Our Microbiome - Who Are We?

Humans have been plagued by exogenous infections for millennia e.g. small pox, TB, 'the plague', cholera, polio, measles, mumps, rubella, influenza, etc. These have largely been controlled by good public health measures, clean water, good sewage systems and vaccinations.

After these, **the next major challenge for humans has been catching endogenous infections from ourselves**, from a tiny portion of our vast numbers of normal healthy bacteria i.e. 'our microbiome' e.g. *Staphylococcus aureus, E. coli,* etc. Since 1943 much of the control of these bacterial endogenous infections has been achieved by large scale use of antibiotics. They have been very effective, perhaps giving us each another 10 years of life on average. But we are now realising that this high usage is not only rapidly breeding antimicrobial resistance, but it is having unintended consequences because antimicrobial usage not only treats the intended organism, but the rest of our microbial microbiome at the same time i.e. collateral damage. It is only relatively recently we are beginning to see some of the wider clinical health implications of this unintended manipulation of our microbiome.

It is thought that we as **humans are made up of about 10 trillion tissue cells** i.e. 'us', with about 23,000 genes. **Plus** each of us, in good health, **also carries about 90 trillion bacterial cells**, thousands of species, millions of genes – and there are interactions amongst them all. We are in effect a multispecies organism.

The importance of the commensal microbiota that colonises the skin, gut, and mucosal surfaces of the human body is being increasingly recognised through a rapidly expanding body of science studying this human microbiome. It is becoming increasingly important for clinicians to have an understanding of the basic concepts of the human microbiome and its relation to human health and disease.

Some of the specific disease states for which the potential role of the human microbiome is becoming increasingly evident, include

- *Clostridium difficile* infection
- inflammatory bowel disease
- colonisation with multidrug-resistant organisms
- obesity
- allergic diseases
- autoimmune diseases
- neuropsychiatric illnesses.

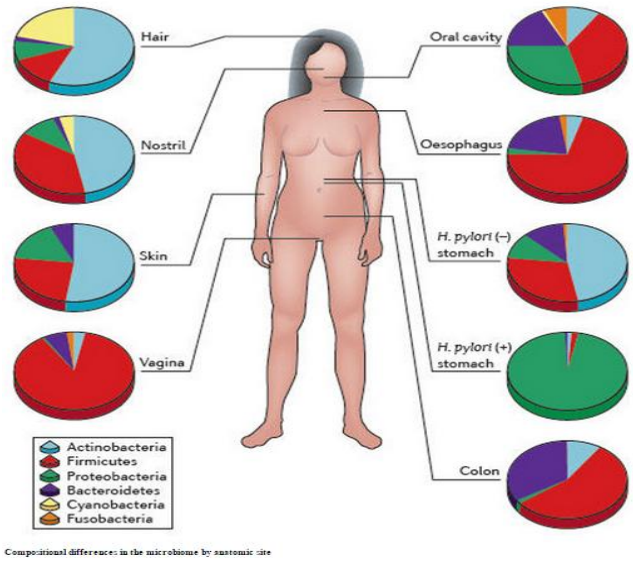
In addition there is an increasing awareness of roles of the microbiome for **restorative therapies** e.g. faecal transplantation therapy in *Clostridium difficile* infection.

The specific balance of microbial diversity within specific anatomical locations will differ among people because of variations such as in hygiene, social behaviours, and genetics.
The gut microbiota may differ at different time points at the same anatomical location within the same person owing to environmental changes. Diet plays a major role in defining the composition of the gut microbiota. In addition, metabolites produced by gut bacteria enter the bloodstream by absorption and enterohepatic circulation. Commensal microbiota produces metabolites that may have a positive effect on the host, including anti-inflammatory and antioxidant activity, regulation of gut barrier function, and production of vitamins and energy sources.

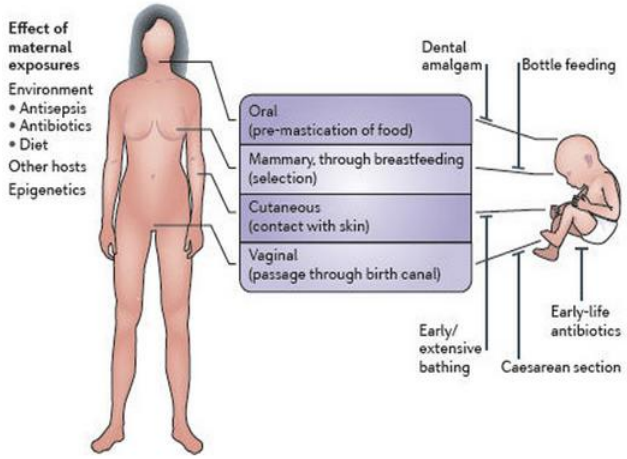
Colonisation with normal commensal organisms begins shortly after birth on exposure to vaginal microbiota. Infants continue to be introduced to new flora through routine activities with other humans, including feeding and play, resulting in the establishment of the microbiome on the skin, gut, and mucosal surfaces.
Introduction and reintroduction of flora continues throughout life from our routine interactions with each other. The establishment of the gut microbiota starts at birth, reaches its maximum diversity at adolescence, and remains stable

until the later stages of life, where the microbiota becomes comparatively less diverse with reduced stability, thus predisposing elderly individuals to conditions associated with decreased diversity, such as *Clostridium difficile* infection.

Several aspects of life in modern society, such as antimicrobials, sanitation, vaccination, and dietary changes, all have profound and lasting effects on our microbiome.



Compositional differences in the microbiome by anatomic site



Examples of association of human conditions with particular microbiota Characteristics:

Disease	Relevant finding
Psoriasis	Increased ratio of Firmicutes to Actinobacteria
Reflux esophagitis	Esophageal microbiota dominated by gram-negative anaerobes Gastric microbiota with low or absent *H. pylori*
Obesity	Reduced ratio of Bacteroidetes to Firmicutes
Childhood-onset asthma	Absent gastric *Helicobacter. pylori* (especially cytotoxin-associated gene (*cagA*) genotype)
IBD (colitis)	Increased *Enterobacteriaceae*
Functional bowel diseases	Increased *Veillonella* and *Lactobacillus*
Colorectal carcinoma	Increased *Fusobacterium spp.*
Cardiovascular disease	Gut microbiota-dependent metabolism of phosphatidylcholine

Perspectives

Inherent complexities in the composition of the microbiome may prevent investigations of microbe associated diseases using classical approaches such as Koch's postulates. Instead of single organisms associated with disease, community characteristics (composition and metagenomic functionality) may be more relevant. The principles of host interaction with pathogens and commensals contain many parallel features, but the nature of the selection for commensalism is more complex and highly dynamic.

The scale of the interface suggests that microbiome–host interactions have important bearings on disease susceptibility, and the microbial effects on the balance of host metabolism and immunity provides an excellent model for the broader phenomenon of disease susceptibility. Modifying disease risk by altering metabolic, immunological, or developmental pathways are obvious strategies.

Given the ongoing extinction with time of our ancient commensal organisms, the future of a healthy human microbiome may include restoration of our ancestral microbial ecology.

There are two types of restoration.

1. restoring ancient organisms (or pathways) in healthy hosts lacking them, as prophylaxis against future imbalances, or
2. restoration could be therapeutic, when the etiologic extinctions and imbalances are recognised

This scientific frontier will require understanding the biology of reintroductions, as well as developing microbial breeding programmes.

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Summary:

- The human microbiome and its relationship to disease is a new and rapidly evolving field of study
- Coevolution of hosts and their microbiomes has led to cooperative interactions in metabolism and homeostasis
- Concepts from community microbial ecology such as resilience, community disturbances, and extinction are useful in understanding the microbiome
- New computational and statistical tools are being actively developed to analyse the large sequence datasets generated by the increasingly powerful technologies
- The taxonomic composition and functional characteristics of the microbiome may allow individuals to be categorised into different microbial patterns, called “enterotypes”, in the gastrointestinal tract
- Although low level taxonomy varies substantially among individuals, higher level taxonomy and functional characteristics appear largely preserved
- Many factors affect the composition of the microbiome over the course of a human lifetime. These include inheritance, mode of infant delivery, diet, and age related changes in adults
- The relationships between the microbiome and several human diseases are being intensively studied for conditions that include colorectal cancer, inflammatory bowel disease, and immunologically mediated skin diseases
- Causal relationships for many of the associations between the microbiome and disease states have yet to be proven
- Understanding the links between the microbiome and human disease may provide prophylactic or therapeutic tools to improve human health – if microbes can make us ill, can they also make us well

Microbiome questions still to be resolved:

1. Understanding microbiome characteristics in relation to families: what is inherited and what is not?

2. Understanding long-term timeframe trends in microbiome composition: what has been lost or gained?

3. For diseases that have changed markedly in incidence in recent decades are changes in the microbiome playing a role? Notable examples include childhood onset asthma, food allergies, type 1 diabetes, obesity, inflammatory bowel disease, autism

4. Do particular signatures of the metagenome predict risk for specific human cancers and other diseases associated with aging? Can these signatures be pursued to better understand oncogenesis (work on *Helicobacter pylori* provides a clear example of this)?

5. How do antibiotics perturb the microbiome— in the short term and long term? Does the route of administration matter?

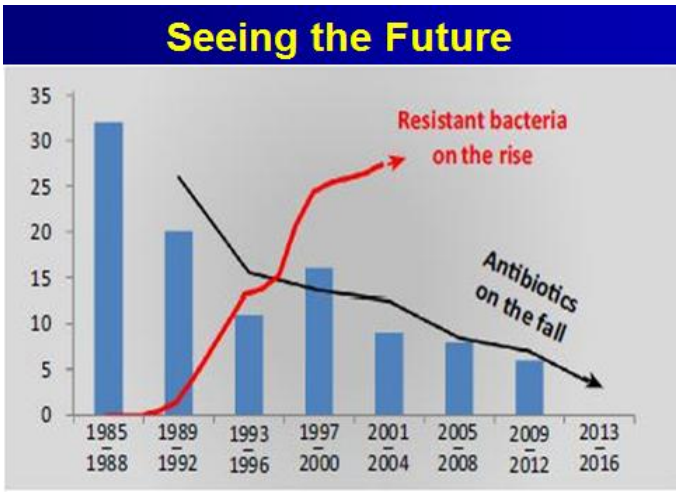
6. How does the microbiome affect the pharmacology of medications? Can we “microtype” people to improve pharmacokinetics and/or reduce toxicity? Can we manipulate the microbiome to improve pharmacokinetic stability?

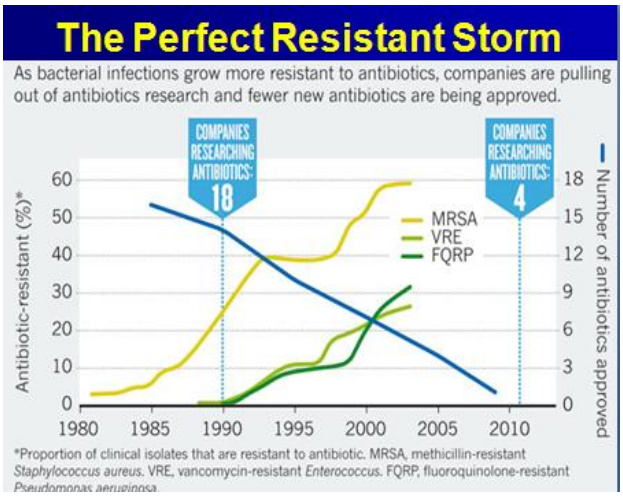
7. Can we harness knowledge of the microbiome to improve diagnostics for disease status and susceptibility?

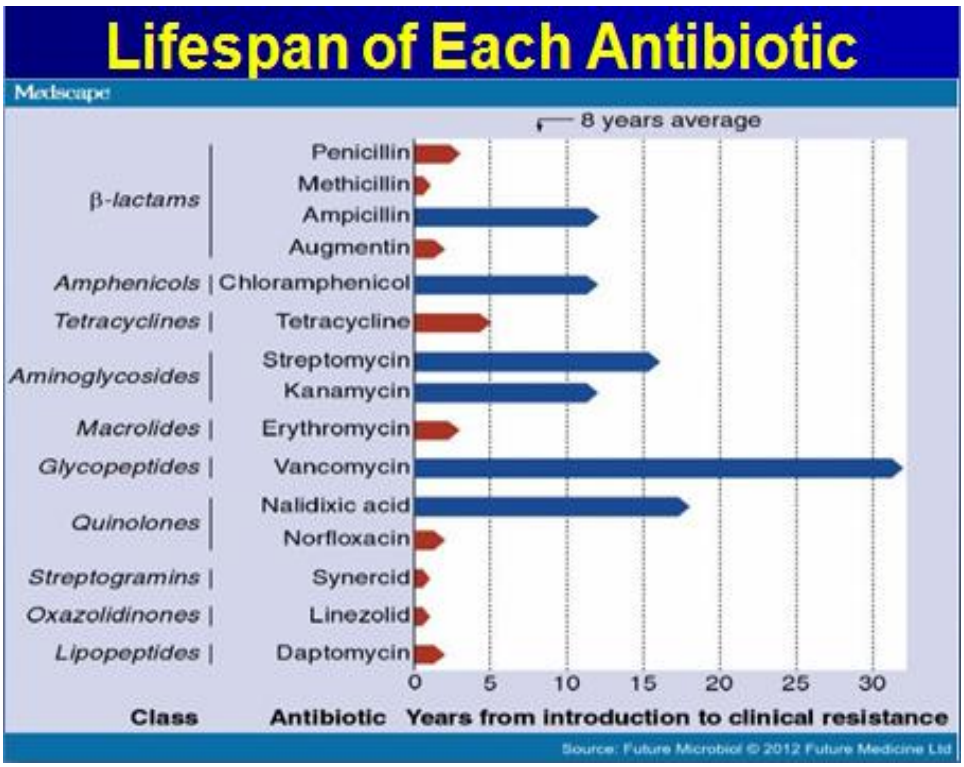
8. Can we harness the close mechanistic interactions between the microbiome and host to provide hints for the creation of new drugs?

9. Can we harness the microbiome to create new narrow spectrum antibiotics?

10. Can we use knowledge of the microbiota to develop true probiotics (and prebiotics)?







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