1.1 THE HUMAN MICROBIOTA

1.1.1 Colonization by microbes

Bacteria, archaea, protozoa, fungi and viruses colonize the entire human body. It is estimated that these microorganisms outnumber the human cells 3:1, and that the combined microbiota may weigh up to five pounds (Sender et al., 2016). Microbes can be found in our oral cavities, skin, urethra, bladder, placenta, lungs and biliary tracts, but the vast majority (70%) colonize the human gastrointestinal tract (GIT). Particularly the small intestine and colon, as these have a relatively large surface area (>200M²) and provide an abundance of nutrients for microbial growth (Ley et al., 2006b). It is projected that the GIT harbours over 2000 different bacterial species and over 10,000 bacterial strains in the combined human population (Almeida et al., 2019). While some of these bacteria can be pathogenic (either inherently or through their metabolites), most are commensal or have a mutualistic relationship with their host and therefore live in peaceful coexistence (Quigley et al 2013).

1.1.2 Gut microbiota composition

The collection of all colonizing microbes is referred to as the human microbiota, which can be classified per phylum, class, order, family, genus, and species. The microbial phyla Firmicutes and Bacteroidetes represent 90% of the gut microbiota. Within the Firmicutes phylum, Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus Clostridium are the predominant genera. Bacteroidetes consist predominantly of the genera Bacteroides and Prevotella (Rinninella et al 2019).

1.1.3 Personal microbiota

While it was initially thought humans are born sterile (Gareau et al 2010), recent studies indicate that the foetus is exposed to some commensal bacteria in utero from the maternal gut which cross the placenta and infiltrate the amniotic fluid (Isolauri et al., 2017). This exposure to colonizing bacteria continues upon birth and throughout the first year of life and has a profound influence on lifelong health. Delivery through the vaginal tract and skin-to-skin contact are vital exposures of an infant to complex microbial communities which form an integral part of the infant’s microbiota later in life (Ley, Peterson & Gordon 2006a). This is underlined by the fact that infants delivered through caesarean section have contrasting microbiota compositions compared to those delivered through the vaginal tract (Ravel et
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Additionally, monozygotic twins have a similar microbiota composition compared to that of their other siblings, suggesting that colonization by maternal microbial communities is more influential in the microbiota formation than host genotypes (Turnbaugh et al., 2009; Turnbaugh et al., 2010). After the initial formation of the microbiota and during the first life year, the composition has low diversity but varies widely between individuals and with time (Rodríguez et al., 2015). After the first year, the microbiota becomes more stable and shows relatively little temporal variability into adulthood. Around the elderly age, the microbiota decreases in diversity again and becomes more susceptible to change (Rodriguez et al., 2015). Throughout life, host and environmental factors, such as diet, medication usage (in particular antibiotics), physical activity, smoking habits and disease, have a strong impact on the composition and diversity of the microbiota (Wen & Duffy, 2017). Figure 1.1 shows an overview of the endogenous microbiota throughout life and the impact of external factors on its composition.

Figure 1.1 Microbiota composition & diversity throughout life.

This Figure illustrates how the gut microbiota composition changes with age and is affected through external host and environmental factors (e.g., antibiotic treatment). By Ottman et al. (2012).
1.1.4 Mutualistic relationships

The gut microbiota is vital to human health and wellbeing as the mutualistic microorganisms within it perform functions that are known to be beneficial. While much remains to be determined about its exact role and mechanism of action, it is frequently reported that the endogenous microbiota may support the host by:

- Protecting the host against pathogens by: (1) competing for binding sites and nutrients, (2) stimulating the host’s antimicrobial compound production, (3) and producing bacteriocins that inhibit the growth of similar or closely related bacterial strains (Kamada et al., 2013).
- Stimulating metabolism and nutritional intake by fermenting dietary carbohydrates into short chain fatty acids (SCFA), such as butyrate, propionate and acetate. These are rich sources of energy that regulate the production of lipids and vitamins, increase colonic pH levels, improve gut integrity, alter cell proliferation, and increase anti-inflammatory, antitumorigenic, and antimicrobial functioning (Macfarlane & Macfarlane (2003); Sartor 2008; Byrne et al 2015; Tan et al 2014).
- Maintaining structural integrity and functioning of the GIT through the: (1) expression of small proline-rich protein 2A (sprr2A) which is required to maintain desmosomes at the epithelial villus (Lutgendorff et al 2008), (2) stimulation of TLR2 mediated signalling which maintain the tight junction functioning (Cario et al., 2007), (3) production of soluble proteins (p40 and p75) that can prevent cytokine induced apoptosis of intestinal epithelial cells (Yan et al., 2011), (4) stimulation of endocannabinoids that control gut barrier functions by decreasing metabolic endotoxemia (Cani et al., 2009), and (5) induction of the transcription factor angiogenin-3 which benefits the development of intestinal microvasculature (Stappenbeck et al., 2002).
- Altering immunomodulatory functioning in tandem with innate and adaptive immune systems. Gut associated lymphoid tissues (GALT), IgA producing B cells, innate lymphoid cells, effector and regulatory T cells, and resident macrophages and dendritic cells are regulated by the gut microbiota in various manners, of which the exact mechanism often remains to be determined (Jandhyala et al 2015).
- Modulating brain chemistry and neuro-endocrine systems through the Gut-Brain-Axis (GBA), the bi-directional biochemical signalling that takes place between the GIT and the central nervous system. Gut microbes can communicate with the GBA through the production of neuroactive and neuroendocrine
molecules such as epinephrine, norepinephrine, serotonin and histamine, thereby regulating anxiety, stress response and memory functioning (Carabotti et al., 2015; Forsythe et al., 2010; Bienenstock et al., 2010).

**Figure 1.2 A senescent gut is a risk factor for disease: an example mediated by the gut-brain-axis.**

This Figure illustrates a healthy and senescent gut microbiota and resulting pathological inflammation. By Nagpal et al (2018).

### 1.1.5 Dysbiosis & disease

There are large variations in the gut microbiota composition between persons and with time. It is therefore difficult to determine what exactly constitutes a healthy microbiome. Nonetheless, it is abundantly clear that ‘dysbiosis’ of the microbiota is associated with increased risk for disease and frailty (Figure 1.2). Dysbiosis is defined as an alteration of the microbiota composition and is frequently associated as a cause or consequence of a disorder. This is underscored by the fact that infants who are hampered in acquiring their gut microbiota early in life, such as per-term infants in an intensive care unit, have an increased change of developing allergies, infections and Irritable Bowel Syndrome (IBS) later in life (Hickey et al., 2012; Hascoët et al., 2011). Moreover, administration of (bacteria depleting) antibiotics
is associated with increased susceptibility to pathogenic colonization (Sekirov et al., 2008), especially during the first year of life, highlighting the importance and protective role of the endogenous microbiota. While cause and effect relationships frequently remain to be determined, strong associations are reported between an altered gut microbiota composition and intestinal disorders such as: Inflammatory Bowel Disease (IBD), IBS, Celiac Disease, *Clostridium difficile* infection (CDI), and Colorectal Cancer (de Vos & de Vos, 2012). Dysbiosis of the gut microbiota may also manifest as a disorder outside the GIT, as the gut microbiota is reported to affect metabolic, biochemical and neural pathways (Carabotti et al 2015). Multiple studies indicate that dysbiosis of the gut microbiota is associated with mental stress, Alzheimer's disease, Parkinson's disease, Autism Spectrum Disorders, and a host of other indications (de Vos & de Vos, 2012; Rinninella 2019). As an altered gut microbiota composition is associated with illness, it propelled the idea that intervention with external microbes may reduce the risk of such disease.

### 1.2 PROBIOTICS

#### 1.2.1 Microbial intervention

It was first postulated that interference with microbes could prevent or treat disease in the early 1900s by Élie Metchnikoff (Metchnikoff, 1908). Medical intervention with fermented foods (containing such microbes), however, is ancient practice (Selhub et al 2014). Metchnikoff hypothesized that host-friendly microbes found in fermented milk could replace harmful microbes in our gut, and thereby promote wellbeing and prolong human life. Indeed, it was later demonstrated that consumption of fermented dairy products is associated with improved GIT health and overall wellbeing (Parvez et al 2006). The host-friendly bacteria found in these fermented foods were called probiotics (Lilley and Stillwell, 1965), a term that is still used in contemporary culture. The World Health Organization defines probiotics as: “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Morelli & Capurso, 2012).

#### 1.2.2 Probiotic applications

Any type of microorganism could potentially be considered a probiotic. Nonetheless, most probiotic products are developed with bacteria, particularly lactic acid producing bacteria such as bifidobacteria and lactobacilli. These are frequently
used in food fermentation processing and can thus be found in many yogurts, cheeses or other fermented foods. Lactic acid bacteria can also be obtained from plant matter, soil or the GIT of humans and animals (Lee et al., 1999; Fontana et al., 2013). To develop successful probiotic applications, it’s generally important that the incorporated bacteria: (1) are neither toxic nor pathogenic, (2) can survive (the acidity and proteolytic activity) of the stomach, (3) are suitable for incorporation in food products or medicine (i.e. able to remain viable after production and processing), and of course (4) confer a health benefit on the host when administered in adequate amounts (Fontana et al., 2013). Although no formal requirements are reported on the minimal ‘adequate amount’ dosage, it is generally accepted that a probiotic product should contain at least $10^8$ Colony Forming Units (CFU) of the bacterial strain.

It is often suggested that probiotics should be able to colonize the GIT in order to convey health benefits on the host. However, many lactic acid bacteria are in fact poor colonizers and tend to have a transient presence that requires continuous consumption of the product (Isolauri et al., 2004). Moreover, while the WHO-definition of a probiotic dictates these microorganisms should be ‘live’, even dead bacteria may convey health benefits as their membrane structures and cell components interact with the host (Adams, 2010).

1.2.3 Clinical evidence

The clinical applications of probiotics have been studied extensively and increasingly over the past decades (Pandey et al., 2015). Evidence comes from in vitro-, animal- and human studies. As the microbiota is involved in numerous systemic pathways and provides the host with a plethora of immunological, metabolic, defensive, neuromodulatory and structural benefits (section 1.1.4), the potential clinical intervention strategies with probiotics are diverse and widespread (van den Nieuwboer, Browne, Claassen., 2016a). Strong associations are found between probiotic intervention and reduced risks for upper respiratory tract infections, Antibiotic Associated Diarrhoea (AAD), infectious diarrhoea and constipation (Kerry et al., 2018; Sánchez et al., 2017). Probiotics also may benefit patients with IBD, IBS, Necrotizing enterocolitis, Obesity, Lactose maldigestion, Atopic Dermatitis, Urinary Tract Infections, and various other indications (Sánchez et al., 2017; Pandey et al., 2015; Marco et al., 2017). In more recent years, the potential role of probiotics has also been studied for the treatment of cancer, carries and a variety of neurological disorders (i.e. Alzheimer, anxiety and depression) (So et al., 2017; Umbrello &
Esposito, 2016; Meurman & Stamatova., 2018). While the therapeutic potential of probiotics is clearly demonstrated by the combined evidence of these studies, compelling evidence is often still warranted per indication (van den Nieuwboer et al., 2016a). Moreover, the effects of probiotics tend to be strain-specific, and the clinical outcomes can thus not be transposed to all probiotics in general but require validation on a strain- or formulation-specific basis (McFarland, Evans & Goldstein., 2018).

### 1.2.4 Mechanism of action

According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), some mechanisms are uncommon among different strains, but others are widespread among strains of the same species (Hill et al., 2014). Individual strains may have multiple mechanisms of action but a comprehensive understanding of these is often lacking (Lebeer et al., 2018). Nonetheless, the following mechanisms of action are frequently ascribed to probiotics (a schematic overview is provided in Figure 1.3):

- Producing metabolites such as short-chain fatty acids and histamine that may improve gut integrity, alter cell proliferation, and increase anti-inflammatory, antitumorigenic, and antimicrobial functioning (Macfarlane & Macfarlane., 2003; Sartor., 2008; Byrne et al., 2015; Tan et al., 2014; Gao et al., 2017; Sanders et al., 2018)

- Enhancing epithelial barrier integrity by stimulating the epithelial mucosal layer, secretory IgA, antimicrobial peptides and the epithelial junction adhesion complex (Anderson et al., 2010; Zyrek et al., 2007; Stetinova et al 2010; Hooper & Stappenbeck., 2003; Otte & Podolsky., 2004; Rao & Samak., 2013)

- Adhering to the mucosal layer and epithelium lining and thereby competitively inhibiting pathogen adhesion and growth (Bermudez-Brito et al., 2012; Hirano et al., 2003)

- Modulating the composition of the host microbiota through adherence and colonization (Motherway et al., 2011; Hemarajata & Versalovic., 2013)

- Inhibiting pathogen virulence gene and protein expression (Corr et al., 2009)

- Producing organic acids such as lactic acid and acetic acid which have a strong inhibitory effect against Gram-negative bacteria (Alakomi et al., 2000; De Keersmaecker et al., 2006; Makras et al., 2006)

- Producing bacteriocins that act against closely related bacteria or food-borne pathogens (Corr et al., 2009; Spinler et al., 2017)
Modulating intestinal and systemic immunity and alter the responsiveness of the intestinal epithelia and immune cells (Yan & Polk., 2011; Thomas and Versalovic, 2010; Bron et al. 2011).

- Altering central nervous system signalling through the Gut-Brain-Axis and the hypothalamic-pituitary-adrenal (HPA) axis (Wang et al., 2016; Bercik et al., 2011; Bravo et al., 2011)
- Modulating gene expression in host tissues at distance from the gastrointestinal tract, such as the liver, by influencing the gene expression of mucins, Toll-like receptors, caspases, nuclear factor-κB, and interleukins (Plaza-Diaz et al 2014; D’argenio et al 2013)
- Producing and supplying vitamins such as vitamin K and water-soluble B vitamins (Gu & Li., 2016; Cani 2018)
- Influencing levels of hormones such as Ghrelin, Leptin, adipsin and adiponectin (Clarke et al., 2014; Kadooka et al., 2010; Mallappa et al., 2012; Ohlson et al., 2008; Mencarelli et al., 2011)
- Synthesising enzymes such as lactase to promote lactose digestion in the small intestine (de Vrese et al., 2001)

Figure 1.3 Known mechanisms whereby probiotics impact the gut microbiota.
This Figure illustrates known mechanisms by which probiotic bacteria may impact on the gut microbiota. By Sharma & Im (2018).
1.2.5 Prebiotics & synbiotics

The effectiveness of probiotics may be enhanced by supplementing the formulation with prebiotics such as Fructooligosaccharide (FOS) and Galactooligosaccharide (GOS). These carbohydrates provide probiotic bacteria with sustenance that may improve their viability. A combination of probiotics with prebiotics is called a synbiotic formulation. Prebiotics can also be administered without probiotics and may benefit the host by providing nourishment to endogenous gut microbes that enables their sustained growth (De Vrese, & Schrezenmeir., 2008; Pandey et al., 2015).

1.2.6 Safety

While there has been substantial debate on the safety of probiotics in the past (Morrow et al., 2012), recent publications clearly indicate that orally consumed probiotics have an excellent safety profile with few reported adverse events (Cabana et al., 2019; Didari et al., 2014). Multiple meta-analyses demonstrate that the consumption of probiotics is safe, even for young children, elderly and immunocompromised patients (Van den Nieuwboer et al., 2014a; Van den Nieuwboer et al., 2014b; Van den Nieuwboer et al., 2015; Larsen et al., 2017). Commonly used lactic acid bacteria are therefore Generally Recognized as Safe (GRAS) for human consumption and have received such, or similar, clearance from regulatory authorities globally (Brodman et al., 2017; Elshaghabee et al., 2017). Nonetheless, the introduction of a novel microorganism without such clearance warrants thorough safety assessments prior to market authorization (Brodman et al., 2017).

1.3 PROBIOTIC MARKET

1.3.1 Products & markets

One of the first commercial probiotic products originated in Japan in 1935. Here, Dr. Minoru Shirota isolated and cultured a lactobacillus strain (\textit{L. casei} Shirota) and used it to produce a fermented probiotic dairy drink called Yakult (Yakult Europe, 2019). The popular drink is still commonly sold and consumed globally to date but has gained tremendous competition as many other probiotic products have flooded the commercial market. These exist in all shapes and forms and are created for both humans and animals (Wang et al., 2016). Typically, we distinguish two types of
commercial products for human consumption: (1) probiotic foods and beverages, such as yoghurts, chocolates and fermented dairy drinks, supplemented with one or multiple probiotic strains (>10^8 CFU) and (2) probiotic dietary supplements, such as capsules, powders or suppositories, which usually contain a variety of probiotics species/strains that are selected based on their viability and potential to prevent a specific disease. However, an increasing number of unsubstantiated products are also reaching the market, such as probiotic shampoos, deodorants and mattresses (Sanders, 2008). The scientific rationale and clinical evidence behind these products are usually marginal. Combined, the probiotic market was estimated at 49 billion dollars in 2018 and is expected to reach 69 billion dollars by 2023 (MarketsandMarkets, 2018; Caselli et al., 2013; Grand View Research, 2016). Moreover, a strong increase is seen in the number of probiotic patent applications that are filed over the past decades, indicative of long-term investment strategies and trust in continued growth of the market (Dixit et al., 2016).

1.3.2 Regulations & health claims

The regulatory landscape for probiotics is diverse and ambiguous. While many probiotics were initially sold as medical devices, primarily due to the relatively low barriers for approval by regulatory bodies, recent policy changes explicitly state that probiotics are no longer recognized as a medical device (EU Directive 2017/745). Many companies therefore need to reclassify their existing products and are looking to develop alternative marketing strategies. Probiotics can also be sold as a medicine, by filing a drug application to organizations like the European Medicine Association (EMA) or the United States’ Food and Drug Administration (FDA) (Van Norman, 2016). These products should then treat, cure or prevent disease in a patient population. Obtaining market authorization for a novel medicine, however, is a costly and lengthy undertaking with enormous monetary investments in clinical trials (Morgan et al., 2011). Most probiotics are therefore sold as nutritional/dietary supplements, and thus are amenable to regulations by food authorities like the European Food and Safety Authority (EFSA). Dietary supplements can be sold on the open market in Europe if they have a Qualified Presumption of Safety (QPS), comparable to the GRAS status in the United States, but to publicly market that a product has specific health promoting properties (i.e. on the product’s packaging), health claim approval needs to be granted first (EFSA, 2016). For such a claim, the EFSA states that a relationship between a specific food and maintenance of good health needs to be established, or a relationship between the food and reduced risk for the disease. The focus is here on healthy populations as opposed
to patients, and the claim should be substantiated with demonstratable changes in generally accepted biomarkers reflecting the risk of disease (EFSA, 2016). While extensive research has been performed with probiotics, most clinical trials have been conducted in patients or subjects at risk of a specific disease rather than a healthy population, complicating the health claim approval process for nutritional supplements (Gibson et al., 2011). Moreover, it is reported a substantial number of clinical trials with a probiotic intervention lack sufficient power, appropriate randomization and blinding, thereby diminishing the weight of the reported evidence (van den Nieuwboer et al, 2016b). To date, no probiotic health claim has been approved by the EFSA and perceived health benefits can thus not be communicated to consumers (Dronkers et al., 2018; Turck et al., 2017; Bröring et al., 2018). Consumers are hence faced with Latin terms on the product’s labelling (i.e. *Lactobacillus rhamnosus* ATCC 53103) as opposed to the intended health indication. As these are not easily understood they create confusion rather than clarity and hamper the probiotic innovation process.

**1.4 INNOVATION PROCESS**

**1.4.1 Defining innovation**

The concept of innovation is complex and polysemous, as there are many academic definitions which vary according to their context (e.g. firm, society or individual) and theoretical background. Baregeh et al (2009) defines innovation as ‘a multi-stage process whereby organizations transform ideas into new and/or improved products, services or processes, in order to advance, compete and differentiate themselves successfully in the marketplace’. This view clearly highlights that the socioeconomic benefits of an organization may drive innovation. However, the implications of these improved products or services may reach well outside the scope of a single firm or marketplace. Innovation in healthcare, for instance, has the potential to drive change and redefine healthcare’s economic and social potential (Weberg et al., 2009). We therefore define probiotic innovation in the present study as: a multi-stage process whereby organizations transform ideas into new or improved products, in order to differentiate themselves successfully in the marketplace and redefine the socioeconomic potential of healthcare.
1.4.2 Microbiota Valorisation & Tech Transfer Cycle

Innovation models can be used as a tool to study valorisation barriers and provide a frame of reference for identifying and advancing change ideas that are most likely to generate value for sustained growth. Innovation systems were initially described as linear or multi-step processes characterized by successive development phases that aim to bridge applied research and socioeconomic benefits (Godin, 2006). These models, however, have been criticised for their perceived one-directionality and lack of iterations (Berkhout et al., 2006). Cyclic innovation models were proposed that take into consideration the multiple feedback loops between industry segments and consortium partners (Berkhout et al., 2010). This concept is used by van den Nieuwboer and colleagues (2016b) to study probiotic innovation barriers, by adapting the Valorisation & Tech Transfer Cycle (Pronker et al., 2013) for research and development on the human microbiota (Figure 1.4). This model distinguishes 3 interrelated segments:

- **The Scientific Discourse**: where the proof of principle of an initial idea is evaluated through empirical research before realizing it through business formation and intellectual property protection.

- **The Development Discourse**: where the proof of concept, safety and efficacy of a product are established through (pre)clinical research trials, before scaling up the product for market introduction.

- **The Market & Society Discourse**: where consumer feedback and unmet medical need articulation feed back into fundamental research and ideation.

We use the Microbiota Valorization & Tech Transfer Cycle (CVM) of van den Nieuwboer and colleagues (2016b) as our conceptual model to study key drivers of the probiotic innovation process and their interrelationship.
PROBLEM STATEMENT & RESEARCH DESIGN

While the probiotic industry has shown tremendous growth over the past decades, the innovation process for probiotics is hampered considerably according to Key Opinion Leaders. Probiotics are not consistently used in clinical practice, no European health claim has been approved to date and there remains a lack of fundamental knowledge on probiotics and their interaction with the host (van den Nieuwboer et al., 2016b).
Figure 1.5 Research Chapters per Innovation Domain.
This Figure portrays the chapters of this thesis, divided over the different domains of the CVM.
To cultivate the therapeutic and socioeconomic benefits of probiotics for consumers and patients, and to stimulate growth of the probiotic market, it is vital that these barriers are addressed and abated, and that new ones are continuously researched.

*This thesis therefore sets out to study key barriers to the probiotic innovation process to advance research & development on live microorganisms for the promotion of human health.*

To attain this objective, a mix methods approach is adopted using a combination of literature studies, quantitative surveys, systematic reviews, meta-analyses, health economic models and in-depth interviews. The CVM is used as a frame of reference on probiotic innovation. For each discourse, prominent barriers to innovation are reviewed and corresponding research objectives formulated (Fig 1.5). An overview of all research objectives, study methods and corresponding chapters of this thesis are described below and in table 1.1.

**1.5.1 Which critical challenges do innovators face when developing probiotic applications?**

Innovators are faced with several persistent challenges throughout the production and development of probiotic applications (Jankovic et al., 2010; van den Nieuwboer et al., 2016b). As our first objective, we therefore aim to identify critical barriers associated with the access to-, research on- and upscaling of probiotic microorganisms (Fig 1.5 Scientific discourse & Upscaling).

In Chapter 2, we explore from a regulatory perspective how the Nagoya Protocol on Access to Genetic Resources restricts research & development on probiotic microorganisms. We review the regulatory framework of the Nagoya Protocol and the barriers associated with the access and utilization lactic acid bacteria for the development of probiotic applications. A literature study is conducted that analyses existing guidance documents on compliance with Nagoya Protocol, and subsequently, a decision framework was developed to guide probiotic innovators.

In Chapter 3, we assess the development risks during production and packaging that may alter the quality of a probiotic product. The most substantiated carrier matrices, factors that influence probiotic functionality during upscaling, and matrix effects on shelf-life, gastrointestinal tract survival and clinical efficacy are reviewed.
1.5.2 What are the barriers and opportunities for bowel habit improvement in nursing homes with probiotic intervention?

Probiotics are not consistently used in clinical practice, despite their apparent clinical potential and increasing prescription rates among medical doctors (van den Nieuwboer et al., 2016b; Ababneh et al., 2019; Browne et al., 2019). This limited use could be ascribed to a lack of safety, efficacy or accessibility of the intervention, as those factors are vital for the success of a probiotic application (Fig 1.5 Evaluation). To advance innovation within Evaluation domain, we therefore aim to determine this potential of probiotics in a population of nursing home residents with regard to bowel habit improvement.

In Chapter 4, we conduct a literature review on studies reporting the effects of probiotic intervention in institutionalized elderly to evaluate the opportunities for bowel habit improvement in nursing homes. Here, we focus on probiotic safety and efficacy. Subsequently, the health economic potential of probiotics in institutionalized elderly with chronic constipation is assessed in Chapter 5 to determine the accessibility/affordability of probiotics for this patient population. To attain this objective, we conduct a meta-analysis of clinical research trials and performed a quantitative survey with nursing home employees (N = 118).

1.5.3 What are the perceptions of physicians and patients towards probiotics?

Negative perceptions and low acceptance among physicians and consumers are key barriers to probiotic innovation, according to van den Nieuwboer and colleagues (2016b). It is crucial to obtain such consumer feedback on the quality and impact of a product after market introduction so that it may be improved for future reference (Fig 1.5 Societal impact & client and consumer feedback). Here, we therefore seek to explore the perceptions of both physicians and patients towards probiotics.

In Chapter 6, a post-marketing study with qualitative interviews is performed to evaluate the attitudes of 23 ulcerative colitis patients towards probiotics and assess the impact of supplementation on their quality of life. The perceptions on probiotics and prescription rates of medical doctors (MD) are subsequently evaluated in Chapter 7 based on a quantitative survey with 415 Dutch MDs. In Chapter 8, a
follow-up survey is performed to evaluate the attitudes of 1318 General Practitioners from eight European countries towards probiotics.

1.5.4 How should research be prioritized for health claim approval in the adult population?

No probiotic health claim has been approved in Europe to date, despite the increasing amount of clinical trials that are being performed with probiotics. Unable to communicate the intended health effects to consumers, this forms a prominent barrier to innovation (de Simone., 2018), which can (in part) be attributed to the wide range of potential therapeutic applications and a diluted distribution of research efforts. Here, we therefore aim to review the current clinical evidence of two of the best documented probiotic strains (*Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12) to prioritize future research for health claim approval (Fig 1.5 Demand Articulation).

In Chapter 9, we review 92 clinical trials that have been performed with LGG and BB-12 over thirteen different health domains. Research priorities for health claim approval are subsequently formulated based on 42 studies that have been performed in healthy adults or patient populations that are considered representative for effects in the general population.

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1.6 AUTHORED WORK


1.7 REFERENCES


