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 ≥ 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 ≥ 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.
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].

RESULTS AND DISCUSSION

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

Prevalence of diarrhoea and constipation 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.

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 heterogeneous 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 categorised 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 4,346 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5). In the analysed studies, 4,346 and 4,642 AE’s (Figure 5).

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.
Efficacy of probiotics in nursing homes to reduce constipation and diarrhoea. Subjects were randomized to receive either the non-coated or double-coated intervention were compared with those during the baseline period. Subjects received the probiotic intervention for 6 weeks after a 3-weeks baseline period without probiotic supplementation. Stool quality and bowel movements during

L. rhamnosus
P. freudenreichii

supplemented with,

1 group receiving juice supplemented with probiotic yogurt. An additional single arm of elderly participants (described in table)

Adults were randomly assigned in a double-blind manner to receive standard yogurt or probiotic yogurt. About the author

Olaf Larsen (1972) is Ass. Professor (0.2 FTE) at the Athena Institute, Vrije Universiteit Amsterdam. He studied chemistry and has a PhD in Biophysics. Following assignments in academia, industry and consulting, Olaf heads since 2012 the Science Department of Yakult Nederland. Since 2016 he combines these activities with a part-time position at the Athena Institute, focusing on the valorisation of microbiota management.

REFERENCES

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Figure 4. Efficacy of probiotics in nursing homes to reduce constipation and diarrhoea.

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).


<table>
<thead>
<tr>
<th>Study</th>
<th>Bowel movements</th>
<th>Stoolwaste</th>
<th>Constipation</th>
<th>Probiotic strain(s) &amp; (dose)</th>
<th>Per rectal set (%)</th>
<th>Study design</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>An et al., 2010 (17)</td>
<td>-</td>
<td>No significant difference in faecal weight and frequency</td>
<td>Lactobacillus GG [6.10^10 log CFU/day]</td>
<td>19</td>
<td>Single Arm</td>
<td>(2 weeks)</td>
<td></td>
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<tr>
<td>Granja et al., 2013 (18)</td>
<td>-</td>
<td>No significant difference in faecal weight</td>
<td>L. acidophilus L2</td>
<td>13</td>
<td>Single Arm</td>
<td>(2 weeks)</td>
<td></td>
</tr>
<tr>
<td>Ouwewand et al., 2002 (19)</td>
<td>-</td>
<td>No significant difference in stool frequency</td>
<td>B. longum 28</td>
<td>22</td>
<td>Double-blind, placebo-controlled, 2 parallel groups</td>
<td>(4 weeks)**</td>
<td></td>
</tr>
<tr>
<td>Pilk-S et al., 2007 (20)</td>
<td>-</td>
<td>No significant difference in bowel movements</td>
<td>B. longum 48 &amp; E. coli 20</td>
<td>179</td>
<td>Double-blind, placebo-controlled, 2 parallel groups</td>
<td>(7 months)</td>
<td></td>
</tr>
<tr>
<td>Van den Nieuwboer et al., 2015 (21)</td>
<td>-</td>
<td>No significant difference in bowel movements</td>
<td>L. casei Shirota</td>
<td>44</td>
<td>Single Arm</td>
<td>(9 weeks)**</td>
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<tr>
<td>Yeun and Lee, 2015 (22)</td>
<td>-</td>
<td>Decrease in number of soft stools</td>
<td>L. casei Shirota, B. longum 28, L. acidophilus</td>
<td>40</td>
<td>Double-blind, placebo-controlled, 2 parallel groups</td>
<td>(2 weeks)**</td>
<td></td>
</tr>
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About the author

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