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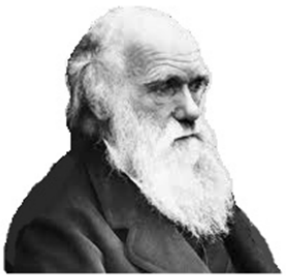

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Human microbiome diversity: implications in health, disease, and applications

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ABSTRACT

The human microbiome is a complex collection of microorganisms, including their genes and the metabolites colonizing the human body, and playing various functions in health and disease. The arrival of culture-independent molecular techniques, such as metagenomics, transcriptomics, proteomics, and metabolomics, have removed the limitations imposed by culture-dependent techniques. These advanced techniques have also brought about some paradigm shifts in what is known about the structural and functional diversities of the human microbiome in health and disease. The dynamics of the human microbiome is implicated in a number of human gastrointestinal and non-gastrointestinal diseases. This makes it a contemporary issue in biological and medical sciences. Of interest, some applications have already emerged for the human microbiome. These include being the source of antimicrobial substances, faecal microbiome therapy, probiotics, prebiotics and phage therapy. Given that a number of factors can alter the host microbiome – such as environment, lifestyle, stage of life, occupation, mode of delivery, therapy, and so on, there is a need for more human microbiome projects that will help to capture these diversities in various continents. Furthermore, for the full impact of the various applications (both, potentials and current) of human microbiome to be felt, there is a need for more studies that will fully elucidate their physiology in humans.

***Keywords*:** Human microbiome, applications of microbiome, gut, health and disease

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1. INTRODUCTION

There is an increasing evidence that we possibly co-evolved with trillions of microorganisms that colonize various niches on and in the human body [1-3]. These various ecosystems include the skin, gastrointestinal tract, airways, urogenital tract, hairs, nails, amongst others. Previously and commonly called "normal flora", the human microbiome is a community of microbes (bacteria, fungi, viruses, archaea, and protozoa) residing on/in humans. It defines the totality of the genome, making up a microbiota [4] and their various metabolites [5]. It is currently estimated that the number of microbes on a human body is over a hundred trillion; out-numbering the human cells (estimated to be about 10 trillion) by a factor of about 10:1. In addition, it is also projected that human harbours about 1 million microbial genes as against the human genome which contains approximately 20,000 genes [6-7].

This complex microbiome plays a number of functions that contribute to the health of humans that begs the question: if we would be able to survive without these myriads of functions they play? The beneficial roles of intestinal microbiome in human health have been categorized by Blum (2017) [8], based on functions into three groups. These include host physiology (adaptive immunity, autoimmunity, inborn immunity, cell propagation, bone density, vascularisation and neurological signalizing), biosynthesis (neurotransmitters, steroid hormone and vitamin B_{12}, bacteriocins production), and metabolism (dietary components, bile salts, drugs and xenobiotics degradation). This is further supported by Mathieu *et al*. (2013) [9] who revealed that *Corynebacterium*, *Staphylococcus*, and *Propionibacterium* were dominant taxa found on the human skin and performed diverse roles, including metabolism of aromatic compounds, virulence/disease, host defense, photosynthesis, amongst others.

The composition of the human microbiome is very a dynamic and complex one that is affected by both, exogenous and endogenous factors. These factors also differ with the various stages of life (infant, adulthood and the elderly) during health and disease. These factors include antibiotics therapy, diet, lifestyle, age, occupation, race, exposure to xenobiotics, mode of delivery, personal hygiene, lifestyle changes, immunological status, and so on [4, 8]. Furthermore, human microbiome has been implicated in phenotypic variation amongst individuals, as much as gene variations in the host genome [10].

Changes in microbial composition at various body sites lead to the changes in the physiology of these microbiomes, resulting in various disease conditions. The implicated diseases include allergic reaction, atherosclerosis, diabetes mellitus, liver diseases, kwashiorkor, thrombosis, cardiovascular diseases, cancer, obesity, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, and neurological diseases, such as autism, depression, Alzheimer's, and Parkinson's [8].

Within the last two decades, there has been a surge and understandably so, in the need to research more into the various microbial ecologies, including the human microbiome [11, 12]. This is driven by the various potential applications of the human microbiome, the gaps that exist in our understanding of their roles in disease and health, as well as the affordability of high- throughput DNA techniques [11, 12].

Some of these studies have changed our perception and concepts of the roles of human microbiome in health and disease, to say the least. Thus, this paper is aimed at providing an overview of the history, current culture-independent microbiome tools, diversity of the human microbiome and their roles in health and diseases, current applications and future perspective.

2. HISTORY AND TOOLS OF HUMAN MICROBIOME STUDY

Culture-based techniques have been around even before the novel discovery of agar as a solidifying medium in the late 19th century by Fanny Hesse [12]. Despite continuous improvements, it is limited in description of microbial diversity as it is not able to capture more than 10% of the overall diversities of the most environments [12-13]. Furthermore, most of the microbes that inhabit the gut are mostly anaerobic bacteria and their cultivation is still limited [14]. The huge diversity of microbes that constitute the "sixth" organ of humans was grossly underexploited with previously and routinely employed culture-based dependent methods [14-17].

Historically, the study of human microbiome started with the use of germ-free mouse models which can be colonized with gut microbes of interest [18]. Later on, fluorescent *in-situ* hybridization (FISH) which allows the quantitative assessment of microbial species was introduced [15]. Other molecular-based techniques that have been used in assessing microbial community include polymerase chain reaction coupled to denaturing gradient gel electrophoresis (PCR-DGGE), terminal restriction fragment length polymorphisms (T-RFLP), and microarray-based techniques [12-14]. The arrival of metagenomics has revolutionized some key concepts in microbial ecology [12-13]. As a culture-independent technique, it is the hallmark of molecular, empirical and bioinformatics advances in genetics. It captures not just the structural composition of the sampled ecosystem, but it also describes the functionality of the microbial structures contained therein using a number of bioinformatics pipelines, such as Kyoto Encyclopedia of Genes and Genome (KEGG), Cluster of Ortholog (COG), PRK (reverse position specific BLAST) and European Bioinformatics Institute (EBI). Most importantly, it is a higher throughput technique than the aforementioned molecular techniques that is more adaptable to bioinformatics analysis [19-22]. The strategies of metagenomics and other molecular techniques have been discussed in a number of reviews [12-14, 16]. Other culture-based independent techniques that have been used in the study of the human microbiome include target gene sequencing, metatranscriptomics, metaproteomics, and metabolomics [23]. It is worthy to note that until the arrival of molecular-based technique, the structural and functional diversity of the human microbiome was largely a *"black box"* [10]. The integration of more than one of these techniques is even possible and comes with better results. A case in this regard is the integration of both, metagenomics and metaproteomics in the study of Crohn's disease where it revealed useful signatures in healthy and non-healthy twin subjects [24]. Also, a combination of quantitative PCR with amplicon sequencing of the 16S rRNA to extract skin microbes revealed new taxa (viruses and eukaryotes), not previously accessible by 16S rRNA sequencing alone [17].

3. HUMAN MICROBIOTA IN THE ERA OF CULTURE-INDEPENDENT TECHNIQUES

There is not a doubt that the culture-independent techniques have allowed researcher to explore much more diversity and functionality of the human microbiome than culture-dependent techniques. Humans were once perceived to be sterile at birth with microbial colonization upon delivery [4]. This conjecture of a sterile womb was a central dogma and held sway for more than a century. However, this paradigm is under challenge by the proponents of the *in- utero* colonization of the fetus. A credence to this position comes from a number of studies, using molecular techniques that assessed microbiota *in-utero* (maternal placenta,

amniotics and mecomium), as reviewed by Perez-Munoz *et al.*, (2017) [25]. As shown in **Figure 1**, opponents believe that the process of colonization of the human gut commences immediately at birth and undergoes a number of successions until it becomes stable in healthy adulthood and more diverse in the elderly (Blum, 2017) [8]. The gut microbiome performs a number of functions that border on metabolism and immunity (host protection and immune system development) [26]. In metabolism, they are involved in the synthesis of vitamins, essential and non-essential amino-acids, and degradation of non-digestible carbohydrates, such as cellulose, pectins, and hemicellulose. In immunity, they are well known for the production of antimicrobial substances with diverse properties [27].

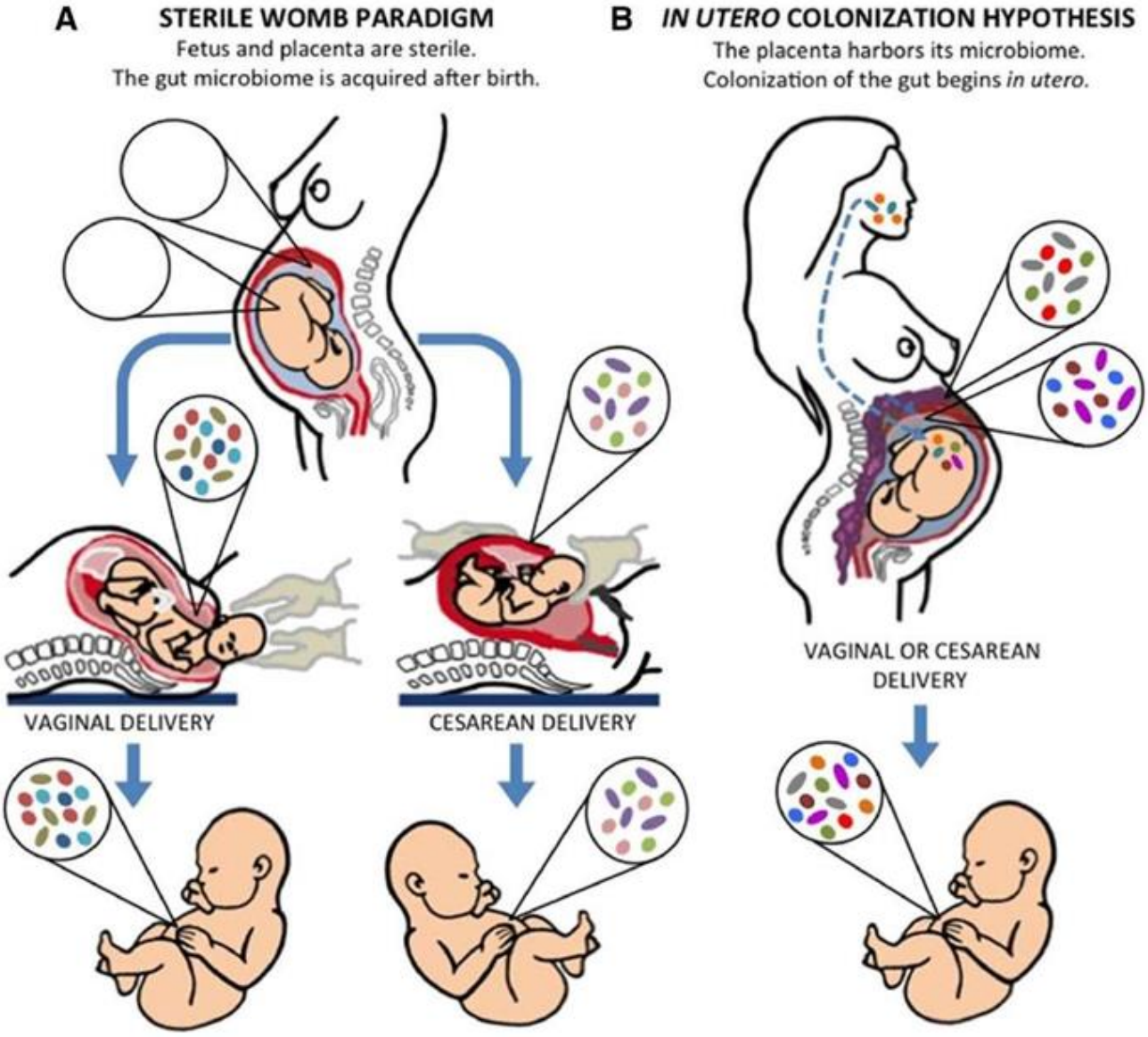

Fig. 1. Diagrammatic representation of the sterile womb and non-sterile womb adapted from Perez-Munoz *et al.* (2017) [25].

The human intestinal microbial community or gut microbiome is the most studied, followed by the skin [11, 28]. Most of the human adult microbiome inhabits the human gut [11] The colon microbes constitutes about 1-2 kg of the total body weight of an adult human and have a cell density of over 10^{11} cells/g content [4, 29]. The total number of microbes in the gut is estimated to be well over 1,000 species, mainly bacteria which contribute over 5,000 different genes [30]. Interestingly, these 1,000 species belong to just a few phyla, namely: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, Cyanobacteria, and Verrucomicrobia. In terms of abundance, the Firmicutes, Bacteroidetes and Actinobacteria remain the most abundant phyla while the Proteobacteria, Fusobacteria and Cyanobacteria are the less represented [31]. Cenit *et al.* (2014) [14] implicated the gut microbiome in obesity, innate and adaptive immune homeostasis, autoimmune and inflammatory diseases, extra-intestinal diseases, such as rheumatoid arthritis, type 1 diabetes, autoimmune encephalomyelitis, and immunodeficiencies [14]. However, a number of studies exist, including the human microbiome project that have revealed the number of species and relative abundance of various taxa, as shown in **Figures 2** and **3**. This shows that the phyla distribution is similar across the oral cavity, skin, airways, and gut. However, the relative abundance differs from site to site. As evident in Figure 1, the urogenital tract is the less diverse in terms of phyla.

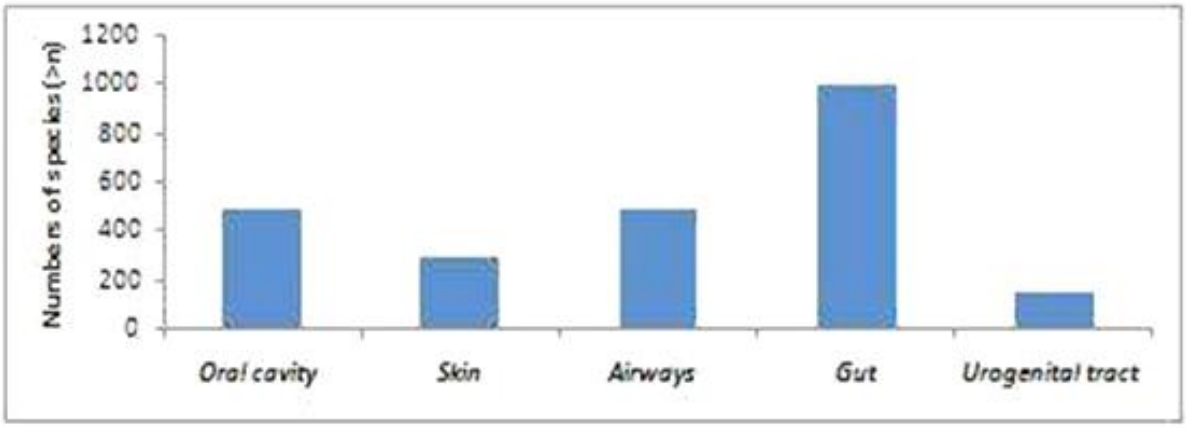

Fig. 2. Approximate number of microbial species in the most studied human body sites.

The urogenital tract represents data for females and was obtained from Argenio and Salvatore (2015) [4].

The human skin is no doubt the largest organ in the body, and as expected, it is colonized by a complex community of microbes, making the skin the second most studied after the gut microbiome [32-33]. Cosseau *et al*. (2016) [34], using metagenomics and diverse culture media, were able to capture the skin diversity much better. Their culture-independent technique detected 45 species-level operational taxonomic units distributed in 30 genera with a high diversity of Proteobacteria while fifty species distributed in 26 genera were identified using diverse culture media belonging to the Actinobacteria and Firmicutes. A study involving the United States and Tanzanian women showed members of the Propionibacteriaceae, Staphylococcaceae, and Streptococceaceae families amongst the US women and soil-associated Rhodobacteraceae and Nocardioidaceae on Tanzanian women, respectively [35]. These findings validate the role of the environment in distribution/diversity of the hand microbiome

[36]. In a related study, Capone *et al*. (2011) [37] showed that early colonization of the skin is dominated by *Staphylococci* which decline before the end of the first year. Furthermore, they also showed that Firmicutes predominate as opposed to that of adults. Another study, using polymerase chain reaction (PCR) and high throughput sequencing approach to access the structural and functional capabilities of the skin microbiome, provided insights into their abilities to utilize various compounds from the human skin. The study further revealed that these were dominated by *Corynebacterium*, *Staphylococcus* and *Propionibacterium* [9]. Elsewhere, metagenomics has been used to study the ecology of the skin where it revealed that the disruptions in its commensal microbiota are associated with progression of many dermatological diseases [38].

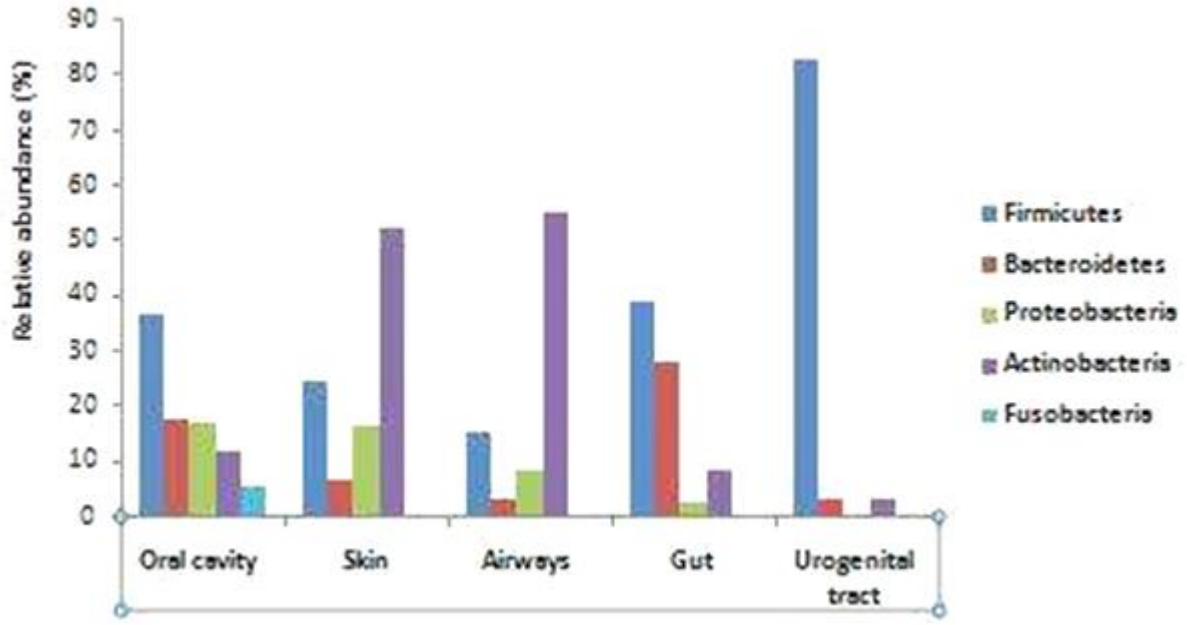

Fig. 3. Microbial composition across the different human body sites. Data culled from Argenio and Salvatore (2015) [4].

Even though, different phyla and their dynamics have been linked to these diseases, the definition of a healthy gut microbiome is debatable. However, a healthy microbiome is defined as one capable of returning to its original baseline structural and functional composition when challenged by factors that are capable of altering them [39]. Although, the metagenome of the human microbiome is much more variable than of the human genome, only a third of these genes are detected in health in humans [2]. This concept is well reviewed by Lloyds-price *et al*. (2016) [2] with a much more comprehensive definition, as captured in **Figure 4**, below. As can be seen from Figure 4, component *a* shows the composition of the gut, skin, mouth, and vagina microbiome in health. Component *b* shows the various functions played by the microbiome and their border on metabolism and immunity. Component *c* shows the impact of ecology on the definition of a healthy microbiome and it shows the impact of geography, host genetics and diet on composition. Component *d* characterizes a healthy microbiome in terms of dynamics from infanthood (unstable) to adulthood (stable) and during perturbation (disease) states [2].

4. THE HUMAN MICROBIOME OUR "SIXTH" ORGAN?

Life is organized, as we all know, in various stages (cells, tissues, organs and systems) in increasing order of complexity. Traditionally, an organ is a group of tissues which is a collection of cells that perform similar function with similar origin. Given such diversity posited above, it is therefore not much of a surprise that the human microbiome has been rightly called the 'missing human organ'. Furthermore, it would not be a complete misnomer to call the human microbiome the sixth most vital and diverse human organ after the brain, heart, kidney, liver, and lungs.

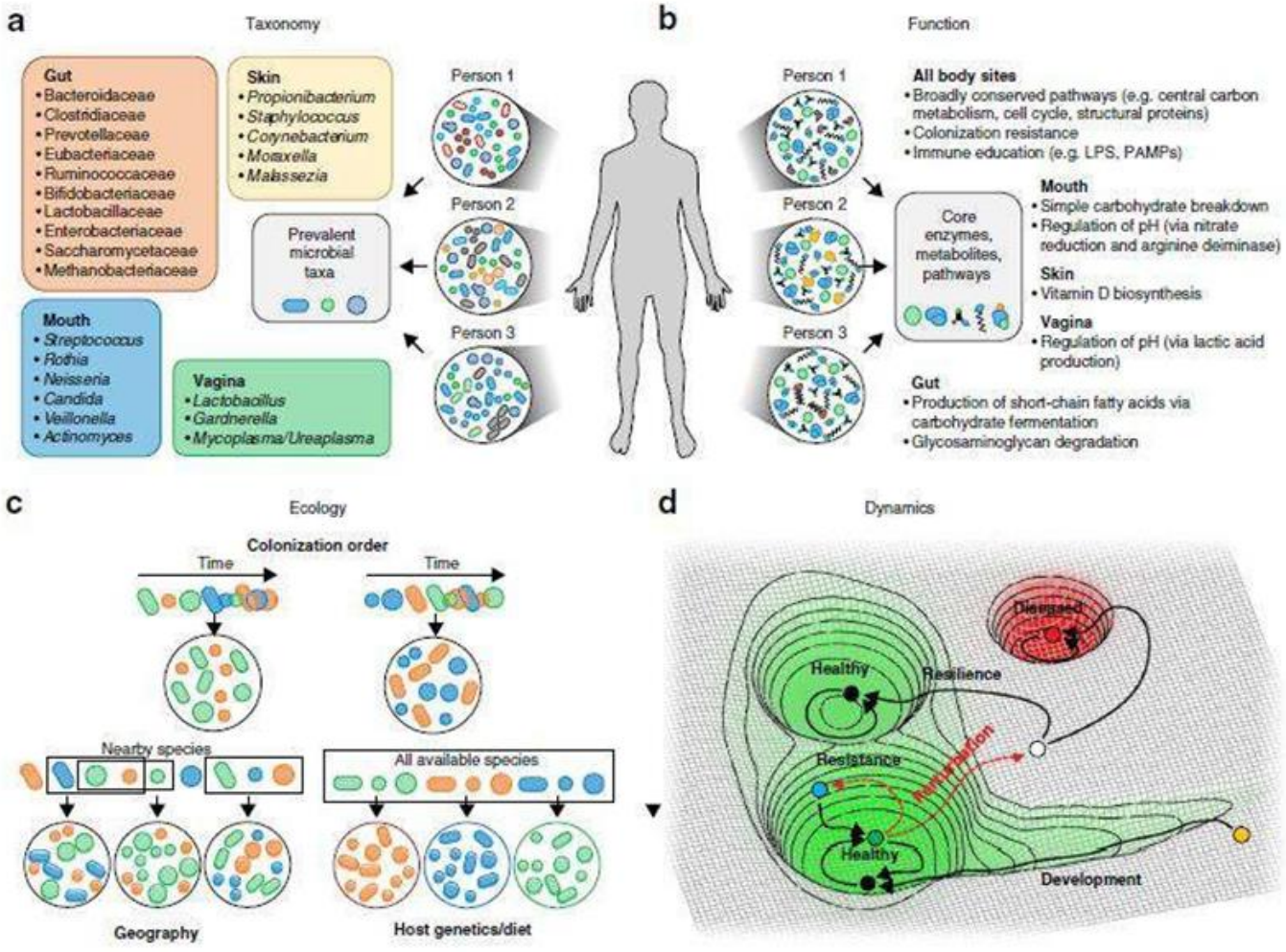

Fig. 4. Shows the definition of a healthy microbiome in terms of: composition, function, dynamics, and ecology represented in the diagram as *a*, *b*, *c*, and *d*, respectively [2].

5. FACTORS THAT AFFECT HUMAN MICROBIOME

The initial colonization processes have been shown to be influenced by a number of factors, such as type of delivery and feeding practices adopted [40-41]. Aging is strongly linked

with a gradual change in microbiome composition (**Figure 5**) between adults and the elderly due to a number of functional and biological changes with time [42].

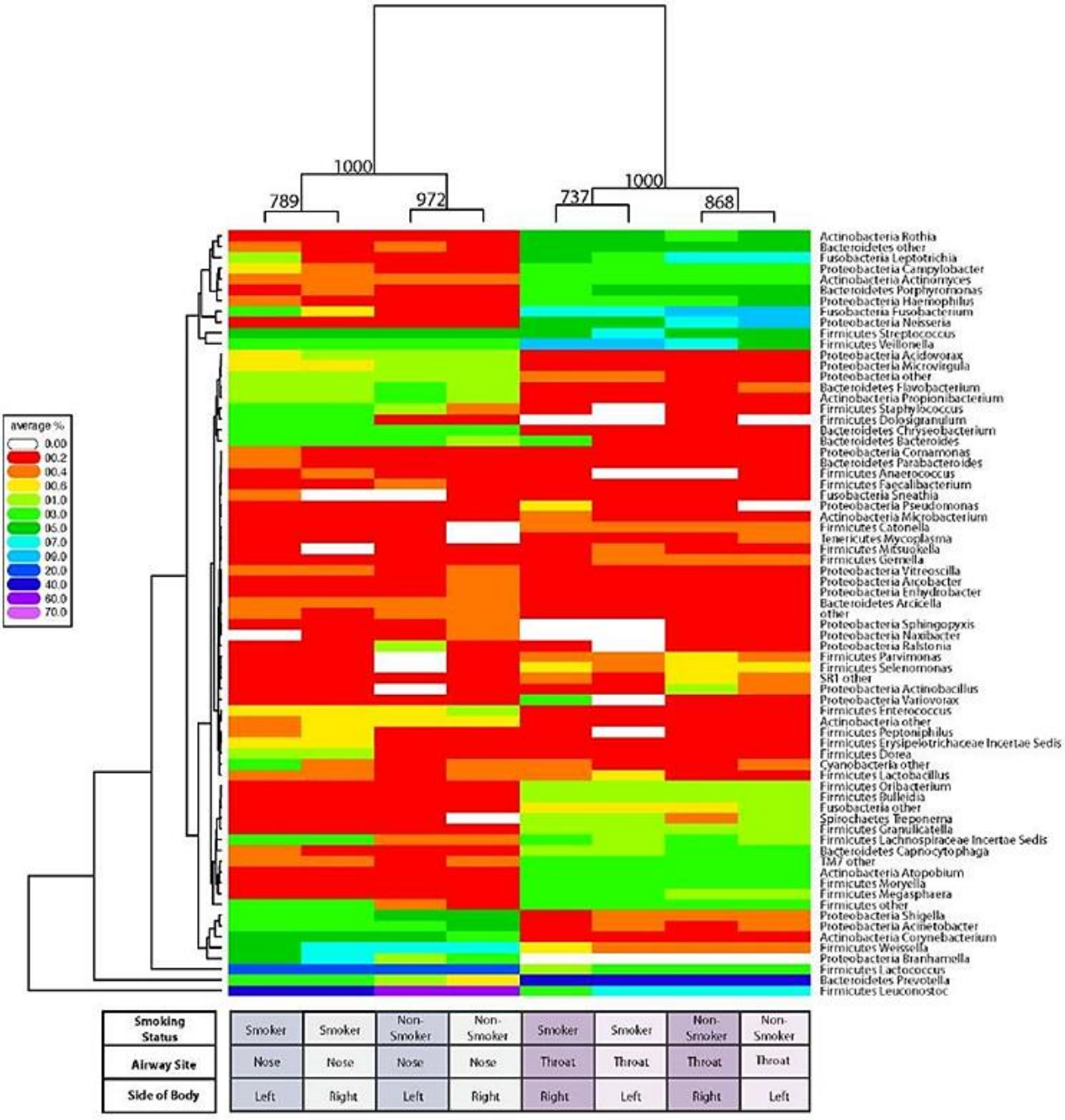

Fig. 5. Abundances of bacterial line ages of oro- and nasopharyngeal communities based on smoking status (Charlson *et al.*, 2010) [47].

It appears to begin at birth, and eventually becomes stable in a healthy adulthood [8]. These factors are divided into endogenous and exogenous factors. Recent evidence has emerged that suggests genetical that genetic variation also influences abundance of certain groups, as far as the intestinal microbiome is concerned [8].

As enumerated by Abubucker *et al*. (2010) [43], these include delivery channels (caesarian or normal vaginal delivery), gestation period, infant hospitalization time on delivery, feeding method (breast milk or type of infant formula), weaning age, malnutrition and therapies received. Other factors that could affect the microbial composition of children under three years of age include undeveloped immune systems, hygiene status, and living conditions of the parents. The most abundant microbial phyla for children under three years of age include Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes in decreasing order of relative abundance. These phyla correspond to those phyla that are associated with the oral cavity, skin, and airways and gut, as shown in Figure 2. In adults, a number of factors also affect the microbial composition and these include diets, travels, therapies, illness, hormonal cycles, and living conditions, as enumerated by Abubucker *et al*. (2010) [43]. Other include general hygiene and living conditions such as shared toilets, clothes and other body items, occupation, lifestyle and behaviours, such as drinking, smoking, sexual activities, drugs or substance abuse, and so on. Factors that influence the microbial composition of the elderly include lower immune systems, lifestyle changes, illness, medication, and diet or nutritional changes [43]. However, the general living conditions and hygiene and extra-curricular activities they are involved could also affect the microbial composition.

Other factors include racial and ethnic differences, and socioeconomic factors [35]. There is also some evidence showing inheritance of microbiota from parents [44]. Anukam (2017) [45] showed that ampicillin reduced the diversity of the gut core taxa with a corresponding increase in *Firmicutes-Bacteroidetes* ratio from 2.4:1 (pre-antibiotics) to 6.5:1 (antibiotics). Furthermore, a high proportion of *Veillonella* species were observed during ampicillin intake and also a stimulation of metabolism, such as carbohydrate (Ascorbate and aldarate), amino acid (D-arginine and D-ornithine), and vitamin (pantothenate and CoA biosynthesis). Similar effect was also seen with fluoroquinolones and β-lactams antibiotics which meaningfully reduced diversity in the gut by twenty-five percent, as well as the main phylogenetic composition from 29 to 12 taxa in faecal samples of patients immediately after treatment [46].

The impact of lifestyle change (smoking) and physiology on oro and nasopharyngeal diversity has been studied by Charlson *et al*. (2010) [47] and some of the results are presented in Figure 4. The results indicate that microbiomes of smokers are more diverse and clustered, together with an enrichment of anaerobic lineages linked to periodontal diseases, and disordered patterns of the upper respiratory tract microbial community in cigarette smokers.

6. MICROBIOME AND DISEASE

There is not a doubt the microbiome concept of disease is gaining popularity. A number of studies have already shown a causal link between microbial composition and a number of disease and the number of such publications are increasing by the day [4, 48]. Qualitative and quantitative changes in this microbial composition also alters the microbial composition and the functional roles they play at those sites that they colonize. These changes have been linked to obesity, immune-related diseases and inflammatory bowel diseases [49-50]. The current perceptive of diseases etiology has revealed that its etiology is not just complex but of

polyfactorial [51]. The various diseases linked to dynamic changes in human microbiomes are well reviewed by a number of authors [8, 26, 28, 52-54]. Thus, we have only provided an overview.

7. INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory bowel diseases, presently associated with changes in host microbiome, include ulcerative colitis and Crohn disease. Although the pathologies of both diseases are not fully known, however, some facts are well known. First, environment, host genetics and microbial community structure are intricately involved in homeostasis and disruption of this delicate balance can lead to IBD. Also, helminthic infection and microbial community have been linked to IBD (Cleynen *et al*., 2016). In their study, they showed an increased incidence of IBD in developed world with a decreased exposure to intestinal parasitic helminthes and alteration of intestinal microbiome. Furthermore, it is posited that there may be many routes to pathology development and a possibility of viral and fungi role [55-56].

8. OBESITY

Obesity is simply body mass index (BMI) that is above 30 kg/m^2 [57]. Current estimates indicate that about 2 billion people are over-weight with a third of them obese. Obesity comes with some health consequences, including diabetes (type 2), cancer, osteoarthritis, work-related disability, and sleep apnea [58]. Apart from obesity, insulin resistance and kwashiorkor are diseases correlated to nutrition, clinical status and microbial dysbiosis [59-60]. An increase in Firmicutes and a decrease of Bacteroidetes levels have been reported in obese individuals, and interestingly, the ratio of the both phyla were observed normalise on weight loss, as seen in lean subjects [62]. A number of ways have been proposed by which gut microbiome may contribute to obesity and these include dietary energy harvest [63], enhancing deposition of fat [64], and triggering systemic inflammation [65]. Furthermore, Tsai and Coyle (2009) [66] have also suggested modification locomotor effect and effect on satiety.

9. ATHEROSCLEROSIS AND THROMBOSIS RISK

Atherosclerosis is an arterial disease that is common and characterized by deterioration and plaques (deposits of cholesterol) formed on the interior of arterial surfaces, this blocking the flow of blood. On the other hand, thrombosis is characterized by the formation or presence of one or more blood clots that may eventually lead to partial or absolute blocking of an artery or vein [67-68].

Recent studies have shown that changes in gut microbial community could trigger both, atherosclerosis and thrombosis [67-68]. In these studies, protein rich foods, such as meat, eggs, yolks, and high dairy foods have been shown to be precursors of trimethylamine (TMA) and trimethylamine N-oxide (TMAO) which are linked to an acceleration of atherosclerosis. TMAO have also been shown to enhance hyperactivity and thrombotic events in animal models.

10. NEUROLOGICAL DISEASES

A number of studies have shown that there is a crucial communication demonstration

between the gut-brain axis and in the modulation and function of the tissue dependent immune cells in the central nervous and as well as the stimulation of the peripheral immune cells elaborated in processes such as neuroinflammation, autoimmunity and neurogenesis. Some of the neurological disorders linked to the gut microbiome include autism spectrum disorders, depression and Alzheimer's or Parkinson's disease [69-71].

11. PERIDONTITIS AND DENTAL CARIES

Amongst the common encountered oral diseases, peridontitis and dental caries are two common oral diseases. These are also amongst the main cause of tooth loss around the world. Most often than not, they are usually diagnosed late and followed by routine expensive and invasive dental care and management. The taxonomic structure of the saliva microbiota has been reported to help differentiate between a healthy and diseased oral person [72-73]. Using metagenomic and metatranscriptomics techniques to access saliva microbiota, Belstrom *et al*. (2017) [53] revealed *Streptococcus* as the principal bacterial genus responsible for a quarter and half of nucleotides (DNA and RNA) reads, correspondingly.

12. MAMMALIAN VIROME IN HEALTH AND DISEASES

Viruses are a part of the human microbiome that is not as well studied as their bacteria counterpart. Mammalian virome is the collection of both, commensals and pathogenic viruses (their DNA and RNA) implicated in evoking immune response from the host. Although no estimates as per the number of virome DNA and RNA, Kim *et al.* (2011) [74] estimated the number of viral particles in human feces to be within the same range as those of their bacteria counterpart ($> 10^9$). As rightly pointed out by Cadwell (2015) [56], the size and diversity of the human virome is simply overwhelming. This diversity is plausible when one looks at the fact that the virome consists of infectious viruses on the human host, viral elements and phages that infects the bacteriome of humans. It has been suggested that the human virome is as important as their bacterial counterpart [75]. Furthermore, millions are chronically and acutely infected by viruses, such as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus in both developing and developed countries which are of great public health significance [76]. It is well known that viral infected cells trigger host manufacture of interferons and other cytokines on recognition by innate immune system and eventually leading to immunomodulation, which is the modification of the immune system by effectors and suppressors. When caused by viruses, immunomodulation has consequences that are far outside antiviral defense, such as alteration of vulnerability to diseases and secondary infection [56]. The human intestinal virome is personalized, stable and dominated by phages [54]. The progression of HIV to AIDS has been linked with an expanded enteric virome, including previously unknown viruses [77].

13. VAGINAL MICROBIOME IN HEALTH AND DISEASES

Just how complex the vaginal microbiome remained elusive until the arrival of culture independent techniques [78] and we are just beginning to understand the roles microbial dynamics play in vaginal health. The effect of vaginal microbiome as a result of factor, such as menses and pregnancy, is not well known. Vaginal flora has been shown to become less stable

during menses with the concentration of non-Lactobacillus species higher during this time [79]. Urogenital infections, such as bacterial vaginosis, urinary tract infection, vaginitis, and vaginal candidiasis are all too common amongst reproductive age women around the world [80-82]. Bacterial vaginosis (BV), for instance, as a complex disease ensues following a change in microbial structure from predominant *Lactobacillus* to aerobes and anaerobes [78-79]. The normal vaginal flora is dominated by *Lactobacillus* species, mainly *L. crispatus, L. jensenii, L. Iners* and *L.s gasseri* (Vasquez *et al.,* 2002). However, in BV *Gardnerella vaginalis, Mycoplasma hominis, Prevotella, Peptostreptococcus, Mobiluncus* and *Bacteroides* species dominate [83-84].

14. CANCER AND HUMAN MICROBIOME

Cancer is no doubt one of the main causes of morbidity and mortality around the world [85-86]. Viruses had long been implicated in various cancers in human, such as cancer of the anus, vulva, vagina, cervix, oropharynx, nasopharynx, liver Kaposi sarcoma, to mention a few with HBV, HCV, Human papillomavirus, Epstein-barr virus, and Kaposi sarcoma-associated virus as associated oncogenic viruses [87]. It is also known that they account for about 20% of cancer cases, and colorectal cancer is one the most studied cancer with causal human microbiome dynamics [88], and there is less uniformity in enriched species and reduced species even with similar samples [89-90]. However, there Fusobacteria in high numbers have been linked to colorectal cancer in earlier studies [91-92].

15. APPLICATIONS OF HUMAN MICROBIOME

A number of applications are emerging already for the human microbiome and these are highlighted below. The idea of treating microbial diseases, with microbes or products, is not completely new and can be traced beyond the pioneering vaccination work of Edward Jenner in the late 18th century. Then came antibiotics therapy with the discovery of penicillin by Alexander Flemings in 1928, and its introduction. One of the major challenges with antibiotics is that of antibiotics resistance, despite advances in combinatorial chemistry, rational drug design and genetics. This has led to the search for alternatives, such as medicinal plants, and more recently, human microbiome [93]. The principle behind the use of human microbiome as a new source of antibiotics discovery is the discovery that the human microbiome can produce antimicrobial substances, such as bacteriocins against closely related bacteria [94]. Interesting, a total of 3,118 small molecules from human genome have been identified from a total of over 14,000 biosynthesis genes clusters [95].

Over a century ago, the father of probiotics, IIya Metchnikov first suggested that the gut microbiome played a significant role in health and disease. Furthermore, he recommended supplementing human diets with lactic acid bacteria. This was as a result of his observation that a regular intake of lactic acid bacteria as contained in fermented dairy products correlated with health and longevity in local Bulgarian peasant population [96]. Probiotics are simply beneficial microbes that assist digestion and also improve host immunity, especially in diarrhoea and infections. Studies have shown that Lactobacillus particularly stand out in this regard. Jones *et al*. (2012) [97], have been able to demonstrate that *Lactobacillus reuteri* they can effectively lower levels of total and LDL-cholesterol, inflammation, and reduce metabolic instability that raise cardiovascular risks. An early attempt to use prebiotics to treat women for BV did not

much promise [84]. Furthermore, interesting clinical improvements have been observed, following faecal transplant in genetically susceptible hosts [98]. Microbiome engineering has been carried out successfully with potential applications in human health and agriculture and as faecal transplant [1]. Other novel but unproven treatments options that have been tried include phage therapy and immune modulation. The use of phage is particularly interesting because it is specific in their target but the main concerned with phages would be resistance. Furthermore, they are self-replicating, thus reducing the costs of producing phage-based therapy when compared to the small molecule therapeutics [99].

16. FUTURE PROSPECTS AND CONCLUSION

Although there are many questions, then answers regarding the various roles of human microbiome may be playing in health and disease and about the factors that shape their dynamics. As next generation technologies continue to increase and improve, we will certainly have a better understanding of the human microbiome in healthy and diseased states. This will certainly enhance its potential and current applications. With the implication of more and more previously unknown microbes in human diseases vis-a-viz their dynamics, we will certainly be seeing novel treatment options for antibiotics, probiotics, and prebiotics. One of the turning points in human microbiome will of course be the correct definition of the microbes that constitute a healthy human microbiome structurally and functionally, not just in the gut and skin, but all other parts of the human body.

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