Chapter 8
Patient Needs and Research Priorities in Probiotics: A Quantitative KOL Prioritization Analysis with Emphasis on Infants and Children

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8.1. Abstract

Due to broad application of probiotics, research efforts are diluted, thus contributing to rejection of health claims. This study aimed to systematically prioritize the unmet needs and research opportunities in infants, children, adults and elderly for probiotics according to their relative importance from a key-opinion-leader (KOL) perspective. In addition, it reveals potential probiotic product characteristics that need improvement from both a patient or consumer and a KOL perspective. Moreover, KOL involvement in the probiotic research & development (R&D) process was assessed. Data was collected by conducting semi-structured interviews and subsequent online questionnaires. The three clinical indications requiring the highest research attention for infants were (infectious) diarrhoea, antibiotic-associated diarrhoea (AAD) and necrotizing enterocolitis (NEC); for children, obesity, AAD and diarrhoea and for adults, AAD, irritable bowel syndrome (IBS) and Alzheimer’s disease. From both a KOL as well as a patient or consumer perspective, clinical evidence needs to be improved for probiotic products. Although the majority of the KOLs consult for and perform research with probiotic companies, they are (surprisingly) not able to sufficiently influence industry research agendas. This study incorporates the insights of KOLs and provides direction in the R&D of probiotics to fulfil unmet medical needs in patients.
8.2. Introduction

An unmet medical need is defined as “a condition whose treatment or diagnosis is not addressed adequately by available therapy” (FDA, 2014). This includes an immediate need for a specific population. It is essential to identify medical needs to realize the optimal health care strategies for both society as well as industry (Weenen et al., 2014; van den Nieuwboer et al., in press). Identification of patient needs proves a valuable factor in the innovation process, and it is unlikely that patient-centered care occurs without a good understanding of patient needs and factors that influence the patients (Richardson et al., 2007). It is therefore key to comprehensively evaluate patients’ needs in order to provide quality care and cure.

The association between an alteration of the microbiome, a dysbiosis, and disease has become increasingly understood, and has led to new insights in potential targets for gut modulation in infants (0-2 yrs), children (2-18 yrs) and adults and elderly (>18 yrs). In every life stage there are strong associations between a dysbiosis of the gastrointestinal tract microbiota and the development of gastrointestinal, metabolic and immunologic diseases. For instance, NEC, late onset sepsis, allergic dermatitis, recurrent wheeze and food allergy are related to enteric dysbiosis (Azad et al., 2015; Berrington et al., 2012; Penders et al., 2007). In the subsequent stage of childhood, diseases that may emerge in the presence of dysbiosis are inflammatory bowel disease (IBD), obesity, diabetes, atopic diseases (e.g. asthma, atopic dermatitis (AD), allergic rhinitis and allergic conjunctivitis) and IBS (Arrieta et al., 2014; Saulnier et al., 2011). Moreover, there are indications that dysbiosis also plays a role in the pathophysiology of neurodevelopmental disorders, such as autism spectrum disorders (ASD), or through the gut-brain axis (GBA) (Arrieta et al., 2014; Cryan and Dinan, 2012; Foster and Neufeld, 2013). The GBA is a reciprocal communication system, which via biochemical signalling pathways, facilitates interaction between the gastrointestinal tract and the brain (Mayer, 2011). In adults, microbial dysbiosis may influence susceptibility to mood disorders, such as anxiety and depression (Cryan and Dinan, 2012). Other adult diseases related to altered gut microbiota include, colorectal cancer, atherosclerosis and non-alcoholic fatty liver disease (de LeBlanc and LeBlanc, 2014). In total there are over 25 diseases, syndromes, or other aberrations that have been associated with the microbiota throughout these life stages (de Vos and de Vos, 2012), thus advocating for a targeted approach with possible interventions by modulating the gut with probiotics. Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill et al., 2014). Currently, the practical use of probiotics is driven by ‘soft’ health effects and promotion of well-being rather than the treatment or prevention of disease symptoms (Foligné et al., 2013).

The application range for probiotic products is very wide and data on effectiveness is piling up. For example, a Cochrane review of well-designed randomized controlled trials (RCT) demonstrated a reduced incidence of upper respiratory tract infections in the probiotic group compared to the placebo (Hao et al., 2011). Another Cochrane review of RCTs compared the effectiveness of probiotics in NEC and showed
that enteral probiotics supplementation significantly reduced the incidence of severe NEC and mortality in preterm infants (AlFaleh and Anabrees, 2014). Probiotic use in treatment or prevention of disease symptoms appears promising for specific diseases and populations, and thereby may potentially address a large number of unmet medical needs. To date, however, medical needs in society are still not yet met as no probiotic products are in routine practice for clinical indications. Research efforts are diluted, and therefore application in medical practice is substandard. The large number of disease areas, potential clinical indications and variety of probiotic strains makes the allocation of the limited resources available within probiotic research both challenging and controversial. This translates into underpowered clinical studies, lack of knowledge in mechanism of action and several other barriers that hamper the innovation process (van den Nieuwboer, in press). As a result, the European Food Safety Authority (EFSA) has been rejecting all claims for probiotic products in the absence of research focus so far (Rijkers et al., 2011). By performing a needs assessment, unmet medical needs can be identified. This is also known as a ‘market pull’, whereby the need or requirement for a new product or a solution to a problem comes from the market through the demand of potential customers or users (e.g. patients). Assessing the medical needs by means of a needs assessment may function as an innovation opportunity for the academic field and the probiotic industry. One way to assess the medical needs is by prioritizing the health research, thus providing researchers clear directions in what research deserves the most attention.

As many communicable and non-communicable diseases may present serious public health threats for humans, it is necessary to prioritize the resources dedicated for clinical research of these diseases (Balabanova et al., 2011). Prioritization has been proven useful in other settings, such as the enteral nutrition market and infectious diseases (Balabanova et al., 2011; Weenen et al., 2014). By assessing health needs, it can aid in future resource allocation and strategic planning at a multidimensional level.

There is often a mismatch between research driven by the interest of scientists, industry and interest groups and the needs of the population. For instance, in pharmaceutical industry, scientific and financial opportunities, and available and required resources mostly drive the drug development priority.

To our best knowledge, a prioritization of patient and consumer needs for probiotics is lacking. Such an overview may provide focus and direction in probiotic research in the academic field to facilitate obtaining health claims for products in treatment or prevention of disease symptoms. The research objective was to prioritize the unmet needs of the infant, children and adult and elderly population to assess the clinical indications that require more research attention in probiotic research. Furthermore, we determined which product characteristics have the highest priority in probiotic development, and evaluated the degree of involvement of KOLs in the probiotic R&D process from a KOL perspective.
8.3. Methods

The design of the study was based on the research prioritization by Weenen et al. (2014) and Balabanova et al. (2011). Since patients and consumers in general are not informed about the potential disease areas that probiotics target, and their function in maintaining health, KOLs were prompted to provide clinical indications that require research priority. During the first stage of the research disease areas, clinical indications and important product characteristics of probiotics were gathered through KOL interviews. Subsequently these clinical indications and product characteristics were ranked according to their priority through an online questionnaire. In addition, KOL involvement in probiotic research & development (R&D) was included.

8.3.1. Semi-structured interviews

Potential disease areas, clinical conditions and product characteristics were compiled by means of semi-structured interviews with KOLs. A KOL is defined as an individual with extensive knowledge in the field of probiotics (research, market, clinical development). Furthermore, the interviews acted as a pilot to validate the questions for the online questionnaire. Open questions were posed on the following topics: patient needs research, innovation opportunities for patient needs and importance of product characteristics. A copy of the interview design can be made available upon request. A total of 25 KOLs were approached for this study, of which, 16 agreed to participate. The participants were selected based on their expertise and relative perspective (academia, industry and regulatory). Saturation curves were used to ensure all conceivable answers were included into this study.

8.3.2. Online questionnaire

Using the data from the semi-structured interviews, an online questionnaire was constructed using the online web survey tool Survey Monkey®. This anonymous online questionnaire was pilot tested and initially distributed among 127 selected KOLs (from different perspectives; practicing medical doctor; MD, researchers, dieticians, regulators, consultants and business developers). Furthermore, KOLs were invited to participate in this research at several international scientific symposia on probiotics; additional KOLs were approached using the snowball-method. Non-respondents received a reminder of the invitation after 7 days to increase the response-rate.
8.3.3. Disease prioritization

The questionnaire consisted of 32 open and closed questions. Clinical indications were ranked by KOLs for infants (0-2 yrs), children (2-18 yrs) and adults and elderly (> 18 yrs). Distinction was made between these population groups based on different diseases affecting at particular stages of life. KOLs were asked to rank three infant, children and adult disease indications ($n=19$; $n=20$; $n=26$ clinical conditions respectively) according to their priority requiring or deserving more research and investigation, with the highest priority receiving a weight of three, the second highest a weight of two and so on. The following formula was used to determine the relative weighted ranking of clinical indications.

$$WR_p = \frac{\sum (n_{r1} * 3) + (n_{r2} * 2) + (n_{r3} * 1)) \times 100}{\sum ((n_{r1} * 3) + (n_{r2} * 2) + (n_{r3} * 1))_{HP}}$$

WR, weighted ranking; P, priority; HP, highest priority; n, number of times; R1/2/3, rank1/2/3.

Cut-off points were applied to differentiate between low priority (0 - 33), medium priority (34 – 66) and high priority (67 – 100). A copy of the questionnaire can be made available upon request.

8.3.4. Product characteristics

Furthermore, KOLs were asked to rank the importance of probiotic products characteristics in general and prioritize the need for product characteristic improvement both from their own and a patient or consumer perspective. Both perspectives were asked from the KOLs to ensure validity and determine the discrepancies between KOLs and patients or consumers. A total of 12 product characteristics (brand reliability, composition, convenience, easy industrial upscaling, efficacy and clinical evidence, formulation, price, product information or labelling, safety, shelf-life, (genetic) stability and taste) were identified and ranked. Composition refers to the selected probiotic strains and dosage, convenience to the ease of use, formulation to the used matrix (lyophilized powder, yoghurt, etc.) and (genetic) stability to maintaining probiotic properties over time. A similar approach as described in section 2.2.1. was used to calculate the relative ranking.
8.3.5. KOL involvement

Using a 5-point Likert-scale, the KOL involvement in the R&D process of probiotics was measured; ranging from 1, not at all, to 5, a very large amount. Involvement could be determined by calculating the mean and median involvement. The difference between KOL involvement was calculated with the Wilcoxon signed-rank test using statistical analysis software (SPSS, version 20). A $P < 0.05$ was considered statistically significant.

8.4. Results

8.4.1. Demographics

Of the 82 participants that initially responded, 52 fully completed the online questionnaire. The majority fulfilled a position as an academic (50%), followed by practicing MD (~26.9%), consultant (~9.6%), industry representative (~9.6%) and dietician (~3.8%). Age groups could be subdivided into 25 – 40 (26.9%), 40 – 55 yrs (55.8%) and > 55 yrs (17.3%). For all population groups, saturation of clinical indications was observed after 12 interviews (see figure 8.1).

The majority of the KOLs researched unmet patient or consumer needs (61.5%). This occurred either through direct contact with patients and consumers (49%), by participating in research programs (27.5%), by conducting questionnaires (17.6%), or via marketing research and through health professionals (5.9%).

The mean perceived extend that KOLs were involved in the academic R&D process of probiotic products, ranging on a five-point Likert-scale from 1 (not at all) to 5 (very large amount), was 2.83 ± SD 1.17 (median of 3.0). Their involvement in the industry R&D process was perceived significantly lower with a mean of 2.54 ± SD 1.29 (median of 2.0; $P<0.01$). Although 62.9% of the KOLs indicated to collaborate with or do research sponsored by probiotic companies, the perceived extent that KOLs can influence research priorities set by probiotic companies was even lower (median of 2.0; mean of 2.37 ± SD 0.96; $P<0.05$).
8.4.2. Clinical indication prioritization

The semi-structured interviews led to the identification of nine major disease areas requiring research attention for probiotics. This concerned allergies, auto-immune disorders, cancer, cardiovascular disease, gastrointestinal disorders, infections (bacterial and viral), metabolic disorders, neurological disorders and general conditions (e.g. acne).
Figure 8.2. Research prioritization for infants, children and adults; low priority (0-33), medium priority (34 – 66) and high priority (67 – 100). AAD, antibiotic-associated diarrhoea; AD, atopic dermatitis; ADHD, attention deficit hyperactivity disorder; CF, common flu; IBD, inflammatory bowel disorder; IBS, irritable bowel syndrome; MS, multiple sclerosis; NEC, necrotizing enterocolitis; OM, otitis media.

For infants the following clinical indications require more research attention: AAD, asthma, AD, autism, coeliac disease, cognition, colic, diabetes (type 1 and 2), diarrhoea (bacterial/viral), food allergy, growth, IBD, malnutrition, NEC, obesity, respiratory infections, seasonal allergy and short bowel syndrome (SBS). The following additional diseases were applicable for children: attention deficit hyperactivity disorder
(ADHD), common flu, constipation, dental health, IBS, metabolic syndrome and otitis media (OM), and for adults/elderly: acne, Alzheimer’s disease, anxiety, bloating, cancer, cardiovascular disease, dementia, depression, multiple sclerosis (MS), schizophrenia, stress and vaginal health.

According to the KOLs, highest priority in probiotic research for infants should be given to diarrhoea (bacterial/viral) followed by AAD and NEC. For children, the highest priority should be given to obesity, followed by AAD and diarrhoea (bacterial/viral) and for adults this concerned AAD, IBS, Alzheimer’s disease and metabolic syndrome. Figure 8.2 illustrates the priority (low – medium – high) for each clinical condition and per population group. Other general effects requiring attention were research on the positive influence of probiotics on the gut in terms of bowel movement and abdominal discomfort (incl. bloating, gas, etc.). Exploring the effect of prenatal probiotic supplementation, how the gut is normally colonized, the effect of probiotics on brain development, reducing side effects of antibiotics by probiotics, effects of probiotics on immunity, metabolism, and infectious diseases. Furthermore it is important to explore the potential of probiotics to improve vaccine efficacy and in combination with other drugs.

8.4.3. Product characteristics

Table 8.1 demonstrates the weighted ranking of the importance of probiotic product characteristics from a KOL and patient perspective, and the need for improvement. Clinical evidence was considered the most important probiotic characteristic from both a KOL as well as a patient perspective, and needs improvement. Other characteristics deemed important from a KOL perspective were composition (strains) and safety. Product characteristics that need improvement were price, composition and product information or labelling. From a patient perspective, safety and price were most important, and improvement is necessary for price, product information or labelling, convenience, brand reliability, shelf-life and safety. When combining both the relative importance and need for improvement into a matrix, it becomes evident which product characteristics deserve the highest priority (Figure 8.3). From both a KOL as a patient or consumer perspective, highest priority is warranted for clinical evidence. From a KOL perspective, composition is assigned to the medium priority group, as from a patient or consumer perspective, this concerns safety and price. Of low priority are stability, convenience, brand reliability, shelf-life, formulation, taste (surprisingly), easy industrial upscaling, product information and labelling, including safety and price from a KOL perspective and composition from a patient or consumer perspective. Although there is a small discrepancy in the medium priority quadrant, both from a KOL and a patient or consumer perspective, KOLs acknowledge there is a need to improve the clinical evidence of probiotic products.
Table 8.1. Weighted importance of probiotic product characteristics from a KOL and patient or consumer perspective

<table>
<thead>
<tr>
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<th>KOL perspective</th>
<th>Patient perspective</th>
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<tr>
<td></td>
<td>Important</td>
<td>Improved</td>
</tr>
<tr>
<td>Efficacy/clinical evidence</td>
<td>100,0</td>
<td>100,0</td>
</tr>
<tr>
<td>Composition</td>
<td>64,3</td>
<td>37,5</td>
</tr>
<tr>
<td>Safety</td>
<td>62,2</td>
<td>26,3</td>
</tr>
<tr>
<td>Stability</td>
<td>18,4</td>
<td>21,3</td>
</tr>
<tr>
<td>Convenience</td>
<td>14,3</td>
<td>22,5</td>
</tr>
<tr>
<td>Price</td>
<td>12,2</td>
<td>41,3</td>
</tr>
<tr>
<td>Brand reliability</td>
<td>10,2</td>
<td>26,3</td>
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<tr>
<td>Shelf life</td>
<td>9,2</td>
<td>27,5</td>
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<tr>
<td>Formulation</td>
<td>8,2</td>
<td>23,8</td>
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<tr>
<td>Taste</td>
<td>7,1</td>
<td>13,8</td>
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<tr>
<td>Easy industrial upscaling</td>
<td>7,1</td>
<td>15,0</td>
</tr>
<tr>
<td>Product information/labelling</td>
<td>5,1</td>
<td>35,0</td>
</tr>
<tr>
<td>Importance</td>
<td>Need for improvement</td>
<td>Efficacy and clinical evidence</td>
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<tr>
<td>High</td>
<td>Safety</td>
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<tr>
<td>Medium</td>
<td>Composition</td>
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<tr>
<td>Low</td>
<td>Stability, convenience, brand reliability, shelf life, formulation, taste, industrial upscaling</td>
<td>Price, product Information and labelling</td>
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**Probiotic product prioritization; KOL perspective**

<table>
<thead>
<tr>
<th>Importance</th>
<th>Need for improvement</th>
<th>Efficacy and Clinical evidence</th>
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<tbody>
<tr>
<td>High</td>
<td>Safety, price</td>
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<tr>
<td>Medium</td>
<td>Composition</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Composition, stability, formulation, taste, industrial upscaling</td>
<td>Convenience, brand reliability, shelf life, product information and labelling</td>
</tr>
</tbody>
</table>

**Probiotic product prioritization; Patient/consumer perspective**

*Figure 8.3. Probiotic product characteristic prioritization from a KOL and a patient/consumer perspective with ‘need for improvement’ plotted against ‘importance’.*
8.5. Conclusion and Discussion

Recently we showed that the innovation process in probiotic research is faulty and due to a lack of research focus, the evidence-base for probiotics is low (van den Nieuwboer et al., in press). The current study systematically evaluated the prioritization of research opportunities in the field of probiotics. Since probiotics can play an important role in the treatment or prevention of several diseases and thereby may fulfil unmet medical needs, research direction and guidance is warranted. Fulfilling these unmet needs should be the primary guide for research innovation and development, instead of commercial interests, to result in a better implementation of probiotics in society. Research opportunities could be subdivided for three population groups; infants, children and adults or elderly. The three clinical indications requiring the highest research attention for infants were (1) diarrhoea, (2) AAD and (3) NEC; for children (1) obesity (2) AAD and (3) diarrhoea and for adults; (1) AAD (2) IBS and (3) Alzheimer's disease. From both a KOL as well as a patient or consumer perspective, clinical evidence needs to be improved for probiotic products. Furthermore this study demonstrated that collaboration between KOLs and industry R&D process is present, however, the perceived extent that KOLs can influence research priorities in industry is low. To ensure that patients’ unmet needs are fulfilled it is desired that KOLs, as patients’ advocates, will have more influence on setting research agendas in industry R&D processes. This could be achieved by improving collaboration between KOLs and industry. In the following sections the clinical conditions requiring the highest priority in probiotic research will be discussed.

8.5.1. Disease prioritization infants and children

8.5.2. Diarrhoea

Diarrhoeal diseases mostly affect people living in low- and middle-income countries, with mortality rates of children (<5 years) reaching 751 thousand deaths a year. Diarrhoea thereby remains the third leading cause of death in children below the age of five (Liu et al., 2012). More than 20 viruses, bacteria and parasites are considered etiological agents in infectious diarrhoea, of which Salmonella, Shigella, and Campylobacter are important examples of bacterial pathogens (Allen et al., 2010). In high-income countries diarrhoea, as a symptom of gastro-enteritis, frequently leads to hospitalization. For instance, in the Netherlands, 1 in 80 children between 0-4 years is hospitalized for gastro-enteritis with diarrhoeal symptoms. This involves significant costs estimated to be around 40 million euros annually (Friesema et al., 2012). The current treatment strategy for acute diarrhoea is administration of oral rehydration solution (ORS). Although ORS interventions have an impact on the mortality, the treatment is solely targeting the dehydration and global coverage is still not sufficient (Unger et al., 2013). Probiotic administration is associated with reduction of the mean duration in diarrhoea. In a meta-analysis with 8,014 subjects, of which 6,489 infants and
children, probiotics demonstrated to reduce the mean duration of diarrhea by one day (mean = 24.76 hours, 95% confidence interval (CI) 15.9 to 33.6 hours) (Allen et al., 2010). In line, Huang and colleagues (2002) concluded in another meta-analysis that co-administration of probiotics with standard rehydration therapy leads to a reduction in diarrhoea duration by approximately one day in otherwise healthy children (<5 years) with acute onset of diarrhoea. Probiotics appear to be safe in treatment of diarrhoea amongst hospitalized children with no known interactions between probiotics and other medications (Floch, 2014l; Rosenfeldt et al., 2004). Similar to children, elderly are susceptible to development of infectious diarrhoea (Allen et al., 2010). The symptoms can have devastating effects on health and quality of life in the elderly (Bennett and Greenough, 1993). Moreover, it may lead to frequent hospitalizations consequently leading to high healthcare costs. The treatment of an elderly patient with diarrhoea is to ensure proper hydrations using ORS (Bennett and Greenough, 1993). Interestingly, probiotics demonstrate the potential to decrease morbidity, healthcare costs, and mortality in patients over the age of 50 (Floch, 2014). These results, both for the young and elderly population are encouraging (van den Nieuwboer, 2015b). Nevertheless, more effectiveness studies are needed to identify the specific dosages, regiments, formulations and timing to be used in infants, children and adults/elderly (Sazawal et al., 2006).

8.5.3. AAD

Disrupting the intestinal microbiota with antibiotics is associated with mild, self-limiting or severe diarrhoea in all age populations. Antibiotic associated diarrhoea (AAD) may present itself as mild to severe colitis, mega colon or death, especially in the case of a Clostridium difficile infection (CDI) (Hempel et al., 2012; Hell et al., 2013). AAD is defined as otherwise unexplained diarrhoea that occurs in association with the administration of antibiotics in as many as 30% of children, and is a significant reason for non-adherence to therapy (Szajewska and Kolodziej, 2015). The incidence of AAD in children is high compared to adults, as paediatric antibiotic usage rates are three times greater compared to adults (Szajewska and Kolodziej, 2015; Xie et al., 2015). In a Cochrane systematic review, Johnston et al. (2011) assessed the efficacy of probiotics in 3,432 children between 0-18 years. Their meta-analysis included subjects receiving probiotics (Lactobacilli spp., Bifidobacterium spp., Streptococcus spp., or Saccharomyces boulardii alone or in combination), placebo, other treatments thought to prevent AAD (i.e. diosmectite or infant formula) or no treatment. The authors concluded that probiotics appear to have a protective effect in preventing AAD in infants and children, especially Lactobacillus rhamnosus and Saccharomyces boulardii were effective to prevent the onset of AAD when ingested in high-dosages (≥5·10⁹ cfu/day) (Johnston et al., 2011). In concordance with these findings, another meta-analysis demonstrated that probiotic treatment reduced the risk of AAD from 28.5% to 11.9% compared to the placebo in children (Relative risk (RR) 0.44, 95% CI 0.25 to 0.77) (Szajewska et al., 2015). None of the included studies that documented on adverse events reported any serious adverse events with probiotic use and the examined strains appeared to be safe in this population (Johnston et al.,
The incidence rate of AAD is also high in the elderly population (Xie et al., 2015). In case AAD as a result of CDI, current treatment with vancomycin is suboptimal (van Nood et al., 2013). Nevertheless, the reduction of AAD by probiotics in this population remains to be demonstrated. In sum, available data on probiotic efficacy in AAD are encouraging for infants and children, yet it is difficult to draw definitive conclusions from current available studies for routine use in practice. This is due to small sample sizes, heterogeneity in probiotic strains, dose, and duration in studies. Future multi-centre, double-blind clinical trials are necessary to determine the optimal probiotic strain(s), the optimal dosing schedule and cost-effectiveness of probiotics (Szajewska et al., 2006). Moreover, future research assessing probiotic efficacy (e.g. incidence and duration of diarrhea) also needs to take into account the types of antibiotics used by patients (Xie et al., 2015).

8.5.4. NEC

NEC is a serious intestinal inflammatory disorder affecting almost 10% of all infants with a low birth weight (<1500 g). It is the most common gastrointestinal emergency in premature infants associated with high mortality and morbidity rates (Berrington et al., 2012; Chen and Walker, 2013). Besides breastfeeding, there are no alternative preventive therapies for NEC (Lee and Polin, 2003). Probiotic administration is associated with a reduction in the incidence of NEC (49.1%). Furthermore, it is associated with reduced overall mortality (26.9%) in very-low-birth-weight (VLBW) infants (Lau and Chamberlain, 2015). To illustrate, a Cochrane review and meta-analysis including 24 RCTs and more than 5000 preterm infants (<1500 gr) investigated probiotic efficacy in treatment and prevention of NEC (AlFaleh and Anabrees, 2014). It demonstrated that both the administration of Lactobacillus species (five trials) and a mixture of probiotics (nine trials) significantly lowered the incidence of severe stage II to III NEC (RR 0.45, 95% CI 0.27 to 0.75; RR 0.37, 95% CI 0.25 to 0.54 respectively). Moreover, administration of prophylactic probiotics significantly reduced mortality (typical RR 0.63, 95% CI 0.50 to 0.81) and NEC related mortality (typical RR 0.38, 95% CI 0.18 to 0.82). Furthermore, the authors showed that the administration of a mixture of probiotics (nine trials) was, in contrast to single species probiotics, significantly more effective in reducing the incidence of mortality (RR 0.62, 95% CI 0.47-0.81) (AlFaleh and Anabrees, 2014). Various mechanisms of action have been proposed, for instance, probiotics may inhibit pathogenic colonization, improve the intestinal barrier function and or regulate the intestinal immune response. Nevertheless, the definite mechanism-of-action of probiotics in NEC remains unclear (Lau and Chamberlain, 2015). In conclusion, there is ample evidence that probiotics are effective in treatment of NEC, yet, probiotic treatment is still not in routine use. To adjust clinical guidelines and to support a change in practice head-to-head comparative studies are required that evaluate the optimal strains dosage, duration and feeding regiment of probiotics to infants susceptible to NEC (Lau and Chamberlain, 2015).
8.5.5. Obesity

Childhood obesity is an emerging problem in many countries worldwide. Approximately 110 million children and adolescents are now classified as overweight or obese and this number is rising. Obesity is consequently becoming one of the greatest global health challenges of this century (Haslam and James, 2005). Childhood obesity is associated with significant health problems, such as cardiovascular disease, type 2 diabetes and metabolic syndrome (e.g. elevated blood pressure, high fasting glucose levels, presence of acanthosis nigricans, and elevated aminotransferase levels (Cali and Caprio, 2008; Haslam et al., 2006). Moreover, up to 80% of obese children become obese adults demonstrating the need for early interventions (Cali and Caprio, 2008). Effective prevention and treatment of obesity is long-term weight loss, which can be achieved by changes in diet, energy intake and increased physical activity. To date, however, these interventions have not been effective to reduce the prevalence of obesity globally (Haslam and James, 2005).

Gut microbiota may participate in the existence of obesity as its composition has significant effect on energy metabolism, glucose metabolism and mucosal and systemic immune responses. For instance, metabolites from the gut microbiota can serve as energy to the host and mediate satiety (Aguirre and Venema, 2015). There is limited evidence that probiotics can mitigate metabolic complications such as obesity in children. A randomized-controlled clinical trial performed by Alisi et al. (2014) in obese children (n=48, mean age 11 yr) with proven non-alcoholic fatty liver disease demonstrated a reduction in body weight and fatty liver severity with consumption of probiotics (VSL#3) compared to placebo in these children. In addition, obesity is highly prevalent in the adult population and 1.1 billion adults are now classified as overweight or obese. In adults, obesity reduces average life expectancy and is a risk factor for cardiovascular and metabolic diseases and several cancers (Haslam and James, 2005). Probiotic intake in overweight adult individuals was associated with decreased abdominal visceral and subcutaneous fat, body weight, and waist circumference (Shen et al., 2013). In contrast, Park and Bae (2015) investigated in their systematic review and meta-analysis the therapeutic efficacy of probiotics compared to placebo. Their analysis included 4 RCTs and demonstrated that probiotics did not show a significant effect on body weight and BMI. In sum, the continuous dramatic increase in obesity worldwide in children and adults confirms the need for new effective intervention strategies for prevention and treatment of obesity and its complications. Probiotics may serve a role to reverse the anticipated trend; however, data on probiotic efficacy on reducing body weight is incomplete. It demands vast amounts of evidence from RCTs and cohort studies over time before probiotic therapies, as a contributing factor to exercise and healthy lifestyle, can be used in clinical practice to help decrease body weight (Aguirre and Venema, 2015). Therefore, more large well-designed studies are necessary to examine the effect of probiotics on body weight in greater detail in both children and adults.
8.5.6. Disease prioritization in adults or elderly

8.5.7. IBS

IBS affects approximately 10-20% adults in developed countries (Whelan and Quigley, 2013). IBS is a functional gastrointestinal disorder characterized by recurrent abdominal pain, bloating and bowel dysfunction (diarrhoea, constipation or an alternation between the two) in the absence of an organic cause. IBS significantly impairs health related quality of life in patients living with the condition (Blagden et al., 2015). Effective pharmacological and behavioural therapies for IBS are available, however these therapies often only provide relief on short term and not all patients respond to available therapies (Ford et al., 2014).

An unbalanced intestinal microbiota and chronic immune activation leads, amongst others, to a low-grade mucosal inflammation whereby it plays a role in the pathogenesis of IBS. Probiotics, by rebalancing the enteric microbiota, may therefore be an attractive treatment option (Ford et al., 2014). A recent systematic review and meta-analysis including 23 RCTs with 2,575 adult patients examined the efficacy of probiotics (Lactobacillus, Bifidobacterium, E. Coli, Streptococcus, Saccharomyces, Lactobacillus) in the treatment of IBS compared to placebo and concluded that probiotics decrease overall symptoms of IBS compared to placebo (RR 0.79; 95 % CI 0.70 – 0.89) with a number needed to treat of 7 (Ford et al., 2014). Moreover, probiotics significantly reduce symptoms of bloating, flatulence and abdominal pain as compared to placebo (respectively, bloating scores, Standardized Mean Difference (SMD) = −0.15; 95 % CI −0.27 to −0.03; flatulence scores, SMD = −0.23; 95 % CI −0.38 to −0.07; abdominal pain SMD = −0.25; 95 % CI −0.36 to −0.14). Although, probiotics have an excellent safety record (van den Nieuwboer et al., 2015a, b), the RR of experiencing any adverse event was significantly higher with probiotics in the studies examined (RR 1.21; 95 % CI 1.02 – 1.44) (Ford et al., 2014). In contrast, Mazurak et al. (2015) concluded that the current available data on probiotic effectiveness in IBS does not allow to perform a methodologically sound meta-analysis due to large heterogeneity of studies (e.g. different bacterial strains, mixtures of strains and dosages). Moreover, in their systematic literature review including 56 RCTs, the authors showed that more than 50% of the trials presented negative outcomes on reducing global symptoms (Mazurak et al., 2015). The debate therefore continues whether probiotics should be recommended for the reduction of IBS symptoms in the adult population. In an attempt to understand the precise role of probiotics in IBS adequately, powered, methodically correct trials with focus on patient selection criteria, treatment duration, probiotic dosages and strains, and the choice of primary and secondary endpoints, are required. In addition, KOLs in our research did not rank IBS as a high research priority for the child population. Nevertheless, we will briefly discuss IBS in children given the significant impact of the syndrome on the daily functioning and quality of life and given that there is no real therapy or satisfying treatment available for children (Mahler, 2015; Santos and Whorwell, 2014). The prevalence of IBS in children and adolescents around the world varies from 6-24% (Hyams et al., 1996; Reshetnikov et al., 2001; Thomson and Dancey, 1996). It enacts a significant psychological and economic
burden on patients’ families and healthcare systems (Hoekman et al., 2015). Probiotics seem to be effective in reducing the intensity of abdominal pain/discomfort and bloating in children and teenagers with IBS. The results on probiotic efficacy in reducing IBS symptoms are, however, based on limited number of studies and there is a high variety of species, strains and dosages of the probiotics used in studies. This indicates the urgency for more research on probiotic efficacy in children and teenagers on which probiotic strains to use in clinical practice for children with IBS. In conclusion, probiotics may exert a positive effect in reduction of IBS symptoms in both child and adult population; however, we need to take a step back and re-evaluate patient selection criteria and primary and secondary outcomes for future research. This will eventually help to generate more evidence on efficacy and will help to define the useful probiotic organisms to use in daily practice.

8.5.8. Alzheimer’s disease

The global prevalence of dementia is high with a prevalence of 24 million individuals suffering from the condition. Alzheimer’s disease is the leading cause of dementia and imposes a major social, medical and economic burden to society [61]. Moreover, with no treatment options, Alzheimer’s disease has become a health- and social-care priority for many high-income countries (Sindi et al., 2015; Prince et al., 2013). Although research on the GBA and gut modulation to mitigate or prevent neurophysiological disorders is still in its infancy, there is increasing evidence that probiotics might play a beneficial role in Alzheimer’s disease management. As mentioned above, the human microbiome is potentially involved in the regulation of several neuro-metabolic and neuro-chemical pathways, thereby connecting the intestines with the central nervous system (Bhattacharjee and Lukiw, 2013). A proposed mechanism on the efficacy for probiotics is for instance the ability of several lactobacilli and bifidobacteria to produce GABA; dysfunctions in signalling of this neurotransmitter are linked to Alzheimer’s disease. Furthermore, in “germ-free” mice the expression of brain-derived neurotrophic factor was reduced, which is also observed in patients with Alzheimer’s disease (Bhattacharjee and Lukiw, 2013). The clinical implications of these findings are yet to be determined. Whether modulating the gut by probiotics will truly be effective in the prevention or improvement of quality of life in of Alzheimer’s disease remains to be determined, nevertheless KOLs believe there is much to gain in this field.

8.5.9. Product characteristics

Both from a patient or consumer and a KOL perspective, the clinical evidence of probiotics is perceived as the characteristic that should receive the highest priority. It seems that the KOL are somewhat in line with the EFSA and FDA in that the current evidence for health claims is insufficient. Due to difficulties inherent
to clinical trials (e.g. interpersonal differences, lack of biomarkers and subtle effects of probiotics, long-term follow up), poor study designs (e.g. underpowered studies, no intention-to-treat analysis, subject selection), heterogeneity between studies (e.g. probiotic preparations, probiotic interventions, study duration) and possible publication bias (e.g. less publication of negative results) it remains difficult to demonstrate efficacy and clinical (van den Nieuwboer et al., in press). From a patient perspective, safety received a medium priority, whereas from a KOL perspective it received a high priority by means of health and a low priority for improvement. Safety is important for products, however, in line with literature, the current probiotic products are safe to use, even in highly susceptible individuals such as infants, children and immune compromised adults (van den Nieuwboer et al., 2015a; van den Nieuwboer et al., 2014a, b). It is likely that the need for safety improvement from a patient perspective illustrates the need to improve perceived notion that probiotics are safe to use.

### 8.5.10. Concluding remarks

It should be noted that not all diseases that can potentially be targeted by probiotics were mentioned and or incorporated in this study, due to the wide variety of application possibilities and new emerging disease targets. One other point of argument could be that the participating KOLs may not accurately represent the unmet need from a patient perspective, as they are not affected by the disease. However, half of KOLs are academics researching unmet patients or consumer needs and more than a quarter had direct contact with patients. More importantly, KOLs as experts in the field of probiotics, and in contrast to patients are familiar to the full potential of probiotics related to different diseases. Therefore, we regard these KOLs perspectives as most useful to prioritize research focus in probiotic research. This study subsequently provides a comprehensive and reliable overview on which clinical indication deserves the highest research attention based on KOLs expertise and expectations (e.g. promising evidence, high burden of disease or no alternative therapy). For all the clinical indications there seems to be a recurrent challenge for every age group. Initial evidence seems promising, however due to severe limitations of study designs, further research is warranted. This prioritization study provides guidance in probiotic research and gives focus to the current diffused and scattered probiotic research. In addition, we recommend enhancing translation of scientific knowledge into clinical applications by investigating probiotics that are or will be accessible to the market as opposed to the current situation where some effective probiotics are not available for third party use or for consumers/patients. Future focused research may then lead to targeted probiotic interventions and probiotic health claims to fulfil unmet medical needs in the infant, child, adults and elderly population.
8.6. Conflict of interest

The authors declare no conflict of interest. In a non-conflicted way pertaining to this study, EC is chairman of the SAB of Christian Hansen (Denmark), the PAB of Pfizer Consumer Health (USA), advisor to Yakult Netherlands BV and Winclove Probiotics B.V. (Netherlands).

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8.8. References


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