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Scales of persistence: transmission and the microbiome

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Abstract

Historically microbiomes have been studied on the scale of the individual host, giving little consideration for the role of extra-host microbial populations in microbiome assembly. However, work in recent years has brought to light the importance of inter-host transmission and its influence on microbiome composition and dynamics. We now appreciate that microbiomes do not exist in isolation, but exchange constituents with the microbial communities of other hosts and the environment. Moving forward, fully understanding the role of transmission in microbiome assembly and dynamics will require a high-resolution view of the colonization and persistence patterns of particular microbial lineages (i.e. strains) across individuals and the environment. Yet, accomplishing this level of resolution will be an immense challenge, requiring improved sampling and bioinformatics approaches as well as employment of tractable experimental models. Insight gained from these investigations will contribute to our understanding of microbiome composition and variation, and lead to improved strategies for modulating microbiomes to improve human health.

Graphical Abstract

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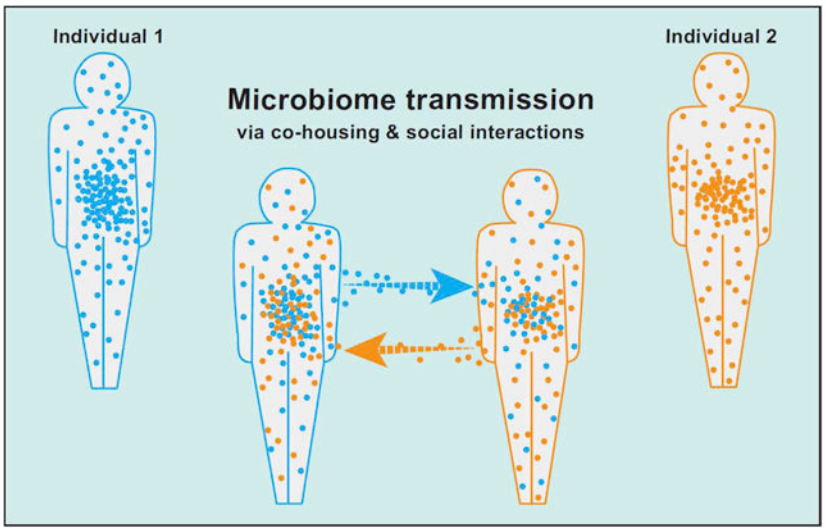

Introduction

Animals are colonized by communities of microorganisms (“microbiomes”) that serve essential roles in host health and development. In particular, the microbiome of the vertebrate gut is incredibly diverse, comprising hundreds of bacterial species representing thousands of different strains [1]. In recent decades, advances in DNA sequencing technologies have enabled extensive profiling of microbiomes and insight into how they vary both across individuals and within individuals over multiple scales of space and time [2]. From these studies, we have come to appreciate the incredibly complex and dynamic nature of these biologically important microbial consortia. In order to harness the microbiome to positively influence human health and treat or prevent microbiome-related diseases, we must be able to reliably predict or modulate microbiome communities. Thus, we must understand the ecological and evolutionary processes that govern microbiome membership and dynamics.

There is growing evidence that the process of transmission can be very important to microbiome composition and dynamics. By “transmission”, we mean the inter-host movement of microbes. Transmission can occur either directly (passed from one host to another via physical contact) or indirectly through various mechanisms. Indirect transmission may include an intermediate period of environmental persistence, and be facilitated by vectors (living) or fomites (non-living). Furthermore, mechanisms of transmission can be defined at a broader, ecological scale (e.g. horizontal vs. vertical transmission, deterministic vs. stochastic), or at a finer scale where genetic or phenotypic features of an organism that are relevant for transmission are identified (e.g. bacterial motility genes, or surface attachment molecules). An in-depth discussion of transmission mechanisms will not be presented here; rather we review recent research that demonstrates the contribution of transmission (by various mechanisms) to microbiome assembly and composition. Overall, this rapidly growing literature demonstrates the need to expand how we study microbiomes to a broader ecological scale, beyond the individual host, providing a

new perspective for thinking about membership of the microbiome and microbial persistence within a host population.

Mounting evidence for the role of transmission in microbiome assembly

Understanding microbiome assembly (i.e. formation of the microbial community at a particular place and time) requires identification of the factors that influence variation across individuals and over time. Surprisingly, studies focused on teasing apart the relative contribution of host genetics and environmental factors on microbiome composition have found only a minor role for genetics in shaping the microbiome [3]. Furthermore, studies attempting to statistically correlate microbiome composition with numerous host factors such as diet, genetics, lifestyle, and clinical information, have not been able to explain more than a minor proportion (<20%) of the total variation across individuals [3–6]. One such study, conducted by Falony et al., included an impressive 503 potential host factors across nearly 4000 individuals, yet could explain only 16.4% of the total variation [6]. These findings highlight that factors or ecological processes not accounted for in these studies influence inter-host variation, and thus microbiome composition and function.

Factors not captured in the design of many of these studies are ones that measure the potential for transmission across individuals, and between individuals and the external environment. For example, they do not measure the extent of an individual's inter-personal network and the type, frequency, and duration of physical interactions. However, several recent studies in both humans [7*–12] and non-human primates [13–16*] provide strong evidence for the contribution of transmission to microbiome assembly, and the need to measure these factors in future studies (Fig. 1). In particular, as discussed by Amato and colleagues in this issue (ref), the field of non-human primate studies is well suited for these endeavors because data on social interaction, shared environment, and other important factors such as diet are directly collected through observation. Tung et al. showed that social networks in wild baboons, and extent of social interaction, could predict microbiome structure, even after controlling for shared environment, diet, and relatedness [16*] (Figure 1a). Consistent with those findings, another study surveyed nine different non-human primate species and found that microbiomes varied with host species, but importantly also by social groups within species [14]. However, this was not seen within social groups of chimpanzees, suggesting that different ecological forces impact their microbiomes and that we should be cautious about generalizing conclusions across species [14].

In the human microbiome field, early studies observed that co-habitation correlated more strongly with microbiome similarity than genetic relatedness [17,18]. This opened the possibility for the role of transmission via a shared environment (Figure 1b); however, this was difficult to decouple from the influence of shared diet and lifestyle. Motivated by this question, more recent studies have designed experiments to better tease this apart. One such study, by Song et al., profiled the microbiomes of 159 people from 60 different families and found that cohabitation significantly influences microbiome composition by decreasing inter-individual variation among household members [7*]. The strongest signal was seen for cohabitating couples. Interestingly, the presence of a dog in the home amplified this homogenizing impact of co-habitation, especially for microbial communities of the skin.

Looking even further into the effects of cohabitation, another study compared spouse and sibling pairs within the same household and found that spouses, especially those who reported having close relationships, shared more microbes than siblings or even spouses with less close relationships [8]. Moreover, they found that close relationships increased microbiome diversity and richness within those individuals. This is consistent with ecological theory demonstrating that dispersal among hosts bolsters microbial diversity [19*].

To get an even finer-resolution picture of the flow of microbes between hosts, improved bioinformatics tools have enabled strain-level resolution from microbiome sequencing data (reviewed in [20]). Achieving this level of phylogenetic accuracy from DNA sequencing data requires especially deep sequencing and specialized alignment and analysis tools, and so is not yet a standard in the field. When applied, however, this can be a powerful approach for tracking patterns of transmission within host populations. This was demonstrated beautifully in a recent study by Brito et al. where the researchers analyzed deeply-sequenced microbiome data from 287 people from 5 villages across the Fiji islands [21*]. Their results not only validate that transmission of strains occurs more frequently within households and between spouses, but also provided several new insights. For example, women's microbiomes were more strongly influenced by inter-personal interactions than men's. They also found no correlation of transmission patterns with specific bacterial phyla. This is suggestive of indirect or stochastic mechanisms of transmission, although these data cannot definitively differentiate between direct and indirect transmission events, or the directionality of transmission.

Harnessing the power of strain tracking from sequencing data, several other studies have made significant contributions to understanding mechanisms of transmission, particularly for investigating horizontal and vertical transmission of strains between mother and infant pairs in the first few months of life [22–25]. Here, vertical transmission is defined as being passed from parent to offspring, and includes those microbes passed via the egg or in the womb (the strictest definition of vertical transmission), but also those transmitted during or shortly after birth (e.g. from the birth canal, during breastfeeding). These studies incorporate longitudinal sampling, offering to date some of the most comprehensive studies for tracking commensal strain transmission and development of the infant microbiome. They highlight that vaginally-born infants acquire more maternal strains than cesarean-born infants [22], that infants are more likely to acquire dominant maternal strains [25] and that early maternally-acquired strains are often later replaced by strains from other sources [22–24]. Future studies like these will continue to illuminate how microbiomes are shaped over time and the mechanisms of transmission and persistence.

Experimental animal models are tractable systems for studying transmission

Laboratory animal models are powerful systems for studying host-microbe interactions, particularly because they confer the ability to control and track features of host-microbe systems that are often not possible in natural settings [26]. A number of studies have used

animal models (e.g. mouse, fly, zebrafish) to explore the role transmission plays in host-microbe interactions [27–31]. Different animal models provide different advantages for the study of transmission; for example, the mouse model is especially well-suited for studying direct (host-to-host) transmission, since mice are coprophagic [32], and the zebrafish has emerged as an especially powerful model for exploring environmentally-mediated transmission [33–35], because the environment external to the host can be sampled and manipulated with relative ease. Invertebrate models with short generation times (e.g. hydra, nematodes, etc.; [36]) are ideal for studying the role of transmission in host-microbe coevolution. The use of animal models in host-microbiome research, including transmission studies, has been reviewed elsewhere [26], Below we provide a few illustrative examples.

An open question in the microbiome field is the relative contribution of vertical (passed from parent to offspring) versus horizontal transmission to microbiome assembly. Moeller et al. investigated this by establishing 17 inbred mouse lines derived from two geographically distinct wild mouse populations and monitoring microbiome composition over many host generations [27]. Lines were maintained separately, but with opportunities for introduction of exogenous microbes through handling and housing conditions. Their data showed the strongest influence of vertical transmission on microbiome composition, however, a small subset of the taxa were correlated with horizontal transmission. Interestingly, vertically transmitted taxa tended to be obligate anaerobes, while horizontally transmitted taxa were more often aerobic, which could be explained by the importance of oxygen tolerance for mechanisms of horizontal transmission. These results contrast with the dominant influence of horizontal transmission for human infant microbiomes at later developmental stages ([23]), again demonstrating that conclusions from these studies may not translate across species.

Using zebrafish as a model, Burns et al. investigated how dispersal among hosts alters microbiome assembly [29*]. To do this, zebrafish of two different genotypes (wild-type and immune-deficient) were reared individually, in groups of the same genotype, or groups of mixed genotypes. Surprisingly, genotype-specific differences in microbiome composition were only apparent when fish were reared in isolation. These effects were mitigated when the fish were co-housed, either with the same genotype or mixed genotypes (Figure 1c). This result shows that the impact of inter-host dispersal on microbiome assembly is greater than the influence of an intact innate immune system. The importance of transmission in the zebrafish system was further demonstrated via the serial passage of a bacterial member of the zebrafish gut microbiome (*Aeromonas* sp.) through axenic zebrafish larvae [28*] (Figure 2a). Rather than adapting to the intra-host environment during serial passage, these bacteria first evolved an increased ability to migrate into the host from the aqueous environment and to transmit from host-to-host (Figure 2b).

Scales of persistence within the microbiome

The field of community ecology has long recognized that ecological dynamics within local communities of species are influenced by dispersal across communities at larger spatial scales, forming the basis of metacommunity theory [37]. This was originally developed in the context of communities of organisms living within abiotic environments (“patches”, e.g.

rock pools). However, recently the concepts and theories born from metacommunity ecology have begun to be applied to the study of animal microbiomes, with the premise that individual hosts serve as patches connected via transmission [38–42]. These theories are now being refined to more appropriately capture the ecological features of host-associated microbiomes, such as feedback between the biotic host patches and the microbiome, and the impact of microbial persistence in the environment on microbiome composition [19*,43].

It is broadly recognized in ecology that one strategy for persistence is to specialize in dispersal between or across communities rather than competing to persist within a single community [44]. Although this has not been well documented in host-microbiome systems, there is evidence that this kind of strategy is employed in free-living microbial communities [45]. Even though the relevance of this for host-associated microbiomes has not been directly demonstrated, it suggests that the continual opportunity for reintroduction via transmission could enable dispersal specialists to persist long term within a network of local comminutes, such as a population of hosts (Figure 3a). For instance, if conditions are unfavorable for persistence within a particular host at a given time, it is possible to persist within the system (i.e. population of hosts and their environment) and have an opportunity to colonize a new host, or re-inoculate the same host when intra-host conditions change (Figure 3b). These dynamics make it difficult to differentiate between species that are capable of persisting long term and ones that are consistently present due to re-inoculation.

While microbiome constituents are often defined in terms of being “resident” or “transient”, it is clear that microbes exist along a spectrum of colonization and persistence, with some able to maintain stable, long-lasting populations in a host, while others are much more short-lived [46–48]. However, current methods for studying the microbiome, particularly microbiome profiling, do not provide a high enough resolution understanding to define the colonization and persistence dynamics of most microbial lineages within and across individuals and their environment (see Box 1). In particular, the most widely used approach is fecal sampling, which does not capture any information about extra-host microbial populations, and furthermore is a poor representation of the community within the host. Nonetheless, in light of the work highlighted here demonstrating that microbiomes are connected via transmission and dispersal, it is clear that there is a need to shift our conceptualization of microbiome membership to one that encompasses the broader ecological context of host-microbe systems and considers microbial persistence at larger spatial scales.

Recognizing the importance of transmission and changing the scale at which we view and study the microbiome has important implications for how we interpret microbiome data. To illustrate, it might be concluded that a low abundance but consistently detected bacterial strain is a fair competitor in the intestine with a small but stable population, when in fact it might be a very poor competitor that maintains its population by continued influx from external sources such as cohabiting individuals or an environmental reservoir. Just as importantly, this broader scale of persistence shifts how we delineate what constitutes an individual’s microbiome—it blurs the lines between hosts and their environment. It also creates an opportunity for feedback within the system such that hosts impact the microbial composition of the environment, which in turn changes the pool from which hosts recruit

potential future colonizers. This intermediate environment could be conceptualized as a "cloud" of host influence within which hosts could enhance transmission across the population and to which microbes could adapt. From this new perspective, we can reimagine how microbes might adapt to being host-associated and the strategies they might use to maintain stable populations not within a particular host, but within a host population over long time periods, even across generations.

Conclusions

The transmission of pathogenic microbes has been studied for many decades but only in recent years are we beginning to understand its relevance for the microbiome. The first observations alluding to the influence of transmission on microbiome assembly came from microbiome profiling studies in humans and non-human primates showing correlations between microbiome composition and cohabitation or social networks. More recently, experiments using animal model systems to test hypotheses about microbiome transmission have substantiated these findings. We now have an appreciation for the relevance of transmission in the ecological and evolutionary dynamics of the microbiome. This has important implications for how we design experiments to study microbiome variation and dynamics and interpret sequencing data. Many questions remain to be answered (see "outstanding questions"). Future work should focus on designing better experimental approaches to elucidate mechanisms of transmission and identify the specific colonization and persistence patterns of microbiome constituents. Furthermore, the bourgeoning microbiome field will benefit from the application of theories and ideas from other fields, such as metacommunity theory from the field of community ecology. Importantly, these insights bring to light a new ecological perspective for studying the microbiome at a larger spatial scale, beyond the individual host.

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Box 1.

The challenges and limitations of microbiome profiling

The majority of microbiome profiling studies use DNA sequencing approaches to analyze microbiome structure and composition. These studies were enabled by advancements in DNA sequencing technologies which allow high-throughput profiling of microbiome samples [49]. However, a sequencing dataset is only as valuable as the tools you have to analyze it, and the challenge of gleaning meaningful information from these complex data is more complicated than one would anticipate. Bioinformatics tools for analysis are continually being developed and refined, and can be tailored to answer specific research questions [50,51]. An enormous amount of genomic information can be acquired from a microbiome sample, yet the limitations of sampling and analysis must be kept in mind when interpreting the data. In essence, the level of resolution that can be achieved is limited in three major ways—spatially, temporally, and taxonomically. Each of these impacts how we interpret the data to understand the complexities and dynamics of the microbiome, especially for tracking individual strains.

Limits of spatial resolution

Spatial resolution in profiling studies is limited by the design and technical aspects of sampling. Fecal sampling is the most common approach for profiling the gut microbiome, primarily due to ease of collection and low cost. However, a fecal sample does not offer a complete representation of the microbial communities within the intestine. Numerous studies have demonstrated that luminal communities, which are primarily represented in fecal samples, are distinct from mucosa-associated communities [52–56]; reviewed in [57]. Furthermore, there are differences in the spatial distribution of taxa along the length of the gut (reviewed in [58]), thus a fecal sample primarily comprises microbes from the distal intestine. As a result, we know little about the microbial communities in the other regions of the intestine, including the proximal colon and the different compartments of the small intestine. In addition, sequencing results can be highly dependent on aspects of the fecal sample preparation, such as homogenization, storage, and DNA extraction [59]. Importantly, few studies sample microbial communities at larger spatial scales outside of hosts, such as from the environment or communities associated with food.

Limits of temporal resolution

Capturing a complete picture of the dynamics of individual strains within the microbiome requires temporal sampling. Temporal resolution can be considered at multiple scales, from hours to years, and even across generations of hosts [60–62]. The majority of microbiome studies sample only a single time point, although decreasing costs of sampling and analysis are leading to more studies that incorporate temporal dynamics into their experimental design.

Limits of taxonomic resolution

Taxonomic resolution is a major challenge in microbiome profiling studies. Until recently, the most common approach for profiling has been targeted 16S rRNA

sequencing [63]. However, bacterial strains encoding near-identical 16S rRNA genes, can have significant differences in content across the rest of the genome [64]. Therefore, 16S rRNA sequencing is generally unable to resolve taxa beyond the species level, although new approaches are being developed to increase this resolution [65,66]. Recent advancements in DNA sequencing technologies have resulted in a marked decrease in cost and efficiency, promoting whole shotgun (i.e. metagenomic) sequencing. These data can provide strain-level resolution of the community, although this requires incredibly deep sequencing and complex analysis tools and so is not yet a standard in the field.

Highlights

- Microbial transmission shapes microbiomes through social networks and co-housing.
- The colonization and persistence dynamics of microbiome members is underexplored.
- Microbiome profiling offers limited spatial, temporal, and taxonomic resolution.
- Animal models provide tractable systems for studying microbiome transmission.
- Microbiome studies should consider ecological contexts beyond individual hosts.

Outstanding questions:

- What are the mechanisms for transmission of microbiomes in different host species?
- What are the time scales on which microbiomes transmit and what factors influence these rates?
- How does transmission affect the colonization and persistence patterns of individual taxa?
- What microbial traits contribute to transmission?
- Are there ecological or evolutionary trade-offs between persistence and transmission?
- Can we distinguish between long-term persistence in individual hosts and serial re-inoculation?
- How do changes in host behavior or environment influence microbiome transmission?

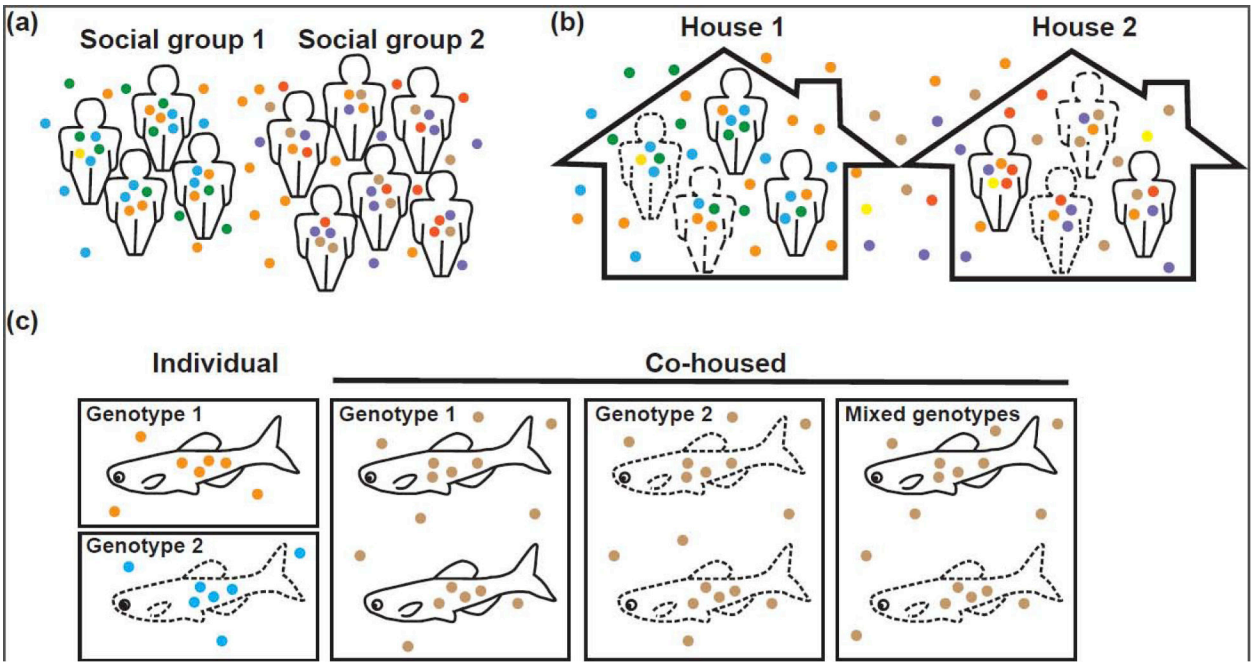

Figure 1. Social groups and co-housing conditions facilitate microbiome transmission across individuals.

In all panels, individuals with similarly-dashed outlines represent close genetic relationships; small filled circles of varying colors represent phylogenetically diverse microbes. (a) Individuals belonging to the same social groups tend to share more microbial species with each other and their environment than individual from other groups. (b) Co-housed individuals have more similar microbiomes than individuals not co-housed, even when they are genetically closely related. (c) Zebrafish of different genotypes housed individually assemble microbiomes that are genotype-specific. However, microbiomes of co-housed fish are different from individually housed fish, irrespective of genotype.

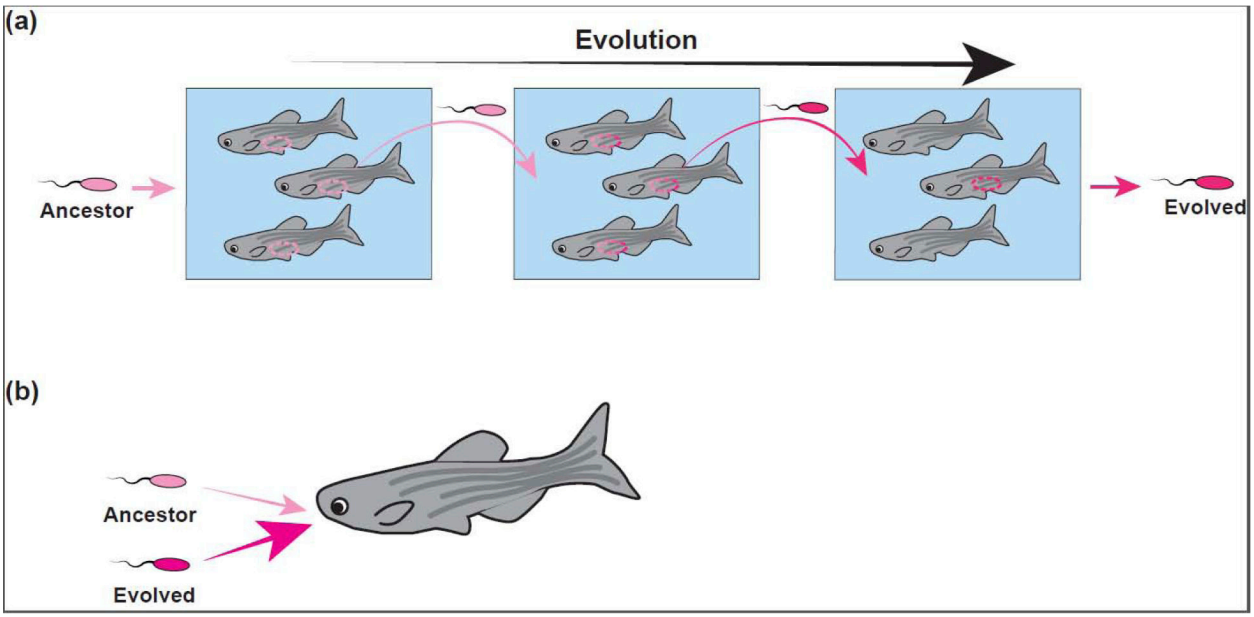

Figure 2. Transmission impacts bacterial evolutionary strategies for optimizing host colonization.

(a) In an experimental evolution study, a bacterial symbiont was passaged through populations of zebrafish, each time selecting gut-associated bacterial populations to inoculate the water of a new host population. (b) The adaptation that evolved first in the experiment was the ability to migrate into the host more quickly than the ancestor.

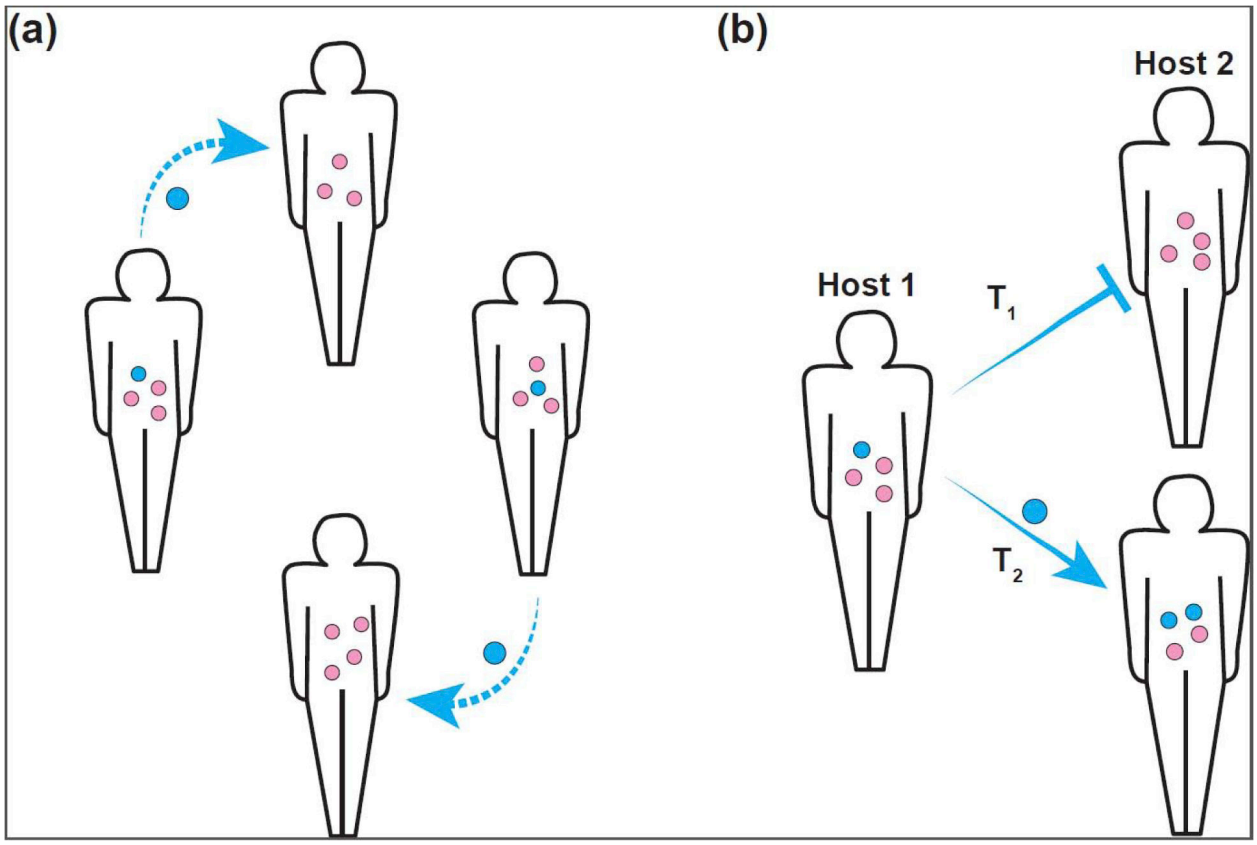

Figure 3. Transmission of dispersal-specialist species within a host population.

(a) Some microbial strains (blue) more readily transmit between hosts than other more long-term resident strains (pink). Through this mechanism, they can persist at a host population level even if they are poor competitors within a single host. (b) Transmission and colonization of a dispersal specialist (blue) may not be successful at one point in time (T_1), however, this microbe can persist within the host population until conditions within the second host allow successful colonization and persistence (T_2).