CHAPTER 7.
Medical Doctors’ Perceptions on Probiotics: *Lack of Efficacy Data Hampers Innovation*

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7.1 ABSTRACT

**Rationale:** The probiotic innovation cycle appears to be hampered and while important barriers have been postulated, the influence of medical doctors (MD) on probiotic innovation remains largely unaddressed.

**Objective:** The present study aims to complement current views on probiotic innovation barriers by reviewing the perceptions of MD on probiotics.

**Methods:** A pilot tested survey was sent to 1676 general practitioners and 741 medical specialists in the Netherlands to address current perceptions.

**Results:** The responses of 208 general practitioners and 207 medical specialists were included in the data-analysis. Half of MD (51%) advised probiotics in their practice, primarily for AAD (74%) and IBS (51%). Lack of evidence was the primary reason for MD not to advise probiotics (53%). Significantly less non-advisers perceived probiotics to be safe (62% vs 82%) and efficacious (24% vs. 64%) compared to advisers, where they primarily used conventional media (radio, television and newspapers) as their source of information (73% vs. 39%). Probiotic efficacy data is the preferred type of future information for all MD (72%).

**Conclusion:** In order to improve the perceptions of MD on probiotics and to advance innovations in this field, more large-scale randomized controlled trials are required that demonstrate probiotic efficacy in adherence with strict Good Clinical Practice guidelines.

**Keywords:** Probiotics; Medical Doctors; Perceptions; Innovation Barriers; Efficacy
7.1.1 Graphical abstract

Do Medical Doctors advise probiotics in their practice?

- YES
  - For what indications?
    - Antibiotic-associated diarrhea (AAD)
    - Irritable Bowel Syndrome (IBS)
  - Perceived safe?
    - 82% Advisers, 62% Non-Advisers
  - Perceived efficacious?
    - 64% Advisers, 24% Non-Advisers
  - Primary information source?
    - Medical associations
    - Scientific journals
  - Most preferred future information types?
    - Efficacy data
      - 2 Advisers, 1 Non-Advisers
    - Mode of Action
      - 40% Advisers, 77% Non-Advisers

- NO
  - For what reasons not?
    - Lack of evidence
    - Lack of awareness
  - Primary information source?
    - Radio, TV, and newspapers

7.2 INTRODUCTION

Dysbacteriosis of the human intestinal microbiome is associated with an increased risk for gastrointestinal disorders including inflammatory bowel disease (IBD), ulcerative colitis, celiac disease and irritable bowel syndrome (IBS) (Brown et al., 2012; Round et al., 2009). It was postulated over a century ago that host-friendly microorganisms found in yogurt and cultured dairy products could alter the intestinal microbiome, proposedly promoting health (Metchnikoff, 1908). This theory flourished in the medical community for some years but the commercialization and social acceptance of these bacteria, which are known today as probiotics, truly emerged in the 1990s. Numerous clinical studies, with various probiotic species, have been conducted since and it appears that probiotics may confer diverse health benefits on the consumer. For instance, the consumption of certain probiotic strains may benefit patients with antibiotic associated diarrhoea (AAD), IBD and necrotizing enterocolitis (NEC) (Sanders et al., 2013; Floch, 2014). Probiotics are furthermore generally considered safe for consumption across all age groups (Borriello et al., 2003; Gueimonde et al., 2004; Van den Nieuwboer et al., 2014a; Van den Nieuwboer et al., 2014b; Van den Nieuwboer et al., 2015). The probiotic industry is therefore expanding rapidly and new probiotic products are constantly...
being developed (Global Market Insights, 2016). However, relatively few probiotic strains are available commercially and probiotics are rarely in routine use in clinical practice. Moreover, all health claims relating to the benefits of probiotic bacteria are rejected by the European Food and Safety Authority (EFSA).

Van den Nieuwboer and colleagues (2016) therefore assessed the barriers and opportunities that influence probiotic innovation from initial concept to customer needs ultimately being met by the final product. Their valorisation model highlights the barriers that hamper probiotic innovation during fundamental scientific research, business development, market introduction and societal need articulation. Difficulty demonstrating clinical efficacy, competition with probiotic products without evidence base and the regulatory approval processes are said to be main innovation barriers (Van den Nieuwboer et al., 2016). However, the impact medical (health care) communities may have on probiotic innovation remains largely unaddressed, while their role could be pivotal. Many patients seek medical- and nutritional advice from their physician and the doctor-patient relationship may drive consumer acceptance and influence public opinion (Lähteenmäki, Lyly, & Urala, 2007). Some studies report that over 80% of medical doctors (MD) perceive probiotics to be safe and would advise them for gastrointestinal disorders (Marzet et al., 2014), which suggests that MD may foster the innovation of probiotic products. Results are however inconsistent and European countries appear to be underrepresented in current literature (Marzet et al., 2014; Oliver et al., 2014; Wheeler et al., 2016;).

The present study therefore aims to complement the current view on probiotic innovation barriers, by reviewing the impact of medical communities on probiotic innovation. To this end, the perceptions of MD on probiotics are reviewed and its implications for the innovation of probiotic products are discussed.

7.3 METHODOLOGY

7.3.1 Data collection

An online questionnaire was developed to review the attitudes of Dutch MD towards probiotics. The questionnaire was created using the SurveyMonkey® software and compromised 15 closed- and 4 open questions. Demographics, frequency of nutritional- and probiotic advice, indications for advice, perceived familiarity
with probiotics, attitudes towards probiotics and current and preferred information sources were addressed. The survey questions were piloted with five MD whose feedback was incorporated into the questionnaire before being sent to participants.

### 7.3.2 Study Population

The online survey invites were sent to 1676 General Practitioners (GP) and 741 Medical Specialists (MS) (gastroenterologists (GAST), elderly care physicians (ECP) and paediatricians (PAED)) who were working in the Netherlands. The databases of the National Academic Research and Collaborations Information System (NARCIS), BSL-Springer, SCEM and Zorgkaart Nederland were used to construct a contact information list. Additionally, a paper version of the survey was filled out by 60 GP at the General Practitioner Fair (Huisartsbeurs) on the 2nd of April 2016 in Utrecht, The Netherlands.

### 7.3.3 Statistical Analysis

The data were collected in a Microsoft Excel (2010) spreadsheet (Microsoft, San Francisco, CA, USA). Statistical analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). Two-tailed Fisher’s exact tests were used to analyse differences between groups. A p-value of < 0.05 was considered to be statistically significant. Open survey questions were analysed through open coding techniques.

### 7.4 RESULTS

#### 7.4.1 Survey respondents’ characteristics

A total of 514 respondents completed the online survey between April 2nd and May 30th, 2016. 99 respondents did not meet the inclusion criteria and were excluded from data-analysis as they were either still in training (n=48), did not complete the survey (n=26) or were from other specializations than the intended study population (n=25). Hence, 415 survey responses of Dutch MD were included in the data-analysis of the present study; 208 GP and 207 MS (117 ECP, 24 GAST and 66 PAED). Each Dutch province was represented by at least 5 MD (average = 35). The demographics of survey participants are presented in Table 7.1.
### Table 7.1 Survey Participant Characteristics

<table>
<thead>
<tr>
<th>Specialization</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>General Practitioners</td>
<td>208 (50%)</td>
</tr>
<tr>
<td>Medical Specialists:</td>
<td>207 (50%)</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>24</td>
</tr>
<tr>
<td>Elderly Care Physicians</td>
<td>117</td>
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<tr>
<td>Pediatricians</td>
<td>66</td>
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#### Age

<table>
<thead>
<tr>
<th>Age</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30 years</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>31-50 years</td>
<td>208 (50%)</td>
</tr>
<tr>
<td>51-64 years</td>
<td>175 (42%)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>20 (5%)</td>
</tr>
</tbody>
</table>

#### Years of practice

<table>
<thead>
<tr>
<th>Years of practice</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 years</td>
<td>93 (23%)</td>
</tr>
<tr>
<td>11-20 years</td>
<td>134 (32%)</td>
</tr>
<tr>
<td>21-30 years</td>
<td>114 (27%)</td>
</tr>
<tr>
<td>≥ 31 years</td>
<td>74 (18%)</td>
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</table>

#### Sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>187 (45%)</td>
</tr>
<tr>
<td>Female</td>
<td>228 (55%)</td>
</tr>
</tbody>
</table>

### 7.4.2 Nutritional and Probiotic Advice

Nutritional advice was provided to patients by 94% of MS and 99% of GP at least sometimes, regularly or often (Figure 7.1 A). Probiotic advice on the other hand was given to patients by 45% of MS and 53% of GP at least sometimes, regularly or often (Figure 7.1 B). No statistical differences were observed between MS and GP with regard to the frequency they provide nutritional or probiotic advice (p > 0.05).

MD that advise the use of probiotics in their practices (49% combined) are referred to as “advisers” from here on out and MD that do not advise the use of probiotics (51%) are referred to “as non-advisers”.
Figure 7.1 Half of medical doctors advise probiotics in their practice.

A) GP and MS were asked how often they provide nutritional advice to patients in their practices. No statistical differences were found between the nutritional advice frequency of GP and MS (Fisher’s exact, p > 0.05). B) GP and MS were asked how often they advise probiotics to patients in their practices. No statistical differences were found between the probiotic advice frequency of GP and MS (Fisher’s exact, p > 0.05)
Figure 7.2 Lack of evidence and awareness are the primary reasons for medical doctors not to advise probiotics.

A) Probiotic advisers were asked to list the medical indications for which they advise the use of probiotics. Multiple answers were allowed. No statistical differences were found between GP and MS with regard to the medical indications for which they prescribe probiotics (Fisher’s exact, p > 0.05). B) GP and MS that do not advise the use of probiotics in their practice were asked to list the reasons why. Multiple answers were allowed. MS significantly more often indicated that it is “Not part of their job” and that there is “No need/indication to advise probiotics” (Fisher’s exact, p < 0.05 both). * p < 0.05.
7.4.3 Indications for Probiotic Advice

The primary indications for which probiotics were recommended were AAD (75% GP vs. 73% MS) and IBS (51% GP vs. 51% MS). A complete overview of indications is presented in Figure 7.2 A. No statistical differences were observed between MS and GP with regard to the indications for which they prescribe probiotics.

7.4.4 Reasons Not to Advise Probiotics

Non-advisers were asked to list the reasons why they do not advise probiotics in their practice. The most important reasons were lack of evidence regarding the efficacy of probiotics (56% GP vs. 50% MS) and personal lack of knowledge on probiotics (31% GP vs. 35% MS). A complete overview of reasons is presented in Figure 7.2 B. MS significantly more often stated that advising probiotics is not part of their job (9% vs. 2%) or that they believe there to be no need (19% vs. 6%) compared to GP (p < 0.05 both).

7.4.5 Perceived Knowledge, Safety and Efficacy

In order to address the perceived familiarity of MD with probiotics, MD were asked to what extent they agree with the following statements: “I am familiar with the mode of action of probiotics”, “The usage of probiotics is safe” and “There is sufficient evidence regarding the efficacy of probiotics for the treatment of specific disorders”. One of the following choice options could be selected: “Disagree”, “Slightly Disagree”, “Slightly Agree” or Agree”. MD that agreed or slightly agreed with these statements were considered: to be familiar with the mode of action of probiotics, to perceive probiotics as safe or to perceive probiotics as efficacious, respectively. Significantly more advisers were familiar with the mode of action of probiotics than non-advisers (83% vs. 55% respectively, p < 0.0005). Furthermore, significantly more advisers deemed probiotics to be safe compared to non-advisers (82% vs. 62% respectively, p < 0.005). More advisers than non-advisers also perceived probiotics to be efficacious (64% vs. 24% respectively, p < 0.0005). An overview of the perceived knowledge, safety and efficacy of advisers and non-advisers is presented in Figure 7.3.
Figure 7.3 Safety, efficacy and mode of action of probiotics is less established according to non-advisers.
Figure 7.3 Continued

A) Probiotic advisers and non-advisers were asked to what extent they agree with the following statement: “I am familiar with the mode of action of probiotics”. The advisers significantly more often “Slightly Agreed” with the statement compared to non-advisers (67% vs. 45%, Fisher’s exact, p < 0.0005), whereas the non-advisers significantly more often stated they “Disagreed” compared to advisers (2% vs. 20%, Fisher’s exact, p < 0.0005). B) Probiotic advisers and non-advisers were asked to what extent they agree with the following statement: “The usage of probiotics is safe”. The advisers significantly more often “Agreed” with the statement compared to non-advisers (26% vs. 13%, Fisher’s exact, p < 0.0005), whereas the non-advisers significantly more often “Slightly Disagreed” (15% vs. 28%, Fisher’s exact, p < 0.005) or “Disagreed” (3% vs. 10%, Fisher’s exact, p < 0.0005) compared to advisers. C) Probiotic advisers and non-advisers were asked to what extent they agree with the following statement: “There is sufficient evidence regarding the efficacy of probiotics for the treatment of specific disorders”. The advisers significantly more often “Agreed” (16% vs. 4%, Fisher’s exact, p < 0.0005) or “Slightly Agreed” (48% vs. 20%, Fisher’s exact, p < 0.0005) with the statement compared to non-advisers, whereas the non-advisers significantly more often “Slightly Disagreed” (25% vs. 38%, Fisher’s exact, p < 0.05) or “Disagreed” (11% vs. 38%, Fisher’s exact, p < 0.0005) compared to advisers. * p < 0.05, ** p < 0.005, *** p < 0.0005.

7.4.6 Information Sources

Traditional media (TV, Radio, Newspaper) were the most important sources of information on probiotics for non-advisers (73%) but not for advisers (39%) (p < 0.0005) (Figure 7.4). Scientific journals (50% vs. 40%), medical associations/colleague experiences (53% vs. 31%), the industry (27% vs. 30%) and symposia (40%
Probiotic advisers and non-advisers were asked to list the sources they used to obtain information on probiotics. Multiple answers were allowed. The advisers, significantly more often than non-advisers, stated they used scientific journals, medical associations/colleague experiences and symposia as their sources of information (Fisher’s exact, \( p < 0.05 \), \( p < 0.0005 \), \( p < 0.005 \) resp.). Whereas the advisers significantly more often used traditional media as a source of information or did not receive any information (Fisher's exact, \( p < 0.0005 \) and \( p < 0.0005 \) resp.). * \( p < 0.05 \), ** \( p < 0.005 \), *** \( p < 0.0005 \).

vs. 24%) were the second most popular sources of information for both advisers and non-advisers, respectively (Figure 7.4). The advisers significantly more often used scientific journals, medical associations and symposia to obtain their information on probiotics compared to non-advisers (\( p < 0.0001 \), \( p < 0.005 \) and \( p < 0.005 \), resp.). Whereas, non-advisers significantly more often stated they obtained no information (11% vs. 2%). A complete overview of sources is presented in Figure 7.4.

### 7.4.7 Information Sources: Subgroup Analysis

MD who were familiar with the mode of action of probiotics, used symposia (40% vs 16%), scientific journals (56% vs 21%), medical associations/colleague experiences (49% vs 25%) and other sources (10% vs. 4%) significantly more often as
Figure 7.5 Medical doctors prefer future information on probiotic efficacy in scientific journals.

A) Probiotic advisers and non-advisers were asked to list the sources they prefer to use in the future to obtain information on probiotics. Multiple answers were allowed. The advisers, significantly more often than the non-advisers, stated that they prefer to use e-learning methods, symposia/information days and e-mails/newsletters to obtain their information on probiotics in the future (Fisher’s exact, p < 0.05, p < 0.05 and p < 0.005 resp.). B) Probiotic advisers and non-advisers were asked to list the type of information on probiotics they wish to obtain in the future.
CHAPTER 7

their source of information than MD who were unfamiliar with the mode of action of probiotics (p < 0.0005, p < 0.0005, p < 0.005 and p < 0.05, resp.). MD who perceived probiotics to be efficacious, used medical associations/colleague experiences (50% vs. 35%), symposia (41% vs. 26%) and other sources (11% vs. 6%) significantly more often than MD who perceived probiotics to be inefficacious (p < 0.05 for all). MD who perceived probiotics to be unsafe significantly more often did not receive any information compared to MD who perceive probiotics to be safe (11% vs. 5%, p < 0.05). MD who were unfamiliar with the mode of action of probiotics significantly more often used conventional media as their source of information (73% vs. 48%) or did not receive any information (21% vs. 1%) compared to MD that were familiar with the mode of action (p < 0.0005 for both). MD who perceived probiotics to be inefficacious also significantly more often used conventional media as their source of information compared to MD who perceive probiotics to be efficacious (64% vs. 45%, p < 0.05).

7.4.8 Future Information: Sources

Scientific journals are the preferred source of information for both advisers and non-advisers to learn about probiotics in the future (50% vs. 51%, resp.). Advisers furthermore preferred e-learning modules (39% vs. 28%), symposia (34% vs. 31%) and e-mails/newsletters (24% vs. 12%) significantly more often than non-advisers as their source of future information (p < 0.05, p < 0.05 and p < 0.005, resp.). A complete overview of preferred sources of future information on probiotics is presented in Figure 7.5 A.

7.4.9 Future Information: Types

Both advisers and non-advisers were primarily interested in future information on the efficacy of probiotics (Figure 7.5 B). However, significantly more advisers were interested in future information on probiotic efficacy than non-advisers (77% vs. 66%, p < 0.05). Future information on the mode of action of probiotics (40% vs. 34%), their safety (25% vs. 25%) and colleague experiences (24% vs. 19%) were also preferred by MD but no statistical differences were observed between advisers.
and non-advisers for these aspects, respectively (p > 0.05). The non-advisers more often did not want to receive additional information at all (27% vs. 18%, p < 0.05). A complete overview of the preferred types of future information is presented Figure 7.5 B.

7.4.10 Future Information: Subgroup Analysis

No statistical differences were observed between MD that prefer future information on either the mode of action, safety or efficacy of probiotics with regard to the source of information they prefer to use in the future (p > 0.05).

7.5 DISCUSSION & CONCLUSION

Positive perceptions of MD on probiotics may stimulate prescriptive behavior, thereby increasing consumer acceptance and fostering probiotic innovation. Most studies report that over 80% of MD perceive probiotics to be efficacious and recommend their use to patients (Cordina et al., 2011; Oliver et al., 2014; Williams & Ciorba, 2010). Our survey results, however, indicate that approximately half of MD advise probiotics in their practice, contrasting studies performed in the United States and the United Kingdom (where 90% and 70% of MD advised probiotics, respectively) (Williams & Ciorba, 2010; Cordina et al., 2011). We argue that conventional media such as radio, television and newspapers have detrimental effects on the perceptions of MD towards probiotics, as they were the primary sources of information for non-advisers (73%) but not for probiotic advisers (39%) (whose primary sources were medical associations (53%) and scientific journals (50%)). The extensive media coverage of the Dutch PROPATRIA trial (Besselink et al., 2008), often littered with miscommunications and misconceptions on probiotics (Foodnews, 2015), is an excellent example of how conventional media may stimulate negative perceptions. In this clinical trial, higher mortality rates in acute pancreatitis patients were attributed to an inefficacious, enterally administered, multi-species probiotic intervention (Besselink et al., 2008). The controversial results of this study fueled an immense discussion on probiotic safety in the Netherlands. It was later argued that the study did not follow Good Clinical Practice (GCP) guidelines (EU Directive, 2005) (Inspectie voor de Gezondheidszorg (Dutch Health Care Inspectorate), 2009), that the combination of proteolytic pancreas enzymes together with the probiotic intervention were the cause of higher mortality rates and that elevated levels of lactic acid produced by bacterial carbohydrate fermentation were a key
contributing factor (Van Baal, 2014; Bongaerts & Severijnen, 2016). Nevertheless, the implications of this study (and more specifically its media coverage) may have fueled long-lasting skepticism on probiotic safety and efficacy in the Netherlands (Mat & Voormolen, 2013).

Despite the fact that 38% of non-advisers perceived probiotics to be unsafe, safety concerns were one of the least important reasons (2%) for MD not to advise probiotics, consonant with previous studies (Williams & Ciorba, 2010; Marzet et al., 2014). Lack of clinical evidence was clearly the primary reason for MD not to advise probiotics (53%) and highlights a fundamental problem in the current innovation cycle. Van den Nieuwboer and colleagues (2016) reported that difficulty demonstrating probiotic efficacy is the most important barrier to innovation according to key opinion leaders. Thus, where medical communities express the need for clinical evidence on the one hand, industry and academia have difficulty demonstrating efficacy on the other hand. Challenges inherent to probiotic research in general (e.g., the relatively subtle effects of probiotics, lack of biomarkers and interpersonal variability of the microbiota), accompanied by the substantial costs of high-powered clinical trials, complicate the process of obtaining solid efficacy data. Moreover, competition with marketed products without evidence base makes probiotic companies reluctant to invest millions in clinical development (Van den Nieuwboer et al., 2016). More quality-controlled trials, however, remain of vital importance as 72% of MD which to obtain future information on the efficacy of probiotic products.

In order to improve MD perceptions on probiotics and to advance innovations in this field, more large-scale randomized controlled trials are required that demonstrate probiotic efficacy in adherence with strict GCP-guidelines. Research funding bodies accompanied by government regulations that further stimulate research and development will foster innovation and reduce the deleterious influence of unsubstantiated probiotic products on the market.

### 7.6 LIMITATIONS

A total of 514 respondents (21%) filled out the present survey out of the 2477 MD who were contacted (of which 415 respondents were fully compliant and included in the data analysis). This relatively low response rate, although common in
survey research, may engender nonresponse bias, potentially influencing the results (Groves & Peytcheva, 2008).

### 7.7 ACKNOWLEDGEMENTS

We thank Prof. Dr. J.F. van den Bosch, (Athena Institute, Vrije Universiteit Amsterdam) who provided insight and expertise during fruitful discussion that greatly assisted the research. We would furthermore like to give special thanks to all MD who participated in this study.

### 7.8 DISCLOSURE STATEMENT

O.F.A. Larsen is also Science Manager at Yakult Nederland B.V.
7.9 REFERENCES


