Prescribing an antibiotic? Pair it with probiotics *J Fam Pract*. 2013:62:148-150.

Potential PURL Review Form: Meta-analysis

SECTION 1: IDENTIFYING INFORMATION

1. Citation	Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012;307:1959-1969.
2. Hypertext link to PDF of full article	http://jama.jamanetwork.com/article.aspx?articleid=1151505
3. First date published study available to readers	May 9, 2012
4. PubMed ID	22570464
5. Nominated By	Jim Stevermer
6. Institutional Affiliation of Nominator	University of Missouri
7. Date Nominated	June 12, 2012
8. Identified Through	InfoPOEMs
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	July 5, 2012
11. Potential PURL Review Form (PPRF) Type	Meta-analysis
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Kate Kirley
14. Reviewer Affiliation	University of Chicago
15. Date Review Due	August 9, 2012
16. Abstract	**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.

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. What types of studies are included in this review?	Randomized controlled trials
2. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.	Question: Are probiotics effective for prevention or treatment of antibiotic-associated diarrhea (AAD)? Probiotics appear effective: pooled (RE) RR 0.58 [0.50-0.68], *P*<.001; pooled RD –0.07 [–0.10 to –0.05]; NNT 13. These results were consistent through a number of sensitivity analyses and subgroup analyses looking at different types of probiotics. Strengths: large number of trials, wide range of patients and clinical scenarios. Weaknesses: overall poor quality of included trials, few trials addressed adverse events.
3. Study addresses an appropriate and clearly focused question - ***select***	Adequately addressed Comments: Questionable whether it makes sense to lump treatment and prevention into one category.

one.

4. A description of the methodology used is included.	Well covered
5. The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered
6. Study quality is assessed and taken into account.	Well covered Comments: Generally poor study quality. Authors assessed the potential for bias, but it is not clear how this bias might affect the results; it appears from their sensitivity analysis—where they only included higher quality trials—that this did not significantly bias the results.
7. There are enough similarities between selected studies to make combining them reasonable.	Well covered Comments: There is huge heterogeneity among trials in terms of probiotic used, original condition being treated with antibiotics, antibiotic used and schedule/duration, and how outcomes were defined. However, subgroup analyses that grouped more clinically similar trials continued to show similar results to the overall pooled result (although could not account for all of the heterogeneity).
8. Are patient-oriented outcomes included? If yes, what are they?	Yes - diarrhea.
9. Are adverse effects addressed? If so, how would they affect recommendations?	Yes - 23 trials evaluated for adverse events and none were observed. However, 59 trials did not report on adverse events. It is unclear whether the absence of adverse events in the trials that did evaluate for adverse events is sufficient to declare the treatment safe; other studies not included here have linked probiotics to serious adverse events.
10. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?	The meta-analysis was funded by RAND. Potential for funding bias is not reported in most of the RCTs included in the analysis.
11. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.	Any patients receiving antibiotics.
12. In what care settings might the findings apply, or not apply?	Medical care setting.

13. To which clinicians or policy makers might the findings be relevant?	Any physicians prescribing antibiotics

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date	Probiotics to prevent antibiotic-associated diarrhea. In: DynaMed [database online]. Available at: www.DynamicMedical.com. Last updated June 18, 2012. Accessed August 8, 2012.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Probiotics are effective in reducing AAD (they specifically cite this article by Hempel).

4. UpToDate excerpts

5. UpToDate citation/access date	Sartor RB. Probiotics for gastrointestinal diseases. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2012. Available at: http://www.uptodate.com. Last updated May 11, 2012. Accessed August 8, 2012.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	There may be benefit, but additional large well-conducted studies are needed.
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	Uses • Antibiotic-induced diarrhea • Efficacy – *Lactobacillus* GG (Culturelle) appears most effective Mechanism of Action • Normal bowel flora inhibit growth of harmful bacteria, stimulate local immunity, promote water reabsorption in colon Adverse Drug Reactions • N/A
8. PEPID citation/access data	Probiotics. In: PEPID [database online]. Available at: http://www.pepidonline.com. Accessed August 8, 2012.
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? Yes, there is important evidence or recommendations that are missing If yes, which PEPID Topic, Title(s): **Probiotics**
10. Other excerpts (USPSTF; other guidelines; etc.)	

11. Citations for other excerpts

12. Bottom line
recommendation or summary
of evidence from other sources
(1-2 sentences)

SECTION 4: CONCLUSIONS

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	3
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	Significant clinical, methodological, and statistical heterogeneity. However, it is not clear from the sensitivity analysis that this heterogeneity would bias the results.
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	3
4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	Certainly relevant, but because of the large heterogeneity it is difficult to say which patients would be most benefited by this intervention—or does it truly benefit any patient taking an antibiotic?
5. Practice-changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)	4
6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	This study reinforces existing evidence. I suspect there is a mixture of practices currently regarding recommending probiotics for this indication.
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care	1

setting)

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)	1
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	
11. Clinical meaningful outcomes or patient-oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)	1
12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.	
13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) Criteria for a Pending PURL: • Valid: Strong internal scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	4
14. Comments on your response in 4.13	Can't decide how large of a problem the heterogeneity is. Also, unclear if this is truly a practice change.