Host microbiota can facilitate pathogen infection

Emily J. Stevens*, Kieran A. Bates, Kayla C. King

Department of Zoology, University of Oxford, Oxford, United Kingdom

* Emily.stevens@zoo.ox.ac.uk

Abstract

Animals live in symbiosis with numerous microbe species. While some can protect hosts from infection and benefit host health, components of the microbiota or changes to the microbial landscape have the potential to facilitate infections and worsen disease severity. Pathogens and pathobionts can exploit microbiota metabolites, or can take advantage of a depletion in host defences and changing conditions within a host, to cause opportunistic infection. The microbiota might also favour a more virulent evolutionary trajectory for invading pathogens. In this review, we consider the ways in which a host microbiota contributes to infectious disease throughout the host’s life and potentially across evolutionary time. We further discuss the implications of these negative outcomes for microbiota manipulation and engineering in disease management.

Introduction

An infection by pathogens (and parasites) can vary from relatively benign to lethal. The degree of harm caused during infection can be driven by aspects of pathogen biology, such as transmissibility [1], infective dose [2], or whether they are facultative/obligate [3], as well as by host biology, and the surrounding biotic or abiotic environment [4]. While hosts can be genetically predisposed to susceptibility [5], disease outcomes can be made worse if hosts have a comorbidity [6] or an impaired or over-reactive immune response [7]. When invading a host, pathogens will also interact with other microbial species [8]. The outcome of infection is thus held in the balance by the complex interactions between a host, its microbiota, and both the biotic and abiotic environment [4].

Microbiota are vital to the functioning of their multicellular host organisms. This realisation has fuelled great interest in the effects of microbes on plant [9] and animal host health [10]. Microbe-mediated protection against infection is a widespread phenomenon across host species [11], with components of the microbiota and their interactions with a host and the wider microbial community mediating susceptibility to invading pathogens and internal pathobionts [12,13]. There are several ways to categorise and define pathogens based on their biology [3]. Here, we use the term “pathobiont” to mean normally harmless components of the microbiota which have pathogenic potential in some contexts [14–16]. We distinguish these from “invading pathogens,” by which we mean pathogens (including parasites) acquired from a source external to the host (i.e., from a different host or from the environment).
It is well established that host microbiota generally play a beneficial role in preventing or fighting infection [17–20]. Microbe-mediated protection can be mediated via resource competition [21,22], interference competition [23], or the host immune response [24,25]. However, the relative magnitude of these benefits might decrease when microbiota components, in some cases, directly or indirectly facilitate the onset of disease caused by invading pathogens or pathobionts (Table 1). Although some invading pathogens can exploit cues or changes in the resource/immunological environment shaped by the microbiota itself, the context of host health is also an important determinant of infection. Diminished host health can remove the beneficial services the microbiota normally provides. Changes in host health can correlate with dysbiosis of host microbiota [26–28], and opportunistic microbiota components can transition to become harmful among the perturbation [26,29–31]. This perturbation and transition of commensals towards pathogenicity can sometimes even be caused by invading pathogens [32,33]. Moreover, protective microbes can become relatively costly to their host in the absence of the invading pathogens they would otherwise suppress [31,34,35] (i.e., the same microbial species is protective in one context, but costly in another; see “Costly protective symbionts”).

To understand the multifaceted contributors to infectious disease, the potentially harmful aspects of the microbiota and its components warrant consideration. Microbe-based therapies for disease are being investigated as alternatives to antimicrobials for a wide range of animal hosts, from endangered amphibians to humans [36–38]. A thorough evaluation of the potential for host microbiota to contribute to infectious disease is necessary to establish their utility in disease management as anti-infective prophylactics, probiotics, and prebiotics. In this review, we will discuss the conditions under which microbiota can promote or worsen infection outcomes, with evolutionary consequences. We will then discuss the implications of this potential to facilitate pathogen invasion and infection from within for microbiota manipulation.

**Promotion of pathogen invaders**

**Microbiota components modify the within-host environment**

**Metabolic environment.** Microbiota metabolites are beneficial to hosts in myriad ways. They help to prime the immune system, act as antimicrobials to combat infection, and aid host metabolism [24,80–82]. However, microbiota metabolites can also provide a convenient and easily attainable source of food for invading pathogens to exploit. Metabolic cross-feeding, in which a product of metabolism from one strain is used by another strain, generates novel niches that may benefit pathogens [83]. This assimilation of resources can enhance energy production within the pathogen, enabling increased virulence and rapid growth, and thus more severe disease. For example, the human gut commensal *Bacteroides thetaiotaomicron* (*Bt*) can exacerbate infection caused by enterohaemorrhagic *Escherichia coli* (EHEC) via metabolic cross-feeding [84]. *Bt* modifies the metabolic environment at the site of EHEC infection, increasing metabolites involved in gluconeogenesis which are then sensed by the virulence-regulating transcription factor Cra. Virulence is up-regulated as a result and, concurrent with invasion of the gut epithelial barrier (also facilitated by *Bt*), EHEC induces a greater degree of host pathology and higher risk of mortality.

Individual species of the microbiota cannot always be pinpointed for their role in facilitating infection. While *Bt* was specifically identified in the previous example as a contributor to EHEC infection [84], microbial metabolites from multiple components of the microbiota can also collectively enhance EHEC virulence [85]. A comparison between human and mouse microbiota metabolites illustrated that the increased severity of EHEC infection in humans, compared to that in mice, is driven by distinct human gut microbiota metabolites [29]. These
metabolites specifically induce increased expression of flagellin in the pathogen, increasing its ability to invade host tissues. Distinct microbial communities can thus shape different infection outcomes via metabolite production.

The metabolic environment within a host is a crucial contributor to the pathogenesis of invading organisms. It can be extensively modified by components of the microbiota to both the detriment and the benefit of the host. Changes in host health can likewise alter the within-host metabolic environment, contributing to disease onset from resident commensals [62]. Given the diversity of species housed by the animal gut, there are complex interactions to pick

Table 1. Summary of the drivers and mechanisms by which the microbiota facilitate harmful infection.

| Pathway to pathogenesis | Driver | Mechanism | Due to change in host health? | Illustrative example | Other relevant references |
|-------------------------|--------|-----------|-----------------------------|---------------------|-------------------------|
| Facilitate pathogenic invaders | Niche exploitation | Invading pathogen cross-feeds off microbiota metabolites | No | Human microbiota metabolites increase severity of *Escherichia coli* infection [29] | [39–43] |
| | | Invading pathogen exploits host transmission of microbiota components | No | Trypanosomatid parasite *Leptomonas pyrrhocoris* exploits host transmission of mutualist Coriobacteriaceae microbial symbionts between firebug hosts to aid its own transmission [44] | [45,46] |
| Provide cues | Pathogens require contact with microbiota to initiate infection | No | Bacterial surface structures (Type 1 fimbiae) bind to proteins at the poles of *Trichuris muris* worms’ eggs and trigger hatching [47] | [48] |
| Alter immunological environment | Microbiota components increase activity of specific immune cells, enhancing susceptibility to infection | No | *Lactobacillus* bacteria in mouse microbiome elevates regulatory T-cell frequencies known to result in greater helmith establishment [49] | | |
| Lower ecological resistance | Lower microbiota diversity reduces colonisation resistance/competitive exclusion | Yes | Loss of specific microbiota components correlate with onset of *Clostridioides difficile* infection in a mouse model [50] | [51–53] |
| Facilitate infection from within | Transitions from (low abundance) commensal to (high abundance) pathobiont | Lower microbiota diversity from biotic or abiotic stress to hosts | Yes | Stress in the brook char fish *Salvelinus fontinalis* induces microbiota dysbiosis, causing reduction in beneficial bacteria and increase in opportunists [28] | [36,54–56] |
| | | Metabolic changes in pathobionts | No | Bacterial nucleoside catabolism of gut luminal uridine to uracil and ribose facilitates the commensal-to-pathogen transition in *Drosophila* microbiota components [57] | [58–60] |
| | | Pathobiont takes advantage of disruption to host homeostasis | Yes | High fat diet and subsequent inflammation in the human gut leads to increase in opportunism from within the microbiota [26] | [61–65] |
| | | Overexpansion of resident pathobiont | Sometimes | Resident *Staphylococcus aureus* overexpansion on the skin corresponds to onset of atopic dermatitis in humans [66] | [67–70] |
| | | Antibiotic treatment | Yes | Antibiotic-mediated alteration of the gut microbiota changes the metabolic profile of this environment to one that favours expansion of *C. difficile* in a mouse model [71] | [72–75] |
| | | Within-host translocation | Disruption to gut barrier function and/or bacterial overgrowth | Yes* | In *Manduca sexta* (tobacco hornworm), disruption of the gut epithelial barrier led to translocation of the gut microbiota component *Enterococcus faecalis*, ultimately leading to sepsis [76] | [32,33,77–79] |

Illustrative examples for each mechanism and other relevant references provided. We highlight whether a change in host health affects the pathogenic potential of the microbiota.

* Infection by invading pathogens can cause this disruption to host health.

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apart. Research is moving towards characterising the functionality of the microbiome by holistically sampling its taxonomic and genomic repertoire in addition to the chemical phenotype. Progress has been made in uncovering pathogen-induced disease phenotypes that are enhanced by the microbiota through application of multi-omics strategies [86,87] (see Table 2). Nonetheless, data integration and interpreting meaningful biological signatures of infection (e.g., biomarkers of infection) remain a challenge [88].

**Immunological environment.** Microbiota can prime the host immune response, altering their susceptibility to invading pathogens. Pathogen infectivity can be indirectly reduced by host microbiota this way [89–93]. Conversely, launching the immune response can inadvertently boost infection by some infectious agents [49]. Reynolds and colleagues [49] found that Lactobacillaceae species abundance in the mouse duodenum positively correlated with susceptibility to the nematode parasite *Heligmosomoides polygyrus* and heightened immunosuppressive regulatory T-cell and Th17 responses. Subsequent treatment of mice with *Lactobacillus taiwanensis*—a rodent commensal dominant in infected mice—elevated regulatory T-cell frequencies and promoted the establishment of *H. polygyrus*. The fact that microbiota composition changed after *H. polygyrus* exposure towards more “helpful” bacterial species suggests that parasites could actively modify the microbiota to improve their survival. This manipulation could occur directly via antimicrobials [94] or by pathogen-induced host inflammation [95]. Physical disruption of the host site might also cause changes in resource availability, shifting microbiota composition [96].

**Invading pathogens might evolve in response to host microbiota**

Microbes can evolve quickly [100] because of their large population sizes and rapid generation times. Microbiota components can evolve within their host’s lifetime with consequences for host health [101]. For example, a mildly pathogenic strain of the gut microbiota component *Enterococcus faecalis* has been shown in nematode hosts to evolve to become more protective due to competitive interactions with a virulent pathogen [23]. Likewise, the pathogen *Candida albicans* was shown to evolve towards protective mutualism when introduced to a new host in a mouse model [102].

**Table 2. Representative examples of omics approaches used to deduce the role of microbiota components in facilitating infection and worsening infection outcomes.**

| Approach                        | Description                                                                 | Example findings                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Proteomics                      | Characterises the protein profile of community being studied. Potential use in identifying biomarkers of infection within the microbiome. | The saliva proteome of human hosts was found to reflect the dynamics of the oral microbiome, including community changes that lead to disease. Identification of biomarkers within the saliva proteome could be used to diagnose oral infections [97]. |
| Metabolomics                    | Elucidates specific metabolites present under study conditions. Gives insight into metabolites required for pathogenesis/mutualism by microbiota components. | Antibiotic-mediated alteration of the human gut microbiota shifts the global metabolic profile in this niche towards one that favours *C. difficile* infection. Specific metabolites were identified that change in abundance following antibiotic treatment. These changes in tandem benefit *C. difficile* [71]. |
| Transcriptomics (also referred to as functional gene expression) | Enables characterisation of the abundance of RNA (transcriptional activity) of both coding and noncoding regions of the genome. This approach is more informative than gene presence/absence. | Differential transcript expression identified in amphibian host populations with different disease history relating to ranavirus infection. Provides information about how hosts respond to infection [98]. |
| Genome-scale metabolic modelling | Integrates genomic information with metabolomics data to create predictive models of metabolism in a given study condition. | Identification of nutrient conditions in a multispecies biofilm model of the human gut that results in *C. difficile*- associated dysbiosis. Statistical modelling predicted the experimentally observed metabolic changes causative of an increase in *C. difficile* abundance and the subsequent decrease in abundance of protective microbiota components [99]. |

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Invading pathogens, in turn, may evolve to overcome or exploit the host microbiota. They can readily overcome barriers to their establishment, including from host resistance [103], antibiotic treatments [104], and vaccines [105]. Theory has shown that pathogens can evolve virulence factors to overcome commensals in the host microbiota, either directly killing their competitors [106] or inducing host inflammation as a form of “proactive invasion” [95]. Experimental evolution approaches in animal model systems have produced mixed evidence on the ability of evolving pathogens to escape suppression by protective microbes. Martinez and colleagues [107] found that niche blocking by Wolbachia in Drosophila melanogaster effectively suppressed the pathogen Drosophila C virus (DCV), which did not evolve to overcome the protective symbiont. In contrast, Rouchet and Vorburger [108] found the parasitoid wasp, Lysiphlebus fabarum, readily counteradapted to the protection given by sympatric Hamiltonella defensa in aphids. A variety of pathogens may have evolved to exploit host microbiota for replication and transmission. Poliovirus and Trichuris muris, for example, have been empirically found to depend on interactions with mouse intestinal microbiota to trigger replication and hatching, respectively, at key host sites [47,48]. Poliovirus was able to better associate with host cells, and its replication was enhanced by up to 500% after binding lipopolysaccharide on enterobacterial surfaces [48]. Similarly, fimbriae on the surface of gut colonisers E. coli and Salmonella typhimurium were found to bind to proteins at the poles of eggs of the parasitic nematode, T. muris. This interaction with enterobacteria provides an essential cue, triggering the emergence of infective larvae [47].

Microbiome-mediated protection can drive the evolution of increased [109] and decreased [110] pathogen virulence. McNally and colleagues [109] found that manipulating the microbiota generated increased competition between commensal competitors and increased the intensity of bacterial warfare. Using theory, they found that stronger competition selected for increased expression of pathogen weapons (virulence factors). Enhanced production of virulence factors by many pathogenic bacteria can inadvertently harm the host. For example, release of Shiga toxin-encoding phage by shigatoxinogenic E. coli [111], and similarly TcdA released by Clostridioides difficile, can clear commensals both directly and via provocation of host inflammation [112,113].

Host microbiota has the potential to influence the evolutionary trajectory of invading pathogens. Manipulating host microbiota offers a promising route to treat or prevent infection, but such approaches should be scrutinised in light of the evolutionary potential of target pathogens.

Harmful infection from within

Transitions of commensal microbes to pathogens. Commensals in the microbiota can transition along the parasite–mutualist continuum [66,76,114]. Transitions towards pathogenicity can be influenced by changes to the within-host environment—onset of illness or compromised immunity [7], diet [26], antibiotic treatment [115], or stress [28,116]—as well as changes in the external environment [28]. Infection by invading pathogens can also induce otherwise commensal bacteria to become pathogenic [33,117].

A well-studied example of a transition to pathogenicity is that of C. difficile, the causative agent of colitis. C. difficile can be at very low abundance in the human gastrointestinal tract. A healthy gut microbiota usually provides colonisation resistance against C. difficile expansion [52]. However, following a period of antibiotic treatment which diminishes the protective power of the microbiota, this bacterium can proliferate extensively to dominate the intestinal niche [71]. In this context, it is a highly problematic pathogen which can cause recurrent disease. Faecal microbiota transplants have proven useful in such cases, whereby the dysbiotic gut...
microbiota of a C. difficile patient is replaced with that of a healthy donor to eliminate the infection [118].

How can these transitions to pathogenicity occur among pathobionts? Metabolic changes in components of the microbiota can underpin the transition. Recent work on the Drosophila gut microbiome demonstrates that catabolism of host gut luminal uridine by pathobionts drives the generation of uracil and ribose. These metabolites respectively trigger an inflammatory host immune response and increased expression of virulence genes in pathobionts. Quorum sensing regulates both processes and is therefore necessary for a transition to virulence. Deletion of genes involved in nucleotide metabolism in strains of enteric Drosophila pathobionts blocked quorum sensing and thus the commensal-to-pathogen transition. Metabolites such as uracil and ribose may therefore act as pathogen-specific indicators, used by metazoan hosts to distinguish good from bad within the gut. Recognition of these indicators equips hosts to modulate immunity and gut-microbe homeostasis in response to changes within the microbiota [58].

In polymicrobial infections, metabolic cross-feeding can be an essential source of nutrients, enhancing the ability of commensal microbes to establish infection. The pathobiont Aggregatibacter actinomycetemcomitans, for example, requires L-lactate produced by the commensal bacterium Streptococcus gordonii to establish polymicrobial periodontal infection in a murine abscess model [119]. A. actinomycetemcomitans also exhibits enhanced respiratory metabolism in the presence of S. gordonii [120], as the latter increases the bioavailability of oxygen to the opportunist by providing electron acceptors. A. actinomycetemcomitans uses these electron acceptors to increase energy yield in the form of ATP production, which promotes increased virulence. With more energy available, the pathobiont can invest in the production of toxins, adhesins, and immunomodulatory proteins, among many other virulence factors [120].

Pathobionts have an array of tools available to adapt to environmental change within their niche [69,121–123]. Factors which contribute to the commensal bacterial lifestyle can be repurposed upon immune compromise in the host or upon nutrient limitation or community disruption of the microbiota. Such changes within the host environment can lead to pathobionts proliferating beyond their niche to invade host tissues [69,123]. Adhesive proteins, for example, are required for asymptomatic colonisation of a new host, yet are also important in attaching to host cells to initiate invasion [123,124]. They can additionally contribute to the development of bacterial biofilms [69,70] to facilitate persistence of an infection under adverse conditions (e.g., antibiotic treatment). Likewise, toxins play a significant destructive role in the onset of disease. Toxins induce host cell lysis and stimulate inflammation, and they are recognised as major drivers of the symptoms of bacterial infection [125]. Recent research has also highlighted the contribution of toxins to pathobiont colonisation or persistence in different niches within the host during asymptomatic carriage, thus they aid both the commensal and pathogenic lifestyles of pathobionts [126]. Gene expression changes underpin transitions to pathogenicity and are driven by the need to adapt to changing conditions [121,122]. Infection can therefore be instigated by pathobionts within the host microbiota, following a transition from commensalism to a pathogenic state.

Costly protective symbionts. In wild animal systems, beneficial microbiota components otherwise known as defensive/protective symbionts have been shown to prevent pathogen establishment and reproduction [127]. They are so effective at defending that the evolution of host resistance is slowed in the face of pathogen infection [128]. Many of these symbionts can, however, impose a physiological burden upon their host that is measured in the absence of an invading threat. [127]. For example, while the endosymbiont Wolbachia in numerous arthropod hosts defends against parasitic viruses [129], bacteria [130], and nematodes [131], Wolbachia in Drosophila fruit flies can cause a reduction in colonised host fertility, fecundity, and
egg hatch rates, mediated by high symbiont densities [31]. A trade-off emerges in many host-microbe systems whereby increased conferred protection means the symbiont can become more pathogenic [34,35] (albeit, see Cayetano and colleagues [132]). Mathé-Hubert and colleagues [133] further showed that the cost of carrying a protective symbiont (Spiroplasma) in pea aphids can be alleviated by concurrent colonisation with a second symbiont (Regiella insecticola), as co-colonisation improves host lifetime reproduction and population growth.

Changes in the abiotic environment can also reveal the costs of these resident protectors in the microbiota. One extreme example is a species of the nematode-infecting bacterium Leucomacter, which under dry laboratory conditions is a protective bacterium against another highly virulent Leucomacter species, but in aqueous conditions causes hosts to become irreversibly fused by their tails leading to death [134]. The abiotic environment can therefore mediate host-associated microbe function to both favour and oppose pathogenicity.

**Microbiota community structure as an early warning signal**

Healthy microbiota community compositions can differ between individuals and population groups and also within individuals over time [135]. It is consequently not always feasible to establish what a “typical” dysbiotic microbiota looks like during infectious disease. However, a recent study in apiculture has demonstrated how early microbiota perturbations can have sustained negative consequences on host development and increase pathogen susceptibility within a population [116]. Schwarz and colleagues administered the commensal species Snodgrassella alvi to newly emerged worker bees as a potential probiotic therapy to protect against the parasite Lotmaria passim. Yet, despite S. alvi being part of the usual core microbiota of bees, inoculation of this species alone in young hosts led to microbiota perturbation, possibly reducing the protective benefits normally conferred and ultimately increasing parasite susceptibility [116].

While microbiota dysbiosis in general may correlate with infectious disease onset, microbial taxonomic signatures for specific infections may not always be a reliable indicator of disease [136]. The Anna Karenina principle [137] (“all happy families look alike, but each unhappy family is unhappy in its own way”) has been applied to explain observations in which microbiota community composition varies more between diseased individuals than healthy individuals. Nonetheless, in some instances, pathologies may be predicted by a specific reduction in certain key taxa. Bacterial vaginosis (BV) in humans is one such example, a condition caused by dysbiosis within the vaginal microbiota that affects approximately one-third of reproductive age women [138]. Vaginal microbiota composition varies across demographics [139], but onset of BV is typically associated with a reduction in Lactobacillus species, accompanied by the dominance of anaerobes and increased alpha diversity [140]. In these lactobacilli-depleted communities, the presence of biogenic amines can increase [141]. These amines, and the microbial community composition with which they are associated, could be useful biomarkers of disease in the early stages of BV development. Indeed, multi-omic approaches have been used to characterise the metabolic profiles corresponding to different symptomatic BV types [142]. Yeoman and colleagues [142] took this approach and identified distinct microbial taxa and metabolites which correlated to 2 different symptomatic BV types (and also to host behaviour). The characteristic odour of BV infection was linked to Dialister spp., the presence of discharge was linked with Mobiluncus spp., and Gardnerella spp. were linked with the symptom of pain. These findings provide both potential diagnostic markers for the onset of disease and insights into the determinants of BV.

Moving beyond correlative relationships between microbes and infections to establishing causation remains a major challenge [143–146]. Due to the complexities of microbial
communities within a host, including the high species richness within a niche and the multitude of microbe–microbe and host–microbe interactions, it is often difficult to attribute specific microbes to a causative role in disease. Furthermore, in some cases, infection may not be attributable to one species, but to polymicrobial interactions which are difficult to pick apart [30]. Host heterogeneity in genotype, lifestyle, and diet further compounds the ability to infer causality. Not all components of the microbiota are culturable in the laboratory setting and are only identifiable as members of the community through sequencing. They are thus often excluded from culture-dependent laboratory experiments aiming to determine causality [86,147–150].

To bridge this gap between correlation and causation in elucidating the relationship between microbiota and infection, current research is benefitting from combining laboratory experiments with multidisciplinary and multi-omic approaches (see Table 2). Tractable, controlled experimental models of defined microbial communities will be important in this transition [151]. Synthetic microbial communities composed of native microbiota components are now being developed for use in model organisms [147,152–154]. Such resources will allow in-depth dissection of host–microbiota interactions in model organisms, using tools which are easily controlled while remaining representative of natural systems. The combination of experimental models with corresponding omics data will further allow functional verification of bacterial phenotypes within the microbiota [155]; this mechanistic insight will be essential in determining causality in microbial infections.

Microbiota manipulation: Always a silver bullet?

Microbial approaches to managing disease in both humans and animals are gaining traction. The application of protective microbes directly to a host, or into a host’s habitat or food source, has been investigated for the control of infectious disease in endangered amphibians [36], aquaculture [156], and apiculture [157] as well as in the prevention and treatment of infectious and noninfectious human disease [38].

Microbe-based solutions have huge potential as alternatives to synthetic drugs [156,158,159]. However, they can sometimes have off-target effects. Studies on amphibian infection reveal the need for identification of these effects associated with probiotic use. Inhibition of the amphibian fungal pathogen Batrachochytrium dendrobatidis (Bd) by bacteria can differ based on pathogen genotype and microbial community composition [160,161]. Single bacterial strains show both growth inhibition or promotion depending on Bd genotype. Becker and colleagues [37] exposed the critically endangered Panamanian golden frog, Atelopus zeteki, to fungal Bd and candidate probiotic bacteria identified based on their Bd inhibitory activity in vitro. Results of the in vivo study showed no difference in Bd-induced mortality in probiotic-treated versus untreated groups. Several probiotics, however, showed a (nonsignificant) trend towards exacerbating Bd-induced mortality when compared to Bd alone. More recently, a probiotic treatment for the emerging fungal pathogen of amphibians Batrachochytrium salamandroides (Bsal) was shown to slow disease progression, but did not improve individual survival within populations [36]. A longer period of infection resulting from treatment was suggested to likely extend the shedding period of Bsal into the environment, increasing its transmission. Research has also shown that colonisation resistance of the native skin microbiota can be metabolically costly and cause amphibians to lose body mass during probiotic treatment for chytridiomycosis [162]. These amphibian studies demonstrate the difficulty in applying protective microbes in the natural environment. There could be a mismatch between in vitro and in vivo outcomes, genetic variation in the effectiveness of protective microbes, or probiotic treatment could alter the infection dynamics in a way that benefits transmission.
Transplantation of entire microbial communities has shown promise in treating human disease. Faecal microbiota transplants are currently used to successfully treat recurrent *C. difficile* infection [118]. However, the long-term and off-target effects of this intervention remain unknown [158]. One potential side effect is the unintentional transfer of pathobionts from donor to recipient [163], for which follow-up studies are lacking [164]. Evidence is also emerging of extra-intestinal and systemic effects of intestinal microbiota replacement [165], including obesity [166], autoimmune disorders [167], and depression [168]. Observations of such varied off-target effects reveal the complex and systemic consequences which microbiota manipulation may have on hosts.

The use of known protective microbes as probiotics also needs to be monitored for unexpected consequences. *Bifidobacterium longum* subsp. *longum* has been investigated for its potential to prevent lethal infection from enteric pathogens. This bacterium is a component of the human gut microbiota which positively modifies the metabolic environment within the gut to inhibit translocation of invading EHEC from the gut to the blood [169]. Severe and ultimately lethal infection is prevented in this manner, but cases of infection caused by this species have been reported [30]. Tena and colleagues [30] reflected that *B. longum* may often be overlooked as a cause of disease in polymicrobial infections due to being labelled as a commensal.

Administration of protective microbes used clinically as probiotics could be particularly problematic for immunocompromised, critically ill, or otherwise vulnerable hosts [170]. Safety concerns include the potential for a probiotic to cause infection by translocation [171], to pass antibiotic resistance genes or other virulence-associated genes onto other microbiota components, and the possibility for production of metabolites that can be toxic [172]. There is also the possibility of permanent colonisation [173] and long-term side effects. Such safety concerns will be essential to account for in cases where probiotic treatments are being investigated to treat vulnerable hosts. Furthermore, the applied probiotic will interact with host microbiota and invading pathogens. As probiotics are inherently "live microorganisms" [174], they retain the ability to evolve, and it is largely unclear how they might change in a new host [175].

**Conclusions**

The “microbiome revolution” is revealing the interconnectedness between a host’s health and its resident microbial species. Microbiota components can form an effective non-immunological line of defence against infection [11,17–20]. Although the microbiota can aid pathogens, worsen infection outcomes, or become harmful themselves in the situations we describe, overall it is acknowledged that the benefits of microbiota substantially outweigh any costs.

There is a need to distinguish the different conditions under which microbiota might facilitate infection. Some pathogens and pathobionts can directly exploit the metabolic and immunological environment shaped by the host microbiota. Whether these outcomes are specific to the interacting host and pathogen species/genotype is unclear. A change in host health status may dictate whether microbiota have the potential to allow for harmful infection [176,177]. Poor health, the application of antibiotics, or infection by invading pathogens might cause a loss of microbiota diversity (and thus protective traits) or physical disruption to the environment allowing for the expansion of harmful microbes. The integration of bioinformatics with lab experiments in model systems will help to characterise genomic, proteomic, and metabolic features of the microbiome in different contexts of infection [147,152,154,155,178,179]. Functional gene expression studies [180–182] and genome-scale metabolic models are also proving increasingly powerful in characterising the microbiota profiles of healthy versus diseased individuals [183,184]. Overall, these approaches will allow predictions to be made about microbial
phenotypes (e.g., metabolic traits, toxin production, and antibiotic resistance) in different contexts and the relevance of these phenotypes to infectious disease.

There are further outstanding questions regarding the contribution of microbiota components to infection in real time. In vitro and in vivo coculture experiments using communities representative of native host microbiota [152] can reveal antagonistic, competitive, and beneficial interactions between species within the microbiota, as well as between microbiota and invading pathogens [185,186]. Interactions between microbiota and host immunity can also be more intricately explored in model animal systems to study the role of the immunological environment in infection promotion [187–189]. With a better understanding of the interactions and dynamic processes that govern the microbiota, it may be possible to predict when harmless components will promote invading pathogens or become pathogenic themselves. Direct experimental tests in tractable systems will help to move our understanding beyond correlations of microbiota structure with infection outcomes and host health.

Thinking on an evolutionary timescale is essential for tackling why pathogens can benefit from the host microbiota. Systems in which pathogenic invaders depend on microbiota to start replicating [47,48] may indicate a coevolutionary relationship in which host-associated microbial species and pathogens cooperate to promote their establishment within the host. The potential for coevolution between protective microbes and pathogens has been demonstrated experimentally [190]. The extent to which pathogen exploitation of microbiome metabolites and immune priming is incidental, or the product of adaptation, remains unclear. Perhaps pathogens can evolve to improve their exploitation of host microbiota. Pathogens might also gain a competitive advantage by modifying their within-host environment (“niche construction” [191]) to select host-associated microbes most favourable to their survival [192]. The long-term effectiveness of a manipulated microbiota will also be vulnerable to pathogen evolution. Does engineering the microbiota or therapeutically applying microbes drive unwanted evolutionary changes in the target pathogen? Reductions in pathogen virulence could be desirable. However, any pathogen adaptation and increased within-host fitness might enhance their transmissibility in the host population. Most of our current understanding of the evolutionary biology in this area is based on theory and empirical work in model systems. Its relevance to human infections is an open question.

Microbiota are an important driver of variation in the prevalence and severity of some infections. Pathogen-suppressive forces generally dominate, but the interactions within the microbiota and between microbiota and invading pathogens are complex and need more direct empirical investigation. Nevertheless, shining a light on the potential ways in which the microbiota can sometimes facilitate infection by pathogens or pathobionts is critical for understanding patterns of infection in natural and applied settings.

References
1. Rafaluk-Mohr C. The relationship between parasite virulence and environmental persistence: a meta-analysis. Parasitology. 2019; 146:897–902. https://doi.org/10.1017/S0031182019000015 PMID: 30777585
2. Leggett HC, Cornwallis CK, West SA. Mechanisms of Pathogenesis, Infective Dose and Virulence in Human Parasites. PLoS Pathog. 2012; 8:e1002512. https://doi.org/10.1371/journal.ppat.1002512 PMID: 22359500
3. Brown SP, Cornforth DM, Mideo N. Evolution of virulence in opportunistic pathogens: generalism, plasticity, and control Trends in Microbiology. 2012; 20:336–42. https://doi.org/10.1016/j.tim.2012.04.005 PMID: 22564248
4. Bernardo-Cravo AP, Schmeller DS, Chatzinotas A, Vredenburg VT, Environmental Factors LA. Host Microbiomes Shape Host–Pathogen Dynamics. Trends Parasitol. 2020; 36:616–33. https://doi.org/10.1016/j.pt.2020.04.010 PMID: 32402837
5. Marquet S, Schurr E. Genetics of Susceptibility to Infectious Diseases: Tuberculosis and Leprosy as Examples. Drug Metab Dispos. 2001; 29:479–83. PMID: 11259336
6. Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: Factors that influence disparities in sepsis. Crit Care Med. 2006; 34:2576–82. https://doi.org/10.1097/01.CCM.0000239114.50519.0E PMID: 16915108
7. Pinsky MR. Dysregulation of the Immune Response in Severe Sepsis. Am J Med Sci. 2004; 328:220–9. https://doi.org/10.1097/00000441-200410000-00005 PMID: 15486537
8. Pallen MJ. The Human Microbiome and Host–Pathogen Interactions. In: Nelson KE, editor. Metagenomics of the Human Body. New York, NY: Springer; 2011. pp. 43–61. https://doi.org/10.1007/978-1-4419-0789-3_3
9. Kurose D, Furuya N, Tsuchiya K, Tsushima S, Evans HC. Endophytic fungi associated with Fallopia japonica (Polygonaceae) in Japan and their interactions with Puccinia polygoni-amphibii var. tovariae, a candidate for classical biological control. Fungal Biol. 2012; 116:785–91. https://doi.org/10.1016/j.fungbiol.2012.04.011 PMID: 22749165
10. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? Front Cell Infect Microbiol. 2012; 2. https://doi.org/10.3389/fcimb.2012.00104 PMID: 22919693
11. Ford SA, King KC. Harnessing the Power of Defensive Microbes: Evolutionary Implications in Nature and Disease Control. PLoS Pathog. 2016; 12:e1005465. https://doi.org/10.1371/journal.ppat.1005465 PMID: 27058881
12. Michel Fons TK Ana Gomez. Mechanisms of Colonisation and Colonisation Resistance of the Digestive Tract Part 2. Bacteria/Bacteria Interactions. Microb Ecol Health Dis. 2000; 12:240–6. https://doi.org/10.1080/089106000750060495
13. Schneitz C. Competitive exclusion in poultry—30 years of research. Food Control. 2005; 16:657–67. https://doi.org/10.1016/j.foodcont.2004.06.002
14. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature. 2008; 453:620–5. https://doi.org/10.1038/nature07008 PMID: 18509436
15. Chow J, Mazmanian SKA. Pathobiont of the Microbiota Balances Host Colonization and Intestinal Inflammation. Cell Host Microbe. 2010; 7:265–76. https://doi.org/10.1016/j.chom.2010.03.004 PMID: 20413095
16. Pathogens HM, Symbionts C. Pathobionts: Discovery and Functional Effects on the Host. ILAR J. 2015; 56:159–62. https://doi.org/10.1093/ilar/ilv007 PMID: 26323625
17. Shanahan F. Gut Microbes: From Bugs to Drugs. Am J Gastroenterol. 2010; 105:275–9. https://doi. org/10.1038/ajg.2009.729 PMID: 20068561
18. Chiu L, Bazin T, Truchetet M-E, Schaeverbeke T, Delhaes L, Pradeu T. Protective Microbiota: From Localized to Long-Reaching Co-Immunity. Front Immunol. 2017; 8. https://doi.org/10.3389/fimmu.2017.01678 PMID: 29270167
19. Lamoué-Smith E, Kelly D, De Cremoux I. Designing bugs as drugs: exploiting the gut microbiome. Am J Physiol Gastrointes t Liver Physiol. 2020 [cited. Feb 2021: 3. https://doi.org/10.1152/ajpgi.00381.2019 PMID: 33264062
20. Britton RA, Cani PD. Bugs as Drugs: Therapeutic Microbes for Prevention and Treatment of Disease. John Wiley & Sons; 2020.
21. Kamada N, Kim Y-G, Sham HP, Vallance BA, Puente JL, Martens EC, et al. Regulated Virulence Controls the Ability of a Pathogen to Compete with the Gut Microbiota. Science. 2012; 336:1325–9. https://doi.org/10.1126/science.1211183 PMID: 22582016
22. Louca S, Doebeli M. Transient dynamics of competitive exclusion in microbial communities. Environ Microbiol. 2016; 18:1863–74. https://doi.org/10.1111/1462-2920.13058 PMID: 26404023
23. King KC, Brockhurst MA, Vasieova O, Paterson S, Bettis A, Ford SA, et al. Rapid evolution of microbe-mediated protection against pathogens in a worm host. ISME J. 2016; 10:1915–24. https://doi.org/10.1038/ismej.2015.259 PMID: 26978164
24. Rooks MG, Garrett WS. Gut microbiota metabolites and host immunity Nat Rev Immunol. 2016; 16:341–52. https://doi.org/10.1038/nri.2016.42 PMID: 27230150
25. Brown EM, Sadarangani M, Finlay BB. The role of the immune system in governing host-microbe interactions in the intestine. Nat Immunol. 2013; 14:660–7. https://doi.org/10.1038/ni.2611 PMID: 23778793
26. Zeng H, Ishaq SL, Liu Z, Bukowski MR. Colonic aberrant crypt formation accompanies an increase of opportunistic pathogenic bacteria in C57BL/6 mice fed a high-fat diet. J Nutr Biochem. 2018; 54:18–27. https://doi.org/10.1016/j.jnutbio.2017.11.001 PMID: 29223827
27. McMurtry VE, Gupta RW, Tran L, Blanchard EE, Penn D, Taylor CM, et al. Bacterial diversity and Clostridia abundance decrease with increasing severity of necrotizing enterocolitis. Microbiome. 2015; 3. https://doi.org/10.1186/s40168-015-0075-8 PMID: 25810906

28. Boutin S, Bernatchez L, Audet C, Déroué N. Network Analysis Highlights Complex Interactions between Pathogen Host and Commensal Microbiota. PLoS ONE. 2013; 8. https://doi.org/10.1371/journal.pone.0068472 PMID: 23476845

29. Tovaglieri A, Sontheimer-Phelps A, Geirnaert A, Prantil-Baun R, Camacho DM, Chou DB, et al. Species-specific enhancement of enterohemorrhagic E. coli pathogenesis mediated by microbiome metabolites. Microbiome. 2019; 7:43. https://doi.org/10.1186/s40168-019-0650-5 PMID: 30890187

30. Tena D, Losa C, Medina MJ, Sáez-Nieto JA. Peritonitis caused by Bifidobacterium longum: Case report and literature review. Anaerobe. 2014; 27:27–30. https://doi.org/10.1016/j.an aero.2014.03.005 PMID: 24657157

31. Martinez J, Ok S, Smith S, Snoeck K, Day JP, Jiggins FM. Should Symbionts Be Nice or Selfish? Antiviral Effects of Wolbachia Are Costly but Reproductive Parasitism Is Not. PLoS Pathog. 2015; 11. https://doi.org/10.1371/journal.ppat.1005021 PMID: 26132467

32. Broderick NA, Raffa KF, Handelsman J. Midgut bacteria required for Bacillus thuringiensis insecticidal activity. PNAS. 2006; 103:15196–9. https://doi.org/10.1073/pnas.0604865103 PMID: 17005725

33. Wei G, Lai Y, Wang G, Chen H, Li F, Wang S. Insect pathogenic fungus interacts with the gut microbiota to accelerate mosquito mortality. PNAS. 2017; 114:5994–9. https://doi.org/10.1073/pnas.1703546114 PMID: 28533370

34. Chröstek E, Marialva MSP, Esteves SS, Weintert LA, Martinez J, Jiggins FM, et al. Wolbachia Variants Induce Differential Protection to Viruses in Drosophila melanogaster: A Phenotypic and Phylogenomic Analysis. PLoS Genet. 2013; 9:e1003896. https://doi.org/10.1371/journal.pgen.1003896 PMID: 24348259

35. Vorburger C, Gouskov A. Only helpful when required: a longevity cost of harbouring defensive symbionts. J Evol Biol. 2011; 24:1611–7. https://doi.org/10.1111/j.1420-9101.2011.02292.x PMID: 21569156

36. Bletz MC, Kelly M, Sabino-Pinto J, Bales E, Van Praet S, Bert W, et al. Disruption of skin microbiota contributes to salamander disease. Proc R Soc B. 2018; 20180758:285. https://doi.org/10.1098/rspb.2018.0758 PMID: 30135150

37. Becker MH, Walke JB, Cikaneck S, Savage AE, Mattheus N, Santiago CN, et al. Composition of symbiotic bacteria predicts survival in Panamanian golden frogs infected with a lethal fungus. Proc R Soc B Biol Sci. 2015; 282:20142881. https://doi.org/10.1098/rspb.2014.2881 PMID: 25788591

38. Crane J, Barthow C, Kang J, Hood F, Stanley T, Wickens K. Probiotics for humans: hoax, hype, hope, or help? J R Soc N Z. 2020; 50:456–69. https://doi.org/10.1108/s13063-020-04322-1 PMID: 32366320

39. Keeney KM, Finlay BB. Enteric pathogens exploit the microbiota-generated nutritional environment of the gut. Curr Opin Microbiol. 2011; 14:92–8. https://doi.org/10.1016/j.mib.2010.12.012 PMID: 21268581

40. Bäumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. Nature. 2016; 535:85–93. https://doi.org/10.1038/nature18849 PMID: 27383983

41. Cameron EA, Frenemies SV. Signaling and Nutritional Integration in Pathogen-Microbiota-Host Interactions. Cell Host Microbe. 2015; 18:275–84. https://doi.org/10.1016/j.chom.2015.08.007 PMID: 26355214

42. Pacheco AR, Sperandio V. Enteric Pathogens Exploit the Microbiota-generated Nutritional Environment of the Gut. Metabolism and Bacterial Pathogenesis. John Wiley & Sons, Ltd; 2015. pp. 279–296. https://doi.org/10.1128/9781555818883.ch13

43. Li M, Wei Z, Wang J, Jousset A, Friman V-P, Xu Y, et al. Facilitation promotes invasions in plant-associated microbial communities. Ecol Lett. 2019; 22:149–58. https://doi.org/10.1111/ele.13177 PMID: 30460736

44. Salem H, Onchuru TO, Bauer E, Kaltenpoth M. Symbiont transmission entails the risk of parasite infection. Biol Lett. 2015; 11:20150840. https://doi.org/10.1098/rsbl.2015.0840 PMID: 26673937

45. Jia D, Mao Q, Chen Y, Liu Y, Chen Q, Wu W, et al. Insect symbiotic bacteria harbour viral pathogens for transovarial transmission. Nat Microbiol. 2017; 2:1–7. https://doi.org/10.1038/nmicrobiol.2017.25 PMID: 28263320

46. Robinson CM. Enteric viruses exploit the microbiota to promote infection. Curr Opin Virol. 2019; 37:58–62. https://doi.org/10.1016/j.coviro.2019.06.002 PMID: 31284078

47. Hayes KS, Bancroft AJ, Goldrick M, Portsmouth C, Roberts IS, Grecins RK. Exploitation of the Intestinal Microflora by the Parasitic Nematode Trichuris muris. Science. 2010; 328:1391–4. https://doi.org/10.1126/science.1187703 PMID: 20538949
48. Kuss SK, Best GT, Etheredge CA, Pruissers AJ, Frierson JM, Hooper LV, et al. Intestinal Microbiota Promote Enteric Virus Replication and Systemic Pathogenesis. Science. 2011; 334:249–52. https://doi.org/10.1126/science.1211057 PMID: 21998395

49. Reynolds LA, Smith KA, Filbey KJ, Marcus Y, Hewitson JP, Redpath SA, et al. Commensal-pathogen interactions in the intestinal tract: lactobacilli promote infection with, and are promoted by. helmint parasites Gut Microbes. 2014; 5:522–32. https://doi.org/10.4161/gmic.32155 PMID: 25144609

50. Buffie CG, Bucci V, Stein RR, McKenney PT, Ling L, Gobourne A, et al. Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. Nature. 2015; 517:205–8. https://doi.org/10.1038/nature13828 PMID: 25337874

51. Sorbara MT, Pamer EG. Interbacterial mechanisms of colonization resistance and the strategies pathogens use to overcome them. Mucosal Immunol. 2019; 12:1–9. https://doi.org/10.1038/s41385-018-0053-0 PMID: 29988120

52. Reeves AE, Theriot CM, Bergin IL, Huffnagle GB, Schloss PD, Young VB. The interplay between microbiome dynamics and pathogen dynamics in a murine model of Clostridium difficile Infection. Gut Microbes. 2011; 2:145–58. https://doi.org/10.4161/gmic.2.3.16333 PMID: 21804357

53. Samarkos M, Mastrogiani E, Kampouropoulou O. The role of gut microbiota in Clostridium difficile infection. Eur J Intern Med. 2018; 50:28–32. https://doi.org/10.1016/j.ejim.2018.02.006 PMID: 29428498

54. Taur Y, Pamer EG. The Intestinal Microbiota and Susceptibility to Infection in Immunocompromised Patients. Curr Opin Infect Dis. 2013; 26:332–7. https://doi.org/10.1097/QCO.0b013e3283630dd3 PMID: 23806896

55. Rojas I-G, Padgett DA, Sheridan JF, Marucha PT. Stress-Induced Susceptibility to Bacterial Infection During Cutaneous Wound Healing. Brain Behav Immun. 2002; 16:74–84. https://doi.org/10.1006/brbi.2000.0619 PMID: 11846442

56. Dai W-F, Zhang J-J, Qiu Q-F, Chen J, Yang W, Ni S, et al. Starvation stress affects the interplay among shrimp gut microbiota, digestion and immune activities Fish Shellfish Immunol. 2018; 80:191–9. https://doi.org/10.1016/j.fsi.2018.05.040 PMID: 29803665

57. Kim E-K, Lee K-A, Hyeon DY, Kyung M, Jun K-Y, Seo SH, et al. Bacterial Nucleoside Catabolism Controls Quorum Sensing and Commensal-to-Pathogen Transition in the Drosophila Gut Cell Host Microbe. 2020; 27:345–357.e6. https://doi.org/10.1016/j.chom.2020.01.025 PMID: 32078802

58. Lee K-A, Kim S-H, Kim E-K, Ha E-M, You H, Kim B, et al. Bacterial-Derived Uracil as a Modulator of Mucosal Immunity and Gut-Microbe Homeostasis in Drosophila. Cell. 2013; 153:797–811. https://doi.org/10.1016/j.cell.2013.04.009 PMID: 23663779

59. Dogan B, Suzuki H, Herlekar D, Sartor RB, Campbell BJ, Roberts CL, et al. Inflammation-associated adherent-invasive Escherichia coli are enriched in pathways for use of propanedio l and iron and M-cell translocation. Inflamm Bowel Dis. 2014; 20:1919–32. https://doi.org/10.1097/MIB.000000000000183 PMID: 25230163

60. Samant S, Lee H, Ghassemi M, Chen J, Cook JL, Mankin AS, et al. Nucleotide Biosynthesis Is Critical for Growth of Bacteria in Human Blood. PLoS Pathog. 2008; 4. https://doi.org/10.1371/journal.ppat.0040037 PMID: 18298099

61. Hopkins MJ, Sharp R, Macfarlane GT. Variation in human intestinal microbiota with age. Dig Liver Dis. 2002; 34:S12–8. https://doi.org/10.1016/s1590-8658(02)80157-8 PMID: 12408433

62. Barreto HC, Sousa A, Gordo I. The Landscape of Adaptive Evolution of a Gut Commensal Bacteria in Aging Mice. Curr Biol. 2020; 30:1102–1109.e5. https://doi.org/10.1016/j.cub.2020.01.037 PMID: 32142696

63. Chatzigiannidou I, Teughe ls W, Van de Wiele T, Boon N. Oral biofilms exposure to chlorhexidine results in altered microbial composition and metabolic profile. NPJ Biofilms Microbiomes. 2020; 6:1–8. https://doi.org/10.1038/s41522-019-0111-8 PMID: 31908831

64. Vötösch D, Willenborg M, Weldearegay YB, Valentin-Weigand P. Streptococcus suis – The “Two Faces” of a Pathobiont in the Porcine Respiratory Tract. Front Microbiol. 2018; 9. https://doi.org/10.3389/fmicb.2018.00480 PMID: 29599763

65. Ryu J-H, Kim S-H, Lee H-Y, Bai JY, Nam Y-D, Bae J-W, et al. Innate Immune Homeostasis by the Homeobox Gene Caudal and Commensal-Gut Mutualism in Drosophila. Science. 2008; 319:777–82. https://doi.org/10.1126/science.1149357 PMID: 18218863

66. Meylan P, Lang C, Mermod S, Johannsen A, Norrenberg S, Hohl D, et al. Skin Colonization by Staphylococcus aureus Precedes the Clinical Diagnosis of Atopic Dermatitis in Infancy. J Investig Dermatol. 2017; 137:2497–504. https://doi.org/10.1016/j.jid.2017.07.834 PMID: 28843230

67. Hajishengallis G, Liang S, Payne MA, Hashim A, Jotwani R, Eskan MA, et al. Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease through the Commensal Microbiota and
68. Hube B. From commensal to pathogen: stage- and tissue-specific gene expression of Candida albicans. Curr Opin Microbiol. 2004; 7:336–41. https://doi.org/10.1016/j.mib.2004.06.003 PMID: 15288621

69. Duell BL, Su Y-C, Riesbeck K. Host–pathogen interactions of nontypeable Haemophilus influenzae: from commensal to pathogen. FEBS Lett. 2016; 590:3840–53. https://doi.org/10.1016/j.febslet.2016.04.003 PMID: 27508518

70. Marks LR, Davidson BA, Knight PR, Hakansson AP. Interkingdom Signaling Induces Streptococcus pneumoniae Biofilm Dispersion and Transition from Asymptomatic Colonization to Disease. MBio. 2013; 4:e00438–13, mBio.00438-13. https://doi.org/10.1128/mBio.00438-13 PMID: 23882016

71. Theriot CM, Koenigsalknecht MJ, Carlson PE, Hatton AM, Li B, et al. Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to Clostridium difficile infection. Nat Commun. 2014; 5:3114. https://doi.org/10.1038/ncomms4114 PMID: 24445449

72. Becattini S, Taur Y, Pamer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. Trends Mol Med. 2016; 22:458–78. https://doi.org/10.1016/j.molmed.2016.04.003 PMID: 27178527

73. Casals-Pascual C, Vergara A, Vila J. Intestinal microbiota and antibiotic resistance: Perspectives and solutions. Hum Microbiol J. 2018; 9:11–5. https://doi.org/10.1016/j.humic.2018.05.002

74. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. J Clin Invest. 2014; 124:4212–8. https://doi.org/10.1172/JCI72333 PMID: 25271726

75. Greenwood C, Morrow AL, Lagomarino AJ, Altaye M, Taft DH, Yu Z, et al. Early Empiric Antibiotic Use in Preterm Infants Is Associated with Lower Bacterial Diversity and Higher Relative Abundance of Enterobacter. J Pediatr. 2014; 165:23–9. https://doi.org/10.1016/j.jpeds.2014.01.010 PMID: 24529620

76. Mason KL, Stepien TA, Blum JE, Holt JF, Labbe NH, Rush JS, et al. From Commensal to Pathogen: Translocation of Enterococcus faecalis from the Midgut to the Hemocoe l of Manduca sexta. MBio. 2011; 2. https://doi.org/10.1128/mBio.00065-11 PMID: 21586646

77. Kitamoto S, Nagao-Kitamoto H, Jiao Y, Gillilland MG, Hayashi A, Imai J, et al. The Intermucosal Connection between the Mouth and Gut in Commensal Pathobiont-Driven Collitis. Cell. 2020; 182:447–462.e14. https://doi.org/10.1016/j.cell.2020.05.048 PMID: 32758418

78. Soares FS, Amaral FC, Silva NLC, Valente MR, Santos LKR, Yamashiro LH, et al. Antibiotic-Induced Pathobiont Dissemination Accelerates Mortality in Severe Experimental Pancreatitis. Front Immunol. 2017; 8. https://doi.org/10.3389/fimmu.2017.01890 PMID: 29375557

79. Caccia S, Lelio ID, Storia AL, Marinelli A, Varricchio P, Franzetti E, et al. Midgut microbiota and host immunocompetence underlie Bacillus thuringiensis killing mechanism. PNAS. 2016; 113:9486–91. https://doi.org/10.1073/pnas.1521741113 PMID: 27506800

80. Wardwell LH, Huttenhower C, Garrett WS. Current Concepts of the Intestinal Microbiota and the Pathogenesis of Infection. Curr Infect Dis Rep 2011; 13:28–34. https://doi.org/10.1007/s11908-010-0147-7 PMID: 21308452

81. McCarville JL, Chen GY, Cuevas VD, Troha K, Ayres JS. Microbiota Metabolites in Health and Disease. Annu Rev Immunol. 2020; 38:147–70. https://doi.org/10.1146/annurev-immunol-071219-125715 PMID: 32340573

82. Hryckowian AJ, Van Treuren W, Smits SA, Davis NM, Gardner JO, Bouley DM, et al. Microbiota-accessible carbohydrates suppress Clostridium difficile infection in a murine model. Nat Microbiol. 2018; 3:662–9. https://doi.org/10.1038/s41564-018-0150-6 PMID: 29682697

83. Roman MS, Wagner A. An enormous potential for niche construction through bacterial cross-feeding in a homogeneous environment. PLoS Comput Biol. 2018; 14:e1006340. https://doi.org/10.1371/journal.pcbi.1006340 PMID: 30040834

84. Curtis MM, Hu Z, Klimko C, Narayanan S, Deberardinis R, Sperandio V. The Gut Commensal Bacteroides thetaiotaomicron Exacerbates Enteric Infection through Modification of the Metabolic Landscape. Cell Host Microbe. 2014; 16:759–69. https://doi.org/10.1016/j.chom.2014.11.005 PMID: 25498343

85. Lustri BC, Sperandio V, Moreira CG. Bacterial Chat: Intestinal Metabolites and Signals in Host-Microbiota-Pathogen Interactions. Andrews-Polymenis HL, editor. Infect Immun. 2017; 85:e00476–17e00476-17. https://doi.org/10.1128/IAI.00476-17 PMID: 28947641

86. Lloyd-Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, et al. Multiomics of the gut microbial ecosystem in inflammatory bowel diseases. Nature. 2019; 569:655–62. https://doi.org/10.1038/s41586-019-1237-9 PMID: 31142855
87. Zierer J, Jackson MA, Kastenmüller G, Mangoi no M, Long T, Telenti A, et al. The fecal metabo lome as a functional readout of the gut microbiome. Nat Genet. 2018; 50:790–5. https://doi.org/10.1038/s41588-018-0135-7 PMID: 29808030

88. Zhang X, Li L, Butcher J, Stintzi A, Fig eys D. Advancing functional and translational micro biome research using meta-omics approaches. Microbiome. 2019; 7:154. https://doi.org/10.1186/s40168-019-0767-8 PMID: 31810497

89. Kwong WK, Mancenido AL, Moran NA. Immune system stimulation by the native gut microbiota of honey bees. R Soc Open Sci. 2017; 4:170003. https://doi.org/10.1098/rsos.170003 PMID: 28386455

90. Muhammad A, Habineza P, Ji T, Hou Y, Shi Z. Intestinal Microbiota Confer Protection by Priming the Immune System of Red Palm Weevil Rhynchophorus ferrugineus Olivier (Coleoptera: Dryophthoridae). Front Physiol. 2019; 10. https://doi.org/10.3389/fphys.2019.01303 PMID: 31681013

91. Cross ML. Microbes versus microbes: immune signals generated by probiotic lactobacilli and their role in protection against microbial pathogens. FEMS Immunol Med Microbiol. 2002; 34:245–53. https://doi.org/10.1111/j.1574-695X.2002.tb00632.x PMID: 12443824

92. Gómez L, Comstock LE. Bacterial antagonism in host-associated microbial communities. Science. 2018; 361. https://doi.org/10.1126/science.aat2456 PMID: 30237322

93. Brown SP, Le Chat L, Taddei F. Evolution of virulence: triggering host inflammation allows invading pathogens to exclude competitors. Ecol Lett. 2008; 11:44–51. https://doi.org/10.1111/j.1461-0248.2007.01125.x PMID: 18021245

94. Li RW, Wu S, Li W, Navarro K, Couch RD, Hill D, et al. Alterations in the porcine colon microbiota induced by the gastrointestinal nematode Trichuris suis. Infect Immun. 2012; 80:2150–7. https://doi.org/10.1128/IAI.00141-12 PMID: 22493085

95. Grassl N, Kulak NA, Pichler G, Geyer PE, Jung J, Schubert S, et al. Ultra-deep and quantitative saliva proteome reveals dynamics of the oral microbiome. Genome Med. 2016; 8:44. https://doi.org/10.1186/s13073-016-0293-0 PMID: 27102203

96. Campbell LJ, Hammond SA, Price SJ, Sharma MD, Garner TWJ, Biro I, et al. A novel approach to wildlife transcriptomics provides evidence of disease-mediated differential expression and changes to the microbiome of amphibian populations. Mol Ecol. 2018; 27:1413–27. https://doi.org/10.1111/mec.14526 PMID: 29420865

97. Phalak P, Henson MA. Metabolic Modeling of Clostridium difficile Associated Dysbiosis of the Gut Microbiota. PRO. 2019; 7:97. https://doi.org/10.3390/pr7020097

98. Koskella B, Demengeot J, Gordo I. Adaptive immunity increases the pace and predictability of evolutionary change in commensal gut bacteria. Nat Commun. 2015; 6:8945. https://doi.org/10.1038/ncomms9945 PMID: 26615893

99. Tso GHW, Reales-Calderon JA, Tan ASM, Sem X, Le GTT, Tan TG, et al. Experimental evolution of a fungal pathogen into a gut symbiont. Science. 2018; 362:589–95. https://doi.org/10.1126/science.aat0537 PMID: 30385579

100. Gandon S, Michalakis Y. Evolution of parasite virulence against qualitative or quantitative host resistance. Philos Trans R Soc Lond B Biol Sci. 2000; 267:985–90. https://doi.org/10.1098/rspb.2000.1100 PMID: 10874747

101. Hughes JM. Preserving the lifesaving power of antimicrobial agents. JAMA. 2011; 305:1027–8. https://doi.org/10.1001/jama.2011.279 PMID: 21343545

102. Bacterial Vaccines LM. Serotype Replacement: Lessons from Haemophilus influenzae and Prospects for Streptococcus pneumoniae. Emerg Infect Dis. 1999; 5:336–45. https://doi.org/10.3201/eid0503.990304 PMID: 10341170

103. Brown SP, Fredrik Ingles R, Taddei F. Evolutionary ecology of microbial wars: within-host competition and (incidental) virulence. Evol Appl. 2009; 2:32–9. https://doi.org/10.1111/j.1752-4571.2008.00059.x PMID: 25567845
107. Martínez J, Bruner-Montero G, Arunkumar R, Smith SCL, Day JP, Longdon B, et al. Virus evolution in Wolbachia-infected Drosophila. Proc R Soc B Biol Sci. 2017; 286 (2019):2019. https://doi.org/10.1098/rspb.2019.2117 PMID: 31662085

108. Rouchet R, Vorburger C. Experimental Evolution of Parasitoid Infectivity on Symbiont-Protected Hosts Leads to the Emergence of Genotype Specificity. Evolution. 2014; 68:1607–1616. https://doi.org/10.1111/evo.12377 PMID: 24495148

109. McNally L, Vale PF, Brown SP. Microbiome engineering could select for more virulent pathogens. bioRxiv. 2015;027854. https://doi.org/10.1101/027854

110. Ford SA, Kao D, Williams D, King KC. Microbe-mediated host defence drives the evolution of reduced pathogen virulence. Nat Commun. 2016; 7:1–9. https://doi.org/10.1038/ncomms13430 PMID: 27845328

111. Gamage SD, Patton AK, Hanson JF, Diversity WAA. Host Range of Shiga Toxin-Encoding Phage. Infect Immun. 2004; 72:7131–9. https://doi.org/10.1128/IAI.72.12.7131-7139.2004 PMID: 15557637

112. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007; 5:339–44. https://doi.org/10.1016/j.cgh.2006.12.027 PMID: 17368233

113. Lima AA, Lyerly DM, Wilkins TD, Innes DJ, Guerrant RL. Effects of Clostridium difficile toxins A and B in rabbit small and large intestine in vivo and on cultured cells in vitro. Infect Immun. 1988; 56:582–8. https://doi.org/10.1128/IAI.56.3.582-588.1988 PMID: 33430528

114. Drew et al. (In press). Microbial evolution and transitions along the parasite–mutualist continuum. Nat Rev Microbiol. 2021.

115. Ayres JS, Trinidad NJ, Vance RE. Lethal inflammasome activation by a multidrug-resistant pathobiont upon antibiotic disruption of the microbiota. Nat Med. 2012; 18:799–806. https://doi.org/10.1038/nm.2729 PMID: 22522562

116. Schwarz RS, Moran NA, Evans JD. Early gut colonizers shape parasite susceptibility and microbiota composition in honey bee workers. Proc Natl Acad Sci U S A. 2016; 113:9345–50. https://doi.org/10.1073/pnas.1606631113 PMID: 27482088

117. Broderick NA, Robinson CJ, McMahon MD, Holt J, Handelsman J, Raffa KF. Contributions of gut bacteria to Bacillus thuringiensis-induced mortality vary across a range of Lepidoptera. BMC Biol. 2009; 7:11. https://doi.org/10.1186/1741-7007-7-11 PMID: 19261175

118. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection. Ann Intern Med. 2016; 165:609–16. https://doi.org/10.7326/M16-0271 PMID: 27547925

119. Ramsey MM, Rumbaugh KP, Whiteley M. Metabolite Cross-Feeding Enhances Virulence in a Model Polymicrobial Infection. PLoS Pathog. 2011; 7:e1002012. https://doi.org/10.1371/journal.ppat.1002012 PMID: 21483753

120. Stacy A, Fleming D, Lamont RJ, Rumbaugh KP, Whiteley M. A Commensal Bacterium Promotes Virulence of an Opportunistic Pathogen via Cross-Respiration. MBio. 2016; 7:e00782-16. https://doi.org/10.1128/mBio.00782-16 PMID: 27353758

121. Proença JT, Barral DC, Gordo I. Commensal-to-pathogen transition: One-single transposon insertion results in two pathoadaptive traits in Escherichia coli-macrophage interaction. Sci Rep. 2017; 7:4504. https://doi.org/10.1038/s41598-017-04081-1 PMID: 28674418

122. Huang G. Regulation of phenotypic transitions in the fungal pathogen Candida albicans. Virulence. 2012; 3:251–61. https://doi.org/10.4161/viru.20010 PMID: 22546903

123. Armistead B, Oler E, Adams Waldorf K, Rajagopal L. The Double Life of Group B Streptococcus: Asymptomatic Colonizer and Potent Pathogen. J Mol Biol. 2019; 431:2914–31. https://doi.org/10.1016/j.jmb.2019.01.035 PMID: 30711542

124. Franklin L, Nobbs AH, Bricio-Moreno L, Wright CJ, Maddocks SE, Sahota JS, et al. The AgI/II Family Adhesin AspA Is Required for Respiratory Infection by Streptococcus pyogenes. PLoS ONE. 2013; 8. https://doi.org/10.1371/journal.pone.0062433 PMID: 2363083

125. Schmitt CK, Meysick KC, O'Brien AD. Bacterial toxins: friends or foes? Emerg Infect Dis. 1999; 5:224–34. https://doi.org/10.3201/eid0502.990206 PMID: 10221874

126. Rudkin JK, McLoughlin RM, Preston A, Massey RC. Bacterial toxins: Offensive, defensive, or something else altogether? PLoS Pathog. 2017; 13. https://doi.org/10.1371/journal.ppat.1006452 PMID: 28934339

127. King KC. Defensive symbionts. Curr Biol. 2019; 29:R78–80. https://doi.org/10.1016/j.cub.2018.11.028 PMID: 30721677
128. Martinez J, Cogni R, Cao C, Smith S, Illingworth CJR, Jiggins FM. Addicted? Reduced host resistance in populations with defensive symbionts Proc R Soc B Biol Sci. 2016; 283:20160778. https://doi.org/10.1098/rspb.2016.0778 PMID: 27335421

129. Osborne SE, Iturbe-Ormaetxe I, Brownlie JC, O'Neill SL, Johnson KN. Antiviral Protection and the Importance of Wolbachia Density and Tissue Tropism in Drosophila simulans. Appl Environ Microbiol. 2012; 78:6922–9. https://doi.org/10.1128/AEM.01727-12 PMID: 22843518

130. Ye YH, Woolfit M, Rancés E, O'Neill SL, McGraw EA. Wolbachia-Associated Bacterial Protection in the Mosquito Aedes aegypti. PLoS Negl Trop Dis. 2013; 7:e2362. https://doi.org/10.1371/journal.pntd.0002362 PMID: 23951381

131. Kambiris Z, Cook PE, Phuc HK, Sinkins SP. Immune activation by life-shortening Wolbachia and reduced filarial competence in mosquitoes. Science. 2009; 326:134–6. https://doi.org/10.1126/science.1177531 PMID: 19797660

132. Cayetano L, Rothacher L, Simon J-C, Vorburger C. Cheaper is not always worse: strongly protective isolates of a defensive symbiont are less costly to the aphid host. Proc Biol Sci. 2015; https://doi.org/10.1098/rspb.2014.2333 PMID: 25473015

133. Mathé-Hubert H, Kaech H, Ganesanandamoorthy P, Vorburger C. Evolutionary costs and benefits of infection with diverse strains of Spiroplasma in pea aphids*. Evolution. 2019; 73:1466–81. https://doi.org/10.1111/evol.13740 PMID: 30990223

134. Hodgkin J, Félix M-A, Clark LC, Stroud D, Gravato-Nobre MJ. Two Leucobacter Strains Exert Complementary Virulence on Caenorhabditis Including Death by Worm-Star Formation. Curr Biol. 2013; 23:2157–61. https://doi.org/10.1016/j.cub.2013.08.060 PMID: 24206844

135. Flores GE, Caporaso JG, Henley JB, Rideout JR, D’Olegra D, Chase J, et al. Temporal variability is a personalized feature of the human microbiome. Genome Biol. 2014; 15:531. https://doi.org/10.1186/s13059-014-0531-y PMID: 25517225

136. Ma Z. (Sam), Li L, Gotelli NJ. Diversity-disease relationships and shared species analyses for human microbiome-associated diseases. ISME J. 2019; 13:1911–9. https://doi.org/10.1038/s41396-019-0395-y PMID: 30894688

137. Zaneveld JR, McMinds R, Vega Thurber R. Stress and stability: applying the Anna Karenina principle to animal microbiomes. Nat Microbiol. 2017; 2:1–8. https://doi.org/10.1038/s41564-017-0121 PMID: 28836573

138. Koumans EH, Sternberg M, Bruce C, McQuillan G, Kendrick J, Sutton M, et al. The Prevalence of Bacterial Vaginosis in the United States, 2001–2004; Associations With Symptoms, Sexual Behaviors, and Reproductive Health. Sex Transm Dis. 2007; 34: 864–869. https://doi.org/10.1097/OLQ.0b013e318074e565 PMID: 17621244

139. Xu J, Peng J-J, Yang W, Fu K, Zhang Y. Vaginal microbiomes and ovarian cancer: a review. Am J Cancer Res. 2020; 10:743–56. PMID: 32266088

140. Nasidinis D, Linhares IM, Ledger WJ, Witkin SS. Bacterial vaginosis: a critical analysis of current knowledge. BJOG. 2017; 124:61–9. https://doi.org/10.1111/1471-0528.14209 PMID: 27396541

141. Nelson TM, Brotman RM, Ravel J, Walk ST, Yeoman CJ. Vaginal biogenic amines: biomarkers of bacterial vaginosis or precursors to vaginal dysbiosis? Front Physiol. 2015; 6. https://doi.org/10.3389/fphys.2015.00253 PMID: 26483694

142. Yeoman CJ, Thomas SM, Miller MEB, Ulanov AV, Torralba M, Lucas S, et al. A Multi-Omic Systems-Based Approach Reveals Metabolic Markers of Bacterial Vaginosis and Insight into the Disease. PLoS ONE. 2013; 8:e56111. https://doi.org/10.1371/journal.pone.0056111 PMID: 23405259

143. Lynch KE, Parke EC, O’Malley MA. How causal are microbiomes? A comparison with the Helicobacter pylori explanation of ulcers. Biol Philos. 2019; 34:1–24. https://doi.org/10.1007/s10539-019-9702-2

144. Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or Exaggerating Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated Rodents. Cell. 2020; 180:221–32. https://doi.org/10.1016/j.cell.2019.12.025 PMID: 31978342

145. Microbiome FMA. Focus on Causation and Mechanism. Cell. 2018; 174:785–90. https://doi.org/10.1016/j.cell.2018.07.038 PMID: 30096310

146. Giovanni MY, Schneider JS, Calder T, Fauci AS. Refocusing Human Microbiota Research in Infectious and Immune-mediated Diseases: Advancing to the Next Stage. J Infect Dis 2020 [cited 1 Feb 2021]. https://doi.org/10.1093/infdis/jiaa706 PMID: 33188418

147. Goodman AL, Kallstrom G, Faith JJ, Reyes A, Moore A, Dantas G, et al. Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. PNAS. 2011; 108:6252–7. https://doi.org/10.1073/pnas.1102938108 PMID: 21436049
148. Yousef NH, Couger MB, McCully AL, Criado AEG, Elshahed MS. Assessing the global phylum level diversity within the bacterial domain: A review. J Adv Res. 2015; 6:269–82. https://doi.org/10.1016/j.jare.2014.10.005 PMID: 26257925

149. Steen AD, Critts-Christoph A, Carini P, DeAngelis KM, Fierer N, Lloyd KG, et al. High proportions of bacteria and archaea across most biomes remain uncultured. ISME J. 2019; 13:3126–30. https://doi.org/10.1038/s41396-019-0484-y PMID: 31388130

150. Gordon JI, Klaenhammer TR. A rendezvous with our microbes PNAS. 2011; 108:4513–5. https://doi.org/10.1073/pnas.1101958108 PMID: 21406595

151. Mooser C, Gomez de Aguero M, Ganal-Vovarburg SC. Standardization in host-microbiota interaction studies: challenges, gnotobiology as a tool, and perspective Curr Opin Microbiol. 2018; 44:50–60. https://doi.org/10.1016/j.mib.2018.07.007 PMID: 30056329

152. Dirksen P, Assie A, Zimmermann J, Zhang F, Tietje A-M, Marsh SA, et al. CeMbio—The Caenorhabditis elegans Microbiome Resource. G3 Genes|Genomes|Genetics. 2020; 10:3025–39. https://doi.org/10.1534/g3.120.401309 PMID: 32669368

153. Bai Y, Müller DB, Srinivas G, Garrido-Oter R, Potthoff E, Rott M, et al. Functional overlap of the Arabidopsis leaf and root microbiota. Nature. 2015; 528:364–9. https://doi.org/10.1038/nature16192 PMID: 26633631

154. Lagkouvardos I, Pukall R, Abt B, Foesel BU, Meier-Kolthoff JP, Kumar N, et al. The Mouse Intestinal Bacterial Collection (miBC) provides host-specific insight into cultured diversity and functional potential of the gut microbiota. Nat Microbiol. 2016; 1:1–15. https://doi.org/10.1038/nmicrobiol.2016.131 PMID: 27670113

155. Forster SC, Kumar N, Anonye BO, Almeida A, Viciani E, Stares MD, et al. A human gut bacterial genome and culture collection for improved metagenomic analyses. Nat Biotechnol. 2019; 37:186–92. https://doi.org/10.1038/s41587-018-0009-7 PMID: 30718869

156. Hoseinifar SH, Sun Y-Z, Wang A, Zhou Z. Probiotics as Means of Diseases Control in Aquaculture, a Review of Current Knowledge and Future Perspectives. Front Microbiol. 2018; 9. https://doi.org/10.3389/fmicb.2018.02429 PMID: 30369918

157. Audisio MC. Gram-Positive Bacteria with Probiotic Potential for the Apis mellifera L. Honey Bee: The Experience in the Northwest of Argentina. Probiotics Antimicrob Proteins. 2017; 9:22–31. https://doi.org/10.1007/s12602-016-9231-0 PMID: 27655068

158. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol. 2019; 16:605–16. https://doi.org/10.1038/s41575-019-0173-3 PMID: 31296969

159. Silva DR, Sardi J de CO, Pitangui NdeS, Roque SM, Silva ACB da, Rosalen PL. Probiotics as an alternative antimicrobial therapy: Current reality and future directions. J Funct Foods. 2020; 73:104080. https://doi.org/10.1016/j.jff.2020.104080

160. Antwis RE, Harrison XA. Probiotic consortia are not uniformly effective against different amphibian chytrid pathogen isolates. Mol Ecol. 2018; 27:577–89. https://doi.org/10.1111/mec.14456 PMID: 29218845

161. Harrison XA, Sewell T, Fisher M, Antwis RE. Designing Probiotic Therapies With Broad-Spectrum Activity Against a Wildlife Pathogen. Front Microbiol. 2020; 10. https://doi.org/10.3389/fmicb.2019.03134 PMID: 32038568

162. Küng D, Bigler L, Davis LR, Gratwicke B, Griffith E, Woodhams DC. Stability of Microbiota Facilitated by Host Immune Regulation: Informing Probiotic Strategies to Manage Amphibian Disease. PLoS ONE. 2014; 9. https://doi.org/10.1371/journal.pone.0087101 PMID: 24489847

163. Lo Vecchio A, Cohen MB. Fecal microbiota transplantation for Clostridium difficile infection: benefits and barriers. Curr Opin Gastroenterol. 2014; 30:47–53. https://doi.org/10.1097/MOG.000000000000023 PMID: 24275671

164. Li Y-T, Cai H-F, Wang Z-H, Xu J, Fang J-Y. Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for Clostridium difficile infection. Aliment Pharmacol Ther. 2016; 43:445–57. https://doi.org/10.1111/apt.13492 PMID: 26662643

165. Cryan JF, O’Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011; 23:187–92. https://doi.org/10.1111/j.1365-2982.2010.01664.x PMID: 21303428

166. Lee P, Yacsynsh BN, Yacsynsh MB. Gut microbiota and obesity: An opportunity to alter obesity through faecal microbiota transplant (FMT). Diabetes Obes Metab. 2019; 21:479–90. https://doi.org/10.1111/dom.13561 PMID: 30328245

167. Rossen EC, Mauri C. A clinical update on the significance of the gut microbiota in systemic autoimmunity. J Autoimmun. 2016; 74: 85–93. https://doi.org/10.1016/j.jaut.2016.06.009 PMID: 27481556
168. Kurokawa S, Kishimoto T, Mizuno S, Masaoka T, Naganuma M, Liang K, et al. The effect of fecal microbiota transplantation on psychiatric symptoms among patients with irritable bowel syndrome, functional diarrhea and functional constipation: An open-label observational study. J Affect Disord. 2018; 235:506–12. https://doi.org/10.1016/j.jad.2018.04.038 PMID: 29684865

169. Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature. 2011; 469:543–7. https://doi.org/10.1038/nature09646 PMID: 21270894

170. Sotoudegan F, Daniali M, Hassani S, Nikfar S, Abdollahi M. Reappraisal of probiotics’ safety in human. Food Chem Toxicol. 2019; 129:22–9. https://doi.org/10.1016/j.fct.2019.04.032 PMID: 31009735

171. Liong M-T. Safety of probiotics: translocation and infection. Nutr Rev. 2008; 66:192–202. https://doi.org/10.1111/j.1753-4887.2008.00024.x PMID: 18366533

172. Butel M-J. Probiotics, gut microbiota and health. Med Mal Infect. 2014; 44:1–8. https://doi.org/10.1016/j.medmal.2013.10.002 PMID: 24290962

173. Marteau P, Shanahan F. Basic aspects and pharmacology of probiotics: an overview of pharmacokinetics, mechanisms of action and side-effects. Best Pract Res Clin Gastroenterol. 2003; 17:725–40. https://doi.org/10.1016/s1521-6918(03)00055-6 PMID: 14507584

174. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11:506–14. https://doi.org/10.1038/nrgastro.2014.66 PMID: 24912386

175. Swain Ewald HA, Ewald PW, Selection N. The Microbiome and Public Health Yale J Biol Med. 2018; 91:445–55. PMID: 30588210

176. Chen YE, Fischbach MA, Belkaid Y. Skin microbiota–host interactions. Nature. 2018; 553:427–36. https://doi.org/10.1038/nature25177 PMID: 29364286

177. Shanahan F. The gut microbiota—a clinical perspective on lessons learned. Nat Rev Gastroenterol Hepatol. 2012; 9:609–14. https://doi.org/10.1038/nrgastro.2012.145 PMID: 22891009

178. Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, Võsa U, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019; 51:600–5. https://doi.org/10.1038/s41588-019-0350-x PMID: 30778224

179. Surana NK, Kasper DL. Moving beyond microbiome-wide associations to causal microbe identification. Nature. 2017; 552:244–7. https://doi.org/10.1038/nature25019 PMID: 29211710

180. Eloe-Fadrosh EA, Brady A, Crabtree J, Drabek EF, Ma B, Mahurkar A, et al. Functional Dynamics of the Gut Microbiome in Elderly People during Probiotic Consumption. MBio. 2015; 6. https://doi.org/10.1128/mBio.00231-15 PMID: 25873374

181. Burke C, Steinberg P, Rusch D, Kjelleberg S, Thomas T. Bacterial community assembly based on functional genes rather than species. PNAS. 2011; 108: 14288–14293. https://doi.org/10.1073/pnas.1101591108 PMID: 21825123

182. Armour CR, Nayfach S, Pollard KS, Sharpton TJA. Metagenomic Meta-analysis Reveals Functional Signatures of Health and Disease in the Human Gut Microbiome. mSystems. 2019; 4. https://doi.org/10.1128/mSystems.00332-18 PMID: 31098399

183. Levy R, Borenstein E. Metabolic modeling of species interaction in the human microbiome elucidates community-level assembly rules. Proc Natl Acad Sci U S A. 2013; 110:12804–9. https://doi.org/10.1073/pnas.1300926110 PMID: 23858463

184. Lu H, Li F, Sánchez BJ, Zhu Z, Li G, Domenzain I, et al. A consensus S. cerevisiae metabolic model Yeast8 and its ecosystem for comprehensively probing cellular metabolism. Nat Commun. 2019; 10:3586. https://doi.org/10.1038/s41467-019-11581-3 PMID: 31395883

185. Frisant T. Co- and polymicrobial infections in the gut mucosa: The host–microbiota–pathogen perspective. Cell Microbiol. 2021; 23:e13279. https://doi.org/10.1111/cmi.13279 PMID: 33040471

186. Hajishengallis G, Lamont RJ. Dancing with the Stars: How Choreographed Bacterial Interactions Dictate Nosocombicity and Give Rise to Keystone Pathogens, Accessory Pathogens, and Pathobionts. Trends Microbiol. 2016; 24:477–89. https://doi.org/10.1016/j.tim.2016.02.010 PMID: 26968354

187. Ford SA, King KC. In Vivo Microbial Coevolution Favors Host Protection and Plastic Downregulation of Immunity. Mol Biol Evol. 2020 [cited 22 Feb 2021]. https://doi.org/10.1093/molbev/msaa292 PMID: 33179739

188. Rosshart SP, Herz J, Vassallo BG, Hunter A, Wall MK, Badger JH, et al. Laboratory mice born to wild mice have natural microbiota and model human immune responses. Science. 2019; 365. https://doi.org/10.1126/science.aaw4361 PMID: 31371577
189. Kissoyan KAB, Drechsler M, Stange E-L, Zimmermann J, Kaleta C, Bode HB, et al. Natural C. elegans Microbiota Protects against Infection via Production of a Cyclic Lipopeptide of the Viscosin Group. Curr Biol. 2019; 29:1030–1037.e5. https://doi.org/10.1016/j.cub.2019.01.050 PMID: 30827913

190. Ford SA, Williams D, Paterson S, King KC. Co-evolutionary dynamics between a defensive microbe and a pathogen driven by fluctuating selection. Mol Ecol. 2017; 26:1778–89. https://doi.org/10.1111/mec.13906 PMID: 27862515

191. Odling-Smee J, Erwin DH, Palkovacs EP, Feldman MW, Laland KN. Niche construction theory: a practical guide for ecologists. Q Rev Biol. 2013; 88:4–28. https://doi.org/10.1086/669266 PMID: 23653966

192. Goddard MR. Quantifying the complexities of Saccharomyces cerevisiae's ecosystem engineering via fermentation. Ecology. 2008; 89:2077–82. https://doi.org/10.1890/07-2060.1 PMID: 18724717