Effective Health Care

Probiotics to Prevent Antibiotic-Associated Diarrhea and *Clostridium Difficile* Diarrhea

Results of Topic Selection Process & Next Steps

The nominator is interested in a new evidence review on probiotics to prevent antibiotic-associated diarrhea and clostridium difficile-associated diarrhea.

We identified five systematic reviews covering the scope of the nomination, therefore, a new review would be duplicative of an existing product. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Probiotics to Prevent Antibiotic-Associated Diarrhea and *Clostridium Difficile* Diarrhea

Nomination Date: 6/21/2018

Topic Brief Date: 6/21/2018

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report

Background

- Antibiotic-associated diarrhea (AAD) is defined as diarrhea associated with antibiotic exposure, up to 8 weeks after antibiotics have been discontinued[1].
- The frequency of AAD in children ranges from 6-80/100. The incidence in adults ranges from 7-33/100 person-years in inpatients and 2.5/100000 person-years in outpatients.
- The treatment of AAD consists of discontinuing or switching the offending antibiotic[1]
- One-third of AAD cases are due to Clostridium difficile.
- Clostridium Difficile-associated diarrhea (CDAD) diagnosis is based on: (1) presence of C. difficile in the stool (e.g., microbial culture, cytotoxin assay, enzyme immunoassay, nucleic acid amplification test, or polymerase chain ribotyping); and (2) the presence of gastrointestinal symptoms (e.g., diarrhea, colitis, etc.) without another etiology being present[1]
- Estimated number of incident C. difficile infections in the United States was 453,000 (95% confidence interval [CI], 397,100 to 508,500). C diff was associated with approximately 29,000 deaths in 2011[2].
- CDAD is treated with antibiotics directed at eradicating clostridium difficile, such as metronidazole and vancomycin

- AAD and CDAD can lead to increased hospitalization, costs of care, and risk of other infections[1].
- Prevention strategies are aimed at decreasing exposure to antibiotics, exposure to clostridium difficile, and measures to improve host defenses. These include measures such as antimicrobial stewardship programs, infection control measures, and probiotics[3].
- While probiotics have been studied for prevention of AAD and CDAD an important potential harms is causing a new infection with organisms in probiotic formulations in hospitalized patients[3]

The key questions for this nomination are:

1. Do probiotics given with antibiotics prevent antibiotic-associated diarrhea?
    a. What strains are most effective?
2. Do probiotics given with antibiotics prevent Clostridium Difficile-associated diarrhea?
    a. What strains are most effective?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, and setting (PICOS) of interest (Table 1).

Table 1. Key Question and PICOS

Key Questions	Probiotics to prevent antibiotic-associated diarrhea (AAD)	Probiotics to prevent Clostridium Difficile-associated diarrhea (CDAD)
Population	Adults (18 years and older) and children (1 month to 18 years old) who will take antibiotics	Adults (18 years and older) and children (1 month to 18 years old) who will take antibiotics
Interventions	Probiotic	Probiotic
Comparators	Other intervention to prevent AAD, usual care	Other intervention to prevent CDAD, usual care
Outcomes	Diarrhea, harms of probiotics	CDAD, harms of probiotics
Setting	Inpatient, outpatient	Inpatient, outpatient

Abbreviations: AAD=antibiotic-associated diarrhea; CDAD=clostridium difficile-associated diarrhea

Methods

We assessed nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication
We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Results

Appropriateness and Importance
This is an appropriate and important topic. See Appendix B for details.

Desirability of New Review/Duplication
A new evidence review would be duplicative of an existing product. We identified five systematic reviews that address the scope of the nomination's questions: three address KQ 1 and four address KQ 2. See Appendix B for details.

Table 2. Key Questions and Results for Duplication

Key Question	Duplication (6/2015-6/2018)
KQ 1: Probiotics and AAD	Total number of identified systematic reviews: 3 • Cochrane SR-2[4, 5] • Other group-1[6]
KQ 2: Probiotics and CDAD	Total number of identified systematic reviews: 4 • AHRQ SR-1[7] • Cochrane SR-2[4, 5] • Other group-1[8]

Abbreviations: AAD=antibiotic associated diarrhea; AHRQ=Agency for Healthcare Research and Quality; CDAD=clostridium difficile-associated diarrhea; KQ=Key Question; SR=systematic review

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be duplicative of an existing product.

References

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Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Estimated number of incident *C. difficile* infections in the United States was 453,000 (95% confidence interval [CI], 397,100 to 508,500). The incidence was estimated to be higher among females, whites, and persons 65 years of age or older. C diff was associated with approximately 29,000 deaths in 2011[2].
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes.
2c. Represents important uncertainty for decision makers	Yes, there is uncertainty about how best to prevent CDAD. In a synthesis of five different C diff guidelines, all but one did not recommend the use of probiotics for primary prevention[9]. A 2017 IDSA guideline published since this synthesis indicated that there was insufficient data to recommend administration of probiotics for primary prevention of outside of clinical trials[3, 10].
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes. There are potential and benefits and harms to the use of probiotics. Harms could include an infection by an organism in the probiotic patients[3, 10].
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. CDAD leads to increased costs of healthcare from $3427-$9960/patient. AAD is also associated with longer hospitalizations, higher healthcare costs, increased risks of mortality and acquiring other nosocomial infections[1]

Selection Criteria	Assessment
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified five systematic reviews that address the scope of the nomination. KQ 1 (AAD and probiotics) • Goldenberg et al (2017)[4]. This Cochrane systematic review addressed probiotics for prevention of AAD and CDAD in adults and children. This review included subgroup analysis based on age, inpatient/outpatient, and probiotic species. • Goldenberg et al (2015)[5]. This Cochrane systematic review addressed AAD and CDAD in children. It included subgroup analysis based on probiotic strain • Blaabjerg et al (2017)[6]. This systematic review focused on probiotics for prevention of AAD in adult and pediatric outpatients taking oral antibiotics. Analysis was also undertaken by strain type, age, and trials of H pylori eradication. KQ 2 (CDAD and probiotics) • Goldenberg et al (2017)[4] • Goldenberg et al (2015)[5] • Butler et al (2016)[7]. This AHRQ EPC systematic review addressed early diagnosis, prevention and treatment of C difficile-associated diarrhea in adults. A range of prevention interventions were included such as probiotics, antimicrobial stewardship, environmental cleaning, and bundled preventive programs. • Shen et al (2017)[8]. This systematic review assessed the use of probiotics in hospitalized adults to prevent CDAD. Secondary analyses examined the effects of probiotic species, dose, timing, formulation, duration, and study quality. We also identified two in-process systematic reviews that can contribute additional information about costs and harms of probiotics • Carina Nakamura, Antony Martin, Dyfrig Hughes, Fabio Miyajima. Economics of interventional measures for Clostridium difficile infection. PROSPERO 2016 CRD42016024893 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016024893 • Rafael da Costa, Andrea de Lorenzo, Cristiane Lamas, Jose Moreira. Infectious complications and mortality after ingestion of probiotics: a systematic review. PROSPERO 2016 CRD42016042289 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016042289

Abbreviations: AAD=antibiotic-associated diarrhea; AHRQ=Agency for Healthcare Research and Quality; CDAD=clostridium difficile-associated diarrhea; IDSA=Infectious Diseases Society of America; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: June 2015 to June 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/