

# Probiotics for the Prevention of CDAD: an idea to flush down the toilet?

François Lefebvre, Lana Moussa, Alex Pozzebon & Emmanuelle Sauvé

Interdisciplinary School of Health Sciences, University of Ottawa



uOttawa

L'Université canadienne  
Canada's university

## Abstract

**Background:** With an aging population, the majority of patients in hospitals tend to be over 50 years old. *Clostridium difficile*, an opportunistic pathogen, is the culprit in a very common condition amongst these older patients, especially in a hospital setting, as a result of the use of broad spectrum antibiotics. This condition is called *Clostridium difficile*-associated diarrhea (CDAD). Literature confirms that about 25% of all antibiotics-associated diarrhea (AAD) are the result of an infection by *C. difficile*, which has a high mortality rate and an increase in the duration of hospitalization. Probiotics are commonly used to prevent diarrhea and restore intestinal flora to its healthy state.

**Research question:** Is the use of probiotics effective as a preventive measure for CDAD in hospitalized individuals over the age of 50? **Objective:** We conducted a literature review in order to determine if the administration of probiotics will help reduce the incidence rate of CDAD in adult patients over 50 years of age.

**Methods:** Two databases were used, PubMed and SCOPUS, to conduct our literature search. The keywords used were: “probiotics”, “prevention”, “clostridium difficile”, “hospital” and “adults”. A total of 49 results were obtained. Articles included had to be in English or French, based on a human population aged 50 or over, not published before the year 2006, peer-reviewed, accessible and had to address CDAD and not just AAD. The articles were also screened for relevance. Upon the application of our relevance criteria, 6 articles were deemed pertinent.

**Results:** Of the 6 relevant articles found, 3 demonstrate a reduction in the incidence of CDAD in hospitals through the use of probiotics, 2 others fail to do so while 1 has inconclusive results.

**Conclusion:** The literature is divided in the effectiveness of probiotics as a preventative measure for CDAD. Further studies are needed.

## Background

*Clostridium difficile* is an opportunistic bacteria that produces spores when subjected to stressful situations which allows them to tolerate extreme conditions such as the alcohol based disinfectants used for hand sanitation<sup>5</sup>. This ability to survive normal hospital cleaning methods is the reason why they are so efficient in hospital environments<sup>5</sup>.

When ingested, the spores germinate into mature *C. difficile* and produce toxins (A and B), inducing the symptoms for *C. difficile*-associated diarrhea or CDAD<sup>5</sup>. Broad spectrum antibiotics alter the flora of the colon mucosa, thus leaving the opportunity for new bacteria, such as *Clostridium difficile*, to become dominant and cause an infection<sup>5</sup>.

*C. difficile* is spread from person to person through the oral-fecal pathway<sup>5</sup>. The spores resist the alcohol based hand sanitizers used by the healthcare workers and can thus be spread throughout the hospital<sup>5</sup>.

Most CDAD cases are reported to be in older individuals (over 50 years of age) because they are more susceptible to be in hospitals, constituting the majority of the patient population<sup>5</sup>.

**Probiotics** are live bacteria and yeasts that are healthy for your gastrointestinal tract. They are often suggested by doctors when patients suffer from digestive problem because they help balance the bacterial ratio<sup>2</sup>.

### Research question

Is the use of probiotics effective as a preventative measure for *Clostridium difficile*-associated diarrhea in hospitalized patients over the age of 50?

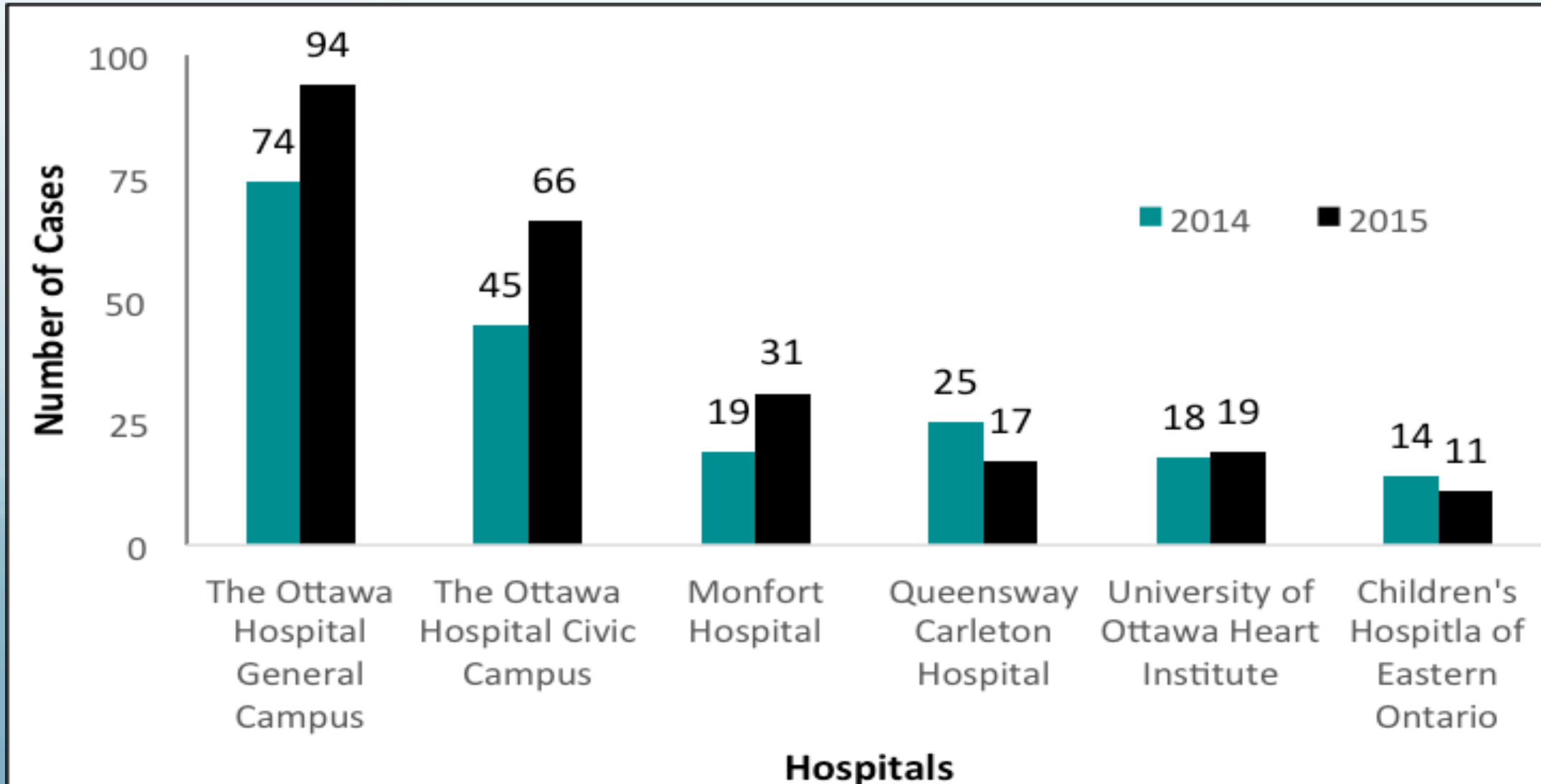
### Objective

This study has conducted a literature review in order to determine if the administration of probiotics will help reduce the incidence rate of CDAD in adult patients over the age of 50 years old.

### Rationale

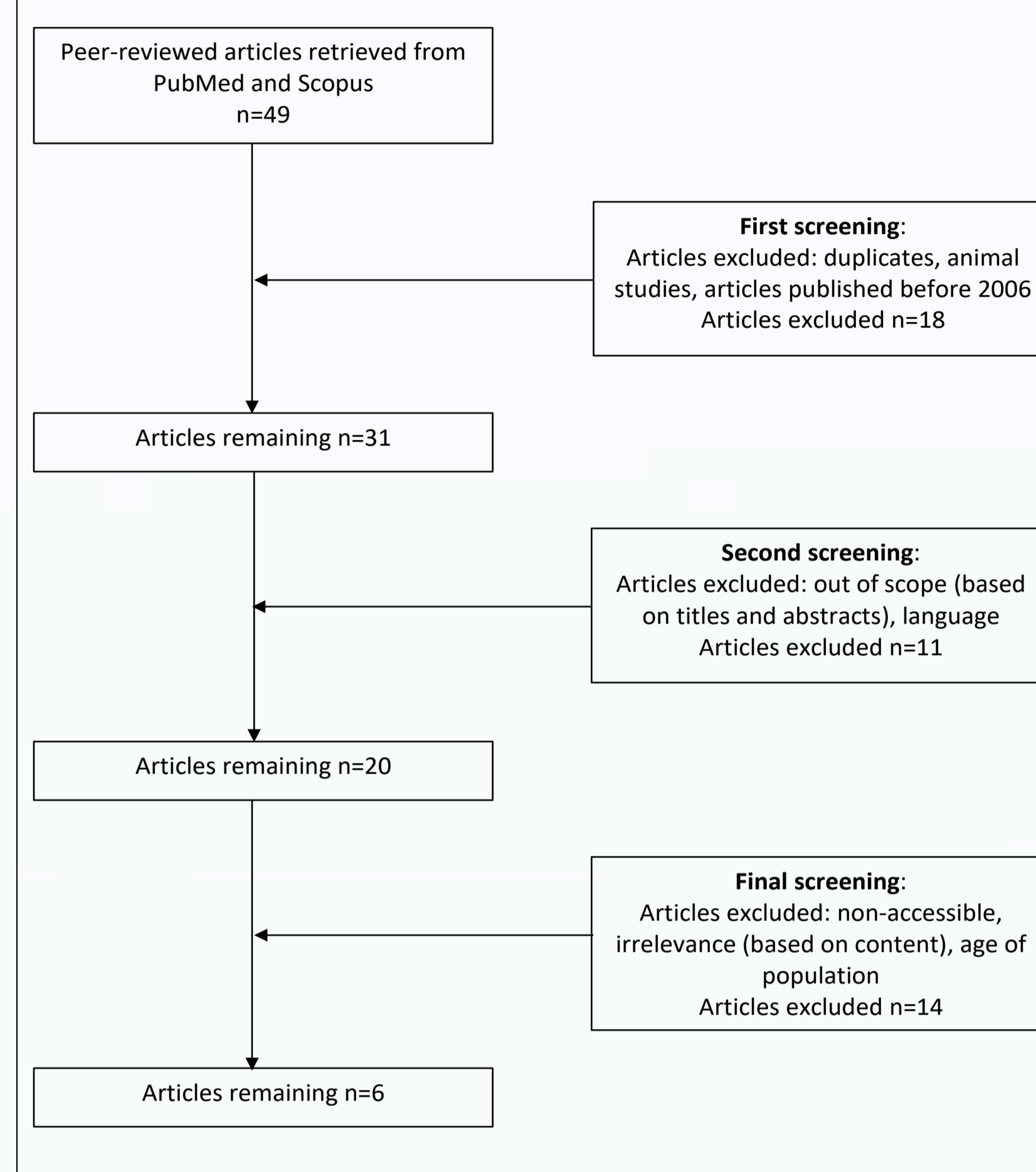
① The incidence rate for in hospital CDAD is on the rise. According to the literature, it affects somewhere between 15-35% of all AAD cases and around 10% of all hospital patients<sup>5</sup>.

② The incidence rate of CDAD outside of hospitals will soon rise as a result of antibiotic overuse<sup>5</sup>. The ability for bacteria to develop resistance to antibiotics will potentially allow it to infect a greater number of people, even those not under antibiotic influence<sup>5</sup>.



**Figure 1.** Comparison of the number of cases of *C. diff.* infections in six Ottawa hospitals in 2014-15  
Data taken from the ministry of Health, Canada

## Methods



**Figure 2.** Application of exclusion criteria

A structured literature search was conducted using two different electronic databases, PubMed and SCOPUS, using the key terms “probiotics” and “prevention” and “clostridium difficile” and “hospital” and “adults”. A total of 37 articles were retrieved from PubMed, and 12 from SCOPUS. Our first set of exclusion criteria removed duplicates, animal studies, studies published prior to the year 2006 and non-peer-reviewed articles, resulting in 31 articles. The articles were then screened for relevance based on their titles and abstracts, and those in languages other than English and French were excluded, resulting in 20 articles. Of the 20 remaining studies, the ones who focused on individuals over the age of 50, and those who were accessible, were included. Also, those who only addressed AAD in general and not CDAD were excluded for irrelevance. Finally, 6 articles remained and were included. The study methods are varied (systematic reviews and RCTs), however all articles are peer-reviewed. The Jadad scale was used to assess the quality of each RCT.

### References

- Allen, S. J., Wareham, K., Wang, D., Bradley, C., Sewell, B., Hutchings, H., ... Phillips, C. J. (2013). A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and clostridium difficile diarrhoea in older people admitted to hospital: A multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). *Health Technology Assessment*, 17(57), 1–130. <https://doi.org/10.3310/hta17570>
- Anderson, H., Aps, N.-G., Bruus, A., Rook, S., Wadstrom, T., & Ward, A. E. (2011). Health effects of probiotics and prebiotics: A literature review on human studies. *Scandinavian Journal of Nutrition/Nutritionforskning*, 45, 58–76. <https://doi.org/10.3402/nfr.v45i0.1790>
- Gao, X. W., Mubasher, M., Fang, C. Y., Reifer, C., & Miller, L. S. (2010). Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1265 and Lactobacillus casei LBC30R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea prophylaxis in adult patients. *The American Journal of Gastroenterology*, 105(7), 1636–1641. <https://doi.org/10.1038/ajg.2010.11>
- Hickson, M., O'Shea, A. L., Mathu, N., Rogers, J. R., Ware, S., Rajuram, C., & Blupitt, C. J. (2007). Use of probiotic Lactobacillus preparation to prevent diarrhea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ (Clinical Research Ed.)*, 335(7610), 80. <https://doi.org/10.1136/bmj.39231.598615.55>
- Khan, F. Y., & Elzaki, A. N. (2014). Clostridium difficile infection: a review of the literature. *Asian Pacific Journal of Tropical Medicine*, 7(10)(Suppl 1), S6–S13. [https://doi.org/10.1016/S1985-7845\(14\)60197-8](https://doi.org/10.1016/S1985-7845(14)60197-8)
- Ouweland, A. C., DongJian, C., Weijian, X., Stewart, M. N. J., Stewart, T., & Miller, L. E. (2014). Probiotics reduce symptoms of antibiotic use in a hospital setting: A randomized dose response study. *Vaccine*, 32(4), 458–463. <https://doi.org/10.1016/j.vaccine.2013.11.063>
- Pozzoni, P., Riva, A., Bellatore, A. G., Amigoni, M., Redaelli, E., Ronchetti, A., ... Colli, A. (2012). Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. *The American Journal of Gastroenterology*, 107(10), 922–31. <https://doi.org/10.1038/ajg.2012.56>
- Xie, C., Li, J., Wang, K., Li, Q., & Chen, D. (2015). Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: A systematic review. *Travel Medicine and Infectious Disease*, 15(3), 128–134. <https://doi.org/10.1016/j.tmaid.2015.03.001>

## Results

Details	Population	Methods	Results	Quality (JADAD)
Allen & al., 2013; UK	N= 1493 cases N= 1488 controls Age group: 65+	<b>Design:</b> Randomized, Double-Blind, Placebo-Controlled Trial, parallel arm trial <b>Disease:</b> AAD & CDAD <b>Intervention:</b> lactobacilli and bifidobacteria <b>Intervention length:</b> 21 days $\alpha=0.05$	<ul style="list-style-type: none"> <li>The development of CDAD was uncommon and occurred in 0.8% of the cases and 1.2% of the controls (RR 0.71; 95% CI 0.34 to 1.47; p = 0.35), but the difference was not statistically significant.</li> </ul>	4.5
Gao, Mubasher, Fang, Reifer, Miller, 2010; USA	N= 86 high dose cases N= 84 control Age group: 50-70	<b>Design:</b> Randomized, Double-Blind, Placebo-Controlled Trial, Dose-ranging study <b>Disease:</b> AAD & CDAD <b>Intervention:</b> Lactobacillus acidophilus, Lactobacillus casei <b>Intervention length:</b> during antibiotics + 5 days $\alpha = 0.05$	<ul style="list-style-type: none"> <li>High dose cases had a lower CDAD incidence (1.2%) vs. low doses cases (9.4%).</li> <li>Each case had a lower CDAD incidence vs. placebo (23.8%)</li> <li>The probiotics were tolerated and effective for reducing CDAD in hospitalized patients on antibiotic</li> </ul>	4
Hickson & al., 2007; UK	N= 69 cases N= 66 controls Age group: 50+	<b>Design:</b> Randomized, Double-Blind, Placebo-Controlled Trial <b>Disease:</b> AAD & CDAD <b>Intervention:</b> Lactobacillus casei, L bulgaricus, and Streptococcus thermophiles <b>Intervention length:</b> 7 days after antibiotics $\alpha=0.001$	<ul style="list-style-type: none"> <li>No one in the cases and 17% in the placebo group had CDAD (P=0.001)</li> <li>Significant reduction in the incidence of CDAD in the cases</li> <li>ARR: 17% (7%-27%)</li> </ul>	4
Ouweland & al., 2014; China	N= 168 high dose cases N= 168 low dose cases N= 167 controls Age group: 50-70	<b>Design:</b> Randomized, Triple-Blind, Placebo-Controlled Trial, Dose-ranging study <b>Disease:</b> AAD & CDAD <b>Intervention:</b> Lactobacillus acidophilus, Lactobacillus paracasei, Bifidobacterium lactis, Bifidobacterium lactis <b>Intervention length:</b> during antibiotics +7 days after antibiotics $\alpha=0.05$	<ul style="list-style-type: none"> <li>CDAD was the 1.8% in both cases and 4.8% in the controls</li> <li>The tested four strain probiotic combination appears to lower the risk of CDAD in a dose-dependent manner</li> </ul>	5
Pozzoni & al., 2012; Italy	N= 241 cases N= 134 control Age group: 50+	<b>Design:</b> Randomized, Double-Blind, Placebo-Controlled Trial <b>Disease:</b> AAD & CDAD <b>Intervention:</b> S. boulardii <b>Intervention length:</b> during antibiotics +7 days after antibiotics $\alpha=0.05$	<ul style="list-style-type: none"> <li>2.0 % of the controls and 2.8% of the cases developed CDAD.</li> <li>OR: 1.40; 95% CI (0.23-8.55)</li> <li>Because of the low number of patients who developed this event during the study, the study was inconclusive</li> </ul>	5
Xie, Li, Wang, Li, Chen, 2015; China	N= varies from 40 to 2981 N <sub>total</sub> = 3562 in 6 studies Age group: 65+	<b>Design:</b> Systematic Review <b>Disease:</b> AAD & CDAD <b>Intervention:</b> Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus and Bacillus <b>Intervention length:</b> varies from 5 days to several weeks $\alpha = 0.05$	<ul style="list-style-type: none"> <li>Probiotics may not reduce the risk of CDAD in older patients</li> </ul>	N/A

**AAD:** Antibiotic-Associated Diarrhea **CDAD:** Clostridium Difficile Associated Diarrhea **ARR:** Absolute Risk Reduction **CI:** Confidence Interval **OR:** Odds ratio **RR:** Relative Risk

**Table 1.** Data extracted from studies included for review

## Discussion & Conclusion

### Discussion

- The results were inconclusive, as 3 reject the null hypothesis, while 3 maintain null hypothesis.
- The studies finding a significant difference tended to be smaller, while the ones finding non-significant results were the larger scale ones, which have a better chance of being representative of the general hospitalised 50 year old population.
- This could mean that the common use of probiotics as a preventative method for CDAD may be useless and a waste of resources, investment may not be a good idea.

### Conclusion

- For hospitalised patients over the age of 50, it is unclear whether the use of probiotics is an effective preventative measure for CDAD.

### Recommendations

- Conduct more studies specific to CDAD in older populations.
- Studies focusing on single strains or strain combinations.
- Open horizons to possible alternative method of prevention (possibly the preventative use of fecal matter transplant, which is currently a treatment option, or something in a similar line of study).
- Focus on eradicating the bacteria itself from hospital setting can be explored.

### Strengths

- No gender or ethnicity exclusion, data can be generalized to all older population, studies conducted in various countries, both industrialised and developing countries.
- All studies found had a satisfactory  $\alpha$  value (0.05 or lower).
- All studies scored a 4 or 5 on the Jadad evaluation, usually losing a point for lack of dropout explanation, debatably less important than the rest.

### Limitations

- Foreign language exclusion bias (excluded Spanish studies only due to language); could search for translations of the studies..
- Ease of access (free and easily accessible)
- Very few studies addressing only CDAD, most include other forms of AAD (confounding).
- Each study uses a separate strain of probiotic, it is very possible that certain probiotics are effective, while others aren't.
- Used Jadad score instead of consort statement for quality evaluation, which is simpler and less specific.