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)

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Scientific summary

Prevention of antibiotic-associated and *C. difficile* diarrhoea

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Scientific summary

Background

Antibiotic-associated diarrhoea (AAD) is diarrhoea that occurs in association with antibiotic treatment without any other cause. It complicates between 5% and 39% of antibiotic courses and occurs within 12 weeks of exposure to antibiotics. Major risk factors include admission to hospital, age ≥ 65 years and exposure to broad-spectrum antibiotics. Antibiotics cause diarrhoea through several mechanisms, including disruption of the gut microbial flora, which impairs colonisation resistance and changes gut physiology, and direct effects on the gut mucosa. The major pathogen associated with AAD is *Clostridium difficile*, which accounts for 15–39% of AAD cases. AAD is usually a mild, self-limiting illness but *C. difficile* diarrhoea (CDD) may result in severe illness with pseudomembranous colitis, toxic megacolon and often death. The frequency and severity of CDD have increased in recent years as a result of the emergence of the hypervirulent 027 strain. In the UK, CDD increases health-care costs by some £4000 per patient affected.

Probiotics are live microbial organisms which, when administered in adequate numbers, are beneficial to health. Probiotics may prevent or ameliorate AAD through several mechanisms, including antipathogen effects, such as secretion of bacteriocins and competition for nutrients and binding sites, and enhancement of the immunological barrier function and integrity of the gut mucosa. Probiotics have rarely led to adverse events even when administered to vulnerable populations, such as preterm infants and people with severe illness.

Although systematic reviews have provided some evidence that probiotics may be effective in preventing AAD, the reviews included trials of many different probiotics (including single strains of bacteria, the yeast *Saccharomyces boulardii* and mixtures of organisms), different administration regimens (including mode of delivery, number of organisms and probiotics combined with prebiotics), and patient populations who were diverse in age and exposure to antibiotics. Thus, the statistical heterogeneity in the results of meta-analysis probably arose from the marked clinical heterogeneity between studies. In addition, follow-up did not always cover the period of risk for AAD and research design and reporting were often poor.

Objectives

The primary objectives were to determine the clinical effectiveness and cost-effectiveness of a high-dose, multistrain probiotic in the prevention of AAD and CDD in older people (aged ≥ 65 years) admitted to hospital. The study was designed to inform whether or not the probiotic should be administered as part of routine health care to older people receiving antibiotics in secondary health care. Therefore, we aimed to undertake a pragmatic study that included participants who would be representative of older people admitted to hospitals in the industrialised world, with causes of diarrhoea identified, and patients managed, according to usual hospital practice. Secondary objectives were to assess the effect of the probiotic on the severity and duration of AAD, the acceptability and serious adverse events (SAEs) of the probiotic preparation and its effect on quality of life (QoL).

Methods

We undertook a multicentre, randomised, double-blind, placebo-controlled, parallel-arm trial.

Setting

We recruited inpatients from five hospitals in two NHS regions in the UK. We recruited from several clinical specialties including those known to have high rates of AAD, such as nephrology and care of the elderly.

Population

Inclusion criteria

- People aged at least 65 years and admitted to hospital.
- People exposed to one or more oral or parenteral antibiotics within the last 7 days or about to start antibiotic treatment.
- Consultant approval to invite the patient to join the study.

Exclusion criteria

People were excluded if they:

- already had diarrhoea, which was defined as three or more watery or loose stools (Bristol Stool Form Scale types 5–7) in the preceding 24 hours
- were sufficiently immunocompromised to require isolation and/or barrier nursing
- had severe illness requiring high-dependency or intensive care
- had a prosthetic heart valve
- had suffered from CDD in the previous 3 months
- had inflammatory bowel disease that had required specific treatment in the previous 12 months
- had suspected acute pancreatitis, which was defined as abdominal pain with serum amylase or lipase greater than three times the institutional upper limit of normal
- had a known abnormality or disease of mesenteric vessels or coeliac axis that may compromise gut blood supply
- had a jejunal tube in situ or were receiving jejunal feeds
- had a previous adverse reaction to probiotics, or
- were unwilling to discontinue their existing use of probiotics.

Participants were allocated sequentially to the probiotic or placebo arm according to a computer-generated random allocation sequence using blocks of variable sizes and stratified by centre.

Intervention

Informed by the findings of meta-analysis, we selected a high-dose, multistrain preparation of lactobacilli and bifidobacteria. The probiotic preparation consisted of a vegetarian capsule containing 6×10^{10} live bacteria as lyophilised powder, two strains of *Lactobacillus acidophilus* [CUL60/National Collection of Industrial, Food and Marine Bacteria (NCIMB) 30157 and CUL21/NCIMB 30156] and two strains of bifidobacteria (*Bifidobacterium bifidum* CUL20/NCIMB 30153 and *Bifidobacterium lactis* CUL34/NCIMB 30172). The placebo capsules were identical in appearance and contained inert maltodextrin powder. The dose was one capsule per day with food, taken between antibiotic doses where possible, for 21 days.

Outcomes

The main outcome measures were the occurrence of AAD within 8 weeks and CDD within 12 weeks of recruitment. Secondary outcomes were severity and duration of AAD, gastrointestinal symptoms, occurrence of pseudomembranous colitis, need for colectomy, duration of hospital stay, QoL, SAEs or death, acceptability of the probiotic and its viability at point of administration, and cost-effectiveness.

Outcomes were assessed by research nurses who were blind to participant allocation. Research nurses followed up participants daily during hospital stay and then weekly by telephone call until 8 weeks post recruitment. We also reviewed laboratory records to identify stools positive for *C. difficile* up to 12 weeks after recruitment. Diarrhoea was defined as three or more watery or loose stools (Bristol Stool Form Scale

types 5–7) in 24 hours. Diarrhoea stools were tested for intestinal pathogens and *C. difficile* according to routine laboratory practice. QoL was assessed by generic Short Form questionnaire-12 items version 2 (SF-12 v2) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires administered at recruitment and at 4 and 8 weeks. Cost-effectiveness was evaluated from the perspective of the UK NHS focusing on the resources used by each participant. Differences between the two arms in costs and outcomes were used in a cost–consequences analysis with cost per quality-adjusted life-year (QALY) gained as the primary outcome.

Results

Patient recruitment was undertaken between 1 December 2008 and 28 February 2012. Out of 17,420 patients screened, 2981 (17.1%) were recruited. The main causes of non-participation were patients' unwillingness to join the trial (52.1%) and presence of exclusion criteria (18.4%). We allocated 1493 participants at random to the probiotic arm and 1488 to the placebo arm. Analysis by treatment allocated covered 2941 (98.7%) participants. The median age of participants was 77.1 years and comorbid illnesses were common; 54.6% participants suffered from hypertension, 24.1% from chronic obstructive pulmonary disease (COPD) and 22.9% from diabetes mellitus. Demographic factors and potential risk factors for AAD at the baseline were similar in the two study arms except for a sex imbalance (52.9% of participants were male in the probiotic arm and 46.2% were male in the placebo arm).

Antibiotic exposure varied between the centres but was similar in the two study arms. The most common indication for antibiotics was the treatment of respiratory, thoracic and mediastinal disorders (34.9% of participants). Antibiotics were prescribed for prophylaxis, mainly for surgical and medical procedures, in 24.3% participants. The most commonly prescribed antibiotics were penicillins (71.8% of participants were prescribed a penicillin and 56.1% of all participants were prescribed a broad-spectrum penicillin) and cephalosporins (24.3% of participants were prescribed cephalosporins). Most participants (78.8%) were exposed to antibiotics from two or more different classes and 62.8% received antibiotics for ≥ 7 days. However, 9.1% received only a single dose of antibiotic.

Non-antibiotic drug treatment was common, and similar, in the two study arms. Overall, 48.1% of participants were receiving an antihypertensive, 40.7% aspirin, 39.4% a proton pump inhibitor (PPI) and 29.7% an angiotensin-converting enzyme (ACE) inhibitor, with many participants receiving a combination of drugs.

Compliance was similar in the two study arms. Nearly all participants (99.6%) took at least one dose of the trial interventions and 52.5% completed the full course of 21 days.

The frequency of AAD (including CDD) was similar in the probiotic (159/1470, 10.8%) and placebo arms [153/1471, 10.4%; relative risk (RR) 1.04; 95% confidence interval (CI) 0.84 to 1.28; $p = 0.72$]. Most episodes of AAD (55.4%) were managed in hospital and stool samples were collected and tested for diarrhoeal pathogens in 58.6% of cases. The frequency and duration of gastrointestinal symptoms during AAD were similar in the two study arms. CDD was an uncommon cause of AAD and occurred in 12/1470 (0.8%) participants in the probiotic and 17/1471 (1.2%) in the placebo arm (RR 0.71; 95% CI 0.34 to 1.47; $p = 0.35$).

In patients with CDD, bloating was less common in the placebo arm (17.6%) than in the probiotic arm (58.3%; risk difference 40.7%; 95% CI 7.4% to 74.0%) but other gastrointestinal symptoms, clinical findings and investigations, and classification of severity of CDD were similar in the two study arms. During follow-up, no patient was identified as having pseudomembranous colitis, toxic megacolon or life-threatening CDD or as having died from CDD.

The frequency of AAD and CDD was similar across the study centres. In covariate analysis, AAD occurred more commonly with longer duration of antibiotic treatment [≤ 8 days compared with > 8 days; odds ratio (OR) 0.48; 95% CI 0.36 to 0.62], antacid therapy (no antacid therapy compared with some antacid therapy; OR 0.74; 95% CI 0.58 to 0.95) and longer duration of hospital stay (< 7 days compared with ≥ 7 days; OR 0.74; 95% CI 0.55 to 0.99). CDD was also more common with longer duration of antibiotic therapy (≤ 8 days compared with > 8 days; OR 0.13; 95% CI 0.03 to 0.55). However, during covariate analysis, taking account of risk factors and the number of days that participants took the trial interventions did not materially alter probiotic effect for either AAD or CDD. Sex was not a risk factor for AAD and did not modulate probiotic effect.

For all participants, the frequency of common gastrointestinal symptoms was similar in the two study arms except for flatus occurring during administration of the trial interventions, which was marginally less common in the placebo arm (10.2%) than in the probiotic arm (12.5%; risk difference 2.3%; 95% CI 0.0% to 4.6%). Duration of hospital stay was similar in the probiotic arm ($n = 1452$; median 4 days, range 1–11 days) and placebo arm ($n = 1447$; median 4 days, range 1–11 days; $p = 0.87$).

The frequency of SAEs and the proportion of participants experiencing at least one SAE were similar in both arms. Across both arms, a SAE resulted in death in 143 participants (4.9%), was life-threatening in 10 participants (0.3%), resulted in prolonged hospitalisation in 447 participants (15.2%), resulted in persistent or significant disability or incapacity in four participants (0.1%) and was considered another significant medical event in 11 participants (0.4%). SAEs took the form of gastrointestinal disorders in 79 (2.7%) participants and infections and infestations in 43 (1.5%).

Perhaps not surprisingly, QoL tended to improve in both arms during follow-up. The change from baseline in EQ-5D index values, visual analogue scale (VAS) and SF-12 v2 scores was similar across both arms except that the change in VAS was less in the probiotic arm than in the placebo arm at 8 weeks (−1.76; 95% CI −3.32 to −0.19). However, this difference of < 2 on the 100-point VAS scale was unlikely to be clinically significant.

Sixty-seven unused trial capsules returned by participants were analysed in an independent laboratory. The 33 capsules allocated as placebo according to the randomisation sequence were inert (contained no viable bacteria) and all 34 capsules allocated as probiotic according to the randomisation sequence had $\geq 1.62 \times 10^{10}$ viable bacteria.

Total health-care cost per patient was remarkably similar in the probiotic arm (£8020; 95% CI £7620 to £8420) and placebo arm (£8010; 95% CI £7600 to £8420). The probiotic was not cost-effective, with an incremental cost-effectiveness ratio (ICER) of £189,662 per QALY. Across both arms, the average duration of hospital stay was 5.58 days (95% CI 2.78 to 8.39 days) longer for patients with AAD than for those without and there was an associated average increase in health-care cost of £4530 (95% CI £3440 to £5620).

Conclusions

We did not find adequate evidence to suggest that probiotic administration was effective in preventing AAD. Although there was a trend towards reduced CDD in the probiotic arm, the administration of this probiotic seems unlikely to benefit older patients exposed to antibiotics. Alternative probiotic preparations may be effective in the prevention of AAD. However, future clinical trials should be guided by a better understanding of the mechanisms underlying AAD and the strain specific effects of probiotics. Furthermore, a probiotic is less likely to be effective where other measures have reduced CDD rates.

Implications for health care

- The high-dose, multistrain preparation of lactobacilli and bifidobacteria evaluated in our study is unlikely to benefit unselected older inpatients exposed to antibiotics.
- The effectiveness of our preparation in preventing CDD was unclear. However, even if it is effective, the falling prevalence of CDD needs more patients to take the probiotic to prevent a single case.
- Clinical judgement regarding the benefits and risks of novel interventions to prevent AAD needs to take account of its reduced frequency as a result of other preventative measures, such as antibiotic stewardship.
- The administration of additional medications to vulnerable older people, many of whom are already taking multiple medications, may not be well tolerated in practice.
- The probiotic preparation was not associated with SAEs in our study. However, surveillance for potentially uncommon adverse events is required in future studies.

Implications for research

- A better understanding of the multiple mechanisms underlying AAD and CDD, and how these vary in specific populations and the strain-specific effects of probiotics, is needed before further clinical trials of specific probiotic preparations are undertaken.
- More research to identify populations at increased risk of AAD and CDD is needed to facilitate the future evaluation of probiotic interventions.
- The design of studies to evaluate the efficacy of alternative probiotics in the prevention of CDD needs to consider the effect of other measures that have reduced the frequency of *C. difficile* infection (CDI) in some health-care institutions.
- Further research into the effect of probiotics on patient QoL will be necessary to better determine patient benefit and cost-effectiveness.

Trial registration

This trial is registered as ISRCTN70017204.

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