IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Efficacy Of Probiotics In The Treatment Of Diarrhoea Of Children

1Indranil Murmu, 2Ankita Ghosh, 3Ayan Mondal, 4Jinia Raychaudhuri, 5Srestha Ray

1Msc in Zoology., 2Msc in Zoology., 3Msc in Zoology., 4M.Sc in Microbiology., 5M.Sc in Biochemistry

1Suri Vidyasagar College, University of Burdwan.,

2Suri Vidyasagar College, University of Burdwan,

3University of Burdwan,

4Maulana Abul Kalam Azad University of Technology,

5Vidyasagar University

Abstract:

Diarrhoea is a symptom, and not a disease. Diarrhoea remains the second leading cause of death in children below 5 years of age; in addition it is also the reason for a considerable morbidity in children of all ages throughout the globe. The use of probiotics in the treatment and prevention of diarrhoeal illnesses, particularly in paediatric populations, has been thoroughly researched during the past few years. The prevention of antibiotic-associated diarrhoea has been the subject of many investigations, both in children and in adults. Most commonly used probiotics were *Lactobacillus GG, Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium ssp, Streptococcus ssp,* and the yeast *Saccharomyces boulardii*.

Probiotics have been tested for a number of clinical uses such as the prevention of antibiotic-associated diarrhoea (AAD), the treatment of various diseases such as *Helicobacter pylori* infection, irritable bowel disease, vaginitis, the prevention of allergies, and necrotizing enterocolitis in newborns. AAD has been the most indicated therapeutic use for probiotics. A common and unwanted side effect of antibiotic therapy is antibiotic-associated diarrhoea (AAD). Disruption of the gut microbiota, decreased intestinal short chain fatty acid (SCFA) concentrations, a buildup of luminal carbohydrates and colonic bile acids, impaired water absorption, and eventually diarrhoea are its hallmarks. Numerous clinical studies have demonstrated the prevention of AAD by probiotics. The hypothesis behind using probiotics for AAD is that they help normalize an unbalanced flora.

Probiotics reduce the risk of AAD through altering the gut microbiota, influencing diet and bile acid metabolism, activating epithelial solute transporters, enhancing intestinal barrier function, and influencing the immune system. Probiotics are frequently suggested in addition to antibiotics, however there is a lack of mechanistic evidence demonstrating how they can prevent AAD.

Keyword: Probiotics, Diarrhoea, Children, Efficacy, Treatment.

Introduction:

The burden of diarrhoeal illness on society is enormous. Diarrhoea causes 1.5 million deaths yearly, or 1% of mortality in children under the age of five, despite advances in case management. Although the bulk of these deaths take place in underdeveloped countries, they are a common cause of medical consultation and hospital admission in Western nations and have a significant social cost in terms of lost productivity for those who are affected and their carers **[1]**.

When ingested, probiotics—also referred to as "good bacteria"—can provide health advantages in a variety of ways. Since most of the health benefits associated with probiotics are either directly or indirectly related to the digestive system, using them to treat or prevent gastrointestinal illnesses is a sensible course of action and may be the most common application of probiotics **[2].**

AAD is more than just a troublesome side effect of antibiotic therapy; it's linked to prescription noncompliance and excessive second-line antibiotic use. Despite the fact that AAD affects people of all ages, children are at higher risk due to the frequency with which they are prescribed antibiotics and the 20–35% rate of diarrhoea linked with antibiotic use in children **[3]**. AAD is characterised as clinically inexplicable diarrhoea that happens after receiving antibiotics. Any antibiotic has the potential to produce AAD, but broad spectrum medications that primarily target anaerobes and are poorly absorbed, such clindamycin, cephalosporins (cefixime and ceftriaxone), and amoxicillin-clavulanate, are more likely to do so **[4]**.

One of the most commonly prescribed uses of probiotics is for the prevention of antibiotic-associated diarrhoea (AAD). Strains from numerous bacterial species have been tested in clinical studies for mitigating AAD including members of the *Bacillus, Bifidobacterium, Clostridium, Lactobacillus, Lactococcus, Leuconostoc, and Streptococcus genera.* Among the fungi, *Saccharomyces boulardii* has also been examined. *Lactobacillus rhamnosus* strain GG and *S. boulardii* strain CNCM I-745 have been most frequently studied **[5,6]**.

Many societies have been using probiotic-rich fermented foods as therapeutic options. Recently, great strides have been made to understand the human gut microbiome and how microbiome imbalances (dysbiosis) lead to several disease conditions. Probiotics are thus attractive as a health-promoting approach to restore the normal intestinal environment **[7]**.

Antibiotic-associated diarrhoea (AAD) prophylaxis is one of the most commonly recommended therapeutic uses for probiotics.

History :

The health benefits of bacteria consumed in food have been known since ages; records dating back to as early as the Persian version of the Old Testament. Noble laureate Elie Metchnikoff in 1908 suggested that products of proteolytic bacterial action on protein resulted in “intestinal autointoxication”. He presented a hypothesis that consumption of yogurt containing *Lactobacillus* lead to reduced number of toxin-producing bacteria in the intestine and thus contributed to the long life of Bulgarian peasants **[8]**. The concept of probiotic is derived from the Greek word meaning “for life” and the term came into practice in 1965 **[9].** Since then the interest in probiotics has grown many folds and currently, the market for probiotics has reached to over 60 billion USD **[10]**.

Scientists reported on the purported health advantages of consuming fermented milk products in the 1800s **[11]**. The exact mechanism of action causing these advantages is still unknown. Louis Pasteur was successful in identifying the bacteria and yeast that cause fermentation, but he disregarded any potential health repercussions **[12]**. Then, in 1905, Elie Metchinikoff, a Russian scientist who had

collaborated with Pasteur, connected Bulgarian longevity not just to the frequent consumption of yoghurt, but also to the *Lactobacilli* employed to ferment it and their presence in the colon **[13]**. After that, in 1906, Henry Tissier discovered *Bifidobacterium* from a baby and hypothesised that it would replace pathogenic bacteria in the stomach **[14]**. The next century observed a rise in research into the microorganisms that help fight disease and promote health. Upon the request of the Food and Agriculture Organisation of the United Nations and with the support of the World. Health Organization, to define probiotics as: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host"**[15]**. The earliest probiotics on the market were single-species products, such as those from the genera *Saccharomyces or Lactobacillus*. The development of probiotics that had a wider range in addition bacteria came next.

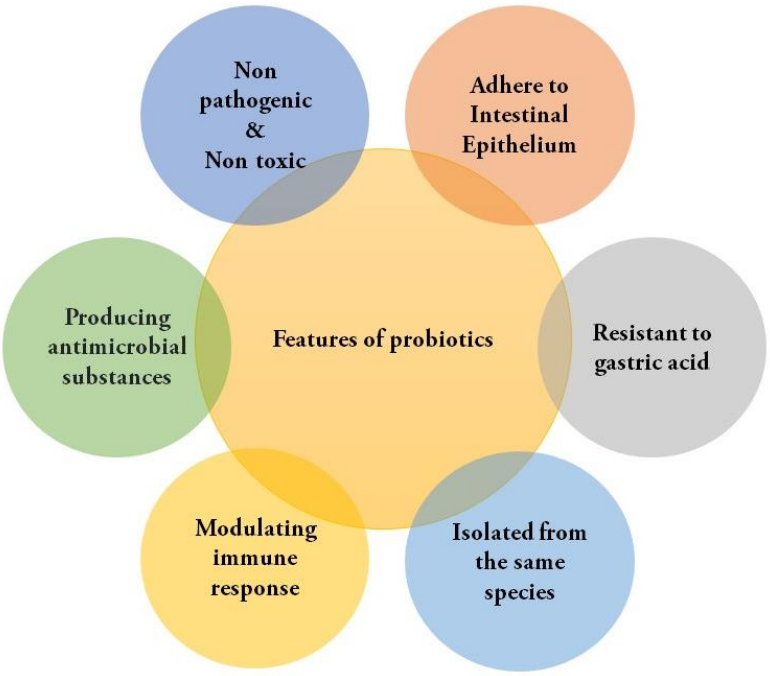
What are Probiotics?

The FAO/ WHO defines probiotic as a "live microorganism which, when administered in adequate amounts, confer a health benefit to the host" **[16]**. Following this, the International Life Science Institute (ILSI) **[17]** and the European Food and Feed Cultures Association (EFFCA) **[18]** have given similar definitions for probiotic: "a live microbial food ingredient that, when consumed in adequate amounts, confers health benefits on the consumers".

Features of Probiotics :

The properties of an ideal probiotic should be **[19]** :

- Origin in human
- Isolated from the same species
- Non-pathogenic
- Contains sufficient number of viable cells
- Unaffected to destruction by technical processing
- Unaffected to destruction by gastric acid and bile
- Adhere to intestinal epithelium
- Able to inhabit the gastrointestinal tract, even if for a short time
- Producing antimicrobial substances
- Modulating immune responses
- Influencing human metabolic activities (i.e. Cholesterol assimilation, vitamin production) and
- Undergone in vivo and in-vitro trials to prove any attributed probiotic effect and documented a clinical benefit.



Common probiotic strain :

Various organisms (bacteria and fungus) have been identified as meeting the diagnostic criteria for probiotics. The common ones are presented in (table 1).

Table 1. Common probiotic strains

Bifidobacterium spp	**Lactobacillus spp**	**Saccharomyces spp**
B. bifidum	*L. acidophilus*	*S. boulardii*
B. breve	*L. casei (rhamnosus)*	
B. lactis	*L. fermentum*	
B. longum	*L. gasseri*	
B. infantis	*L. johnsonii*	
B. adolescents	*L. lactis*	
B. paracasei		
B. plantarum		
B. reuteri		

The indigenous flora of the intestines :

Only 10% of the estimated 1014 cells in the human body that are not bacteria. Mammal gastrointestinal tracts are complex, dynamic, and diversified ecosystems made up of interactions between nonpathogenic, aerobic and anaerobic microorganisms. The colony is stable and has 400 different species. The luminal flora accounts for 40% of the faecal weight and the majority of the gut organisms, however the presence of these organisms in the faeces does not always indicate an important host-microbial symbiosis with the mucosal bound flora **[20]**. The newborn's intestines becomes populated with germs within the first few days following birth. The gut is initially inoculated with a wide variety of bacteria, including *bifidobacteria*, *enterobacteria*, *bacteroids*, *clostridium*, and gram-positive *cocci*. Later, the flora rapidly changes based on the birth method, gestational age, and food (breastfeeding/formula feeding). At 48 hours of life, breastfed babies delivered vaginally exhibit similar colonisation to babies delivered vaginally and fed formula, indicating similar "inoculums". However, by 7 days, only 22% of breastfed newborns and 61% of formula-fed infants have *B. fragilis* colonisation **[21]**. It's interesting to note that nutrition only plays a little effect in the composition of the faecal flora in older children and adults **[22]**.

Up to 65% of people have fungi in their faeces, with the most common genus being Candida. It indicates that under typical conditions, the normal bacterial flora inhibits the pathogenic colonisation of yeast. However, antibiotics would cause the faecal flora to change or disappear, which would cause yeast to proliferate in large quantities **[23]**.

Mechanism of action of probiotics in diarrhoea :

Probiotics are live microorganisms that provide health benefits when consumed in adequate amounts. They are often referred to as "good" or "beneficial" bacteria because they can help restore and maintain a healthy balance of gut microbiota. Probiotics can play a role in preventing and treating diarrhoea by several mechanisms:

- **Restoring Gut Microbiota Balance**: Diarrhoea is often caused by an imbalance in the gut microbiota, usually due to an overgrowth of harmful bacteria or a decrease in beneficial bacteria. Probiotics, when consumed, can help replenish the gut with beneficial bacteria, restoring the microbial balance and promoting a healthier gut environment **[24]**.

- **Production of Beneficial Substances**: Probiotic bacteria can produce various compounds, such as short-chain fatty acids, antimicrobial substances, and bacteriocins, which have antimicrobial properties. These substances can help inhibit the growth of harmful bacteria and pathogens in the gut, reducing the severity and duration of diarrhoea **[25]**.

- **Competition with Pathogens**: Probiotics can compete with pathogenic bacteria for nutrients and adhesion sites in the gut lining. By occupying these sites, probiotics can prevent harmful bacteria from attaching and colonizing the intestinal walls, limiting their ability to cause infections and diarrhoea **[26]**.

- **Modulation of the Immune System**: Probiotics can interact with the gut-associated immune system, helping to regulate immune responses. They can promote the production of anti-inflammatory cytokines while reducing the production of pro-inflammatory cytokines. This balanced immune response can aid in controlling inflammation and promoting healing during diarrhoeal episodes **[27]**.

- **Enhanced Gut Barrier Function**: Probiotics can strengthen the intestinal barrier by promoting the synthesis of tight junction proteins, which help maintain the integrity of the gut lining. A stronger gut barrier can prevent harmful substances and pathogens from leaking into the bloodstream and reduce inflammation and diarrhoea **[28]**.

- **Fermentation of Fiber**: Some probiotic strains can ferment dietary fiber in the colon, producing short-chain fatty acids (SCFAs). SCFAs nourish the colon cells and promote a healthier environment, which can lead to reduced diarrhoea symptoms **[29]**.

It's important to note that the effectiveness of probiotics in preventing and treating diarrhoea can vary depending on the probiotic strains used, the individual's health condition, and the underlying cause of diarrhoea. If you're considering using probiotics for diarrhoea, it's best to consult with a healthcare professional to ensure you choose the most appropriate probiotic strain and dosage for your specific situation **[30]**.

Probiotics uses:

Probiotics are helpful microorganisms that have been found to provide a variety of health advantages. As a result, probiotic foods and supplements have gained popularity as all-natural remedies for a variety of illnesses, including digestive problems like diarrhoea **[31]**.

❖ *Probiotics for diarrhoea of viral origin:*

Around the world, viral agents, with Rotavirus being the most significant, are to blame for acute diarrhoeal episodes in children. According to a Cochrane database of systematic reviews, *Lactobacillus* can reduce the duration of acute rotavirus diarrhoea by 29 hours (95% CI 16-42 hours) and the frequency of stools by 1.25 per day (95% CI 0.4-2.1) on day 2 after the intervention. Grandy et al **[32]** investigated the effects of *S. boulardii* alone or in combination with two different strains of *Lactobacillus* and three additional probiotics on rotavirus diarrhoea. Both products appeared to be connected to a shortening of the diarrhoeal episode. However, one of only four intervention groups who received *S. boulardii* in a Turkish trial discovered benefit in terms of shorter duration of diarrhoea **[33]**.

Despite the fact that a number of therapy trials have found alternative viral agents that are not rotaviruses **[34,35]**, few individual isolates have been found, and no studies have documented the primary or secondary effects of probiotic administration for acute diarrhoeal episodes caused by viruses other than rotavirus.

In a similar vein, research on the prevention of diarrhoeal disease has typically been unable to show evidence of immunity to particular viral agents. Adenovirus detection from stool samples was less common in a cohort treated with *Lactobacillus GG*, according to a Peruvian study on the prevention of diarrhoea in children aged 6-29 months **[36]**.

On the other hand, Sur et al. discovered no differences between the recovery rates for adenovirus, rotavirus, norovirus, or astrovirus for children from a poor urban context in India receiving L. casei Shirota compared to a control group **[37]**.

Children with HIV (Human immunodeficiency virus) infection are a special population group who are more vulnerable to diarrhoeal illnesses as a result of various infections. The outcomes of published studies on the utility of probiotics in treating diarrhoea in this population have been mixed; some [38,39] but not others [40,41], finding efficacy. In a sizable study of Malawian kids who had severe acute malnutrition a multicomponent probiotic containing *lactobacilli* or a placebo was randomly assigned to participants, more than 40% of whom were HIV positive. The rate of diarrhoea among probiotic patients did not decrease, according to the study **[42]**.

A multicomponent probiotic containing *lactobacilli* or a placebo was randomly assigned to participants, more than 40% of whom were HIV positive. The rate of diarrhoea among probiotic patients did not decrease, according to the study.

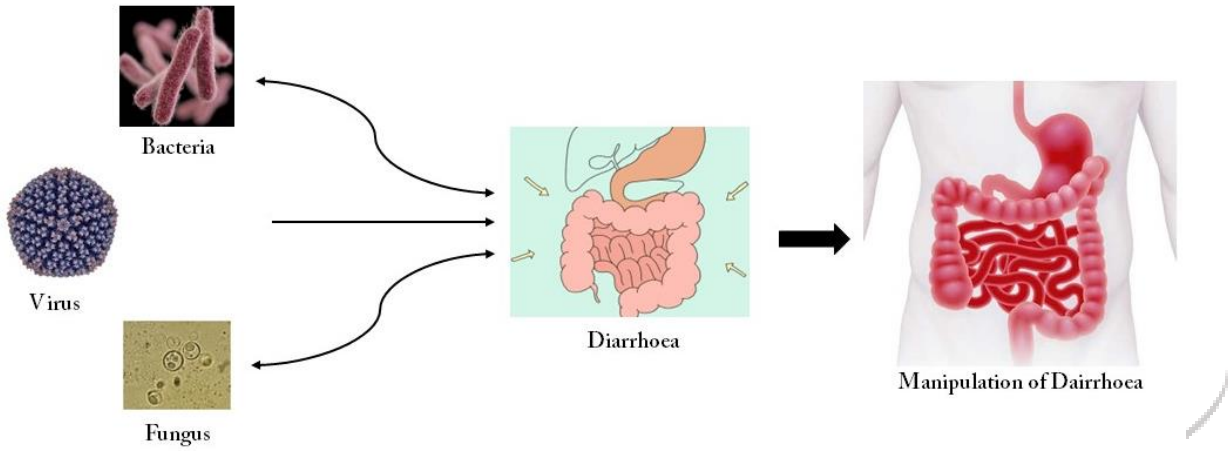
❖ *Probiotics for bacterial diarrhoea:*

In two investigations using *Lactobacillus rhamnosus GG*, the 'invasive' infections Salmonella or Shigella, which affect 15-20% of youngsters, were not found to be protected **[43]**. When LGG was co-treated with trimethoprim-sulfamethoxazole during an outbreak of Shigella dysentery in Estonia, the only trial that dealt directly with bacterial disease, the diarrhoea had earlier resolved **[44]**. For 20 kids who had pathogenic *E. coli* cultured from their stool, Hwe et al **[45]** described an improvement in stool consistency. *Escherichia faecium* was one of three probiotic species in a Taiwanese study, but it was not found to significantly shorten the length of diarrhoea caused by Salmonella or Campylobacter **[46]**. Many research using combination probiotics (*S. boulardii* or *E. coli* Nissle 1917) in middle-income countries demonstrate overall efficacy for groups with large (10–20%) contributions from pathogenic species, but little information is available to quantify efficacy by diarrhoeal pathogen **[47,48,49,50]**.

Although other bacteria (including pathogenic *E. coli*), virus, and protozoal species were recovered at comparable rates, a large community prevention study from India **[37]** found a decrease in diarrhoeal sickness with Aeromonas and Cryptosporidium species among *Lactobacillus casei* Shirota recipients. Another study from urban India found protection from dysentery, which is indicated by a parental history of bloody diarrhoea, but no effect on the total incidence of diarrhoea **[51]**.

❖ ***Probiotics for parasitic diarrhoea:***

S. boulardii was administered in a Cuban research on children with chronic diarrhoea, 35 of whom had giardia cysts in their stools **[52]**. 25 Turkish children who received *Saccharomyces* have reported less bloody diarrhoea and a decreased rate of cyst excretion on day 5 in cases of amoebic dysentery **[53]**. Probiotics were associated with increased rates of clinical cure and cyst elimination from the stool in a study of 48 symptomatic Blastocystis hominis children **[54]**.



❖ ***Probiotics for clostridium difficile associated diarrhoea (CDAD):***

Antimicrobial drugs cause the vast majority of *C. difficile* infections. The biggest risk occurs when drugs with a high potential for abuse are administered impact on the typical gastrointestinal microflora **[55]**. Within two months of the initial episode, the likelihood of recurrences or reinfections is estimated to be 15-35% **[56]**. In a few uncontrolled investigations and in one study, the effectiveness of *Lactobacillus GG* to prevent recurrences of Clostridium difficile-associated diarrhoea (CDAD) has been examined and the trial's final results have not yet been published **[57]**. L. plantarum (299V) has been tested for its effectiveness in preventing repeated episodes of CDAD in a small, double-blind, placebo-controlled study **[58]**. Recurrences were observed in four of the eleven patients who received metronidazole and the probiotic strain and in six of the nine patients who received the antibiotic and a placebo. For the treatment of recurrent *C. difficile colitis, Saccharomyces boulardii* has been tested in two minor open trials. Vancomycin was administered for 10 days and *Sac. boulardii* for 30 days to 13 patients; none of them experienced any further recurrences **[59]**.

Antibiotics are often recommended medications that may disrupt the gastrointestinal microflora, which may in turn impair resistance to various pathogenic pathogens like the bacterium *C. difficile*. This could result in CDAD, a potentially harmful complication caused by *C. difficile*. Probiotics are live microorganisms, and it is thought that they may balance the gastrointestinal flora, preventing this disorder.

Several studies have shown that various probiotics are safe and effective in preventing CDAD in this area. Probiotics may considerably lower the risk of CDAD by 64%, according to an SR from the Cochrane Collaboration that included 23 clinical studies and 4213 people. In the probiotic group, the incidence of CDAD was 2.0%, compared to 5.5% in the control group that received no treatment or a placebo **[60]**.

Probiotics are shown to significantly lower the incidence of CDAD by 66%, according to further SRs and MAs that included 20 RCTs and 3818 participants. 33 episodes per 1000 people would be avoided by probiotic prophylaxis in a population with a 5% incidence of CDAD **[61]**.

Regarding therapy, an MA published in 2012 examined the effectiveness of probiotics in treating CDAD and concluded that probiotics are helpful in treating this condition **[62]** despite the fact that only a small number of the included studies had been created particularly to assess this procedure.

According to the limited controlled clinical trials on CDAD prevention *Sac. Boulardii* is an effective adjuvant in the treatment of recurrent CDAD,. But more research is required, and it's important to understand the pathophysiology and risk factors for CDAD **[57]**.

❖ ***Antibiotic associated diarrhoea (AAD):***

Due to the rising frequency of AAD and the resulting strain on the healthcare system, probiotic research for the treatment of AAD is expanding. Up to one-third of patients receiving antibiotic treatment experience AAD, a frequent adverse effect of antibiotic use **[63]**. Antibiotics can exacerbate diarrhoea through a variety of processes and causes.

Altering the diversity of gut bacteria: While killing and focusing on diseases, antibiotics also affect the symbiotic bacteria essential to the gut microbiome. The immune environment may be significantly changed by this decline in bacterial diversity in the GI tract. This increases the patient's susceptibility of opportunistic infections and enables pathogens to outcompete microorganisms in a competitive environment **[64,65,66]**.

Age of patient: Any patient population can develop AAD, but children are especially vulnerable. Antibiotic usage in this population may have a longer-lasting, more significant impact on the microbiome, including an increase in Proteobacteria and a decline in the diversity of Actinobacteria since the baby microbiome is not fully matured **[65]**.

Spectrum of antibiotics: Antibiotic traits such its mode of action, pharmacokinetics, and dose can not only affect the intended pathogen but can have unexpected effects like AAD. AAD rates are higher when broad-spectrum antibiotics like clindamycin, which are particularly effective against anaerobes, are used. Conversely, narrow-spectrum antibiotics often result in reduced rates of AAD **[67,68]**.

Metabolic disturbances: Nutrition and metabolism are significantly influenced by the gut microbiome. However, certain carbohydrates are digested by bacteria and converted into short-chain fatty acids (SCFAs), which are then absorbed in the small intestine. Extra non-absorbable carbohydrates stay in the gut after antibiotics kill and lyse these bacteria. As they travel to the large intestine, these non-absorbable carbohydrates osmotically absorb water. Osmotic diarrhoea eventually results from this **[68]**.

Loss of colonization resistance: The capacity of bacteria to repel pathogenic germs from colonising is known as colonisation resistance. Bile acids, sugars, and amino acids are just a few of the metabolites that the gut microbiota controls. The defence against infections is aided by these metabolites. One such is the control of *Clostridium difficile* by secondary bile acids. The growth of *C. difficile* is inhibited by secondary bile acids, which are generated by gut bacteria. Secondary bile acids are reduced as a result of antibiotics' destruction of the gut flora. *C. difficile* can then thrive as a result of this **[68]**.

Patients experience AAD from the beginning of treatment and it can linger for up to two months after it is finished **[69]**. According to the majority of clinicians, diarrhoea is characterised by three or more watery or loose bowel movements each day for at least two days in a row.While patients can receive antibiotics in both inpatient and outpatient settings, primary care doctors typically write the majority of antibiotic prescriptions **[70]**. According to studies, the majority of antibiotic use, particularly in outpatient settings, may be unnecessary. Antibiotic overprescription is now being addressed by raising awareness. However, when antibiotic medication is required, having a reliable, practical, and secure technique to avoid adverse effects like AAD is helpful **[71]**. Probiotics have recently gained popularity among AAD patients as a safe alternative to lessen the negative effects of antibiotics on gastrointestinal function **[72]**.

- **Probiotics in Preventing AAD**

There are many different strains of probiotics on the market, many of which have undefined advantages. Numerous probiotic strains have undergone testing. The probiotic genera *Lactobacillus, Saccharomyces*, and *Bifidobacterium* have undergone the greatest research **[73]**. Probiotics are thought to help normalise an imbalanced flora, which is the theory underlying its use to reduce the pathophysiology and symptoms of digestive diseases **[74]**.

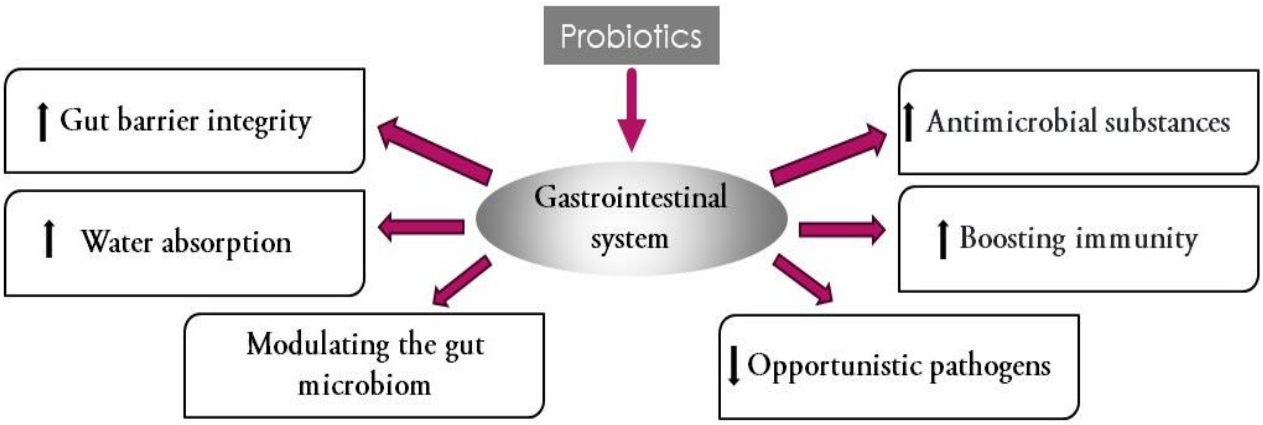


***Figure**. Hypothesized role of probiotics in the treatment of AAD. Upward and downward arrows inside the word boxes indicate increase and decrease, respectively.*

Boosting immunity: Probiotic microorganisms have been demonstrated to enhance the humoral immune response by raising the amount of IgM-, IgG-, and IgA-secreting cells, though the precise method is still unclear. In addition, they generate immunological responses that are not targeted, including activating macrophages **[75]**.

Increasing gut barrier integrity: The mucus layer, epithelium, and underlying lamina propria make up the heterogeneous intestinal barrier. These use tight junctions, multi-protein complexes that function as a physical barrier against gut bacteria. A leaky gut results from defective tight junctions, which enhance the epithelium's permeability. Numerous gastrointestinal disorders, including celiac disease, irritable bowel syndrome, and irritable bowel disease, are brought on by a leaky gut. Probiotics can increase the production of ZO-1 and occludin protein, preserving the integrity of the intestinal barrier **[76]**.

Producing antimicrobial substances: Gram-positive and gram-negative bacteria can be inhibited by a number of chemicals that probiotics produce. These compounds consist of bacteriocins, organic acids, and hydrogen peroxide. This has the potential to modify bacterial metabolism, limit the generation of toxins, and lower the quantity of harmful bacteria **[77,78]**.

Modulating the gut microbiome: It has been demonstrated that using probiotics can restore gut microbiome dysbiosis. When a patient is subjected to extreme circumstances like protracted antibiotic medication, excruciating physical stress, and persistent sickness, dysbiosis may develop Lactic acid and short-chain fatty acids are produced during the metabolism of complex carbohydrates by probiotics. As a result, bacterial translocation is decreased, tight junction integrity is increased, and mucin synthesis is prompted **[79]**.

Increasing water absorption: AQP1, 3, 4, and 8 are the most abundantly expressed aquaporins, which are water-channel membrane proteins, in the colon. These proteins can be broken down by pathogenic bacteria, which can also cause stools to contain more water and make people dehydrated. Aquaporin expression has been demonstrated to rise as a result of probiotic use, increasing the colon's ability to absorb water **[80]**.

Decreasing opportunistic pathogens: By creating inhibitory compounds like bacteriocins, inhibiting adhesion sites on the surfaces of the intestinal epithelial cells, and competing for nutrition, probiotics reduce the population of pathogenic bacteria. These systems are crucial for infection prevention and management. The capacity of probiotics to co-aggregate can result in a protective barrier that stops harmful bacteria from colonising the epithelium **[81]**.

❖ ***Acute gastroenteritis:***

- ***Probiotics for traveller's diarrhoea:***

Depending on the destination, travellers get acute diarrhoea anywhere from 5% to 50% of the time. [82,83]. 80% of cases are caused by bacterial infections. One of the seven varieties of *E. coli* that cause diarrhoea is the most prevalent infection **[84,82]**.

Several studies have suggested that *lactobacilli* may be useful in preventing travellers from developing diarrhoea. Only one study using a combination of strains (containing *Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium bifidum, and Streptococcus thermophilus*) found that the reduction in the overall incidence of diarrhoea was statistically significant **[85]**.

One MA **[86]** study found that some probiotics are safe and effective in preventing traveller's diarrhoea and predicted that up to 85% of these cases might be avoided using probiotics. However, these findings were not supported by a second meta-analysis **[87]**.

S. boulardii provided some protection for travellers visiting a variety of locations, including North Africa, South America, India, and Turkey **[88]** There have been several attempts to do meta-analysis using these data, with estimates of risk ratios that are just slightly in favour of probiotics (RR estimates between 0.85 and 0.93) but with confidence ranges that are near or encompass the point of equivalent **[89,90,91]**.

- ***Probiotics for diarrhoea in children:***

Children's nosocomial diarrhoea has been tested for its resistance to probiotic strains. In hospitalised children, prophylactic administration of *Lactobacillus GG* has been demonstrated to dramatically lower the risk of illnesses, particularly rotavirus gastroenteritis (2.2% compared with 17%, P 0.02) **[92]**. *Lactobacillus GG* was shown to be ineffective whereas breastfeeding was effective in preventing nosocomial rotavirus infections in a different trial that examined the effects of the same strain similarly prepared and breastfeeding **[93]**.

Evaluation of the prophylactic use of *Lactobacillus GG* to prevent diarrhoea in malnourished children from a developing country **[94]**. However, the protective impact varied across children of various ages and between breastfed and nonbreastfed infants. No benefits were seen in the youngest infants, whereas breastfed 18–19-month–old infants showed a strong protective impact. Breastfed children were shown to have significantly greater diarrhoea when given *Lactobacillus GG* in the eldest age group of 30-41-month-old children.

❖ ***Randomized control trials (RCT):***

Probiotics are helpful in preventing AAD, according to previous studies **[95]**. However, a large portion of the earlier reviews were concentrated on the inpatient setting, which has different antibiotic treatment modalities, medication administration methods, and potential pathogen exposures. Since then, comprehensive reviews and meta-analyses have been conducted to weigh the advantages and drawbacks of probiotics in preventing AAD for people of all ages in an outpatient context. Probiotics were being tested for the prevention of AAD in an outpatient context in 17 prospective, randomised controlled studies with placebo, active, or no-treatment control arms, according to a meta-analysis by Blaabjerg et al. **[96]**.

It has been found that probiotics have a preventive effect to stop AAD in the outpatient environment for all ages. Probiotics decreased the risk of AAD from 3631 patients by 51% (RR 0.49; 95% CI 0.36 to 0.66; I2 = 58%) while appearing to have no increased risk of adverse effects. 11 (95% CI, 6 to 13) people were required to be treated in total (NNT) in order to prevent one episode of diarrhoea. Although bias, definitions of diarrhoea, types of infections, and the type of antibiotic used differed, this should be taken into account when interpreting the results of the study.

The clinical correlation between meta-analysis and RCT results determines how valuable the data are. It can be difficult to choose a suitable probiotic product given the large amount of information. In order to accurately measure efficacy outcomes and assist physicians in making the best treatment choices, expert consensus and current recommendations advise that reviews and meta-analyses display outcome data through probiotic strain sub-groups **[97,98,99]**. Though, direct strain comparisons are uncommon, and the strain is frequently evaluated for the same reason. Clinicians can more effectively target their treatments by evaluating and synthesising data from rcts by strain.

Side effect:

There were hardly any reports of side effects of probiotics in human. But there is a possibility that the bacteria or yeast in probiotics could occasionally result in infections itself in persons with extremely weakened immune systems or specific severe conditions **[114]**.

Safety of probiotics:

Since years, probiotics have been used safely. There are few increased risks of negative effects, according to meta-analysis **[100]**. Abdominal pain, nausea, lack of appetite, headaches, and flu-like symptoms are a few side effects that have been documented in RCTs investigating the use of probiotics in the prevention of AAD. The symptoms, however, are most likely the result of an underlying infection or the adverse effects of an antibiotic. Data from clinical trials, instances, and experimental models have shown potential dangers **[101]**.

It's crucial to remember that different probiotic strains have varied therapeutic effects and maybe varying safety profiles. The probiotic organism used in commercial preparations and the other ingredients of that product have an impact on how safely it can be used. Probiotics may be to blame for gastrointestinal adverse effects such cramping and nausea as well as systemic infections, colon ischemia, excessive inflammation, and gene transfer between probiotics and microbiome bacteria. Despite the rarity of these findings, it is advised that researchers who perform clinical trials including probiotics keep a close eye out for any negative effects and identify any patients who may be more vulnerable **[102-109]**.

Probiotics are generally accepted as safe (GRAS) and well tolerated in humans, but case reports have shown bacteremia and fungemia subsequent to probiotics. For instance, it has been reported that a 1-year-old immunocompetent infant who received *S. boulardii* for gastroenteritis eventually developed fungemia **[110]**. Eight immunocompromised patients with positive blood cultures for *Lactobacillus* after liver transplants were reported by the Mayo Clinic **[111]**. Additionally, probiotic strains of *Lactobacillus GG* were

discovered to be bacteremic in two infants with short bowel syndrome **[112]**. Antibiotic resistance may develop over time from long-term usage of probiotics under the pressure of antibiotic selection, and the resistance gene may spread to other bacteria **[113]**.

Future perspective:

The underdeveloped world would be significantly impacted by a low-cost probiotic intervention that could, even with modest efficacy, lower the chances of diarrhoea in infancy. There will be a lot of work required for its widespread implementation, assuming effectiveness for the prevention and treatment of childhood diarrhoea in these settings is established.

Since probiotics were formally established, research on the administration of microbes to alter the human microbiome and enhance health has been accelerating. New preventative therapy strategies for diarrhoea caused by antibiotics and other gastrointestinal illnesses are greatly encouraged by the possibility to modify these microbial ecosystems. However, there are few practical probiotic usage recommendations that include strain- and disease-specific advice. Numerous studies demonstrate the benefits of using probiotics to treat AAD, but larger placebo-controlled studies are still needed to: (i) ascertain the species and doses most effective for prevention; (ii) demonstrate effectiveness in preventing AAD; and (iii) determine the impact on length of hospital stay and cost-effectiveness. Moving forward, research should concentrate on strain-specific dose requirements, safety considerations, and patient variables that can assist doctors in selecting the best probiotics for treating diarrhoea brought on by antibiotics and other gastrointestinal illnesses.

Carried out an evaluation of probiotics for AAD in the pediatric population. While the use of *B. clausii* as a single probiotic was not advised, *L. rhamnosus GG* and *S. boulardii* were strongly advised for usage in avoiding AAD in children. The Canadian Paediatric Society advised doctors to think about recommending probiotics for AAD, although they should be cautious of the slight risk of invasive infections with some strains, especially while treating immunocompromised patients. Additionally, they suggested that the federal government mandate probiotics manufacturers to produce labelling that are accurate and comprehensive and preserve the high quality of the goods.

Given that *C. difficile* is the major cause of infectious antibiotics associated diarrhoea, several clinical recommendations for the use of probiotics are reviewed in relation to *C. difficile* infection. Globally, there are different recommendations for the use of probiotics in the treatment of AAD, including that connected to a *C. difficile* infection. For instance, the American College of Gastroenterology (ACG) guidelines advised against the use of probiotics for the prevention of both primary and recurring infections of *C. difficile*. On the other side, the American Gastroenterological Association (AGA) recommended using certain organisms, like *S. boulardii*, or combinations of strains, like *L. acidophilus* CL1285 and *L. casei*, for both adults and children receiving antibiotic treatment. They also advised against using probiotics in individuals with serious illnesses or those who were worried about the probiotics' price.

Reference:

1. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. Lancet. 2013; 381 (9875) : 1405-16 .
2. De-Vrese M, Marteau PR. Probiotics and prebiotics: effects on diarrhoea. J Nutr. 2007; 137 (S3) : 803S-11S .
3. McFarland LV, Ozen M, Dinleyici EC, Goh S: Comparison of pediatric and adult antibiotic-associated diarrhoea and Clostridium difficile infections. World J Gastroenterol 2016, 22:3078-3104.
4. Agamennone V, Krul CAM, Rijkers G, Kort R: A practical guide for probiotics applied to the case of antibiotic-associated diarrhoea in The Netherlands. BMC Gastroenterol 2018, 18:103.
5. Capurso L: Thirty years of Lactobacillus rhamnosus GG: a review. J Clin Gastroenterol 2019, 53:S1-S41.

6. Czerucka D, Rampal P: Diversity of Saccharomyces boulardii CNCM I-745 mechanisms of action against intestinal infections. World J Gastroenterol 2019, 25:2188-2203.
7. Martin, R.; Langella, P. Emerging Health Concepts in the Probiotics Field: Streamlining the Definitions. Front. Microbiol. 2019, 10, 1047.
8. Metchnikoff II. The prolongation of life: optimistic studiesSpringer Publishing Company: New York; 2004.
9. Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. Science. 1965; 147 (3659) : 747-8 .
10. Probiotic Ingredients Market by Function (Regular, Preventative, Therapy), Application (Food & Beverage, Dietary Supplements, & Animal Feed), End Use (Human & Animal Probiotics), Ingredient (Bacteria & Yeast), and by Region - Global Trends & Forecast to 2020. . .
11. Tamime, A.Y. Fermented milks: A historical food with modern applications—A review. Eur. J. Clin. Nutr. 2002, 56 (Suppl. 4), S2–S15.
12. Barnett, J.A. A history of research on yeasts 2: Louis Pasteur and his contemporaries, 1850–1880. Yeast 2000, 16, 755–771.
13. Metchnikoff, E. Lactic acid as inhibiting intestinal putrefaction. In The Prolongation of Life. Optimistic Studies; G.P. Putnam's Sons: New York, NY, USA, 1908; Chapter V; pp. 161–183.
14. Tissier, H. Treatment of intestinal infections using bacterial flora of the intestine. Crit Rev. Soc. Biol. 1906, 60, 359–361.
15. FAO/WHO. Guidelines for the Evaluation of Probiotics in Food; Joint FAO/WHO Working Group: London, ON, Canada, 2002.
16. Joint FAO/WHO Working Group, Joint FAO/WHO Working Group. Guidelines for the evaluation of probiotics in foodWorld Health Organization, ON, Canada: Food and Agriculture Organization: London; 2002.
17. Roberfroid MB. Concepts In Functional Foods. Nutrition Today. 1999; 34 (4) : 162-65 .
18. Bourdichon F, Casaregola S, Farrokh C, Frisvad JC, Gerds ML, Hammes WP, Harnett J, Huys G, Laulund S, Ouwehand A, Powell IB. Food fermentations: microorganisms with technological beneficial use. International journal of food microbiology 2012 Mar. 15; 154 (3) : 87-97 .
19. Borchers AT, Selmi C, Meyers FJ, Keen CL, Gershwin ME. Probiotics and immunity. J Gastroenterol. 2009; 44 (1) : 26-46 .
20. Teitelbaum JE, Wyllie R, Hyams JS. Indigenous flora. Pediatric Gastrointestinal and Liver Disease, 4th Edition. Philadelphia: Elsevier Inc. 2011;28-38. . .
21. Long S, Swenson R. Development of anaerobic fecal flora in healthy newborn infants. J Pediatr. 1977; 91 : 298-301 .
22. Simon G, Gorbach S. The human intestine microflora. Dig Dis Sci. 1986; 31 : 127-62 .
23. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science. 2005; 308 (5728) : 1635-8 .
24. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F, at al. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Paediatr Drugs. 2015; 17 (3) : 199-216 .
25. Castagliuolo I, Riegler MF, Valenick L, LaMont JT, Pothoulakis C. Saccharomyces boulardii protease inhibits the effects of Clostridium difficile toxins A and B in human colonic mucosa. Infect Immun. 1999; 67 (1) : 302-7 .
26. de Vrese M, Stegelmann A, Richter B, Fenselau S, Laue C, Schrezenmeir J. Probiotics compensation for lactase insufficiency. Am J Clin Nutr. 2001; 73 (Suppl 2) : 421S-429S .
27. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. 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 (8) : 506-14 .
28. Lebeer S, Vanderleyden J, De Keersmaecker SC. Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. Nat Rev Microbiol. 2010; 8 (3) : 171-84 .
29. Sherman PM, Ossa JC, Johnson-Henry K. Unraveling mechanisms of action of probiotics. Nutr Clin Pract. 2009; 24 (1): 10-4.

30. Yan F, Polk DB. Probiotics as functional food in the treatment of diarrhoea. Curr Opin Clin Nutr Metab Care. 2006; 9(6):717-21.
31. Beneficial Properties of Probiotics Lye Huey Shi,1,* Kunasundari Balakrishnan,2 Kokila Thiagarajah,3 Nor Ismaliza Mohd Ismail,4 and Ooi Shao Yin1 PMCID: PMC5031164 PMID: 27688852 2016 Aug; 27(2): 73–90. doi: 10.21315/tlsr2016.27.2.6
32. Grandy G, Medina M, Soria R, Terán CG, Araya M. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children BMC Infect Dis. 2010; 10 : 253 .
33. Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose-free formula in children with rotavirus diarrhoea: are they effective? Pediatr Int. 2011; 53 (5) : 677-82 .
34. Szymański H, Pejcz J, Jawień M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three Lactobacillus rhamnosus strains--a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006. 15; 23 (2) : 247-53 .
35. Chen CC, Kong MS, Lai MW, Chao HC, Chang KW, Chen SY, et al. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhoea. Pediatr Infect Dis J. 2010; 29 (2) : 135-8 .
36. Oberhelman RA, Gilman RH, Sheen P, Taylor DN, Black RE, Cabrera L, et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhoea in undernourished Peruvian children. J Pediatr. 1999; 134 (1) : 15-20 .
37. Sur D, Manna B, Niyogi SK, Ramamurthy T, Palit A, Nomoto K, et al. Role of probiotic in preventing acute diarrhoea in children: a community-based, randomized, double-blind placebo-controlled field trial in an urban slum. Epidemiol Infect. 2011; 139 (6) : 919-26 .
38. Heiser CR, Ernst JA, Barrett JT, French N, Schutz M, Dube MP. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhoea. J Int Assoc Physicians AIDS Care (Chic). 2004; 3 (4) : 121-9 .
39. Anukam KC, Osazuwa EO, Osadolor HB, Bruce AW, Reid G. Yogurt containing probiotic Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 helps resolve moderate diarrhoea and increases CD4 count in HIV/AIDS patients J Clin Gastroenterol. 2008; 42 (3): 239-43.
40. Salminen MK, Tynkkynen S, Rautelin H, Poussa T, Saxelin M, Ristola M, et al. The efficacy and safety of probiotic Lactobacillus rhamnosus GG on prolonged, noninfectious diarrhoea in HIV Patients on antiretroviral therapy: a randomized, placebo-controlled, crossover study. HIV Clin Trials. 2004; 5 (4) : 183-91 .
41. Trois L, Cardoso EM, Miura E. Use of probiotics in HIV-infected children: a randomized double-blind controlled study. J Trop Pediatr. 2008; 54 (1) : 19-24 .
42. Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, et al. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. Lancet. 2009; 374 (9684) : 136-44 .
43. Shornikova AV, Isolauri E, Burkanova L, Lukovnikova S, Vesikari T. A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. Acta Paediatr. 1997; 86 (5) : 460-5 .
44. Sepp E, Tamm E, Torm S, Lutsar I, Mikelsaar M, Salminen S. Impact of a Lactobacillus probiotic on the fecal microflora in children with Shigellosis. Microecol Ther. 1999; 23 (1) : 74-80 .
45. Htwe K, Yee KS, Tin M, Vandenplas Y. Effect of Saccharomyces boulardii in the treatment of acute watery diarrhoea in Myanmar children: a randomized controlled study. Am J Trop Med Hyg. 2008; 78 (2) : 214-6 .
46. Chen CC, Kong MS, Lai MW, Chao HC, Chang KW, Chen SY, et al. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhoea. Pediatr Infect Dis J. 2010; 29 (2) : 135-8 .
47. Kurugöl Z, Koturoğlu G. Effects of Saccharomyces boulardii in children with acute diarrhoea. Acta Paediatr. 2005; 94 (1) : 44-7 .

48. Henker J, Laass M, Blokhin BM, Bolbot YK, Maydannik VG, Elze M, et al. The probiotic Escherichia coli strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. Eur J Pediatr. 2007; 166 (4) : 311-8
49. Henker J, Laass MW, Blokhin BM, Maydannik VG, Bolbot YK, Elze M, et al. Probiotic Escherichia coli Nissle 1917 versus placebo for treating diarrhoea of greater than 4 days duration in infants and toddlers. Pediatr Infect Dis J. 2008; 27 (6) : 494-9 .
50. Vivatvakin B, Kowitdamrong E. Randomized control trial of live Lactobacillus acidophilus plus Bifidobacterium infantis in treatment of infantile acute watery diarrhoea. J Med Assoc Thai. 2006; 89 (Suppl 3) : S126-33
51. Sazawal S, Dhingra U, Hiremath G, Sarkar A, Dhingra P, Dutta A, et al. Prebiotic and probiotic fortified milk in prevention of morbidities among children: community-based, randomized, double-blind, controlled trial. PLoS One. 2010; 5 (8) : e12164 .
52. Castaneda C, Garcia E, Santa Cruz M, Fernandez M, Monterrey P. Effects of Saccharomyces boulardii in children with chronic diarrhoea, especially cases due to giardiasis. Rev Mex Pueric Pediatr. 1995; 2 : 12-16 .
53. Mansour-Ghanaei F, Dehbashi N, Yazdanparast K, Shafaghi A. Efficacy of saccharomyces boulardii with antibiotics in acute amoebiasis. World J Gastroenterol. 2003; 9 (8) : 1832-3 .
54. Dinleyici EC, Eren M, Dogan N, Reyhanioglu S, Yargic ZA, Vandenplas Y. Clinical efficacy of Saccharomyces boulardii or metronidazole in symptomatic children with Blastocystis hominis infection. Parasitol Res. 2011; 108 (3) : 541-5 .
55. Barbut F, Petit JC. Epidemiology of Clostridium difficile-associated infections. Clin Microbiol Infect 2001; 7: 405–10.
56. Barbut F, Richard A, Hamadi K, Chomette V, Burghoffer B, Petit JC. Epidemiology of recurrences or reinfections of Clostridium difficile-associated diarrhoea. J Clin Microbiol 2000; 38: 2386–8.
57. Surawicz CM. Probiotics, antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in humans. Best Pract Res Clin Gastroenterol 2003; 17: 775–83.
58. Wullt M, Hagslatt ML, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficileassociated diarrhoea: a double-blind, placebo-controlled trial. Scand J Infect Dis 2003; 35: 365–7.
59. Surawicz CM, McFarland LV, Elmer G, Chinn J. Treatment of recurrent Clostridium difficile colitis with vancomycin and Saccharomyces boulardii. Am J Gastroenterol 1989; 84: 1285–7.
60. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhoea in adults and children. Cochrane Database Syst Rev. 2013:CD006095.
61. Johnston BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhoea: a systematic review and metaanalysis. Ann Intern Med. 2012;157:878---88.
62. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhoea: a systematic review and metaanalysis. JAMA. 2012;307:19
63. McFarland, L.V. Diarrhoea associated with antibiotic use. BMJ 2007, 335, 54–55.
64. Milner, E.; Stevens, B.; An, M.; Lam, V.; Ainsworth, M.; Dihle, P.; Stearns, J.; Dombrowski, A.; Rego, D.; Segars, K. Utilizing Probiotics for the Prevention and Treatment of Gastrointestinal Diseases. Front. Microbiol. 2021, 12, 689958.
65. Ianiro, G.; Tilg, H.; Gasbarrini, A. Antibiotics as deep modulators of gut microbiota: Between good and evil. Gut 2016, 65, 1906–1915.
66. Mekonnen, S.A.; Merenstein, D.; Fraser, C.M.; Marco, M.L. Molecular mechanisms of probiotic prevention of antibiotic-associated diarrhoea. Curr. Opin. Biotechnol. 2020, 61, 226–234.
67. McFarland, L.V.; Surawicz, C.M.; Stamm, W.E. Risk factors for Clostridium difficile carriage and C. difficile-associated diarrhoea in a cohort of hospitalized patients. J. Infect. Dis. 1990, 162, 678–684.
68. Silverman, M.A.; Konnikova, L.; Gerber, J.S. Impact of Antibiotics on Necrotizing Enterocolitis and Antibiotic-Associated Diarrhoea. Gastroenterol. Clin. N. Am. 2017, 46, 61–76.

69. McFarland, L.V. Epidemiology, risk factors and treatments for antibiotic-associated diarrhoea. Dig. Dis. 1998, 16, 292–307.
70. Goossens, H.; Ferech, M.; Vander Stichele, R.; Elseviers, M. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. Lancet 2005, 365, 579–587.
71. Hayes, S.R.; Vargas, A.J. Probiotics for the Prevention of Pediatric Antibiotic-Associated Diarrhoea. Explore 2016, 12, 463–466.
72. Mills, J.P.; Rao, K.; Young, V.B. Probiotics for prevention of Clostridium difficile infection. Curr. Opin. Gastroenterol. 2018, 34, 3–10.
73. Hempel, S.; Newberry, S.J.; Maher, A.R.; Wang, Z.; Miles, J.N.; Shanman, R.; Johnsen, B.; Shekelle, P.G. Probiotics for the prevention and treatment of antibiotic-associated diarrhoea: A systematic review and meta-analysis. JAMA 2012, 307, 1959–1969.
74. Wieers, G.; Belkhir, L.; Enaud, R.; Leclercq, S.; Philippart de Foy, J.M.; Dequenne, I.; de Timary, P.; Cani, P.D. How Probiotics Affect the Microbiota. Front. Cell. Infect. Microbiol. 2019, 9, 454.
75. Isolauri, E.; Sutas, Y.; Kankaanpaa, P.; Arvilommi, H.; Salminen, S. Probiotics: Effects on immunity. Am. J. Clin. Nutr. 2001, 73, 444S–450S.
76. La Fata, G.; Weber, P.; Mohajeri, M.H. Probiotics and the Gut Immune System: Indirect Regulation. Probiotics Antimicrob. Proteins 2018, 10, 11–21.
77. Atassi, F.; Servin, A.L. Individual and co-operative roles of lactic acid and hydrogen peroxide in the killing activity of enteric strain Lactobacillus johnsonii NCC933 and vaginal strain Lactobacillus gasseri KS120.1 against enteric, uropathogenic and vaginosis-associated pathogens. FEMS Microbiol. Lett. 2010, 304, 29–38.
78. Zavisic, G.; Petricevic, S.; Radulovic, Z.; Begovic, J.; Golic, N.; Topisirovic, L.; Strahinic, I. Probiotic features of two oral Lactobacillus isolates. Braz. J. Microbiol. [Publ. Braz. Soc. Microbiol.] 2012, 43, 418–428.
79. Patel, R.; DuPont, H.L. New approaches for bacteriotherapy: Prebiotics, new-generation probiotics, and synbiotics. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2015, 60 (Suppl. 2), S108–S121.
80. Zhang, W.; Zhu, B.; Xu, J.; Liu, Y.; Qiu, E.; Li, Z.; He, Y.; Zhou, H.; Bai, Y.; Zhi, F. Bacteroides fragilis Protects Against Antibiotic-Associated Diarrhoea in Rats by Modulating Intestinal Defenses. Front. Immunol. 2018, 9, 1040.
81. Rolfe, R.D. The role of probiotic cultures in the control of gastrointestinal health. J. Nutr. 2000, 130, 396S–402S.
82. Girardin M, Seidman EG. Indications for the use of probiotics in gastrointestinal diseases. Dig Dis. 2011;29:574---87.
83. Islam SU. Clinical uses of probiotics. Medicine (Baltimore). 2016;95:e2658.
84. Sullivan Å, Nord CE. Probiotics and gastrointestinal diseases. J Intern Med. 2005;257:78---92.
85. Black F, Anderson P, Orskov J, Gaarlev K, Laulund S. Prophylactic efficacy of Lactobacili on traveller's diarrhoea. Travel Med. 1989; 7 : 333-5 .
86. McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhoea. Travel Med Infect Dis. 2007;5:97---105.
87. Takahashi O, Noguchi Y, Omata F, Tokuda Y, Fukui T. Probiotics in the prevention of traveler's diarrhoea: meta-analysis. J Clin Gastroenterol. 2007;41:336---7.
88. Kollaritsch H, Kremsner P, Weidermann G, Scheiner O. Prevention of traveler's diarrhoea: comparison of different non-antibiotic preparations. Travel Med Int. 1989; 6 : 9-17 .
89. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 2006; 6 (6) : 374-82 .
90. McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhoea. Travel Med Infect Dis. 2007; 5 (2) : 97-105 .
91. Takahashi O, Noguchi Y, Omata F, Tokuda Y, Fukui T. Probiotics in the prevention of traveler's diarrhoea: meta-analysis. J Clin Gastroenterol. 2007; 41 (3) : 336-7 .
92. Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhoea in infants. J Pediatr 2001; 138:361–5.

93. Mastretta E, Longo P, Laccisaglia A et al. Effect of Lactobacillus GG and breast-feeding in the prevention of rotavirus nosocomial infection. J Pediatr Gastroenterol Nutr 2002; 35: 527–31
94. Oberhelman RA, Gilman RH, Sheen P et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhoea in undernourished Peruvian children. J Pediatr 1999; 134: 15–2
95. Goldenberg, J.Z.; Lytvyn, L.; Steurich, J.; Parkin, P.; Mahant, S.; Johnston, B.C. Probiotics for the prevention of pediatric antibiotic-associated diarrhoea. Cochrane Database Syst. Rev. 2015, 12, CD004827.
96. Blaabjerg, S.; Artzi, D.M.; Aabenhus, R. Probiotics for the Prevention of Antibiotic-Associated Diarrhoea in Outpatients-A Systematic Review and Meta-Analysis. Antibiotics 2017, 6, 21.
97. Hill, C.; Scott, K.; Klaenhammer, T.R.; Quigley, E.; Sanders, M.E. Probiotic nomenclature matters. Gut Microbes 2016, 7, 1–2.
98. Chatterjee, S.; Kar, P.; Das, T.; Ray, S.; Gangulyt, S.; Rajendiran, C.; Mitra, M. Randomised placebo-controlled double blind multicentric trial on efficacy and safety of Lactobacillus acidophilus LA-5 and Bifidobacterium BB-12 for prevention of antibiotic-associated diarrhoea. J. Assoc. Physicians India 2013, 61, 708–712.
99. Glanville, J.; King, S.; Guarner, F.; Hill, C.; Sanders, M.E. A review of the systematic review process and its applicability for use in evaluating evidence for health claims on probiotic foods in the European Union. Nutr. J. 2015, 14, 16.
100. Sanders, M.E.; Akkermans, L.M.; Haller, D.; Hammerman, C.; Heimbach, J.T.; Hörmannsperger, G.; Huys, G. Safety assessment of probiotics for human use. Gut Microbes 2010, 1, 164–185.
101. Doron, S.; Snydman, D.R. Risk and safety of probiotics. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2015, 60 (Suppl. 2), S129–S134.
102. Bassetti, S.; Frei, R.; Zimmerli, W. Fungemia with Saccharomyces cerevisiae after treatment with Saccharomyces boulardii. Am. J. Med. 1998, 105, 71–72.
103. Cherifi, S.; Robberecht, J.; Miendje, Y. Saccharomyces cerevisiae fungemia in an elderly patient with Clostridium difficile colitis. Acta Clin. Belg. 2004, 59, 223–224.
104. Ohishi, A.; Takahashi, S.; Ito, Y.; Ohishi, Y.; Tsukamoto, K.; Nanba, Y.; Ito, N.; Kakiuchi, S.; Saitoh, A.; Morotomi, M.; et al. Bifidobacterium septicemia associated with postoperative probiotic therapy in a neonate with omphalocele. J. Pediatrics 2010, 156, 679–681.
105. McFarland, L.V.; Surawicz, C.M.; Greenberg, R.N.; Elmer, G.W.; Moyer, K.A.; Melcher, S.A.; Bowen, K.E.; Cox, J.L. Prevention of beta-lactam-associated diarrhoea by Saccharomyces boulardii compared with placebo. Am. J. Gastroenterol. 1995, 90, 439–448.
106. Besselink, M.G.; van Santvoort, H.C.; Buskens, E.; Boermeester, M.A.; van Goor, H.; Timmerman, H.M.; Nieuwenhuijs, V.B.; Bollen, T.L.; van Ramshorst, B.; Witteman, B.J.; et al. Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. Lancet 2008, 371, 651–659.
107. Vaarala, O. Immunological effects of probiotics with special reference to lactobacilli. Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol. 2003, 33, 1634–1640.
108. Veckman, V.; Miettinen, M.; Pirhonen, J.; Siren, J.; Matikainen, S.; Julkunen, I. Streptococcus pyogenes and Lactobacillus rhamnosus differentially induce maturation and production of Th1-type cytokines and chemokines in human monocyte-derived dendritic cells. J. Leukoc. Biol. 2004, 75, 764–771.
109. Dessart, S.R.; Steenson, S.L. High frequency intergeneric and intrageneric transfer conjugal transfer of drug resistance plasmids in Leuconostoc mesenteroides ssp. cremoris. J. Dairy Sci. 1991, 74, 2912–2919.
110. Platincx M, Legein J, Vandenplas Y. Fungemia with Saccharomyces boulardii in a 1-year-old girl with protracted diarrhoea. J Pediatr Gastroenterol Nutr. 1995; 21 : 113-5 .
111. Patel R, Cockeril FR, Porayko MK, et al. Lactobacillemia in liver transplant patients. Clin Infect Dis. 1994; 18 : 207-12 .
112. Kunz A, Noel J, Fairchol M. Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. J Pediatr Gastroenterol Nutr. 2004; 38 : 557-8 .

113. Dai M, Lu J, Wang Y, Liu Z, Yuan Z. In vitro development and transfer of resistance to chlortetracycline in Bacillus subtilis. J Microbiol. 2012; 50 (5) : 807-12 .

114. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev 2010; (11): CD003048.