Integrating research on bacterial pathogens and commensals to fight infections—an ecological perspective

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The incidence of antibiotic-resistant bacterial infections is increasing, and development of new antibiotics has been deprioritised by the pharmaceutical industry. Interdisciplinary research approaches, based on the ecological principles of bacterial fitness, competition, and transmission, could open new avenues to combat antibiotic-resistant infections. Many facultative bacterial pathogens use human mucosal surfaces as their major reservoirs and induce infectious diseases to aid their lateral transmission to new host organisms under some pathological states of the microbiome and host. Beneficial bacterial commensals can outcompete specific pathogens, thereby lowering the capacity of the pathogens to spread and cause serious infections. Despite the clinical relevance, however, the understanding of commensal–pathogen interactions in their natural habitats remains poor. In this Personal View, we highlight directions to intensify research on the interactions between bacterial pathogens and commensals in the context of human microbiomes and host biology that can lead to the development of innovative and sustainable ways of preventing and treating infectious diseases.

Introduction

Increasing recognition of the human microbiome integrity as a health requirement is drastically changing the appreciation of bacterial microbiome members and their interactions, among themselves and with the host. This change in understanding has placed the principles of microbial ecology at the centre of innovative approaches for prevention and treatment of major human diseases. Microbiome signatures inferred from metagenome analyses are under consideration as biomarkers in the diagnosis of different diseases, ranging from different types of cancer, such as colon or breast cancer, to autoimmunity disorders, such as rheumatoid arthritis or psoriasis. Faecal microbiota transplantation is effectively used in the treatment of infections with *Clostridioides difficile* and supplementation of microbiome members (eg, *Akkermansia muciniphila*) or microbiome products (eg, short chain fatty acids) have shown promise in improving health outcomes in both metabolic disorders and cancers.[1,2] The ecological principles of microbial fitness, competition, and evolution established in the context of environmental bacterial communities are now being increasingly applied to host-associated microbiomes. However, fundamental differences exist between environmental and human-associated microbial ecosystems.[3] Many environmental microbiomes represent expansive, unrestricted ecosystems and often have an unlimited life span that poses a minimal barrier to microbial spread. In contrast, host-associated microbiomes, such as those in the human gut, are restricted ecosystems with a short life span. Host-associated microbiomes demand specific bacterial mechanisms for transmission across individuals and generations and for temporary persistence outside their preferred living conditions.[4] Furthermore, hosts expose microbial colonisers to stressors other than environmental habitats, particularly via their mucosal immune system.[5]

Historically, research on host-associated microbial ecosystems has been limited to separate investigations on neutral or mutualistic bacterial commensals and harmful pathogens by different research groups. Consequently, the current understanding of these different groups of host-associated bacteria is highly asymmetrical, with a strong bias towards pathogens, hindering a comprehensive understanding of the human microbiome ecology. Despite the extensive interaction of these groups of bacteria in their natural habitats, experimental research on the interaction of commensals and pathogens is scarce.[6] For instance, typical pathogens can be found as virtually domesticated members of human microbiomes, whereas commensals can collude with pathogens, such as in polymicrobial infections.

Although the conventional differentiation between commensal and pathogenic microorganisms remains an important criterion in infection medicine, in the ecological context, the inherent overlaps in the properties of these groups of microorganisms render this differentiation inadequate.[7] Beneficial commensalism and antagonistic pathogenicity represent the opposite ends of a range of bacterial behaviours (figure 1), although few bacterial microbiome members can show real pathogenic behaviour. Many bacterial species or clones can dynamically change their capacity to function as commensals or pathogens, depending on their environmental context and the host physiological state, which further complicates the distinction (figure 1). For instance, microbiome dysbiosis and host immune defects can transform *Enterococcus faecium* from a virtually innocuous member of the intestinal microbiome to a cause of bloodstream infections.[8] Moreover, a single horizontal gene transfer event can shift the balance between commensal and pathogenic lifestyles, such as when a prophage-encoded toxin becomes the major virulence factor of enterohaemorrhagic *Escherichia coli* or of skin-colonising and oropharynx-colonising *Corynebacterium diphtheriae*.[9]

The dynamic change between commensalism and pathogenicity in facultative bacterial pathogens challenges the current, often inconsistent use of the term infection. We suggest reserving the term infection for pathological conditions caused by the emergence of a bacterial strain in a

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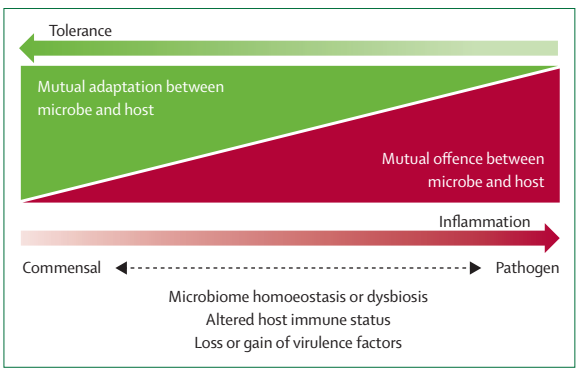

Figure 1: **Continuum of commensal versus pathogenic bacterial behaviour**
Bacterial microbiome members differ in their adaptation to a specific host organism and expression of proinflammatory or other host cell-manipulating molecules. Some commensals can thus become accidental pathogens when immunological tolerance and microbiome homoeostasis are disturbed or when the commensals acquire new virulence genes by means of horizontal gene transfer. Likewise, professional pathogens can adopt commensal lifestyles as long as proinflammatory and aggressive virulence factors are not expressed or are neutralised under conditions of microbiome and immune homoeostasis.

specific organ tissue. Such conditions can include, for instance, induction of diarrhoea by food-borne or waterborne *Shigella flexneri* in the colon, abscesses by *Staphylococcus aureus* in the skin, or pneumonia by *Streptococcus pneumoniae* in the lung. Consequently, in this Personal View, we refer to bacteria that regularly cause infections as pathogens and those that do not as commensals, although we do acknowledge that the terms have their limitations and do not describe all types of microbe–host antagonisms appropriately. The blurred distinction between pathogens and commensals also challenges Koch's postulates, which suggest a monocausal relationship between a particular microorganism and the corresponding disease.[1] In reality, however, some diseases arise from indirect effects of multiple bacterial species, when microbiome imbalance rather than the mere presence of such species causes a specific pathological state that is not regarded as a typical infection.[7]

Rapid advances in microbiome science together with new technologies have set the stage for a new phase of microbiology that integrates research on bacterial pathogens and commensals, moving beyond reductionist approaches.[10] To investigate how changes in environmental contexts affect the dynamic behavioural changes of bacterial microbiome members, microbiologists from diverse backgrounds should collaborate and combine their expertise in complementary disciplines such as systems biology, natural product chemistry, mucosal immunology, and clinical infectious diseases. These new approaches might help to answer some of the most relevant and obvious questions: Why do only a few host-associated bacteria commit a substantial portion of their genetic information to manipulating and harming host cells? What are the ecological perks for such professional pathogens to express virulence factors? Why do some commensals turn into accidental pathogens that cause diseases when the microbiome composition is disturbed or the host immune defence is compromised (table 1)? How can the current knowledge of ecological principles be used to develop effective prevention and treatment methods for infections, especially those caused by antibiotic-resistant and difficult-to-treat pathogens? Can microbiomes be optimised to foster health-promoting probiotic bacteria or disarm pathogens specifically, while allowing commensals to remain unharmed (table 2)?[25] In the following section, we discuss alignment of research directions addressing the survival mechanisms of commensal and pathogenic bacteria.

Future research on commensal bacteria inspired by that on pathogens

Owing to their high clinical relevance and comparative ease of cultivation and manipulation, major bacterial pathogens such as *S flexneri*, *S aureus*, and *S pneumoniae* have been studied for decades and to a much larger extent than typical host-associated commensals.[11,12,26] In contrast, major human-associated commensals, for instance those from the genera *Bacteroides*, *Clostridium*, and *Cutibacterium*, have been investigated by few laboratories. Indeed, most of the human microbiome members remain challenging to cultivate and are not genetically tractable.[27] A few of the commensals that can become accidental pathogens under particular circumstances, such as nosocomial clones of *E coli*, *E faecium*, or *Staphylococcus epidermidis*, have been studied to some extent, but why these specific bacteria cause invasive infections more frequently than the other more innocuous commensals remains unclear (table 1).[8,21,28]

An increasing body of evidence suggests that some commensal bacteria are important for human health.[29] For instance, by producing specific antibacterial compounds, commensal clones of *Blautia producta* inhibit and exclude *E faecium* and those of *Staphylococcus lugdunensis* inhibit and exclude *S aureus*.[30,31] Intestinal *Bacillus subtilis* releases an inhibitory compound that blocks the colonisation capacity of *S aureus*[32] or virulence factor expression in *Enterococcus faecalis*.[33] Some commensals can also produce compounds that have direct beneficial effects on their host organism (figure 2), promoting, for instance, the success of tumour therapies.[34,35] Research on pathogens can help to understand the biology of such beneficial commensals and enlist them against bacterial infections (table 2). Many important properties of commensals can vary among individual strains, depending, for instance, on acquisition or loss of mobile genetic elements, such as genomic islands encoding resistance or fitness traits.[36] Established approaches for clone-specific classification of pathogens such as sequence typing schemes could be applied to commensals as well. These approaches could help to enhance the current diagnostic strategies to a new level of personalised infection medicine by monitoring not only the presence of specific harmful pathogens but also the absence of specific beneficial commensals such as those protecting against colonisation by potential pathogens (table 2).

Like most of the major bacterial pathogens, many commensals are also specific to particular host species.[37]

	Human carriage, prevalence in human population	Typical transmission routes	Typical infectious diseases that promote transmission	Typical infectious diseases that do not promote transmission
Professional pathogens				
Shigella flexneri[11]	Colon, carriage usually transient	Faecal–oral	Diarrhoea	Arthritis
Staphylococcus aureus[12]	Nares, 20–30%, carriage often transient	Skin–skin	Purulent skin abscesses, impetigo, wound infections	Deep-seated abscess, bloodstream infection
Neisseria gonorrhoeae[13]	Genitourinary tract; carriage usually transient	Sexual contact, skin–skin	Urethritis	..
Streptococcus pyogenes[14]	Throat, 15–20% in children, low in adults	Oral–oral, skin–skin	Pharyngitis, impetigo	Scarlet fever, rheumatic fever, bloodstream infection
Streptococcus pneumoniae[15]	Throat, 27–65% in children, low in adults	Oral–oral	Bronchitis, pneumonia, sinusitis	Bloodstream infection, meningitis
Bordetella pertussis[16]	Throat, carriage usually transient	Oral–oral	Whooping cough	..
Accidental pathogens				
Enterococcus faecium[8,17]	Colon, 23–62%	Faecal–oral	..	Bloodstream infection
Escherichia coli[18,19] (commensal strains)	Colon, 61%	Faecal–oral	..	Urinary tract infection, bloodstream infection
Helicobacter pylori[20]	Stomach, 43% of adults in the global population	Oral–oral, faecal–oral	..	Gastric ulcer, gastric cancer
Staphylococcus epidermidis[21]	Skin and nasopharynx, virtually any human	Skin–skin	..	Implant-associated and bloodstream infections
Cutibacterium acnes[22]	Skin and nares, virtually any human	Skin–skin	..	Putative contribution to acne inversa
Streptococcus sanguinis[23]	Oral cavity, virtually any human	Oral–oral	..	Endocarditis
Neisseria meningitidis[24]	Nasopharynx, 5–24%	Oral–oral	..	Meningitis

Table 1: **Examples of human-adapted potential professional or accidental pathogens**

The adaptation processes leading to host specificity possibly serve as a strategy to increase bacterial fitness in competition with other less well-adapted microorganisms. The underlying mechanisms are only poorly understood for pathogens and largely unclear for apathogenic commensals.[38] Continued colonisation of a specific host often depends on effective adhesion to epithelial binding motifs such as surface proteins, proteoglycans, or glycolipids.[39] Although corresponding bacterial adhesins have been studied to some extent in many of the major pathogens,[40] such mechanisms in commensal microbes are being explored only now.

Bacterial survival on epithelial surfaces is limited by mucosal host-defence mechanisms, including production of IgA, antimicrobial peptides and lipids, and reactive oxygen and nitrogen compounds.[5] Innate and adaptive immune mechanisms, initiated by sensing of microbe-associated molecular pattern molecules or detection of microbial antigens by mucosal leukocytes, aid in the processes of mucosal immunity, leading to the release of proinflammatory or anti-inflammatory signalling and effector molecules.[41] Continued colonisation of the host depends on the ability of bacteria to either tolerate antimicrobial immune effectors or reduce their expression by inducing immunological tolerance.[5] Bacteria with increased tolerance to antimicrobial host effectors can even induce and exploit antimicrobial host responses to eliminate more susceptible competitors. Antagonistic interference with other members of the microbiome, depending on host immune reactions, has been documented for *S epidermidis*[42] and *Salmonella enterica* Typhimurium.[43] Extensive studies have shed light on the immune-evasion mechanisms of major pathogens, but whether commensals use similar or different strategies remains unknown.[44] For instance, some intestinal commensals blunt innate immune responses by producing non-inflammatory flagellin proteins that silence the human Toll-like receptor 5 or short-chain fatty acids that can induce regulatory T cells at mucosal surfaces, to facilitate immunotolerance.[45] However, the underlying control mechanisms can be disturbed and might lead to diseases in situations when the host is unable to initiate tolerance and responds with inflammation, such as when oral commensals colonise the gut ectopically.[46]

Overall, bacterial interactions within host-associated ecosystems rely to a large extent on secreted factors, which can be released either as individual, soluble molecules via specialised secretion systems or as components of membrane vesicles (figure 2). For this reason, secreted virulence factors of bacterial pathogens have been investigated intensively. In contrast, how the secreted primary or secondary metabolites or protein mediators of commensals modulate interactions with pathogens and the host has been addressed by few studies.[47] These studies have shown, for instance, how some commensals release molecules such as bacteriocins that eliminate pathogens such as *S aureus*[48] or generate nutrients that promote expansion of pathogens such as *C difficile* (figure 2),[49] thereby highlighting a novel layer of complexity in host-associated microbial ecosystems.

Expanding knowledge on fitness mechanisms of facultative human pathogens

Many major bacterial human pathogens are not obligate pathogens but colonise human or animal body surfaces as common microbiome members, without causing disease (table 1).[50] Indeed, acute infections are rare episodes in the

	Intervention measures
Therapy	• Develop narrow-spectrum anti-infectives, including phage therapies, and specific antivirulence and antifitness drugs, to spare important commensals and preserve microbiome integrity. • Choose antibiotics wisely on the basis of either presence or absence of resistance genes in commensal or pathogenic microbiome members.
Prevention	• Colonise individuals at risk with pathogen-excluding commensals, to reduce risk of severe, microbiome-derived infections. • Consider that non-antibiotic drugs coadministered to polymorbid individuals can inhibit beneficial commensals, thereby increasing the risk of infections. • Develop pathogen-eradicating mucosal vaccines.
Surveillance	• Focus particularly on prevalence and evolution of virulence factors in clonal lineages of professional pathogens that promote lateral spread. • Monitor evolution and spread of commensals bearing antimicrobial resistance-conferring mobile genetic elements.

Table 2: **Perspectives for microbiome ecology-instructed approaches against bacterial infections**

otherwise largely commensal lifestyles of most of these facultative pathogens. However, research has largely focused on the virulence mechanisms of pathogens such as *S flexneri*, *S aureus*, and *S pneumoniae*, and the mechanisms that steer the fitness of these organisms in competition with other microbiome members during commensal behaviour remain neglected.[51] From the perspective of microbes, whether and which types of infections are indeed advantageous for bacteria or should rather be regarded as accidental events, without benefits for their long-term evolutionary success over several host generations (figure 3), remains unclear.

A deeper understanding of bacterial infections is more important now than ever, considering the increasing global burden of antimicrobial resistance and bacterial infections.[52] The current knowledge of bacterial infections is restricted to few model pathogens such as *S aureus*[12] and *S pneumoniae*.[15] In contrast, some of the notorious antibiotic-resistant bacterial species, named ESKAPE pathogens according to the first letters of the genera of the following pathogen species, *E faecium*, *S aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*,[53] have been explored in much less detail. Antibiotic resistance mechanisms usually represent fitness burdens in the absence of antibiotic selection pressure, but some of the ESKAPE pathogens have evolved resistance traits that are maintained even outside of health-care settings. Compensatory mutations that overcome fitness burdens of resistance can contribute to the success of resistant clones and spread of resistance.[54] Why such community-associated meticillin-resistant *S aureus* or vancomycin-resistant *E faecium* spread and expand so effectively at the expense of their antibiotic-susceptible siblings remains a mystery.[55,56]

Ecological concepts are common in the field of general and environmental microbiology but have not been widely applied to the understanding of pathogenic bacteria.[43] The success of a bacterial clone in competition with other microbiome members depends on various mechanisms, including the capacity to use growth-limiting nutrients, profit from growth-promoting common goods such as polymer-hydrolytic enzymes or trace metal-scavenging metallophores from other bacteria, withstanding antimicrobial molecules released by microbial community members, or adhering to a few epithelial attachment sites.[6,51] The long-term ecological success of a bacterial species or clone results from the combined effect of the proliferation of the species within a specific host organism and the spread of the species to new host organisms (figure 3). To investigate the proliferation of a species within a specific host organism, a range of research strategies on mutual or antagonistic interactions should be adopted, from studies on commensals to the investigation of major professional and accidental pathogens. To investigate the spread of a species to new host organisms, the processes of transmission to new host organisms need to be explored using innovative experimental approaches. Bacteria colonising or infecting human or animal hosts can use two different strategies—vertical transmission (from parents to offspring) or lateral transmission (via social interactions) to new host organisms.[3] The mechanisms underlying these modes of transmission have so far been largely neglected in both commensals and pathogens. Vertical transmission promotes microbe–host adaptation and is typically used by commensals, whereas lateral transmission is common among many pathogens. However, the development of individual microbiomes can rely on both strategies, with the two strategies contributing differently to the transmission of different bacterial species. Indeed, a 2022 study indicates that members of a bacterial microbiome differ in their propensity to spread either vertically or laterally.[57] For instance, the patterns for the lateral spread of epidemic pathogen clones have been studied in detail for *Helicobacter pylori*,[20] *S pneumoniae*,[15] and *S aureus*.[12] Although these patterns have been often well documented by public monitoring programmes, the mechanisms steering the survival outside host organisms and invasion of the microbiomes of new hosts remain largely unclear. Accordingly, why some bacterial microbiome members spread only slowly and predominantly in the vertical direction and others disseminate quickly from individual to individual, even in larger human populations, is unknown.

The epidemic spread of major pathogens is probably linked to the types and severity of the infection that the pathogens cause (table 1, figure 3). The contribution of disease characteristics to bacterial spread is most obvious for inducers of diarrhoea such as *S flexneri*, which profits from spread via contaminated sewage.[11] Other common manifestations of infections might serve similar purposes. The typical infections caused by *S aureus*, purulent skin and wound infections, lead to the emergence of massive numbers of *S aureus* cells on body surfaces, to support host-to-host spread via skin contacts.[12] Similar mechanisms can enable the rapid host-to-host spread of urogenital pathogens such as *Neisseria gonorrhoeae*.[13] Airway infection-causing *Bordetella pertussis*, *Streptococcus pyogenes*, or *S pneumoniae* spread via aerosols released from coughing or sneezing individuals. Whether and how the severity of disease contributes to pathogen fitness by supporting dissemination has been discussed, for instance, in the context of

SARS-CoV-2,[58] but has not been systematically assessed for bacterial pathogens. Notably, most professional bacterial pathogens are not core members of human microbiomes and colonise humans only transiently (table 1), which necessitates them to have effective lateral spreading mechanisms. Continued colonisation by professional human pathogens (for instance, *S flexneri* and *N gonorrhoeae*) is rare or found only in a small portion of the human population (for instance, for *S aureus*) or in specific age groups (for instance, *S pyogenes* or *S pneumoniae*), suggesting that maintenance of an extensive virulence armoury involves substantial fitness burdens in competition with other microbiome members.

Accidental pathogens such as *E faecium* and *S epidermidis* express factors that aid their immune-evasion capacity, but hardly any aggressive toxins, which can contribute to these pathogens having higher prevalence and persistence in human microbiomes than most professional pathogens (table 1).[8,21] Because accidental pathogens cause infections predominantly in immunocompromised individuals, accidental pathogens are also often referred to as opportunistic pathogens. However, this term is also frequently used for professional pathogens such as *S aureus* and *S pneumoniae*, which cause other and more severe types of infections (typically bloodstream infections) in immunocompromised individuals than in immunocompetent individuals.[12,15] Accordingly, professional pathogens can also sometimes cause accidental infections that do not promote pathogen spread. Accidental human infections can also arise from pathogens such as *Legionella pneumophila*[59] or *Vibrio cholerae*,[60] which are adapted to non-human hosts and infect humans only under specific environmental conditions.

Integrative understanding of fitness of bacterial commensals and pathogens can help with infection prevention

Investigating commensals and pathogens together, in their natural contexts, can help to identify better ways of controlling microbes and fight infections and other microbiome-associated disorders. Commensal bacteria seem to have far more complex consequences for infectious diseases than previously assumed (figure 2). Some commensal species use active defence strategies such as release of antimicrobial bacteriocins or elimination of other bacteria by contact-dependent type-V, type-VI, or type-VII secretion systems, which can differ widely in their specificity for particular target species.[48,61] Moreover, commensals can use more subtle inhibitory strategies to increase their ecological success against pathogen colonisation, based on metabolic interference. Commensal bacterial communities can block access of pathogens such as *K pneumoniae* and *S* Typhimurium to nutrients in a collaborative manner that depends on the diversity of the community and its metabolic overlap with the pathogen.[62] Alternatively, pathogen exclusion can result from sequestration of essential trace metals by commensal-released metallophores[63] or the production of inhibitory metabolites. For example, some gut commensals can convert primary bile acids into secondary bile acid metabolites that inhibit outgrowth of spores of the intestinal pathogen *C difficile*.[64]

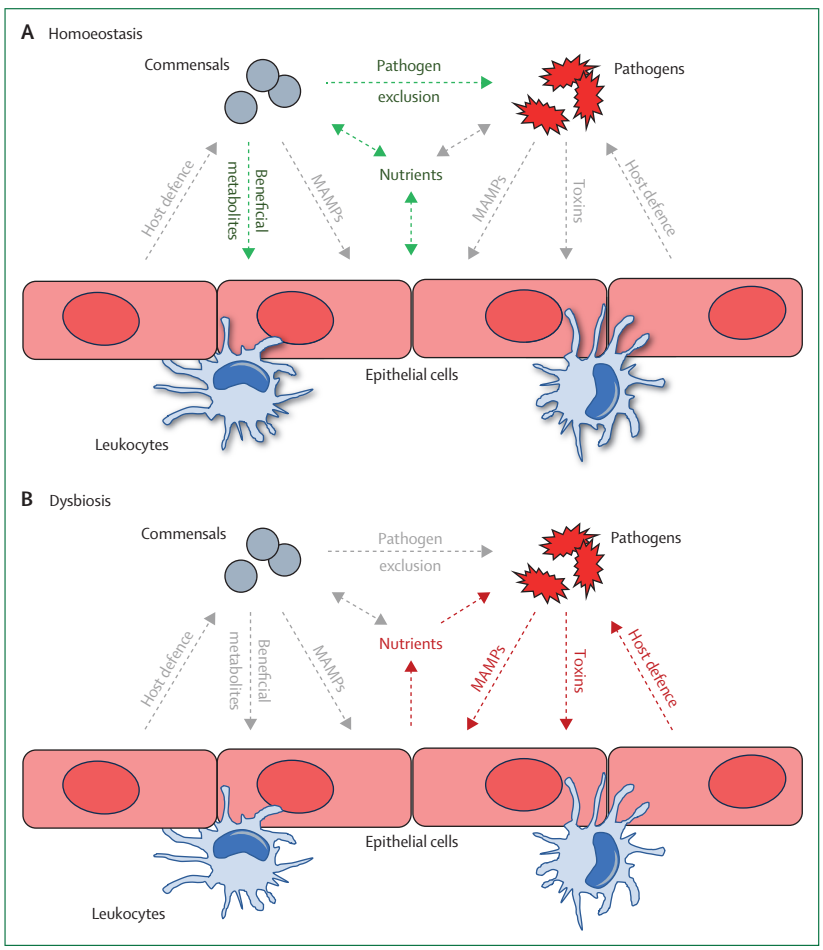

Figure 2: **Complex interplay among commensals, pathogens, and the host**
Well adjusted activities of commensals and host cells contribute to homoeostasis (green arrows; **A**), whereas expansion of pathogenic bacteria can disrupt homoeostasis (red arrows; **B**). Mutual exchange or sequestration of nutrients by commensals and pathogens and host cell activation by MAMPs can affect homoeostasis or dysbiosis in multiple ways (grey arrows). MAMPs=microbe-associated molecular patterns.

Microbiome restoration by faecal microbiome transfer is an effective strategy to treat *C difficile* infections. The success of faecal microbiome transfer is at least in part due to the restoration of a beneficial bacterial community and its metabolites that inhibit *C difficile* growth.[64] However, faecal microbiome transfer is difficult to standardise, and its value against that of other pathogens remains unclear.[25] Using defined commensal clones or communities for microbiome editing approaches could produce more consistent results and enable personalised strategies adjusted to a specific microbiome composition. Preclinical and clinical trials are currently evaluating the use of commensal-based life therapeutic products for preventing colonisation by antibiotic-resistant pathogens in individuals at risk (table 2).[25] However, the same commensals that protect from pathogen colonisation are often more susceptible to

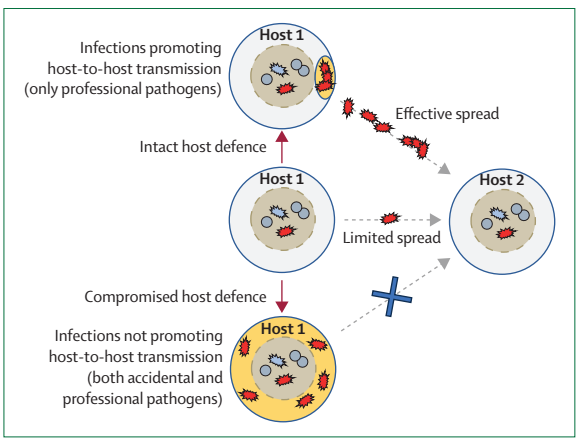

Figure 3: **How do infections support host-to-host spread of professional bacterial pathogens?**
Bacterial commensals that colonise humans spread continuously to new host organisms, usually vertically, with low activity. Professional pathogens (in red) can cause localised infections (small yellow circle) that promote host-to-host spread. In immunocompromised individuals, accidental pathogens can also cause infections; however, these infections usually do not promote transmission and can even limit the life expectancy of a host organism (large yellow circle). In addition, professional pathogens can cause such accidental infections in immunocompromised individuals, and these infections are often more severe than those caused in immunocompetent hosts.

antibiotics than the targeted pathogens,[65] which can abolish the beneficial effects of the commensals and fuel dysbiosis-associated diseases during antibiotic therapy. Systematic evaluation of the antibiotic susceptibility of crucial groups of commensals and incorporation of such knowledge into personalised, microbiome-based antibiotic stewardship regimens are essential to minimise collateral damage to the microbiome by broad-spectrum antibiotics. In addition to conventional antibiotics, many intestinal commensals can also be inhibited by multiple human-targeted non-antibiotic drugs.[66] Such unexpected drug side-effects need to be taken into account in the future, particularly in multimorbid individuals requiring polypharmacy (table 2). The microbiome itself has been revealed to be a rich source of new classes of antimicrobials with unusual properties and modes of action.[30,47,67] Systematic identification and characterisation of such innovative compounds can be a promising strategy for the discovery of new agents that prevent or eliminate pathogen colonisation.

In clinical practice, antibiotic treatment strategies rely largely on broad-spectrum antibiotics, which impose massive selection pressure on not only the pathogens but also most commensals. Consequently, commensals have a crucial role in the evolution of resistance mechanisms and in resistance gene transfer to pathogens (figure 2).[68] Interspecies horizontal transfer of resistance genes appears to be frequent during antibiotic therapy, for instance, via broad-host range conjugative plasmids and transducing phages, even within specific host organisms.[69] Ecological imbalances that support co-blooming of some members at the expense of others within the gut microbiome can increase plasmid transfer efficiency by increasing the contact frequency of plasmid donors and recipients.[70] Public surveillance systems should, therefore, focus on the evolution and spread of not only resistant clones of major pathogens but also key commensal species once the commensals have been identified as major resistance transmitters (table 2).

With the implementation of ecological concepts to infection research, important steps could be taken towards the identification of the Achilles heels among typical pathogens. These pathogens can then serve as targets for intelligent antifitness drugs, to render pathogens more susceptible to the antagonistic mechanisms of beneficial commensals or host-defence effectors.[71] Such targets cannot be found in screening programmes relying on in-vitro growth of pathogens in isolation. Their identification requires cultivation within relevant model communities, which still need to be established. Since mouse models are often of little value for the study of strictly human-specific pathogens, controlled human challenge models have been established, which might open new avenues, for instance for the prevention of shigellosis.[72] Understanding the ecological benefit of virulence will be crucial to identifying virulence factors that are important for host-to-host spread of professional pathogens. Targeting such virulence mechanisms with antivirulence compounds that are yet to be developed could help to limit the contagiousness and epidemic spread of pathogens (table 2).[71]

Mucosal immunity plays a crucial role in neutralising pathogens while tolerating commensals.[5] Whether and how the invasiveness of microbiome members affects the activation of innate and adaptive host-defence mechanisms, including regulatory T cells and immunoglobulins, is only beginning to be understood now.[41] In addition, the induction of specific IgA at mucosal surfaces remains to be fully understood, and whether IgA promotes or impairs colonisation by IgA-bound bacteria remains largely unclear. Depending on the specific antigen and bacterial species, IgA can probably have opposing roles.[73–75] Although many promising surface antigens of pathogens have been identified, those of most commensals remain largely unknown. However, commensals and pathogens at times share key surface antigens,[76] which could pose challenges to developing effective vaccines against bacterial pathogens that overcome immunological tolerance. Knowledge of antigenic epitopes of pathogens and commensals can inform the development of mucosal vaccines for preventive and therapeutic approaches against potentially pathogenic microbiome members (table 2). There is currently no vaccine for most of the ESKAPE pathogens,[77] which calls for the development of new approaches for control of pathogens, based on the ecology-instructed enlistment of commensals and immune responses.

Contributors
LM, CS-T, REL, HB-O, HL, NZ, SW, and AP conceptualised the Personal View. AP wrote the original draft. All authors provided critical review and edits of the Personal View.

Declaration of interests
We declare no competing interests.

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