OPINION

The resilience of the intestinal microbiota influences health and disease

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Abstract | The composition of the intestinal microbiota varies among individuals and throughout development, and is dependent on host and environmental factors. However, although the microbiota is constantly exposed to environmental challenges, its composition and function in an individual are stable against perturbations, as microbial communities are resilient and resistant to change. The maintenance of a beneficial microbiota requires a homeostatic equilibrium within microbial communities, and also between the microorganisms and the intestinal interface of the host. The resilience of the healthy microbiota protects us from dysbiosis-related diseases, such as inflammatory bowel disease (IBD) or metabolic disorder. By contrast, a resilient dysbiotic microbiota may cause disease. In this Opinion article, we propose that microbial resilience has a key role in health and disease. We will discuss the concepts and mechanisms of microbial resilience against dietary, antibiotic or bacteriotherapy-induced perturbations and the implications for human health.

The 'insurance hypothesis' states that biodiversity insures ecosystems against decreases in their functionality and is applicable to most natural ecosystems. In the gut, this hypothesis implies that the rich diversity of the intestinal microbiota (the community of microorganisms that reside in the gut) is crucial and protective for sustaining a microbial equilibrium (a stable composition of species in the microbiota) and for the integrity of the mucosal barrier[1–4]. This complex ecosystem of intestinal bacterial communities is characterized by a capacity for self-regeneration, which is also known as the resilience phenomenon. Thus, the intestinal microbiota has the ability to restore its equilibrium after an external perturbation, such as infection with a pathogen or antibiotic treatment.

The theoretical concept of resilience (BOX 1), which is generally described as the capacity of an ecosystem to recover from a modulating perturbation, comprises four crucial layers: latitude, resistance, precariousness and panarchy[5] (BOX 1). These layers will be explained in the context of the intestinal microbiota during health and disease. Perturbations are important modulating elements of all ecosystems (BOX 1). In the gut these perturbations can include acute infectious diarrhoea, dietary life events (for example, phases of malnutrition) and treatment with antibiotics. Although many studies have associated host-specific factors with alterations to the microbiome (for example, through the association of specific genotypes or studies in genetically modified mice), relatively little is known about the context-dependent mechanisms (for example, environmental factors, diet and infection) that control the longitudinal stability and dynamics of the microbiome. In accordance with this, few reviews have explored the concept of microbial resilience[6–8].

In this Opinion article, we focus on the interactions between bacteria, the host and the environment that enable microbial resilience against dietary, antibiotic or bacteriotherapy-induced perturbations, and the implications of microbial resilience for human health. We briefly consider resilience in health and disease before introducing the ecological concepts that explain resilience of the microbiota and consider the mechanisms that contribute to this. Last, we propose how resilience may affect the microbiota during development, antibiotic treatment and bacteriotherapy.

Concepts of microbial resilience

The microbial communities that reside in the human gut are constantly exposed to environmental perturbations. Throughout human evolution, the intestinal microbiota has been challenged by nutrient intake from diverse energy sources and constant exposure to new bacteria, fungi, protozoa and viruses. In the past 50 years, societal and cultural changes have added exposure to antibiotics and the constituents of processed foods and hygiene products (for example, emulsifiers and artificial sweeteners) as novel perturbations of microbial ecology, which have spread with the globalization of the Western industrialized lifestyle[9,10].

Complex ecosystems, such as the microbial communities in the gut, are thought to be able to attain a limited number of stable equilibrium states[7] (BOX 1). The term 'state' actually reflects a dynamic equilibrium, which undergoes constant minor fluctuations that are usually associated with distinct functions (ecosystem services; BOX 1). If ecosystem services are beneficial to the host, the functioning of the ecosystem (including the host) may be considered as a complex symbiosis. However, if the stable equilibrium state is associated with detrimental services then it is considered to be in a state of 'dysbiosis' (BOX 1). Dysbiosis occurs when the microbiota crucially contributes to the manifestation or continuation of a given disease that cannot be attributed to a single bacterial species[11–13]. For example, the intestinal microbiota may contribute to the development of chronic disorders, such as metabolic syndrome or inflammatory bowel disease (IBD).

Thus, understanding the mechanisms of microbiota stability in the face of continuous perturbations is important for human health (FIG. 1).

In ecology, a perturbation is defined as a causal event that can change the immediate environment or directly change the community[14], and can vary in magnitude, rhythmicity and context. Perturbations are often categorized as pulses or presses, depending on their duration[15] (BOX 1). In general, pulse disturbances are discrete short-term events, whereas presses are long-term or continuous.

To understand the reactions to perturbations in the gut, as a complex ecosystem, it is important to understand two general principles of ecology. First, 'resistance' defines the attribute of a given ecosystem to stand unchanged in the face of a disturbance[16] (BOX 1). Second, the term 'resilience' describes the amount of stress that a system can tolerate before its homeostatic state shifts towards a new equilibrium that potentially has different functions and services[7,17] (BOX 1). In this definition, resilience is a complex feature of ecosystems[18,19] that comprises several crucial components (FIG. 2). First, resistance is an important first layer of resilience, as it describes how easily a system can shift away from its stable state. (FIG. 2a,b) Second, the latitude of changes is defined as the maximum extent that a system can be shifted by a perturbation before it loses its property to recover to the initial stable state. Third, the state of precariousness describes the distance from the initial homeostatic state to a threshold of no return (also known as the latitude of changes; FIG. 2d). Fourth, the term 'panarchy' describes the influence that the organizational state of a population (within an ecosystem) has on its ability to cope with stress. For example, in the gut this would relate to the density and spatiotemporal organization of bacterial subgroups[20], which may affect interactions at the population level (FIG. 2). Facing a continuous (press) perturbation (for example, a permanent change in nutrient availability caused by a shift from a carbohydrate-rich diet to a protein-rich diet)[21,22], the composition of the microbiota may adopt a new beneficial or detrimental state (known as 'regime shift'; FIG. 2c,d). In addition, it is part of the plasticity of the normal microbiota to deliver ecosystem services when confronted with a changing environment (known as 'adaptation'; FIG. 2c).

There is a strong relationship between species diversity and ecosystem stability (BOX 1), which is known as the insurance hypothesis. This refers to the buffering capacities of the community to return to a stable equilibrium in response to a perturbation, either through a single stabilizer or through multiple means[23,24]. A community that contains many species is less susceptible to perturbation. This is because as several species compete for the limited resources, these well-adapted species limit the influx or overgrowth of other species[7]. Thus, high diversity and functional redundancy seem to be important factors of microbial resilience. Interestingly, a decreased diversity in the microbiota is associated with several diseases, including obesity, diabetes[25–28], chronic IBD[2,29–32] or recurrent infection with *Clostridium difficile*[33]. A complex and diverse microbiota can be classified into 'enterotypes' or enterogradients, an example of the non-random assemblage of the gut communities. These are clusters of community types that are characterized by the dominance of signature bacterial taxa, including *Bacteroides* and Lachnospiraceae[34,35]. Enterotype-like clusters were observed in humans, chimpanzees[36] and mice[21,37], and shifts between clusters, which correlated with nutritional intake, were demonstrated in longitudinal studies. It has been debated whether the observed clusters are truly discrete or whether they represent gradients around extremes. However, evidence suggests that a distinct number of optimal metabolic assembly states may exist, depending on the main

Box 1 | Crucial terms of the concept of microbial resilience

- Latitude: the maximum degree a system can be shifted by a perturbation before it loses its property to recover to the initial stable state.
- Precariousness: the distance of the initial homeostatic state to a threshold of no return.
- Panarchy: the influence an organizational state of a population (in an ecosystem) has on its ability to cope with stress.

Terms of perturbation

- Perturbation: an external event that causes a distinct selective pressure on the intestinal ecosystem[15,110], also called a disturbance.
- Pulse perturbation: a defined perturbation that is present for a shorter period of time[15] (for example, a short course of antibiotics).
- Press perturbation: a continuous perturbation with a constant level that is maintained over a longer period of time[15] (for example, a permanent shift in dietary patterns or moving to a location with different hygiene conditions).

Terms of response

- Ecosystem stability: the property of a system to maintain or return to an initial state after a disturbance. Stable communities in an ecosystem can be defined in different ways, including the taxonomical or functional persistence of populations through perturbations or over time[111,112]. Over time, the microbiota of an individual may fluctuate to a certain extent, but in the absence of a severe perturbation the microbiota profiles of an individual cluster together distinct from other individuals[113,114]. Thus, microbial stability refers to a dynamic equilibrium.
- Resistance: a measure that describes the property of a community to remain unchanged during a perturbation, sometimes described as a part of resilience[7].
- Resilience: the property of a microbial community that defines how fast, and to what extent, it will recover its initial functional or taxonomical composition following catastrophic perturbation[19].

Terms of functional outcomes

- Stable equilibrium state: a possible dynamic equilibrium that a microbial community may reach during development or after a disturbance[7]. The term takes into account the concept that a limited number of alternative equilibria can be realized, given the requirements of the intestinal habitat. Communities are likely to return to their initial 'attractor' state. The stability of such an equilibrium is unsteady and undergoes constant spontaneous fluctuations.
- Ecosystem service: a term that describes the benefits of the bacterial–host mutualism to its individual members[115]. It often refers only to the net beneficial output of the microbial consortia for the human host.
- Dysbiosis: a term that describes an ill-defined state of the intestinal microbial community, which leads to the loss of intestinal host–microbial balance[116]. It is typically related to a loss of diversity and low-grade spontaneous inflammation at the mucosal barrier. Importantly, this state is linked to numerous human diseases and may itself be highly resilient to external perturbation (for example, therapy).

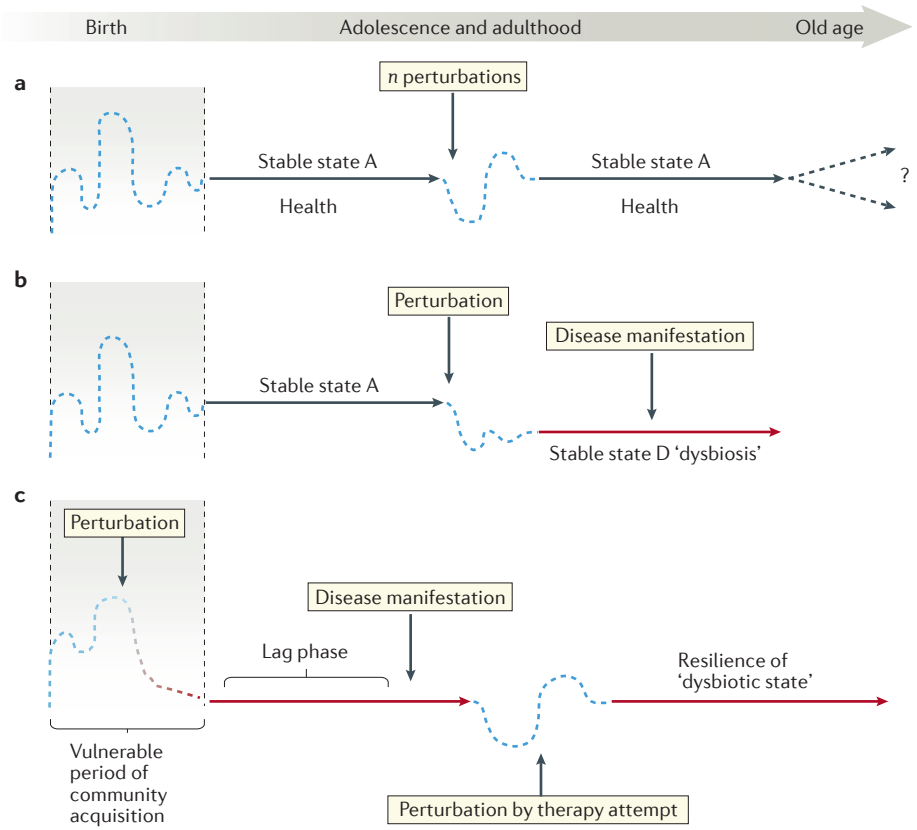

Figure 1 | **Schematic representation of resilience phenomena in health and disease. a** | The structure of the microbial community of an individual is established during the first months of life. During this period of time, larger fluctuations may occur and the individual is particularly vulnerable to external perturbations. Usually, an equilibrium state (stable state A) is attained in adolescence, which remains relatively stable over the lifetime of a healthy host. The depicted stability in the absence of perturbations is, in reality, also subject to constant minor fluctuations. Even in the face of catastrophic external perturbations (*n* perturbations), the intestinal microbiota has a remarkable ability to restore its functional state (stable state A), owing to a marked capacity for self-regeneration (the resilience phenomenon). **b** | Permanent shift to a detrimental equilibrium state (stable state D) termed 'dysbiosis' can occur when resilience of the original community fails. Dysbiosis represents an ill-defined loss of the typical intestinal host–microbial balance and is associated with numerous systemic and local human disorders, from chronic infections or inflammatory diseases (for example, inflammatory bowel disease) to metabolic syndrome. **c** | Disturbances during the vulnerable period may potentially exert long-lasting changes to the structure of the microbial ecosystem, possibly causing a predisposition to chronic disease, which manifests after a lag phase. It is conceivable that such early changes could lead to especially strong resilience of the dysbiotic communities, which would make attempts to restore a normal physiological state particularly difficult.

type of dietary energy at a given time (that is, whether energy is in the form of plants and fibre, or protein and fat of animal origin)[38]. Interestingly, a slight enrichment of inflammatory markers was observed in individuals who have the *Bacteroides*-dominated state, and *in silico* analyses indicated that individuals with the *Bacteroides* enterotype have lower functional redundancy, which suggests lower resilience[39].

Taken together, the resilience of the microbiota determines whether a particular perturbation will permanently shift its stable state or whether it will return to its initial homeostatic state following a disturbance. This has obvious implications for human health. For example, when travelling to a country that has a different level of hygiene or diet, having a healthy microbiota conformation that has high resilience to exogenous challenge might mean protection from food poisoning and infection. Furthermore, when an individual becomes sick with a gastrointestinal infection, resilience also suggests a quick recovery of the microbiota and a fast restoration of normal ecosystem services (that is, of the digestive properties of the gut)[40–43]. In addition, antibiotic treatment (a marked stressor of the microbiota) may lead to the overgrowth of previously rare pathobionts, which are otherwise harmless bacteria that, under certain conditions, can cause disease. However, a highly resilient microbiota can recover to its healthy state. This could be through competition that decreases the number of pathobionts and restores initial homeostasis. In light of the contribution of the microbiota to human disease states, resilience also has a dark side. The acquisition of an unhealthy and dysbiotic microbiota that has a high resilience potential may contribute to the chronicity of human microbiota-associated diseases, such as IBD, obesity and metabolic syndrome.

Mechanisms that shape resilience

Resilience and resistance (BOX 1) are intrinsic properties of communities, including communities of microorganisms. Thus, the composition and diversity of the microbiota are drivers of its resilience potential. Four mechanisms (reviewed in REF. 44) contribute to the assembly of the microbiota: dispersal (new genetic variation; for example, from mutation or the introduction of new organisms), diversification (the movement of organisms through space), drift (stochastic changes over time) and selection (fitness-dependent changes). Perturbations can come under one or more of these categories. For example, the mode of childbirth (that is, vaginal delivery or caesarean section) can cause dispersal (because it influences the transmission of microorganisms from mother to offspring) but also affects selection (by enhancing or diminishing the pool of microorganisms that the offspring can select from). As internal (within the community; for example, among species in the gut microbiota) and external (environmental factors that act on the community; for example, nutrient availability or host immune responses) selection are strong factors for determining the structure of microbial communities, we will focus on these mechanisms in the next sections.

External selection mechanisms. External, mostly host-derived selection mechanisms crucially contribute to the development of microbiota communities[45] (FIG. 3). Importantly, in contrast to a passive abiotic environment, the host can actively shape ecological niches in the gut. Furthermore, many of these shaping principles (for example, mucus composition) are modified in a context-dependent manner following

perturbation. In this sense, the host actively contributes to the resilience potential of the microbiota. First, the host uses several specific effector mechanisms, which have presumably evolved to protect against colonization by pathogens or to select for a beneficial microbiota. These include the controlled release of antimicrobial components of the immune system, such as antimicrobial peptides[46], reactive oxygen species and immunoglobulins. In addition, the production of a specialized mucus layer functions as a protective barrier but also acts as a nutrient source and substrate for bacterial adhesion[47–50] (FIG. 3). The regeneration and differentiation of the epithelial layer, which is responsible for producing most of these effectors, is tightly regulated by bacterial[51,52] and host-intrinsic signalling pathways (for example, signalling mediated by interleukin-22 (IL-22))[53]. Second, the host also controls other important environmental factors and physiochemical properties of the gastrointestinal tract, such as the transit time (peristalsis), pH, bile secretion and the input of metabolic products (nutrition or secondary metabolites), thereby determining the local niche and growth conditions, and thus the composition of the microbiota[20,35,54,55]. An important factor for colonization is the microenvironmental presence of oxygen, which may inhibit the growth of oxygen-sensitive bacteria[56,57]. This factor could determine the succession of bacterial colonizers in the neonatal period or after a perturbation. In support of this, direct colonization of germ-free mice with a strictly anaerobic species of bacteria often fails, whereas secondary colonization with the same species works well after primary colonization with a facultative anaerobic species of bacteria. This is presumably due to the consumption and depletion of oxygen by the primary colonizer, which then facilitates secondary colonization[58]. Diurnal changes in the concentrations and activity of the microbiota are currently emerging as prominent features for the maintenance of host–bacteria symbiosis. Crucial elements of these changes are a cyclic reduction of bacterial load through expulsion[59] (that is, by defecation in the case of the intestinal tract)[54,60] and pulsed nutrient intake[61,62] (FIG. 3).

Internal selection mechanisms. Internal selection mechanisms are the interactions among the microorganisms that comprise the microbiota and drive its community

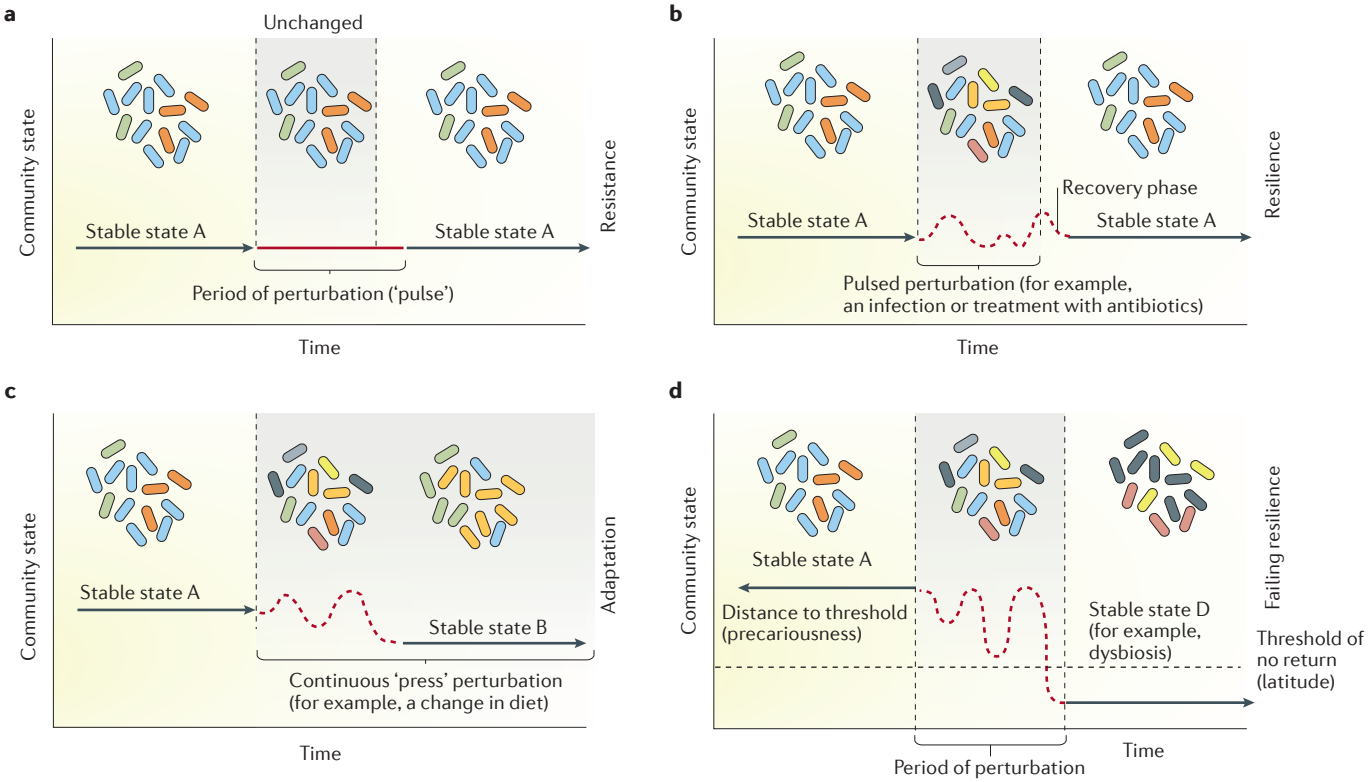

Figure 2 | **Conceptual elements that govern the stability of the intestinal ecosystem.** Several principles contribute to stable ecosystem services of the intestinal ecosystem. **a** | The microbial community withstands an external short-term perturbation ('pulse') without any noticeable change in composition or functional genetic elements (such as a change in gene expression). This theoretical case would refer to a perfectly 'resistant' community. **b** | A short-term 'pulse' disturbance, such as inflammation, infection, acute diarrhoea, dietary life events or antibiotic treatment, disrupts community composition. After a lag phase or recovery, a resilient community returns to normal function and composition (stable state A). **c** | A long-term 'press' perturbation requires the community of microorganisms to adapt its function and can lead to the community adopting an alternative stable and beneficial state (stable state B). It can be assumed that if the selection pressure is released, the alternative state will shift to another stable equilibrium that reflects the plasticity of the ecosystem. **d** | Failing resilience of the initial microbial community (stable state A) facing a perturbation may also lead to an alternative stable but detrimental state ('resilient dysbiosis'; stable state D). The latitude of change describes the threshold of no return, past which the microbial community cannot return to its initial compositional state (stable state A). Precariousness is defined as the magnitude of community shift that is necessary to reach the threshold (for example, the point of no return will be easier to reach in a community that has non-redundant functions, as loss of a function cannot be compensated for). Panarchy is another important layer of resilience that is not depicted in the scheme, as it refers to the spatial and temporal organization of the microbiota, which may be very different in the gut under different conditions; for example, owing to changes in transit time.

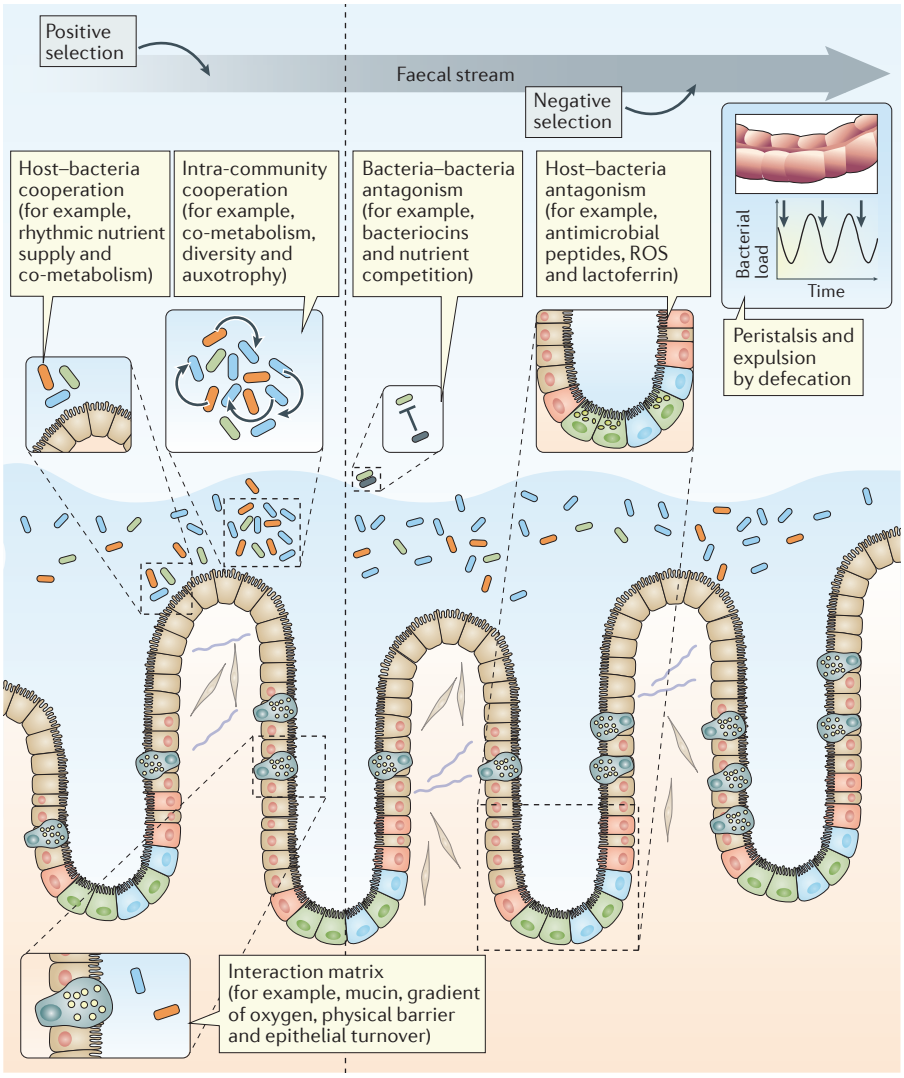

Figure 3 | **Mechanisms of resilience.** Several selection mechanisms guide the stability and resilience of microbial consortia in the intestinal habitat. This includes positive selection from the faecal stream, or by host–bacteria or bacteria–bacteria cooperation. Negative selection mechanisms comprise direct bacteria–bacteria antagonism and the context-dependent expression of antibacterial effectors by the host (for example, reactive oxygen species (ROS) and antimicrobial peptides from specialized Paneth cells). The matrix of the interaction is delivered mainly by intestinal epithelial cells, which secrete the mucus layer. Their regeneration (stem cells (blue) and proliferating zone (red)) and differentiation potential (goblet cells (grey), enterocytes (light brown) and Paneth cells (green)) influence positive and negative selection. Biological rhythms, such as nutrient intake (positive selection) and expulsion by defecation (negative selection; reduction of bacterial load), lead to physiological fluctuations in the microbial communities and are an important principle of the ecosystem.

structure and resilience potential (reviewed in REF. 63). In the intestinal environment, microorganisms can cooperate and compete for resources. For example, auxotrophic bacteria cannot directly synthesize crucial compounds by metabolizing dietary nutrients and rely on the fermentation products of other primary metabolizers, thus creating cooperative metabolic chains (such chains may also involve metabolites produced by the human host). By contrast, several microorganisms may inhabit the same regional or ecological niche and therefore compete for resources; for example, by colonizing the mucus layer and using the same energy substrates[20]. In addition to these factors, a substantial proportion of community members may be dormant or inactive at any given moment in time[64,65]. Dormancy describes a strategy used by organisms to enter a reduced state of metabolic activity[64,66]. Dormancy strategies may be common among communities that live in temporally dynamic environments, as they promote compositional stability in fluctuating conditions[64–66]. Last, bacteria also produce effectors of direct antagonism, such as quorum sensing or quenching molecules, antibiotics or other toxic substances (for example, bacteriocins and metal ion binding proteins), which prevent the growth of competitors, especially at high cellular densities[67–69] (FIG. 3). Together, external and internal selection factors have the potential to substantially affect the resilience of microbial ecosystems in the gut.

Resilience during development

The mammalian newborn contains a simple gut microbial community that has low diversity, low bacterial load (that is the number of microorganisms) and low resilience; therefore, it can be considered a blank sheet for external colonization. Thus, after delivery, any environmental microorganism that the newborn is exposed to that meets the physicochemical requirements of the intestinal environment[45] can colonize the baby. This includes, for example, bacteria from the vaginal and skin microbiota of the mother and/or from breast milk[70]. Succession of the developing microbiota is directional, which means that the growth of certain species requires prior growth of other species. This is, in part, controlled by negative feedback loops, in which one organism alters the environment (for example, by its metabolic activity) so that its own fitness decreases and the fitness of a competing species increases. The genetic make-up of the host is another important factor for determining the succession and selection process of the developing microbiota[71]. This is shown by studies in mice, which have demonstrated the influence of innate immune receptors, mucus or antimicrobial gene loss-of-function variants in the acquisition of the early microbiota[72,73]. Owing to the initially oxidative environment, facultative anaerobic bacteria, such as members of the Proteobacteria phylum, including *Escherichia coli* or *Lactobacillus* spp., are primary colonizers of the intestines of infants. Once established, these bacteria decrease the oxygen concentration in the intestines and thereby promote their own replacement through successive colonization by anaerobic bacteria, such as members of the Bacteroidetes, Actinobacteria and Firmicutes phyla. Therefore, the composition of the gut microbiota markedly fluctuates early in life (FIG. 1), but within the first three years of life microbial diversity increases and the community structure stabilizes. The microbiota is then presumed to steadily

increase its resilience while maturing into an adult-like state[74–76]. Until the microbiota reaches the adult equilibrium, environmental factors, such as mode of delivery (vaginal or caesarean), diet, hygiene and medications (for example, antibiotics), may substantially affect its establishment and maturation[35,55,70,77,78]. Controlled longitudinal experiments are required to investigate the molecular and environmental determinants of the development of the early microbiota in greater detail. Perturbations in the microbiota early in life seem to be particularly important and may have long-lasting effects on host health.

Resilience and antibiotics

The use of antibiotics substantially affects the microbiota. However, although some studies indicate that antibiotics only have transient effects on the microbiota[79], others suggest that antibiotic use permanently changes the microbiome and disturbs gut homeostasis and pathways that modulate the immune response[80–84]. Whether these antibiotic-induced differences in the microbiota and host physiology revert or remain after treatment may depend on whether individuals receive a single dose of antibiotics or whether they are chronically exposed, and also on the age of exposure[85]. It remains unclear whether all of the observed effects on the intestinal microbiota are consequences of the direct action of antibiotics or are the result of secondary effects (such as altered physiochemical parameters in the intestine or the tuning of immune responses). It is also possible that the resilience of the microbiota could affect the response to treatment with antibiotics. Several observational studies have investigated resilience phenomena after antibiotic perturbation in humans. Human volunteers who were treated with the broad-spectrum antibiotic ciprofloxacin for 5 days showed rapid shifts in the community composition of their distal gut microbiota. Although the gut microbiota stabilized following treatment, it remained altered compared with its unperturbed native form. This was due to the failed recovery of several bacterial taxa (for example, *Bacteroides dorei*, *Akkermansia muciniphila* and several *Roseburia* spp.), which suggests that this altered state may also lack several previous community functions[80]. Another study showed that 7 days of administration of clindamycin (another broad-spectrum antibiotic) resulted in a loss of diversity in *Bacteroides* spp. that was not restored, even 2 years after treatment[82]. Furthermore, the widely used antibiotic amoxicillin not only decreases the abundance of *Lactobacillus* spp. in the proximal and distal small intestine but also decreases the expression of MHC class I and class II genes or antimicrobial peptides[84]. Short-term (3 days) treatment with the locally acting antibiotic paromomycin led to incomplete resilience, and thus changes to the composition of the microbiota, in almost all individuals in a healthy volunteer study, but also changed the mucosal antibody repertoire[81]. This demonstrated that lasting effects on the microbiota and intestinal immune responses can be introduced by a single catastrophic perturbation. Similarly, mice treated with paromomycin for 3 days showed that diversified B cell clones were rapidly distributed to other organs (for example, from the gut to the mammary glands). This implies that crosstalk between intestinal mucosal immune cells and the perturbed non-resilient microbiota is an important mechanism for instructing antibody-dependent systemic immune processes[83].

Infection with *C. difficile* is a particularly relevant clinical example of failing resilience, as it almost exclusively affects immunocompromised individuals (for example, newborns and the elderly) after the administration of broad-spectrum antibiotics, such as clindamycin, cephalosporins or fluoroquinolones[33]. Infection with *C. difficile* is often associated with decreased microbial diversity and is thought to occur when there is little competition from commensal microorganisms, thus enabling colonization and overgrowth of the pathogen. Interestingly, a recent report demonstrated that antibiotic-induced depletion of the microbiota specifically led to a decrease in the production of secondary bile acids, which usually inhibit spore germination and the growth of *C. difficile*, thus enabling its colonization[86].

Antibiotic use within the first year of life is associated with an increased risk of the development of chronic inflammatory diseases, such as allergy and asthma[87], IBD[88,89] or metabolic syndrome[90,91] later in life. Paradoxically, antibiotic use per capita is most intensive throughout the first 2 years of life[92]. It is tempting to speculate that failing resilience and an associated decrease in functional redundancy of the intestinal microbiota may be crucial for the observed association. However, the exact mechanisms as to how antibiotic press perturbations (BOX 1) of intestinal microbial communities translate into complex disease aetiologies remain to be determined.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is the transfer of stool, or portions of stool, from a donor to the gastrointestinal tract of a recipient[93]. This approach may transfer certain physiological properties of the donor to the new host, which are thought to depend on the metabolic functions of the transmitted microbial consortia. Animal experiments have shown that the range of transmissible phenotypes is broad, affecting many organ systems other than the intestinal tract[94–96].

FMT is effective at modifying the gut microbiota and acts as a short-term pulse perturbation (acting as dispersal and selection), followed by a recovery or resilience period. Engraftment, which means the colonization success of the transferred microbiota, occurs quickly, with recipient microbial communities resembling the composition of the donor. Notably, FMT has been used to successfully treat recurrent *C. difficile* infection (RCDI) and it leads to the resolution of gastrointestinal symptoms within 2–3 days post-FMT[97–99]. After a transient engraftment of community members from the microbiota of the donor and a concurrent increase in diversity, the microbiome of the recipient generally returns to baseline after FMT, but some donor-specific species can be identified up to 3 months post-FMT in the recipient[98–100]. In a recent study in humans that investigated strain engraftment, donor and recipient strains could coexist; however, the success of colonization was greater for conspecific strains (that is, donor strains that belong to the same species as those present in the microbiota of the recipient) than new species[98]. However, over time, the recipient microbiota gradually returns to its baseline-like state. Given the current lack of conclusive therapeutic effects of FMT for complex diseases (such as IBD), a single short-term perturbation of the dysbiotic microbiota of a patient might be insufficient, but instead repeated FMTs may be required to ensure stable engraftment and a therapeutic value[101].

Clinically, FMT has gained much attention since its use as a procedure to treat RCDI. First described in 1958 as a treatment for pseudomembranous colitis[102] (an inflammation of the colon that is associated with an overgrowth of *C. difficile*), a recent seminal clinical study demonstrated more than 90% clearance of infection after FMT, with several other groups replicating this remarkable success rate[98,103,104]. The overall clinical efficacy in the treatment of RCDI has prompted a wider clinical use of FMT

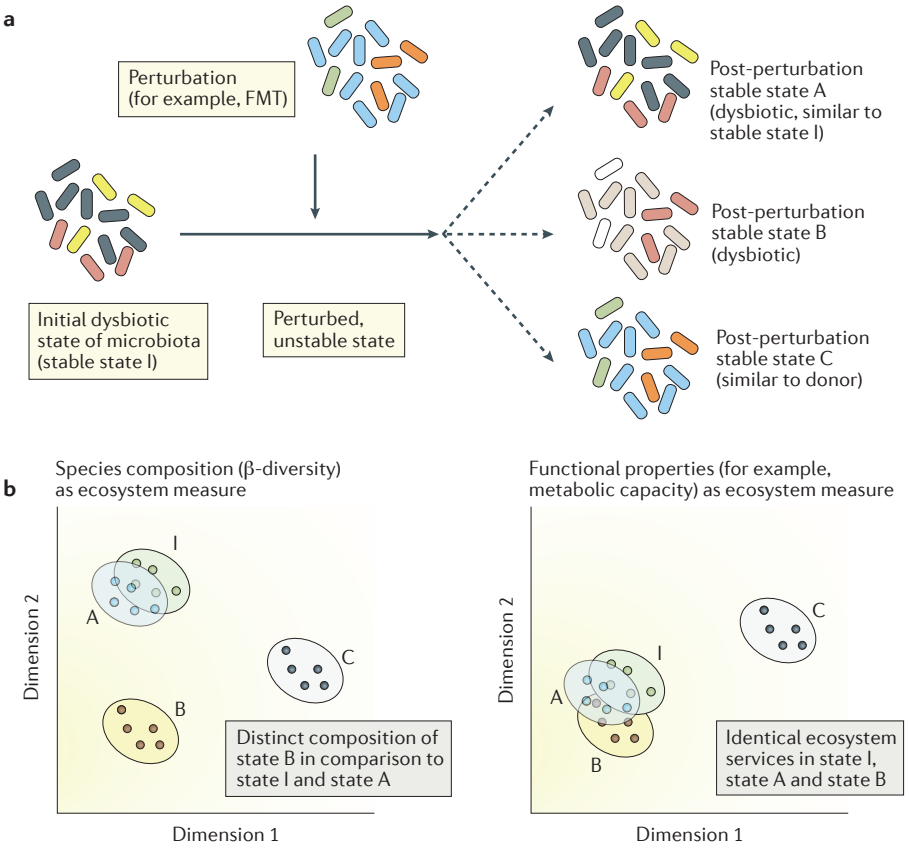

Figure 4 | **Faecal microbiota transplantation as a perturbation to a resilient dysbiotic community.** The interaction between two microbial consortia during bacteriotherapy (for example, faecal microbiota transplantation (FMT)) may be regarded as a complex pulse perturbation, which is carried out to transfer the functional properties of the donor community to a recipient host. **a** | Several hypothetical outcomes are possible. First, the host communities return to their initial dysbiotic state (stable state I and stable state A), as the perturbation is too weak and the transferred microorganisms do not permanently succeed. Second, owing to host intrinsic or environmental factors, the final outcome is the selection of an alternative, but still dysbiotic, state (stable state B). Although distinct in composition, the microbial community would still carry out the detrimental ecosystem service. Third, resilience of the donor community (stable state C) in the new habitat would define a new interaction with long-term transfer of the beneficial properties. **b** | Hierarchical level of the definition of resilience. Resilience can be defined at the species or taxonomical level. In this sense, full recovery would only be obtained if the abundance and composition of the microbiota are identical to its initial state after a perturbation. In conventional β-diversity analyses (left panel; this visualizes the similarity in the composition and abundance of species between different samples), the alternative dysbiotic state B or the eubiotic (healthy) state C would simply be recognized as two distinct distant community types. At the functional level (right panel), the communities in state B and state C are clearly separated. In turn, a functional definition of resilience could hypothetically mean complete elimination of initial bacterial taxa from the microbiota, but full recovery of biological functions and symbiotic interactions with the host. Understanding the functional elements that are necessary for stable homeostasis and correct ecosystem services will thus be important for designing rational bacteriotherapy approaches.

for more complex disease phenotypes in which dysbiosis of the gut microbiota contributes to the disease process; for example, type II diabetes mellitus[93], irritable bowel syndrome[105] or IBD[106–108]. However, the first results for these complex diseases are ambiguous and highlight the differences between treating a chronic infection by a single species of bacteria (low diversity and low latitude) and altering the intricate metabolic and inflammatory properties of a complex intestinal microbial consortium (dysbiosis with high resilience potential) as a whole (FIG. 4).

An important consideration for the transfer of complex bacterial communities is the taxonomic level used to analyse the dynamic equilibrium state before and after the intervention. This is particularly important when considering personalized microbiota interventions as a therapy in the future. How should we measure the 'dysbiotic' state, which has to be shifted in a patient with inflammatory bowel disease? What level of organization (for example, species, family or phylum) has to be corrected and how can we select the microbial elements that are required for individual 'correction' of the ecosystem? Several outcomes of an FMT bacteriotherapy are possible that emphasize the importance of the hierarchical level of observation (FIG. 4). First, the dysbiotic communities are highly resilient and, after a short period of perturbation, return to a highly similar composition (full resilience). Second, after an initial perturbation and owing to intrinsic characteristics of the host or lifestyle factors, a new community is selected that is distinct in composition but shares functional properties (functional resilience), thus dysbiosis persists. Last, the transmitted communities stably colonize and establish a novel eubiotic (healthy) microbiota that has distinct functional properties (resilience of the donor community). Interestingly, recent work showed that the transfer of sterile-filtered faecal material successfully ameliorates RCDI symptoms[109], which indicates that bacterial components, metabolites or bacteriophages may mediate the effects of FMT. Therefore, it is necessary to improve our limited knowledge of the dynamics and molecular language of the forced interaction between two potentially resilient bacterial communities (donor and recipient) during FMT. This will enable the identification of the crucial factors and signalling networks that are involved, which could ultimately lead to the safe and stable transmission of a desired phenotype into the recipient host.

Conclusions and outlook

A stable homeostatic interaction with our microbiota is a key requirement for a healthy human physiology. Resilience and resistance (BOX 1) of the gut ecosystem are important elements of this dynamic equilibrium. Investigating the resilience mechanisms that govern long-term community stability and stable ecosystem services while understanding the countless perturbations of a lifetime are important to understand the full complexity of the intestinal physiology. Although presumably linked to several diseases, from chronic infections to metabolic syndrome and IBD, the exact functional details of failing resilience and the methods for predicting its essential components (resistance, latitude, state of precariousness and panarchy) in a clinical setting remain to be determined.

Furthermore, an important factor that affects microbial composition and resilience is often overlooked: the interactions between microorganisms, either through competition, antimicrobial agents or metabolic networks. Promoting the resilience of beneficial microbiota assemblies or decreasing the resilience of dysbiotic microbiota communities is a promising option to support a healthy human physiology. Thus, improving our understanding of microbial resilience towards external perturbations will be a key requirement for microbiome-directed precision medicine; for example, by pre-selecting and designing suitable, functionally selected microbial communities or by the stratification of patients according to the properties of their microbial communities to maximize treatment success. Therefore, modulation of the microbiota remains a promising therapeutic option for the treatment of complex diseases, but much more must be learned to make this vision a reality, in which understanding resilience might be key.

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1. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature* **486**, 207–214 (2012).
2. Qin, J. *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65 (2010).
3. Faith, J. J. *et al.* The long-term stability of the human gut microbiota. *Science* **341**, 1237439 (2013).
4. Caporaso, J. G. *et al.* Moving pictures of the human microbiome. *Genome Biol.* **12**, R50 (2011).
5. Walker, B., Holling, C. S., Carpenter, S. R. & Kinzig, A. Resilience, adaptability and transformability in social–ecological systems. *Ecol. Soc.* **9**, 5 (2004).
6. Moya, A. & Ferrer, M. Functional redundancy-induced stability of gut microbiota subjected to disturbance. *Trends Microbiol.* **24**, 402–413 (2016).
7. Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K. & Knight, R. Diversity, stability and resilience of the human gut microbiota. *Nature* **489**, 220–230 (2012).
8. Greenhalgh, K., Meyer, K. M., Aagaard, K. M. & Wilmes, P. The human gut microbiome in health: establishment and resilience of microbiota over a lifetime. *Environ. Microbiol.* **18**, 2103–2116 (2016).
9. Chassaing, B. *et al.* Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* **519**, 92–96 (2015).
10. Suez, J. *et al.* Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* **514**, 181–186 (2014).
11. Henle, J. in *Pathologische Untersuchungen* 1–82 (Hirschwald,1840).
12. Koch, R. Die Ätiologie der Tuberkulose [German]. *Berliner Klinische Wochenschrift* **19**, 428–445 (1882).
13. Singh, V. P., Proctor, S. D. & Willing, B. P. Koch's postulates, microbial dysbiosis and inflammatory bowel disease. *Clin. Microbiol. Infect.* **22**, 594–599 (2016).
14. Shade, A. *et al.* Fundamentals of microbial community resistance and resilience. *Front. Microbiol.* **3**, 417 (2012).
15. Bender, E. A., Case, T. J. & Gilpin, M. E. Perturbation experiments in community ecology: theory and practice. *Ecology* **65**, 1–13 (1984).
16. Oliver, T. H. *et al.* Biodiversity and resilience of ecosystem functions. *Trends Ecol. Evol.* **30**, 673–684 (2015).
17. Gunderson, L. H. Ecological resilience — in theory and application. *Annu. Rev. Ecol. Syst.* **31**, 425–439 (2000).
18. Holling, C. S. & Gunderson, L. in *Panarchy: Understanding Transformations in Human and Natural Systems* 25–62 (Island Press, 2002).
19. Holling, C. S. Resilience and stability of ecological systems. *Annu. Rev. Ecol. Syst.* **4**, 1–23 (1973).
20. Sommer, F. & Backhed, F. Know your neighbor: microbiota and host epithelial cells interact locally to control intestinal function and physiology. *Bioessays* **38**, 455–464 (2016).
21. Wang, J. *et al.* Dietary history contributes to enterotype-like clustering and functional metagenomic content in the intestinal microbiome of wild mice. *Proc. Natl Acad. Sci. USA* **111**, E2703–E2710 (2014).
22. David, L. A. *et al.* Diet rapidly and reproducibly alters the human gut microbiome. *Nature* **505**, 559–563 (2014).
23. McNaughton, S. J. Diversity and stability of ecological communities: a comment on the role of empiricism in ecology. *Am. Nat.* **111**, 515–525 (1977).
24. Naeem, S. & Li, S. Biodiversity enhances ecosystem reliability. *Nature* **390**, 507–509 (1997).
25. Ley, R. E., Turnbaugh, P. J., Klein, S. & Gordon, J. I. Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022–1023 (2006).
26. Turnbaugh, P. J. *et al.* A core gut microbiome in obese and lean twins. *Nature* **457**, 480–484 (2009).
27. Ley, R. E. *et al.* Obesity alters gut microbial ecology. *Proc. Natl Acad. Sci. USA* **102**, 11070–11075 (2005).
28. Furet, J. P. *et al.* Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* **59**, 3049–3057 (2010).
29. Manichanh, C. *et al.* Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* **55**, 205–211 (2006).
30. Willing, B. P. *et al.* A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. *Gastroenterology* **139**, 1844–1854.e1 (2010).
31. Ott, S. J. *et al.* Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut* **53**, 685–693 (2004).
32. Lepage, P. *et al.* Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. *Gastroenterology* **141**, 227–236 (2011).
33. Chang, J. Y. *et al.* Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile*-associated diarrhea. *J. Infect. Dis.* **197**, 435–438 (2008).
34. Arumugam, M. *et al.* Enterotypes of the human gut microbiome. *Nature* **473**, 174–180 (2011).
35. Zhernakova, A. *et al.* Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science* **352**, 565–569 (2016).
36. Moeller, A. H. *et al.* Chimpanzees and humans harbour compositionally similar gut enterotypes. *Nat. Commun.* **3**, 1179 (2012).
37. Horst, K. *et al.* Risk stratification by injury distribution in polytrauma patients — does the clavicular fracture play a role? *Patient Saf. Surg.* **7**, 23 (2013).
38. Wu, G. D. *et al.* Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108 (2011).
39. Vieira-Silva, S. *et al.* Species–function relationships shape ecological properties of the human gut microbiome. *Nat. Microbiol.* **1**, 16088 (2016).
40. Schreiber, S., Rosenstiel, P., Albrecht, M., Hampe, J. & Krawczak, M. Genetics of Crohn disease, an archetypal inflammatory barrier disease. *Nat. Rev. Genet.* **6**, 376–388 (2005).
41. Hsiao, A. *et al.* Members of the human gut microbiota involved in recovery from *Vibrio cholerae* infection. *Nature* **515**, 423–426 (2014).
42. Schwab, C. *et al.* Longitudinal study of murine microbiota activity and interactions with the host during acute inflammation and recovery. *ISME J.* **8**, 1101–1114 (2014).
43. Buffie, C. G. *et al.* Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. *Infect. Immun.* **80**, 62–73 (2012).
44. Nemergut, D. R. *et al.* Patterns and processes of microbial community assembly. *Microbiol. Mol. Biol. Rev.* **77**, 342–356 (2013).
45. Seedorf, H. *et al.* Bacteria from diverse habitats colonize and compete in the mouse gut. *Cell* **159**, 253–266 (2014).
46. Salzman, N. H. *et al.* Enteric defensins are essential regulators of intestinal microbial ecology. *Nat. Immunol.* **11**, 76–83 (2010).
47. Sommer, F. *et al.* Altered mucus glycosylation in core 1 O-glycan-deficient mice affects microbiota composition and intestinal architecture. *PLoS ONE* **9**, e85254 (2014).
48. Johansson, M. E. *et al.* The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc. Natl Acad. Sci. USA* **105**, 15064–15069 (2008).
49. Hooper, L. V., Littman, D. R. & Macpherson, A. J. Interactions between the microbiota and the immune system. *Science* **336**, 1268–1273 (2012).
50. Wehkamp, J. *et al.* Reduced Paneth cell α-defensins in ileal Crohn's disease. *Proc. Natl Acad. Sci. USA* **102**, 18129–18134 (2005).
51. Mathewson, N. D. *et al.* Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat. Immunol.* **17**, 505–513 (2016).
52. Nigro, G., Rossi, R., Commere, P. H., Jay, P. & Sansonetti, P. J. The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell protection and links microbes to gut epithelial regeneration. *Cell Host Microbe* **15**, 792–798 (2014).
53. Lindemans, C. A. *et al.* Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration. *Nature* **528**, 560–564 (2015).
54. Hadizadeh, F. *et al.* Stool frequency is associated with gut microbiota composition. *Gut* **66**, 559–560 (2016).
55. Falony, G. *et al.* Population-level analysis of gut microbiome variation. *Science* **352**, 560–564 (2016).
56. Alam, A. *et al.* The microenvironment of injured murine gut elicits a local pro-restitutive microbiota. *Nat. Microbiol.* **1**, 15021 (2016).
57. Pedron, T. *et al.* A crypt-specific core microbiota resides in the mouse colon. *mBio* **3,** e00116-12 (2012).
58. Gillilland, M. G. III *et al.* Ecological succession of bacterial communities during conventionalization of germ-free mice. *Appl. Environ. Microbiol.* **78**, 2359–2366 (2012).
59. Wier, A. M. *et al.* Transcriptional patterns in both host and bacterium underlie a daily rhythm of anatomical and metabolic change in a beneficial symbiosis. *Proc. Natl Acad. Sci. USA* **107**, 2259–2264 (2010).
60. Sender, R., Fuchs, S. & Milo, R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol.* **14**, e1002533 (2016).
61. Thaiss, C. A. *et al.* Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* **159**, 514–529 (2014).
62. Thaiss, C. A. *et al.* Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell* **167**, 1495–1510.e12 (2016).
63. Faust, K. & Raes, J. Microbial interactions: from networks to models. *Nat. Rev. Microbiol.* **10**, 538–550 (2012).
64. Jones, S. E. & Lennon, J. T. Dormancy contributes to the maintenance of microbial diversity. *Proc. Natl Acad. Sci. USA* **107**, 5881–5886 (2010).
65. Pedros-Alio, C. Marine microbial diversity: can it be determined? *Trends Microbiol.* **14**, 257–263 (2006).

66. Lennon, J. T. & Jones, S. E. Microbial seed banks: the ecological and evolutionary implications of dormancy. *Nat. Rev. Microbiol.* **9**, 119–130 (2011).
67. Tait, K. & Sutherland, I. W. Antagonistic interactions amongst bacteriocin-producing enteric bacteria in dual species biofilms. *J. Appl. Microbiol.* **93**, 345–352 (2002).
68. LaSarre, B. & Federle, M. J. Exploiting quorum sensing to confuse bacterial pathogens. *Microbiol. Mol. Biol. Rev.* **77**, 73–111 (2013).
69. Tan, C. H. *et al.* Community quorum sensing signalling and quenching: microbial granular biofilm assembly. *NPJ Biofilms Microbiomes* **1**, 15006 (2015).
70. Dominguez-Bello, M. G. *et al.* Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc. Natl Acad. Sci. USA* **107**, 11971–11975 (2010).
71. Sommer, F. & Backhed, F. The gut microbiota — masters of host development and physiology. *Nat. Rev. Microbiol.* **11**, 227–238 (2013).
72. Rehman, A. *et al.* Nod2 is essential for temporal development of intestinal microbial communities. *Gut* **60**, 1354–1362 (2011).
73. Rakoff-Nahoum, S. *et al.* Analysis of gene–environment interactions in postnatal development of the mammalian intestine. *Proc. Natl Acad. Sci. USA* **112**, 1929–1936 (2015).
74. Koenig, J. E. *et al.* Succession of microbial consortia in the developing infant gut microbiome. *Proc. Natl Acad. Sci. USA* **108** (Suppl. 1), 4578–4585 (2011).
75. Palmer, C., Bik, E. M., DiGiulio, D. B., Relman, D. A. & Brown, P. O. Development of the human infant intestinal microbiota. *PLoS Biol.* **5**, e177 (2007).
76. Yatsunenko, T. *et al.* Human gut microbiome viewed across age and geography. *Nature* **486**, 222–227 (2012).
77. Russell, S. L. *et al.* Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep.* **13**, 440–447 (2012).
78. Dominguez-Bello, M. G. *et al.* Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat. Med.* **22**, 250–253 (2016).
79. Subramanian, S. *et al.* Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature* **510**, 417–421 (2014).
80. Dethlefsen, L. & Relman, D. A. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc. Natl Acad. Sci. USA* **108** (Suppl. 1), 4554–4561 (2011).
81. Heinsen, F. A. *et al.* Dynamic changes of the luminal and mucosa-associated gut microbiota during and after antibiotic therapy with paromomycin. *Gut Microbes* **6**, 243–254 (2015).
82. Jernberg, C., Lofmark, S., Edlund, C. & Jansson, J. K. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME J.* **1**, 56–66 (2007).
83. Lindner, C. *et al.* Diversification of memory B cells drives the continuous adaptation of secretory antibodies to gut microbiota. *Nat. Immunol.* **16**, 880–888 (2015).
84. Schumann, A. *et al.* Neonatal antibiotic treatment alters gastrointestinal tract developmental gene expression and intestinal barrier transcriptome. *Physiol. Genomics* **23**, 235–245 (2005).
85. Biedermann, L. & Rogler, G. The intestinal microbiota: its role in health and disease. *Eur. J. Pediatr.* **174**, 151–167 (2015).
86. Theriot, C. M., Bowman, A. A. & Young, V. B. Antibiotic-induced alterations of the gut microbiota alter secondary bile acid production and allow for *Clostridium difficile* spore germination and outgrowth in the large intestine. *mSphere* http://dx.doi.org/10.1128/mSphere.00045-15 (2016).
87. Risnes, K. R., Belanger, K., Murk, W. & Bracken, M. B. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. *Am. J. Epidemiol.* **173**, 310–318 (2011).
88. Shaw, S. Y., Blanchard, J. F. & Bernstein, C. N. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am. J. Gastroenterol.* **105**, 2687–2692 (2010).
89. Kronman, M. P., Zaoutis, T. E., Haynes, K., Feng, R. & Coffin, S. E. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics* **130**, e794–e803 (2012).
90. Azad, M. B., Bridgman, S. L., Becker, A. B. & Kozyrskyj, A. L. Infant antibiotic exposure and the development of childhood overweight and central adiposity. *Int. J. Obes. (Lond.)* **38**, 1290–1298 (2014).
91. Boursi, B., Mamtani, R., Haynes, K. & Yang, Y. X. The effect of past antibiotic exposure on diabetes risk. *Eur. J. Endocrinol.* **172**, 639–648 (2015).
92. Blaser, M. J. Antibiotic use and its consequences for the normal microbiome. *Science* **352**, 544–545 (2016).
93. Vrieze, A. *et al.* Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **143**, 913–916.e7 (2012).
94. Bäckhed, F. *et al.* The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101**, 15718–15723 (2004).
95. Couturier-Maillard, A. *et al.* NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. *J. Clin. Invest.* **123**, 700–711 (2013).
96. Vijay-Kumar, M. *et al.* Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* **328**, 228–231 (2010).
97. Hamilton, M. J., Weingarden, A. R., Unno, T., Khoruts, A. & Sadowsky, M. J. High-throughput DNA sequence analysis reveals stable engraftment of gut microbiota following transplantation of previously frozen fecal bacteria. *Gut Microbes* **4**, 125–135 (2013).
98. Li, S. S. *et al.* Durable coexistence of donor and recipient strains after fecal microbiota transplantation. *Science* **352**, 586–589 (2016).
99. Manichanh, C. *et al.* Reshaping the gut microbiome with bacterial transplantation and antibiotic intake. *Genome Res.* **20**, 1411–1419 (2010).
100. Fuentes, S. *et al.* Reset of a critically disturbed microbial ecosystem: faecal transplant in recurrent *Clostridium difficile* infection. *ISME J.* **8**, 1621–1633 (2014).
101. Grinspan, A. M. & Kelly, C. R. Fecal microbiota transplantation for ulcerative colitis: not just yet. *Gastroenterology* **149**, 15–18 (2015).
102. Eiseman, B., Silen, W., Bascom, G. S. & Kauvar, A. J. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* **44**, 854–859 (1958).
103. van Nood, E. *et al.* Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N. Engl. J. Med.* **368**, 407–415 (2013).
104. Broecker, F., Klumpp, J. & Moelling, K. Long-term microbiota and virome in a Zurich patient after fecal transplantation against *Clostridium difficile* infection. *Ann. NY Acad. Sci.* **1372**, 29–41 (2016).
105. Vermeire, S. *et al.* Donor species richness determines faecal microbiota transplantation success in inflammatory bowel disease. *J. Crohns Colitis* **10**, 387–394 (2016).
106. Colman, R. J. & Rubin, D. T. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J. Crohns Colitis* **8**, 1569–1581 (2014).
107. Moayyedi, P. *et al.* Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* **149**, 102–109.e6 (2015).
108. Rossen, N. G. *et al.* Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology* **149**, 110–118.e4 (2015).
109. Ott, S. J. *et al.* Efficacy of sterile fecal filtrate transfer for treating patients with *Clostridium difficile* infection. *Gastroenterology* **152**, 799–811.e7 (2016).
110. Rykiel, E. J. Towards a definition of ecological disturbance. *Aust. J. Ecol.* **10**, 361–365 (1985).
111. Worm, B. & Duffy, J. E. Biodiversity, productivity and stability in real food webs. *Trends Ecol. Evol.* **18**, 628–632 (2003).
112. Relman, D. A. The human microbiome: ecosystem resilience and health. *Nutr. Rev.* **70**, S2–S9 (2012).
113. Costello, E. K. *et al.* Bacterial community variation in human body habitats across space and time. *Science* **326**, 1694–1697 (2009).
114. David, L. A. *et al.* Host lifestyle affects human microbiota on daily timescales. *Genome Biol.* **15**, R89 (2014).
115. Costello, E. K., Stagaman, K., Dethlefsen, L., Bohannan, B. J. & Relman, D. A. The application of ecological theory toward an understanding of the human microbiome. *Science* **336**, 1255–1262 (2012).
116. Tamboli, C. P., Neut, C., Desreumaux, P. & Colombel, J. F. Dysbiosis in inflammatory bowel disease. *Gut* **53**, 1–4 (2004).

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Competing interests statement

The authors declare no competing interests.