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UTILITY OF PROBIOTICS FOR MAINTENANCE OR IMPROVEMENT OF HEALTH STATUS IN OLDER PEOPLE – A SCOPING REVIEW

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Abstract: *Objective:* To evaluate the available evidence on probiotic use in older adults from human studies. *Design:* systematic review. *Methods:* The databases Embase, CINAHL and Medline were searched in December of 2017 for studies in humans where probiotics were used to modify a health outcome in older people. The quality of studies was evaluated using the Critical Appraisal Skills Program (CASP) assessment tool and the Cochrane Risk of Bias Assessment tool. *Participants:* Subjects aged over sixty years either through specified selection criteria or where the mean participant age was greater than sixty. *Interventions:* Probiotic supplements. *Measurements:* Pre-specified clinically measurable health outcomes in age related conditions. *Results:* 1210 articles were identified. After quality assessment and selection criteria were applied, 33 articles were identified to be included for review. As these studies cover a variety of applications and used customised protocols accordingly, meta-analysis was not possible and synthesis is in narrative form. *Conclusions:* A growing body of research has applied commercially available probiotic preparations across care settings for age related conditions including gut dysmotility, osteoporosis, common infectious diseases and cognitive impairment. Although methodologies vary, randomised controlled trials have reproduced results in these areas, and so warrant consideration of probiotics as a low risk adjuvant treatment for specific indications in the elderly.

Key words: Human, elderly, older person, probiotic, health.

Introduction

Normal ageing is associated with homeostenosis, or narrowing of the physiological reserve, in any organ system. In the immune system, this manifests as the phenomenon of immunosenesence. Decreased cellularity of bone marrow has the effect of a reduction in major cell populations, which comprise the adaptive immune system. Mature lymphocytes show a lesser degree of diversity and lower proliferative response to stimulation (1). There is a higher level of background activation of the innate immune system. In what may be a compensatory mechanism in response to decreased lymphocyte activity, there is an attenuated response to antigen challenges as well as in response to cellular damage (2).

The gastrointestinal tract is subject to physiological changes with age, impacting its essential functions in nutrient absorption and immune defence (3). A loss of CD4+ T-cells brings with it persistent activation of innate immunity and potentially dysfunctional immunosenesence (4). The gut microbiota also provides a range of ecological, metabolic and immunomodulatory functionalities that contribute to host health (5). Notably, the composition of the elderly gut microbiota differs from that of young adults and these changes are coincident with the onset of old age (3, 6, 7). In this setting, the gut microbiome composition is more heavily influenced by environmental factors such as diet and antibiotic use than in young adult life (8). Considering the critical role of the gut microbiota in influencing host health through its interaction the gut epithelium and immune system at this site (9) the risk for age onset health consequences could be potentially be ameliorated by modulating the structure-function activity of the microbiota.

The public widely consumes Probiotic-based interventions (5). Probiotics, as defined by the World Health Organisation, are live microbes that confer a health benefit to the host when administered in sufficient doses (10). The most common strains are typically affiliated with the genera *Lactobacillus* and *Bifidobacterium*.

Animal studies have shown significant effects in using probiotics in aged animal models, modulating inflammation and oxidative stress and this work has elucidated complex host-microbe interactions behind these effects (11-13). As several recent review articles cover the effect on various biochemical, serological and microbiological effects of probiotic use (14-16), this review reports on translational studies to date where clinical outcome measures are available.

Key areas where human studies are available include prevention of common infectious diseases, reduction of in-hospital complications including perioperative complications and improvement of gut function. This review examines the evidence from these studies to highlight the clinical conditions across care settings where probiotic supplementation have been studied for potential utility.

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Table 1
Inclusion and Exclusion Criteria

	Included	Excluded
Publication type	Published in peer review journal	Review
	Full text in English	Editorial
		Conference abstract
		'Grey' literature
Study design	Experimental design	Observational study
	Human study	Case series
	Using probiotics	Case report
		Animal study, in vitro study
Population	Mean age > 60 years	Mean age <60 years
Outcome measure	Clinically measurable health metric	Serology or microbiology results only, without direct clinical correlate

Methods

Search Strategy

Embase, CINAHL and Medline databases were searched in December 2017 for articles published in peer review journals between 2007 and 2017. Search terms used were elder, older people, older person, ageing, geriatr*, gerontol* or frail* AND probiotic*. Review articles, editorials and conference presentations were excluded. Titles were screened for relevance before review at an abstract level according to inclusion and exclusion criteria (see Table 1).

The Critical Appraisal Skills Program (CASP) assessment tool produced by the Institute for Health Sciences, Oxford(17), for randomised controlled trials was used to evaluate the quality of included studies at abstract level and the Cochrane Risk of Bias tool was used to further evaluate studies selected for full text review.

Data extraction was systematic including, study design, number of participants, intervention, outcome measures, and direction of change (increase, decrease or no change).

Results

The literature search identified 1210 articles and 66 duplicate articles were removed. After application of the inclusion and exclusion criteria, sixty articles were reviewed in full. On full-text review articles were further excluded where they did not have an experimental study design, did not measure clinical outcomes, or where the mean age of the cohort was less than sixty years. The remaining thirty-three studies were included for review. The variety of investigational product and treatment protocols prohibited meta-analysis. Furthermore, although studies may list the same clinical outcome, such as diarrhoea or constipation, the definition of these terms varied between study protocols and this likely influenced the overall result. Therefore these studies have been compared in a narrative discussion.

Ambulatory care

Interventions focused on community-dwelling older adults with probiotic supplementation have targeted use as a preventative health strategy. Nine studies were identified investigating applications in bone health, the metabolic syndrome, prevention of infection and cognition.

Common infectious diseases. Investigation into the microbiome's role in immune function has lead researchers to translate this role to prevention of common infectious diseases.

Two large double blind randomised placebo controlled trials demonstrated favourable results for long-term administration (>5 months) on prevention of infection. Shinkai and colleagues enrolled 300 participants into three arms: a placebo group, low dose (2 x 109 cells), and high dose (2 x 1010) *Lactobacillus pentosus* for twenty weeks. Participants demonstrated a dose-dependent decrease in incidence of the common cold corresponding to improved health perception (18). Guillemard et al conducted a randomised controlled trial of 1072 community dwelling adults with a mean age of 76. They administered Actimel (*Lactobacillus casei* 1010 colony forming units, *Streptococcus thermophilus* and *Lactobacillus delbrueckii subsp. Bulgaricus* 109 colony forming units) for three months and observed a significantly reduced duration but not incidence of upper respiratory tract infection in this time, with mean duration of illness being 7.4 days in the treatment group compared to 9.8 days in controls with cumulative duration of illness over the treatment period being 9.1 days in the treatment group versus 21.1 days in controls (19). A lower intensity regime where an intervention group took *Bacillus subtilis* for ten days before an eighteen-day break for four cycles showed no change in the rate or duration of common infectious diseases (20). Taken together these results indicate that effect in prevention of common infectious diseases including the common cold is likely dose-dependent with the strongest signal being in high dose treatment for five consecutive months.

In prevention of recurrent urinary tract infection, a salient

Table 2
Ambulatory Care

Author/Year	Design	Investigational Product	Population	Outcome Measure	Direction of Change
Barreto 2014	Case-control n=24	*Lactobacillus plantarum*	Postmenopausal women with metabolic syndrome	HOMA-IR Waist circumference, systolic/ diastolic BP	↓ (-)
Beerepoot 2012	Double blind non-inferiority trial n=252	*Lactobacillus rhamnosus, Lactobacillus reuteri*	Women with recurrent urinary tract infection	Mean symptomatic UTI Antibiotic resistance	↓ ↓
Benton 2007	Randomised double-blind placebo controlled trial n=124	*Lactobacillus casei Shirota strain* (Yakult)	Community dwelling adults	Mood Memory Verbal fluency	(-) (-) (-)
Guillemard 2010	Randomised, double blind controlled parallel study n=1072	*Lactobacillus casei*	Community dwelling adults	Incidence of CID Duration of CID Cumulative duration	(-) ↓ ↓
Lefevre 2015	Randomised double-blind placebo controlled trial n=100	*Bacillus subtilis*	Community dwelling adults	Frequency of CID Duration of CID Intensity of CID	(-) (-) (-)
Lei 2016	Randmosed double blind placebo controlled trial, n=417	*Lactobacillus casei Shirota strain* (Yakult)	Patients aged over 60 years with distal radius fracture	Functional recovery: disability of the arm, shoulder and hip (DASH) score	↑
Makino 2010	Meta-analysis of two studies	*Lactobacillus bulgaricus*	Community dwelling adults	Incidence of common cold	↓
Shinkai 2013	Randomised double blind placebo controlled trial, n=300 parallel arms (placebo, low dose and high dose)	*Lactobacillus pentosus*	Community dwelling adults > 65 years	Incidence of common cold Overall health related quality of life (SF-36) Health perception subset	↓ ↓ (-) ↑ in high dose group
Valentini Neto 2013	Randomised double blind placebo controlled trial, n=17	*Fructooligossacarides, Lactobacillus paracasei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium lactis*	Community dwelling adults aged 60 to 75 years	Body composition (skin folds, waist circumference, calf circumference)	(-)

study in 2012 enrolled 252 post-menopausal women who had on average 7 urinary tract infections in the previous year. After twelve months treatment with *Lactobacillus reuteri* participants had an average of 3.3 urinary tract infections compared to 2.9 in those treated with trimethoprim-sulfamethoxasole. Although this did not meet predefined non-inferiority criteria, of note was the major difference in antibiotic resistance of faecal E. coli: after one month of antibiotic prophylaxis resistance to trimethoprim and ampicillin rose from 20-40% of colony forming units to 80-95% where no change occurred in the treatment group (21).

Metabolic syndrome

The metabolic syndrome, as defined by the cluster of cardiovascular risk factors including excess abdominal adiposity, hyperlipidaemia, hypertension and elevated blood glucose, is more prevalent with age. In a case-control study (n=24) of post-menopausal women with metabolic syndrome, consumption of *Lactobacillus plantarum* resulted in decreased blood glucose, homocysteine and LDL cholesterol levels but no change in waist circumference or blood pressure (22). In another study (n=17) consumption of a Synbiotic (both a pre and probiotic) for three-months did not affect any change in body composition compared to controls (23). As yet, there are no reports of whether change in serological markers might reduce cardiovascular disease.

Osteoporosis

A key health determinant in older age is osteoporosis and fragility fractures. Based on earlier work in animal studies, Lei et al., (24) examined the impact of probiotic consumption on functional recovery after distal radius fracture. Four hundred and seventeen participants underwent a six-month course of treatment with *Lactobacillus casei* (Yakult) in conjunction with outpatient therapy. In the treatment group, functional recovery occurred earlier with performance at three months being equivalent to the control group at six months.

Cognition

Benton et al., (25) examined whether a probiotic could improve mood and cognitive performance in an elderly population (mean age 61.8 years). Here, 124 participants were randomised to placebo or a fermented milk drink of *Lactobacillus casei* (Yakult) as part of a three-week intervention. No significant group differences were reported following cognitive assessment using metrics of episodic memory, long-term recall and verbal fluency with mood assessed on visual analogue scales. There was a trend toward

Table 3
Inpatient Care

Author/Year	Design	Investigational Product	Population	Outcome Measure	Direction of Change
Akatsu 2013	Double blind, randomised controlled trial, n=45	*Bifidobacterium longum*	Enterally fed inpatients > 65 years	Body temperature Bowel motion form and frequency	(-) (-)
Allen 2013	Double blind, randomised placebo controlled trial n=2981	*Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium bifidum*	Inpatients > 65 years exposed to parenteral antibiotics	Antibiotic associated diarrhoea Clostridium difficile diarrhoea	(-) (-)
Dietrich 2014	Observational pilot study n=257	*Lactobacillus casei* (Actimel)	Inpatients exposed to antibiotics, mean age 70.8 years	Antibiotic associated diarrhoea Duration of diarrhoea	↓
Dietrich 2014	Randomised open label study	*Lactobacillus casei* (Actimel versus Yakult)	Inpatients exposed to antibiotics, mean age 70.8 years	Antibiotic associated diarrhoea Duration of diarrhoea	(-) ↓
Fukushima 2007	Double blind, randomised controlled trial n= 24	*Lactobacillus johnsonii*	Enterally fed inpatients > 70 years	Body temperature Duration of infection Stool form and frequency	(-) ↓ (-)
Hickson 2007	Randomised double blind, placebo controlled trial n=135	*Lactobacillus casei, Lactobacillus bulgaricus, Streptoccocus thermophiles* (Actimel)	Inpatients over 50 years (mean age 70.7) exposed to antibiotics	Incidence of antibiotic associated diarrhoea Incidence of clostridium difficile diarrhoea	↓ ↓
Mallina 2017	Clinical trial with historical control n= 105 in intervention	*Lactobacillus casei, Lactobacillus bulgaricus, Streptoccocus thermophiles* (Actimel)	Patients over 70 years undergoing surgery for hip fracture with > 3 days antibiotic exposure	Antibiotic associated diarrhoea Clostridium difficile diarrhoea	(-) (-)
Song 2010	Randomised placebo controlled trial n=214	*Lactobacillus rhamnosus* (Lacidofil)	Patients admitted with respiratory infection treated with antibiotics, mean age 61	Antibiotic associated diarrhoea	(-)
Wright 2015	Randomised placebo-controlled trial n=87	*Lactobacillus casei Shirota strain* (Yakult)	Patients over 60 years admitted to subacute geriatric unit	Incidence of diarrhoea Duration of diarrhoea Prescription of aperients	(-) (-) (-)
Zaharoni 2011	Randomised double blind placebo controlled trial, n= 243	*L. plantarum, L. paracasei, L. bulgaricus, L. acidophilus, B. breve, B. longum, B. infantis, S. thermophiles* (VSL#3)	Patients > 65 years admitted to an orthopaedic rehabilitation unit	Incidence of constipation Use of laxatives > 1 day Incidence of diarrhoea	(-) ↓ (-)

the most depressed participants improving in mood, which did not reach statistical significance, and without direct comparison to a control group of depressed individuals it would be unclear how much of this could relate to other trial related factors such as intensive follow up (25).

Inpatient care

Sixteen studies applied probiotics in the inpatient care setting. One of the first applications to emerge as a therapeutic target was in prevention of antibiotic-associated diarrhoea. More recently a number of regimes have been trialled for potential effect on gut epithelial function applied to recovery after gastrointestinal surgery, measuring recovery of bowel function and incidence of postoperative infection.

Antibiotic-associated diarrhoea

The potential for probiotics to mitigate the effects of antibiotic associated diarrhoea has lead to a number of randomised, placebo-controlled trials in this area. Here, six studies were examined where the mean age of participants was over sixty years. Overall, results have been positive in studies where the incidence of antibiotic associated diarrhoea were high and this is likely attributable to study design.

Hickson and colleagues in 2007 performed a randomised, double blinded placebo-controlled trial of 135 hospitalised inpatients with a mean age of 74 years. They employed a multi-species probiotic drink for their intervention containing *Lactobacillus casei, L bulgaricus*, and *Streptococcus thermophilus*. Measures of both incidence of diarrhea (as defined by protocol criteria for stool frequency, volume and consistency) and *Clostridium difficile* infection were reported. The study found a difference in antibiotic associated diarrhea (12% compared to 34%) as well as *C. difficile* associated diarrhea (none in the treatment group compared to 17% in controls) with an overall number needed to treat to prevent diarrhea of 5 (26). Song and colleagues also performed a randomized, double-blinded placebo-controlled trial in 214 patients being treated as inpatients for respiratory tract infection with intravenous antibiotics. The treatment group was administered *Lactobacillus rhamnosus* and *Lactobacillus acidophilus*. The incidence of antibiotic associated diarrhea was not significantly different between groups however the treatment group had improved stool consistency and frequency compared to controls (27). Several more recent studies showed

Table 4
Perioperative care

Author/Year	Design	Investigational Product	Population	Outcome Measure	Direction of Change
Horvat 2010	Double blind placebo controlled trial, n=68 with parallel arms of prebiotic, symbiotic and placebo	*Pediacoccus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei subsp. Paracasei, Lactobacil- lus plantarum plus* prebiotic plant fibers (Synbiotic 2000)	Patients admitted for abdominal surgery for adenocarcinoma, mean age 62-65 years	Days to first flatus Days to first stool	(-) (-)
Liu 2011	Randomised double blind placebo controlled trial, n=114	*Lactobacillus plantarum, lactobacillus acidophilus, bifidobacterium longum*	Patients undergoing colectomy for colorectal carcinoma, mean age 65 years	Postoperative infection Surgical site infection Duration of antibiotics Time to first defecation Incidence of diarrhoea Time on fluid vs solid diet	↓ (-) ↓ ↓ ↓ (-)
Mitsuyoshi 2013	Randomised double blind placebo controlled trial, n=48	*Lactobacillus casei Shirota strain* (Yakult)	Patients over 70 years undergoing surgery for gastrointestinal or hepato-biliary cancers	Any infectious complication Bacteraemia	(-) (-)
Pellino 2013	Randomised double blind placebo controlled trial, n=18	*L. plantarum, L. paracasei, L. bulgaricus, L. acidophilus, B. breve, B. longum, B. infantis, S. thermophiles* (VSL#3)	Patients over 70 years undergoing laparoscopic colectomy for colorectal cancer	Stool frequency Social functioning	↓ ↑
Yang 2016	Randomised double blind placebo controlled trial, n=60	*Bifidobacterium longum, Lactobacillus acidophilus, Enterococcus faecalis* (Bifico)	Patients undergoing surgery for colorectal cancer, mean age 63 years	Days to first flatus Days to first defecation Time on fluid vs solid diet Duration of pyrexia Length of antibiotic therapy	↓ ↓ (-) (-) (-)
Zhang 2012	Randomised double blind placebo controlled trial, n=60	*Bifidobacterium longum, Lactobacillus acidophilus, Enterococcus faecalis*	Patients for radical resection of colorectal cancer, mean age 64.65 years	Total postoperative infective complications Bacteraemia	↓ ↓

no difference between incidences of antibiotic associated diarrhea for *Clostridium difficile* diarrhea in hospitalized inpatients (28-30). In each of these studies the authors noted the incidence of antibiotic associated diarrhea was significantly lower than in the earlier study by Hickson et al (26). This may reflect change in antibiotic prescribing practice in the intervening time as well as the fact that enrollment was not targeted at patients admitted for an infection requiring antibiotics. This raises the possibility that treatment related risk factors for antibiotic associated diarrhea might identify patients who could benefit from probiotics however more research is required to address this question.

Treatment of constipation

Maintenance of regular bowel habit remains a daily task in hospital-based care of the elderly. Although probiotics have been explored in this group to relieve constipation and maintain regularity of bowel habit, results have showed no major change when compared to placebo although trends toward improved stool form and reduced use of laxatives have been reported (30-33). This contrasts with studies in younger adults and older adults in residential aged care, most likely due to the multifactorial nature of gut dysmotility in the acute hospital setting.

Recovery of gut function after surgery

Clinical trials have replicated results showing that a short course of probiotic therapy can impact gut function after surgery however these studies are small in scale. No gold standard perioperative regime is available at present and studies to date have used a variety of multi-species probiotic preparations with or without a prebiotic ingredient. Four studies enrolling a total of 260 participants were identified.

VSL#3 was used by Pellino and colleagues in a double-blind, placebo-controlled trial of patients over 70 years undergoing elective colorectal surgery. The treatment group received the multispecies probiotic supplement for four weeks. Stool diary showed fewer bowel motions in the treatment group compared to placebo and this corresponded to improved social functioning on the SF-36 quality of life scale, which was statistically significant. Though numbers were small (n=18) these results were borne out whether the ileocecal valve was spared or not (34).

Bifico, which contains *Enterococcus faecalis*, *Bifidobacterium longum* and *Lactobacillus acidophilus*, has also been trialled in the perioperative setting. Yang and colleagues found that with pre-treatment of five days followed by seven days post-operative treatment recovery of bowel function improved. Days to first flatus (3.27 vs. 3.66) and first bowel movement (3.87 vs. 4.53) were significantly reduced in the treatment group and incidence of diarrhoea was lower (each with a p-value of <0.05). There was no significant change in

Table 5
Residential Aged Care

Author/Year	Design	Investigational Product	Population	Outcome Measure	Direction of Change
Akbari 2016	Randomised double blind placebo controlled trial, n=60	*Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum*	Aged care residents with Alzheimer's dementia	Change in MMSE after three months	↑
An 2010	Clinical trial comparing treatment to lead-in control period, n=19	*Lactobacillus acidophilus, Pediococcus pentosaceus, Bifidobacterium longum*	Aged care residents with chronic constipation	Stool frequency and form	(-)
Fonolla 2017	Ransomised double blind placebo controlled trial, n=98	*Lactobacillus coryniformis*	Aged care residents receiving seasonal influenza vaccine	Symptoms of respiratory tract infection Incidence of influenza-like illness	↓ ↓
Kraft-Bodi 2015	Randomised double blind placebo controlled trial, n=174	*Lactobacillus reuteri*	Denture wearing aged care residents	High candida count on plaque Gingivitis Plaque level	↓ (-) (-)
Nagata 2011	Case-control study, n=77	*Lactobacillus casei Shirota* (Yakult)	Aged care residents in facilities affected by a norovirus outbreak	Transmission of norovirus Duration of fever	(-) ↓
Nagata 2016	Randomised double blind placebo controlled trial, n=88	*Lactobacillus casei Shirota (Yakult)*	Aged care residents	Days with fever Incidence of constipation Incidence of diarrhoea	↓ ↓ ↓ at 3 months, no change by 6 months
Van Den Nieuwboer 2015	Clinical trial with lead-in control period, n=44	*Lactobacillus casei Shirota* (Yakult)	Aged care residents	Frequency of bowel movement Percentage of ideal stool type Incidence of diarrhoea	(-) ↑ ↓
Van Puyenbroeck 2012	Randomised double blind placebo controlled trial, n=737	*Lactobacillus casei Shirota* (Yakult)	Aged care residents receiving seasonal influenza vaccine	Days with respiratory symptoms Incidence of severe respiratory tract infection	(-) (-)

surgical site infection or hospital acquired infection (35). Liu et al reported similar outcomes using a multispecies preparation containing *Lactobacillus plantarum, Lactobacillus acidophilus and Lactobacillus longum*. Patients in the treatment arm had a shorter time to defecation, lower incidence of diarrhoea, less cramping and abdominal distension as well as shorter duration of pyrexia where any infection did occur (36). One contrary study using a synbiotic preparation showed no change (37) but overall the direction of results appears to be positive.

Postoperative infection

Three studies examined the incidence of postoperative infection after gastrointestinal surgery. Zhang et al found that postoperative infections were reduced from 33.3% in controls to 10% in the treatment group following a three-day preoperative course of a multispecies preparation (n=60, p=0.05)(38). In periampullary neoplasms, a similar reduction in infection rate lead to a difference in mortality of 26% in controls versus zero in the treatment group (p=0.02) (39). Mitsoyushi et al. used Biolactis powder (Yakult, containing *Lactobacillus casei* and *Bifidobacterium breve* plus prebiotic galacto-oligosaccharides) and reported that postoperative infectious complications were 12% in the treatment group versus 36% in controls, which fell short of statistical significance (p=0.06) but was suggestive of a significant clinical effect (40). Of note, none of the studies reviewed in full that utilised probiotics in the perioperative setting reported serious adverse events related to their use.

Residential aged care

Residents of aged care facilities generally represent an older and frailer population than is typically represented in clinical trials. Conducting trials in this population can be challenging due to ethical considerations in obtaining informed consent as well as results being confounded by a higher rate of multimorbidity. As such, this review has included open label studies with a lead-in control period and one case-control study.

Treatment of constipation

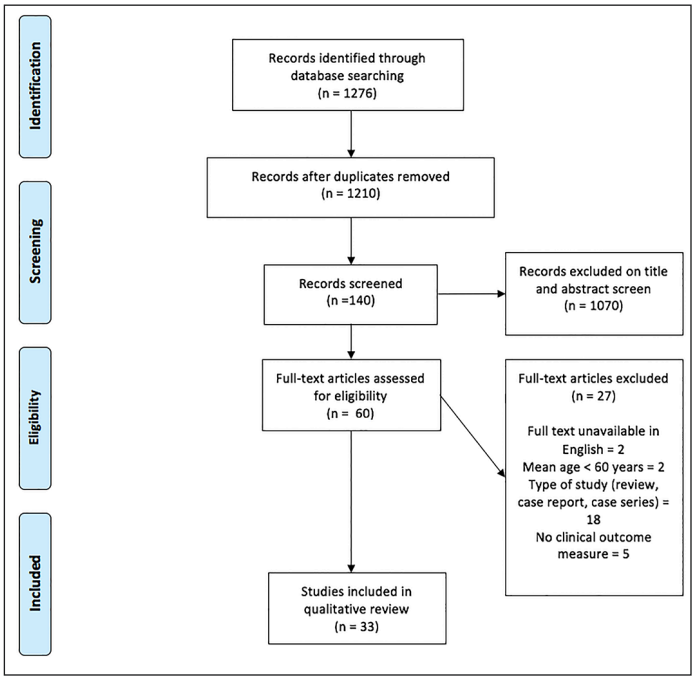
Two open label studies have examined the effect of probiotics in relief of constipation. Van Den Nieuwboer et al enrolled 135 participants that kept a stool diary for three weeks leading up to treatment with *Lactobacillus casei* Shirota strain (Yakult), and then throughout the treatment period of three weeks. Only 44 participants of 135 had completed data for analysis, but this number was enough to show an increased proportion of ideal stool types and decrease in constipation in this period (p=0.01)(41). The major cited by the authors for incomplete data were that subjects who were normally assisted

to toilet, allowing nursing staff to record stool frequency, had been toileting themselves (an everyday pitfall in bowel management of the elderly). A similarly designed study of 19 aged care residents showed an increase in stool frequency but without reaching statistical significance (42).

Oral candidiasis

Another application has been in prevention of oral candidiasis through competitive inhibition with non-invasive probiotic strains. Here, a study using multispecies Lactobacillus supplements have shown decreased incidence of Candida spp. isolation from saliva (16% in treatment versus 92% in placebo) however there was no change in visible plague or gingivitis (43). The investigators hypothesized that lower candida growth may still lead to lower rates of opportunistic infection though this was not directly answered by the study.

Figure 1
PRISMA Flow Diagram



Common infectious diseases

Residents of residential aged care facilities are susceptible to transmission of infectious diseases through the nature of shared living facilities and carer contact. A case-control study of 77 residents of an aged care facility during a norovirus outbreak using *Lactobacillus casei* Shirota strain (Yakult) showed no change in the rate of transmission but a reduction in duration of febrile illness from 2.9 days in controls to 1.5 days in the treatment group ($p < 0.05$) (44). Following this, investigators conducted a randomised controlled trial also using Yakult in 72 aged care residents measuring days with fever and days with diarrhoea over six months showing a reduction in febrile days and a decrease in diarrhoea at three months though this was not borne out at six months (45).

Separately, Fonolla and colleagues found a significant decrease in respiratory tract infection and influenza-like illness. Ninety-eight residents of an aged care facility were randomised to placebo or treatment with *Lactobacillus coryniformis* from two weeks prior to seasonal influenza vaccine. The primary outcome was seroconversion, which was significantly improved in the treatment group, corresponding with a statistically significant reduction in incidence of respiratory symptoms ($p=0.007$) and consumption of analgesics ($p=0.008$) over the five-month follow-up period (46). In contrast, using *Lactobacillus casei* Shirota strain (Yakult) in 737 aged care residents, Van Puyenbroeck et al showed no difference after three weeks treatment before seasonal influenza vaccine when measuring days with respiratory symptoms or incidence of severe respiratory tract infection (46, 47). A limitation of both these studies is that information is not available on the incidence of confirmed influenza or the genotype to know if the seasonal vaccine afforded immunity in the trial period and so a conclusion on the impact of probiotics on influenza in residential aged care cannot be drawn at this stage.

Cognition in dementia

The potential impact of probiotic treatments on cognitive function is discussed to a disproportionate degree relative to the available clinical evidence. Only one study was identified directly examining the efficacy of a multispecies probiotic supplement in aged care residents with Alzheimer's dementia. Akbari et al enrolled 60 aged care residents with an average baseline mini-mental state exam score of 8.47 in controls and 8.67 in the treatment group. The average score in the treatment group was 10.57 at the end of three months where the controls had declined on average to a score of 8.00 ($p=0.01$) (48).

Discussion

In this scoping review, we found evidence that probiotics have been investigated in relation to gut and immune system function across a range of care settings.

Probiotics in the prevention of common infectious disease when provided long term (>5 months) reduced the duration and frequency of symptoms. This effect is seen most clearly in institutional settings amongst the oldest cohorts corresponding to what is already known of the ageing immune system, with the decline in adaptive immune response seen from the seventh decade onwards (49) which coincides with restriction of gut microbiome species(3, 50). In prophylaxis against urinary tract infection the reduction seen in incidence of symptomatic infection without long-term antibiotics conveyed the additional benefit of significantly less antibiotic resistance.

In osteoporosis treatment the benefit in calcium absorption and osteogenesis demonstrated in animal models (51, 52) has translated into clinically significant results. Earlier recovery of upper limb fracture shows this effect can result in improved functional status. There is theoretical appeal in improving

bone density through stimulation of endogenous pathways for osteogenesis given the long-term pitfalls of anti-resorptive therapy where density can come at the expense of tensile strength (53, 54).

Not measured in individual studies but of interest from an individual patient perspective are the indirect effects of reducing the burden of common illnesses amongst the elderly population. Where an upper limb fracture occurs in a dominant arm or the patient is dependent on upper limb weight bearing for mobility this improvement could have a significant impact on an individual's function. The same could be said for when respiratory or urinary tract infection precipitate delirium in an individual. In essence, where the physiology of ageing creates homeostenosis, a demonstrated reduction in the frequency and duration of common or predictable physiological stressors may be of benefit in maintaining overall health status.

Mood and cognition have been examined as therapeutic targets, per the idea of the "gut-brain-axis" but this concept remains largely a theoretical one at this stage (55). Discussion and reviews abound which comment on potential molecular mechanisms for this but clinical trials are lacking. In the one clinical trial identified, the effect did reach statistical significance. Like many other interventions in this area, results may be interpreted in two ways. It could be argued that the change from a score of 8.67 to 10.57 would be unlikely to improve a patient's quality of life. Conversely, when compared to deterioration in the same amount of time or added to a multifaceted treatment plan this change could be seen as clinically significant. As always, an individual approach is required but it appears that probiotics may have a role in supportive care of patients with Alzheimer's dementia.

In an inpatient context numerous factors combine to impair gut function. Immobility, polypharmacy, changes in diet, exposure to antibiotics and gastrointestinal surgery all contribute to disturbance in gut motility and epithelial function (56-58). This arena shows the greatest diversity in research methodologies when it comes to implementation of probiotics. More recent studies in the use of probiotics for prevention of antibiotic associated diarrhoea showed no significant difference and that may be owing to the decreased incidence in more recent cohorts, possibly related to changes in prescribing practice over the last ten years.

Several multispecies strains have been implemented in the management of patients undergoing gastrointestinal surgery. Here it appears there is an earlier recovery of gut function after surgery with improvement in indicators of motility such as time to first flatus and defecation. Potentially corresponding to benefit in maintenance of gut epithelial function, probiotic use was shown to reduce postoperative infection. Importantly, despite probiotics commencing prior to surgery and continuing in the early postoperative period in most protocols there were no reported incidence of bacteraemia caused by probiotic strains, nor any serious adverse events related to probiotics.

Studies to date have effectively linked modulation of the gut microbiome to specific indications. While work continues into the mechanisms behind these effects, translational work in older populations is beginning to add information on relevant patient-centred outcomes. A future direction for research that might lend further clarity to results is relating the observed effects to the baseline characteristics of the host. Typically in studies of older populations an arbitrary age group of participants over sixty or sixty-five years is chosen for pragmatic reasons but this cohort can have greater physiologic heterogeneity compared to healthy young adults. Patient characteristics such as the level of background inflammation, age, nutritional status and frailty status have the potential to answer whether certain conditions have an impact on effect size and improve generalizability to specific populations.

This review covers translational research from the last ten years where probiotics have been trialled in humans. There exists a large body of grey literature in this area, which was excluded from review, as were articles where the full text was not available in English. Due to the array of methodologies used, including within the same clinical application, meta-analysis could not be performed.

Conclusion

There is a clinical need in the care of the elderly for interventions that can impact on morbidity and quality of life with low treatment burden. Probiotics have thus garnered significant research interest. As a preventative intervention, probiotics have the benefit of low cost, ease of administration, widespread availability and tolerability.

Studies have implemented a range of protocols and no standard model for intervention exists currently. In future it is possible that probiotic interventions are tailored to the indication, patient age or even individualised. However, a range of commercially available products is available with corresponding randomised controlled trials to inform clinicians though the size of these studies remains small. Where goals of care to minimise treatment burden in an individual or vulnerability exists to exposures in a healthcare or institutional setting, there is plausibly scope to consider probiotics as an adjuvant treatment in older patients for certain conditions.

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