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Probiotics for the prevention of antibiotic associated diarrhea: a systematic review

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Probiotics for the prevention of antibiotic associated diarrhoea: a systematic review

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

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West Midlands Health Technology Assessment Collaboration (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility) of the intervention.

Conflicts of interest

The authors all declare that they have no conflicts of interest.

Contribution of the authors

This review was planned by RST and MC with assistance from all authors. IS developed the search strategy, undertook the searches, appraised the articles, and extracted the data. IS analysed the data with the help of RST and MC. Writing up the report was principally done by IS with input from all members of the review team. In particular, RST advised on systematic review methods and DJW advised on important clinical aspects of antibiotic associated diarrhoea and the current service provision.

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West Midlands Regional Evaluation Panel

Recommendation

Recommended – but a definitive RCT is needed to take forward this important research subject

Anticipated expiry date:

The advice contained in the report is current until 2010 or until a definitive RCT is reported.

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FIGURES

ABBREVIATIONS

AAD	Antibiotic associated diarrhoea
CDAD	Clostridium difficile associated diarrhoea
CI	Confidence interval
NNT	Number needed to treat
OR	Odds ratio
RR	Relative risk
SE	Standard error

1. Summary

Background

Antibiotic associated diarrhoea (AAD) is a potential side effect of antibiotic treatment, due to disturbance of the gastrointestinal flora. Infection with Clostridium difficile, a gram-positive toxin producing bacterium can lead to more severe diarrhoea, which can result in pseudo membranous colitis and in some cases death. It is estimated that between 5 to 39% of patients receiving antibiotic treatment develop diarrhoea, generating immense costs for the health care system. There were 43682 cases of C. difficile in the UK in 2004, having a large impact on the health care system; furthermore, considering the severe health impacts and frequent recurrences, these figures are worrying. There are no clear national guidelines for the treatment of AAD. Although the treatment of C. difficile associated diarrhoea with oral metronidazole and vancomycin is effective, recurrences do still occur.

Probiotics are non-pathogenic bacteria or yeast, which have a beneficial influence on the gastrointestinal micro flora. A number of studies have shown that probiotics can prevent the development of AAD in a variety of populations and settings. Two previous systematic reviews have addressed the question of the preventive impact of probiotics on AAD. However, these reviews are out of date and did not address the impact of probiotics on C. difficile.

Aims

To assess the clinical effectiveness and cost effectiveness of probiotics for the prevention of AAD.

Methods

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, DARE, Science Citation Index and NHS EED were searched for relevant studies. Randomised controlled trials were included that examined the effect of probiotics on the incidence of AAD and C. difficile. Trials were included if they compared any from of antibiotic treatment supplemented with probiotics compared to placebo, no therapy or active comparator. There were no restrictions on study population age or the setting of the trial. Studies were excluded if they examined the effect of probiotics as treatment for diarrhoea. Data on study and patient characteristics, outcomes, direction of effect and quality were extracted by one reviewer and checked by a second reviewer. Key trial quality criteria were assessed using standard checklists. Numerical pooling of data was performed where possible and a random effect

meta-analysis model applied where there was evidence of statistical heterogeneity. Statistical heterogeneity across studies was explored with stratified meta- analyses and meta-regression

Identified studies

A total of 23 randomised controlled trials were included Trials were conducted between 1977 and 2005, across a variety of populations, settings and assessed different types of probiotics and antibiotics.

Clinical Effectiveness

The results of this review suggest that probiotics can significantly decrease the incidence and duration of AAD by 52% (95% CI: 37% to 63%) and by 0.6 days (95% CI: 0.04 to 1.11) respectively. The benefit of probiotics is found in the comparison with placebo or no treatment (RR=0.48, 95% CI 0.37 – 0.63, NNT=8) However, the incidence of AAD did not differ between probiotic and active comparator groups (RR: 1.45, 95% CI: 0.91 to 2.30). Furthermore, the incidence of C. difficile associated diarrhoea was reduced by 46% (95% CI: 14%-76%, NNT= 36). However, colonisation by C. difficile did not differ between the probiotic and placebo groups (RR: 0.95; 95% CI: 0.66-1.36).
Probiotics have no effect on the severity and time to developing symptoms of diarrhoea. There were no reports with adverse events with probiotics.

Cost effectiveness

No cost effectiveness studies were found and there was little information on the potential costs of probiotics. One study quoted a cost of £3.64 per treatment course of two weeks at 2002 prices (currency conversion Euro to £ for 2005).

Conclusion

Probiotics appear to be effective in the prevention of AAD including C. difficile and have little or no harmful effects. Given the low cost of a course of treatment and their potential to reduce downstream healthcare resource utilisation, probiotics may well be cost saving.

2. Introduction

Antibiotic associated diarrhoea (AAD) has been recognised as an important side effect of antibiotic treatment since 1950 and the evolution of broad-spectrum antibiotics. AAD was considered as mild, until patients who were treated with Clindamycin presented with pseudo membranous colitis. In 1978 Clostridium difficile had been identified as the agent for pseudo membranous colitis and from that time point onwards, research has been widely carried out leading to a better understanding of the mechanisms of AAD.[1] C. difficile-associated diarrhoea (CDAD) in particular can have major impacts in terms of health impact for the patient and corresponding impact on the health care system. Probiotics are non-pathogenic bacteria or yeast, which have a beneficial influence on the gastrointestinal micro flora. Increasing knowledge about the aetiology of AAD and the working mechanisms of probiotics indicated the possible link and clinical benefit that could be achieved. Since the 1970s, a number of studies have been conducted to determine the preventive as well as the therapeutic effect of probiotics on AAD and C. difficile associated diarrhoea.
Although two systematic reviews have shown the benefit of probiotics on AAD, a number of uncertainties remain.

- What is the magnitude of the effect of probiotics in preventing AAD and in particular the effect on *C. difficile* associated diarrhoea?
- What patient groups should receive probiotics as supplements to their antibiotic treatment?
- Which, if any, particular antibiotics are best suited to probiotic supplementation?
- Is there a relative advantage of one probiotic versus others?
- Is there a clinical effective dosage of probiotics, therefore a threshold dosage, and is the timing of probiotic administration important?
- What is the cost effectiveness of probiotics?

3. Background

3.1 Underlying health problem

AAD is clinically defined as three or more mushy or watery stools per day, following and/or during antibiotic treatment.[2] The antibiotics disrupt the equilibrium of the normal gut flora by altering some of the physiological functions of the micro flora.[1] Results of this disturbance are changes in colonic carbohydrate digestion, decreased short-chain fatty acid absorption and osmotic diarrhoea.[3] Furthermore, the resistance to colonization can be influenced, enabling pathogenic organisms such as *C. difficile* to emerge.[3] Although *C. difficile* is the most prominent pathogenic cause of AAD, other reported infectious causes include *Clostridium perfringens*, *Klebsiella oxytoca*, *Candida species* and *Staphylococcus aureus*.[2]

Most of the presentations of clinical AAD are uncomplicated, but it can also be associated with colitis including fever, vomiting, abdominal pain, hypoalbuminemia and leukocytosis.[4] It occurs in hospitalised and outpatient settings and in most cases the discontinuation or replacement of the inciting antibiotic can be effective.[1] One of the major risk factors for the occurrence of AAD is the age of the patient. Patients younger than 6 years and older than 65 years are reportedly at higher risk.[1,2] AAD can be related to nearly all antibiotics, particularly if the anaerobic intestinal flora forms part of their antibacterial spectrum. The exceptions are vancomycin and aminoglycosides.[1 5] (see Appendix page 55)

The more severe cases of AAD are especially associated with *C. difficile* infection; the treatment therefore may require additional antibiotics such as metronidazole or glycopeptides to treat the diarrhoea.[1]

C. difficile is a Gram-positive anaerobic bacterium that, in its infectious form, produces two toxins, an enterotoxin A and a cytotoxin B, which causes colitis. It is likely to cause a spectrum of largely but not exclusively hospital-acquired diseases, often consequent to antibiotic exposure. The spectrum of disease ranges from asymptomatic colonization of the intestinal flora, diarrhoea, colitis, and pseudo membranous colitis to death.[6] The produced toxins inflame the colon, which results in an influx of white blood cells. In more severe cases, the toxins damage the tissues of the inner lining of the colon. The mixture of dead tissues and white blood cells (pus) appears like a white membranous patch covering the inner lining of the colon. This form of severe colitis is called pseudo membranous, as the patches appear like membranes, but are not true membranes.[7,8] *C. difficile* associated disease is the term used to describe the symptomatic manifestations due to the colonisation with *C. difficile*, such as i.e. diarrhoea or colitis, but not the asymptomatic carriage. The antibiotics, which are especially related with *C. difficile* associated diarrhoea, are cephalosporins and clindamycin.[9] Colonisation with *C. difficile* is not necessarily associated with diarrhoea, only if toxins A

and/or B are detectable in the faeces and diarrhoea is present, clinical steps have to be undertaken. Symptoms can occur as mild diarrhoea, similar to the diarrhoea found in general AAD where no specific therapy is needed for recovery.[5] However, nearly all cases of colitis and pseudo membranous colitis are associated with a *C. difficile* infection.[9]

The most important complication with *C. difficile* associated diarrhoea is the frequency of recurrences, which leads to increased antibiotics consumption, prolonged stays in hospitals and other medical complications.[4] The recurrence of *C. difficile* infections has been an increasing problem in recent years, the probability reaching up to 47% of patients treated with oral metronidazole.[10,11] In recurrent forms of pseudo membranous colitis, a severe form of *C. difficile* associated diarrhoea; the mortality rates increase significantly and range between 10% to 38%.[4,5,12]

3.2 Epidemiology and burden of disease

Antibiotic associated diarrhoea: general considerations

Data on the incidence or prevalence of AAD in the UK are lacking. Nevertheless, data on the number of antibiotic prescriptions in the UK is available which can be used to at least estimate the extent of the problem. The incidence of AAD differs with the antibiotic used and has been reported to vary from 5% to 39% of patients receiving antibiotic treatment.[1,4,12] Based on the number of antibiotic prescriptions in the UK in 2000 has been 36,9 million, the number of antibiotic associated diarrhoeic events ranges somewhere between 1,8 million to 14,4 million events per year.[13 14]

***C. difficile* associated diarrhoea:**

C. difficile infection is probably responsible for about 10% to 20% of all AAD and is currently one of the most common nosocomial infections.[5,12]The number of reported *C. difficile* infections increased from 20,556 reports in 2000 to 28,819 in 2002 in England, Wales and Northern Ireland.[6] It is not clear how much of the increase represents increased ascertainment and increases in number of contributing laboratories. Nevertheless, in 2004 there were 43682 reported cases in the UK.[15] These numbers demonstrate the importance for preventive approaches, as *C. difficile* associated diarrhoea has considerable impact on health, health care consumption and costs regarding the health problem of AAD. In contrast to general AAD, younger age (< 6-years) is not related with a higher risk of *C. difficile* associated diarrhoea. However, much higher rates of detected *C. difficile* associated diarrhoea occur in the elderly. In 2002 eighty-two per cent of all reported cases in England, Wales and Northern Ireland concerned patients aged 65 or over.[6] In a Swedish study 42% of cases of *CDAD* presented in the community, half of whom had no history of hospitalisation in

the previous month, and an Irish study reported that 11% of cases presenting had no history of hospitalisation in the previous 60 days.[16,17]

3.3 Current service provision

AAD is in most patients associated with mild symptoms that are self-resolving and are managed by cessation of the antibiotic therapy or the replacement with a low risk antibiotic. Only when more severe diarrhoea is observed, including *C. difficile* associated diarrhoea, is an additional antibiotic to treat the *Clostridium bacterium* encouraged (see appendix page 56).[1,5] Generally, patients older than 65 who develop diarrhoea are tested for *Clostridium* (*difficile*). Diarrhoeal samples in younger patients are tested only if there are additional risk factors present or the clinician has reasonable suspicion for the diagnosis.
There are several diagnostic tools available, but the most sensitive one is by culturing stool on selective medium. It is important to be able to detect toxin A and toxin B to make the clinically important distinction between asymptomatic carriers and the manifestation of the disease. Once the diagnosis *C. difficile* associated diarrhoea is confirmed, the treatment with oral metronidazole or vancomycin is started as they have high rates of efficacy with response rates up to 97 per cent.[9] Although the treatment of *C. difficile* associated diarrhoea and colitis with antibiotics (vancomycin or metronidazole) is effective, recurrences occur in a small number of patients.[2,12]*C. difficile* associated diarrhoea can results in prolonged stays in hospitals and associated diagnostic and treatment costs. Wilcox et al state that the additional costs for *C. difficile* infected patients in a medical ward exceeds £4000 per case.[18] Using the Hospital & Community Health Services (HCHS) Pay & Prices Index this inflates to £5643 for 2005. A prolonged hospital stay of 21 days and resulting additional costs of diagnostics and treatment mainly generated these costs. The costs of recurrences were not included in this calculation.

3.4 Description of new intervention

Probiotics are ‘live organisms which when administered in adequate amounts confer a health benefit on the host’.[19]A single probiotic intervention can include more than one species of bacteria, such as *Bifidobacteria* and *Lactobacilli*, which are both part of the normal human intestinal flora, or yeast such as *Saccharomyces* species.[20] The virulence of probiotics compared to other pathogens that can occur in the intestinal gut flora is very low.

Although the specific mechanisms of how probiotics influence the intestinal flora are not fully understood, it is widely agreed that there is a beneficial effect. Some invoke stimulation of the immune system of the intestinal tract or suppression of the growth of enteric pathogens by competition for nutrients and adherence sites or the production of antimicrobial agents. [1,12,20,21]There have been some reports of severe infections caused by probiotic ingestion, usually in severely ill or immune-suppressed patients. [20]

3.5 Existing systematic reviews on prevention of antibiotic-associated diarrhoea by probiotics

At the outset of this report, a scoping search of the literature was undertaken. This search identified two existing systematic reviews[14,22] The 'bottom line' of both reviews was a beneficial effect of probiotics in the prevention of AAD. However, both emphasize the need for the collection of further data including the cost effectiveness of probiotics. Cremonini et al[14] reported that a pooled relative risk for incidence of AAD across seven studies was 0.40 (95% CI: 0.27 to 0.57) in favour of probiotic treatment over placebo. D'Souza et al[22]found a pooled odds ratio for the incidence of AAD of 0.37 (95% CI: 0.26 to 0.53). Methodological quality of the two systematic reviews was assessed using a modified version of the Oxman and Guyatt scale.[23,24] Quality was expressed as an overall score with a maximum of 18. Both reviews were judged to be of moderate quality. The review by D'Souza scored 11 points and Cremonini scored 15 points. Details of the quality assessment criteria and the scoring are provided in the appendix page 57.

There were other limitations with these systematic reviews:

- Search dates: Both reviews concluded their searches in 2001 and therefore do not include more recently published studies.
- Evidence identified: Both reviews identified 11 trials. However, only 5 trials were common between the two reports. Given that the searches of both reviews were performed at a similar time period and employed similar inclusion and exclusion criteria, the reason for this lack of consistency is unclear.
- Outcomes assessed: Data synthesis and presentation of both reviews was restricted to the prevention of diarrhoeic events. C. difficile associated diarrhoea was not reported.
- Exploration of heterogeneity: Although both reviews identified statistical heterogeneity, no formal exploration of this heterogeneity was undertaken.

4. Aims and objectives of review

The aim of this report was to assess the clinical and cost effectiveness of probiotics in the prevention of AAD.

Specific objectives of the report were:

- To assess the impact of probiotics on the prevention of *C. difficile* associated diarrhoea.
- To explore differences in the effects of probiotics across different patient groups, healthcare settings, different formulations and doses of probiotics

5. Methods for review of clinical effetiveness

5.1 Search strategy

The two previously published systematic reviews were used as source of trials.[14,22] In addition a full bibliographic search for primary and ongoing studies was also undertaken. Details of the databases searched are shown in Table 1, and full details of the search strategies are presented in the appendix pages 59 and 102. Additionally, the citation lists were inspected for further relevant studies. No language restrictions were applied.

Table 1 Bibliographic and other databases searched

Search and date conducted	Databases	Date and year(s) or issue searched
Primary completed and ongoing research (April 2005)	MEDLINE	1966 - April 2005
	EMBASE	1980 – April 2005
	CINAHL	1982 – April 2005
	The Cochrane Central Register of Controlled Trials (CENTRAL)	2005 Issue 2 No date restriction
	NHS Economic Evaluation Database (NHS EED)	No date restriction
	DARE	No date restriction
	Science citation index	
Ongoing research only (May 2005)	National Research Register	2005 Issue 2
	Current controlled trials	20/05/2005
	ISRCTN register	
	ClinicalTrials.gov	20/05/2005
	Current controlled trials meta register	20/05/2005
Updated search (June 2005)	MEDLINE	Updated on 9th of June
	EMBASE	
	The Cochrane Central Register of Controlled Trials (Central)	

5.2 Inclusion and exclusion criteria

Study design

Randomised controlled trials (RCTs), assessing the preventive effectiveness of probiotics for AAD.

Study population

Individuals of any age receiving antibiotic treatment for any indication, including healthy volunteers.

Intervention

Any form of type of probiotic administration.

Comparator

Any comparator without probiotic.

Outcomes

Inclusion of one of the more the following outcomes.

Primary outcome

- Incidence of AAD

Secondary outcomes

- Incidence, duration and time to developing symptoms of AAD
- Incidence of C. difficile infection (only asymptomatic carriage)
- Incidence of C. difficile associated diarrhoea
- Incidence of recurrent C. difficile associated diarrhoea
- Health-related quality of life
- GP visits, hospital admissions and costs
- Serious adverse events (including pseudo membranous colitis and mortality)
- Days of work lost by patient or carer

Studies where excluded where: (1) probiotics were used as a treatment for AAD; (2) studies where the antibiotic treatment of diarrhoea (e.g. *C. difficile* associated diarrhoea) was supplemented with probiotics.

Inclusion and exclusion criteria were applied by a single reviewer (IS).

5.3 Quality assessment strategy

Quality assessment of included studies was performed to identify threats to the internal validity.

A checklist based on the Jadad scale[25] (Appendix page 61) was used to assess the quality of the included trials An overall quality was score calculated based on methods of randomisation, blinding and handling of withdrawals. In addition, concealment and intention to treat analysis were also assessed (see Appendix page 62). Quality was assessed by a single reviewer (IS) and checked by a second (RT or MC).

5.4 Data extraction strategy

A standard data extraction form was developed to extract data on study characteristics, quality and results. Data from all included studies was extracted by a single reviewer and checked by a second. Where due a lack of reporting, there was uncertainty about trial quality or outcomes, the study authors were contacted.

5.5 Review analysis and data synthesis

Results were tabulated according to outcome. Where possible, outcomes were pooled across studies using meta-analysis. Random effects models were used when statistical significant heterogeneity ($P \leq 0.10$) was detected and results were displayed using Forest plots.
Results for dichotomous outcomes were expressed as n/N (number of patients experiencing the event/total of population of patients) and relative risk (RR); continuous outcomes were expressed as the weighted mean.
Funnel plots and inferential tests (Egger and Begg) were used to assess publication bias.
Results for studies with an active comparator and for studies with a placebo comparator are presented separately throughout.

Several of trials reported outcome data at more than one time point. Where no total incidence of diarrhoea was given and it could not clearly be assumed that incidences of later time points were only of new patients, the first time point outcome was included in the general meta-analysis for the incidence of AAD.

Detailed exploration of heterogeneity across trials in the primary outcome (AAD) was undertaken. This included stratified meta-analysis and meta-regression. To analyse the influence of different follow up times a stratified meta-analysis was used. For this analysis, all the recorded time points per study were included and displayed for 1,2, and more than 3 weeks, using forest plots. A test for heterogeneity was used to compare the three strata and examine the predictive value of time on the effect size.

Considering clinical and quality characteristics of the individual studies resulted in 9 *pre hoc* defined meta-regression covariates:

- Setting: Hospital, primary care or experimental
- Age: Children (<18 years), adults (18-65 years), elderly (>65 years) and adults/elderly (>18 years)
- Probiotics type: *S.boulardii, L GG*, Lactinex, Other combinations
- Study quality: Jadad score
- Intention to treat: Yes, no
- Comparator: Placebo (or no therapy), active comparator
- Time: Time point of outcome measurement
- Publication year: <2000, ≥2000
- Adequate study: C ‘adequate’ or ‘inadequate’

Univariate and multivariate meta-regression was undertaken. The covariate ‘comparator’ was analysed separately.

Results are reported as means and 95 percent confidence intervals. All analyses were conducted using Stata version 7.0 (Stata Corp., College Station, Texas, USA) ; MetaWin version 2.0 (Statistical Software for Meta-Analysis, Sinaur Associates, Sunderland, USA) and Comprehensive Meta-Analysis (Biostat, Englewood, USA). Detail of the data manipulation necessary for some trials is described in the appendix page 104.

6. Clinical effectiveness results

6.1 Quantity and quality of identified studies

6.1.1 Quantity of identified studies

The two existing systematic reviews identified a total of 11 trials that were retrieved for further assessment.[26-36] In addition, a total of 849 citations were identified by the bibliographic searches. Following application of inclusion and exclusion criteria and exclusion of duplicate citations, the number of potential studies was reduced to 170. These studies were further assessed and 146 were excluded for a variety of reasons detailed in appendix page 65. A total of, 23 trials were finally included for review. Of these, 10 trials were identified from the previous systematic review, 13 from bibliographic database searches. This process is summarised in Figure 1.
In addition, 2 ongoing trials were identified; further information is listed in appendix page 101.
Details of the 23 included trials are given in appendix page 71.

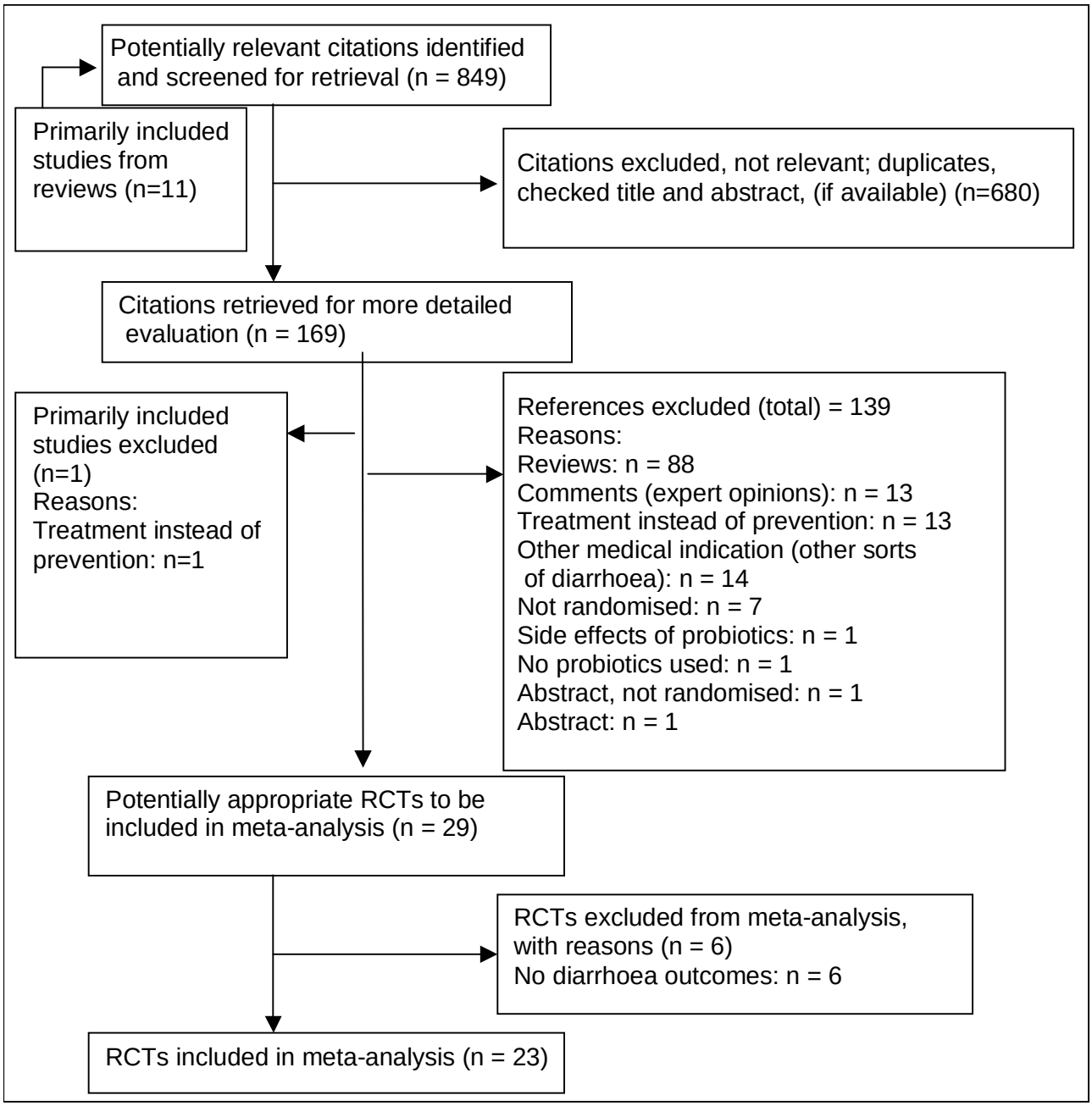


Figure 1 Flow diagram of inclusion process

6.1.2 Study characteristics

The included study characteristics, details of study drugs and the quality of studies are summarized in Table 2 to Table 4.

Sample size

The study size varied between 18 and 616 participants, with a total number of patients of 3365 from all included studies.

Setting

Twelve studies were performed in a hospital setting, 9 in a primary care setting and 2 studies were experimental. Of the 12 hospital based studies, two were also carried out in outpatient clinics or centres. They were nevertheless regarded as hospital-based studies for the statistical analysis.

Study participants & antibiotics used

The age of the study population ranged from some months to over 90 years old.
There were 7 studies in children (<18 years), 7 studies in adults (18-65 years), 3 studies in elderly (>65 years) and 4 studies in adults/elderly (>18 years). The study conducted by Adam[26] included patients older than 15 years; nevertheless it was classified as 'adult population' based on the mean age reported. One study[37], could not be classified because no age of study participants was reported.
There were diverse reasons for antibiotic medication in the studies; mostly it included various forms of infectious disorders but also the eradication therapy for Helicobacter pylori, acute emergencies and even healthy volunteers. The antibiotics used in the trials also show a large variety, but mainly broad-spectrum antibiotics from the categories of the beta-lactams, tetracylines, macrolides and amino-glycosides are being studied (appendix page 55).

Probiotics used

The probiotics used in the included studies can roughly be divided into bacteria and yeasts. All yeast studies used *S. boulardii* as study drug. The use of bacteria as study drug shows a larger variety, including:

- *Lactobacillus acidophilus, L. bulgaricus, L. delbrueckii ssp. bulgaricus, L. GG, L. sporongens,*
- *Bifidobacterium clausii, B. bifidum, B. longum, B. lactis, B. infantis,*
- *Streptococcus salivarius ssp. thermophilus*,

There were 7 studies using *S. boulardii*, 15 studies using one or more forms of bacteria, and 1 study[38], used both bacteria and yeast. The most frequently used bacterial probiotic was *L. GG* used by 6 studies.

Table 3 provides information about the antibiotics and probiotics used. Apart from the broad range of different bacteria used as a probiotic study drug, the dosage varies over the different studies. This is equally the case for bacteria and yeast and shows the difficulties of grouping the probiotic drugs by dosage.

Comparators

Of the 23 studies, only 3 compared the effectiveness of probiotics in preventing AAD with an active comparator, 19 studies had a placebo comparison and only one study had a control group with no other intervention (no placebo). The active comparators were: Diosmectite (dioctahedral smectite, a natural clay with adsorbant properties and claimed to be usefull as an anti diarrhoeal agent), and oligosaccharides in two studies. The oligosaccharides used occur naturally in inulin-rich plants and are poorly digested by the human body, but have been shown to stimulate the growth of Bifidobacteria in vitro and in vivo. The oligosaccharides belong to the class of prebiotics, which are defined as a 'non-digestible' food ingredient that selectively promotes the growth of one, or a limited number of bacteria in the colon.[32,39] Due to their possible active effect on the prevention of diarrhoea, prebiotics were regarded as an active comparator treatment.

Study duration

The study duration is rather short, as can be expected by an event as diarrhoea, which has no long duration of its own. The duration ranges from 6 days to 3 months, but most studies have no longer follow-up than 3 weeks.

Outcomes

The outcomes collected by the studies are also shown in Table 2. Only one study[40], does not report the incidence of antibiotic-associated diarrhoea, for all other studies, this is the most important primary outcome. Ten, 7, and 2 studies collected the Outcomes of Duration, Severity, and Incubation period of AAD respectively. 7 studies report the incidence of *C. difficile* associated diarrhoea, but only 6 studies provide the correct information for meta-analysis. No other outcomes, such as costs, health-related quality of life, days of work, were reported.

Table 2 General characteristics of studies

Author/ Year/ Country	Setting	Study population*	Group size I = Intervention C = Control	Reason for antibiotic medication	Probiotics used	Comparator	Follow up (total study duration)	Outcomes collected**					
								AAD	D	S	TS	CD	CDAD
Adam/ 1977/ France[26]	Primary Care	Adults (older than 15)	I = 199 C = 189	Infections of the upper/lower respiratory tract	S. boulardii	Placebo	Approximately 7 days	√		√			
Gotz/ 1979/ US[29]	Hospital	Adults/Elderly (range 18-88)	I = 36 C = 43	Not stated	L. acidophilus and L. bulgaricus	Placebo	Not stated	√	√				
Monteiro/ 1981/ Portugal[37]	Hospital	Not stated	I = 121 C = 119	Diverse infections, e.g. Bronchus-pulmonary, oto-rhinological or post surgery infections	S. boulardii	Placebo	6 days	√					
Surawicz/ 1989/ US[33]	Hospital	Adults/Elderly	I = 116 C = 64	Not stated	S. boulardii	Placebo	Apr. 3 weeks	√	√	√		√	√
Tankanow/ 1990/ US[34]	Primary care	Children‡	I = 15 C = 23	Common medical disorders, e.g. otitis media, pharyngitis	L. acidophilus, L. bulgaricus	Placebo	10-12 days	√	√				
Nord/ 1997/ Sweden[40]	Experimental	Adults	I = 11 C = 12	Healthy volunteers	*L. acidophilus, B. bifidum, L. delbrueckii subsp. bulgaricus, Streptococcus salivarius subsp. thermophilus*	Placebo	4 weeks					√	

Author/ Year/ Country	Setting	Study population*	Group size I = Intervention C = Control	Reason for antibiotic medication	Probiotics used	Comparator	Follow up (total study duration)	Outcomes collected**					
								AAD	D	S	TS	CD	CDAD
Lewis/ 1998/ UK[30]	Hospital	Elderly	I = 33 C = 36	Acute admission to the general medical ward	*S. boulardii*	Placebo	Median 7 days (up to 10 days)	√				√	√
Arvola/ 1999/ Finland[28]	Health Care Centre or Hospital	Children‡	I = 61 C = 58	Acute respiratory infections	*L. GG*	Placebo	3 months	√	√	√		√	√
Benhamou/ 1999/ France[41]	Primary Care	Children‡	I = 327 C = 289	Infection of the upper and/or lower respiratory tract	*S. boulardii*	Diosmetice (DS) in form of sachet, 6g/day for children between 1-2 years; 9g/day for children >2 years. Placebo capsule	6-10 days	√					
McFarland/ 1995/ US[31]	Hospital	Adults/Elderly (18-70)	I = 97 C = 96	Not stated	S. boulardii	Placebo	7 weeks	√	√	√	√	√	√
Madeo/ 1999/ UK[39]	Hospital	Elderly	I = 30 C1 = 18 C2 = 18	Common medical disorders e.g. chest infections, urinary tract infections	*L. acidophilus* and *Bifidum-bacterium*	Group1: Sachet with: 9.1 g fructose, 9.1 g FOS and 1.8 g apricot powder Group2: Sachet with 9.1 g fructose, 9.1 g maltodextrin and 1.8 g apricot powder	25 days	√	√		√		

Author/ Year/ Country	Setting	Study population*	Group size I = Intervention C = Control	Reason for antibiotic medication	Probiotics used	Comparator	Follow up (total study duration)	Outcomes collected**					
								AAD	D	S	TS	CD	CDAD
Vanderhoof / 1999/ US[35]	Primary Care	Children‡	I = 93 C = 95	Acute infectious disorders (minor infections) of the upper and lower respiratory tract, the urinary tract, soft tissues or skin	*L GG*	Placebo	10 days	√	√				
Orrhage/ 2000/ Sweden[32]	Experim ental	Adults	I = 10 C1 = 10 C2 = 10	None, healthy volunteers	*B. longum* and *L acidophilus*	Group 1: placebo milk supplement with 15 g oligofructose Group 2: placebo milk supplement	21 days	√				√	
Armuzzi*1/ 2001/ Italy[27]	Primary Care	Adults	I = 30 C = 30	Helicobacter pylori positive, asymptomatic	*L. GG*	Placebo	3 weeks	√					
Armuzzi/ 2001/ Italy[42]	Primary Care	Adults	I = 60 C = 60	Helicobacter pylori positive, asymptomatic	*L.GG*	No placebo	5 weeks	√		√			
Thomas/ 2001/ US[43]	Hospital	Adults/Elderly (18-93)	I = 133 C = 134	Presumed or proven infection	*L. GG*	Placebo	3 weeks	√					√
Cremonini/ 2002/ Italy[38]	Primary Care	Adults	I1 = 21 I2 = 21 I3 = 21 C = 20	H. pylori positive, asymptomatic	Group 1: *L. GG* Group 2: *S. boulardii* Group 3: *L. acidophilus* and *B. lactis*	Placebo	3 weeks	√					
Jirapinyo/ 2002/ Thailand[44]	Hospital	Children‡	I = 8 C = 10	Sepsis or meningitis	*L. acidophilus* and *B. infantis*	Placebo	1 week	√	√		√		

Author/ Year/ Country	Setting	Study population*	Group size I = Intervention C = Control	Reason for antibiotic medication	Probiotics used	Comparator	Follow up (total study duration)	Outcomes collected**					
								AAD	D	S	TS	CD	CDAD
La Rosa/ 2003/ Italy[45]	Primary Care	Children‡	I = 48 C = 50	Infections, e.g. pharyngitis, tonsillitis, otitis media, bronchitis	*L. sporongens*	Placebo	2 weeks	√	√				
Nista/ 2004/ Italy[46]	Primary Care	Adults	I = 54 C = 52	H. pylori positive, asymptomatic	*B. clausii*	Placebo	4 weeks	√		√			
Plummer/ 2004/ UK[47]	Hospital	Elderly	I = 69 C = 69	Acute emergencies requiring treatment with antibiotics	*L. acidophilus* and *B. bifidum*	Placebo	20 days	√				√	√
Corrêa/ 2005/ Brazil[48]	Hospital	Children‡	I = 80 C = 77	Not stated	*B. lactis* *S. thermophilus*	Placebo	30 days	√	√	√			
Kotowska/ 2005/ Poland[49]	Hospital and out-patient clinic	Children‡	I = 119 C = 127	Acute otitis media and/or respiratory tract infection	*S. boulardii*	Placebo	3 weeks	√					√

* Categories are: ‡ Children <18** Adults 18-65 Elderly 66 + Abbreviations: AAD Incidence of Antibiotic-associated diarrhoea D Duration of AAD

Table 3 Characteristics of study drugs

Author	Antibiotic used	Dosage, schedule, duration of antibiotics	Probiotics used	Dosage, schedule, duration of probiotics	Comparator
Adam[26]	Beta-lactams (penicillins, ampicillin, amoxicillin, cephalosporins) and tetracyclines	Treatment for at least 5 days	*S. boulardii*	4 gel capsules per day, for duration of antibiotic treatment	Placebo
Gotz[29]	Ampicillin	Not stated	*L. acidophilus and L. bulgaricus (Lactinex)*	4 times daily one packet for the first 5 days of ampicillin treatment (20 doses in total)	Placebo
Monteiro[37]	Several antibiotics, beta-lactam antibiotics and tetracyclines	Not stated	*S. boulardii*	4 times daily one capsule for 6 days	Placebo
Surawicz[33]	Several antibiotics: e.g. penicillin, other single agents, multiple agents containing clindamycin, or TMP or cephalosporins	Not stated	*S. boulardii*	250 mg capsule bid. twice a day (- 1g lyophilised S. boulardii); until 2 weeks after antibiotic treatment **=> 1 g/day**	Placebo
Tankanow[34]	Amoxicillin	Not stated	*L. acidophilus, L. bulgaricus (Lactinex)*	1 g packets ($5.1x10^8$ cfu per packet) 4 times/day for 10 days **=> $2.04x10^9$/day**	Placebo
McFarland[31]	B-lactam antibiotics (medium-to-broad spectrum penicillin's, combination penicillin's [penicillins with a β-lactamase inhibitor] or any cephalosporin	Treatment for at least 48 hours	*S. boulardii*	1g ($3x10^{10}$ cfu) per day administered as 2x250 mg capsules bid. continued until 3 days after the antibiotic treatment was discontinued. The maximum duration was 28 days. **=>$3x10^{10}$/day**	Placebo
Nord[40]	Clindamycin	150 mg 4times/day for 7 days	*L. acidophilus, B. bifidum, L. delbrueckii subsp. bulgaricus, Streptococcus salivarius subsp. thermophilus*	3 capsules ($3x10^9$ cfu per capsule) 2 times/day for 14 days **=>$6x10^9$/day**	Placebo

Author	Antibiotic used	Dosage, schedule, duration of antibiotics	Probiotics used	Dosage, schedule, duration of probiotics	Comparator
Lewis[30]	Not stated	Not stated	*S. boulardii*	113 mg twice daily during antibiotic treatment **=>226 mg/day**	Placebo
Arvola[28]	Penicillin; Amoxicillin; Cephalosporins; Erythromycin; Trimetoprim-sulpha	Dosage was divided into 2 or 3 doses, given every 8 hours, for 7-10 days	*L. GG*	$2x10^{10}$ cfu in capsules, b.d., during antimicrobial treatment **$4x10^{9}$/day**	Placebo
Benhamou[41]	Amoxicillin clavulonic acid; cefradoxil, josamycin, erythromycin + sulfafurazol, cefixim	Treatment for 6-10 days	*S. boulardii*	226 mg per capsule 1 capsule/day for the duration of antibiotic treatment 1 placebo sachet **=>226 mg/day**	Diosmetice (DS) in form of sachet, 6g/day for children between 1-2 years; 9g/day for children >2 years Placebo capsule
Madeo[39]	Co-amoxycliv; Flucloxacillin; Augmentin; Ampicillin; Clarithromycin; Cefotaxime; Metronidazole; Cefuroxime; Cephadrine; Magnapen; Trimethoprin; Ciproflaxicin	Not stated	*L. acidophilus and Bifidobacterium*	Combined with 8,5g FOS (fructo-oligosaccharides), 2 g apricot powder and 9.1 g fructose; the product was administered on sachet per day, for 15 days	Group 1: Sachet consisted of : 9.1 g fructose, 9.1 g FOS and 1.8 g apricot powder Group 2: Sachet with 9.1 g fructose, 9.1 g maltodextrin and 1.8 g apricot powder
Vanderhoo[35]	Amoxicillin; Amoxicillin/ clavulanate potassium; Cefprozil; Clarithomycin; Ciprofloxacin; Cefotaxime; Penicillin; Cephalothin; Erythromycin; Tetracycline; Trimethoprim; Sulfamethox.	10 days	*L. GG*	Children weighing<12 kg: 1 capsule ($1x10^{10}$cfu/capsule) once daily for 10 days Children weighing >12 kg: 2 capsules once daily for 10 days **=>$1x10^{10}$-$2x10^{10}$/day**	Placebo

Author	Antibiotic used	Dosage, schedule, duration of antibiotics	Probiotics used	Dosage, schedule, duration of probiotics	Comparator
Orrhage[32]	Cefpodoxime proxetil	2x 100 mg/day for 7 days	*B. longum and L acidophilus*	250ml of a fermented milk supplement containing $5x10^7$ to $2x10^8$ cfu/ml of B. longum and $2x10^8$ to $3x10^8$ cfu/ml of L. acidophilus once daily for 21 days (additionally: 15g oligofructose) **=> max. $5x10^8$/day**	-Group 1: placebo milk supplement with 15 g of oligofructose -Group 2: placebo milk supplement FOS (fructo-oligosaccharides both groups for 21 days
Armuzzi*1[27]	Triple therapy: Rabeprazole Clarithromycin Tinidazol	Rab. 20 mg b.d. Clar. 500 mg b.d. Tin. 500 mg b.d. For 7 days	*L. GG*	$6x10^9$ of viable bacteria bid. for 14 days **=>$12x10^9$/day**	Placebo
Armuzzi [42]	Triple therapy: Pantoprazole Clarithromycin Tinidazol	Pan. 40 mg b.d. Clar. 500 mg b.d. Tin. 500 mg b.d. For 7 days	*L. GG*	Freeze dried powder ($6x10^9$ cfu) bid. for 14 days **=> $12x10^9$/day**	No placebo
Thomas[43]	Penicillins, cephaolsporins, carbapenems, Fluoroquinolones, macrolides, aminoglycosides, glycopeptides, tetracycline, others	Not stated	*L. GG*	1 capsule twice daily for 14 days; Capsules contained $10x10^9$ cfu of live L. GG **=> $1x10^{10}$/day**	Placebo
Cremonini[38]	Triple therapy: Clarithromycin; Tinidazole; Rabeprazol	Clar. 500 mg b.d. Tini. 500 mg b.d. Rab. 20 mg b.d. For 7 days	-Group 1: *L. GG* -Group 2: *S. boulardii* -Group 3: *L. acidophilus* and *B. lactis*	-*L. GG*: 1 sachet bid. ($6x10^9$ cfu per sachet) -*S. boulardii*: 1 sachet bid. ($5x10^9$ per sachet) -*L. acidophilus* + *L. lactis*: 1 sachet bid. ($5x10^9$ per sachet) all groups for 2 weeks **=> $3.2x10^{10}$/day**	Placebo
Jirapinyo[44]	One or more than one broad spectrum antibiotics	Not stated	*L. acidophilus and B. infantis*	1 capsule three times a day, for 7 days	Placebo

Author	Antibiotic used	Dosage, schedule, duration of antibiotics	Probiotics used	Dosage, schedule, duration of probiotics	Comparator
La Rosa[45]	Amoxicillin clavulanic acid; Cephalosporin; Erythormycin (or other macrolides)	10 days of therapy	*L. sporongens*	$5.5x10^8$ cfu per capsule (and 250 mg fructo-oligosaccharide) 1 capsule/day for 10 days **=> $5.5x10^8$**	Placebo
Nista[46]	Triple therapy: Clarithromycin; Amoxicillin; Rabeprazol	Clar. 500 mg b.d. Amox. 1 g b.d. Rab. 20 mg b.d. For 7 days	*B. clausii*	1 vial/day ($2x10^9$ spores per vial) for 14 days **=> $2x10^9$/day**	Placebo
Plummer[47]	Not stated	Not stated	*L. acidophilus and B. bifidum*	$2x10^{10}$ cfu per capsule 1 capsule/day for 20 days **=> $2x10^{10}$/day**	Placebo
Corrêa[48]	Penicillin, ampicillin, oxacillin, amoxicillin (+ clavulanic acid), cephalosporin	Not stated	*B. lactis, Streptococcus thermophilis*	Minimum of 500 ml of formula/day = $1x10^7$ cfu/g of contents for 15 days **=> $1x10^7$/day**	Placebo
Kotowska[49]	Cefuroxime axetil; Amoxicillin (+clavulanate); Cefuroxime; Penicillin; Clarithromycin; Roxithromycin	Not stated	*S. boulardii*	250 mg *S. boulardii*, bid. for the duration of the antibiotic treatment **=> 500 mg/day**	Placebo

Table 4 Quality assessment results

Author	Randomisation	Allocation concealment	Blinding	Blinding method	Withdrawals (%)	Intention to treat used	Score on Jadad scale
Adam[26]	Acceptable	Not acceptable	Double	Acceptable	0%	Yes	5
Cremonini[38]	Acceptable	Acceptable	Double	Acceptable	Intervention1: 0% Intervention2: 4.5% Intervention3: 0% Control: 4.8%	No	5
Kotowska[49]	Acceptable	Acceptable	Triple	Acceptable	Intervention: 9.8% Control: 7.3%	No	5
La Rosa[45]	Acceptable	Acceptable	Double	Acceptable	Intervention: 20.0% Control: 16.7%	Yes	5
Madeo[39]	Acceptable	Not reported	Double	Acceptable	0%	Yes	5
Thomas[43]	Acceptable	Acceptable	Double	Acceptable	Intervention: 12.5% Control: 10.7%	Yes	5
Vanderhoof*[35]	Acceptable	Acceptable	Double	Acceptable	Intervention: 7.9% Control: 5.9%	No	5
Armuzzi*1[27]	Not acceptable	Acceptable	Double	Acceptable	0%	Yes	4
Arvola[28]	Acceptable	Not reported	Double	Acceptable	Intervention: 31.5% Control: 25.6%	No	4
Benhamou[41]	Not acceptable	Not reported	Double	Acceptable	Intervention: 16.4% Control: 25.5%	No	4
Corrêa[48]	Not acceptable	Not reported	Double	Acceptable	Intervention: 8.8% Control: 6.1%	No	4
Gotz[29]	Not acceptable	Not reported	Double	Acceptable	Intervention: 25.0% Control: 14.0%	No	4
Jirapinyo[44]	Not acceptable	Not reported	Double	Acceptable	0%	Yes	4
Lewis*[30]	Not acceptable	Acceptable	Double	Acceptable	Intervention: 8.3% Control: 0%	No	4
McFarland[31]	Not acceptable	Acceptable	Double	Acceptable	0%	Yes	4

Author	Randomisation	Allocation concealment	Blinding	Blinding method	Withdrawals (%)	Intention to treat used	Score on Jadad scale
Nista[46]	Acceptable	Not reported	Double	Not acceptable	Intervention: 10.0% Control: 13.3%	Yes	4
Nord[40]	Not acceptable	Acceptable	Double	Acceptable	0%	Yes	4
Surawicz*[33]	Not acceptable	Not reported	Double	Acceptable	Intervention: 27.0% Control: 59.7%	No	4
Tankanow*[34]	Not acceptable	Acceptable**	Double	Acceptable**	Intervention: 50% Control: 23.3%	No	4**
Monteiro*[37]	Not acceptable	Not reported	Double	Not acceptable	Intervention: 19.3% Control: 20.7%	No	3
Orrhage[32]	Not acceptable	Not reported	Double	Not acceptable	Intervention: 10.0% Control1: 0% Control2: 0%	No	3
Plummer*[47]	Not acceptable	Not reported	Double	Not acceptable	Intervention: 8.0% Control: 8.0%	No	3
Armuzz[42]	Not acceptable	Not acceptable	Not blinded	Not blinded	0%	Yes	2

* Randomised group size not stated, assumed that patients were equally distributed over the two groups.
** Information completed by contacting authors

Randomisation: Acceptable = well described, method really random
Not acceptable = not well described, uncertain if method really random
Allocation concealment: Acceptable = concealment method applied and well described
Not acceptable = concealment method applied and not well described
Not reported
Blinding: Single/double/triple
Not blinded
Not reported
Blinding method: Acceptable = well described,
Not acceptable = not well described
Not blinded

6.1.3 Quality assessment and threats to validity

The results for selected quality assessment items are shown in Table 4 above. Trials were assessed according to their overall Jadad score (1= poor quality to 5=high quality; see appendix page 61). Nineteen studies were judged to be of good quality (i.e. ≥ 4 out 5). Three trials were judged to be of moderate quality (3/5) and one was of poor quality (2/5). Although these Jadad scores indicate a generally good level of quality across trials, an assessment of individual dimensions of quality gives a rather less positive picture.

Nine (39%) studies were judged to have 'acceptable' randomisation, 10 (44%) 'acceptable' concealment, 18 (78%) had 'acceptable' blinding methods, 17 (74%) studies had acceptable level (≤ 20%) of withdrawal and 10 (44%) of the studies used an 'intention to treat' analysis To assess the use of 'intention to treat' analysis, the following criteria was used: only studies reporting an intention to treat analysis and studies that had no withdrawals (therefore resulting in de facto intention to treat analysis) were considered. Studies where withdrawals were not included in the analysis were not considered 'intention to treat-studies'. Only 10 out of the 23 (43%) of studies were being considered 'acceptable' across all five criteria.

6.2 Primary outcomes: Incidence of diarrhoea

6.2.1 Meta-analysis of primary outcome data: Incidence of diarrhoea (AAD)

The pooling of studies was performed separately for those studies that used an active comparator (Figure 2) and for those that used either placebo or no therapy (Figure 3).
No significant difference in AAD between probiotic and an active comparator was observed (RR: 1.45, 95% CI: 0.91 to 2.30). There was no evidence of statistically significant heterogeneity (p-value = 0.816).
Of the 19 placebo or no therapy studies, eleven reported a significant reduction of the risk of AAD in the probiotic-treated group. The pooled relative risk was statistically significant (RR: 0.48, 95% CI: 0.37-0.63; random effects; $p < 0.001$). There was evidence of significant statistical heterogeneity (p= 0.002).

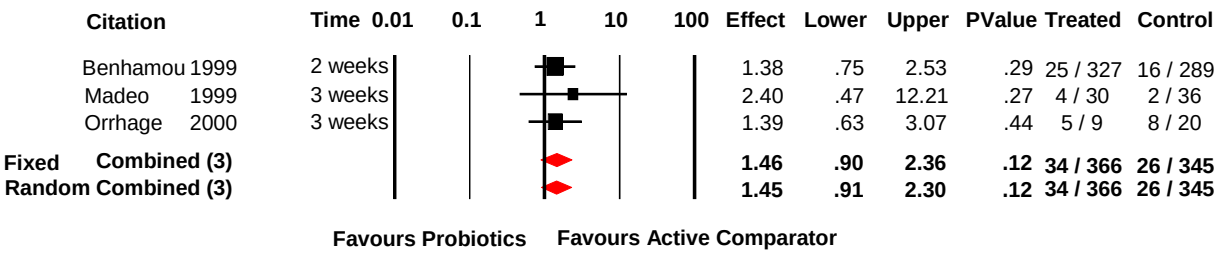


Figure 2 Meta-analysis: studies with an active comparator

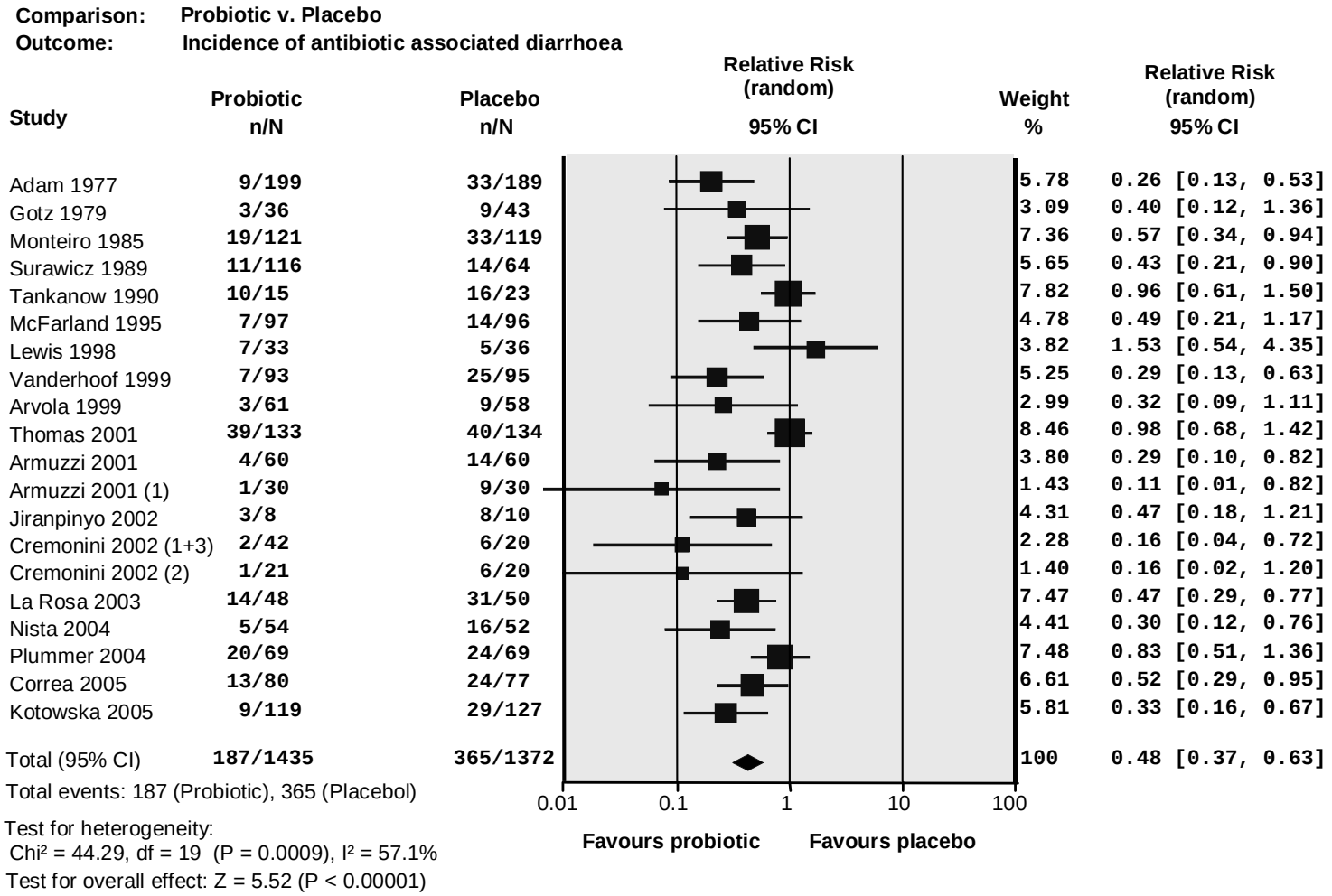


Figure 3 Meta-analysis: studies with placebo and no therapy as comparator

6.2.2 Stratified meta-analysis for different time points

Several studies reported outcomes for more than one time point. AAD outcome was pooled separately at 1-week, 2-weeks, and at 3 or more weeks (Figure 4 and Table 5). The pooled relative risk (with 95% CI) of AAD with probiotics at each time point was 0.38 (95% CI: 0.28 to 0.52); 0.50 (95% CI: 0.30 to 0.84) and 0.61 (95% CI: 0.43 to 0.85) respectively. Thus it appears the beneficial effect of probiotics decreases over the course of time. Nevertheless this effect remained at 3 weeks and after the point of starting the intervention. Table 5 summarizes the results of the stratified meta-analysis, also reporting the observed heterogeneity in the individual strata, which is not significant for the strata of 1 and more than 3 weeks. A significant test of heterogeneity (p=0.012) between the three strata confirmed that follow up time was a predictor of the probiotic treatment effect.

Table 5 Results of the stratified meta-analysis for different time points

Time point of outcomes	Number of studies (n)	RR (95% CI)	Heterogeneity
1 week	9	0.38 (0.28-0.52)	Chi-squared = 8.32 p = 0.403
2 weeks	8	0.50 (0.30-0.85)	Chi-squared = 17.68 p = 0.013
≥3 weeks	9	0.61 (0.43-0.85)	Chi-squared = 12.82 p = 0.118

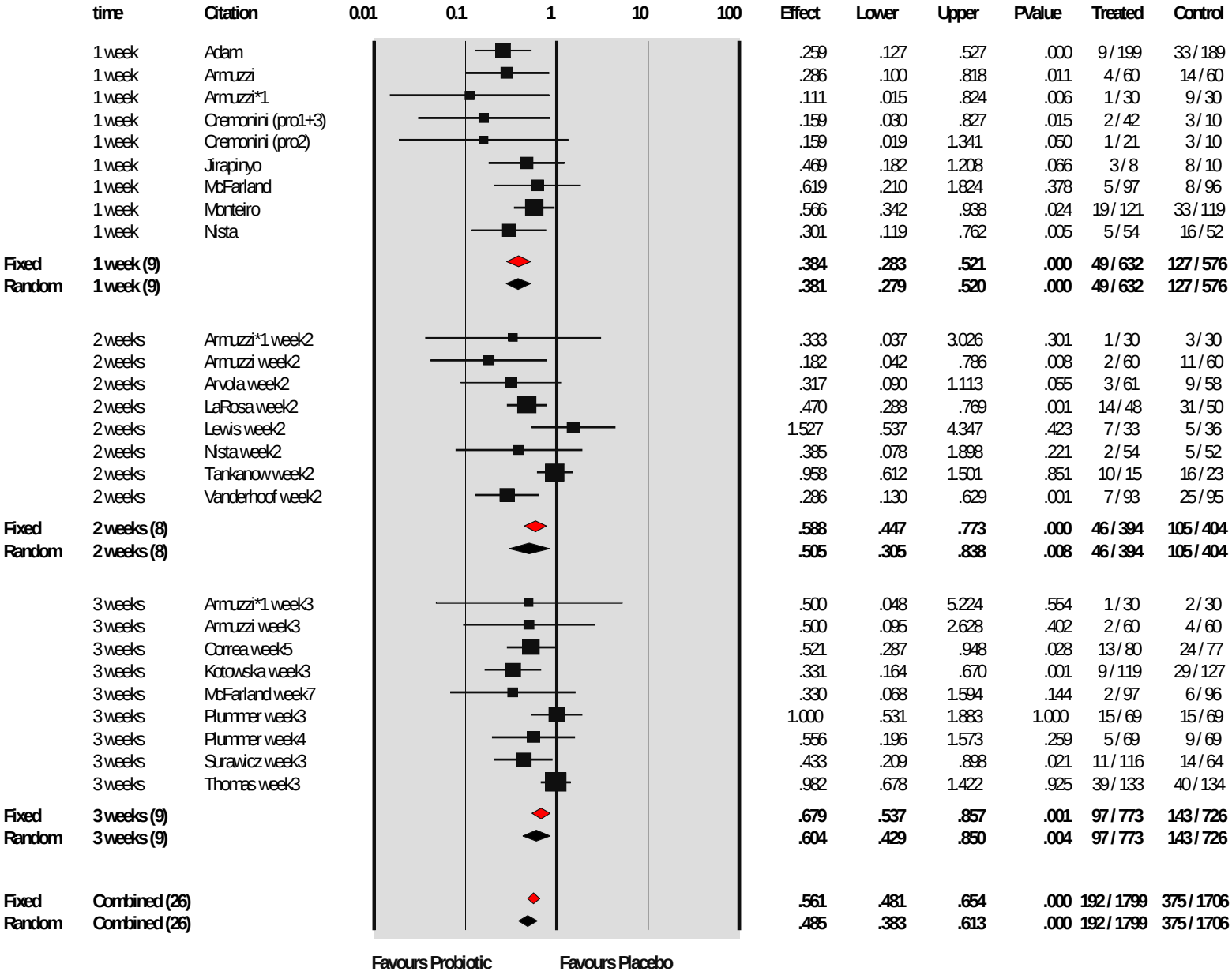
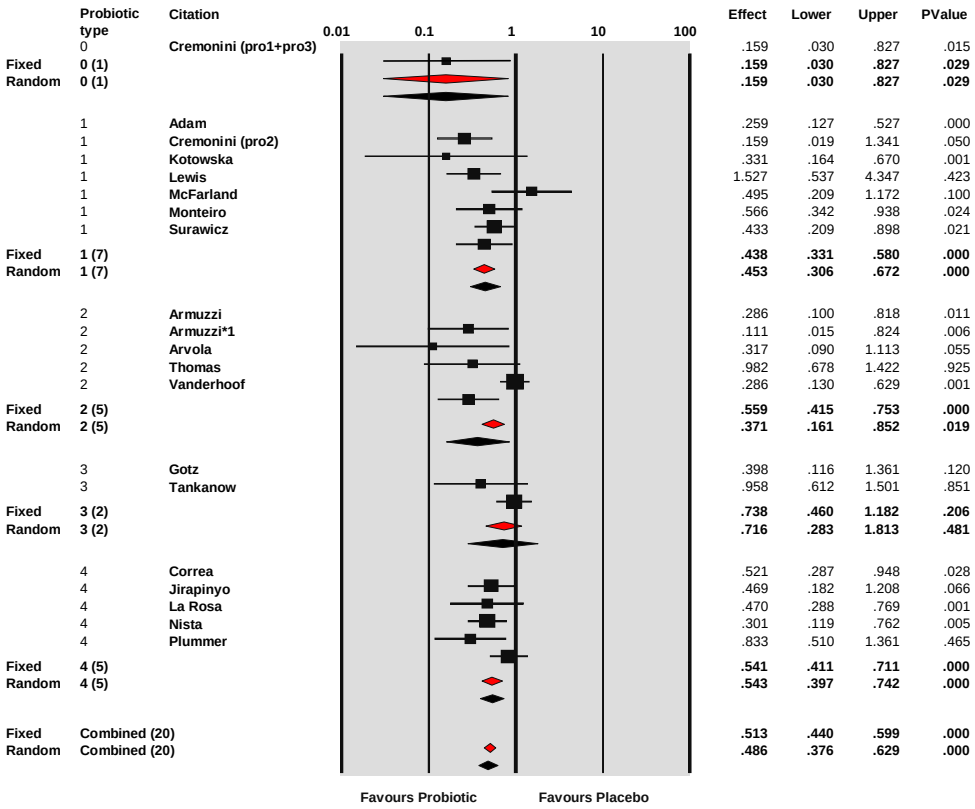


Figure 4 Meta-analysis of incidence of diarrhoea at 1, 2, and more than 3 weeks

6.2.3 Stratified meta-analysis for different types of probiotic

The different probiotic preparations used by the studies were grouped and analysed to examine the specific effects on the incidence of diarrhoea. Figure 5 shows the pooled relative risk for AAD for trials using *S. boulardii, L. GG*, Lactinex (*L. acidophilus* and *L. bulgaricus*) and other preparations (including e.g. *Bifidobacteria, Streptococcus*, and various combinations).

Only the Lactinex preparations failed to show a statistically significant reduction in AAD although there were only 2 trials in this case. As the bacteria group of the study by Cremonini[38]could not be classified, because of the combination of *L. GG* and a *Lactobacillus* and *Bifidobacterium* combination, it was not included in this analysis. The authors stated in their report, that there was no statistical significance between the effectiveness of these two different study drugs.



Legend: group 1: *Saccharomyces boulardii* group 2: *Lactobacillus GG* group 3: Lactinex group 4: other combinations

Figure 5 Stratified meta-analysis for different probiotics.

Given the statistically significant heterogeneity identified in incidence of AAD across placebo-controlled studies, stratified meta-analysis and meta-regression were used to explore the potential associations between treatment effect and study characteristics.

The stratified meta-analysis of the various trial levels of covariates and univariate meta-regression (Table 7) indicated only time of follow up to be a significant predictor of effect size. Nevertheless, this effect over time failed to reach statistical significant in the multivariate meta-regression. No other covariates were found to be statistically associated with the effect size.

Table 6 Subgroup analysis and meta-regression for covariate 'comparator'

Variable	Stratified analysis	RR (95% CI)	Univariate regression	Multivariate regression
Comparator	Placebo (n=20)	0.48 (0.37-0.62)	p= 0.002	p= 0.003
	Active (n=3)	1.45 (0.91-2.30)		

Table 7 Subgroup analysis

Variable	Stratified analysis	RR (95% CI)	Univariate regression	Multivariate regression
Setting	Hospital (n=1)	0.60 (0.46-0.79)	p= 0.074	p=0.342
	Non-hospital (n=9)	0.36 (0.22-0.59)		
Age*	Children (n=7)	0.48 (0.33-0.70)	p= 0.902	p= 0.648
	Adults (n=6)	0.26 (0.17-0.41)		
	Elderly (n=2)	0.94 (0.58-1.51)		
	Adults-elderly (n=4)	0.61 (0.36-1.03)		
Probiotics type	*S. Boulardii* (n=7)	0.46 (0.32-0.67)	p= 0.339	p= 0.534
	L. GG (n=5)	0.37 (0.16-0.85)		
	Lactinex(n=2)	0.72 (0.28-1.81)		
	Other combinations (n=5)	0.54 (0.40-0.74)		
Study quality	<4 (n=3)	0.60 (0.37-0.97)	p= 0.457	p= 0.877
(Jadad score)	≥4 (n=17)	0.48 (0.35-0.64)		
Intention to treat	Yes (n=8)	0.42 (0.27-0.67)	p= 0.511	p= 0.467
	No (n=12)	0.55 (0.40-0.74)		
Publication year	<2000 (n=9)	0.50 (0.34-0.75)	p= 0.881	p= 0.298
	≥2000 (n=11)	0.49 (0.35-0.69)		
Time*	1 week (n=9)	0.39 (0.29-0.53)	p= 0.044	p=0.092
	2 weeks (n=5)	0.59 (0.32-1.06)		
	≥ 3 weeks(n=5)	0.61 (0.41-0.92)		
'Adequate	Yes (n=8)	0.40 (0.25-0.63)	p= 0.181	p= 0.607
studies'	No (n=12)	0.58 (0.44-0.77)		

Subgroup analysis performed only for studies with placebo comparator
* 1 study (Gotz) did not report any age or time point of measurement

6.2.5 Publication bias

To assess publication bias in AAD outcome, two statistical tests were carried out:
a] The Begg and Mazumdar adjusted rank correlation test; this test looks for correlation between effect size and study variance; in the absence of publication bias no correlation would be expected but when small studies with near null effect sizes are missing from the sample (publication bias) a correlation becomes evident.
b] Egger regression asymmetry test; this test regresses standardised effect size against study precision (1/SE) and predicts the presence of bias if the 95% confidence intervals of intercept fail to encompass a zero standardised effect size).

A funnel plot was also examined (Figure 6). Both a non-significant (at $p < 0.05$) Begg and Mazumdar test ($p = 0.091$) and a fairly symmetrical funnel plot suggested there was only moderate evidence of publication bias. However, in contrast the Egger test (Figure 7) indicated significant statistical heterogeneity ($p = 0.026$). Contradictory results from this pair of tests is not unusual as Begg's test lacks statistical power for small numbers of studies.

Given these contradictory findings, a 'fail safe' analysis using the Rosenthal's method was performed in Meta Win. This method assesses the possibility of publication bias by calculating the 'fail safe N': the number of studies showing no benefit, therefore without any treatment effect, which would be needed to increase the P value for the meta-analysis to above 0.05. When this test was used, N was found to be 180; nearly 8 times more studies than included in the meta-analysis would be needed to shift the p-value. Therefore, it was concluded that publication bias was unlikely.

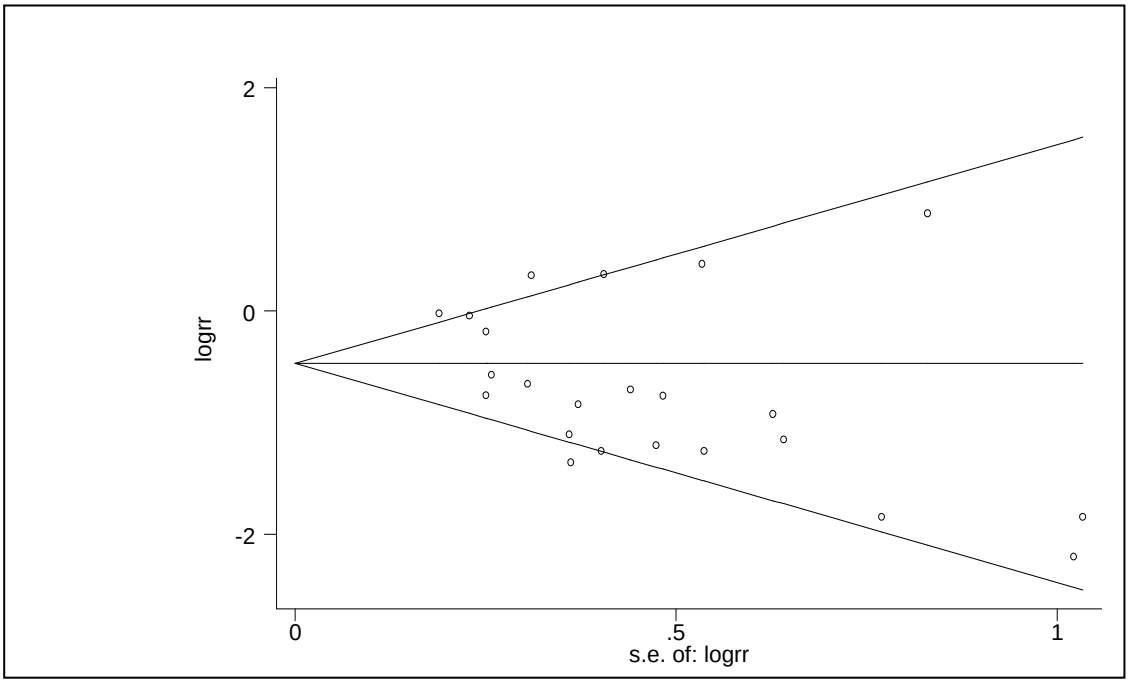


Figure 6 Begg's funnel plot with 95% CI

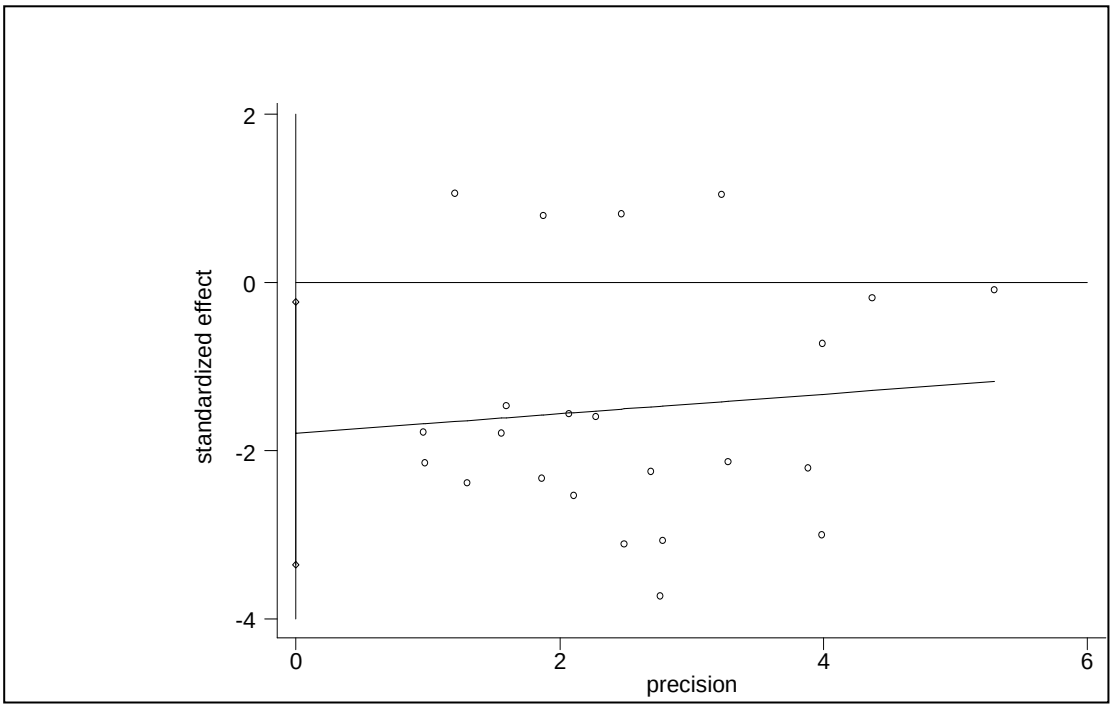


Figure 7 Egger's regression plot for publication bias

6.3 Secondary outcomes

6.3.1 Meta-analysis of the incidence of *C difficile*

The pooled result of the meta-analysis regarding the incidence of *C. difficile* carriage ( ) does not show a significant effect of probiotics (relative risk 0.95, 95% CI: 0.66 to 1.36). However, there was a reduction in the incidence of *C. difficile* associated diarrhoea (relative risk: 0.54 95% CI: 0.24 to 0.86, NNT= 36). For this outcome, all studies compared probiotics to placebo. There was no evidence of significant statistical heterogeneity (p-value = 0.756) (see Figure 9). However, there was evidence of clinical heterogeneity regarding the classifications of *C. difficile* associated diarrhoea in the included studies. The definition of the presence of *C. difficile* associated diarrhoea was based on various tests and assays. All studies determined the presence of *C. difficile* toxins, however only two studies tested for toxins A and B[47,49], one study used only toxin A[28,47]and the other three studies did not clarify on which toxin their analysis was based.[31,33,43,47]

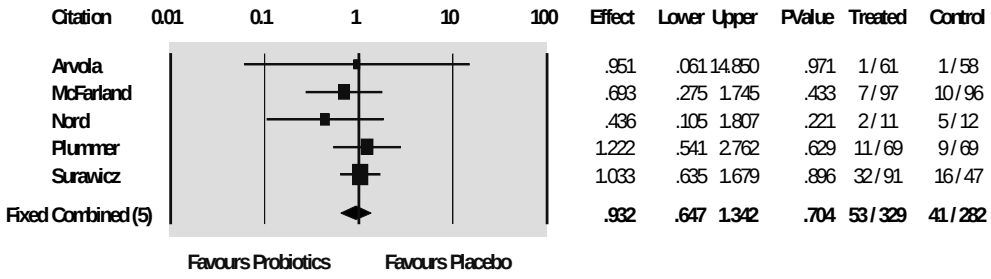


Figure 8 Meta-analysis of incidence of *C difficile* carriage

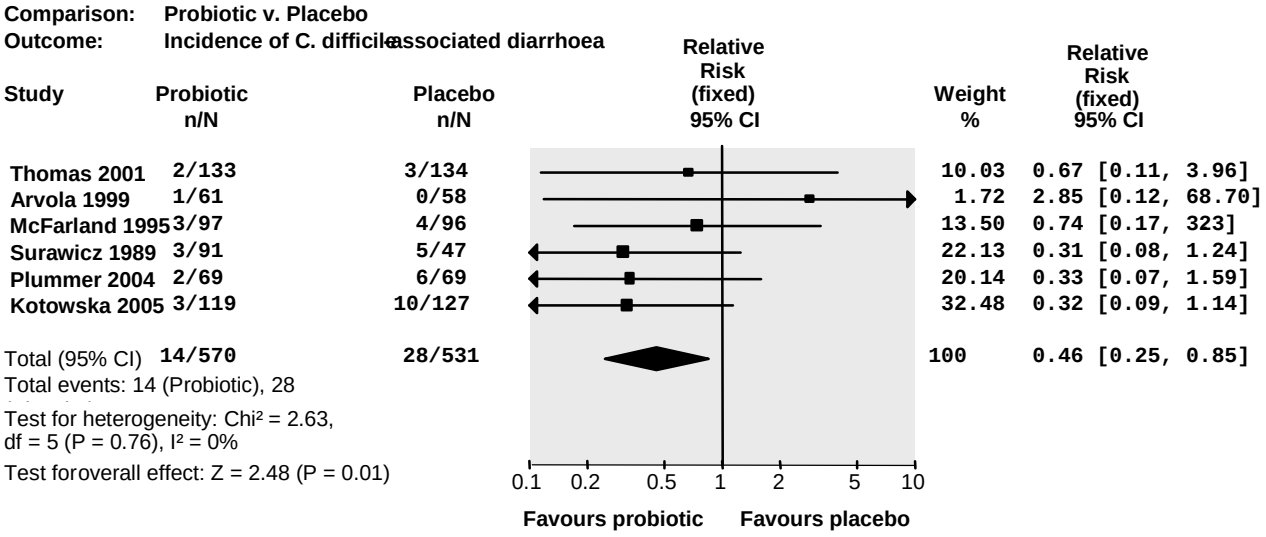


Figure 9 Meta-analysis of incidence of *C difficile* associated diarrhoea

6.3.2 Duration, Severity and Time to developing symptoms of AAD

Duration of diarrhoea

The duration of diarrhoea was reported as the mean number of days of a diarrhoeic event in 6 studies. As shown in Figure 10, there was a significant reduction in the mean duration of diarrhoea of 0.58 days (95% CI: -1.11 to -0.04) with probiotics. There was no evidence of significant statistical heterogeneity, (p-value 0.147).The mean duration of diarrhoea as reported by the included studies varied between 0.7 and 5.9 days. The study by McFarland et al[31] ported duration of diarrhoea as median days rather than mean days. A median duration of 3.0 and 4.0 days for the probiotic group and control group was reported at one week of follow-up, and 2.5 and 18.0 days at 7 weeks of follow up. According to a t-test they found no significant effect of probiotic, however the large t-values reported (24.5 and 26) suggest that there may have been miscalculation; for these reasons this study was not included in the meta-analysis.

Tankanow et al[34] reported additional information on the duration that could not be quantified as above and therefore was not included in the pooled analysis. Nevertheless, this study also appears to support the effectiveness of probiotics on the duration of diarrhoea. They state, that of the 10 patients having diarrhoea in the probiotic group 2 patients (20%) had diarrhoea throughout the study period (10-12 days), 4 patients (40%) had diarrhoea early in the course of the therapy, which improved in the course of the therapy and 4 patients (40%) were recorded to have sporadic diarrhoea in the intervention group. In the control group, 5 out of 16 patients (31%) had diarrhoea throughout the study period, 8 patients (50%) had diarrhoea early in the therapy course; and 2 patients (12.5%) had sporadic diarrhoea. One patient (6%) in the control group developed diarrhoea in the last two days of study.

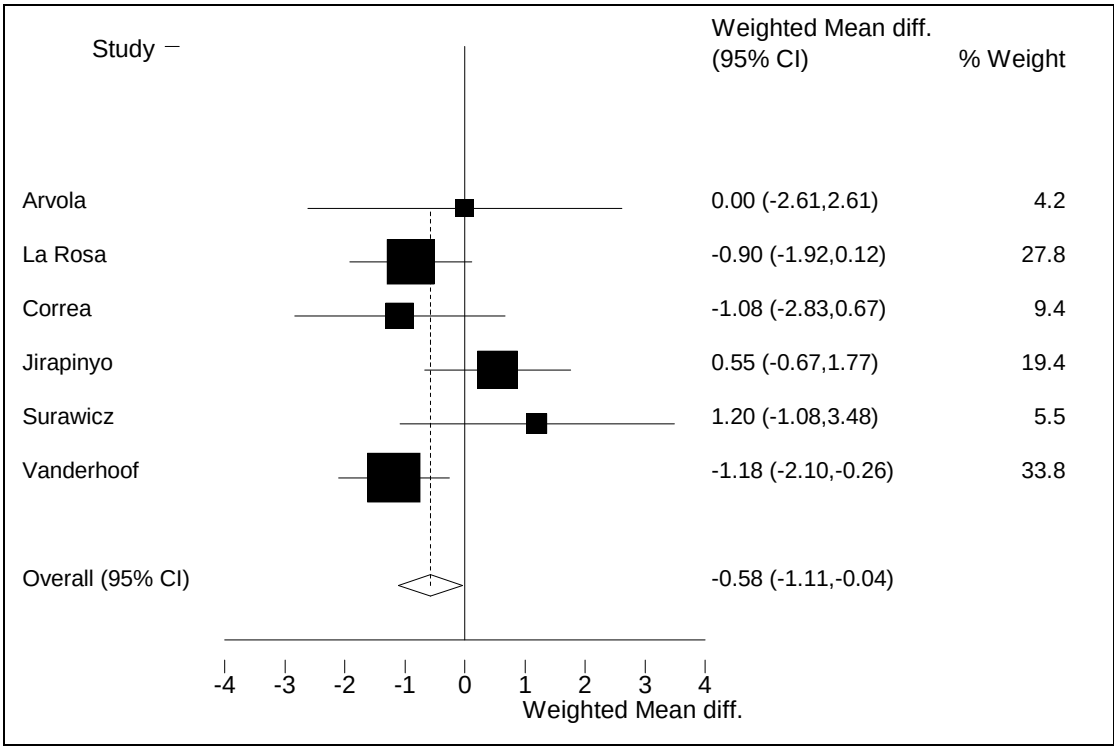


Figure 10 Meta-analysis of duration in days of AAD

Severity of diarrhoea

Severity of diarrhoea was assessed on the assumption that a higher number of stools indicate more severe diarrhoea. Only three studies reported this outcome in a way that could be used for meta-analysis as shown in Figure 11. The effect of probiotic supplementation on the severity of the diarrhoeic events is found not to be statistically significant; the weighted mean difference is 0.61 (95% CI = -0.16 to 1.39).

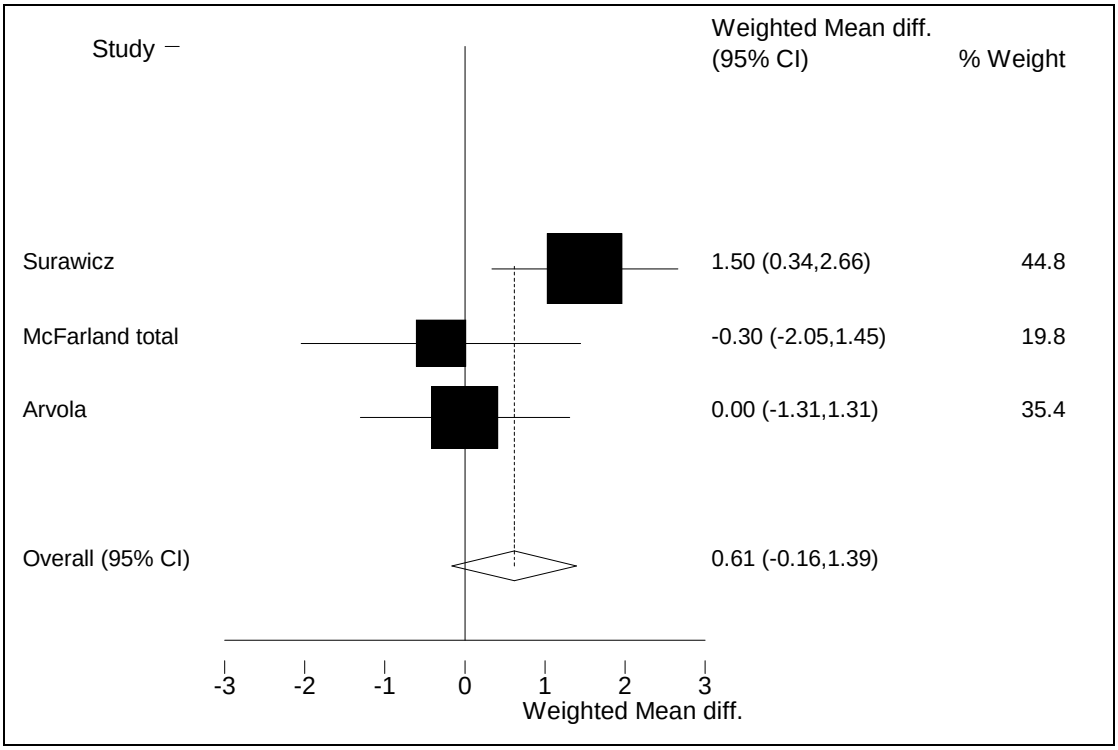


Figure 11 Meta-analysis of severity of AAD (mean number of stools / day

Information on the severity of diarrhoea was given by four additional studies, which used different outcome measures. Corrêa et al[48] used the absolute numbers of patients that exhibited dehydration as an indication of the severity. They reported that 9 of 13 patients in the probiotic and 23 of 24 patients in the control group were classified as dehydrated.
The studies conducted by Nista[46], Armuzzi[42] and Adam[26] all used categorical outcome measures to classify severity. A scoring classification of 'mild, moderate and severe diarrhoea' was used by all three studies, but the criteria for scoring the different classes were not identical.
Nista[46] rated the intensity of symptoms using a scale, in which 0,1,2 and 3, respectively corresponded to absent, mild, moderate and severe symptoms. The results for the first week of follow-up are for the probiotic group: 0.01 ± 0.04, and for the control group: 0.16 ± 0.4, this difference was significant (p-value = 0.01). The same relation can be found for the second and third week of follow-up.
In the study conducted by Armuzzi [42], a similar rating scale was used. (For more detailed information see appendix page 71) The reported results for the probiotic and control group are respectively: Probiotics: 4/4 patients recorded mild diarrhoea; no one had worse than mild symptoms; Controls: 11/14 patients recorded mild symptoms, 3/14 patients recorded moderate diarrhoea.

Adam et al[26] used an even more complex method. They determined the severity of diarrhoea on the basis of 3 different items that were scored and used to generate an overall number, which indicated the severity. The items consisted of the difference of the number of stools per day, the difference according to consistency and the difference according to the colour. In the probiotics group 8/9 patients had mild diarrhoea and 1/9 severe. In the control group, 17/33 patients had mild diarrhoea, 15/33 had moderate diarrhoea and 1/33 had severe symptoms.

Time to developing symptoms of diarrhoea

Only two studies reported the time until onset of diarrhoea. Due to the small study size and flaws in the calculation of outcomes in these studies, no meta-analysis was performed. The study by McFarland et al[31] reported a longer time to onset of diarrhoea in the probiotic group of approximately 4 days after 1 week of follow-up. After seven weeks of follow-up, the mean difference was approximately 8 days longer time to onset for the probiotic group compared to the placebo.

Jirapinyo et al[44] reported a shorter time to developing symptoms for patients in the probiotics group of approximately 1.5 days. These contradictory findings do not allow for a conclusion regarding the effect of probiotics on the time to developing symptoms of diarrhoea.

7. Cost effectiveness results

No studies relating to the cost or cost-effectiveness of probiotics in preventing AAD and/or *C. difficile* infections were identified.

Given the lack of formal economic evaluative data, the remainder of this section reports the results of additional bibliographic searches to assist an outline analysis as to the potential cost-effectiveness of prevention of AAD and/or *C. difficile* infections with probiotic therapy. We searched for studies reporting (1) on the cost effectiveness of probiotic treatment of AAD, (2) costs of *C. difficile* associated diarrhoea and (3) the costs of probiotic supplementations.

Cost effectiveness of probiotic treatment

Bibliographic searches identified a single study examining the cost-benefit of the treatment of unspecified diarrhoea with *S. boulardii* in comparison with no treatment.[50] This study undertook a cost-benefit analysis based on the assumption, that treatment with *S. boulardii* reduced AAD by approximately one day. This duration is similar to the reduction of 0.6 days found in our systematic review. Based on a currency conversion to UK pounds, the savings per patient in direct healthcare costs with probiotics were reported £22.42 (at 1989 prices). Combining indirect (productivity savings) and direct costs showed possible savings of £175.98 per patient. These savings were primarily achieved due to one day of reduced diarrhoea, leading to a smaller percentage of patients' hospitalised and shorter absence from work.

Costs of *C. difficile* infection

A UK study by Wilcox et al advises that patients with an *C. difficile* associated diarrhoea stayed significantly longer in hospital than controls (mean 21.3 days), including an average 14 days in a side room. The increased cost of with *C. difficile* associated diarrhoea was in excess of £4000 per case.[18] Using the Hospital & Community Health Services (HCHS) Pay & Prices Index this inflates to £5643 for 2005. The additional costs consisted mainly of hotel cost due to a prolonged stay in hospital. The authors concluded that these high costs justify expenditure on control measures to reduce the incidence of this infection.

Costs of probiotics

Probiotics are classified as foods or food supplements; however, they could in theory be prescribed on the NHS on a named-patient basis. As no information about prescription

patterns of probiotics is available, the assumption arises, that consumers directly buy most probiotic preparations. At time of writing this review, there is no legislative regulation of the quality of commercially available preparations, which makes it difficult to determine the specific costs of a ‘working product’. Foods (e.g. yoghurts, drinks) and supplements containing probiotics are available from supermarkets and pharmacies, but these are in general not the preparations assessed in published trials. Nevertheless, it can be reported, that the costs for all different probiotics preparations are very low and generally range somewhere between £0.25 - £1.00 per day.[2,38]

8. Discussion and Conclusions

8.1 Review findings

This systematic review identified a total of 23 RCTs of the effectiveness of probiotics in the prevention of AAD. Of these, 18 compared probiotics to placebo or no therapy and three compared probiotics to active comparators (Diosmectite, a natural clay with reputed anti diarrhoeal properties, and oligosaccharides). No studies were identified of the costs or cost effectiveness of probiotics in the prevention of AAD. The key findings are summarised as follows:

Antibiotic associated diarrhoea

Compared to placebo probiotics were associated with a relative reduction in the incidence of AAD of 52% (95% CI: 37% to 63%) i.e. a number needed to treat (NNT) of 8. A high level of statistical heterogeneity was observed. Stratified meta-analysis and meta-regression indicated that the effects of probiotics were consistent across trial follow up, trial settings (i.e. hospital vs. primary care), patient age, type of probiotic, and various dimensions of the methodological quality of trials.

The three head to head comparisons of probiotics to other preventative strategies of Diosmectite (a natural clay) and oligosaccharides, showed no significant difference in AAD prevention with probiotics, however the studies numbered only 3.

This review found that reported baseline risk of incidence of AAD was higher in young children and elderly, in line with findings in the literature (see section 3.2 page 11 and Appendix page 103).

Duration, Severity and Time to developing symptoms of AAD

The trials in this report used various ways of reporting these outcomes, which made the quantitative pooling of results across trials problematical.

The duration of diarrhoea was reported fairly consistently across trials and the pooled result showed a decrease in diarrhoea of 0.6 days (95% CI; 0.04 to 1.11) in the group of patients receiving probiotics compared to those that received placebo. Considering the duration of non-complicated diarrhoea rarely exceeds a week (see section 6.3.2 page 44), this appears to represent a clinically important reduction in the duration of diarrhoea.

The impact of probiotics on the severity of diarrhoea was unclear. The pooled result of the meta-analysis did not show a significant effect. However, the studies using a categorical

scale to express the severity, and were therefore not included in the meta-analysis, observed a significant effect of probiotics in reducing the severity of diarrhoea. Patients receiving probiotics had predominantly mild diarrhoea and only very rarely more severe forms, which were observed in the control group (Section 6.3.2 page 44).[42,46]The time to developing symptoms of diarrhoea could not be meta-analysed, as only two studies reported outcomes, and no meta-analysis was performed. The results of the two studies are contradictory; therefore, no trend of the effect of probiotics on the time to onset of diarrhoea is visible. Nevertheless, it has to be stated, that McFarland found a large difference in time to developing symptoms at seven weeks of follow-up (Section 6.3.2).[31]

C. difficile

Compared to placebo, probiotics do not prevent the colonisation of the intestine with *C. difficile* (RR: 0.95; 95% CI: 0.66 to 1.36). Nevertheless there was a relative reduction of some 46% (95% CI 14% to 76%) in the incidence of *C. difficile* associated diarrhoea with probiotic administration i.e. NNT of 36 patients. It has to be considered that there was clinical heterogeneity, especially in the classification of *C. difficile* associated diarrhoea. Therefore, these results have to be analysed carefully. Although the mechanisms with which probiotics prevent *C. difficile* associated diarrhoea are not fully understood, it is assumed that they influence the immune system and compete with pathogens for adhesion sites in the intestines. Czerucka et al [51] reported that *S. boulardii* synthesized a serine protease that is able to degrade toxins A and B and their respective receptors on the colonic mucosa. Additionally, *S. boulardii* was found to enhance the intestinal immune response to toxin A. The oberservations appear to support the finding of this review that there was no significant reduction in *C. difficile* carriage due to probiotics, but that the occurrence of *C. difficile* associated diarrhoea was significantly reduced. The asymptomatic carriage of *C. difficile* is not seen as the major health care problem, Spencer states, that although the asymptomatic carriage of *C. difficile* may carry epidemic strains to cause disease in others, carriers themselves do not appear to be at high risk of illness; prophylactic treatment with metronidazole or vancomycin is therefore not justified. [52] The mechanisms with which probiotics prevent the development of disease from asymptomatic carriage appear therefore to be able to reduce the health care impact of *C. difficile* infections.

Adverse Effects

In the identified studies, probiotics were not associated with any adverse effects in patients; they are well tolerated by the majority of recipients. However, there have been a few isolated reports of severe infections arising from probiotic ingestion in immune-suppressed or debilitated patients.[53-55] Adverse events included fungemia, caused by *S. boulardii* and

infections of the liver and endocarditis by *L. rhamnosus GG*. [6,20] Marteau et al,[56] who reviewed the tolerance of probiotics, state that probiotics should not be used in powder form in intensive care units, strict hygiene rules concerning probiotics use have to be followed and they should not be used in severely ill patients unless a medical indication is given and tolerance is monitored properly.

8.2 Strengths and limitations of the review

The principle strength of this report was its comprehensiveness both in terms of the extent of searching and inclusion of outcomes. Compared to the previously published reviews by D'Souza and Cremonini,[22,38] 13 more RCTs have been identified. In contrast to previous systematic reviews, the present study sought information on the duration, severity and time to developing symptoms of AAD, and *C. difficile* infection.

This report has three principle limitations, one methodological (i.e. substantial statistical heterogeneity between studies) – and two related to the included trials (i.e. lack of standardisation in outcomes and the methodological quality).

As a consequence of the broad search strategy and inclusion criteria, the included trials spanned a wide range of populations, probiotics and setting. As a result significant statistical heterogeneity was observed in the treatment effect of probiotics on the primary outcome of AAD. Traditionally quantitative pooling of trials is not undertaken in such circumstances. However, given the policy focus of this report, it was deemed appropriate to pool the trials using a random effects model and undertake a detailed exploration of the reasons for this statistical heterogeneity.

There was a considerable lack of standardisation in the reporting of diarrhoea-associated outcomes (such as severity and duration of diarrhoea) across trials. Therefore for a number of outcomes it was only possible to pool the results of a sub-sample of trials. However, a narrative summary of the findings of all trials was also undertaken. For the outcome severity of diarrhoea, there were some discrepancies in the conclusions of these two approaches, as the meta-analysis showed no effect whereas the narrative summary of the other studies did find a significant reduction of severity in the intervention group.

Finally, trial quality was noted to vary considerably and this assessment was hampered by poor reporting. Poor methodological trial quality is known to introduce treatment bias. Nevertheless in this review we found no clear evidence of an association in the magnitude of treatment effect of probiotics and trial quality.

8.3 Implications for clinical practice

The results of this review suggest that probiotics may be effective for preventing AAD, reducing the duration of diarrhoea and most importantly, preventing the incidence of *C. difficile* associated diarrhoea. The cost of a probiotic preparation is assumed to be less than £1 per day,[2,38] and an average antibiotic treatment period is generally within the region of 1 to 3 weeks.[57]Assuming probiotics are taken as supplements for the whole course of antibiotic treatment and some time beyond, a cost of approximately £30 per course seems reasonable. Based on the number needed to treat to prevent *C. difficile* associated diarrhoea of approximately 36, and a costs per case in excess of £4000 (cost inflates to more than £5000 for 2005; see section 7 page 48), the intervention would be cost-neutral if every patient would generate costs of around £111 (36 x 111 = £3,996). Given an assumed cost per £30 per course, it would be appear that probiotics are potentially cost saving. This analysis is probably conservative as probiotics will not only decrease the costs of *C. difficile* associated diarrhoea, but also decrease the incidence and duration of general AAD. Probiotics are likely to be most effective and cost effective in high-risk populations who require taking antibiotics such as young children, the elderly and those with significant morbidity.
There are some issues that need to be considered in implementing the use of probiotics in everyday clinical practice. First, the variability of probiotic preparations and doses used in the analysed studies makes it difficult to determine the 'best' probiotic for a specific patient group. However, this review shows that *S. boulardii* and *L. GG* may be effective for the prevention of AAD. These findings are in line with results of Surawicz et al.[12] The effectiveness of other combinations (i.e. combinations of different *Bifidobacteria* or *Lactobacilli*) was less clear from this review, as there were insufficient trials using these combinations. Data on the effectiveness of these preparations are therefore limited.

Second, due to the lack of regulation of probiotics, it is difficult to determine which probiotic preparation consists of a sufficient amount of the right bacteria or yeast. Therefore, specific attention should be given on freely available probiotic products in the UK to assess their implementation capability.
The two identified ongoing trials examine the effectiveness of probiotics administered in the form of yoghurts. The results will give important information on the applicability of these products.

8.4 Implications for future research

Although there is already a substantive body of RCT evidence that demonstrates the benefit of probiotics, further research is required. In particular, there is a need for further well-designed and better-reported studies that examine the impact of probiotics on health-related quality of life, downstream healthcare resources and costs in different settings (i.e. hospital and primary care). In addition, further studies are needed that examine the optimal dose and formulation of probiotics for use in clinical practice. Further research to identify patient groups in which the additional treatment with probiotics should be implemented is needed. In addition well-designed cost effectiveness studies are required.

9. Appendices

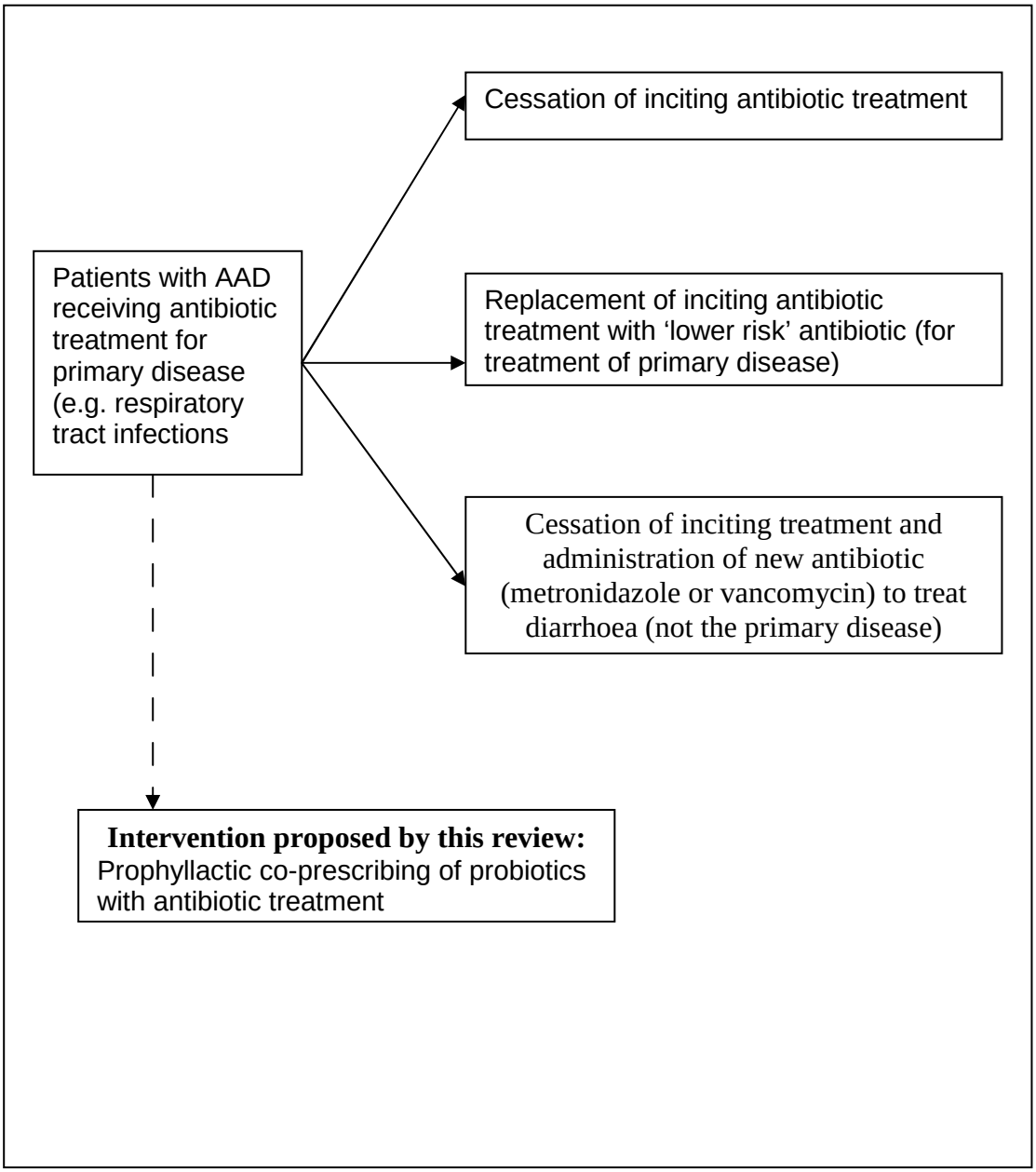
9.1 Appendix 1. Table of antibiotics

Classification of antibiotics

Category	Examples	Characteristic	Indication
Beta-lactam	Penicillin, Cephalosporin, Amoxicillin and Ampicillin	a large class of natural and semi synthetic antibiotics with a lactam ring	Tonsillitis, pneumonia, bronchitis, infections of skin, etc.
Tetracycline	Doxycycline, Minocycline and Tetracycline	a yellow crystalline broad-spectrum antibiotic produced naturally or synthetically.	Urinary tract infections, gonorrhoea, acne, chlamydia, etc.
Aminoglycoside	Streptomycin and Neomycin	a group of antibiotics that inhibit bacterial protein synthesis and are active especially against gram-negative bacteria	Severe or serious bacterial infections
Macrolide and Clindamycin	Erythromycin and clindamycin	• several antibiotics containing a macro cyclic lactone ring that are produced naturally and inhibit bacterial protein synthesis • an antibiotic obtained naturally and effective especially against gram-positive bacteria	• severe or serious bacterial infections, such as: Tonsillitis, pneumonia, bronchitis, infections of skin, etc • Dental prophylaxis, staphylococcal bone and joint infections, peritonitis, etc.
Sulphonamide/ trimethoprim	Co-trimoxazole	• any of various synthetic organic bacteria-inhibiting drugs that are sulphonamides closely related chemically to sulphanilamide • a synthetic antibacterial drug used alone especially to treat urinary tract infections and Pneumocystis carinii pneumonia and in combination with sulfamethoxazole to treat these as well as other infections (as shigellosis or acute otitis media)	• Urinary tract infections, typhus, shigellosis, trachoma, respiratory tract infections, etc.
Quinolone	Ciprofloxacin, Levofloxacin and Ofloxacin, Moxifloxacin	any of a class of synthetic antibacterial drugs that are derivatives of hydroxylated quinolines and inhibit the replication of bacterial DNA	Urinary tract infections, respiratory tract infections, gastrointestinal infections and infections of skin and soft parts.
Other antibiotics (selection)	• Metronidazole	• an antiprotozoal and antibacterial drug	• vaginal trichomoniasis, amoebiasis, and infections by anaerobic bacteria
	• Vancomycine	• an antibiotic derived naturally, that is effective against gram-positive bacteria	• used especially against staphylococci resistant to methicillin
	• Colistin	• a polymyxin produced by a bacterium of the genus *Bacillus* and used against some gram-negative pathogens	• especially of the genera *Pseudomonas, Escherichia, Klebsiella,* and *Shigella*

Source:Farmacotherapeutisch kompas, http://www.fk.cvz.nl/

9.2 Appendix 2. Treatment options for patients with AAD



9.3 Appendix 3. Criteria to asess quality of reviews

Modified version of the Oxman & Guyatt scale to assess the quality of reviews.[23,24]

1. Were the search methods used to find evidence on the primary question(s) stated?
    - *Yes*, **description of databases searched, search strategy, and years reviewed.** *2 points*
    - *Partially*, **description of methods not complete.** *1 point*
    - *No*, **no description of search methods.** *0 points*
2. Was the search for evidence reasonably comprehensive?
    - *Yes*, **at least one computerized database searched as well as a search of unpublished or non-indexed literature.** *2 points*
    - *Can't tell*, **search strategy partially comprehensive, at least one of the strategies were performed.** *1 point*
    - *No*, **search not comprehensive or not described well.** *0 points*
3. Were the criteria used for deciding which studies to include in the review reported?
    - *Yes*, **in- and exclusion criteria clearly defined.** *2 points*
    - *Partially*, **reference to in- and exclusion criteria can be found but are not defined clearly enough.** *1 point*
    - *No*, **no criteria defined.** *0 points*
4. Was bias in the selection of articles avoided?
    - *Yes*, **issues influencing selection bias were covered. Two of three of the following bias avoiding strategies were used: two or more assessors independently judged study relevance and selection using predetermined criteria, reviewers were blinded to identifying features of the study, and assessors were blinded to treatment outcome.** *2 points*
    - *Can't tell*, **only one of the strategies used.** *1 point*
    - *No*, **selection bias was not avoided or was not discussed.** *0 points*
5. Were the criteria used for assessing the validity for the studies that were reviewed reported?
    - *Yes*, **criteria defined.** *2 points*
    - *Partially*, **some discussion or reference to criteria.** *1 point*
    - *No*, **validity or methodological quality criteria not used or not described.** *0 points*
6. Was the validity for each study cited assessed using appropriate criteria?
    - *Yes*, **criteria used addressed the major factors influencing bias.** *2 points*
    - *Partially*, **some discussion, but not clearly described predetermined criteria.** *1 point*
    - *No*, **criteria not used or not described.** *0 points*
7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?
    - *Yes*, **qualitative and quantitative methods are acceptable.** *2 points*
    - *Partially*, **partial description of methods to combine and tabulate; not sufficient to duplicate.** *1 point*
    - *No*, **methods not stated or described.** *0 points*
8. Were findings of the relevant studies combined appropriately relative to the primary question of the overview?
    - *Yes*, **combining of studies appears acceptable.** *2 points*
    - *Can't tell*, **should be marked if in doubt.** *1 point*

- *No*, **no attempt was made to combine findings, and no statement was made regarding the inappropriateness of combining findings.** *0 points*

9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?

- *Yes*, **data were reported that support the main conclusions regarding the primary question(s) that the overview addresses.** *2 points*
- *Partially, 1 point*
- *No*, **conclusions not supported or unclear.** *0 points*

10. How would you rate the scientific quality of this overview?

- **Adding up the scores from question 1-9. Maximum quality score is 18 points.**

Methodological scored of Review articles

	D'Souza		Cremonini	
Question	Answer	score	Answer	score
Q 1	Yes	2	Yes	2
Q 2	Can't tell	1	Yes	2
Q 3	Partially	1	Yes	2
Q 4	Can't tell	1	Can't tell	1
Q 5	No	0	Partially	1
Q 6	No	0	Partially	1
Q 7	Yes	2	Yes	2
Q 8	Yes	2	Yes	2
Q 9	Yes	2	Yes	2
Q 10	Major flaws	11	Minor flaws	15

9.4 Appendix 4. Search strategy

Search strategy MEDLINE

#	Search History	Results
1	Bifidobacterium/ or probiotics.mp. or PROBIOTICS/ or Lactobacillus acidophilus/	3606
2	(s boulardii or saccharomyces boulardii).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	163
3	SACCHAROMYCES/ or saccharomyces.mp.	73043
4	(l acidophilus or lactobacillus acidophilus).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	1310
5	LACTOBACILLUS/ or lactobacillus.mp.	10813
6	(l rhamnosus gg or lactobacillus rhamnosus gg).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	60
7	bacillus subtilis.mp. or Bacillus subtilis/	18556
8	1 or 2 or 3 or 4 or 5 or 6 or 7	103013
9	diarrhea.mp. or exp DIARRHEA/	47131
10	diarrhoea.mp.	13276
11	gastrointestinal diseases.mp. or exp Gastrointestinal Diseases/	464927
12	(c difficile or clostridium difficile).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	3650
13	colitis/ or enterocolitis/ or enterocolitis, pseudomembranous/	12279
14	9 or 10 or 11 or 12 or 13	502275
15	8 and 14	1739
36	Randomized controlled trial filter medline	632888
37	15 and 36	276
38	limit 37 to humans	276

Search strategy Cochrane Library

ID	Search	Hits
#1	**probiotic*** in **All Fields** in **all products**	227
#2	MeSH descriptor **Probiotics** explode all trees in **MeSH products**	134
#3	**"s boulardii"** in **All Fields** in **all products**	3
#4	**"saccharomyces boulardii"** in **All Fields** in **all products**	37
#5	**"l acidophilus"** in **All Fields** in **all products**	4
#6	**"lactobacillus acidophilus"** in **All Fields** in **all products**	86
#7	**"l rhamnosus gg"** in **All Fields** in **all products**	1
#8	**"lactobacillus rhamnosus gg"** in **All Fields** in **all products**	7
#9	**"bacillus subtilis"** in **All Fields** in **all products**	26
#10	**lactobacillus** in **All Fields** in **all products**	436
#11	**saccharomyces** in **All Fields** in **all products**	97
#12	MeSH descriptor **Lactobacillus** explode all trees in **MeSH products**	288
#13	MeSH descriptor **Saccharomyces** explode all trees in **MeSH products**	54
#14	(**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13**)	635
#15	MeSH descriptor **Diarrhea** explode all trees in **MeSH products**	1621
#16	**diarrhea** in **All Fields** in **all products**	5850
#17	**diarrhoea** in **All Fields** in **all products**	5850
#18	MeSH descriptor **Gastrointestinal Diseases** explode all trees in **MeSH products**	14209
#19	**"gastrointestinal disease"** in **All Fields** in **all products**	261
#20	**colitis** in **All Fields** in **all products**	1038
#21	MeSH descriptor **Enterocolitis, Pseudomembranous** explode all trees in **MeSH products**	83
#22	**"c difficile"** in **All Fields** in **all products**	9
#23	**"clostridium difficile"** in **All Fields** in **all products**	128
#24	MeSH descriptor **Clostridium Infections** explode all trees in **MeSH products**	181
#25	MeSH descriptor **Clostridium difficile** explode all trees in **MeSH products**	43
#26	(**#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25**)	19727
#27	(**#14** AND **#26**)	212

9.5 Appendix 5. Jadad Scale

Instrument used to assess quality of randomised controlled trials.
Adapted Jadad scale[25]

1. Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items:
A score of 1 point for each 'yes' and 0 points for each 'no'.

1 additional point was given if:
For question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.)
And:
If for question 2 the method of double blinding was well described and it was appropriate (identical placebo, active placebo, dummy, etc.)

The following guidelines were used for assessment:

1. Randomisation
   A Method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigator could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
2. Double blinding
   A study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned and well described.
3. Withdrawals and dropouts
   Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points. An exception is made, if the presented data clearly describes that there have been no withdrawals.

9.6 Appendix 6. Data extraction form

Trial details	Trial ID		
	Author		
	Year of publication		
	Centres and location		
	Co-Author		
	Subsidizer		
	Study start and end dates		
	Type of trial design		
	Setting of study		
	Definition and diagnostic criteria for diarrhoea		
	Definition and diagnostic criteria for C. difficile associated diarrhoea		
	Antibiotic(s) used		
	Antibiotic duration, dosage and schedule		
	Probiotic(s) used		
	Probiotic duration, dosage and schedule		
	Reason for antibiotic medication		
	Control(s)		
Quality assessment			Jadad Scale (Yes=1 point, No=0)
	Was assignment of treatment described as random?		
	Was method of randomisation well described and appropriate?		
	Was the method really random?		
	Was allocation of treatment concealed?		
	What was concealment method?		
	Was the study described as double blind?		
	Who was blinded to treatment?		
	Was method of blinding adequately described?		
	Were withdrawals stated?		
	Were reasons for withdrawals stated?		
	Was ‘intention-to-treat’ used?		

	Score on Jadad Scale, total (0-5)						
	Comments						
Eligibility criteria	Inclusion criteria						
	Exclusion criteria						
Baseline characteristics			Probiotics group			Control group	
	Number randomised						
	Number analysed						
	Age						
	Male:female						
	Allergies to antibiotics						
	Duration of antibiotic treatment						
	C. difficile carrier						
	Dietary differences						
	Comments						
Outcomes And Results	Number of measurement points						
	Primary outcome(s) including time points if repeated		Incidence of diarrhoea	Duration of diarrhoea (or severity of diarrhoea)	Incidence of C. difficile carriers	Incidence of C. difficile infection	Incidence of recurrent C. difficile infection
		Probiotics					
		Control					
		Probiotics					
		Control					
		Probiotics					
		Control					
		Probiotics					
		Control					
		Probiotics					

		Control					
	Other primary outcome(s)						
	Secondary outcome(s)	Quality of life	GP visits	Hospital admissions	Costs	Days of work	Days of work by carer (when child is patient)
	Other secondary outcome(s)						
	'Ad hoc' outcomes (if emphasised and not in methods)						
	Effect size						
	Direction of effect						
	Comments						
		Probiotics	Control				
	Median follow-up						
	Withdrawals including reasons where specified						
	Comments (including whether unadjusted results reported)						
Adverse events	Criteria for reporting						
	Events: Pseudomembranous colitis Mortality Others						
	Comments						
General comments on study							

9.7 Appendix 7. List of excluded studies

Reference List

Sorted by reasons of exclusion:

Abstracts:

1. Potts L, Lewis SJ, Barry R. Randomised double blind placebo controlled study of the ability of saccharomyces boulardii to prevent antibiotic related diarrhoea [abstract]. *Gut* 1996;**38 Suppl 1**:A61.

2. Elmer G. Prospective study in prevention by Saccharomyces boulardii of diarrhea secondary to antibiotic therapy. *Medecine et Chirurgie Digestives* 1988;**. 17**.

Comments:

3. Hotz J,.Hotz J . [Prevention of antibiotic-associated diarrhea by Saccharomyces boulardii: a prospective study]. [German]. *Zeitschrift fur Gastroenterologie* 1990;**28**:259-60.

4. Arnheim K. Saccharomyces boulardii in Clostridium difficle infections. *Zeitschrift fur Allgemeinmedizin* 1995;**. 71**.

5. Awasthi S. Lactobacillus GG reduced diarrhoea incidence in children treated with antibiotics. *Evidence Based Medicine* 2000;**. 5** .

6. Huntley AL,.Martin KW. Probiotics show promise for prevention and treatment of diarrhoea. *FOCUS ALTERN.COMPLEMENT THER.* 2001;**2002 Dec; 7**:358-9.

7. Beckly J, Lewis S, Beckly J, Lewis S. Probiotics and antibiotic associated diarrhoea. The case for probiotics remains unproved.[comment]. *BMJ* 2002;**325**:901.

8. Probiotics prevent diarrhoea due to antibiotic treatment, review says. *Pharmaceutical Journal* 2002;**. 268**:15.

9. Battle M, Teare L, Law S, Fulton J. Probiotics and antibiotic associated diarrhoea - Lactulose is effective. *British Medical Journal* 2002;**325**:901-2.

10. Donohoe M. Lactobacillus casei-fortified yoghurt reduces the severity and duration of diarrhoea in healthy children. *FOCUS ALTERN.COMPLEMENT THER.* 2002;**1999 Dec; 4**:204-5.

11. Shaughnessy A,.Shaughnessy A. Probiotics use decreases antibiotic-associated diarrhea. *Am.Fam.Physician* 2003;**67**:1782.

12. Well-proven biotherapeutic agent (Perenterol) for the prevention and treatment of diarrhea. *MMW Fortschr.Med.* 2003;**. 145**:24.

13. Mack DR,.Lebel S. Role of probiotics in the modulation of intestinal infections and inflammation. *Current Opinion in Gastroenterology* 2004;**. 20**.

14. Probiotics should be more widely used in our hospitals. *NURS.TIMES* 2004;**2004 Mar 30-Apr 5; 100**:16-7.

15. Studies confirm efficacy of probiotics for diarrhea. *NUTR.MD* 2005;**D.. 2001 Oct; 27**:5.

No probiotic used:

16. Lode H, Von Der HN, Ziege S, Borner K, Nord CE. Ecological effects of linezolid versus amoxicillin/clavulanic acid on the normal intestinal microflora. *Scandinavian Journal of Infectious Diseases* 2001; **. 33**.

Not randomised:

17. Linquette M, May JP, Linquette M, May JP. [Clinical trial of a combination of tetracycline chlorhydrate and yeast]. [French]. *Lille Med.* 1966;**11**:1056-7.

18. Colombel JF, Cortot A, Neut C, Romond C, Colombel JF, Cortot A *et al*. Yoghurt with Bifidobacterium longum reduces erythromycin-induced gastrointestinal effects. *Lancet* 1987;**2**:43.

19. Michielutti F, Bertini M, Presciuttini B, Andreotti G, Michielutti F, Bertini M *et al*. [Clinical assessment of a new oral bacterial treatment for children with acute diarrhea]. [Italian]. *Minerva Medica* 1996;**87**:545-50.

20. Ahuja MC, Khamar B, Ahuja MC, Khamar B. Antibiotic associated diarrhoea: a controlled study comparing plain antibiotic with those containing protected lactobacilli. *Journal of the Indian Medical Association* 2002;**100**:334-5.

21. Seki H, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A *et al* . Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI. *Pediatrics International* 2003;**. 45**.

22. Erdeve O, Tiras U, Dallar Y, Erdeve O, Tiras U, Dallar Y. The probiotic effect of Saccharomyces boulardii in a pediatric age group. *Journal of Tropical Pediatrics* 2004;**50** :234-6.

23. Oleinichenko EV, Mitrokhin SD, Nonikov VE, Minaev VI. [Effectiveness of acipole in prevention of enteric dysbacteriosis due to antibacterial therapy]. [Russian]. *Antibiotiki.i Khimioterapiia.* 1999;**44**:23-5.

Other medical indication:

24. Yost RL, Gotz VP, Yost RL, Gotz VP. Effect of a lactobacillus preparation on the absorption of oral ampicillin. *Antimicrobial Agents & Chemotherapy* 1985;**28**:727-9.

25. Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH, Saavedra JM *et al*. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet* 1994;**344**:1046-9.

26. Stotzer PO, Blomberg L, Conway PL, Henriksson A, Abrahamsson H, Stotzer PO *et al*. Probiotic treatment of small intestinal bacterial overgrowth by Lactobacillus fermentum KLD. *Scandinavian Journal of Infectious Diseases* 1996;**28**:615-9.

27. Bleichner G, Blehaut H, Mentec H, Moyse D, Bleichner G, Blehaut H *et al*. Saccharomyces boulardii prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial. *Intensive Care Medicine* 1997;**23**:517-23.

28. Sullivan A, Palmgren AC, Nord CE. Effect of Lactobacillus paracasei on intestinal colonisation of Lactobacilli, Bifidobacteria and Clostridium difficile in elderly persons. *Anaerobe.* 2001;**7**:67-70.

29. Mattar AF, Drongowski RA, Coran AG, Harmon CM. Effect of probiotics on enterocyte bacterial translocation in vitro. *Pediatric Surgery International* 2001;**. 17**.

30. Szajewska H,.Mrukowicz JZ. Analysis of evidence for clinical efficacy of probiotic products registered in Poland in the treatment and prevention of acute infectious diarrhea in infants and young children (Provisional record). *Pediatria.Polska.* 2002;**77**:495-500.

31. Hopkins MJ,.Macfarlane GT. Changes in predominant bacterial populations in human faeces with age and with Clostridium difficile infection. *J.Med.Microbiol.* 2002;**. 51**.

32. Mansour-Ghanaei F, Dehbashi N, Yazdanparast K, Shafaghi A, Mansour-Ghanaei F, Dehbashi N *et al*. Efficacy of saccharomyces boulardii with antibiotics in acute amoebiasis. *World Journal of Gastroenterology* 2003;**9**:1832-3.

33. Duggan C, Penny ME, Hibberd P, Gil A, Huapaya A, Cooper A *et al*. Oligofructose-supplemented infant cereal: 2 randomized, blinded, community-based trials in Peruvian infants. *American Journal of Clinical Nutrition* 2003;**77**:937-42.

34. Chouraqui JP, Van Egroo LD, Fichot MC, Chouraqui JP, Van Egroo LD, Fichot MC. Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings.[see comment]. *Journal of Pediatric Gastroenterology & Nutrition* 2004;**38**:288-92.

35. Sullivan A, Johansson A, Svenungsson B, Nord CE, Sullivan A, Johansson A *et al*. Effect of Lactobacillus F19 on the emergence of antibiotic-resistant microorganisms in the intestinal microflora. *Journal of Antimicrobial Chemotherapy* 2004;**54**:791-7.

36. Naaber P, Smidt I, Stsepetova J, Brilene T, Annuk H, Mikelsaar M. Inhibition of Clostridium difficile strains by intestinal Lactobacillus species. *J.Med.Microbiol.* 2004;**53**:551-4.

37. Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M , Mikolajczyk W, Szajewska H *et al*. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. *Journal of Pediatrics* 2001;**138**:361-5.

Not a preventive study:

38. Wunderlich PF, Braun L, Fumagalli I, D'Apuzzo V, Heim F, Karly M *et al*. Double-blind report on the efficacy of lactic acid-producing Enterococcus SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *Journal of International Medical Research* 1989;**17**:333-8.

Reviews:

39. Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J, Jr. Clostridium difficile-associated diarrhea and colitis. *INFECT.CONTROL HOSP.EPIDEMIOL.* 195;**1995 Aug; 16**:459-77.

40. Robertson J. In children receiving antibiotics, does coadministration of Lactobacillus GG reduce the incidence of diarrhea?... commentary on Vanderhoof JA, Whitney DB, Antonson DL, et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J PEDIATR 1999;135:564-568. *WJM WEST J.MED.* 397;**2000 Dec; 173**:397.

41. Gagan MJ. Review: probiotics are effective in preventing antibiotic associated diarrhoea. *EVID.BASED NURS.* 1916;**2003 Jan; 6**:16.

42. Posani T. Clostridium difficile: causes and interventions. *CRIT CARE NURS.CLIN.NORTH AM.* 1921;**2004 Dec; 16**:547-51.

43. Vanderhoof JA. Probiotics: future directions... Probiotics in Health and Disease, proceedings of symposium held in San Diego, CA, April, 2000. *American Journal of Clinical Nutrition* 1933;**2001 Jun; 73**:1152S-5S.

44. Braswell B,.O'Connell CB. Advisor forum. Pseudomembranous colitis. *CLIN.ADVIS.* 1938;**2004 Nov; 7**:38.

45. Isolauri E. Probiotics in human disease... Probiotics in Health and Disease, proceedings of symposium held in San Diego, CA, April, 2000. *American Journal of Clinical Nutrition* 1946;**2001 Jun; 73**:1142S-6S.

46. Birdsall TC. Gastrointestinal candidiasis: fact or fiction? *ALTERN.MED.REV.* 1948;**1997 Oct; 2**:346-54.

47. Saavedra JM. Clinical applications of probiotic agents... Probiotics in Health and Disease, proceedings of symposium held in San Diego, CA, April, 2000. *American Journal of Clinical Nutrition* 1955;**2001 Jun; 73**:1147S-51S.

48. Liang MEK. Clostridium difficile infection. *REV.CLIN.GERONTOL.* 1969;**2003 Feb; 13**:1-9.

49. Kopp-Hoolihan L. Prophylactic and therapeutic uses of probiotics: a review. *J.AM.DIET.ASSOC.* 1976;**2001 Feb; 101**:229-41.

50. Robertson J. Lactobacillus GG reduced diarrhoea incidence in antibiotic treated children... commentary on Vanderhoof JA, Whitney DB, Antonson DL et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J PEDIATR 1999 Nov;135:564-8. *EVID.BASED NURS.* 1976;**2000 Jul; 3**:76.

51. Lidbeck A,.Nord CE. Lactobacilli in relation to human ecology and antimicrobial therapy. *International Journal of Tissue Reactions* 1991;**. 13**.

52. Ultra-levure in the annual congress of the American Gastroenterological Association. *Gazette Medicale* 1993;**. 100**.

53. Pothoulakis C,.LaMont JT. Clostridium difficile colitis and diarrhea. *Gastroenterol.Clin.North Am.* 1993;**. 22**.

54. Mazza P. The use of Bacillus subtilis as an antidiarrhoeal microorganism. *Bollettino Chimico Farmaceutico* 1994;**. 133**.

55. Harris AD. Review: probiotics are effective in preventing antibiotic-associated diarrhea. *ACP J.CLUB* 1995;**2002 Nov-Dec; [137]** :95.

56. Elmer GW, Surawicz CM, McFarland LV, Elmer GW, Surawicz CM, McFarland LV. Biotherapeutic agents. A neglected modality for the treatment and prevention of selected intestinal and vaginal infections.[see comment]. [Review] [81 refs]. *JAMA* 1996;**275**:870-6.

57. Sibal A,.Davison SM. Saccharomyces boulardii - Scope for use in gastrointestinal disorders. *Singapore Paediatric Journal* 1996;**. 38**.

58. Broussard EK,.Surawicz CM. Probiotics and prebiotics in clinical practice. *NUTR.CLIN.CARE* 1996;**2004 Jul-Sep; 7**:104-13.

59. Eddy JT, Stamatakis MK, Makela EH, Eddy JT, Stamatakis MK, Makela EH. Saccharomyces boulardii for the treatment of Clostridium difficile-associated colitis. *Ann.Pharmacother.* 1997;**31**:919-21.

60. McFarland LV,.Elmer GW. Pharmaceutical probiotics for the treatment of anaerobic and other infections. *Anaerobe* 1997;**. 3**.

61. Rappenhoner B, Pfeil T, Rychlik R. On the socioeconomic cost structure of the diarrhea treatment - A cost benefit analysis of saccharomyces boulardii. *Med.Welt* 1997;**. 48**.

62. Lewis SJ, Freedman AR, Lewis SJ, Freedman AR. Review article: the use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. [Review] [144 refs]. *Alimentary Pharmacology & Therapeutics* 1998;**12**:807-22.

63. Famularo G, De Simone C, Matteuzzi D, Pirovano F. Traditional and high potency probiotic preparations for oral bacteriotherapy. *Biodrugs* 1999;**. 12**.

64. Williams CN. Clostridium difficile diarrhea. *Can.J.Gastroenterol.* 1999;**. 13**.

65. Surawicz CM,.McFarland LV. Pseudomembranous colitis: Causes and cures. *Digestion* 1999;**. 60**.

66. Mombelli B, Gismondo MR, Mombelli B, Gismondo MR. The use of probiotics in medical practice. [Review] [56 refs]. *Int.J.Antimicrob.Agents* 2000;**16**:531-6.

67. Bergogne-Berezin E,.Bergogne-Berezin E. Treatment and prevention of antibiotic associated diarrhea. [Review] [25 refs]. *Int.J.Antimicrob.Agents* 2000;**16**:521-6.

68. Rolfe RD,.Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. [Review] [85 refs]. *J.Nutr.* 2000;**130**:396S-402S.

69. de Roos NM, Katan MB, de Roos NM, Katan MB. Effects of probiotic bacteria on diarrhea, lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. [Review] [80 refs]. *American Journal of Clinical Nutrition* 2000;**71**:405-11.

70. Marchand J,.Vandenplas Y. Micro-organisms administered in the benefit of the host: Myths and facts. *European Journal of Gastroenterology & Hepatology* 2000;**. 12**.

71. McFarland LV. A review of the evidence of health claims for biotherapeutic agents. *Microbial Ecology in Health & Disease* 2000;**. 12**.

72. Penna FJ, Filho LAP, Calcado AC, Junior HR, Nicoli JR. Up-to-date clinical and experimental basis for the use of probiotics. *Jornal de Pediatria* 2000;**. 76**.

73. Vanderhoof JA. Probiotics and intestinal inflammatory disorders in infants and children. *Journal of Pediatric Gastroenterology & Nutrition* 2000;**. 30**.

74. Brar HS,.Surawicz CM. Pseudomembranous colitis: An update. *Can.J.Gastroenterol.* 2000;**. 14**.

75. Elmer GW,.Elmer GW. Probiotics: "living drugs". [Review] [102 refs]. *Am.J.Health-Syst.Pharm.* 2001;**58**:1101-9.

76. Madsen KL. The use of probiotics in gastrointestinal disease. *Can.J.Gastroenterol.* 2001;**. 15**.

77. Playne M,.Salminen S. Can antibiotic associated diarrhoea be alleviated by probiotics? *Today's Life Science* 2001; **. 13**.

78. Andersson H, Asp N-G, Bruce A, Roos S, Wadstrom T, Wold AE. Health effects of probiotics and prebiotics a literature review on human studies. *Scandinavian Journal of Nutrition/Naringsforskning* 2001;**. 45**.

79. McNaught CE,.MacFie J. Probiotics in clinical practice: A critical review of the evidence. *Nutrition Research* 2001;**. 21**.

80. O'Sullivan GC. Probiotics. *British Journal of Surgery* 2001;**. 88**.

81. Marteau PR, De Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. *American Journal of Clinical Nutrition* 2001;**. 73**.

82. Wilcox MH,.Dave J. Treatment options in Clostridium difficile infection. *Reviews in Medical Microbiology* 2001;**. 12**.

83. Vanderhoof JA,.Young RJ. The role of probiotics in the treatment of intestinal infections and inflammation. *Current Opinion in Gastroenterology* 2001;**. 17**.

84. Probiotics for antibiotic-associated diarrhoea. *Bandolier* 2001;**2002 Oct; 9**:1-2.

85. Marteau P, Seksik P, Jian R, Marteau P, Seksik P, Jian R. Probiotics and health: new facts and ideas. [Review] [30 refs]. *Curr.Opin.Biotechnol.* 2002;**13**:486-9.

86. Cremonini F, Di Caro S, Santarelli L, Gabrielli M , Candelli M, Nista EC *et al*. Probiotics in antibiotic-associated diarrhoea. *Digestive & Liver Disease* 2002;**34 Suppl 2**:S78-S80.

87. Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G *et al*. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. [Review] [39 refs]. *Alimentary Pharmacology & Therapeutics* 2002;**16**:1461-7.

88. Saavedra JM, Tschernia A, Saavedra JM, Tschernia A. Human studies with probiotics and prebiotics: clinical implications. [Review] [45 refs]. *Br.J.Nutr.* 2002;**87 Suppl 2**:S241-S246.

89. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ, D'Souza AL, Rajkumar C *et al*. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis.[see comment]. [Review] [22 refs]. *BMJ* 2002;**324**:1361.

90. Marteau PR,.Marteau PR. Probiotics in clinical conditions. [Review] [112 refs]. *Clin.Rev.Allergy Immunol.* 2002;**22**:255-73.

91. Isolauri E, Kirjavainen PV, Salminen S, Isolauri E, Kirjavainen PV, Salminen S. Probiotics: a role in the treatment of intestinal infection and inflammation?. [Review] [55 refs]. *Gut* 2002;**50 Suppl 3**:III54-III59.

92. -D-, apos-, Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis (Structured abstract). *BMJ* 2002;**324**:1361-4.

93. Schneider S. Probiotics in prevention of antibiotic associated diarrhoea: Meta-analysis. *Nutrition Clinique et Metabolisme* 2002;**. 16**.

94. Joyce AM,.Burns DL. Recurrent Clostridium difficile colitis: Tackling a tenacious nosocomial infection. *POSTGRAD.MED.* 2002;**. 112**:01.

95. Piche T. Antibiotic-associated diarrhea. *Hepato-Gastro* 2002;**. 9**.

96. Probiotics: Preventing antibiotic associated diarrhoea. *Medicine Today* 2002;**. 3**.

97. Barbut F,.Meynard JL. Managing antibiotic associated diarrhoea: Probiotics may help in prevention. *British Medical Journal* 2002;**. 324**:08.

98. Gionchetti P, Rizzello F, Campieri M. Probiotics in gastroenterology. *Current Opinion in Gastroenterology* 2002;**. 18**.

99. Gosar JG. Saccharomyces boulardii in the prevention of pseudomembranous colitis. *J.PHARM.TECHNOL.* 2002;**. 18**.

100. Shaughnessy A. Can probiotics decrease the likelihood of antibiotic-associated diarrhea? *EVID.BASED PRACT.* 2002;**2003 Feb; 6**:3.

101. Goossens D, Jonkers D, Stobberingh E, van den BA , Russel M, Stockbrugger R *et al*. Probiotics in gastroenterology: indications and future perspectives. [Review] [135 refs]. *Scand.J.Gastroenterol.Suppl* 2003;15-23.

102. Reid G, Jass J, Sebulsky MT, McCormick JK, Reid G, Jass J *et al*. Potential uses of probiotics in clinical practice. [Review] [152 refs]. *Clin.Microbiol.Rev.* 2003;**16**:658-72.

103. Shanahan F,.Shanahan F. Probiotics: a perspective on problems and pitfalls. [Review] [18 refs]. *Scand.J.Gastroenterol.Suppl* 2003;34-6.

104. Pillai A,.Nelson R. Probiotics for Clostridium difficile-associated colitis in adults. *Pillai.A, Nelson.R.Probiotics.for Clostridium.difficile.associated.colitis.in adults.The Cochrane Database of Systematic Reviews: Protocols.2003 Issue.4 John.Wiley.& Sons., Ltd.Chichester, UK DOI.: 10.1002./14651858.CD004611.* 2003.

105. Ouwehand AC. Probiotics: Time to move beyond Metchnikoff? *Drug Discovery Today* 2003;**. 8**:01.

106. Surawicz CM. Probiotics, antibiotics-associated diarrhoea and Clostridium diffucile diarrhoea in humans. *Baillieres Best Pract.Res.Clin.Gastroenterol.* 2003;**. 17**.

107. McConaghy JR. Do probiotics decrease antibiotic-associated diarrhea? *Journal of Family Practice* 2003;**. 52**:01.

108. Lestin F, Pertschy A, Rimek D. Fungemia after oral treatment with Saccharomyces boulardii in a patient with multiple co-morbidities. *Dtsch.Med.Wochenschr.* 2003;**128**:2531-3.

109. Surawicz CM. Antibiotic-associated diarrhea in children: How many dirty diapers? *Journal of Pediatric Gastroenterology and Nutrition* 2003;**37**:2-3.

110. Vanderhoof JA, Young RJ, Vanderhoof JA, Young RJ . Current and potential uses of probiotics. [Review] [53 refs]. *Ann.Allergy Asthma Immunol.* 2004;**93**:S33-S37.

111. Fox CH, Dang G, Fox CH, Dang G. Probiotics in the prevention and treatment of diarrhea. [Review] [28 refs]. *J.Altern.Complement Med.* 2004;**10**:601-3.

112. Hamilton-Miller JM,.Hamilton-Miller JMT. Probiotics and prebiotics in the elderly. [Review] [60 refs]. *Postgrad.Med.J.* 2004;**80**:447-51.

113. Johnston BC, Wiebe N, Crumley E, Supina A, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Johnston.BC, Wiebe.N., Crumley.E., Supina.A, Vohra.S.Probiotics.for the prevention.of pediatric antibiotic.associated.diarrhea.The Cochrane Database of Systematic Reviews: Protocols.2004.Issue.2 John.Wiley.& Sons., Ltd.Chichester, UK DOI.: 10.1002./1465* 2004.

114. Hull MW,.Beck PL. Clostridium difficile - Associated colitis. *Can.Fam.Physician* 2004;**50**.

115. Naaber P,.Mikelsaar M. Interactions between lactobacilli and antibiotic-associated diarrhea. *Advances in Applied Microbiology* 2004;**. 54**.

116. Koornhof HJ. Probiotics - How functional are they? *South African Medical Journal* 2004;**. 94**.

117. Fontana M,.Martelli L. Probiotics in paediatric gastroenterology. *Medico e Bambino* 2004;**. 23**:31.

118. Fedorak RN,.Madsen KL. Probiotics and prebiotics in gastrointestinal disorders. *Current Opinion in Gastroenterology* 2004;**. 20**.

119. Beaugerie L,.Petit JC. Antibiotic-associated diarrhoea. *Baillieres Best Pract.Res.Clin.Gastroenterol.* 2004;**18**:337-52.

120. Cherifi S, Robberecht J, Miendje Y. Saccharomyces cerevisiae fungemia in an elderly patient with Clostridium difficile colitis. *Acta Clinica Belgica* 2004;**59**:223-4.

121. Berrington A, Borriello SP, Brazier J, Duckworth G, Foster K, Freeman R *et al*. National Clostridium difficile standards group: Report to the department of health. *J.Hosp.Infect.* 2004;**56**:1-38.

122. Sullivan A, Nord CE, Sullivan A, Nord CE. Probiotics and gastrointestinal diseases. [Review] [107 refs] . *J.Intern.Med.* 2005;**257**:78-92.

123. Ohl ME, Stevermer JJ, Meadows S. What are effective therapies for Clostridium difficile-associated diarrhea? *Journal of Family Practice* 2005;**. 54**.

124. Hunter M. When antibiotics go wrong. *GASTROINTEST.NURS.* 2005;**2004 Apr; 2**:14-7.

125. Van Niel CW. Probiotics: Not just for treatment anymore. *Pediatrics* 2005;**115**:174-7.

126. TRICKS OF THE TRADE. *EMERG.MED.* 2006;**2004 Jun; 36**:6.

Side effects of probiotics:

127. Lherm T, Monet C, Nougiere B, Soulier M, Larbi D, Le Gall C *et al*. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Medicine* 2002;**. 28**.

Treatment:

128. Satta A, Delplano A, Cossu P, Cossellu S, Satta A, Delplano A *et al*. [Treatment of enterocolitis and other intestinal disorders with a Bifidobacterium bifidum and Lactobacillus acidophilus combination]. [Italian]. *Clin.Ter.* 1980;**94**:173-84.

129. Chapoy P,.Chapoy P. [Treatment of acute infantile diarrhea: controlled trial of Saccharomyces boulardii]. [French]. *Ann.Pediatr.(Paris)* 1985;**32**:561-3.

130. Surawicz CM, McFarland LV, Elmer G, Chinn J, Surawicz CM, McFarland LV *et al*. Treatment of recurrent Clostridium difficile colitis with vancomycin and Saccharomyces boulardii. *American Journal of Gastroenterology* 1989;**84**:1285-7.

131. Höchter W, Chase D, Hagenhoff G. Saccharomyces boulardii in Treatment of Acute Adult Diarrhoea. Efficacy and Tolerance. *Munchener.Medizinische Wochenschrift* 1990;**132**:188-92.

132. Drug-induced diarrhea treated with acidophilus. *NURSES DRUG ALERT* 1992;**1994 Dec; 18**:92.

133. McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA *et al*. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease.[erratum appears in JAMA 1994 Aug 17;272(7):518]. *JAMA* 1994;**271**:1913-8.

134. Goerg KJ, Schlorer E, Goerg KJ, Schlorer E. [Probiotic therapy of pseudomembranous colitis. Combination of intestinal lavage and oral administration of Escherichia coli]. [German]. *Dtsch.Med.Wochenschr.* 1998;**123**:1274-8.

135. Elmer GW, McFarland LV, Surawicz CM, Danko L, Greenberg RN, Elmer GW *et al*. Behaviour of Saccharomyces boulardii in recurrent Clostridium difficile disease patients. *Alimentary Pharmacology & Therapeutics* 1999;**13**:1663-8.

136. Surawicz CM, McFarland LV, Greenberg RN, Rubin M , Fekety R, Mulligan ME *et al*. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. *Clinical Infectious Diseases* 2000;**31**:1012-7.

137. Pochapin M,.Pochapin M. The effect of probiotics on Clostridium difficile diarrhea.[see comment]. *American Journal of Gastroenterology* 2000;**95**:S11-S13.

138. Sudarmo SM, Ranuh RG, Rochim A, Soeparto P, Sudarmo SM, Ranuh RG *et al* . Management of infant diarrhea with high-lactose probiotic-containing formula. *Southeast Asian Journal of Tropical Medicine & Public Health* 2003;**34**:845-8.

139. Gaon D, Garcia H, Winter L, Rodriguez N, Quintas R, Gonzalez SN *et al*. Effect of Lactobacillus strains and Saccharomyces boulardii on persistent diarrhea in children. *Medicina* 2003;**63**:293-8.

140. Wullt M, Hagslatt ML, Odenholt I, Wullt M, Hagslatt MLJ, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. *Scandinavian Journal of Infectious Diseases* 2003;**35**:365-7.

9.8 Appendix 8. Data extracted

9.8.1 Information on study characteristics

Trial ID	***31***	***50***	***88***
Author	***Plummer S[1]***	***La Rosa M***	***Cremonini F***
Year of publication	*2004*	*2003*	*2002*
Centres and location	*[1]Cultech Ltd., York Chambers [2]Addenbrooke`s Hospital, Department of Gastroenterology, Cambridge UK*	*Department of Pediatrics, Universita degli Studi di Cantania, Catania*	*Department of Internal Medicine, University Cattolica del Sacro Cuoro, Policlinico Gemelli, Roma, Italy*
Co-Author	*Weaver MA[1]; Harris JC[1]; Dee P[2]; Hunter J[2]*	*Bottaro G; Gulino N; Gambuzza F; Forti Di F; Ini G; Tornambe E*	*DiCaro S; Covino M; Armuzzi A; Gabrielli M; Santarelli L; Nista EC; Cammarota G; Gasbarrini G; Gasbarrini A*
Subsidizer	*Not stated*	*Not stated*	*Associazione Ricerca in Medicina, Bologna, Italy*
Study start and end dates	*March 1999 – July 2000*	*December 2001 to April 2002*	*Not stated*
Type of trial design	*Double-blind, placebo-controlled study*	*Multicentre, randomised, double-blind, placebo controlled study*	*Randomised placebo-controlled, double blind trial*
Setting of study	*Hospital Setting*	*Primary care setting*	*Primary care setting*
Definition and diagnostic criteria for diarrhoea	*Not stated*	*Based on the frequency and consistency of stool, defined as at least 2 bowel movements with an 'poltacea' or watery stool for one day(starting 24 hours after start of treatment)*	*Not stated*
Definition C. Difficile associated diarrhoea	*Toxin positive and diarrhoea*	*Not stated*	*Not stated*
Antibiotic(s) used	**Not stated**	*Amoxicillin-acid clavulanico; cephalosporin; Erythromycin (or other macrolide); others*	*Rabeparzole, clarythromicin and tinidazole (triple therapy scheme)*
Antibiotic duration, dosage and schedule	*Not stated*	*10 days of therapy*	*Rabeprazole 20 mg b.i.d.(twice a day); Clarythromicin 500 mg b.i.d.; Tinidazole 500 mg b.i.d. for 7 days*
Probiotic(s) used	*Lactobacillus acidophilus and Bifidobacterium bifidum ($2x10^{10}$ cfu)*	*Lactobacillus sporongens*	*Lactobacillus GG, Saccharomyces boulardii, Lactobacillus acidophilus and Bifidobacterium lactis*
Probiotic duration, dosage and schedule	*1 capsule/day for 20 days*	*L. sporongens (550 000 000 ufc) and 250 mg fructo-oligosaccharide Administered once daily for 10 days, preferably in the mornings in the form of a gel capsule*	*Group 1: L. GG b.i.d. during antibiotic week and for 1 wk after ($6x10^9$ per sachet) Group 2: S. boulardii given b.i.d. during antibiotic week and 1 wk thereafter ($5x10^9$ per sachet) Group 3: L. acidophilus + B. lactis b.i.d. during antibiotic wk and 1 wk after ($5x10^9$ per sachet)*
Reason for antibiotic medication	*Acute emergencies requiring treatment with antibiotics*	*Mainly: pharyngitis, tonsillitis, otitis media, bronchitis*	*H. pylori positive*
Control(s)	**Inactive carrier**	*Placebo, indistinguishable in shape and every other aspects, same schedule as probiotic*	*Placebo administered with the same regimen of probiotic preparations*

Trial ID	***97***	***136***	***147***
Author	***Jirapinyo P***	***Thomas MR***	***Armuzzi A***
Year of publication	*2002*	*2001*	*2001*
Centres and location	*Departments of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*	*Division of Community Internal Medicine, Division of Area General Internal Medicine, Division of Infectious Diseases and Internal Medicine, Section of Biostatistics and the Advanced General Medicine Fellowship, Mayo Clinic, Rochester, Minnesota USA*	*Departments of Internal Medicine, Hygiene and Medical Pathology, Catholic University, Rome, Italy* *Human Nutrition, Tor Vergata University, Rome, Italy*
Co-Author	*Thamonsiri N; Densupsoontorn N; Wongarn R*	*Litin SC; Osmon DR; Corr AP; Weaver AL; Lohse CM*	*Cremonini F; Bartolozzi F; Canducci F; Candelli M; Ojetti V; Cammarota G; Anti M; Lorenzo de A; Pola P; Gasbarrini G; Gasbarrini A*
Subsidizer	*Not stated*	*In part by a grant from ConAgra Foods, Inc, Omaha, Nebraska, USA*	*Not stated*
Study start and end dates	*Not stated*	*July 1, 1998 to October 31, 1999*	*September 1999 –31. January 2000*
Type of trial design	*Double-blind, randomised placebo-controlled trial*	*Prospective, randomised, double-blind, placebo-controlled trial*	*Single centre, double blind, prospective, randomised, placebo-controlled trial*
Setting of study	*Hospital setting*	*Hospital setting*	*Primary care setting*
Definition and diagnostic criteria for diarrhoea	*Not stated*	*Either watery or liquid stools (bowel movement consistency of 1, 2, or 3 on the Stool Consistency Continuum, composed of 8 line drawings depicting stools varying from watery to hard and dry) for 2 or more consecutive days in a patient with normal stools (≤1 per day) at baseline or 3 or more bowel movements more than the patient's normal daily number of bowel movements, regardless of consistency.*	*Not stated*
Definition C. Difficile associated diarrhoea	*Not stated*	*Not stated*	*Not stated*
Antibiotic(s) used	*One or more than one broad spectrum antibiotics*	*Penicillins, cephaolsporins, carbapenems, Fluoroquinolones, macrolides, aminoglycosides, glycopeptides, tetracycline, azoles*	*Triple therapy for H.pylori, consisting of: rabeprazol, claritthromcin and tinidazole*
Antibiotic duration, dosage and schedule	*Not stated*	*Not stated*	*7 day therapy, 20 mg rabeprazole (before breakfast and dinner); 500 mg clarithromycin (half an hour after breakfast and dinner); 500 mg tinidazole (half an hour after breakfast and dinner)*
Probiotic(s) used	*L. acidophilus and Bifidobacterium infantis (Infloran)*	*Lactobacillus GG (CAG Funtcional Foods, Omaha, Nebraska)*	*Lactobacillus GG*
Probiotic duration, dosage and schedule	*1 capsule three times a day, for 7 days test drug (and placebo) had to be given within 24 hours of admission to the study and not later than 24 hours following antibiotic administration*	*1 capsule twice daily for 14 days, beginning within 24 hours of the institution of antibiotic therapy.* *Capsules contained $10x10^9$ cfu of live L. GG and inulin as filler*	*$6x10^9$ of viable bacteria Lactobacillus GG, 2 hours after breakfast and dinner, mixed with water for 14 days (from Giflorex, Errekappa, Euroterapici S.p.A. Milan, Italy)*
Reason for antibiotic medication	*Sepsis or meningitis*	*Presumed or proven infection*	*Helicobacter pylori positive, otherwise healthy volunteers*
Control(s)	*Placebo capsules, which contained a small amount of sugar and followed the same dosing schedule*	*Placebo appeared idenctical to the active capsules, but only contained the inulin filler. Same schedule as probiotics*	*The same proton pump inhibitor and antibiotic regimen plus probiotic-matched placebo*

Trial ID	**159**	***194***
Author	**Orrhage K**	***Arvola T***
Year of publication	2000	*1999*
Centres and location	Departments of Microbiology, Pathology and Immunology and Surgery, Huddinge University Hospital, Karolinska Institutet, Stockholm, Sweden	*Medical School, University of Tampere and the Departments of Pediatrics, Tampere University Hospital, Tampere, Finland*
Co-Author	Sjöstedt S; Nord CE	*Laiho K; Torkkeli S; Mykkänen H; Salminen S; Maunula L; Isolauri E*
Subsidizer	By grant from Arla, Stockholm, Sweden	*Finnish Foundation for Gastroenterological Research* *Medical Research Fund of Tampere University Hospital* *Emil Aaltonen Foundation* *Acadamy of Finnland*
Study start and end dates	Not stated	*Not stated*
Type of trial design	Randomised double-blind parallel group study	*Randomised controlled trial*
Setting of study	Experimental setting, healthy volunteers	*Health care centre or hospital*
Definition and diagnostic criteria for diarrhoea	Not stated	*At least three watery or loose stools per day for a minimum of 2 consecutive days.*
Definition C. Difficile associated diarrhoea	Not stated	*Not stated*
Antibiotic(s) used	Cefpodoxime proxetil	*Penicillin, Amoxicillin, Kephalosporins Erythromycin, Trimetoprim-sulpha*
Antibiotic duration, dosage and schedule	2 x 100mg/day in tablets, orally for 7 days	*Duration 7-10 days, the dosage was divided into 2 or 3 doses, given every 8 to 12 hours.*
Probiotic(s) used	Bifidobacterium longum BB536, Lactobacillus acidophilus NCFB 1748 bd	*Lactobacillus GG*
Probiotic duration, dosage and schedule	250 ml of a fermented milk supplement containing $5x10^7$ to $2x10^8$ cfu/ml of B.longum and $2x10^8$ to $3x10^8$ cfu/ml of L. acidophilus once daily for 21 days. Additionally, 15g of oligofructose was given.	*$2x10^{10}$ colony forming units (cfu) in capsules , twice daily, during antimicrobial treatment*
Reason for antibiotic medication	None, healthy volunteers	*Treatment of acute respiratory infections*
Control(s)	2 control groups: placebo milk supplement with 15g of oligofructose for 21 days placebo milk supplement without oligofructose for 21 days All milk products contained the yoghurt culture bacteria Lactobacillus delbrueckii subsp. Bulgaricus LBU 108 (10^7-10^8 cfu/ml) and Streptococcus salivarius subsp. thermophilus STH 482 (10^8-10^9 cfu/ml)	*Placebo capsule*

Trial ID	***251***	***255***	***268***
Author	***Tankanow RM***	***Surawicz CM***	***Gotz V***
Year of publication	*1990*	*1989*	*1979*
Centres and location	*Department of Pharmacy Services, University of Michigan Hospitals, University of Michigan College of Pharmacy; USA*	*Departments of Medicine, Medicinal Chemistry, Epidemiology, and Biostatistics, University of Washington, Seattle, Washington*	*The New York Hospital, New York Cornell University, Medical College, New York City, USA*
Co-Author	*Ross MB; Ertel IJ; Dickinson DG; McCormick LS; Garfinkel JF*	*Elmer GW, Speelman P, McFarland LV, Chinn J, Belle van G*	*Romankeiwicz JA, Moss J, Murray HW*
Subsidizer	*Hynson, Westcott, and Dunning Products*	*Laboratoire Biocodex, Montrouge, France*	*By a grant from Hynson, Westcott and Dunning*
Study start and end dates	*Recruitment during 13 month period*		*February 1977 to April 1978*
Type of trial design	*Randomised, double-blind, placebo-controlled trial*	*Prospective, double-blind, randomised controlled trial*	*Double-blind, randomised controlled trial*
Setting of study	*Local paediatric practice*	*Hospital setting*	*Hospital setting*
Definition and diagnostic criteria for diarrhoea	*One or more abnormally loose bowel movements per day throughout the study period of one to ten days.*	*Change in bowel habit, with 3 or more loose or watery stools per day for at least 2 days*	*≥3 bowel movements more than the patient's normal daily number of bowel movements, regardless of consistency*
Definition C. Difficile associated diarrhoea	*Not stated*	*A minimum of 3 stools was considered necessary to determine if a patient became infected with C. difficile. (Protocol: stool specimens from patients who developed diarrhoea only C. difficile positive stools were tested for cytotoxin.)*	*Not stated*
Antibiotic(s) used	*Amoxicillin*	*Several antibiotics: e.g. penicillin, other single agents, multiple agents containing clindamycin, or TMP or cephalosporins*	*Ampicillin (oral, injectable or both)*
Antibiotic duration, dosage and schedule	*Doses were based on the physicians' clinical experience and were consistent with the manufacturers' dosing guidelines*	*Not stated*	*Not stated*
Probiotic(s) used	*Lactobacillus acidophilus, Lactobacillus bulgaricus (both in on preparation = Lactinex) Lactinex was supplied by Hynson, Westcott and Dunning Products*	*S. boulardii*	*Lactobacillus acidophilus and Lactobacillus bulgaricus (Lactinex granules) By: Hynson, Westcott and Dunning, Baltimore, MD*
Probiotic duration, dosage and schedule	*Lactinex granules (1 g packets) 4 times daily for ten days (5.1x10^{8} cfu per 1 g packet)*	*250 mg capsule b.i.d. twice a day (- 1g lyophilised S. boulardii) initiation within 48 hours of antibiotics and confirmation for 2 weeks after antibiotic treatment*	*4 times daily one packet for the first 5 days of ampicillin treatment (20 doses in total)*
Reason for antibiotic medication	*Diagnosis of disease, where amoxicillin is reasonable therapy Mainly: Otits media, pharyngitis*	*Not stated*	*Not stated*
Control(s)	*Placebo, consisting of lactose*	*Placebo; an inert composition formulated to be indistinguishable from the capsules of yeast.*	*Placebo (same dosage, schedule)*

Trial ID	***195***	***205***	***231***
Author	***Vanderhoof JA***	***Lewis SJ***	***McFarland LV***
Year of publication	*1999*	*1998*	*1994*
Centres and location	*Department of Pediatrics, University of Nebraska, Omaha* *Black Hills Pediatrics Children's hospital, Rapid City, South Dakota* *Departments of Pediatrics and Psychology, Creighton University, Omaha, Nebraska* *USA*	*Department of Medicine, Bristol Royal Infirmary, Bristol, UK*	*Department of Medicinal Chemistry, University of Washington, Biocodex, Inc., Division of Gastroenterology, Department of Medicine, Harborview Medical Centre, Seattle, Washington* *Department of Infectious Disease, Division of Medicine, University of Kentucky, Lexington, Kentucky*
Co-Author	*Whitney DB; Antonson DL; Hanner TL; Lupo JV; Young RJ*	*Potts LF; Barry RE*	*Surawicz CM, Greenberg RN, Elmer GW, Moyer KA; Melcher SA; Bowen KE; Cox JL*
Subsidizer		*United Bristol Health Care Trust*	*Funded by grants to University of Kentucky, University of Washington, and St. Louis University Medical Centre from Laboratoires Biocodex, Montrouge, France*
Study start and end dates	*Not stated*	*Not stated*	*March 1989 – December 1992*
Type of trial design	*Randomised, double-blind, placebo-controlled trial*	*Randomised double-blind, placebo-controlled trial*	*[Randomised] Double-blinded, placebo-controlled parallel group study*
Setting of study	*Primary care, paediatric practice*	*Hospital setting*	*Hospital setting, high risk group of patients*
Definition and diagnostic criteria for diarrhoea	*Presence of at least 2 liquid stools per day on at least 2 observation periods during the course of the study.*	*3 or more loose stools within a 24 h period*	*A change in bowel habit with at least 3 loose stools/day for at least 2 consecutive days. Definition for antibiotic-associated diarrhoea: diarrhoea associated with at least on β-lactam antibiotic with no other aetiology of diarrhoea identified (medications, lactose intolerance, nasogastric tube feeding, enemas)*
Definition C. Difficile associated diarrhoea		*Analysis for C. difficile toxin by a cell culture technique with positive result*	*Diarrhoea with detected C. difficile toxin*
Antibiotic(s) used	*Amoxicillin, Amoxicillin/clavulanate potassium, Cefprozil, Clarithomycin, Ciprofloxacin, Cefotaxime, Penicillin, Cephalothin, Erythromycin, Tetracycline, Trimethoprim, Sulfamethoxazole*	*Not stated*	*β-lactam antibiotics either alone or with another antibiotic; β-lactam antibiotics included medium-to-broad spectrum penicillin's, combination penicillin's (penicillin's with aβ-lactamase inhibitor), or any cephalosporin*
Antibiotic duration, dosage and schedule	*10 days*	*Not stated*	*Antibiotic treatment for at least 48 hours (oral or intravenous)*
Probiotic(s) used	*Lactobacillus GG (from CAG Functional Foods in Omaha, Nebraska)*	*Saccharomyces boulardii (Ultra-Levure, Biocodex, Montrouge, France)*	*Saccharomyces boulardii*
Probiotic duration, dosage and schedule	*Children weighing < 12kg : 1 capsule ($1x10^{10}$ cfu/capsule) once daily for 10 days* *Children weighing > 12kg: 2 capsules ($1x10^{10}$ cfu/capsule) once daily for 10 days*	*113 mg twice daily throughout the time that every patient received antibiotics*	*1g ($3x10^{10}$ cfu) per day (2 x 250mg capsules, twice a day), continued until 3 days after the antibiotic was discontinued; the maximum duration was 28 days*
Reason for antibiotic medication	*Acute infectious disorders (minor infections) of the upper or lower respiratory tract, the urinary tract, soft tissues, or skin.*	*Acute admission to the general medical ward*	*Not stated*
Control(s)	*Placebo capsule, composed of inulin*	*Placebo*	*Placebo*

Trial ID	***302***	***310***	***395***
Author	***Benhamou PH***	***Nord CE***	***Nista EC***
Year of publication	*1999*	*1997*	*2004*
Centres and location	*Département de Gastro-entérologie Pédiatrique, Hôpital Saint Vincent de Paul, Paris* *Glyrpa (Groupe Lyonnais de Recherche en Pédiatrie Ambulatoire), Lyon* *Institiut IPSEN, Paris, France*	*Department of Microbiology and Surgery, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden*	*Departments of Internal Medicine and Medical Pathology, Catholic University, Rome, Italy*
Co-Author	*Berlier P; Danjou G; Plique O; Jessueld D; Dupont C*	*Lidbeck A; Orrhage K; Sjöstedt S*	*Candelli M; Cremonini F; Cazzato IA; Zocco MA; Franceschi F; Cammarota G; Gasbarrini G; Gasbarrini A*
Subsidizer		*Not stated*	*Not stated*
Study start and end dates	*October 1993 to July 1997*	*Not stated*	*November 2001 to June 2002*
Type of trial design	*Double-blind, randomised controlled trial*	*Randomised, double-blind, parallel-group study*	*Single centre, double-blind, prospective, randomised, placebo-controlled.*
Setting of study	*Primary care setting*	*Experimental – Healthy volunteers*	*Primary care setting*
Definition and diagnostic criteria for diarrhoea	*More than 3 liquid stools per day*	*Not stated*	*Not stated*
Definition C. difficile associated diarrhoea		*Not stated*	*Not stated*
Antibiotic(s) used	Amoxicillin (+ clavulate), cefradoxil, josamycin, erytomycin + sulfafurazol, cefixim	*Clindamycin (Dolacin, Upjohn, Kalamazoo, Michigan, USA*	*Triple therapy based on: clarithromycin, amoxicillin, rabeprazole*
Antibiotic duration, dosage and schedule	*Treatment for 6-10 days*	*150 mg Clindamycin with meals, 4 times a day for 7 days*	*Clarithromycin 500 mg b.d. , amoxicillin 1 g b.d., rabeprazole 20 mg b.d. for 7 days*
Probiotic(s) used	*Saccharomyces boulardii*	*L. acidophilus La-CH5, Bifidobacterium bifidum Bb-12, L. delbrueckii subsp. bulgaricus Lb-Y27, Streptococcus salivarius subsp. thermophilus St – Y31 (Christian Hansen Biosystems, Denmark)*	*B. clausii, (Enterogermina, Sanofi-Synthelabo OTC, Milan, Italy)*
Probiotic duration, dosage and schedule	*226 mg per day one hour before a meal, in form of gel capsules; for the duration of the antibiotic treatment* *A placebo sachet (similar in look to the sachet for the control group)*	*3 capsules (3x10^{9} cfu per capsule) after meal twice a day for 14 days, starting at the same time as the antibiotic.* *Daily dose: 2x10^{10} cfu*	*1 vial t.d.s. (each vial containing 2x10^{9} spores of B.clausii) for 14 days, during eradication therapy and 1 week thereafter*
Reason for antibiotic medication	*Infection of the upper and/or lower respiratory tract*	*None, healthy volunteers*	*Helicobacter pylori eradiction*
Control(s)	*Diosmetice (DS) in form of a sachet, 6 g/day for children between 1 and 2 years of age; 9 g/day for children above 2 years* *A placebo gel capsule, similar in looks to the ones the probiotic group gets*	*Placebo capsule, administered following same schedule as probiotic group*	*Placebo, identical in colour, size, shape, weight and taste, same schedule as probiotic*

Trial ID	***786***	***897***	***930***
Author	***Monteiro E***	***Madeo M***	***Kotowska M***
Year of publication	*1981*	*1999*	*2005*
Centres and location	*College of Medicine of Lisbon, College of Ciencias Medical of Lisbon, Civil Hospital of Lisbon, College of Medicine of Porto, Porto. College of Medicine of Coimbra, Coimbra, Portugal*	*Public Health Laboratory Service, Hull Royal Infirmary, Hull, UK*	*Department of Pediatric Gastroenterology and Nutrition, The Medical University of Warsaw, Warsaw, Poland*
Co-Author	*Fernandes JP; Vieira MR; Correia JP; Caetano JM; Ribeiro T; et al.*	*Whitlock M; Martin CR*	*Albrecht P; Szajewska H*
Subsidizer	*Not stated*	*Not stated*	
Study start and end dates	*Not stated*	*Inclusion period was 2 month, no specific date stated*	*November 2002 to May 2004*
Type of trial design	*Double blind, randomised, placebo-controlled trial*	*Prospective, double-blind randomised controlled trial*	*Double blind, randomised, placebo controlled clinical trial*
Setting of study	*Hospital setting*	*Hospital setting*	*Hospital setting (paediatric hospitals and out-patient clinics)*
Definition and diagnostic criteria for diarrhoea	*Transit disturbance (assumed that this refers to diarrhoea) = more than 2 stools per day during study period*	*Bowels opened three or more times more than usual in 24 hours and consisted of a watery (liquid) stool.*	*≥3 loose or watery stools/day for ≥48h occurring during or up to 2 weeks after the antibiotic therapy. AAD was furthermore restricted to absence of rotavirus and a negative stool culture.*
Definition C. difficile associated diarrhoea	*Not stated*	*If diarrhoea was present a sample was examined for pathogens and C. difficile toxin*	*Toxins A and B were identified by immunoassay*
Antibiotic(s) used	*Tetracyclines and betalactamases*	*Co-amoxycliv, Flucloxacillin, Augmentin, Ampicillin, Clarithromycin, Cefotaxime, Metronidazole, Cefuroxime, Cephadrine, Magnapen, Trimethoprin, Ciproflaxicin*	*Cefuroxime axetil, Amoxicillin (+clavulanate), cefuroxime, penicillin, clarithromycin, roxithromycin*
Antibiotic duration, dosage and schedule	*Therapeutical dosage, orally*	*Oral or intravenous antibiotics,*	*Oral or intravenous,*
Probiotic(s) used	*S. boulardii*		*Saccharomyces boulardii*
Probiotic duration, dosage and schedule	*1 capsule, 4 times daily for 6 days*		*250 mg S. boulardii, orally twice daily for the duration of the antibiotic treatment*
Reason for antibiotic medication	*Broncho-pulmonary infections, oto-rhinological infections or infections occurring after surgery.*		*Acute otitis media and/or respiratory tract infection*
Control(s)	*Placebo, same schedule as probiotic*		*Placebo consisting of Saccharum lactis (250 mg)*

Trial ID	963	964
Author	***Armuzzi A***	***Adam J***
Year of publication	*2001*	*1977*
Centres and location	*Departments of Internal Medicine, Hygiene and Medical Pathology, Catholic University, Rome, and Department of Human Nutrition, Tor Vergata University, Rome, Italy*	*Not stated*
Co-Author	*Cremonini F; Ojetti V; Bartolozzi F; Canducci F; Candelli M; Santarelli L; Cammarota G; De Lorenzo A; Pola P; Gasbarrini G; Gasbarrini A*	*Barret A, Barret-Bellet C*
Subsidizer	*Not stated*	*Not stated (Laboratoires Biocodex)*
Study start and end dates	*May 1 to July 31 1999*	*Not stated*
Type of trial design	*Single-centre, open, prospective, randomised trial*	*Randomised placebo controlled, double blind trial*
Setting of study	*Primary care setting*	*primary care*
Definition and diagnostic criteria for diarrhoea	*Not stated*	*diarrhoea was defined as a minimum of 2 points, calculated with a specific method that took the frequency, the consistency and the colour into account.* *The formula is as follows: (Differences apply to measures before treatment and after treatment)* *difference of the number of stools x points* *+ difference according to consistency (normal 0, soft 1, liquid 2) x points* *+ difference according to the colour (normal 0, abnormal 1) x points* *0-2 points - no diarrhoea* *3-4 pts - mild diarrhoea* *5-6 pts moderate diarrhoea* *7 + pts important diarrhoea.*
Definition C. difficile associated diarrhoea	*Not stated*	*Not stated*
Antibiotic(s) used	*Triple therapy consisting of: pantoprazole, clarithromycin, and tinidazole*	*Beta-lactams (penicillins, ampicillin, amoxicillin, cephalosporins) and tetracyclines*
Antibiotic duration, dosage and schedule	*Pantoprazole 40 mag b.i.d. (before breakfast and dinner), clarithromycin 500 mg b.i.d. (0.5 h after breakfast and dinner), tinidazole 500mg b.i.d. (0.5 h after breakfast and dinner)*	*duration of at least 5 days.*
Probiotic(s) used	*Lactobacillus GG (Gilflorex, Errekappa Euroterapici S.p.A., Milan, Italy)*	*S. boulardii (Ultra-Levure)*
Probiotic duration, dosage and schedule	*Freeze dried powder containing L. GG (6x10^9 cfu) b.i.d. (2h after breakfast and dinner, mixed with water) for 14 days, during and the week after eradication therapy.*	*4 gel capsules per day for the duration of antibiotic treatment.*
Reason for antibiotic medication	*Helicobacter pylori eradication therapy*	*infections of the upper and/or lower respiratory tract (e.g. bronchitis, sinusitis etc.)*
Control(s)	*Only antibiotics, no placebo*	*placebo, same schedule as probiotics*

Trial ID	***965***
Author	***Correa NBO***
Year of publication	*2005*
Centres and location	*Departamento de Pediatria, Faculdade de Medicina, and Departamento de Microbiologia, Instituto de Ciencias Diologicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais; and Departamento de Pediatria e Puericultura, Universidade Federal de Goias, Goiania, Brazil*
Co-Author	*Péret Filho LA; Penna FJ; Lima FMLS; Nicoli JR*
Subsidizer	*Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq), Brasilia, DF, Brazil, and Nestlé Brasil Ltda, Sao Paulo, Brazil*
Study start and end dates	*Not stated*
Type of trial design	*Double blind RCT*
Setting of study	*Hospital*
Definition and diagnostic criteria for diarrhoea	*change in bowel habits with the passage of 3 or more liquid stools per day for at least 2 consecutive days.*
Definition C. Difficile associated diarrhoea	*Not stated*
Antibiotic(s) used	*Penicillin, ampicillin, oxacillin, amoxicillin, cephalosporin, amoxicillin + clavulanic acid, others*
Antibiotic duration, dosage and schedule	*venous or oral*
Probiotic(s) used	*B. lactis, S. thermophilis*
Probiotic duration, dosage and schedule	*10^{7} cfu/g powdered formula of B. lactis; 10^{6} cfu/g of S. thermophilis; minimum of 500 ml of formula/day => 10^{7} cfu/g of contents for 15 days*
Reason for antibiotic medication	*Not stated*
Control(s)	*Placebo*

9.8.2 Information on quality assessment

Trial ID	*31*		*50*		***88***		***97***		***136***	
Author	***Plummer S1***		***La Rosa M***		***Cremonini F***		***Jirapinyo P***		***Thomas MR***	
		Jadad Score (yes=1 point, no=0)		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**
Was assignment of treatment described as random?	Yes	*1*	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***
Was method of randomisation well described and appropriate?	*No*	*0*	***Yes***	*1*	*Yes*	*1*	*No*	*0*	*Yes*	*1*
Was the method really random?	*Not stated*		*Yes, computerised list, provided by a randomisation computer programme*		Yes		*Randomisation list, but not further described*		*A randomisation schedule was generated by the Section of Biostatistics and stratified on 3 parameters, including baseline daily bowel movement frequency, use of ß-lactams as initial antibiotic therapy, and age at entry.*	
Was allocation of treatment concealed?	*Not stated*		Not stated		*Yes*		*Not stated*		*Yes*	
What was concealment method?	*Not stated*		*At the first visit, the parents were given the study drug and an diary*		*Computer list kept & generated by pharmacy, a marked numbered box with the sachets /pnt was designated.*		*Not stated*		*A pharmacist who at no time had direct contact with the patients or investigators dispensed active and placebo capsules according to randomisation schedule*	
Was the study described as double blind?	*Yes*	*1*	***Yes***	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*
Who was blinded to treatment?	*Not stated*		*Don't know*		*Patient, investigator*		*Not stated*		*Patients, investigators*	
Was method of blinding adequately described?	*No*	*0*	***Yes***	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*
Were withdrawals stated?	*Yes*	*1*	***Yes***	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*
Were reasons for withdrawals stated?	No		Yes		*Yes*		*No one was lost to follow-up*		*Yes*	
Was intention to treat' used?	*No, 150 pnts were randomised, only 138 were included in the analyses*		Yes		*No, analyses per protocol*		*Yes*		*Yes*	
Score on Jadad Scale, total (0-5)	*3*		5		*5*		*4*		*5*	
Comments	*Withdrawals are stated in the abstract, but no reasons for withdrawal were given*				*Did not state that analyses were per protocol, but they used only the data of those patients, who completed the follow-up period*		*Small number of patients, short method section*		*Authors describe in paper that they use a intention to treat analysis, but their results are only presented for the 267 patients who completed the study, the 34 drop-outs were not taken into the analysis*	

Trial ID	***147***		***159***		***194***		***195***		***205***	
Author	***Armuzzi A***		***Orrhage K***		***Arvola T***		***Vanderhoof JA***		***Lewis SJ***	
		Jadad Score (yes=1 point, no=0)		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**		**Jadad Score (yes=1 point, no=0)**
Was assignment of treatment described as random?	Yes	*1*	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***
Was method of randomisation well described and appropriate?	*No*	*0*	*No*	*0*	***Yes***	*1*	*Yes*	*1*	*No*	*0*
Was the method really random?	*Don`t know*		*Not stated*		*Yes*		*Yes*		*Not stated*	
Was allocation of treatment concealed?	*Yes*		*Not stated*		*Not stated*		*Yes*		*Yes*	
What was concealment method?	*Closed envelopes*		*Not stated*		*Not stated*		*Product randomisation by blinded numeric codes was performed by the supplier before the product was shipped to the investigation site. Codes were kept by the supplier until all data were collected. The L. GG and placebo were packed in identical bottles with identical capsule covers.*		*Medical management of each volunteer was by attending physician and not influenced by the study. Nursing staff was dispensing the medication to the subject. The trial capsules were prepacked by the pharmacy.*	
Was the study described as double blind?	*Yes*	*1*	*Yes*	*1*	*No*	*0*	*Yes*	*1*	*Yes*	*1*
Who was blinded to treatment?	*Patients and investigator*		*Not stated*		*Patients (parents)*		*Patient, investigator*		*Patients, clinicians (nurses and physicians)*	
Was method of blinding adequately described?	*Yes*	*1*	*No*	*0*	***Yes***	*1*	*Yes*	*1*	*Yes*	*1*
Were withdrawals stated?	*Yes*	*1*	*Yes*	*1*	***Yes***	*1*	*Yes*	*1*	*Yes*	*1*
Were reasons for withdrawals stated?	*Nobody was lost to follow up, this was additionally assessed through a tablet count at the end of the therapy*		*Yes, one patient excluded because of treatment with another antimicrobial agent*		*Yes*		*Yes, primarily because of antibiotic non-compliance or inability of investigator to contact the primary caregiver at the assigned follow-up time.*		*Yes*	
Was intention to treat' used?	*No withdrawals- therefore at discussion*		*No*		*No*		*No*		*No*	
Score on Jadad Scale, total (0-5)	*4*		*3*		*4*		*5*		*4*	

Trial ID	*147*	*159*	*194*	*195*	*205*
Author	***Armuzzi A***	***Orrhage K***	***Arvola T***	***Vanderhoof JA***	***Lewis SJ***
Comments	*Volunteers came from a medical background; all were personnel of a catholic teaching hospital in Rome, working as physicians, etc, so this could explain zero loss to follow up.*		*Intention to treat is not used, study pop'n without patients who were lost to follow up was used for analysis.*		*3 patients lost to follow-up, those were not included in the analyses*

Trial ID	*231*		*251*		*255*		*268*		*302*	
Author	***McFarland LV***		***Tankanow RM***		***Surawicz CM***		***Gotz V***		***Benhamou PH***	
		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)
Was assignment of treatment described as random?	Yes	*1*	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***
Was method of randomisation well described and appropriate?	*No*	*0*	*No*	*0*	*No*	*0*	*No*	*0*	*No*	*0*
Was the method really random?	*Randomisation within three age groups for each centre. Not clear if this concluded in a true randomisation. (Age groups were: 18-44; 45-69; or 70-99)*		*Not clear*		*Not clear*		*Not clear*		*Not clear*	
Was allocation of treatment concealed?	*Yes, Laboratoires Biocodex packed the study drug (probiotic, placebo); this was concealed to investigators*		*Yes*		*Not stated*		*Not stated*		*Not clear*	
What was concealment method?	*Blinded study kits*		*Drug company blinded the foil packs of lactobacilli (active or placebo). The packs were packed into boxes and those boxes numbered. Drug company also provided randomisation code, which was given to investigators in sealed envelope, which could only be opened upon emergency.*		*Not stated*		*Not stated*		*Not clear*	
Was the study described as double blind?	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*
Who was blinded to treatment?	*Investigator, patient*		*Investigators, patients*		*Not stated*		*Patients, Clinicians*		*Patient, investigator*	
Was method of blinding adequately described?	*Yes*	*1*	Yes	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*

Trial ID	***231***		***251***		***255***		***268***		***302***	
Author	***McFarland LV***		***Tankanow RM***		***Surawicz CM***		***Gotz V***		***Benhamou PH***	
Were withdrawals stated?	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*
Were reasons for withdrawals stated?	*Yes*		*Yes*		*Yes*		*Yes*		*No*	
Was intention to treat' used?	*Yes*		*No*		*No*		*No*		*No*	
Score on Jadad Scale, total (0-5)	*4*		*4*		*4*		*4*		*4*	
Comments			*No description of blinding, apart from title, randomisation method not described, concealment not described, nearly half of the population lost to follow up or other drop outs*		*It is not clear who was blinded, apart from patients*					

Trial ID	***310***		***395***		***786***		***897***		***930***		***963***	
Author	***Nord CE***		***Nista EC***		***Monteiro E***		***Madeo M***		***Kotowska M***		***Armuzzi A***	
		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)
Was assignment of treatment described as random?	Yes	*1*	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***	***Yes***	***1***
Was method of randomisation well described and appropriate?	*No*	*0*	*Yes*	*1*	*No*	*0*	*Yes*	*1*	*Yes*	*1*	*No*	*0*
Was the method really random?	*Not clear*		*Yes (permuted blocks randomisation)*		*Not clear*		*Not very clear*		*Yes*		*Not clear*	
Was allocation of treatment concealed?	*Not clear*		*Yes*		*Not stated*		*No*		*Yes*		*Not clear*	
What was concealment method?	*Not stated*		*Permuted block randomisation*		*Not stated*		*Not stated*		*An independent subject prepared the randomisation schedule and oversaw the packaging and labelling of trial treatments.*		*'Closed envelopes'*	
Was the study described as double blind?	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*No*	*0*
Who was blinded to treatment?	*Not clear*		*Don't know*		*Can't tell*		*Patient, investigator*		*All investigators, participants, outcome assessors and data analysts*		*Nobody*	

Trial ID	***310***		***395***		***786***		***897***		***930***		***963***	
Author	***Nord CE***		***Nista EC***		***Monteiro E***		***Madeo M***		***Kotowska M***		***Armuzzi A***	
Was method of blinding adequately described?	*Yes*	*1*	*No*	*0*	*No*	*0*	*Yes*	*1*	*Yes*	*1*	*No*	*0*
Were withdrawals stated?	*Yes*	*1*	*Yes*	*1*	*Yes*	*1*	*Yes*		*Yes*	*1*	*Yes*	*1*
Were reasons for withdrawals stated?	*No withdrawals*		*Yes*		*Yes*		*No withdrawals*		*Yes*		*No withdrawals*	
Was intention to treat' used?	*Yes*		*Yes, but also a 'Per-protocol analysis' was performed*		*No*		*Yes (assuming, because all patients remained at fu)*		*No*		*Yes*	
Score on Jadad Scale, total (0-5)	*4*		*4*		*3*		*5*		*5*		*2*	
Comments	*No withdrawals, therefore no reasons stated.*		*Method of blinding and allocation concealment not described.*								*No withdrawals mentioned, therefore assumed, that all subjects were included in the analysis* *Based on the tablet/sachet count after bringing back the medication containers, all subjects who finished therapy were '100% adherent' with respective protocol.*	

Trial ID	***964***		***965***	
Author	***Adam J***		***Correa NBO***	
		Jadad Score (yes=1 point, no=0)		Jadad Score (yes=1 point, no=0)
Was assignment of treatment described as random?	Yes	*1*	***Yes***	***1***
Was method of randomisation well described and appropriate?	*Yes*	*1*	*No*	*0*
Was the method really random?	*Yes, randomisation tables, the same tables applied to all different centres.*		*Not clear*	
Was allocation of treatment concealed?	*Yes*		*Not stated*	
What was concealment method?	*randomisation table was used to number the batches (study product). According to this table, the treatment was given*		*Not stated*	
Was the study described as double blind?	*Yes*	*1*	*Yes*	*1*
Who was blinded to treatment?	*investigators, patients*		*patients, investigator*	
Was method of blinding adequately described?	*Yes*	*1*	*Yes*	*1*
Were withdrawals stated?	*Yes*	*1*	*Yes*	*1*
Were reasons for withdrawals stated?	*No loss to follow-up reported*		*Yes*	
Was intention to treat' used?	*Yes (because no follow-up loss, assumed)*		*No*	

Trial ID	*964*	*965*
Author	***Adam J***	***Correa NBO***
Score on Jadad Scale, total (0-5)	*5*	*4*
Comments	*Not definitely sure about Jadad score, if blinding is appropriate and if there are withdrawals mentioned or not.*	

9.8.3 Inclusion exclusion criteria

Trial ID	*31*	*50*	*88*	*97*	*136*
Author	***Plummer S[1]***	***La Rosa M***	***Cremonini F***	***Jirapinyo P***	***Thomas MR***
Inclusion criteria	*Patients with acute emergencies*	*Written informed consent by parents* *Patients between 4 months and 15 years* *Presence of an infection which makes a therapy with Erythromycin or other macrolides, amoxicillinacid/clavulan or cephalosporins necessary*	*Subjects underwent H. pylori testing and tested positive* *Free of GI symptoms at enrolment* *Wished to be treated for H. pylori* *Gave written informed consent, answered a questionnaire on GI and extraintestinal symptoms, drug history and reactions.*	*In patients diagnosed with either sepsis or meningitis* *Ages ranged from 1 to 36 months* *Receiving high doses of one or more than one broad spectrum antibiotics* *Written informed consent by parents*	*Admitted to a general internal medicine inpatient service at Saint Marys Hospital, Rochester* *Received intravenous or oral antibacterial agents for a presumed or proved infection*
Exclusion criteria	*Patients on a course of antibiotics lasting longer than 20 days*	*Gastrointestinal infection* *Other pathologic infections that have influence on the GI tract* *Chronic 'defecation' problems that demand parenteral feeding* *Antibiotic treatment 15 days preceding inclusion into study*	*Recorded occurrence of any symptoms* *Incidentally used any drug associated with GI side effects* *Occurrence of fever or flu-like syndrome* *Use of a calcium channel blocker* *Use of L-thyroxine* *Occasional use of laxatives* *Use of anticholinergic drugs*	*Presence of diarrhoea before the study* *Conditions where enteral feeding was contraindicated* *Patients in a moribund condition* *Patients with either primary or secondary immunodeficiency*	*Treatment with an antibiotic for more than 24 hours prior to enrolment or at any time within the prior 2 weeks* *Age younger than 18 years* *Diagnosis of C. difficile colitis within the previous 3 months* *Underlying long-term gastrointestinal tract disease characterized by diarrhoea or unformed stools* *Tube feeding* *Use of an ileostomy or colostomy* *Residence outside the United States* *Inability to speak or read English* *Inability to provide informed consent* *Immunocompromised state* *Administration of antibiotics as prophylaxis of infection only*

Trial ID	*147*	*159*	*194*	*195*	*205*	*231*
Author	***Armuzzi A***	***Orrhage K***	***Arvola T***	***Vanderhoof JA***	***Lewis SJ***	***McFarland LV***
Inclusion criteria	*Helicobacter pylori positive* *Volunteers from hospital*	Healthy volunteers No history of gastrointestinal, hepatic or renal diseases	*No antimicrobial medication during the previous 3 month* *No need for intravenous antimicrobial treatment* *No gastrointestinal disorders*	*Being evaluated for symptoms of acute infection of the upper and lower respiratory tract, the urinary tract, soft tissues, or skin during the month of September.* *Prescription for a 10 day antibiotic course*	*Prescribed antibiotics in last 24 hours*	*Consecutive adult impatient receiving new prescription of β-lactam antibiotics for at least 48 hr* *18 years or older* *Written informed consent* *No diarrhoea less than 24 hours after enrolment*
Exclusion criteria	*Symptomatic subjects (dyspeptic symptoms)*	Other antibiotic medication		*Any chronic disease* *Serious acute infection* *Diarrhoea at time of antibiotic initiation*	*Taken antibiotics within previous 6 weeks* *Pre-existing bowel pathology* *Fed by a naso-gastric tube* *Unable to given written consent*	*Antibiotic started > 72 hours of interview* *Immunosuppression* *Antibiotic given for < 48 hours* *Catastrophic illness* *No telephone* *Discharged before interview* <*18 yr old* *oral anti-fungal medication* *refused participation* *patients receiving only penicillin G or penicillin V (narrow spectrum penicillin's)*

Trial ID	*251*	*255*	*268*	*302*	*310*
Author	***Tankanow RM***	***Surawicz CM***	***Gotz V***	***Benhamou PH***	***Nord CE***
Inclusion criteria	*Patients between age of 6 months to six years diagnosed with disease where amoxicillin treatment is reasonable* *Inclusions for efficacy analyses: patients completed at least five days of antibiotic and Lactinex/placebo therapy*	*Inpatients receiving new antibiotic prescriptions* *Adult patients* *Written informed consent*	*Ampicillin treatment* *Medical inpatient of the New York Hospital*	*Upper and/or lower respiratory tract infection which required an antibiotic therapy of 8 ±2 days*	*Volunteers*
Exclusion criteria	*Currently had diarrhoea or an underlying disease with diarrhoea as a conventional factor.* *Not eating a normal diet prior to the history of the present illness* *Colostomy or ileostomy* *Nourishment by breast milk only* *Sensitivity or contraindication to amoxicillin, lactinex, lactose or milk products* *Receiving drugs known to interact with amoxicillin to a clinically significant extent (such as carbamazepine, theophylline, aminobenzoic acid, and methotrexate)*	*Diarrhoea within the preceding week or within 24h of the start of the study* *Immune compromise (i.e. AIDS, recent or ongoing chemotherapy, or radiation therapy)* *Renal failure requiring dialysis, pregnancy, antibiotic therapy for < 3 days* *Patients receiving the following medications were also excluded: vancomycin or metronidazole (used to treat C. difficile diarrhoea)* *Antifungal antibiotics (could inactivate the yeast)* *Lactulose (was known a priori to cause diarrhoea)* *Patients who were monitored for < 8 days were considered to have an insufficient follow-up to allow diarrhoea to develop and were excluded from the analyses*	*Colostomy, ileaostomy, an underlying disease, having diarrhoea as a constitutional factor, receiving multiple antibiotics, not eating a normal diet.*	*Severe illness, such as immune suppression, cancer, renal insufficiency or liver damage etc.)* *Diarrhoea on the day of inclusion or the preceding week* *Antibiotic treatment in the preceding 2 weeks before inclusion* *Presence of a purulent otitis media infection justifying a paracentesis treatment*	*Antibiotic treatment during last 3 month* *Consumption of lactic acid bacteria-fermented products for 2 weeks prior to the study* *Other medication during investigation period* *History of GI, hepatic or renal disease*

Trial ID	***395***	***786***	***897***	***930***	***963***
Author	***Nista EC***	***Monteiro E***	***Madeo M***	***Kotowska M***	***Armuzzi A***
Inclusion criteria	*Aged between 18 –65 years* *Free of gastrointestinal symptoms in the previous 3 months* *Affected by gastric H. pylori infection as confirmed by a C-urea breath test* *Patients under chronic drug treatment were considered suitable if they had been receiving such treatment for >3months.* *All patients signed a written informed consent.*	*Patients submitted to the hospital with diverse infections* *Use of antibiotics from the groups of the tetracyclines and betalactams*	*Patients were recruited from 6 elderly wards where they were admitted to* *Commenced oral or intravenous antibiotic therapy* *Granted informed consent*	*Age between 6 months to 14 years* *Acute otitis media and/or respiratory tract infection* *Started short-term treatment with oral or intravenous antibiotics within 24 of enrolment*	*Healthy asymptomatic volunteers, working at the Gemelli Hospital in Rome as physicians, biologists, nurses or administrative personnel.* *Subjects attended a screening program for the assessment of the prevalence and risk factors for H. pylori infection among healthcare workers.* *Those H. pylori-positive asymptomatic subjects who wished to be cured were included in the study.*
Exclusion criteria	*Recent (within the previous 3 months) use of anti-microbial agents, bismuth compounds, proton pump inhibitors and H_2 receptor antagonists, laxatives, anti-diarrhoeals, other probiotic preparations, alcohol or illicit drug abuse.* *Patients with acute or chronic gastrointestinal diseases, or with major concomitant diseases including psychiatric disorders and pregnant or lactating women were also excluded from the study.*	*Not stated*	*Not stated*	*Presence of a severe or generalized bacterial infection* *Antibiotic treatment within the previous 2 months* *Prophylactic antibiotic treatment* *Use of a probiotic product for medicinal purposes within the previous 7 days* *Immunodeficiency* *Chronic gastrointestinal disease* *Acute or chronic diarrhoea*	*Presence of dyspeptic symptoms and active organic disease* *Taking of any medication at time of enrolment*

Trial ID	***964***	***965***
Author	***Adam J***	***Correa NBO***
Inclusion criteria	*older than 15 years* *antibiotic treatment for at least 5 days for lower or upper respiratory infections* *selected antibiotic had to belong to group of either tetracyclines or beta-lactams* *had to be used orally*	*age: 6-36 months* *inpatients receiving antibiotics*
Exclusion criteria	*younger than 15 years* *receiving any other treatments aiming at the digestive system* *patients with abdominal disorders, or candidose* *psychologically not very reliable* *any other antibiotics other than the 2 defined above* *any other addition of antibiotic therapy with 'digestive medicines'*	*breast feeding* *diarrhoea episode* *antibiotics use 3 weeks before trial* *diarrhoea within 12 hours of trial* *inability to consume 500 ml of formula/day* *existence of underlying pathology (e.g. sepsis, custic fibrosis, renal insufficiency)*

9.8.4 Information on baseline characteristics

Trial ID	***31***		***50***		***88***				***97***		***136***		***147***	
Author	***Plummer S[1]***		***La Rosa M***		***Cremonini F***				***Jirapinyo P***		***Thomas MR***		***Armuzzi A***	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic 1*	*Probiotic 2*	*Probiotic 3*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*150*		*60*	*60*	*21*	*22*	*21*	*21*	*8*	*10*	*152*	*150*	*30*	*30*
Number analysed	*69*	*69*	*48*	*50*	*21*	*21*	*21*	*20*	*8*	*10*	*133*	*134*	*30*	*30*
Age	*Elderly*		*6.6 years (range: 0,4-13.2)*	*6.7 years (range: 0.9-14.4)*	*97 patients enroled, age range 18-61 years*				*8.6 months (2-36)*	*5.7 months (2-24)*	*57.2 years ± 18.0 (20-93)*	*54.4 years ± 17.4 (18-86)*	*Mean age 40 ± 12 years*	
Male:female			*34:25*	*31:28*	*43:54*				*5:3*	*7:3*	*68:65*	*75:59*	*25:35*	
Allergies to antibiotics					*Not stated*						*Not stated*		*Not stated*	
Duration of antibiotic treatment	*20 days*	*20 days*			*7 days*	*7 days*	*7 days*	*7 days*			*11.9 ±5.9 days*	*12.5 ±5.0 days*	*7 days*	*7 days*
C. difficile carrier					*Not stated*								*Not stated*	
Dietary differences					*Not stated*								*Not stated*	
Comments	*C.difficile carrier 'comparable' in both groups, in total 8 patients.*				*Baseline characteristics were not furhter stated*						*The treatment and placebo group were similar in terms of demographics and medical profiles at enrolment. There were no significant differences in indications for antibiotic treatment, use of over-the-counter medications at enrolment, or comorbidities between patients receiving Lactobacillus GG and placebo.*		*No further information on the two groups given, no 'table 1 with general characteristics*	

Trial ID	***159***			***194***		***195***		***205***		***231***	
Author	***Orrhage K***			***Arvola T***		***Vanderhoof JA***		***Lewis SJ***		***McFarland LV***	
Study group	*Probiotic*	*Control 1*	*Control 2*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*10*	*10*	*10*	*89*	*78*	*202 randomised*		*72 patients randomised*		*97*	*96*
Number analysed	*9*	*10*	*10*	*61*	*58*	*92*	*95*	*33*	*36*	*97*	*96*
Age	*Mean age 28 years (range 21-50 years)*			*4.7 (2 weeks to 11.8 years)*	*4.4 (2 weeks to 12.8 years)*	*3 years 11 months*	*4 years*	*75 years (71-81)*	*77 years (70-85)*	*(randomised age groups) 1)18-44 years 2) 45-69 3)≥ 70*	
										1) 64 2) 25 3)8	*1)62 2) 24 3) 10*
Male:female	*4:6*	*4:6*	*4:6*	*Not stated*		*43:50*	*42:53*	*Not stated*		*62:35*	*63:33*
Allergies to antibiotics	*Not stated*			*Not stated*				*Not stated*		*Not stated*	
Duration of antibiotic treatment	*7 days*	*7 days*	*7 days*	*Not stated*		*10 days*	*10 days*	*6 days (5-8)*	*7 days (6-10)*	*Not stated*	
C. difficile carrier				*Not stated*				*Not stated*		*Not stated*	
Dietary differences				*Not stated*				*Not stated*		*Not stated*	
Comments				*No difference between males, females, due to study population being children. The groups were comparable in clinical diagnosis, antimicrobial agents used, history of antibiotic use and mode of day care*		*Not specifically stated, how many patients of the probiotic or control group were lost to follow-up. Two groups also comparable regarding diagnosis for antibiotic treatment and antibiotic used.*		*Narrative: between groups no difference in sex, age, duration of antibiotic use, length of hospital stay, number or type of antibiotics taken.*		*There were 4 different hospitals involved, which also differed in patient characteristics. Patients from the four sites were generally similar except for differences in age, number of medications, and APACHE index (a modified standard index to quantitate the patient's basic health status to stratify acutely ill patients). Patients at St. Louis University were significantly older, had higher APACHE index scores, and received more antibiotics and medications; but none of these factors resulted in a higher frequency of AAD. Patients at the University of Kentucky had a significantly lower frequency of AAD, were older, had higher APACHE scores, and had significantly lower frequency of C. difficile. To judge if bias was introduced by treatment assignment, a comparison of the group of patients receiving S.boulardii and the group receiving placebo was performed. No statistically significant differences were noted in the patients assigned to S. boulardii compared with patients given placebo.*	

Trial ID	***251***		***255***		***268***		***302***		***310***		***395***	
Author	***Tankanow RM***		***Surawicz CM***		***Gotz V***		***Benhamou PH***		***Nord CE***		***Nista EC***	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*60*		*318*		*48*	*50*	*391*	*388*	*11*	*12*	*60*	*60*
Number analysed	*15*	*23*	*116*	*64*	*36*	*43*	*327*	*289*	*11*	*12*	*54*	*52*
Age	*29 ± 17 months*		*48.6 years*	*45.4 years*	*65 years (19-86)*	*64 years (24-88)*	*2.40 years± 0.05*	*2.44 years ± 0.05*	*29.5 years (range:21-54)*		*46.2 years ± 12.83*	*43.1 years ± 13.36*
Male:female	*22:16*		*66% male*	*73% male*	*22:21*	*13:23*	*55.24% male*	*53.05 % male*	*3:8*	*4:8*	*33:27*	*25:35*
Allergies to antibiotics	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*	
Duration of antibiotic treatment	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*7 days*	*7 days*	*7 days*	*7 days*
C. difficile carrier	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*	
Dietary differences	*Not stated*		*Not stated*						*Not stated*		*Not stated*	
Comments	*Apple cider and fruit are frequently associated with diarrhoeal episodes and were consumed by several children who subsequently experienced an increased number of loose stools. Conversely, bulk-forming foods, such as bran, were also consumed, which may have decreased the incidence of diarrhoea. In addition, yoghurt contains Lactobacillus, which, if consumed in sufficient quantities, could have skewed the data.*		*High loss to follow up, patients excluded from analysis due to not being monitored longer than 8 days*		*No difference in age, dose of ampicillin, number of doses of the study drug; however, more women than men in the study population Median total ampicillin dose (g): Probiotic: 29 (4.75-176) Control: 16 (5-108)*		*No differences between the groups concerning height, weight, temperature or the type of infection There were also no differences in the antibiotics administered between the two groups*				*There were no significant differences in age and baseline symptom scores (all patients were symptom free at enrolments) between the placebo and the B. clausii groups. On the contrary, a higher prevalence of male gender was observed in B. clausii group an female gender in placebo group.*	

Trial ID	***786***		***897***			***930***		***963***		***964***		***965***	
Author	***Monteiro E***		***Madeo M***			***Kotowska M***		***Armuzzi A***		***Adam J***		***Correa NBO***	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control 1*	*Control 2*	*Probiotic*	*Control*	*Probiotic*	*Control*	Probiotic	Control	Probiotic	Control
Number randomised	*300*		*30*	*18*	*18*	*132*	*137*	*60*	*60*	199	189	87	82
Number analysed	*121*	*119*	*30*	*18*	*18*	*119*	*127*	*60*	*60*	199	189	80	77
Age	*Not stated*		*81 years*	*82 years*	*90 years*	*58.8 months ± 44 (6.2-178)*	*55.8 months ± 43.5 (5.2-182)*	*36.8 years ± 10*	*37.0 years ±*	39.27 years ± 2.25	37.59 years ± 2.84	21.94 months ± 9.84	22.19 months ± 10.70
Male:female	*Not stated*		*11:19*	*4:14*	*3:15*	*66:66*	*82:55*	*28:32*	*26:34*	96:103	96:93	27:53	33:44
Allergies to antibiotics	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Duration of antibiotic treatment	*6 days*	*6 days*	*5 days*	*5 days*	*5 days*	*Not stated*		*7 days*	*7 days*	6.80 ± 0.24 days	6.84 ± 0.25 days	Not stated	
C. difficile carrier	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Dietary differences	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Comments						*There were no differences between the groups concerning diagnosis and antibiotics used, or the route of administration or the setting of the study*							

9.8.5 Information on outcomes

Trial ID	***31***		***50***		***88***				***97***		***136***		***147***	
Author	***Plummer S[1]***		***La Rosa M***		***Cremonini F***				***Jirapinyo P***		***Thomas MR***		***Armuzzi A***	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic 1*	*Probiotic 2*	*Probiotic 3*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*150*		*60*	*60*	*21*	*22*	*21*	*21*	*8*	*10*	*152*	*150*	*30*	*30*
Number analysed	*69*	*69*	*48*	*50*	*21*	*21*	*21*	*20*	*8*	*10*	*133*	*134*	*30*	*30*
Age	*Elderly*		*6.6 years (range: 0,4-13.2)*	*6.7 years (range: 0.9-14.4)*	*97 patients enroled, age range 18-61 years*				*8.6 months (2-36)*	*5.7 months (2-24)*	*57.2 years ± 18.0 (20-93)*	*54.4 years ± 17.4 (18-86)*	*Mean age 40 ± 12 years*	
Male:female			*34:25*	*31:28*	*43:54*				*5:3*	*7:3*	*68:65*	*75:59*	*25:35*	
Allergies to antibiotics					*Not stated*						*Not stated*		*Not stated*	
Duration of antibiotic treatment	*20 days*	*20 days*			*7 days*	*7 days*	*7 days*	*7 days*			*11.9 ±5.9 days*	*12.5 ±5.0 days*	*7 days*	*7 days*
C. difficile carrier					*Not stated*								*Not stated*	
Dietary differences					*Not stated*								*Not stated*	
Comments	*C.difficile carrier 'comparable' in both groups, in total 8 patients.*				*Baseline characteristics were not furhter stated*						*The treatment & placebo groups were similar in demographics & medical profiles at enrolment. No significant differences in indications for antibiotic treatment, or use of over-the-counter medications, or comorbidities at enrolment .*		*No further information on the two groups given, no 'table 1 with general characteristics*	

Trial ID	***159***			***194***		***195***		***205***		***231***	
Author	***Orrhage K***			***Arvola T***		***Vanderhoof JA***		***Lewis SJ***		***McFarland LV***	
Study group	*Probiotic*	*Control 1*	*Control 2*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*10*	*10*	*10*	*89*	*78*	*202 randomised*		*72 patients randomised*		*97*	*96*
Number analysed	*9*	*10*	*10*	*61*	*58*	*92*	*95*	*33*	*36*	*97*	*96*
Age	*Mean age 28 years (range 21-50 years)*			*4.7 (2 weeks to 11.8 years)*	*4.4 (2 weeks to 12.8 years)*	*3 years 11 months*	*4 years*	*75 years (71-81)*	*77 years (70-85)*	*(randomised age groups) 1)18-44 years 2) 45-69 3)≥ 70*	
										1) 64 2) 25 3)8	*1)62 2) 24 3) 10*
Male:female	*4:6*	*4:6*	*4:6*	*Not stated*		*43:50*	*42:53*	*Not stated*		*62:35*	*63:33*
Allergies to antibiotics	*Not stated*			*Not stated*				*Not stated*		*Not stated*	
Duration of antibiotic treatment	*7 days*	*7 days*	*7 days*	*Not stated*		*10 days*	*10 days*	*6 days (5-8)*	*7 days (6-10)*	*Not stated*	
C. difficile carrier				*Not stated*				*Not stated*		*Not stated*	
Dietary differences				*Not stated*				*Not stated*		*Not stated*	
Comments				*No difference between males, females, due to study population being children. The groups were comparable in clinical diagnosis, antimicrobial agents used, history of antibiotic use and mode of day care*		*Not specifically stated, how many patients of the probiotic or control group were lost to follow-up. Two groups also comparable regarding diagnosis for antibiotic treatment and antibiotic used.*		*Narrative: between groups no difference in sex, age, duration of antibiotic use, length of hospital stay, number or type of antibiotics taken.*		*There were 4 different hospitals involved, which also differed in patient characteristics. Patients from the four sites were generally similar except for differences in age, number of medications, and APACHE index (a modified standard index to quantitate the patient's basic health status to stratify acutely ill patients). Patients at St. Louis University were significantly older, had higher APACHE index scores, and received more antibiotics and medications; but none of these factors resulted in a higher frequency of AAD. Patients at the University of Kentucky had a significantly lower frequency of AAD, were older, had higher APACHE scores, and had significantly lower frequency of C. difficile. To judge if bias was introduced by treatment assignment, a comparison of the group of patients receiving S.boulardii and the group receiving placebo was performed. No statistically significant differences were noted in the patients assigned to S. boulardii compared with patients given placebo.*	

Trial ID	***251***		***255***		***268***		***302***		***310***		***395***	
Author	***Tankanow RM***		***Surawicz CM***		***Gotz V***		***Benhamou PH***		***Nord CE***		***Nista EC***	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Number randomised	*60*		*318*		*48*	*50*	*391*	*388*	*11*	*12*	*60*	*60*
Number analysed	*15*	*23*	*116*	*64*	*36*	*43*	*327*	*289*	*11*	*12*	*54*	*52*
Age	*29 ± 17 months*		*48.6 years*	*45.4 years*	*65 years (19-86)*	*64 years (24-88)*	*2.40 years± 0.05*	*2.44 years ± 0.05*	*29.5 years (range:21-54)*		*46.2 years ± 12.83*	*43.1 years ± 13.36*
Male:female	*22:16*		*66% male*	*73% male*	*22:21*	*13:23*	*55.24% male*	*53.05 % male*	*3:8*	*4:8*	*33:27*	*25:35*
Allergies to antibiotics	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*	
Duration of antibiotic treatment	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*7 days*	*7 days*	*7 days*	*7 days*
C. difficile carrier	*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*		*Not stated*	
Dietary differences	*Not stated*		*Not stated*						*Not stated*		*Not stated*	
Comments	*Apple cider and fruit are frequently associated with diarrhoeal episodes and were consumed by several children who subsequently experienced an increased number of loose stools. Conversely, bulk-forming foods, such as bran, were also consumed, which may have decreased the incidence of diarrhoea. In addition, yoghurt contains Lactobacillus, which, if consumed in sufficient quantities, could have skewed the data.*		*High loss to follow up, patients excluded from analysis due to not being monitored longer than 8 days*		*No difference in age, dose of ampicillin, number of doses of the study drug; however, more women than men in the study population Median total ampicillin dose (g): Probiotic: 29 (4.75-176) Control: 16 (5-108)*		*No differences between the groups concerning height, weight, temperature or the type of infection There were also no differences in the antibiotics administered between the two groups*				*There were no significant differences in age and baseline symptom scores (all patients were symptom free at enrolments) between the placebo and the B. clausii groups. On the contrary, a higher prevalence of male gender was observed in B. clausii group an female gender in placebo group.*	

Trial ID	***786***		***897***			***930***		***963***		**964**		**965**	
Author	***Monteiro E***		***Madeo M***			***Kotowska M***		***Armuzzi A***		**Adam J**		**Correa NBO**	
Study group	*Probiotic*	*Control*	*Probiotic*	*Control 1*	*Control 2*	*Probiotic*	*Control*	*Probiotic*	*Control*	Probiotic	Control	Probiotic	Control
Number randomised	*300*		*30*	*18*	*18*	*132*	*137*	*60*	*60*	199	189	87	82
Number analysed	*121*	*119*	*30*	*18*	*18*	*119*	*127*	*60*	*60*	199	189	80	77
Age	*Not stated*		*81 years*	*82 years*	*90 years*	*58.8 months ± 44 (6.2-178)*	*55.8 months ± 43.5 (5.2-182)*	*36.8 years ± 10*	*37.0 years ±*	39.27 years ± 2.25	37.59 years ± 2.84	21.94 months ± 9.84	22.19 months ± 10.70
Male:female	*Not stated*		*11:19*	*4:14*	*3:15*	*66:66*	*82:55*	*28:32*	*26:34*	96:103	96:93	27:53	33:44
Allergies to antibiotics	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Duration of antibiotic treatment	*6 days*	*6 days*	*5 days*	*5 days*	*5 days*	*Not stated*		*7 days*	*7 days*	6.80 ± 0.24 days	6.84 ± 0.25 days	Not stated	
C. difficile carrier	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Dietary differences	*Not stated*		*Not stated*			*Not stated*		*Not stated*		Not stated		Not stated	
Comments						*There were no differences between the groups concerning diagnosis and antibiotics used, or the route of administration or the setting of the study*							

9.8.6 Information on withdrawals and adverse events

Trial ID	*31*	*50*		*88*		*97*	*136*		*147*	
Author	*Plummer S*[1]	*La Rosa M*		*Cremonini F*		*Jirapinyo P*	*Thomas MR*		*Armuzzi A*	
Group		*Probiotic*	*Control*	*Probiotic*	*Control*		*Probiotic*	*Control*	*Probiotic*	*Control*
Median follow-up	*Not stated*	*Not stated*		*3 weeks*	*3 weeks*	*Not stated*	*21 days*	*21 days*	*3 weeks*	*3 weeks*
Withdrawals including reasons where specified	*Not stated*	*4/60* *2 patients were lost to follow up* *2 patients were lost due to other reasons*	*6/60* *1 patient developed a severe abdominal colitis* *1 patient withdrew the consent* *2 patients were lost to follow up* *2 patients were lost due to other reasons*	*1 patient excluded from the S. boulardii group (Probiotics 2) because of incomplete adherence to the antibiotic treatment because of self-reported lack of motivation (1/21)*	*1 patient excluded because of inadequate filling of symptom reports in week 1 and 3 of the study. (1/20)*	*Not stated, not observed*	*16/150* *Dropped out (n=9)* *Insufficient follow-up (n=7)*	*19/152* *Dropped out (n=14)* *Insufficient follow-up (n=4)* *Discontinued antibiotic after 1 dose (n=1)*	*None*	*None*
Comments		*For 12 patients it was not possible to obtain effectiveness evaluation, due to not filled in questionnaires. So 110 patients were 'left' subtracting the withdrawals, but only 98 were included in ITT analysis.*								
Adverse events	*Not stated*	*Reported in the diary, possible side effects caused by the study drugs* *1 patient in the placebo group developed 'coliche addominali' (abdominal colitis?)*		*No major side effects leading to treatment discontinuation were observed.*		*Not observed*	*Not observed*		*Not observed*	

Trial ID	*159*		*194*		*195*		*205*		*231*	
Author	*Orrhage K*		*Arvola T*		*Vanderhoof JA*		*Lewis SJ*		*McFarland LV*	
Group	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*	*Probiotic*	*Control*
Median follow-up	*21 days*	*21 days*	*3 months*	*3 months*	*10 days*	*10 days*	*6 days*	*7 days*	*7 weeks*	*7 weeks*
Withdrawals including reasons where specified	*1/10, due to* treatment with another antimicrobial agent	*0*	*28/89 difficulties in the transportation of study samples*	*20/78 difficulties in the transportation of study samples*	*14/202 children did not complete the study, primarily because of antibiotic non-compliance or inability of the investigators to contact the primary caregiver at the assigned follow up time.*		*3 patients failed to complete the stud because they did not wish to have stool specimens collected.*		*25/193 patients were censored during the study drug period* *39/193 were censored during the follow-up period* *Of these patients:* *28/64 were lost to follow-up* *27/64 received a new antibiotic prescription poststudy drug* *4/64 developed adverse reactions (nausea or constipation)* *3/64 died* *2/64 received oral nystatin*	
Comments					*None of the participants failed to complete the 10 day course of antibiotics because of a change in stool consistency or frequency. There were no failures resulting from untoward effects of either L. GG or placebo.*					
Adverse events	*No serious adverse events observed during study*		*Not observed*		*No events observed*		*No adverse events stated, no side effects due to S. boulardii observed*		*No severe adverse events observed. There were no significant adverse reactions with the exception that placebo patients reported more intestinal gas (n= 7, 7.4%) than S.boulardii treated patients (n= 0, p= 0.01) and significantly more patients given placebo reported fever (n= 5, 5.3%) compared with S.boulardii treated patients (n= 0, p= 0.04).* *None of the patients with AAD had endoscopic examiniations, so it is unknown if colitis or pseudomembranous colitis was present.* *However, in patients with C. difficile disease, the diarrhoea was sufficiently severe in 57% of the patients to require treatment with vancomycin or metronidazole.*	

Trial ID	*251*	*255*	*268*	*302*		*310*	*395*	
Author	*Tankanow RM*	*Surawicz CM*	*Gotz V*	*Benhamou PH*		*Nord CE*	*Nista EC*	
Group				*Probiotic*	*Control*		*Probiotic*	*Control*
Median follow-up	*Not stated*	*Not stated*	*Not stated*	Not stated		*28 days*	*4 weeks*	*4 weeks*
Withdrawals including reasons where specified	*5 patients did not return their daily log forms therefore lost to follow-up* *17 patients dropped out of the study within the first 5 days; reasons were:* *- children refusing to take the study medication due to taste* *- adverse reactions* *- non-compliance* *- parents not comfortable with having children in a study*	*138/318 could not be evaluated, due to:* *never received study drug or missed > 3 doses (26 patients)* *developed diarrhoea within 24 hours of starting study (15 patients)* *< 72 h of antibiotic therapy (12 patients)* *exclusion drug started (2 patients)* *monitored for < 8 days (74 patients)*	*19/98 were excluded* *4 patients: discharged early without study medication*	*64/391*	*99/388*		*6/60* *-3 patients did not start the assigned treatment* *-3 patients did not return the first diary* *not relevant, because ITT population results are data extracted [-4 patients were not included in the per protocol analysis because they did not return the second diary or because of withdrawal or poor compliance (i.e. <80% of the vials were recoverded)]*	*8/60* *-3 patients did not start the assigned treatment* *-5 patients did not return the first diary* *not relevant, because ITT population results are data extracted [-2 patients were not included in the per protocol analysis because they did not return the second diary or because of withdrawal or poor compliance (i.e. <80% of the vials were recoverded)]*
Comments		*The hospital serves a large indigent population that tended to be noncompliant and difficult to follow after discharge. Characteristics of the 180 completed patients were compared with the 138 unevaluable patients and there were no significant differences in demographics between these two groups.*						
Adverse events	*No severe adverse events observed* *Adverse effects other than diarrhoea were: rash, gas, buring, hiccups, constipation, increased phlegm production, vomiting and 'chest pain'*	*Not observed*	*Not stated*	*Not stated*		*No serious adverse events observed*	*Not observed*	

Trial ID	*786*	*897*	*930*		*963*	*964*	*965*	
Author	*Monteiro E*	*Madeo M*	*Kotowska M*		*Armuzzi A*	*Adam J*	*Correa NBO*	
Group			*Probiotic*	*Control*			*Probiotic*	*Control*
Median follow-up	*6 days*	*Follow up was up to 10 days after biotherapeutic treatment (in total 25 days from start of study)*	*2 weeks following antibiotic treatment*	*2 weeks following antibiotic treatment*	*5 weeks*	*Not directly stated, mean duration of probiotics was 7 days for both groups, therefore assumed that follow up around 1 week*	*30 days*	*30 days*
Withdrawals including reasons where specified	*60 patients failed to fulfil the study protocol*	*No withdrawals*	*12/132 patients lost to follow up: non-acceptance of the study product* *1/132 patient lost to follow up due to damage to the study product*	*10/137 patients lost due to non-acceptance of the study product*	*None*	*No withdrawals*	*7/87* *5 = insufficient ingestion of probiotic formula* *1 = impossibility of oral alimentation after transfer to intensive care*	*5/82* *4 = loss of follow-up* *1 = impossibility of oral alimentation after transfer to intensive care*
Comments			*The analysis was based on allocated treatment, excluding those patients lost to follow-up, all of the other participants for which outcome data were available were analysed according to the intervention to which they were assigned, whether or not they received it.* *A potential problem with this type of analysis is that, unless the absence of an observation is independent of outcome, missing responses can lead to bias. Therefore, for both primary outcome measures, the researchers investigated the effect of various methods of handling missing responses in trials. That is , they compared outcomes in both treatment groups assuming: (i) all patients in both groups with an unknown outcome to have had either a good or a poor outcome, (ii) extreme case favouring of S. boulardii and (iii) extreme case favouring of placebo*					
Adverse events	*Not stated*	*Not stated*	*No severe adverse events were observed*		*Not observed*	*Not stated*	*Not observed*	

9.9 Appendix 9 Details of ongoing studies

Source	Project record	Description	Project organisation	End date
National Research Register	**Publication ID:** N0515143152 **NRR data provider:** North West London Hospitals NHS Trust **Region:** London Regional Office	**Title:** The efficacy of probiotics in the prevention of antibiotic-associated diarrhoea **Principal research question:** The aim is to determine whether a probiotic yoghurt containing Lactobacillus can prevent the onset of antibiotic associated diarrhoea in elderly hospital in-patients. **Methodology:** prospective, double-blind, placebo-controlled trial	**Lead centre name:** Dr Mary Hedison Charing Cross Hospital **Start date:** 12 Jan 2004	1 Dec 2005
National Research Register	**Publication ID:** N0016106821 **NRR data provider:** Hammersmith Hospital NHS Trust **Region:** London Regional Office	**Title:** Efficacy of Probiotics in the prevention of Antibiotic-associated Diarrhoea **Principal research question:** Can the use of live bacterial yoghurt supplement prevent the onset of antibiotic-associated diarrhoea and *C. difficile* infection? **Methodology:** randomised controlled trial **Sample group description:** 200 **Outcome measure description:** Proportion of patients free of diarrhoea in active & placebo groups, average length of stay compared in the two groups.	**Lead centre name: T**his record is from the lead centre of a multi-centre study **Start date:** 25 March 2002	1 April 2003 (still ongoing)

9.10 Appendix 10 Search strategy for economic studies

Database: Ovid MEDLINE(R) <1966 to May Week 3 2005>
Search Strategy:
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1 Bifidobacterium/ or probiotics.mp. or PROBIOTICS/ or Lactobacillus acidophilus/ (3762)
2 (s boulardii or saccharomyces boulardii).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (166)
3 SACCHAROMYCES/ or saccharomyces.mp. (74425)
4 (l acidophilus or lactobacillus acidophilus).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1336)
5 LACTOBACILLUS/ or lactobacillus.mp. (10983)
6 (l rhamnosus gg or lactobacillus rhamnosus gg).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (62)
7 bacillus subtilis.mp. or Bacillus subtilis/ (18739)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (104815)
9 diarrhea.mp. or exp DIARRHEA/ (47645)
10 diarrhoea.mp. (13406)
11 gastrointestinal diseases.mp. or exp Gastrointestinal Diseases/ (469962)
12 (c difficile or clostridium difficile).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3704)
13 colitis/ or enterocolitis/ or enterocolitis, pseudomembranous/ (12397)
14 9 or 10 or 11 or 12 or 13 (507729)
15 8 and 14 (1808)
16 economics/ (23835)
17 exp "costs and cost analysis"/ (115152)
18 cost of illness/ (6848)
19 exp health care costs/ (23976)
20 economic value of life/ (4426)
21 exp economics medical/ (9631)
22 exp economics hospital/ (13296)
23 economics pharmaceutical/ (1461)
24 exp "fees and charges"/ (21473)
25 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (204467)
26 (expenditure$ not energy).tw. (8894)
27 (value adj1 money).tw. (371)
28 budget$.tw. (9194)
29 or/16-28 (307412)
30 15 and 29 (28)
31 from 30 keep 1-28 (28)

The database OHE HEED (May 2005) was also searched iteratively using the following terms: bifidobacterium, probiotics, lactobacillus acidophilus, boulardii, saccharomyces, lactobacillus, rhamnosus, bacillus subtilis. Records were sampled and those matching the populations were retrieved.

9.11 Appendix 11 Baseline risk of AAD for different age groups

Risk factors for the development of AAD are supposed to be age younger than 6 years and older than 65 years. This could have an influence on the effect that probiotics have in preventing diarrhoea, as the baseline risk, and therefore incidence rate, could be different for the different age groups. The incidence rates of the baseline risk of the placebo groups have been calculated for the different age groups. After weighting for study size, it can be advised, that there is a higher incidence rate for children compared to adults (41.4% compared to 23.7%). The incidence rate for elderly appears to be higher as well, but no definite conclusions can be made as there are only two studies considering elderly patients.

Age group	Included studies	Incidence rate per study (%)	Weight	Pooled incidence rate
Children	Tankanow	69.6	4.00	42.5
	Arvola	15.5	3.00	
	Vanderhoof	26.3	5.00	
	Jirapinyo	80.0	2.83	
	La Rosa	62.0	5.57	
	Corrêa	31.2	4.90	
	Kotowska	22.8	5.39	
Adults	Adam	17.5	5.74	25.0
	Armuzzi*1	30.0	3.00	
	Armuzzi	23.3	3.74	
	Cremonini	30.0	2.45	
	Nista	30.8	4.00	
Elderly	Lewis	13.9	2.24	28.2
	Plummer	34.8	4.90	
Adults/elderly	Gotz	20.9	3.00	23.1
	Surawicz	21.9	3.74	
	McFarland	14.6	3.74	
	Thomas	29.9	6.32	

9.12 Appendix 12 Data manipulation

The study conducted by Cremonini used three different probiotic types as intervention, of these one yeast and two different bacteria. For the analysis, the study results have been split into the bacteria groups (named: Cremonini pro1 + pro3) and the yeast group (named Cremonini pro2), both arms were compared to the halved placebo group. The two bacterial probiotic preparations used in the study were not separated; this would have resulted in very small group sizes, as there was only one placebo group. Therefore, the bacterial groups of this study could not be taken into account for the subgroup analysis of probiotics types, because one group used *L. GG* and the other a combination of other bacteria.
Where possible, the outcomes of an intention to treat approach were selected for the analysis, if this was unclear or not performed; any other results were included and noted.
To assess the effectiveness of probiotic supplementation in the prevention of diarrhoea, the duration and severity of diarrhoeic events as well as the incubation period were analysed. The analysis of these outcomes includes only the studies using placebo as comparator. As not all studies reported the standard deviations, these were calculated where possible. For the study by Madeo it was not possible to calculate standard deviations, as no range or p-value for the outcomes of interest were stated. Several studies reported categorical values for the severity of diarrhoea, which could not be included in the pooled analysis; they are therefore reported separately.
The standard deviations were given by La Rosa and Correa, two studies reported a t-value from which the pooled standard deviation could be calculated and two studies (Surawicz and McFarland) reported a range which was used for the calculation of a pooled standard deviation. Only one study (Vanderhoof) reported a p-value of an analysis of variance, from which again a pooled standard deviation was retrieved.

10. REFERENCES

1 Bergogne-Berezin E, Bergogne-Berezin E. Treatment and prevention of antibiotic associated diarrhea. *Int J Antimicrob Agents* 2000; **16**(4):521-526.
2 Hoegenauer C, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and Management of Antibiotic-Associated Diarrhea. *Clinical Infectious Diseases* 1998; **27**:702-710.
3 Surawicz CM. Probiotics, antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in humans. *Best Practice & Research in Clinical Gastroenterology 17(5):775-83,* 2003.
4 Marteau PR, De Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. *American Journal of Clinical Nutrition* 2001; **. 73**(2 SUPPL.).
5 Gronczewski CA, Katz JP. Clostridium Difficile Colitis. *emedicine* 2003.
6 Berrington A, Borriello SP, Brazier J, Duckworth G, Foster K, Freeman R, *et al*. National Clostridium difficile standards group: Report to the department of health. *Journal of Hospital Infection* 2004; **56**:1-38.
7 Lee D, Marks J. Clostridium Difficile Colitis. *Medicine Net* 2005.
8 Wilcox MH. Clostridium difficile infection and pseudomembranous colitis. *Baillieres Best Pract Res Clin Gastroenterol* 2003; **17**(3):475-493.
9 Bartlett JG. Antibiotic-Associated Diarrhea. *N Engl J Med* 2002; **346**(5):334-339.
10 Pepin J, Alary ME, Valiquette L, Raiche E, Ruel J, Fulop K, *et al*. Increasing Risk of Relapse after Treatment of Clostridium difficile Colitis in Quebec, Canada. *Clinical Infectious Diseases* 2005; **40**:1591-1597.
11 Musher D.M., Aslam S., Logan N., Nallacheru S., Bhaila I., Borchert F., *et al*. Relatively Poor Outcome after Treatment of Clostridium difficile Colitis with Metronidazole. *Clinical Infectious Diseases* 2005; **40**:1586-1590.
12 Surawicz CM. Probiotics, antibiotics-associated diarrhoea and Clostridium diffucile diarrhoea in humans. *Baillieres Best Pract Res Clin Gastroenterol* 2003; **. 17**(5).
13 Wrigley T, Tinto A, Majeed A. Age- and sex-specific antibiotic prescribing patterns in General Practice in England and Wales, 1994 to 1998. *Health Statistics Quarterly* 2002; **14**:14-20.
14 Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, *et al*. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Alimentary Pharmacology & Therapeutics* 2002; **16**(8):1461-1467.
15 Health Protection Agency. Reports of Clostridium difficile isolated from faecal specimens under the voluntary reporting scheme: England, Wales, and Northern Ireland 1990-2004.
http://www hpa org uk/infections/topics_az/clostridium_difficile/vol_data htm 2005.
16 Kyne L, Merry C, O'Connell B, Keane C, O'Neill D. Community-acquired Clostridium difficile infection. *J Infect* 1998; **36**(3):287-288.
17 Karlstrom O, Fryklund B, Tullus K, Burman LG. A prospective nationwide study of Clostridium difficile-associated diarrhea in Sweden. The Swedish C. difficile Study Group. *Clin Infect Dis* 1998; **26**(1):141-145.
18 Wilcox MH, Cunniffe JG, Trundle C, Redpath C. Financial burden of hospital-acquired Clostridium difficile infection. *Journal of Hospital Infection 34(1):23-30,* 1996.
19 Joint FAO/WHO Working Group. Guidelines for the evaluation of probiotics in food; Joint FAO/WHO Working Group. *WHO* 2002.
20 Anon. Probiotics for gastrointestinal disorders. *Drug & Therapeutics Bulletin 42(11):85-8,* 2004.
21 Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews (2):CD003048,* 2004.

22 D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ, D'Souza AL, Rajkumar C, *et al*. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; **324**(7350):1361.
23 Oxman AD, Guyatt GH, Singer J, Goldsmith CH, Hutchison BG, Milner RA, *et al*. Agreement among reviewers of review articles. *Journal of Clinical Epidemiology 44(1):91-8,* 1991.
24 Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *Journal of Clinical Epidemiology 44(11):1271-8,* 1991.
25 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials 17(1):1-12,* 1996.
26 Adam J, Barret A, Barret-Bellet C. Essais clinique contrôlés en double insu de l'Ultra-Levure Lyophilisée. Étude multicentrique par 25 médecins de 388 cas. *Gaz Med Fr* 1977; **84**:2072-2078.
27 Armuzzi A, Cremonini F, Bartolozzi F, Canducci F, Candelli M, Ojetti V, *et al*. The effect of oral administration of Lactobacillus GG on antibiotic-associated gastrointestinal side-effects during Helicobacter pylori eradication therapy. *Alimentary Pharmacology & Therapeutics* 2001; **15**(2):163-169.
28 Arvola T, Laiho K, Torkkeli S, Mykkanen H, Salminen S, Maunula L, *et al*. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* 1999; **104**(5):e64.
29 Gotz V, Romankiewicz JA, Moss J, Murray HW, Gotz V, Romankiewicz JA, *et al*. Prophylaxis against ampicillin-associated diarrhea with a lactobacillus preparation. *Am J Hosp Pharm* 1979; **36**(6):754-757.
30 Lewis SJ, Potts LF, Barry RE, Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of Saccharomyces boulardii in the prevention of antibiotic-related diarrhoea in elderly patients. *Journal of Infection* 1998; **36**(2):171-174.
31 McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Moyer KA, Melcher SA, *et al*. Prevention of beta-lactam-associated diarrhea by Saccharomyces boulardii compared with placebo. *American Journal of Gastroenterology* 1995; **90**(3):439-448.
32 Orrhage K, Sjostedt S, Nord CE, Orrhage K, Sjostedt S, Nord CE. Effect of supplements with lactic acid bacteria and oligofructose on the intestinal microflora during administration of cefpodoxime proxetil. *Journal of Antimicrobial Chemotherapy* 2000; **46**(4):603-612.
33 Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, van Belle G, *et al*. Prevention of antibiotic-associated diarrhea by Saccharomyces boulardii: a prospective study. *Gastroenterology* 1989; **96**(4):981-988.
34 Tankanow RM, Ross MB, Ertel IJ, Dickinson DG, McCormick LS, Garfinkel JF, *et al*. A double-blind, placebo-controlled study of the efficacy of Lactinex in the prophylaxis of amoxicillin-induced diarrhea. *DICP* 1990; **24**(4):382-384.
35 Vanderhoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ, *et al*. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. *Journal of Pediatrics* 1999; **135**(5):564-568.
36 Wunderlich PF, Braun L, Fumagalli I, D'Apuzzo V, Heim F, Karly M, *et al*. Double-blind report on the efficacy of lactic acid-producing Enterococcus SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *Journal of International Medical Research* 1989; **17**(4):333-338.
37 Monteiro E, Picao FJ, Vieira MR. Double blind clinical trial on the effect of Ultra-levure in the prophylaxis of antibiotic induced gastrointestinal and mucocutaneous disorders. *Acta Medica Portuguesa* 1981; **. 3**(2).
38 Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, *et al*. Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. *American Journal of Gastroenterology* 2002; **97**(11):2744-2749.

39 Madeo M, Whitlock M, Martin CR. A randomized controlled trial comparing Lactobacillus combined with Bifidobacterium bifidum against fructo-oligosaccharides in reducing the incidence of antibiotic-associated diarrhoea: a preliminary investigation. *Clinical Effectiveness in Nursing* 1910; **1999 Jun; 3**(2):83-87.

40 Nord CE, Lidbeck A, Orrhage K, Sjostedt S. Oral supplementation with lactic acid-producing bacteria during intake of clindamycin. *Clinical Microbiology and Infection* 1997; **3**:124-132.

41 Benhamou PH, Berlier P, Danjou G, Plique O, Jessueld D, Dupont C. Antibiotic-associated diarrhoea in children: A computer monitored double-blind outpatients trial comparing a protective and a probiotic agent. *Medecine et Chirurgie Digestives* 1999; **28**:163-168.

42 Armuzzi A, Cremonini F, Ojetti V, Bartolozzi F, Canducci F, Candelli M, *et al*. Effect of Lactobacillus GG supplementation on antibiotic-associated gastrointestinal side effects during Helicobacter pylori eradication therapy: a pilot study. *Digestion 63(1):1-7,* 2001.

43 Thomas MR, Litin SC, Osmon DR, Corr AP, Weaver AL, Lohse CM, *et al*. Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. *Mayo Clinic Proceedings* 2001; **76**(9):883-889.

44 Jirapinyo P, Densupsoontorn N, Thamonsiri N, Wongarn R, Jirapinyo P, Densupsoontorn N, *et al*. Prevention of antibiotic-associated diarrhea in infants by probiotics. *J Med Assoc Thai* 2002; **85 Suppl 2**:S739-S742.

45 La Rosa M, Bottaro G, Gulino N, Gambuzza F, Di Forti F, Ini G, *et al*. Prevention of antibiotic-associated diarrhea with Lactobacillus sporogens and fructo-oligosaccharides in children. A multicentric double-blind vs placebo study. *Minerva Pediatr* 2003; **55**(5):447-452.

46 Nista EC, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, *et al*. Bacillus clausii therapy to reduce side-effects of anti-Helicobacter pylori treatment: Randomized, double-blind, placebo controlled trial. *Alimentary Pharmacology & Therapeutics* 2004; **. 20**(10):15.

47 Plummer S, Weaver MA, Harris JC, Dee P, Hunter J, Plummer S, *et al*. Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. *International Microbiology* 2004; **7**(1):59-62.

48 Correa NBO, Peret Filho LA, Penna FJ, Lima FMLS, Nicoli JR. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. *Journal of Clinical Gastroenterology Vol 39* 2005; **39**(5):385-389.

49 Kotowska M, Albrecht P, Szajewska H. Saccharomyces boulardii in the prevention of antibiotic- associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Alimentary Pharmacology & Therapeutics* 2005; **21**(5):583-590.

50 Rappenhoner B, Pfeil T, Rychlik R. On the socio-economic cost structure of the diarrhoea treatment: a cost benefit analysis of Saccharomyces boulardii. *Medwelt* 1997; **48**:38-44.

51 Czerucka D, Rampal P. Experimental effects of Saccharomyces boulardii on diarrheal pathogens. *Microbes & Infection 4(7):733-9,* 2002.

52 Spencer RC. Clinical impact and associated costs of Clostridium difficile-associated disease. *Journal of Antimicrobial Chemotherapy 41 Suppl C:5-12,* 1998.

53 Lherm T, Monet C, Nougiere B, Soulier M, Larbi D, Le GC, *et al*. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Med* 2002; **28**(6):797-801.

54 Bassetti S, Frei R, Zimmerli W. Fungemia with Saccharomyces cerevisiae after treatment with Saccharomyces boulardii. *American Journal of Medicine 105(1):71-2,* 1998.

55 Cassone M, Serra P, Mondello F, Girolamo A, Scafetti S, Pistella E, *et al*. Outbreak of Saccharomyces cerevisiae subtype boulardii fungemia in patients neighboring those treated with a probiotic preparation of the organism. *Journal of Clinical Microbiology 41(11):5340-3,* 2003.

56 Marteau P, Seksik P. Tolerance of probiotics and prebiotics. *Journal of Clinical Gastroenterology 38(6 Suppl):S67-9,* 2004.
57 World Health Organization DoCDSaR. Prevention of hospital-aquired infections; A practical guide, 2nd edition. *WHO/CDS/CSR/EPH/2002 12* 2002.

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