HYPOTHESIS

The equilibria that allow bacterial persistence in human hosts

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We propose that microbes that have developed persistent relationships with human hosts have evolved cross-signalling mechanisms that permit homeostasis that conforms to Nash equilibria and, more specifically, to evolutionarily stable strategies. This implies that a group of highly diverse organisms has evolved within the changing contexts of variation in effective human population size and lifespan, shaping the equilibria achieved, and creating relationships resembling climax communities. We propose that such ecosystems contain nested communities in which equilibrium at one level contributes to homeostasis at another. The model can aid prediction of equilibrium states in the context of further change: widespread immunodeficiency, changing population densities, or extinctions.

When two organisms occupy the same habitat, a conflict or a series of compromises ensues. Sometimes there are elements of both, and interactions range from a 'cold-war'-type conflict to peaceful coexistence. Many of the most intense conflicts are accidental (for example, when a microbe finds itself in a niche (or host) to which it is unaccustomed), and the interactions are often short term (leading to the eradication of the microbe or the death of the host). More complex are the relationships between hosts and microbes that have evolved together, each with adaptations tied to the biology of the other, often leading to nonlinear interactions[1].

We focus on a specific class of such relationships, persistent infections, resulting from the pairing of a microbe and host that have survived the challenges of co-habitation. It is a phenotype defined by its success. Because these relationships are fundamentally different compared with either accidental or short-term co-evolved interactions, our goal is to clarify the key principles. The central concept we explore is that persistence represents the evolved selection for balancing host and microbial interests, resulting in an equilibrium that, by definition, is long-term but not necessarily forever stable. We hypothesize that maintenance of this equilibrium requires a series of evolved, nested equilibria to achieve the overall homeostasis.

The framework of such persistence is illustrated by examination of three bacterial species (*Helicobacter pylori*, *Salmonella typhi* and *Mycobacterium tuberculosis*) that are human-specific, despite causing well-recognized biological costs to their hosts[2–4]. These particular host–microbial interactions are representative of different classes of persistent infection (Fig. 1). We focus on bacterial infections of humans because of their importance and because of the knowledge already gained through their study[5]; however, the principles should be general to other microbes and other hosts.

Relationships between persistent microbes and their hosts span many spatial scales and timescales. At a microscopic timescale are the individual elements of both microbe and host reactive cell (immunocyte) populations, together with their intra-host evolution and interactions. The mesoscopic (physiological/ecological) scale involves population dynamics and interaction consequences for both host and transmission. At the macroscopic scale, host evolutionary changes occur[1].

We propose that microbial persistence represents a co-evolved series of nested equilibria, operating simultaneously on each of these multiple scales, to achieve an overall homeostasis. The composite equilibria of host and microbe may be considered as a 'holobiont'[6] (that is, organisms living together in symbiosis), regardless of whether there is mutualism[7]. Such relationships would resemble climax communities that have achieved stability under prevailing conditions. In the following sections, we consider elements critical

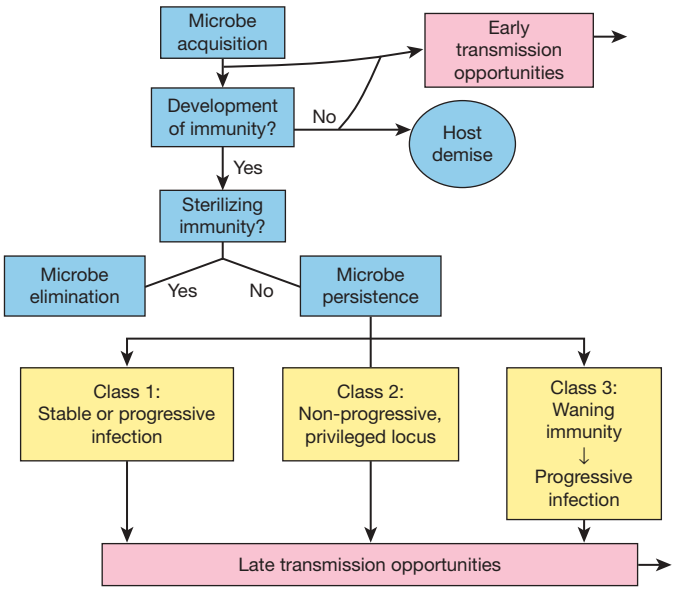

Figure 1 | Classes of microbial persistence. Because inter-host transmission is required for obligate host-associated microparasites, our model is organized according to transmission strategy. After microbial acquisition, there can be early transmission until effective immunity develops. For microbes able to resist immune elimination, late transmission may occur via progressive infection (class 1), non-progressive infection with carriage (class 2), or development of progressive infection in hosts with declining immunity (class 3). *H. pylori*, *S. typhi* and *M. tuberculosis* are representative human-associated microbes belonging to these three classes, respectively. Early and late transmission are biological trade-offs.

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Table 1 | Mechanisms used by persistent bacteria against host responses

Category	Principle	Example
Stealth	Intracellular location	*Chlamydia* species
	Sequestration (foreign body)	*Staphylococcus aureus*
	Molecular mimicry	*Escherichia coli* (K1 capsule)
	Low antigenicity (surface antigen)	*Treponema pallidum*
	Low expression of stimuli of innate responses	*Salmonella typhi* (Vi)
	Antigen masking	*Neisseria gonorrhoeae*
Variation	Surface-exposed antigens	*Bacteroides fragilis*
		Borrelia burgdorferi
Anti-defence	Antibody-absorbing	*Staphylococcus aureus* (protein A)
	IgA protease	*Haemophilus influenzae*
	Inhibition of phagocytosis	*Staphylococcus aureus*
	Resistance to phagocyte killing	*Salmonella*
	Disarming macrophages	*Yersinia* spp. (YOPs)
	Killing of macrophages	*Mycobacterium tuberculosis*
	Disarming T cells	*Helicobacter pylori* (VacA)

This Table is adapted from refs 52–54. YOPs, *Yersinia* outer proteins.

to the development of the equilibria, including generation of host immunity and its neutralization by persistent microbes (microscale); variation among populations of microbes and host cells (mesoscale); the parameters that affect inter-host microbial transmission (macroscale); and most critically, the types of rules governing the equilibria.

Immunity and microbial escape

Immunity, defined as the resistance of a host to the endogenous propagation of microbes, is mediated by innate or adaptive recognition[8]. Innate mechanisms are based on selection of hosts recognizing stereotypical structures, whereas adaptive immunity involves intra-host memory against encountered threats. Just as microbial populations evolved mechanisms to regulate group activities (for example, quorum sensing), processes evolved in hosts to regulate their immunocyte populations. In addition to upregulatory networks, regulatory T cells (T_R cells) have the ability to secrete chemical signals that limit T-helper 1 (T_H1) and T_H2 cellular responses[9–11]. Dedicated T_R cells[11,12] suppress auto-intolerance and limit the immunopathogenesis accompanying infections, probably selected by reducing tissue injury from infections[9]. The balance between T_R and T-effector cells affects infectious disease pathogenesis in individual hosts and at specific life-cycle stages[9].

By definition, persistent microbes have successful strategies to sufficiently thwart host responses to gain a niche. Many such microbial adaptations have been recognized, involving stealth, antigenic variation and anti-defence strategies (Table 1). Host responses may be narrow, with a single immune clone out-competing the others (immunodominance), or broad, in which multiple immune clones develop; efficient control of persistent infection correlates with narrow responses[13,14].

However, there is a balance between microbial immune evasion and maintaining growth fitness. The evolved microbial genome[15–17] reflects the tensions between these selective pressures[18,19]. For example, *H. pylori* both downregulates T-cell responses by secreting VacA[20], and upregulates mucosal signal transduction pathways by injecting into epithelial cells a protein (CagA) with tyrosine phosphorylation domains interacting with host cellular kinases and phosphatases[21–23]. Clonal variants within individual hosts differ in the number of phosphorylation domains, affecting interaction intensity[24]. The gene (*cagY*) encoding the injection system pilus protein possesses complex repetitive DNA regions that undergo intragenic recombination, creating antigenic variants[25]. Persistent *H. pylori* populations have been selected for their ability to manipulate T_R function[26].

Microbial transmission dynamics

For host-adapted microbes, transmission to new hosts is required. This concept is captured by the term R_0, which quantifies the transmission potential of a microparasite as the average number of secondary infections occurring when a single infectious host is introduced into a universally susceptible host population[27]. A simple way to define R_0 explicitly, on the basis of a standard model of epidemic transmission[28,29], is given by the equation:

$$R_0 = BN/(\alpha + b + v),$$

where BN is the transmission rate (a function of the population size, N), α is the rate of mortality owing to the microbe (a measure of virulence), b is the rate of mortality in the host population independent of the microbe (a measure of lifespan), and v is the rate at which hosts recover from the infection (a measure of immunity). In other formulations of R_0, although transmission rate is a function of B and N, the size of the population becomes more determinative[30]. When $R_0 > 1$, microbial transmission is sustained; when $R_0 < 1$, transmission goes to extinction.

The level of virulence is set by competition among microbes of the same species, because they always have the same host population number (N) at any given time. If the parameters of the R_0 equation are independent of one another, then the direction of evolution would be away from virulence towards commensalism, as selection would favour highly transmissible ($B \rightarrow$ large), persistent ($v \rightarrow 0$) commensals ($\alpha \rightarrow 0$) or symbionts ($\alpha \rightarrow -$large)[29]. However, if B and α are directly (and positively) related, then selection could favour some level of virulence ($\alpha > 0$) in the microbial population[27]. The effects of the introduction of myxoma virus to the rabbit population in Australia provides experimental support for this scenario[31].

There is further meaning to each of the terms of the R_0 equation. In much earlier times, when human populations were small[32], N was limiting, which selected against pathogens that had high mortality (α) (Table 2). With the rise of civilization[33,34], population growth, crowding and improved transportation, the number and proximity of susceptible hosts grew, which permitted more pathogenic organisms to flourish. Similarly, host variation (for example, immunodeficiencies increasing microbial number) affects B (the rate of transmission), thereby increasing R_0.

The basis for a host–microbe equilibrium model

Microbial success in a host requires the ability to grow and overcome the host's defences. The microbe must be able to access sufficient nutrients, overcome physical forces (such as the peristalsis of the gastrointestinal tract) and thwart innate or adaptive host defence molecules; these are host 'signals' to which the microbe must adapt. Conversely, microbial metabolites, toxins and anti-defence molecules, and physical adherence to host cells are microbial 'signals' to the host. The host-derived and microbial-derived signals may be either unlinked or linked. In the unlinked model, when the host wins, the microbe is eliminated, but if the microbe wins, the host dies. An

Table 2 | Ontogeny of microbe acquisition in human pre-history/history

Time-line of human history (yr BP)	Effective population size	Major source of microbial transmission	Nature of immunity	Example	Persistence
Most ancient (>50,000)	Isolated hunter-gatherers (<100)	Maternal/intrafamilial	Ineffective	*Bacteroides* species, *H. pylori*	Active
Intermediate (10,000–50,000)	Communicating hunter-gatherer groups (<100 to 10,000)	Long-term carriers	Containment but not elimination	*M. tuberculosis*, *S. typhi*, varicella-zoster virus	Latency
Recent (<10,000)	Large societies (>500,000)	Acutely ill persons	Life long	Measles	No
Very recent (<200)	>10 million	Acute infection	Serotype-specific	Pandemic influenza	No

alternative model, based on linked signals between microbe and host, implies selective pressure favouring co-evolved phenotypes[35,36], and is most applicable to persistent organisms (Fig. 2). In such a model, the host sequesters the bacterium into a discrete compartment (for example, the lumen of the gastrointestinal tract, the interior of a gallstone, the centre of a granuloma) that is surrounded by responding host cells that do not permit the microbe to extend into adjacent tissues[35–39]. A linkage between host and microbial signals and the achievement of persistence implies that equilibrium (homeostasis) has been reached.

The equilibrium model

To understand the principles permitting persistent equilibrium, we developed deterministic mathematical models[35,36]. Although we used *H. pylori* (Box 1) as the model organism, the underlying principles should be broadly generalizable. The essential feature of the model is that there must be both positive and negative feedback between the host and microbe; only with negative feedback can equilibrium (persistence) be achieved. The constructed model[36] encompasses five prototypic populations that are followed over time (Supplementary Information). There are two microbial subpopulations: bacteria that are free-living in the gastric mucus or are adherent to host cells. In a broader sense, these two populations also represent any two classes of bacterial cells that vary in the intensity of their host interactions. The model also defined a concentration of microbial effector molecules signalling the host, and a concentration of host-derived nutrients that benefit the microbes. Finally, the model included host immunity, governed by its response rate, ultimate capacity and the differential effect of the two microbial subpopulations with high or limited interaction. In this model, immunity limits microbial populations by restricting growth rates; immunity can be defined as lowering net microbial replication. By limiting replication, the autoregulatory network leads to either transient or persistent *H. pylori* colonization[36]. This model produced equilibrium solutions under a wide range of relevant biological variation. We propose that host status is also critical in determining the types of equilibrium reached with *S. typhi* (Box 2) and *M. tuberculosis* (Box 3).

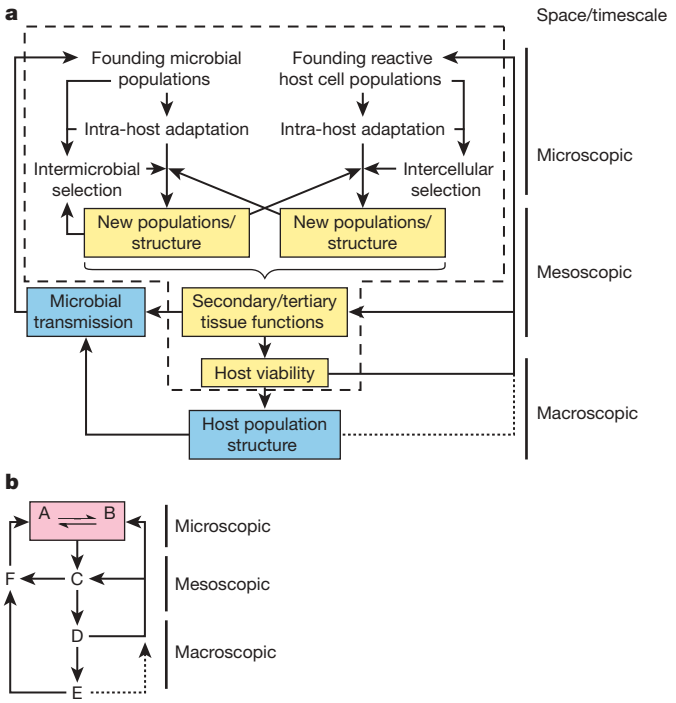

Figure 2 | A model for microbial persistence in metazoan hosts. **a**, Schematic with model elements. After founding microbes are acquired, new populations/population structure reflect intra-host adaptation, influenced by both intermicrobial selection (a product of microbial competition and cooperativity) and by the population of host reactive (immune) cells, which determine the resource space and structure. A parallel phenomenon describes the selection of host reactive cell populations. Events within the host are inside the dashed box. These microevolutionary events represent the first (microscopic) scale of the interaction (as adapted from ref. 1). For persisting organisms, these two interlocking phenomena have co-evolved and in their sum affect secondary tissue functions (for example, immune adjuvancy, hormone levels) that affect microbial transmission. These second scale (mesoscopic) interaction events influence host viability (for example, pathogens, through disease, or symbionts via resistance to pathogens or to famine). On the macroscopic (host evolutionary) interaction timescale, these events affect host population structure, which then governs microbial transmission and selection for host genotypes (shown by dotted lines). In this model, host population size and structure are important selectors for the types of microbes that can be successful. **b**, General schematic of the model. (See text for further discussion of elements A–F.)

Box 1 | Model 1: *Helicobacter pylori*

Helicobacter pylori, a Gram-negative bacterium that colonizes the human stomach as its sole environmental niche[23], has redundant (faecal–oral, oral–oral, vomitus–oral) transmission routes and notable biological success: (1) present in humans for >50,000 yr; (2) cosmopolitan (world-wide) in distribution; (3) nearly universal in all developing societies; (4) colonization essentially life-long; (5) dominant single species (>70% of clones) in the human stomach; and (6) multiple strains often colonizing the same host[55–60]. Once established in a host, *H. pylori* populations develop persistence, often life-long, with concomitant host responses. Although *H. pylori* enhances risk for lethal gastric cancer and peptic ulceration, these generally occur late in life[2]. Equilibrium involves stimulating host inflammation to provide nutrients[35–37]. Although *H. pylori* actively replicates in the human stomach for decades, persistence eventually may lead to progressive gastric atrophy[61], which reduces or eliminates its own colonization; thus, too much inflammation is maladaptive.

H. pylori has many characteristics favouring gastric colonization, outcompeting other microbes, and regulating and reducing specific immune responses[20,62–64]. Adaptive *H. pylori* genomic features include pathogenicity islands and numerous contingency genes[65], with variable expression based on binary switches[16]. On the basis of endogenous mutation and recombination[58], facilitated by natural competence for DNA uptake[66], *H. pylori* cells have high genomic plasticity, providing numerous phenotypic variants capable of colonizing diverse and changing niches[40]. Within-host dynamics between *H. pylori* competition[67] and cooperation[40] are an important tension (microscopic scale); success at this level provides one basis for the next stratum of equilibrium (Fig. 2), and the emergence of phenotypic variants[24,25] interacting with immunocytes[26] provides another basis.

At mesoscopic and macroscopic scales, the success of *H. pylori* in human populations reflects either low virulence or possible symbiosis early in life; essentially all of its negative consequences occur after reproductive age. Potential *H. pylori* benefits to young hosts include protection against diarrhoeal diseases and asthma, and metabolic regulation via gastric leptin and ghrelin[23,68–70].

Consistent with an ESS, host population structure influences *H. pylori* transmission. The family has been central[71], with early transmission opportunities from infected children[72], especially older siblings, later opportunities when girls become mothers (less so, but present from fathers), and later still, as an old age consequence of gastric atrophy and hypochlorhydria[73] (class 1 in Fig. 1). With low *H. pylori* virulence, there is little competition between early and late transmission (Fig. 1). Gastric *H. pylori* colonization is a prototypic ESS, as it effectively controls *H. pylori* cheaters, and essentially excludes all other bacteria from the stomach[56] for the bulk of an individual's life, well into the post-reproductive years, with probable early life benefits and little cost to hosts. However, the use of antibiotics in the 20th century may have eliminated an ESS that has existed since time immemorial.

Strain variation and the control of cheaters

The equilibrium model predicts that each microbial phenotypic variant develops different host interactions[35,36,40]. Bacterial variants often

Box 2 | Model 2: *Salmonella typhi*

Unlike all other known *Salmonella* species, *S. typhi* and the closely related *S. paratyphi A* are obligate pathogens of humans[74]. Because transmission is faecal–oral (often with food or water intermediates), the ability of *S. typhi* to enter the faecal stream by thwarting host phagocyte function[75,76] is critical. Under conditions of poor hygiene, *S. typhi* can infect large populations, but as those who survive natural infection (about 80%) develop permanent immunity, the pool of susceptible hosts is rapidly exhausted. However, some hosts become asymptomatic biliary carriers (for example, 'Typhoid Mary'), capable of life-long *S. typhi* transmission. Although the humoral and cellular immunity that develops[77,78] protects these hosts from disease, it is insufficient to sterilize the lumen of the gallbladder and biliary tract, especially when gallstones are present[79]; the stone becomes the segregated niche that enables life-long *S. typhi* carriage (class 2 in Fig. 1).

Genomic analysis of *S. typhi* has provided tools to understand its evolution[80]. The ancestral *S. typhi* haplotype arose after human migrations out of Africa (50,000 yr BP), but before the Neolithic period (10,000 yr BP)[74,81], when effective human population sizes were relatively small. Long persistence of individual haplotypes, neutral population structure and global transmission[74] are population correlates of a stable lifestyle with high biological success. *S. typhi* isolates show low genomic variation[74,80] consistent with stable immune interactions at the microscopic scale (Fig. 2). The effects of *S. typhi* on biliary tract function (mesoscopic scale) with stable carrier state development increase mean inter-host transmission time, allowing for spread within and between human groups when small populations were insufficient to sustain direct spread of acute infection. The long-term carrier keeps *S. typhi* extant in a population until new generations of susceptible hosts can be introduced to the organism (macroscopic level). As human populations grew along rivers[33,34], faecal contamination of portable water by a carrier could transmit *S. typhi* to distant downstream communities. Spread from carriers initiates epidemic cycles, seeding populations for generations to come.

Box 3 | Model 3: *Mycobacterium tuberculosis*

Mycobacterium tuberculosis, the cause of tuberculosis, is usually transmitted from diseased hosts via cough-borne aerosols[82]. Once acquired by the respiratory route, *M. tuberculosis* establishes a pulmonary parenchymal focus, but in most hosts, life-long latency develops, with low likelihood for disease. This raises the question of how latency is established.

The essential site for *M. tuberculosis* persistence is within the granuloma, a complex structure of bacteria and host multinucleated cells and infected macrophages, encircled by both activated and non-activated macrophages and T cells. The granuloma has a central caseous necrotic core that harbours mycobacteria and dead host cells[83,84]. In this environment, host cells and mycobacteria can interact for the host's lifetime[85], with bacterial replication[86,87] but controlled growth. Mathematical models[88–93] of the conditions favouring latency have defined two bacterial subpopulations (intracellular and extracellular) with distinctive growth rates and signals to host cells, and different macrophage-response states and T-cell and cytokine contributions[92]. An equilibrium maintains low bacterial levels and controls tissue damage, based on macrophage activation and control[83,84,93]. This is the locus for the microscopic scale of the general model (Fig. 2).

The models predict that disease reactivation occurs when the granulomas no longer effectively control extracellular bacterial growth; when intracellular management predominates, local tissue damage and bacterial dissemination are reduced. The models also predict that the signalling that occurs between host cells and their intracellular bacteria facilitate granuloma maintenance, and that the slow mycobacterial growth rate favours latency[85,88–91,93]. Thus, *M. tuberculosis* has evolved slow growth rates and the ability to survive inside macrophages, while hosts who minimize tissue damage from potentially over-zealous immune responses have been selected[75,83,85].

However, with ageing or other immunodeficiencies, infection within the granuloma is no longer suppressed, net bacterial growth accelerates, and disease occurs (mesoscopic scale)[82,94]. This 'reactivation' form of tuberculosis is most common, creating new opportunities for transmission via coughing, often decades after the organism was acquired (class 3 in Fig. 1). With both early and late transmission possibilities, *M. tuberculosis* can skip generations of human hosts, an effective strategy for host populations of small size (macroscopic scale). The global population structure of *M. tuberculosis*, defined by phylogeographic lineages associated with sympatric human populations[95], provides evidence for its co-evolution with humans, as does the disproportion of allopatric tuberculosis cases involving compromised hosts[96]. That host population characteristics determine the extent of clinical tuberculosis in a community[97] is consistent with the remarkable genomic conservation of *M. tuberculosis*[17,98]. As predicted, certain 'cheater' events, such as utilization of forbidden sites (for example, development of tuberculous meningitis), cause host demise without transmission; strains exhibiting such phenotypes would be selected against.

arise through mutation, intragenomic recombination, or horizontal gene transfer[40,41]. When hosts harbour more than one strain simultaneously, these compete, but often also cooperate (through genetic exchange and specialized function)[42,43]. The model indicates that for competitors to persist, each must occupy an exclusive niche, or face eventual elimination[35,36]. An implicit limitation of an equilibrium model is the emergence of individuals ('cheaters') that break the rules to their own advantage[44].

Game theory provides solutions for how nature can resolve this dilemma. A cheater may be defined as a player that changes strategy unilaterally. A Nash equilibrium is a strategy profile in a game with $\geq$2 players in which none can gain by changing strategy unilaterally[45]. A subset of the Nash equilibrium is the evolutionarily stable strategy (ESS)[46,47], which when present in a population resists invasion by a competing alternative strategy. We propose that co-evolved persistent microbe–host systems have developed ESSs, which preclude cheater success.

What boundaries would ensure ESS maintenance? Because the persistence model is based on linked regulation of host and microbial signals, a cheater is a variant signalling for resources but not halting its growth when the resources are provided, as the equilibrium requires. One solution to this problem is that penalties for transgression have evolved in the ESS that ultimately lower cheater fitness. Penalties can involve crossing thresholds to induce new host responses. A host response whereby bacterial growth triggers new innate or adaptive responses with subsequent amplification would be effective, as any growth advantage for the cheater would be temporary and local. Because a novel mutant can escape the specific immunity directed towards a predominant strain, ecosystem stability might favour microbes with low mutation rates[48]. However, the penalty mechanism, affecting all strains of the microbe including cheaters, does not permit mutational escape. Regulatory T cells are a class of immunocyte that could closely modulate host responses to microbial perturbations[9–11], but multiple mechanisms exist (Supplementary Information).

A general model of microbial persistence in hosts

Despite the enormous microbial variation that exists, our prior mathematical modelling and examination of three cases of microbial persistence (Boxes 1–3) indicate that a general hypothesis for persistence in metazoan hosts can be developed. In complex ecosystems, such as within humans, the model depends on a series of evolved equilibrium relationships, nested in one another and interconnected, and operating simultaneously over three different biological scales. The model proposed represents an ESS, and has six major components (identified as A–F; Fig. 2).

Element A represents the microbial populations persisting in a particular tissue or host compartment (Fig. 2a). The composition and structure of the population is based on the founding populations, the intra-host generation of variation, the selection imposed by the competing (and cooperating) microbes, and the selection

imposed by the host. The composition and population structure of the reactive host cells involved in innate and adaptive immunity (element B) is based on principles parallel to those governing the microbial cells (founders, variants generated, selective pressure from competing/cooperating cells) and the selection exerted by the persisting microbes. Thus, the two populations (A and B) are interdependent, and exist in a linked dynamic equilibrium.

The nature of this primary (microscale) host–microbial equilibrium shapes tissue function (element C, mesoscale), which ultimately affects both host viability (element D, macroscale) and microbial transmission (element F, mesoscale). Pathogenic microbes damage tissue, leading to coughing, vomiting or diarrhoea, favouring their own transmission. Conversely, the tissue effects of symbionts are protective (for example, metabolic or immune), selecting for the hosts that carry them.

The (negative or positive) effects on host viability select for host genes in elements B and C, influencing population structure (element E), which through extinction vortices also affects the host gene pool (elements B and C). The host population structure affects microbial transmission (element F), influencing the founding microbial populations in new hosts; small host population size selects against virulence, and short lifespans select against late-transmitting microbes.

This is a dynamic model of co-evolved hosts and microbes (Fig. 2b), requiring multiple scales, flexible across a range of conditions, and useful for understanding both symbionts and pathogens. In reality, there is no fixed distinction between the two; their biological behaviour is defined by their ecological context.

Discussion

Microbial transmission—central to the maintenance of persistent host-adapted infections—is considered as being vertical across generations or horizontal across populations. Typically, indigenous (commensal) organisms are transmitted vertically from mother to child, whereas pathogens are transmitted horizontally. However, there are intermediate cases[49], because an individual is more likely to cough on family members than on strangers, and the microbes transmitted from mother to offspring may be affected by her environmental exposures. R_0 dynamics can be affected by mixed vertical and horizontal transmission, as well as by demographic changes, such as number of births per woman.

Transfer of a microbe to a host genetically related to the previous host occurs with vertical, but not necessarily horizontal, transmission; as pandemic infections become more frequent in the modern world, horizontal transmission has an enhanced role. Microbial genomes are plastic, with extensive intra-host variation[37,38]; strains partly adapted to a new host owing to passage through a genetically related previous host may yield different outcomes than strains from unrelated persons[50].

As predicted by the R_0 equation, with small effective population sizes the long hunter-gatherer stage of human evolution was a bottleneck for highly virulent human pathogens. Small population sizes selected for symbionts or for pathogens that could be transmitted decades after infecting a host, after new susceptible individuals had been introduced into the population via births (Table 2). In contrast, high-virulence pathogens would have been driven to extinction by the demise of their isolated host populations. However, with the larger effective population sizes that have developed since the rise of agriculture[33,34], more virulent pathogens have been appearing. Our rapidly changing human context, including widespread immunodeficiencies and jet travel, is continuing to alter the selection for human-adapted microbes.

For example, the proportion of hosts newly infected with *M. tuberculosis* who develop progressive tuberculosis and become immediately infectious, who reactivate the infection late, or who never reactivate, is dependent on the immunocompetence of the host population. Host characteristics unevenly distributed across the population, including malnutrition and HIV infection, affect the proportions of individuals in each compartment and thus, the transmission profiles. Similarly, because tuberculosis reactivation rates are age-dependent, general improvements in health that lead to increased proportions of elderly persons in the population affect outcomes. Conversely, reactivation of lethal infections tends to keep overall host lifespan under close regulation. Nevertheless, for microbes like *M. tuberculosis*, there is also a cost to latency, because competing mortality limits transmission. As HIV has become more common, there has been selection towards progressive primary tuberculosis.

As illustrated by *M. tuberculosis*, the evolution of a persistent parasite that uses latency as part of its transmission strategy integrates the transmission rates for all stages in the host life cycle, keeping net $R_0 > 1$. The balance between early and late opportunities for transmission is context specific, dependent on host variables including effective population size, age structure, distribution of immunocompetence and previous selection for resistance. Similarly for symbionts, context matters. A microbe that induces iron deficiency may be symbiotic in regions where malaria is holoendemic[51], but without malaria may decrease host fitness. Because context is all-important in evolution, the multiple scales on which persistent parasitic and symbiotic infections operate provide substrate for the dynamic solutions that unfold.

We propose a new model based on ESSs, a subset of Nash equilibria, to explain the common features of microbial persistence in their human hosts. That the model was consistent with the observed biology of three bacteria (*H. pylori*, *S. typhi* and *M. tuberculosis*) with highly dissimilar genomic and lifestyle features supports its generalizability. Importantly, the model applies to both pathogens and commensals, and can be used to understand the direction of virulence as the context of human ecology changes.

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