

Consumers have quickly adopted probiotics and wide spread acceptance has created an industry with worldwide sales of \$25-30 billion. U.S. sales of probiotics increased to \$2.14 billion by 2017, attesting to consumer belief in their efficacy for the treatment or prevention of a variety of health conditions. [Statistica 2018] Consumers are familiar with probiotics in a variety of commonly purchased foods such as yogurt, kefir, cheeses, kimchi, pickles, and sauerkraut as well as probiotic supplements available in liquid, packet and capsule form.

Probiotics are the third most commonly used dietary supplement in the U.S. with 4 million adults having used probiotics in the previous 30 days, based on results from a 2012 National Health Interview Survey. Approximately 300,000 children used probiotics during the same time span, making probiotics one of the top three natural products used by children. Probiotic usage has increased 4-fold between 2007 and 2012 and their use is only expected to grow. [NIH 2016]

As usage expands, more data are needed to advance the field of probiotics among the various stakeholder groups: the medical community/scientists, consumers/patients, industry and regulators. All parties have an interest in improving human lives by harnessing the benefits of probiotic therapy.

It is important to distinguish probiotics from prebiotics; the latter are food ingredients, typically selectively fermented nondigestible fiber, that stimulate the growth or activity of

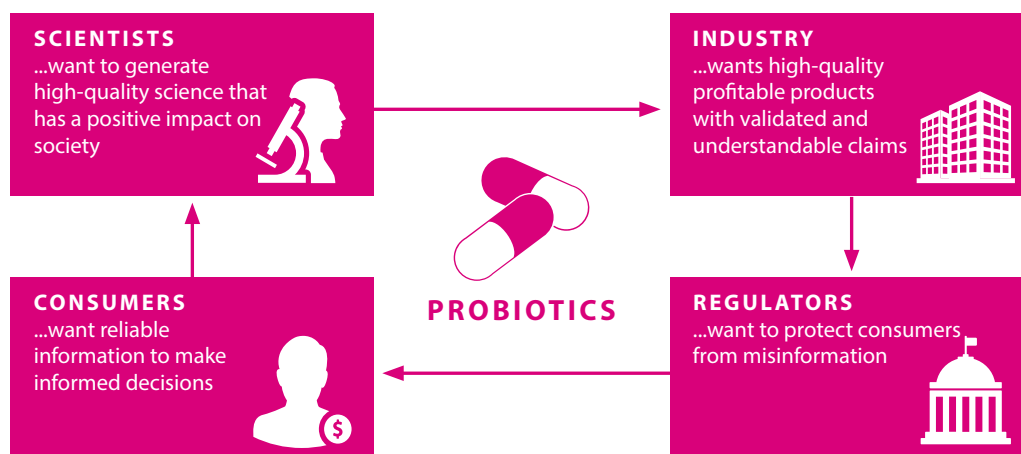


Figure 1. Objectives of stakeholders in the probiotic field. These objectives are compatible, so there is no apparent reason for obstruction of probiotic product development and marketing. Importantly, all stakeholders must work together performing their respective duties so that society benefits from the scientific advances in the field of probiotic research. [Hill 2014].

beneficial bacteria. [Hill 2014] Foods containing prebiotics include legumes, asparagus, onions, garlic, leafy greens (such as chicory and dandelions) bananas, oatmeal, barley and whole grains.

Quality Control – Not all Probiotic Products are Equal

Reliability is a concern as probiotics vary tremendously between brands. Although some probiotic strains have demonstrated efficacy, not all probiotics are equal. In addition, the same strain in one brand's formulation is not a "generic" equal to that strain marketed in a different brand. Not all marketed probiotics have a sufficiently high colony forming content, and data for many species lack rigorous study. [Reid 2000].

Survivability of bacteria is also critical, so probiotic products must contain strains that can resist high levels of acidity in the digestive tract. Not all probiotic products contain active cultures that can survive stomach bile in the human digestive tract. And, if these probiotics contain bile-sensitive strains they may have virtually no probiotic activity. [Danisco TM 48-23]]

Proper storage and handling is important because many probiotics contain live cultures with cells that die at a faster rate if left unrefrigerated. If probiotics are exposed to high temperatures, they may degrade and the live cultures can perish. Many over-the-counter (OTC) probiotics are shipped and stored unrefrigerated, falling short in providing the number of live cell counts that experts maintain are required to provide a benefit to their users.

Some products employ continuous refrigeration, however, only Florajen has a Cold Chain Commitment™ so that cell counts remain potent and consistent on a daily basis, for patients who are trying to restore GI or vaginal flora. These probiotics are kept cold throughout the manufacturing and pharmacy distribution process and until it reaches the patient. No storage and transport method has been proven to work better than refrigeration.

Probiotic manufacturers should also adhere to Good Manufacturing Practices (GMP). The Florajen line of probiotics are manufactured in compliance with GMP standards. Clearly, healthcare professionals need to be confident that the probiotic product recommended will deliver the

proper quantity of live strains – and the health benefit – they expect for their patients.

Mechanism of Action – Species Matter

The Human Microbiome Project, an interdisciplinary effort begun ten years ago by the National Institutes of Health, has helped us gain a more sophisticated understanding of the role played by microbiota in the human body. These microorganisms can be found in the epidermis, GI tract, vaginal and respiratory tracts, and an imbalance of these microbiota plays a role in disease development. [Tiano 2013]

Probiotics are widely thought to provide health benefits by inhibiting the growth of pathogenic bacteria. Although the mechanism of action is not certain, it is postulated that probiotics alter pH and exert immunomodulating activity.

Lactobacillus and Bifidobacterium species are among the most studied probiotics. Lactobacillus are lactic acid producing probiotics that are part of the body's normal flora. Bifidobacterium strains are normally found in the human colon and produce short chain fatty acids, a critical component of gut health. Taken orally, these strains are believed to pass through the gut and bind to the epithelial mucosa, preventing the attachment of pathogenic organisms and act by:

- Lowering the pH and inhibiting the growth of pathogenic organisms by producing acidic compounds (ex., lactic acid, hydrogen peroxide, acetic acid and propionic acid)
- Binding to the mucosa in the intestine; they may also prolong their time in the intestine and prevent attachment of coliform pathogens to the intestinal mucosa [Islam 2016]

Proposed Probiotic Mechanisms of Action

- Bind to intestinal mucosa
- Interact with intestinal mucosa and immune system
- Modulate immune response
- Protect against colonization of pathogen enteric microorganisms providing "colonization resistance"

Source: Danisco TM 2054-2e, TM 48-2e

The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus panel recognized that probiotics exert their activity on the human microbiome with different underlying mechanisms. The current understanding of probiotic mechanisms among experts is that some mechanisms (ex., inhibition of pathogens or the production of useful metabolites or enzymes) can be considered widespread among classes of probiotics, other

mechanisms may only be specific to strains or species (ex., effect on the immune system) and some probiotic strains may have multiple mechanisms. The panel recognized the concept of 'core' benefits of probiotics based on the preponderance of data from hundreds of human studies and numerous positive meta-analyses that suggest some generalizations on health benefits that can be made beyond strain-specific effects. [Hill 2014].

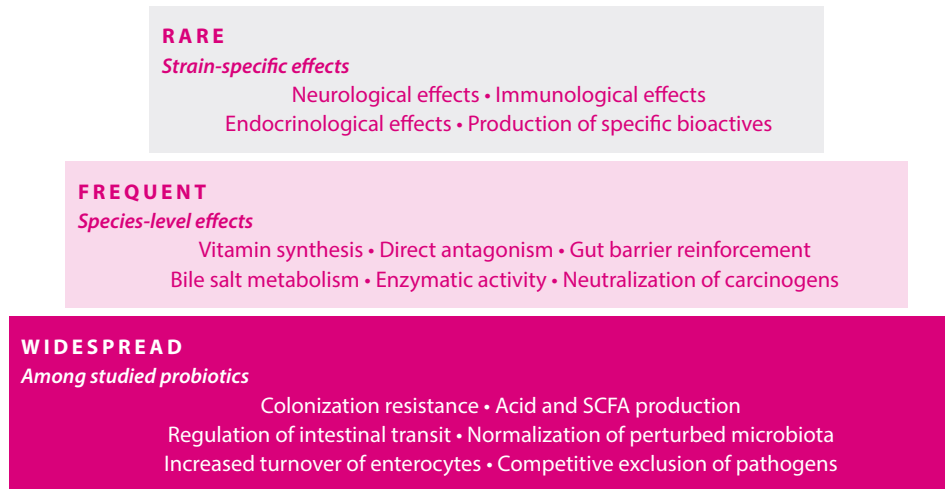


Figure 2. Possible distribution of mechanisms among probiotics. Some mechanisms might be widespread among commonly studied probiotic species; others may be rare and present in only a few strains in a given species. Evidence is accumulating on a cross-section of probiotic strains that suggest some generalizations can be made beyond strain-specific effects. Abbreviation: SCFA, short-chain fatty acid. [Hill 2014].

Multi-strain probiotic products may have increased efficacy, especially when they include individual strains that have supportive data, but most experts would like to see evidence. It makes intuitive sense that products containing several differently acting strains may have complementary activity that may provide additional health benefits to patients. Additionally, there are data showing that probiotics confer health benefits among the general population as well as to the elderly. [Gill 2001]

While there is greater weight for their use in some conditions than in others, further study is needed to optimize how the different probiotic strains can be used alone or in combination to manage disease.

Safety and Probiotics

There is limited published data on safety for the many probiotic strains currently available. The Agency for Healthcare Research and Quality (AHRQ) conducted an

evidence-based literature review on the safety of probiotics and published the results in 2014. The report concluded there was no evidence of significant adverse events overall in the short term but also that there was little data on the long-term safety of these products. [Hempel 2011] Despite this paucity of data, reputable organizations as diverse as the NIH and Harvard Medical School recommend probiotics as safe and tolerable for use by healthy adults with little risk of side effects.

This literature is consistent with other reports that probiotic use is generally safe with few side effects, most being minor (ex., gastrointestinal) within the first few days of treatment. Studies in healthy adults using probiotics for up to 5 months also demonstrated no adverse events. [Cox 2014] There are few, if any studies in people who may be more at risk, such as infants and adults with serious underlying disease. Patients with concomitant diseases and the immunocompromised may be more susceptible to potential side effects from a probiotic regimen. These patients should consult with their physician to discuss risks and benefits of probiotics.

Florajen Brand of Probiotics

There is reliable and compelling scientific evidence behind the probiotic strains contained in high quality brands such as Florajen. The active strains in the various Florajen formulations are high concentrations of the same well-studied microorganisms (*Lactobacillus* and *Bifidobacterium* species) normally found in the healthy human body. The *Lactobacillus* and *Bifidobacterium* species used in Florajen formulations are safe and well tolerated with no reported drug interactions or serious adverse events.

Florajen products contain strains such as *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Bifidobacterium lactis* that are known to survive contact with bile acids. [Danisco TM27-2e; Danisco TM48-2e; Gilliland 1978] Dosage of cultures in Florajen products greatly exceed the 1×10^9 CFU minimum number of viable cells to provide activity (see table to the right). Florajen products are refrigerated to ensure freshness and the viability of the live cultures. Florajen can be stored for up to 2 weeks without refrigeration and still maintain efficacy because the products contain high levels of viable cultures.

In addition, the Florajen product line addresses many safety concerns because it is manufactured completely in the U.S. under strict GMP (Good Manufacturing Practice) guidelines in properly certified facilities with independent testing for safety, quality and potency of live cultures. Florajen products are dairy free, non-GMO and gluten free: Florajen products contain less than 5 parts per million (gluten), while the FDA definition requires less than 20 part per million to qualify as gluten-free.



Florajen Family of Products

Florajen Digestion (formerly Florajen 3)

15 billion live cultures per capsule

Lactobacillus acidophilus

Bifidobacterium lactis

Bifidobacterium longum

Florajen Women

15 billion live cultures per capsule

Lactobacillus acidophilus

Lactobacillus rhamnosus

Florajen Kids

6 billion live cultures per capsule

Lactobacillus acidophilus

Bifidobacterium lactis

Lactobacillus rhamnosus

Florajen Acidophilus

Over 20 billion live cultures per capsule

Lactobacillus acidophilus

Source: Data on file Clarion Brands

Evidence for Probiotic Therapeutic Uses

Probiotics are now widely used by healthcare professionals to manage a number of medical conditions. They are nutritional supplements and are not intended to diagnose, treat or mitigate disease. Probiotics such as Florajen are specifically formulated to provide nutrients which support healthy, normal microbial balance needed by the human body.

The use of probiotics has become mainstream with their inclusion in the guidelines of several medical societies as adjunctive therapy, particularly in digestive diseases (such as antibiotic induced diarrhea), respiratory infections, vaginal conditions and allergic conditions such as atopic dermatitis and allergic rhinitis. Because the most important source of early human immune-microbial interaction is the gut microbiota, the development of allergic disease has been associated with variations in microorganisms in the first months of life. [Forsberg 2016]

Key Supporting Evidence	Author/Reference
American Academy of Pediatrics guidelines: provide clinicians with a review and recommendations regarding the medical uses of probiotics	Armstrong C. AAP reports on use of probiotics and prebiotics in children <i>American Family Physician</i> Apr 2011, 83:7
American College of Gastroenterology recommendations including use of probiotics for managing IBS and constipation	Ford AC , Moayyedi P, Lacy BE, Lembo AJ , Saito YA , Schiller LR, Soffer EE, Quigley E. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation <i>Am J Gastroenterol</i> 2014; 109:52 – S26
International Diseases Society of America 2017 Clinical Practice Guidelines for Diagnosis and Management of Infectious Diarrhea	Shane, Andi L., Mody, Rajal K., Crump, John A., Tarr, Phillip I., Steiner, Theodore S., Kotloff, Karen, Langley, Joanne M. , Wanke, Christine, Warren, Cirle Alcantara, Cheng, Allen C., Cantey, Joseph, Picking, Larry K. 2017 IDSA Guidelines for the Diagnosis and Management of Infectious Diarrhea <i>CID</i> 2017:1-36
The International Scientific Association for Probiotics and Prebiotics Expert Consensus Document	Hill C., Guarner F. Reid G., Gibson GT., Merenstein DJ., Pot B., Morelli L, Canani RF., Flint HJ, Salminen S., Calder PC., Sanders, ME., The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic <i>Nat. Rev. Gastroenterol. Hepatol.</i> 2014, 11: 506-514
Probiotics in Functional Constipation (Cochrane Meta-analysis)	Dimidi E, Christodoulides S, Fragkos K C, Scott M, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials <i>The American Journal of Clinical Nutrition</i> , 100:4, 1 October 2014, 1075–1084
Probiotics in Acute Upper Respiratory Tract Infection (Cochrane Review)	Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. <i>Cochrane Database Syst Rev.</i> 2015 Feb 3;2
Probiotics for Prevention of Antibiotic Associated Diarrhea and Treatment of CDAD	McFarland, Lynne V. Meta-Analysis of Probiotics for the Prevention of Antibiotic Associated Diarrhea and the Treatment of Clostridium difficile <i>Disease Am J Gastroenterology</i> 2006 Apr 101(4):812-22.
Probiotics for Prevention of CDAD (Cochrane Review)	Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. <i>Cochrane Database of Systematic Reviews</i> 2013, Issue 5
Probiotics in IBS (Review and meta-analysis)	Hoveyda N, Heneghan C, Mahtani K R, Perera Rafael, Roberts N, Glasziou P. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome <i>BMC Gastroenterology</i> 2009, 9:15
Practice Guidelines in CDAD	Surawicz Christina M. Brandt Lawrence J, Binion David G., Ananthakrishnan Ashwin N., Curry Scott R., Gilligan Peter H., McFarland Lynne V. Mellow Mark., Zuckerbraun Brian S Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections <i>Am J Gastroenterol</i> 2013; 108:478–498
World Allergy Organization recommendation about probiotic supplementation for prevention of allergy	Fiocchi A et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics <i>World Allergy Organization Journal</i> 2015, 8:4
Probiotics in Allergic Rhinitis (Review and meta-analysis)	Zajac A, Adams AS, Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis, <i>International Forum of Allergy and Immunology</i> , 2015, 5(6): 524-532

Probiotic Value in Digestive Health in Adults and Children

There is a solid body of scientific literature supporting the use of probiotics in providing nutrients to maintain digestive health in patients who have GI symptoms such as constipation, bloating, altered bowel function and pain associated with Irritable Bowel Syndrome (IBS). [Ciorba M 2012] The natural bacteria in children’s intestines are important in digesting food, destroying pathogenic microorganisms that cause disease, producing essential vitamins and contributing to immune function. If children do not possess the appropriate microbial flora and balance at birth or through breastfeeding, or if antibiotic use disrupts the balance, probiotic supplementation (such as **Florajen Kids**) may help establish and maintain healthy microbiota.

Probiotics may also help patients with acute infectious diarrhea: a Cochrane meta-analysis on the use of probiotics in acute infectious diarrhea indicates that probiotics can shorten the mean duration of diarrhea, and reduce stool frequency and diarrhea severity. [Allen 2010]. An animal

study in China looking at *Lactobacillus acidophilus* NCFM in rotavirus diarrhea suggests that it may provide some immunity as well as reducing rotavirus diarrhea [Liu 2014].

Florajen Digestion (a multi-strain probiotic product containing *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Bifidobacterium longum*) and **Florajen Kids** (a multi-strain probiotic containing *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Lactobacillus rhamnosus*) have demonstrated benefits in digestive health and enhancing immunity.

It is important to reiterate that Florajen is labeled as a nutritional supplement and is not intended to diagnose, treat or mitigate disease. Nonetheless, Florajen is specifically formulated to provide nutrients which support healthy, normal gut flora. In many of the studies, endpoints such as reduced antibiotic side effects are evaluated as indicators of healthy GI flora. Additionally, there are studies which evaluate the ingredients in Florajen, at comparable quantities. These studies provide evidence for the health promotion claims made for Florajen.

Health Benefits	GI and Colon Health	Diarrhea	Constipation	Nausea	Bloating	Immune System	Lactose Intolerance
Reduces GBS colonization [Ephraim E]; Improves colon health by shifting predominant bacteria and production of short-chain fatty acids of fecal microbiota [Ringel-Kulka 2011] [Danisco A/S TM 55-1e]	X						
Reduces duration and severity of diarrhea; reduces risk of diarrhea and fever [Hemalata R.,2014]		X					
Improves symptoms related to constipation (increases frequency and ease of bowel movements) [Favretto 2013]			X				
Reduces nausea [Safdar 2008]				X			
Reduces bloating associated with functional bowel disorders [Ringel-Kulka T, 2011; Danisco A/S. TM 58-1e.]					X		
Improves GI health and well-being [Danisco A/S. TM 54-2e]; Improves function of immune system [Maneerat S.,2013; Danisco A/S. TM 55-1e.]; Strengthens body’s natural defense [Danisco A/S. TM 58-1e.]; Offers immune function benefits [Sanders M 2001; Danisco A/S. TM 48-2e. & TM 54-2e.]						X	
Enhances lactose tolerance and improves lactose digestion [Sanders M 2001]							X

Antibiotic Associated Diarrhea (AAD)

The pathology of AAD is predicated by antibiotics killing off normal microorganisms, allowing the overgrowth of pathogenic bacteria that lead to infection and illness. Probiotics used adjunctively with antibiotics or prophylactically are believed to redress that balance. A meta-analysis of probiotics looked at 31 randomized control trials in preventing AAD and showed that probiotic combinations helped prevent AAD [McFarland 2006]

Several guidelines recognize the role probiotics may play to promote GI health by increasing the beneficial bacteria in the gut. The Infectious Disease Society of America (IDSA) 2017 guidelines recommend probiotic use when prescribing antibiotics to reduce the symptoms of AAD, although the results depend on the probiotic strains and products used. *Lactobacillus* and *Bifidobacterium* strains have been used to manage AAD. [Shane 2017]

- The American Academy of Pediatrics (AAP) recognizes preventive beneficial effects of probiotics reducing the risk of AAD in children. [Armstrong 2010]

C. difficile-associated Diarrhea (CDAD)

The American College of Gastroenterology recognizes the growing evidence that altered colonic microbiota is a major factor in the pathophysiology of *C. difficile* infection and notes that probiotics have been used adjunctively with antimicrobial therapy. Opportunistic infections by *C. difficile* are a leading cause of nosocomial diarrhea associated with long length of stays and large hospital outbreaks. The morbidity and mortality associated with *C. difficile* results in recurrent hospitalizations thus driving up healthcare costs estimated at \$3.2 billion. Further study into this topic has been recommended to enhance the body of evidence. [Surawicz 2013]

There is some evidence that the use of probiotic combinations of *lactobacilli* and *bifidobacterium*, when added to antimicrobial treatment regimens, may restore flora and GI health in hospitalized patients. [Ref 10 Graul] A Cochrane meta-analysis reviewing 23 randomized controlled studies (4,213 patients) suggested that probiotic use significantly reduced the risk of CDAD by 64% and that there was moderate evidence supporting short term use of probiotics in CDAD prevention [Goldenberg 2013]

A recently presented poster at ASM-ICAAC 2017, evaluated the in vitro effect of a probiotic combination of 15B live

cultures of *Lactobacillus acidophilus*, *Bifidobacterium lactis* Bi-07 and *Bifidobacterium longum* BI-05 on the growth and production of *Clostridium difficile* toxin at 5 different pH levels. The study demonstrated that the probiotic combination reduced toxin production by *C. difficile* by more than 90%, suggesting the probiotics significantly suppressed toxin development, compared to the comparator; *C. difficile* without probiotic. [Ref Bina]

An in vitro study completed in July 2018, replicated the in vitro study that assessed the growth and production of *Clostridium difficile* toxin at 5 different pH levels. This study, however, tested the new **Florajen Digestion** (over 15 billion live cultures of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Bifidobacterium longum*) and **Florajen Kids** (over 6 billion live cultures of *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*) probiotic formulations. The study demonstrated that the probiotic combinations in **Florajen Digestion** and **Florajen Kids**, reduced toxin production by *C. difficile* by more than 90%, suggesting these probiotics significantly suppressed toxin development, compared to the comparator; *C. difficile* without probiotic. [Ref Bina 2]

IBS Symptoms, Bloating and Constipation

There is some evidence that probiotics can provide health benefits to patients with other GI conditions by providing nutrients that support healthy, normal microbial balance. Two of the most common functional bowel disorders include Irritable Bowel Syndrome (IBS) and functional constipation, with a worldwide prevalence of 15% and 14% respectively. [Ford 2014]

A meta-analysis in the treatment of IBS concluded that probiotics may have a role in alleviating some symptoms of IBS. [Hoveyda 2009] There are data showing benefit in managing bloating, poor digestion and abdominal pain [Ringel-Kulka 2014] as well as constipation, where the presence of *Bifidobacterium lactis* HN019 and *Lactobacillus acidophilus* NCFM may shorten colonic transit times and relieve constipation. [Magro 2014]. The American College of Gastroenterology (ACG) recommendations include probiotics as adjunctive therapy with antimicrobial agents for Irritable Bowel Syndrome, noting that overall, probiotics can improve global symptoms, bloating, and flatulence in IBS for many patients. [Ford 2014]

Constipation is a common problem afflicting more adults than diarrhea and creating a healthcare burden. The Harvard

Medical School estimates that approximately 14% of adults experience constipation annually, resulting in 2.3 million office visits [Corliss 2017] and at a healthcare cost per patient ranging from \$1,912 to \$7,522. Recent literature

supports the use of probiotics to improve bowel health. *Bifidobacterium*, contained in many probiotic regimens, appeared to increase weekly bowel movements and soften stools. [Dimidi 2014]

Supportive Data on Probiotic Use in GI Health/Diarrhea, IBS Symptoms and Constipation

Author/Reference	Summary
Danisco A/S. <i>Bifidobacterium longum</i> BI-05. TM 27-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	<i>Bifidobacterium longum</i> BI-05 is well suited for intestinal survival as it is tolerant of acid and bile and adheres to intestinal mucosa
Danisco A/S. <i>Bifidobacterium lactis</i> Bi-07. TM 55-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	<i>Bifidobacterium lactis</i> Bi-07 is well suited for use in GI health and well-being
Danisco A/S. <i>Bifidobacterium lactis</i> HN019- a probiotic with proven efficacy. TM 58-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	<i>Bifidobacterium lactis</i> HN019 is well suited in GI health particularly in the area of immune system modulation
Favretto D., Pontin B., Moreira T. Effect of the consumption of a cheese enriched with probiotic organisms (<i>Bifidobacterium lactis</i> Bi-07) in improving symptoms of constipation. <i>Arg Gastroenterol</i> 2013, Vol. 50 no.3	Fresh cheese containing <i>Bifidobacterium lactis</i> Bi-07 improved constipation symptoms
Waller P, Gopal P, Leyer G, Ouwehand A, Reifer C, Stewart M, Miller L. Dose-response effect of <i>Bifidobacterium lactis</i> HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. <i>Scandinavian Journal of Gastroenterology</i> , 2011; 46: 1057-1064	Demonstrated that <i>Bifidobacterium lactis</i> HN019 short term therapy may reduce the frequency of functional gastrointestinal symptoms without adverse effects
Danisco A/S. HOWARU <i>Rhamnosus</i> . TM 2053-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	HOWARU <i>Rhamnosus</i> or <i>Lactobacillus rhamnosus</i> HN001 is well suited with immune-enhancing properties
Danisco A/S. <i>Lactobacillus acidophilus</i> LA-14. TM 48-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	<i>Lactobacillus acidophilus</i> LA-14 is well suited for use in GI health as it is acid and bile tolerant and may have immunomodulating activity
Danisco A/S. <i>Lactobacillus acidophilus</i> NCFM-a probiotic with proven efficacy. TM 54-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark	<i>Lactobacillus acidophilus</i> NCFM is well suited for use in GI health as it is acid and bile tolerant and may have immunomodulating activity
Gilliland S.E., Speck M.L., Nauyok G.F., Giesbrecht F.G. Influence of consuming nonfermented milk containing <i>Lactobacillus acidophilus</i> on fecal flora of healthy males. <i>Journal of Dairy Science</i> 1978, Volume 61, Number 1	<i>Lactobacillus acidophilus</i> survives in the intestinal tract
Liu, F., Wen K., Li G., Yang X., Kocher J., Bui T., Jones D., Pelzer K., Clark-Deener S., Yuan L. Dual functions of <i>Lactobacillus acidophilus</i> NCFM as protection against rotavirus diarrhea. <i>J Pediatr Gastroenterol Nutr.</i> 2014, Feb; 58 (2):171-8	<i>Lactobacillus acidophilus</i> NCFM has demonstrated that appropriate strains and doses may reduce rotavirus diarrhea and enhance the immune response

Author/Reference	Summary
Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel J, Ardid D, Desreumaux P. <i>Lactobacillus acidophilus</i> modulates intestinal pain and induces opioid and cannabinoid receptors. <i>Natural Medicine</i> , 2007. Volume 13, Number 1.	Study of <i>Lactobacillus acidophilus</i> activity on cannabinoid receptors in the intestinal epithelial cells may provide insight in the treatment of abdominal pain and irritable bowel syndrome
Graul T, Cain A, Karpa K. Lactobacillus and bifidobacterial combinations: A strategy to reduce hospital-acquired Clostridium difficile diarrhea incidence and mortality. <i>Medical Hypotheses</i> , 2009. Volume 73, 194-198	<i>Clostridium difficile</i> nosocomial infection may be managed by Lactobacillus and Bifidobacteria combination probiotics
Hill C., Guarner F. Reid G., Gibson GT., Merenstein DJ., Pot B., Morelli L, Canani RF., Flint HJ, Salminen S., Calder PC., Sanders, ME., The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic <i>Nat. Rev. Gastroenterol. Hepatol.</i> 2014, 11: 506-514	Recommendations of the ISAPP consensus committee on probiotics and prebiotic uses
Magro, D., Oliveira L., Bernasconi I., Ruela M., Credidio L., Barcelos I., Leal R., Ayrizono M., Fagundes J., Teixeira L., Ouwehand A., Coy C. Effect of yogurt containing polydextrose, <i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> HN019: a randomized, double blind, controlled study in chronic constipation <i>Nutrition Journal</i> 2014, 13:75	<i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> HN019 significantly shortened colonic transit time after 2 weeks and may be a therapeutic option to treat constipation
Ringel-Kulka T, Palsos OS, Maier D, Carroll I, Galanko JA, Leyer G, Ringel Y. Probiotic bacteria <i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. <i>J. Clin Gastroenterol</i> 2011 Jul;45(6):518-25	Demonstrated improvement in abdominal bloating, supporting the role of <i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> Bi-07 in managing functional bowel disorders (FBD)
Safdar N, Barigala R, Said A, McKinley L. Feasibility and tolerability of probiotics for prevention of antibiotic-associated diarrhea in hospitalized US military veterans. <i>Journal of Clinical Pharmacy and Therapeutics</i> . 2008. Volume 33, 663-668	A pilot study that focused on military veterans demonstrated that this elderly population with multiple comorbidities and medications tolerated the Florajen formulation
Zanten G, Knudsen A, Ryotio H, Forssten S, Lawther M, Blennow A, Lahtinen S, Jakobsen M, Svensson B, Jespersen L. The effect of selected synbiotics on microbial composition and short-chain fatty acid production in a model system of the human colon. <i>PLOS ONE</i> , October 2012. Volume 7, Issue 10, e47212	Demonstrated that probiotic combinations can shift predominant bacterial strains in the colon, potentially able to affect the microbiota for health purposes

Increase in Allergic Diseases

Allergic diseases have seen a worldwide increase creating a huge healthcare and cost burden. The “hygiene hypothesis,” first proposed in 1989 by David Strachan, suggests that in the more affluent, hygienic areas of the world, a lack of microbial exposure has increased the prevalence of allergy and autoimmune disease. [Strachan 1989] Greater understanding of the human microbiome has led to the study of how the intestinal gut flora are related to sensitization

and the body’s immune response. Probiotics may address this issue, providing a useful adjunct in allergic conditions such as eczema and atopic sensitization. [Wickens 2013] Interestingly, some data suggests a lack of Bifidobacteria can be seen in children exhibiting food allergies, thereby raising awareness of the important role these organisms play in the human microbiome and the positive role probiotic supplementation can play. [Kirjavaninen 2001]

Eczema and Atopic Sensitization

Early supplementation with *Lactobacillus rhamnosus* HN001 appears to confer a protective effect against the development of eczema and possibly atopy in high risk infants up to age 6 years, reducing cumulative prevalence by over 40%. The probiotic effect on atopic sensitization may be attributed to immunomodulating activity and its ability to enhance the gut barrier function. [Wickens 2013] *Lactobacillus rhamnosus* HN001 and HN019 strains appear to be safe and well tolerated in this population. [Dekker 2009]. Recently, the World Allergy Organization recognized the likely benefit of using probiotics and issued guidelines recommending the use of probiotics in pregnant and lactating women to prevent eczema in infants who are at high risk of developing an allergy. [Fiocchi 2015]

Allergic Rhinitis

Because probiotics have demonstrated immunomodulating activity, their use has been encouraged in immune-mediated and allergic disease. *Lactobacillus acidophilus* and *Bifidobacterium lactis* are two strains that have been studied in allergic rhinitis. [Ouwehand 2009]

There are several studies that have shown probiotic utility in allergic rhinitis. A Cochrane meta-analysis published in 2015 evaluated the effects of probiotics by reviewing 23 randomized controlled trials. Of these, 17 out of 23 studies demonstrated a significant clinical benefit associated with probiotic use. Despite the variability of the study designs and outcome measures, the conclusions were that patients suffering from allergic rhinitis may benefit from probiotics in improving symptoms and improving patient quality of life. [Zajac 2015]

Respiratory Symptom Control

The use of probiotics in preventing respiratory symptoms of cold and flu, particularly in children, is gaining attention. *Lactobacillus acidophilus* and *Bifidobacterium lactis* are two strains that have been studied for their health benefit in reducing cold and influenza symptoms. A study by Leyer et al, demonstrated that daily supplementation with some probiotic strains for 6 months in children may reduce the severity of respiratory illness: reducing episodes of fever,

rhinorrhea and cough, reducing antibiotic prescriptions and the number of days of school lost to illness. With the AAP Public Health Advisory recommending against the use of popular cough and cold remedies in children under 2 years old, probiotic prophylaxis may obviate the need to use pharmacologic agents for symptom relief in children. [Leyer 2009]

This concept is also supported by a Cochrane Review that evaluated a dozen studies of probiotics preventing upper respiratory tract infections (URTI). The meta-analysis concluded that probiotics performed better than placebo, reduced the number of episodes and mean duration of URTI, and reduced antibiotic use and school absences. [Hao 2015]

Vaginal Health

The human vagina hosts a range of microbiota from a pool of over 50 species with lactobacilli being the most common. Vaginal health can be disrupted by a variety of natural as well as human causes. Menopause, diabetes, the use of oral contraceptives and spermicides can upset the delicate balance of microbiota, causing yeast infections and bacterial vaginosis. Antibiotics are another culprit, with up to 25% of women reporting vaginal side effects after administration. [Wright 2013] Probiotic supplementation with a product such as **Florajen Women** may help restore and maintain a healthy balance of vaginal flora and appropriate vaginal pH, as well as overall GI health.

Florajen Women (a multi-strain probiotic containing *Lactobacillus acidophilus* and *Lactobacillus rhamnosus*) has demonstrated benefits in maintaining vaginal health and restoring vaginal pH.

The interest in using lactic-acid producing probiotic strains to promote vaginal health is based on the role played by these microorganisms in maintaining the body's normal low vaginal pH (<4.5) which protects against the growth of pathogenic bacteria. A recent study by Davide De Alberti et al, looked at the consumption of a *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* La-14 combination with bovine lactoferrin by healthy women and confirmed the presence of these strains of lactobacilli in the vagina. This health benefit should be further explored. [Alberti 2015]

Supportive Data on Probiotic Use in Immunity/Related Conditions and Vaginal Health

Author/Reference	Summary
Alberti D., Russo R., Terruzzi F., Nobile V., Ouwehand A. Lactobacilli vaginal colonization after oral consumption of Respecta complex: a randomized controlled pilot study. <i>Arch Gynecol Obstet</i> 2015	<i>Lactobacillus rhamnosus</i> HN001, <i>Lactobacillus acidophilus</i> La-14 were studied in healthy women and determined that these consumed strains were detected in the vagina
Dekker J, Wickens K, Black P, Stanley T, Mitchell E, Fitzharris P, Tannock G, Purdie G, Crane J. Safety aspects of probiotic strains <i>Lactobacillus rhamnosus</i> HN001 and <i>Bifidobacterium animalis</i> subsp. <i>Lactis</i> HN019 in human infants aged 0-2 years. <i>International Dairy Journal</i> , 2009. Volume 19 149-154	<i>Lactobacillus rhamnosus</i> HN001 and <i>Bifidobacterium lactis</i> HN019 are safe and well tolerated in young children
Goldin B, Gorbach S. The effect of milk lactobacillus feeding on human intestinal bacterial enzyme activity. <i>The American Journal of Clinical Nutrition</i> , May 1984. Volume 39, 756-761	<i>Lactobacillus acidophilus</i> causes alteration of intestinal bacteria and appears to suppress fecal bacterial enzymes involved in the production of carcinogens in the intestine
Petersen ER, Claesson MH, Schmidt EG, Jensen SS, Ravin P, Olsen J, Ouwehand AC, Kristensen NN. Consumption of probiotics increases the effect of regulatory T cells in transfer colitis. <i>Inflamm Bowel Dis</i> . January 2012. Volume 18(1): 131-42. doi: 10.1002/ibd.21709. Epub 2011 Apr 14.	<i>Lactobacillus acidophilus</i> NCFM appears to have immunomodulating activity
Sanders M, Klaenhammer T. Invited Review: The scientific basis of <i>Lactobacillus acidophilus</i> NCFM functionality as a probiotic. <i>J. Dairy Sci.</i> , 2001. Volume 84 319-331	<i>Lactobacillus acidophilus</i> NCFM demonstrated efficacy and was safe and well tolerated, including in young children
Leyer G, Shuguang L, Mubasher M, Reifer C, Ouwehand A. Probiotic effects on cold and influenza-like symptoms incidence and duration in children. <i>Pediatrics</i> , 2009. 124;e172-e179	Daily supplementation for 6 months with probiotics (<i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> Bi-07) was safe and effective in reducing the incidence and duration of rhinorrhea, fever and cough in children, reduced the incidence of antibiotic use and reduced the number of missed school days
Wickens K., Black, P. N., Stanley T. V., Mitchell E.A., Fitzharris P., Tannock G.W., Purdie G., Crane J. A differential effect of 2 probiotics in the prevention of eczema and atopy: A double-blind, randomized, placebo-controlled trial. <i>J Allergy Clin Immunol</i> October 2008, Volume 122, Number 4	Supplementation with <i>Lactobacillus rhamnosus</i> HN001 in young children confers protection against the development of eczema
Wickens K., Stanley T. V., Mitchell E.A., Barthow C., Fitzharris P., Purdie G., Siebers R., Black P.N., Crane J. Early supplementation with <i>Lactobacillus rhamnosus</i> HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? <i>Clinical Experimental Allergy</i> 2013 43, 1048-1057	Daily supplementation with <i>Lactobacillus rhamnosus</i> HN001 demonstrated a protective effect against eczema when dosed for the first 2 years of life and extended up to 4 years

CONCLUSION

The study of the human microbiome is increasing our understanding of the role microorganisms play in the human body and particularly in disease. Our greater knowledge is opening new frontiers in the role that probiotic products can play to promote health benefits, and reduce symptoms and side effects that are indicators of poor GI and vaginal health.

Healthcare professionals should review specific probiotic strains that have been studied and are most likely to confer health benefits. The Florajen line of probiotics, for patients age 6 months and up, was developed using culture combinations based on bacterial strain data.

In addition to delivering the right strains, it is critical to ensure that patients receive an efficacious dose and a

safe, high quality product with live cultures. The Florajen probiotic line, for example, is manufactured under Good Manufacturing Practices (GMP) and is shipped and stored at retail under refrigeration to ensure potency. The Florajen Cold Chain Commitment™ ensures that patients trying to restore flora have potent and consistent cultures on a daily basis. No other method to keep cultures alive has proven more effective than refrigeration. Florajen can be stored at room temperature up to 2 weeks and maintain effectiveness.

Multi-strain probiotics with high culture counts of live bacteria, such as the Florajen product line, are an exciting new approach for GI and vaginal health, because they can draw upon the strength of their individual components to provide complementary activity and health benefits.



REFERENCES

- Alberti D., Russo R., Terruzzi F., Nobile V., Ouwehand A. Lactobacilli vaginal colonization after oral consumption of Respecta complex: a randomized controlled pilot study. *Arch Gynecol Obstet* 2015
- Anderson L. Common Side Effects from Antibiotics, and Allergies and Reactions <https://www.drugs.com/article/antibiotic-sideeffects-allergies-reactions.html>, Accessed April 19, 2018
- Antibiotic-associated diarrhea. Mayo Clinic website. Accessed April 4, 2017 <http://www.mayoclinic.org/diseases-conditions/antibiotic-associated-diarrhea/symptoms-causes/dxc-20229977>
- Armstrong C. AAP reports on use of probiotics and prebiotics in children *American Family Physician* Apr 2011, 83:7
- Bina, Paul Effect of Probiotic on Clostridium difficile growth and toxin production at different pH Values. Data on file
- Bina, Paul. Effect of Probiotic on Clostridium difficile growth and toxin production at different pH values for Florajen Digestion and Florajen Kids' formulations. July 2018, Data on file
- CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. Available at <http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>. Accessed March 5, 2018.
- Centers for Disease Control and Prevention. Antibiotic Use in Nursing Homes. Nov 5, 2013. <http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/nursing-homes.html>
- Ciorba, Matthew A. A Gastroenterologists's Guide to Probiotics *Clinical Gastroenterology and Hepatology* 2012; 10:960-968
- Corliss, J. Probiotics May Ease Constipation. Harvard Health Publications, Harvard Medical School website. <https://www.health.harvard.edu/blog/probiotics-may-ease-constipation-201408217377> Accessed April 10, 2018
- Cox AJ, West NP, Horn PL, Lehtinen MJ, Koerbin G, Pyne DB, Lahtinen SJ, Fricker PA, Cripps AW. Effects of probiotic supplementation over 5 months on routine haematology and clinical chemistry measures in healthy active adults. *Eur J Clin Nutr* July 2014, doi:10.1038/ejcn.2014. 137
- Danisco A/S. *Bifidobacterium longum* BI-05. TM 27-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Danisco A/S. *Bifidobacterium lactis* Bi-07. TM 55-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Danisco A/S. *Bifidobacterium lactis* HN019- a probiotic with proven efficacy. TM 58-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Danisco A/S. HOWARU Rhamnosus. TM 2053-1e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Danisco A/S. *Lactobacillus acidophilus* LA-14. TM 48-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Danisco A/S. *Lactobacillus acidophilus* NCFM-a probiotic with proven efficacy. TM 54-2e. Edwin Rahrs Vej 38. DK-8220 Brabrand, Denmark
- Dekker J, Wickens K, Black P, Stanley T, Mitchell E, Fitzharris P, Tannock G, Purdie G, Crane J. Safety aspects of probiotic strains *Lactobacillus rhamnosus* HN001 and *Bifidobacterium animalis* subsp. *Lactis* HN019 in human infants aged 0-2 years. *International Dairy Journal*, 2009, 19:149-154
- Dimidi E, Christodoulides S, Fragkos K C, Scott M, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials *The American Journal of Clinical Nutrition*, 100:4, 1 October 2014, 1075–1084
- Ephraim E, Schultz R, Duster M, Warrack S, Spiegel C, Safdar N. In-vitro evaluation of the antagonistic effects of the probiotics *Lactobacillus Rhamnosus* HN001 and Florajen 3 against Group B Streptococci.
- Favretto D., Pontin B., Moreira T. Effect of the consumption of a cheese enriched with probiotic organisms (*Bifidobacterium lactis* Bi-07) in improving symptoms of constipation. *Arg Gastroenterol* 2013, 50 (3)
- Fiocchi, A, Pawankar R, Cuello-Garcia C, Kangmo A, Al-Hammadi S, Agarwal A, Beyer, K, Burks, W, Canonica GW, Ebisawa M, Gandhi S, Karmenwa R, Lee BW, Li H, Prescott, S, Riva, JJ, Rosenwasser L, Sampson H, Spigler M, Terracciano L, Vereda-Ortiz A, Wasserman S, Yepes-Nunez JJ, Brozek JL, Schunemann HJ. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. *World Allergy Organization Journal* 2015, 8:4
- Ford AC , Moayyedi P, Lacy BE, Lembo AJ , Saito YA , Schiller LR, Soffer EE, Quigley E. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation *Am J Gastroenterol* 2014, 109:S2 – S26
- Forsberg A, West CE, Jenmalm MC. Pre- and probiotics for allergy prevention: time to revisit recommendations? *Clin Exp Allergy*. Dec 2016, 46(12):1506-1521
- Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews* 2013, Issue 5.

- Gill H., Rutherford K., Cross M. Dietary probiotic supplementation enhances natural killer cell activity in elderly: an investigation of age-related immunological changes. *Journal of Clinical Immunology* 2001, 21(4)
- Gilliland S.E., Speck M.L., Nauyok G.F., Giesbrecht F.G. Influence of consuming nonfermented milk containing *Lactobacillus acidophilus* on fecal flora of healthy males. *Journal of Dairy Science* 1978, 61(1)
- Goldin B, Gorbach S. The effect of milk lactobacillus feeding on human intestinal bacterial enzyme activity. *The American Journal of Clinical Nutrition*, May 1984, 39:756-761
- Graul T, Cain A, Karpa K. Lactobacillus and bifidobacterial combinations: A strategy to reduce hospital-acquired *Clostridium difficile* diarrhea incidence and mortality. *Medical Hypotheses*, 2009, 73:194-198
- Hanson L, Vusse V, Duster M, Warrack S, Safdar N. Feasibility of oral prenatal probiotics against maternal group B *Streptococcus* vaginal and rectal colonization. *JOGNN* 2014, 43:294-304
- Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2015 Feb 3;2
- Hemalata R., Ouwehand A., Forssten S., Geddan J., Mamidi R., Bhaskar V., Radhakrishna K. A community-based randomized double blind controlled trial of *Lactobacillus paracasei* and *Bifidobacterium lactis* on reducing risk for diarrhea and fever in preschool children in an urban slum in India. *European Journal of Nutrition & Food Safety* 2014, 4(4): 325-341
- Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JNV, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, Smith A, Roth E, Polak J, Motala A, Perry T, Shekelle PG. *Safety of Probiotics to Reduce Risk and Prevent or Treat Disease*. Evidence Report/Technology Assessment No. 200. AHRQ Publication No. 11-E007. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Accessed March 7, 2018 <https://www.ahrq.gov/research/findings/evidence-based-reports/probiotsum.html>
- Hill C., Guarner F, Reid G., Gibson GT., Merenstein DJ., Pot B., Morelli L, Canani RF., Flint HJ, Salminen S., Calder PC., Sanders ME., The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic *Nat. Rev. Gastroenterol. Hepatol.* 2014, 11: 506-514
- Hoveyda Nourieh, Heneghan Carl, Mahtani Kamal R Perera Rafael, Roberts Nia Glasziou Paul, *BMC Gastroenterology* 2009, 9:15
- How to Prevent Diarrhea While You Take Antibiotics. Cleveland Clinic website. Accessed April 4, 2017 <https://health.clevelandclinic.org/2015/04/how-to-prevent-diarrhea-while-you-take-antibiotics/>
- Joint Commission. New Antimicrobial Stewardship Standard *Joint Commission Perspectives*, July 2016, 36:7
- Islam SU. Clinical uses of probiotics. *Medicine* 2016, 95:e2658
- Leyer G, Shuguang L, Mubasher M, Reifer C, Ouwehand A. Probiotic effects on cold and influenza-like symptoms incidence and duration in children. *Pediatrics*, 2009, 124:e172-e179
- Liu, Fangning, Wen Ke, Yang, Xingdong, Kocher, Jacob, Bui, Tammy, James, Dorothy, Pezler, Kevin, Clark-Deener, Sherrie, and Yuan, Lijuan Dual Functions of *Lactobacillus acidophilus* NCFM as Protection Against Rotavirus Diarrhea, *JPGN* 2014, 58:169-176
- Magro, D., Oliveira L., Bernasconi I., Ruela M., Credidio L., Barcelos I., Leal R., Ayrizono M., Fagundes J., Teixeira L., Ouwehand A., Coy C. Effect of yogurt containing polydextrose, *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* HN019: a randomized, double blind, controlled study in chronic constipation *Nutrition Journal* 2014, 13:75
- Maneerat S., Lehtinen M., Childs C., Forssten S., Alhoniemi E., Tiphaine M., Yaqoob P., Ouwehand A., Rastall R. Consumption of *Bifidobacterium lactis* Bi-07 by healthy elderly adults enhances phagocytic activity of monocytes and granulocytes. *Journal of Nutritional Science* 2013, 2:e44, 1-10
- McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Dig Dis*. 1998;16(5):292-307 <https://www.ncbi.nlm.nih.gov/pubmed/9892789>
- McFarland, LV. Meta-Analysis of Probiotics for the Prevention of Antibiotic Associated Diarrhea and the Treatment of *Clostridium difficile* Disease *Am J Gastroenterology* Apr 2006, 101(4):812-22
- National Institutes of Health. The basics of probiotics. *NIH Medline Plus* Winter 2016 Issue: Volume 10 Number 4 Page 22 <https://medlineplus.gov/magazine/issues/winter16/articles/winter16pg22.html> Accessed March 7, 2018
- NIH National Center for Complementary Health Approaches in the US. Most used natural products. <https://nccih.nih.gov/research/statistics/NHIS/2012/natural-products/biotics> Accessed March 7, 2018
- Ouwehand AC, Nermes M, Collado MC, Rautonen N, Salminen S, Isolauri E. Specific probiotics alleviate allergic rhinitis during the birch pollen season. *World J of Gastroenterol* 2009; 15(26): 3261-3268
- Petersen ER, Claesson MH, Schmidt EG, Jensen SS, Ravin P, Olsen J, Ouwehand AC, Kristensen NN. Consumption of probiotics increases the effect of regulatory T cells in transfer colitis. *Inflamm Bowel Dis*. January 2012, (1): 131-42

- Reid, Gregory. In vitro testing of *Lactobacillus acidophilus* NCFM as a possible probiotic for the urogenital tract. *International Dairy Journal*. 2002, 10:415-419
- Ringel-Kulka T, Goldsmith, JR, Carroll IM, Baroos SP, Palsom O, Jobin C, Ringel Y. *Lactobacillus acidophilus* NCFM affects colonic mucosal opioid receptor expression in patients with functional pain – a randomized clinical study. *Aliment Pharmacol Ther*. 2014 Jul; 40(2):200-7
- Ringel-Kulka T, Palsom OS, Maier D, Carroll I, Galanko JA, Leyer G, Ringel Y. Probiotic bacteria *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. *J. Clin Gastroenterol* Jul 2011;45(6):518-25
- Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel J, Ardid D, Desreumaux P. *Lactobacillus acidophilus* modulates intestinal pain and induces opioid and cannabinoid receptors. *Natural Medicine*, 2007, 13(1)
- Safdar N, Barigala R, Said A, McKinley L. Feasibility and tolerability of probiotics for prevention of antibiotic-associated diarrhea in hospitalized US military veterans. *Journal of Clinical Pharmacy and Therapeutics*. 2008, 33: 663-668
- Sanders M, Klaenhammer T. Invited Review: The scientific basis of *Lactobacillus acidophilus* NCFM functionality as a probiotic. *J. Dairy Sci.*, 2001,84:319-331
- Shane, Andi L., Mody, Rajal K., Crump, John A., Tarr, Phillip I., Steiner, Theodore S., Kotloff, Karen, Langley, Joanne M., Wanke, Christine, Warren, Cirle Alcantara, Cheng, Allen C., Cantey, Joseph, Picking, Larry K. 2017 IDSA Guidelines for the Diagnosis and Management of Infectious Diarrhea CID 2017, 1-36
- Sheih Y., Chiang B., Wang L., Liao C., Gill H. Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* HN001. *Journal of the American College of Nutrition* 2001, 20(2):149-156
- Statista. Retail sales value of probiotic functional foods worldwide from 2012 to 2104. <https://www.statista.com/statistics/252941/probiotic-products-sales-worldwide-by-region>, Accessed March 3, 2018
- Statista. US dollar sales of probiotic supplements 2014-2020ps://www.statista.com/statistics/492591/dollar-sales-probiotic-supplements-united-states, Accessed March 8, 2018
- Surawicz Christina M. Brandt Lawrence J, Binion David G., Ananthakrishnan Ashwin N., Curry Scott R., Gilligan Peter H., McFarland Lynne V. Mellow Mark., Zuckerbraun Brian S Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium diffi cile* Infections *Am J Gastroenterol* 201; 108:478–498
- Tannock G., Munro K., Harmsen H., Welling G., Smart J., Gopal P. Analysis of the fecal microflora of human subjects consuming a probiotic product containing *Lactobacillus rhamnosus* DR20. *Applied and Environmental Microbiology* June 2000, 66(6): 2578-2588.
- Tiano J, The Human Microbiome Project, The Catalyst (National Institutes of Health), 2013, 21(6):1
- Vanderhoof JA, et al . *Lactobacillus* GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr*. 1999;135(5):564-568 <https://www.ncbi.nlm.nih.gov/pubmed/10547243>
- Waller P, Gopal P, Leyer G, Ouwehand A, Reifer C, Stewart M, Miller L. Dose-response effect of *Bifidobacterium lactis* HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scandinavian Journal of Gastroenterology*, 2011, 46: 1057-1064
- Wickens K., Black, P. N., Stanley T. V., Mitchell E.A., Fitzharris P, Tannock G.W., Purdie G., Crane J. A differential effect of 2 probiotics in the prevention of eczema and atopy: A double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* October 2008, 122,(4)
- Wickens K., Stanley T. V., Mitchell E.A., Barthow C., Fitzharris P, Purdie G., Siebers R., Black P.N., Crane J. Early supplementation with *Lactobacillus rhamnosus* HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? *Clinical Experimental Allergy* 2013, 43: 1048-1057
- Wright JJ, Paauw DP. Complications of Antibiotic Therapy. *Medical Clinics of North America*, July 2013, 97(40):667-679
- Zajac A, Adams AS, Turner JH. A systematic review and emta-analysis of probiotics for the treatment of allergic rhinitis, *International Forum of Allergy and Immunology*, 201, 5(6) 524-532
- Zanten G, Knudsen A, Ryotio H, Forssten S, Lawther M, Blennow A, Lahtinen S, Jakobsen M, Svensson B, Jespersen L. The effect of selected synbiotics on microbial composition and short-chain fatty acid production in a model system of the human colon. *PLOS ONE*, October 2012, 7(10): e47212