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Microbiota succession throughout life from the cradle to the grave

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Abstract | Associations between age and the human microbiota are robust and reproducible. The microbial composition at several body sites can predict human chronological age relatively accurately. Although it is largely unknown why specific microorganisms are more abundant at certain ages, human microbiota research has elucidated a series of microbial community transformations that occur between birth and death. In this Review, we explore microbial succession in the healthy human microbiota from the cradle to the grave. We discuss the stages from primary succession at birth, to disruptions by disease or antibiotic use, to microbial expansion at death. We address how these successions differ by body site and by domain (bacteria, fungi or viruses). We also review experimental tools that microbiota researchers use to conduct this work. Finally, we discuss future directions for studying the microbiota's relationship with age, including designing consistent, well-powered, longitudinal studies, performing robust statistical analyses and improving characterization of non-bacterial microorganisms.

Human-associated microbiotas are communities of bacteria, fungi, protists, archaea and viruses (often referred to as the bacteriome, mycobiome, protistome, archaeaome and virome, respectively) that live on and/or inside the human body. We know far more about how bacterial communities change across age groups than about fungi, archaea, protists or viruses, but that does not necessarily translate to bacteria being of disproportionate importance. Microbial communities exist on every mucosal surface in the human body, and each body site within a person has a unique ecology[1–3]. Each individual's human-associated microbial community is unique compared with that of all other humans[4]. Human-resident microorganisms encode an estimated 2 million to 20 million genes, whereas the human genome encodes an estimated 20,000 to 25,000; therefore, the microbiome represents up to 99.9% of the genetic capacity in the human body[5]. During each stage of life from birth to death and decomposition, microbial communities act as a dynamic component of the body. Investigating the natural and induced changes in our microbiota has the potential to revolutionize our understanding of human biology.

Microbial succession is defined as a change in the presence, relative abundance or absolute abundance of one or more organisms within a microbial community. Microbial succession processes can be deterministic or stochastic. Factors that drive deterministic succession fall into three categories: abiotic factors (for example, pH or redox potential)[6], environmental factors (for example, cross-feeding[7], diet[8] or travel[9]) and biological factors (for example, innate and adaptive immunity)[10]. Stochastic succession is defined as microbial community changes that are not the consequence of environmentally determined fitness (also called 'ecological drift')[11,12]. Whether microbial succession is more deterministic or stochastic is driven by several factors in the formation of the community, including birth mode, travel, diet (for example, human breast milk) and antibiotics[13–17]. There are three main stages of microbial succession that naturally occur across human life during normal or healthy ageing.

The first stage, primary succession, begins at birth when pioneer species first establish the community, and this stage is followed by rapid changes in the microbial community. The rate of change decreases from birth until childhood, and many intermediate species exist between birth and late childhood[13–15] (FIG. 1, columns 2–4). Primary succession ends at the formation of a climax community, thought to be achieved by adolescence and largely sustained through adulthood; this community is characterized by its relative stability[18,19] (FIG. 1, column 4). Although the microbiota is stabler in adulthood than in childhood, there is still variability, fuelling the debate over the existence of a climax community in the human microbiota[20]. Natural variation in the adult microbiota exists on the timescale of hours (circadian rhythms)[21] to years (ageing), but microbiotas are relatively stable except in the presence of a disturbance, such as a change in diet or medications. The next stage, secondary succession, occurs when part of nearly all of a pre-existing

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Keystone community members
Microbial species that have an exceedingly large impact on the stability, or recovery after perturbation, of the whole ecosystem.

Alpha diversity
A measure of within-sample diversity.

Beta diversity
A measure of similarity between samples.

stable community is altered or removed, followed by regeneration of the community to either the same state or a different state. This can happen either deliberately, through medical treatments such as antibiotics[22,23], or spontaneously, through diseases such as infection with *Vibrio cholerae*[24]. Secondary succession in humans is characterized by at least some period of a stochastic process dominating. In induced conditions, such as a single course of antibiotics, the community follows a process similar to primary succession, in which parts of the existing microbial community act as 'microbial memory' and help re-establish a community similar to the one that existed before. This process is thought to be driven by keystone community members[25,26] rather than the pioneer microorganisms that drive primary succession (FIG. 1, columns 5–7). Third, final succession is part of the natural host senescence and death. During old age, the microbial community again succeeds at an increased rate of change, producing a community composed of fewer total members, usually with increased relative abundance, and sometimes total dominance, of the phylum Proteobacteria (also known as Pseudomonadota)[27,28] (FIG. 1, column 8).

Unlike the human genome, which is encoded at birth and cannot be altered during life (at least with current technology), each of these unique microbiota changes can be deliberately modified across time. Within an individual, the specific body site location, the geographical location and the individual's age have the strongest relationship with the healthy microbiota of any physiological or demographic variable measured to date[18]. Age drives both alpha diversity and beta diversity in human microbiotas (FIG. 2 and Supplementary Fig. 1). Studying each stage of succession enables researchers to address how human-associated microbial communities are formed and maintained. By understanding these processes, we may better understand how to manage microbiotas as we age and in relation to human health. Although the methods to measure and describe microbial communities are an area of active development, standard practices do exist, making it possible to integrate results across cohorts.

Primary succession in early life

The first factors that shape a human microbiota come from the mother during fetal development. The fetus is exposed to metabolites produced by the mother's microbial community through the placenta, which imprint its immune system and can affect both the normal microbiota and also various aspects of pathology later in life (immune imprinting described in[29])[30–32]. The composition and transfer of these metabolites to the fetus can be impacted by the mother's health, diet and use of antibiotics during pregnancy[33–39]. For example, the mother's gut microbiota ferments dietary fibre, resulting in short-chain fatty acids such as acetate which have been observed to cross the placenta[33]. Acetate in the fetal tissue affects epigenetic imprinting linked to the generation of regulatory T cells in adults, which are associated with protection from the development of asthma later in life[33]. Microbial metabolites (including short-chain fatty acids) and ligands regulate the host aryl hydrocarbon receptor (AHR), which helps to shape the neonatal microbial and immune development[34,40–42]. Maternal antibiotic use and gastrointestinal tract-related diseases such as inflammatory bowel disease (IBD) are also thought to increase the risk of pathology in offspring later in life by imprinting of the fetal immune system[43–46]. However, these links have been studied only in non-human experiments. In one case, germ-free mice colonized by microbiotas from either pregnant mothers with IBD or their newborn baby went on to develop the aberrant microbiota and immune development indicative of IBD[45]. The mother's microbiota and immune system are also altered during pregnancy[47,48]. The mother's vaginal microbiota becomes more diverse, consisting of many microorganisms conventionally found at other body sites[49]. The maternal immune system during pregnancy forms cooperative interactions with the fetus, including transferring IgG antibodies across the placenta (reviewed in REFS.[50,51]) (FIG. 3a).

The beginning of the human microbial community and the start of primary succession occur at birth with the seeding of the newborn from the mother's microbiota. There is some debate about whether the microbiota obtained at birth originates from both vaginal and faecal sources, through mixing, or whether the vaginal microbiota itself is pluripotent at birth and is the main source of microbial pioneers (that is, the first species to colonize, setting the stage for other species later in succession)[49,52–54]. Regardless of the exact maternal source, this stage is characterized by pioneer bacterial species such as *Lactobacillus*, *Enterobacter*, *Escherichia*, *Bacteroides*, *Parabacteroides* and *Prevotella*, which then colonize their conventional body sites: the gut, mouth and skin[15,18,55,56]. Many pioneer bacteria are facultative anaerobes, which deplete oxygen and thereby enable obligate anaerobes to colonize each environment later. At first, each body site of a newborn is relatively undifferentiated, but pioneer microorganisms quickly begin initiating a cascade of body site-dependent microbial diversity, and at least the bacteria at each site can be easily distinguished by the fourth to sixth week of life[1,13] (FIG. 3b).

The development of the bacterial community in the human gut has been well studied (reviewed in REF.[57]). *Bifidobacterium* spp. are dominant until they give way to a combination of *Bifidobacterium*, *Clostridium* and *Bacteroides* spp. by the end of the first year of life. This is followed by a greater increase in the abundance of

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Bacteroides spp., a more diverse set of genera within the phylum Firmicutes (also known as Bacillota; for example, *Clostridia*, *Faecalibacterium*, *Ruminococcus* and *Veillonella*) and a relative decrease in the abundance of species such as those in the genus *Bifidobacterium*[14,15,52]. *Bifidobacterium* spp. catabolize human milk oligosaccharides (HMOs) from the mother's breast milk, which is believed to begin imprinting the immune systems for life[58–61]. Most recently, a study found functional links between bacteria such as *Bifidobacterium* spp. containing genes required for catabolism of HMOs and the infant immune development. In particular, faecal waters from infants that received *Bifidobacterium infantis* EVC001 polarized naive T cells differently from faecal waters from the control group, in a manner associated with decreased intestinal inflammation[58]. However, species in other genera, such as Bacteroides and Akkermansia, can also degrade HMOs[62]. By the age of 3–6 years, the gut bacterial community converges to the climax community sustained throughout adulthood. This community of microorganisms is one of the densest and most diverse ecologies known[63,64]. Usually, only two bacterial phyla are dominant in an average healthy person during this time: Firmicutes and Bacteroidetes[65].

The virome, mycobiome and archaeaome are far less explored than the bacteriome during the course of human gut development. Throughout life, the mycobiome accounts for far fewer total numbers than the

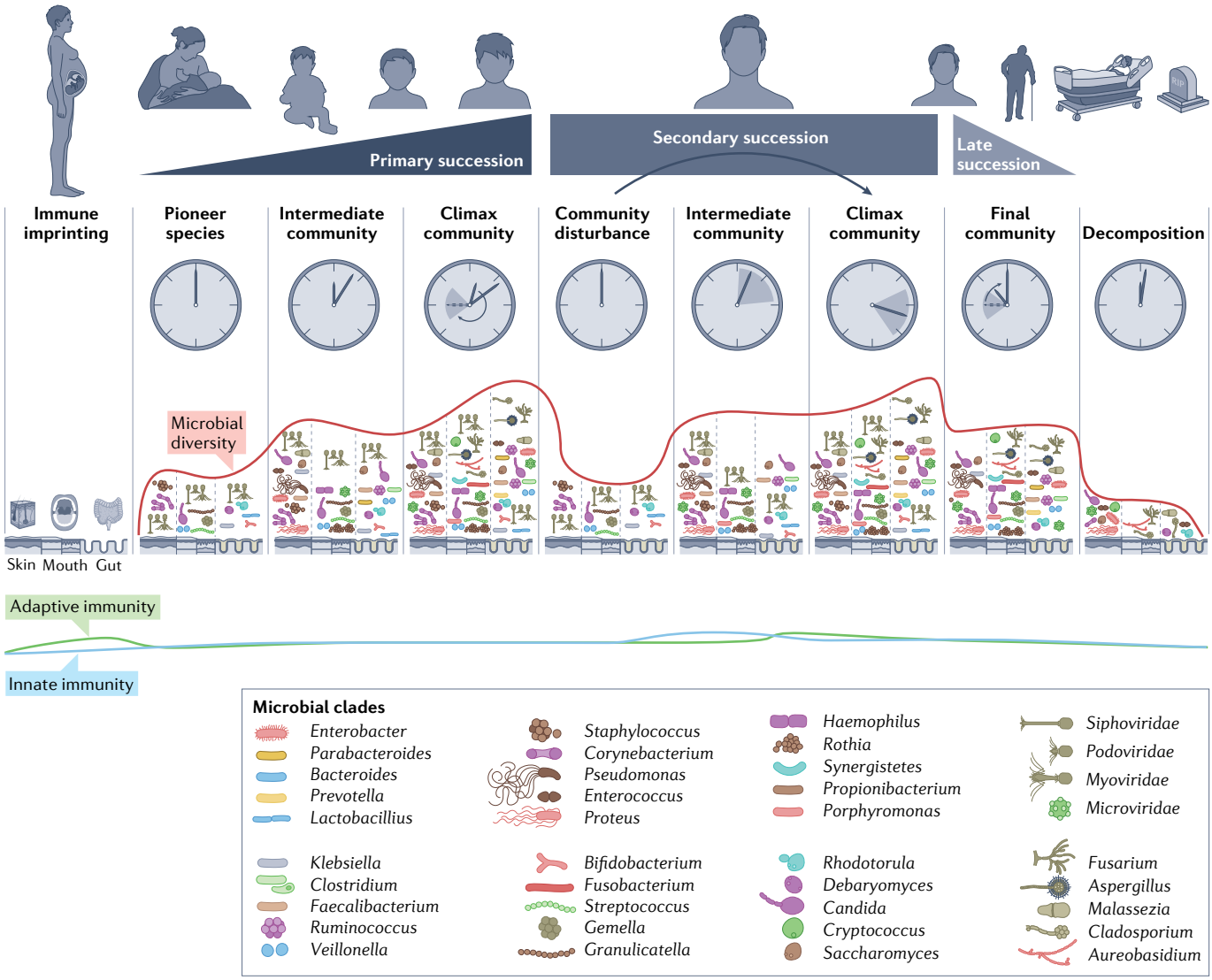

Fig. 1 | **The succession of the human microbiota from conception to death.** The diversity of resident bacteria, fungi and viruses changes across human life stages. The analogue clock represents the relative time of the host age at which each microbial community stage develops. Immune imprinting begins before birth through the mother's microbiota and its metabolites (first column). Initial colonization of pioneer species begins at birth, and body site-specific microbial communities emerge (second column). These communities continue to increase in complexity until they reach a relatively stable community structure (third and fourth columns). Secondary successions of these microbial communities can occur from internal and external perturbations (fifth column). Intermediate species of microorganisms re-establish the initial community and reach a steady state again (sixth and seventh columns). At late age, the community goes through a final succession and changes as the host nears natural death (eighth column). The last stage of microbial succession occurs at putrefaction and decomposition. During this stage, diversity further declines and, during the first 24–48 h, many of the human microbiota structures are conserved, but then quickly begin to erode (ninth column). The relative strength of adaptive immunity (green line) and innate immunity (blue line) across different stages of life and microbial succession (bottom) is shown.

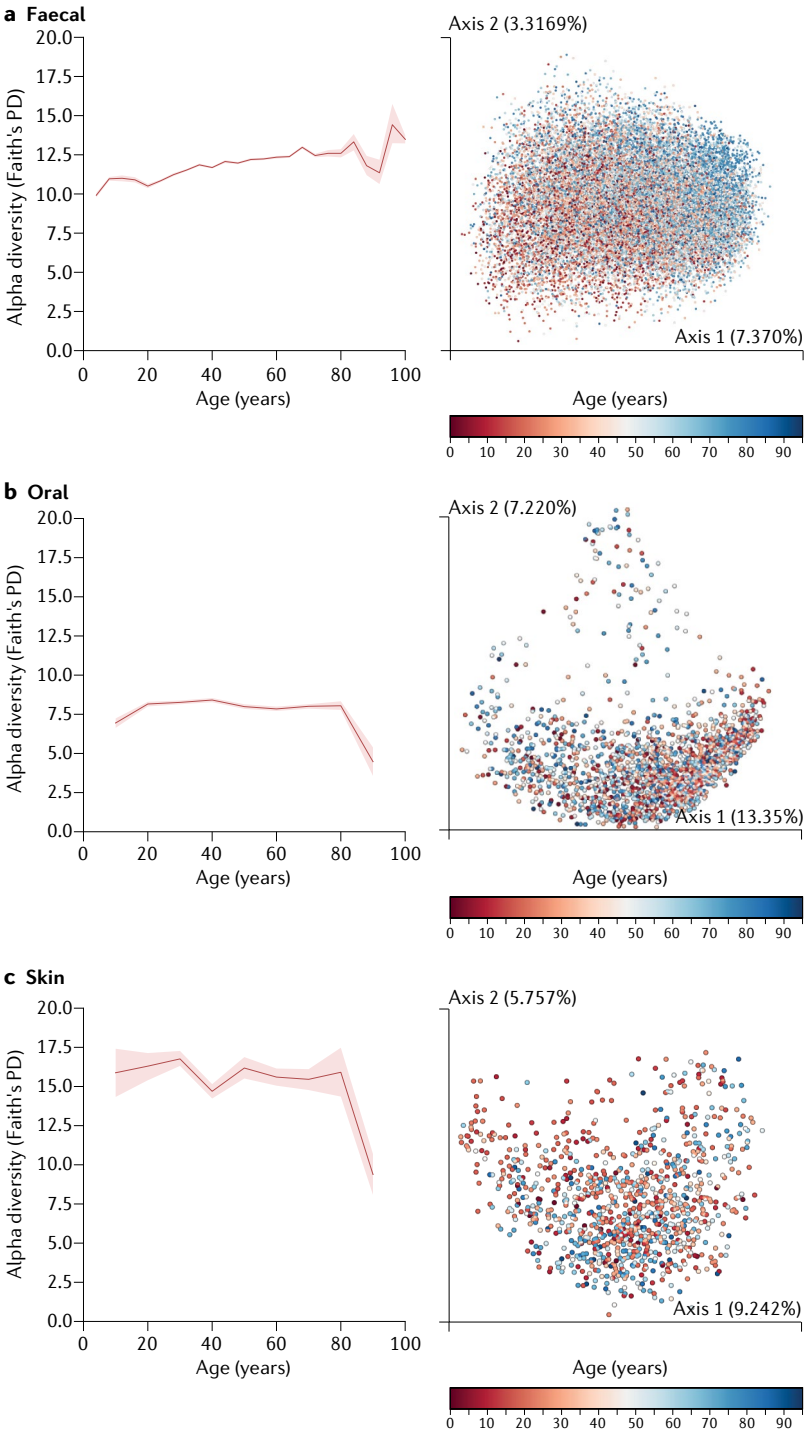

Fig. 2 | **Measurements of bacterial diversity across age.** The bacterial diversity and phylogenetic history of the human faecal (part **a**), oral (part **b**) and skin (part **c**) microbiotas from childhood to old age measured in the data set of the American Gut Project, a citizen science project containing 21,919 faecal, 1,920 oral and 998 skin microbiota samples with 16S ribosomal RNA gene amplicon sequencing[56]. Alpha diversity, a quantitative measure of the number of different types of microorganisms in a sample, measured through Faith's phylogenetic diversity (PD) alpha diversity metric across age (left column). The UniFrac beta diversity principal coordinate analysis, a method for comparing the similarity of microbial communities where spatially close dots represent similar samples and spatially distant dots represent dissimilar samples, coloured by age (right column).

bacteriome or virome. The fungal community in the first few days of life contains a high abundance of *Rhodotorula* and *Debaryomyces* spp., followed in the next month by *Candida*, *Cryptococcus* and *Saccharomyces* spp.[2,66]. By adulthood, the dominant fungal genera are *Aspergillus*, *Candida* and *Saccharomyces*[67–69]. The archaeal gut community during development is not well understood, but archaea are some of the earliest colonizers but in low abundance[70]. Early-colonizing archaea include the genera *Methanosphaera* and *Methanobrevibacter*[70]. The viral community, consisting mainly of phages, is numerous in the first week of life[71]. The phage families *Siphoviridae*, *Podoviridae* and *Myoviridae* are prevalent immediately after birth, primarily in lysogenic form (integrated into the bacterial genome)[72,73]. By the fourth month of life, the phage order *Caudovirales* grows in abundance and members are more often lytic (infectious phage particles or actively replicating phages)[74–76]. In adults, *Caudovirales* and *Microviridae* dominate the gut phage community, but the phage gut virome is highly specific to the individual, and much is still unknown about its succession (reviewed in REF.[77]). Unlike phages, the gut virome of eukaryote-infecting viruses is mostly associated with pathology both in children (for example, gastroenteritis)[78] and in adults[79]. Recently, some eukaryote-infecting viruses have also been observed in low abundance both in healthy children and in healthy adults but their timing and prevalence are unknown[72,73,80] (FIG. 3b–d, gut columns).

The oral bacteriome has a high prevalence of members of the genera *Streptococcus*, *Gemella*, *Granulicatella* and *Veillonella* at birth[81]. In the following months, the genera *Lactobacillus* and *Fusobacterium* also become prevalent. The abundance of *Staphylococcus* peaks at around 3 months of life and then steadily decreases, giving way to a higher abundance of *Gemella*, *Granulicatella*, *Haemophilus* and *Rothia* spp.[82]. After the formation of teeth, the oral microbiota shifts again, to have a higher abundance of the phyla Fusobacteriota, Synergistetes, Tenericutes, Saccharibacteria (TM7) and SR1 into adulthood[83–86]. The oral mycobiome is believed to harbour less fungal diversity than the skin and gut[2]. *Candida* spp. are the first fungal colonizers of the oral cavity, on the first day of life[87,88]. Very little is known of the intermediate oral fungal community, but by adulthood *Candida*, *Cladosporium*, *Aureobasidium*, *Aspergillus*, *Fusarium* and *Cryptococcus* spp. have high prevalence[89]. The oral archaeaome during development is not well understood, but the adult oral cavity harbours many archaeal methanogens, including of the genus *Methanobrevibacter*[90–92]. To our knowledge, not much is currently known about the colonization of the oral cavity by viruses in human infants. In adults, similarly to the gut, the most common phage group is Caudovirales[4,93,94]. The eukaryotic oral viral community is generally viewed as pathological in nature (for example, Coxsackie A virus, Morbillivirus, Rubulavirus and human papillomavirus), and there are no longitudinal studies of viral

community composition[95]. However, many eukaryotic viral taxa have also been observed in asymptomatic and otherwise healthy adults[96] (FIG. 3b–d, oral columns).

The skin bacterial community contains a high abundance of the mother's vaginal *Lactobacillus* spp. at birth[13,49]. By week 4–5 the infant skin microbiota resembles the adult skin microbiota, but continues to become more site specific into adolescence, with dominant genera such as *Staphylococcus* and *Corynebacterium* across sites and *Pseudomonas*, *Enterobacter*, *Enterococcus*, *Proteus* and *Klebsiella* at specific sites (for example, armpit versus forearm)[1,97]. In the skin mycobiome, species of the genera *Malassezia*, *Candida*, and *Saccharomyces* are most prevalent in the first 30 days of life[2,98,99]. Little is known about the exact compositions of the intermediate community, but the adult mycobiome often has a high abundance of *Malassezia* species, with estimates ranging from 75% to 90% of the total fungal community composition[2,100]. Little is known of the development of the archaeal community of the skin, but archaea constitute around 4% of the adult community[101]. Broadly, the adult archaeal skin community is represented by the

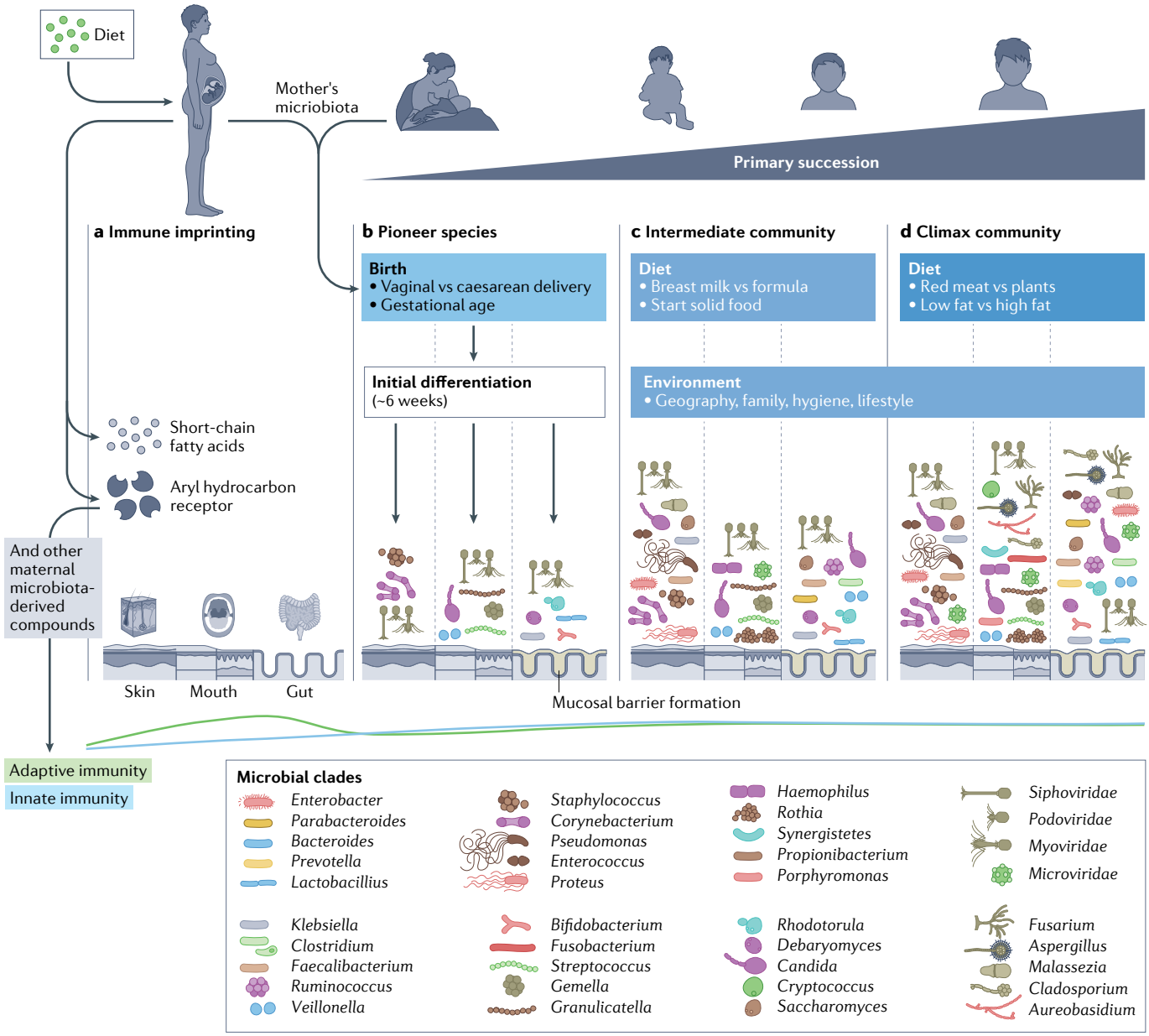

Fig. 3 | **Primary succession in utero and during early life.** The future of the yet-to-be-colonized fetus is set on an initial community assembly trajectory through the priming of each body site by the mother's imprinting on the fetal immune system. Metabolites such as short-chain fatty acids (for example, acetate) and other microbial compounds can be transferred to the fetus through the placenta and influence immune development. The mother's diet and health also influence these metabolites (panel **a**). Upon birth, the microbial community quickly differentiates by body site (panel **b**). During this initial colonization, the pioneer species and the community development of the next 4 years can be impacted by birth mode and gestation time. The following intermediate community is shaped by the diet, such as the consumption of breast milk or formula, and the environment (panel **c**). Finally, the stable climax community is again shaped by the diet and the environment (panel **d**). The key (bottom) is composed of fungal, bacterial and viral clades shown in differing colours and distinct representative morphologies. The presence or absence of different clades represents the description in the main text.

Secondary bile acids
Bile acids that have been altered by the microbiota.

phyla Thaumarchaeota and Euryarchaeota. The archaeal family Halobacteriaceae and genus *Methanobrevibacter* are also found on adult human skin[102,103]. Unlike the gut and oral cavity, the healthy skin microbiota harbours relatively little known viral diversity, and few studies has been devoted to it, likely due to the technical limitations associated with low-biomass samples[104]. However, there are some naturally residing viral populations on the skin[105] (FIG. 3b–d, skin columns).

Several factors shape and differentiate microbial community development in the first few years of life. Birth mode and maternal antibiotic use are among the best-studied and clearest factors that influence the human microbial community. However, microbial development can lead to unique outcomes, even in cohabitating identical twins, likely due to many unknown or stochastic processes[106]. The process of natural microbial community establishment can be disrupted, in all body sites, through caesarean delivery and perinatal and neonatal antibiotic exposure[13–15,107–109]. This finding highlights the importance of the vaginal microbial community, which naturally contains a high abundance of *Lactobacillus* spp. but is altered during puberty, menopause and pregnancy, and is central to female health (reviewed in REFS.[110,111]). Several of the best-sampled infant development studies, commonly abbreviated as DIABIMMUNE[14] ECAM[15] and TEDDY[108], followed up infants for the first 2 and 3 years of life, and focused on the impacts of antibiotic use or birth mode. In all aforementioned studies, infants born vaginally had higher relative abundance of *Bacteroides* spp. than those born by caesarean delivery. The lack of a natural pioneer microbiota to establish the microbial community results in a more variable community composition thought to be driven more by a stochastic process than a deterministic process, with the effects of birth mode on microbial community composition still observable until the fourth year of life[112,113]. An exception to the impact of birth mode is preterm birth, likely due to the high use of antibiotics in the first few days of life, which is characterized by an unstable microbial development regardless of the birth mode (reviewed in REF.[114]). This alteration in the natural development of the infant microbiota is associated with increased risks of infections, immune diseases, obesity and neuroendocrine abnormalities[107,115–125]. Second, breastfeeding has a large effect on microbiota development compared with other factors[108]. The use of formula compared with breastfeeding leads to a higher-diversity and less deterministic microbial community[126]. For example, given the natural dominance of Bifidobacteriaceae in the gut at birth, the lack of certain HMOs as a primary nutrient source can lead to instability in the initial colonization[58]. However, much of the multi-omics integration of the microbiota, milk metabolome and immune system development is an area of active and rapidly advancing research[127]. In addition to HMOs, breast milk also contains other immunomodulatory compounds, such as lipopolysaccharide from Gram-negative bacteria, secretory IgA, innate immune factors, antimicrobial peptides and prebiotic factors[34,128–131]. Finally, all of these factors impact human immune development. Microorganism-associated molecular pattern recognition receptors (for example, Toll-like receptors[132] and NOD-like receptors[133]) interact with microbiota-derived molecules (for example, lipopolysaccharide), metabolites such as short-chain fatty acids (which interact with GPR43, GPR41 and GPR109)[33] and secondary bile acids (which interact with FXR)[134] to directly impact immune development[135,136]. Together, many of these factors contribute to the development of a unique, relatively stable microbial community of bacteria, fungi and viruses, which persists for a large part of the human lifespan.

Secondary succession in adult life

Although the adult microbial community is largely stable compared with the big changes that occur during primary succession in infancy, the community can be perturbed and pushed away from the climax community state. The understanding of the microbiota during health and disease is a deepening and disease-specific research field[99,137,138]. The genomes of certain bacteria evolve across time in healthy adults, demonstrating that functional and compositional evolution occur in a steady state during secondary succession[139] (FIG. 4a). There are also natural short-term changes that occur in the adult microbiota on timescales of a day to months or years (FIG. 4a). One well-characterized example of short-term changes is the circadian rhythm in microbial community composition. Human gene expression and immune activation linked to the circadian rhythm[140], and the abundance and composition of bacteria within the gut microbiota also follow this pattern[21]. Bacterial families showing a diurnal cycle in mice include Ruminococcaceae, Lachnospiraceae, Muribaculaceae (S24-7), and Verrucomicrobiaceae, but little is known about equivalent cycles in humans because they produce faeces less frequently than do mice[141]. In the mouth, daily oscillations in whole groups of fungi and bacteria coincide with brushing[142]. On the skin, daily fungal and bacterial alterations coincide with washing and depend on personal care products[143,144]. A well-studied example of changes that occur on the scale of weeks to years is diet-driven alteration of the gut microbiota. Diet has a large effect on microbial communities, and can include natural and reversible changes in the community (reviewed in REF.[145]). For example, the Hadza tribe of Tanzania, who eat a diet rich in meat and tubers in the dry season but a diet rich in honey and berries during the wet season, exhibit large seasonal fluctuations in genera such as *Bacteroides*[8,145,146]. The large influence of diet in shaping the microbiota may also play a role in human health (reviewed in REF.[147]), and much work is being dedicated to understanding how specific dietary components, and dietary patterns overall, influence the microbiota and its impact on health. For example, Western diets, with high levels of red meat, have been linked to all-cause mortality[148]. The gut microbiota can act in a deleterious manner to convert L-carnitine, which red meat is rich in, to trimethylamine, and the liver converts trimethylamine into trimethylamine *N*-oxide, which is hypothesized to promote atherosclerosis[149]. The gut microbiota can also act in a protective manner, for example, by cleaving carcinogenic molecules from

red meat before they are absorbed in the gut, protecting from inflammation[146]. Besides diet, many other factors help to shape the adult microbiota, including genetics, geography, host factors such as metabolic disease and medicines (reviewed in REF.[150]).

Secondary successions that occur due to a disruption in the microbial community have been studied and reviewed extensively. Of the many factors that disrupt the microbiota, antibiotics are among the strongest, often with individually variable recovery after treatment[22,23]. The ability of the gut microbial community to rebound after antibiotic treatment is thought to depend on specific community members, such as *Bacteroides thetaiotaomicron* and *Bifidobacterium adolescentis*[25,26]. Disease itself can also disrupt the microbiota, whether the change is initiated within the microbial community (overgrowth of a pathogen), from the host or from a combination of factors (reviewed in REF.[10]) (FIG. 4b). Many other diseases in the gut, such as IBD, disrupt the microbial community but do not reach a new stable community composition,

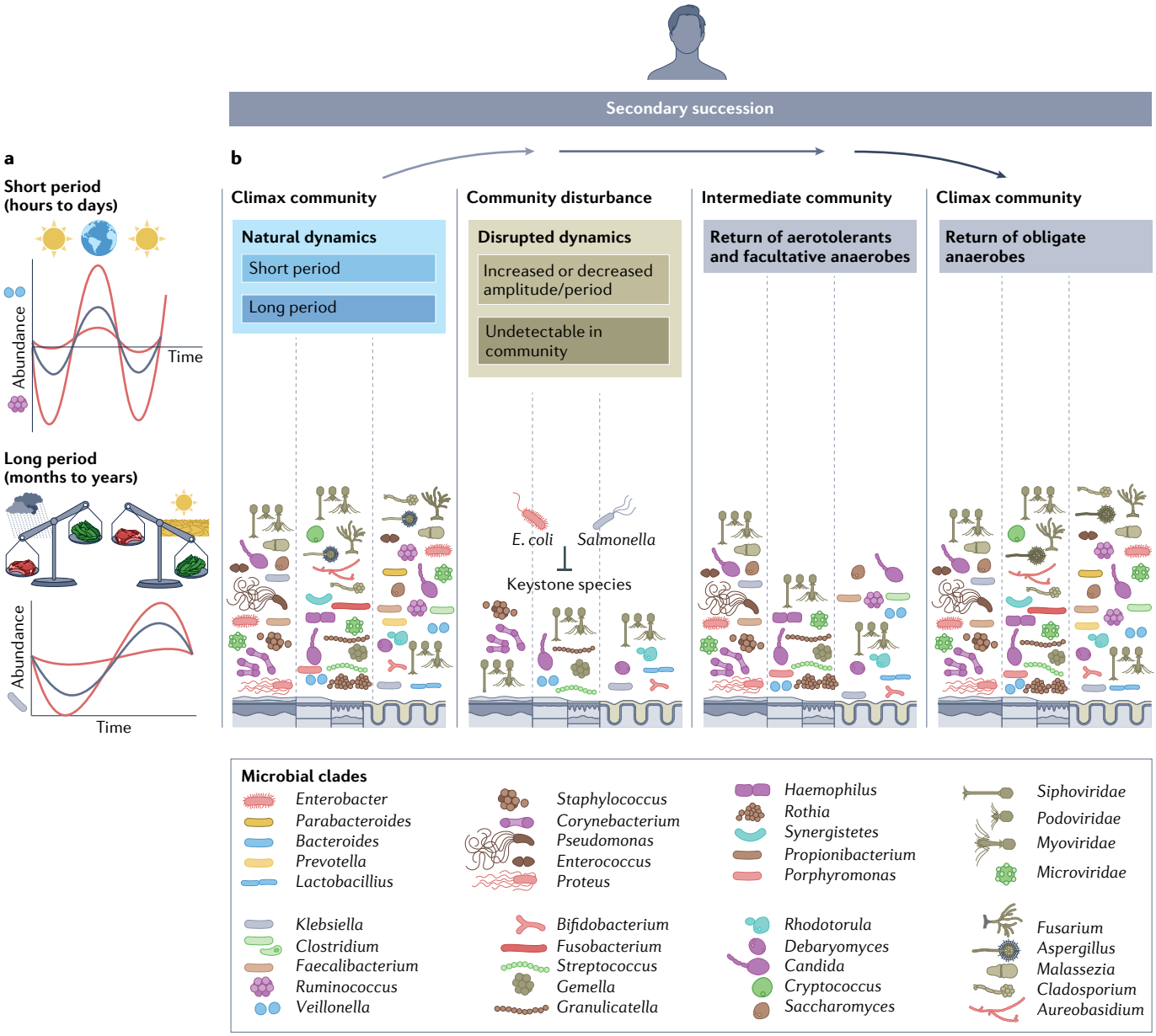

Fig. 4 | **Secondary succession in adolescence and adult life.** Compared with microbial community assembly in primary succession and human development, the microbial community in adulthood is relatively stable. There are natural dynamics and changes to this community, such as microbial oscillations that correlate with host circadian rhythms by day and night or changes in the diet or season (panel **a**). Secondary succession occurs when there is a disturbance, which can have many causes, with antibiotics being one of the clearest examples. This disruption can cause microbial community members to be lost or fall below the level of detection and large changes in microbial dynamics, such as the amplitude or periodicity. During this stage, keystone species, similarly to pioneer species, play a key role in preventing the overgrowth of opportunistic pathogens. Soon after, the intermediate community forms with the return of aerotolerant taxa and facultative anaerobes. Finally, the community resembles the initial community with the return of obligate anaerobes (panel **b**). The key (bottom) is composed of fungal, bacterial and viral clades shown with differing colours and distinct representative morphologies. The presence or absence of different clades represents the description in the main text. *E. coli*, *Escherichia coli*.

but rather continue to be chronically unstable in the absence of intervention (reviewed in REF.[151]). On the skin, atopic dermatitis is characterized by a bloom in *Staphylococcus aureus* and a decrease in bacterial diversity, induced by immune-mediated inflammation[152]. A decrease of abundance of the fungal genus *Malassezia* is observed during such *S. aureus* blooms[153], and vice versa, a fungal abundance increase leads to a decrease of abundance of *S. aureus*, which may be in part due to the ability of the fungi to produce proteases that digest *S. aureus* biofilms and reduce the bacterium's ability to evade the immune system[154]. Similar cross-kingdom interactions also exist in the mouth; for example, colonization of the fungus *Candida albicans* is dependent on bacterial biofilms, but at the same times bacterial genera such as *Pseudomonas* and *Staphylococcus* form competitive and synergistic relationships, respectively (reviewed in REF.[155]). These examples highlight how microbial community interactions and successions cross domains and also interact with the host but are still not fully understood due to their complicated nature of higher-order interactions (reviewed in REF.[156]).

Obstacles to microbial community recovery after a disturbance have led many researchers to explore the possibility of interventions for targeted restoration of the microbiota. Microbial community restoration involves directed reseeding or enrichment or depletion of certain species, with the intent to induce recovery of a microbial community close to that from before the disturbance. This can be attempted through probiotics, prebiotics, antibiotics or other drugs, transplantation of the complete microbial consortia from a healthy individual[157] or a combination of these. Although these therapies can be highly effective for restoring a healthy microbial community in certain well-characterized contexts[158,159], they are often limited by a lack of mechanistic knowledge of their interaction with the existing community[160], or by their ability to engraft only transiently[161]. To address the mechanisms, researchers have focused on two areas. The first area involves gaining a better understanding of how communities are assembled. For example, the study of human development helps identify how microbial communities assemble during development and the impact of that assembly later in life[13,49,52,162]. Second, new methods are being developed for determining mechanisms by exploring microbial community interactions both computationally[163] and experimentally, including high-throughput co-culturing[164,165] and genome editing of microbial communities[166]. To address transience, two main approaches have been applied. First, the transient and individualized impact of microbial community therapeutics is driven by the individual nature of each person's microbiota[167]. Therefore, precision medicine, where community alteration is targeted to each person's unique microbiota, holds great promise. For example, personalized nutrition based on microbial community compositions effectively modified postprandial blood glucose in a blinded randomized controlled intervention[168]. Second, going beyond the bacteriome to explore the virome and mycobiome, and their interkingdom interactions, holds great promise. For example, phage therapy has already been used in severe cases of drug-resistant bacterial infections[169], and is highly specific to the target bacterial strains[170]. While exciting, most such interventions are still in their preliminary phases of research and are cost-prohibitive at scale.

Late succession in late life

Ageing due to both biological programming and accumulation of damage throughout life impacts every aspect of cellular function, and the microbiota is no exception[171]. With advanced age, the gut microbiota alpha diversity decreases and the beta diversity (variation between individuals) increases[19,28,69,172,173]. Much is still unknown about the microbiota in old age, and the literature has been somewhat contradictory (for example, Claesson et al.[174] reported increased abundance of *Bacteroides* spp. in adults aged 65 years and older, contradicting other studies), and most research has focused on gut bacteria. Generally, the community succession observed in the gut is a decrease in the abundance of bacterial genera dominant and prevalent in younger adults (aged 25–45 years), such as *Bifidobacteria*, *Bacteroides* and *Lactobacillus*, often with a decrease in the ability to fend off blooms of opportunistic bacteria such as Enterobacteriaceae and *Clostridium* spp.[65,174,175]. Skin bacteria of the genera *Cutibacterium* (formerly *Propionibacterium*) and *Staphylococcus* decrease in abundance in those aged 65 years and older, with a greater abundance of *Corynebacterium* being observed[176]. In the oral body site, *Rothia* and *Streptococcus* spp. dominate the core oral bacterial community, with consistent decreases in the abundance of *Porphyromonas*, *Treponema* and *Faecalibacterium* spp.[177,178]. The gut mycobiome in old age is characterized by an increased dominance of *Penicillium*, *Candida*, *Aspergillus* and *Saccharomyces* spp.[67,69,179]. In the skin and oral body sites, very few studies exist, but old age is characterized by a decreased abundance of *Malassezia* spp. in the skin and *Candida* spp. in the oral cavity[180]. In gut phages, dominance of *Siphoviridae* in adulthood gives way to dominance of *Microviridae*, *Podoviridae* and crAssphages in old age[19]. In contrast to gut bacterial, fungal and phage populations, eukaryotic viral diversity stays constant after childhood throughout the rest of life[19] (FIG. 5a).

Due to the high variability between individuals, the focus of research into microbial succession in old age has primarily been in the comparison of healthy and unhealthy ageing. It remains unclear whether the microbiota has a mechanistic role in healthy ageing or is just a strong indicator of other variables, such as diet, exercise and medications (reviewed in[181]). However, in those who live longer and healthily, commonalities can be observed in sustained retention of those taxa highly prevalent in healthy adults such as *Bacteroides* spp.[182]. However, centenarians exhibit a more unique microbiota with increased alpha diversity and greater inter-individual differences in community composition, complicating the comparison between 'healthy' and 'unhealthy' ageing[28,172,173] (FIG. 5b). Secondary bile acids are enriched in centenarians and may also have a role in healthy ageing[183]. Although promising, this area of research is still underpowered and emerging.

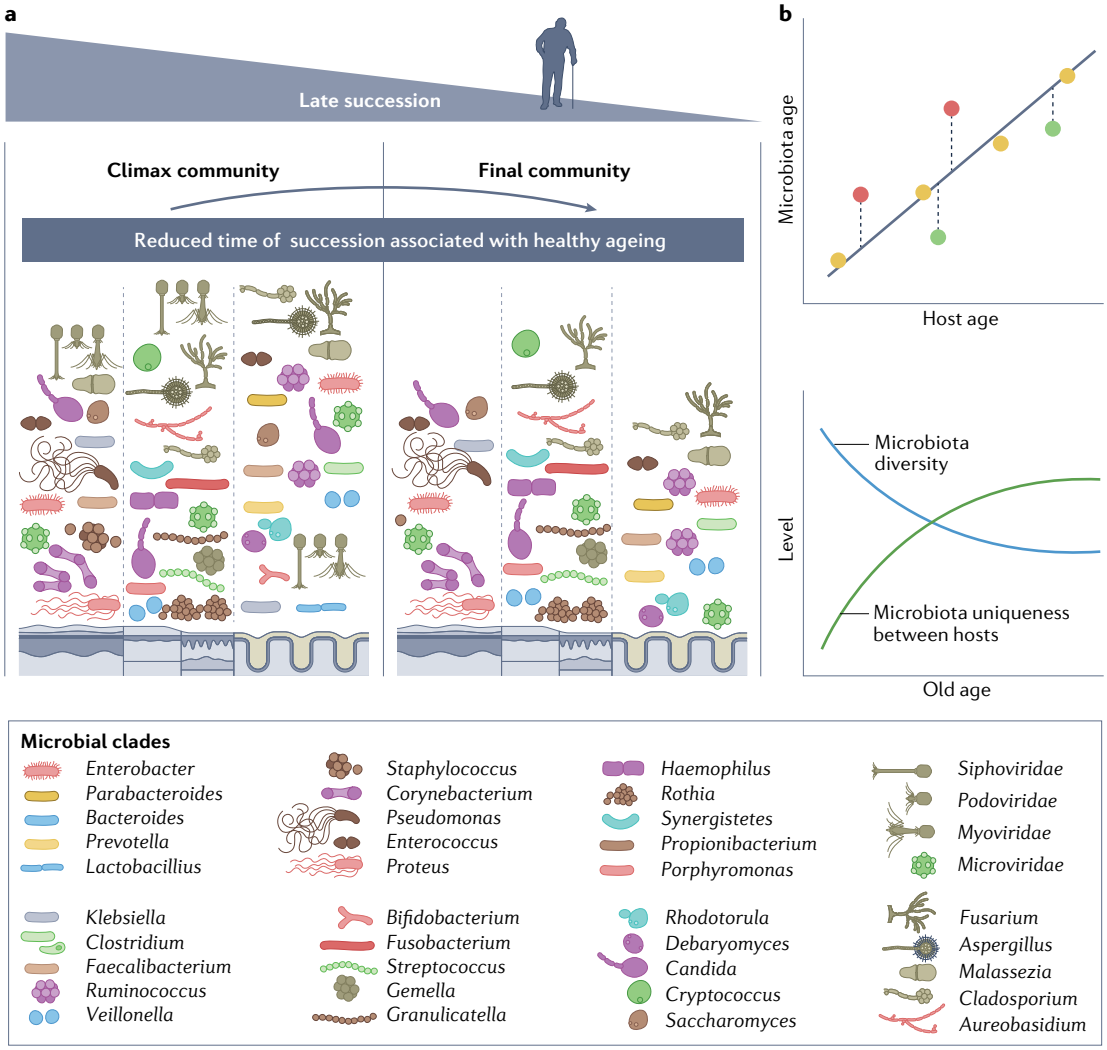

Fig. 5 | **Late succession approaching the end of life.** The adult stable microbial community transitions to a final community in old age (panel **a**). The exact timescale of 'old age' depends on several other host-related factors, such as disease, but most literature to date defines 'older adults' as those aged 65 years and older. Healthy ageing is generally associated with a delayed transition to the final community (panel **b**, top). The final community characteristics are lower alpha diversity and increased uniqueness compared across different people of the same age (panel **b**, bottom). The key (bottom) is composed of fungal, bacterial and viral clades shown with differing colours and distinct representative morphologies. The presence or absence of different clades represents the description in the main text.

The microbiota after death

Microbial succession does not end with the death of an individual, and host death can be viewed primarily as an ecological disturbance of the microbiota. Immediately following cessation of the heart, tissues begin to break down due to the lack of oxygen[184,185]. Cellular functions continue until all the remaining oxygen is depleted and carbon dioxide is no longer able to be transported from the tissue[184,185]. The intracellular build-up of carbon dioxide creates a hypoxic, acidic environment, leading to cell rupture[185,186]. Cellular components, such as enzymes (for example, lipases), leak into the surroundings, where they further facilitate tissue breakdown in a process called 'autolysis'[186]. Autolysis triggers a cascade of microbial processes responsible for tissue breakdown (that is, putrefaction) by eliminating the immune system, loosening cellular junctions and providing nutrients to the microbiota[185–187]. During the first few days to weeks of decomposition, putrefaction is performed mostly by bacteria, but fungi have an increased role as decomposition progresses[188–191] (FIG. 6a). However, little is known about the virome succession and functional role during this process.

The human microbiota is relatively stable during the first 24–48 h after death, with distinct body site microbial ecologies[191], alpha diversity patterns by age[191] and identifiable personalized skin microbiota signatures[192]. Afterwards, the cascade of environmental changes facilitates a microbial succession that alters the human body and microbiota in a way that no longer resembles a living individual (unless the body is cooled or frozen). The dearth of environmental constraints previously encountered in host life enables rapid changes in the relative abundance of microorganisms[189,191,193] as well as movement across body sites[187,194,195]. Migrating bacterial groups become pioneer species that translocate from

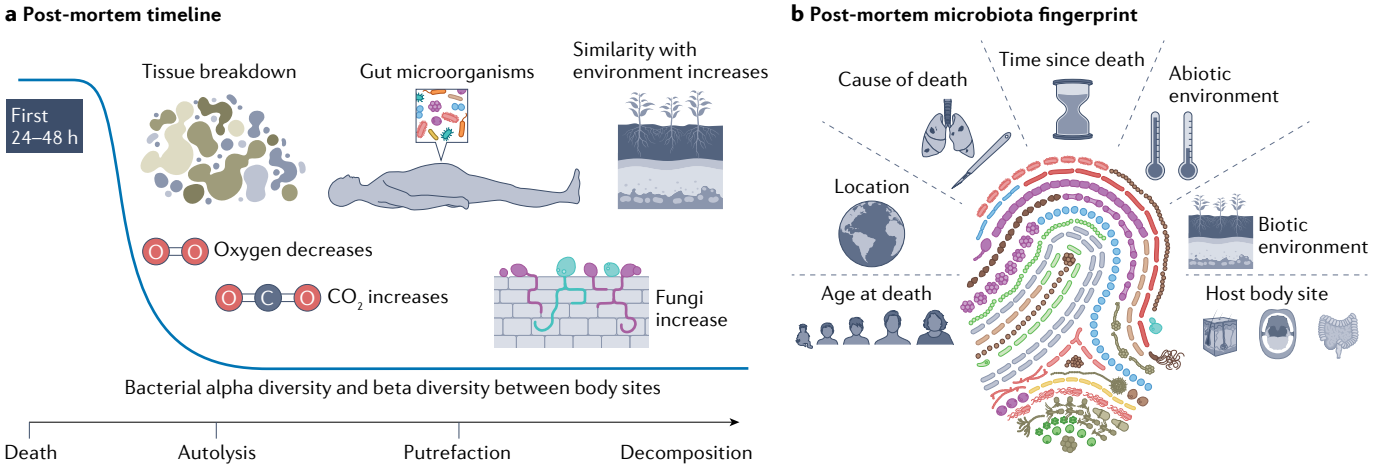

Fig. 6 | **The microbiota after death.** After death the microbiota is relatively stable in the first 24–48 h. The tissue then begins to break down during autolysis, leading to bloom in the gastrointestinal microbiota and a decrease in alpha diversity and a decrease in beta diversity between body sites. During putrefaction, the role of fungi increases, and the microbiota of the body becomes more similar to the microbiota of the surrounding environment (part **a**). The post-mortem microbiota is unique to each body and is distinct between bodies on the basis of the time since death, cause of death, environment, location and age at death, and, at the beginning, between body sites (part **b**).

the intestinal tract to extraintestinal sites, participating in either primary succession or secondary succession depending on the body site[195,196]. As the time after death increases, alpha diversity of communities generally decreases (as is expected with nutrient pulses) and community composition (that is, beta diversity) becomes more similar across body sites[189,197,198]. The gut and the skin are the two best-studied human post-mortem microbial ecologies. Interestingly, the post-mortem community succession in the gut follows trends also detected in old age, with decreases in the relative abundance of *Bacteroides* and *Lactobacillus* spp. and an increase in the relative abundance of *Clostridium* spp. and taxa in the family Enterococcaceae[190,193,197,199]. The post-mortem composition and succession of skin microbial communities depends on the external environment. For example, if exposed to soil, most post-mortem microorganisms, as well as nematodes, assemble from soil communities[189].

The microbiota of death has attracted increased attention due to its implications for forensic investigations. The consistent temporal patterns of succession associated with multiple individuals and body sites are evidence that the post-mortem microbiota may serve as a bioindicator of the post-mortem interval[189,193,197,198,200]. Post-mortem interval estimations are more accurate during the earlier stages of decomposition (that is, the first 2–3 weeks after death), when microbial succession includes rapid turnover of community members[197,201], but are still useful in later stages of decomposition (for example, in bone), when few lines of evidence exist for estimating the post-mortem interval[202,203]. Connections with the cause of death and microbial presence have also been demonstrated[191]. For example, increased detection of *Rothia* spp. was found in the oral microbiota of individuals who died of heart disease[191]. Moreover, skin microbiota shedding may contribute to trace evidence by connecting individuals with items they have interacted with such as mobile phones[192,204]; however, the time this unique signature can be accurately matched to an individual depends on the object's material and use[192] (FIG. 6b).

Conclusions and outlook

In this Review, we have described the current understanding of human resident microbial community composition across ages and different body sites. The many connections between human health and our microbial community composition are bringing an increasing interest in interventions. Interventions that focus on the whole microbial community, rather than the enrichment or elimination of a single species, require an understanding of how these communities are formed and maintained. Through studying microbial communities across the human lifespan, we may better understand these complex interactions and how to effectively push the community to a desired composition for the host. Moreover, as discussed here, these insights are being applied in several other areas, such as in forensics.

Although this Review has focused on the microbiota and its associations with healthy ageing, many conditions have been associated with accelerated ageing, and are just beginning to be studied in a microbiota context, a key example being schizophrenia[205]. Social determinants of health have a major impact on health, ageing and longevity, in the context of both healthy ageing and pathological ageing. These factors include education, poverty, occupation, discrimination and social connections[206]. Since many of these factors have also been linked to the microbiota, understanding the role of these social determinants and how to modify their effects to promote healthy ageing will be an important topic for future research linking the microbiota and ageing.

Despite the enormous effort and resources being put into characterizing the microbiota, we have just

Box 1 | **Sampling and quantifying microbial communities**

Study design and sample collection

The human microbiota is dynamic[209]. With this in mind, it is important to design a sampling strategy that can capture the temporal and spatial variability of the microbiota, particularly when these fluctuations are relevant to the scientific questions asked. Cross-sectional studies collect a single sample from each individual, while repeated-measures studies collect samples at multiple time points or body sites. With time, the frequency of sampling should be tuned to the phenomenon researchers are attempting to observe. For example, murine circadian rhythm studies typically collect faecal samples every 2–4 h (REF.[210]), while in inflammatory bowel disease, sampling patients between three times and five times over a period of weeks can improve disease classification[211]. In other applications, such as studying the effect of particular treatments on an individual's microbiota, it may be relevant to perform an '*n*-of-one' study, in which the same participant is repeatedly probed for resultant changes in his or her microbiota; samples collected before treatment are regarded as individual-level controls[212].

It is also important to consider that the microbiota of a population is highly dependent on geography and ethnicity. For example, one of the microorganisms most highly associated with age in a large Chinese cohort was not detected at all in a large American cohort[153]. Another specific example pertains to the 'built environment' of urbanized societies; urbanized populations generally have less exposure to environmental microorganisms and higher use of household antimicrobials, resulting in significant shifts compared with the human microbiota from rural societies[213]. These considerations are particularly relevant for the microbiota field, as most public microbiota data come from urbanized North American and European populations[183]. Therefore, conclusions from existing data sets may not generalize well to the global population.

Data generation

The main categories of sequencing data that are generated from human microbiota and microbiome studies are amplicon sequencing data and shotgun sequencing data. In amplicon sequencing, the PCR products (amplicons) of established hypervariable regions are deeply sequenced, enabling identification and measurement of community members by matching to their individual 'barcodes'. There are two choices to be made here: the gene to amplify and which portion of that gene to amplify. Commonly amplified regions of microbial genomes include the 16S ribosomal RNA gene for bacteria, the 18S ribosomal RNA gene for eukaryotic microorganisms and internal transcribed spacer for fungi. The choice of the hypervariable region within each specific gene to amplify depends on the particular microorganism to be captured, but broadly, commonly used ones include the V4 region from the Earth Microbiome Project[214]. In shotgun sequencing, all microbial DNA is sequenced instead of only PCR products, enabling a more specific taxonomic classification of microorganisms. Because it does not rely on any marker genes, shotgun sequencing is less biased than amplicon sequencing is towards certain sets of microorganisms. However, shotgun sequencing is considerably more expensive and requires substantially more computational power, making amplicon sequencing attractive in cases in which the increased resolution of shotgun sequencing is not required. An additional concern and outstanding problem in the field is privacy and ensuring that public metagenomic data cannot be used to identify study participants[215].

Pairing sequencing data with other analyses

Performing amplicon or metagenomic sequencing in conjunction with other techniques, including other omics techniques, can enrich one's understanding of both microbiota and host. Techniques such as quantitative PCR and fluorescence-activated cell sorting provide more context for relative abundances by anchoring them to a reliable absolute abundance measure[185,186]. Enzyme-linked immunosorbent assay (ELISA) and single-cell sequencing can pair well with metagenomic sequencing by providing host cell type or host immune information[187]. Culturomics enables the researcher to experimentally verify genomic predictions of function or activity, as well as to turn the microorganisms into probiotics[188]. Microbially produced metabolites or proteins, the downstream effectors of the microbiota, can be probed through metabolomics and proteomics, respectively[189]. Finally, host genomics and transcriptomics are increasingly paired with amplicon and/or metagenomic data to provide insight into connections between host gene expression and the microbiota.

Metadata

Finally, it is paramount to collect data from the participants surveyed. Some important categories of metadata for general microbiota studies include demographics, clinical information (that is, other conditions and antibiotic use) and dietary information; however, the exact metadata used will differ by study. Practices for producing standardized metadata should be adopted so that results are reusable and reproducible[216].

scratched the surface. Moreover, many current challenges and limitations exist, such as skewed geographical sampling, privacy concerns and outstanding issues with data standardization (BOX 1). There are also large disparities in our understanding of microbial kingdoms, mainly due to technical difficulties in characterizing taxa other than bacteria[207]. The gaps in understanding virome and mycobiome community structure and cross-kingdom interactions are an area of exciting research driven by technical advances that increase the accuracy and decrease the cost of DNA sequencing. However, contradictions in the field are abundant, especially in those observations driven purely by sequencing data, and more robust analyses are key to consolidating knowledge in the field (for example, log ratios)[208] (BOX 1). Studying species beyond relative taxonomic compositions through high-throughput cultivation, metagenomics, transcriptomics and metabolomics is a rapidly expanding area of research that is key to filling in gaps in our understanding[163].

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