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The application of ecological theory towards an understanding of the human microbiome

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Abstract

The human microbial ecosystem plays a diversity of roles in human health and disease. Each individual can be viewed as an island-like “patch” of habitat occupied by microbial assemblages formed by the fundamental processes of community ecology, i.e., dispersal, local diversification, environmental selection, and ecological drift. In this review, we consider how community assembly theory, and as an example, metacommunity theory, could be used to help explain the dynamics of the human microbiome, and in particular, compositional variability within and between hosts. We explore three core scenarios of human microbiome assembly: development in infants, representing assembly in previously unoccupied habitat; recovery from antibiotics, representing assembly after disturbance; and invasion by pathogens, representing assembly in the context of invasive species. Judicious application of ecological theory may lead to improved strategies for maintaining and restoring the microbiota, and the crucial health-associated ecosystem services that it provides.

Each human is an assemblage composed not only of somatic cells but also of many symbiotic species. The abundant and diverse microbial members of the assemblage play critical roles in the maintenance of human health by liberating nutrients and/or energy from otherwise inaccessible dietary substrates, promoting differentiation of host tissues, stimulating the immune system, and protecting the host from invasion by pathogens. A number of clinical disorders are associated with alterations in host-associated microbial communities (the ‘microbiota’), including obesity, malnutrition, and a variety of inflammatory diseases of the skin, mouth, and intestinal tract. Thus, the human body can be viewed as an ecosystem, and human health as a product of ecosystem services delivered, in part, by the microbiota.

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There is growing interest in the use of theoretical methods to study microbial community ecology, and in particular, host-associated microbiota (1, 2). Recent discoveries of unexpected variation in the composition of the microbiome of healthy individuals (3–5) highlight the importance of identifying the processes that could possibly give rise to such variation. Ecological theory seeks to explain and predict observable phenomena, such as temporal and spatial patterns of diversity. The concept put forth in the late nineteenth and early twentieth centuries that ‘everything is everywhere, but the environment selects’ had a powerful impact on thinking about microbial community assembly (8), but a more recent appreciation of other ecological processes (such as diversification and dispersal limitation) suggests that this conceptualization was overly simplistic. Here, we explore how community assembly theory could be used to understand the human-associated microbiota and its role in health and disease. We focus on three scenarios relevant to the assembly of the human microbiome: assembly in previously unoccupied habitats (e.g., postnatal development), reassembly following disturbance (e.g., following antibiotic treatment), and assembly in the context of invasion (e.g., by a pathogen).

Ecological processes within humans

The essential building blocks of community assembly theory encompass the processes that create and shape diversity in local assemblages: dispersal, *in situ* diversification, environmental selection, and ecological drift (6). In addition, coevolution provides another lens through which to view the human-microbial ecosystem (7), although in this review we focus on shorter-term dynamics at the level of individual hosts.

Dispersal, or the movement of organisms across space, is a fundamental process by which diversity accumulates in local microbial communities. Dispersal tends to emphasize a view of the human body as an “island”, a patch of habitat that is continually sampling the pool of available colonists. The list of available colonists may be influenced by microbial traits—those affecting dispersal efficiency, transmission routes, and “ex-host” survivability—and by patterns of host contact and carriage, among other factors. Controlling infectious disease transmission depends on accurate models of host-to-host microbial dispersal (9), and these could guide investigations into the dissemination of the human microbiome. Selection favors efficient dispersal in pathogens, but perhaps less so among beneficial bacteria, because the host is harmed by the first and not by the second; for beneficial microbes, transmission routes such as direct or close contact may be more important. Notably, the density and spatial arrangement of host habitat patches has been highly dynamic throughout human history.

A second process operating in microbial communities is local diversification. Unlike in most plant and animal communities, this process can take place over short ecological time-scales for microbes. Large microbial population sizes, high growth rates, and strong selective regimes, all of which can be found in the human body, facilitate rapid microbial adaptation via mutation or recombination. Recombination via horizontal gene transfer may be especially common among members of the human microbiota, especially those sharing the same ecological niche (e.g., body site) (10). Microbial diversification may also be driven by

interactions with phage in the human body. Dispersal and diversification may interact (11); for example, immigration may suppress adaptive radiations (12).

Relative abundances in local communities are shaped over time by a third process, environmental selection. When considering environmental selection, or niche-based interactions, the human body can be viewed in two ways. First, it can be viewed as a "habitat filter", a collection of resources and conditions allowing the growth of some microbes, but not others, emphasizing the selection of microbial traits that permit survival and growth in the host. In this view, the host shapes the microbiota, but not the other way around. Body temperature is an example of such filtering, since microbes alter body temperature (causing fever) only when they transgress host anatomic boundaries. Second, the human body and its symbionts may be viewed as a community of interacting cells. This view differs from the habitat filter view in that it assumes strong feedbacks between hosts and microbes, and among microbes. This view assumes that the host shapes the microbiota, and vice versa. Interactions between the host immune system and the microbiota might be best represented by this view (see accompanying review by Hooper *et al.*). Importantly, the overall patterns that arise from dispersal and environmental selection (niche-based interactions) can vary as a function of the spatial scale over which these processes occur (13).

In addition to selection-driven changes, species abundances may fluctuate due to a fourth process, known as ecological drift, or demographic stochasticity. As a result of this process, low-abundance species (e.g., recent immigrants, antibiotic sensitive strains, or strains occupying niches with low carrying capacity) are more likely to proceed towards local extinction and become lost from the system, unless they have (or can gain) a competitive advantage, access to a different niche, or become replenished by dispersal from outside the community. Thus, dispersal can effectively "rescue" species from the brink of local extinction, or thereafter.

Finally, the human habitat can be understood as a host-symbiont "holobiont", and as such, an ecological system under selection to minimize conflict between individual members. This view emphasizes the dominant role of co-evolution in the assembly and dynamics of the human ecosystem and reminds us that long- and short-term selective pressures on the human microbiota are not necessarily aligned. Any mutualistic trait that imposes a cost on the microbes that express it – such as producing dedicated molecules to interfere with pathogens or modulate host immune activity – represents a trade-off between the immediate selection against that cost and the long-term selection in favor of mutualism (7).

In summary, different views of humans as microbial habitats make different assumptions about the processes most important to the assembly and dynamics of human microbiome. Community assembly can be conceptualized as being niche-based, dispersal-limited, historically contingent, or random, depending on the relative contributions of habitat conditions, colonist availability, arrival order (and timing), or chance-driven events, respectively, in shaping observed patterns (Fig. 1). Metacommunity theory integrates the four processes described above and provides a useful framework for considering community assembly in the human body (6).

Metacommunity theory and the human microbiome

Various theoretical frameworks are used to study community assembly, and one key framework is neutral theory (16) in which it is assumed that dispersal, diversification, and ecological drift are purely chance-driven processes. It is a neutral model because it invokes neither environmental selection nor inherent differences in species' ability to disperse or diversify. Although neutral theory on it's own is quite valuable in testing this null hypothesis, a broader framework for the assembly of the human microbiome might accommodate alternative theories, and combine the strengths of transmission dynamic models (e.g., inclusion of host contact and carriage dynamics) with those of community ecology (e.g., focus on communities, rather than individual pathogens). One such approach is metacommunity theory (17), which could be especially useful for modeling host-associated communities.

Metacommunity theory views the world as a collection of patches, or spatially distinct areas of suitable habitat surrounded by a matrix of unsuitable habitat. These patches each contain a community of organisms, and these spatially distinct communities are connected together to form a metacommunity by the dispersal of organisms from patch to patch. Human populations can be viewed likewise, with host-to-host dispersal linking microbial communities. Metacommunity theory is especially helpful for understanding the relative importance of dispersal and environmental selection in shaping host-associated communities (1), an issue that has received relatively little attention in studies of the human microbiome.

The predictions of metacommunity theory depend on the frequency and extent of dispersal, differences in the traits of individual organisms, and the degree to which patches vary in their environmental conditions (17, 18). Dispersal can be infrequent and localized, or widespread and frequent, as discussed above. In some metacommunity models, patches are assumed to be essentially identical, and that movement among patches determines variation in community membership (e.g., "patch dynamics" model). Such models might be especially appropriate for populations of closely related hosts. Other models assume that patches vary strongly in their available niches, and that variation in community membership results at least in part from environmental selection (e.g., underpinned by host genetics or diet) (e.g., "species-sorting" model).

Metacommunity theory enables one to predict the conditions under which community dynamics within a patch are driven by immigration from outside versus local adaptation. Low dispersal rates favor adaptation within a patch and high dispersal favors immigration. This concept could be useful, for example, in understanding responses to antibiotic use. If acquisition of antibiotic resistance were primarily a result of immigration, then interventions focused on quarantine and hygiene would be more effective than those focused on altering antibiotic duration or dose (see "An ecological approach to managing invasions" below).

While metacommunity theory has been used to elucidate the drivers of non-host associated microbial community membership and dynamics (19–21), it has rarely been used to study host-associated communities (22, 23), e.g., to explore the stringency of host selection and its dependence on the microbial group or the age of the host. Ultimately this information will

result in a better understanding of how microbes are “filtered” by the host and, conversely, how microbes evade this filtering. This information is crucial if clinicians are to directly manipulate host-associated communities, through, for example, the design of probiotics capable of evading host filtering and establishing within a host.

The effective application of metacommunity theory (and assembly theory, in general) to the human microbiome requires a preliminary understanding of how the microbiome varies across hosts and over time. In the subsequent discussion, we review our current understanding of this variation, focusing on the dynamics of communities in newly created habitats (e.g., neonatal colonization), following disturbance (e.g., after antibiotic treatment) and following invasion (e.g., by a pathogen). We chose these scenarios because they represent and reveal the fundamental types of assembly relevant to human health.

Postnatal acquisition and development of the human microbiome

Babies are born essentially sterile, and acquire their microbiome from their surroundings. The postnatal assembly of the human microbiota plays an important role in infant health, providing resistance to pathogen invasion, immune stimulation, and other important developmental cues early in life (24). Acute and chronic disorders, such as necrotizing enterocolitis, antibiotic-associated diarrhea, malnutrition, inflammatory bowel disease, and asthma have been linked to inadequate, inappropriate, or disrupted postnatal microbiome acquisition and development (25). Mechanisms controlling the appearance of bacteria in healthy infants have been studied for well over a century (26), and many have likened microbiome development to ecological succession (24, 27). Succession, as a mode of community assembly, has largely emphasized niche-based processes, being described often as orderly and predictable, but the importance of stochastic and/or historical events has also long been recognized.

In the absence of microbial invasion of the amniotic cavity, which is thought to be a rare, pathologic condition, rupture of membranes signals the moment when microbes, most likely of maternal vaginal origin, first gain access to the neonate. Vaginally delivered infants clearly receive a strong input of vaginal, and possibly other urogenital or fecal microbiota as they pass through and exit the birth canal (28, 29). Vaginal microbiome composition in non-pregnant, reproductive age women is highly dynamic, and is characterized by at least five compositional classes delineated by different, dominant *Lactobacillus* species, or a lack of *Lactobacillus* dominance. There is frequent class switching over time, including to and from compositions indicative of bacterial vaginosis, even in the absence of symptoms (4, 30, 31). Whether these dynamics occur similarly in pregnant and postpartum women has important implications for the initial colonization of vaginally delivered infants; if they do, infant-to-infant variation in the composition of initial colonists may be imposed in some cases by maternal vaginal microbiome class at the time of delivery. Likewise, maternal gut microbiome types (5, 32) may also determine the pool of colonists available to vaginally-delivered infants at birth. Thus, variation among neonate microbiomes may reflect variation in maternal microbiomes, but this has not been widely tested for maternal habitats other than the vagina. At the time of delivery, microbiomes do not differ consistently among infant

body sites (28), implying that sampling is driving initial community assembly, with minimal filtering by the infant host.

Delivery mode also determines microbial exposure at the time of birth. For example, infants delivered by cesarean section do not receive contributions from the vaginal microbiota, and instead, are exposed initially to what appears to be ambient skin microbiota (28). Incidental exposures to maternal (or other) gut or vaginal microbiota may occur later in cesarean section infants, at low density or low frequency, but may be inadequate for outcompeting already established strains. For example, cesarean section infants display reduced abundances and/or incidences of colonization by the genera *Bacteroides* and *Bifidobacterium* early in development relative to infants born by vaginal delivery (33, 34). The effects of delivery mode can persist for months, and may have consequences for infant health; cesarean section infants have a higher risk for some immune-mediated diseases (35, 36). The ambient environment may also play a role in colonization at delivery; infants delivered at home versus the hospital were colonized differently at 1 month of age (34). Thus, dispersal limitation imposed by certain medical interventions may contribute to inter-individual variation early in life.

Over the first few months – roughly up until the first solid foods are introduced – a well constrained range of stereotypical bacteria appear in the feces (distal gut), diversity generally increases, and aerobes are thought to be supplanted by facultative and then strict anaerobes (24). Exclusive breast-feeding selects for increased abundance of particular *Bifidobacterium* species whose genome sequences reflect specialized use of human milk oligosaccharides and similar host-derived substrates (37), or for other bacteria such as *Bacteroides* that could compete for the same ecological niche (38). Strikingly, during this early phase, microbiota composition is highly dynamic within and between infants (3, 24, 39–41), with temporal variation characterized by periods of relative stability (for varying lengths of time) punctuated by abrupt shifts in composition and structure. In some cases, these shifts can be linked with life events that likely impose environmental selection such as fever, formula feeding, or antibiotic therapy (3, 40, 42). Extraordinarily parallel transitions observed in a pair of dizygotic twins suggest that exposures (shared exposures in their case) can also play an important role during this phase, driving within and between infant variation (3). This finding emphasizes the need to better understand how infants sample their environment over time, e.g., whether outside-of-host environmental reservoirs or direct host exchange paradigms prevail, and with regard to the frequency and extent of dispersal (as discussed above). Abrupt shifts might reflect opportunistic invasions by better-adapted species or changes in filtering by the host. An infant's unique developmental path through this early unstable phase may have longer-term health implications. For example, recent work has shown that colonization during the neonatal period has a particularly important effect on mucosal immune development (43).

The introduction of solid foods and weaning are associated with the onset of a transition towards an adult-like gut microbiome. Differences due to early exposures such as delivery mode fade as microbiota compositions become more canalized. Life events like illness, diet modification, and antibiotic therapy can still impose disturbances, although specific compositions appear to recover. Taxa characteristic of the adult eventually establish, but the

process of microbial community assembly appears to extend past the first year of life and into childhood (3, 40). If there is an imprint of microbial flow from parents to children, it is either difficult to detect at early ages and/or else emerges gradually later in life. In one study, fecal patterns of bacterial taxonomic diversity in one year olds were not found to be significantly more similar to those of their parents than to those of unrelated adults (3); but in another study, patterns of microbial diversity in adult twins were slightly more similar to those of their mother (44). These findings suggest that we acquire microbes from competing sources other than, or in addition to, our family members. Further, there may be strong selection for an individualized microbiota. Describing the adult state as "stable" may not suffice when stability is defined as the permanent coexistence of locally occurring species, because even adult gut composition appears to change slightly over time (46). In summary, microbiome assembly in newly created habitats likely involves a gradual shift from conditions under the strong influence of dispersal limitation, and stochastic, and/or historical factors, towards conditions increasingly influenced by environmental selection (e.g., by diet), with weaning as a strong catalyst, and with development towards adult-like composition continuing into childhood.

Community assembly following disturbance: antibiotics as a paradigm

The assembly of human-associated microbial communities does not, in general, proceed smoothly to a stable climax state which then resists further changes in composition. Disturbances often remove or kill some fraction of the community, providing an opportunity for remaining community members or new colonists to increase in abundance. For example, personal oral hygiene removes bacterial biofilm from teeth, and an antibiotic affects not only the targeted pathogen but also members of the normal microbiota (Fig. 2A). The former case represents a deliberate attempt to interrupt the development of microbial communities that might be associated with periodontitis, the latter case, an inadvertent consequence of modern medicine. In addition to directly inducing a shift in the community state, disturbance may also involve a change in the community's habitat parameters, e.g., host diet (Fig. 2B). In many cases, a crucial unknown is resilience – that is, the degree to which the post-disturbance community returns to its former state (47). While most work on community resilience has considered resilience in terms of community taxonomic composition, assessment of community function and ecosystem services may be even more important.

The effect of antibiotics on the gut microbiota serves as a paradigm for disturbances in human-associated communities. Antibiotics are now one of the most common and important forms of disturbance of the human microbiota; on any given day, approximately 1–3% of people in the developed world are exposed to pharmacologic doses of antibiotics (48). Over the past several decades there has been increasing concern about the spread of antibiotic resistance among pathogens, as well as growing concern that antibiotic use may disrupt the host-microbe interactions that contribute to human health.

Antibiotic therapy is meant to achieve a sufficient concentration of the drug for a sufficient duration in a particular body site so that the targeted pathogen is eliminated. Even if this aim were always attained, the antibiotic will be found at a range of concentrations at many locations in the body, depending on the mode of administration and its pharmacodynamic

properties. Where members of the indigenous microbiota are exposed to antibiotics that affect their growth without killing them, there is selection for resistance. Human gut and oral communities are recognized as reservoirs for the evolution and horizontal transfer of antibiotic resistance determinants, including to pathogens (10, 49, 50). However, antibiotic resistance among the microbiota is one of several mechanisms that may act to enhance the resilience of the indigenous communities, hence preserving their beneficial ecosystem services. Others may include population-level resistance via stress-response signaling (51), and the existence of dormant persister cells (52) or refugium-like locations (e.g., mucus layer).

Only a handful of studies have employed cultivation-independent surveys to examine the consequences of therapeutic doses of antibiotics on the human gut microbiota (53–57). While these studies have examined different antibiotics and employed a range of sampling strategies, durations and analytical approaches, they all have found that antibiotic treatment alters the composition of the gut microbiota, and that the abundance of most taxa begins to return to prior levels within several weeks. However, the studies are also consistent in showing that various taxa recovered to different extents, and that some do not recover over the duration of the study. The antibiotic effect is greater than the routine temporal variability of community composition (53, 54, 56). Some studies have revealed that the composition of strains within a taxon is sometimes altered, even if the overall relative abundance of taxon members returns to pre-antibiotic levels. In both of the studies that involved measurements of the prevalence of antibiotic resistant strains, elevated levels of resistance persisted to the end of the study (55, 56).

Overall, research suggests that the human gut microbiota of generally healthy adults is largely, but not entirely, resilient to short courses of antibiotic therapy, while clinical evidence indicates that extended or repeated courses are more likely to result in serious complications such as the invasion and bloom of *Clostridium difficile* (58). Perhaps over short courses of antibiotics, a sufficient, although possibly quite small number of residual cells from most of the large, pre-existing populations survives to recolonize the gut. An increasing number of these residual cells may be lost with longer or repeated courses of antibiotics. Thus, reassembly of the microbial community following extended antibiotic treatment may require colonization from outside the host, a process that would likely be more variable and require a longer period of time than reassembly via the filtering of existing populations in the host. In addition, the microbiome may be highly vulnerable to invasion by, or blooms of pathogens during recovery after disturbance, because resources are in high abundance and resident populations are low. The longer recovery time required following extended antibiotic treatment could lead to a higher probability of invasion by pathogenic strains. One can envision a more enlightened strategy for clinical use of antibiotics that includes pre-treatment estimates of a patient's microbial community resilience, e.g., based on the use of a standardized disturbance and monitoring of key community products, mapping of the community stability landscape, and assessment of the likelihood for community displacement and adoption of a disadvantageous, altered state. Assessments of elevated risk, or of loss of resilience might then prompt efforts at restoration (see associated review by Lemon K *et al.*, STM).

Little is known regarding the response of the microbiome to frequent antibiotic use. When disturbances take place of greater magnitude or frequency than that to which a community has had an opportunity to adapt, ecological surprises may occur (59). Such frequent disturbances may allow the persistence of microbial taxa that are inferior competitors within a given host, but that are maintained across hosts because they have traits that result in widespread and frequent dispersal, i.e., “fugitive” taxa. Such a scenario is analogous to the patch dynamics paradigm of metacommunity theory (17).

Assembly of the human microbiome in the context of invaders (pathogens)

It is naïve to consider only the interactions between host and pathogen when predicting the likelihood of microbial disease. The latter, for our purposes, is defined as infection of, and proliferation within a host by a species that, in so doing, elicits some sort of pathology. It may be useful to view the pathogen as an invasive species, and the consequences of invasion as a special case of community assembly. Like invasive species in more traditionally studied settings, whether a species can invade a particular community depends largely on niche opportunities: the filters imposed by the abiotic environment and the resistance of the community to colonization by an exotic species (60). A successful invasion involves the dispersal of an invader to a new community, initial colonization, and proliferation, steps influenced by the same processes as community assembly more generally.

The environment created by the host determines the number of potential niche opportunities. The nature of this environment is influenced by a number of conditions, including “abiotic” factors such as oxygen levels, pH, and temperature, as well as the abundance and types of available resources, such as the composition of the host’s diet (61) and carbon sources provided directly by the host, such as mucosal poly- and oligosaccharides (62). In addition, the host immune system acts as an important environmental filter to limit the spatial extent of the microbiota’s available niches. The main functions of the mucosal immune system are to create an inhospitable buffer zone between the microbiota and the host epithelium, and to minimize the incidence of systemic inflammation that would normally be induced in the face of so many bacterial products (63, 64) (see associated review by Hooper L *et al.* Science). The immune system performs these functions through three general mechanisms: i) physical barriers such as the inner mucus layer of the colon and stomach, which is generally impenetrable to bacterial cells (65); ii) antimicrobial peptides and mucosal antibodies in the mucus layer that further hinder bacterial colonization of the epithelium (63); and iii) innate and adaptive immune responses within the regional lymphatic tissues (64). Inflammation is an important disturbance that alters the host-associated environment. These three mechanisms, in most healthy hosts, select for bacterial species that do well at or near mucosal surfaces or strong barriers such as the skin. However, host filtering is not the only factor influencing the ability of pathogens to invade the host-microbiota community.

One of the most important roles of the microbiota in mediating host-pathogen interactions is protection of the host from pathogen invasion, or ‘colonization resistance’ (64, 66). Protection is achieved through induction of the innate and adaptive branches of the immune system, creating an environment that is unfavorable to pathogens (illustrated by the observation that axenic mice (67) and zebrafish (68) have diminished immune responses and

impaired barriers to infection), and through direct competition (or community filtering – e.g., by lowering vaginal pH). In the latter case, pathogens are kept at bay by competition with the microbiota for space and resources. This protective effect is demonstrated by the increased susceptibility to infection of hosts that have had their microbiota altered by antibiotics, a phenomenon well documented by Miller and Bohnhoff in the early 1960s with *Salmonella* invasion of mice pretreated with antibiotics (69). The ability of certain anaerobes to limit the invasion and growth of *Clostridium perfringens* in a diet-dependent manner is an example of competition for resources (70). *Bifidobacterium breve* produces an exopolysaccharide (EPS) that protects it from the immune response; this allows it to compete for space and colonize the mouse gut at high loads in both the lumen and at the epithelial surface without inducing inflammation (71). Even if invaders do gain a foothold, the indigenous microbiota can block lethality: in mice, some *B. longum* strains can protect against enterohemorrhagic *E. coli*-mediated death by inhibiting translocation of Shiga toxin from lumen to blood (72).

By viewing pathogens as invasive species we see that the contexts in which they are able to cause disease are the same as those required for any other species that invades and proliferates in a community. Niche opportunities can result from exploiting novel or overly abundant resources (from the host's food), out-competing a commensal species for the same resource, or perhaps most importantly, exploiting niches left open after a disturbance. The importance of exploiting disturbance is well illustrated by the increasing number of cases of disease caused by *Clostridium difficile* (73). *C. difficile* is a "weedy", both native and exotic species that can rapidly fill niches once they are vacant, but in most cases is eventually removed or kept at low abundance in the absence of a disturbance. *Salmonella enterica* serovar Typhimurium is an example of an exotic invasive that exploits disturbance, but in this case, it also causes the disturbance it exploits. *S.* Typhimurium expresses many virulence factors that create inflammation in the mammalian intestine. A mutant *S.* Typhimurium strain lacking these virulence factors is unable to invade the gut community and cause disease; however, if inflammation is provided by some other mechanism, otherwise avirulent strains are able to invade the host communities (74). Inflammation likely reduces the abundances of other bacteria that would compete with pro-inflammatory pathogens for space. As one possible mechanism, inflammation causes the intestine to produce tetrathionate which *S.* Typhimurium utilizes as an electron acceptor for respiring ethanolamine, a carbon source that cannot be exploited by other bacteria, thus avoiding competition for nutrients (75). By causing acute inflammation, the pathogen is able to alter the native microbiota and effectively colonize and proliferate.

In contrast to the above examples, a reduction in disturbance frequency can also promote invasion by pathogens, as evident in cases of cystic fibrosis. Patients with cystic fibrosis produce thickened mucus, which inhibits the ability of the cilia to remove foreign material from normally sterile lung airways. This lack of constant removal (i.e., impaired innate immune host filtering mechanism), among other factors, allows for the establishment of bacterial communities that would normally not be able to persist at that site (76).

In summary, predicting the success and outcome of infection by pathogens can be aided by framing the issue as an ecological problem of community assembly. Invasion ecology

highlights the importance of niche opportunities as determinants of success of invasion, and the manipulation of which might help in pathogen control and disease prevention. Experimental models using gnotobiotic organisms such as mice and zebrafish will be helpful in understanding the role of community diversity, as well as the role of particular community members in conferring colonization resistance through indirect inhibition and resource competition. In addition, the frequency and magnitude of disturbance plays a crucial role in facilitating both the colonization by exotic invasives as well as the expansion of native species. Finding ways, through prebiotics, probiotics, or pharmabiotics, to alter pathogen or other bacterial species abundances (or to inhibit their detrimental effects on the host) in a specific manner without causing additional disturbance to the community will be very important for preventing and treating disease caused by invasive species.

Translating ecological understanding into clinical practice

An improved understanding, informed by ecological theory, of how microbiomes assemble could alter clinical practice by changing the perspective clinicians bring to the treatment of infectious disease. The traditional perspective has been to think of the human body as a battleground, on which physicians attack pathogens with increasing force, occasionally having to resort to a scorched earth approach to rid a body of disease. Although this perspective has been very successful for several diseases, it has come at a great cost. Even for those diseases for which it has worked, the collateral damage can be severe. As we have discussed, antibiotics often kill beyond the target organisms (54) and can increase the chance of invasion by unwanted organisms (such as *C. difficile* (73)).

The body-as-battleground approach ignores the community context of infectious disease, and does not take into account our increasing knowledge regarding the assembly of the human microbiome. We suggest that it is time for clinicians to abandon the war metaphor (77). Given the ecological parallels between assembly of the human microbiome and assembly of other ecological communities, we suggest that human medicine has more in common with park management, than it does with battlefield strategy. To effectively manage a plant or animal community requires a multipronged approach of habitat restoration, promotion of native species, and targeted removal of invasives. We describe below some examples of how such a human-as-habitat approach might alter clinical practice.

An ecological approach to managing invasions

An understanding of the dominant mechanisms of community assembly could directly alter how clinicians treat infectious disease. Consider, for example, the rise of drug-resistant pathogens during the course of drug treatment. We can consider this a “special case” of community assembly, much as we did invasion by a pathogen (see above). We can ask: what is the relative importance of dispersal, diversification, environmental selection and ecological drift in the successful invasion by this drug-resistant strain? If the source of these strains is primarily through random sampling of the external environment, then the most effective preventative strategy may be quarantine and enhanced hygiene. In contrast, if such strains arise primarily through diversification of resident taxa, then multi-drug treatment may be more effective (to make successful evolution more difficult). If the drug-resistant

strains are already present at the outset of treatment and increase in abundance via environmental selection, then drug cycling may be the most effective treatment to reduce the overall competitive advantage of the resistant strains. If drug-resistant strains establish primarily through ecological drift, then disturbance may be crucial to their establishment (freeing up ecological “space” for their invasion). In this case, reducing disturbance of the resident microbiota may be most effective. In this way, a detailed understanding of the relative importance of different community assembly processes can be used to tailor the treatment of disease.

Health as a product of ecosystem services

Humans benefit from a variety of processes supplied by natural ecosystems. Collectively these benefits are known as ecosystem services (78). There is growing evidence that human health is a collective property of the human body and its associated microbiome, and thus could be considered a net effect of ecosystem services. We envision clinical medicine focused on managing the human body and its associated microbiome to preserve these ecosystem services. How might this be accomplished? In general ecology, the management of an ecosystem service requires four basic steps (79): i) identification of ecosystem service providers (ESPs; taxa that provide specific ecosystem services) and characterization of their functional roles; ii) determination of how community context influences the function of these providers; iii) assessment of key environmental factors influencing the provision of services; and iv) measurement of the spatial and temporal scales at which these providers and their functions operate. This general framework would work equally well for human health-associated ecosystem services. If studies of the human microbiome were structured around these four priorities, the development of an ecological approach to medicine could be accelerated. Progress has been made in identifying ESPs (“biomarkers”; see associated review by Lemon *et al.* STM); for example, declines in *Faecalibacterium prausnitzii* are associated with inflammatory bowel disease, and this organism may be an ESP for health in the human gut (80).

Adaptive management of the human body

Transitioning clinical practice from the body-as-battleground to the human-as-habitat perspective will require rethinking how one manages the human body. In the management of plant and animal communities, a system-level approach known as “adaptive management” has become popular. This approach is a structured, iterative process of decision-making, one that utilizes system monitoring to continually update management decisions (79). It has been successfully used to manage biodiversity in a variety of habitats, including communities in highly disturbed environments impacted by overfishing and by climate change (79). For the human body, we envision that this approach would involve monitoring of the microbiome during health, to establish a healthy baseline, with more intensive monitoring during disease and treatment. This will require the development of new diagnostic tools that are both accurate and sufficiently rapid to inform decisions regarding therapeutics (see associated review by Lemon *et al.* STM). Such diagnostics are not yet feasible, but given recent advances in our ability to survey the human microbiome, this possibility is not far in the future, especially if we are able to identify particular components of the human microbiome that contribute disproportionately to the maintenance of human health. An adaptive

management approach to clinical medicine is the ultimate in personalized medicine, with treatments tailored to individuals based on diagnostic changes in an individual's microbiome, and continually adjusted through regular monitoring. Such an information-intensive approach, guided by ecological theory, has the potential to revolutionize the treatment of disease.

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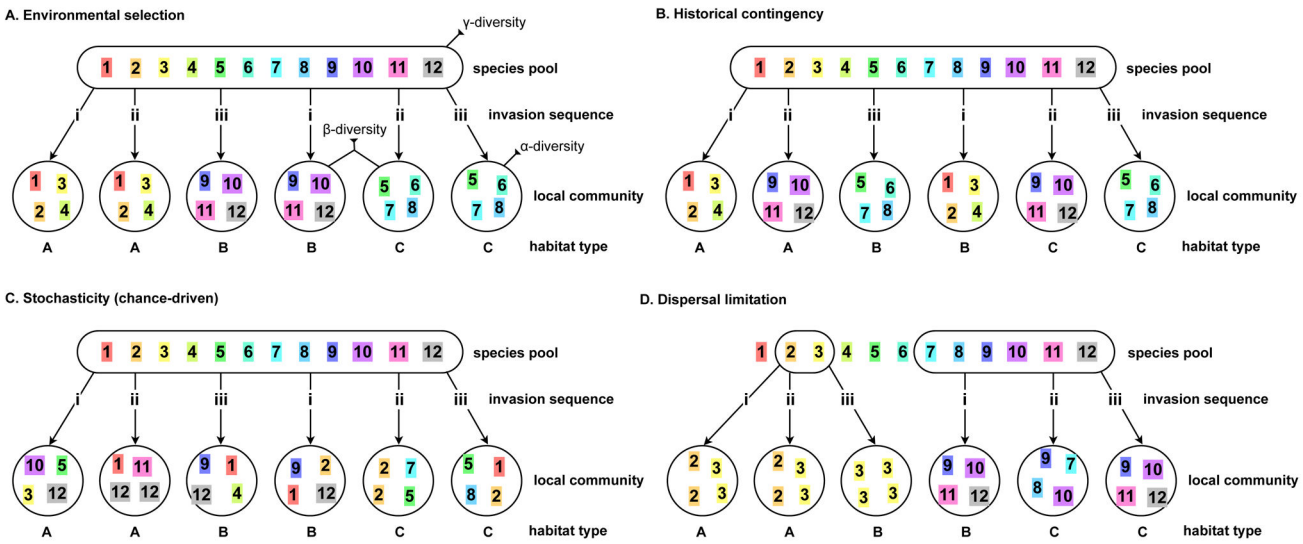

Figure 1. Alternative community assembly scenarios could give rise to the compositional variations observed in the human microbiota

Each panel shows the assembly of local communities in different habitat types from a pool of available species. In A–C, each local community has access to all available colonists, but the order of invasion varies. In A, local species composition is determined primarily by environmental selection: regardless of invasion order, habitats with initially similar conditions select for similar assemblages. In B, the opposite is true: regardless of initial habitat conditions, historical contingencies (i.e., differences in the timing and order of species invasions) determine assemblage composition. In C, neither habitat nor history matter: local communities assemble via random draws from the species pool. In D, dispersal barriers result in local communities that assemble from different species pools. For each of the pools, local communities may assemble as in A, B, or C. The meaning of three different diversity measures is shown in Panel A: gamma diversity refers to the "regional" species pool, i.e., the total diversity of the local communities connected via dispersal; beta diversity refers to the differences between local communities (species turnover); and alpha diversity refers to the diversity within a local community. Although multiple scenarios are likely to apply to any real-world setting, one may dominate. For example, differences between body habitats may be best explained by environmental selection (A), differences between siblings for the same habitat may be best explained by historical contingency (B), differences between monozygotic twins prior to weaning highlight the role of stochasticity (C), and differences between infants born by Cesarean section versus vaginal delivery are likely to be explained by dispersal limitation. Adapted from Chase (14) and Fukami (15).

NOTE TO ART EDITORS: In this figure, circles representing local communities could be changed to human forms (outlines).

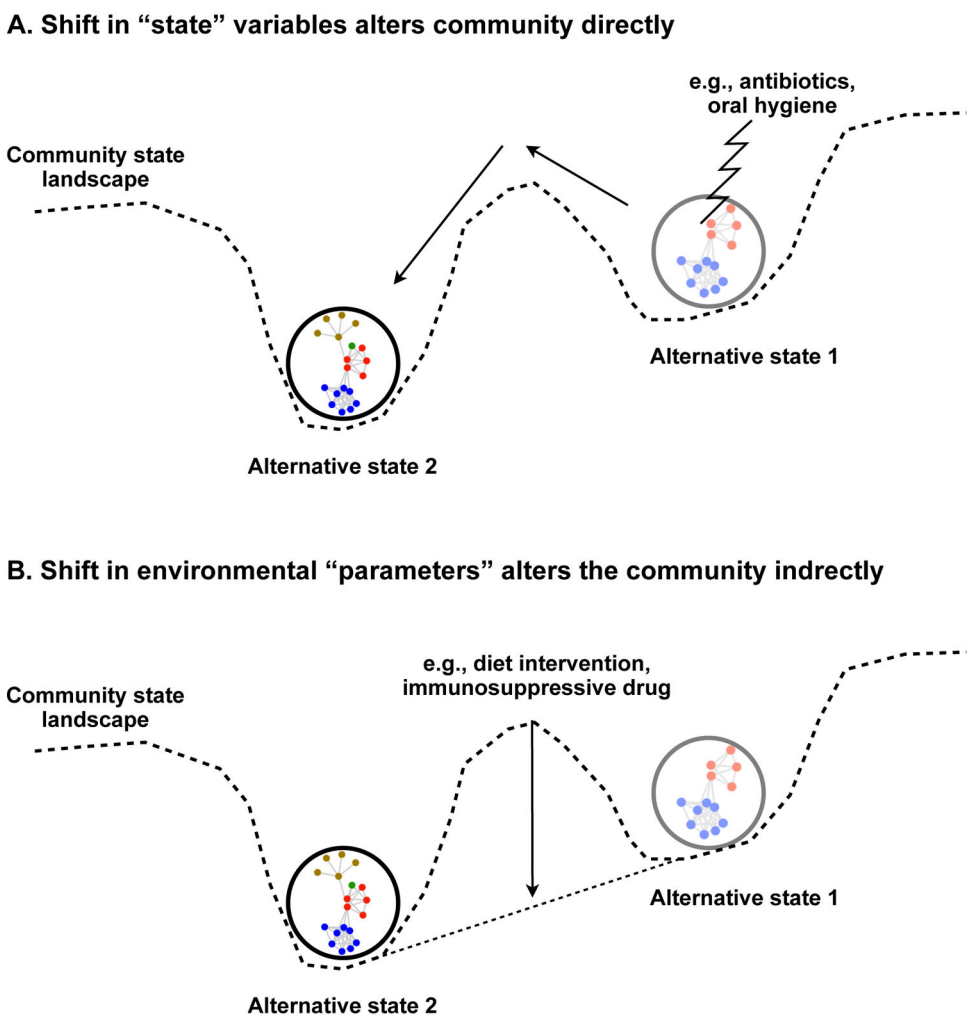

Figure 2. Disturbance can be illustrated using a stability landscape schematic

The ball represents the community and the changing horizontal position of the ball represents the changing community state. The depth of a basin indicates the likelihood of a community remaining in that basin despite frequent "buffeting" by minor disturbance (50), and hence, the relative stability of the community state. Disturbance can alter (A) the community directly by changing its composition or activity, or (B) indirectly by changing the environmental parameters. In either case, the community can shift to an alternative state. In reality, continuous feedback between the community and its environment means that they change together. See Lemon *et al.* (accompanying STM manuscript) for applications to therapy.

NOTE TO ART EDITORS: In this figure, the landscape line could be solid and the curves smoothed. The arrows in A could be curved to match landscape.