Effect of probiotic use on antibiotic administration among care home residents: a randomized clinical trial

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Key Points

Question Does a dose of a daily oral probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* reduce cumulative systemic antibiotic administration days for all-cause, acute infections in care home residents?

Findings In this randomized clinical trial that included 310 participants, this daily probiotic combination, compared with placebo, did not significantly reduce antibiotic administration over 1 year (mean cumulative antibiotic administration days, 12.9 days vs 12.0 days).

Meaning The findings do not support the use of probiotics for reducing antibiotic administration in older adults living in care homes

Abstract

IMPORTANCE Probiotics are frequently used by residents in care homes (residential homes or nursing homes that provide residents with 24-hour support for personal care or nursing care), although the evidence on whether probiotics prevent infections and reduce antibiotic use in these settings is limited.

OBJECTIVE To determine whether a daily oral probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* compared to placebo reduces antibiotic administration in care home residents.

DESIGN, SETTING, AND PARTICIPANTS Placebo-controlled randomized trial of 310 care home residents aged 65 years and older recruited from 23 care homes in the UK between December 2016 and May 2018, with last follow up on 31st October 2018.

INTERVENTIONS Study participants were assigned to receive a daily capsule containing a probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* (total cell count per capsule $1.3x10^{10}$ - $1.6x10^{10}$) (n=155), or daily matched placebo (n=155), for up to one year.

MAIN OUTCOME MEASURE The primary outcome was cumulative antibiotic administration days for all cause infections measured from randomization for up to one year.

RESULTS Among 310 randomized care home residents (mean age 85.3 years; 66.8% women), 195 (62.9%) remained alive and completed the trial. Participant diary data (daily data including study product use, antibiotic administration, and signs of infection) were available for 97.4% randomized to placebo and 98.7% randomized to the probiotic group.

Care home residents randomized to the probiotic group had a mean cumulative systemic antibiotic administration days of 12.9 days (95% CI: 0 to 18.05), and those randomized to placebo, 12.0 days (95% CI: 0 to 16.95) (absolute difference = 0.9 days, 95% CI: -3.25 to 5.05 days; adjusted incidence rate ratio = 1.13, 95% CI: 0.79 to 1.63, P=.50). A total of 120 care home residents experienced 283 adverse events, including 78 (58.6%) hospitalizations in the placebo group and 94 (62.7%) in probiotic group. There were 32 deaths (20.6%) in the placebo group and 33 (21.3%) in the probiotic group.

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CONCLUSIONS AND RELEVANCE Among care home residents in the UK, a daily dose of a probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* did not significantly reduce antibiotic administration for all-cause infections. These findings do not support the use of probiotics in this setting.

TRIAL REGISTRATION The trial is registered with the ISRCTN, Registry number ISRCTN16392920.

Background

Global sales of probiotics are estimated at over $40 billion and are projected to reach over $64 billion by 2023.[1] The US hospital and nursing home market for probiotics was estimated at $92.4 million in 2016, and is projected to expand at an estimated compound annual growth rate of 9.3% from 2017 to 2025.[2] Probiotics are often promoted for health indications[3] and may be an inexpensive and safe intervention to reduce antibiotic use and resistance through preventing infections.[4 5]

A systematic review of probiotics to reduce antibiotic use for common infections in infants and children included 17 RCTs that evaluated 13 probiotic formulations of *Lactobacillus* and *Bifidobacterium* strains singly or combined, and found that probiotic use was associated with reduced risk of antibiotic prescription relative to placebo.[6] A further systematic review of 20 RCTs in otherwise healthy children and adults found that use of *Lactobacillus* and *Bifidobacterium* probiotic strains was associated with reduced duration of respiratory illness in children.[7] However, the quality of this supporting evidence was variable, and the authors called for additional well-designed studies to substantiate the findings and explore effects in other population groups.[6,7]

With the aging population, care homes are an increasingly important care sector; care home residents are more prone to infections and consume more antibiotics than the general population,[8] increasing the risk of antimicrobial resistance and poor outcomes.[9] The Probiotics to reduce infections in care home residents(PRINCESS) trial was designed to test the hypothesis that daily administration of a combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. Lactis BB-12* probiotics to care home residents would reduce cumulative systemic antibiotic administration days for all-cause, acute infections.

Methods

Trial Design

This study was designed as a multicenter, parallel, individually randomized, placebo controlled, double-blind clinical trial, and was conducted between December 2016 and May 2018 in UK care homes. The trial was approved by the Research Ethics Committee (REC) for Wales (Wales REC 6) recognized by the UK Ethics Committee Authority (14/WA/1106), which approved all recruitment sites. National Health Service (NHS) Health Boards and Clinical Commissioning Groups gave Research and Development approval to sites. Informed, written consent was obtained from those participants with capacity to do so, and for those who lacked capacity to provide consent, a consultee (either a legal representative or guardian) could complete a consultee declaration for participation on their behalf. The protocol has been published,[10] and the final protocol, amendments, and statistical analysis plan are available in Supplement 1.

Participants

Care home residents in this trial included those living in residential, nursing, and dual registered homes. Care home residents were eligible if they were aged 65 years or older. Exclusions were being immunocompromised (ongoing immune-suppressants; long-term, high-dose, oral, intramuscular or intravenous steroids), or taking ongoing, regular probiotics. Full eligibility criteria are provided in eAppendixes 1 of Supplement 2.

Treatment allocation

Participants were randomized using an online process in a 1:1 ratio using minimization to balance groups by care home and resident sex, with a random component set at 80%.

Procedures

Nurses registered with the UK Nursing and Midwifery Council, blind to group allocation, visited each care home each week, and recorded weekly diary data for each participant in an online database, including the amount of study product (probiotic or placebo) taken each day; signs of infection; use of antibiotics including route; diarrhea; hospitalization; and serious or trial-related adverse events. Data were obtained from participants' daily medical administration records, care home clinical records, observation of the participant, discussion with the participant or their friends and family, care home staff, and hospital discharge summaries. EQ-5D (health utility) and ICEpop CAPability measure for Older people (ICECAP-O) (wellbeing) questionnaires were collected at baseline, a 3-month follow-up point and a follow-up point as close to 12-months as the study would allow (some participant follow-up was truncated). Participants were asked to provide stool and saliva samples at baseline, 3-months, and up to 12-months, but this was not a requirement for participation.

Interventions

Participants were allocated a daily oral probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* (total cell count per capsule of between $1.3x10^{10}$ to $1.6x10^{10}$), or a matched placebo (containing maltodextrin, microcrystalline cellulose, magnesium stearate, and silicon dioxide), as a capsule once daily while the care home resident remained in the study (see eAppendixes 2 of the Supplement). The study product was not administered while care home residents were away from care homes such as when hospitalized, after withdrawal from the study.

Outcomes

The primary outcome was cumulative systemic antibiotic administration days for all cause infections, defined as the total number of days of systemic antibiotic administration as recorded in care home medical records and hospital discharge summaries and with the denominator calculated as the total number of days participants were observed in the study.

Secondary outcomes included: total number of days of antibiotic administration for each infection category recorded in care home medical records (urinary tract infection, gastrointestinal infection, respiratory tract infections (divided into upper and lower respiratory tract infections post hoc after the Trial Management Group decided it would be more informative to evaluate these outcomes separately), skin and soft tissue infection, unexplained fever, and other); number, site, duration (mean and cumulative) of infection; duration of diarrhea when oral antibiotics were taken and not taken,; antibiotic-associated diarrhea; incidence of *Clostridioides difficile* infection; antibiotic sensitivity of stool Gram-negative *Enterobacteriaceae* and vancomycin resistant enterococci (VRE), and counts of *Lactobacillus rhamnosus* and *Bifidobacterium animalis subsp. Lactis*; oral *Candida* spp; self- and/or proxy reported health-related quality of life measured by EQ-5D-5L (index value range from -0.594 (worst) to 1 (best); health status range from 0 (worst) to 100 (best)) and ICECAP-O (range from 0 (worst) to 1 (best));[11] number and duration of hospital stays, and; deaths. eAppendix 3 of Supplement 2 provides further details on the derivation of some outcomes.

Statistical analyses

An estimated 330 participants from 20 UK care homes would provide 90% power at the 5% level to demonstrate a 10% relative reduction in cumulative systemic antibiotic administration days, assuming a mean cumulative systemic antibiotic administration days of

17.4 days and a 10% reduction in the probiotic group to 15.6 days per resident-year.[8] We considered a 10% reduction feasible and clinically important,[12] because physician targeted interventions to reduce antibiotic use for respiratory tract infections have been associated with an average reduction in antibiotic prescriptions of 11.6%;[13] longer duration of antibiotic exposure has been associated with increased risk of subsequent infections with drug-resistant organisms[14]; approximately 20% of all antibiotics prescribed in primary care in England are considered inappropriate,[15] and the UK government initiative was to halve inappropriate prescribing, amounting to a 10% relative reduction.[16]

This sample size accounted for 30% of participants contributing no outcome data (i.e. randomized but contributing to neither the numerator or denominator). Our target sample size was adjusted after a planned interim assessment of outcome data availability after 3 months (33 participants) to be at least 258. Assuming a mean number of days for which primary outcome data could be available (i.e. accounting for follow-up time) of approximately 250 days, this would provide at least 82% power to detect a 10% relative reduction in cumulative systemic antibiotic administration days.

Primary and secondary comparative analyses were pre-specified and included all randomized participants who provided outcome data, analyzed in the group to which they were randomized without imputation to account for loss of observation time. The mean cumulative systemic antibiotic administration days per resident-year was compared between groups by fitting a two-level negative binomial regression model, accounting for participants nested within care homes, the length of time observed, and the sex of care home residents. Similarly, the majority of secondary outcome analyses (cumulative systemic antibiotic administration days by infection type, rates of infections, rates of diarrhea) involved the between-group comparison of rate variables using two-level Poisson or negative binomial regression

(depending on the presence of over-dispersion). The decision to analyze lower and upper respiratory tract infections separately was made post hoc by the Trial Management Group because reporting lower respiratory tract infections separately was considered important, as these infections typically cause greater morbidity in the study population than upper respiratory infections. The consistency of conclusions drawn from the primary analysis was investigated by conducting the following pre-specified sensitivity analyses: i.) including prophylactic antibiotic use in the definition of cumulative systemic antibiotic administration days; ii.) ignoring periods of hospitalization from both the numerator and denominator; iii.) handling data truncated due to death from infection by imputing participants as having been administered antibiotics for the remainder of the time they should have been observed in the trial (a composite strategy)[17]; iv.) accounting for study product consumption (see eAppendix 4 of Supplement 2). Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. For all analyses, two-sided 95% confidence intervals and p-values were calculated. P-values <.05 were considered statistically significant. Statistical analyses were conducted using IBM SPSS version 25 and STATA version 15. Further details of statistical analyses are provided in eAppendix 4 of Supplement 2.

Results

Participants

310 care home residents, 155 in each group, were randomized from 23 care homes in the UK between December 2016 and May 2018. Due to slower than anticipated recruitment, follow-up was truncated for 106 care home residents, with these care home residents followed-up for between 147 and 362 days in total. Among the 199 participants who remained alive, had not withdrawn from the study, and could have had a second follow up at 12-months post-randomization (or earlier for those whose follow-up was truncated), responses were available for 195 (98.0%) care home residents, 98 in the probiotic group and 97 in the placebo group (Figure 1). The mean age was 85.3 years (SD 7.39) years; 33.2% (103/310) were men and 66.8% (207/310) were women; 65.8% (204/310) lacked capacity to consent. Care home residents in trial groups were well matched for these and most other characteristics at baseline, including stool sample culture for probiotic organisms. However, more care home residents in the probiotic group had *Clostridioides difficile* cultured from their stool (6/83) compared to the placebo group (0/75) (Table 1). Care home residents allocated to the probiotic group contributed 39,798 person days (mean number of days per probiotic participant = 252.4, SD = 110.51) and care home residents allocated to placebo contributed 37,974 person days (mean days = 242.9, SD = 115.24). The primary cause of unobserved data was truncation due to death, with post-randomization deaths occurring in 33 care home residents allocated to probiotic and 32 allocated to placebo (total number of unobserved days due to death = 7,578 and 6,978 respectively). Other reasons for unobserved data were care home residents being away from the care home (114 days in placebo group and 56 days in probiotic group), waiting for a capacity assessment (zero in placebo group and 7 days in probiotic group), and data not collected for unknown reason (972 days in placebo group and 1898 in probiotic group). 305 (98.4%) care home residents contributed to the

primary analysis and secondary analyses relating to infections and diarrhea, with 5 care home residents excluded from these analyses due to death or withdrawal following randomization and prior to contributing data.

Intervention fidelity

302 (97.4%) care home residents initiated at least 1 dose of study product, 98.1% (152/155) in the placebo group and 96.8% (150/155) in the probiotic group. Of the remaining 8 care home residents, 5 withdrew following randomization and 3 died soon after randomization. For the 302 care home residents who initiated at least one study product dose, a median of 97.8% (IQR 93.56 to 99.45) full or partial doses were taken, and 89.4% (65,525/77,772) were either swallowed as capsules, or sprinkled on food (that was not hot) prior to ingestion.

Significantly more stool samples from care home residents randomized to probiotic were found to contain *Lactobacillus rhamnosus* than samples from those randomized to placebo at three-months post-randomization (47/56 – 83.9% versus 19/52 – 36.5%, absolute risk difference = -47.4%, 95% CI: -64.8 to -29.0%; AOR = 9.19, 95% CI: 3.51 to 24.07, P < .001), mean concentrations were 7.04×10^5 (SD = 3.05×10^6) for those randomized to probiotic and 4.67×10^4 (SD = 2.77×10^5) in placebo. This finding persisted at the second follow-up time point (27/37 – 73.0% versus 9/29 – 31.0%, absolute risk difference = -41.9%, 95% CI: -66.1 to -17.7%; AOR = 6.41, 95% CI: 2.14 to 19.20, p = .001), mean concentrations 1.52×10^5 (SD = 5.27×10^5) in probiotic versus 1.40×10^4 (SD = 4.31×10^4) in the placebo group.

Care home residents randomized to probiotic provided stool samples containing *Bifidobacterium animalis subsp. Lactis* significantly more frequently than those randomized

to placebo at 3 months (29/56 – 51.8% versus 2/52 – 3.8%, absolute risk difference = -47.9%, 95% CI: -65.0 to -30.9%; AOR = 26.90, 95% CI: 5.94 to 121.66, p < .001), mean concentrations 1.72 x 10^6 (SD = 5.11 x 10^6) in the probiotic group and 2.88 x 10^4 (SD = 1.71 x 10^5) in the placebo group. This finding persisted at the second follow-up time point (21/37 – 56.8% versus 2/29 – 6.9%, absolute risk difference = -49.9%, 95% CI: -73.0 to -26.7%; AOR = 21.96, 95% CI: 2.97 to 162.43, p = .002) with mean concentrations 2.15 x 10^5 (SD = 4.45 x 10^5) in the probiotic group versus 3.62 x 10^2 (SD = 1.86 x 10^3) in the placebo group.

There were 202 (66.2%) care home residents who were prescribed at least one non-prophylactic antibiotic, 69.1% (105/155) in the placebo group and 63.4% (97/155) in the probiotic group. 336 courses of non-prophylactic antibiotics were prescribed in the placebo group and 287 in the probiotic group.

Primary outcome

Care home residents randomized to probiotic had a mean cumulative systemic antibiotic administration days of 12.9 (95% CI: 0 to 18.05), and care home residents randomized to placebo had a mean cumulative systemic antibiotic administration days of 12.0 (95% CI: 0 to 16.95). The distribution was positively skewed with 37% of residents having 0 days due to not being administered antibiotics (eFigure 1). The absolute difference in cumulative systemic antibiotic administration days was 0.9 days (95% CI, -3.25 to 5.05 days) and the adjusted incidence rate ratio (IRR) was 1.13 (95% CI, 0.79 to 1.63; P =.50). Death due to infection was reported for 12 care home residents in the probiotic group and 6 in the placebo group, with 6 care home residents in the probiotic group and 1 in placebo group taken antibiotic up until death. Further details of sensitivity analyses for the primary outcome measure are provided in eTable 1 to eTable 3 of Supplement 2.

Secondary outcomes

Care home residents allocated to a daily oral probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* were administered significantly more antibiotics for lower respiratory tract infections than those randomized to placebo (mean 6.2 days in probiotic group compared to 4.0 days in placebo group; absolute difference = 2.2 days, 95% CI: -0.41 to 4.81 days; adjusted IRR=1.42, 95% CI: 1.05 to 1.93, P=.02). There was no statistically significant difference between groups in antibiotic use for urinary tract infections (mean 7.1 days versus mean 6.7 days; absolute difference = 0.4 days, 95% CI: -2.81 to 3.61 days; adjusted IRR = 1.17, 95% CI: 0.75 to 1.84, p =.48), upper respiratory tract infections (mean 3.3 days versus mean 3.4 days; absolute difference = 0.1 days, 95% CI: -2.09 to 2.29 days; adjusted IRR = 1.13, 95% CI: 0.71 to 1.78, P=.61), skin infections (mean 3.4 days versus mean 3.7 days; absolute difference = 0.3 days, 95% CI: -2.20 to 2.80 days; adjusted IRR = 0.92, 95% CI 0.54 to 1.57, P=.76), and duration of infection (median 6 days versus median 5 days; adjusted mean difference = 0.08, 95% CI -0.001 to 0.16, P=.05) (see eFigure 2). Unexplained fever was not reported for any participants during the trial (Table 2).

Care home residents allocated to the probiotic group had statistically significantly lower self-reported generic wellbeing/capability scores at three months (mean score 0.72 versus mean score 0.69; absolute difference = 0.03, 95% CI: -0.05 to 0.11; adjusted mean difference= -0.06, 95% CI: -0.11 to -0.001, P=.05). There were no statistically significant differences for other self-report and proxy wellbeing and quality of life outcomes (Table 3).

There was no statistically significant difference between groups in terms of care home residents being hospitalized at least once during the post-randomization study period (42/152 – 27.6% in probiotic group versus 36/153 – 23.5% in placebo group; absolute risk difference = -4.1%, 95% CI: -13.9 to 5.7%; adjusted odds ratio = 1.25, 95% CI: 0.74 to 2.11, P=.41), number of hospital stays (mean 0.4 versus 0.3; absolute difference = 0.08, 95% CI: -0.06 to 0.22; adjusted IRR = 1.17, 95% CI 0.72 to 1.90, P=.53), cumulative number of hospital days (mean 4.5 days versus mean 5.4 days; absolute difference = 0.9 days, 95% CI: -2.77 to 4.57 days; adjusted IRR = 1.00, 95% CI 0.43 to 2.29, P=1.00), or death (33/155 – 21.3% versus 32/155 – 20.6%; absolute risk difference = -0.6%, 95% CI: -9.7 to 8.4%; adjusted odds ratio = 1.03, 95% CI 0.59 to 1.80, P=.90) (Table 3). Similarly, there was no statistically significant between-group differences for incidence of antibiotic-associated diarrhea (mean 0.8 versus mean 0.6; absolute difference = 0.2, 95% CI: -0.16 to 0.50; adjusted IRR = 1.39, 95% CI 0.79 to 2.46, P=.25) and cumulative days of antibiotic-associated diarrhea (mean 6.8 days versus mean 4.4 days; absolute difference = 2.4 days, 95% CI: -2.00 to 6.71 days; adjusted IRR = 1.83, 95% CI: 0.95 to 3.54, P=.07) (Table 3).

There were no statistically significant differences between groups with regards to Enterobacterales resistant to at least 1 of the tested antibiotics in stool samples (3 months: 37/55 – 67.3% in the probiotic group versus 39/52 – 75.0% in the placebo group; absolute risk difference = 7.7%, 95% CI: -9.5 to 25.9%; adjusted odds ratio 0.61, 95% CI 0.24 to 1.56, P=.30, second follow-up: 23/33 – 69.7% versus 19/27 – 70.0%; absolute risk difference = 0.7%, 95% CI: -22.6 to 24.0%; adjusted odds ratio 0.76, 95% CI 0.20 to 2.89, P=.68), or in the presence of oral candida (3 months: 88/113 – 77.9% versus 80/105 – 76.2%; absolute risk difference = -0.2%, 95% CI: -11.3 to 10.9%; adjusted odds ratio 1.23, 95% CI 0.54 to 2.83, P=.62, second follow-up: 70/85 – 82.4% versus 57/76 – 75.0%; absolute risk difference = -

7.4%, 95% CI: -20.0 to 5.3%; adjusted odds ratio 1.27, 95% CI 0.50 to 3.21, P=.62). Analysis of the outcome measures related to candidiasis are provided in eTable 4 of Supplement 2. Three stool samples were positive for vancomycin resistant enterococci at baseline, 3 month, and final follow-up time point. Further details of analysis of microbiology outcome measures are provided in eTable 5 of Supplement 2.

At 3-months post-randomization, 7 of the 107 stool samples tested (6.5%) were positive for *Clostridioides difficile*, with a greater number detected in samples belonging to care home residents randomized to probiotic than placebo (6/55 10.9% versus 1/52 1.9%, absolute risk difference = -9.0%, 95% CI: -18.4 to 0.4%; AOR = 6.51, 95% CI: 0.75 to 56.57, p = .09). At the second follow-up, 2/64 samples tested (3.1%) yielded *Clostridioides difficile*. Both of these samples were from care home residents randomized to probiotic.

Subgroup effects

There were no statistically significant different intervention effects for any of the pre-specified subgroups. Further details are provided in eTable 6 of Supplement 2.

Adverse Events

120 care home residents experienced 283 adverse events, including 78 (58.6%) hospitalizations in the placebo group and 94 (62.7%) in probiotic group, and 32 deaths (24.1%) in the placebo group and 33 (22.0%) in the probiotic group (Table 3). Three trial-related AEs were identified and all were in the placebo group; 1 stopped the study product because of choking risk, another because they reported the study product made their diarrhea worse, and another because the study product made them feel bloated.

Discussion

This double blind, placebo controlled clinical trial found that the administration of a daily dose of the probiotic combination, *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* to care home residents did not result in significantly fewer cumulative systemic antibiotic administration days for all-cause, acute infections.

Prior studies of probiotics have produced contradictory findings and have been criticized for poor design, selective reporting, poorly described and verified outcomes, inadequate reporting of harms, and poor ascertainment of outcomes.[3] In this trial, a registered nurse blind to randomization status visited study participants each week to complete participant diary data from multiple sources, with data for only 1.3% of eligible study days missing,, and probiotic organisms were identified more often and in greater counts in the stool of care home residents in the probiotic group.

A recent meta-analysis on the effectiveness of probiotics in preventing infections in older adults included 15 studies covering 5,916 participants with mean age of 75.21 years.[18] Three of the included studies recruited institutionalized older adults: Mane and colleagues randomized 50 participants to receive low, or high daily dose of *Lactobacillus plamtarum* or placebo for up to 12 weeks, and found that the high dose significantly increased the percentages of markers of immunogenicity, and significantly lowered incidence of infections.[19] Van Puyenbroeck and colleagues randomized 737 nursing home residents to receive a fermented milk containing *Lactobacillus casei Shirota* or placebo for 176 days, and found no significant effect on the number of days with respiratory symptoms or anti-influenza antibody titers after influenza vaccination.[20] Nagata and colleagues randomized 72 residents and staff members of facilities for older adults to receive *Lactobacillus casei*

Shirota in fermented milk or placebo each day for six months, and found a lower incidence of fever and improved bowel movements in those taking the probiotic.[21] The authors of the review concluded that the overall quality of evidence was poor, and that it did not support the use of probiotics for reducing infections in older adults, that safety outcomes were similar between probiotics and placebo, and that more research was needed.[18]

A subsequent, double blind, placebo controlled pilot trial of *Lactobacillus rhamnosus GG* or placebo daily for 6 months to prevent respiratory infections in 209 nursing home residents identified laboratory-confirmed respiratory viral infections in 14 (15.0%) and 21 (22.9%) in the placebo and probiotic groups respectively, and called for a larger trial.[5]

A large trial of hospitalized patients found no benefit from short term lactobacilli and bifidobacteria with regard to antibiotic associated diarrhea,[22] which conflicted with findings from several systematic reviews.[23]

This trial found no beneficial effect of probiotic use compared with placebo on antibiotic use overall, or for the main categories of infections that commonly affect the population studied, duration of infections, health utility and wellbeing, hospitalizations, death, antibiotic-associated diarrhea, or carriage of antibiotic resistant stool organisms. However, participants who were randomized to the probiotic group were administered significantly more antibiotics for lower respiratory tract infections, had a small but statistically significant lower self-reported generic wellbeing/capability scores at 3 months, and a pre-specified sensitivity analysis found a significant increase in cumulative systemic antibiotic days. These findings should be interpreted with caution, given multiple testing. However, this study does not rule out harm from probiotics. Certain probiotics may delay the return of the host gut microbiome

to its normal state after antibiotic treatment,[24] and a retrospective, single center study found probiotic exposure was associated with *Clostridioides difficile* infection in hospitalized patients.[25]

Limitations

This study has several limitations. First, although all care home residents remaining in the trial were followed up for at least 6 months, some had their follow-up truncated before the originally planned twelve months due to longer than expected study set-up. Second, a higher than expected proportion of stool cultures were positive for the study probiotics at baseline, and probiotic organisms were isolated from some of the stool samples obtained from the placebo group at follow-up, albeit at low counts. More sensitive microbiological techniques may partially explain isolation of these organisms at low counts, Exposure to the probiotic organisms in the placebo group would dilute any between-group differences in outcomes. Third, infection related outcomes were not based on standard definitions, as presentation of infections in this population is often non-specific, and care home residents were not tested for etiology using microbiological sampling. This may limit generalizability of some secondary outcomes. Fourth, given a lower than expected event rate, this study was underpowered to detect statistical significance for the minimal clinically important difference in the primary outcome. Fifth, these findings are not necessarily generalizable to other probiotics or probiotic combinations, or applicable to other populations, since the effects of probiotic supplementation may be strain specific and vary according to setting, immune status, and age.

Conclusion

Among care home residents in the UK, a daily oral probiotic combination of *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* did not significantly reduce

antibiotic administration for all-cause infections. The findings do not support the use of probiotics in this setting.

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The Trial Steering Committee members were Professor Steve Iliffe, FRCGP (University College London), Professor Glenn R. Gibson, PhD (University of Reading), Dr Jonathan Sandoe, FCRPath (University of Leeds), Dr Meena Rafiq, MBBS (University College London), Robin Willmott (General Manager Millbrook Lodge Care Home), and the members of the Independent Data Monitoring Committee were Dr Stephen Bremner PhD (Brighton and Sussex Medical School), Dr Neil Haslam FRCP (Royal Liverpool and Broadgreen University Hospitals NHS Trust) and Dr Matthew Ridd, PhD (University of Bristol).

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Figure 1: Enrollment, randomization, and follow-up

672 **Table 1: Participant characteristics at baseline**

Characteristic	**Probiotic (N=155*)**	**Placebo (N=155*)**
Age, mean (SD), year	85.1 (7.6)	85.6 (7.21)
Sex, n (%)		
Male	52 (33.5)	51 (32.9)
Female	103 (66.5)	104 (67.1)
Lacks mental capacity to consent†, n (%)	98 (63.2)	106 (68.4)
Has mental capacity to consent†, n (%)	57 (36.8)	49 (31.6)
Duration of residency in care home, median (IQR) N, year	1 (0, 2) 153	1 (0, 3) 154
Height, mean (SD) N, cm	162 (7.8) 70	165 (8.8) 74
Weight, median (IQR), kg	60 (52.1, 70.6)	63 (55.6, 72.9)
Ulna length‡, mean (SD) N, cm	25 (2.5) 152	26 (2.5) 150
Mid upper arm circumference§, mean (SD) N, cm	27 (4.5) 151	27 (4.1) 150
Clinical frailty scale‖		
Very fit to managing well	13 (8.4)	18 (11.6)
Vulnerable to moderately frail	64 (41.3)	51 (32.9)
Severely frail to terminally ill	78 (50.3)	86 (55.5)

Characteristic	**Probiotic (N=155*)**	**Placebo (N=155*)**
Prescribed antimicrobials in the last four weeks, n (%)	45 (29.0)	37 (23.9)
Used a proton pump inhibitor in the last four weeks, n (%)	61 (39.4)	52 (33.5)
Used a laxative in the last four weeks, n (%)	75 (48.4)	85 (54.8)
Used Vitamin D in the last four weeks, n (%)	50 (32.3)	44 (28.4)
Stool sample - *Lactobacillus rhamnosus* growth on plate, n/N (%)	28/83 (33.7)	19/75 (25.3)
Stool sample - *Bifidobacterium animalis subsp. lactis* growth on plate, n/N (%)	3/83 (3.6)	4/75 (5.3)
Stool sample – Growth of *Clostridioides difficile*, n/N (%)	6/83 (7.2)	0/75 (0.0)

*Unless otherwise specified.

†If participants lacked capacity to consent, a consultee advised about their participation in accordance with the governing legislation

‡Measure between the point of the elbow and the midpoint of the prominent bone of the wrist.

§Measure the distance between the bony protrusion on the shoulder and the point of the elbow, mark the midpoint and measure around the arm at this point.

||Clinical frailty scale assesses the level of fitness or frailty of older adult, scores range from 1 to 8: (1-3) very fit to managing well, (4-6) vulnerable to moderately frail, and (7-8) severely frail to terminally ill.

688 **Table 2: Between-group differences for infection-related outcome measures***

689

Analysis	**Probiotic (n=155)**	**Placebo (n=155)**	**Absolute difference, 95% CI**	**Adjusted incidence rate ratio, 95% CI**	**p-value**
Primary outcome No. (%) with data	152 (98.1)	153 (98.7)			
Cumulative antibiotic administration days, mean (SD)	12.9 (18.4)	12.0 (18.6)	0.9 (-3.3 to 5.1)	1.1 (0.8 to 1.6)	.50
Secondary outcome No. (%) with data*	152 (98.1)	153 (98.7)			
Cumulative systemic antibiotic administration days for urinary tract infection†, mean (SD)	7.1 (15.0)	6.7 (13.6)	0.4 (-2.8 to 3.6)	1.2 (0.8 to 1.8)	.48
Cumulative systemic antibiotic administration days for upper respiratory tract infections, mean (SD)	3.3 (9.4)	3.4 (10.1)	0.1 (-2.1 to 2.3)	1.1 (0.7 to 1.8)	.61

Analysis	Probiotic (n=155)	Placebo (n=155)	Absolute difference,	Adjusted incidence	p-value
Cumulative systemic antibiotic administration days for lower respiratory tract infections, mean (SD)	6.2 (14.6)	4.0 (7.6)	2.2 (-0.4 to 4.8)	1.4 (1.1 to 1.9)	.02
Cumulative systemic antibiotic administration days for skin infections, mean (SD)	3.4 (8.7)	3.7 (13.1)	0.3 (-2.2 to 2.8)	0.9 (0.5 to 1.6)	.76
Incidence of any infection, mean (SD)	2.5 (2.5)	2.4 (2.7)	0.1 (-1.3 to 1.5)	1.0 (0.8 to 1.2)	.92
Incidence of urinary tract infections, mean (SD)	0.8 (1.4)	0.8 (1.4)	0 (-0.3 to 0.3)	1.1 (0.6 to 2.1)	.68
Incidence of gastrointestinal infections, mean (SD)	0.03 (0.2)	0.04 (0.2)	0 (0 to 0.1)	0.8 (0.2 to 2.6)	.68
Incidence for upper respiratory tract infections, mean (SD)	0.4 (0.8)	0.5 (0.9)	0.1 (-0.1 to 0.3)	0.8 (0.5 to 1.2)	.31
Incidence for lower	0.6 (1.0)	0.5 (0.9)	0.1 (-0.1 to	1.2 (0.8 to	.41

Analysis	Probiotic (n=155)	Placebo (n=155)	Absolute difference,	Adjusted incidence	p-value
respiratory tract infections, mean (SD)			0.3)	1.7)	
Incidence for skin infections, mean (SD)	0.6 (1.2)	0.5 (1.1)	0.1 (-0.2 to 0.4)	1.2 (0.7 to 2.0)	.49
At least one infection, n (%)	111 (73.0)	102 (66.7)	0.1 (0 to 0.2)	1.4 (0.8 to 2.4) ‡	.20
Duration of infection for those with at least one infection§, median (IQR) N	6 (4, 9) 111	5 (3, 7) 102	0.9 (-0.4 to 2.2)	0.1 (0 to 0.2) **	.05
Cumulative number of infection days per person-year††, median (IQR)	13 (0, 27)	8 (0, 25)	1 (-7.1 to 9.1)	1.1 (0.8 to 1.5)	.67

*Cumulative systemic antibiotic administration days for gastrointestinal infection was not reported due to a small number of participants having gastrointestinal infection (two participants in probiotic group and zero in placebo group).

†Cumulative infection-site specific antibiotic administration days were rate variables expressed per person year. The numerator was the number of days that an antibiotic was administered for a specific infection (as indicated in the care home medical records) and the denominator was the period of exposure days.

‡ Adjusted odds ratio, 95% CI

§Duration of infection was calculated by dividing the number of infection days by the total number of infections. See eFigure 2 for the distribution.

**Adjusted mean difference, 95% CI

††Cumulative number of infection days was a rate variable expressed as infection days per person year, with the number of suspected infection days as the numerator over the period of exposure days. During weekly visits, Research Nurses would record whether care home residents displayed signs of infection (and if so what infection/s), following discussions with Care Home Staff. This was asked and recorded separately to whether a care home resident received an antibiotic on a given day.

709 **Table 3: Between-group differences for secondary outcome measures***

710

Secondary Analysis	**Probiotic (n=155)**	**Placebo (n=155)**	**Absolute difference, 95% CI**	**Adjusted difference, 95% CI†**	**p-value**
3-months EQ-5D index value*‡					
Self-report, mean (SD) N	0.6 (0.3) 49	0.6 (0.2) 43	0 (-0.1 to 0.2)	Mean: -0.1 (-0.1 to 0)	.13
Proxy, mean (SD) N	0.5 (0.3) 130	0.5 (0.3) 129	0 (-0.1 to 0.1)	Mean: 0 (-0.1 to 0)	.66
3-months EQ-5D health status*§					
Self-report, mean (SD) N	65 (18.3) 44	65 (20.6) 42	0.1 (-8.1 to 8.3)	Mean: -0.3 (-8.0 to 7.5)	.95
Proxy, mean (SD) N	71 (19.1) 128	70 (20.6) 130	0.4 (-4.4 to 5.2)	Mean: 0.4 (-4.1 to 4.8)	.87
Second follow-up EQ-5D index value*‡					

Secondary Analysis	**Probiotic (n=155)**	**Placebo (n=155)**	**Absolute difference, 95% CI**	**Adjusted difference, 95% CI†**	**p-value**
Self-report, mean (SD) N	0.6 (0.4) 38	0.6 (0.3) 31	0 (-0.2 to 0.2)	Mean: 0 (-0.1 to 0.1)	.92
Proxy, mean (SD) N	0.5 (0.3) 97	0.5 (0.3) 95	0 (0 to 0.1)	Mean: 0 (-0.1 to 0.1)	.79
Second follow-up EQ-5D health status*§					
Self-report, mean (SD) N	65 (21.4) 34	66 (21.5) 29	0.5 (-10.1 to 11.1)	Mean: 24.4 (-1267.9 to 1316.6) ‖	.97
Proxy, mean (SD) N	65 (21.8) 98	64 (21.0) 96	0.6 (-5.4 to 6.6)	Mean: 0.6 (-4.9 to 6.2)	.82
3-months ICECAP-O value¶					
Self-report, mean (SD) N	0.7 (0.2) 47	0.7 (0.2) 40	0 (-0.1 to 0.1)	Mean: -0.1 (-0.1 to -0)	.05
Proxy, mean (SD) N	0.7 (0.2) 117	0.7 (0.2) 118	0 (0 to 0.1)	Mean: 0 (0 to 0)	.85

Secondary Analysis	**Probiotic (n=155)**	**Placebo (n=155)**	**Absolute difference, 95% CI**	**Adjusted difference, 95% CI†**	**p-value**
Second follow-up ICECAP-O value¶					
Self-report, mean (SD) N	0.7 (0.3) 35	0.7 (0.2) 27	0.1 (-0.1 to 0.2)	Mean: -0.1 (-0.2 to 0)	.15
Proxy, mean (SD) N	0.7 (0.2) 84	0.7 (0.2) 90	0 (-0.1 to 0.1)	Mean: 0 (-0.1 to 0)	.69
Ever been hospitalized, n/N (%)	42/152 (27.6)	36/153 (23.5)	0 (-0.1 to 0.1)	OR: 1.3 (0.7 to 2.1)	.41
Death, n (%)	33 (21.3)	32 (20.6)	0 (-0.1 to 0.1)	OR: 1.0 (0.6 to 1.8)	.90
Number of hospital stays, mean (SD) N	0.4 (0.7) 152	0.3 (0.6) 153	0.1 (-0.1 to 0.2)	IRR: 1.2 (0.7 to 1.9)	.53
Cumulative number of hospital days, mean (SD) N	4.5 (12.5) 152	5.4 (19.4) 153	0.9 (-2.8 to 4.6)	IRR: 1.0 (0.43 to 2.29)	1.00
Incidence of antibiotic-associated diarrhea, mean (SD) N	0.8 (2.0) 152	0.6 (1.8) 153	0.2 (-0.2 to 0.5)	IRR: 1.4 (0.8 to 2.5)	.25

Secondary Analysis	**Probiotic (n=155)**	**Placebo (n=155)**	**Absolute difference, 95% CI**	**Adjusted difference, 95% CI†**	**p-value**
Cumulative days of antibiotic-associated diarrhea, mean (SD) N	6.8 (22.3) 152	4.4 (16.1) 153	2.4 (-2.0 to 6.7)	IRR: 1.8 (1.0 to 3.5)	.07
Incidence of all-cause diarrhea, mean (SD) N	1.8 (3.9) 152	1.6 (3.5) 153	0.2 (-0.6 to 1.1)	IRR: 1.1 (0.7 to 1.6)	.80
Cumulative days of all-cause diarrhea, mean (SD) N	4.4 (10.2) 152	4.4 (10.8) 153	0 (-2.3 to 2.4)	IRR: 1.2 (0.78 to 2.0)	.39
At least one all-cause diarrhea, n/N (%)	64/152 (42.1)	61/153 (39.9)	0 (-0.1 to 0.1)	OR: 1.0 (0.6 to 1.8)	.89
Mean duration of diarrhea episodes for those with at least one diarrhea, mean (SD) N	1.4 (0.6) 64	1.4 (0.6) 61	0.1 (-0.1 to 0.3)	Mean: 0.1 (-0.1 to 0.2)	.27

*Self-report EQ-5D-5L and ICECAP – O completed by participants who had capacity. Proxy EQ-5D-5L and ICECAP – O completed by relatives on behalf of participants

†Mean: Adjusted mean difference; OR: Adjusted odds ratio; IRR: Adjusted incidence rate ratio

‡EQ-5D index values can range from -0.594 to 1, with a higher score indicating better health utility

§EQ-5D health status can range from 0 to 100, with a higher score indicating better overall health

‖Transformed outcome (power of 2)

¶ICECAP-O score can range from 0 to 1, with a higher score indicating higher capability