JAMA | Original Investigation

Effect of Probiotic Use on Antibiotic Administration Among Care Home Residents
A Randomized Clinical Trial

Christopher C. Butler, MD; Mandy Lau, BSc; David Gillespie, PhD; Eleri Owen-Jones, PhD; Mark Lown, PhD; Mandy Wootton, PhD; Philip C. Calder, PhD; Antony J. Bayer, BM ChB; Michael Moore, MSc; Paul Little, MD; Jane Davies, PhD; Alison Edwards, MSc; Victoria Shepherd, PhD; Kerenza Hood, PhD; F. D. Richard Hobbs, MBChB; Mina Davoudianfar, BA; Heather Rutter, BSc; Helen Stanton, BSc; Rachel Lowe, PhD; Richard Fuller, BMBS; Nick A. Francis, PhD

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 with placebo reduces antibiotic administration in care home residents.

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

INTERVENTIONS Study participants were randomized 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, 1.3×10^{10} to 1.6×10^{10}) (n = 155), or daily matched placebo (n = 155), for up to 1 year.

MAIN OUTCOMES AND MEASURES The primary outcome was cumulative antibiotic administration days for all-cause infections measured from randomization for up to 1 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 98.7% randomized to the probiotic group and 97.4% randomized to placebo. Care home residents randomized to the probiotic group had a mean of 12.9 cumulative systemic antibiotic administration days (95% CI, 0 to 18.05), and residents randomized to placebo had a mean of 12.0 days (95% CI, 0 to 16.95) (absolute difference, 0.9 days [95% CI, −3.25 to 5.05]; 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 (150 adverse events in the probiotic group and 133 in the placebo group). Hospitalizations accounted for 94 of the events in probiotic group and 78 events in the placebo group, and deaths accounted for 33 of the events in the probiotic group and 32 of the events in the placebo group.

CONCLUSIONS AND RELEVANCE Among care home residents in the United Kingdom, 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 ISRCTN Identifier:16392920

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 92

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christopher C. Butler, FMedSci, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, (christopher.butler@phc.ox.ac.uk).

JAMA. 2020;324(1):47-56. doi:10.1001/jama.2020.8556

The global human probiotics market size was more than $34 billion (US dollars) in 2015, and may be worth $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 randomized clinical trials (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 populations.[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.

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 vs 12.0).

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

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 3; recognized by the UK Ethics Committee Authority [15/WA/0306]), which approved all recruitment sites. National Health Service (NHS) health boards and clinical commissioning groups gave research and development approval to sites. Written informed 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 elsewhere,[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 eAppendix 1 in 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 and blind to group allocation made weekly visits to each care home and recorded weekly diary data for each participant in an online database. Participant data included 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, and discussion with participants or their friends and family, care home staff, and hospital discharge summaries. The EuroQol Group 5-Dimension Self-Report (EQ-5D) for health utility and the Icepop Capability Measure for Older People (ICECAP-O) well-being questionnaires were collected at baseline, at 3-month follow-up, and at the 12-month follow-up point (or 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, month 3, and at 12-month follow-up (or as close to 12 months as the study would allow), but this was not a requirement for participation.

Interventions

Participants were randomized to receive a daily oral probiotic combination of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp *lactis* BB-12 (total cell count per capsule, 1.3×10^{10} to 1.6×10^{10}) or a matched placebo (capsule containing maltodextrin, microcrystalline cellulose, magnesium stearate, and silicon dioxide) once daily (eAppendix 2 in Supplement 2). The study product was not administered while care

home residents were away from care homes, such as when hospitalized or 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, with the denominator calculated as the total number of days participants were observed in the study.

Secondary outcomes were the 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, and duration of infection (mean and cumulative values reported); 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- or proxy-reported (or both) health-related quality of life measured by EQ-5D-5L (index value range, −0.594 [worst] to 1 [best]); health status range, 0 [worst] to 100 [best]) and ICECAP-O (range, 0 [worst] to 1 [best])[11]; number and duration of hospital stays; and deaths. eAppendix 3 in Supplement 2 provides further details on the derivation of some outcomes.

Statistical Analyses

An estimated 330 participants from 20 care homes in the UK would provide 90% power at the 5% level to demonstrate a 10% relative reduction in cumulative systemic antibiotic administration days, assuming a mean number of cumulative systemic antibiotic administration days of 17.4 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 a mean 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 a UK government initiative to halve inappropriate prescribing would amount to a 10% relative reduction.[16]

This sample size accounted for 30% of participants contributing no outcome data (ie, randomized but contributing to neither the numerator or denominator). The 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 (ie, 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.

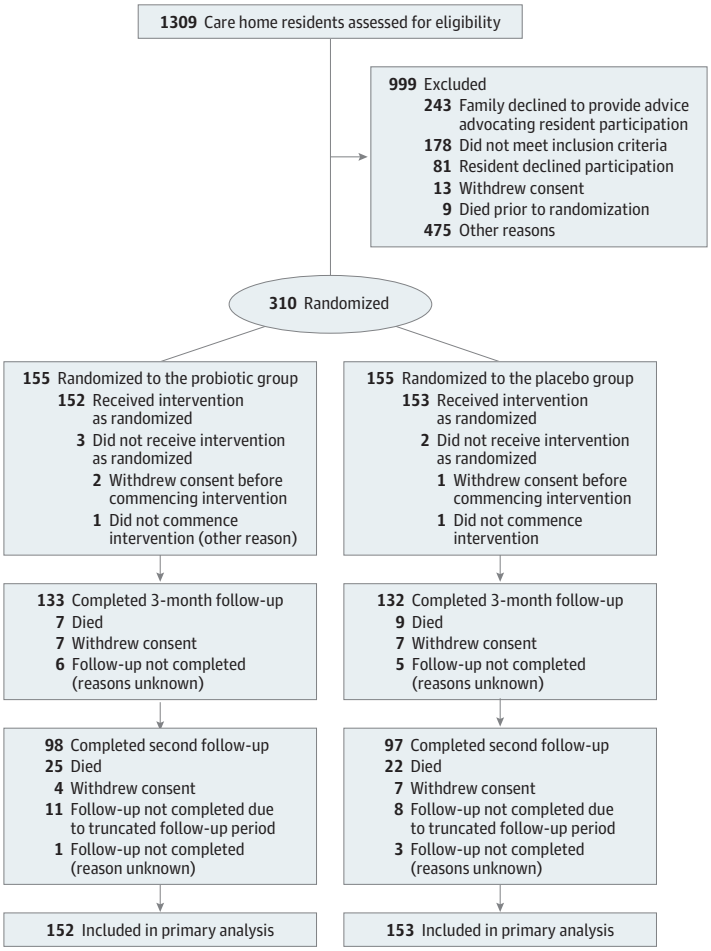
Primary and secondary comparative analyses were prespecified and included all randomized participants who provided outcome data, analyzed in the group to which they were randomized without imputation to account for loss of observation time. The mean cumulative systemic antibiotic administration days per resident-year was compared between groups by fitting a 2-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 2-level Poisson or negative binomial regression (depending on the presence of overdispersion). 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 tract infections. The consistency of conclusions drawn from the primary analysis was investigated by conducting the following prespecified sensitivity analyses: (1) including prophylactic antibiotic use in the definition of cumulative systemic antibiotic administration days; (2) ignoring periods of hospitalization from both the numerator and denominator; (3) 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]; and (4) accounting for study product consumption (see eAppendix 4 in Supplement 2). Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. For all analyses, 2-sided 95% CIs and *P* values were calculated. *P* values of less than .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

Of 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 undergone a second follow up at 12 months postrandomization (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. Enrollment, Randomization, and Follow-up of Care Home Residents



(**Figure**). The mean (SD) age was 85.3 (7.39) years; 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 *C difficile* cultured from their stool (6/83 [7.2%]) compared with the placebo group (0/75) (**Table 1**). Care home residents allocated to the probiotic group contributed 39 798 person days (mean [SD] number of days per probiotic participant, 252.4 [110.51]) and care home residents allocated to placebo contributed 37 974 person days (mean days, 242.9 [115.24]). The primary cause of unobserved data was truncation due to death, with postrandomization deaths occurring in 33 care home residents randomized to the probiotic group and 32 randomized to receive placebo (total number of unobserved days due to death, 7578 for the probiotic group and 6978 for the placebo group). Other reasons for unobserved data were resident absence from the care home (56 days in the probiotic group and 114 days in the placebo group), waiting for a capacity assessment (7 days in the probiotic group and zero in the placebo group), and data not collected for an unknown reason (1898 days in the probiotic group and 972 days in the placebo group). There were 305 (98.4%) care home residents who 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

Among study participants, 302 (97.4%) initiated at least 1 dose of study product (152 [98.1%] in the placebo group and 150 [96.8%] 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 1 study product dose, a median of 93.3% (interquartile range [IQR], 93.56% to 99.45%) full or partial doses were taken, and 89.4% (68 356/73 302) were either swallowed as capsules or sprinkled on food (that was not hot) prior to ingestion, 4.4% (3258/73 302) in liquid form, and 2.3% (1688/73 302) by method unknown.

At 3 months postrandomization, significantly more stool samples were found to contain *Lactobacillus rhamnosus* among care home residents randomized to the probiotic group vs from those randomized to the placebo group (83.9% [47/56] vs 36.5% [19/52]; absolute risk difference [ARD], -47.4% [95% CI, -64.8%

to -29.0%]; adjusted odds ratio [AOR], 9.19 [95% CI, 3.51 to 24.07]; $P < .001$), and mean (SD) concentrations were 7.04×10^5 (3.05×10^6) for those randomized to the probiotic group and 4.67×10^4 (2.77×10^5) in the placebo group. This finding persisted at the second follow-up time point, with stool samples containing *Lactobacillus rhamnosus* in 73.0% (27/37) of participants in the probiotic group vs 31.0% (9/29) of participants in the placebo group (ARD, -41.9% [95% CI, -66.1% to -17.7%]; AOR, 6.41 [95% CI, 2.14 to 19.20]; $P = .001$), mean (SD) concentrations, 1.52×10^5 (5.27×10^5) in the probiotic group vs 1.40×10^4 (4.31×10^4) in the placebo group (eTable 5 in Supplement 2).

Care home residents randomized to the probiotic group provided stool samples containing *Bifidobacterium animalis* subsp *lactis* significantly more frequently than those randomized to placebo at 3 months (51.8% [29/56] vs 3.8% [2/52]; ARD, -47.9% [95% CI, -65.0% to -30.9%]; AOR, 26.90 [95% CI, 5.94 to 121.66]; $P < .001$), mean (SD) concentrations, 1.72×10^6 (5.11×10^6) in the probiotic group and 2.88×10^4 (1.71×10^5) in the placebo group. This finding persisted at the second follow-up time point (56.8% [21/37] in the probiotic group vs 6.9% [2/29]; ARD, -49.9% [95% CI, -73.0% to -26.7%]; AOR, 21.96 [95% CI, 2.97 to 162.43]; $P = .002$), with mean (SD) concentrations of 2.15×10^5 (4.45×10^5) in the probiotic group vs 3.62×10^2 (1.86×10^3) in the placebo group (eTable 5 in Supplement 2).

There were 202 (66.2%) care home residents who were prescribed at least 1 nonprophylactic antibiotic (63.4% [97/155] in the probiotic group vs 69.1% [105/155] in the placebo group). There were 287 courses of nonprophylactic antibiotics prescribed in the probiotic group vs 336 courses in the placebo group.

Table 1. Participant Characteristics at Baseline of Care Home Residents

Characteristic	Probiotic (n = 155)[a]	Placebo (n = 155)[a]
Age, mean (SD), y	85.1 (7.6)	85.6 (7.21)
Men	52 (33.5)	51 (32.9)
Women	103 (66.5)	104 (67.1)
Consent provided by proxy[b]	98 (63.2)	106 (68.4)
Consent self-provided[b]	57 (36.8)	49 (31.6)
Years of residency in care home, median (IQR)[c]	1 (0-2)	1 (0-3)
Height, mean (SD), cm[d]	162 (7.8)	165 (8.8)
Weight, median (IQR), kg	60 (52.1-70.6)	63 (55.6-72.9)
Ulna length[e], mean (SD), cm	25 (2.5)	26 (2.5)
Mid-upper arm circumference, mean (SD), cm[f]	27 (4.5)	27 (4.1)
Clinical frailty scale[g]		
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)
Prescribed antimicrobials in the last 4 weeks	45 (29.0)	37 (23.9)
Used a proton pump inhibitor in the last 4 weeks	61 (39.4)	52 (33.5)
Used a laxative in the last 4 weeks	75 (48.4)	85 (54.8)
Used vitamin D in the last 4 weeks	50 (32.3)	44 (28.4)
Lactobacillus rhamnosus growth on plate, No./total No. (%)[h]	28/83 (33.7)	19/75 (25.3)
Bifidobacterium animalis subsp *lactis* growth on plate, No./total No. (%)[h]	3/83 (3.6)	4/75 (5.3)
Growth of *Clostridioides difficile*, No./total No. (%)[h]	6/83 (7.2)	0/75

[a] Values are reported as No. (%) unless otherwise specified. Some characteristic categories, as indicated by footnote, did not count all group participants.

[b] If participants lacked capacity to consent, a consultee (legal representative or guardian) advised about their participation in accordance with the governing legislation.

[c] Categorical count included 153 in the probiotic group and 154 in the placebo group.

[d] Categorical count included 70 in the probiotic group and 74 in the placebo group.

[e] Indicates length between the point of the elbow and the midpoint of the prominent bone of the wrist. Categorical count included 152 in the probiotic group and 150 in the placebo group.

[f] Indicates the distance between the bony protrusion on the shoulder and the point of the elbow, marking the midpoint and measuring around the arm at this point. Categorical count included 151 in the probiotic group and 150 in the placebo group.

[g] Scale assesses the level of fitness or frailty in an older adult (score ranges and interpretations: 1-3, very fit to managing well; 4-6, vulnerable to moderately frail; and 7-8, severely frail to terminally ill).

[h] Assessed from participant stool samples.

Primary Outcome

Care home residents randomized to the probiotic group had a mean (SD) of 12.9 (18.4) cumulative systemic antibiotic administration days (95% CI, 0 to 18.05 days), and care home residents randomized to the placebo group had a mean of 12.0 (18.6) cumulative systemic antibiotic administration days (95% CI, 0 to 16.95 days). The distribution was positively skewed, with 37% of residents having 0 days due to not being administered antibiotics (eFigure 1 in Supplement 2). 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 taking an antibiotic until death. Further details of sensitivity analyses for the primary outcome measure are provided in eTable 1, eTable 2, and eTable 3 in Supplement 2.

Secondary Outcomes

Care home residents randomized to receive 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 the placebo group (mean 6.2 days in the probiotic group vs 4.0 days in the 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 were no statistically significant between-group differences in antibiotic use for urinary tract infections (mean 7.1 days in the probiotic group vs mean 6.7 days in the placebo group; 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 in the probiotic group vs mean 3.4 days

Table 2. Between-Group Differences for Infection-Related Outcome Measures[a]

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, mean (SD), days	12.9 (18.4)	12.0 (18.6)	0.9 (-3.25 to 5.05)	1.13 (0.79 to 1.63)	.50
Secondary outcome, No. (%) with data[a]	152 (98.1)	153 (98.7)			
Cumulative systemic antibiotic administration, mean (SD), days					
For urinary tract infection[b]	7.1 (15.0)	6.7 (13.6)	0.4 (-2.81 to 3.61)	1.17 (0.75 to 1.84)	.48
For upper respiratory tract infections[b]	3.3 (9.4)	3.4 (10.1)	0.1 (-2.09 to 2.29)	1.13 (0.71 to 1.78)	.61
For lower respiratory tract infections[b]	6.2 (14.6)	4.0 (7.6)	2.2 (-0.4 to 4.8)	1.4 (1.1 to 1.9)	.02
For skin infections[b]	3.4 (8.7)	3.7 (13.1)	0.3 (-2.20 to 2.80)	0.92 (0.54 to 1.57)	.76
Incidence of infection, mean (SD), No. per person					
Of any infection	2.5 (2.5)	2.4 (2.7)	0.1 (-1.3 to 1.5)	1.0 (0.8 to 1.2)	.92
Of urinary tract infections	0.8 (1.4)	0.8 (1.4)	0 (-0.3 to 0.3)	1.1 (0.6 to 2.1)	.68
Of gastrointestinal infections	0.03 (0.2)	0.04 (0.2)	0 (0 to 0.1)	0.8 (0.2 to 2.6)	.68
Of upper respiratory tract infections	0.4 (0.8)	0.5 (0.9)	0.1 (-0.1 to 0.3)	0.8 (0.5 to 1.2)	.31
Of lower respiratory tract infections	0.6 (1.0)	0.5 (0.9)	0.1 (-0.1 to 0.3)	1.2 (0.8 to 1.7)	.41
Of skin infections	0.6 (1.2)	0.5 (1.1)	0.1 (-0.2 to 0.4)	1.2 (0.7 to 2.0)	.49
≥1 Infection, No. (%)	111 (73.0)	102 (66.7)	0.1 (0 to 0.2)	1.4 (0.8 to 2.4)[c]	.20
Duration of infection for those with ≥1 infection, mean (SD)[d]	6.8 (4.7)	6.0 (4.9)	0.9 (-0.4 to 2.2)	0.1 (0 to 0.2)[e]	.05
Cumulative number of infection days per person-year, mean (SD)[f]	22 (30.8)	21 (40.7)	1 (-7.1 to 9.1)	1.1 (0.8 to 1.5)	.67

Abbreviation: IQR, interquartile range.

[a] Cumulative systemic antibiotic administration days for gastrointestinal infection was not reported due to a small number of participants having gastrointestinal infection (2 participants in the probiotic group and 0 in the placebo group).

[b] Cumulative infection-site–specific antibiotic administration days were rate variables expressed per person-year. The mean rates were calculated by dividing the number of days that an antibiotic was administered for a specific infection (as indicated in the care home medical records) by the period of exposure days.

[c] Indicates adjusted odds ratio (95% CI).

[d] Duration of infection was calculated by dividing the number of infection days by the total number of infections. Values in this category are based on a count of 111 in the probiotic group and 102 in the placebo group. See eFigure 2 in Supplement 2 for the distribution.

[e] Indicates adjusted mean difference (95% CI).

[f] 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, record which infection[s]) following discussions with care home staff. This was asked and recorded separately from whether a care home resident received an antibiotic on a given day.

in the placebo group; 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 in the probiotic group vs mean 3.7 days in the placebo group; 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 in the probiotic group vs median 5 days in the placebo group; adjusted mean difference, 0.08 [95% CI, -0.001 to 0.16]; *P* = .05; **Table 2**; eFigure 2 in Supplement 2). Unexplained fever was not reported for any participants during the trial.

Care home residents allocated to the probiotic group had statistically significant lower self-reported generic well-being/capability scores at 3 months (mean score, 0.72 in the probiotic group vs mean score, 0.69 in the placebo group; 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-reported and proxy well-being and quality of life outcomes (**Table 3**).

There were no statistically significant between-group differences for being hospitalized at least once during the post-randomization study period (42/152 [27.6%] in probiotic group vs 36/153 [23.5%] in placebo group; absolute percentage risk difference, -4.1% [95% CI, -13.9% to 5.7%]; adjusted OR, 1.25 [95% CI, 0.74 to 2.11]; *P* = .41), number of hospital stays (mean [SD], 0.4 [0.7] in the probiotic group vs 0.3 [0.6] in the placebo group; 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 [SD], 4.5 [12.5] days in the probiotic group vs 5.4 [19.4] days in the placebo group; 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* >.99), or death (33/155 [21.3%] in the probiotic group vs 32/155 [20.6%] in the placebo group; absolute percentage risk difference, -0.6% [95% CI, -9.7% to 8.4%]; AOR, 1.03 [95% CI, 0.59 to 1.80]; *P* = .90) (Table 3). Similarly, there were no statistically significant between-group differences for incidence of antibiotic-associated diarrhea (mean 0.8 vs 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 vs 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).

Table 3. Between-Group Differences for Secondary Outcome Measures

Secondary analysis	Probiotic (n = 155)	Placebo (n = 155)	Absolute difference (95% CI)	Adjusted difference (95% CI)[a]	*P* value
3-mo EQ-5D index value[b,c]					
Self-report, mean (SD) [No.]	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) [No.]	0.5 (0.3) [130]	0.5 (0.3) [129]	0 (-0.1 to 0.1)	Mean, 0 (-0.1 to 0)	.66
3-mo EQ-5D health status[b,c]					
Self-report, mean (SD) [No.]	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) [No.]	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[b,c]					
Self-report, mean (SD) [No.]	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) [No.]	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[b,c]					
Self-report, mean (SD) [No.]	65 (21.4) [34]	66 (21.5) [29]	0.5 (-10.1 to 11.1)	Mean, 24.4 (-1267.9 to 1316.6)[d]	.97
Proxy, mean (SD) [No.]	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-mo ICECAP-O value[e]					
Self-report, mean (SD) [No.]	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) [No.]	0.7 (0.2) [117]	0.7 (0.2) [118]	0 (0 to 0.1)	Mean, 0 (0 to 0)	.85
Second follow-up ICECAP-O value[e]					
Self-report, mean (SD) [No.]	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) [No.]	0.7 (0.2) [84]	0.7 (0.2) [90]	0 (-0.1 to 0.1)	Mean, 0 (-0.1 to 0)	.69
No. ever hospitalized/total No. (%)	42/152 (27.6)	36/153 (23.5)	0 (-0.1 to 0.1)	OR, 1.25 (0.74 to 2.11)	.41
Death, No. (%)	33 (21.3)	32 (20.6)	0 (-0.1 to 0.1)	OR, 1.03 (0.59 to 1.80)	.90
No. of hospital stays, mean (SD)[f]	0.4 (0.7)	0.3 (0.6)	0.08 (-0.06 to 0.22)	IRR, 1.17 (0.72 to 1.90)	.53
Cumulative No. of hospital days, mean (SD)[f]	4.5 (12.5)	5.4 (19.4)	0.9 (-2.77 to 4.57)	IRR, 1.00 (0.43 to 2.29)	>.99
Incidence of antibiotic-associated diarrhea, mean (SD)[f]	0.8 (2.0)	0.6 (1.8)	0.2 (-0.16 to 0.50)	IRR, 1.39 (0.79 to 2.46)	.25
Cumulative days of antibiotic-associated diarrhea, mean (SD)[f]	6.8 (22.3)	4.4 (16.1)	2.4 (-2.00 to 6.71)	IRR, 1.83 (0.95 to 3.54)	.07
Incidence of all-cause diarrhea, mean (SD)[f]	1.8 (3.9)	1.6 (3.5)	0.2 (-0.6 to 1.1)	IRR, 1.1 (0.7 to 1.6)	.80
Cumulative days of all-cause diarrhea, mean (SD)[f]	4.4 (10.2)	4.4 (10.8)	0 (-2.3 to 2.4)	IRR, 1.2 (0.78 to 2.0)	.39
≥1 All-cause diarrhea episode, No./total No. (%)	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 ≥1 episode, mean (SD), No. of persons	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

Abbreviations: EQ-5D-5L, EuroQol Group 5-Dimension Self-Report; ICECAP-O, Icepop Capability Measure for Older People; IRR, incidence rate ratio; OR, odds ratio.

[a] Column includes adjusted mean difference, adjusted OR, and adjusted IRR values and 95% CIs (indicated as mean, OR, and IRR).

[a] Column includes adjusted mean difference, adjusted OR, and adjusted IRR values and 95% CIs (indicated as mean, OR, and IRR).

[b] Responses by proxy were completed by relatives, consultees, (or the legal representative or guardian) on behalf of participants without capacity to self-report.

[c] EQ-5D index values range from −0.594 to 1 (higher score indicates better health utility), and EQ-5D health status values range from 0 to 100 (higher score indicates better overall health).

[d] Indicates transformed outcome (power of 2).

[e] ICECAP-O score ranges from 0 to 1 (higher score indicates higher capability).

[f] Analysis for this category included 152 participants in the probiotic group and 153 in the placebo group.

There were no statistically significant between-group differences with regards to *Enterobacterales* resistant to at least 1 of the tested antibiotics in stool samples at 3 months (37/55 [67.3%] in the probiotic group vs 39/52 [75.0%] in the placebo group; ARD, 7.7% [95% CI, -9.5% to 25.9%]; AOR, 0.61 [95% CI, 0.24 to 1.56]; *P* = .30), at second follow-up (23/33 [69.7%] in the probiotic group vs 19/27 [70.0%] in the placebo group; ARD, 0.7% [95% CI, -22.6 to 24.0%]; AOR, 0.76 [95% CI, 0.20 to 2.89]; *P* = .68), in the presence of oral candida at 3 months (88/113 [77.9%] in the probiotic group vs 80/105 [76.2%] in the placebo group; ARD, -0.2% [95% CI, -11.3 to 10.9%]; AOR, 1.23 [95% CI, 0.54 to 2.83]; *P* = .62), at second follow-up (70/85 [82.4%] in the probiotic group vs 57/76 [75.0%] in the placebo group; ARD, -7.4% [95% CI, -20.0% to 5.3%]; AOR, 1.27 [95% CI, 0.50 to 3.21]; *P* = .62). Analysis of the outcome measures related to candidiasis are provided in eTable 4 in Supplement 2. Three stool samples were positive for vancomycin-resistant *Enterococci* at baseline, 3 months, and at the final follow-up time point. Further details of analysis of microbiology outcome measures are provided in eTable 5 in Supplement 2.

At 3 months postrandomization, 7 of the 107 stool samples tested (6.5%) were positive for *C difficile*, with a greater number detected in samples belonging to care home residents randomized to the probiotic group than the placebo group (6/55 [10.9%] vs 1/52 [1.9%]; ARD, -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 of 64 samples tested (3.1%) yielded *C difficile*. Both of these samples were from care home residents randomized to the probiotic group.

Subgroup Effects

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

Adverse Events

A total of 120 care home residents experienced 283 adverse events (150 adverse events in the probiotic group and 133 in the placebo group). Hospitalizations accounted for 94 events in the probiotic group and 78 events in placebo group, and deaths accounted for 33 of the events in the probiotic group and 32 of the events in the placebo group (Table 3).

Three trial-related adverse events were identified and all were in the placebo group; study product was stopped because of choking risk for 1 participant, because of participant-reported worsening diarrhea for another, and because of participant-reported bloating for the third.

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 5916 participants with a mean age of 75.21 years.[18] Three of the included studies recruited institutionalized older adults: Mañé and colleagues[19] randomized 50 participants to receive a 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. Van Puyenbroeck and colleagues[20] 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. Nagata and colleagues[21] randomized 72 residents and staff members of facilities for older adults to receive *Lactobacillus casei Shirota* in fermented milk or placebo each day for 6 months and found a lower incidence of fever and improved bowel movements in those taking the probiotic. The authors of the review concluded that the overall quality of evidence was poor, that the evidence 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 well-being, 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 small but statistically significant lower self-reported generic well-being/capability scores at 3 months, and a prespecified 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 *C 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 12 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 nonspecific, 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.

Conclusions

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.

ARTICLE INFORMATION

Accepted for Publication: May 6, 2020.

Author Affiliations: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Bldg, University of Oxford, Oxford, United Kingdom (Butler, Hobbs, Davoudianfar, Rutter); Centre for Trials Research, Cardiff University, Heath Park, Cardiff, United Kingdom (Lau, Gillespie, Owen-Jones, Davies, Edwards, Shepherd, Hood, Stanton, Lowe); Primary Care and Population Sciences Unit, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, United Kingdom (Lown, Moore, Little, Fuller, Francis); Specialist Antimicrobial Chemotherapy Unit, Public Health Wales Microbiology, University Hospital of Wales, Heath Park, Cardiff, United Kingdom (Wootton); NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom (Calder); Division of Population Medicine, School of Medicine, Neuadd Meirionnydd, Cardiff University, Cardiff, United Kingdom (Bayer).

Author Contributions: Drs Butler and Gillespie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Butler, Lau, Gillespie, Calder, Bayer, Moore, Little, Shepherd, Hood, Hobbs, Lowe, Fuller, Francis.
Acquisition, analysis, or interpretation of data: Lau, Gillespie, Owen-Jones, Lown, Wootton, Calder, Moore, Little, Davies, Edwards, Shepherd, Hood, Hobbs, Davoudianfar, Rutter, Stanton, Lowe, Francis.
Drafting of the manuscript: Butler, Lau, Gillespie, Calder, Davies, Edwards, Shepherd, Rutter, Fuller, Francis.
Critical revision of the manuscript for important intellectual content: Butler, Gillespie, Owen-Jones, Lown, Wootton, Calder, Bayer, Moore, Little, Davies, Shepherd, Hood, Hobbs, Davoudianfar, Stanton, Lowe, Francis.
Statistical analysis: Lau, Gillespie, Hood, Francis.
Obtained funding: Butler, Gillespie, Calder, Bayer, Moore, Shepherd, Hood, Hobbs, Fuller, Francis.
Administrative, technical, or material support: Butler, Owen-Jones, Lown, Wootton, Bayer, Davies, Edwards, Shepherd, Davoudianfar, Rutter, Stanton, Lowe, Fuller.
Supervision: Gillespie, Owen-Jones, Calder, Moore, Little, Hood.
Other - research nurse role: Davies.

Conflict of Interest Disclosures: Dr Butler reported grants from the Efficacy and Mechanism Evaluation (EME) program, which is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), being part of a publicly funded research consortia that includes industrial partners, and funding from the NIHR Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at the University of Oxford, Oxford, UK, in partnership with Public Health England during the conduct of the study; grants from NIHR Health, the NIHR Health Technology Assessment Programme, Roche Molecular Diagnostics, NIHR Health Protection Research Unit on Health Care Associated Infections and Antimicrobial Resistance; and personal fees from Pfizer, Roche Molecular Diagnostics (advisory board participation), and Janssen Pharmaceuticals (advisory board participation) outside the submitted work; and being a salaried general medical practitioner in the Cwm Taf Morgannwg University Health Board, an NIHR senior investigator, and clinical director of the University of Oxford Primary Care and Vaccines Clinical Trials Collaboration and the NIHR Oxford Community Medical Technology and Invitro Diagnostics Co-operative. Dr Hobbs reported partial funding from the NIHR School for Primary Care Research, the NIHR Collaboration for Leadership in Health Research and Care Oxford, the NIHR Oxford Biomedical Research Centre, and the NIHR Oxford MedTech and In-Vitro Diagnostics Co-operative. Dr Gillespie reported grants from NIHR/MRC EME during the conduct of the study. Dr Owen-Jones reported grants from NIHR EME during the conduct of the study. Dr Lown reported grants from NIHR during the conduct of the study. Dr Calder reported grants from NIHR during the conduct of the study; personal fees from Chr Hansen, and nonfinancial support from Chr Hansen outside the submitted work. Dr Bayer reported grants from NIHR during the conduct of the study. Dr Moore reported grants from NIHR during the conduct of the study. Dr Shepherd reported grants from NIHR EME during the conduct of the study. Dr Hood reported grants from NIHR EME during the conduct of the study. Dr Lowe reported grants from NIHR EME and nonfinancial support from Chr Hansen during the conduct of the study. Dr Francis reported grants from NIHR/MRC EME during the conduct of the study. No other disclosures were reported.

Funding/Support: This project was funded by the EME program, which is funded by the MRC and NIHR, with contributions from Chief Scientist Office—Scotland, Health and Care Research Wales, and the Health and Social Care Research and Development Division (part of the Public Health Agency) Northern Ireland (grant 13/95/10, Probiotics to Reduce Infections in Care Home Residents [PRINCESS]). Chr Hansen provided the probiotic combination and matched placebo capsules at no cost to the study.

Role of the Funder/Sponsor: The funding and sponsoring organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. In addition, they had no right to veto publication or to control the decision regarding to which journal the paper was submitted.

Disclaimer This report presents independent research commissioned by the NIHR. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the National Health Service; the NIHR; the NIHR Evaluation, Trials, and Studies Coordinating Centre; the Health Technology Assessment program, or the Department of Health.

Additional Contributions: In addition to the authors, the PRINCESS trial team comprised the following: Katy Addison, MA, Cathy Lisles, MSc, Charlotte Scoble, HND, Sam Clarkstone, BSc, Rachael Lee, MA (Centre for Trials Research, Cardiff University); and Irene Noel, MSc, Bernadette Mundy, Diploma in Professional Studies Nursing, Belinda I'Anson, Diploma in Nurse, Johanna Cook, MSc, and Julie Allen, BA (Nuffield Department of Primary Health Care Sciences, University of Oxford). Alun Toghill and James Downs were the public and patient involvement representatives on the Trial Management Group. George Lewith, DM, of the University of Southampton, helped develop the research question, obtain the funding, and implement the study, but died during the course of the trial. The Trial Steering Committee members: Steve Iliffe, FRCGP (University College London), Glenn R. Gibson, PhD (University of Reading), Jonathan Sandoe, MD, FCRPath (University of Leeds), Meena Rafiq, MD, MBBS (University College London), Robin Willmott (general manager Millbrook Lodge Care Home), and members of the independent data monitoring committee were Stephen Bremner, PhD (Brighton and Sussex Medical School), Neil Haslam, MD, FRCP (Royal Liverpool and Broadgreen University Hospitals NHS Trust), and Matthew Ridd, PhD (University of Bristol). Two UK Clinical Research Collaboration–registered clinical trials units led study delivery: the Centre for Trials Research (receives funding from Health and Care Research Wales and Cancer Research UK, Cardiff University, and University of Oxford Primary Care and Vaccines Clinical Trials Collaboration. Jennifer Richards, BSc, and Leanne Davies, BSc, (Specialist Antimicrobial

Chemotherapy Unit, Public Health Wales at the University Hospital of Wales) processed and analyzed the microbiology samples. The following Clinical Research Networks and NHS Trusts helped identify care homes from which participants were recruited and data were collected: Yorkshire and Humber CRN (Magdalen Park Care Home and Westfield Park Care Home); West Midlands CRN (Berwood Court Care Home and Southcrest Nursing Home); Thames Valley and South Midlands CRN (Rosebank Care Home and Churchfields Care Home); Northumbria Healthcare NHS Foundation Trust (Ashington Grange Care Home and Castleview Care Home); and Derbyshire Healthcare NHS Foundation Trust (Ashbourne Lodge Care Home and Milford House Care Home). Research staff from Cwm Taf Morgannwg University Health Board carried out data collection in Greenhill Manor Care Home and Ysguborwen Care Home. All of these individuals involved in the study provided their assistance without any compensation beyond their usual salary.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Global Market Insights Inc. Probiotics Market Size to Exceed USD 64 Billion by 2023. Published 2016. Accessed October 06, 2019. https: //www.prnewswire.com/news-releases/probiotics-market-size-to-exceed-usd-64-billion-by-2023-global-market-insights-inc-578769201.html

2. Grand View Research. US Hospital and Nursing Home Probiotics Market Size, Share & Trends Analysis Report By Channel (Hospitals, Nursing Homes), by Function (Gut Health, Immunity, Wellness), and Segment Forecasts, 2018-2025. Published 2018. Accessed 06 October 2019. https://www.grandviewresearch.com/industry-analysis/us-hospital-nursing-home-probiotics-market

3. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25(5):716-729. doi:10.1038/s41591-019-0439-x

4. Ouwehand AC, Forssten S, Hibberd AA, Lyra A, Stahl B. Probiotic approach to prevent antibiotic resistance. *Ann Med*. 2016;48(4):246-255. doi:10.3109/07853890.2016.1161232

5. Wang B, Hylwka T, Smieja M, Surrette M, Bowdish DME, Loeb M. Probiotics to prevent respiratory infections in nursing homes: a pilot randomized controlled trial. *J Am Geriatr Soc*. 2018;66(7):1346-1352. doi:10.1111/jgs.15396

6. King S, Tancredi D, Lenoir-Wijnkoop I, et al. Does probiotic consumption reduce antibiotic utilization for common acute infections? a systematic review and meta-analysis. *Eur J Public Health*. 2019;29(3):494-499. doi:10.1093/eurpub/cky185

7. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. *Br J Nutr*. 2014;112(1):41-54. doi:10.1017/S0007114514000075

8. Gillespie D, Hood K, Bayer A, et al. Antibiotic prescribing and associated diarrhoea: a prospective cohort study of care home residents. *Age Ageing*. 2015;44(5):853-860. doi:10.1093/ageing/afv072

9. Vihta KD, Stoesser N, Llewelyn MJ, et al. Trends over time in *Escherichia coli* bloodstream infections, urinary tract infections, and antibiotic susceptibilities in Oxfordshire, UK, 1998-2016: a study of electronic health records. *Lancet Infect Dis*. 2018;18(10):1138-1149. doi:10.1016/S1473-3099(18)30353-0

10. Owen-Jones E, Lowe R, Lown M, et al. Protocol for a double-blind placebo-controlled trial to evaluate the efficacy of probiotics in reducing antibiotics for infection in care home residents: the Probiotics to Reduce Infections iN CarE home reSidentS (PRINCESS) trial. *BMJ Open*. 2019;9(6):e027513. doi:10.1136/bmjopen-2018-027513

11. Couzner L, Crotty M, Norman R, Ratcliffe J. A comparison of the EQ-5D-3L and ICECAP-O in an older post-acute patient population relative to the general population. *Appl Health Econ Health Policy*. 2013;11(4):415-425. doi:10.1007/s40258-013-0039-8

12. Cook JA, Julious SA, Sones W, et al. DELTA^2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. *BMJ*. 2018;363:k3750. doi:10.1136/bmj.k3750

13. van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. *Br J Gen Pract*. 2012;62(605):e801-e807. doi:10.3399/bjgp12X659268

14. Hillier S, Roberts Z, Dunstan F, Butler C, Howard A, Palmer S. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. *J Antimicrob Chemother*. 2007;60(1):92-99. doi:10.1093/jac/dkm141

15. Smieszek T, Pouwels KB, Dolk FCK, et al Potential for reducing inappropriate antibiotic prescribing in English primary care. *J Antimicrob Chemother*. 2018;73(suppl_2):ii36-ii43. doi:10.1093/jac/dkx500

16. Davies SC. Reducing inappropriate prescribing of antibiotics in English primary care: evidence and outlook. *J Antimicrob Chemother*. 2018;73(4):833-834. doi:10.1093/jac/dkx535

17. European Medicines Agency Committee for Medicinal Products for Human Use. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Published February 17, 2020. Accessed October 6, 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

18. Wachholz PA, Nunes VDS, Polachini do Valle A, Jacinto AF, Villas-Boas PJF. Effectiveness of probiotics on the occurrence of infections in older people: systematic review and meta-analysis. *Age Ageing*. 2018;47(4):527-536. doi:10.1093/ageing/afy006

19. Mañé J, Pedrosa E, Lorén V, et al. A mixture of Lactobacillus plantarum CECT 7315 and CECT 7316 enhances systemic immunity in elderly subjects: a dose-response, double-blind, placebo-controlled, randomized pilot trial. *Nutr Hosp*. 2011;26(1):228-235.

20. Van Puyenbroeck K, Hens N, Coenen S, et al. Efficacy of daily intake of Lactobacillus casei Shirota on respiratory symptoms and influenza vaccination immune response: a randomized, double-blind, placebo-controlled trial in healthy elderly nursing home residents. *Am J Clin Nutr*. 2012;95(5):1165-1171. doi:10.3945/ajcn.111.026831

21. Nagata S, Asahara T, Wang C, et al. The effectiveness of lactobacillus beverages in controlling infections among the residents of an aged care facility: a randomized placebo-controlled double-blind trial. *Ann Nutr Metab*. 2016;68(1):51-59. doi:10.1159/000442305

22. Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2013;382(9900):1249-1257. doi:10.1016/S0140-6736(13)61218-0

23. Butler CC, Duncan D, Hood K. Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea? *BMJ*. 2012;344:e682. doi:10.1136/bmj.e682

24. Suez J, Zmora N, Zilberman-Schapira G, et al Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell*. 2018;174(6):1406-1423.e1416. doi:10.1016/j.cell.2018.08.047

25. Carvour ML, Wilder SL, Ryan KL, et al. Predictors of Clostridium difficile infection and predictive impact of probiotic use in a diverse hospital-wide cohort. *Am J Infect Control*. 2019;47(1):2-8. doi:10.1016/j.ajic.2018.07.014