

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

REVIEW

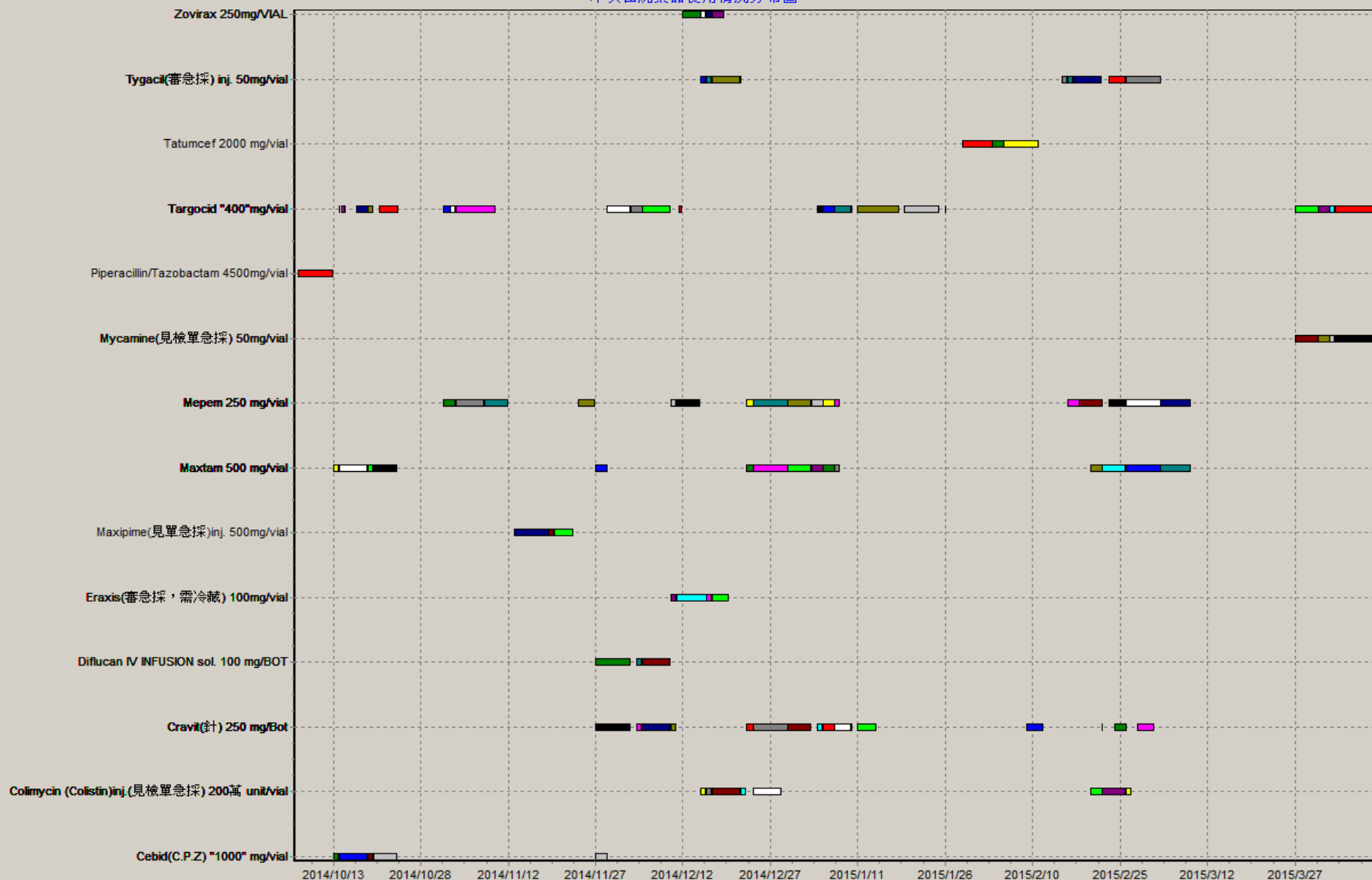
Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: A systematic review

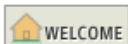
Chunhong Xie ^{a,1}, Jiajing Li ^{a,1}, Kejia Wang ^{b,1}, Qinqin Li ^a,
Daorong Chen ^{a,*}

^a Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

^b Department of Gastroenterology, Banan People's Hospital of Chongqing, Chongqing, China

本次住院藥品使用情況分布圖





Journal Summary List

[Journal Title Changes](#)

Journals from: search Full Journal Title for 'TRAVEL MEDICINE AND INFECTIOUS DISEASE'

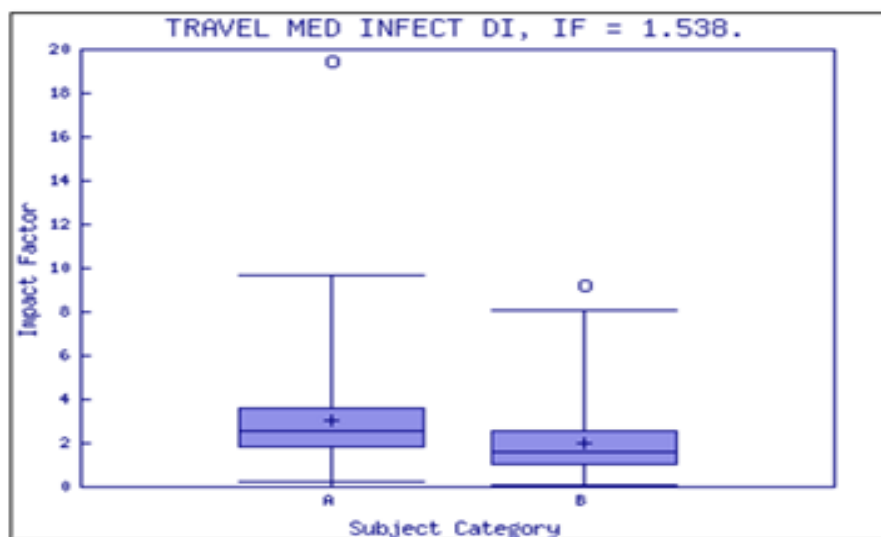
Sorted by:

Journals 1 - 1 (of 1)

Page 1 of 1

Ranking is based on your journal and sort selections.

Mark	Rank	Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data ⁱ						Eigenfactor [®] Metrics ⁱ	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor [®] Score	Article Influence [®] Score
<input type="checkbox"/>	1	TRAVEL MED INFECT DI	1477-8939	518	1.538		0.387	62	4.5	0.00205	



Key

A - INFECTIOUS DISEASES

B - PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH



Introduction

- * Antibiotic-associated diarrhea (AAD) is one of the most common intestinal complications.
- * This occurs in 5% ~ 39% of patients, depending on the population and type of antibiotic.
- * It is more common in older patients (age >65 years), and broad-spectrum antibiotics, such as clindamycin, cephalosporins and fluoroquinolones.
- * Clostridium difficile, an important infectious cause of AAD, accounts for 15 - 39% of all AAD cases.

Introduction

- * The clinical presentations of AAD may range from mild, uncomplicated diarrhea to more severe colitis, and may even result in toxic megacolon or death, particularly in *C.difficile* infections.
- * AAD may also put patients at risk for developing other nosocomial infections, hospital stays, medical care costs, and diagnostic procedures.
- * At present, several meta-analyses and systematic reviews have been conducted to evaluate the efficacy of probiotics in prevention of AAD in adult and paediatric patients, but such a study of older patients has not been carried out.

步驟 1：系統性文獻回顧探討的問題為何？

研究族群 / 問題 (Population/ Problem)	older patients (age > 65 years) treated with antibiotics
介入措施 (Intervention)	Interventions based on the genera Lactobacillus, Bifidobacterium, Saccharomyces, Strepto-coccus, Enterococcus, and Bacillus, alone or in combination
比較 (Comparison)	Placebo
結果 (Outcomes)	Risk ratios (RRs) for AAD and CDD relative to placebo or absence of treatment

AAD was diarrhea occurring in association with antibiotic therapy and without detection of diarrhea pathogens or an alternative explanation (e.g. laxative treatment).

CDD: stool positive for C. difficile toxins were diagnosed.

步驟 2：系統性文獻回顧的品質如何？(FAITH)

PP.02

2. Methods

2.1. Data sources and literature search strategy

A comprehensive search of PubMed, EMBASE, CENTRAL, CINAHL, and ISI Web of Science from date of their inception to May 2014 was conducted with the following keywords: probiotics, diarrhoea, antibiotic therapy, older, and randomised controlled trials (RCTs), *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*. For example, the PubMed search text was:

[(probiotics OR *lactobacillus* OR LGG OR *bifidobacterium* OR *Saccharomyces boulardii* OR *saccharomyces* OR *streptococcus* OR *enterococcus* OR *bacillus*) AND (antibiotic*) AND (diarrhoea OR diarrhoea) AND (aged OR elderly OR senior* OR geriatric* OR retire* OR pension* OR old*)] AND (Clinical Trial [ptyp]). No language restrictions were applied. Additional trials were obtained by scanning the reference lists of all identified records.

步驟 2：系統性文獻回顧的品質如何？(FAITH)

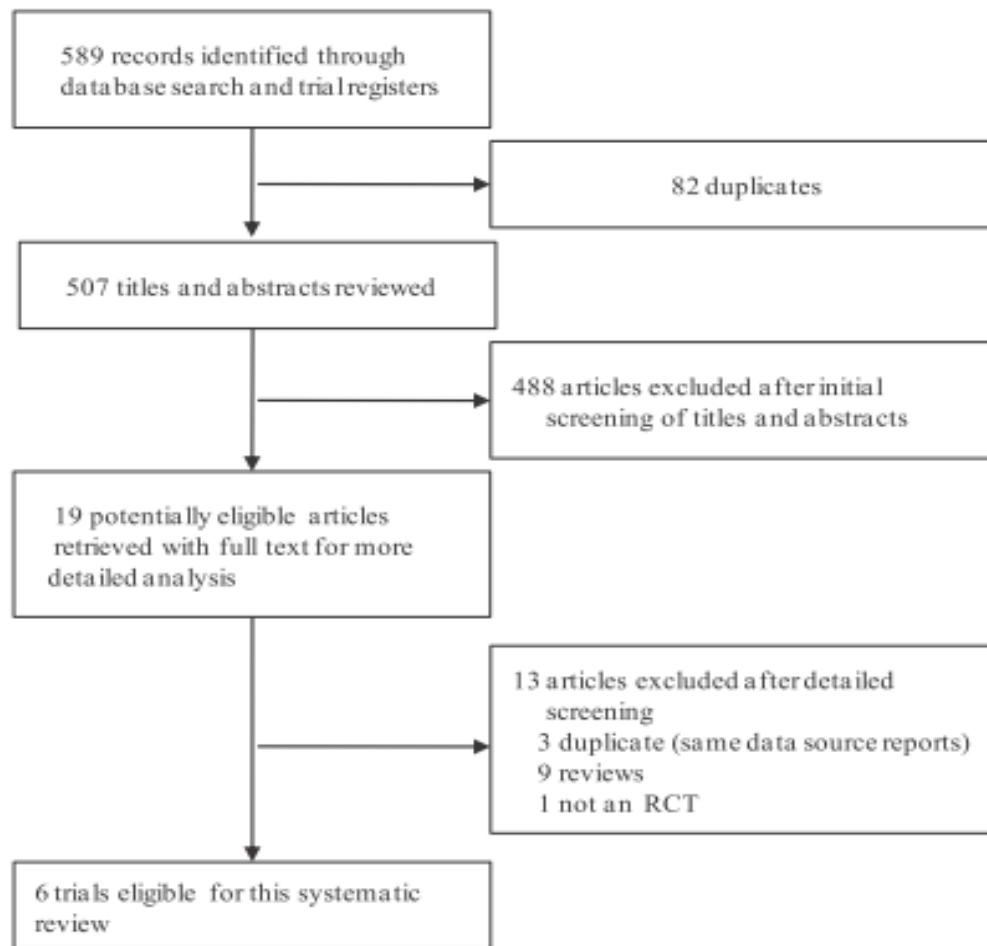


Figure 1 Summary of trial identification and selection.

評讀結果：V 是 ☐否 ☐不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

Table 1 Characteristics of studies included in the systematic review.

Author, year	Patients	Age [range, mean] (years)	Antibiotic/ indication	Probiotics genus, dose, and duration	Diarrhoea definition and report type
Allen et al., 2013 [23]	2981	70–84, 77.1	Various	Two strains of <i>Lactobacillus acidophilus</i> (CUL60 and CUL21) and two strains of <i>Bifidobacterium</i> (<i>Bifidobacterium bifidum</i> CUL20 and <i>B lactis</i> CUL34), 6×10^{10} cfu/d for 21 d	≥ 3 Loose stools within 24 h or as stools described as looser than normal in participants unable to use the scale; staff recorded
Lewis et al., 1998 [44]	69	70–85, 76.04	Various	<i>Saccharomyces cerevisiae</i> (<i>boulardii</i>) lyo, 226 mg/d for 5–10 d	≥ 3 Loose stools within 24 h; staff reported
Li et al., 2010 [45]	247	65–103, 81.48	Various	<i>Bacillus licheniformis</i> , 1.5×10^9 cfu/d for 14d or more	≥ 3 Loose stools within 24 h; staff reported
Plummer et al., 2004 [46]	138	≥ 65 , NA	NA	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium bifidum</i> (Cultech strains), 2×10^{10} cfu/d for 20 d	NA; staff recorded
Safdar et al., 2008 [47]	40	NA, 69.07	Various	<i>Lactobacillus acidophilus</i> (Florajen), 6×10^9 cfu/d for 14 d	≥ 3 Loose stools within 24 h; staff recorded
Wright et al., 2014 [48]	87	66–101, 85.50	Various	<i>Lactobacillus casei</i> Shirota strain, 130 mL/d for mean 29 d	≥ 3 Loose stools within 24 h; staff recorded

步驟 2：系統性文獻回顧的品質如何？(FAITH)

2.4. Data extraction and quality assessment

Two investigators (C.X. and K.W.) independently extracted trial details pertaining to the participants, antibiotic and probiotic interventions and controls, and results regarding diarrhoea, using a standardized form, and discrepancies. We also extracted other relevant outcomes such as the severity of diarrhoea or measures of stool consistency. Any discrepancies regarding individual study inclusion, data extraction and interpretation were resolved by a third investigator (D.C.). The studies with strong interrater agreement (κ statistic = 0.90) were assessed. We applied the Cochrane Risk of Bias tool to assess the studies' methodological quality [30].

3.2. Quality assessment

The overall quality of studies was rated as moderate, even though many reports did not provide details about randomization and allocation concealment. Only one included trial met the criteria for a high risk of bias (Fig. 2).

評讀結果：□是 V否 □不清楚

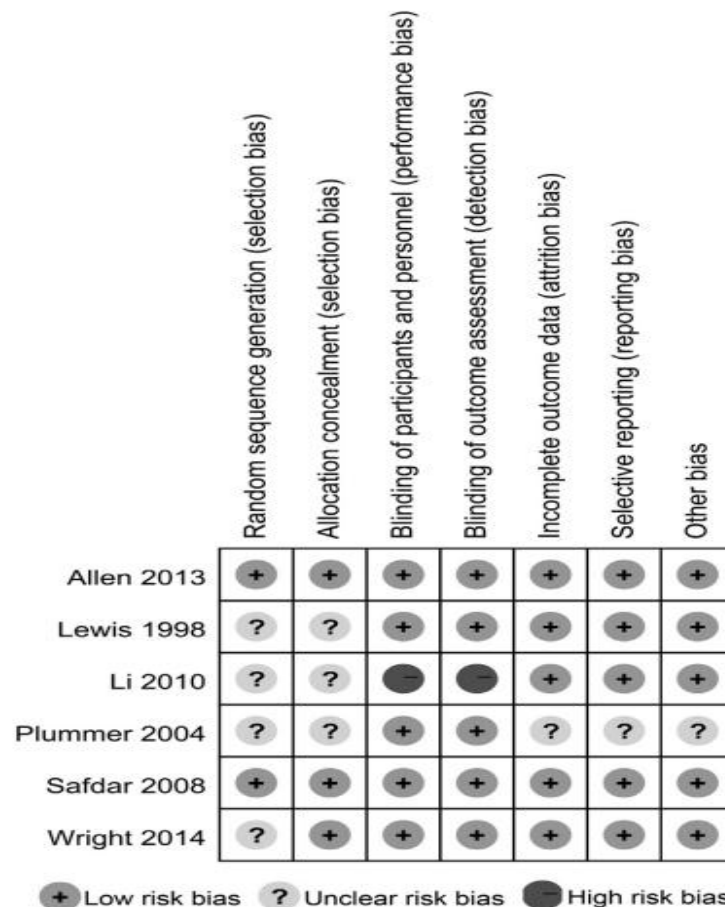


Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

步驟 2：

系統性文獻回顧的品質如何？(FAITH)

Table 2 Effects of studies included in the systematic review.

Author, year	Interventions		Incidence of AAD n (N)		RR (95% CI) for AAD	Incidence of CDD n (N)		RR (95% CI) for CDD
	Probiotic	Control	Probiotic	Control		Probiotic	Control	
Allen et al., 2013 [23]	Mixture of <i>Lactobacillus acidophilus</i> CUL60, CUL21, <i>Bifidobacterium bifidum</i> CUL20 and <i>B lactis</i> CUL34	Placebo	159/1470	153/1471	1.04 (0.84–1.28)	12/1470	17/1471	0.71 (0.34–1.47)
Lewis et al., 1998 [44]	<i>Saccharomyces cerevisiae</i> (boulardii) lyo	Placebo	7/33	5/36	1.53 (0.54–4.35)	5/33	3/36	1.82 (0.47–7.02)
Li et al., 2010 [45]	<i>Bacillus licheniformis</i>	No treatment	15/110	34/124	0.50 (0.29–0.86)	NA	NA	NA
Plummer et al., 2004 [46]	Mixture of <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium bifidum</i> (Cultech strains)	Placebo	15/69	15/69	1.00 (0.53–1.88)	2/69	5/69	0.40 (0.08–1.99)
Safdar et al., 2008 [47]	<i>Lactobacillus acidophilus</i> (Florajen)	Placebo	4/23	6/16	0.46 (0.16–1.38)	0/23	1/16	0.24 (0.01–5.45)
Wright et al., 2014 [48]	<i>Lactobacillus casei</i> Shirota strain	Placebo	5/41	4/46	1.40 (0.40–4.87)	NA	NA	NA

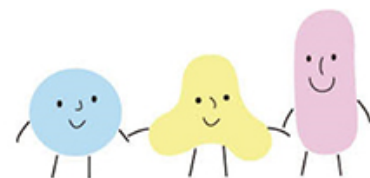
AAD = Antibiotic-associated diarrhoea, CDD = *Clostridium difficile* diarrhoea, RR = Risk ratios, CI = Confidence interval.

評讀結果：□ 是 □否 V不清楚

菌種	主要作用部位	作用機轉
菲卡利斯菌(F) <i>Streptococcus faecalis</i> 	 小腸上部~下部	<ul style="list-style-type: none"> ● 活性乳酸菌，能迅速增殖幫助嗜酸乳桿菌(A)&比菲德氏菌(B)加速發育 ● 迅速將腸內菌叢正常化
嗜酸乳桿菌(A) <i>Lactobacillus acidophilus</i>		<ul style="list-style-type: none"> ● 可產生大量乳酸，抑制有害菌增殖
比菲德氏菌(B) <i>Bifidobacterium bifidum</i> 	小腸下部~大腸	<ul style="list-style-type: none"> ● 製造乳酸及醋酸，抑制害菌(革蘭氏陰性菌)發育 ● 提高巨噬細胞活性，提高整腸效果 ● 促進腸管運動，軟化糞便

適應症

腸內異常發酵、急慢性腸炎、下痢、消化不良、鼓腸、綠便



Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea

A Systematic Review and Meta-analysis

Susanne Hempel, PhD

Sydne J. Newberry, PhD

Alicia R. Maher, MD

Zhen Wang, PhD

Jeremy N. V. Miles, PhD

Roberta Shanman, MS

Breanne Johnsen, BS

Paul G. Shekelle, MD, PhD

THE USE OF ANTIBIOTICS THAT disturb the gastrointestinal flora is associated with clinical symptoms such as diarrhea, which occurs in as many as 30% of patients.^{1,2} Symptoms range from mild and self-limiting to severe, particularly in *Clostridium difficile* infections, and antibiotic-associated diarrhea (AAD) is an important reason for nonadherence with antibiotic treatment.³

Probiotics are microorganisms intended to have a health benefit when consumed. Synbiotics refer to preparations in which probiotic organisms and prebiotics (nondigestible food ingredients that may benefit the host by selectively stimulating bacteria in the colon) are combined.

Potentially, probiotics maintain or restore gut microecology during or after

Context Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

Objective To evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea (AAD).

Data Sources Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA) and references of included studies and reviews were screened from database inception to February 2012, without language restriction.

Study Selection Two independent reviewers identified parallel randomized controlled trials (RCTs) of probiotics (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus*) for the prevention or treatment of AAD.

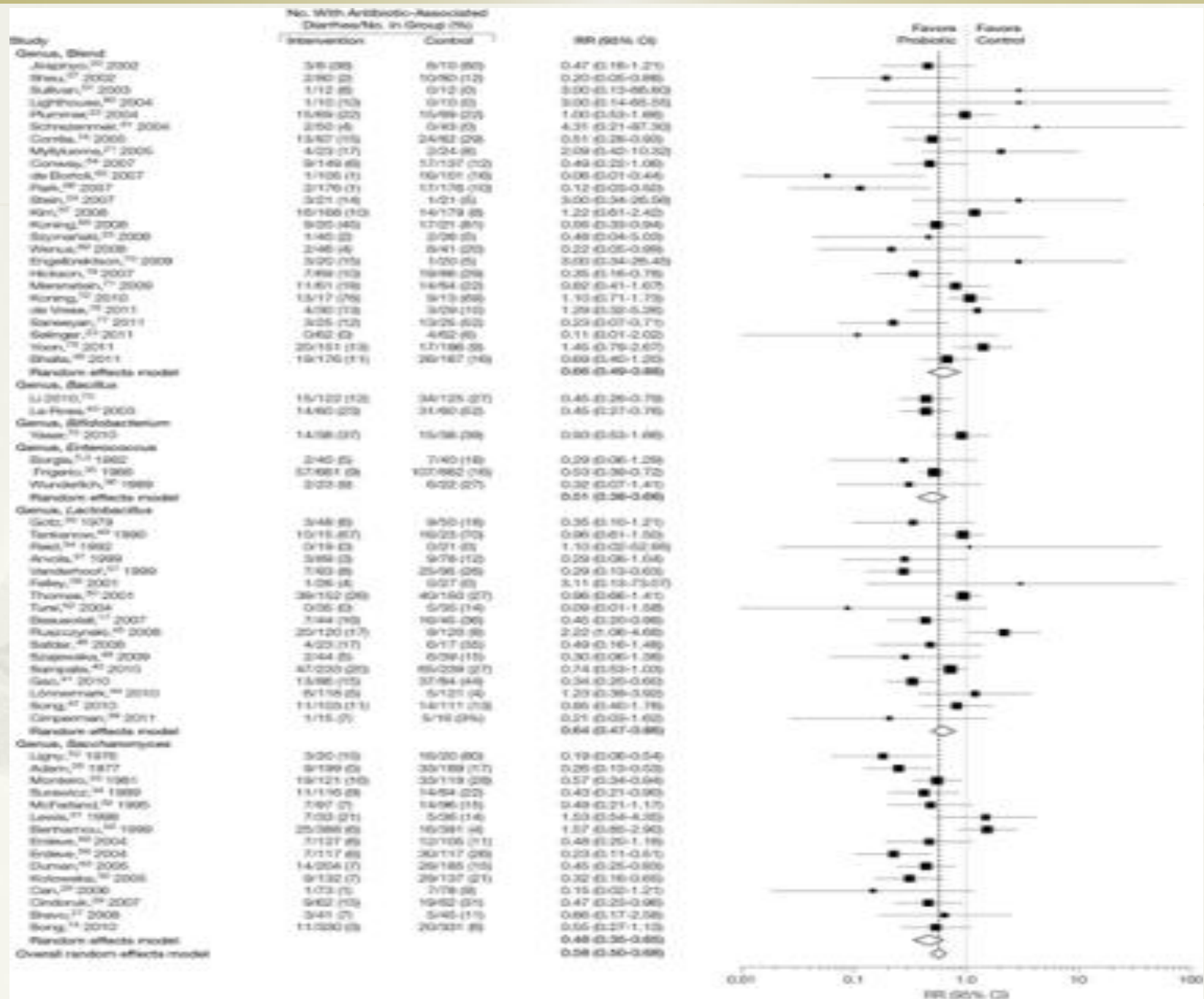
Data Extraction Two independent reviewers extracted the data and assessed trial quality.

Results A total of 82 RCTs met inclusion criteria. The majority used *Lactobacillus*-based interventions alone or in combination with other genera; strains were poorly documented. The pooled relative risk in a DerSimonian-Laird random-effects meta-analysis of 63 RCTs, which included 11 811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68; $P < .001$; I^2 , 54%; [risk difference, -0.07; 95% CI, -0.10 to -0.05], [number needed to treat, 13; 95% CI, 10.3 to 19.1]) in trials reporting on the number of patients with AAD. This result was relatively insensitive to numerous subgroup analyses. However, there exists significant heterogeneity in pooled results and the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

Conclusions The pooled evidence suggests that probiotics are associated with a reduction in AAD. More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics.

JAMA. 2012;307(18):1959-1969

www.jama.com



Main Conclusions

- * A total of 82 RCTs met inclusion criteria. The majority used *Lactobacillus* -based interventions alone or in combination with other genera; strains were poorly documented.
- * The pooled relative risk in random-effects meta-analysis of 63 RCTs, which included 11811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68; $P < .001$; I^2 , 54%; number needed to treat, 13; 95% CI, 10.3 to 19.1])
- * However, there exists significant heterogeneity in pooled results and the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

Discussion

- * There was a lots of patients elder age > 65 whom provided Miyarisan (40 mg/pk) TID.
- * Does it really beneficial or effective for AAD prevention.

Clinical Discussion

* 感染科醫師

1. 年長者腹瀉原因很多，臨床上投與益生菌治療抗生素相關腹瀉效果因人而異。高風險病人或過去病史有易感AAD者，會考慮投與益生菌治療的。
2. 目前研究中真正有效的益生菌並未在市面上販售，服用後效果與益生菌遭受胃酸程度相關，除了須自費藥價的考量，臨床上未發現明顯副作用。
3. 有研究佐證，益生菌用於病毒性腹瀉之證據力較高。

* 營養

益生菌在腸道的生長或存活，除了跟活菌、死菌、細菌數量相關，益菌生是提供益生菌的食物來源，坊間有些產品結合複方的益生菌及益菌生，以提高效果。

Clinical Discussion

* 護理

1. 病人發生AAD給予益生菌的同時，也會同時使用止瀉劑，如何確定是益生菌或止瀉藥產生的效果。
2. 藥師在衛教病人服用抗生素治療時，並不建議給予益生菌，與現行的臨床處置有衝突，臆測是因為無法確認民眾購買益生菌種類及抗生素使用的的多樣性，而有所差異。
3. 此文章納入的六篇臨床試驗品質並不是很好，而唯一顯著風險下降的Li (2010)，呈現誤差值大，未來還有研究的空間。
4. 益生菌用於抗生素相關腹瀉，是預防性或治療性之用途？定義不同，需先分辨清楚。

是否建議使用抗生素的病人，使用 益生菌以預防抗生素引起的腹瀉？



Thanks

