ENVIRONMENTAL AND INTERNAL MICROBIOME SESSION

This is a report of the session on Environmental and Internal Microbiome that took place on 6th October 2016 in Brussels, in the framework of the European OneHealth/EcoHealth workshop organised by the Belgian Community of Practice Biodiversity & Health which is facilitated by the Belgian Biodiversity Platform

Session coordinator: Lucette Flandroy, in collaboration with Ellen Decaestecker.
Beside the speakers and posters presenters mentioned in the Presentations section below, the session included the following participants in the workshop: Cristina Romanelli,
Vlatko Ilieski, Vujadin Kovacevic, Martine Röhl, Esther Schelling, and Bernard Taminiau.

INTRODUCTION

The session aimed at discussing the effects of environmental, food-grade and commensal microbes on human, animal and plant health, in an integrative approach, in order to identify links between environmental and internal microbiome with human health and disease. The session and its discussions largely focused on:

- The effects of gut bacteria on human health through the activation of interrelated physiological systems
- The role of the microbiome on the host adaptation and evolution in its natural environment
- The extent to which influences of genetics and environment may affect the internal human microbiome
- The impact of various lifestyle factors, including diet, pharmaceutical products consumption and exposure to environmental chemical substances on the gut microbiome
- The similarities and correlations between functions of human, animal, and plant microbiomes
- The importance of microbial biodiversity for human health in the context of the interlinked environmental and internal microbiome
- The need for medical, nutritional, environmental, agricultural, land use planning, architectural and social interventions aiming at increasing microbial biodiversity in the environment and human exposure to beneficial microbes
- Policy recommendations.

PRESENTATIONS

The session had several presentations illustrating the current knowledge on those various aspects on the microbiome.

Introductory presentation (Ilkka Hanski' s legacy to allergy research: the environment-microbiota-health axis) from Lasse Ruokolainen (University of Helsinki, Finland) summarised the current knowledge and knowledge gaps relatively to the importance of contact with environmental microbes to avoid skin and respiratory tract allergic manifestations. Various subsequent presentations in this session illustrated correlations between disturbed gut microbiome (dysbiosis) and chronic pathologies, in particular cardiometabolic disorders (including obesity and diabetes) (with Dr. Maria-Carlotta Dao and Hubert Plovier), cancer (with Prof. Theofilos Poutahidis), psycho-neurological disorders (with Dr. Gerard Clarke). Interactions with host health of the intestinal microbiome, mostly tackled in this session, were viewed as a paradigm for exploring the whole-body microbiota, including that of skin and respiratory tract already evoked but also that of reproductive systems and upper gastrointestinal tract.

The notion of "normal" or "healthy" gut microbiome was presented by Prof Jeroen Raes and discussed taking into account the various potential determinants of our microbiome. Current medical intervention using fecal microbiota to counteract health problems due to intestinal dysbiosis was exposed by Prof. Xavier Stephenne. Large consortia of research on the human microbiome at the European and international levels and their objectives were reminded by Dr. Kathleen D'Hondt and by the poster of Dr. Yolanda Sanz and Alfonso Benitez-Paez.

The session participants listening to presentations

Knowledge on the plants microbiomes and their relationship to human microbiome and health, and to food conservation, were presented by Prof. Gabrielle Berg, by the poster of Prof. Sébastien Massart, and by Prof. Bernard Taminiau. The adaptation provided to invertebrates by their gut microbiota was illustrated by Prof. Ellen Decaestecker and may suggest adaptation brought to humans by their microbiota. Prof. Eeva Furman concluded with a presentation on the concrete environmental and social actions that can be developed on the basis of the current knowledge and that should be more promoted by political decisions.

DISCUSSIONS

During and after the presentations, discussions were based on a questionnaire that had been sent and completed before the workshop by the future participants of the session. The overarching questions were, in substance:

- What is known about *coherence* and evidence for *causal relationships* between the microbiome and physiological parameters linked with chronical diseases?
- What is known about the *mode of action* of the internal microbiome?
- What is known about respective influence of *genetics* and *environment* on our internal microbiome?
- What is known about *positive and negative environmental influences* on our internal microbiome?
- Is the current knowledge concerning positive effects of the microbiome on our physiology sufficient to undertake *concrete actions* about it?

Gerard Clarke presenting the links between the gut microbiome and brain function

- Which *further research* is needed and under which favorable conditions?
- Which *policy recommendations* can be made, based on the existing knowledge?

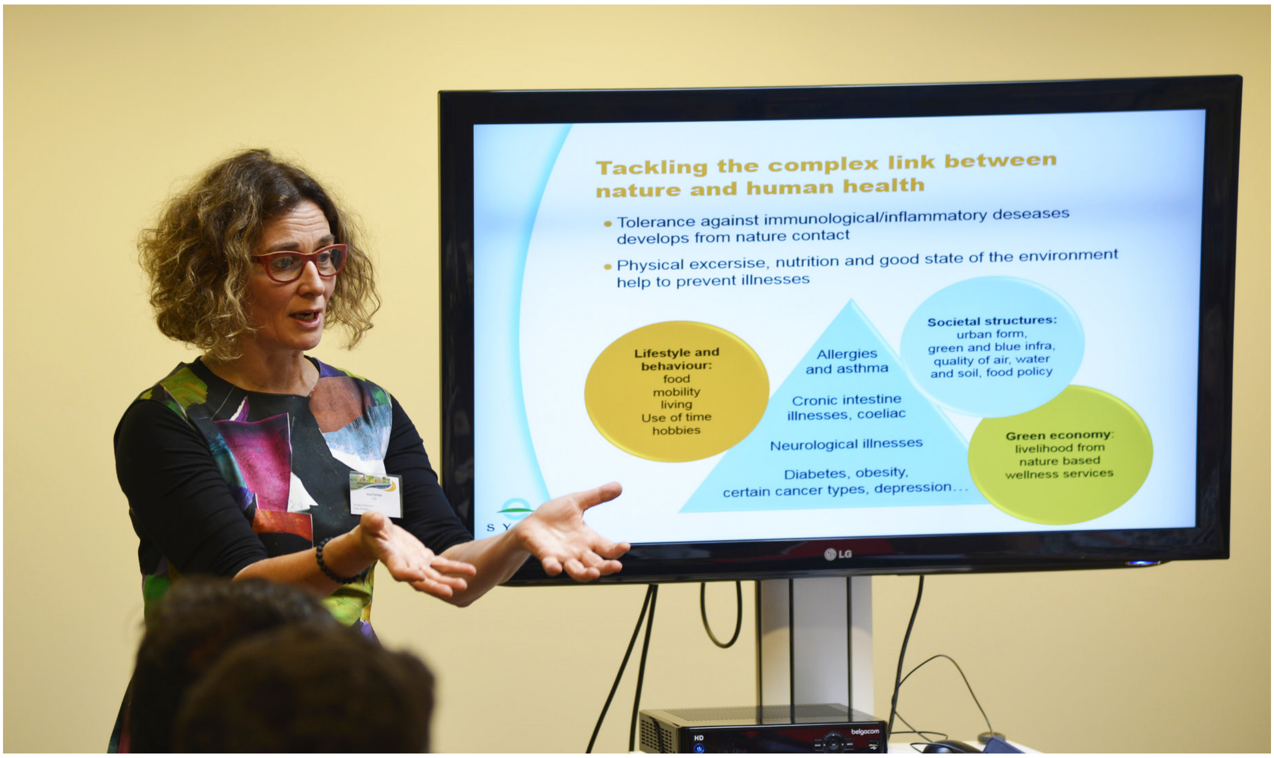
Essential points made during discussions:

- The evidence linking disturbed gut microbiome (dysbiosis) and chronic pathologies (non-communicable diseases-NCDs) as evident by both human and animal studies is strong.
- Some important aspects of associations

between gut microbiota and NCDs have been elucidated, and common patterns of action start to be understood. Still, the precise mechanisms that enable a beneficial gut microbiome to prevent NCDs remain to be fully characterised.

- Defining a general *"health-promoting"* versus *"disease-predisposing"* gut microbiome is difficult, if not irrelevant. An ideal gut microbiome might differ depending on various factors such as age, geographical situation, diet, and genetics. Moreover, the resulting metabolome might be more important than the underlying pattern of organisms.
- Animal models are valuable experimental platforms to discover biological phenomena and mechanisms of host-microbiome interactions. Research in animals thus far highlights the important role of internal microbiome in health and disease. Such data, however, cannot easily be directly translated to humans. There is a need for more human clinical studies.
- Convincing epidemiological data and evidence from animal experiments suggest that the high environmental microbial biodiversity conferring humans with rich exposure to environmental microbes is linked to a good health status (*"biodiversity hypothesis"*). Whether a rich microbial biodiversity ensures a good balance between several complementary physiological functions needs to be investigated further.
- Particular microbial species have been shown to confer protection from NCDs by counteracting gut dysbiosis in animal models.
- Inflammation, whether chronic or acute, is a common pathogenic link between the disturbed gut microbiome and the various NCDs mentioned during the presentations.

- The immune system has a central role in the axis connecting the gut microbiota with effects on tissues located distant from the gut.
- Accumulating evidence suggests that beneficial bacteria and microbial products activate interrelated immune, endocrine and central nervous system pathways that promote overall good health to prevent or even counteract NCDs.
- Killed / inactivated forms of key microbes, and structural bacterial components, may have anti-inflammatory and health-promoting effects. Bacterial products (postbiotics) hold promise as bioactive compounds.
- It is not known what are the precise relative contributions of genetics, environment, and lifestyle factors, to the composition of our gut microbiome. Although diet has an obvious effect, host genetics and interpersonal variation as well as other environmental factors can have a profound impact.
- Epigenetic effects of the microbiota on the host genome have been described, and might explain some transgenerational inheritance of the impacts of the microbiome. There seems to be a critical window during early mammalian development, including the *in utero* period, during which environmental factors can cause epigenetic modulation of the genome. A well substantiated transgenerational hypothesis is emerging.
- Early life rich microbial exposures seem to promote overall health later in life. Accumulating data support both *"hygiene"* and *"biodiversity"* hypotheses. Along these lines, natural childbirth and breast feeding, and direct contact with nature in early infancy are recognised as important factors for promoting a childhood deprived of allergic pathologies and a potential lifelong healthfulness.
- Later in life, however, the link between microbes dominating the microbiota in early infancy and health status is still less clear but knowledge is progressing. Further impacts



Eeva Furman presenting links between contact with nature/microbiome/human health and potential concrete environmental and social actions

of living habits might interfere with the initial status established during perinatal period. The gut microbiota in human adults is more resilient than in early life and seems largely defined by its progressive acquisition and stabilisation through long term dietary habits and our general living environment.

- Green and blue areas in the living surrounding promote beneficial exposure to microbial biodiversity from the natural environment, especially in cities and buildings.
- The differential ability of various building materials to harbor variable microbial loads and their relationship with health should be scrutinised.
- Studying plant microbiome provides lessons for animal and human microbiota and vice versa.
- As with human and animal microbiome,

high microbial biodiversity in the soil, naturally coexisting with a high plant biodiversity, is generally accompanied by a good health of the plants grown on that soil.

- The effects of edible plant microbiota (endophytes and exophytes) on human health are generally overlooked and should be studied more carefully. The effect of edible plant storage and refrigeration has been shown to profoundly alter its microbiota. (The use of preservative bacterial strains in food product to control food spoilage is under study). Further research is needed to address whether this phenomenon may connect with the popular notion that eating seasonal food is good for health. The high microbial diversity of fermented food should also be better studied in relation with its impacts on health.
- Understanding the role of gut microbiota in evolutionary interactions is relatively complicated. Although the study of these mechanisms is still in its infancy, it may provide an opportunity to better understand host-microbiota interactions, as well as their ecological and evolutionary impacts. *Daphnia* is an interesting model system that showcases the symbiotic co-evolution and adaptation of organisms with their microbiome. The ecotoxicological model of *Daphnia* shows that the gut microbiota of these small crustaceans confers resistance against toxins produced in the water by cyanobacteria.
- Fecal transplantation has been used in many different countries and brings good results against diarrhea caused by overgrowth of multi-resistant *Clostridium difficile*. Convincing data for other therapeutic applications are however currently lacking. More standardisation is needed to make this technique operational. Cryo-preservation banks of fecal material should be constituted to improve the research in this field. Such banks would enable epidemiological studies and enhance both safety and efficacy. The characteristics of the microbiota in each sample could be linked to clinical

results in the recipient. The strategy would also be improved if we could develop our capacity to grow the consortia of beneficial bacteria in laboratory conditions to ensure safety and reproducibility.

- The effects of a) antibiotics, b) other pharmaceutical compounds *(e.g. laxatives, hormones and immunosuppressive compounds)*, c) food additives *(e.g. sweeteners and emulsifiers)*, d) cosmetics, and e) environmental pollution, pesticides and endocrine disruptor chemicals, on the composition of the gut microbiota should be monitored more closely for both separate and combined cumulative adverse effects on health.

CONCLUSIONS AND RECOMMENDATIONS

In summary, accumulating evidence suggests that **host health** *(would it be human, animal or plant)* is **deeply influenced by its microbiota** that constitutes a complementary genome. Our understanding is improving on the precise mechanisms of action of the human microbiome. This helps to explain how the various physiological systems interact with the microbiota and why microbiome disturbances link with current increase of NCDs occurrence. NCDs have become a heavy burden in industrialised countries and alarmingly increase in developing countries as well. Present knowledge suggests that, in addition to genetic factors, the microbiota composition depends on environmental microbial load and diversity, dietary practices and nutrition, medication, hygiene practices and lifestyle. Agricultural food production systems could influence our internal microbiota, through diverse pathways. Importantly, our internal microbiome might have transgenerational impacts on the health of our progeny, in particular through effects during foetal life. However, to solidify these initial data, more **research is still necessary to unravel the role of host genetics and environment** on the human microbiome. The impact of different foods, diets, agricultural systems, environmental surroundings, pharmaceutical medications and environmental chemical substances on the composition and functionality of our microbiome should be better characterised. Future research on this field should focus on revealing how these factors may affect human microbiota either directly or through modulating the environmental microbiome. Understanding how environmental factors impact the human microbiome and health in the context of host genetics and defining the *"healthy"* microbiome along these lines, may revolutionise disease prevention and therapy. **More interdisciplinary research** is needed to elucidate these interactions and their consequences on human health. General and specialised medical doctors and veterinarians *(including oncologists, neurologists, neuro-gastro-endocrinologists, diabetologists, allergologists, pneumonologists, rheumatologists, psychiatrists)* and other health care professionals *(nutritionists, food hygiene specialists, psychologists)* should collaborate with biologists, microbiologists, immunologists, zoologists, ethologists, anthropologists, biotechnologists, bio-informaticians, engineering specialists, botanists, environmentalists, ecologists, phytopathologists, agronomists, as well as with architects, sociologists and political scientists. Education during the university studies should adjust to prepare scientists for such a wide interdisciplinary collaboration requiring innovative *"big picture"* thinkers.

Solidifying the importance of the microbiome in the context of the wide OneHealth/EcoHealth perspective, with such studies, could eventually lead to the design of novel disease prevention strategies at the population level.

Integration of different concerned policy sectors should preferably aim towards promoting **transnational interdisciplinary research** studies. This implies integration between health, environment, agriculture, food security and nutrition, land use planning and housing policy sectors.

Gabriel Berg concluding her presentation on plant microbiome, its similarities and potential impacts for human health, with an artistic slide symbolising "Networking provide key to success"

Policy makers should also support general **public information/education** towards adapting lifestyles that take in account a **holistic vision of microbes** in the environment and their connection with human health, while **avoiding** at the same time **exaggerated press messages** on *"good"* microbe influences or compromising hygiene practices and rational use of traditional medication.

The **current knowledge** on the importance of our internal microbiome composition for our health, and its relationship with the environment, is **reinforcing** the reasons why policy makers should further **promote** access to and **contact with nature,** with **high biodiversity,** especially in urban areas.

Coherently with the OneHealth/EcoHealth approach, **healthy ecosystems** may be key to disease prevention, and should be viewed as a fundamental pillar of **cost-effective healthcare**, especially in a time of economic and environmental crisis.

Finally, it should be noted that research and implementation of knowledge on the microbiome could constitute an integrating living element between national and supra-national policies, such as EU policies, but can also contribute to **integrated realisation of several Sustainable Development Goals (SDGs) of the UN 2030 Agenda:**

- **SDG 2** (aimed at promoting sustainable agriculture, food security and improved nutrition)
- **SDG 3** (aimed at ensuring healthy lives for all, reducing communicable and NCdiseases)
- **SDG 6** (aimed at ensuring sustainable management of water and sanitation for all. It should indeed not be forgotten that microbes participate in metabolising toxics and pollutants)
- **SDG 11** (aimed at making cities and human settlements inclusive, safe, resilient and sustainable)
- **SDG 14** (aimed at conservation and sustainable use of the oceans, seas and marine resource for sustainable development. Marine ecosystems indeed contain quantities of microbial resources, still poorly known but probably useful in water as in terrestrial ecosystems life cycles, and for industrial developments)
- **SDG 15** (aimed at protecting, restoring, and promoting sustainable use of terrestrial ecosystems, reverse land degradation and halt biodiversity loss).

Indirectly through influence on the previous ones, implementation of other SDGs would also be enhanced by taking benefit of integrated knowledge on the microbiome: SDG 1 (reduce poverty); SDG 8 & 9 (sustainable economic growth, industrialisation innovation); SDG 10 (reduce inequalities); SDG 13 (combat climate change).

Videos and presentations accessible at:
http://www.biodiversity.be/health/58