

the gut microbiome. However, across host species, a handful of Bacteria and Archaea, with known importance for health, have emerged as heritable and associate with host genes related to immunity and diet. These interactions may be fairly sensitive to diet, making the gut microbiome a tractable therapeutic target. The field of microbiome GWAS is in its infancy. Developments in sample acquisition, data generation, and analysis will continue to reveal informative and biologically relevant associations between taxa and host genetic variants. These associations, which underlie interactions yet to be described, are the signatures of an ongoing coevolution between host and microbiome.

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REVIEW

Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens

Eric G. Pamer

The intestinal microbiota, which is composed of diverse populations of commensal bacterial species, provides resistance against colonization and invasion by pathogens. Antibiotic treatment can damage the intestinal microbiota and, paradoxically, increase susceptibility to infections. Reestablishing microbiota-mediated colonization resistance after antibiotic treatment could markedly reduce infections, particularly those caused by antibiotic-resistant bacteria. Ongoing studies are identifying commensal bacterial species that can be developed into next-generation probiotics to reestablish or enhance colonization resistance. These live medicines are at various stages of discovery, testing, and production and are being subjected to existing regulatory gauntlets for eventual introduction into clinical practice. The development of next-generation probiotics to reestablish colonization resistance and eliminate potential pathogens from the gut is warranted and will reduce health care–associated infections caused by highly antibiotic-resistant bacteria.

Antibiotic treatment has saved millions of lives. Penicillins, sulfa drugs, macrolides, aminoglycosides, quinolones, cephalosporins, and carbapenems are used to “target” pathogens that cause potentially lethal infections, resulting in marked reductions in morbidity and mortality. None of these antibiotics, however, are selective for pathogens, and their administration leads to collateral destruction of commensal bacterial populations constituting the microbiota. Furthermore, many pathogens have acquired resistance to antibiotics, reducing treatment options and cure rates in a broadening range of clinical settings. The impact of broad-spectrum antibiotics on commensal inhabitants of our mucosal surfaces, in particular the gastrointestinal tract, has increasingly been the focus of laboratory investigation (1–3). It is well appreciated that a side effect of antibiotic treatment is increased susceptibility to a range of bacterial infections (4). An intact microbiota can exclude invading bacteria by direct and indirect mechanisms that, in aggregate, provide “colonization resistance.”

Although not a new idea, administration of live bacteria to compensate for loss of commensal microbes and colonization resistance after antibiotic treatment is becoming increasingly plausible, largely because the bacterial species that promote high-level colonization resistance to infection are being defined (5–9). The effectiveness of these bacterial species is impressive, and (for the most part) these organisms are not associated with disease states, nor do they express virulence factors associated with pathogenic bacteria. This review summarizes recent studies identifying protective commensal bacterial species and discusses the need for a development path for

these potential next-generation probiotics that demonstrates their effectiveness, ensures their safety, and promotes their eventual production, distribution, and affordability.

Colonization resistance mediated by commensal bacteria

Not long after antibiotics were introduced for the treatment of bacterial infections, investigators noted that antibiotic administration to animals markedly reduced colonization resistance against a range of pathogens. Early studies demonstrated that antibiotic administration to mice or hamsters rendered these animals more susceptible, by as much as six orders of magnitude, to infection by common enteric pathogens (10–13). More than 50 years ago, it was found that loss of obligate anaerobic bacterial populations from the lower gastrointestinal tract strongly correlated with susceptibility to infection, which suggests that these commensal organisms were providing colonization resistance (13). Compositional analyses of colonic microbial populations in humans after antibiotic treatment demonstrated that loss of obligate anaerobes frequently results in expansion of γ -proteobacteria and enterococci; these findings suggest that the complex, pre-antibiotic commensal microbiota suppresses the expansion of the oxygen-tolerant bacterial species (14, 15).

Microbiota destruction and antibiotic-resistant infections

Increasing antibiotic resistance, according to the World Health Organization, is one of the most important threats to human health (www.who.int/entity/drugresistance/en). Bacterial resistance to antibiotics has become a formidable problem for the treatment of many infections. A subset of these infections—indeed, some of the most antibiotic-resistant forms—occur in hospitalized patients, where they achieve very high densities that facilitate patient-to-patient spread. Extended-spectrum β -lactamase (ESBL)–producing Enterobacteriaceae,

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carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant enterococci (VRE), and *Clostridium difficile* are listed by the Centers for Disease Control and Prevention (CDC) as urgent and serious threats, and they have become so common within hospitals that donning of gloves and gowns to visit patients is now practically routine.

A seminal clinical study investigating the impact of different antibiotics on the density of colonization by VRE demonstrated that an antibiotic's ability to destroy obligate anaerobes correlates with VRE expansion (16). A critical point is that the antibiotic that promotes expansion of an antibiotic-resistant bacterial species may not be the one it is resistant to (such as vancomycin in the case of VRE), but rather an antibiotic that kills bacterial species that provide colonization resistance. The density of colonization by VRE approaches 10^{10} colony-forming units per gram of intestinal content, which leads to high rates of transmission within a hospital setting. Studies focusing on patients undergoing bone marrow transplantation demonstrated that many patients develop intestinal domination with VRE and that bacteremia strongly correlates with preceding intestinal domination (2). Administration of an antibiotic with high specificity for obligate anaerobic bacteria was the major risk factor for development of VRE intestinal domination (17).

Antibiotic-resistant Enterobacteriaceae were also found to dominate the intestinal tract in bone marrow transplant patients and to correlate with the development of bacteremia (17). It remains unclear whether bacterial species that confer coloni-

zation resistance to VRE similarly protect against Enterobacteriaceae such as antibiotic-resistant *Klebsiella pneumoniae*. However, at least in mouse models, reestablishment of a normal microbiota in VRE- or *K. pneumoniae*-dominated mice by transplantation of feces from antibiotic-naïve mice leads to the elimination of both bacterial species (18). With respect to VRE domination, deep 16S rRNA gene sequence analysis demonstrated a strong correlation between the presence of bacteria belonging to the *Barnesiella* genus and colonization resistance to VRE (8). Whether *Barnesiella* strains directly mediate VRE clearance or work together with other commensal bacterial species to establish colonization resistance remains to be determined. Although the effectiveness of the microbiota in protecting humans against infection by antibiotic-resistant bacteria is unknown, two recent reports suggest that reestablishment of a diverse microbiota reduces intestinal colonization by VRE and antibiotic-resistant *Escherichia coli* (19, 20).

Clostridium difficile is perhaps the best-known pathogen associated with infections that follow antibiotic-mediated damage to the microbiota. The ability of normal fecal microbiota to provide colonization resistance against *C. difficile* has been suspected for many decades but was finally proven in a randomized study (21). Tvede and colleagues demonstrated nearly 30 years ago that administration of a cocktail of 10 commensal bacterial species, including some obligate anaerobic bacteria, could cure *C. difficile* infection in patients (22). Subsequent studies from several laboratories have demonstrated that even smaller consortia

of commensal bacterial species can provide protection against *C. difficile* infection (5–7, 9). A recent study identified *C. scindens*, an obligate anaerobic bacterial species that inhabits the colon and that has the rare ability to convert primary to secondary bile salts, as highly associated with resistance to *C. difficile* colitis in mice and humans (7). Administration of *C. scindens* to susceptible mice corrected the deficiency in secondary bile salts and rendered them more resistant to *C. difficile* colitis. Other studies have demonstrated that commensal bacterial strains can introduce sialic acids into the gut lumen, a potential energy source for invading pathogens, and that antibiotic administration transiently increases sialic acid levels, thereby enhancing *C. difficile* growth (23).

Microbiota-mediated colonization resistance against pathogens such as VRE, *K. pneumoniae*, and *C. difficile* is often indirect—for example, by inducing antibacterial factors such as RegIIIγ (24), a C-type lectin that selectively kills Gram-positive bacteria (25), or by modifying host factors such as bile salts to render them toxic to other bacteria (7) (Fig. 1). On the other hand, inhibition can be more direct, such as by nutrient depletion (26, 27) or potentially by direct attacks (e.g., by the type 6 secretion systems harbored by some bacterial species that enable them to attack and kill other bacterial species) (28). Although the mechanisms underlying colonization resistance are complex and remain incompletely defined, there is little doubt that high levels of colonization resistance can be induced by transfer of specific commensal bacteria to vulnerable individuals, and that the degree of colonization resistance—with reductions in colonization density exceeding six orders of magnitude—resembles the degree of resistance induced by some of the most effective vaccines. Thus, from a clinical standpoint, the development of commensal bacteria as preventive and therapeutic agents is a high priority.

Correcting colonization resistance to reduce antibiotic-resistant infections

A document published in 2013 by the CDC outlined the major antibiotic-resistant pathogens that are continuing to emerge as threats to human health (www.cdc.gov/drugresistance/threat-report-2013). Recommendations to combat the progression of antibiotic resistance included barrier and hygiene approaches to reduce transmission, limits on antibiotic use, and development of new and more effective antibiotics. A major concern with these approaches, however, is that antibiotic resistance has grown despite their implementation. Recently, the White House provided a national action plan for combating antibiotic-resistant bacteria, which included specific milestones that introduced the potential role of the microbiome and the microbiota in combating antibiotic resistance (www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf). The plan calls for the “characterization of the gut microbiome of at least one animal species raised for food, to determine

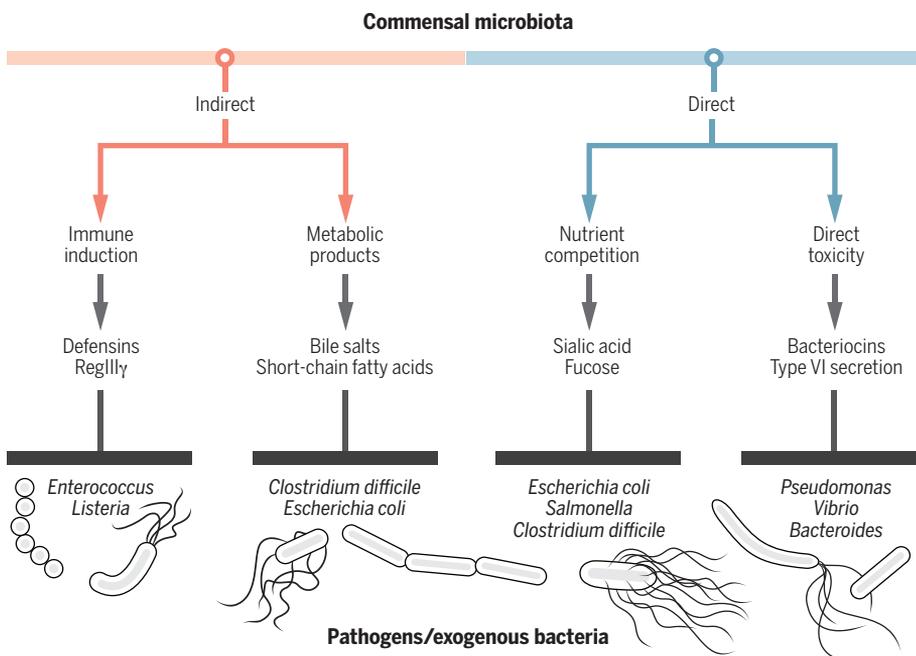


Fig. 1. The intestinal commensal microbiota provides colonization resistance against a wide range of pathogens by indirect and direct mechanisms. Commensal bacteria activate innate immune defenses in the mucosa, produce or modify host-derived metabolites, deplete nutrients, or produce substances that are directly toxic to competing bacteria. These mechanisms in aggregate can induce a high level of resistance against colonization by exogenous bacteria.

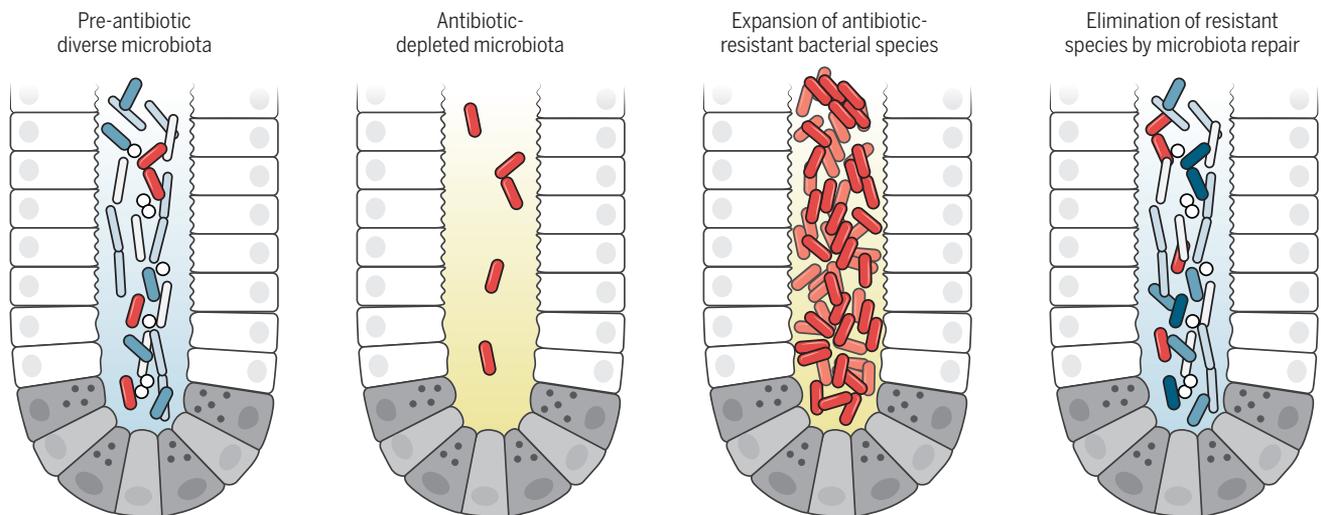


Fig. 2. Antibiotic treatment eliminates many commensal bacterial species from the gut lumen and reduces antimicrobial defenses. Antibiotic-resistant bacterial species can thrive, undergo expansion, and traverse the intestinal epithelial barrier. Antibiotic-induced microbiota defects and the resulting loss of colonization resistance can be corrected by administration of commensal bacterial species.

how antibiotic treatments disrupt normal gut bacteria and how animal growth might be promoted—and bacterial diseases might be treated—without using antibiotics. USDA, in consultation with NIH and CDC, will support research to map the gut microbiome using metagenomic techniques and big data analysis tools” and “developing products that restore or preserve beneficial bacteria in human and animal microbiomes and prevent colonization with harmful bacteria (e.g., probiotics, prebiotics, or synthetic microbiota).”

The mention within the White House document of microbiome-derived probiotics as a potential intervention for dealing with antibiotic resistance is important, and the proposed NIH support for basic and clinical studies to investigate the relationship between the microbiome and antibiotic resistance will undoubtedly move this field forward and lead to new probiotic agents. Although commensal bacterial strains that confer colonization resistance are referred to as probiotics below, they differ substantially from probiotics that are currently marketed. Recent studies confirm the original suggestion that obligate anaerobes are the major contributors to colonization resistance (5–7).

Probiotics: From Metchnikov to Activia

The idea that administration of live bacteria to humans can lead to health benefits likely originated with Élie Metchnikov, a Nobel laureate in 1908. Toward the end of his career, he became fascinated with the longevity of yogurt-eating people in Bulgaria (29). He postulated that lactate-producing bacteria were health-promoting and that other bacteria inhabiting the host were responsible for age-related decompensation and tissue destruction. A century later, this general notion remains popular and has led to the concept that certain bacteria—in particular, lactate-producing genera such as *Lactobacillus*—promote health and thus are referred to as probiotics (30). Other pro-

biotic bacteria, such as Bifidobacteria, have similarly been proposed to enhance health and have recently been associated with enhanced responses to cancer immunotherapy (31) and resistance to infection by enteropathogenic *Escherichia coli* (32) in animal models. Despite the popularity of these probiotics, there is little solid evidence in humans of their effectiveness in enhancing health, promoting longevity, or reducing infections.

Worldwide, probiotics are a big business, with more than \$30 billion in sales annually. Because specific health claims are not made, most probiotics are not regulated as drugs by the U.S. Food and Drug Administration. However, at times manufacturers cross the line, as occurred with Activia yogurt in 2010. In that case, ingestion of Activia, which contains *Bifidobacterium*, was advertised to reduce bowel transit time, but the claim had not been substantiated by clinical studies (www.fda.gov/news-events/press-releases/2010/12/dannon-agrees-drop-exaggerated-health-claims-activia-yogurt) and was challenged by the U.S. Federal Trade Commission. The exaggerated health claims were dropped and the parent company, Danone, was fined roughly \$35 million.

The limited regulation of probiotics has occasionally resulted in exaggerated claims that have left at least some health professionals skeptical of the entire field. The recently characterized bacterial species that constitute a small fraction of the commensal microbiota but have been shown in the laboratory to provide colonization resistance will be new members of the probiotic club; presumably, specific claims about their benefits will be substantiated by careful clinical studies to demonstrate safety and effectiveness.

Next-generation probiotics: Clinical studies of safety and effectiveness

Movement of laboratory discoveries to the clinic requires clinical trials, safe manufacturing, distribution, and, ultimately, delivery to the patient.

Development and safe delivery of a medicine consisting of live bacteria poses special but not unprecedented challenges. For example, live *Mycobacterium bovis* BCG is currently being used and is FDA-approved for treatment of superficial bladder cancer (www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM163039.pdf), and live bacterial vaccines such as the typhoid vaccine (www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm201437.htm) have been developed and administered. Because next-generation probiotics will make health claims (i.e., to treat or prevent a disease), the FDA will regulate their progression to the clinic. Probiotic bacteria that treat or prevent *C. difficile* or that reduce intestinal colonization with highly antibiotic-resistant pathogens would be classified as drugs and should therefore be rigorously tested for effectiveness and safety.

That said, there are many different stringencies of FDA regulation, depending on the potential risks associated with the drug and the specificity of the health claims. Food supplements are regulated by the FDA, but mostly at the level of ensuring proper branding and lack of “adulteration” (www.fda.gov/Food/DietarySupplements). Commercially available homeopathic agents make specific health claims but have generally not been regulated by the FDA because of their assumed lack of toxicity. However, even homeopathic agents occasionally result in toxic reactions (33). The line distinguishing a health claim that defines a substance as an FDA-regulated drug versus a claim that is more general and not requiring FDA regulation is, to say the least, unclear.

Clinical studies to demonstrate safety and effectiveness leading to eventual FDA approval are expensive and are generally beyond the capacity of an academic research laboratory. Giving companies incentives to perform these studies requires some form of protection, usually defining a drug

as intellectual property through a patent that prevents, for a defined period of time, competitors from producing and selling the same drug without having shouldered the development costs. Intellectual property can be thought of as a creation or invention that resulted from intellectual creativity that yielded a material, or property, that did not exist prior to its invention. In the field of biomedicine, a typical example of intellectual property is an engineered antibody that can be administered as a clinically beneficial drug.

The patenting of a natural product, by contrast, is more controversial and may have an adverse impact on its clinical development. For example, after the sequencing of the human genome in 2001, it was possible to patent individual genes, which restricted the ability of other investigators to study these genes and held back research groups and potential competitors from developing diagnostic tests (34). The U.S. Supreme Court struck down the ability to patent genes in 2013. Bacterial strains that have been genetically manipulated to modify or enhance a specific function have been patented since 1981 (US 4259444 A). Whether unmanipulated bacterial strains isolated from human donors can be patented and protected as intellectual property is unclear. Recently, however, a patent has been issued to protect a consortium of genetically unmanipulated bacterial spores isolated from human feces (US 8906668 B2).

Given the potential difficulties associated with patenting bacterial species, commercial development of colonization resistance–promoting bacterial strains will be challenging. One example of an unpatented drug being brought forward is Taxol, a natural product (paclitaxel) that was purified from the Pacific yew and is an effective treatment for some cancers (35). In this case, production and delivery of Taxol by a major pharmaceutical company was promoted by an unusual 5-year guarantee of exclusivity that was extended another 5 years through a series of legal maneuvers.

Producing and delivering probiotic bacteria

Unlike chemical drugs, whose composition and purity can be determined with precision, live bacteria must be cultured, often in complex media, and, even if maintained in pure form, can mutate and either gain or lose functions upon extended culturing. Thus, guaranteeing uniformity, purity, and effectiveness becomes a substantial challenge that can be overcome with a high level of vigilance. Repopulating the human gut with commensal bacterial species has been performed by infusion of fecal material to the upper gastrointestinal tract by nasogastric tube (27) and to the lower gastrointestinal tract by colonoscopy or enema (36). Recently, capsules containing spores isolated from human feces have been administered orally and have effectively treated recurrent *C. difficile* infection (37). These results suggest that administration of probiotic commensal bacteria can occur by different routes; orally administered capsules likely represent the simplest approach.

The most common role of next-generation probiotics will likely be preventive rather than therapeutic. Routine administration of bacterial consortia

to hospitalized patients to optimize resistance against infection with antibiotic-resistant pathogens, or to individuals traveling to areas where enteric infections are common, is certainly conceivable (Fig. 2). Replenishment of microbiota after treatment with antibiotics is another intervention that would likely reduce secondary infections. Because these commensal bacterial species have a long history of inhabiting the human intestine and are not associated with diseases or infections, it is unclear whether the FDA might regulate them as loosely as homeopathic agents (33). Similarly, it remains unclear whether next-generation probiotics should be made available on store shelves for over-the-counter purchase or whether they will require a physician prescription.

For now, clinical studies need to be performed to establish effectiveness and safety, and such studies require funding. Extensive analyses of the intestinal microbiota have revealed the impact of distinct commensal bacterial populations on the development of obesity (38), metabolic syndrome (39), intestinal inflammation (40), autoimmunity (41), and potentially even psychoneurologic states (42). The broad impact of commensal bacterial species on a wide range of health issues will require consideration in settings of microbiota reconstitution with designer microbial consortia. Thus, studies of next-generation probiotics will require long-term follow-up to evaluate study participants for development of obesity, metabolic syndrome, or autoimmune diseases and to monitor long-term colonization by probiotic agents.

Conclusion

The discovery that a subset of commensal bacteria can provide colonization resistance against many of the most threatening antibiotic-resistant pathogens causing disease in patients is exciting, and their development as preventive or therapeutic agents is important. For now, we remain in the discovery phase, but commercial interests are already growing, and companies are positioning themselves within the context of the existing rules and regulations for drug development. A rush to protect bacterial strains or consortia as intellectual property is under way and may promote their development as important therapies in the battle against antibiotic-resistant pathogens. On the other hand, as occurred with the patenting of genes, declaring bacterial strains isolated from the microbiota intellectual property may restrict their development. Unlike conventional drugs, commensal bacterial species have coevolved with us and are a normal part of the human superorganism. Indeed, these microbial populations are the product of tens of millions of years of coevolution with humans, and thus their safety might be considered well established. Indeed, it is their absence that is associated with susceptibility to a wide range of infections.

Although protective commensal bacterial strains developed for the resurrection of a healthy microbiota will be considered drugs, the established regulatory hurdles for conventional drug development require recalibration for these normal components of the human superorganism. The

clinical development of these strains and their affordability will also be affected by whether they can be declared intellectual property. The potential for these next-generation probiotics in enhancing resistance to infection and reducing antibiotic-resistant infections is real, and their development should be supported by research funding, as proposed by the White House national action plan, and by the delineation of a regulatory path that balances concerns about safety with expediency.

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Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens

Eric G. Pamer (April 28, 2016)

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