Precision Biotics®

Clinical Evidence Summary

Gastrointestinal Health and Antibiotic-Associated Diarrhoea.

Probiotic strains **BB-12®** and **LA-5®**

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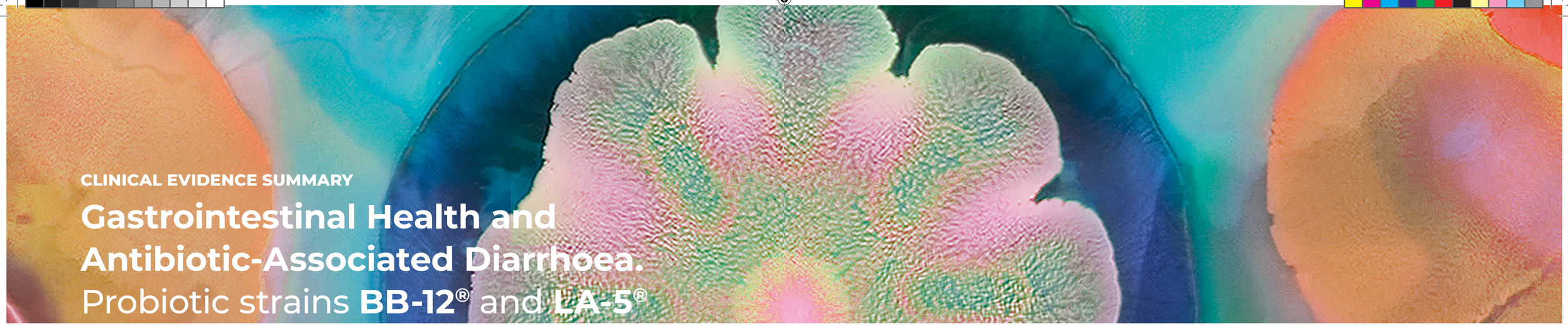

CLINICAL EVIDENCE SUMMARY

Gastrointestinal Health and Antibiotic-Associated Diarrhoea.

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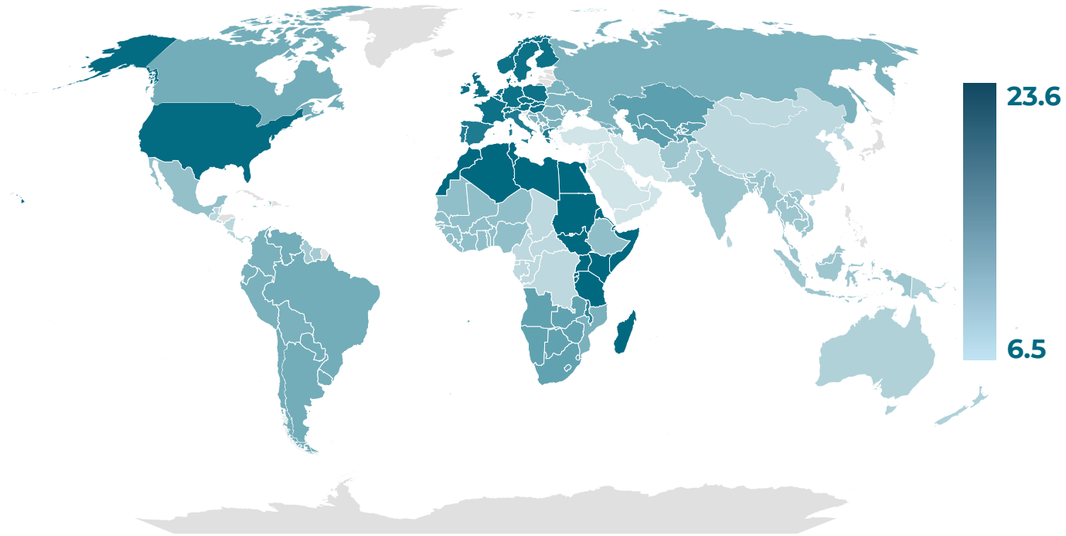
Key Points

- Antibiotics are widely prescribed to treat or prevent some types of bacterial infections with up to 6.5% of people globally using them daily[1].
- Antibiotic-associated diarrhoea (AAD) affects 5-35% of patients on antibiotics[2], with higher rates observed in those on broad-spectrum antibiotics[3].
- *H. pylori* infection affects over half the global population[4]. Current *H. pylori* treatment includes proton pump inhibitors (PPI) and a combination of antibiotics. Both treatments are associated with diarrhoea (approximately 30% of patients)[5-8] and other gastrointestinal issues[9].
- The combination of *Bifidobacterium animalis*, **BB-12®** and *Lactobacillus acidophilus*, **LA-5®** probiotics strains has been associated with significant reductions in the duration and severity of AAD in adults[7,10].

Gut health and antibiotic use

Antibiotics are widely prescribed to treat or prevent some types of bacterial infections but they are ineffective against viral infections, including common conditions such as colds, flu, coughs, and sore throats[11]. A recent spatial modelling study showed that the global antibiotic consumption increased 46% between 2000 and 2018[12].

Antibiotic consumption estimates by GBD super-region and GBD region, for the year 2018



Rate of total antibiotic consumption (DDD per 1000 per day, 95% UI)
DDD=defined daily doses. GBD=Global Burden of Disease. UI=uncertainty interval.

Image adapted from Browne et al., 2021[12].

Specifically, in the U.K., despite a decline in antibiotic prescription rates since 2013, the country still prescribes antibiotics at notably higher levels compared to other European nations[13]. In primary care, where 80% of all antibiotics are prescribed, prescriptions increased by 2.6% in 2023[14].

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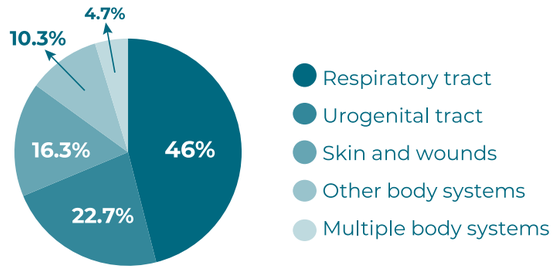
Why are people prescribed antibiotics?

In the U.K., people are prescribed antibiotics for a variety of reasons as displayed below[15]:



46% of total prescribed antibiotics

Respiratory tract (RT)*

- **10.4%** Cough
- **8.2%** Lower RT infections
- **7.7%** Sore throat
- **6.7%** Upper RT infections
- **5.6%** Ear related symptoms
- **7.4%** Other

*including ear, nose and throat (ENT)

22.7% of total prescribed antibiotics

Urogenital tract

- **20.6%** Urinary tract
- **1.5%** Genital tract
- **0.6%** Unspecific

16.3% of total prescribed antibiotics

Skin and wounds

- **2.3%** Boil, cyst, abscess
- **2.2%** Unspecific
- **2.1%** Wounds
- **2.0%** Cellulitis
- **1.5%** Acne
- **1.2%** Ingrown/infected nail
- **1.0%** Bites
- **4.0%** Other symptoms

Antibiotic-associated diarrhoea

The use of antibiotics is associated with a range of negative side effects, with 35% of users experiencing issues such as diarrhoea[2]. AAD likely results from the disruption of the natural protective gut microbiota[2,10]. The incidence of AAD is 5 - 35%[2], with higher rates observed when broad-spectrum antibiotics are used[3]. AAD affects both children and adults[10], with significant implications for overall well-being[5,16], highlighting the need for effective prevention strategies.

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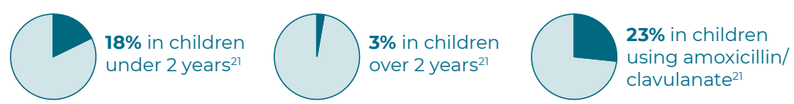
AAD can occur from a few hours after starting antibiotic therapy up to eight weeks after stopping it[2]. Typically, AAD begins around five days after starting antibiotics and lasts between 2 to 41 days, with a median duration of four days[17]. The impact of antibiotics on the gut microbiota has been shown to last much longer that was first thought, with changes observed up to four years after certain treatments such as *H. pylori* eradication medicines[18,19].

Antibiotic-associated diarrhoea is most frequently observed in young children and elderly people

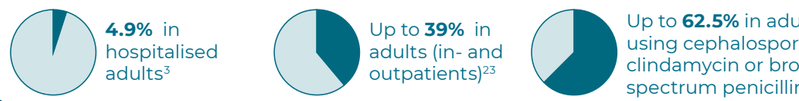
In children, AAD incidence is up to 11%, usually starting 5.3 days after beginning antibiotics and lasting an average of four days. Children under two years have a higher incidence (18%) compared to those over two years (3%). Certain antibiotics, particularly amoxicillin/clavulanate, increase AAD rates to 23% in children[20,21].

In adults, AAD incidence ranges from 5% to 35%[2] and between 15%-34% in the elderly, especially among hospitalised patients[2,22]. AAD in these patients contributes to increased healthcare costs, mortality, morbidity, and longer hospital stays[23-25].

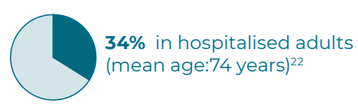
AAD in children



AAD in young adults

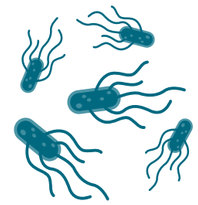


AAD in older adults



The *H. pylori* challenge

The use of antibiotics is particularly relevant for treating *H. pylori* infections, which affect more than half of the population worldwide[4] and presents a higher prevalence in the developing countries[26].



The current standard treatment for *H. pylori*, known as 'triple therapy', includes a combination of a proton pump inhibitor (PPI) and two antibiotics, typically amoxicillin and clarithromycin[27,28]. Both the PPIs and the antibiotics are risks factors associated with the development of AAD, potentially increasing its incidence by about two-fold[17].

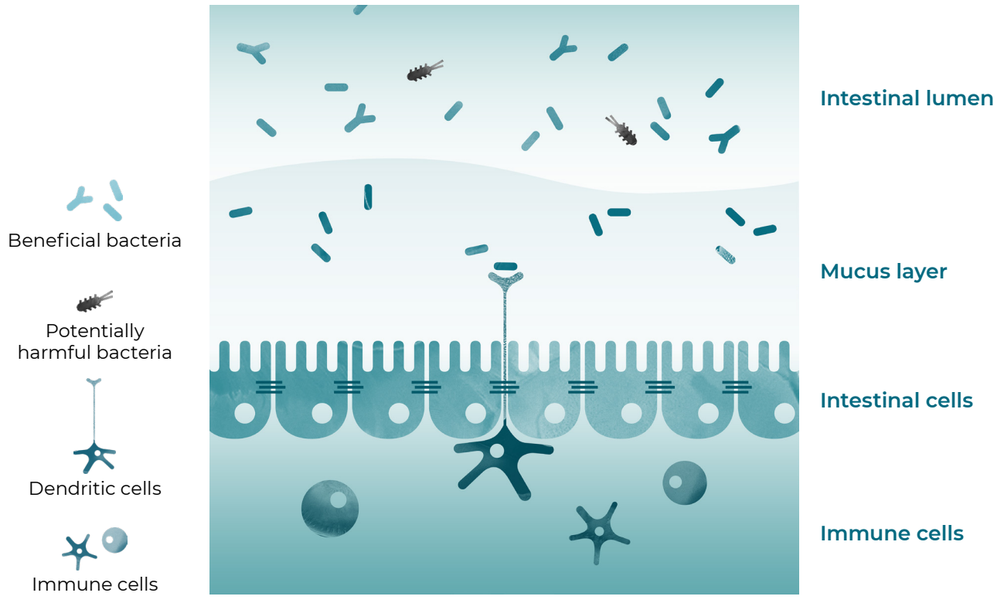
Probiotics and the gut microbiota

The diversity and activity of the gut microbiota is crucial for maintaining various aspects of health, including digestion, nutrient absorption, immune function, and protection against pathogens[24].

A balanced gut microbiota typically features a rich diversity of beneficial bacteria that help in fermenting dietary fibres, producing essential nutrients and modulating the immune system[29]. Antibiotic use often disrupts the composition and functionality of the gut microbiota and can lead to dysbiosis, which is associated with various gastrointestinal disorders, including AAD[29].

Several studies have demonstrated that the use of probiotics can significantly reduce the risk of AAD in adults, with relative risk reductions ranging from 0.43[24] to 0.47[30].

BB-12® and LA-5® and the proposed mechanism of action*



Bifidobacterium animalis, BB-12®

Bifidobacterium animalis, **BB-12®** strain is the most researched *Bifidobacterium* probiotic strain. Many scientific studies have been published, on both preclinical and clinical investigations. Proposed mechanisms of action of **BB-12®**:

1. Production of anti-microbial substances[31,32] and competition with unwanted bacteria for adhesion sites in the intestine[33]*
2. Upregulation of mucus production and tight junction genes[34]*, supporting the intestinal barrier function
3. Modulation of the microbiota by changing the relative abundance of several bifidobacterial species[35]

Scientific information. For healthcare professionals only.

Lactobacillus acidophilus, LA-5®

Lactobacillus acidophilus, **LA-5®** strain has been used in food and dietary supplements since 1979 and it has been object of study in many scientific publications. Proposed mechanisms of action of **LA-5®**:

1. Competition with harmful bacteria for adhesion sites in the intestine[36]*
2. Immune response regulation by the activation of immune cells[37,38]*

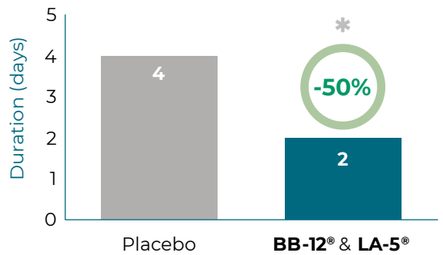
**Proposed mode-of-actions are based on in vitro or animal data.*

Clinical evidence

A randomised, double-blind, placebo-controlled multicentre trial investigated the efficacy and safety of administering 2 x 10^9 colony forming units (CFU) of *Bifidobacterium animalis*, **BB-12®** and 2 x 10^9 CFU of *Lactobacillus acidophilus*, **LA-5®** probiotic strains per day. Adults (18-70 years old) on antibiotics were given probiotic capsules or a placebo over a two-week period. The study assessed, among other parameters, the duration and severity of AAD[10].

Population	Sample size	Probiotic	Comparator	Duration
Adults (18-70 years old) On antibiotics (cefradoxil or amoxycilin)	n= 167 placebo n= 176 probiotic	2 x 10^9 CFU of **BB-12®** and 2 x 10^9 CFU of **LA-5®**	Placebo	2 weeks

Duration of loose stools

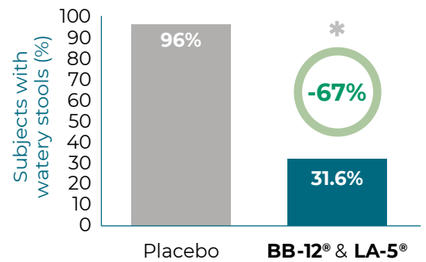


* p < 0.01 between intervention and placebo

An intervention with the **BB-12®** and **LA-5®** strains led to a significant reduction in the number of days with loose stools (p<0.01). This effect represented a 50% improvement, with the intervention group averaging just two days of symptoms, compared to four days in the placebo group.
These data refers only to participants experiencing AAD.
Placebo: n= 26/167 (15.56%)
Probiotic: n= 19/176 (10.79%)

The severity of AAD was assessed by the incidence of watery stools. The intervention with 2 x 10^9 CFU of each of **BB-12®** and **LA-5®** led to a significant reduction in the percentage of subjects experiencing watery stools (p<0.001). The intervention resulted in a 67% decrease, with 96% of the placebo group reporting watery stools, compared to only 31.6% in the intervention group.
These data refers only to participants experiencing AAD.
Placebo: n= 26/167 (15.56%)
Probiotic: n= 19/176 (10.79%)

Incidence of watery stools (indicative of severe diarrhoea)

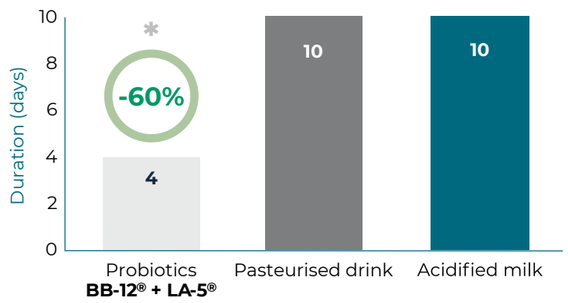


* p < 0.001 between intervention and placebo

A randomised, double-blind, controlled study was conducted over eight weeks involving adults aged 18-65 years undergoing *H. pylori* eradication treatment. The intervention was a yoghurt drink containing 0.25 x 10^9 CFUs each of the *Bifidobacterium animalis*, **BB-12®** and *Lactobacillus acidophilus*, **LA-5®** probiotic strains per day. Comparators included a pasteurised yogurt drink (without live bacteria) and chemically acidified milk to separately analyse the effects of the probiotics and pH. The study assessed the incidence and duration of AAD and gastrointestinal (GI) discomfort[7].

Population	Sample size	Probiotic	Comparator	Duration
Adults (18-65 years old) being treated for *H. pylori* (500 mg Clarithromycin, Clacid™, 1 g Amoxicillin, Amoxypen™ + Omeprazol 20 mg Antra 20™).	n= 30 probiotic n= 29 placebo n= 29 acidified milk	0.25 x 10^9 CFU of **BB-12®** and 0.25 x 10^9 CFU of **LA-5®**	Pasteurised drink Acidified milk	8 weeks

Duration of loose stools



* p < 0.05 compared to pasteurised and acidified milk.

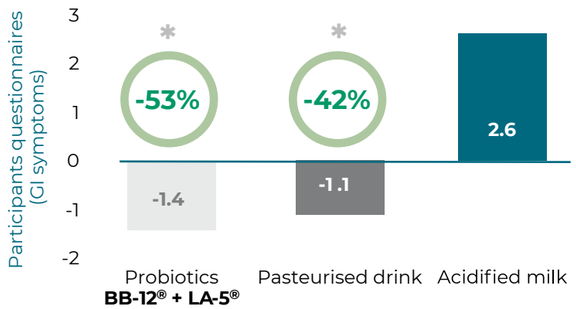
The intervention with **BB-12®** and **LA-5®** strains led to a significant reduction in the number of days with loose stools compared to the pasteurised drink and acidified milk groups (p<0.05).

This resulted in a 60% improvement, with the probiotic group averaging four days of symptoms, compared to ten days for the pasteurised and acidified milk groups.

GI discomfort was evaluated through participant questionnaires on GI symptoms. Both the probiotics intervention and pasteurised drink groups showed a significant reduction in symptom scores compared to the acidified milk group (p<0.05).

The reduction was greater in the probiotics group (53%) than in the pasteurised drink group (42%).

Total symptom score



* p< 0.05 in comparison with the acidified milk

Summary

- The use of probiotic formulations to prevent or reduce AAD has profound implications for clinical practice. The high incidence of AAD, particularly in children and the elderly, highlights the need to for preventative strategies. Studies have shown the effectiveness of certain probiotics in reducing the risk and incidence of AAD[24,30]. A range of mechanisms may underly this benefit, such as helping to restore the protective ability of the gut microbiota, inhibiting gut pathogens and stimulating the immune system[39,40].
- Specifically, the combination of *Bifidobacterium animalis*, **BB-12®** and *Lactobacillus acidophilus*, **LA-5®** strains has been associated with significant reductions of the duration and severity of AAD:
  - AAD duration shortened by 50%-60% [7,10]
  - Incidence of severe diarrhoea reduced by 67% in people with AAD[10]
- The use of probiotics in conjunction with antibiotic treatment could serve as a standard adjunctive management approach, particularly in populations at higher risk of AAD. The approach could help to maintain the protective function of the gut microbiota during and after a course of antibiotics.
- Healthcare providers should consider incorporating probiotics into treatment regimens for patients undergoing antibiotic therapy, especially those on broad-spectrum antibiotics or triple therapy for *H. pylori*.

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