

REVIEW SUMMARY

MICROBIOTA

Vulnerability of the industrialized microbiota

Justin L. Sonnenburg* and Erica D. Sonnenburg*

BACKGROUND: The collection of trillions of microbes inhabiting the human gut, called the microbiome or microbiota, has captivated the biomedical research community for the past decade. Intimate connections exist between the microbiota and the immune system, central nervous system, and metabolism. The growing realization of the fundamental role that the microbiota plays in human health has been accompanied by the challenge of trying to understand which features define a healthy gut community and how these may differ depending upon context. Such insight will lead to new routes of disease treatment and prevention and may illuminate how lifestyle-driven changes to the microbiota can impact health across populations. Individuals living traditional lifestyles around the world share a strikingly similar microbiota composition that is distinct from that found in industrialized populations. Indeed, lineages of gut microbes have cospeciated with humans over millions of years, passing through hundreds of thousands of generations, and lend credence to the possibility that our microbial residents have shaped our biology throughout evolution.

Relative to the “traditional” microbiota, the “industrial” microbiota appears to have lower microbial diversity, with major shifts in membership and functions. Individuals immigrating from nonindustrialized to industrialized settings or living at different intermediate states between foraging and industrialization have microbiota composition alterations that correspond to time and severity of lifestyle change. Industrial advances including antibiotics, processed food diets, and a highly sanitized environment have been shown to influence microbiota composition and transmission and were developed and widely implemented in the absence of understanding their effects on the microbiota.

ADVANCES: Here, we argue that the microbiota harbored by individuals living in the industrialized world is of a configuration never before experienced by human populations. This “new,” industrial microbiota has been shaped by recent progress in medicine, food, and sanitation. As technology and medicine have limited our exposure to pathogenic microbes, enabled feeding large populations inexpensively, and

otherwise reduced acute medical incidents, many of these advances have been implemented in the absence of understanding the collateral damage inflicted on our resident microbes or the importance of these microbes in our health. More connections are being drawn between the composition and function of the gut microbiota and alteration in the immune status of the host. These

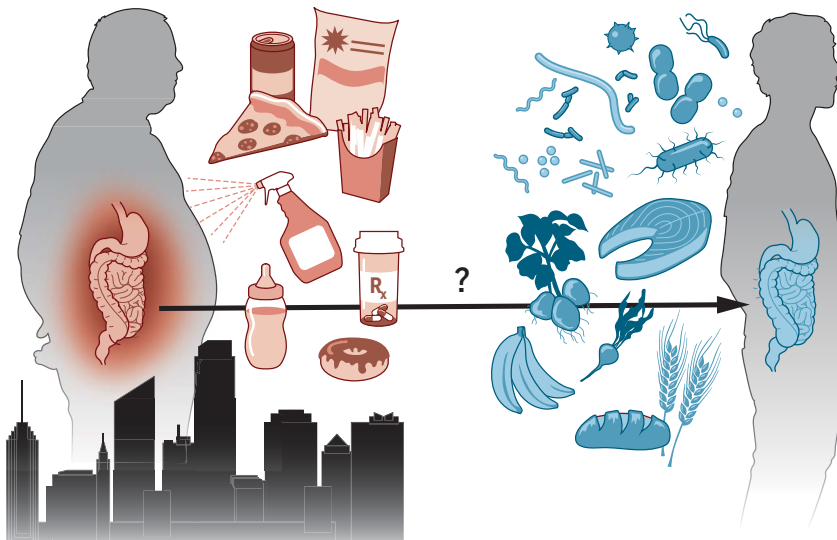
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relationships connect the industrial microbiota to the litany of chronic diseases that are driven by inflammation. Notably, these diseases spread along with the lifestyle

factors that are known to alter the microbiota. While researchers have been uncovering the basic tenets of how the microbiota influences human health, there has been a growing realization that as the industrial lifestyle spreads globally, changes to the human microbiota may be central to the coincident spread of non-communicable, chronic diseases and may not be easily reversed.

OUTLOOK: We suggest that viewing microbiota biodiversity with an emphasis on sustainability and conservation may be an important approach to safeguarding human health. Understanding the services provided by the microbiota to humans, analogous to how ecosystem services are used to place value on aspects of macroecosystems, could aid in assessing the cost versus benefit of specific microbiota dysfunctions that are induced by different aspects of lifestyle. A key hurdle is to establish the impact of industrialization-induced changes to the microbiota on human health. The severity of this impact might depend on the specifics of numerous factors, including health status, diet, human genotype, and lifestyle. Isolating and archiving bacterial strains that are sensitive to industrialization may be required to enable detailed study of these organisms and to preserve ecosystem services that are unique to those strains and potentially beneficial to human health. Determining a path forward for sustainable medical practices, diet, and sanitation that is mindful of the importance and fragility of the microbiota is needed if we are to maintain a sustainable relationship with our internal microbial world. ■



Industrialization affects the human gut microbiota. Aspects of lifestyle, including those associated with industrialization, such as processed foods, infant formula, modern medicines, and sanitation, can change the gut microbiota. Major questions include whether microbiota changes associated with industrialization are important for human health, if they are reversible, and what steps should be taken to prevent further change while information is acquired to enable an informed cost-versus-benefit analysis. It is possible that a diet rich in whole foods and low in processed foods, along with increased exposure to nonpathogenic microbes, may be beneficial to industrial populations.

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Vulnerability of the industrialized microbiota

Justin L. Sonnenburg^{1,2*} and Erica D. Sonnenburg^{1*}

The human body is an ecosystem that is home to a complex array of microbes known as the microbiome or microbiota. This ecosystem plays an important role in human health, but as a result of recent lifestyle changes occurring around the planet, whole populations are seeing a major shift in their gut microbiota. Measures meant to kill or limit exposure to pathogenic microbes, such as antibiotics and sanitation, combined with other factors such as processed food, have had unintended consequences for the human microbial ecosystem, including changes that may be difficult to reverse. Microbiota alteration and the accompanying loss of certain functional attributes might result in the microbial communities of people living in industrialized societies being suboptimal for human health. As macroecologists, conservationists, and climate scientists race to document, understand, predict, and delay global changes in our wider environment, microbiota scientists may benefit by using analogous approaches to study and protect our intimate microbial ecosystems.

Ecosystems change. Seasonal or periodic fluctuations may occur over short time scales, trajectories of lasting change can occur over time, and sudden perturbations can result in instability or new stable states. Ecosystems can also reach tipping points at which biodiversity crashes, invasive and opportunistic species take over, and the services expected of the original ecosystem are lost, which may result in further damage and/or extinctions. Each human is an ecosystem composed of thousands of species and trillions of members, the host body of *Homo sapiens* being just one of those species. Most of these community members are microorganisms that reside in the gut, which is the focus of this article. Sequencing of the microbiota shows that human microbiomes are composed of a stunning array of species and functional diversity. An intricate set of interactions, just now being mapped, connects microbial species within a microbiota to one another and to human biology and is beginning to show how profoundly these microbes influence our health.

The first steps in human microbiota assembly occur upon birth, with microbes vying to colonize environment-exposed surfaces in and on the body. This process is influenced by many factors, including mode of birth, nutrition, environment, infection, and antibiotic exposure (1, 2). Specific taxa of microbes have co-diversified with *Homo sapiens*, consistent with vertical transmission over hundreds of thousands of generations (3). The millions of years of association have provided ample opportunities for our biology and theirs to evolve (4).

Intimate connections between the microbiota and the human immune system, nervous system, and metabolism have been revealed over the past decade (5–9). The specific microbes that first colonize the infant gut and the ensuing succession of the community can irreversibly influence mucosal and systemic immune development (10). Orchestrating the assembly of a health-promoting gut microbiota or manipulating a mature community to alter human physiology has vast therapeutic potential, which has captured the attention of the biomedical community. Beyond the importance of the microbiota to human health, recent research has also demonstrated its vulnerability. This ecosystem is susceptible to change by selective forces (11, 12). For example, a single course of one type of antibiotic can decimate and reshape the gut microbiota (13). Exciting research is racing to identify disease treatments using microbiome manipulation, but less focus has been placed on how to protect the microbiota from damage that may be deleterious to human health (14).

The germ theory of disease, formalized in the 1860s by Louis Pasteur, portrayed microbes as an enemy to be controlled and eradicated. The subsequent “war” on microbes deploying hand washing, sterile surgical techniques, and antibiotics has saved countless lives. In 1900, pneumonia, tuberculosis, and infectious enteritis were the three leading causes of mortality in the United States, accounting for almost one-third of all deaths (15). By the end of the millennium, these infectious disease killers were replaced by chronic diseases, including heart disease, cancer, and stroke, which offered evidence of our ability to effectively manage “germs.” However, the inverse relationship of infectious and chronic disease rates may share a similar underlying cause. Consistent with tenets of the hygiene hypothesis, limited expo-

sure to microbes may result in defects in immune function and/or regulation, leading to an increasing burden of allergic and autoimmune diseases. In light of our new knowledge about the role of the microbiota in health, the war on microbes likely needs to be reconsidered in less combative terms. The profound success of germ-killing techniques and drugs developed in the past century that have minimal acute side effects has led to overuse. The rise of superbugs that are resistant to antibiotics and chemical bactericides reveals that there is a cost to our war on microbes (16). However, the longer-term and less obvious costs to human health of disrupting the microbiota may come from chronic metabolic and immune diseases. Although intimate, the communities that live in our guts are hard to study, and at present we do not fully understand the health impact of the differences in the microbiota observed between human populations.

Microbiota composition, diversity, and gene content in industrialized peoples vary substantially from that of more traditional rural populations and likely from that of our ancient ancestors, indicating that aspects of our lifestyle are changing our resident microbes (4, 17–20). Antibiotics are not the only potential contributor to this effect. Other recent changes in practice, including Caesarean section (C-section) delivery, infant formula, and consumption of industrially produced foods, have all been shown to influence the gut microbiota of humans (21–23). Although these technological and medical advances have had undeniable benefits (especially for emergency health care), their implementation and widespread use have occurred without an understanding of their impact on our resident microbial communities. At one extreme, microbiota shifts coincident with industrialization may have no impact (or even a beneficial impact, for example, by removing or reducing microbes with pathogenic potential) on human health and longevity. At the other extreme, the microbiota alterations observed in industrialized populations may be a major contributor to the misregulation of the human immune system that drives chronic inflammation (4, 24). Noncommunicable diseases (NCDs), such as stroke, heart disease, some cancers, chronic kidney disease, diabetes, and dementias, all of which are fueled by chronic inflammation, are associated with the worldwide expansion of industrialized lifestyles and are predicted to create a global health crisis in the coming century (25, 26).

In many ways, the rapid changes experienced by the microbiota of urban humans are analogous to those observed in macroecosystems throughout the world (27). Over time and with tremendous efforts to generate and analyze data, a global scientific consensus has emerged that human-induced climate change

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will have a devastating impact on Earth's species and ecosystems if not curtailed and reversed (28, 29). Likewise, as we become increasingly cognizant of the importance of the microbiota in dictating the duration and extent of our health, it is vital that we reframe our relationship with microbes and use strategies similar to the sustainability and biodiversity conservation efforts under way around the globe. What steps should we take now to protect resident microbes, given the current data and range of possible outcomes?

The gut: A rapidly changing ecosystem

That the gut ecosystem would change in response to marked lifestyle alterations is not surprising. What is notable is that the microbiota of traditional populations share taxa that have been lost or reduced in individuals living in the industrialized world, which we have termed "VANISH" (volatile and/or associated negatively with industrialized societies of humans) taxa (Fig. 1A) (30). A study comparing the industrialized microbiota with that of three Nepalese populations living on a gradient from foraging to farming showed the shift in microbiota composition that takes place as populations depart from a foraging lifestyle (31). Intermediate states of lifestyle change toward urbanization are accompanied by less extreme but evident changes in the microbiota (Fig. 1, B and C).

Similarly, a longitudinal study of individuals immigrating from a Thai refugee camp to the United States showed a loss of VANISH taxa within months of immigrating (32). The longer the immigrants lived in the United States, the more profound the changes. In addition to changes in microbial membership, functional differences in the microbiota correspond to lifestyle. Traditional populations such as the Hadza, a hunter-gatherer group living in Tanzania, like the immigrants from Southeast Asia, harbor microbiota with a larger and more diverse collection of carbohydrate active enzymes (CAZymes) than their industrial counterparts. CAZymes digest complex plant polysaccharides, characteristic of traditional dietary fiber intake (32, 33). By comparison, the microbiota of U.S. residents are enriched in CAZymes that degrade host mucus, which serves as a backup food source for gut microbes when dietary fiber is limited, a hallmark of the industrialized diet (33, 34). The selection of mucus-utilizing bacteria in industrialized populations is evident in the enrichment of *Akkermansia muciniphila* (a mucin-loving bacterium in the phylum Verrucomicrobia) that was found in a worldwide comparison of industrialized and nonindustrialized microbiomes (Fig. 1A) (33). Whether the loss or reduction of VANISH taxa cause or contribute to the growing burden of NCDs in humans remains to be determined. However, determin-

ing the potential importance of VANISH taxa to human biology will require efforts to maintain their diversity before it is lost (35, 36).

An ecosystem vulnerable to industrialization

We must not forget how the attempted eradication of pathogenic microbes with antibiotics, increased sanitation, and medicalized birth has saved countless lives. Other features of industrialized life, such as the Western diet and infant formula, have added convenience, increased human productivity and met the food demands of a growing population. The development and widespread implementation of these technological advances occurred before there was an understanding of their effect on the microbiota and the significance of the microbiota to human health. One difficulty in understanding the effects of different aspects of industrialization on the human gut microbiota is that so many lifestyle factors covary. Below, we summarize studies that have sought to disentangle facets of the industrialized lifestyle that change the microbiota.

The development and use of antibiotics have accompanied human population growth, industrialization, and rapid technological advances. Antibiotics have become the prototypic factor associated with industrialization that negatively affects the gut microbiota. Antibiotic resistance and increased susceptibility to enteric pathogens are well-known negative effects of antibiotic use. Accumulating data also show that oral antibiotic use has long-term effects on the composition of the gut microbiota (37). Just 5 days of ciprofloxacin was shown to decimate the gut microbial community, which only recovered slowly over the ensuing weeks and months (13). Recoveries were individualized, were incomplete, and differed in their kinetics (13). Similarly, other studies have shown that antibiotics can have a long-term impact on the microbiota—perhaps we should not be surprised because most of these medicines were originally designed to have broad-spectrum effects (38).

For most of human existence, humans consumed food and water laden with microbes, some of which caused disease. But humans also routinely consumed benign bacteria, both through incidental environmental exposure (e.g., from dirt or unsanitized food or on the skin) and from fermented foods (39). The recent shift to consuming largely sterile food and water has likely also influenced the microbiota. For example, the source of drinking water was significantly associated with microbiota composition in the cross-sectional study of Nepalese individuals living on a lifestyle gradient, as well as the Hadza (31). As industrial populations removed microbes from drinking water, the burden of diseases such as cholera and other waterborne illnesses decreased. Recent studies in mice suggest that

sanitization in the form of cage cleaning does exacerbate extinctions in the microbiota after perturbation (40). The industrialized human microbiota also bears the hallmarks of sanitation, showing greater interindividual differences in microbiota composition (an indication of less microbe sharing between people) compared with traditional human populations in Papua, New Guinea, where individuals share more bacterial species with one another (20). Risking increased infectious diseases by reducing standards of sanitation would be misguided, but a better understanding of how hygienic practices shape our microbiota and the resulting impact on human health is needed. Restoring the consumption of non-disease-causing microbes may ameliorate diseases that are common among populations that consume sterile food and water (41).

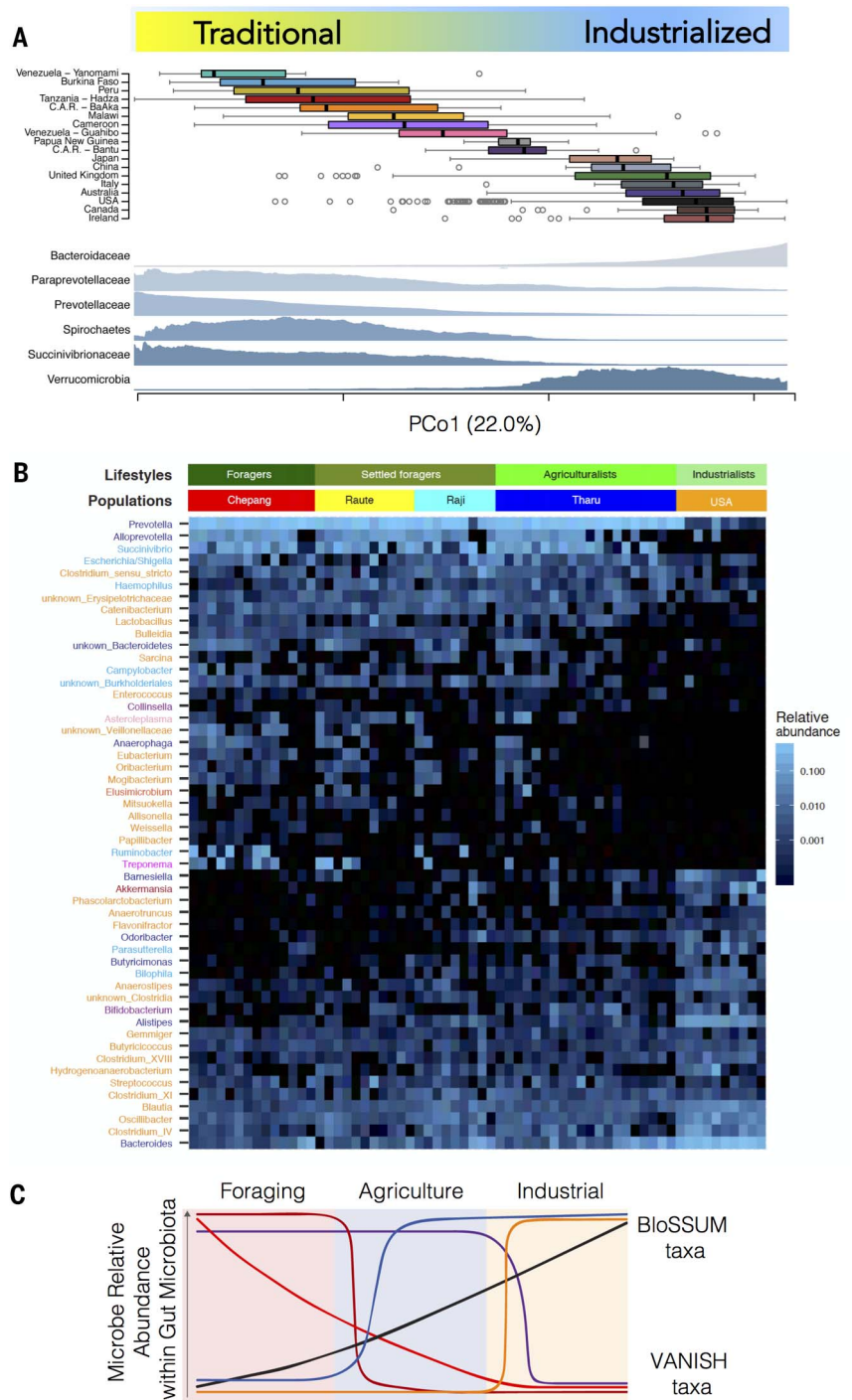
Antibiotics and sanitation are intended to limit exposure to pathogenic microbes, but other practices such as the Western diet and C-section births that are not targeted at microbe control may nevertheless be having a profound effect on the microbiota.

Diet is a major driver of the composition and metabolic output of the microbiota (42–44). Humans have shifted from a diet of exclusively wild animals and gathered foods to one of domesticated livestock and agricultural produce (10,000 to 20,000 years ago) to a more recent shift to industrially produced foods, including chemically managed livestock and produce and sterilized, ultraprocessed foods containing preservatives and additives (45, 46). These shifts have resulted in a food supply capable of supporting a growing human population, but perhaps at the cost of the population's health (47).

One notable change to foodstuffs is the unintentional depletion of a major form of sustenance for the microbiota: microbiota-accessible carbohydrates (MACs; the complex carbohydrates found in the dietary fiber of edible plants such as legumes, whole grains, vegetables, nuts, etc.) (42). A high-MAC diet was commonplace when humans exclusively foraged for nutrition, and low-MAC diets have been associated with lower microbiota diversity and poor markers of health in humans and in animal models (48–50). The paucity of MACs in the industrialized diet was compensated for by additional protein, simple carbohydrates, and fat, which had the effect of altering the composition and functional output of the microbiota (43, 51). The use of additives such as emulsifiers and non-nutritive sweeteners is pervasive in industrialized food. Both have been shown to alter microbiota composition and promote intestinal inflammation. In addition, emulsifiers promote adiposity and non-nutritive sweeteners alter the metabolic output of the microbiota toward one that resembles that of type 2 diabetics (21, 52).

Fig. 1. The gut microbiota mirrors lifestyle across traditional and industrial populations.

(A) Aggregation of gut microbiota composition from multiple studies separated by principal component analysis of Bray–Curtis dissimilarity of 16S rRNA enumerations [adapted from Smits *et al.* (33)]. Top panel: The first principal component explains 22% of the variation in the data from 18 populations living lifestyles spanning from uncontacted Amerindians in Venezuela (top) to fully industrialized populations in Australia, the United States, Canada, and Ireland (bottom). Bottom panel: Mapping the relative abundance of bacterial families on PCo1 reveals global patterns in the VANISH taxa, which are associated negatively with industrialized societies, and BloSSUM taxa (bloom or selected in societies of urbanization/modernization), such as the Bacteroidaceae and Verrucomicrobia. **(B)** Heat map adapted from Jha *et al.* (31) displaying taxa that change across lifestyles in one geographic location (Nepal) of individuals living as foragers (Chepang), settled foragers (Raute, Raji), or agriculturalists (Tharu) versus industrialized individuals in the United States. **(C)** Model adapted from Jha *et al.* (31) of strain loss and/or reduction versus gain and/or increase across a lifestyle gradient. Different patterns of changing abundance correspond with specific aspects of lifestyle that change as populations move away from foraging and toward urbanization. The model could also reflect the historical progression of industrialized humans from foraging (*Homo sapiens* arose ~200,000 to 300,000 years ago) to agriculture (starting 10,000 to 20,000 years ago) to industrialization (starting 100 to 200 years ago).



Small changes to the microbiota have the capacity to amplify over generations. For example, mice fed a low-MAC diet showed reduced microbiota diversity that compounded over generations. Restoration of a high-MAC diet was not sufficient to regain microbiota diversity, which indicated that species within the microbiota had gone extinct during the four-generation length of the experiment (50). In another study, antibiotic treatment of pregnant mice altered the microbiota of

the offspring and resulted in metabolic derangement that predisposed the pups to diet-induced obesity (53). Similarly, C-section delivery in humans results in colonization of the infant with microbes derived from skin instead of the mother's vaginal microbiota (54). Acute perturbations from diet, antibiotics, and medical practices could have been propagated over generations and synergized with heightened hygiene and sanitation to result in the population-wide ecosystem re-

configurations observed today. The effects of other factors associated with an industrialized lifestyle on the microbiota, including increased sedentary behavior, stress, exposure to new chemicals (e.g., plastics, herbicides, and pesticides), and social isolation, have only begun to be explored (55–57).

Microbiota change: Good, bad, or neither?

It is not a given that the microbiota found in traditional populations, which likely shares

more commonality with that of our ancient ancestors, would improve the health of a person living in an industrialized society (4). For example, several members of a traditional gut microbiota, such as parasites, are frank pathogens. Some functions of a traditional microbiota may have beneficial effects in the context of a traditional lifestyle but may not in a more urbanized context. We have simplified these points and recognize that some parasites may confer “benefits” to human health, but how benefit is defined may depend on context and the individual. For example, parasites that protect against intestinal inflammatory diseases may cause opportunistic infections in immunocompromised individuals (58).

While remaining agnostic about broad connections between change in the microbiota and human health, it is worth considering underlying evolutionary principles that might predict whether microbiota changes are likely to be beneficial, deleterious, or neutral. A very conservative view is that until we have a good understanding of which microbes or communities are beneficial or deleterious, including how context determines this answer, we should recognize that (i) our resident microbes have the potential to affect our health in profound ways and (ii) individual lifestyle and/or medical choices and population-level lifestyle, medical, and dietary choices can change these communities. Similar to early, albeit insufficient, steps to address climate change before the full scope of the problem was understood, such as developing renewable alternatives to fossil fuels, a hedge against potential catastrophe seems warranted. In the case of our gut microbes, acting to minimize unintended loss of biodiversity is likely a wise strategy until we know more. We discuss possible strategies below.

An important question is whether loss or reduction of resident, codiversified microbes and associated functions could have a negative health impact on humans. Some properties of the human microbiota appear to have been stable during much of human evolution before industrialization. It is expected that the combined biology and genome of the human body and its commensal microorganisms would have coevolved to maximize human reproductive success (fitness) during that time (59). Because industrialized humans are interested in a long, healthy life, it is worth asking whether long life is consistent with the reproductive success of early humans. The reproductive success of modern hunter-gatherers corresponds to being long lived (as demonstrated by evidence supporting the patriarch hypothesis); therefore, the components of the microbiome that lived within humans throughout most of our existence as a species likely promote biology consistent with a long, healthy life (60).

From the microbial point of view, a bacterial species is chiefly concerned with making more of itself. Therefore, it is worth considering whether it is possible for members of the microbiota that increase host health and longevity to arise. In other words, the question is not only whether the interests of host and microbiota are aligned (i.e., to promote a long, healthy life of the host), but whether microbes that promote the health and longevity of their hosts are retained and favored over evolutionary time.

Gut-resident microbes that improve host health and life span are most likely to arise when the health-promoting function does not incur a short-term fitness cost to themselves (61, 62). For example, imagine a microbial pathway that not only generates energy for the microbe by fermenting a dietary complex carbohydrate but also produces a fermentation end product that can be absorbed by the host and play beneficial metabolic and/or regulatory roles. These microbes would contribute to host health without incurring a fitness cost and could be selected over time as a result of host fitness, longevity, and transmission to offspring and other individuals. We might expect that loss of these coevolved microbes and associated functions would have a negative health impact.

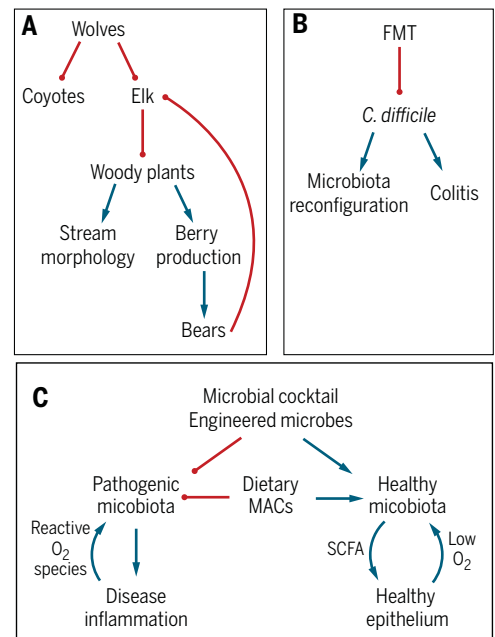
The industrialized microbiota could be considered better adapted to an industrialized host lifestyle by harboring more resistance to antibiotics and being less proficient at dietary fiber degradation. However, such a microbiota may not be optimized for our health.

Fig. 2. Interaction networks in Yellowstone and the gut microbiota. (A) Gray wolves were introduced into Yellowstone National Park in 1995 to control the swelling elk population (105). The rewilding of Yellowstone set off a trophic cascade that resulted in a decreasing elk population (thereby promoting new growth in aspens), an increase in berries available to bears, and stream morphology changes caused by increased woody plants (64). This provides an example of how wildlife management can be used to restore a more diverse and perhaps functional ecosystem, as well as how reintroduction of species into a habitat can lead to unanticipated changes to that ecosystem. (B) Rewilding of a *C. difficile*-infected microbiota by FMT results in largely predictable outcomes in host health, but the specifics of the resulting microbiota composition are difficult to predict. (C) Long-term strategies for managing the microbiota include precision approaches of adding defined cocktails of microbes, engineered bacterial species, and improving ecosystem habitat quality. For example, increasing dietary MACs encourages commensal growth and provides fermentation end products such as butyrate to the epithelium, which can help keep oxygen tensions lower in the gut and prevent the growth of facultative anaerobes with pathogenic potential (106).

Strategies to protect and, when appropriate, restore the microbiome

Learning how to minimize harm to an ecosystem is an easier prospect than rebuilding one that has deteriorated; however, the realization of an ecosystem’s importance often only becomes apparent after major change has taken place. In the case of the gut microbiota, we may have to confront the daunting task of reconfiguring an ecosystem that we are just beginning to understand. Biodiverse ecosystems are characterized by complex networks of interactions; delete or add one node and the cascade of changes through the network of interactions can be difficult to anticipate. Predicting ecosystem changes from species reintroduction, such as wolves into Yellowstone National Park, is a challenge long faced by conservation biologists (63, 64) (Fig. 2A).

Fecal microbiota transplantation (FMT) is an example of how ecosystem remodeling through multispecies rewilding can be applied to the gut microbiota. In this procedure, all of the bacterial species of a healthy human donor’s stool microbiota are introduced into a diseased recipient in an attempt to reconfigure a maladaptive ecosystem (Fig. 2B) (65). FMT has been highly effective in treating *Clostridium difficile* infection (CDI) refractory to conventional antibiotic-based treatment (66). Although this procedure cures CDI, the addition of hundreds of microbial species into an equally complex, although disrupted, ecosystem results in an unpredictable community that is composed of strains from the donor,



recipient, and other sources (67, 68). CDI represents an extreme case of ecosystem disruption; therefore, the lack of precision in dictating the resulting community after ecosystem rewilding is clinically tolerable, as almost any resulting microbiota configuration lacking or minimizing *C. difficile* is preferred. However, FMTs are not an ideal long-term solution for the treatment of many diseases. In many cases, they are simply ineffective, and in others, the unintended consequences may include transmission of antibiotic-resistant microbes or other infectious agents and the transference of unwanted phenotypes from the donor (69). Gut microbiota rewilding through FMT has currently only been consistently successful for *C. difficile* cases. Similar to cases of animal reintroduction in macroecosystems, success as defined by the ability of these reintroduced species to thrive has been mixed (70).

Targeted rewilding through discrete changes in habitat quality or the introduction of specific species chosen based on known interactions may be a more predictable and successful approach to ecosystem management in a disrupted gut microbiota. Habitat quality is a key element of success in macroecosystem restoration and is also an important consideration in the gut (71). Ecosystems are made up of interacting species and their physicochemical environment. Factors that influence the suitability of the gut habitat, including temperature, pH, osmolality, redox status, water activity, and chemical and nutrient availability, will likely affect the success of microbiota reconfiguration efforts. Mice chronically infected with *C. difficile* can be effectively treated using a diet containing MACs. This simple change to habitat quality enabled the recovery of a robust indigenous community and re-established important functions such as short-chain fatty acid (SCFA) production (72). Diet can also create a niche for a newly introduced microbial strain to colonize. For instance, feeding mice the seaweed polysaccharide porphyran allowed engraftment of a porphyran-utilizing *Bacteroides* strain (73). This example of engrafting a new species into a microbiota may provide a strategy that can be extended to help targeted rewilding (Fig. 2C).

An additional challenge to managing ecosystems is identifying the features within an ecosystem that are “beneficial” and thus worthy of conservation. One strategy used by ecologists is to assess the “services” provided by an ecosystem. Ecosystem services, popularized in the Millennium Ecosystem Assessment, enable value to be placed on different components of an ecosystem (74). For example, if a lake provides fresh drinking water and recreation (swimming, fishing), then pollution of that lake would put those services in jeopardy. Likewise, we can consider the ecosystem services supplied by the gut microbiota (75) (Fig. 3).

However, determining whether a microbiota ecosystem service is beneficial is difficult enough in itself, and establishing whether this benefit is universal or specific to a subpopulation of people or even only one individual, a developmental period of life, or during disease or reproduction adds complexity. For example, extraction of calories was an important microbiota ecosystem service rendered in the preindustrialized world, but when eating modern, calorie-dense foods, this service becomes less important.

Studying microbiota configurations in different contexts may reveal associations that are positive for human health. For example, work on the gut microbiota in individuals undergoing immunotherapy to treat cancer has shown associations between specific microbiota components and improved outcomes (76). Although many specifics remain to be determined, these findings are consistent with the ability of different microbiotas and their services, such as SCFA production, to alter host immune status and function. Unfortunately, such observational work is usually conducted on people living in industrialized countries and therefore is limited in the microbiota configurations and features that are queried.

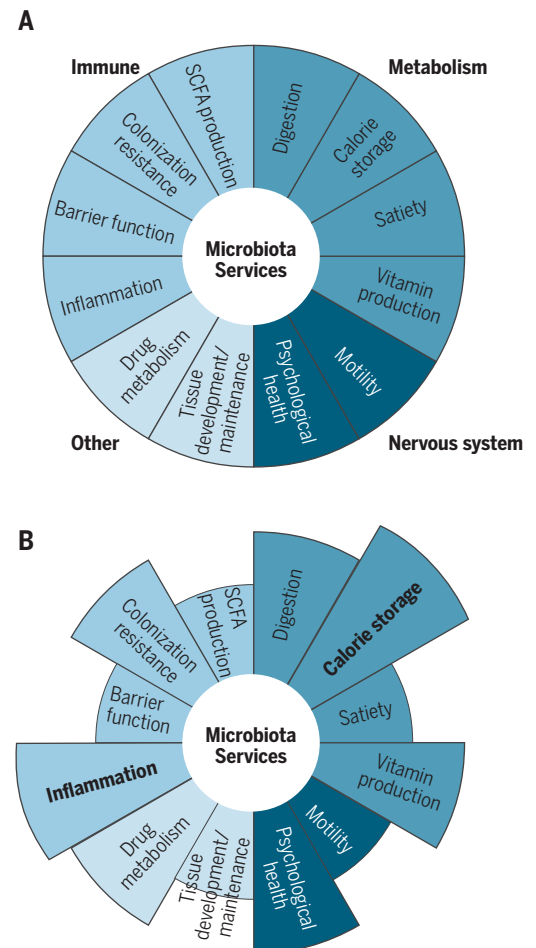
If humans have developed a dependence upon microbiota services that have been lost during industrialization, then might reintroduction of these services be analogous to complementing a lost portion of human biology and provide broad benefit? Even if this is not the case, given the recent success of prophylactic antibiotics in low- and middle-income countries in improving health and reducing mortality in children, rewilding the microbiota after treatment using defined key strains may become a standard treatment to aid in ecosystem recovery (77). Should this be the case, then considerations of how to make reintroductions self-sustaining, especially in the face of spreading industrialization, will be important.

Toward a more sustainable relationship with our microbiota

The goals of a managed microbiota should be to optimize ecosystem services to prevent disease and improve health and longevity. Optimization requires precise, targeted approaches that consider an individual’s genotype, microbiome, or subcategory of disease. Given the large global health impact, strategies to protect the microbiome in all populations should

Fig. 3. Ecosystem services of the gut microbiota.

Identifying the benefits provided by the gut microbiome to human health is one way to determine when the ecosystem is functioning well. (A) List of benefits provided by the gut microbiota. This list is not intended to be comprehensive, and the categorization is only one of many possibilities, but it is presented as a potentially useful framework for conceptualizing how to value specific features of microbiota. (B) Current data suggest that, along with the shift in the composition of the industrialized microbiota, certain services may be lost or out of balance, resulting in suboptimal states of host physiology or disease. A more nuanced understanding of which services are beneficial and in what context will be enabled by longitudinal high-dimensional profiling of microbiome and host biology combined with long-term monitoring of health in humans.



Box. Sustainable ecosystem management approaches.

As we continue to learn of the multitude of benefits afforded by our microbial symbionts, developing alternative strategies to manage microbial ecosystems will enable us to promote short- and long-term public health priorities simultaneously (87). Listed here are a few examples of successes in using beneficial microbes to manage microbial ecosystems.

Wound healing

Sterility in skin-injury repair has been viewed as an important factor in effective wound healing. However, maintaining a sterile wound-healing environment is a difficult prospect considering the exposure of most wounds to the environment (88). Recent evidence suggests that populating wounds with commensal microbes can reduce infections after surgery and minimize the need for antibiotic treatment (89). Similar strategies are also being tested in treating skin conditions including atopic dermatitis (clinical trial NCT03018275) and acute wounds (90).

Probiotics in hospital cleaning

Health care-associated infections are pervasive in both high- and low-income countries and are a leading cause of death in the United States (91). Germicidal treatments of hospital surfaces are not completely effective, leaving behind dangerous pathogens, some of which can inhabit surfaces for months and also lead to increasing antibiotic resistance. The use of probiotic-containing cleaners can be an effective, alternative method to decontaminate hospital surfaces that does not select for antibiotic-resistant strains (92).

Food safety

Concerns over increasing antibiotic resistance, consumption of antibiotic-laden meat, and antibiotic-induced reduction of natural resistance to pathogens have led to the exploration of alternatives to antibiotics in livestock. Probiotic use in chickens has resulted in better growth rates, reductions in pathogen load and antibiotic resistance genes, and improved egg quality (93, 94). Probiotics have also been used to prevent infections and improve milk production in dairy cows and to aid growth in beef cattle (95). Use of probiotics is also beneficial in aquaculture, improving water quality, resistance to pathogens, and growth (96).

Fighting infections in humans

There is growing evidence that the use of beneficial bacteria is a promising path forward for managing pathogenic microbes in humans (97). Probiotics can reduce the duration and severity of infectious diarrhea and may be an effective alternative to antibiotics in the treatment and prevention of bacterial vaginosis (98, 99). A synbiotic mixture of *Lactobacillus plantarum* and fructo-oligosaccharides reduced the incidence of sepsis and lowered rates of respiratory tract infection in a cohort of infants from rural India (100). The use of bacteriophage to control pathogens, especially those that are resistant to multiple antibiotics, is another emerging alternative with recent success (101).

Priming an ecosystem to fight cancer

Antibiotics are commonly used in cancer treatment to minimize the risk of infection in a patient population with a disrupted immune system. However, in animal models, antibiotic treatment can alter the microbiota in ways that reduce treatment efficacy (102, 103). In fact, specific manipulation of the microbiota improved immunotherapy-based tumor control in a mouse model of melanoma (102, 103). Optimization of the microbiota to optimize immune status, whether augmenting immunotherapy or enabling bone marrow transplantation, will likely be integral to the future treatment of diseases such as cancer.

C-section delivery

Given newly acquired data about the importance of early microbiota assembly in the health of the infant, a rethinking of medicalized birth is warranted. A recent pilot study showed that infants delivered by C-section who were seeded with their mother's vaginal microbes developed microbiota more closely resembling those of vaginally delivered infants (104). Future studies are required to determine whether vaginal seeding after C-section delivery provides any lifelong health benefit to the infant.

be considered to maximize the palette of microbial and molecular tools available. Efforts are under way to archive the microbial diversity found in the gut of humans around the globe (35, 36). Whether these efforts will result in new therapeutics remains to be seen, but at

the very least they provide a time capsule of microbial diversity in a rapidly industrializing world. Industrialization of the microbiome, and its accompanying loss or reduction of certain species, can occur on a time scale of months within an individual, creating some

urgency for the banking of vulnerable species (78). An additional challenge is navigating the changing restrictions on the distribution of bacterial strains for research and therapeutic development while protecting the rights and recognizing the contribution of the people from which they came (79, 80).

Reshaping ingrained aspects of industrialized societies to moderate practices that have negative impacts on the microbiota will be a challenge but will be more practical than reversion to preindustrial practices (see Box: Sustainable ecosystem management approaches). Antibiotic use will remain an important aspect of industrial life; however, regulation in clinical and agricultural settings is needed to maintain efficacy and to protect the microbiome. Similarly, rationally engineered microbial “cocktails” or fermented foods could offer safe microbe exposure to compensate for sanitization. Government subsidies similar to those provided for certain crops could be justified to make MAC-rich and fermented foods cheaper and more widely available. Until food policy reflects the findings of biomedical research, short-term solutions, such as supplementing processed foods with MACs or probiotic bacteria, could provide a gradual progression toward health-optimizing food systems in industrialized countries.

Expanding cohort and interventional studies in humans from a wide representation of humans while simultaneously documenting microbiome and health changes is key for healthy, sustainable microbiota. Numerous associations have been made between the microbiota and human disease, but additional microbiome datasets from longitudinal, prospective observational and interventional studies of humans will provide insight into causal relationships. High-resolution measurements of host biology, including “omics” approaches and high-dimensional immune profiling, will be important to elucidate the specific lifestyle practices that lead to the most meaningful microbiome changes for human health (44, 81, 82). Animal models informed by human-derived data can be used to perform controlled studies with the goal of developing strategies to rebuild and maintain a healthy microbiota (83).

A connection with the greater ecosystem

Some of the specific forces that are bad for Earth appear also to harm our microbiota. For example, animal meat production removes forest habitat for pasture and results in increased methane production. Excessive meat consumption has been coupled to trimethylamine-*N*-oxide (TMAO) production by the microbiota, and TMAO is a risk factor for cardiovascular events (84). It may be wise to approach climate and health and microbiota sustainability simultaneously to identify solutions that align

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