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SYSTEMATIC REVIEW

Effectiveness of probiotics on the occurrence of infections in older people: systematic review and meta-analysis

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Abstract

Background: infectious diseases in older people are associated with higher mortality rates and probiotics have been hypothesised to reduce the occurrence of infection.
Objectives: to assess the effectiveness and safety of probiotics in the occurrence of infections in older adults in comparison to placebo.
Methods: a systematic review and meta-analysis of randomised placebo-controlled trials were conducted on 30 December 2016 using Medline, Embase, CENTRAL, Web of Science and LILACS databases. Efficacy outcomes were: occurrence of infection, quality of life, mortality and mean duration of infection per episode. Safety outcomes were adverse events. Data were analysed using relative risk ratios with 95% confidence intervals. Relative risk ratios were pooled where more than three estimates were available.
Results: fifteen articles were included, with a total of 5,916 participants with a mean age of 75.21 years. The effect of probiotics was not significantly different from that reported for placebo on the occurrence of infection, adverse events, mortality or mean duration of infection episodes (relative risk (RR) 0.90, 95% confidence interval (CI) 0.76 to 1.08; RR 1.01, 95% CI 0.91 to 1.12; RR 1.09, 95% CI 0.70 to 1.72; MD −0.35, 95% CI −1.57 to 0.87, respectively).
Conclusion: the current low-quality evidence does not support the use of probiotics for the reduction in the occurrence of infection in older adults, however, the safety outcomes were similar between probiotics and placebo. Further research is required to confirm these findings.

PROSPERO: CRD42014013707

Keywords: *probiotics, aged, aged 80 and over, infection, systematic review, older people*

Background

Infectious diseases (ID) in older people are more frequent, usually more severe, and associated with higher mortality rates and functional impairment than in younger adults [1]. There were more than 21 million infection-related hospitalisations among older US patients between 1990 and 2002, with an upward trend in hospitalisation rates related to increasing admissions of patients older than 75 years old [2]. The burden of ID on older adult visits to US emergency departments in 2011–12 was higher than the rates observed for myocardial infarction and congestive heart failure combined [3].

The prevention of ID in older people is generally confined to adherence to immunisation, sanitation and hygiene measures. Probiotics are live microorganisms, usually sold as dietary supplements, which, when administered in adequate amounts, confer a health benefit on the host. They are thought to modulate immune functions through interaction with lymphoid and epithelial gut cells, competitive exclusion and production of anti-microorganism metabolites [4, 5]. Probiotics

are often used in older patients for the prevention of non-infectious diarrhoea secondary to antibiotics, and to reduce the occurrence of *Clostridium difficille*-associated diarrhoea (CDD). In fact, the role of probiotics in the occurrence of other IDs has been extensively studied in a younger population [6, 7].

Randomised clinical trials (RCT) and systematic reviews (SR) have consistently found benefits related to probiotic consumption on the occurrence, duration and severity of ID in paediatric patients when compared to placebo [5–7]. Although age-related immunosenescence is associated with higher ID rates in older patients [8], the effectiveness of probiotics on the prevention of infection in older age groups remains controversial [9–15]. A SR recently found no evidence of the benefit of probiotics in reducing the incidence of CDD in older people, but the authors only included hospitalised patients from five studies [16].

The purpose of this SR was to assess the effectiveness and safety of probiotics in the occurrence of infections in older adults in comparison to placebo.

Methods

Criteria for considering studies for this review

The review protocol was registered on PROSPERO (CRD42014013707) and has been previously published [17]. The review complied with the recommendations of the *Methodological Expectations of Cochrane Interventions Reviews*, and with the principles of the *PRISMA* statement.

Only RCTs were included, observational designs and non-standard experimental designs (such as cluster and crossover RCTs) were not considered.

The studies must have recruited people aged 65 years or older, regardless of sex, comorbidities or functional or cognitive status. In studies conducted with mixed populations (individuals under and over 65 years), only data relevant to the older group were included whenever possible. Individuals could be living in the community or in long-term care units, with no clinical or laboratory signs nor diagnosis of infection at baseline. Participants could be hospitalised at recruitment, but patients that developed nosocomial infections were excluded. When data were not available, the authors were contacted for additional information.

As the pattern and severity of ID in subgroups of older people that are critically ill and immunosuppressed or experiencing oncologic and post-operative conditions may be substantially different and heterogeneous, these studies were excluded from this analysis.

Any intervention that involved specific and identified probiotic strains at an effective dose regimen (at least 10^7 colony-forming units/gram) [17] was acceptable. Interventions could involve single or multiple strains, using single or multiple doses, alone or in combination with prebiotics, any duration of treatment and commercially available preparations or compound products were acceptable. Only placebo comparators were considered, studies that used other pharmacological interventions or no intervention for comparison were not considered. Studies where other drugs were administered prior to randomisation were considered eligible. For studies with two or more active arms, only data relevant to the highest intervention dose were included.

Studies were included if they reported at least one of the following outcome measures:

- **Primary outcomes**: Occurrence of infection; incidence of adverse events; mortality; quality of life.
- **Secondary outcomes**: Duration of episodes of infection; occurrence of visits to emergency departments; occurrence of antibiotic use; duration of antibiotic treatment; occurrence of hospitalisation; duration of hospitalisation.

Search methods for identification of studies

This review aimed to identify all relevant studies, regardless of language, publication period or status. The electronic search was conducted by the first author (PAW), while searches for unpublished trials, reference lists and grey literature were performed by two authors (PAW, PJFVB). Specially designed and tested search filters were used to identify RCTs in Medline [18]. The full search strategy composed of the following terms (and their main synonyms): aged; aged 80 and over; probiotics; *lactobacillus*; *lactococcus*; *bifidobacterium*; *enterococcus*; *streptococcus*; *saccharomyces* and infection prevention, as shown in the appendices. The following databases were searched on 30 December 2016:

- Cochrane Central Register of Controlled Trials (CENTRAL, 2016, issue 12)
- Medline (Pubmed), 1946-onwards
- EMBASE (Elsevier), 1974-onwards
- Science Citation Index Expanded and the Conference Proceedings Citation Index on Web of Science (Thomson Reuters), 1945-onwards
- Latin American and Caribbean Health Science (LILACS), 1982-onwards.

The WHO International Clinical Trial Registry Platform, Clinical Trials and the metaRegister of Controlled Trials for ongoing studies were also searched. In addition, experts and pharmaceutical and probiotic companies were contacted for further information on grey literature and unpublished RCTs. Conference proceedings and Google Scholar were also searched for additional studies.

A reference management software was used to manage the records retrieved; duplications among the different databases were highlighted by the software, and checked manually by the first author (PAW). Two authors (PAW, PJFVB) independently assessed all titles and abstracts, obtained full texts for potentially relevant studies and applied the eligibility criteria. Any discrepancies regarding eligibility were resolved by consensus. If more than one publication reported data from the same participants, the most detailed study was used.

Data were included as stated in the published papers whenever possible; where data were insufficiently reported, the authors were contacted for clarification. Data from eligible studies were extracted by two independent reviewers (PAW, PJFVB) using a pre-tested extraction form. A study flow diagram was created using the PRISMA model (Figure 1) to map out the number of records identified, included and excluded, a table with excluded studies and justification is available in the appendices.

Details of included RCTs were extracted; they are available in the appendices and summarised in Table 1. Three reviewers (PAW, PJFVB and VSN) independently assessed methodological information using Cochrane's tool for risk of bias assessment [18], adopting the criteria outlined in the appendices. Disagreements were resolved by consensus.

Data collection and analysis

The appropriate unit of analysis was the individual patient. For all outcomes, where possible, an intention-to-treat analysis was performed, otherwise the available case analysis was used. The statistical heterogeneity was assessed using the I^2 statistic, interpreted according to the Cochrane Handbook [18], and considered substantial if I^2 was greater than 50%. If there were ten or more studies in the meta-analysis (MA), reporting biases were investigated using funnel plots and reasons for asymmetry were considered if they were noted.

The Review Manager software (RevMan 5.3®) was used to calculate summary statistics using a random-effects model. For continuous data, the mean difference (MD) was provided if outcomes were measured in the same way among trials and standardised mean difference (SMD) if not. For dichotomous data, the results were presented as a summary risk ratio (RR) with 95% confidence intervals (CI). Where substantial heterogeneity was present, potential explanations were considered including subgroup analysis, and sensitivity analyses were conducted based on the risk of bias in which studies with the highest level of bias or unclear bias for allocation concealment and completeness of outcome data were excluded.

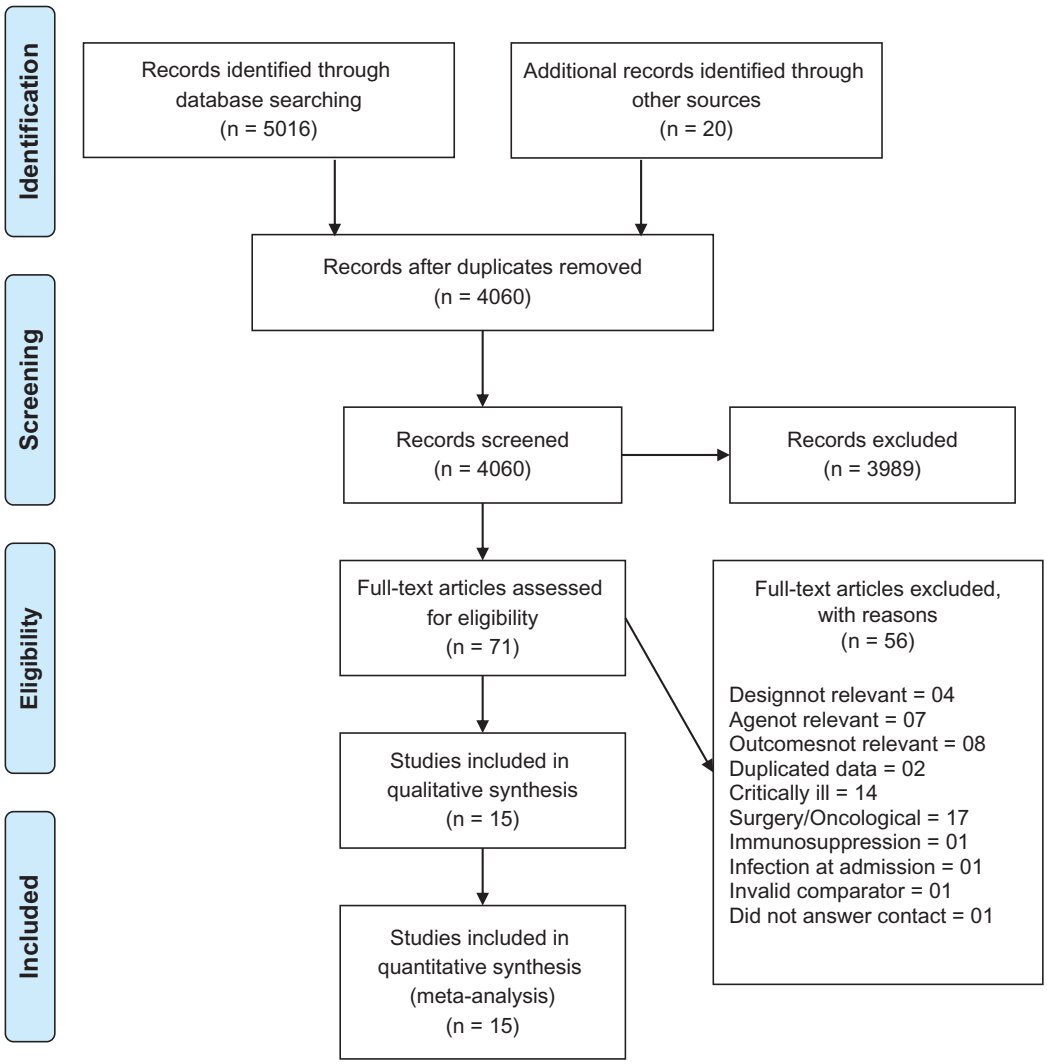

Figure 1. Study flow diagram.

Table 1. Main characteristics of included studies

References	Country and duration	Population, Intervention, Comparator, Outcome (P.I.C.O.)	Main findings
Allen 2013	UK 1 December 2008 to 30 May 2012	Elderly inpatients exposed to antibiotics in the preceding 7 days; multi-strain probiotic; placebo; occurrence of AAD and CDD	CDD was as uncommon cause of AAD (0.8% in the probiotic group, 1.2% in placebo group [RR 0.71; 95% CI 0.34 to 1.47; $P = 0.35$].). Frequency of serious AE was similar in the two groups, none attributed to participation in the trial
Auinguer 2013	Germany October 2010 to May 2011	Healthy adults with recurring common colds; single probiotic strain; placebo; incidence of common cold	Probiotic reduced the number of symptomatic common cold infections by 25% compared to placebo ($P = 0.041$). Data on elderly subgroup were provided by authors and there was no difference between groups in this age group
Beausoleil 2007	Canada September 2003 to May 2004	Adult inpatients who were expected to take at least 3 days of any systemic antibiotic;multi-strain probiotic; placebo; occurrence of AAD/CDD	Daily administration of probiotics was safe and effective in the prevention of AAD; 1 patient in probiotic group and 7 in placebo group developed CDD (assay performed on only 2 patients in intervention group and on 13 in placebo group)
Fujita 2013	Japan 30 November 2009 to 30 June 2010	Elderly users of day care facilities; single-strain probiotic; placebo; occurrence of URTI	The number of persons diagnosed with acute URTIs was similar in both groups. Mean duration of infection per event was found to be shorter in probiotic group (3.71 × 5.40 days)
Fukushima 2007	Japan Winter seasons 2002–2003	Bed-ridden inpatients (>70 years) with dementia and using total enteral nutrition—multi-strain probiotic; placebo; incidence of infection	The percentage of days with infections significantly decreased (15.4% vs. 5.7%) in the probiotic group comparing the run-in period with intervention period; the reduction was greater than that of the control group ($P = 0.047$)
Guillemard 2010	France 2 November 2006 to 4 May 2007	Non-institutionalised elderly older than 70 years; multi-strain probiotic; placebo; occurrence of common infectious diseases	Probiotic intervention significantly reduced the average duration per episode of CID (6.5 v. 8d; $P = 0.008$) and the cumulative duration of CID (7 v.8d; $P = 0.009$). The cumulative numbers of CID were not different between groups
Hickson 2007	England November 2002 to January 2005	Inpatients aged 50 years and over who were prescribed antibiotics; multi-strain probiotic; placebo; incidence of AAD and CDD	Nine/53 patients in control group had CDD versus none/56 in intervention group ($P = 0.001$); absolute risk reduction was 17%, NNT = 6
Lewis 1998	England Duration not clearly stated	Elderly inpatients who were prescribed antibiotics; single-strain probiotic; placebo; occurrence of AAD and CDD	There was no difference in the incidence of CDD between groups ($I = 5/33$; C = 3/36)
Mañé 2011	Spain Winter 2006 and Spring 2007	Institutionalised elderly; multi-strain probiotic; placebo; infection occurrence and survival rates	Incidence of infection showed a significant lowering in the high probiotic dose group. Mortality was greater in placebo versus both probiotic groups
Nagata 2016	Japan September 2009–2010	Institutionalised elderly; single-strain probiotic; placebo; infections and fever occurrence	Long-term consumption of probiotic may be useful for decreasing risk of infection among long-term care elderly (number of days with fever/2 weeks after 6th month consumption was 1.1 vs. 2.5 at intervention and placebo group, respectively)
Pozzoni 2012	Italy April 2009 to July 2010	Inpatients aged 50 years and over who had not yet started receiving antibiotics or who were prescribed antibiotics <48 h; single-strain probiotic; placebo; incidence of AAD and CDD	Five cases of CDD occurred, two in the placebo group (2%) and three in the probiotic group (2.8%); the probiotic was not effective in preventing AAD/CDD
Safdar 2008	USA November 2003 to June 2005	Adult inpatients aged 18 years and older who were prescribed antibiotics for at least 72 h; single-strain probiotic; placebo; incidence of AAD and CDD	Probiotic intervention was well tolerated, without major adverse events AE; CDD occurred in only one patient in placebo group; of seven patients tested ($I = 3$; $P = 4$; $P = 0.27$)
Shinkai 2013	Japan March to July 2010	Elderly living in the community; single-strain probiotic; placebo; occurrence of common cold	The accumulated incidence rate of common cold was 47.3% in placebo group and 29% in high-dose intervention group ($P = 0.012$); QoL (SF-36) was higher in intervention groups ($P = 0.016$)
Thomas 2001	USA July 1998 to October 1999	Adult inpatients aged 18 years and older who were prescribed antibiotics for at least 72 h; single-strain probiotic; placebo; incidence of AAD and CDD	Probiotics did not reduce the rate of occurrence of AAD ($P = 0.93$). Too few patients had positive diagnosis of CDD to assess between-group differences
Van Puyenbroeck 2012	Belgium Winter 2007-2008	Institutionalised elderly; single-strain probiotic; placebo; occurrence of RTI	Probiotic had no statistically or clinically significant effect on protection against respiratory symptoms

AAD; antibiotic associated diarrhoea; AE; adverse events; CDD; *Clostridium difficile* diarrhoea; CI; confidence interval; CID; common infectious diseases; URTIs; upper respiratory tract infections; NNT; number necessary to treat; PPA; per-protocol analysis; QOL; quality of life; RR; risk ratio; RTI; respiratory tract infections.

Subgroup analyses for the following were considered where possible:

- Age (65–80 years; older than 80 years)
- Coexistence environment (institutionalised, hospitalised, community-dwelling)
- Type of probiotics (combinations of probiotics, probiotics plus prebiotics, individual strains)
- Type of infection.

For each outcome, a tabulated summary of the findings was produced to report the intervention effect and a measure of the certainty of the evidence using the GRADE approach, including a narrative description, when necessary. The evidence was downgraded from 'high' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Minor changes were applied to the original protocol [17], with the intention of improving the sensitivity of results, and to adapt them to GRADE standards: (i) trials whose patients had been recruited in a hospital setting were included; (ii) studies whose population had been recruited from critically ill, immunocompromised, oncologic or surgical patients were excluded and (iii) quality of life and mortality were included as primary outcomes, rather than secondary outcomes.

RESULTS

Results of the search, excluded and included studies

The search retrieved 5,036 studies (Figure 1), of which, 15 articles were included (Table 1). Fifty-six RCTs (appendices) were excluded as there were oncological studies or included post-operative patients (17 studies).

The included studies enrolled 5,916 participants (intervention = 2,959; control = 2,957) from nine countries (Table 1), with a mean age of 75.2 years and a median follow-up time of 319 days (204.75–631.50). Eight studies recruited inpatients [11, 13, 15, 19–23], investigating the effect of probiotics on the prevention of CDD; in three RCTs, patients were admitted from long-term care institutions evaluating respiratory tract infections (RTI [9] or all ID (AID) [10, 24]), and in four reports, participants were living in the community (RTI [12, 25, 26] and AID [14], respectively).

Eight reports enrolled only older patients [9–14, 24, 25], corresponding to 86.3% of the participants. The mean age in four out of the six remaining studies was greater than 65 years old [19–22]; one author provided non-published data on an older person [26], and in one report, the randomisation schedule was generated using a rule that included age at entry (<65 vs. ≥65 years) [23].

Two RCTs [10, 11] recruited solely functional dependent older participants (n = 96); one of them [11] exclusively enrolled bed-ridden dementia patients. Three studies [9, 14, 24] enrolled independent older patients (n = 1,843), while most studies did not register functional capacity or cognitive status. No study used probiotics associated with prebiotics.

Risk of bias in included studies

Six studies did not clearly report the random sequence generation nor the allocation concealment [10, 11, 15, 19, 24, 25]. Blinding of the outcome assessment was insufficiently reported in nine RCTs [9–11, 14, 19, 22–24, 26], and six studies were judged as having a high risk of bias for incompleteness of outcome data due to a high rate of exclusions and/or attrition [9, 10, 20, 21, 24]. Two studies [11, 23] were judged to be at high risk for other bias due to clear involvement with probiotic manufacturers. The other eight RCTs were unclear, as the authors declared that they received only the support of the industry, without their participation in the organisation, planning or execution of the research.

There was not enough information to fully assess the potential for selective reporting bias for most of the included trials, therefore they were judged as being an unclear risk. In the five studies where the protocol was available [10, 13, 21, 26], all outcomes were reported as intended (appendices). Most studies [9–12, 14, 19, 20, 22–24, 26] were funded or supported by probiotic industries.

Effect of interventions

See **Summary of findings** (Table 2) for main comparisons.

- *Occurrence of infection*: The effect of probiotics on the occurrence of infection was not significantly different from placebo (13 trials, 5,820 participants: RR 0.86, 95% CI 0.70 to 1.07; I^2 = 39%; Figure 2). When only trials that enrolled older adults were included, there was still no evidence of a significant effect (9 trials, 5,225 participants, 735 events: RR 0.92, 95% CI 0.77 to 1.09; I^2 = 27%). The subgroup analysis did not change the heterogeneity and the sensitivity analysis did not change the outcome result (RR 0.92, 95% CI 0.76 to 1.12). The funnel plot (appendices) for this outcome was asymmetric due to the lack of publication of 'positive results' for placebo in smaller studies. However, this asymmetry would probably have no impact on the results of the present MA.
- *Adverse events*: There was no significant difference between probiotics and placebo in terms of adverse events (RR 1.01, 95% CI 0.91 to 1.12; I^2 = 0%). Data were available for 5,310 participants from 9 trials, for a total of 1,098 events (probiotics 554; placebo 544). The most common adverse events reported were related to gastrointestinal disorders: constipation, abdominal pain and cramping, flatulence, nausea and gas bloating, with almost no cases of serious adverse events related directly to probiotic use.
- *Mortality*: The effect of probiotics on general mortality was not significantly different from that reported for the placebo (5 trials, 669 participants, 77 events: RR 1.09, 95% CI 0.70 to 1.72; I^2 = 5%). It is important to highlight that mortality was described by a very small number of studies (13.2% of the population in this review).

Table 2. Summary of findings table

	Number of participants (studies)	Quality assessment					Illustrative comparative risks (95% CI)			
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Assumed risk control	Corresponding risk probiotics	Relative effect (95% CI)	Quality of evidence
							Study population			
Occurrence of infection	5,927 (13 studies)	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	134 per 1,000	116 per 1,000 (94–144)	RR 0.86 (0.7 to 1.07)	⊕⊕◯ Low[a]
Adverse events	5,082 (6 studies)	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	215 per 1,000	217 per 1,000 (196–241)	RR 1.01 (0.91 to 1.12)	⊕⊕◯◯ Low[b]
Mortality	669 (5 studies)	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[c]	None	110 per 1,000	120 per 1,000 (77–189)	RR 1.09 (0.7 to 1.72)	⊕◯◯◯ Very low[c]
Mean duration of infection	1,406 (7 studies)	Very serious[d]	Serious[d]	No serious indirectness	No serious imprecision	None	The mean duration of infection per episode in the intervention group was 0.35 lower (1.57 lower to 0.87 higher)			⊕◯◯◯ Very low[c]

To determine a GRADE quality of the evidence, the GRADE approach begins by assigning findings to one of two starting levels of quality depending on the study design. Randomised trials are high quality, while observational studies are low quality. Additionally, two other levels exist; moderate and very low. This gives four levels: High, Moderate, Low and Very low. Studies can then be up-or downgraded based on certain factors:
(i) Risk of bias (−1 if serious risk of bias, −2 if very serious risk of bias); (ii) Inconsistency or heterogeneity of evidence (−1 if serious inconsistency, −2 if very serious inconsistency); (iii) Indirectness of evidence (−1 if serious, −2 if very serious); (iv) imprecision of results (−1 if wide confidence interval, −2 if very wide confidence interval) and (v) Publication bias (−1 if likely, −2 if very likely).
Quality of Evidence: ⊕⊕⊕⊕ = High quality: the authors are very confident that the true effect lies close to that of the estimate of the effect; ⊕⊕⊕◯ = Moderate quality: the authors are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ⊕⊕◯◯ = Low quality: the authors' confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; ⊕◯◯◯ = Very low quality: the authors have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Six out of 13 studies were judged as high risk for incomplete outcome data, and another 3 were judged as unclear for the same criterion. Too many studies were also judged as having unclear risk of bias for other critical domains (sequence generation, allocation concealment, blinding of outcome assessor and involvement with manufacturers).

[b]A significant number of studies were judged as unclear or high risk of bias for critical domains (sequence generation, allocation concealment, blinding of outcome assessor, involvement with manufacturers).

[c]The confidence interval was large, and the sample size for this outcome (as well as the number of events) was too small, and did not met the optimum size of information. Only 5 out of 15 included studies described mortality as a primary endpoint.

[d]Too many studies were judged as having unclear or high risk of bias for a number of critical domains, namely incomplete outcome data, sequence generation, allocation concealment, blinding of outcome assessor and involvement by manufacturers. The estimate effects showed different magnitudes, the confidence intervals presented small or no overlaps, with a high level of heterogeneity.

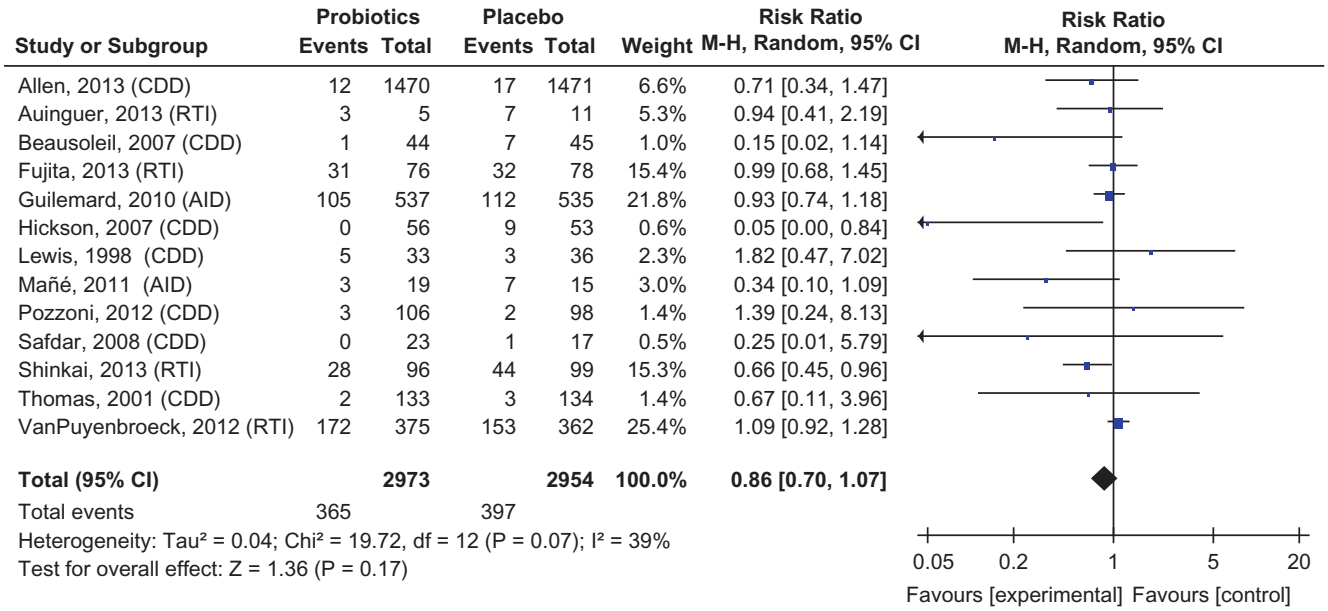

Figure 2. Comparison between intervention (probiotics) versus placebo for the primary outcome of *occurrence of infection* (alphabetically ordered studies). CDD; *Clostridium difficile* diarrhoea; RTI; respiratory tract infection; AID; all infectious diseases.

- *Quality of life (QoL)*: Three [13, 14, 25] trials described QoL as an outcome, but only two [13, 25] provided data for comparison analysis. Data were available for 3,136 participants. As QoL was measured using different scales, the SMD was used (SMD −0.09, 95% CI −0.99 to 0.81, I^2 = 97%).
- *Mean duration of infection per episode*: Probiotics were not significantly different from placebo with regard to the mean duration of ID episodes (7 trials, 1,406 participants, MD −0.35, 95% CI −1.57 to 0.87, I^2 = 86%). There were no differences between groups of types of probiotics, settings and types of ID during subgroup analyses to examine heterogeneity; insufficient data limited our analysis by age group. Sensitivity analysis did not significantly change the estimate of effect.
- The appendices contain additional information. Unfortunately, the included studies did not provide sufficient data for any description of the other secondary outcomes [17].

Discussion

Summary of the main findings

This systematic review of probiotics for occurrence of ID in older adults found 15 completed RCTs, including three larger trials (more than 500 subjects), enrolling 5,916 participants. While five studies did not provide data related to older participants, the mean age of their samples was over 65 years, and they accounted for less than 15% of the total participants of this SR.

Participants were recruited from long-term care institutions and community settings, or during short-term hospital admissions, and were represented by independent older patients. Primary studies investigated the effect of probiotics on the prevention of respiratory tract infections, *C. difficile* diarrhoea and on common IDs. Despite the high clinical heterogeneity among the primary studies, it is important to highlight that ID in older patients is a complex entity, probably no single intervention would result in a direct effect of a binary outcome. Factors such as seasonal changes in contact, social structure, vaccination, nutrition, frailty, immunosenescence and setting may enhance susceptibility to infection in this population [27]. One previous SR found moderate quality evidence that probiotics are both safe and effective for preventing CDD in infants and adults [28]; in this review, besides focusing in older patients and in more infections than just CDD, population and comparators were also different.

Overall, when compared to placebo, probiotics did not significantly reduce the occurrence of IDs in older patients, with a low quality of evidence. Of note, there was a consistent effect that did not change during sensitivity or subgroup analysis, and a narrow confidence interval, that did not cross damage or benefit thresholds. In addition, probiotics did not seem to reduce the mean duration of an infection episode (very low quality of evidence). There were no differences in the occurrence of infection in the subgroup analyses according to age, coexistence environment and types of infection and probiotic.

Although poorly described, the effect of probiotics on general mortality did not seem to differ from that of the placebo (very low quality of evidence). This SR did not find differences between probiotics and placebo regarding adverse events, with a low quality of evidence.

QoL was described by only two studies, each of which showed opposite results, which may justify the high heterogeneity found despite the large sample analysed for this outcome. Unfortunately, QoL remains a rather neglected outcome in studies conducted with older patients.

There were very few studies evaluating the prevalence and budget impact of the consumption of probiotics, especially in older people; an American study with 1,976,167 discharges found that probiotics were used in 51,723 hospitalisations in 2012 [29] . Probiotics were previously found to be better than placebo in reducing the mean duration of RTIs [5], reduced the risk of developing CDD by 59.5% (especially among hospitalised patients) [30], and were considered a cornerstone for the prevention of some infections in paediatric patients[6] . However, RCTs of probiotics for infection prevention in older people yielded unclear results.

Limitations of the review

Unfortunately, the primary data of older people from five trials were not available and this information might have changed some endpoints. Also, it was not possible to perform a subgroup analysis with the age groups 65–80 years and >80 years. Consequently, assumptions cannot be made about the long-term safety of probiotics in older people or about their effect on critically ill older patients.

Despite persistent requests, no authors provided information on ongoing trials. The clinical heterogeneity of the interventions and infections studied may have contributed to the lack of statistical significance, therefore a fixed-effect model was not possible. Furthermore, the follow-up period was variable in each study, and there was a lack of information related to vaccination and routine hygiene measures, which may have influenced the ID outcomes.

Implications for practice and research

On average, older adults suffer between two to five episodes of mild infection per year, including upper RTI, flu, digestive and urinary tract infections [1]. The use of over-the-counter medications to prevent an ID is trivial, but costs, safety and the risk of drug interactions exist, and may be a concern for public health due to the high incidence and recurrence rates of ID in this age group. It is interesting to note, however, that this intervention was not associated with adverse effects.

The current data on the effectiveness of the probiotics in older people are insufficient. Future research should focus on specific strains, investigating the effect of dosing and timing on potential benefits. Furthermore, clinically relevant efficacy outcomes should be used instead of laboratory surrogates, with better descriptions of the safety outcomes, as well as costs and efficacy for public health.

Conclusion

The current low quality of evidence does not support the use of probiotics for the reduction of the occurrence of infection in older patients, despite a good safety profile. Consequently, there is no simple solution for the problem of ID in older patients and unique infection-control interventions may not be realistic.

Key points

- This systematic review and meta-analysis assessed the effectiveness and safety of probiotics in comparison to placebo in the occurrence of infections in older adults.
- The current evidence, which is of low quality, does not support the use of probiotics for the reduction of the occurrence of infection in older people.
- The current evidence, which is of very low quality, suggests that the mean duration of an infection episode is not affected by probiotics.
- The evidence, which is of low quality, suggests that probiotics have a safety profile similar to placebo.

Supplementary Data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of Interest

None declared.

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