Probiotics to reduce antibiotic administration in care home residents aged 65 years and older: the PRINCESS RCT

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Scientific summary

The PRINCESS RCT

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Scientific summary

Background

Probiotics are being marketed for their potential health benefits, but studies often produce contradictory findings and have been criticised for methodological weaknesses. Nevertheless, systematic reviews of randomised controlled trials have found that probiotics reduce the risk of common infections in infants and children and the duration of infections in otherwise healthy children and adults. Care homes are an increasingly important sector of care, and care home residents are particularly prone to infections and have a high level of antibiotic use. Infections in care home residents may have particularly severe consequences for individuals, with a long-lasting impact on health-related quality of life. Furthermore, antibiotic treatment for these infections may drive antimicrobial resistance. Probiotics are cheap and feasible to administer in care homes and are considered to be safe. Few studies of probiotics to reduce antibiotic use, and the risk and duration of infections, have been carried out in older people, and we were not able to identify a rigorous trial of the effect of probiotics on antibiotic use by care home residents.

Objective

The PRINCESS (Probiotics to Reduce Infections iN CarE home reSidentS) trial was designed to evaluate the effect of a dose of daily oral probiotics on cumulative systemic antibiotic administration days for all-cause, acute infections.

Design

The PRINCESS trial was a double-blind, individually randomised, placebo-controlled trial that assessed the effect of a daily oral probiotic combination of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12 on cumulative systemic antibiotic administration days (primary outcome) for infection in care home residents aged $\geq$ 65 years for up to 12 months. The trial had an imbedded qualitative evaluation and two mechanistic substudies: an immunology substudy and an influenza vaccine substudy.

Setting

The trial was conducted in care homes in the UK, recruiting from 23 care homes between December 2016 and May 2018.

Participants

The participants were care home residents aged $\geq$ 65 years who were willing and able to give informed consent for participation or who had a consultee to provide advice about participation if they lacked capacity to consent.

Intervention

Participants received a capsule, to be taken orally, every day, containing a probiotic combination of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12, or a matched placebo, for up to 1 year.

Main outcome measures

Primary outcome measure

The primary outcome measure was cumulative systemic antibiotic administration days for all-cause infections. This was ascertained from the total number of days of systemic antibiotic administration as recorded in care home medical records and hospital discharge summaries. This was collected retrospectively by the research nurses during weekly visits to care home residents.

Secondary outcome measures

Secondary outcomes included:

- infection – the total number of days of antibiotic administration for each infection type (respiratory tract infection, urinary tract infection, gastrointestinal infection, unexplained fever and other); number, site and duration of infection; use of antimicrobials; and estimation of incidence and duration of antibiotic-associated diarrhoea
- stool microbiology – detection of *Clostridium difficile*, antibiotic-resistant Gram-negative Enterobacterales, vancomycin-resistant enterococci, *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12
- oral microbiology – semi-quantitative count of the amount of *Candida* spp.
- health and well-being – measured using the self- and/or proxy-reported health-related quality of life EuroQol-5 Dimensions, 5-level version; self- and/or proxy-reported ICEpop CAPability measure for Older people
- hospitalisations – number and duration of all-cause hospital stays
- mortality – number of deaths.

Mechanistic immunology outcomes

Mechanistic immunology outcomes included:

- influenza vaccine efficacy – assessed via the haemagglutination inhibition assay and antibody titres
- full blood count and measurement of immune cell phenotypes, plasma cytokines and chemokines
- cytokine and chemokine response in whole blood stimulated ex vivo by toll-like receptor 2 and 4 agonists
- monocyte and neutrophil phagocytosis of *Escherichia coli*
- serum vitamin D levels.

Methods

Following enrolment and baseline data collection, care home residents were individually randomised to receive probiotic or placebo preparation in a 1 : 1 ratio using minimisation variables of the care home from which a resident was recruited and the sex of the care home resident. The study product was administered daily, and capsules could be swallowed whole, opened and sprinkled onto warm or cold (but not hot) food or dissolved in warm or cold (but not hot) liquid. Optional samples of saliva and stool were obtained at baseline and at the 3- and 12-month reviews. Optional blood samples were obtained at baseline and, for those participating in the immunology substudy, at the 12-month review. As a result of time limitations, some participants had a truncated follow-up and received either a

baseline assessment and 3-month follow-up or a baseline assessment, a 3-month follow-up and a second follow-up between 6 and 10 months post randomisation. A subset of care home residents provided blood samples for the influenza vaccine substudy. These pre- and post-vaccination samples were scheduled around the participant's annual flu vaccination.

Data were collected weekly for up to 52 weeks following randomisation. Research nurses visited care home residents weekly to retrospectively collect data and conduct the 3- and 12-month reviews. Participants were reviewed weekly for signs of infection, incidence of diarrhoea, antibiotic use, hospitalisations and adverse events, and changes to capacity status. The dose taken of the study product (full dose or partial dose) and method of ingestion (capsule/in food/in liquid/unknown) were also recorded.

Qualitative interviews were conducted with groups who participated in the trial. This included family members/friends who had provided advice on behalf of a care home resident about participation (consultee), family members/friends who experienced the resident's participation in the trial, and research nurses and care home staff who had been involved in the research activities required to recruit care home residents, or collecting research data for the trial. Interviews were audio-recorded and transcribed. Qualitative data were analysed using framework analysis.

Results

Three hundred and thirty-two care home residents were recruited to participate in the PRINCESS trial from 23 care homes in the UK. A total of 318 residents completed baseline data collection, and 310 were randomised. Weekly participant diary data were available for 97.4% of participants randomised to placebo and for 98.7% randomised to the probiotic combination. Longer than expected study set-up time meant that follow-up had to be truncated after 6 months for some participants. We captured daily probiotic or placebo (known as study product) usage data for a total of 77,772 days, with > 92% of study product recorded as having been taken in the full dose. Screening of the pre- and post-probiotic stool samples from participants who volunteered for this additional aspect of the study confirmed that the probiotic organism was found more often and in increased numbers in the stools of those participants allocated to probiotic treatment at both 3 months (for *Lactobacillus rhamnosus* GG, odds ratio 15.7, 95% confidence interval 2.77 to 88.37, $p = 0.002$; for *Bifidobacterium animalis* subsp. *lactis* BB-12, odds ratio 49.0, 95% confidence interval 6.20 to 387.23, $p < 0.001$) and at the second follow-up (for *Lactobacillus rhamnosus* GG, odds ratio 8.1, 95% confidence interval 1.56 to 42.35, $p = 0.013$; for *Bifidobacterium animalis* subsp. *lactis* BB-12, odds ratio 36.0, 95% confidence interval 3.96 to 327.50, $p = 0.001$) than at baseline.

We found no evidence that administration of a daily dose of the probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12 reduced cumulative systemic antibiotic administration days for all-cause, acute infections in care home residents (odds ratio 1.13, 95% confidence interval 0.79 to 1.63; $p = 0.495$). All secondary outcomes were consistent with the main finding, with some evidence of potentially worse outcomes from probiotic supplementation. Adverse events were similar between the groups in terms of both the percentage of people experiencing at least one event and the type of events experienced.

Conclusions

The PRINCESS trial has provided clear evidence that administration of a daily dose of the probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12 does not reduce cumulative systemic antibiotic administration days for all-cause, acute infections in care home residents.

All secondary outcomes were consistent with the main finding, including effects on duration of infections, hospitalisations, death, antibiotic-associated diarrhoea, health status, capability and quality of life.

Implications for health care

Based on these findings, care home residents should not be advised to consume a combination of the probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12 each day. We are not able to draw conclusions about the effects of other probiotics or probiotic combinations because certain effects of probiotics may be strain specific. Neither are we able to indicate that these findings are applicable to other populations in different settings, and probiotic supplementation may vary according to immune status and age.

Future research implications

As probiotics are a feasible and cheap potential intervention, further rigorous efficacy, mechanisms and effectiveness trials of other probiotics and in other population groups and settings may be indicated regarding antibiotic use and susceptibility to common infections. Potential harms should be carefully studied in such trials.

Trial registration

This trial is registered as ISRCTN16392920.

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This report

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