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For Those On Antibiotics

How probiotics can prevent and treat antibiotic-associated diarrhoea

This CPD module is for the use of Pharmacists and Pharmacy Professionals

Reviewed by **Dr Gemma Walton** PhD

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CPD

Module summary

Antibiotics cause numerous adverse events, including antibiotic-associated diarrhoea (AAD). As AAD arises from disruption of the gastrointestinal (GI) microbiome, the use of probiotics is clinically rational and supported by the NHS. This module summarises the evidence that probiotic supplementation prevents and shortens the duration of AAD.

Learning objectives

After studying the clinical review and completing the online assessment, you should:

- Appreciate the epidemiology, causes and consequences of AAD
- Be familiar with the mechanisms of action of probiotics in AAD
- Be familiar with the evidence that probiotic supplementation prevents and shortens the duration of AAD
- Feel confident recommending a probiotic alongside antibiotics in practice

Reviewed by Dr Gemma Walton PhD

Next steps

- Read the clinical review
- Complete the online assessment
- Receive CPD certificate

This learning module can be used towards CPD for revalidation with the General Pharmaceutical Council (GPhC)

References provided at the end of the module.

Date of Publication: September 2022

Pre-learning reflection

Please take a moment to answer these pre-learning questions. Once completed, click 'next step' below to start this module. These answers will be logged on your CPD certificate, which will be emailed to you on completion as evidence of your learning.

Are you familiar with antibiotics' effects on the microbiome and the clinical consequences, particularly AAD?

On average, how often do you prescribe or dispense antibiotics each day?

Alternatively, if you are not a prescriber: how many people do you see each day who are receiving antibiotics?

What advice to you offer patients and caregivers who ask about AAD?

How often do you proactively suggest using a probiotic supplement alongside antibiotics to reduce the risk of common GI side effects?

Date of Publication: September 2022

Definitions

Term	Definition
Probiotics	Live bacteria and yeasts that when consumed in adequate amounts benefit human health; probiotics are usually added to yoghurts or used as food supplements[1]
Prebiotics	Substrates (some carbohydrates and fibre) that the host's microorganisms use selectively and that confer a health benefit[2]
Microbiome	The collective genomes (genetic sequences) of micro-organisms in a particular area of, for example, the skin, gut or vagina[1]
Microbiota	The community of microorganisms in a specific area, such as parts of the gastrointestinal tract, skin and vagina[1]

References provided at the end of the module.

Date of Publication: September 2022

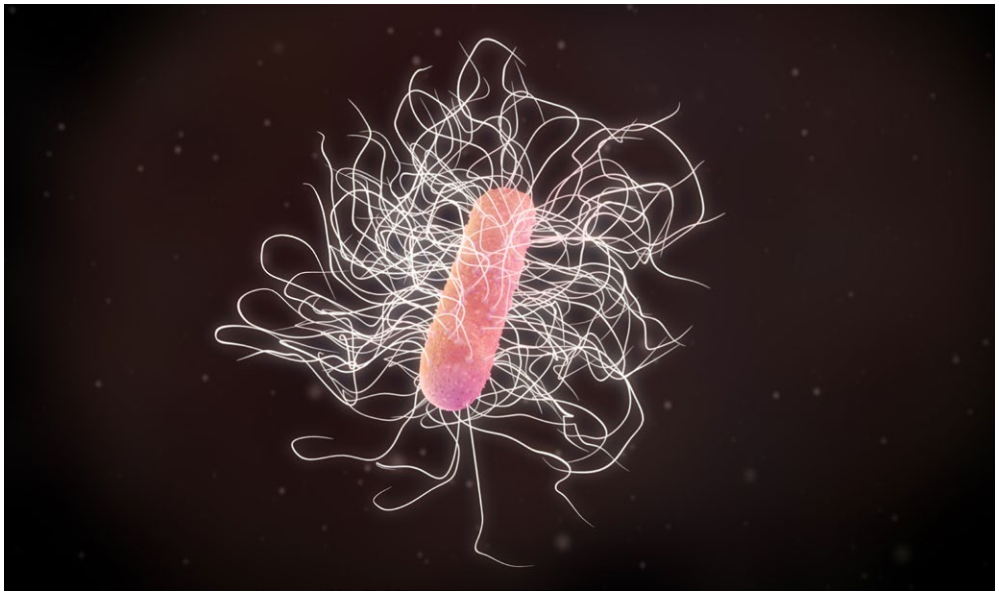
Antibiotics: benefits and risks

Improved nutrition, hygiene and sanitation, and less overcrowded housing help prevent and reduce transmission of infections. Together with these changes, antibiotics add, on average, 20 years to life expectancy[3]

However, antibiotics are associated with numerous short-term (within 90 days of the start of treatment) adverse events, including: gastrointestinal, dermatological, musculoskeletal, haematological, hepatobiliary, renal, cardiac and neurological side effects[4]

In children younger than 2 years of age, antibiotics have been associated with longer-term adverse events including increased risks of eczema, asthma and other allergic diseases, inflammatory bowel disease and obesity[5]

Appropriate use of antibiotics along with antimicrobial stewardship helps minimise these negative effects and slow the spread of antibiotic resistance[3]



Antibiotics increase the risk of *Clostridium difficile* (recently renamed *Clostridioides difficile*) infections[2]

References provided at the end of the module.

Date of Publication: September 2022

Epidemiology of AAD

Between 2% and 35% of people taking antibiotics experience diarrhoea. The incidence depends on the definition, the antibiotic (eg AAD is more common with broad-spectrum than narrow-spectrum antibiotics), co-morbidities and other patient-related factors[6-9]

AAD may develop during or up to two months after the end of antibiotic treatment[7,9]

Between 2% and 35% of people taking antibiotics experience diarrhoea

References provided at the end of the module.

Date of Publication: September 2022

Causes of AAD

AAD and other common side-effects follow disruption of normally protective bacteria in the GI microbiome[1-4]

The GI microbiome usually recovers to baseline within a few weeks after antibiotic treatment ends. Some studies suggest, however, that changes to the microbiome may persist for 2 to 6 months.[3,4] Some bacteria, however, may be lost and do not recover[1,2]

Overgrowth of various bacteria can cause AAD[1,3,5]

- *C. difficile* is responsible for 10% to 30% of AAD cases[1,6]
- The aetiology is not known for about two-thirds of AAD cases[9]

References provided at the end of the module.

Date of Publication: September 2022

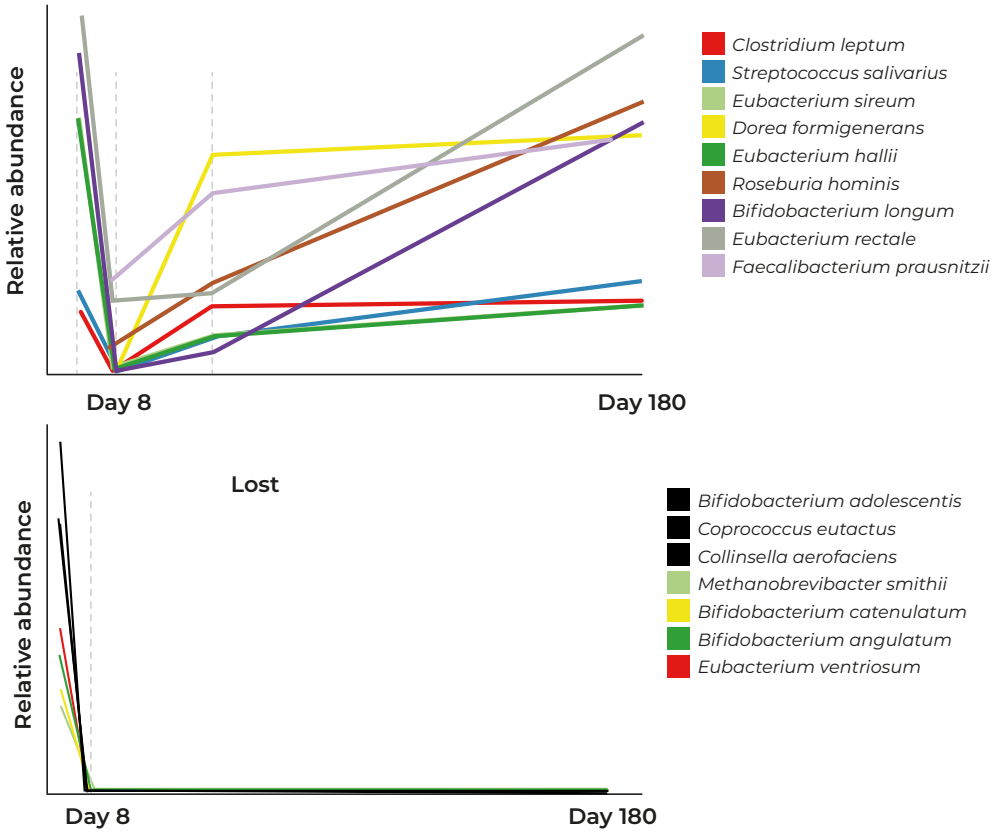
Causes of AAD

In one study, 12 healthy men received four days treatment with meropenem, gentamicin and vancomycin[12]

The study showed short-term increases in the numbers of several potential pathogens including *Escherichia coli*, *Klebsiella* and *Enterococcus*. Populations of 'healthy' *Bifidobacterium* species and butyrate-producing* bacteria decreased. Some of these did not return to their pre antibiotic levels (top graph)

Nine common species with beneficial properties, which were present before treatment with antibiotics, could not be detected in most subjects after 180 days (bottom graph)

* Butyrate is a short-chain fatty acid which is: an energy source for certain cells in the colon; regulates transepithelial fluid transport; reduces mucosal inflammation and oxidative status; bolsters the epithelial defence barrier; and influences visceral sensitivity and intestinal motility[13]



Adapted from Ramirez[4] after Palleja[7]

Relative abundance of species recovered after four-day antibiotic treatment over a 180-day follow-up

References provided at the end of the module.

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Causes of AAD

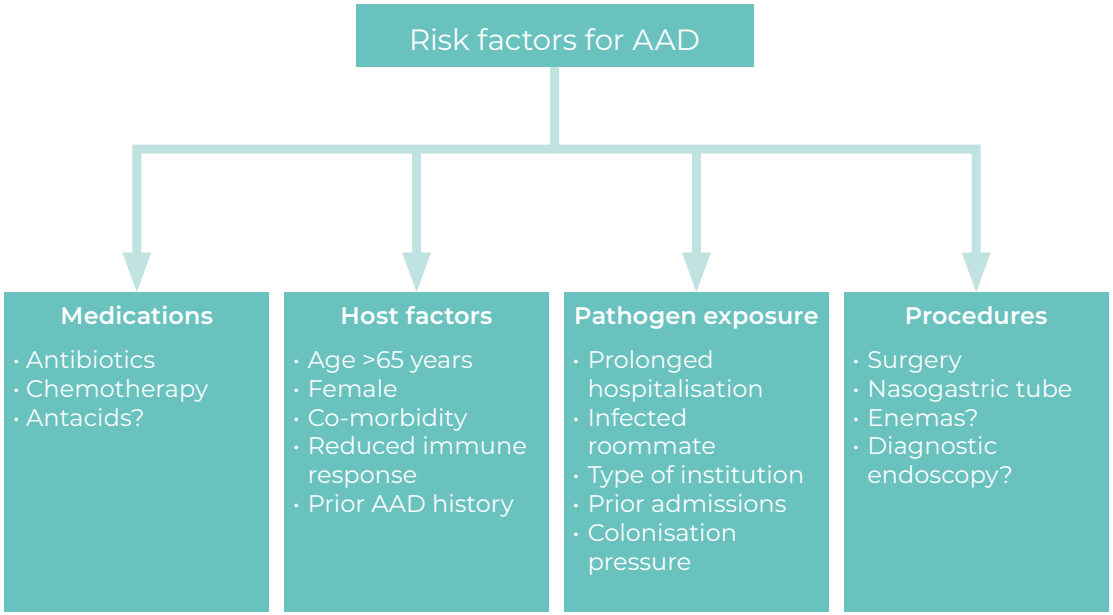
In addition to pathogen overgrowth, disruption of normally protective bacteria in the GI microbiome alters digestion and fermentation of carbohydrates in the colon[9]

Reduced metabolism of carbohydrates and bile salts can contribute to AAD[7]

Broad-spectrum antibiotics reduce short-chain fatty acid levels, which can, with the unfermented carbohydrates induce osmotic diarrhoea[9]

Antibiotics and toxins from *C. difficile* may modulate the enteric nervous system, which may lead to diarrhoea[9]

Factors that increase the risk of AAD include: the type of antibiotic or other drug; patient-related factors; exposure to pathogens; and procedures that disrupt normal colonic microbiota[9]



Adapted from McFarland[9]

Risk factors for AAD[9]

References provided at the end of the module.

Date of Publication: September 2022

Consequences of AAD

AAD may prolong hospital stay, increase the risk of other infections[7] and be distressing for patients. AAD complications can range from mild loose stools to fulminant pseudomembranous colitis (95-99% of cases caused by *C. difficile*), toxic megacolon, perforation, shock and death[8,9]

Antibiotic use may have longer-term consequences, including inflammatory bowel disease and food intolerances, especially if antibiotics are introduced during the first 2 years of life[14-17]

AAD may lead to reduced compliance and premature discontinuation of the antibiotic, which undermines efficacy[8,17] and could encourage antimicrobial resistance

References provided at the end of the module.

Date of Publication: September 2022

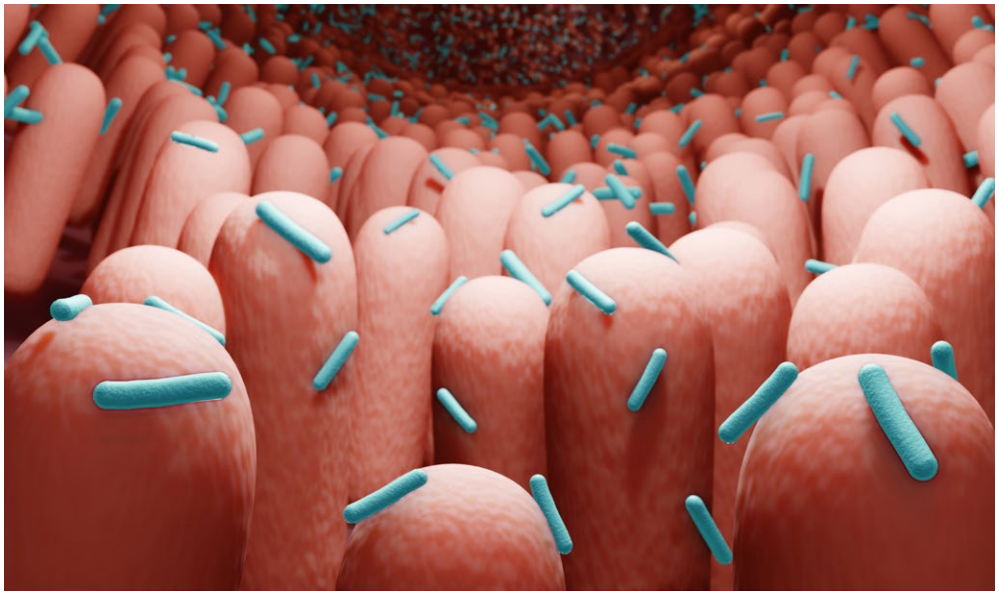
Management of AAD

Mild cases of AAD may respond to, for instance, rehydration or switching antibiotic.[7] Treatment of more severe AAD, which typically involves *C. difficile*, requires further courses of antibiotics (eg vancomycin or metronidazole)[18]

Antimicrobial stewardship and good hygiene in healthcare settings help reduce the risk of AAD[7]

As AAD arises from disruption of the GI microbiome, the use of probiotics is clinically rational[7,8,17]

- A systematic review reported that adjunct probiotics (most studies used *Lactobacillus*) reduced AAD risk by 42%[17]
- The NHS comments that "There's some evidence that probiotics may be helpful in some cases, such as helping prevent diarrhoea when taking antibiotics"[19]



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Date of Publication: September 2022

The story so far...

- Between 2% and 35% of people taking antibiotics experience antibiotic-associated diarrhoea (AAD)[6-9]
- AAD follows disruption of the GI microbiome, which usually recovers to baseline within a few weeks after antibiotic treatment ends; in some people, changes persist for 2 to 6 months. One study demonstrated that antibiotics resulted in the complete loss of nine potentially beneficial species[1-4,12]
- AAD may prolong hospital stay, increase the risk of other infections and be distressing for patients[8-9]
- AAD may lead to reduced compliance and early discontinuation of the antibiotic, which undermines efficacy and could encourage microbial resistance[8,17]
- Antibiotic use may have longer-term consequences, especially if antibiotics are introduced in the first 2 years of life[5]
- As AAD arises from disruption of the GI microbiome, the use of probiotics is clinically rational and acknowledged by the NHS[1-4,19]

Please click to continue the module

References provided at the end of the module.

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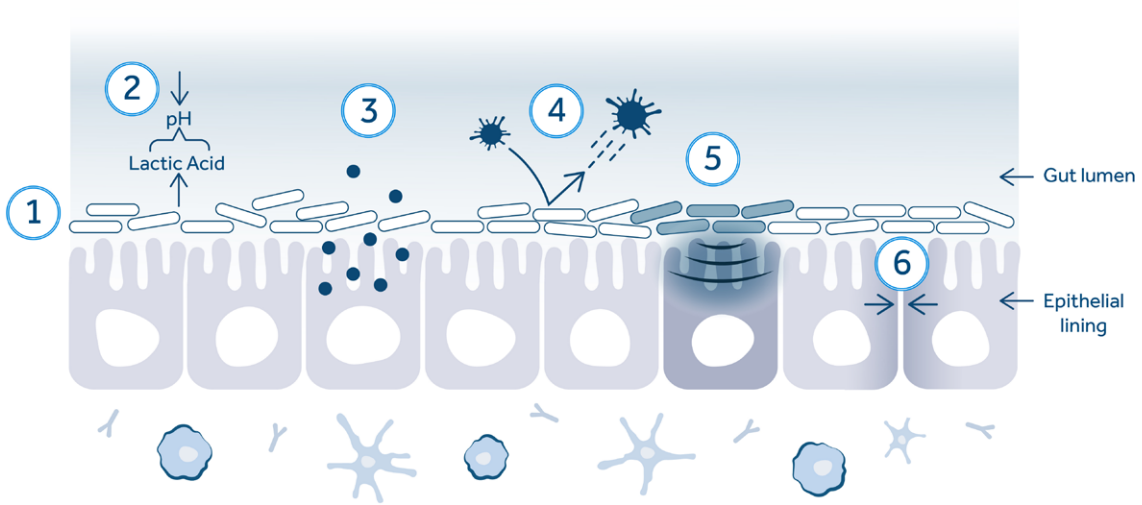
Probiotic mechanisms of action in AAD

Probiotics have several actions that maintain or restore the GI microbiome during or after antibiotic treatment; but the benefits are strain specific (see next slide)[8,17,20-22]



1. Probiotics bind to the mucosal lining where they fortify the barrier and encourage the growth of resident bacteria
2. Probiotics lower colonic pH, which favours the growth of non-pathogenic species
3. Beneficial bacteria produce short-chain fatty acids (SCFAs) to encourage a healthy epithelial lining. Reduced SCFAs concentrations are associated with diarrhoea
4. Probiotics reduce pathogen adherence to epithelial and mucosal cells through competitive inhibition and the production of antimicrobial substances. They can exert anti-toxinic effect against several toxin-producing pathogens
5. Probiotics can modulate immune cells and inflammation (enhance anti-inflammatory action and calm proinflammatory responses)
6. Probiotics can help support gut cell integrity (tight junctions), cell turnover and enterocyte health and encourage peristalsis. These changes counteract the increase in intestinal permeability often induced by antibiotics

These mechanisms support a healthy microbial composition, especially during antibiotics

SCFA: Short chain fatty acid

References provided at the end of the module.

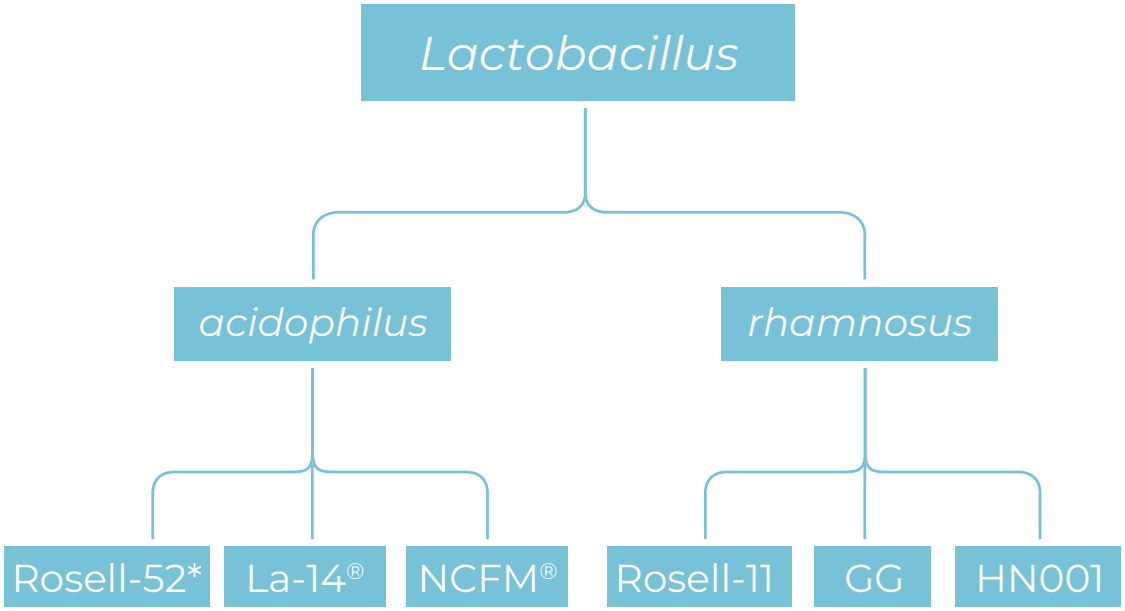
Date of Publication: September 2022

The importance of strain specificity

The World Health Organisation (WHO) notes that probiotics' effects are strain specific, commenting: "Strain identity is important to link a strain to a specific health effect"[28]

Healthcare professionals "need to consider which probiotic strain is supported by evidence from clinical trials, as not all probiotics have equal effectiveness"[8]

Correctly identifying the strain (not only the genus and species) in studies of AAD is "paramount"[8]



Microbes can be classified based on genetics and characteristics. Biologically important ranks include genus, species and strain.

***L. helveticus* Rosell-52 used to be classified as an acidophilus and is often still referred to as *L. acidophilus* Rosell-52**

References provided at the end of the module.

Date of Publication: September 2022

L. rhamnosus Rosell-11 and *L. acidophilus* Rosell-52 protects against AAD

A comprehensive review of studies on *L. rhamnosus* Rosell-11 and *L. acidophilus* Rosell-52 found that this combination of probiotics was effective against various GI conditions, including AAD[24]

Children receiving the combination* experienced, compared with children on antibiotics alone, a:[24]

- 1.5-fold lower incidence of AAD
- 2-fold shorter duration of diarrhoea
- 8-fold less *C. difficile* toxins
- 10-fold less *C. difficile* carriage
- No reported side effects

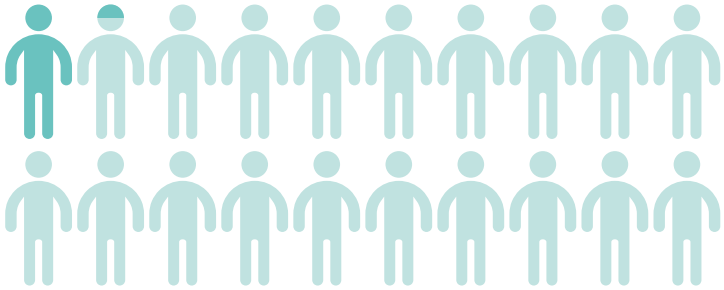
The combination led to improved appetite, normalised stool consistency, reduced GI discomfort and helped resolve glossitis (swollen and inflamed tongue) [24]

In another study, AAD occurred in significantly fewer people receiving the combination compared with controls: 12.8% and 44.8% respectively[24]

Duration of diarrhoea was significantly shorter in the treatment group compared with controls: 2.6 and 5.9 days respectively[24]

*One to three capsules a day, 2×10^9 colony forming units per capsule

***L. rhamnosus* Rosell-11 and *L. acidophilus* Rosell-52**



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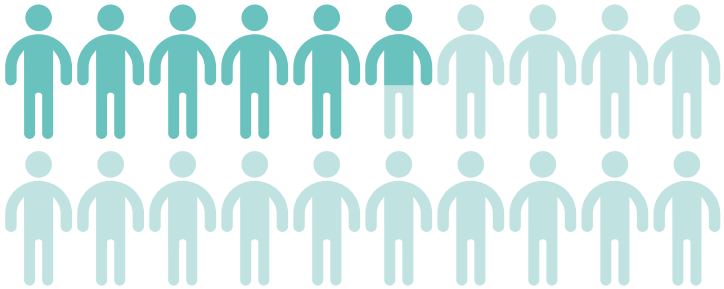


One of the studies reported found an 80% reduction in the risk of AAD when *L. rhamnosus* Rosell-11 and *L. acidophilus* Rosell-52 was added to antibiotic treatment[24]

References provided at the end of the module.

Date of Publication: September 2022

L. rhamnosus Rosell-11 and *L. acidophilus* Rosell-52 improve antimicrobial outcomes[24-27]

Significantly reduces AAD incidence and duration when taken alongside antibiotics

Significantly reduces *C. difficile* carriage and levels of associated toxins

Improved *Helicobacter pylori* eradication

Improves other GI-related side effects of antibiotic therapy including reduced appetite and gastrointestinal discomfort

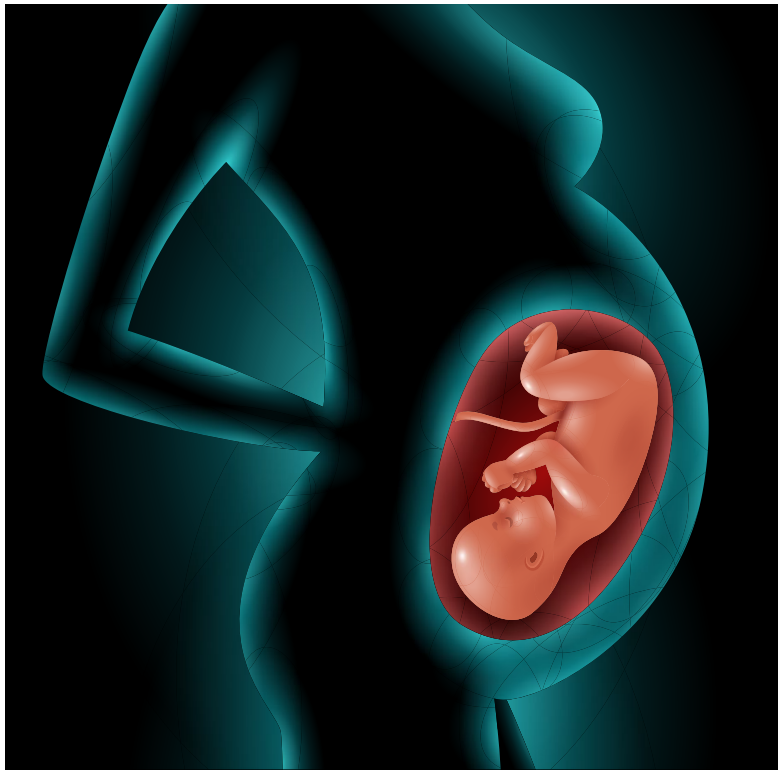
References provided at the end of the module.

Date of Publication: September 2022

L. rhamnosus Rosell-11 and *L. helveticus** Rosell-52 after caesarean section[24]

In a randomised, controlled study, 96 women undergoing caesarean section (CS) were given prophylactic antibiotics plus a probiotic combination: *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52, which resulted in:

A reduced risk of AAD



89.3% of patients receiving *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 had a balanced vaginal microbiome, compared to none of the controls

Establishment of a neonatal microbiome similar to that of a vaginally born infant

Supplementation with *L. rhamnosus* Rosell-11 and *L. helveticus* Rosell-52 before CS may reduce the incidence of opportunistic infections of the vaginal microbiome up to 3-fold. The same supplement given after CS was associated with a 1.3-fold reduction in the incidence. Both treatments reduced the risk of disrupted microbiome in the mother and infant

***L. helveticus* Rosell-52 used to be classified as an acidophilus and is often still referred to as *L. acidophilus* Rosell-52**

References provided at the end of the module.

Date of Publication: September 2022

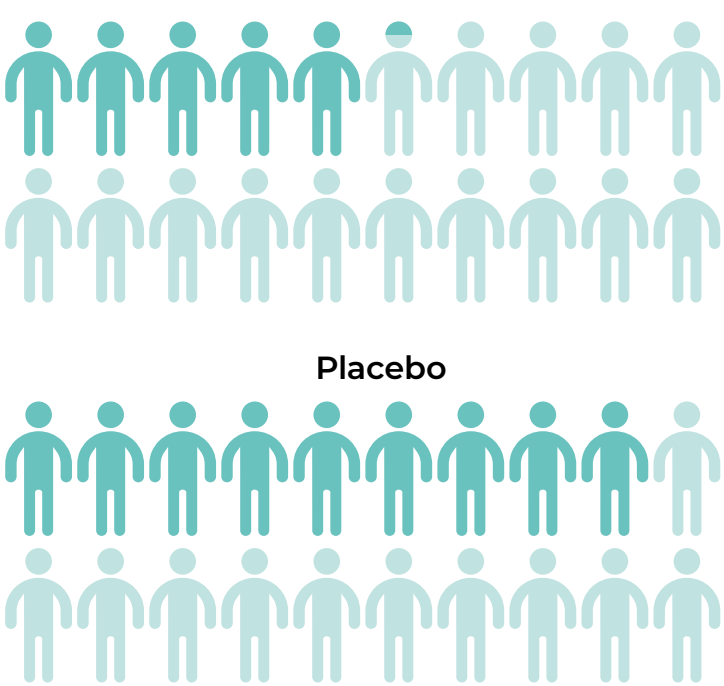
Saccharomyces boulardii can prevent AAD

***S. boulardii*, a fungi (yeast), was discovered in 1920 and is now widely used as a probiotic. A meta-analysis concluded that "*S. boulardii* can be strongly recommended for the prevention of AAD"[21]**

A meta-analysis* of 10 randomised, controlled trials in adults found that *S. boulardii* approximately halved the rate of AAD (relative risk 0.47); a statistically significant difference [21]

A meta-analysis* of six randomised, controlled trials in adults found that various different probiotics† reduced the risk of *C. difficile* infections by 40% (relative risk 0.59); a statistically significant difference [21]

Probiotics can reduce the risk that *C. difficile* infections will recur. In one study, 26% of patients taking *S. boulardii* had a recurrence of *C. difficile* infection compared with 45% given placebo, another statistically significant difference [21]



Recurrence rates of *C. difficile* infections in people receiving *S. boulardii* probiotic or placebo

* A meta-analysis is a statistical technique that combines results from multiple scientific studies

† *S. boulardii*, *L. rhamnosus* GG, *Lactobacillus planatarum* 299v, and a mix of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*

References provided at the end of the module.

Date of Publication: September 2022

Multi-strain probiotics can prevent AAD

A multi-strain probiotic* reduced the risk of AAD in 350 children (aged 3 months to 18 years), when given during antibiotic treatment and for 7 days after[28]

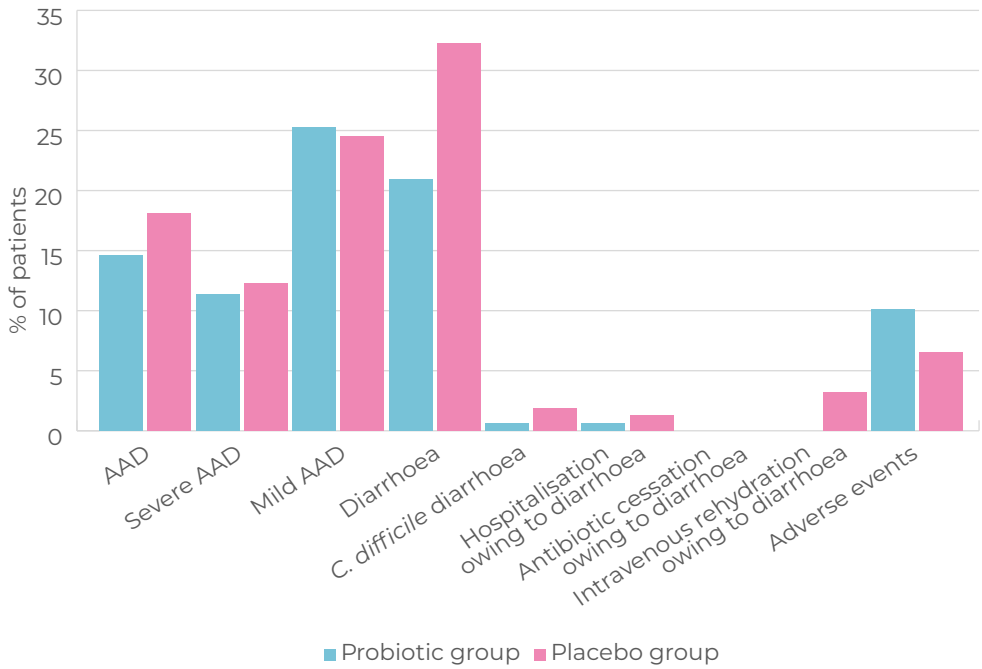
Compared with placebo, the probiotic reduced the risk of AAD (3 or more loose or watery stools per day over 24-hour) by 19% which was not significant[28]

Children in the probiotic group had a significant 35% lower risk of diarrhoea regardless of the aetiology[28]

No significant differences were observed between the groups for most of the secondary outcomes, including adverse events (see right) [28]

The definition of AAD influences the clinical trial results and should be considered when interpreting the results[28]

* **Multi-strain formula**: *B. bifidum* W23, *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W37, *L. acidophilus* W55, *Lactocaseibacillus paracasei* W20, *Lactoplantibacillus plantarum* W62, *Lactocaseibacillus rhamnosus* W71 and *Ligilactobacillus salivarius* W24, for a total dose of 10 billion colony-forming units daily



Outcomes with a multi-strain probiotic used to manage AAD[28]

References provided at the end of the module.

Date of Publication: September 2022

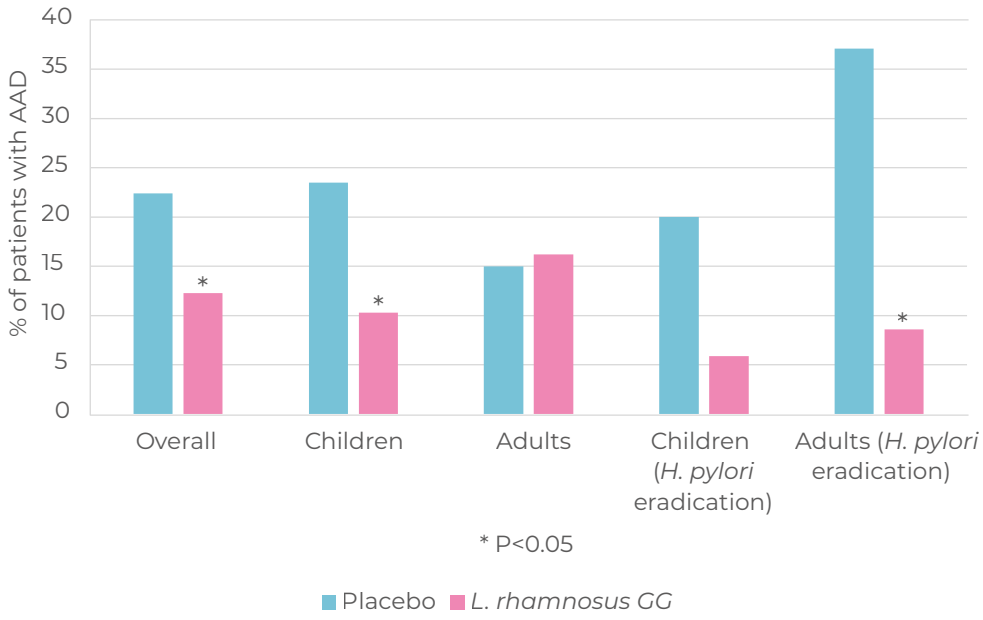
Lactobacillus rhamnosus GG can prevent AAD in children and adults

***L. rhamnosus* GG prevented AAD in children and adults treated with antibiotics for any reason, according to a meta-analysis of 12 randomised controlled studies involving 1499 patients[29]**

Treatment with *L. rhamnosus* GG compared with placebo or no additional treatment significantly reduced AAD risk by 51%[29]

This difference was significant in children and a subset of adults receiving antibiotics as part of *H. pylori* eradication[29]

These results are part of a body of evidence that makes *L. rhamnosus* GG one of the most researched probiotics for children[30]



Effect of *L. rhamnosus* GG in the prevention of AAD[29]

References provided at the end of the module.

Date of Publication: September 2022

Lactobacillus rhamnosus GG can prevent AAD in children

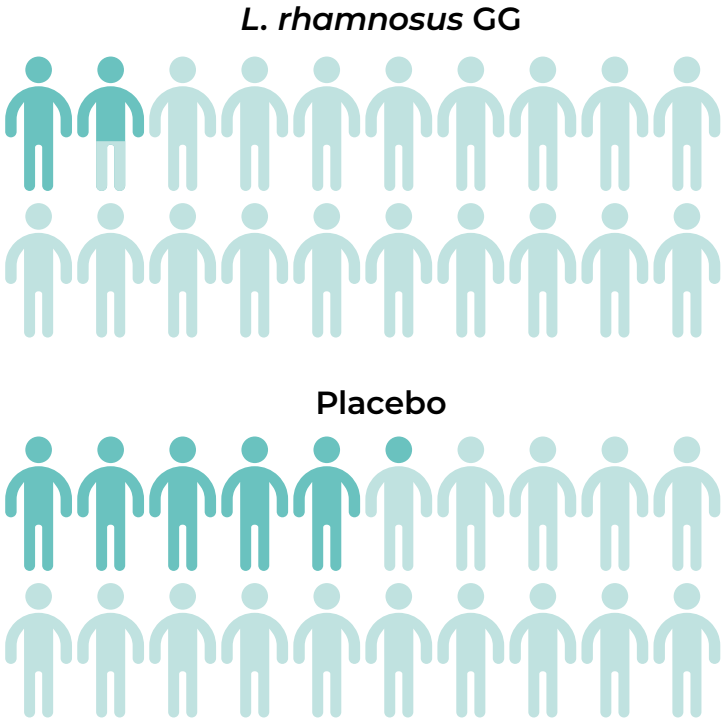
L. rhamnosus GG reduces AAD incidence in children treated with oral antibiotics for common childhood infections[31]

A study enrolled 202 children between 6 months and 10 years of age who received *L. rhamnosus* GG* or placebo; 188 children completed the study[31]

26% of patients who received placebo and 8% who received *L. rhamnosus* GG had AAD (at least two liquid stools per day on at least two occasions during the 10-day study) [31]

Mean stool consistency significantly improved (see graph) [31]

The mean duration of AAD was 5.88 days in the placebo group and 4.70 days in those who received *L. rhamnosus* GG, a statistically significant difference[31]



Rates of AAD in people receiving *L. rhamnosus* GG or placebo[31]

*1-2x10[10] colony forming units a day

References provided at the end of the module.

Date of Publication: September 2022

Summary

- Between 2% and 35% of people taking antibiotics experience AAD; as AAD arises from disruption of the GI microbiome, the use of probiotics is clinically rational and supported by the NHS[6-9,14,19]
- Probiotics have several actions that maintain or restore the GI microbiome during or after antibiotic treatment; but the benefits are strain specific[8,17,20-22]
- A meta-analysis of 10 randomised, controlled trials in adults found that *S. boulardii* approximately halved the rate of AAD[21]
- *L. rhamnosus* GG can prevent AAD in children and adults as well as improving appetite, normalising stools, reducing GI discomfort and resolving glossitis[24]
- A comprehensive review of studies found that the probiotic combination *L. rhamnosus* Rosell-11 and *L. acidophilus* Rosell-52 was effective against various GI diseases, including significantly reducing the incidence and duration of AAD when taken alongside antibiotics, and reducing the incidence of vaginal dysbiosis associated with antibiotic treatment[24]

Please click to continue the module

References provided at the end of the module.

Date of Publication: September 2022

Assessment

Now that you have reviewed the learning, please complete the following multiple choice questions to test what you've learnt and receive your CPD certificate

QUESTION 1:

Clostridium difficile is responsible for what proportion of AAD cases?

- ◯ 10-30%
- ◯ 30-50%
- ◯ 50-70%
- ◯ 70-90%

References provided at the end of the module.

Date of Publication: September 2022

Assessment

ANSWER 1:

Clostridium difficile is responsible for what proportion of AAD cases?

- (●) 10-30%
- ( ) 30-50%
- ( ) 50-70%
- ( ) 70-90%

References provided at the end of the module.

Date of Publication: September 2022

Assessment

QUESTION 2:

Is this statement: "In some people, changes to the GI microbiome persist for 2 to 6 months after antibiotic treatment ends"

- ◯ True?
- ◯ False?

References provided at the end of the module.

Date of Publication: September 2022

Assessment

ANSWER 2:

Is this statement: "In some people, changes to the GI microbiome persist for 2 to 6 months after antibiotic treatment ends"

- (●) True
- ( ) False

References provided at the end of the module.

Date of Publication: September 2022

Assessment

QUESTION 3:

Which of the following contribute to probiotics' beneficial effects in AAD?

- ◯ Anti-inflammatory action
- ◯ Countering the increase in intestinal permeability induced by antibiotics
- ◯ Inhibiting pathogen adherence to epithelial and mucosal cells
- ◯ Influencing tight junctions
- ◯ Lowering colonic pH
- ◯ All of the above

References provided at the end of the module.

Date of Publication: September 2022

Assessment

ANSWER 3:

Which of the following contribute to probiotics' beneficial effects in AAD?

- ◯ Anti-inflammatory action
- ◯ Countering the increase in intestinal permeability induced by antibiotics
- ◯ Inhibiting pathogen adherence to epithelial and mucosal cells
- ◯ Influencing tight junctions
- ◯ Lowering colonic pH
- ◉ All of the above

References provided at the end of the module.

Date of Publication: September 2022

Assessment

QUESTION 4:

In a meta-analysis *S. boulardii* approximately halved the rate of AAD. But is *S. boulardii*:

- ◯ A bacterium?
- ◯ A fungus?

References provided at the end of the module.

Date of Publication: September 2022

Assessment

ANSWER 4:

In a meta-analysis *S. boulardii* approximately halved the rate of AAD. But is *S. boulardii*:

- ○ A bacterium
- ◉ A fungus

References provided at the end of the module.

Date of Publication: September 2022

Assessment

QUESTION 5:

L. rhamnosus Rosell-11 and *L. acidophilus* Rosell-52 improve which of the following outcomes?

- ◯ Appetite and gastrointestinal discomfort
- ◯ *C. difficile* carriage and levels of associated toxins
- ◯ *H. pylori* eradication
- ◯ Incidence and duration of AAD when taken alongside antibiotics
- ◯ All of the above

References provided at the end of the module.

Date of Publication: September 2022

Assessment

ANSWER 5:

L. rhamnosus Rosell-11 and _L. acidophilus_ Rosell-52 improve which of the following outcomes?

- ◯ Appetite and gastrointestinal discomfort
- ◯ *C. difficile* carriage and levels of associated toxins
- ◯ *H. pylori* eradication
- ◯ Incidence and duration of AAD when taken alongside antibiotics
- ◉ All of the above

References provided at the end of the module.

Date of Publication: September 2022

Post-learning reflection

Please take a moment to answer these post-learning questions. These answers will be logged alongside your pre-learning responses on your CPD certificate which will be emailed to you on completion as evidence of your learning.

What are the three most important messages you have learnt? How will you apply this knowledge to your clinical practice?

How confident do you now feel to advise patients about probiotics to prevent and treat AAD?

What else do you feel you need to know about the role of probiotics in the prevention and treatment of AAD? How will you continue to improve your knowledge?

Date of Publication: September 2022

References and further reading

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Date of Publication: September 2022

Advertorial

Introducing Optibac For Those On Antibiotics

Optibac
Trusted friendly bacteria

An expertly formulated digestive supplement with highly researched probiotic strains to support those on antibiotics.

Contains **4.5 billion probiotics** per capsule, including ***Lactobacillus rhamnosus*** **Rosell-11**, ***Bifidobacterium lactis*** **Lafti B94** & ***Lactobacillus acidophilus/helveticus*** **Rosell-52**.

Key benefits

Includes probiotic strains scientifically proven to survive to reach the gut alive even when **taken at the same time as antibiotics**[1]. Also clinically proven to:

✓ **Reduce antibiotic associated side effects[1]:**

- Significantly lowers the risk of antibiotic associated diarrhoea (AAD)
- Significantly reduces the duration of AAD
- Improves other GI associated side effects, including reduced appetite, discomfort and glossitis

✓ **Support the microbiome during antibiotics[1]:**

- Significantly decreases the carriage of *C. difficile* and associated toxins
- Improves outcomes of *H. pylori* eradication therapy
- Maintains a balanced vaginal microbiome during antibiotics and reduces opportunistic infections

Recommended by HCPs and pharmacists, Optibac For Those On Antibiotics is vegan, gluten-free and suitable during pregnancy. It can be taken once daily at the same time as antibiotics.

1. Foster et al. (2011) A comprehensive post-market review of studies on a probiotic product containing Lactobacillus helveticus (acidophilus) R0052 and Lactobacillus rhamnosus R0011. Beneficial Microbes. 2, 4. 319-334.

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Please rate the overall quality of this CPD module:

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Before completing this module, how likely were you to recommend probiotics alongside antibiotics, especially to prevent or treat AAD?

◯ Very likely ◯ Likely ◯ Neither likely or unlikely ◯ Very unlikely

After completing this module, how likely are you to recommend probiotics alongside antibiotics, especially to prevent or treat AAD?

◯ Very likely ◯ Likely ◯ Neither likely or unlikely ◯ Very unlikely

Before completing this module, how likely were you to recommend Optibac Probiotics alongside antibiotics, especially to prevent or treat AAD?

◯ Very likely ◯ Likely ◯ Neither likely or unlikely ◯ Very unlikely

After completing this module, how likely are you to recommend Optibac Probiotics alongside antibiotics, especially to prevent or treat AAD?

◯ Very likely ◯ Likely ◯ Neither likely or unlikely ◯ Very unlikely

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PHARMACY ACADEMY

At the heart of clinical education

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