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PROBIOTICS FOR PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHOEA IN CHILDREN: A SYSTEMATIC REVIEW

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1. INTRODUCTION

Antibiotics save lives, and they also upset the gut. A child who is given amoxicillin for an ear infection or a macrolide for a chest infection has a real chance of developing loose stools within days, sometimes within hours. Estimates of the frequency of antibiotic-associated diarrhoea (AAD) in children vary widely, from a few per cent to more than a fifth, depending on the drug, the setting and the definition used [1, 2, 3]. Most episodes are mild and settle after the course ends. Even so, they cause nappy rash,

Abstract

Diarrhoea is one of the commonest adverse effects of antibiotic treatment in childhood, and probiotics are widely used to prevent it. This review summarises published randomised trials, meta-analyses, guidelines and safety reports on probiotics for the prevention of antibiotic-associated diarrhoea in children, and it reports no new data. Pooled analyses suggest that selected strains, mainly Lactobacillus rhamnosus GG and Saccharomyces boulardii at adequate doses, lower the risk of diarrhoea roughly by half, whereas other strains and products have not shown benefit. Evidence for preventing Clostridioides difficile infection in children is weaker. Strain specificity, variable definitions of diarrhoea, small trials and sparse safety data in vulnerable children limit the strength of recommendations.

dehydration, missed school and parental worry, and they sometimes lead to the antibiotic being stopped early, which carries

its own risks. Clinicians also see the other side of the problem, which is that parents who have watched a child suffer through one bad course of antibiotics are often keen to try anything that might prevent a repeat, and the pharmacy counter is frequently where that question is first asked.

Probiotics, defined as live microorganisms that confer a health benefit when given in adequate amounts, are the most frequently proposed preventive measure [4]. Paediatricians, pharmacists and parents alike reach for a sachet or a yogurt drink with the first dose of the antibiotic. The idea is intuitive: if antibiotics disturb the resident bacteria, replacing or supporting them should protect the gut. Intuition is not evidence, however, and the probiotic category covers many different organisms, doses and formulations. A claim that probiotics prevent AAD has to be tested strain by strain, product by product, and in the age group where the advice will be used. Marketing language adds to the confusion, since labels such as friendly bacteria or gut balance carry no information about strain, dose or evidence. For this reason the review separates what is known for named organisms from what is merely asserted for the product category as a whole.

A substantial body of randomised trials now exists. Several meta-analyses have pooled them, a Cochrane review focused specifically on children has been updated, and a European paediatric society has issued recommendations [5, 6, 7]. These sources broadly agree on the headline, which is that some probiotics reduce the risk of AAD, but they differ in how strongly they phrase it and in what they say about individual products. For a clinician advising a family, that gap between a general statement and a specific recommendation matters. Telling a parent that a named product has trial support is not the same as telling them probiotics work. Guidance is more cautious still, and it tends to be restricted to named organisms at named doses. Reading the primary trials alongside the summaries shows how much depends on a handful of strains tested repeatedly, while many commercial products have little or no direct paediatric evidence [4, 7].

This narrative review brings the published evidence together and reports no new data. It describes how antibiotics change the intestinal microbiota, summarises the trials and meta-analyses on prevention of AAD and of *Clostridioides difficile* infection in children, compares the strains and doses tested, and discusses safety and practical use. The evidence is presented as a synthesis of other people's work, using the cited reviews and trials, and conclusions are limited to what those sources support. Special attention is given to the quality of the evidence, because several well-known limitations affect how far the pooled results can be trusted. The article is organised around the questions a pharmacist or paediatrician would actually ask: why does AAD happen, who is at risk, does prevention work, which product, is it safe, and where is the evidence weakest. The same questions structure the table and the figure that follow.

2. MECHANISMS AND RISK FACTORS

The healthy colon holds trillions of bacteria that ferment dietary fibre, produce short-chain fatty acids, compete with pathogens for nutrients and space, and train the immune system [8]. Broad-spectrum antibiotics reduce this community and change its balance. Studies using molecular methods have shown large shifts in faecal microbiota in people with AAD, with loss of diversity and expansion of a few resistant groups [9]. Recovery is often incomplete. After repeated courses of a fluoroquinolone, for example, volunteers did not return to their starting composition within the weeks of observation, and the response differed markedly from person to person [10]. Short-chain fatty acids also feed colonocytes, so a fall in their production can weaken the barrier and promote water loss, a mechanism that links the microbial shift directly to the clinical symptom of watery stools.

Diarrhoea can arise through more than one route. Loss of fermenting bacteria reduces short-chain fatty acid production, so that carbohydrates and bile acids reach the colon in larger amounts and draw water into the lumen. Some antibiotics have direct effects on gut motility, and clavulanic acid is the textbook example, stimulating small-bowel

transit. Overgrowth of toxin-producing organisms accounts for a minority of cases but the most serious ones. *Clostridioides difficile* is the best known and can cause colitis of varying severity, from mild illness to pseudomembranous disease [1, 11]. This diversity of mechanisms hints at why one probiotic may succeed where another fails. In young children the situation is complicated by an immature microbiota that is still being established, so the same antibiotic can disrupt a community that has not yet reached its adult stability. How much that matters for long-term health is a separate and unresolved question.

Risk is not evenly distributed. Aminopenicillins combined with a beta-lactamase inhibitor, cephalosporins and clindamycin are most often linked with diarrhoea, and risk rises with longer courses and with combined therapy [2, 3]. In children, younger age, previous episodes, hospital admission and attendance at group childcare have been reported as risk factors in some studies, although the data are not consistent. An outpatient study in French children found that the type of antibiotic and the age of the child mattered, and that most cases appeared during treatment rather than afterwards [3]. These observations help to define who might benefit most from prevention. Practical risk assessment is therefore imprecise. No validated score exists for predicting AAD in an individual child, and recommendations about who should receive a probiotic have usually been framed around the antibiotic prescribed and the child's circumstances rather than a formal risk model [1, 2].

Definitions complicate everything. Some trials count three or more loose stools in 24 hours, others use two, others rely on parent reports or hospital records, and the time window ranges from the course of treatment to several weeks after it. A child with two soft stools on day four would be a case in one study and a non-case in another. Such differences inflate or deflate event rates and add to heterogeneity in meta-analysis. Consensus definitions have been suggested by expert groups, but older trials predate them, and even recent ones do not always apply them consistently [5, 7]. Clear

definitions are especially important when trial results are combined, because a pooled estimate is only as meaningful as the common ground between the studies that feed it. Reviewers have tried to handle this by using the investigators' own definition and then testing alternatives in sensitivity analyses [5, 6].

3. EVIDENCE FROM TRIALS AND META-ANALYSES

The early paediatric evidence came from small randomised trials, and a meta-analysis of randomised trials in children published in 2006 found that probiotics reduced the risk of AAD, with *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* showing the clearest effects [12, 13]. A larger meta-analysis across age groups, including 63 randomised trials, reported a clear reduction in the risk of AAD with probiotics and estimated that a modest number of patients would need to be treated to prevent one case [5, 14]. Reviews of this kind do not distinguish well between children and adults, so paediatric data must be read separately. Because these early reviews drew on trials of mixed quality and mixed products, their positive messages were treated as promising rather than conclusive, and the call for better-designed and better-reported trials was already clear. Similar conclusions had been drawn from reviews of probiotics in infectious diarrhoea [13].

The Cochrane review dedicated to children is the key reference. Its most recent version included over twenty trials, with several thousand participants, and found that the risk of AAD was roughly halved with probiotics compared with placebo or no treatment, with moderate certainty of evidence [6]. The benefit was seen mainly at higher daily doses, around five billion colony-forming units or more, and the reviewers noted that sub-group findings by strain were exploratory. Results were presented as relative risks with confidence intervals that excluded no effect, while the baseline risk in control groups varied considerably between trials, which means that absolute benefit in an individual child may differ. Dose-response was explored by comparing trials above and below the threshold, which is a crude approach, because trials differ in many other ways. The finding

is consistent but not proof, and the authors rightly framed it as a hypothesis to test in dedicated dose-ranging studies [6, 7].

Meta-analyses restricted to single organisms point in the same direction for the two best-supported agents. A systematic review of *Saccharomyces boulardii* found a reduction in AAD in both children and adults, with an apparently larger benefit in children [15]. For *Lactobacillus rhamnosus* GG, an early randomised trial in children treated for respiratory infections likewise found less antibiotic-associated diarrhoea than with placebo [16]. Network meta-analysis, which compares several products indirectly, has also ranked certain single-strain products and mixtures among the more effective options, though indirect comparisons carry additional uncertainty and should be read as hypothesis-generating [17, 18]. These reviews overlap heavily in the trials they include, so agreement between them is less independent than it seems. Counting four reviews that reach the same answer is not the same as having four independent confirmations, a point that is often missed in summary tables [5, 6].

Not all trials are positive, and failures are informative. A randomised trial of *Lactobacillus reuteri* DSM 17938 in children receiving antibiotics found no meaningful preventive effect, even though the organism has shown benefit in other paediatric gut conditions [19]. In adults, a large trial in older hospital inpatients using a multi-strain lactobacilli and bifidobacteria preparation (PLACIDE) found no reduction in AAD or in *C. difficile* diarrhoea [20]. Adult data cannot simply be carried over to children, but the trial is a useful warning that an apparently well-designed probiotic can still fail, and that publication of negative trials matters for the credibility of the field. The contrast with the positive results for *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* is a useful reminder of why strain-level thinking is necessary. A product containing a closely related organism is not a lesser version of the same thing; it is a different intervention that requires its own evidence [4, 7].

Results are collected in table 1, where entries are organised by the type of evidence and the

organism studied. The pattern is fairly clear. Pooled analyses lean positive, the best-supported agents are *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, other organisms have inconsistent or negative results, and expert guidance has converged on a cautious recommendation for those two organisms (fig. 1). The table cannot show variation in dose, formulation, antibiotic or age of children, so it gives a summary and not a prescribing guide [5, 6, 7]. Tailored use of a single table cannot capture everything, so readers who plan to apply the findings should consult the original trials and the guidance cited there. The ESPGHAN position on probiotics in acute gastroenteritis shows the same strain-by-strain approach applied to a related condition [21].

Food-based delivery has also been explored. Probiotic yogurts and fermented milk drinks are attractive to families because they are familiar and inexpensive, and trials in children have tested them as alternatives to capsules and sachets [22]. The difficulty is that the viable count in a commercial product can vary with storage and shelf life, and that the dose in a typical serving is not always known. Where a product is sold as a food rather than a medicine, regulators do not require the same proof of strain identity and content, so the quality of evidence for a specific brand can be thin. Independent assessment of viable counts in such foods would be welcome [22, 23].

Table 1: Published evidence on probiotics for antibiotic-associated diarrhoea in children

Evidence source or organism	Reported finding	Ref.
Meta-analysis of trials 63 randomised trials, all ages	Probiotics reduced the risk of antibiotic-associated diarrhoea; benefit not fully explained by dose or strain.	[5]
Cochrane review Paediatric trials	Risk roughly halved with moderate certainty, mainly at higher daily doses.	[6]
Meta-analysis of paediatric trials	Reduced risk, with the clearest effect for two organisms.	[12]
<i>Lactobacillus rhamnosus</i> GG	Randomised trial in children on antibiotics found less diarrhoea than placebo.	[16]

Evidence source or organism	Reported finding	Ref.
Saccharomyces boulardii	Meta-analysis found lower risk of diarrhoea, with apparently larger benefit in children.	[15]
Lactobacillus reuteri DSM 17938	No meaningful preventive effect in children receiving antibiotics.	[19]
Multi-strain preparation Older adult inpatients	No reduction in antibiotic-associated or C. difficile diarrhoea in a large trial.	[20]
Probiotics and C. difficile	Lower incidence of C. difficile-associated diarrhoea, with few paediatric trials.	[24, 25]
ESPGHAN working group	Consider Lactobacillus rhamnosus GG or Saccharomyces boulardii; other organisms not recommended.	[7]
Guidance on hospital use	Evidence for nosocomial diarrhoea limited and strain dependent.	[26]
Probiotic sepsis reports	Sepsis described in children with central lines or complex illness.	[27]

4. STRAINS, DOSE AND CLOSTRIDIODES DIFFICILE

Strain specificity is the central principle of probiotic science, and it is easy to say and hard to apply. Two products that both contain Lactobacillus can behave quite differently, and evidence for one strain does not carry over to another of the same species. The consensus statement on the term probiotic stresses that the genus, species and strain should be identified, and that effects should be demonstrated for the actual product [4]. In practice, that means that a recommendation for Lactobacillus rhamnosus GG is a recommendation for that strain, not for any lactobacillus product on the shelf. Manufacturers sometimes combine several species in the hope of broader effect, but combinations complicate interpretation, since a positive trial of the mixture does not show which component was active, nor does it demonstrate that every component is needed [23, 28].

The paediatric guidance from the European society for paediatric gastroenterology,

hepatology and nutrition (ESPGHAN) working group came to a measured position. It suggested that Lactobacillus rhamnosus GG or Saccharomyces boulardii be considered for children receiving antibiotics, with a recommendation that was graded as of moderate strength and based on moderate-quality evidence, and it did not recommend other organisms in the absence of supporting trials [7]. The working group also gave dose guidance that mirrors the pooled analyses, namely at least five billion colony-forming units per day for lactobacilli, and about 250 to 500 mg per day of the yeast. The position is revisited as new trials appear, and the wording reflects a deliberate trade-off between enthusiasm and the limits of the data. Guidance of this kind is more useful to practitioners than a bare statement that probiotics help, because it names the options and the dose [6, 15].

Timing and duration are less well studied than dose. Most trials started the probiotic at the same time as the antibiotic and continued it until the end of the course, and some for a week or so beyond. Whether an earlier start would help, or whether continuing for longer would protect against late-onset diarrhoea, is largely unexplored. Spacing the probiotic a couple of hours from a bacterial antibiotic is common advice, and it makes sense for lactobacilli, which are susceptible to many antibacterials, but the yeast is not affected by antibacterials and can be given at the same time [28, 29]. Evidence for these practical points comes largely from pharmaceutical reasoning and small studies of survival in the presence of antibacterials, not from clinical trials comparing different timing schedules, so they should be offered as sensible practice and not as proven rules [8, 28].

Prevention of Clostridioides difficile infection is a separate question with its own literature. A meta-analysis of randomised trials in adults and children reported that probiotics lowered the incidence of C. difficile-associated diarrhoea, with the relative reduction larger in studies with a high baseline risk [25]. The Cochrane review on this topic, which included both children and adults, reached a similar conclusion with moderate certainty but noted that few trials included children,

and that the product tested in the largest trials had not been tested in younger age groups [24]. Infection guidelines for adults did not recommend routine probiotic use at the time of their publication [11]. For children, evidence is thinner still, since the largest trials in this area were conducted in adults, and extrapolating from adults to younger age groups assumes similar microbial and immunological responses, an assumption that needs to be tested [20, 25]. Food-based delivery, for example probiotic yogurt, has also been trialled in children [22].

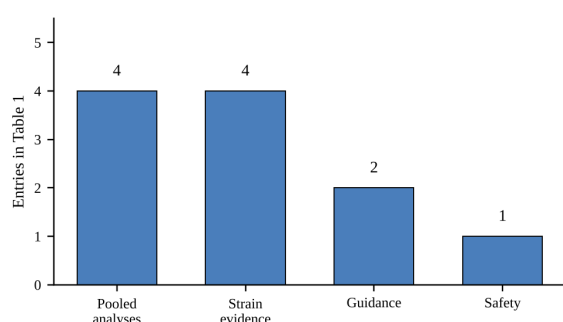


Fig. 1: Number of entries in table 1 by type of evidence

Product quality is a recurring practical problem. Independent analyses of commercial probiotic products have found that some contain fewer viable organisms than labelled, a different strain from the one stated, or contaminants. A practical guide aimed at clinicians offered a way to choose a product by listing strains with evidence of benefit for each condition and checking that the preparation in the pharmacy matched them [23]. For a pharmacist, this is a familiar job: verify the identity, confirm the dose per day, check the expiry and storage conditions, and make sure the labelled strain matches the one in the trials. Pharmacy staff can also help by keeping a record of the products they stock and the evidence behind each one, so that advice is consistent across the team [23, 30].

5. SAFETY AND PRACTICAL USE

In otherwise healthy children, probiotics are well tolerated and serious harm is rare. Mild gas, bloating or a change in stool pattern are the most commonly mentioned effects. Systematic reviews of safety conclude that the evidence of adverse events in trials is reassuring, but they also point out that many trials do not report harms carefully, so the

absence of reported problems is weaker evidence than it appears [30, 31]. The data are least informative exactly where concern is greatest, namely in very ill or immunosuppressed patients who are underrepresented in trials. Safety reporting should include not only serious events but also tolerability, adherence to the product and discontinuation, since these shape real-world acceptability. Reviews recommend that trials of probiotics adopt the same adverse event standards as drug trials [30, 31].

Case reports describe bacteraemia and fungaemia linked to probiotic organisms. Sepsis due to *Lactobacillus rhamnosus* GG has been described in children with underlying conditions such as short bowel syndrome or congenital heart disease, often in the presence of a central venous catheter [27]. Fungaemia from *Saccharomyces* has been reported in critically ill patients, and contamination of the hospital environment during preparation of sachets is a recognised hazard. Regulators have drawn attention to the gap in oversight of products marketed as supplements, as opposed to drugs [30]. Because of these reports, probiotics are generally avoided in children with central lines, severe immunodeficiency or critical illness. These cases are uncommon relative to the number of doses given, and causation is sometimes uncertain, but they are severe enough to justify caution. Pharmacists asked about probiotics for a child with a complex medical history should refer the question to the treating team rather than answering from product leaflets [26, 27].

The question of whether routine probiotic use leaves the gut better or worse after antibiotics has recently been raised. In a human study with healthy adult volunteers, a multi-strain probiotic colonised the gut but delayed the return of the normal mucosal microbiome after antibiotics, whereas autologous faecal transplant restored it quickly [32]. The study was small and not in children, and it did not measure diarrhoea, so it cannot be used to argue against probiotic use for AAD. It does show that the effect on the microbiota is not necessarily the straightforward restoration that marketing implies, and it deserves follow-up in paediatric populations. Where a

microbiota effect of this kind occurs, it may also depend on the product, the dose and the host, so one study should not be overinterpreted. Researchers have argued for more direct comparison of the microbiome and clinical outcomes in the same trial participants [10, 32].

What does this mean in practice for a pharmacist or paediatrician? When an antibiotic is genuinely needed, the first step is to question whether the spectrum is as narrow as it could be, and whether the course length is justified. If a family wants to add a probiotic, one of the two best-supported agents at a trial-tested dose is a defensible option for an otherwise healthy child [7]. Counselling should include the reasons, the expected modest size of the benefit, how to store the product, and when diarrhoea should prompt medical review, such as blood in the stool, fever, persistent vomiting or signs of dehydration. Written advice helps, because parents tend to forget details given verbally at the counter. A short leaflet that names the strain, dose and duration, and lists warning signs, supports safer use and also leaves a record of what was recommended [7, 23].

Cost and access also deserve attention. Probiotic products are rarely reimbursed and prices differ greatly, so families bear the expense. In settings where antibiotic prescribing is frequent and the burden of diarrhoea is high, a small absolute risk reduction may not justify routine use, whereas in a child with a high-risk profile, such as a long course of a broad-spectrum antibiotic, the case is stronger. An honest discussion with parents about the likely size of benefit helps to align expectations and avoids the impression that a probiotic makes antibiotic overuse harmless. Honest counselling also protects the child's family from spending money on products with no supporting trial, and it reinforces the message that antibiotics should be used only when needed [6, 7].

Hospital settings raise additional points. The ESPGHAN working group also reviewed probiotics for the prevention of nosocomial diarrhoea in children and found the evidence limited and strain dependent [26]. Meta-analytic data for healthcare-associated diarrhoea support a benefit for *Lactobacillus*

rhamnosus GG, mainly for rotavirus gastroenteritis, but these results are distinct from AAD and should not be merged with it [33]. Infection control teams generally prefer to avoid opening probiotic sachets near immunosuppressed patients, and hospital formularies may reasonably restrict their use to defined indications. Policies of this sort protect vulnerable patients without excluding the many for whom probiotics are reasonable [27, 30].

6. LIMITATIONS AND FUTURE DIRECTIONS

The certainty of the evidence needs to be stated honestly. When assessed with the GRADE framework, reviews usually rate the quality of evidence for AAD prevention as moderate at best, because of risk of bias in individual trials, inconsistency between them and imprecision [6, 34]. Substantial heterogeneity is common in these analyses, and it is not fully explained by dose or strain [35]. Funnel plots suggest that small positive trials are overrepresented, and many trials were sponsored by the manufacturer of the product tested. None of this invalidates the findings, but it argues for caution when quoting numbers. Reporting quality is another problem. Many trials do not describe allocation concealment clearly, and some do not explain how missing data were handled, which complicates assessment of the risk of bias and raises the possibility that the observed effect is somewhat exaggerated [6, 34].

The trials also differ in what they actually measured. Parent-reported loose stools, laboratory confirmation of *C. difficile* toxin, duration of diarrhoea and need for hospital care are all outcomes that matter, but very few trials report more than one. Patient-important outcomes such as school absence, parental time off work or antibiotic discontinuation are almost never reported. Without them, it is hard to know whether a reduction in the rate of mild loose stools translates into a benefit that families and health services would value, or simply shifts the borderline between normal and abnormal stools. This matters for decision making, since the value of preventing an event depends on its consequences. A product that

prevents mild loose stools but not hospital admission may still be worth using, but the justification should be explicit and not assumed [5, 6].

Several research questions remain open. Head-to-head trials of the leading strains in comparable populations would clarify whether *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* are equivalent. Dose-ranging studies in children, with prespecified definitions of diarrhoea, would settle the minimum effective amount. Trials in high-risk groups, such as children on prolonged courses or those in hospital, are needed to find where the benefit is greatest. Finally, studies of next-generation products and well-defined microbial consortia should be judged by the same standards, with transparent reporting of strain identity, dose and viability [4, 28]. Further, independent replication is rare. The same research groups produced many of the positive trials of the leading strains, and confirmation by unrelated teams, ideally with public pre-registration, would add credibility that pooled statistics cannot supply [15, 16].

Regulation and professional practice also need to catch up. Product labels should identify strains by their full designations and state the number of viable organisms at the end of shelf life, not at manufacture. Guideline groups should update their recommendations regularly and be explicit about the certainty of the underlying evidence. For pharmacists, who are often the first person parents ask, concise decision aids that name the supported strains, doses and exclusions would be more useful than general statements that probiotics are safe and effective [7, 23, 30]. Recommendations that clearly separate evidence for prevention in healthy children from evidence for hospital settings or for treatment of established diarrhoea would also reduce confusion, since the same probiotic may have different roles in each [7, 26, 33].

Finally, there is a need for better thinking about the goals of prevention. If the main aim is to spare children and families an unpleasant episode, then even a modest relative risk reduction has value when the product is cheap and safe. If the aim is to reduce serious

complications such as *C. difficile* colitis, trial designs must be adequately powered for rarer outcomes. Clarifying which of these purposes a particular recommendation serves would make the evidence easier to apply and guard against overstatement [6, 25]. Both goals are legitimate; the difficulty arises when evidence for one is quoted in support of the other [24, 25].

7. CONCLUSION

The published evidence supports a modest but real benefit of selected probiotics in preventing antibiotic-associated diarrhoea in children. Pooled analyses suggest that the risk is roughly halved with *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii* at adequate daily doses, and a European working group has accordingly advised that these two agents may be considered [5, 6, 7]. Other strains have not shown the same benefit, and the effect cannot be generalised to probiotics as a class. Evidence for preventing *C. difficile* infection in children is encouraging in pooled data but thin in children specifically [24, 25].

Practical use should therefore be selective. Choose a named strain with trial support, confirm dose and product quality, avoid use in children with central lines, severe immunodeficiency or critical illness, and counsel families about the likely size of benefit [7, 23, 27]. Future work should focus on head-to-head comparisons, clear definitions of diarrhoea, patient-important outcomes and longer follow-up, so that recommendations can rest on stronger evidence than is currently available. Probiotics should also never be allowed to stand in for prudent antibiotic prescribing, which remains the first line of prevention [1, 2].

8. ABBREVIATIONS

AAD-Antibiotic-associated diarrhoea,
CFU-Colony-forming units,
ESPGHAN-European Society for Paediatric
Gastroenterology, Hepatology and Nutrition,
GRADE-Grading of Recommendations,
Assessment, Development and Evaluations,
LGG-*Lactobacillus rhamnosus* GG,
RCT-Randomised controlled trial, *C.*
difficile-*Clostridioides difficile*

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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