

Shifting trends in pathogen dynamics on a changing planet

Paul A. Hoskisson · Jack T. Trevors

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Abstract In this perspective we offer views on how microbial activities may change in response to the impact of human activities and an increasing human population. New knowledge is forthcoming in microbiology and immunology on the biology of emerging pathogens. With the exposure of human populations to changing environments, through climate change and human encroachment into previously unpopulated areas, there is likely to be increased incidences of diseases caused by existing, emerging and previously unrecognised pathogens.

Keywords Pathogen · Emerging infection · Climate change · Microorganisms

How do we define a pathogen in a dynamic world?

Living organisms can interact in several ways; often defined in broad terms as symbionts, commensals and

parasites. Symbiotic relationships are where both interacting organisms receive a benefit from interacting, often with one partner unable to survive alone, commensal relationships result in one organism benefiting from the interaction but without causing harm to its partner and finally parasitic relationships result in one interacting organism benefiting at the expense of the other (pathogenesis). However, the more we understand the natural ecology of these organisms and their interactions with existing and potential hosts in a changing environment, it becomes evident that novel pathogens are emerging which may not fit classical definitions, such as not adhering to Koch's well known postulates or resulting in chronic carrier status (Casadevall and Pirofski 2000). Equating causal associations with disease is an important step in identifying emerging pathogens and builds on the fundamental work of Koch (Fredericks and Relman 1996). Gaining an awareness of these problems is vital for our future understanding of pathogenicity and disease emergence.

The virulence of an organism is not a fixed trait (Ebert and Bull 2003). This is exemplified by the range of effects on a host during infection by certain diseases, ranging from asymptomatic carriage through to severe acute illness. We know that microbial pathogens sense and respond to their environment in a variety of ways, and the diversity of disease effects experienced is a reflection of this response to individual hosts and niches. Whether these changes are regulatory or evolutionary, modern epidemiology suggests that

P. A. Hoskisson (✉)
Strathclyde Institute of Pharmacy and Biomedical
Science, University of Strathclyde, Royal College,
204 George Street, Glasgow, UK
e-mail: paul.hoskisson@strath.ac.uk

J. T. Trevors
School of Environmental Sciences, University of Guelph,
50 Stone Road East, Guelph, Ontario N1G 2W1, Canada
e-mail: jtrevors@uoguelph.ca

epidemic disease begins when a transmissible pathogen becomes present in a sufficiently large population of susceptible hosts (Lipsitch and Moxon 1997). However studies of virulence and transmissibility of disease can exhibit some striking relationships. Decoupling virulence from transmission can highlight the links and the complex relationships between the transmission stages; adaptation for transmission, movement between hosts and colonisation. This is particularly true of diseases caused by environmental organisms (e.g., *Legionella pneumophila* and *Clostridium tetani*), zoonotic and emerging infections (Levin and Svanborg 1990). If the link between virulence and transmission efficiency is removed then virulence should evolve to a minimum value and transmission would evolve to a maximum (Levin and Pimentel 1981), essentially resulting in commensalism. However when linking these two factors, a trade off between high rates of transmission and high host mortality is experienced (Antia et al. 1994). This is essentially what occurs during adaptation to a novel host, due to the intrinsic selection pressure of reducing host availability through reduction of the host population (Mosquera and Adler 1998). Underlying this adaptation is the differential rate of mutation between the rapidly evolving pathogen and their relatively slowly evolving hosts. Therefore this would suggest that extreme virulence is an ancestral characteristic indicative of a recent association with a novel host (Ho Sui et al. 2009) and may reflect the high levels of mortality and morbidity in emergent diseases.

Species hops, skips and jumps

Emerging diseases have renewed interest in the evolutionary and ecological mechanisms that promote parasite adaptations to novel hosts. Emerging diseases can be defined as those caused by organisms which have recently increased in virulence, those infecting a novel host and or those that occur in a new geographical location (Giraud et al. 2010). Emerging diseases may reflect primarily ecological rather than evolutionary changes in the host–pathogen relationship and understanding the factors that drive their emergence is of great interest. This was elegantly tested by Benmayor et al. (2009) using a bacteria–bacteriophage model to test the hypothesis that adaptation from the normal host to novel hosts

requires an increase in mutant pathogens with improved performance on the novel host and reduced selective pressure to infect novel hosts. Crucial to this hypothesis is the provision of susceptible hosts through mixing of two populations. These subtle changes in host mixing dynamics appeared to support the hypothesis, but only under very specific conditions. The work of these authors suggests that switches to novel hosts occur only when there are small changes in contact rates between two host species.

One of the keys to this population mixing in the environment is the presence of a reservoir species in which the pathogen is already established (Woolhouse et al. 2005). This scenario has led to some of the most significant and ongoing disease epidemics of humans, wild and domestic animals and plants of the last 100 years such as HIV/AIDS, SARS coronavirus, *Escherichia coli* O157:H7, *Phytophthora infestans* and *Brachychochytrium dendrobatidis* (Woolhouse et al. 2005). These pathogen reservoirs can also result in the preconditioning of a pathogen for virulence. A good example of this is the passage of human pathogens through environmental amoebae, which activate ‘virulence genes’ to enable survival inside these environmental hosts. Amoebae are emerging as useful experimental tools for the study of the intracellular behaviour of pathogens as many of their prey endocytosis and digestion mechanisms are conserved with those of macrophages (Cosson and Soldati 2008). These mechanisms may however facilitate the pre-conditioning of organisms in the environment such as *L. pneumophila* (Huws et al. 2008) and *Mycobacterium avium* (Danelishvili et al. 2007), activating virulence genes to enable them cause infections in humans. This suggests that some virulence genes, as we recognise them (e.g. vacuole escape mechanisms and toxin production) are in fact ancestral anti-predator responses to facilitate survival in the environment.

Impacts of local and global changes on emerging pathogens

Key changes in the host ecology and environment can have profound effects on the natural history of potential pathogens; encroachment into primary forests for farming and urbanisation of these areas has

lead to emergence of diseases such as Ebola (Morvan 2000) and Hendra virus (Field et al. 2001). Changes in host behaviour such as travel can also affect emerging disease patterns (as exemplified by the recent rapid spread of Influenza H1N1 across the world due to air travel and the spread of diseases such as smallpox through the new world in the sixteenth and seventeenth centuries). Likewise, population displacements due to war and famine affect disease outbreaks, as do changes in leisure patterns resulting in, for example increases in tick-borne diseases in walkers (Randolph 2001). Changes in the host genotype and phenotype can also have a profound effect on susceptibility of hosts, notably including immunosuppression, due to drugs or other infections (e.g., HIV/AIDS), or in-breeding of livestock resulting in loss of genetic diversity (Woolhouse et al. 2005). Additionally the evolutionary selective pressures acting on specific pathogens can be altered through the use of vaccination and antibiotic drugs. Examples of this include the rise in *Clostridium difficile* infections due to the use of fluoroquinolones in the clinic (Deshpande et al. 2008).

The changes in immune status of the host due to vaccination may also predispose to infections by new pathogens through mechanisms such as the loss of cross immunity, where protective or partially protective immune responses to one pathogen induced by vaccination or exposure (e.g., BDG against TB) are lost due to evolution of pathogens or the host. Woolhouse et al. (2005) also cites further examples such as Leprosy and TB, Yaws and Syphilis, and vivax and falciparum malaria. Mechanisms such as this may explain the rises in non-toxicogenic *Corynebacterium diphtheriae* infections in immunised populations (Reacher et al. 2000), where the vaccine targets the toxin, encoded on a mobile bacteriophage, and may select against these strains in immunised hosts. The suggestion that immune hosts can drive evolution and selection for virulence in pathogens, reducing the protective effects of vaccination and putting unvaccinated individuals at greater risks in a mixed population has also been made for a range of other organisms (Mackinnon et al. 2008). Hypotheses such as that immunity selects for higher rates of host exploitation can be tested experimentally, and was verified for malaria (Mackinnon et al. 2008). The targeting of specific stages of a pathogen lifecycle

may have profound effects on selection of those pathogens, enhancing virulence of other life stages and must be considered when conceiving vaccine strategies. Moreover it is also important to improve understanding of the factors behind why, historically, combating certain microbial diseases such as Scarlet Fever (*Streptococcus pyogenes*), Smallpox and Polio through the introduction of improved public health, vaccination and drugs has been successful, yet other disease (notably Tuberculosis and Malaria) still remain a significant threat to public health (Cohen 2000) and continue to present significant challenges to biomedical researchers.

Industrialisation, global pollution, loss of biodiversity and habitats, population growth and all other human activities are having profound effects on the earth's climate resulting in a net increase in temperature (Caldeira and Kasting 1992). It is expected that the global temperature will rise by 2–5°C in the next decade, with the effects being felt by all species on the planet (Garcia-Solache and Casadevall 2010). This may lead to expansion of the geographical range of many species, including those which can cause infectious disease either alone or through vector-borne transmission, leading to the exposure of naïve hosts to novel pathogens. High profile examples such as the expansion of Blue-tongue virus in Europe, which spread northwards between 1998 and 2005 by 800 km, associated mainly with the expansion of the midge *Culicoides imicola* from Africa and Asia (Randolph and Rogers 2010), exemplify the potential for expanded distributions of vector borne disease. Fungal diseases such as Cryptococcosis may spread due to climate change, as it is prevalent in 30% of African HIV/AIDS patients, yet only in 10–15% of patients in temperate regions (Garcia-Solache and Casadevall 2010). Little known and poorly studied diseases such as *Nocardia* mastitis, prevalent in animals in sub-Saharan Africa (Maldonado et al. 2004), may expand their range northwards into naïve temperate livestock. Increases in sea temperatures have been postulated as potentially enhancing factors in the spread of infectious diseases such as cholera (Colwell 1996). The spread of the emerging waterborne pathogen, *Vibrio vulnificus* has also been linked to global climate change, through increasing sea temperatures in the Mediterranean basin (Paz et al. 2007).

Perspective summary

It is evident that the definition of a pathogen in simple terms, as an organism which receives benefit from a relationship, at the expense (i.e. damage) of another is useful. However, what are less obvious are the factors that modulate pathogenicity; such as exposure of naïve hosts being a major factor in the emergence of new diseases. This exposure can be as a result of changing environmental, ecological, behavioural and evolutionary conditions. Fine changes in the equilibrium of hosts and potential pathogens in their natural niches are resulting in the emergence of novel diseases in naïve populations. These changes are likely to accelerate in the future due to continuing pressures of global climate change, rapidly expanding human populations either due to housing or expansion of agriculture resulting in encroachment into previously unpopulated natural areas. In the future we are likely to see further emergence of novel pathogens and the increasing recognition of environmental microorganisms as potential pathogens due to human activities. Climate change may also allow pathogens to move into new environmental niches where they previously were not a concern. This will place an increasing demand on water and sewage treatment, the protection of crops from plant pathogens, and humans and other animals from newly emerging pathogens. The challenge for microbiologists and public health personnel is to identify and address these risks early for the protection of human and environmental health and agricultural crops (van Elsas et al. 2010). It is also important to understand the capacity of microorganisms to evolve quickly via horizontal gene transfer and mutation, and become resistant to antibiotics and acquire new toxin producing genes for example.

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