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Evolution of pathogens in a man-made world

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Abstract

Human activities have resulted in substantial, large-scale environmental modifications, especially in the past century. Ecologists and evolutionary biologists are increasingly coming to realize that parasites and pathogens, like free-living organisms, evolve as the consequence of these anthropogenic changes. Although this area now commands the attention of a variety of researchers, a broad predictive framework is lacking, mainly because the links between human activities, the environment and parasite evolution are complex. From empirical and theoretical examples chosen in the literature, we give an overview of the ways in which humans can directly or indirectly influence the evolution of different traits in parasites (*e.g.* specificity, virulence, polymorphism). We discuss the role of direct and indirect factors as diverse as habitat fragmentation, pollution, biodiversity loss, climate change, introduction of species, use of vaccines and antibiotics, ageing of the population, etc. We also present challenging questions for further research. Understanding the links between anthropogenic changes and parasite evolution needs to become a cornerstone of public health planning, economic development and conservation biology.

Keywords: ecology of health, human activities, infectious diseases, parasite evolution, protected areas, virulence

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Introduction

Parasite-induced damage to hosts is of great significance to humans, both as hosts themselves and as exploiters of hosts (livestock, crops). If we measure virulence (damage to host) only by the crude measure of host mortality, the scale of importance is made plain. Globally, parasites (defined broadly as infectious agents of disease) are responsible for 19% of all human mortality (World Health Organization 2004). In recent decades, the burden of infectious diseases has even increased in many countries because of the emergence of new pathogens and the re-emergence of old pathogens newly resistant to current methods of control (Woolhouse & Gowtage-Sequeria 2005). The picture was not always so bleak. The development and widespread use of new vaccines and antibiotics in the 1950s and 1960s led to an unprecedented decline in numerous deadly parasites and pathogens in developed countries, with one infectious disease, smallpox, even driven to extinction. As a measure of this historic success, in 1969 the US Surgeon General was able to declare that the war against pestilence had been won (Fig. 1, Anker & Schaaf 2002).

Over the last 20 years, this confidence has been shattered. New diseases like severe acute respiratory syndrome (SARS) and acquired immune deficiency syndrome (AIDS) grab headlines, while others like tuberculosis (TB), once thought banished, have returned newly resistant to existing treatments. While the scientific breakthroughs driving the first 'war against pestilence' came almost entirely from the biomedical sciences, there is now an increasingly influential body of ideas emerging from the fields of ecology and evolution. The logic behind this new input is clear — pathogenic microbes readily evolve in response to new drugs (Palumbi 2001), and the spread of pathogens, new and old, depends on their ecology (shaped by human activities ranging from air travel to bioterrorism) (Ferrari *et al*. 2006).

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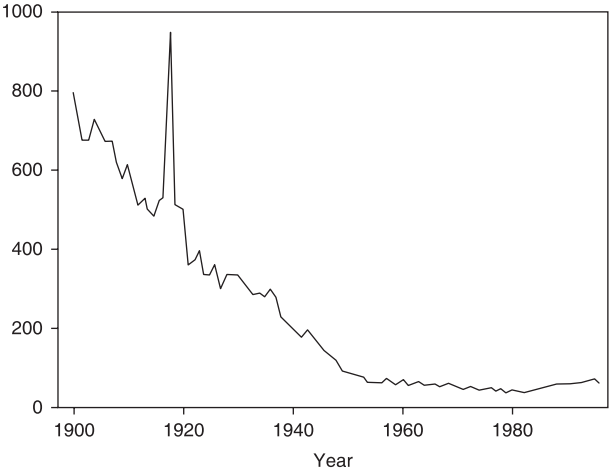

Fig. 1 US mortality rates (per 100 000) attributable to infectious diseases during the 20th Century. In 1900, approximately 1/3 of all deaths were due to infectious diseases (primarily pneumonia, TB and diarrhoea). Note the dramatic spike in mortality associated with the Influenza Pandemic of 1918 (highlights ongoing risk of novel pathogens). Also note definite rebound since 1980, attributable to AIDS and remerging (drug resistant) pathogens. Taken from Armstrong *et al*. (1999).

The evolution of drug resistance is only one dimension of parasite adaptation to human intervention. More generally, a great deal of theoretical attention has been paid to the question of how much harm a parasite should impose on its host, as a function of the parasite's ecology (shaped in part by biomedical interventions). Parasite-induced harm to the host, or virulence (Ebert & Hamilton 1996; Poulin & Combes 1999) is commonly assumed to be an inevitable side-effect of exploitation and transmission to another host, presenting the parasite with the challenge of balancing a trade-off between increasing transmission and rising virulence (Anderson & May 1982; Dieckmann *et al*. 2002; but see Ebert & Bull 2003 for an alternative view). The evolutionary study of virulence is currently attracting increasing interest, undoubtedly because of its strong implications for many areas, including human public health strategy and conservation biology. Understanding parasite evolution is thus not just an academic pursuit; it offers a conceptual framework to professionals in many fields and should contribute to decision-making.

Predicting the conditions that cause parasites to evolve in one direction or another, or to become more or less harmful to their hosts is of central importance in biological sciences, not only because of applied aspects of parasitology such as epidemiology and medicine, but also for purely fundamental reasons given the wide range of ways in which parasites interfere with the ecology and the evolution of free-living organisms (host regulation, sexual selection, life-history traits, invasion processes, etc. see Thomas *et al*. 2005 and 2007 for reviews). Parasites evolve but the exact contribution of human activities to this phenomenon remains an open question to which there is no simple answer at the moment. It is well established that human activities, especially in the past century, have resulted in substantial large-scale habitat and climate modifications. It is also widely recognized that such phenomena have major, sometimes dramatic, effects on the ecology and the evolution of living organisms. However, compared to the huge effort that researchers have devoted to explore the consequences of these changes on the ecology and/or on the evolution of free-living organisms, considerably less attention has been paid to parasitic organisms. In addition to altering global ecology, technology and human population growth also affect the evolutionary trajectories of disease organisms in many ways (Palumbi 2001), although the direction and magnitude of these effects remain difficult to predict (Altizer *et al*. 2003). However, at this stage, speculation has proven more attractive than data collection, and as a consequence, predictions remain at best simplistic, and at worst misleading. We review here some of the current evidence of the interactions between human activities and parasite evolution and explore avenues for further research.

Why should human activities influence parasite evolution?

Lessons from the past

The idea that humans, during their evolution, have influenced the evolutionary ecology of many parasite species is not new. Humans have suffered from multiple infectious diseases for millions of years from their origin to the present. It is well established that the range of diseases humans have been exposed to has changed considerably from early human populations nearly 4 millions years ago to Neolithic humans that lived on Earth *c.a.* 10 000–8000 years ago, and thereafter to modern humans living today in megalopolises (Armelagos *et al*. 1996). For instance, the habitat of early hominids was probably restricted to the tropical savannah. Then, during the course of human evolution, the habitat expanded gradually into the more temperate zones. Hominids thus transported some other diseases *en route* with the human expansion, and acquired new pathogen agents living in the newly colonized territories (Guégan *et al*. 2007). Traditional human populations lived in small, sparsely settled communities, where population sizes and densities remained very low. Human communities were too small to support endemic pathogens, but they were infected by various zoonoses (*e.g*. sleeping sickness, avian tuberculosis and leptospirosis) (Armelagos *et al*. 1996). With the agricultural revolution about 10 000 years ago, increasing sedentarity and larger population groupings resulted in an increase in the diversity and severity of

infectious diseases such as influenza, measles, mumps, or smallpox (Armelagos *et al*. 1996). The domestication of animals also provided a supply of vectors and greater exposure to zoonotic diseases (Polgar 1964). Human populations have constantly moved, transformed habitats, and created new ways of living and eating, thus generating new pathways for diseases to invade and spread into communities.

The human population is currently predicted to grow by another 2–4 billion people by 2050 (United Nations 2001), and environmental changes such as climate shifts and landscape modification are accelerating at an unprecedented pace. Terms such as 'climate warming', 'habitat loss' or 'biodiversity' have now joined the vernacular vocabulary. The threat of pandemics, for instance following the recent spread of highly pathogenic microbes like H5N1 influenza virus, is a key social preoccupation. We are facing an important epidemiological transition, potentially impacting on human adaptation and/or survival if those disease agents have the potential to be transmitted on a global scale. Understanding the links between anthropogenic changes and parasite evolution needs to become a key concern of public health planning, economic development and conservation biology.

Human activities can a priori influence the evolutionary trajectories of parasites in different ways, directly or indirectly by altering components of the environment of parasites. The environment of parasites is made of at least two dimensions which are ecologically different: the host (i.e. the immediate environment) and the habitat of the host (the ecosystem) (Thomas *et al*. 2002). For practical purposes, anthropogenic changes that may affect parasite evolution can be divided into three broad types, most of them being indirect (Fig. 2).

Change within human hosts

Anti-parasite drugs and parasite drug-resistance. The evolution of resistance to drugs is probably the best-known example that humans can directly drive the evolution of parasites. Resistance is a near inevitable consequence of the use of antiparasitic drugs (Palumbi 2001). The most commonplace example is the rapid acquisition of resistance to antibiotics in bacteria (Baquero & Blasquez 1997), further documented indirectly by geographical correlations between levels of antibiotic prescription and resistance (Goossens *et al*. 2005).

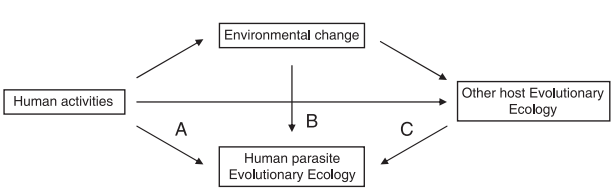

Fig. 2 Links between human activities and evolutionary ecology of parasites.

Similar examples also abound in livestock hosts. The routine use of anthelmintics against parasites of sheep and cattle has imposed new pressures on adult helminths for many parasite generations. Resistance to some anthelmintics has evolved quickly (Sangster 1999), but these have been replaced by other types of drugs so that the increased adult parasite mortality is maintained. We may thus expect other adaptive changes in parasite populations that have been exposed to anthelmintics for several years (see Buckling *et al*. 1997; Skorping & Read 1998; Leignel & Cabaret 2001; Poulin 2007). For instance, if adult parasite lifespan decreases, it is predicted that selection should favour a shorter prepatent period, that is an earlier age at maturity. Such a process then allows the parasite to produce eggs before the host is given anthelmintics (Poulin 2007).

There is considerable evidence that the virulence of human parasites and diseases has evolved jointly with transmission routes, and that the treatment of diseases can influence virulence, by favouring more or less virulent strains (Barlow & Nathwani 2005; Vazquez *et al*. 2007). Elderly people are often immunocompromised and they are assisted by a full panoply of medications. These treatments undeniably lead to the selection of drug resistance in many categories of pathogens. The grouping of patients in 'elderly care homes' may constitute production units of 'pathogen resistant ecosystems', which will represent a new and complex public health problem as the population ages (Renaud *et al*. 2005). We expect that pathogens produced in these ecosystems, many of which may be drug resistant, will spill out to attack other age groups of the population (i.e. infants, toddlers and children). Modern humans live longer, at least in industrialized countries, where the number of elderly is rapidly increasing (Morris & Potter 1997). This leads to an increasingly large group of hosts ripe for exploitation. To our knowledge, health policies have not yet considered this ecological problem.

Surgical interventions. Medical and surgical developments (*e.g.* catheters, fibroscopy, prosthesis, organ transplants associated with antirejection medicine, immunosuppressive drugs, etc.) are generating new environments in hospital ecosystems that are colonized now by new parasite and pathogen flocks (Renaud *et al*. 2005). The addition of exogenous material essentially leads to the establishment of new ecosystems inside the body. These new niches can subsequently be colonized by pathogens such as group C *Streptococcus*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Histoplasma capsulatum* (Gillespie 1997; Kleshinski *et al*. 2000) and SARS virus.

Change within human host communities

Human contact networks and parasite transmission. For most of their evolutionary history, human populations lived in

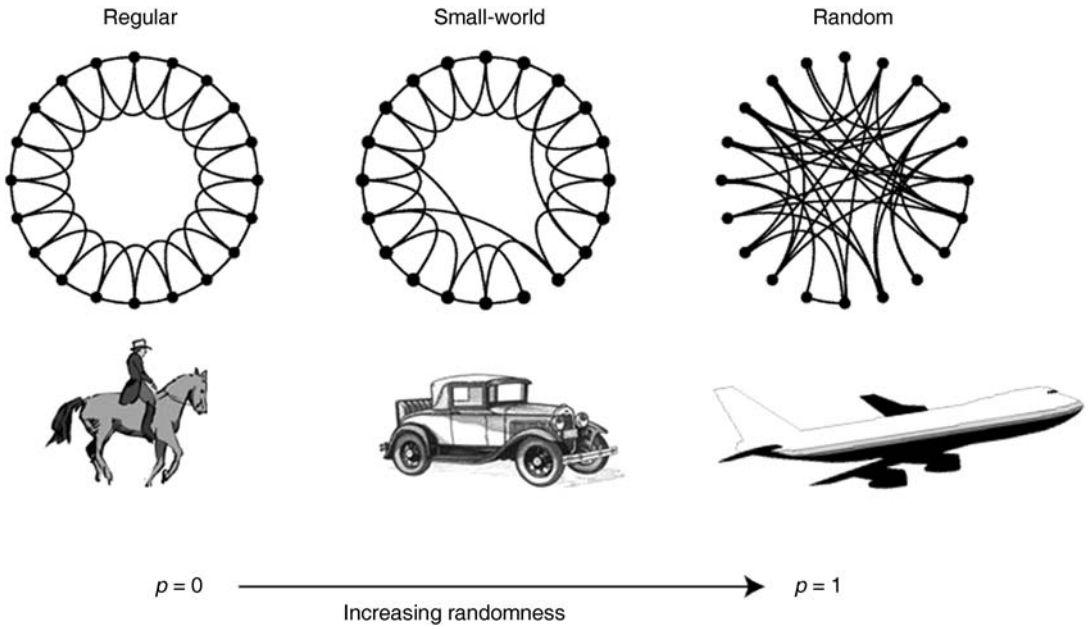

Fig. 3 Development of 'travel man-made ecosystems' consequences: connection topology from a regular ring lattice to a random network. The intermediate connection is called small 'world' network, and infectious diseases spread more easily in small-world networks that in regular lattices (modified from Watts & Strogatz 1998).

small and isolated populations. Things are, as we know, rather different nowadays. Developing travel considerably altered the connections between different inhabited areas (Fig. 3). Within the last 300 years, transportation has played a major role in shaping disease patterns by bringing larger segments of human populations into close contact with pathogens at an accelerated rate (Renaud *et al*. 2005; Guégan *et al*. 2007). Such a phenomenon has major implications for parasite dispersal and hence evolution (Boots & Sasaki 1999).

Modern social networks (Wasserman & Faust 1994) can be described as 'small worlds', characterized by significant long-distance connections reducing the mean number of social links between two individuals (Watts & Strogatz 1998). It follows that infection networks may also show 'small world' connections in modern societies. In agreement with this, it is interesting to note that the same pathogen genotype has often been isolated from two distant regions of the world, worldwide dissemination being attributable either to a single clone as for leprosy (Monot *et al*. 2005), or to some geographically ubiquitous strains as in measles (Riddell *et al*. 2005). The rapid and seasonal spread of a predominant influenza subtype among human populations is the best evidence of worldwide dissemination of the disease, because of increasing human contact networks (Brownstein *et al*. 2006; Nelson & Holmes 2007). Similarly, although still controversial, the most likely explanation for the recent and rapid spread of the highly pathogenic avian influenza H5N1 virus throughout the world is human activity (Gauthier-Clerc *et al*. 2007).

When infections occur predominantly locally, theoretical models predict a lower virulence than when transmission occurs predominantly randomly both within and between populations (Boots & Sasaki 1999). As a result of changing patterns of contact due in particular to innovations in transportation, one can argue that we have shifted from a regular lattice (characterized by local interactions only) to increasingly 'small world' networks (Renaud *et al*. 2005). Watts & Strogatz (1998) suggested that infectious diseases spread more easily in small-world networks than in 'regular' lattices, therefore changing contact patterns would have strong consequences for pathogen dispersal (Ferrari *et al*. 2006; Meyers 2006) and consequently for the evolution of virulence and resistance. Changing contact patterns would likewise impact the movement of all categories of vectors that are responsible for pathogen transport. Planes and boats constitute new opportunities for vector and pathogen dispersal (Renaud *et al*. 2005). Even if there are likely to be many cases where diseases failed to emerge from contact with a disease-bearing organism, transcontinental travel and pet transport will increase in the future. In this context, we need to be increasingly aware of the implications of the international exotic pet trade, which may be an efficient pathway for disseminating those infectious diseases around the globe (Di Giulio & Eckburg 2004).

Another important problem raised by the dispersal of parasites is the risk of pathogen evolution through interspecific hybridization. Fungi from the same geographical area often exhibit strong genetic barriers (sexual or asexual) to

interspecific hybridization. These barriers probably maintain gene combinations conferring optimal adaptation to the local ecological niche, and also prevent the spread of harmful genetic elements, such as viruses, between species (Brasier 2000). However, such barriers might not exist, or might be weaker, between fungi that have remained geographically isolated. There is thus a greater possibility of hybridization when fungi spread beyond their normal geographical ranges. Human influences have increased the chances of such occurrences. Immigration of fungal pathogens into new areas is likely to bring them into contact with resident, related species, especially those with a similar host or vector type. Although the potential for hybridization between residents and immigrants depends on several factors, it happens sometimes. Possible outcomes range from the acquisition of a single gene by one parent to a full species hybrid incorporating the genomes of both parents (Brasier 1995). The evolutionary potential of a population is proportional to its level of phenotypic, as well as genotypic, variation. It is now apparent that hybridization between fungal pathogens can produce a devastating array of phenotypes.

Environmental changes favouring transmission. Like free-living organisms, parasites and pathogens can colonize and evolve in new environments. Even if it is of course not their intention, humans routinely create novel habitats for parasites, and these new habitats can then in turn function as ongoing sources of infection for humans, even if the pathogen cannot maintain itself by transmission between human hosts (Sokurenko *et al*. 2006). For instance, microbes can contaminate and thrive in air-conditioning units and cooling towers; this can result in other health problems for workers and visitors such as respiratory sensitization and building-related illness, or 'sick building syndrome' (Renaud *et al*. 2005). The development of medical technology in hospital ecosystems has lead to the development of cohorts of opportunistic pathogens which exploit these new ecosystems. Diseases emerging in hospital ecosystems are known under the terminology 'Nosocomial infections'. Hospitals are the source of many diseases because patients are often immunocompromised, and because infected people converge on hospitals. The majority of nosocomial infections have an endemic origin (i.e. inside the hospital), where infection comes from a microorganism present in the ecosystem, with surgical or other medical intervention rendering it infectious. Nosocomial infections are even more alarming in the 21st century as antibiotic resistance spreads.

Humans not only create new habitats for parasites, but also for vectors. For instance, old tyres become excellent habitats for the larvae of different mosquito species, especially *Aedes* spp. which are the vectors of the dengue virus. In addition, worn and waste tyres are being traded throughout the world, and are responsible for the introduction of mosquitoes in different countries (Renaud *et al*. 2005).

Environmental changes hindering transmission. Finally, it is important to recognize the tremendous successes (and ongoing challenge in the developing world) of diverse public health measures such as the introduction of clean chlorinated water and vaccines in driving the reduction and even eradication of many infectious diseases (Fig. 1, Armstrong *et al*. 1999). However, although vaccination generally prevents successful pathogen transmission, imperfect or 'leaky' vaccines can also have unplanned consequences: if used repeatedly, they can select for higher levels of virulence (Gandon *et al*. 2001; Gandon *et al*. 2003; André & Gandon 2006). More generally, vaccination can influence the evolution of pathogens through various phenomena, both long-term and short-term ones. Because of the protection conferred by vaccine, hosts die less, thereby relieving the parasite of the potential fitness costs of prematurely shortened infections. Thus, host populations with high levels of immunity can maintain more virulent pathogens than naïve host populations can (Gandon *et al*. 2001). Vaccine-acquired host immunity may also result in lower parasite loads that reduce resource competition among parasites inside the host, but increase the competition for enemy-free space (*e.g*. by immune evasion). As pointed out by Mackinnon & Read (2004), this could lead to more aggressive parasites racing to stay ahead of proliferating immune responses. Along the same idea, it could also lead to the evolution of novel antigenic variants that have a selective advantage only in immunized hosts.

Change among nonhuman hosts

Farming. Agricultural processes have widely disturbed ecological parameters in natural ecosystems modified for food development; they are responsible for the emergence and spread of new parasite and pathogen species, and also for changes in host–parasite interactions. The ecology of industrial farming also raises the problem of hygiene. The very high densities of animals packed into very small areas, together with the increase of stress factors, are particularly favourable to the propagation of virulent agents once they appear. The highly pathogenic avian influenza H5N1 virus, discovered in Asia at the end of 1996, appeared in poultry farms and is only the latest example (it will not be the last), of a transfer of pathogen from animals to humans facilitated by farming practices.

Wildlife. As a consequence of various changes in human land use, many animal populations are displaced into new environments, which are often ecologically different from those of their source with respect to many factors. Such displacements of domestic and /or wild animals across the

globe can first be implicated in the spread of various pathogens, for example West Nile virus and H5N1. In addition, reserves are in many cases an effective means of protecting wildlife from threats, but they can, in certain circumstances, favour the most virulent strains of pathogens. Protected areas often encompass a very small portion of the total surface area potentially suitable (Dompka 1996). In addition, even when they appear relatively large in terms of surface area, the true optimal size of protected areas remains a relative parameter as it mainly depends on the number/type of species present. The overcrowding of animals in reserves is a topic that currently attracts increasing attention among conservationists. Such a phenomenon may indeed create foci for the production and maintenance of virulent parasites, which can potentially spill out to attack hosts from other areas or other species (Lebarbenchon *et al*. 2006). The likelihood and impact of an epidemic increases with host density because density determines contact rates between infected and uninfected individuals. Infectious agents require a threshold host density for transmission. Reducing the spatial extent of available habitat is indeed likely to select for virulent strains and trigger disease outbreaks by pushing parasites and hosts closer together. In extreme cases, this type of phenomenon favours the emergence of new diseases since increased interspecific contacts, and/or the elimination of the preferred host species, may then result in parasites jumping species. Because of the stress resulting from overcrowding, individuals may be in poor conditions and may provide 'stepping stones' for the evolution of pathogens. Humanity continuously encounters new pathogens of animal origin because anthropogenic changes often increase the pathogen's opportunities to enter the human population and to generate subsequent human-to-human transmission (Antia *et al*. 2003). The past decade has even seen the emergence and resurgence of many infectious diseases around the world with the majority of them being zoonoses (Guégan *et al*. 2007). HIV, Ebola and new hanta viruses in humans are believed to have arisen through that route. The independent emergence of two Human Immunodeficiency Virus strains, that is HIV-1 and HIV-2, from two distinct Simian Immunodeficiency Virus progenitors in two widely separated geographical areas, from the chimpanzee in Central Africa for HIV-1 (Keele *et al*. 2006) and from the sooty mangabey in West Africa for HIV-2 (Santiago *et al*. 2005), is just an illustration of the huge diversity of locally adapted microbial forms in wildlife that can transfer to humans. The Ebola virus was discovered to originate from bats (Leroy *et al*. 2005). The Severe Acute Respiratory Syndrome (SARS) provoked by an RNA virus, a coronavirus, was identified as coming from Palm civets *Paguma larvata* living in the Himalayas and feeding in China (Guan *et al*. 2003). Similarly, Arena and Hantaan viruses causing haemorrhagic fevers in humans are common in wild rodent species all over the world. The expansion and the encroachment of humans into new environments still increase the probability of contact with new parasites.

In theory, the successful emergence of a pathogen requires the pathogen's reproductive number, R_0, to exceed one (i.e. exceed the replacement level) in the new host (Anderson & May 1991). The pathogen's reproductive number corresponds to the average number of new infections resulting from the introduction of one infected individual in a population of susceptible hosts. There are a number of ways in which R_0 can increase, some of which are under human influence. Ecological changes such as changes in host density or behaviour can increase R_0, as can genetic changes in the pathogen population or in the population of its new host. In addition, Antia *et al*. (2003), showed that factors such as ecological changes, even when they increase the R_0 value of the pathogen to a level not sufficient to cause an epidemic (i.e. R_0 still less than one), can greatly increase the length of stochastic chains of disease transmission. These long transmission chains provide an opportunity for the pathogen to adapt to human hosts, and thus for the disease to emerge.

As illustrated by recent mathematical developments (Hochberg *et al*. 2000), density or demographic differences across geographical landscapes can produce selection mosaics in interacting species, with virulent parasites being most likely to be found in habitats where host-population density is the highest. As long as protected areas are synonymous with high-density areas, their potential role in amplifying pathogen demography will remain. The use of treatments or vaccines, if available, in protected areas is only likely to lead to the selection of resistance.

Lebarbenchon *et al*. (2006) suggested that one way to explore how virulence in parasites is connected to the shape and the size of reserves would be to manipulate variables influencing host densities in large experimental areas and to measure the resulting consequences on parameters linked to virulence. Alternatively, several studies have shown that grouping (as a behavioural trait) may vary between populations, and/or can also be selected for in certain species (see Krause & Ruxton 2002). Such situations could be used to explore the parasitic consequences of overcrowding. Species comparisons may also allow far-reaching conclusions regarding the relationships between social organization and ecological parameters like parasitism. For instance, animals that regularly and naturally congregate at extremely high densities on small areas (*e.g*. pinnipeds, penguins or shorebirds) provide fruitful biological situations to consider. Indeed, because social congregation on islands is somewhat analogous to protected areas in terms of isolation, but also results from thousands of years of evolution, these species might help to predict long-term ecological and parasitological consequences of overcrowding (Lebarbenchon *et al*. 2006).

Global change

Several recent studies on pathogens of forests and human crops, for which long-term data exist, show sensitivity of some pathogens and vectors to climate factors (Harvell *et al*. 2002). It is therefore likely that pathogens affecting wild populations will experience similar climate-driven changes. The most notable prediction of anthropogenic global change is widespread increases in average temperatures. Given that distributions and performances of parasites (as for all species) are bounded by suitable climatic conditions, climate changes are expected to alter the ecology and geographical distribution of parasitic diseases (Lafferty & Kuris 2005 for a review). For instance, van Riper *et al*. (1986) demonstrated that the highest incidence of malaria in Hawaii birds occurs in wet midelevation forests (between 900 m and 1500 m) where populations of *Culex* mosquitoes overlap with highly susceptible native birds. Climate warming is expected to (i) increase pathogen development rates, transmission and number of generations per year and survival rates; (ii) relaxing overwintering restrictions on pathogen life cycles; and (iii) modifying host susceptibility to infection (Harvell *et al*. 2002). Although most host-parasite systems are predicted to experience more frequent or severe disease impacts with warming, some parasites should however, be more sensitive to warming than others. Temperature is particularly important when hosts are ectotherms that do not actively regulate their temperature. Pathogen taxa with 'external' stages (helminth worms, vector-transmitted pathogens like protozoa and reservoir-borne diseases like many viruses) should have also more opportunity to interact with climatic conditions, as the host's range and its environmental requirements constrain the parasitic range. According to Woolhouse & Gowtage-Sequeria (2005), 58% of a total set of 1407 recognized species of human pathogens are zoonotic, and thus are constrained by the animal host's spatial range. At the moment, a majority of zoonotic and vector-borne pathogens are endemic to tropical zones, but such a picture could change following temperature alterations.

Change in temperature is also expected to modify the ecology of host–parasite interactions in subtle ways. Most fitness traits for hosts and their parasites will exhibit a peak performance at a thermal optimum. If the relationship between performance and temperature differs between host and parasite, the resulting gene by gene by environment interaction will either increase or decrease disease at a given temperature, at least on the level of the individual host. For example, the optimal temperature of a fungal pathogen is higher than the optimal temperature of its sea fan host, placing the sea fan at risk to global warming. The number of host–parasite associations in this case is not known at the moment but potentially high. Of course, with global warming happening gradually, the optimal temperature of pathogens can evolve. And it can do so more rapidly than that of the host, given the fact that generation times of pathogens are often orders of magnitude shorter than those of their hosts.

Precipitation is another aspect of climate that may change with environmental degradation. Increased precipitation should favour waterborne parasites as well as those requiring vectoring by biting arthropods with juvenile aquatic stages (*e.g.* mosquitoes). Modellers have used the association between climate and mosquito distributions along with predicted patterns of climate change to further predict that the potential for malaria transmission will greatly expand in the future. Humidity associated with increased precipitation should favour some parasites, especially nematodes transmitted by eggs or with free-living juvenile stages; elsewhere, though, higher temperatures will desiccate soils. Increased aridity should impair the transmission of parasites with stages that live in soil. Change in temperature and precipitation interact with parasitism in complex ways, making it difficult to generalize broadly about its effects on disease (Lafferty & Kuris 2005). One possible bridging solution to this gap is to separate the independent and interactive effects of multiple climate drivers on disease impact (Harvell *et al*. 2002).

Another anthropogenic global environmental change that has been plaguing our planet is pollution in its many forms. Although in part responsible for climate change, chemical pollution can also have more direct effects on the ecology and evolution of pathogens. Toxic chemicals are now ubiquitous in the environment, especially in freshwater ecosystems. They are known to directly affect host susceptibility, through reduced immunocompetence, as well as the infective stages of pathogens outside their host (Poulin 1992). This can have obvious evolutionary impacts. For instance, we now have much empirical evidence showing that pollutants reduce the lifespan of the free-living infective stages of many pathogens (Pietrock & Marcogliese 2003), and that the survival of infective stages in the external environment is a key driver of the evolution of pathogen virulence (Walther & Ewald 2004). The harsher conditions for infective stages resulting from pollution affect transmission success and may be selecting for pathogen strains with different levels of virulence.

Discussion

Darwinian medicine

In this review, we have focused on the lessons of ecology and evolution for our understanding of infectious diseases. The application of evolutionary theory to the medical sciences has been organized under the banner of 'Darwinian Medicine' (Williams & Nesse 1991; Stearns & Ebert 2001). Applied to infectious diseases, Darwinian Medicine

considers the interaction between host and parasite as a potentially long-lasting struggle between largely opposing strategies of replication. The key applied interest of this approach is that it allows a predictive framework for the direction this struggle will take, allowing in principle the design of medical and public health measures that if not ensuring eradication can at least favour less virulent strains (Ewald 1994; Dieckmann *et al*. 2002).

Virulence management

The emerging field of 'virulence management' (Dieckmann *et al*. 2002) is now the dominant theoretical-evolutionary approach to the study of parasite virulence. The 'virulence management' approach is characterized by a focus on the epidemiological scale, focusing on complexities on the host population scale (*e.g.* patterns of transmission and host death), at the expense of complexities on the within-host level. Typically, virulence is viewed as an unavoidable side effect of parasite exploitation and transmission to a new host (Dieckmann *et al*. 2002; for a critique see Ebert & Bull 2003). A central and significant challenge in the study of parasite virulence is to use ecological and evolutionary theory to integrate the intricacies of within-host interactions between host and pathogen into this broader epidemiological framework, to derive *predictions* of the relationship between parasite exploitation, virulence and transmission (Ganusov *et al*. 2002; Alizon & Van Baalen 2005; André & Gandon 2006; Gilchrist & Coombs 2006; S.P. Brown, L. Le Chat, F. Taddei, in preparation). Looking within the host raises a number of significant theoretical challenges, such as capturing explicit immunological dynamics (S. Alizon, in preparation), parasite–parasite interactions (Brown *et al*. 2002; Gardner *et al*. 2004; Brown *et al*. 2006a), fine-scale (cellular) spatial structure (Brown *et al*. 2006b) and a merging of ecological and evolutionary timescales (Alizon & van Baalen 2005). The rewards of an integrated experimental and theoretical pro-ramme are substantial; insights derived from these problems will be of direct practical relevance to both the short-term (ecological) and long-term (evolutionary) management of infectious diseases.

But perhaps the greatest challenge towards the construction of a predictive framework of pathogen evolution will be the integration of multiple species interactions within one set of models. A limitation of the current 'virulence management' models is their focus on one-host/one-parasite systems (but see Gandon 2004; Restif & Grenfell 2006; for exceptions). In reality, any given host–parasite interaction is just one of many interconnected interactions within a complex network of host and parasite species. Although simple one-host/one-parasite systems are more easily tractable mathematically, ignoring the broader community context probably means that we are overlooking several important evolutionary phenomena. As we aim to anticipate and control any change in diseases resulting from man-made ecosystem changes, we will need to take this complexity into account.

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References

Alizon S, van Baalen M (2005) Emergence of a convex trade-off between transmission and virulence. *The American Naturalist*, **165**, E155–E167.

Altizer S, Harvell D, Friedle E (2003) Rapid evolutionary dynamics and disease threats to biodiversity. *Trends in Ecology & Evolution*, **18**, 589–596.

Anderson RM, May RM (1982) Coevolution of hosts and parasites. *Parasitology*, **85**, 411–426.

Anderson RM, May RM (1991) *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press, Oxford, UK.

André J-B, Gandon S (2006) Vaccination, within-host dynamics, and virulence evolution. *Evolution*, **60**, 13–23.

Anker M, Schaaf D (2002) WHO Report on global surveillance of epidemic-prone infectious diseases. WHO/CDS/CSR/ISR/2000.1, World Health Organisation, Geneva, Switzerland.

Antia R, Regoes R, Koella JC, Bergdtrom CT (2003) The role of evolution in the emergence of infectious diseases. *Nature*, **426**, 658–661.

Armelagos GC, Barnes KC, Lin J (1996) Disease in human evolution: the re-emergence of infectious disease in the third epidemiological transition. *National Museum of Natural History Bulletin for Teachers*, **18**, 1–6.

Armstrong GL, Conn LA, Pinner RW (1999) Trends in infectious disease mortality in the United States during the 20th Century. *Journal of the American Medical Association*, **281**, 61–66.

Baquero F, Blasquez J (1997) Evolution of antibiotic resistance. *Trends in Ecology & Evolution*, **12**, 482–487.

Barlow G, Nathwani D (2005) Is antibiotic resistance a problem? A practical guide for hospital clinicians. *Postgraduate Medical Journal*, **81**, 680–692.

Boots M, Sasaki A (1999) Small worlds' and the evolution of virulence: infection occurs locally and at a distance. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **266**, 1933–1938.

Brasier CM (1995) Episodic selection as a force in fungal microevolution with special reference to clonal speciation and hybrid introgression. *Canadian Journal of Botany*, **73**, S1213–S1221.

Brasier C (2000) The rise of the hybrid fungi. *Nature*, **405**, 134–135.

Brown SP, Hochberg ME, Grenfell BT (2002) Does multiple infection select for increased virulence? *Trends in Microbiology*, **10**, 401–405.

Brown SP, Le Chat L, De Paepe M, Taddei F (2006a) Ecology of microbial invasions: amplification allows virus-carriers to invade more rapidly when rare. *Current Biology*, **16**, 2048–2052.

Brown SP, Cornell SJ, Sheppard M, *et al*. (2006b) Intracellular demography and the dynamics of Salmonella typhimurium infections. *PLoS Biology*, **4**, e349.

Brownstein JS, Wolfe CJ, Mandl KD (2006) Empirical evidence for the effect of airline travel on inter-regional influenza spread in the United States. *PLoS Medicine*, **3**, e401.

Buckling AGJ, Taylor LH, Carlton JM-R, Read AF (1997) Adaptive changes in Plasmodium transmission strategies following chloroquine chemotherapy. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **264**, 553–559.

Di Giulio DB, Eckburg PB (2004) Human monkeypox: an emerging zoonosis. *Lancet Infectious Diseases*, **4**, 15–25.

Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K (2002) Adaptive dynamics of infectious diseases. In: *Pursuit of Virulence Management*. Cambridge studies in adaptive dynamics, Cambridge University Press, Cambridge, UK.

Dompka V (1996) *Human Population, Biodiversity and Protected Areas: Science and Policy Issues*. American Association for the Advancement of Science, Washington, DC.

Ebert D, Bull JJ (2003) Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *Trends in Microbiology*, **11**, 15–20.

Ebert D, Hamilton WD (1996) Sex against virulence: the coevolution of parasitic diseases. *Trends in Ecology & Evolution*, **11**, 79–82.

Ewald PW (1994) *Evolution of Infectious Disease*. Oxford University Press, Oxford, UK.

Ferrari MJ, Bansal S, Meyers LA, Bjørnstad ON (2006) Network frailty and the geometry of herd immunity. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **273**, 2743–2748.

Gandon S (2004) Evolution of multihost parasite. *Evolution*, **58**, 455–469.

Gandon S, Mackinnon MJ, Nee S, Read AF (2001) Imperfect vaccines and the evolution of pathogen virulence. *Nature*, **414**, 751–756.

Gandon S, Mackinnon M, Nee S, Read A (2003) Imperfect vaccination: some epidemiological and evolutionary consequences. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **270**, 1129–1136.

Ganusov VV, Bergstrom CT, Antia R (2002) Within-host population dynamics and the evolution of microparasites in a heterogeneous host population. *Evolution*, **52**, 213–223.

Gardner A, West SA, Buckling A (2004) Bacteriocins, spite and virulence. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **271**, 1529–1535.

Gauthier-Clerc M, Lebarbenchon C, Thomas F (2007) Recent expansion of highly pathogenic avion influenza H5N1: a critical review. *Ibis*, **149**, 202–214.

Gilchrist MA, Coombs D (2006) Evolution of virulence: interdependence, constraints, and selection using nested models. *Theoretical Population Biology*, **69**, 145–153.

Gillespie WJ (1997) Prevention and management of infection after total joint replacement. *Clinical Infectious Diseases*, **25**, 1310–1317.

Goossens H, Ferech M, van der Stichele R, Elseviers M (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*, 365, 579–587.

Guan Y, Zheng BJ, He YQ, *et al*. (2003) Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*, **302**, 276–278.

Guégan JF, Prugnolle F, Thomas F (2007) Global spatial patterns of infectious diseases and human evolution. In: *Evolution in Health and Diseases* (eds Stearns S, Koella J). Oxford University Press, Oxford, UK. In press.

Harvell CD, Mitchell CE, Ward JR, *et al*. (2002) Climate warming and disease risks for terrestrial and marine biota. *Science*, **296**, 2158–2162.

Hochberg ME, Gomulkiewicz R, Holt RD, Thompson JN (2000) Weak sinks could cradle mutualistic symbioses — strong sources should harbour parasitic symbioses. *Journal of Evolutionary Biology*, **13**, 213–222.

Keele BF, Heuverswyn FV, Li Y*et al*. (2006) Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science*, **313**, 523–526.

Kleshinski J, Georgiadis GM, Duggan JM (2000) Group C streptococcal infection in a prosthetic joint. *Southern Medical Journal*, **93**, 1217–1220.

Krause J, Ruxton GD (2002) *Living in Groups*. Oxford University Press, New York.

Lafferty KD, Kuris AM (2005) Parasitism and environmental disturbances. In: *Parasitism and Ecosystems* (eds Thomas F, Renaud F, Guégan J-F). Oxford University Press, Oxford, UK.

Lebarbenchon C, Poulin R, Gauthier-Clerc M, Thomas F (2006) Parasitological consequences of overcrowding in protected areas. *Ecohealth*, **3**, 303–307.

Leignel V, Cabaret J (2001) Massive use of chemotherapy influences life traits of parasitic nematodes in domestic ruminants. *Functional Ecology*, **15**, 569–574.

Leroy EM, Kumulungui B, Pourrut X, *et al*. (2005) Fruit bats as reservoirs of Ebola virus. *Nature*, **438**, 575–576.

Mackinnon MJ, Read AF (2004) Immunity promotes virulence evolution in a malaria model. *PloS Biology*, **2**, 1286–1292.

Meyers LA (2006) Predicting epidemics on directed contact networks. *Journal of Theoretical Biology*, **240**, 400–418.

Monot M, Honore N, Garnier T, *et al*. (2005) On the origin of leprosy. *Science*, **308**, 936–937.

Morris JG, Potter M (1997) Emergence of new pathogens as a function of changes in host susceptibility. *Emerging Infectious Diseases*, **3**, 435–441.

Nelson MI, Holmes EC (2007) The evolution of epidemic influenza. *Nature Reviews Genetics*, **8**, 196–205.

Palumbi SR (2001) Humans as the world's greatest evolutionary force. *Science*, **293**, 1786–1790.

Pietrock M, Marcogliese DJ (2003) Free-living endohelminth stages: at the mercy of environmental conditions. *Trends in Parasitology*, **19**, 293–299.

Polgar S (1964) Evolution and the ills of mankind. In: *Horizons of Anthropology* (ed. Tax S), Aldine Publishing Co., Chicago, Illinois.

Poulin R (1992) Toxic pollution and parasitism in freshwater fish. *Parasitology Today*, **8**, 58–61.

Poulin R (2007) *Evolutionary Ecology of Parasites*. Princeton University Press, Princeton, New Jersey.

Poulin R, Combes C (1999) The concept of virulence: interpretations and implications. *Parasitology Today*, **15**, 474–475.

Renaud F, de Meeüs T, Read AF (2005) Parasitism in man-made ecosystems. In: *Parasitism and Ecosystems* (eds Thomas F, Renaud F, Guégan J-F). Oxford University Press, Oxford, UK.

Restif O, Grenfell BT (2006) Integrating life history and cross-immunity into the evolutionary dynamics of pathogens. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **273**, 409–416.

Riddell MA, Rota JS, Rota PA (2005) Review of the temporal and geographical distribution of measles virus genotypes in the prevaccine and postvaccine eras. *Virology Journal*, **2**, 87.

van Riper C, van Riper SG, Goff ML, Laird M (1986) The epizootiology and ecological significance of malaria in Hawaiian land birds. *Ecological Monographs*, **56**, 327–344.

Sangster NC (1999) Anthelmintic resistance: past, present and future. *International Journal for Parasitology*, **29**, 115–124.

Santiago ML, Range F, Keele BF, *et al*. (2005) Simian immunodeficiency virus infection in free-ranging sooty mangabeys (*Cercocebus atys atys*) from the Taï forest, Côte d'Ivoire: implications for the origin of epidemic human immunodefiency virus type 2. *Journal of Virology*, **79**, 12515–12527.

Skorping A, Read AF (1998) Drugs and parasites: global experiments in life history evolution? *Ecology Letters*, **1**, 10–12.

Sokurenko EV, Gomulkiewicz R, Dykhuizen DE (2006) Source-sink dynamics of virulence evolution. *Nature Reviews Microbiology*, **4**, 548–555.

Stearns SC, Ebert D (2001) Evolution in health and disease. *Quarterly Review of Biology*, **76**, 417–432.

Thomas F, Brown SP, Sukhdeo M, Renaud F (2002) Understanding parasite strategies: a state-dependent approach? *Trends in Parasitology*, **18**, 387–390.

Thomas F, Renaud F, Guégan JF (2005) *Parasitism and Ecosystems*. Oxford University Press, Oxford, UK.

Thomas F, Guégan JF, Renaud F (2007) Ecologie et Evolution des systèmes parasités. De Boeck Université, Paris, France.

Vazquez JA, Enriquez R, Abad R, Alcala B, Salcedo C, Arreaza L (2007) Antibiotic resistant meningococci in Europe: any need to act?. *FEMS Microbiology Reviews*, **31**, 64–70.

Walther BA, Ewald PW (2004) Pathogen survival in the external environment and the evolution of virulence. *Biological Reviews*, **79**, 849–869.

Wasserman S, Faust K (1994) *Social Network Analysis: Methods and Applications*. Cambridge University Press, Cambridge, UK.

Watts DJ, Strogatz SH (1998) Collective dynamics of 'small world networks'. *Nature*, **393**, 440–442.

Williams GC, Nesse RM (1991) The dawn of Darwinian medicine. *Quarterly Review Biology*, **66**, 1–22.

Woolhouse MEJ, Gowtage-Sequeria S (2005) Host range and emerging and reemerging pathogens. *Emerging Infectious Diseases*, **11**, 1842–1847.

World Health Organization (2004) *The World Health Report 2004 — Changing History, 'Annex Table 2: Deaths by Cause, Sex and Mortality Stratum in WHO Regions, Estimates For 2002'*. World Health Organization, Geneva, Switzerland.

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