House of Lords Science and Technology Committee Inquiry on Ageing: Science, Technology and Healthy Living

Written evidence submitted by the Society for Applied Microbiology
19th September 2019

The House of Lords Science and Technology Committee has launched a new inquiry into Ageing: Science, Technology and Healthy Living. The committee is seeking evidence regarding the scientific understanding of the ageing process, and how areas of research could lead to treatments for delaying or managing the negative effects of ageing.

SfAM has hereby prepared a concise response to the inquiry emphasising the importance of considering the role of the microbiome in the ageing process and also the increased risk of infectious disease associated with ageing. This written submission draws upon insights from experts in the field of microbiology including:

- Professor Glenn Gibson - Institute of Cardiovascular and Metabolic Research at the University of Reading.
- Dr Ben Mullish - Clinical Research Fellow in the Department of Metabolism, Digestion and Reproduction at Imperial College London and Honorary Speciality Registrar in Gastroenterology and Hepatology at St Mary's Hospital, Imperial Healthcare NHS Trust.
- Dr Marina Ezcurra - Lecturer in Molecular Biosciences at the University of Kent and group leader of the Microbiome research laboratory.
- Dr Lindsay Hall - Group leader in early life microbiota-host interactions at the Quadram Institute.
- Professor Simon Carding - Group leader in gut microbes in health and disease at the Quadram Institute.
- Professor Julian Marchesi - Faculty of Medicine, Department of Metabolism, Digestion and Reproduction at Imperial College London, and Professor of Human Microbiome Research at Cardiff University.
- Dr Linda Thomas - Scientific Consultant and Secretariat for the British Society of Gastroenterology's Gut Microbiota for Health Expert panel.
- Professor Christine Dodd - Chair in Food Microbiology, Faculty of Science, University of Nottingham.

Introduction and summary

1. Ageing is defined as the regression of physiological function with increasing age (Flatt, 2012). The ageing process is associated with a loss of physical barriers and immune efficiency, which results in an increased risk of infectious disease in elderly individuals, often worsened by other health factors such as malnutrition and immobility (Kendall *et al*., 2006). This is particularly evident by the increased susceptibility of the elderly to foodborne pathogens, including *Norovirus*, *Salmonella* and *Campylobacter*, when compared to healthy adults (Lund, 2015). In addition, gaining increased interest within the field is the role of the gut microbiome in the ageing process. Throughout the ageing process there is considerable impact on the

physiology of the intestinal tract (Drozdowski & Thomson, 2006). A healthy intestinal tract relies on a dynamic equilibrium between the intestinal immune system and the gut microbiota (Round & Mazmanian, 2009). Decreased intestinal motility (i.e. age-related constipation), low-level chronic inflammation (i.e. inflammaging) and nutritional behavioural changes in older people results in alterations in the gut microbiota (Candela *et al.*, 2014). This is significant because there is increasing evidence to suggest a direct correlation between the gut microbiome, diet, healthy ageing and disease (Claesson *et al*, 2012; Zapata & Quagliarello, 2016).

Of the questions put forward by the House of Lords Science and Technology committee, particular focus on the part of SfAM is on the following:

1. **How complete is the scientific understanding of the biological processes of ageing and their epidemiologies (including the relative roles of genetics, epigenetics, lifestyle, environment, etc.)?**

2. There is increasing medical/ scientific interest in the apparent correlation between the composition of the gut microbiota, diet, and health in older people (Claesson *et al.*, 2012); however, this has principally been correlative data, and has not firmly demonstrated a direct relationship between, e.g. alteration in diet, change in gut microbiota and effects upon the biological processes of aging. Despite this, it is well-recognised that populations of beneficial gut bacteria, like bifidobacteria, decline with age, from approximately 60-70% within the healthy infant gut, decreasing considerably to between 0-5% in old age (Figure 1) (Arboleya *et al.*, 2016). This opens up increased risk of infection, elevated gut inflammatory response and possible links to cognitive state (Picard *et al.*, 2005).

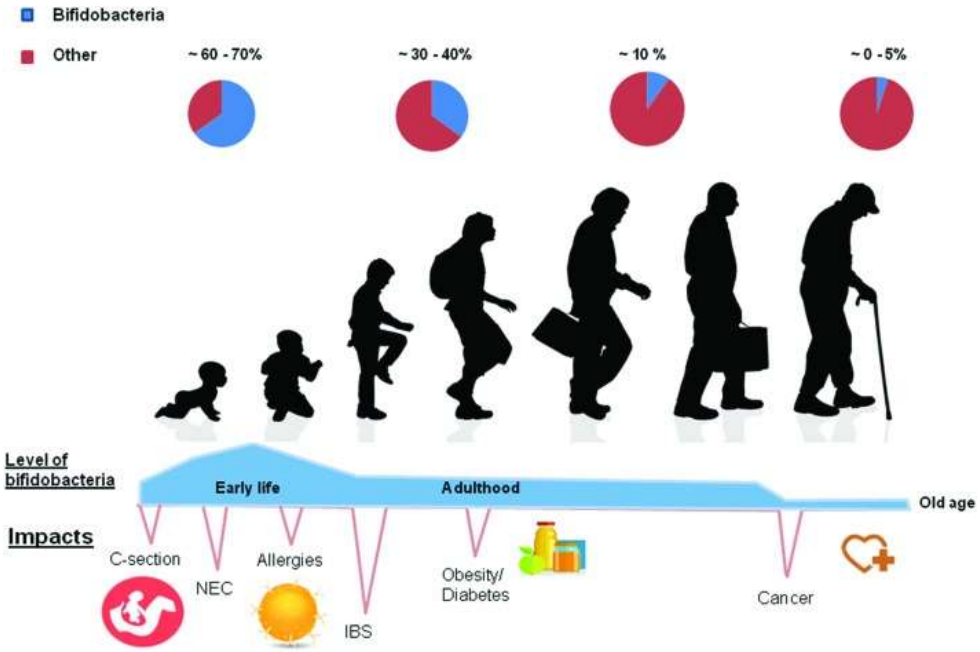

Figure 1: Bifidobacteria Abundance: From the Infant to the Aged Microbiota. Levels of bifidobacteria through the various stages of the life cycle. These are highest at birth but during adulthood the levels of bifidobacteria decline whilst remaining relatively stable and decrease further in old age.

3. The human microbiome is complex and difficult to study, despite the recent developments in whole genome sequencing. However, very recently and principally using mouse models of progeria (genetic disorder in which symptoms resembling aspects of aging are manifested at an early age) and the use of faecal microbiota transplant (FMT) within these models, there is the suggestion that the gut microbiota may directly contribute to length of life and health status in older age (Bárcena *et al*., 2019). However, these are relatively early studies and principally based in mice, and therefore need validation in humans. There are also studies which suggest specialised metabolites from the microbiome have beneficial physiological effects during old age (Levy *et al*., 2017). Continued research over the coming years, will show the extent to which we can manipulate and utilise our microbiome, and there is already significant activity both in the academic and industrial sectors.

4. It is apparent that there is a need for an increased number of longitudinal human studies investigating the link between the gut microbiota and healthy ageing. There are some international efforts to longitudinally profile the gut microbiota and to try and link microbiota changes to clinical outcomes in the profiled people for example the Canadian paediatric study (https://childstudy.ca/). Within the UK, researchers at the Quadram Institute are looking for pregnant mothers at less than 22 weeks of gestation to take part in the PEARL Study (Pregnancy & Early Life) to understand how the transmission of beneficial microbes affects health and development of the infant (https://quadram.ac.uk/pearlstudy/). There has been no older person/elderly equivalent longitudinal study, which may be due to logistical challenges including setting up, recruiting and following up elderly subjects.

2. How firm is the scientific basis for public health advice about healthy lifestyles to increase health span, including physical health and mental health?

5. The gut microbiome is the vast collection of microbes present in all of us (it is thought that we have 100 trillion microbes living in and on us, of which 95% live in the gut; and we have ten times more bacterial cells than human ones). The gut microbiome is known to impact markedly upon human health and welfare with an array of disorders susceptible to intervention by changing the microbiome through diet. As elderly persons have a "compromised" microbiome their health has been better managed using prebiotics and probiotics. In particular, the former of these reduced inflammation, stoked immunity and fortified the gut microbiota towards a more resilient community (Kamada *et al*, 2013; Belkaid & Hand, 2015). Probiotics are live microbes in the diet, while prebiotics (a UK science invention) are growth enhancers for positive bacteria already in the gut.

6. The microbiota of pre-term babies and infants has been well documented through both culture techniques and more recently using high throughput molecular techniques, but there have been relatively few studies dealing with the changes in the intestinal microbiota during the ageing process. Understanding the changes that occur in older people will facilitate the development of nutritional and therapeutic

strategies to reduce or reverse these processes and maintain a healthy colon (Woodmansey *et al.*, 2004). Essentially, there is correlative data between gut microbiota, diet and health in old age, but very little mechanistic data showing that these variables are directly linked.

7. Although the evidence based on metagenomic studies suggests a rich and diverse microbiome is associated with health and youth, it is currently too early to give public health advice on how to maintain a healthy microbiome. Work over the coming years will clarify the dietary and lifestyle measures that are needed. It is likely that this advice will be on the same lines of what is already in place, as the evidence is pointing towards that having a varied plant-based diet free of processed and sugary foods is the basis for a microbiome that promotes health.

3. Which developments in biomedical science are anticipated in the coming years, in time to contribute to the Government's aim of five more years of healthy and independent life by 2035?

8. The microbiome is becoming an increasingly attractive target for potential therapeutics and has a huge potential to improve health of the elderly. There is a potential for probiotics and prebiotics to be utilised to restore the microbial imbalance in the gut microbiota associated with the ageing process (Voreades *et al*., 2014). For example, research has shown that probiotics can successfully increase the levels of beneficial *Bifidobacterium* and *Lactobacillus* species in elderly individuals, whilst inhibiting pathogenic organisms (Toward *et al.*, 2012). Probiotic supplementation can also be supported through prebiotics, as they provide fermentable food sources to stimulate the growth of specific bacterial species (O'Conner *et al.*, 2014). *In vitro* studies have suggested that probiotic/prebiotic combinations can modulate the gut microbiota in elderly subjects causing a major shift in the levels of *Bifidobacterium* and *Lactobacillus* species, resulting in a healthier colon (Likotrafiti *et al*., 2014). Prebiotics alone, including fructooligosaccharides (FOS) such as inulin, have been shown to have bifidogenic effects in elderly subjects (Guigoz *et al*., 2002). In another example, a recent Japanese study demonstrated that ingesting fermented milk products containing the probiotic *Lactobacillus casei* strain Shirota (LcS) enhanced intestinal motility, facilitating defecation in older people who recurrently suffered from infrequent bowel movements (Aoyagi *et al*., 2019).

9. Despite such findings, research into the effects of probiotics and prebiotics on the elderly gut microbiome is still limited. Future work, must involve an evaluation of current methodologies and the development of mutually agreed selection criteria and mechanistic models (Voreades *et al*., 2014). The use of safe interventions, like probiotics to elicit positive changes in the microbiome and concomitant health outputs, forms part of the remit of the newly launched All Party Parliamentary Group on the Gut Microbiome.

10. A second approach to restoring a healthy gut microbiota in elderly individuals is through faecal microbiota transplantations (FMT), however FMT is not clinically validated to date for applications other than the treatment of *Clostridiodes difficile*-associated diarrhoea due to the number of potential associated risks (Khoruts *et al.*, 2010). The biggest challenges within microbiome research is to determine cause-effect relationships and to design microbiome-based therapies that are able to achieve predictable outcomes on the microbial community and host health. If successful, such interventions have the potential to improve the health of the elderly and reduce the burden on the health care system (Lynch *et al.*, 2015).

11. Alternatively, completely bypassing the microbiome and instead utilising microbial compounds and metabolites as pharmaceuticals offers a more controlled approach. Research over the past few years has revealed that the intestinal microbial community exerts much of its impact on host physiology through the secretion of small molecules that modulate cellular and organismal functions of the host, targeting host genes and proteins. These small molecules serve as an effective means of communication in host-microbe interactions. Rather than targeting the aberrant microbial composition, exogenous administration or inhibition of metabolites has the potential to counteract and correct the negative effects of imbalances of the microbiome.

12. Metabolite-based interventions are therapeutically attractive for several reasons. Metabolites are physiologically abundant at high concentrations, and thus the potential for toxicity is low. In contrast to the administration of live organisms, their dosage and routes of administration follow the principles of pharmacokinetics. Moreover, metabolites are present at most body sides and thus suitable for different routes of administration. Additionally, metabolites are generally stable in the systemic circulation and thus amenable for scalable modulation of their concentration.

13. As the mechanistic contribution of the gut microbiota to human health developments is revealed, we are also likely to have improved understanding of methods of manipulating the gut microbiota to improve health outcomes. This may include, for instance, the evidence-based demonstration of particular forms of diet manipulation, probiotic supplementation, forms of FMT, and/or other interventions that cause sustainable changes in the gut microbiota which may directly affect health in old age/ impact upon the aging process. Researchers at the Quadram institute are seeking healthy people aged over 60 for a new major microbiome study taking place in the UK (Example 1). The findings from this study will help scientists understand the role of gut microbes in the ageing process and facilitate the development of new strategies to manage the negative effects of ageing (https://quadram.ac.uk/motionstudy/).

Example 1: The MOTION Study
The MOTION study is a new longitudinal cohort study being conducted at The Quadram Institute and the Norfolk and Norwich University Hospitals. The MOTION study is looking into the microbiome of the ageing gut and its effect on human gut health and cognition. The study is investigating gut microbes and the role they play in healthy ageing and, in particular, declining mental health and risk of developing dementia. The researchers will be investigating the different types of microbes including bacteria and viruses that live in the gut and how these affect our brain and mental processes as we age. This longitudinal study will answer a key question of whether the age-related decline in cognitive function is associated with changes in the intestinal microbiome. This knowledge will be extremely useful in increasing our understanding of the factors involved in declining physical and mental health in old age, and in the development of new strategies and therapies that can help maintain mental health during old age.

14. Research on treatments based on the microbiome is only in its infancy, and the coming 20 years might yield completely novel approaches to promoting healthy ageing. Interestingly, there is strong evidence that metformin, an ageing treatment currently undergoing clinical trials, acts through interactions with the gut microbiome (Wu *et al*., 2017). This illustrates the potential of the microbiome as a means for promoting healthy ageing and opens up the possibility that other existing drugs might be acting through the microbiome without our knowledge.

15. Even though it is likely that most of the ageing treatments that are under development will not pass clinical trials, development of one or a few successful treatments could have a massive impact on the health of our ageing population and might well contribute to the Government's target of adding 5 years of health by 2035. Further studies, and importantly increased funding to academic and industrial research in the ageing field will increase the likelihood of this being successful. This may be accomplished through funding via the Industrial Strategy Challenge fund: Innovate UK: Live longer, better, healthier.

4. What technologies will be needed to facilitate treatments for ageing and ageing related diseases, and what is their current state of readiness?

16. If microbiota-related interventions develop, these are likely to be dietary, or involve preparation of mixtures of microbes or their associated metabolites, phages, etc. The technologies are already in place for this. Prebiotics and probiotics for elderly persons are likely to be used more for prophylactic rather than therapeutic reasons. Both have been tested and efficacious forms should be put into mainstream health management for vulnerable groups like the elderly. There are also advantages for resisting hospital infections like *C. difficile*. Research on the gut-brain axis for humans is burgeoning - we do know that gut microbes produce neurotransmitters that can act positively or negatively. Again, dietary intervention can be used to influence this effectively. Trials on depression,

anxiety, autism and dementias are reported and/or ongoing. This has much relevance for the aged population.

17. There are exciting studies showing an association between the microbiome and age-related diseases and frailty, but there is a lack of understanding of underlying mechanisms and treatments. If the field is to make significant progress, systematic approaches using simple and inexpensive models are needed. There is a massive need for high-throughput platforms allowing unbiased screening approaches of microbial strains and microbial metabolites. In addition, using multiple model systems, such as cell lines, nematodes, flies, and short-lived vertebrates such as killifish, combined with rodents would be highly beneficial to establish evolutionary conservation and identify interventions that are likely to be translatable to humans.

About the Society for Applied Microbiology

The Society for Applied Microbiology (SfAM) is the oldest microbiology society in the UK, representing a global scientific community that is passionate about the application of microbiology for the benefit of the public. Our Members work to address issues involving the environment, human and animal health, agriculture and industry. SfAM works in partnership with sister organizations and microbiological bodies towards enabling microbiologists to inform policymaking within the UK, in Europe and worldwide.

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