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Emerging viruses

Editorial overview

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Infectious diseases have continued to plague human existence from the dawn of civilization. While some human pathogens co-evolved as *Homo sapiens* evolved from our non-human primate ancestors, most of the microbial agents causing disease were likely acquired subsequently from wild or domestic animals. These infectious disease emergences occurred in waves related to the major transitions that occurred during human civilization. The first and most important of these ‘historical’ transitions was associated with the change from a hunter-gatherer existence, with familial groups of 30–40 or less, to a pastoral lifestyle with domesticated livestock, pets and peri-domestic animals such as rodents (*ca.* 10,000 years ago). This led to the emergence of many of the endemic communicable diseases that remain with us today such as measles, chickenpox, diphtheria, influenza A, mumps, rotavirus and smallpox [1–3]. The other major transitions that impacted on the spread of infectious diseases was the period of European exploration and the discovery of the new World (*ca.* AD 1500) and the period we are currently living through – one of unprecedented human population growth and associated ecological and environmental change [2]. Thus, population migrations, urbanization and other social and demographic changes and the resulting ecological impact, the increase in international travel and trade, change in patterns of animal husbandry practices and microbial adaptation all contributed to the emergence of the currently endemic communicable diseases that have affected mankind for the last 10,000 years.

During the last century, some of these factors potentially promoting emergence of infectious disease have undergone a quantum-change, thereby accelerating the process of novel infectious disease emergence or re-emergence. The proportion of the human population that lives in an urban environment increased from 13% in 1900 to 49% by 2005 and over 15 cities now host populations of over 10 million inhabitants. International journeys that took weeks or months by sea are completed in a day (i.e. within the incubation periods of almost all infectious diseases) and it is estimated that over 700 million people travel by air every year. HIV-1 and 2 arose from cross-species transmission to humans of simian immunodeficiency viruses of chimpanzees (*Pan troglodytes*) and sooty mangabeys (*Cercocebus atys*) to humans, probably as a consequence of the bush-meat trade [4]. While such inter-species transmissions probably have gone on for millennia, increasing human mobility and changing lifestyles provided the opportunity for HIV to develop into the global health threat it currently is.

Intensive animal husbandry has led to unprecedented densities of livestock with decreasing genetic diversity. Live animals are transported hundreds of miles across international borders for human consumption, not all such transport is legal or regulated. Increasing urbanization has led to the

development of 'wet markets' harboring a large diversity of live animal species, domestic livestock as well as more exotic species, within large urban environments. These factors contributed to the emergence of SARS and the spread of the highly pathogenic avian influenza (HPAI) H5N1 [9]. Intensive animal husbandry practices such as the feeding of meat and bone meal containing neurological tissue to cattle provided the route for the emergence of Bovine Spongiform Encephalopathy (BSE) that subsequently transmitted to humans resulting in a variant Creutzfeldt–Jakob disease. The unprecedented increase in trade in animals as pets contributed to the recent introductions of West Nile virus and monkeypox to North America.

The technological innovations designed to improve human lifestyle and comfort have also been exploited by microbes to give rise to emerging diseases. *Legionella* had long been a parasite of a protozoal host with no significance for human disease until the proliferation of air-conditioning cooling towers provided a new niche for the bacterium and its protozoal host and a means to generate aerosols that bring the bacterium into interaction with the respiratory tract of susceptible individuals leading to the emergence of Legionnaires' disease [5]. The use of xenotransplantation (where animal organs may be introduced into an immunocompromised host) has been hotly debated but has so far been (rightly) rejected because of the potential risk of generating new infectious diseases.

Emerging and re-emerging infectious diseases are defined as those that have newly appeared in the human population or those that had previously existed but are rapidly increasing in incidence or geographic spread. In 2003, an Institute of Medicine Report entitled 'Microbial threats to human health' concluded that 'One can safely predict that infectious diseases will continue to emerge' and that depending on the adequacy of our response 'the situation could lead to a catastrophic storm of microbial threats.' [6]. This report, though many years in development, was formally published in early 2003, in the midst of the global SARS outbreak which provided a real-time and real-life example of the point being made. An analysis of emerging infectious disease incidents over the period 1940–2004 demonstrated that with the exception of emergence of antibiotic resistant bacteria, viruses are the major contributor to such episodes. Many of these had zoonotic origins, whether from wildlife or from domestic animal reservoirs [7].

Diseases such as Ebola, Hendra and Nipah emerge episodically to cause limited outbreaks, albeit ones with worryingly high case fatality. SARS spread worldwide in 2003 before it was successfully contained by public health interventions, while the 2009 pandemic H1N1 virus rapidly spanned the globe within weeks or months of its emergence and has now become an endemic disease.

In today's world of instant-news, even those outbreaks that do not establish themselves as long-term human pathogens can have huge impact. The cost is not measured only as human mortality and morbidity but is also felt in terms of veterinary, economic, social and political consequences. The direct economic costs of SARS in Asia in 2003 is estimated to be US\$ 30 billion, the Nipah outbreak in Malaysia in 1999 cost approximately US\$ 625 million, plague in India in 1995 cost US\$ 1.7 billion, while the bovine spongiform encephalopathy outbreak between 1990 and 1998 outbreak cost the UK US\$ 39 billion [8].

Many emerging infectious diseases are caused by RNA viruses. The high mutation rates and the plasticity of their genomes make them particularly fit to cross species barriers and adapt to new hosts. Dzak and Lipkin outline the nature of the challenge we face. Recent developments in molecular diagnostics provide dramatic improvements in our capacity to identify and characterize novel pathogens associated with outbreaks of emerging infections. However, an astute clinical and epidemiological awareness is required to distinguish the unusual from the banal so that these intensive and expensive technologies and expertise are deployed to maximum effect. Shifting the focus from responding to a novel disease to recognizing such threats in the animal reservoir and pre-empting their emergence is the ultimate future goal. This is however poses formidable challenges. New diagnostic tools are exponentially increasing our understanding of the viral (and other microbial) diversity found in wild life and domestic livestock. Prioritizing the microbes that we find to identify those that pose significant threat to human health is a much greater challenge. We still yet poorly understand the ecological, viral and host factors that lead to zoonotic infections and know even less about what it takes for a pathogen to become efficiently transmissible from human-to-human, that is, become epidemic. Retrospective studies that re-construct episodes of past disease emergence is particularly instructive in this regard. Bolles, Baric and colleagues review what has been learnt about the emergence of SARS. The biological determinants of transmission of viruses in humans is still poorly understood, even with well established human respiratory pathogens. Sorrell and Fouchier try to address this formidable challenge, using influenza as a case-study. In an animal or even in a single clinical specimen, RNA viruses exist as 'mutant swarms' of genetic diversity rather than as a uniform genetic template. The development, role and consequence of such viral quasi-species for pathogenesis and transmission are explored by Borderria and Vignuzzi. Bats are increasingly recognized as important reservoirs of emerging viral infections, SARS, Nipah, Hendra, rabies, ebola and Marburg being just a few examples. Whether this is simply a 'numbers-game' (the diversity of bat species is only second to that of rodents) or a result of an unusual

host-virus interaction is discussed by Wang and Poon. Case studies of Henipaviruses (Kung and Field) and lyssa viruses (Rupprecht *et al.*) and presented.

While this issue of the journal does not set out to cover all emerging viral pathogens, for example, HIV, Marburg, ebola, ebola-Reston are not included due to constraints on space, our selection of topics for this issue was directed at addressing particular challenges that are generally illustrative and provide insights into a field, that is itself, rapidly evolving.

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