

Translating probiotic science into practice

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Abstract: Scientific and clinical evidence on the health effects of probiotics has expanded rapidly in recent years and points towards benefits for a number of specific health conditions, particularly those related to the gut. Healthcare professionals are important conduits in the transfer of evidence-based messages on probiotics, but research indicates many do not consider themselves to have good knowledge in this area. To identify potential solutions that support healthcare professionals the British Nutrition Foundation held a one-day roundtable event on 7 February 2019 to gather expert views on the content of, and best delivery mode for, evidence-based resources to guide healthcare professional advice about the use of probiotics. This report describes the main themes emerging from the discussions and the group's recommendation for the development of a UK-focused online toolkit for healthcare professionals, which assimilates, appraises and translates current scientific knowledge of probiotics to promote evidence-based practice for the benefit of patients.

Keywords: Probiotics, gut health, microbiome, microbiota, immunity, healthcare professionals

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Introduction

The gut microbiota contributes significantly to health and there is increasing evidence that it plays a role in the aetiology and development of a number of non-communicable diseases. However, there is still much to be learnt about these relationships (Marchesi *et al.* 2016; Lynch & Pedersen 2016) and the strength of the evidence in relation to specific health disorders varies greatly (*e.g.* Parker *et al.* 2018). Advances in understanding of human gut physiology have opened potential for the development of novel therapies to improve health. One such approach is the use of probiotics, defined by the Food and Agriculture Organization/World Health Organization (FAO/WHO) in 2001 as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' (FAO/WHO 2001); a definition reiterated and modified slightly by the International Scientific Association for Probiotics and Prebiotics (ISAAP) in 2014 (Hill *et al.* 2014). With nearly 24 000 scientific papers and over 2300 clinical trials published in relation to probiotics (according to PubMed, April 2019), evidence is mounting for the potential benefit of probiotics for a number of specific health disorders, particularly those related to the gut (Sanders *et al.* 2018).

Despite a European Union (EU) regulatory framework that restricts the use of the term 'probiotics' in commercial communications (see Box 1), public interest in the health benefits of probiotics is expanding rapidly. Google trends data show that 'probiotic' as a search term in the UK has doubled in the last 5 years (<http://bit.do/eMrDF>) and the global market, estimated at USD 49.4 billion (GBP 37.4 billion) in 2018, is projected to reach USD 69.3 billion (GBP 53.1 billion) by 2023 (Markets and Markets 2019). Advertisements, friends, family, journalists and the internet are reported by the general public as common sources of information on probiotics (Dimidi *et al.* 2019; Hedin *et al.* 2010) and scientific accuracy of knowledge in this area amongst this group can be variable. To help people with specific conditions where evidence indicates that probiotics may be a helpful (adjunctive) therapy and to inform those who may consider using probiotics for a condition that lacks supporting evidence, a need exists to provide the public with reliable, up-to-date information on probiotic efficacy to support informed choices.

Healthcare professionals (HCPs) are well placed to disseminate evidence-based information about the role of probiotics in health. Some research in the UK indicates that HCPs often advise patients to take probiotics for a range of gastrointestinal issues (Jordan *et al.* 2015), usually as an adjunct therapy (Dimidi *et al.* 2019). However, a UK study of 1830 HCPs showed that only 23.4% of dietitians, 7.4% of community nurses, 6.3% of GPs and 4.5% of practice nurses consider themselves to have good understanding in this area (Johnson *et al.* 2016). With an evidence base that is rapidly advancing alongside interest from the public, and studies demonstrating that probiotic effects are typically condition- and species/strain-specific, HCPs will need more support in keeping abreast of emerging research so that they are able to provide accurate and up-to-date information to their patients about the probiotics they might consider using, for which conditions and why.

In order to identify potential solutions to support HCPs in this area, on 7 February 2019, the British Nutrition Foundation (BNF) held a one-day roundtable event to gather expert views on the content of, and best delivery mode for, evidence-based resources for HCPs about the role of probiotics in healthcare. Participants were selected to provide insight and expertise from a range of sectors including academia, dietetics, health charities, nursing, retail and General Practice. The event was opened with a presentation summarising where evidence exists for a potential health benefit of probiotics. This was followed by group discussions on key information that should be communicated to HCPs about probiotics from this evidence base and how this should be delivered, so that they are better able to provide up-to-date, evidence-based advice on the topic. The main themes emerging

from the roundtable discussions and the recommendation for developing a UK-focussed probiotics toolkit for HCPs are described below.

Box 1: European Union regulation in relation to health claims about probiotics

- In the European Union, **Regulation (EC) No 1924/2006** came into effect on 1 July 2007 to ensure that nutrition and health claims made about foods are clear, accurate and based on scientific evidence, and that consumers are not misled by false, ambiguous or misleading claims (EC 2006).
- The Regulation covers all foods, drinks, and dietary supplements and applies to nutrition and health claims made in commercial communications (*e.g.* labelling, advertising).
- The Regulation does not apply to nutrition and health claims made in non-commercial communications (Article 1). This includes advice/information from healthcare professionals on consumption of food products in relation to health where the objective is to provide information for the benefit of the consumer rather than the benefit of the manufacturer or retailer (Department of Health 2011).
- The European Food Safety Authority Panel on Dietetic products, Nutrition and Allergies (EFSA NDA Panel) is responsible for evaluating the scientific evidence supporting nutrition and health claims.
- A health claim is defined as any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents, and health.
- The EFSA NDA Panel considers that the population group for which health claims are intended is 'the general (healthy) population or specific subgroups thereof, for example, elderly people, physically active subjects, or pregnant women' (EFSA 2011).
- Health claims must not attribute to any foodstuff the property of preventing, treating or curing a human disease, or referring to such properties (Article 7 of Regulation (EC) No 1169/2011). Therefore, health claims targeted at people with specific diseases are outside the scope of the Regulation.
- In the 2007 European Commission (EC) Guidance on the implementation of the Regulation, the EC stated that the term 'probiotic' should be considered a health claim as it *implies* a health benefit (EC 2007). In other words, stating 'contains probiotic' (or similar) on a product is not considered the same as saying 'contains ingredient X'. It implies that the product contains a substance that may be beneficial for health.
- Despite 129 health claim submissions since 2007, no health claims for probiotics have been approved by the EFSA NDA Panel (see <https://bit.ly/2gFecif>). Therefore, no claims on probiotics are listed on the EU register as authorised for use.
- Most submitted claims were in regard to general improvements in gut health or immune function. Claims were rejected on the basis of one or more of the following:
 - the probiotic-containing product was not sufficiently defined and characterised for a scientific assessment of the claimed effect;
 - the scientific evidence assessed in support of the claimed effect did not substantiate the claim;
 - the claimed effect for the probiotic-containing product was not sufficiently defined;
 - and/or the claimed effect for the probiotic-containing product was not considered a beneficial physiological effect as required by the Regulation.
- Health claims in relation to probiotics as beneficial for people with specific diseases are outside the scope of the Regulation and this is where the majority of evidence for the benefits of probiotics lies (Salminen & van Loveren 2012). However, certain population groups with diseases, such as those with Irritable Bowel Syndrome, may be considered an appropriate study group to substantiate certain health claims intended for the general (healthy) population, and this is assessed on a case-by-case basis by the EFSA NDA Panel (EFSA 2011).

Setting the scene – a summary of the presentation on the evidence for health benefits of probiotics

The possibility that lactobacilli in fermented drinks are beneficial to health was first identified in the early 20th century by Elie Metchnikoff (Mackowiak 2013), but it was not until nearly 60 years later that the term 'probiotic' was introduced. Since then, the definition of probiotic has gone through numerous iterations, the most recent of which was agreed by an expert panel during an ISAPP consensus meeting as: 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (Hill *et al.* 2014).

Regulations in the EU in relation to health claims about probiotics are summarised in Box 1. Currently there is no legal framework in the EU defining probiotic bacteria or the food category 'probiotics'. However, both FAO/WHO and ISAPP have produced guidelines to determine whether a product can be considered a probiotic (FAO/WHO 2002; Sanders *et al.* 2018). These include that it 1) must be alive when administered; 2) must have undergone controlled evaluation to document health benefits in the target host; 3) must be a taxonomically defined microbe(s); and 4) must be safe for its intended use. Many types of probiotics are available, including single or mixed microbe strains, most commonly from the genera *Lactobacillus* and *Bifidobacterium*.

Probiotics have been hypothesised to benefit various aspects of health. Broad areas studied that are considered to be supported by good evidence indicating a benefit include gut health (Sánchez *et al.* 2017) and immune function (*e.g.* Yan & Polk 2011). Emerging evidence exists for urogenital health (Hanson *et al.* 2016), bodyweight management (Croversy *et al.* 2017) and mental health/cognitive function (Dolan *et al.* 2016). Only a limited number of studies suggest benefits to dental, heart and skin health.

Specific health conditions for which there is supporting evidence from systematic reviews and meta-analyses of a potential benefit of probiotics mainly concern the gastrointestinal tract. These include antibiotic associated diarrhea (*e.g.* Agamennone *et al.* 2018), *Clostridium difficile* infection (*e.g.* Johnston *et al.* 2012), *Helicobacter pylori* infection (*e.g.* Ritchie & Romanuk 2012), Irritable Bowel Syndrome (IBS) (*e.g.* Ford *et al.* 2018), acute infectious diarrhoea (*e.g.* Allen *et al.* 2010), necrotizing enterocolitis (*e.g.* AlFaleh & Anabrees 2014), pouchitis (*e.g.* Ritchie & Romanuk 2012), constipation and transit time (*e.g.* Dimidi *et al.* 2014), infant colic (Sung *et al.* 2018) and the inflammatory bowel disease, Ulcerative Colitis (*e.g.* Peng *et al.* 2019; Derwa *et al.* 2017). There is also some evidence for a role for probiotics in preventing upper respiratory tract infections (*e.g.* Hao *et al.* 2015). Other conditions for which there are, as yet, no meta-analyses but some evidence of a benefit include lactose maldigestion (EFSA 2010) and dyspepsia (Igarashi *et al.* 2017).

Scientific literature on the relationship between probiotics and health is increasing rapidly but many research gaps, questions and issues remain. These include data on the appropriate dose and duration of use; a full understanding of strain specific effects and the relative effectiveness of single preparations vs. mixtures; knowledge of the mechanisms underpinning the relationships between probiotics and health; and the quality assurance and characterisation of all products on the market.

Translating probiotic science to practice – what to communicate to healthcare professionals

Roundtable participants discussed the information that HCPs require from the scientific literature on probiotics in order to provide advice about their use. The target group for advice on probiotics was highlighted as an important first consideration. Interest in probiotics tends to fall into three distinct categories: disease treatment (*i.e.* restoration of health), disease prevention (*i.e.* maintenance of health) and health 'optimisation' (*i.e.* the optimal ability to live well). The group considered the role of HCPs in providing advice in these three areas. It was acknowledged that the current evidence base is principally aligned with disease treatment and that HCP contact with patients is invariably in the

context of treatment, although in the UK the ‘making every contact count’ agenda encourages HCPs to have brief conversations with patients on how they might make positive improvements to their health or wellbeing and increased funding for preventive medicine has recently been proposed (www.longtermplan.nhs.uk/). It was concluded that providing HCPs with information about the role of probiotics in the treatment of specific health conditions rather than maintenance or ‘optimisation’ of general health is currently most appropriate.

The group acknowledged the challenge of uniting a probiotics evidence base that is nuanced - the health condition, population group, microbe strain, dose and probiotic form (*i.e.* food or supplement) are all important for deriving accurate clinical messages – with the reality of medical practice where both contact time with patients and time to devote to research on probiotics alongside other treatment options is limited, often necessitating a ‘topline’ message approach. It was agreed that a measure of the quality and quantity of evidence (including where no evidence exists) is essential and that this information should be presented in a summary form to facilitate quick clinical decision making. Given the variability of quality of the evidence base and the rate of new publications in the area, focusing on systematic reviews and meta-analyses was considered to be appropriate and this is standard in healthcare practice. However, while systematic reviews and meta-analyses allow summaries of a large number of studies and can indicate the size and direction of the effects, it was acknowledged that species- or strain- specific effects, reflecting the varying microbiological and physiological properties of different species and strains, may result in underestimation of the benefits of probiotics (Whelan 2014). Thus, findings from systematic reviews and meta-analyses require critical appraisal to tease out effects of individual species or strains in order to apply the findings to practice. Healthcare professionals may lack the training and time to do this and it was agreed that a simple scoring system within the resource is needed to allow HCPs to quickly appraise the strength of the evidence plus some practical points to complement research findings. It was agreed that information on the evidence should be provided in a layered way with options to access ‘topline’ messages about the potential benefit of probiotics for a specific health condition and also to ‘drill down’ and access more detailed information and individual papers, when required. Participants advised that HCP interest will predominantly be in those conditions for which there is the strongest evidence for a benefit from probiotics (currently, these mainly relate to gut health), but that identifying conditions for which there is limited, or no, evidence will also be important for advice given in practice.

Other scientific information judged to be important to communicate to HCPs was the characteristics of probiotic-containing products that have been shown to have beneficial effects. These include the brand/product name, microbial strain(s) they contain, in what form they are sold (*i.e.* food or supplement), dose provided and the recommended duration of treatment (where this information is available). Healthcare professionals may also need information on the population groups in which probiotics have been shown to have a benefit (*e.g.* elderly with a diagnosed health condition) and inclusion/exclusion criteria of the studies. Although it was acknowledged that safety concerns are low for probiotics, the group stressed that providing HCPs with information on side-effects/adverse events and at-risk groups (*e.g.* those who are immunosuppressed) was essential. It was noted that HCPs would benefit from some general ‘demystifying’ information about probiotics, including their proposed mechanisms of action, generic functions (*e.g.* immunomodulatory effects, vitamin production) and an explanation of the scientific terminology [*e.g.* microbiome, microbiota, colony forming unit (CFU)].

Translating probiotic science to practice – how to communicate to healthcare professionals

To inform discussions on how best to communicate with HCPs about the probiotics evidence base, the group identified potential barriers to the communication of evidence-based messages in this area.

Themes that emerged from these discussions indicate that obstacles exist in four broad interconnected areas: regulations on use of the term probiotics; guidance on probiotic use; HCP knowledge, skills and resources; and consumer/patient knowledge and behaviours. These are summarised in Box 2.

Box 2: Barriers to the communication of evidence-based messages about probiotics as identified in four interconnecting areas by the roundtable participants

Regulations on use of the term probiotics

The European Union Nutrition and Health Claims Regulation means the term 'probiotics' cannot be used in commercial communications with the general public about probiotic products, until such time as a successful health claim is authorised (see Box 1)

Guidelines on probiotics use

There is minimal guidance on use of probiotics from the National Institute for Health and Care Excellence (NICE) and other learned bodies working with Healthcare professionals (HCPs)

There is conflicting information on probiotics in sources HCPs use for clinical guidance (*e.g.* NHS website, NHS clinical commissions, Cochrane reviews)

A scientifically credible, independent, authoritative voice on probiotics is not well established in some countries

HCP knowledge, skills and resources

HCP interest and knowledge in the area is variable

HCPs may lack time to find and read research papers and keep up to date with emerging research

HCPs may have difficulty translating evidence from the numerous clinical trials into advice for an individual patient with his or her own specific needs

HCPs may view probiotics as an alternative/complementary therapy and this could mean probiotics are not given due consideration

HCPs may have concerns over safety and side-effects due to lack of information

Consumer/patient knowledge and behaviours

Consumer interest in probiotics appears to be in illness prevention or health 'optimisation' but evidence is stronger for the benefit of probiotics in treatment of specific health conditions

Complementary practitioners and health 'gurus', via media and social media, are dominating the conversation on probiotics rather than the scientific community

When patients are recommended a probiotic for treatment of a specific condition, availability of the particular type recommended may be an issue

When probiotics are chosen as a therapy, adherence may be an issue and use sporadic. Thus, probiotic protocols shown to be effective in trials are typically not replicated in practice

The price of probiotics and health literacy of certain population groups may restrict access to probiotics as a potential therapy and widen health inequalities

Probiotic products tend to be seen as interchangeable and appreciation of strain or product specific effects may be lacking

Overall, the group agreed that at the heart of many issues is the absence of an authoritative, comprehensive, accessible and actionable source of information summarising the evidence base on probiotics. In the UK, guidance from recognised health authorities on the use of probiotics is limited. Despite the number of clinical trials in the area, there are very few guidance documents or evidence summaries from the National Institute for Health and Care Excellence (NICE) that refer to probiotics. The NHS Choices website, the UK's leading health website, funded by the Department of Health and Social Care, goes nowhere near reflecting the full scope of current scientific knowledge on probiotics, stating only that: 'There's some evidence that probiotics may be helpful in some cases (*e.g.* helping prevent diarrhoea when taking antibiotics) and helping to ease some symptoms of IBS. But there is little evidence to support many health claims made about them (*e.g.* help treat eczema). But for most people, probiotics appear to be safe. If you want to try them, and you have a healthy immune system, they shouldn't cause any unpleasant side effects' (NHS 2019).

A selection of evidence-based resources on probiotics currently available for HCPs was considered by the group. It was highlighted that a considerable amount of information is available but this is fragmented and the quality variable. Discussed in some detail were resources developed by ISAPP (<https://isappscience.org/infographics/>), the British Dietetic Association (BDA) (www.bda.uk.com/foodfacts/probiotics.pdf) and Skokovic-Sunjic and colleagues entitled the 'Clinical Guide to Probiotic Products in Canada' (<https://bit.ly/2H2ySOI>) (a version for the US is also available: <https://bit.ly/2ExPcDE>). Resources from ISAPP and the BDA were noted for effectively providing the background information necessary to facilitate decision making by HCPs about recommending probiotics as a possible treatment. The Clinical Guide to Probiotic Products in Canada, an online database summarising evidence on the benefits of probiotic effects for specific conditions, was commended for its high level of detail and flexibility of use. It grades evidence for the health benefits of a range of probiotic products and provides references to the relevant trials. Information about the product brand names, probiotic strains, dosage forms (capsule, fermented drink *etc.*) and daily doses, in relation to the specific health conditions for which benefits have been shown, is tabulated and users can filter by clinical application. It was highlighted that the Canadian database includes information only on commercial formulations available in Canada and that a UK version would need to be developed. The methodology of Skokovic-Sunjic and colleagues could be adapted for this version but the group agreed that thought would need to be given to the grading of the evidence, as they focused on the clinical question of 'what works' and therefore only presented the number of positive studies in the area rather than the totality of the evidence, including studies where probiotics did not show clinical benefit. If a UK version of the database is to be developed, an evaluation of the evidence that includes some measure of consistency of findings was suggested and the group advised that a focus on specific conditions, for which systematic reviews and meta-analyses are already available, would be one way of achieving this. An annual review of the evidence would be required to capture new studies as they emerge.

It was reiterated that any future UK resource would benefit from a 'layering' of information. More general information on the gut microbiota and the function of probiotics (as per the ISAPP and BDA resources mentioned above) could be combined with 'topline' messages about probiotic benefits, plus detailed information from specific trials on their effects (as per the Skokovic-Sunjic *et al.* guide) and links to the trials cited for those requiring detail. Providing flexibility in the level of information accessed would ensure that the needs of HCPs from different disciplines, with varying levels of background knowledge and diverse patient needs, are served.

Discussions ensued on appropriate delivery modes for the proposed UK toolkit on probiotics (the database plus background information) for HCPs. The consensus view was it should take the form of an online resource (a website and/or an 'app'), which could also serve as a repository or central 'hub' for other relevant evidence-based resources in the area. The merit of developing user-friendly leaflets, or factsheets, to be handed out to patients was debated. Some of the group considered this format redundant because healthcare is moving to paperless systems, while others argued it has value as it can forestall common patient questions and may be attractive to certain patient groups who do not readily engage with digital media, therefore supporting inclusivity. Consideration would need to be given to the information included in any print-outs designed for patients/the general public to ensure that requirements of the EC Nutrition and Health Claims Regulation were met (see Box 1). The value of input from HCPs in the development of any new resources on the potential benefits of probiotics was emphasised, as well as input from patients themselves. It was recognised that the co-design of health-related resources with end-users can require significant time and financial investment and that the biggest gains were likely to be had from involving these groups at the outset rather than at the end-stage as reviewers of the developed materials.

To improve knowledge and the application of probiotics in the UK, the group agreed that there would need to be consistency between health information providers that include probiotics in their remit (*e.g.* British Nutrition Foundation and GUTS UK) and any new educational toolkit developed will need to be backed by a programme of dissemination activities targeted at key stakeholders. A number of ideas were suggested on how to reach and engage HCPs. A need was identified to educate HCPs about recent advances in probiotic science because knowledge and opinions can be outdated or misinformed. Ensuring that specialist and senior HCPs, such as consultants working in gastroenterology, are 'on-board' and engaged with any new resource developed was considered important so that the messages 'trickle down' and reach other HCPs working in the area. The group agreed there is scope for training HCPs on the potential health benefits of probiotics, including embedding modules in pre-registration courses as well as CPD opportunities for qualified professionals, but also acknowledged the challenge of competing with other learning priorities. Training could be in the form of conference symposia, online training modules (accredited through the colleges), webinars and study days. A newsletter for HCPs on probiotics research was suggested as one way of generating interest in the area, as well as articles in medical journals. Educating patient groups and the public was also suggested as important as this would encourage them to approach HCPs for information on this topic. This could be achieved through partnership with those working in public engagement, such as Science Museums and the Wellcome Trust. Retailers and manufacturers were highlighted as other key stakeholders who would be important to engage with, to ensure that those probiotic-containing products for which evidence of a benefit exists, are readily available for patients.

Recommendations and next steps

Consensus was reached that there is a need in the UK for an online toolkit for HCPs, which assimilates, appraises and translates current scientific knowledge on the potential benefits of probiotics for specific health conditions, and highlights where no evidence for a benefit exists. A two-stage approach was advised for the development of this resource. The first tranche of work could establish a central online repository/hub for evidence-based resources on probiotics, and determine which resources currently available are suitable for inclusion, based on an evidence-based approach. The second tranche could develop a UK version of the Canadian database. This should include layered information on: the gut microbiome and broad probiotic functions as an introduction; the effects of probiotics on specific health conditions, including 'topline' actionable, practical messages; a measure of the quality

and consistency of the research; the characteristics of the probiotics studied (brand name, strain, form) and the therapeutic protocols (dosage); population groups studied; any safety issues; and links to the relevant research papers. Next steps were discussed and the following suggestions made.

1. Establish an advisory committee to provide guidance on the content of the online toolkit and dissemination programme, and explore partnership work and funding options (*e.g.* with charities, Research Councils, and the NHS) and possible ways of working with industry and other stakeholders which would ensure that the scientific integrity and impartiality of information provided remained intact.
2. Establish a working group to facilitate the development of the online toolkit and dissemination activities, which would begin with an audit and review of the probiotic resources currently available.

Conclusions

The evidence base on the health benefits of probiotics has expanded rapidly in recent years and accumulating research points towards potential benefits for a number of health conditions, particularly those related to the gut. Healthcare professionals are critical for the transfer of evidence-based messages about probiotics as treatment options for patients, as well for clarifying where probiotics might not be helpful. The roundtable participants explored how the gap could be bridged between the science on probiotics and their application in practice, via HCPs. A need was identified in the UK for a trusted, comprehensive and accessible source of information on probiotics to enable HCPs to provide actionable messages tailored to the specific health condition and characteristics of individual patients. Participants considered the types of information that HCPs would need from the scientific evidence base and how this information should be delivered, with recommendations made for the development of an online probiotics toolkit. The hope is that this will help improve knowledge about probiotics, promote evidence-based practice in the area and encourage use where they can be helpful adjuncts to treatment regimens for the benefit of patients.

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