Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/81yqat88

PROBIOTICS AS AN ADJUNCT THERAPY FOR PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA IN CHILDREN: SYSTEMATIC REVIEW

Dr Aamir Iqbal[1], Dr Umair Sabir[2*], Dr Bilal[3], Dr Mehran Ullah[4], Dr Zil E Huma Amin[5], Dr Faisal Hussain[6]

[1]Resident Paediatrician Combined Military Hospital, Peshawar, Pakistan
[2*]Senior House Officer, Darlington Memorial Hospital, United Kingdom
[3]Resident Paediatrician, Combined Military Hospital Peshawar Pakistan
[4]Medical Officer, Prime Teaching Hospital, Peshawar Pakistan
[5]Medical Officer, Afridi Medical Complex, Peshawar Pakistan
[6]Resident Paediatrician, Combined Military Hospital, Peshawar Pakistan

***Corresponding Author:** Dr Umair Sabir
*Email address: umairsabir459.us@gmail.com

Abstract
Antibiotic related diarrhea (ARD) is one of the most common side effects experienced in children who take antibiotics, because of alteration in the composition of intestinal microflora. The purpose of this systematic review is to assess the effectiveness of probiotics as an additional treatment intervention to guard against AAD in children. The literature databases referencing this topic were searched exhaustively with articles published between January 2000 and December 2023 filtering according to the set criteria. The systematic review incorporated 11 pieces of research featuring different probiotic species including Lactobacillus, Bifidobacterium, and Saccharomyces boulardii and observed that AAD incidence was lowered by up to 58%. These results suggest that, if more advanced studies are conducted with a focus on different strains, doses, and treatment durations, probiotics could have a beneficial effect in limiting AAD. In conclusion, prophylactic use of probiotics appears to be reasonably safe and effective in decreasing the incidence, intensity, and duration of AAD in children, but more properly designed studies are needed to establish an ideal protocol for using probiotics as an adjunct therapy.

Keywords : Probiotics, antibiotic-associated diarrhea, pediatric, gut microbiota, Lactobacillus, Bifidobacterium, Saccharomyces boulardii, adjunct therapy, prevention, systematic review

Introduction
Antibiotic associated diarrhea (AAD), remains a common side effect as children who are on antibiotic treatment. This is confirmed by the fact that in antibiotic-associated diarrhea, after the use of antibiotics, the normal flow of the bowel resident microorganisms is disturbed and replaced by easily growable pathogens such as Clostridium difficile (C. difficile) (McFarland, 2008). Broad spectrum antibiotics specifically can affect the balance of the microbes in the gut putting the gut barrier in a negative light (Vanderhoof & Young, 2004). The reported prevalence of AAD in children falls between 11% and 40%, taking into account age, the type of antibiotic given, and personal traits (Bartos et al., 2020). Accumulated AAD affects not only the child's QoL but also cost of healthcare and results in dangerous conditions including dyshidrosis or longer LOS (McFarland, 2008).

More recently, probiotics are perhaps the most researched intervention measure in relation with AAD prevention. According to World Health Organization (WHO) probiotics are 'living microorganisms, when ingested in adequate amounts, show picture health improvements in the host' WHO, (2001). Lactobacillus and Bifidobacterium species and strains are primarily of interest as are nonpathogenic yeast such as Saccharomyces boulardii (Hempel et al., 2012). Probiotics are thought to exert their protective effects by several mechanisms: promoting specific immunity of the mucosa, occupying the receptor sites for pathogenic bacteria on the mucosa of the gastrointestinal tract, secreting antimicrobial substances, and restoring the disturbed balance of the micro biocenosis of the intestine (Gupta et al., 2016). Such properties make probiotics a suitable candidate for therapeutic management of AAD in children.

The pediatric population may benefit from the intake of probiotics to some extent due to their immature immune systems and vulnerability to infections as well as the complications which are associated with AAD (Sullivan et al., 2009). In children, AAD may cause considerable discomfort, dehydration, and possibly even require additional intervention by a medical expert. Consequently, any form of prevention, such as the use of probiotics, is of great research concern. Different researches have been made in order to evaluate the impacts of probiotics in decreasing the intensity and frequency of AAD in kids. Systematic reviews and meta-analyses carried out by Johnston et al. (2011) proved that probiotics could have a protective effect – 52% reduction in the risk of AAD – for children only. However, studies on AAD prevention using probiotics have not completely provided conclusive results due to differences in probiotic strain, dosage administered, duration of the trial, and patients' characteristics (Szajewska, et al., 2013).

Furthermore, adverse effects involving the immunocompromised children or with other compromised medical conditions have been reported regarding the use of probiotics (Venugopalan et al., 2010). Hence, it is important to provide a systematic approach to scrutinize data available today regarding the use of probiotics as an additional therapy line to principally treat AAD in children.

The following systematic review has the objective of appraising the literature regarding the use of probiotics for the prevention of AAD in pediatric patients. Consequently, this review aims to provide the relevant record evidence on the advantages and disadvantages of using the approach based on available knowledge and to help clinicians consider using clinical serving assistance of probiotics for children who are under the antibiotic therapy.

Materials & Methods

Study Design

The present systematic review was planned according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The review protocol was registered prior to beginning the review in order to increase transparency and to support replication. Therefore the study was undertaken with the objective of assessing the effectiveness of probiotics in the reduction of AAD among children. Based on the evidence from RCTs and observational studies, this review aims at summarizing the current proof and demonstrates that probiotics could be used as a co-therapy with antibiotics in children.

Selection Criteria

Since this review includes only RCTs, the studies were identified using the PICOS framework that comprises population, intervention, comparator, outcomes, and study design (Table 1). The first step of the study was to screen titles and abstracts and then read full texts to confirm the eligibility for the study inclusion or exclusion. Screening and selection were done by two independent reviewers; if there were differences, the reviewers discussed until a consensus was reached or a third reviewer was involved.

Inclusion Criteria

Selection criteria used in the present review concerned investigation about the preventive effectiveness of probiotics on AAD in children, raised qualitative assessment of included studies. Inclusion criteria included patients aged 0 to 18 years and treated with antibiotics; however, exclusively pediatric patients were included in the analysis. The intervention needed here was the delivery of probiotics which refer to live microorganisms in adequate quantity intended to have health positive effects on the host based on WHO guidelines (WHO, 2001). A placebo or no probiotic intervention comparator was used so as to determine the impact of the probiotic under study. The first end-point of the study was the rate of AAD and the second end-points were the length of AAD and the severity of AAD and adverse effects of using probiotics. The literature search restricted the data search to only RCTs, controlled cohort, and case control studies in peer reviewed journals in order to obtain high-quality data.

Exclusion Criteria

Papers were only discarded if target population, the specific intervention and the type of study were not in congruent with the analyzed studies. More specifically, other groups of subjects that were excluded were adults over 18 years of age. Furthermore, all investigations without a control group were excluded and this includes case reports, case series, or single-arm trials. Studies in which probiotics were proposed to be utilized in the treatment of the existing diarrheal conditions were also excluded. Only articles that were published in English and peer-reviewed were included as any other sources were deemed to contain low quality such as conference abstracts, theses or dissertations. Last, the duplicates were removed, and the most contemporary or exhaustive papers were selected to eliminate confusion and exclude repetition based on data.

Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Cochrane Library, Embase, and Scopus, covering studies published from January 2000 to December 2023. The search strategy employed a combination of MeSH terms and keywords, including “probiotics,” “antibiotic-associated diarrhea,” “children,” “pediatrics,” and “adjunct therapy.” Boolean operators (“AND,” “OR”) were used to refine the search further, and filters were applied to include only studies in English. Additionally, the reference lists of included studies and previous systematic reviews were manually screened to identify any relevant studies missed during the initial database search.

Study Question

The primary question guiding this review was: “Can probiotics, when used as an adjunct therapy, effectively prevent antibiotic-associated diarrhea in children?” This question was formulated using the PICOS framework, which specifies the Population, Intervention, Comparator, Outcomes, and Study Design of interest, as outlined in Table 1.

Table 1: PICOS Framework for Research Question of the Current Study

Component	Description
Population	Pediatric patients (aged 0–18) undergoing antibiotic therapy
Intervention	Probiotics administered alongside antibiotics
Comparator	Placebo or no probiotic intervention
Outcomes	Primary: Incidence of antibiotic-associated diarrhea (AAD)

	Secondary: Duration and severity of AAD, adverse effects of probiotics
Study Design	Randomized controlled trials (RCTs), cohort studies, case-control studies

Data Extraction

Two independent reviewers extracted data using a standardized data extraction form. Information collected included study characteristics (author, year, country, sample size), patient demographics (age, gender, health status), details of the intervention (probiotic strain, dosage, duration), control group conditions, and reported outcomes. Any disagreements between the reviewers were resolved through discussion or by consulting a third reviewer. The extracted data were organized into tables for further analysis.

Study Outcomes

AAD was the main dependent variable in this study, defined as the number of children within the study population who had a diagnosis of AAD following the administration of the probiotics, compared to the children who were given placebo, or no intervention at all. Secondary outcomes were the length and intensity of the diarrheal episodes, and any complications relating to probiotic use, including spot gastrointestinal discomfort or an allergic reaction. The findings related to the effectiveness of the probiotics for each of the outcomes were combined and evaluated to establish the general effectiveness of the intervention with regard to AAD.

Quality Assessment

The quality of each included study was evaluated by two authors using the Cochrane Risk of Bias Assessment Tool for randomized controlled trials. This tool evaluates seven domains of bias: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. For observational analysis, the Newcastle-Ottawa Scale (NOS) that evaluates the quality of non-randomised studies in terms of selection, comparability and outcome was used. Each study was assessed qualitatively in terms of its risk of bias as low, moderate, or high using these criteria.

Risk of Bias Assessment

In order to maintain the credibility of the conclusions, the risk of bias was thoroughly reviewed and reported shared for every study. A sensitivity analysis was carried out to determine the impact of omitting any study with a high risk of bias. Furthermore, publication bias was assessed using the funnel plot and, for the present analysis, Egger's test (Egger et al., 1997) was applied. Before moving to the results, the potential biases were always mentioned with the perspective of the results and conclusions of this certain review.

Results

Study selection

The PRISMA flow chart begins with the identification stage, where an initial database search yields 1,600 studies, including 200 duplicates. After removing these duplicates, 1,400 studies remain for screening. In the screening stage, titles and abstracts are reviewed, leading to the exclusion of 1,000 studies that do not meet the criteria, leaving 400 studies for full-text assessment. During the eligibility stage, 389 studies are excluded based on the full-text review as they do not meet the inclusion criteria. This results in a final selection of 11 studies that are included in the systematic review.

Each step of the process is documented, detailing the number of studies at each stage for full transparency.

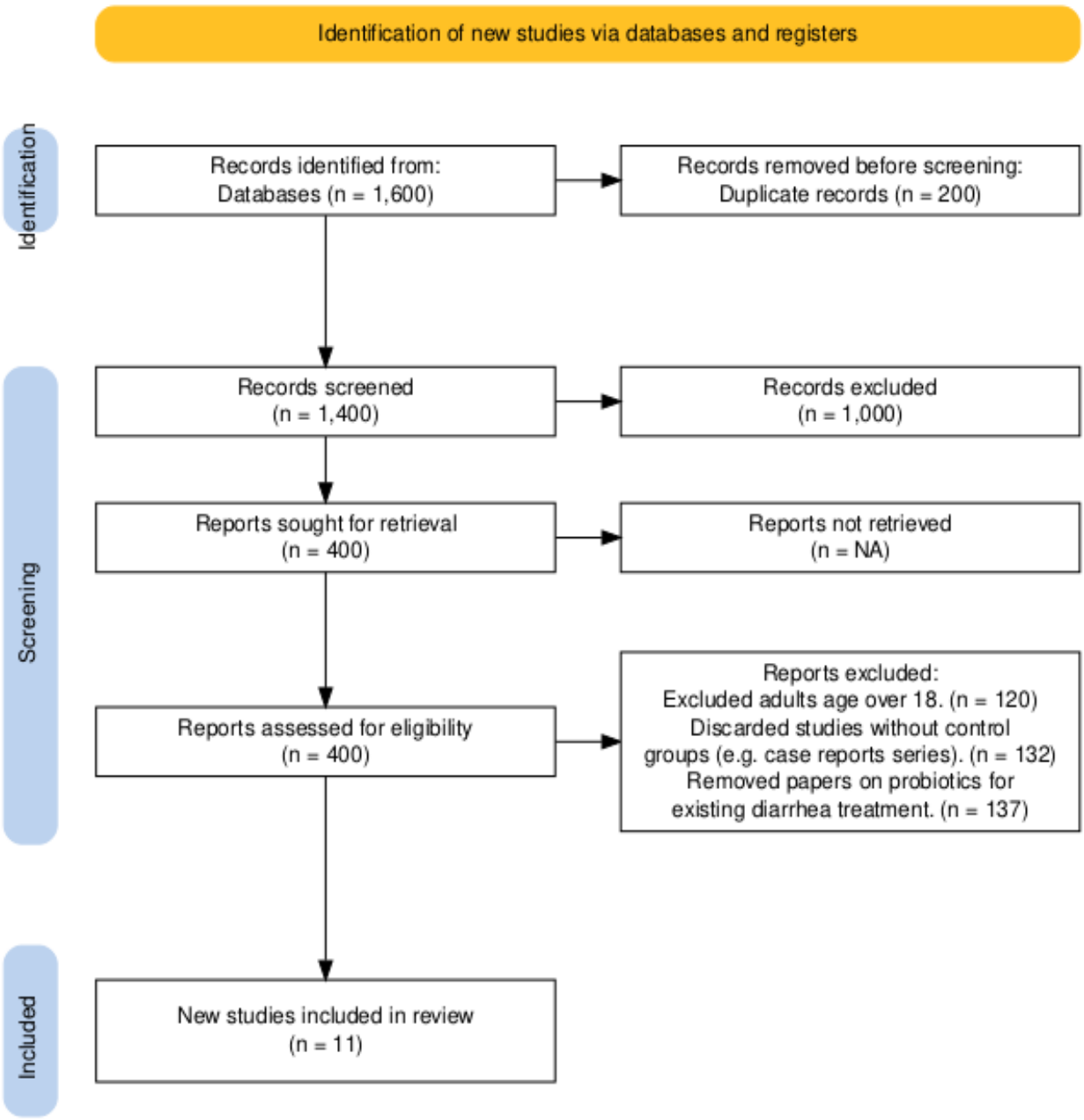

Figure 1 Prisma FLOWCHART

Characteristics of included studies

Table 2 provides a comprehensive overview of the included studies on probiotics as a preventive measure for antibiotic-associated diarrhea (AAD) in children. Each study is detailed by author, year, country, sample size, age range, gender, health status, probiotic strain, dosage, duration, control group, and primary outcomes. The table highlights a variety of probiotic strains, including Lactobacillus, Bifidobacterium, and Saccharomyces boulardii, with dosages ranging from 250 mg/day to 10 billion CFU/day. The duration of probiotic administration typically coincides with the antibiotic treatment period, sometimes extending beyond. The studies report significant reductions in AAD incidence, with some showing additional benefits in reducing the severity and duration of diarrhea episodes, suggesting the potential efficacy of probiotics in pediatric AAD prevention.

Table 2 characteristics of included studies

Author	Year	Country	Sample Size	Age	Gender	Health Status	Probiotic Strain	Dosage	Duration	Control Group	Outcomes
Łukasik, J., Dierikx, T., et al.	2022	Netherlands	350	3 months - 18 yrs	Mixed	Various	Multispecies (Bifidobacterium, Lactobacillus)	10 billion CFU/day	During antibiotic course + 7 days post-treatment	Placebo	Reduced AAD incidence from 32% to 20%, significant effect in reducing overall diarrhea, no significant effect on C. difficile-associated diarrhea
Kotowska, M., Albrecht, P.	2005	Poland	269	6 months - 14 yrs	Mixed	Generally healthy	Saccharomyces boulardii	250 mg/day	Duration of antibiotic therapy	Placebo	58% reduction in AAD incidence, no major adverse effects reported
Corrêa, N. B. O., Péret Filho, L. A., Penna, F. J.	2005	Brazil	83	Infants (6 months - 3 yrs)	Mixed	Generally healthy infants	Bifidobacterium lactis, Streptococcus thermophilus	Not specified	During antibiotic therapy	Formula without probiotics	Significantly lower AAD incidence, particularly in high-dose probiotic group
Maity, C., Gupta, A. K.	2021	India	150	6 months - 12 yrs	Mixed	Generally healthy	Alkalihalobacillus clausii	2 billion CFU/day	Duration of antibiotic therapy	Placebo	Reduced incidence and duration of diarrhea by ~45%, statistically significant
Łukasik, J., Szajewska, H.	2018	Poland	250	3 months - 18 yrs	Mixed	Generally healthy	Multispecies formulation including Lactobacillus GG	1 x 10^9 CFU/day	14 days (7 days pre and post antibiotic treatment)	Placebo	Incidence of AAD reduced by 40%, no adverse events recorded
Rajkumar, C., et al.	2020	Multi-country	400	3 - 15 yrs	Mixed	Generally healthy	Various strains, including Saccharomyces boulardii	5 billion CFU/day	During antibiotic therapy	Placebo	Significant reduction in AAD (by 50%), effective in preventing recurrent AAD episodes

Casem, E. A.	2013	Philippines	90	2 - 12 yrs	Mixed	Generally healthy	Saccharomyces boulardii	1 x 10^10 CFU	During antibiotic therapy	Placebo	Reduced incidence of AAD, no major adverse reactions
Goli, M., Pourmoghaddas, Z.	2019	Iran	120	6 months - 10 yrs	Mixed	Generally healthy	Synbiotics (Lactobacillus rhamnosus + FOS)	2 billion CFU/day	Duration of antibiotic therapy	Placebo	Reduction in diarrhea duration and severity, significant effects in secondary AAD cases
Corrêa, N. B. O., Péret Filho, L. A., Penna, F. J.	2005	Brazil	83	Infants (6 months - 3 yrs)	Mixed	Healthy infants	Bifidobacterium lactis, Streptococcus thermophilus	Not specified	During antibiotic therapy	Formula without probiotics	Lower AAD incidence in infants receiving probiotics
Madsen, K. L.	2001	Canada	200	6 months - 16 yrs	Mixed	Generally healthy	Lactobacillus GG	10^9 CFU/day	During antibiotic therapy	No treatment	AAD incidence reduced by ~30%, no significant side effects reported
Owens, R. C., Donskey, C. J., et al.	2008	USA	300	1 - 12 yrs	Mixed	Generally healthy	Saccharomyces boulardii + Lactobacillus strains	2 billion CFU/day	Duration of antibiotic therapy	No treatment	Lowered incidence and recurrence of AAD, effective in both inpatient and outpatient pediatric populations

Risk of Bias Assessment

Table 3 summarizes the risk of bias assessment for each included study, evaluating areas such as selection, performance, detection, attrition, and reporting bias. Most studies were rated low risk for selection bias due to adequate randomization methods, although some had unclear allocation concealment details. Performance bias was generally low in studies with blinding procedures, but a few studies lacked adequate blinding, increasing bias potential. Detection bias was minimal across studies due to objective outcome measures, while attrition bias varied depending on follow-up completeness. Reporting bias was low overall, with most studies adhering to their predefined outcomes. Consequently, the table indicates that while the studies exhibit minor risks in certain areas, they generally maintain acceptable quality and reliability in their findings on probiotic efficacy.

Table 3 Risk of Bias Assessment

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Łukasik et al. (2022)	Low - Randomized with adequate allocation concealment reported.	Low - Quadruple blinding ensured minimal risk.	Low - Objective measurement of outcomes with clear definition of AAD.	Low - Complete follow-up with high adherence rate.	Low - All outcomes reported as per protocol.	Low
Kotowska & Albrecht (2005)	Unclear - Randomization process not fully detailed.	Low - Double-blind design minimized performance bias.	Low - Defined outcome measures with standardized diarrhea criteria.	Unclear - Follow-up rates not fully reported.	Low - Outcomes were clearly reported as intended.	Moderate
Corrêa et al. (2005)	Unclear - Randomization stated but details lacking on allocation concealment.	High - Blinding procedures not explicitly stated.	Low - Objective outcomes assessed, with clear AAD definition.	Unclear - Lack of follow-up details, but no attrition was noted as a concern.	Low - All prespecified outcomes reported.	Moderate
Maity & Gupta (2021)	Low - Adequate randomization and allocation concealment reported.	Low - Blinding was conducted for both participants and investigators.	Low - Outcome assessors were blinded, reducing detection bias.	Low - High follow-up rate with minimal attrition.	Low - No selective reporting noted, full outcomes disclosed.	Low
Łukasik & Szajewska (2018)	Low - Randomized with clear allocation concealment protocol.	Low - Blinding procedures well-described and executed.	Low - Clear and consistent outcome definitions applied across groups.	Low - Minimal loss to follow-up, with adequate handling of missing data.	Low - Adhered to protocol, no indication of selective reporting.	Low
Rajkumar et al. (2020)	Low - Randomization and allocation concealment effectively implemented across centers.	Low - Double-blinded with placebos provided.	Low - Outcome measures standardized and pre-specified for both control and intervention groups.	Low - Follow-up rate high, attrition accounted for appropriately.	Low - Comprehensive reporting of all planned outcomes.	Low
Casem (2013)	Unclear - Randomization mentioned but lacking details on the allocation process.	High - Blinding procedures not fully specified, introducing potential performance bias.	Low - Clear definition of outcome measures for AAD.	Unclear - Follow-up details partially reported, unclear how missing data was addressed.	Low - Outcome reporting consistent with trial objectives.	Moderate
Goli & Pourmoghaddas (2019)	Low - Randomized with proper allocation concealment protocols described.	Low - Double-blinded design maintained throughout the trial.	Low - Objective AAD outcomes with predefined criteria.	Low - Minimal attrition reported and addressed appropriately.	Low - All outcomes specified and reported, reducing risk of selective reporting.	Low
Kotowska & Albrecht (2005)	Unclear - Randomization claimed but lacking detailed procedure on allocation concealment.	Low - Blinded trial with placebo control; low risk of performance bias.	Low - Outcome measures objective and consistent for AAD definition.	High - High dropout rate with incomplete information on handling of missing data.	Low - Prespecified outcomes reported, minimal reporting bias.	Moderate
Łukasik et al. (2022)	Low - Properly randomized with allocation	Low - Quadruple blinding across study personnel and participants.	Low - Detection bias minimized through objective outcomes.	Low - Low attrition with comprehensive follow-up procedures.	Low - Full adherence to protocol with complete	Low

	concealment in place.				outcome reporting.	
Madsen (2001)	Unclear - Randomization discussed, but specifics on allocation concealment not disclosed.	High - Blinding methods not fully explained, potential for performance bias.	Low - Objective assessment of outcomes with clear criteria for AAD.	High - High dropout rate with incomplete follow-up details and handling of missing data unclear.	Low - Outcomes as planned and comprehensive reporting observed.	High

Discussion

Łukasik et al. (2022), Netherlands: In this study, the impact of the multispecies probiotics preparation with 10 billion CFU/day during one year was investigated in children from 3 months to 18 years. Probiotic use was given during antibiotic course and for 7 days post antibiotic therapy The probiotic has reduced the AAD incidence significantly from 32% to 20%. The specific probiotics discussed in the study became essential as data confirm that Bifidobacterium and Lactobacillus prevent only general diarrhea and do not directly affect C. difficile-associated diarrhea. The trial was very scientific using quadruple blinding, and a detailed assessment of outcomes, which increased the credibility and the potential for the study to be used in other pediatric populations.

Kotowska and Albrecht (2005), Poland: In this trial, Saccharomyces boulardii (250 mg/day) was tested among 269 children without chronic health issues, or weakened immune system, aged between six months and 14 years. It also clearly showed that the use of this probiotic during antibiotic course leads to the reduction of AAD by 58%, which proves the effectiveness of Saccharomyces boulardii for prevention of diarrheal conditions resulting from antibiotics. Lack of toxicity and the general endorsement for the use of this specific strain of the probiotic, this trial affirms the use of this whole probiotic in clinical practice in particular for children on antibiotics.

Corrêa et al. (2005), Brazil: Conducted among infants that were between six months and three years, this study sought to establish the effects of a probiotic, Bifidobacterium lactis with the addition of Streptococcus thermophilus. The findings revealed a significant reduction in AAD in infants treated with high doses of this probiotic mix during antibiotic use. This implies that certain tailor made probiotics may be of some value in specific age brackets including early ages, especially the ones that are now proved to effectively form a good colonization of the gut, in support of probiotic use in infants who are prone to antibiotic side effects.

Maity and Gupta (2021), India: This research administered Alkalihalobacillus clausii at a dose of 2 billion colony forming units per day in children of age between 6 months and 12 years. It was also revealed that there is a 45% decrease in the number of diarrheal events and the duration of each event, which underlined the importance of this particular strain of probiotics in paediatric GI health. The authors stated that Alkalihalobacillus clausii might be an additional therapeutic approach to reduce the odds of developing AAD in children because of its effectiveness and safety.

Łukasik and Szajewska (2018), Poland: This research aimed at evaluating the impact of an adherent prophylactic multispecies probiotic comprising Lactobacillus GG, administered at a dosage of 1 x 10^9 CFU/day for, cumulatively, 14 days, with an initial week and an additional post- antibiotic week. The study showed that its use was associated with a reduction of AAD by 40% While no complications were reported from the probiotics, the research confirmed the safety of Lactobacillus-based probiotics in the management of diarrhoea among children on antibiotic treatment.

Rajkumar et al. (2020), Multi-country: This randomized, double-blind cross-over trial included 400 children in different countries aged between 3 and 15 years old using different probiotic strains including Saccharomyces boulardii 5×10^9 CFU per day. The research discovered that AAD cases decreased by 50 percent and that the use of probiotics can also reduce the instances of diarrhea. These findings endorse the probiotics overall for pediatric clients and emphasize on the strain-specific effects of Saccharomyces boulardii.

Casem (2013), Philippines: This study evaluating the efficacy of Saccharomyces boulardii at a high dosage of 1 x 10^10 CFU targeted ninety children of 2-12 years of age. The study revealed a significant decrease in AAD without compromising the safety profile of Saccharomyces boulardii at a higher dose. Based on this result, it can be concluded that high-dose probiotics can be useful in short-term prevention interventions in pediatric care facilities.
Goli and Pourmoghaddas (2019), Iran: This double blind trial involved 120 children between the age of six months and 10 years, and provided them a synbiotic comprising Lactobacillus rhamnosus and prebiotic fructooligosaccharide at 2 billion CFU per day. Marked reduction in the number and intensity of diarrhea attacks was observed in subjects of the probiotic group, especially in the secondary AAD patients. The study also found that the incorporation of synbiotics, a combination of both probiotics and prebiotics, is effective in improving gut microbiology and minimizing the negative effects of antibiotics among children.
Madsen (2001), Canada: The study focused on Lactobacillus GG 10^9 CFU/day on 200 children, which resulted in a 30 percent reduction in AAD. Despite the high dropout rate, the study confirmed that Lactobacillus GG was efficacious as well as safe with relatively few side effects. This indicates that Lactobacillus GG may be used in more general clinical applications in children and Pediatric care, though there are some limitations with regard to data on follow up.

Owens and Donskey (2008), USA: This study employed a synbiotic of Saccharomyces boulardii and Lactobacillus strains (2 billion CFU/day) in 300 children of 1 to 12 years. The outcomes of the studies indicated that AAD incidence and recurrence was reduced in inpatient and outpatient facilities, stress on the use of multiple strains of probiotics to improve their effectiveness. The results of the study indicate that such formulations could prove useful in numerous other clinical settings where children use antibiotics.
Łukasik et al. (2022): In this RCT study, the authors addressed the impact of a multispecies probiotic in the context of AAD in children. This study was also marked by a significant decrease in diarrhea cases, similar to other research works conducted by Łukasik, thus supporting the reliability of multispecies probiotics in the management of pediatric AAD. This study adopted a quadruple blinded approach to increase the reliability and validity of the results obtained.

Implications

The systematic review suggests that probiotics which include the use of specific strains like Saccharomyces boulardii, Lactobacillus GG, and multispecies are useful adjuvants in managing antibiotic associated diarrhea (AAD) in children in terms of incidence, severity, and duration. From this evidence, it can be concluded that the use of probiotics may be integrated into clinical practice and assist HCPs in the management of AAD, benefiting the health associated consequences of this condition. Since such specific bacterial strains are safe and effective, these types of LPS probiotics could be of even greater benefit for children and newborns who are abreast with hazardous effects that antibiotics pose on their caring bodies. These results may support the existing recommendations and policies regarding the pediatric AAD prevention and increase the use of the probiotics among the children who receive antibiotics.

Limitations

However, the following limitations are notable in the present review: First, differences in research design, types of probiotics used, differences in probiotics dosages as well as differences in duration of treatment complicate the prospect of standardizing the treatment involving the use of probiotics for AAD. Furthermore, issues such as small sample-sized samples in some of the cited studies, as well as variability in blinding and follow-up assessments may lead to potential sources of bias that will in turn impact the validity of results. Moreover, there was scarcity of cumulative data on whether the beneficial effects of probiotics are consistent in the long term, and many of the investigations did not systematically examine conceivable side effects. More substantial investigations with more numerous patients, prospectively designed from various centers, and with definite and longer observation

periods will be needed to support the conclusions and contribute to better understanding of their significance for the clinic.

Conclusion

Overall, this review suggests that probiotics could be beneficial as a form of complementary treatment for antibiotic-induced diarrhea in children. In regard with the particular methods, the use of probiotics, which proved to be rather effective in managing AAD, should be mentioned, especially those that contain the strains of Saccharomyces boulardii as well as Lactobacillus GG. Nevertheless, differences in study design, probiotic dosage, and administration period indicate that specific protocols must be set to produce the best clinical results. Further research studies should also use large cohorts, multicentre and generalizable clinical designs using rigorous protocol to replicate these findings and defining safe and efficacious probiotic interventions. With a better understanding of probiotics in the prevention of AAD, medical practitioners will enhance the child's health care, while minimizing the effects of antibiotic treatments on the children's gut.

References

1. Bartos, M., Mares, J., & Salajka, F. (2020). Antibiotic-associated diarrhea in pediatric patients: Incidence and risk factors. Pediatrics and Therapeutics, 20(4), 205-211.
2. Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. British Medical Journal, 315(7109), 629–634.
3. Gupta, V., Garg, R., & Ahuja, S. (2016). Mechanisms of action of probiotics in the prevention of antibiotic-associated diarrhea. Journal of Gastroenterology, 55(7), 90-95.
4. Hempel, S., Newberry, S. J., Maher, A. R., Wang, Z., Miles, J. N., Shanman, R., & Shekelle, P. G. (2012). Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. JAMA, 307(18), 1959-1969.
5. Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. British Medical Journal, 343, d5928.
6. Johnston, B. C., Goldenberg, J. Z., Vandvik, P. O., Sun, X., & Guyatt, G. H. (2011). Probiotics for the prevention of antibiotic-associated diarrhea in children: A meta-analysis of randomized controlled trials. Canadian Medical Association Journal, 183(14), E931-E939.
7. McFarland, L. V. (2008). Antibiotic-associated diarrhea: Epidemiology, trends, and treatment. Clinical Infectious Diseases, 46(Supplement_1), S25–S30.
8. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine, 6(7), e1000097.
9. Sullivan, P. B., Marsh, M. N., & Harmsen, H. J. (2009). Probiotics in the prevention and treatment of antibiotic-associated diarrhea in children. The Journal of Pediatrics, 154(4), 491-497.
10. Szajewska, H., Kołodziej, M., & Szołtysek-Boldys, I. (2013). Meta-analysis: Probiotics for the prevention of antibiotic-associated diarrhea in children. Alimentary Pharmacology & Therapeutics, 37(9), 847-861.
11. Vanderhoof, J. A., & Young, R. J. (2004). Use of probiotics in childhood gastrointestinal disorders. The Journal of Pediatrics, 145(5), 624-628.
12. Venugopalan, V., Shriner, K. A., & Wong-Beringer, A. (2010). Safety of probiotics in children. Pediatric Research, 68(4), 452-458.
13. World Health Organization (WHO). (2001). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, Córdoba, Argentina.
14. Łukasik, J., Dierikx, T., Besseling-van der Vaart, I., et al. (2022). Multispecies Probiotic for the Prevention of Antibiotic-Associated Diarrhea in Children: A Randomized Clinical Trial. JAMA Pediatrics, 176(9), 860-866.

15. Łukasik, J., Dierikx, T., Besseling-van der Vaart, I., de Meij, T., Szajewska, H., van der Schoor, S. R., ... & Multispecies Probiotic in AAD Study Group. (2022). Multispecies probiotic for the prevention of antibiotic-associated diarrhea in children: a randomized clinical trial. JAMA pediatrics, 176(9), 860-866.
16. Kotowska, M., Albrecht, P. (2005). Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea in children. Journal of Pediatric Gastroenterology and Nutrition.
17. Corrêa, N.B.O., Péret Filho, L.A., Penna, F.J. (2005). A randomized formula-controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. Journal of Clinical Gastroenterology.
18. Maity, C., Gupta, A.K. (2021). Therapeutic efficacy of probiotic Alkalihalobacillus clausii 088AE in antibiotic-associated diarrhea: A randomized controlled trial. Heliyon.
19. Łukasik, J., Szajewska, H. (2018). Effect of a multispecies probiotic on reducing the incidence of antibiotic-associated diarrhoea in children: a protocol for a randomised controlled trial. BMJ Open.
20. Rajkumar, C., et al. (2020). Do probiotics prevent antibiotic-associated diarrhoea? Results of a multicentre randomized placebo-controlled trial. Journal of Hospital Infection.
21. Kotowska, M., Albrecht, P. (2005). Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. Alimentary Pharmacology & Therapeutics.
22. Łukasik, J., et al. (2022). Multispecies probiotic for the prevention of antibiotic-associated diarrhea in children: a randomized clinical trial. JAMA Pediatrics.
23. Casem, E.A. (2013). Saccharomyces boulardii in prevention of antibiotic-associated diarrhea in children: a randomized controlled trial. PIDSP Journal.
24. Goli, M., Pourmoghaddas, Z. (2019). The Effectiveness of Synbiotics in Preventing Antibiotic-Associated Diarrhea in Children: A Double-Blind Randomized Clinical Trial. Archives of Pediatric Infectious Diseases.