Probiotics for Antibiotic-Associated Diarrhoea (PAAD): a prospective observational study of antibiotic-associated diarrhoea (including *Clostridium difficile*-associated diarrhoea) in care homes

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Scientific summary

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Scientific summary

Background

With an ageing population, and demand for long-term care in the UK expected to rise by up to 150% over the next 50 years, the need for evidence to support and inform best practice in care homes has never been more of a priority.

Current evidence suggests that between 5% and 10% of residents in care homes will be prescribed antibiotics for a presumed infection at any one time. Antibiotic use has consequences for residents' quality of life (QoL), cost of care and risk of subsequent infections being antibiotic resistant. By disrupting the normal flora of the gut, antibiotic treatment sometimes causes diarrhoea. Despite older patients with frequent hospitalisations and high comorbidity being at greatest risk of developing antibiotic-associated diarrhoea (AAD), little is known about the frequency and type of antibiotics prescribed in care homes in the UK, or about the incidence and aetiology of AAD. *Clostridium difficile* (Hall and O'Toole 1935) Prévot 1938-associated diarrhoea (CDAD) is the most commonly identified cause of AAD.

Probiotics given in conjunction with antibiotic treatment have been suggested as a cheap and safe intervention for the prevention of AAD and CDAD, as they reinforce the human intestinal barrier and help maintain the commensal gut flora.

Objectives

This two-stage study aimed first to establish the frequency and importance of AAD in care homes before evaluating an intervention targeted at preventing the condition.

Our objectives for stage 1 were to:

- conduct a prospective systematic ascertainment of all antibiotics used, AAD and outcome over a 12-month period
- determine asymptomatic carriage of *C. difficile*
- estimate the risk of AAD from particular antibiotics
- pilot and develop trial procedures, including modelling of consent procedures
- test the acceptability and feasibility of administering VSL#3 (a probiotic)
- allow an appraisal of the estimated sample size for a randomised controlled trial (RCT) of probiotics given with antibiotics to prevent AAD.

Our objectives for Probiotics for Antibiotic-Associated Diarrhoea (PAAD) stage 2 were:

- Primary
    - to assess the effectiveness of probiotics taken in conjunction with antibiotic treatment in reducing the incidence of AAD

- Secondary
  - to assess the effectiveness of probiotics taken in conjunction with antibiotic treatment in reducing the incidence of CDAD
  - to evaluate the impact of probiotics taken in conjunction with antibiotic treatment on functional status and quality QoL
  - to evaluate the cost-effectiveness of probiotics taken in conjunction with antibiotic treatment in reducing the incidence of AAD.

However, a major study [probiotic lactobacilli and bifidobacteria in AAD and *C. difficile* diarrhoea in the elderly (PLACIDE)] addressing a similar question as PAAD stage 2, but in hospitals, reported shortly prior to commencement of care home resident recruitment. The findings of PLACIDE were considered to be applicable to care home residents. A decision was therefore taken not to proceed with PAAD stage 2.

Methods

Probiotics for Antibiotic-Associated Diarrhoea stage 1

A prospective observational cohort study was conducted in care home residents in South Wales. Residents were eligible for the study if they had been admitted to the care home for at least 24 hours, had a planned admission for at least 1 month and written consent could be provided; or, if residents lacked capacity, advice was taken from a consultee about whether or not the resident would wish to participate in the study.

At study entry the medical history for each recruited resident was recorded and a stool sample was collected. All antibiotics prescribed for the resident after recruitment were recorded. Following an antibiotic prescription, staff recorded the bowel motions of residents (time and consistency of stool) for the period that antibiotics were prescribed, and for an additional 8 weeks. We defined AAD as three or more loose stools in a 24-hour period during this follow-up period. When loose stools occurred, stool samples were collected and sent to a central laboratory to test for *C. difficile*.

To fit a 95% confidence interval to an AAD rate of 25% $\pm$ 10%, we estimated that a minimum of 270 care home residents from nine care homes would be required.

An interim analysis was conducted to provide initial evidence of the burden of antibiotic prescribing and AAD in care homes and to provide estimates for the calculation of a sample size for PAAD stage 2 RCT. Specific criteria for the progression from PAAD stage 1 to PAAD stage 2 were defined and agreed a priori.

Qualitative study exploring practical and ethical issues of conducting research in care home settings

To understand the views of a range of stakeholders, a qualitative study was conducted. The qualitative study participants consisted of residents, relatives, care home staff and general practitioners (GPs) who had a responsibility for the general medical care of residents and who may be asked to assess eligibility for research studies. We recruited participants through care homes that participated in the aforementioned observational study. Data collection was undertaken through a combination of face-to-face interviews with residents, relatives and GPs and with focus groups among care home staff.

Data were collected on the various merits and problems associated with a number of models of consent that could be used for a trial that lasts a reasonably long period, and also covered how discussions regarding consent should take place. Participants were asked what time frame they felt advanced consent should cover and for their opinion on what should happen should the resident lose (and potentially regain) capacity during a research trial.

Probiotics for Antibiotic-Associated Diarrhoea stage 2

A multicentre double-blind placebo-controlled individually randomised trial was proposed.

Participants were eligible for inclusion if they had been prescribed an oral antibiotic for an acute infection and they had been admitted to the care home for at least 24 hours, had a planned admission for at least 1 month, written consent could be provided (by the participant or a personal legal representative) and, if they regularly consumed probiotics, they were willing to discontinue probiotic use for the duration of the trial.

Participants were deemed ineligible for the trial if they had previously been randomised into the trial, they had a usual stool pattern of 'diarrhoea' (as per our previous definition), they both lacked capacity and were a regular user of probiotics, or they had a medical condition listed as an exclusion criterion.

Participants would be randomised to receive a prescription of VSL#3 (a probiotic containing eight different strains of potentially beneficial bacteria), to be taken as one sachet twice a day for 21 days, or a matched placebo, to be started within 72 hours of a new, acute prescription of an antibiotic.

The primary outcome was the occurrence of at least one episode of AAD during the 8 weeks following randomisation (defined as per PAAD stage 1).

Secondary outcomes included:

- occurrence of CDAD
- duration, frequency and recurrence of AAD
- health-related QoL was also to be measured using the European Quality of Life-5 Dimensions as a self-reported or proxy measure
- health-care resource use.

The proposed sample size was 400 residents (200 per arm). This would provide 80% power at the 5% significance level to detect a 50% relative reduction in the incidence of AAD in those given probiotic intervention alongside antibiotic treatment. This was based on an estimated AAD incidence of 25% in the placebo arm and is adjusted to allow for a 20% drop-out rate.

Results

Probiotics for Antibiotic-Associated Diarrhoea stage 1

A total of 279 residents were recruited from 10 care homes: four nursing, four residential and two dual-registered homes. Residents had a median age of 86 years and the majority were female. Approximately 29% had capacity to consent for themselves.

Stool samples were obtained at study entry from 81% of residents. An average of 2.2 isolates was cultured per sample, with *Escherichia coli* (Migula 1895) Castellani and Chalmers 1919, *Enterococcus* spp. (ex Thiercelin and Jouhaud 1903) Schleifer and Kilpper-Bälz 1984 and *Pseudomonas* Migula 1894 the three most commonly cultured isolates. Over half of the samples contained antibiotic-resistant isolates. Enterobacteriaceae species resistant to ciprofloxacin were found in 47% of samples. There was wide variation in the proportion of participants providing stool samples containing antibiotic-resistant isolates between different types of care homes. The odds of residents carrying antibiotic-resistant isolates in their stools at study entry increased with age and previous antibiotic use and were significantly lower for participants in residential homes than for those in nursing homes. *C. difficile* was cultured in 7% of samples, with the prevalence varying from 0% in some care homes to 19% in others.

The incidence of antibiotic prescribing was 2.16 prescriptions per resident-year. Antibiotics were prescribed for a variety of indications. Urinary tract infection (UTI) was the most common indication, followed by

upper respiratory tract infection (URTI). The most commonly prescribed antibiotics were amoxicillin and trimethoprim. There was no obvious marked seasonal variation. The odds of being prescribed an antibiotic was higher for residents who had been prescribed antibiotics in the 4 weeks prior to study entry and lower for residents in dual-registered homes than in nursing homes.

The incidence of AAD was 0.57 per year for those residents who were prescribed antibiotics. The odds of developing AAD were higher for those residents prescribed co-amoxiclav and lower for residents in residential homes than for those in nursing homes. Time from antibiotic prescription to first AAD episode was shorter in residents prescribed co-amoxiclav and who routinely wore incontinence pads. Time to first AAD episode was longer in residents from residential homes than those in nursing homes.

For only 55 of the 447 episodes of AAD were corresponding microbiological data available from stool samples. *C. difficile* was cultured in eight of these samples, all of which came from residents in the same care home. However, no ribotype was found in more than one resident, indicating that the *C. difficile* cultured was not the result of an outbreak.

Qualitative study exploring practical and ethical issues of conducting research in care home settings

In total, interviews were conducted with 14 residents, 14 relatives and 10 GPs. Two parallel focus groups were conducted with 19 care home staff members.

While the majority of residents were happy to be consented just once, relatives, staff and GPs felt that a verbal rechecking of consent at regular intervals should be performed.

Staff and relatives generally felt that if a resident lost capacity during the trial, his or her relative or legal representative should be notified of the resident's participation and current situation.

Probiotics for Antibiotic-Associated Diarrhoea stage 2

At the interim analysis point in PAAD stage 1, all progression (stop/go) criteria for PAAD stage 2 were sufficiently met, so progression to a RCT was considered justified. The process required to set up the RCT was lengthy and resource intensive, largely because the trial involved a clinical trial of an investigational medicinal product (IMP). However, as we were about to open PAAD stage 2 to recruitment of care home residents, new evidence emerged from the PLACIDE trial regarding the clinical effectiveness of probiotics in reducing the incidence of AAD and CDAD in older hospital inpatients. The PLACIDE study recommended that no further studies assessing probiotics for AAD should be undertaken until further evidence is generated regarding which strains maybe effective in reducing AAD (in vitro evidence). As a result, discussion took place with members of the Trial Management Group, Trial Steering Committee and the Health Technology Assessment funding programme, and the decision was made not to progress to the recruitment phase of PAAD stage 2.

Research prioritisation workshop findings

Following the decision not to progress with PAAD stage 2, a workshop was arranged with members of staff from care homes that participated in the study (both PAAD stage 1 and during the set-up of PAAD stage 2) to elicit and rank research priorities for the care home sector.

A total of 23 topics were identified at the workshop, which included a spectrum of service delivery themes and more specific health-related questions. The topics that were identified as the highest research priority were improving communication between care home staff and hospital staff during admission or discharge of a resident, how care home staff can best be kept up to date with staff development and evidence updates, and the best methods of diagnosing UTIs in this population and collecting reliable urine samples in female residents.

Conclusions

Residents of care homes are frequently prescribed antibiotics and frequently experience diarrhoea following their antibiotic prescription. Not all episodes of diarrhoea following antibiotic use can be ascribed to antibiotics, and our study does not seek to demonstrate causality, merely association. CDAD was detected in about 15% of episodes with associated stool samples. Residents in nursing homes were most likely to be prescribed antibiotics and experience AAD, but the size of the differences may in part be due to the intensity of monitoring of residents in these types of homes, rather than clinical differences in the residents. Residents of care homes, in particular nursing homes, have high levels of carriage of antibiotic-resistant organisms, particularly ciprofloxacin-resistant species. Recent antibiotic use was associated with an increased likelihood of residents carrying antibiotic-resistant organisms in their stool. *C. difficile* was more common in nursing homes, but there was little suggestion of clustering of type by home.

Residents, relatives, care home staff and GPs are generally supportive of older adults in care homes participating in research studies. However, respondents were concerned about the best way of facilitating this, and about the amount of detail that participants can reasonably understand and retain from consent discussions.

Setting up a RCT in a care home setting was a complex and resource-intensive process, during which period scientific evidence emerged which impacted on the justification for conducting PAAD stage 2. Continuing engagement with care homes has resulted in establishing research priorities in the care home setting.

Implications for health care

Antimicrobial stewardship is an important issue in care homes. Close attention needs to be paid to the necessity of antibiotic treatment, taking the risk of side effects such as diarrhoea and the development of antimicrobial resistance into full consideration.

Recommendations for research

There is an urgent need for the provision of evidence to support and inform best practice in care homes. A greater understanding of the appropriateness (e.g. type, dose and duration) of antibiotic prescribing in this setting is needed in order to develop antimicrobial stewardship interventions. Conducting and disseminating research in this setting is challenging, particularly when the research involves IMPs. These challenges need to be overcome if meaningful evidence-based care is to be implemented. Research priorities identified by care home staff include the need to improve the communication between care home and hospital staff, improving the provision of current relevant evidence to care home staff and methods for diagnosing UTIs in this population.

Those planning analogous research in care homes may wish to consider:

- consulting an 'expert' with experience of working in a care home at the design stage of the study
- allowing plenty of time to initially approach care homes, set up the sites, recruit residents and undertake the study
- ensuring that processes are easy for staff to complete and where possible following their own processes, so as to not add to staff workload
- embedding additional study staff or employing research nurses in the care homes to collect information from residents and carry out any sampling.

Trial registration

The study is registered as ISRCTN7954844.

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