



# Probiotics for healthy ageing: Innovation barriers and opportunities for bowel habit improvement in nursing homes

**KEYWORDS:** Probiotics, elderly, nursing homes, bowel habits, innovation cycle, safety.

**Abstract** As aging is associated with changes in the diversity and composition of the microbiota, resulting in increased susceptibility to constipation and diarrhoea, probiotics seem to be a promising intervention to modulate and (partially) restore the gut microbiota and its associated disorders. Here, we review the current state of probiotic innovation for elderly nursing home residents with respect to bowel habit improvement. By systematically exploring all aspects of the innovation cycle, including unmet patient needs, efficacy, safety, and health economics, we revealed the main barriers and corresponding opportunities for probiotic valorisation within this domain. Although our results indicate that there is a clear unmet patient need and that probiotic intervention may be both efficacious and safe in improving the bowel habits of elderly residents in nursing homes, only few clinical studies have addressed this problem. High quality clinical studies are required to further drive the probiotic innovation cycle within this domain.

## INTRODUCTION

The world population is rapidly ageing. Whereas in 1950 about 8% of the total world population was 60 years or older, it is projected that in 2050 this number has increased to more than 20%. For the developed countries, this number even goes up to a staggering ~30% (1). Aging comes at a price, as it is considered to be a risk factor for disease (2,3). The associated costs pose a burden on the economy, as health care expenditures rise with age (4,5). It has currently been demonstrated that ageing is associated with a decline in the composition and quality of the gut microbiota (6). Nursing home residents are an extra vulnerable group, that is negatively affected by the dietary patterns in this type of institutions. Recent studies show that nursing home residents are frailer and exhibit higher comorbidity compared to community dwelling elderly (7). As elderly nursing home residents experience a higher comorbidity, they also experience a more pronounced reduction in quality of life (8), and pose an extra burden on healthcare expenditures when compared to elderly without comorbidity (9). Hence, there seems to be an unmet health need within nursing home care to improve quality of life by reducing (co-) morbidity, and as such lower the associated healthcare costs. In this respect, probiotic products could be of potential benefit, as these substances are known to have the potential to modulate and restore the gut microbiota (10). However, despite its potential, probiotic usage is still limited within the medical community (11). This might be a result of a seriously hampered valorisation cycle, as indicated by Key Opinion Leaders (12). A study on patient needs and probiotic research prioritization indicated that gastrointestinal diseases like (antibiotic-

associated) diarrhoea were considered top priority (13). To date, no information on the valorisation cycle for probiotics usage within elderly care is available, despite the huge unmet need. Hence, this paper sets out to recapitulate the current position of probiotics within elderly care, focussing on the improvement of bowel habits within nursing homes. The complete innovation cycle of probiotics will be considered, and topics that will be reviewed are: the different disease types that are currently being studied within the elderly population using probiotics, probiotic efficacy, safety, costs-reduction and consumer acceptance. Insight into the valorisation cycle allows for the identification of barriers and corresponding opportunities, which promotes selective intervention to improve probiotic innovation.

## METHODS

Literature searches were performed using the Pubmed, Medline and Science Direct databases. Only articles in the English language on clinical trials using probiotics with elderly aged  $\geq 60$  years were deemed eligible for inclusion. Searches were performed using the following keywords in the title and/or abstract: "Probiotic", and "elderly", "senior", "geriatric", "retired", "institutionalized", "long-term care", "nursing home", "residential home", "rest home", and "aged-care". Reviews and non-clinical trials were removed from the search results. In case of unclarity on the age range of subjects included, the average age was used and when  $\geq 60$  years old, the paper was included for analysis. Trials with heat-killed microorganisms were excluded as these substances do not obey the definition of probiotics being live microorganisms.

Prevalence of diarrhoea and constipation in nursing homes and healthy adult populations were systemically obtained by including relevant search terms (e.g. "diarrhoea", "constipation", "prevalence" and "nursing home").

Adverse events were analysed according to the Common Terminology Criteria for Adverse Events [CTCAE v. 4.0] (14).

## RESULTS AND DISCUSSION

The complete innovation cycle for probiotic products is illustrated in the figures below.

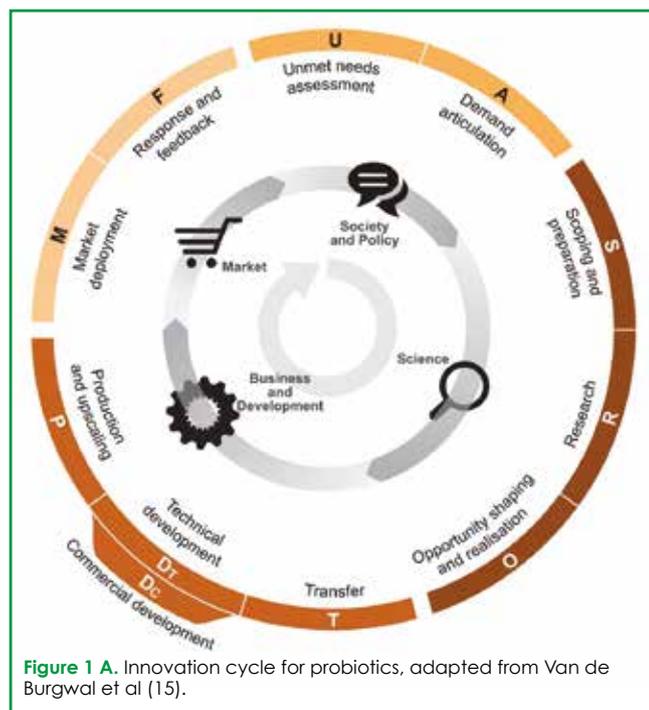


Figure 1 A. Innovation cycle for probiotics, adapted from Van de Burgwal et al (15).

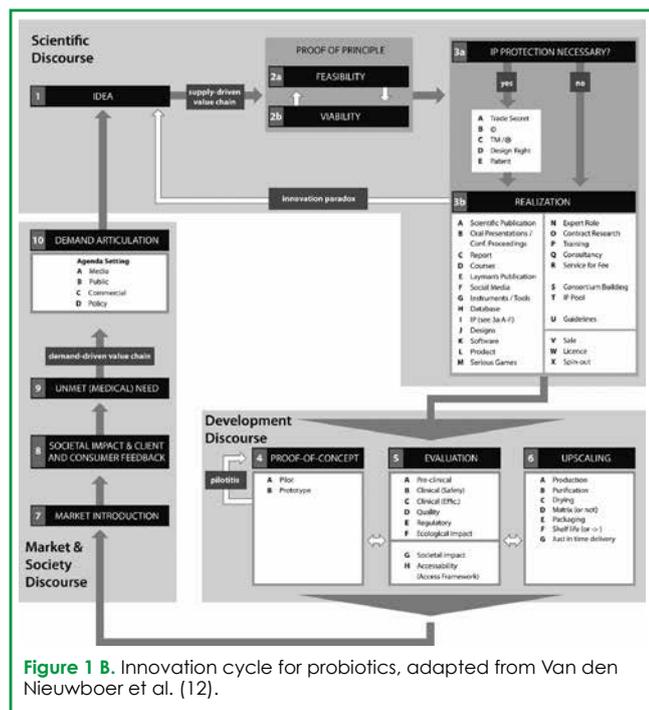


Figure 1 B. Innovation cycle for probiotics, adapted from Van den Nieuwboer et al. (12).

According to this model, unmet health needs and the corresponding demands for new products drive scientific research on probiotics, fuelling the prototyping and upscaling of new probiotic products. These products are subsequently being evaluated by the customers after market introduction. This again results in the articulation of new or additional unmet needs with corresponding demands for new products, providing again input for new research aiming at new probiotic products matching the updated unmet needs. This cycle is hampered for probiotics innovation, and as such calls for a detailed specification of the inherent barriers with corresponding opportunities in order to drive this cycle (12).

### Prevalence of constipation and diarrhoea in nursing homes: the underlying unmet need within the valorisation cycle

In order to identify the magnitude of the unmet need for bowel habit improvement in nursing homes, we analysed the prevalence of both constipation and diarrhoea for this type of institutions, as displayed in Figure 2 (weighted average of 4 diarrhoea and 6 constipation trials, respectively). The unmet health need for bowel habit improvement in nursing home residents seems to be higher with respect to constipation (62%, weighted average) when comparing the prevalence with that of the general population (median 16%, Mugie et al (16)), although the range within the general population is wide (0.7% to 79%). Data on the prevalence of diarrhoea in the general population is not readily available. The data clearly demonstrate the current unmet health need.

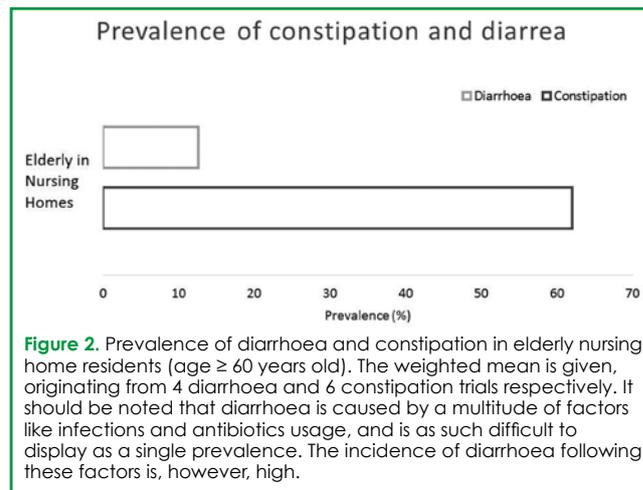


Figure 2. Prevalence of diarrhoea and constipation in elderly nursing home residents (age ≥ 60 years old). The weighted mean is given, originating from 4 diarrhoea and 6 constipation trials respectively. It should be noted that diarrhoea is caused by a multitude of factors like infections and antibiotics usage, and is as such difficult to display as a single prevalence. The incidence of diarrhoea following these factors is, however, high.

### The valorisation cycle: science

In order to investigate the current state of probiotics research in elderly in general and nursing homes in particular, we canvassed all clinical trials on this topic, of which the results are displayed in Figures 3a and 3b.

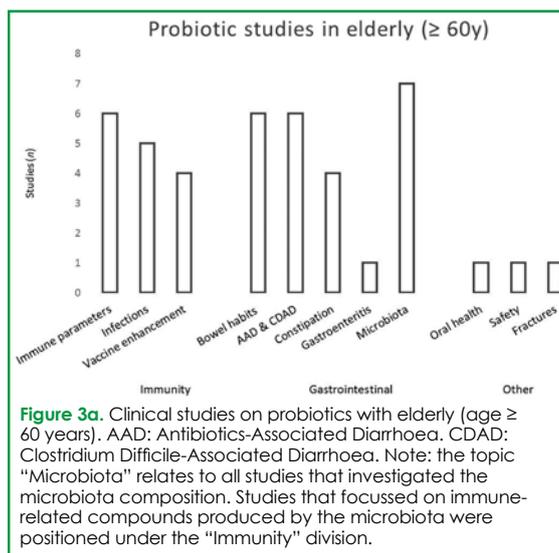
The results show that gastrointestinal-related trials are in the majority, followed by studies on immune improvement. Bowel habits (including constipation and diarrhoea) constitute a major research topic within this respect. Studies on immune improvement are more heterogenous as compared to gastrointestinal improvement, and range from, e.g., upper-respiratory infections to vaccination support. Our results clearly demonstrate that studies using probiotics in nursing homes are scarce. Hence, despite the high unmet need, there seems to be a mismatch with the limited amount of effort to meet this need by utilizing probiotics research.

### Efficacy of probiotics: Proof of concept within the valorisation cycle

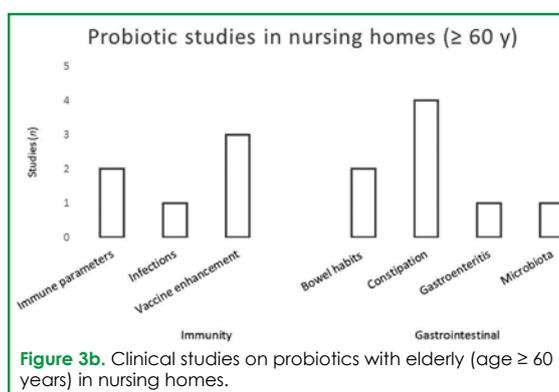
Figure 4 displays the efficacy of probiotics to improve bowel habits in nursing homes, for diarrhoea and constipation respectively. In general, the studies published until now all use small sample sizes, and hence position them within the pilot phase, having limited statistical solidity. The studies are also heterogeneous in setup with differences in types of primary outcomes, intervention times, dosages, populations, probiotic strains and product types. These two shortcomings form a barrier to innovation. Earlier studies already indicated that the efficacy of a probiotic product depends on both the strain and matrix used (23), making it impossible to compare these studies in order to generalize the efficacy of probiotics for either constipation or diarrhoea within the framework of a meta-analysis. Hence, the current evidence of probiotic efficacy for diarrhoea and constipation in nursing homes is still insufficient, although these studies indicate that the perspective looks promising. Large scale double-blind placebo controlled trials are needed to substantiate these preliminary results posing an opportunity for the probiotics community (clinical evaluation of the efficacy of the proofs of concepts within the valorisation cycle, also see Figure 1).

### Safety evaluation of probiotics within the elderly: business development within the valorisation cycle

Although safety of probiotic products does not seem to be a topic of great concern for medical doctors (anymore) (11), and safety data for even immune compromised persons indicate that probiotics usage is safe (14), no exhaustive safety data on probiotics usage amongst the elderly population is presented yet. Therefore, we categorized the Adverse Events (AE) reported in all trials on probiotics with elderly according to the CTCAE (version 4.0) classification. Analysis of 42 clinical studies in the elderly population (age range of 60-103y) with a median duration of 30 days reported a total of 4.642 AE's (Figure 5). In the analysed studies, 4.346 and 3.954 participants were allocated to the probiotic treatment or control group respectively. Dosages of the 51 applied probiotic strains ranged from  $6.5 \times 10^7$  –  $9.0 \times 10^{11}$  CFU per day. Most of the AEs could be categorized as gastrointestinal disorders (CTCAE-7). None of the studies reported serious AE that were related to the study product. Apart from a higher incidence in flatulence and unrelated nasogastric tubing in the probiotic group (24), there were no statistical significant differences in the total number of AEs between the probiotic and control group (Fisher's exact test, two-sided,  $p=0.06$ ). Although current data is insufficient to make conclusive remarks, it indicates that the evaluated probiotic strains are safe for elderly in the setting of clinical trials at their respective dosage. However, it should be noted that AEs are not always systematically documented and reported in probiotic research (14), which could potentially result in underreporting bias.



**Figure 3a.** Clinical studies on probiotics with elderly (age ≥ 60 years). AAD: Antibiotics-Associated Diarrhoea. CDAD: Clostridium Difficile-Associated Diarrhoea. Note: the topic "Microbiota" relates to all studies that investigated the microbiota composition. Studies that focussed on immune-related compounds produced by the microbiota were positioned under the "Immunity" division.



**Figure 3b.** Clinical studies on probiotics with elderly (age ≥ 60 years) in nursing homes.

### Customer feedback within the valorisation cycle: cost reduction.

To date, only limited data is available on the cost effectiveness of probiotics usage. For elderly, Lenoir Wijnkoop et al. estimated that probiotics introduction to prevent antibiotics-associated diarrhoea potentially could save £339 per hospitalized elderly patient over the age of 65 years (25). To the best of our knowledge, no such information is available for nursing home residents with respect to both reduction of constipation and diarrhoea. Hence, in order to complete a "business case" for probiotics usage in this type of setting, studies are urgently needed that address these cost aspects.

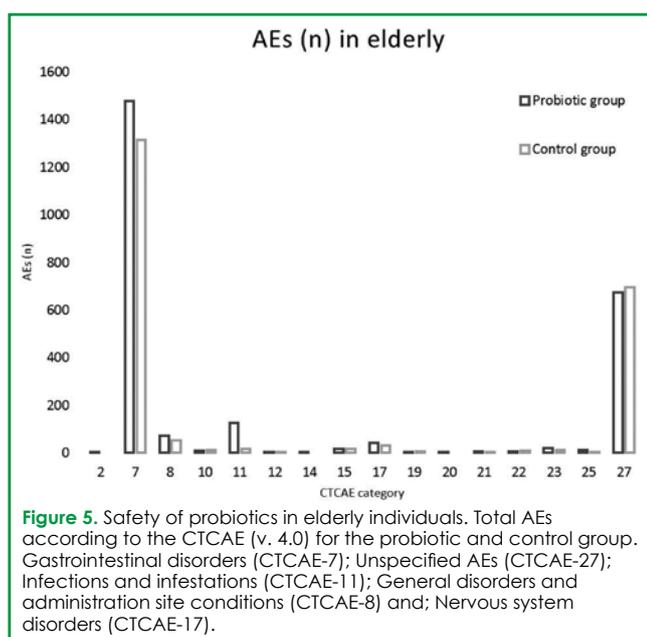
### CONCLUSION

Probiotics are acclaimed to have the potential to positively effect indications associated with dysbiosis, such as constipation and diarrhoea, which are generally more pronounced upon ageing. The role of probiotics in iatrogenic bowel irregularities has been previously evaluated (26), discussing its potential towards unmet health needs together with associated cost

benefits. Prevalence data on bowel habit disorders amongst the elderly population indicate a clear unmet health need. Despite this unmet health need, probiotic evidence to improve bowel habits for a nursing home population seems to be still in its infancy. Difficulties inherent to research in nursing homes in general such as obtaining informed consent, involving staff members and, most importantly, obtaining regulatory and ethical approval (27, 28), make it challenging to perform clinical trials in a nursing home setting and currently prevent rapid progress. Although the results of preliminary studies seem promising, no solid evidence is given yet due to the heterogeneity of the data currently provided. Large-scale, double-blind, placebo-controlled trials are needed, providing both a barrier and corresponding opportunity within the valorisation cycle. Possible costs reductions of probiotics usage in this setting are not given at all yet, most likely contributing to a diminished "prescription rate" of the medical doctors involved. Safety data, however, seem promising but should be further substantiated by more homogeneous data, provided by large scale trials adhering to strict Good Clinical Practice guidelines. Overall, the valorisation cycle for probiotic usage within nursing homes to improve bowel habits seems to be predominantly hampered within the business development phase, particularly in the proof of concept phase. However, for successful innovation, all steps within the complete innovation cycle should be taken. Given the current progress, the potential of probiotics to improve bowel habits of elderly residents in nursing homes seems promising but requires substantially more quality research and increasing cooperation between researchers, nursing homes and ethics- and regulatory committees.

Study	Bowel movements	Diarrhoea	Constipation	Probiotic strain(s) (& dose)	Per protocol set (N)	Study design (& duration)
An et al., 2010 (17)	-	-	No significant difference in defecation frequency or state of stools	<i>L. acidophilus</i> [LH] CBT, <i>Pediococcus pentosaceus</i> [PP] CBT, <i>B. longum</i> SPM 1205 (6.0 × 10 <sup>11</sup> CFU/g)	19	Single Arm (2 weeks)
Granata et al., 2013 (18)	-	-	Reduction in constipation status (p=0.001); Reduced pain during evacuation (p=0.002); Reduced time needed for evacuation (p=0.004)	<i>L. rhamnosus</i> GG (6.90 log CFU/g)	12	Single Arm (4 weeks)*
Ouwehand et al., 2002 (19)	-	-	Increase in average defecation frequency per week (p<0.05) in LGG+PJS group	<i>L. rhamnosus</i> LC705 (1-2 × 10 <sup>8</sup> CFU/ml) + <i>P. freudenreichii</i> shermanii JS (2-4 × 10 <sup>8</sup> CFU/ml) OR <i>L. reuteri</i> ING1 (3.6 × 10 <sup>6</sup> CFU/ml) (200ml)	22	Open-label 3 parallel groups (4 weeks)**
Pitkälä et al., 2007 (20)	More normal bowel movements (p=0.003)	No significant difference in diarrhoea	-	<i>B. longum</i> 46 + <i>B. longum</i> 2C (10 <sup>9</sup> CFU/day) OR <i>B. lactis</i> Bb-12 (10 <sup>9</sup> CFU/day)	179	Double-blind, placebo-controlled, 2 parallel groups (7 months)
van den Nieuwboer et al., 2015 (21)	No significant difference in bowel movements	Lower percentage diarrhoea stool types per week (p<0.05)	Lower percentage constipation stool types per week (p<0.01)	<i>L. casei</i> Shirota (6.5 × 10 <sup>9</sup> CFU per day)	44	Single Arm (9 weeks)***
Yeun and Lee, 2015 (22)	-	-	Decrease in hard or lumpy stools (p<0.05); Increased defecation frequency per week (p<0.01)	Non- or double-coated: <i>B. bifidum</i> (KCTC 12199BP) + <i>B. lactis</i> (KCTC 11904BP) + <i>B. longum</i> (KCTC 12200BP) + <i>L. rhamnosus</i> (KCTC 12202BP) + <i>L. acidophilus</i> (KCTC 11906BP) + <i>S. thermophilus</i> (KCTC 11870BP) (2.5-5 × 10 <sup>8</sup> CFU day)	40	Double-blind, 2 parallel groups (2 weeks)****

**Figure 4.** Efficacy of probiotics in nursing homes to reduce constipation and diarrhoea. \* Adults were randomly assigned in a double-blind manner to receive standard yogurt or probiotic yogurt. An additional single arm of elderly participants (described in table) received only the probiotic yogurt. \*\* Subjects were divided into 3 groups: 1 control group receiving non-supplemented juice; 1 group receiving juice supplemented with *L. reuteri*, and 1 group receiving juice supplemented with *L. rhamnosus* and *P. freudenreichii*. \*\*\* Subjects received the probiotic intervention for 6 weeks after a 3-weeks baseline period without probiotic supplementation. Stool quality and bowel movements during the intervention were compared with those during the baseline period. \*\*\*\* Subjects were randomized to receive either the non-coated or double-coated probiotic intervention. No placebo group was utilized.



**Figure 5.** Safety of probiotics in elderly individuals. Total AEs according to the CTCAE (v. 4.0) for the probiotic and control group. Gastrointestinal disorders (CTCAE-7); Unspecified AEs (CTCAE-27); Infections and infestations (CTCAE-11); General disorders and administration site conditions (CTCAE-8) and; Nervous system disorders (CTCAE-17).

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