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Feature Review

Understanding Immunity through the Lens of Disease Ecology

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As we describe the immune system in ever more exquisite detail, we might find that no matter how successful, this approach will not be sufficient to understand the spread of infectious agents, their susceptibility to vaccine therapy, and human disease resistance. Compared with the strict reductionism practiced as a means of characterizing most biological processes, I propose that the progression and outcome of disease-causing host–parasite interactions will be more clearly understood through a focus on disease ecology.

Predicting the Outcome of Host–Pathogen Interactions

If immunology as a discipline attempts to understand our resistance to parasitism and its associated diseases, the field is still in its infancy. Consider the fact that despite our extensive knowledge of the general principles and many details of mammalian immunity, this knowledge gives us almost no predictive power. As an illustration, parasitic agents that jump to a novel host almost invariably exhibit an unpredictable virulence, and this is often due to uncharted, species-specific differences in mechanisms of immunity [1–3]. Furthermore, the virulence can be attenuated or exaggerated, but rarely do different species experience the same infectious agent with exactly the same pathology. For example, of the 31 species of the genus *Mammarenavirus*, most cause mild pathology in their natural murid hosts and do not cause an apparent infection in human beings. However, seven of the 31 species are known to cause hemorrhagic fever in human beings with mortality rates between 15% and 30%. The other Mammarenaviruses either do not replicate in human cells or, like lymphocytic choriomeningitis virus, cause moderate pathology and are eventually cleared [4]. Similar severe hemorrhagic zoonoses can be transmitted by but some of the viruses from the Bunyaviridae (e.g., Hanta) [5], Filoviridae (e.g., Ebola) [6], Flaviviridae (e.g., dengue) [7], and Paramyxoviridae (e.g., Hendra) [8] virus families (National Center for Emerging and Zoonotic Infectious Diseases, http://www.cdc.gov/vhf/virus-families/index.html). Each such zoonotic infection that results in severe disease with or without an emerging epidemic may be understood as a mechanistic failure of the immune system [3]; an alternative is to analyze infectious disease through the lens of host–pathogen co-evolution, and view zoonotic infections as an ecosystem out of balance.

As a field, we have described a vast number of immunity mechanisms in ever greater detail, but putting this information into the context of disease susceptibility at different scales is less advanced. It may involve bridging epidemiology, disease ecology, and immunology, each of which uses different tools and has a different culture. The understanding of epidemic disease spread largely arises from mathematical modeling that is difficult to empirically test in laboratory or field studies [9]. Disease ecology, including the co-evolution of hosts and pathogens, itself combines two intertwined but historically distinct fields of study, ecology and evolution, each of which is characterized by almost overwhelming complexity. Finally, there is immunology, which

Trends

Immunology has characterized many defense mechanisms that resist parasitism, but resistance is only one factor determining the outcome infection.

Resistance to infection is a property of host immunity, but varies for each infectious agent.

Severity of disease is a property of an infectious agent, but depends on the host.

The principles underlying these interactions are best understood and applied through an understanding of host and pathogen ecology and co-evolution.

Unlike co-evolved infections, the spread and severity of zoonotic infections are unpredictable.

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is largely experimental and founded on fantastic biological phenomena [10]. Perhaps these cultural differences have impeded a more holistic understanding of the immune system and its role in the landscape of parasitism. In essence, we can take the immune system apart and intricately describe its components, but putting these components back together to understand individual or community health is a much greater challenge. From Strogatz [11] quoting E. O. Wilson, 'The greatest challenge today, not just in cell biology and ecology but in all of science, is the accurate and complete description of complex systems. Scientists have broken down many kinds of systems. They think they know most of the elements and forces. The next task is to reassemble them, at least in mathematical models that capture the key properties of the entire ensembles' [11,12].

Evolution of the diverse mechanisms of immunity has been driven by unrelenting selective pressures placed on host organisms by the world of biological parasites: transposons, viruses, prions, bacteria, the diverse single-cell eukaryotes collectively referred to as protists, fungi, helminths, and arthropod ectoparasites. Parasitism is a continual and fundamental property of life where a loss of one or more evolved immune mechanisms often results in opportunistic, parasite-induced disease and mortality [13–17]. Thus, a common perception is that an absence of pathology-associated infections is a signature of effective host immunity, or more emphatically, that 'any life-threatening infection results from a primary immunodeficiency' [18]. This notion is incomplete as it lacks the perspective of host–pathogen co-evolution. Importantly, virulence is a property of the parasitic organism, but it is only revealed in specific hosts [19], and likewise, the immune system is a property of the host, but its effectiveness depends on the infectious agent.

This illustrates an important concept. The immune system, in all its many manifestations, can and does limit parasitism, especially by environmental microbes that have not been selected for survival and replication as infectious agents. However, it is not a defense shield generally able to resist all manner of infectious agents. As the aforementioned examples illustrate, rapidly evolving parasites and their more slowly evolving hosts forge a relationship that is balanced between parasite virulence and host survival. Depending on the selection pressures governing a parasite's replication and transmission, the evolved virulence can be 'life threatening' to the host. Moreover, when host–pathogen co-evolution is taken out of the equation (e.g., by zoonotic transmission), balance is lost, and the ability of the immune system to resist or clear infection is presently unpredictable. The question is, what determines this balance, and could we ever understand the principles sufficiently to 'capture the key properties of the entire ensembles?' In this review, I attempt to describe the ways in which immunity can be placed into a broader ecological context, highlighting the principles that determine the spread and severity of infectious disease [20,21].

The Host Response to Parasitism

There are three responses that affect parasitism in the most general sense: avoidance, resistance, and tolerance. Avoidance arises from complex behavioral traits presumably selected to minimize contact with infected individuals or other environmental sources of infection [22,23]. For example, *Caenorhabditis elegans* forages on bacteria found in decomposing organic matter, and this behavior includes a learned avoidance response triggered by the presence of products from pathogenic bacteria such as *Serratia marcescens* and *Pseudomonas aeruginosa* [24–26]. *N*-Formyl peptide receptors present on vomeronasal sensory neurons in mice are capable of mediating olfactory detection and response, presumably to avoid prokaryotic pathogens [27]. Perhaps the most experiential example is the physiological response that arises from the detection of putrescent chemicals such as putrescine and cadaverine – attractants to animals that eat or lay eggs in dead things, repellants to others [28,29]. No doubt avoidance is deeply rooted in biological behavior, and it is initiated by diverse environmental cues, many of which have yet to be discovered.

The study of resistance to parasitism, until recently, has been the entire focus of immunology. Mechanisms of resistance include barriers to initial infection, clearance of a primary infection, and the acquisition of immunity to reinfection. In keeping with an ever-present selective advantage to minimizing parasitism, the mechanisms are extensive, varied, and inventive. They are amenable to reductionist study at the atomic, cellular, and organismal levels, and as a field we have found fantastic biological novelty and described physiological and genetic processes, such as V(D)J recombination, found nowhere outside the immune system. The basic components of immunity are conserved over evolutionary time, and yet, as described earlier, an infectious agent can exhibit very different virulence when infecting different species, even those as similar as chimpanzees and human beings. However, avoidance and resistance only explain part of the host–parasite experience; there are many infectious parasites that are not avoided, and to which there is little or no effective resistance.

For the entire world of biological parasites characterized by persistence, there exists another strategy. These agents can parasitize a host for long periods, often for life. Although a host immune response occurs, it is ineffective with respect to parasite clearance, and often it does not confer immunity to reinfection. Moreover, upon infection with such an agent, the immune system can be subject to self-imposed attenuation, presumably selected as a means to avoid fruitless immunopathology – an evolutionary acknowledgement that for this, and perhaps other forms of parasitism, resistance is futile. The ability of a host to co-exist with a range of both acute and persistent infectious parasites, with limited disease severity, has been termed tolerance, a concept akin to, but distinct from self-tolerance that prevents the immune system from causing self-destruction [30–34]. Although appreciated in animals only recently, tolerance is a concept that has been studied in plants for decades [35,36].

What selects for resistance or tolerance, disease severity, or persistence in a long-evolved host–pathogen interaction, and how does that differ from a zoonotic infection? Another way of addressing this issue is to ask what influences the co-evolution of hosts and their parasites, and what causes some parasites to evolve toward commensalism, whereas others evolve or maintain high virulence? Finally, is the disease experience of human beings exceptional?

Trade-Off Theory and the Evolution of Parasite Virulence

Theoretical epidemiology provides mathematical understanding of some of the most basic processes guiding disease spread within a population and the evolution of virulence in individual hosts (what follows is a description without the mathematics of epidemiological modeling; the intrepid reader is referred to the *magnum opus* of Anderson and May [37]). These studies are based on a simple infection model using ordinary differential equations to track the abundance of three different classes of hosts over time: susceptible, infected, and recovered (SIR) [38]. This analysis gave rise to the cornerstone of epidemiology, that is, trade-off theory [39]. Trade-off theory replaced the long-held avirulence hypothesis, that is, for a particular host, a pathogen tends to evolve to a benign state wherein it becomes a commensal – the idea being that there is always a selective advantage for the parasite to keep its host alive. By contrast, trade-off theory derives from the acknowledgement that virulence (and its associated depression of a host population), transmission, length of infection, and parasite spread are linked [39].

Virulence is the cost of infection to the host. It could result from mortality or some loss of reproductive success, but it is assumed to be associated with the rapidity and extent of in-host parasite replication. Transmission rate is simply the rate at which a parasite is successfully spread from host to host, and transmission can occur over the length of infection that is determined by a combination of the host life span, the death rate due to infection, and the rate of parasite clearance. The fitness of the parasite lies in its basic reproductive number, R_0, equal to the number of new infections caused by each infected host. The 'trade-off' is that as in-host

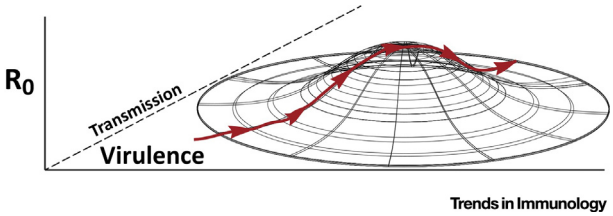

Figure 1. An Idealized Landscape of Trade-Off Theory. Depending on population density, size, and structure, as well as the mode of parasite transmission, the success of a parasite within a host population also depends on the virulence. As in-host reproduction and virulence increase, so does transmission, but at some point, this is outweighed by a decrease in the time of infection, which in turn, can decrease the basic reproductive ratio, R_0. The red arrows exemplify how R_0 might vary with transmission and virulence for a particular infectious agent.

reproduction increases, transmission rate increases, and so does virulence. As virulence increases, the length of infection decreases and fewer transmission events occur (Figure 1). R_0 is thus determined by a trade-off between the opposing properties of virulence and transmission versus length of infection (Box 1).

To determine the validity of their model, Anderson and May reanalyzed the evolution of viral (Ectromelia) or bacterial (*Pasteurella muris*) virulence extracted from a 15-year experiment starting in the 1920s involving between 100 000 and 200 000 mice – possibly the most extensive and ambitious experimental epidemiological analysis ever undertaken [40,41]. In closed environments manipulated only by the introduction of a pathogen and the regular addition of susceptible mice, the mortality rate and host population census were measured. From this, the disease mortality rate of the extant pathogen could be determined for different rates of host influx. Remarkably, the observed disease mortality rate was almost identical to that predicted by the theory to cause the maximum host population depression. Thus, despite the simplifications built into the SIR model, it closely tracked the evolution of pathogen virulence in a large and dense mouse community. In other words, the pathogens evolved to a virulence that maximized their spread within the mouse population [41].

The most famous real-world test of trade-off theory arose from biological control experiments in which the myxoma virus from the South American tapeti (*Sylvilagus brasiliensis*) was released separately in Australia and France to control the European rabbit population (*Oryctolagus cuniculus*). Myxoma virus causes a relatively benign cutaneous fibroma in its natural host, but

Box 1. Trade-Off Theory

The easiest way to think about trade-off theory is to imagine a parasite with a low rate of replication, and thus a low virulence and long duration of infection. As more rapidly replicating parasites dominate the infection, the virulence increases, but the duration of infection decreases. At some point, virulence would be high enough that the host could die before transmitting the parasite, and such an overly virulent parasite would cease to be maintained in the population. Previous to the recent epidemic in West Africa, this characterized the overly virulent Ebola outbreaks in human beings – clusters of infection that would 'fade-out' after causing the death of a few hundred people [55]. A mutation or mutations in the Ebola glycoprotein increased primate infectivity (while diminishing infectivity in bat cells) without a substantial increase in virulence; the primate-evolved virus was thus able to persist in human populations by spreading more rapidly [56,57]. Conversely, if the starting population of parasites evolved to a subthreshold replication rate, the duration of infection would be long, but little or no transmission would be achieved. Again, the parasite would die out. The idea is that for some value of infectivity, replication, and virulence, R_0 is maximal, and it is toward this that the parasite tends to evolve (Figure 1). Of course, this is a simplification and fails to account for the success of persistent parasites. Many parasitic agents have evolved to an endless length of infection, and yet find the means to maintain infectivity – either continuously or sporadically. While trade-off theory has been challenged for its simplifications and certain details [58], it presently constitutes the most effective means of describing theoretical and practical aspects of disease propagation [9,59].

the standard laboratory strains of myxoma virus exhibited a fatality rate of >99% in rabbit members from the same phylogenic family (Leporidae) [42] – a reminder of the unpredictability of zoonoses. Released in Australia in 1950, over the following 30 years, the spreading virus evolved to an intermediate virulence (with 70–95% fatality rate) in laboratory rabbits along with an extended time of infection [43–45]. Remarkably, a very similar pattern was replicated in France upon release of a separate myxoma virus strain [46]. There also occurred a co-evolutionary increased resistance in the wild rabbit population, presumably caused by the severe selective pressures of a highly lethal disease epidemic. In addition, there was some evidence for a resulting compensatory rebound of myxoma virulence [47] in a manner reminiscent of a 'red queen' effect [48–52]. I note that these attempts at biological control did not eliminate the target population, nor could they.

A molecular analysis of myxoma strains re-isolated from Australia and Europe revealed that the phenotypic attenuation was caused by unique mutations in viruses isolated from different geographic locations, and several of these mutations appeared to diminish the immune inhibitory virulence factors of the natural virus [53]. As would be predicted within the framework of trade-off theory, the virus evolved a phenotypic attenuation of virulence that favored an increased time of infection, but did not evolve toward avirulence [54].

Host Population Density, Size, and Structure Determines Disease Virulence

Population Density and Size

The success of trade-off theory arising as an emergent property of a simple one-on-one host parasite interaction model has led to a huge literature describing how different real-world parameters would be predicted to affect the dynamics of disease spread and virulence. From these models and empirical experience, a major predictor of parasite spread and virulence arises from host population characteristics: density, size, and spatial structure. As noted earlier, transmission of a parasite not only depends on in-host replication to increase transmission potential, but also depends on the frequency of transmission, and this in turn depends on the contagiousness of the agent and, importantly, the probability of an infected host coming into contact with a susceptible individual. This latter parameter depends, to a first approximation, on the density of the host population.

Modeling the dynamics of an epidemic reveals that virulence at the beginning of an epidemic, when the density of susceptible hosts is maximum, is greater than at the endemic phase of an epidemic when the density of susceptible hosts has diminished due to infection-related mortality or the appearance of recovered immune hosts [60]. The denser the population, the more rapidly the parasite can spread, and the less selective pressure there is for an extended time of infection. It follows that parasite virulence evolves to higher levels when invading a higher density host population, and conversely, as host population density decreases, the length of infection required to maintain a parasite in the population would approach the life of the host, that is, persistence [61].

This idea is embedded in the massive Greenwood *et al.* experiments. Pathogen virulence, as measured by disease mortality rate, changed with different rates of added uninfected mice, which in turn altered the density of the susceptible hosts [40,41]. Another example comes from laboratory passage of virus stocks. If a virus is serially passaged by injection of fluids from an infected animal into a naïve host, the cost of virulence and diminished time of infection is entirely eliminated, and essentially, the density of hosts is unlimited. This is known to increase virulence since the only selective pressure on the virus is rate of replication [62]. By contrast, passaging viruses in tissue culture also selects for the most rapidly replicating viruses, but without a selection the immune system might impose other cell-intrinsic mediators such as interferons. This latter process ultimately gives rise to an attenuated viral strain that can be used as a

vaccine [63]. Finally, layered on top of density is the much more complex notion of host diversity, and theoretical and experimental studies show that transmission and virulence decrease in the face of increased host diversity [64].

The size of the population is another important parameter that affects maintenance of a parasite in the population. This comes from the notion that, for acutely infectious diseases that are cleared with sterilizing immunity, recovered hosts no longer contribute to the density of susceptible hosts. Thus, with time, the basic reproductive rate falls until the disease is extinguished from the population. In this case, empirical data preceded theory. Disease incidence studies revealed a 2-year periodicity of measles epidemics and the tendency of the disease to 'fade-out' in communities of less than 200 000–500 000 people [65,66].

Mathematical modeling affirmed that an oscillation is consistent with requirement for births to provide a sufficient density of susceptible hosts to reignite an epidemic. Moreover, in populations beneath a threshold size, the renewal of susceptible hosts would not occur rapidly enough, and the infectious agent would be predicted to fade-out [66]. A corollary to this observation was the realization that diseases such as measles 'did not predate the rise of the great river valley civilizations some 5000–6000 years ago . . . it seems necessary to presume, therefore, that measles virus evolved sometime within the past 6000 years' [66]. More generally, maintenance of acutely infectious agents that are cleared with sterilizing immunity requires a large and dense population of hosts, and thus the expectation was that in small diffusely populated aboriginal societies with little to no contact with the world at large, the disease profile should be similar to preagricultural hunter-gatherers, and substantially different from that of the 'developed' world. Studies by Black [67] on people of the Amazon basin showed that there was serological evidence for persistent viruses including herpes simplex, varicella, Epstein-Barr virus, hepatitis B, and cytomegalovirus, infections that are largely inapparent, but little evidence for the acute epidemic diseases that dominated the densely populated world prior to mass vaccination. Epidemiological theory along with observational and experimental data is consistent with the basic idea that the evolution of virulence or disease severity is strongly influenced by host population factors including size and density.

Disease Spread Depends on the Interconnectedness of a Population: It Is a Small World after All

In real-world disease epidemics, unlike caged mice, the population is not perfectly mixed. Interactions occur based on geographic proximity as well as social, familial, and biological connections. Thus, host density, as it influences virulence of an infectious agent and its evolution to overcome host immunity, should contain information about the spatial structure of a population and the forms of interaction that can result in pathogen transmission [68].

A basis for understanding the flow of information, such as disease spread through a population, comes from graph theory often referred to as network theory [11,69,70] or from the point of view of statistical mechanics, percolation theory [71–73]. Although beyond the scope of this review, network analyses hold the promise of understanding epidemics as nonlinear complex systems, and may reveal emergent and generalizable properties of epidemic spread. Work carried out over the past two decades has revealed two such properties that characterize many different types of networks including the propagation of infectious diseases through human populations. One is that modern society is highly clustered, that is, there is a high probability that your connections are themselves connected, but it also exhibits characteristics of a 'small-world network' in which there is a very short path length between any two individuals. This is the popular notion that each of the billions of people in the world is separated by, at most, 6 degrees [74–76].

A second attribute of modern society is that the number of interactions that characterize each individual (the degree distribution) does not follow a normal distribution. Rather, the number of 'friends' or 'connections' possessed by each person is extremely heterogeneous and more closely follows a (truncated) power law (an example of a 'heavy-tailed' distribution). That is, most people have small number of connections, whereas some directly interact with many people [72,77]. A simplified way to looking at this is that for disease spread there would exist highly connected individuals who would be sure to propagate an epidemic [78–81]. Mathematical modeling indicates that no matter how inefficient the transmission of a disease, in a network with a heavy-tailed distribution, an epidemic is likely to permanently take hold. Unless factors such as avoidance and resistance completely prevent infection, which they do not, it would seem that population density, size, and structure are key to understanding virulence and spread of disease.

Disease Virulence and Modes of Transmission

In trade-off theory, as described earlier, high levels of parasite replication represent a cost to the host in terms of life span, but in addition, an important factor is the ability of an infected host to spread disease [82,83]. If infection affects host mobility, at least for a class of agents transmitted by proximity or direct contact, virulence would inversely impact parasite spread. The natural extension of this concept is that virulence and time of infection are closely associated with the form of parasite transmission whether it be skin-to-skin exposure, respiratory droplets, water contamination, venereal contact, or exchange of fluids. An additional factor is the stability of parasitic agents in the environment such that the time of host infection is diminished or eliminated as a selective pressure (Box 2).

The message is that we can fairly accurately deduce characteristics of co-evolved host–pathogen interactions from the density and structure of the host population and the

Box 2. Mechanisms of Transmission

If contracting one of the many viruses that results in cold symptoms made you feel like staying in bed, transmission would be limited. Colds are thus bothersome but benign. However, if the agent is spread by a vector, then this limitation is eliminated. In fact, if anything, an immobilized malarial host might make a better target for voracious mosquitos. Without a penalty due to reduced host mobility, a vector-transmitted parasite would be expected to evolve to higher levels of virulence. Mathematical models appear to support this idea to an extent; however, another factor affecting virulence might be the dose of parasites delivered by a 'flying syringe' [9,84].

Another example of the dependence of virulence on transmission is the spread of infections that require exchange of body fluids, usually in the form of sexual intercourse. In this case, the network upon which the parasitic agents spread is limited to sexual partners, and sometimes further limited to sexual encounters in which blood is exchanged. All of these infectious agents, for example, *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), hepatitis C virus (hepatitis), HIV (AIDS), are characterized by persistence, meaning that they are not cleared through mechanisms of resistance, and they exhibit low virulence at least for a period we deduce is needed for multiple sexual encounters. Although categorizing HIV as low virulence is counterintuitive, the median time for progression to AIDS in untreated infected individuals is 8–9 years [85] – ample time for an infected individual to transmit the virus to susceptible hosts. HIV would not have caused a worldwide epidemic, where more than 60 million people have been infected, if it had a short incubation period and time to death, or exhibited characteristics of measles or influenza that are cleared within weeks. There is a similarity between venereal infectious agents and those that are endemic in a low-density diffuse population. Both need to cause persistent infections where contagion may occur only rarely.

In addition to the means of transmission, another factor is the resilience of the parasite outside an infected host. *Bacillus anthracis* (anthrax disease) is a spore-forming bacillus that is stable in environment for decades. A healthy and mobile susceptible host can thus contract disease from an environmental repository of *B. anthracis* (in the form of an anthrax-deceased corpse). Similarly, *Variola* virus (smallpox) can remain infectious for years, such that it may have constituted an early instance of biological warfare as waged by the British against Native Americans [86,87]. Of course, it too displays a remarkably high virulence. Environmental stability combined with water-borne transmission makes *Vibrio cholerae* (cholera) a particularly difficult pathogen [88]. Diarrhea and vomiting that occur within hours of infection constitute an effective means of propagating an epidemic via compromised water sources. For all of these parasitic agents, virulence can evolve without trade-offs.

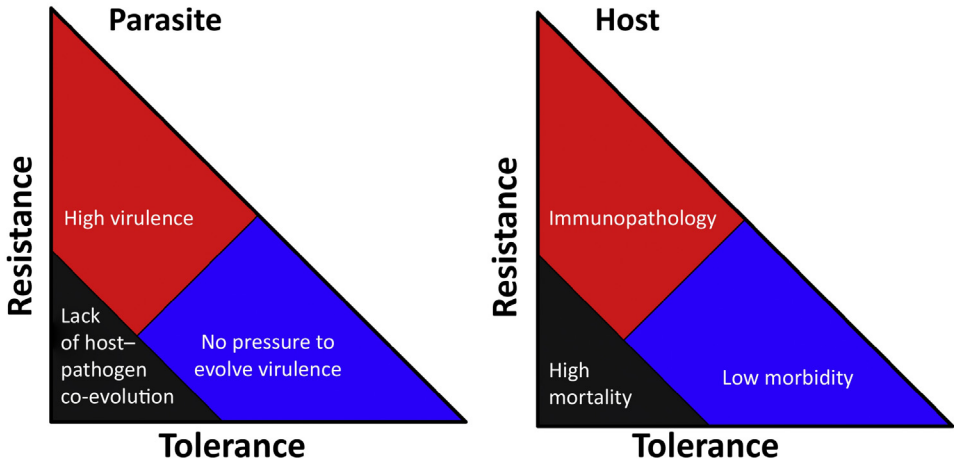

Figure 2. Phase Space Showing Resistance versus Tolerance for Hosts and Their Pathogens. Depending on the resistance or tolerance exhibited by the host, parasites are under more or less pressure to evolve virulence, that is, mechanisms to overcome immunity. Strong resistance is associated with host immunopathology and increased selective pressure for virulent parasites. Tolerance results in widespread, but inapparent infection within the population. The absence of effective resistance and tolerance, as might be found in a zoonotic infection, would be associated with the potential for high host mortality.

mechanisms of disease transmission. Parasites that remain endemic within a dispersed, low-density population evolve persistence, and would be expected to elicit a degree of tolerance, whereas those parasites that exhibit acute infectivity and rapid transmission would likely elicit a stronger resistance response. Tolerance and resistance, in turn, correlate with immunopathology experienced by the host, and, in addition, affect the selection of virulence in the parasite (Figure 2). Yet, this knowledge comes about without any information concerning the specifics of the parasite in question, whether RNA virus or protozoan. More importantly for immunologists, it does not require knowledge of the specifics of immunity; in fact, the rich inventory of innate and acquired immunity mechanisms thus far charted does not presently appear to be helpful in determining the virulence or time-of-infection for a host-adapted parasitic agent.

The Unique Human Experience Illustrates the Fundamental Concepts of Disease Ecology

These concepts have been applied by epidemiologists and social scientists to understand important aspects of human disease [66,89–91]. In particular, they appear to explain the incidence of infectious disease in human beings, the epidemics that swept across Eurasia for millennia, and the massive population contraction of Native Americans following European contact in the 16th century. In addition, I believe our unique human disease experience set the stage for a focus of immunological studies on acute, resolving infectious agents. Only recently, perhaps triggered by the HIV epidemic, there has been an increased interest in persistent infectious agents. Yet, there is still mystery surrounding the existence of persistent viruses, 'How some viruses manage to persist despite the impressive immune armamentarium of the host, without causing overt disease, is a great unsolved mystery in immunobiology' [92].

By one accounting there are approximately 1400 species of infectious agents (excluding ectoparasites) that can infect human beings, and of these, 100–150 are plausibly capable of causing human epidemics [1,93]. No more than 100 species are specialized to infect human beings; some of these were recently acquired and became uniquely human adapted (like HIV or *Plasmodium falciparum*), whereas others have a long, co-evolved relationship with vertebrates,

including human beings (many of the herpes family viruses). A majority of potential parasitic agents are zoonotic.

A reasonable surmise is that the human species is unique in altering its own ecosystem in the geologic blink of an eye. In particular, radical changes in human population density and structure occurred. Available genetic evidence indicates that our Paleolithic ancestors lived as diffuse bands of hunter-gatherers barely holding on to species existence [94,95]. A few thousand individuals seeded the world outside of Africa approximately 50 000 years ago, and the population then grew at the relatively constant annual rate of 0.04% [96], consistent with a European population of less than 1 million inhabitants in 10 000 years BCE, or about 1 person per 10 km^2 [97]. Alternatively, based on archeological sites, climate, and the ethnography of hunter-gathers, the population of Upper Paleolithic Europe was estimated to be approximately 100 000–300 000 people [98].

Such a sparse network of human hosts did not have worldwide connections, and as Black [67] proposed, individual bands were not large enough to sustain acute epidemic disease. Over a period of several thousand years, corresponding with the domestication of plants and animals, a segment of the population became concentrated within densely situated urban populations. As a consequence of this ecological revolution we dramatically increased the frequency and number of direct and casual contacts, and at the same time, sampled all of the parasitic agents to be found in domesticated birds as well as in herd animals such as cows, goats, horses, and sheep.

The rise of civilization was a recipe for the selection and evolution of infectious agents that would cultivate 'crowd epidemic diseases' as deduced by Black and others [66,89,99,100]. The host population in walled cities was densely connected, as in a regular network, so that each individual had dozens of contacts that we can assume occurred almost constantly. Each interactive cluster was further connected by travel and trade so that human hosts constituted a small-world network on which parasites could widely spread. Through births and immigration, cities could sustain acute diseases, albeit as oscillating epidemics that eventually took the form of childhood diseases. In parallel, agriculture invaded and altered habitats such that insect vectors could flourish and contact burgeoning human populations. Furthermore, human beings had no co-evolved relationship with the infectious agents found in newly domesticated species, let alone all of the wild game that were brought down by increasingly sophisticated weapons. Thus, as we now know, the infectivity and virulence of these agents would be individually unpredictable, but likely to include a proportion of parasites that were able to cause disease and be transmitted within dense human populations.

This was the perfect recipe for 'virgin soil epidemics' [101], that is, the introduction of a contagious infectious agent into a population in which no one is immune. The epidemic diseases that ensued, for example, measles, mumps, rubella, chickenpox, smallpox, were selected for the rapid propagation within a dense and large population. Often, they were contagious via casual contact, usually through expelled respiratory droplets, and they could infect many new hosts in a short period. They were thus under no selective pressure to evolve persistence, hence our common (mis) conception of the transient nature of infectious disease. This gave rise to the idea that most diseases are cleared (they are not), and the mysteries surrounding the existence of persistent infectious agents.

Other agents were spread via open waste that flowed through cities until well into the 20th century, and still other agents were harbored and spread by commensal rodents and their vectors. As described by McNeill in 'Plagues and Peoples', microparasite-caused epidemics swept almost continuously through Europe, the Middle East, and East Asia [89,99].

Industrialization allowed us to create megalopolises such that the smallpox death toll for the first two-thirds of the 20th century is estimated at 300 million people, a significant percentage of the world's population [102].

History records that these diseases were not present in the Americas, Polynesia, or New Zealand at the time of first European contact despite the presence of large and dense cities in the Western Hemisphere. These societies were cut off from Eurasia as the last ice age receded and Beringia was once again submerged sometime after 17 000 years BCE, and this constitutes another indication that the great Eurasian epidemic diseases are of recent origin. Why the Americas failed to develop their own crowd-epidemic diseases is unknown, but the answer may include a lack of large herd animals suitable for domestication [99]. With exposure, all the ravages of millennia rained down at once upon disease-naïve inhabitants, causing population losses between 50% and 90% [103,104]. European contact resulted in multiple virgin soil epidemics horrifically played out over a great segment of the world's population.

A prediction from this line of reasoning is that the killer epidemics, which circulated through Eurasia or Africa for thousands of years, should have left a genetic imprint that would not be found in Native Americans or Polynesians. This is indeed the case. The strongest genetic signature of disease has been caused by malaria in the form of hemoglobinopathies and other tolerance alleles found at high frequency only in those parts of the world in which malaria was endemic for thousands of years [105]. Although *P. falciparum* appears to have entered the human population from gorillas on the order of 365 000 years BCE [106], many of these resistance alleles appear to be less than 5000 years old [107,108]. Other derived alleles that recently swept Eurasia under strong selection for resistance to epidemic diseases appear to cause a hyperactive immune system such that they are associated with multiple autoimmune and inflammatory diseases [109–116].

A half century ago everyone expected their children to experience the ravages of measles, mumps, rubella, chicken pox, influenza, and other infections that had evolved into the 'childhood' diseases. This was traumatic enough that even as a small child, not knowing anything about the dynamics of disease epidemics, I wondered why I had to experience all of these diseases as well as an almost continuous string of less severe 'colds' and enteropathies (we called them all stomach flu), when all the while our pets appeared to remain perfectly healthy. If human beings are just exceptionally intelligent animals, I wondered, why should we be sick so often? The answer is to be found in our unnaturally rapid alteration of population density and structure, our close association (often involving killing and exchange of blood) with so many different other species, and our small-world population structure. I assert the likely possibility that because of our unique ability to change our ecosystem, for the past few thousand years, we human beings have been the most diseased species on earth.

Acute versus Persistent Infectious Agents and Vaccines

Evolution by natural selection is at once the basis of all biological understanding and almost impossibly complex. Still, if there is any concept in biology more fraught with complexity, it is host–pathogen co-evolution. It entails the selection for host immunity mechanisms under pressures of independently co-evolving parasitic organisms or viruses. The host is under selective pressure to be fit relative to other members of its species, and the parasites are in a life or death pursuit of new hosts within which they can replicate. The problem is multidimensional. Still, there are very general concepts that may take immunology beyond a host-specific analysis of innate and acquired mechanisms of resistance.

One way to study disease and explain our inability to clear certain infections is to ask, what were the pressures that drove the evolution of an infectious agent in question? What is the structure

of its natural host population? How is it transmitted? Can it remain endemic as an acutely infectious agent, or does it require persistence? What is its host range and how does virulence change with different hosts? These questions have direct relevance to the investigation of disease treatments, especially the development of vaccines that might convey resistance (see Outstanding Questions).

Consider, for example, the 24 infectious agents to which we have successfully produced vaccines (Table 1). They overwhelmingly cause acute diseases that either kill the host or they are cleared with sterilizing immunity. We can deduce, from more than a century of experience, that if there is acquired immunity associated with natural disease clearance, an effective vaccine can be readily formulated – I do not know of an exception to this. Effective, in this case, means that the vaccine confers individual resistance and herd immunity such that a human-specific disease tends to fade-out of the population. Examples include smallpox, polio, measles, mumps, rubella, and others, but this only applies if human beings are the sole host and the agent in question is an obligate parasite. If there are one or more reservoir species, as for rotaviruses, or the agent in question is a saprophytic environmental bacterium, such as *Clostridium tetani*, then vaccination may confer individual protection, but it will not substantially diminish disease risk in the population. The converse is not true. Acute disease resolution with sterilizing immunity is not a prerequisite for the development of a vaccine. The clear exceptions thus far are hepatitis B virus and human papillomavirus.

For most of the major chronic human infectious agents, there are no effective vaccines. These parasites are too numerous to list, but include examples from each of the aforementioned categories. Just considering the chronic human viruses, there are very few to which we have been able to produce an effective vaccine (Table 2) – and not for lack of trying. After more than 30 years (and a huge fortune invested), we are still not very close to producing an effective vaccine to prevent HIV infection, and I contend that the problem lies with an early lack of acknowledgment that acutely resolving and persistent diseases present very different challenges to mechanisms of resistance. Indeed, tolerance rather than resistance may be the operative response to these diseases. Measles virus is under no selective pressure to remain persistent, and so has not evolved the means to avoid elimination by acquired immunity (although it does suppress the immune system for about 2 years [117]). By contrast, HIV, and similar lentiviruses, is under selective pressure to remain infectious for the time required for vertical or venereal transmission. Unfortunately, it appears to do this via a high replication rate and an error-prone polymerase such that each patient produces a many-fold mutant-saturated viral genome – every day [118]. The result is a phylogeny of HIV isolated from a single person that looks like that of influenza viruses isolated over 30 years from human population, that is, continuous strong immune selection acting on a great sequence diversity without preventing virus spread [119].

Immunology and Disease Ecology

The question posed at the beginning of this review concerns the possibility of reassembling the immune response to infectious agents from the component parts. As I have described, if this is at all feasible, the solution will not lie exclusively with general properties of the host immune system. It must include the evolutionary history of the host–pathogen interaction. For a long co-evolved host–pathogen interaction, the progression and outcome of an infection depends on selective pressures for pathogen endemicity within a population. The consequences of this host–pathogen co-evolution vary from an acute infection followed by sterilizing immunity to long-term persistence or latency. We may be able to assemble the course of an infection from an understanding of the host–pathogen ecology, a survey of the virulence strategies encoded by the pathogen, and a general knowledge of the immune system.

Table 1. Diseases for Which Vaccines Are Available (United States)

Disease	Transmission	Incubation	Contagious (acute vs chronic)	Etiologic agent	Sterilizing immunity	Effective vaccine
Anthrax	Inhalation, ingestion, other	1–2 months	None (acute)	*Bacillus anthracis* spores	Yes	Yes
Chicken pox	Respiratory	10–21 days	6–8 days (acute)	Varicella-zoster virus (α-herpes)	No[a]	Yes
Diphtheria	Respiratory	2–5 days	2–4 weeks (acute)	*Corynebacterium diphtheriae*	Yes	Yes
Hepatitis A	Ingestion	2–6 weeks	2–6 months (acute)	Hepatitis A virus (Picornavirales)	Yes	Yes
Hepatitis B	Bodily fluids, perinatal	60–150 days	Variable (can be chronic)	Hepatitis B virus (Hepadenavirus)	Yes	Yes
Haemophilus influenzae diseases	Respiratory	Unknown	Carriers (acute)	*H. influenzae*	Yes, adults	Yes
Genital warts, cancers of epithelia	Contact	Unknown	Active lesions (chronic)	Human papilloma virus	Unknown	Yes types 16, 18
Influenza A	Respiratory	1–3 days	5–7 days (acute)	Influenza A virus	Yes (specific to serogroup)	Yes (specific to serogroup)
Japanese encephalitis	Vector	5–15 days	Not contagious (acute)	Japanese encephalitis virus (Flavivirus)	Yes	Yes
Measles (rubeola)	Respiratory	9–12 days	Approximately 4–9 days (acute)	Morbillivirus	Yes	Yes
Meningococcal disease	Respiratory (close contact)	3–7 days	Until resolved (acute)	*Neisseria meningitides*	Partial	Partial
Mumps	Respiratory	16–18 days	15 days (acute)	Mumps virus	Yes	Yes
Pertussis (whooping cough[a])	Respiratory	7–14 days	5 weeks (acute)	*Bordetella pertussis*	Yes (partial)	Yes (varies with number of vaccinations)
Pneumococcal disease	Respiratory	High percentage of carriers	Unknown (acute)	*Streptococcus pneumoniae*	Not understood	Yes
Polio	Ingestion (fecal–oral)	3–6 days; paralysis 7–21 days	7–10-day symptoms (acute)	Poliovirus (Picornaviridae enterovirus)	Yes	Yes
Rabies	Saliva to blood	Weeks to months	No human transmission (acute)	Rabies virus (*Lyssavirus*)	Not applicable since survival is almost nil	Yes
Rotavirus	Fecal–oral	2 days	3 days following recovery (acute)	Rotavirus (Reoviridae Sedoreovirinae)	No	Partial
Rubella	Respiratory	14–21 days	17 days (acute)	Rubella virus (Togavirus)	Yes	Yes
Shingles	Recrudescence	Years	Active lesions (chronic-latent)	Varicella	No	Partial, 51–67% effective
Small pox	Respiratory	12 days	>40 days (ordinary) (acute)	*Variola major*	Yes	Yes
Tetanus	Skin lesions	3–21 days	No human transmission (acute)	*Clostridium tetani*	No	Yes
Tuberculosis	Respiratory-active disease	Variable	Years (acute or chronic)	*Mycobacterium tuberculosis*	Yes[a]	Variably effective
Typhoid	Fecal–oral	6–30 days	1 month (acute)	*Salmonella typhi*	No	Partial
Yellow fever	Vector	3–6 days	Not contagious (acute)	Yellow fever virus	Yes	Yes

[a]Largely protective antibodies are induced by infection or vaccination, but the virus persists in a latent form and can reactivate to cause shingles.

Table 2. Presently Known Human Persistent Viruses[a]

Virus	Transmission	Family	Genome	Vaccine	Notes
Adenoviruses	Respiratory droplets, direct conjunctival inoculation, fecal–oral – stable virion	Adenoviridae	dsDNA	Yes, types 4,7	>67 adenoviruses (human types in 7 species cause several diseases). Latency in adenoids, tonsils, continually shed in feces. Human co-evolution
BK virus (BKV) and JC virus (JCV)	BKV: unknown, saliva or urine JCV: contaminated water	Human polyomavirus	dsDNA	No	Immunocompromised people: BKV, renal dysfunction; JCV, progressive multifocal leukoencephalopathy
Hepatitis B virus	Body fluids	Hepadenavirus	dsDNA and ssDNA	Yes	Chronic or latent, can result in hepatitis, cirrhosis, hepatocellular carcinoma
Hepatitis C virus	Blood, birth	Flavivirus	ssRNA	No	Hepatitis, cirrhosis Liver cancer
Herpes simplex virus-1 (human herpes virus 1)	Contact with reactivated lesions	α-Herpes (Herpesviridae)	dsDNA	No	Cold sores
Herpes simplex virus-2 (human herpes virus 1)	Contact with reactivated lesions	α-Herpes	dsDNA	No	Genital herpes
Varicella zoster virus (human herpes virus 3)	Respiratory droplets, contact with blisters	Related to α-herpes	dsDNA	Yes	Acute chickenpox is cleared, virus remains latent, and may cause shingles
Epstein-Barr virus (human herpes virus 4)	Saliva and genital secretions	γ-Herpes (herpesviridae)	dsDNA	No	Infects about 90% of human beings (Burkitt's lymphoma, mononucleosis, others)
Cytomegalovirus (human herpes virus 5)	Urine saliva, blood, semen, breast milk	β-Herpes (herpesviridae)	dsDNA	No	Infects most human beings
Human herpes virus-6 and 7	Saliva	β-Herpes (herpesviridae)	dsDNA	No	6a: Neurovirulent 6b, 7: Exanthema subitum
Kaposi's sarcoma-associated herpesvirus (human herpes virus 8)	Saliva, blood, venereal contact	β-Herpes	dsDNA	No	Cause of Kaposi's sarcoma
Human hepegivirus 1 (pegivirus, hepatitis G)	Blood	Flavivirus	ssRNA	No	Not known to be pathogenic
HIV	Blood, semen, vaginal fluid, breast milk	Lentivirus (Retroviridae)	ssRNA	No	Acquired immunodeficiency disease
Human papilloma viruses (HPVs)	Venereal contact	Papilloma virus	dsDNA	Yes	>170 types; HPV16 and HPV18 cause 70% of cervical cancer cases
Human T-cell lymphotropic virus 1 and 2	Blood, venereal contact, breast milk	Deltaretrovirus	ssRNA	No	T-cell leukemia and lymphomas
Measles virus (latent)	Respiratory droplets	Morbillivirus	ssRNA	Yes	Behaves as acute infection and rarely persists causing subacute sclerosing panencephalitis in $1/10^5$ infected cases
B19 virus: Parvovirus	Respiratory droplets	Parvovirus	dsDNA	No	B19 can cause chronic hemolytic anemia

[a]Abbreviations: dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; ssDNA, single-stranded DNA; ssRNA, single-stranded RNA.

By contrast, for a zoonotic infection, neither the pathogen nor the host is entirely prepared for the interaction, and hence the outcome is unpredictable. In particular, if there is a productive infection, the ensuing immune response may be over-reactive (often via some component of innate immunity) and cause immunopathology, or it may be in some way inadequate, resulting in direct pathogenesis. Each case is idiosyncratic, but surely predicting the rate of pathogen clearance, disease severity, or the onset of an epidemic will require more than even 'complete' knowledge of the mechanisms of immunity [3,120,121].

A newly emerged disease epidemic originates from an opportunity for interspecies contact and infection, pathogen replication and transmission, and a selection for variants that more effectively disseminate within the affected host population. It depends on events that occur across multiple spatial and temporal scales: from molecular and cellular events that allow for initial replication to the large-scale demographics and mobility of the host population [122]. These parameters combined with the others reviewed earlier may be interdependent such that the time course of pathogen spread and the effects on the host population exhibit decidedly nonlinear dynamics [122–124]. For example, a modeling exercise using real-world assumptions and simple differential equations that track the spread of different strains of a pathogen with time showed that altering only two parameters, the ratio of the time of infection to the lifetime of the host and the antigenic cross-reactivity between different strains of a pathogen, would result in entirely different epidemic outcomes. The strains of the infectious agent present within the novel host population could become diverse and stable, could exhibit cyclic or chaotic fluctuations over time, or could resolve to a single dominant endemic strain [123]. Considering that there are many ways in which time of infection, lifetime of the host, and the cross-reactivity of pathogen strains might be influenced at different temporal and spatial scales, a real-world prediction of an epidemic will be a major future challenge.

Nonetheless, as the components of immunity important for a particular pathogen have been characterized in more detail, and models have become more sophisticated, there has been progress in quantitative modeling of in-host pathogen replication, the effectiveness of an immune response, and the potential for epidemic spread of infection [125,126]. Unfortunately, the needed quantitative information to construct such models is at best presently available for a particular pathogen infecting inbred, specific pathogen-free mice. How this translates to natural hosts or human beings is still difficult to know; however, advances in this regard allow genetically modified mice to harbor components of the innate and adaptive human immune system, and as such, begin to provide the means of pretesting an infectious agent for replication dynamics and the potential for immune clearance [127,128]. Combined with an accommodation for natural microbiota [129,130], there is the potential to experimentally replicate a human–pathogen interaction. In addition, studies of the immune populations present in blood or in the tissues of transplant donors at the time of death are now providing information on the make-up of the human immune system correlated with age and infection history, and further, how it compares with that of mice [129–133]. A combination of increasingly sophisticated experimental models, a knowledge of the disease ecology of a given infectious agent, and mathematical models of in-host and between-host propagation may begin to fulfill Wilson's challenge to capture the key properties of the entire ensembles.

Outstanding Questions

Are there general principles dictating the severity of zoonotic infections?

Which form or forms of immunity most commonly restrict replication and spread within a novel host population?

Do some forms of parasitism exhibit wider host tropism and have greater potential to cause emergent diseases?

Are there forms of avoidance in mammals that have yet to be discovered?

How is the immune system directed to attenuate resistance and follow a course of tolerance?

Can experimental model organisms be constructed that more closely recreate natural human–pathogen interactions?

Is the reassembly of the component parts of the immune system to capture the key properties of the entire ensemble a realistic goal?

References

1. Taylor, L.H. *et al.* (2001) Risk factors for human disease emergence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 356, 983–989
2. Woolhouse, M.E. *et al.* (2005) Emerging pathogens: the epidemiology and evolution of species jumps. *Trends Ecol. Evol.* 20, 238–244
3. Mandl, J.N. *et al.* (2015) Reservoir host immune responses to emerging zoonotic viruses. *Cell* 160, 20–35
4. Zapata, J.C. and Salvato, M.S. (2013) Arenavirus variations due to host-specific adaptation. *Viruses* 5, 241–278
5. Ermonval, M. *et al.* (2016) What do we know about how Hantaviruses interact with their different hosts. *Viruses* 8, E223
6. Holmes, E.C. *et al.* (2016) The evolution of Ebola virus: insights from the 2013–2016 epidemic. *Nature* 538, 193–200
7. Screaton, G. *et al.* (2015) New insights into the immunopathology and control of dengue virus infection. *Nat. Rev. Immunol.* 15, 745–759
8. Wild, T.F. (2009) Henipaviruses: a new family of emerging Paramyxoviruses. *Pathol. Biol. (Paris)* 57, 188–196
9. Cressler, C.E. *et al.* (2016) The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. *Parasitology* 143, 915–930
10. Silverstein, A.M. (2009) *A History of Immunology* (2nd edn), Elsevier
11. Strogatz, S.H. (2001) Exploring complex networks. *Nature* 410, 268–276
12. Wilson, E.O. (1998) *Consilience: The Unity of Knowledge,* Vintage Books, p. 85
13. Hoffmann, J.A. *et al.* (1996) Innate immunity in higher insects. *Curr. Opin. Immunol.* 8, 8–13
14. Brennan, C.A. and Anderson, K.V. (2004) *Drosophila*: the genetics of innate immune recognition and response. *Annu. Rev. Immunol.* 22, 457–483
15. Ayres, J.S. *et al.* (2008) Identification of *Drosophila* mutants altering defense of and endurance to *Listeria monocytogenes* infection. *Genetics* 178, 1807–1815
16. Choi, O. and Rutschmann, S. (2012) Dissecting immunity by germline mutagenesis. *Immunology* 137, 124–130

17. Casanova, J.L. (2015) Severe infectious diseases of childhood as monogenic inborn errors of immunity. *Proc. Natl. Acad. Sci. U. S. A.* 112, E7128–E7137
18. Casanova, J.L. and Abel, L. (2007) Primary immunodeficiencies: a field in its infancy. *Science* 317, 617–619
19. Casadevall, A. and Pirofski, L. (2001) Host-pathogen interactions: the attributes of virulence. *J. Infect. Dis.* 184, 337–344
20. Sadd, B.M. and Schmid-Hempel, P. (2009) Principles of ecological immunology. *Evol. Appl.* 2, 113–121
21. Archie, E.A. *et al.* (2009) Infecting epidemiology with genetics: a new frontier in disease ecology. *Trends Ecol. Evol.* 24, 21–30
22. Cremer, S. *et al.* (2007) Social immunity. *Curr. Biol.* 17, R693–R702
23. de Roode, J.C. and Lefèvre, T. (2012) Behavioral immunity in insects. *Insects* 3, 789–820
24. Beale, E. *et al.* (2006) *Caenorhabditis elegans* senses bacterial autoinducers. *Appl. Environ. Microbiol.* 72, 5135–5137
25. Pradel, E. *et al.* (2007) Detection and avoidance of a natural product from the pathogenic bacterium *Serratia marcescens* by *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. U. S. A.* 104, 2295–2300
26. Meisel, J.D. *et al.* (2014) Chemosensation of bacterial secondary metabolites modulates neuroendocrine signaling and behavior of *C. elegans*. *Cell* 159, 267–280
27. Rivière, S. *et al.* (2009) Formyl peptide receptor-like proteins are a novel family of vomeronasal chemosensors. *Nature* 459, 574–577
28. Oaten, M. *et al.* (2009) Disgust as a disease-avoidance mechanism. *Psychol. Bull.* 135, 303–321
29. Curtis, V. *et al.* (2011) Disgust as an adaptive system for disease avoidance behaviour. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 366, 389–401
30. Schneider, D.S. and Ayres, J.S. (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nat. Rev. Immunol.* 8, 889–895
31. Råberg, L. *et al.* (2009) Decomposing health: tolerance and resistance to parasites in animals. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 364, 37–49
32. Little, T.J. *et al.* (2010) The coevolution of virulence: tolerance in perspective. *PLoS Pathog.* 6, e1001006
33. Sears, B.F. *et al.* (2011) The economy of inflammation: when is less more? *Trends Parasitol.* 27, 382–387
34. Medzhitov, R. *et al.* (2012) Disease tolerance as a defense strategy. *Science* 335, 936–941
35. Schafer, J.F. (1971) Tolerance to plant disease. *Annu. Rev. Phytopathol.* 9, 235–252
36. Baucom, R.S. and de Roode, J.C. (2011) Ecological immunology and tolerance in plants and animals: tolerance in plants and animals. *Funct. Ecol.* 25, 18–28
37. Anderson, R.M. and May, R.M. (1992) *Infectious Diseases of Humans: Dynamics and Control,* Oxford University Press
38. Kermack, W.O. and McKendrick, A.G. (1991) Contributions to the mathematical theory of epidemics – I. 1927. *Bull. Math. Biol.* 53, 33–55
39. Anderson, R.M. and May, R.M. (1982) Coevolution of hosts and parasites. *Parasitology* 85, 411–426
40. Greenwood, M. *et al.* (1936) Experimental epidemiology. Medical Research Council Special Report Series. *JAMA* 107, 1971–1972
41. Anderson, R.M. and May, R.M. (1979) Population biology of infectious diseases: part I. *Nature* 280, 361–367
42. Fenner, F. and Ratcliffe, F.N. (1965) *Myxomatosis,* Cambridge University Press
43. Fenner, F. (1953) Changes in the mortality-rate due to myxomatosis in the Australian wild rabbit. *Nature* 172, 228–230
44. Fenner, F. (2010) Deliberate introduction of the European rabbit, *Oryctolagus cuniculus*, into Australia. *Rev. Sci. Tech.* 29, 103–111
45. Marshall, I.D. and Fenner, F. (1960) Studies in the epidemiology of infectious myxomatosis of rabbits. VII. The virulence of strains of myxoma virus recovered from Australian wild rabbits between 1951 and 1959. *J. Hyg. (Lond)* 58, 485–488
46. Kerr, P.J. (2012) Myxomatosis in Australia and Europe: a model for emerging infectious diseases. *Antiviral Res.* 93, 387–415
47. Kerr, P.J. *et al.* (2015) Myxoma virus and the Leporipoxviruses: an evolutionary paradigm. *Viruses* 7, 1020–1061
48. Van Valen, L. (1973) A new evolutionary law. *Evol. Theory* 1, 1–30
49. Ebert, D. and Hamilton, W.D. (1996) Sex against virulence: the coevolution of parasitic diseases. *Trends Ecol. Evol.* 11, 79–82
50. Hedrick, S.M. (2004) The acquired immune system: a vantage from beneath. *Immunity* 21, 607–615
51. Decaestecker, E. *et al.* (2007) Host-parasite 'Red Queen' dynamics archived in pond sediment. *Nature* 450, 870–873
52. Lively, C.M. (2010) An epidemiological model of host-parasite coevolution and sex. *J. Evol. Biol.* 23, 1490–1497
53. Kerr, P.J. *et al.* (2012) Evolutionary history and attenuation of myxoma virus on two continents. *PLoS Pathog.* 8, e1002950
54. André, J.B. *et al.* (2003) Within-host parasite dynamics, emerging trade-off, and evolution of virulence with immune system. *Evolution* 57, 1489–1497
55. Legrand, J. *et al.* (2007) Understanding the dynamics of Ebola epidemics. *Epidemiol. Infect.* 135, 610–621
56. Diehl, W.E. *et al.* (2016) Ebola virus glycoprotein with increased infectivity dominated the 2013–2016 epidemic. *Cell* 167, 1088–1098 e6
57. Urbanowicz, R.A. *et al.* (2016) Human adaptation of Ebola virus during the West African outbreak. *Cell* 167, 1079–1087 e5
58. Bull, J.J. and Lauring, A.S. (2014) Theory and empiricism in virulence evolution. *PLoS Pathog.* 10, e1004387
59. Alizon, S. *et al.* (2009) Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *J. Evol. Biol.* 22, 245–259
60. Bull, J.J. and Ebert, D. (2008) Invasion thresholds and the evolution of nonequilibrium virulence. *Evol. Appl.* 1, 172–182
61. Lively, C.M. (2006) The ecology of virulence. *Ecol. Lett.* 9, 1089–1095
62. Ebert, D. (1998) Experimental evolution of parasites. *Science* 282, 1432–1435
63. Sabin, A.B. and Boulger, L.R. (1973) History of Sabin attenuated poliovirus oral live vaccine strains. *J. Biol. Stand.* 1, 115–118
64. Johnson, P.T. *et al.* (2013) Biodiversity decreases disease through predictable changes in host community competence. *Nature* 494, 230–233
65. Bartlett, M.S. (1960) The critical community size for measles in the United States. *J. R. Stat. Soc. A* 123, 37–44
66. Black, F.L. (1966) Measles endemicity in insular populations: critical community size and its evolutionary implication. *J. Theor. Biol.* 11, 207–211
67. Black, F.L. (1975) Infectious diseases in primitive societies. *Science* 187, 515–518
68. Haraguchi, Y. and Sasaki, A. (2000) The evolution of parasite virulence and transmission rate in a spatially structured population. *J. Theor. Biol.* 203, 85–96
69. Erdös, P. and Rényi, A. (1960) On the evolution of random graphs. *Bull. Inst. Int. Stat.* 38, 343–347
70. Karoński, M. (1982) A review of random graphs. *J. Graph Theory* 6, 349–389
71. Callaway, D.S. *et al.* (2000) Network robustness and fragility: percolation on random graphs. *Phys. Rev. Lett.* 85, 5468–5471
72. Albert, R. and Barabási, A.-L. (2002) Statistical mechanics of complex networks. *Rev. Mod. Phys.* 74, 47–97
73. Miller, J.C. (2009) Percolation and epidemics in random clustered networks. *Phys. Rev. E Stat. Nonlinear Soft Matter Phys.* 80, 020901
74. Milgram, S. (1967) The small-world problem. *Psychol. Today* 1, 61–67
75. Travers, J. and Milgram, S. (1969) An experimental study of the small world problem. *Sociometry* 32, 425–443
76. Watts, D.J. and Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. *Nature* 393, 440–442

77. Zuev, K. *et al.* (2016) Hamiltonian dynamics of preferential attachment. *J. Phys. A Math. Theor.* 49, 105001
78. Pastor-Satorras, R. and Vespignani, A. (2001) Epidemic spreading in scale-free networks. *Phys. Rev. Lett.* 86, 3200–3203
79. May, R.M. and Lloyd, A.L. (2001) Infection dynamics on scale-free networks. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 64, 066112
80. Boguñá, M. *et al.* (2003) Absence of epidemic threshold in scale-free networks with degree correlations. *Phys. Rev. Lett.* 90, 028701
81. Barthélemy, M. *et al.* (2004) Velocity and hierarchical spread of epidemic outbreaks in scale-free networks. *Phys. Rev. Lett.* 92, 178701
82. Ewald, P.W. (1983) Host-parasite relations, vectors, and the evolution of disease severity. *Annu. Rev. Ecol. Syst.* 14, 465–485
83. Ewald, P.W. (1995) The evolution of virulence: a unifying link between parasitology and ecology. *J. Parasitol.* 81, 659–669
84. Day, T. (2001) Parasite transmission modes and the evolution of virulence. *Evolution* 55, 2389–2400
85. Veugelers, P.J. *et al.* (1994) Determinants of HIV disease progression among homosexual men registered in the Tricontinental Seroconverter Study. *Am. J. Epidemiol.* 140, 747–758
86. Fenn, E. (2000) Biological warfare in eighteenth-century North America: beyond Jeffery Amherst. *J. Am. Hist.* 86, 1552–1580
87. Walther, B.A. and Ewald, P.W. (2004) Pathogen survival in the external environment and the evolution of virulence. *Biol. Rev. Camb. Philos. Soc.* 79, 849–869
88. Bailey, D. (2011) *Cholera,* Rosen Publishing
89. McNeill, W.H. (1976) *Plagues and Peoples,* Anchor Press/Doubleday
90. Galvani, A.P. (2003) Epidemiology meets evolutionary ecology. *Trends Ecol. Evol.* 18, 132–139
91. Armelagos, G.J. *et al.* (2005) Evolutionary, historical and political economic perspectives on health and disease. *Soc. Sci. Med.* 61, 755–765
92. Virgin, H.W. *et al.* (2009) Redefining chronic viral infection. *Cell* 138, 30–50
93. Woolhouse, M. and Gaunt, E. (2007) Ecological origins of novel human pathogens. *Crit. Rev. Microbiol.* 33, 231–242
94. Bocquet-Appel, J.-P. *et al.* (2005) Estimates of Upper Palaeolithic meta-population size in Europe from archaeological data. *J. Archaeol. Sci.* 32, 1656–1668
95. Li, H. *et al.* (2011) Inference of human population history from individual whole-genome sequences. *Nature* 475, 493–496
96. Zahid, H.J. *et al.* (2016) Agriculture, population growth, and statistical analysis of the radiocarbon record. *Proc. Natl. Acad. Sci. U. S. A.* 113, 931–935
97. Goldewijk, K.K. *et al.* (2010) Long-term dynamic modeling of global population and built-up area in a spatially explicit way: HYDE 3. 1. *Holocene* 20, 565–573
98. Tallavaara, M. *et al.* (2015) Human population dynamics in Europe over the Last Glacial Maximum. *Proc. Natl. Acad. Sci. U. S. A.* 112, 8232–8237
99. Diamond, J.M. (1997) *Guns, Germs, and Steel: The Fates of Human Societies,* pp. 199–214, W.W. Norton
100. Wolfe, N.D. *et al.* (2007) Origins of major human infectious diseases. *Nature* 447, 279–283
101. Crosby, A.W. (1976) Virgin soil epidemics as a factor in the aboriginal depopulation in America. *William Mary Q.* 33, 289
102. Fenner, F. (1993) Smallpox: emergence, global spread, and eradication. *Hist. Philos. Life Sci.* 15, 397–420
103. Black, F.L. (1992) Why did they die? *Science* 258, 1739–1740
104. Mann, C.C. (2005) *1491: New Revelations of the Americas before Columbus,* Albert A. Knopf
105. Hedrick, P.W. (2011) Population genetics of malaria resistance in humans. *Heredity (Edinb)* 107, 283–304
106. Baron, J.M. *et al.* (2011) A revised timeline for the origin of *Plasmodium falciparum* as a human pathogen. *J. Mol. Evol.* 73, 297–304
107. Carter, R. and Mendis, K.N. (2002) Evolutionary and historical aspects of the burden of malaria. *Clin. Microbiol. Rev.* 15, 564–594
108. Hedrick, P.W. (2012) Resistance to malaria in humans: the impact of strong, recent selection. *Malar. J.* 11, 349
109. Zhernakova, A. *et al.* (2010) Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection. *Am. J. Hum. Genet.* 86, 970–977
110. Zhernakova, A. *et al.* (2011) Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet.* 7, e1002004
111. Yang, H. *et al.* (2012) IFIH1 gene polymorphisms in type 1 diabetes: genetic association analysis and genotype-phenotype correlation in Chinese Han population. *Autoimmunity* 45, 226–232
112. Vasseur, E. *et al.* (2012) The evolutionary landscape of cytosolic microbial sensors in humans. *Am. J. Hum. Genet.* 91, 27–37
113. Sironi, M. (2013) Pathogen-driven selection in the human genome. *Int. J. Evol. Biol.* 2013, 204240
114. Laayouni, H. *et al.* (2014) Convergent evolution in European and Rroma populations reveals pressure exerted by plague on Toll-like receptors. *Proc. Natl. Acad. Sci. U. S. A.* 111, 2668–2673
115. Ramos, P.S. *et al.* (2014) Genes associated with SLE are targets of recent positive selection. *Autoimmune Dis.* 2014, 203435
116. Quach, H. *et al.* (2016) Genetic adaptation and neandertal admixture shaped the immune system of human populations. *Cell* 167, 643–656 e17
117. Mina, M.J. *et al.* (2015) Vaccines. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* 348, 694–699
118. Perelson, A.S. *et al.* (1996) HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* 271, 1582–1586
119. Grenfell, B.T. *et al.* (2004) Unifying the epidemiological and evolutionary dynamics of pathogens. *Science* 303, 327–332
120. Murphy, F.A. (1998) Emerging zoonoses. *Emerg. Infect. Dis.* 4, 429–435
121. Han, B.A. *et al.* (2016) Global patterns of zoonotic disease in mammals. *Trends Parasitol.* 32, 565–577
122. Peters, D.P. *et al.* (2004) Cross-scale interactions, nonlinearities, and forecasting catastrophic events. *Proc. Natl. Acad. Sci. U. S. A.* 101, 15130–15135
123. Gupta, S. *et al.* (1998) Chaos, persistence, and evolution of strain structure in antigenically diverse infectious agents. *Science* 280, 912–915
124. Gupta, S. and Anderson, R.M. (1999) Population structure of pathogens: the role of immune selection. *Parasitol. Today* 15, 497–501
125. Handel, A. *et al.* (2010) Towards a quantitative understanding of the within-host dynamics of influenza A infections. *J. R. Soc. Interface* 7, 35–47
126. Banerjee, S. *et al.* (2016) Estimating biologically relevant parameters under uncertainty for experimental within-host murine West Nile virus infection. *J. R. Soc. Interface* 13, 20160130
127. Rongvaux, A. *et al.* (2014) Development and function of human innate immune cells in a humanized mouse model. *Nat. Biotechnol.* 32, 364–372
128. Saito, Y. *et al.* (2016) Peripheral blood $CD34^+$ cells efficiently engraft human cytokine knock-in mice. *Blood* Published online August 19, 2016. http://dx.doi.org/10.1182/blood-2015-10-676452
129. Beura, L.K. *et al.* (2016) Normalizing the environment recapitulates adult human immune traits in laboratory mice. *Nature* 532, 512–516
130. Reese, T.A. *et al.* (2016) Sequential infection with common pathogens promotes human-like immune gene expression and altered vaccine response. *Cell Host Microbe* 19, 713–719
131. Farber, D.L. *et al.* (2016) Immunological memory: lessons from the past and a look to the future. *Nat. Rev. Immunol.* 16, 124–128
132. Urrutia, A. *et al.* (2016) Standardized whole-blood transcriptional profiling enables the deconvolution of complex induced immune responses. *Cell Rep.* 16, 2777–2791
133. Brodin, P. and Davis, M.M. (2017) Human immune system variation. *Nat. Rev. Immunol.* 17, 21–29