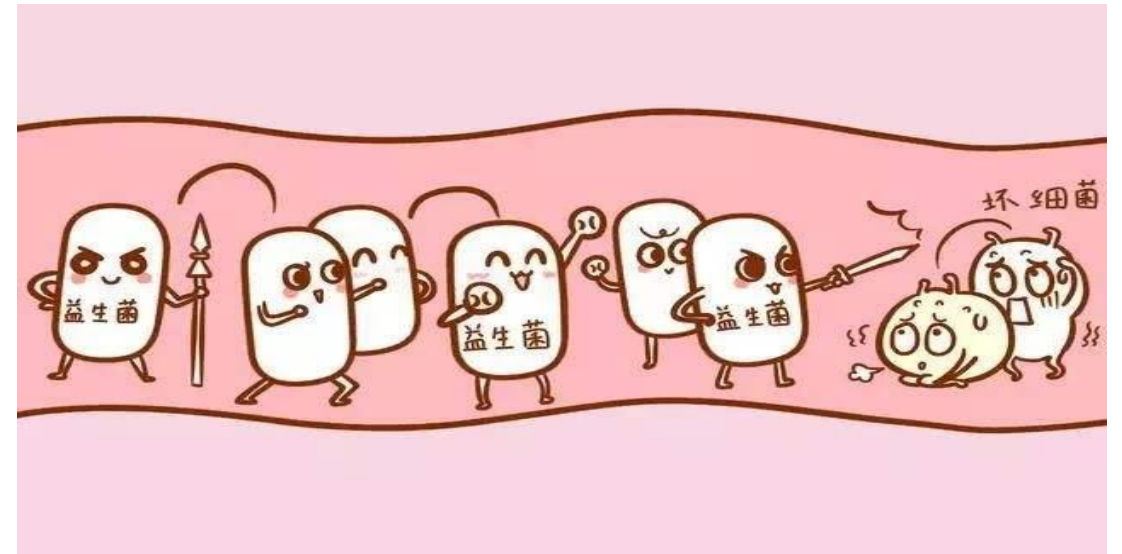# 早期常規使用益生菌能否有效預防抗生素引起之腹瀉？

Journal Club

引言人：王佳珮 護理師

報告日期：2021年10月26日
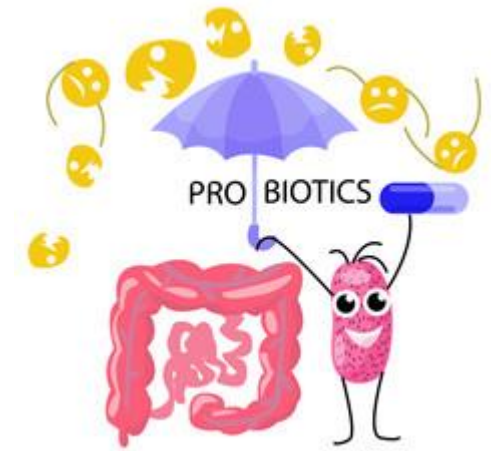
Background Knowledge--AAD

- Antibiotic-associated diarrhea(AAD)抗生素相關腹瀉定義：
  自使用抗生素治療開始至停藥6-8週期間所發生之腹瀉
- 成人盛行率約30%
- 致病機轉：
  (1)the direct effect of antibacterial agents on the intestinal mucosa
  (2)the interference on the intestinal flora ecosystem leads to normal
     metabolic dysfunction and overgrowth of pathogens(esp.
     Clostridioides difficile困難梭狀芽孢桿菌)
- 易導致AAD之抗生素種類：Piperacillin-Tazobactam、Clindamycin、
 Cephalosporins、Fluoroquinolones(Levofloxacin)、Penicillins

Background Knowledge--Probiotics

- 益生菌(Probiotics)：
- A live microorganism
- 應用於AAD相關機轉

  (1)altering the gut microbiota composition and metabolism

  (2)modulating the solute secretion and absorption

  (3)improving the intestinal barrier function and intestinal immune

     responses

Background Knowledge--Probiotics

- 使用益生菌能對腸道產生的益處包含：
  1.抑制病原菌的生長或侵襲腸道上皮組織。
  2.改善腸道屏障功能。
  3.調節免疫系統：誘導保護性細胞因子，
     抑制促炎細胞因子(proinflammatory
     cytokines)。
- 目前常被研究的菌種包含：
  乳桿菌屬(Lactobacillus)、
  雙歧桿菌屬(Bifidobacterium)、酵母菌屬
  (Saccharomyces)、埃希氏菌屬(Escherichia)
  、梭狀桿菌屬(Clostridium)、與鏈球菌屬
  (Streptococcus)等。

益生菌保護腸道的機制

與病原菌競爭食物

本身會產生抗菌物質

與病原菌競爭
黏附到腸道細胞的位置

保護腸道屏障

營養麵包

免疫細胞　促進人體的免疫　樹突狀細胞　腸道細胞
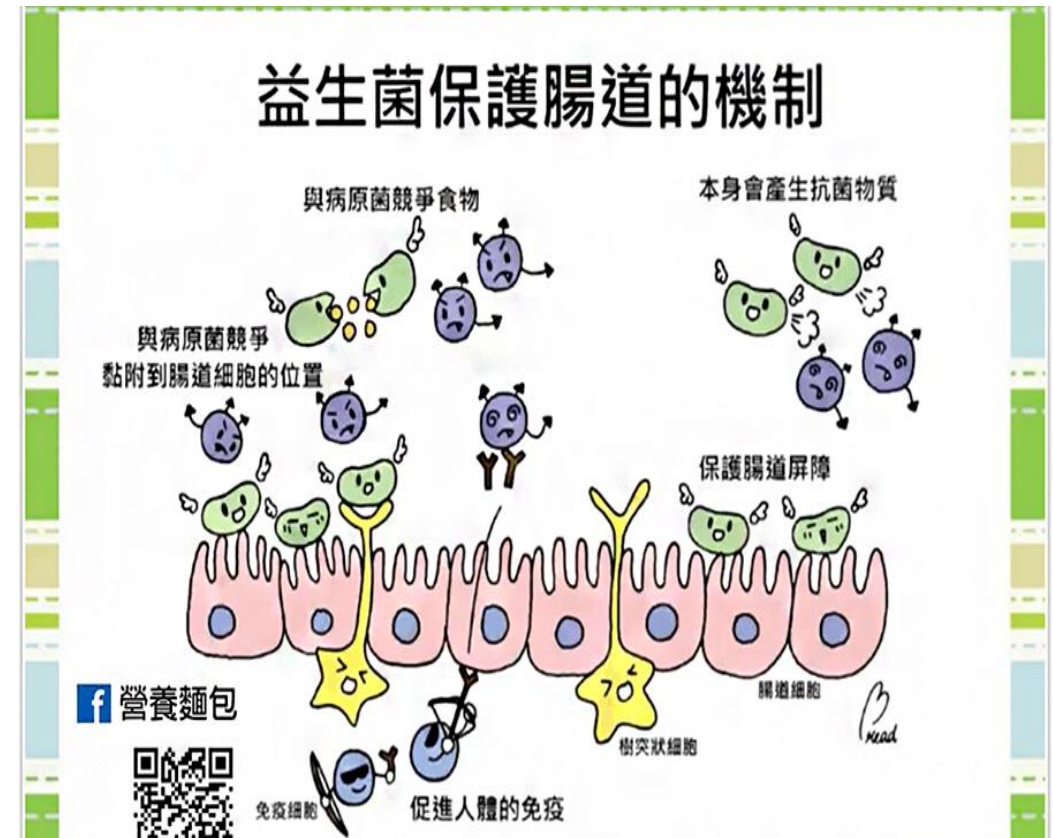
PICO問題：
早期常規使用益生菌能否有效預防抗生素引起之腹瀉？

- P：使用抗生素治療的病人

- I：早期常規使用益生菌

- C：無早期常規使用益生菌

- O：腹瀉程度，不良反應
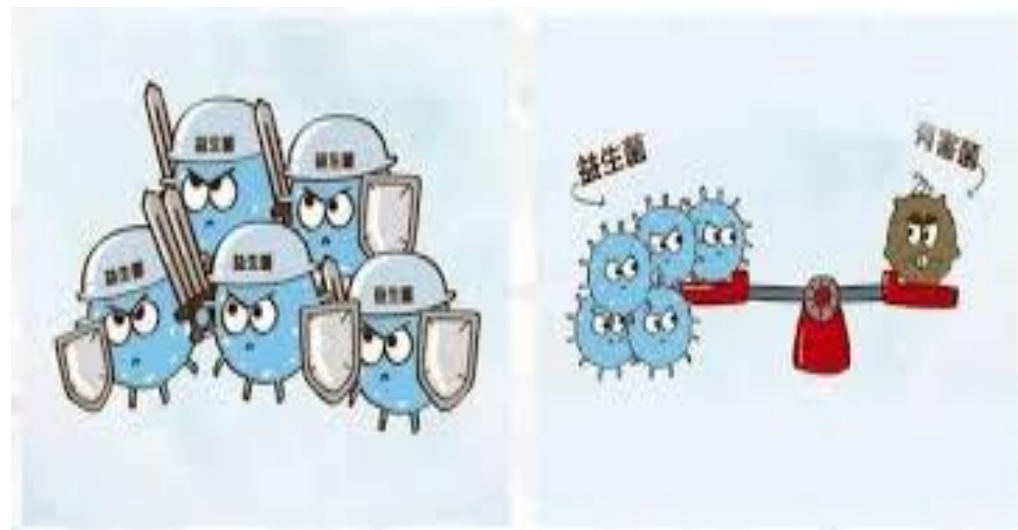
Probiotics for the Prevention of Antibiotic-associated Diarrhea in Adults
A Meta-Analysis of Randomized Placebo-Controlled Trials

Wanqian Liao, MM,*† Chongxiang Chen, MD,*†
Tianmeng Wen, MBBS,‡ and Qingyu Zhao, MD*†

- Journal Impact Factor 3.062(2020)

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)：

- 介入措施 (Intervention)：

- 比較 (Comparison)：

- 結果 (Outcomes)：

- adults prescribed antibiotics for various reasons (inpatients and outpatients)

- Probiotics(primarily included *Lactobacillus*、*Saccharomyces*、*Bifidobacterium* and *Streptococcus*

- Placebo

- Occurrence of AAD and adverse events，analyze probiotic duration、dosage、and time from antibiotic to probiotics

步驟 2：系統性文獻回顧的品質如何？(FAITH)

- F - 研究是否找到 (Find) 所有的相關證據？(p474)
- 評讀結果：V是　　否　　不清楚

Database	The PubMed，EMBASE，Web of Science and Cochrane Library
Language	any language
Search terms	Mesh terms and key words：probiotic(s), diarrhea, anti-bacterial agents, antibiotic(s), antibiotic-associated diarrhea, placebo, randomized, randomized controlled trial
Inclusion criteria	(1)Patients limited to the adults both inpatients and outpatients who were prescribed antibiotics for various reasons with probiotics(experimental groups) or placebo(control group) (2)Providing the occurrence of AAD (3)The study designed as RCT
Exclusion criteria	(1)Duplicate studies, animal researches, preclinical studies, and case reports (2)Unknown probiotics composition (3)not-blinded trials (4)Existing diarrhea in baseline or containing laxative-related diarrhea

PRISMA flow diagram (p469)
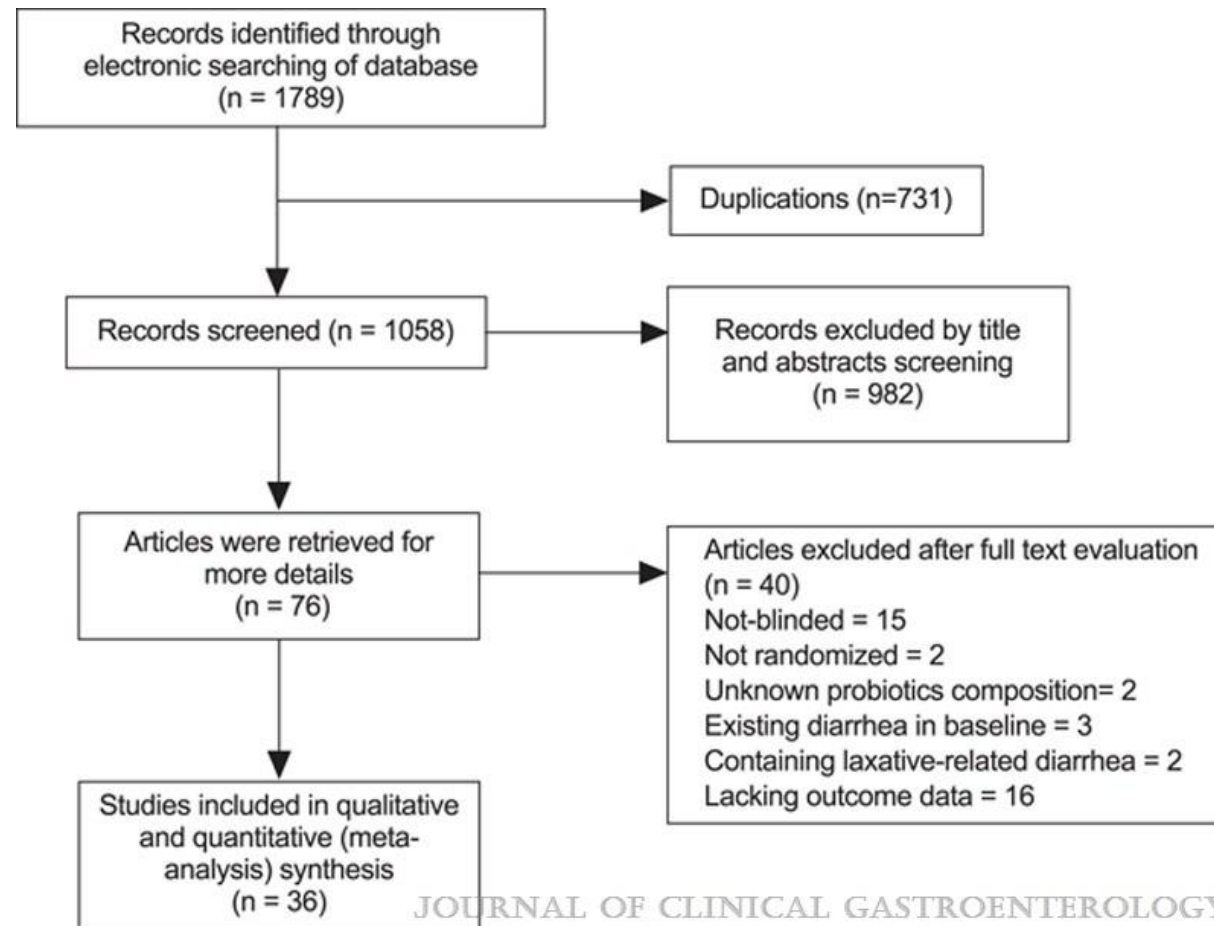
步驟 2：系統性文獻回顧的品質如何？(FAITH)

- A－文獻是否經過嚴格評讀 (Appraisal)？(p.474-475)

  評讀結果：V是　　否　　不清楚

- The data extraction was conducted using the standardized form by 2 independent researchers

- The Cochrane Handbook for Systematic Review of Interventions was applied to assess the quality of the selected studies

- 2 researchers assessed the eligibility and quality of each article independently，any discrepancies were resolved through consensus，adjudicated with the support of the third investigator

步驟 2：系統性文獻回顧的品質如何？(FAITH)

I - 是否只納入 (Included) 具良好效度的文章？(p475)

- 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)

- T - 作者是否以表格和圖表「總結」 (Total up) 試驗結果？(p.470-473)
- 評讀結果：V是　　否　　不清楚

TABLE 1. Characteristics of Enrolled Studies

References	Risk of Bias (Based on Cochrane Handbook)	Setting	Sample Size (Treatment Group; Placebo Group)	Mean Age/ Range (Treatment Group; Placebo Group)	Diarrhea Definition	Antibiotic (s)	Time From Antibiotic to Probiotic, d	Probiotic Species	Dosage Per Day	Probiotic Duration (d)	Follow-up Period (From the Cessation of Antibiotics Treatment)
Armuzzi et al[18]	Low	Adults, asymptomatic	30/30	40	NR	H. pylori eradication	0	Lactobacillus GG	1.2×10^{10} CFU	14 d, AC†+7	3 wk
Thomas et al[19]	Low	Adults, in-patient	133/134	57.2/54.4	Other definition	Various	1	Lactobacillus GG	1×10^{10} CFU	14 d	1 wk
Cremonini et al[20]	Low	Adults, asymptomatic	63/20	18-61	NR	H. pylori eradication	0	Lactobacillus GG, Saccharomyces boulardii, or the combination of L. acidophilus and Bifidobacterium lactis	6×10^9, 5×10^9, or 5×10^9 CFU	14 d, AC+7	3 wk
Nista et al[21]	Unclear	Adults, asymptomatic	54/52	46.0/43.0	NR	H. pylori eradication	0	Bacillus clausii	6×10^9 CFU	14 d, AC+7	3 wk
Can et al[22]	Unclear	Adults, in-patient	73/78	25-50	NR	Various	2	S. boulardii	1×10^{10} CFU	Various, AC	4 wk
Beausoleil et al[23]	High	Adults, in-patient	44/45	68.8/72.9	WHO*	Various	2	A combination of L. acidophilus and L. casei	2.5×10^{10} CFU for the first 2 days, 5×10^{10}v CFU for the remaining days	Various, AC	3 wk
Cindoruk et al[24]	Unclear	adults	62/62	45.82/47.56	NR	H. pylori eradication	0	S. boulardii	1000 mg	14 d, AC	6 wk
Hickson et al[25]	Unclear	Adults, in-patient	57/56	73.7/73.9	Other definition	Various	2	A combination of L. casei, S. thermophilus	1.94×10^{10}, 1.94×10^{10}, and 1.94×10^9 CFU,	Various, AC +7	4 wk

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allen 2013	159	1470	153	1471	6.1%	1.04 [0.84, 1.28]
Armuzzi 2001	1	30	8	30	0.8%	0.13 [0.02, 0.94]
Beausoleil 2007	7	44	16	45	3.1%	0.45 [0.20, 0.98]
Bekar 2011	11	46	18	36	3.9%	0.48 [0.26, 0.88]
Bravo 2008	3	41	5	45	1.5%	0.66 [0.17, 2.58]
Can 2006	1	73	7	78	0.7%	0.15 [0.02, 1.21]
Chatterjee 2013	19	176	26	167	4.2%	0.69 [0.40, 1.20]
Chotivitayatarakorn 2017	0	54	5	54	0.4%	0.09 [0.01, 1.60]
Cimperman 2011	1	13	5	10	0.8%	0.15 [0.02, 1.12]
Cindoruk 2007	9	62	19	62	3.4%	0.47 [0.23, 0.96]
Cremonini 2002	3	63	6	20	1.6%	0.16 [0.04, 0.58]
Ehrhardt 2016	21	246	17	231	3.9%	1.16 [0.63, 2.14]
Evans 2016	20	80	26	80	4.5%	0.77 [0.47, 1.26]
Francavilla 2013	4	44	12	43	2.2%	0.33 [0.11, 0.93]
Gao 2010	37	171	37	84	5.2%	0.49 [0.34, 0.71]
Haghdoost 2017	7	88	3	88	1.5%	2.33 [0.62, 8.73]
Helps 2015	16	44	14	41	4.1%	1.06 [0.60, 1.90]
Hickson 2007	7	57	19	56	3.1%	0.36 [0.17, 0.79]
Jiang 2018	2	111	18	111	1.4%	0.11 [0.03, 0.47]
Koning 2008	9	19	15	19	4.3%	0.60 [0.35, 1.02]
Lonnermark 2010	6	80	5	83	1.9%	1.25 [0.40, 3.92]
Manfredi 2012	4	73	14	76	2.1%	0.30 [0.10, 0.86]
Nista 2004	5	54	16	52	2.5%	0.30 [0.12, 0.76]
Ouwehand 2014	54	336	41	167	5.3%	0.65 [0.46, 0.94]
Padilla 2013	4	29	6	30	1.9%	0.69 [0.22, 2.19]
Pozzoni 2012	16	106	13	98	3.5%	1.14 [0.58, 2.24]
Rajkumar 2020	106	549	103	577	5.9%	1.08 [0.85, 1.38]
Romeo 2019	8	74	15	73	3.0%	0.53 [0.24, 1.16]
Selinger 2013	5	117	10	112	2.2%	0.48 [0.17, 1.36]
Shafaghi 2016	3	38	7	38	1.6%	0.43 [0.12, 1.53]
Shavakhi 2013	2	90	10	90	1.3%	0.20 [0.05, 0.89]
Song 2010	4	103	8	111	1.9%	0.54 [0.17, 1.74]
Thomas 2001	39	133	40	134	5.2%	0.98 [0.68, 1.42]
Trallero 2019	5	18	5	18	2.1%	1.00 [0.35, 2.87]
Wenus 2008	2	34	8	29	1.3%	0.21 [0.05, 0.93]
Wright 2015	5	41	4	46	1.7%	1.40 [0.40, 4.87]
Total (95% CI)		**4807**		**4505**	**100.0%**	**0.62 [0.51, 0.74]**
Total events	605		734			

Heterogeneity: Tau² = 0.14; Chi² = 84.23, df = 35 (P < 0.00001); I² = 58%
Test for overall effect: Z = 5.06 (P < 0.00001)
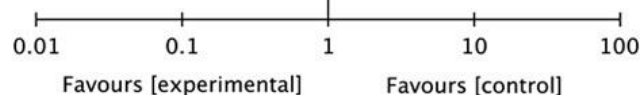
- H – 試驗的結果是否相近 – 異質性 (Heterogeneity)？
- 評讀結果：V是　否 不清楚

Overall Effect of Probiotics

As substantial heterogeneity was observed among the included studies ($P < 0.1$, $I^2 = 58\% > 50\%$), we calculated the overall AAD rate using a random effect model. Probiotics reduced the incidence of AAD by 38% (RR, 0.62; 95% CI, 0.51-0.74) in comparison with placebo (Fig. 4).

Forest plot for the overall effect of probiotics (p.476)
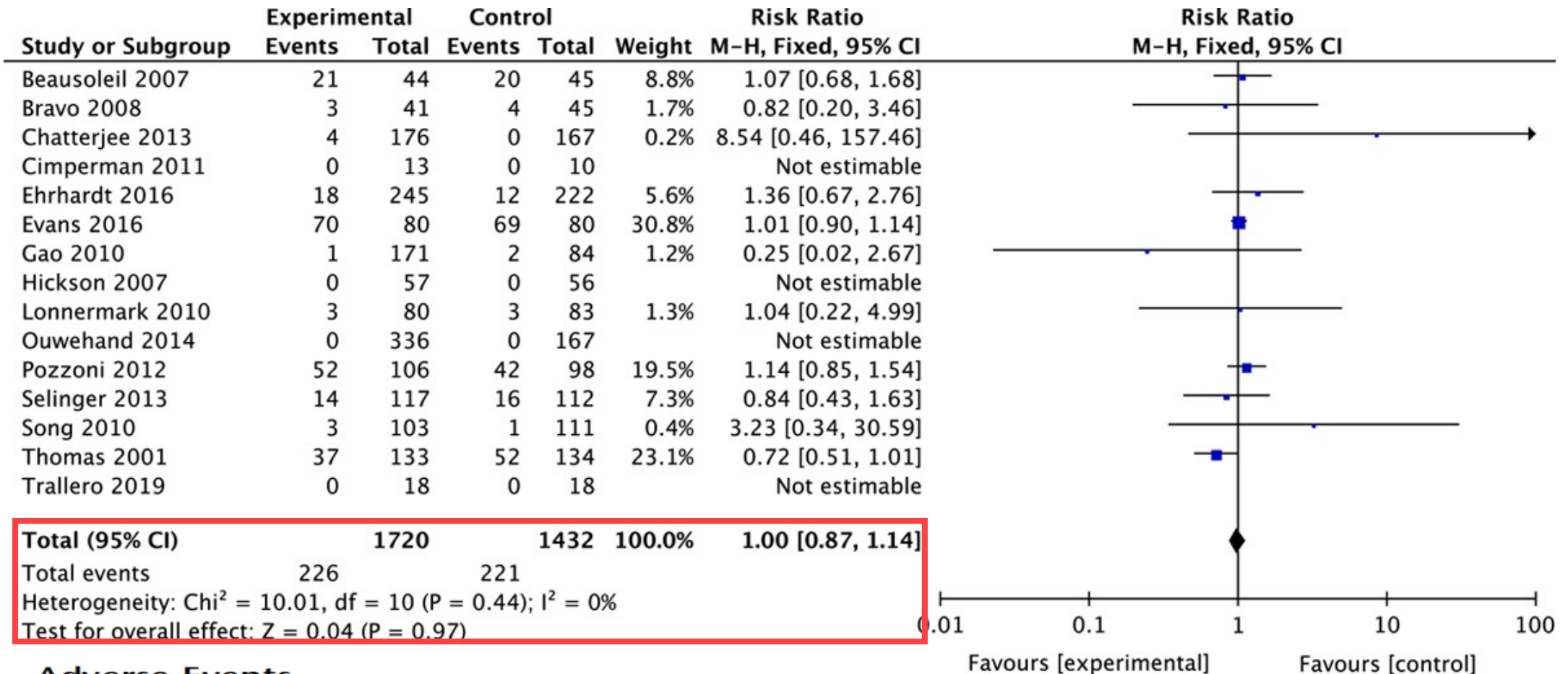
TABLE 2. The Results of Subgroup Analyses

Subgroup	No. Trials	Effect Estimate		Heterogeneity Test	P for Interaction
		Risk Ratio	95% CI	I^2, P	
Overall effect	36	0.62	0.51-0.74	58%, <0.1	—
Risk of bias					
Low risk	13	0.72	0.55-0.93	59%, 0.003	0.25
Unclear risk	18	0.57	0.42-0.77	63%, 0.0002	
High risk	5	0.45	0.27-0.76	0%, 0.82	
Diarrhea definition					
WHO definition	8	0.74	0.55-0.99	64%, 0.007	0.27
Adjusted WHO definition	6	0.64	0.37-1.11	30%, 0.21	
Others	22	0.53	0.40-0.70	63%, <0.01	
Reasons for antibiotics treatment					
For *H. pylori* eradication	13	0.36	0.25-0.53	31%, 0.13	0.0007
For other reasons	23	0.75	0.63-0.90	49%, 0.005	
Participant setting					
Hospital	16	0.75	0.60-0.94	61%, 0.0007	0.64
Community	4	0.69	0.51-0.92	0%, 0.92	
No. antibiotics					
One	8	0.62	0.52-0.75	0%, 0.84	0.68
Others	28	0.58	0.45-0.75	64%, <0.01	
Probiotic duration					
During antibiotics treatment	12	0.42	0.31-0.58	10%, 0.34	0.006
At least 1 week after antibiotics	16	0.74	0.58-0.95	55%, 0.004	
No. probiotics species					
One	15	0.64	0.44-0.93	56%, 0.004	0.86
Mixture	20	0.61	0.49-0.76	60%, 0.0003	
Probiotic dosage (CFU/d)					
$\geq 10^{10}$	14	0.77	0.60-0.98	52%, 0.01	0.05
$< 10^{10}$	12	0.49	0.33-0.72	43%, 0.06	
Follow-up duration (from the cessation of antibiotics treatment) (wk)					
≥ 4	14	0.64	0.47-0.86	64%, 0.0006	0.45
< 4	20	0.54	0.41-0.72	57%, 0.0008	
Probiotic species					
Lactobacillus	12	0.67	0.50-0.91	44%, 0.05	0.10
S. boulardii	6	0.69	0.39-1.22	47%, 0.09	
Lactobacillus+Bifidobacterium	6	0.82	0.57-1.17	56%, 0.04	
Other (mixed) species	12	0.41	0.27-0.63	71%, <0.01	
Time from antibiotic to probiotic (d)					
< 2	22	0.54	0.43-0.67	43%, 0.02	0.03
2-7	13	0.79	0.60-1.03	52%, 0.01	

H. pylori indicates Helicobacter pylori; S. boulardii, Saccharomyces boulardii.

- H – 試驗的結果是否相近 – 異質性 (Heterogeneity)？
- 評讀結果：∨是　　否　　不清楚

Sensitivity analysis revealed that the pooled RR of probiotic effectiveness was robust. No single study significantly affected the overall effect.

Forest plot of adverse events

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI
Beausoleil 2007	21	44	20	45	8.8%	1.07 [0.68, 1.68]
Bravo 2008	3	41	4	45	1.7%	0.82 [0.20, 3.46]
Chatterjee 2013	4	176	0	167	0.2%	8.54 [0.46, 157.46]
Cimperman 2011	0	13	0	10		Not estimable
Ehrhardt 2016	18	245	12	222	5.6%	1.36 [0.67, 2.76]
Evans 2016	70	80	69	80	30.8%	1.01 [0.90, 1.14]
Gao 2010	1	171	2	84	1.2%	0.25 [0.02, 2.67]
Hickson 2007	0	57	0	56		Not estimable
Lonnermark 2010	3	80	3	83	1.3%	1.04 [0.22, 4.99]
Ouwehand 2014	0	336	0	167		Not estimable
Pozzoni 2012	52	106	42	98	19.5%	1.14 [0.85, 1.54]
Selinger 2013	14	117	16	112	7.3%	0.84 [0.43, 1.63]
Song 2010	3	103	1	111	0.4%	3.23 [0.34, 30.59]
Thomas 2001	37	133	52	134	23.1%	0.72 [0.51, 1.01]
Trallero 2019	0	18	0	18		Not estimable
Total (95% CI)		**1720**		**1432**	**100.0%**	**1.00 [0.87, 1.14]**
Total events	226		221			

Heterogeneity: Chi^2 = 10.01, df = 10 (P = 0.44); I^2 = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

Favours [experimental]   Favours [control]

Adverse Events

A total of 15 studies described adverse events, mainly involving nausea, bloating, and dyspepsia. Four of them reported no adverse events either in the probiotics group or in the placebo, and 2 registered serious adverse events but not attributable to probiotics. There were no statistically significant increased adverse events in the probiotics group (RR, 1.00; 95% CI, 0.87-1.14; $P=0.97$) (Fig. 5).

步驟 2：系統性文獻回顧的品質如何？(FAITH)
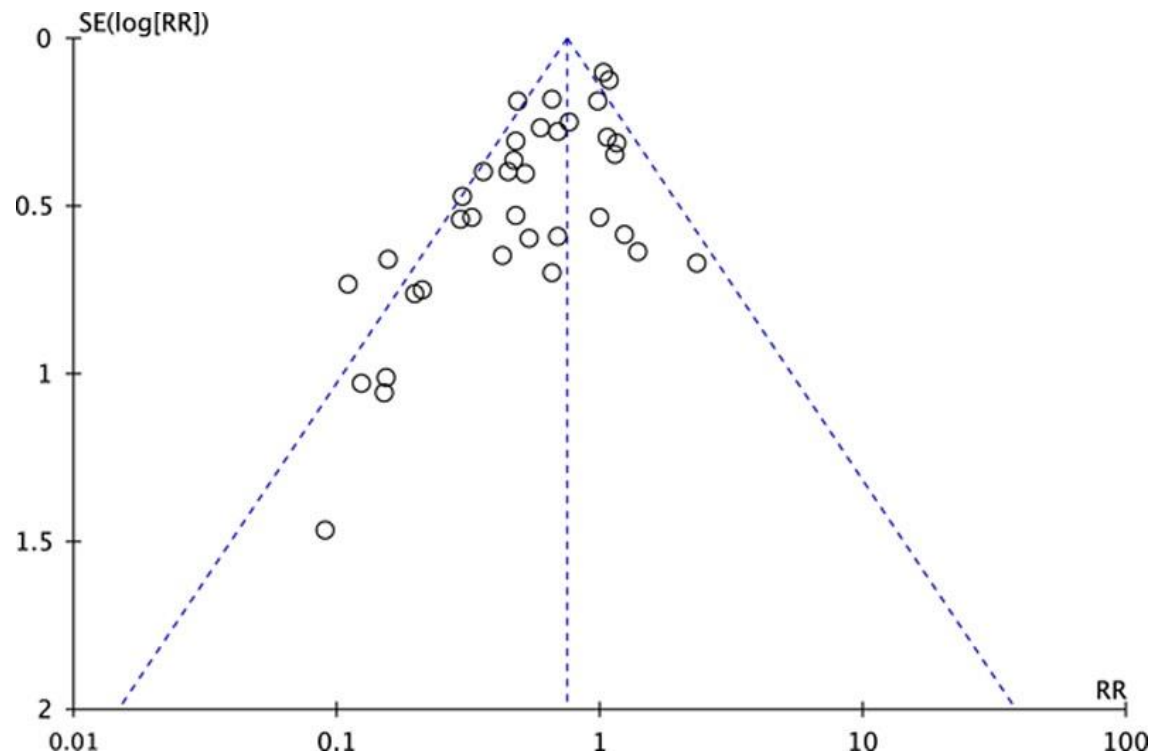
Funnel plot of publication bias. RR indicates relative risk;
SE, standard error.

Publication Bias

The funnel plot, Begg test, and Egger test were applied to assess the publication bias of the enrolled studies. These results provided evidence of publication bias (Begg test: $z = 2.36$, $Pr > |z| = 0.018 < 0.05$; and Egger test: $t = -4.77$; 95% CI, -2.40 to -0.97; $P < 0.05$). We use the trim and fill method to correct the publication bias and yielded the same pooled RR of 0.62 as initial outcomes, which suggested that results of the overall effect were stable, and publication bias had few effects on the results. Therefore, our asymmetric funnel plot may be caused by other reasons such as studies with low quality or small sample size (Fig. 6).

總結

	FAITH系統性文獻回顧快速評讀表		結果
F	研究是否找到 (Find) 所有的相關證據？	至少二個主要資料庫(PubMed，EMBASE，and Cochrane Library)，加上文獻引用檢索(Web of Science)，不限英文，使用 MeSH 字串及一般檢索詞彙(text words)。	是
A	文獻是否經過嚴格評讀 (Appraisal)？	以the Cochrane Risk of Bias assessment tool進行嚴格評讀，並以表格呈現各篇納入文獻品質	是
I	是否只納入 (Included) 具良好效度的文章？	由二位研究員獨立進行評讀，意見不一時由第三位進行裁定	是
T	作者是否以表格和圖表「總結」 (Total up)	Table (characteristics of enrolled studies, subgroup analysis), forest plot of probiotics overall effects and adverse events	是
H	試驗的結果是否相近－異質性 (Heterogeneity)？	因異質性大套用random effect model，進行sensitivity analyses and subgroup analyses，funnel plot、Begg test、Egger test to assess publication bias	是

Conclusion

Eligible studies	36 RCTs, n=9312 (low risk:13, unclear:18, high risk:5)
Overall effect	Probiotics reduced AAD incidence by 38% in comparison with placebo
Reasons for antibiotics treatment	Helicobacter pylori eradication had a higher efficacy than those used antibiotics for other reasons
Probiotic duration	Equal to the antibiotics course is more effective than prolong use
Probiotic dosage	Daily dose of probiotics < 10^10 CFU (low dose) is more effective in AAD prevention
Time from antibiotic to probiotic	Within the first 2 days of antibiotic treatment is more beneficial to prevent diarrhea
Adverse events	No statistically significant increased adverse events

BMJ Open

Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis

Clare Goodman [iD],[1] Georgia Keating,[2] Ekavi Georgousopoulou,[1] Charlotte Hespe [iD],[1] Kate Levett [iD][1]

- Journal Impact Factor 2.692(2020)

Liao et al., 2021		Goodman et al., 2021
To assess the effect of probiotics on preventing antibiotic-associated diarrhea in adults	Objective	To evaluate existing evidence for the use of probiotics in preventing antibiotic-associated diarrhea(AAD) in adults
The PubMed，EMBASE，Web of Science and Cochrane Library	Search strategy	CINAHL Plus, EMBASE, MEDLINE (Ovid), Web of Science, Google scholar databases, grey literature and clinical trial registers, reference list search
Any language	Language	English only
Mesh terms and key words：probiotic(s), diarrhea, anti-bacterial agents, antibiotic(s), antibiotic-associated diarrhea, placebo, randomized, randomized controlled trial	Search terms	Boolean keywords / search terms： *intervention* (Probiotic or fermented milk or fermented yoghurt or lactic acid bacteria or lactobacillus or..) *Outcome* (Incidence or prevalence or occurrence or reduction or improvement or prevention or alleviation or episode* or occasion)AND (Diarrh* or antibiotic-associated diarrh* or clostridium difficile associated diarrh* or pseudomembranous colitis ornosocomial diarrh* or infectious diarrh*). mtitl.

Liao et al., 2021		Goodman et al., 2021
(1)adults both inpatients and outpatients who were prescribed antibiotics for various reasons with probiotics or placebo (2)Providing the occurrence of AAD(mainly WHO definition) (3)The study designed as RCT	Inclusion criteria	(1)RCTs comparing probiotic use(any strain, dose or formulation)to placebo, alternative dose, alternative probiotic strain or no treatment, for the prevention of diarrhea in adults receiving antibiotic therapy (2)Primary outcome measure-incidence of AAD (defined by authors) during the antibiotic treatment or follow-up phases
(1)Duplicate studies, animal researches, preclinical studies, and case reports (2)Unknown probiotics composition (3)not-blinded trials (4)Existing diarrhea in baseline or containing laxative-related diarrhea	Exclusion criteria	(1)Studies examined probiotics for treatment of AAD (2) Studies of paediatric populations (3)Duplicate, unfinished,non-randomized study design, different outcome measures studies
the Cochrane Risk of Bias tool	Quality assessment	the Cochrane Risk of Bias tool The overall quality of the evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach
36 RCTs (9312 participants) adults, (low risk:13, unclear:18, high risk:5)	No of studies included	42 RCTs (11305 participants), age 15-85 y/o 6/42 low risk of bias, 36/42 unclear or high risk

Liao et al., 2021		Goodman et al., 2021
Probiotics reduced AAD incidence by 38% in comparison with placebo	Overall results	The pooled RR of 0.63 (RR=0.63 (95% CI 0.54 to 0.73), p<0.00001) indicates that over one-third less likely to develop AAD. NNT=20
Probiotic duration equal to the antibiotics course is more effective than prolong use	Probiotic duration	
high-dose probiotics (≥10^10 CFU/d) were statistically less effective than low dose probiotics (P= 0.05<0.10)	Probiotic dosage	higher dose group demonstrated a significant reduction in the relative risk of AAD(RR 0.54 (95% CI 0.38 to 0.76), p=0.0004)
Within the first 2 days of antibiotic treatment is more beneficial to prevent diarrhea	Time from antibiotic to probiotic	
No statistically significant increase	Adverse events	No serious adverse events
	other	• variation in the probiotic formulation ie, tablets, powder, yoghurt or fermented milk • The following probiotic strains demonstrated significant reduction in AAD：L. acidophilus(嗜酸乳桿菌), L. paracasei(副乾酪乳桿菌), etc. • participants with a moderate or high baseline risk for developing AAD demonstrated 39% and 45% risk reduction, respectively

Discussion
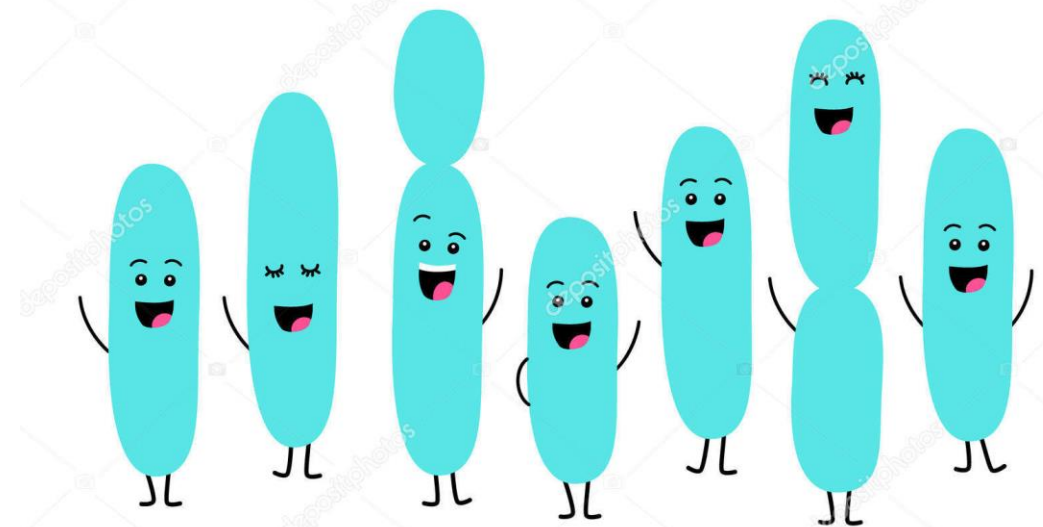
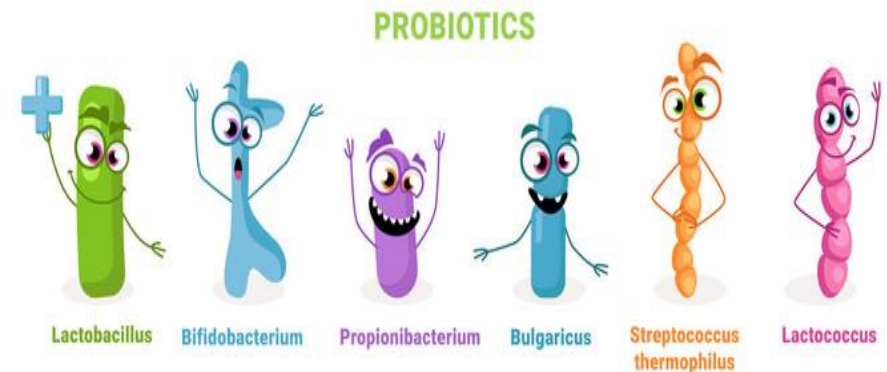PROBIOTICS BACTERIA FAMILY

● 是否贊成接受抗生素治療的病人，常規早期使用益生菌，以預防抗生素引起的腹瀉？

同意：5票　　仍有疑慮：16票　　不同意：0票

許怡苹 下午1:02
黃色

10A黃色3票

陳秀鉛9A病房 下午
黃色

黃湀萍第二加護病房
黃色

PROBIOTICS

Lactobacillus　Bifidobacterium　Propionibacterium　Bulgaricus　Streptococcus thermophilus　Lactococcus