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PATTERNS OF ECOLOGICAL CHANGE AND EMERGING INFECTIOUS DISEASE IN THE AUSTRALASIAN REGION

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Abstract

An unusually rapid and widespread increase in apparently new and changing infectious diseases has occurred globally over the past four decades. This has also been a time of accelerated global ecological change. Associations between the two phenomena are unclear: emerging infectious diseases (EIDs) are reported more frequently in wealthy countries, with greater capacity for resources for surveillance and detection than less affluent centres, even though the latter are often undergoing accelerated socioecological change. Here, a series of transdisciplinary studies is reviewed that test the hypothesis that specific ecological change accounts for a significant component of the rise in EIDs in the Australasian region. Amongst the range of mechanisms, factors such as wildlife adaptation to changing landscapes and selection for antimicrobial resistance appear to be of major significance. However, exploring multi-scale complex relationships is a challenge to epidemiology. The importance of framing the scale of relationships and limitations of available data are discussed. Despite obstacles, insight into approaches to mitigating disease risk at a landscape level is expanding.

Introduction – Global Patterns, Global Questions

The past four decades have seen an unusually rapid and widespread increase in apparently new and changing infectious diseases in humans, domesticated animals, wildlife and plants. Some 335 novel or re-emerging infectious diseases of humans have been described since the 1940s (Jones et al., 2008). The majority of these 'emerging infectious diseases' (EIDs) – defined as infectious diseases

that are novel or expanding in pathogenicity and range (Morse, 1995) – have occurred since the 1970s. The increase in EIDs has coincided with an acceleration of anthropogenic ecological change, defined as a change in interactions among living organisms with each other and with their environments, driven by the increasing global human population. Links between the two phenomena have been postulated (McMichael, 2004).

The rise in EIDs has been linked broadly to changing ecosystems; climate and weather; economic development and land use; human demographics and behaviour; international travel and commerce; poverty and social inequality; breakdown in public health measures; lack of political will; intent to harm (such as bioterrorism); and the impacts of new technologies and industries (Smolinski et al., 2003). This multitude of potential influences on pathogen, vector and host(s) has also been discussed in terms of complex social–ecological systems (Wilcox and Colwell, 2005). The socioecological system perspective on disease causation reinforces a broader discussion of anthropogenic ecological change as systemic health risk (e.g. McMichael and Wilcox, 2009). Understanding the role of ecological change poses many challenges for epidemiology. Many of the speculated relationships are not easily tested. Available ecological information may describe a dynamic of interest at a scale other than that at which disease is understood, and multiple influences may act and interact across multiple scales. This chapter describes our approach to assembling a robust evidence base to understand the role of ecological change in EIDs of the Australasian region. By framing issues at appropriate scales and exploring relationships where data are available, we hope to add complexity and insight progressively.

Reviews of EIDs alert us to two major areas of ecological change resulting in new human–pathogen interactions. Approximately 20 per cent of global (human) EIDs are antimicrobial-resistant (AMR) pathogens and 75 per cent are zoonoses, most from wildlife, particularly wild mammals (Taylor et al., 2001; Jones et al., 2008). A modest overlap between these two groupings also exists. The small remainder includes environmental pathogens, opportunistic pathogens (such as those affecting immunocompromised individuals) and other less easily grouped diseases. These patterns potentially tell us much about our changing ecological impact.

Human influence on the selection of AMR is complex, but a direct relationship is clear. Prescriptions of antibiotics began in the 1930s and AMR was recognised shortly thereafter, steadily increasing until now, where multidrug-resistant organisms are common and widespread, including in many intensive livestock production systems (Levy and Marshall, 2004). Belatedly, research has turned to understanding the role of antibiotics and AMR in the natural systems in which they evolved. We are also only beginning to understand the lability and significance of environmental contamination with human and animal

drug-resistant organisms (Finley et al., 2013). Similarly, there are many issues surrounding the rise in anti-fungal, malarial, parasitic and viral resistance, and in vectorcidal resistance following their widespread use.

The relationship between the rise in (wildlife) zoonoses and anthropogenic ecological change is less obvious. The traditional view of zoonotic and crowd diseases arising from ancient humanity's shift to densely populated agrarian settlements with domesticated animals (e.g. McNeill, 1976) sheds little light on the rise, now, of zoonotic pathogens of wild animals. There is a reported positive association between high mammal diversity, human density and zoonotic infectious diseases of wildlife origin (Jones et al., 2008; Morand et al., 2014), but it is difficult to undertake detailed global assessments. Data on EID emergence are usually more comprehensive in developed temperate regions, as are data on many other potential explanatory variables (such as the role of ecological and sociodemographic parameters).

Exploring the importance of ecological change as a driver of EIDs is complicated by many factors. Advances in diagnostic technology, surveillance, fundability of research and even digital search engines have had (incompletely quantified) influence on the number of EIDs reported. According to one study, reporting of EIDs peaked in the 1980s (once the underlying reporting bias for papers from less-developed countries (LDCs) was addressed). This was a decade associated with taxonomical reclassification and diagnosis of novel co-infections with HIV/AIDS (Jones et al., 2008).

The rise in numbers of EIDs is not necessarily accompanied by an increase in the burden of disease. HIV/AIDS is unique in its combined novelty, significance and the proliferation of novel co-infections recognised during and since the 1980s. Many other EIDs are of minor or only potential population health importance, or of importance primarily for their scientific novelty, a fact that undermines research on novel EIDs in countries struggling to address other major health impacts (Butler, 2012). Many of the most important human EIDs (e.g. multi-drug-resistant tuberculosis and malaria) are old scourges with new twists. HIV/AIDS also illustrates the lag period that may follow ecological changes, and the spatially and temporally dispersed social changes that may result in infectious disease emergence. For this disease, the events that led to ancestral virus spilling from non-human primates to humans appear to have occurred in the early 20th century (or perhaps even prior to this) (Sharp et al., 2001). Social and demographic changes in the late 20th century gave rise to a global pandemic.

Even as a signal of ecological change, human EIDs only tell part of the story. EIDs of plants and animals not involved in human disease transmission receive much less research and reporting effort, but are also a feature of recent decades. Wheat rust Ug99, white spot baculovirus syndrome of shrimp and

porcine respiratory and reproductive syndrome are examples of EIDs that have arisen from, and caused collapse in, intensively produced human food production (Singh et al., 2011; Wang et al., 2006; Zhou et al., 2008). Intensive livestock production has proven to be a highly effective amplifier of zoonotic disease (Liverani et al., 2013). Infectious diseases of wildlife are also emerging in vulnerable species, degraded ecosystems and where least expected. The pandemic amphibian chytridiomycosis is responsible for multiple species extinctions even in pristine habitats; Tasmanian Devil Facial Tumour has decimated its marsupial carnivore host, a species not long ago regarded as a pest. Although there has been a vigorous literature on EIDs as a global phenomenon in a changing world, our understanding is biased to one host (humans) and to well-resourced developed countries.

Patterns of EIDs in the Australasian Region

To examine the hypothesis that ecological change accounts for a substantial component of the rise in zoonotic EIDs, a series of transdisciplinary studies based on the Australasian region were designed by the author under the doctoral supervision of Professors Tony McMichael and Adrian Sleigh and Dr Peter Black (McFarlane et al., 2011, 2012, 2013, 2014). These studies reflected Tony's support for research that explored the awkward, important issues, and for epidemiology that – in an inventive and insightful way – sought to address these challenges. The postulated drivers of EIDs examined in these studies have a history and forward trajectory, and cannot be considered in isolation from other processes. In this way, each study contributed detail to the complex systems perspective of socioecological change as a health risk that Tony's work brought to global research.

The EID literature for Australasia is dominated by reports published by the sparsely populated, developed country, Australia. The region also includes smaller, developed New Zealand and the developing Melanesian nations. This region adjoins that of the adjacent, densely populated, rapidly developing Southeast Asia and East Asia to its north, which have been the origin of numerous EIDs of global concern, including highly pathogenic avian influenza (H1N1) of poultry origin and SARS (severe acute respiratory syndrome) coronavirus and Nipah viruses of bat origin. These adjoining regions have important social and ecological influences on Australasia. In Australia, other bat-borne viruses and zoonotic arboviruses, including the southern expansion of Japanese Encephalitis Virus, are of concern (Mackenzie, 2001).

A systematic literature review of the databases Scopus, CABI and Web of Science for 1973–2010, using search terms 'emerging infectious disease(s)' and 'emerging communicable diseases(s)' of humans and animals by country (25) and region, identified a large number of articles (Australasia (n = 192), Southeast Asia (n = 257) and East Asia (n = 491)). China, Japan, Australia, Hong Kong and Taiwan were the subject of >100 papers each; South Korea, Indonesia, Thailand, Malaysia, Singapore, New Zealand and Vietnam were the subject of 16–99 papers; the remaining countries featured in <16 papers. Four diseases were the topic of large numbers of articles: SARS coronavirus (n = 125), highly pathogenic avian influenza (n = 49), amphibian chytridiomycosis (n = 20) and HIV/AIDS (n = 18). Across the regions, interest in zoonoses was high. However, ecological factors were rarely discussed as the primary focus of an EID article (n = 33).

A total of 104 emerging or re-emerging human diseases were reported in the reviewed literature (McFarlane et al., 2012; Morand et al., 2014). Zoonotic diseases (n = 70) accounted for 67 per cent of the total of these diseases, and 63 per cent of these were zoonoses of wildlife origin (n = 44). AMR (n = 14) and environmental pathogens (n = 9) accounted for 14 per cent and 9 per cent of EIDs, respectively. There were also 53 EIDs of livestock and 23 EIDs of wildlife reported. The collective Asian–Australasian region contains one-third of the human population and approximately one-third of globally reported human EIDs (Jones et al., 2008).

In Australia, the country with the largest EID literature in the region, 90 diseases (59 diseases of humans, of which 30 were zoonoses; 12 diseases of domestic animals; 18 diseases of terrestrial wildlife) meet the criteria for emerging or re-emerging diseases in the interval 1973–2010 (McFarlane et al., 2013). Of the human diseases, 51 per cent are zoonotic (66 per cent of these from wildlife), 15 per cent are classified as environmental pathogens and 10 per cent are AMR pathogens. Non-wildlife zoonoses (n = 10) include food-borne disease, AMR and canine pathogens. The majority of the remainder of human EIDs are re-emerging and/or re-identified viruses. A full list is available as online supplementary material (McFarlane et al., 2013).

The large volume of EID literature from Australia, including that of animal disease, reflects Australia's capacity to research and report EIDs. The small number of EIDs reported in the rest of Australasia – and in proportion to the population in Southeast Asia and East Asia – make intra- and interregional comparisons problematical. Reporting bias appears to be acting strongly against those countries to the east and north of Australia where fewer EIDs (and hence available data) have been reported and where socioecological change is occurring rapidly and extensively.

EIDs identified through the literature review were examined further with reference to ecological change. First, we examined the characteristics of the wildlife hosts of zoonotic EIDs identified from the multi-region literature review to gain insight into changing human–animal relationships. Second, we looked at the patterns of infectious disease emergence and ecological change within Australia's own tumultuous post-colonisation history. Third, we looked in detail at a particular Australian zoonosis, Hendra virus disease, thus providing the opportunity to study ecological drivers at both the broad and finer scales.

Biodiversity Change, Synanthropy and Zoonotic Disease in the Asian–Australasian Regions

In the first study, we found that the identified (mammalian) hosts of emerging zoonoses of wildlife origin across the Australasian–Asian regions were proportionate in terms of their taxonomic distribution to total mammals in the study region, as reported by the International Union for the Conservation of Nature (IUCN, 2012). However, wildlife hosts were 15 times more likely (OR = 15.02; 95 per cent CI 5.87, 38.41) to be associated ecologically with humans and human-modified environments (i.e. to be synanthropic) than to be restricted to intact natural habitat (McFarlane et al., 2012). These wildlife hosts were also more likely (relative to non-host species) to be species classified as being at little or no conservation risk. While some hosts were also species consumed as bushmeat, or were encountered at the leading edge of natural vegetation clearances, hosts were found overwhelmingly to be species that could exploit anthropogenic ecological change.

The relationship between synanthropy and EID hosts can be understood with reference to biodiversity change in the ecologically diverse Asian–Australasian regions. Approximately one-third of global terrestrial mammal species (n = 1,823) occur here: about one-quarter of these utilise human modified environments (the trait used to define synanthropic species in our study). The majority of hosts are not at conservation risk, and many are classified as pest and invasive species (IUCN, 2012). Almost half of the total 1,823 species are in a conservation risk category and threatened from extensive land clearing, hunting, the impact of invasive species or extreme weather events or climate (IUCN, 2012). Anthropogenic ecological change is taking a heavy toll on many species, but is selecting inadvertently for those that can live with people or exploit human environments. By this process, human exposure to synanthropic species, their numbers and their pathogens may be increased.

Synanthropy is a characteristic of a diverse range of species. For example, in Australia some 30 species of bats, 22 species of the largest marsupial order (kangaroos, possums, etc) and less than 10 species each of rodents, insectivorous marsupials, bandicoots, introduced hoofed mammals, carnivores, rabbits and hares make their homes in human-modified environments. Of these, some 20 species of bats and 0–5 species in the other orders find useful resources in urban environments.

The predominance of bats in urban environments is observed in (all) other regions globally – often greater in diversity than synanthropic rodents by an order of magnitude (IUCN, 2012). This is of particular interest because of the unforeseen emergence of numerous EIDs from bats in the past two decades. Nipah virus emerged in Malaysia in 1999 in a piggery where mangoes were co-produced, with the fruit crop providing a ready food source for local fruit bats (Johara et al., 2001). The principle host bat species commonly roosts and feeds in mainland orchards and coconut palm groves in preference to remnant native forest (IUCN, 2012). SARS coronavirus emerged from insectivorous horseshoe bats in southern China in 2003 after amplification in farmed civet cats, and possibly racoon dogs. These bats (and carnivores) are sold in local wet markets, but they are also synanthropic species. Horseshoe bats roost in the artificial caves created by roadworks, and multiple spillovers back and forth to domestic animals have been demonstrated prior to 2003 (Lau et al., 2010).

Elsewhere, synanthropic rodents and shrews have emerged as hosts of novel pathogens (e.g. hantaviruses), or with other novel hosts in new environments as hosts of re-emerging diseases (e.g. alveolar echinococcosis, leptospirosis, cutaneous leishmaniasis). Primate sources of 'monkey malaria' (Plasmodium knowlesi), Mi Tri and Zika viruses and the zoonotic reservoir of Chikungunya virus in Southeast Asia are macaques, particularly the highly synanthropic long-tailed macaques in the south and rhesus monkeys in the north (McFarlane et al., 2012).

Change in the diversity and number of synanthropic wildlife over time is difficult to assess, potentially limiting this as an explanation of how anthropogenic ecological change contributes to the rise in wildlife EIDs. However, global land transformation occurred very slowly from the first agricultural settlements some 10,000 years ago until its acceleration in the 20th century. The proportion of global (ice-free) land remaining in its natural state is now estimated to be 22 per cent (two-thirds of this in cold and dry regions with low productivity), having passed the 50 per cent mark (half natural, half human modified) some time in the first half of the 20th century (Ellis, 2011). Land transformation has continued to accelerate, and it is in the latter part of the 20th century that the pressure has been greatest on wild species to adapt to human environments.

Even so, ecological change has not occurred uniformly across the globe. Certainly, in Australia, there was no urban or Western-style agricultural land use, or associated synanthropic wildlife (with the exception of the dingo), before European colonisers displaced its predominantly hunter–gatherer Indigenous inhabitants over 225 years ago (McFarlane et al., 2013).

Recent Patterns of Development and Disease in Australia

The second study looked at the evidence for a relationship between ecological change and EIDs within (data-rich) Australia. In this country, the interval of post-hunter–gatherer land-use change is shorter and better documented than most other regions, and it is also an island continent. Since colonisation in 1788, Australia has lost approximately 50 per cent of its forest and woodland cover, with much of the rest degraded (Bradshaw, 2012). Its mammals, primarily highly endemic marsupials, experienced the highest extinction rate in the developed world. Agricultural and pastoral enterprises now account for 61 per cent of land use, and there is an extensive mining sector. The majority (87 per cent) of the population of 23 million is concentrated in urban centres that are located predominantly in the high-rainfall, biodiverse coastal regions.

Multiple emergences of indigenous zoonotic and vector-borne diseases have occurred after dramatic intervals of natural vegetation removal in the past, and in the recent decades that define EIDs, in Australia (see McFarlane et al., 2013, for full details, figures and references). Loss of natural habitat through land-use change affects zoonotic disease transmission by changing the density or abundance of disease-related organisms; the species composition of communities; the life cycle of vectors or pathogens; exposure pathways or by selection pressure on organisms that results in increased pathogen virulence (Myers and Patz, 2009). As land-use change intensifies and natural elements and processes are replaced by industrial food production and urban development – a major transition of the late 20th century in Australia, as elsewhere – do we see an increased rate of infectious disease emergence?

Our study found a positive temporally sequenced and biologically plausible association with land-use change (the majority with the extreme transitions) for approximately 22 per cent of Australian EIDs reported in the literature since 1970 (McFarlane et al., 2013). However, it is difficult to establish land-use change–EID causality beyond this or to quantify attribution for most diseases, and certainly not at a multi-disease level. Many processes are too complex or distally acting to demonstrate specificity, consistency or biological gradient, if indeed these

metrics are relevant. For some diseases, the effect of land-use change may be incremental and reversible. For environmental pathogens such as *Burkholderia pseudomallei* (the cause of melioidosis) or *Mycobacterium ulcerans* (the cause of Buruli ulcer), the relationships between land-use change and disease emergence may be relatively straightforward. However, extreme stages of land-use change lead to state shifts in ecological communities that are irreversible. This makes many land-use change–EID effects one way and limits traditional analyses.

A striking example of ecological transformation relates to the increasing urbanisation of the four flying fox (fruit bat) species of the Australian mainland and the emergence of zoonotic Hendra virus, Australian bat lyssavirus (ABLV) and Menangle virus. All four bat species have been affected by natural vegetation clearing and have increased their reliance on vegetation in urban and peri-urban coastal areas. However, the relationships between habitat loss, urbanisation and disease emergence are incompletely understood, and are complicated further by the southern range extension (and contraction) of two species. Hendra, ABLV and Menangle viruses have been present in flying foxes prior to their emergence as human and animal disease and are endemic across their hosts' geographic ranges, an area collectively larger than that in which the diseases have been observed.

For Hendra virus disease, the relatively small number of geographically dispersed outbreaks since 1994 (most of the c.50 outbreaks have occurred since 2011) have challenged analysis of the ecological drivers of emergence. A temporal and spatial association between recent large-scale loss of habitat and Hendra emergence, most frequently in Queensland, can be demonstrated at a coarse scale (Bradshaw, 2012; McFarlane, 2013). However, temporally and geographically proximal, quantifiable environmental factors in local Hendra emergence have not been demonstrated beyond the proximity of horses to flying fox camps and seasonality at higher latitudes (McFarlane et al., 2011). The effect of urbanisation on virus dynamics has been modelled for Hendra virus and can explain periodic outbreaks of that disease (Plowright et al., 2011). Incorporating hypotheses from multiple disciplines including the ecological factors discussed here (and others, including viral factors, bat ecology, horse management) at the multiple scales relevant to each variable is now being undertaken to build the complex picture of why this disease has emerged (Plowright et al., 2015). Future Risks and Research

Our understanding of ecological change and EIDs is scarcely beyond the conceptual mapping stage at this time. Meta-analyses risk simplifying risk factors, and data are often poor where ecological change is most dramatic. Other large-scale processes are also potentially important. Social factors within the Australasian–Asian region that have not been discussed here include the rising human population; the rapidly increasing wealth, resource and consumer

demands of developing economies; the growth in intensive animal production systems (growth in pig, poultry and aquaculture production has been globally significant in East and Southeast Asia in recent decades; Thornton, 2010); patterns of human and livestock movement; changing diets; and improvements and failures in diagnostic, reporting and biosecurity measures.

Conceptual mapping of causal EID relationships is valuable by itself and gives insights into future risk. The rising human population, resource demand and the limited availability of new agricultural land is driving the intensification of land use. A dominant, simplified human ecosystem with large numbers of few species (dominated by humans, domestic animals, invasive and synanthropic wildlife) must affect the nature and patterns of zoonotic disease outbreaks. Livestock already make up a staggering 20 per cent of terrestrial animal biomass, 85 per cent of which is pig and poultry, increasingly within intensive production systems (Steinfeld et al., 2006; FAO, 2011). Zoonotic diseases are predicted to remain a substantial burden for urban and subsistence livestock keepers and intensive production units with inadequate biosecurity (Steinfeld et al., 2008; Grace et al., 2012).

It is difficult to predict the future importance of wildlife as hosts of EIDs. Ongoing loss of biodiverse equatorial forests is a potential source of future novel zoonotic risk, but we are currently close to the limit of remaining unconverted productive land outside these rainforest zones (Ellis, 2011). New opportunities for wildlife pathogen amplification may arise as new centres of intensive livestock production develop (e.g. in Africa) (Butler and McFarlane, 2011). Research continues to focus on the role of biodiversity to generate and/or regulate zoonotic disease emergence. However, this must take into account the clumped spatial distribution of biodiversity and the majority, simplified, human-dominated ecosystems in which this is embedded. Climate change may reshuffle vectors, wildlife, agriculture and people so that new opportunities for wildlife zoonoses emerge or reduce population immunity to existing risks (McMichael et al., 2006). It is also possible that the observed rise in EIDs of wildlife origin is a transient phenomenon marking the end stages of wildlife displacement and demise.

Widespread AMR, reduced investment in developing new antimicrobials and ever larger numbers of humans with impaired immune systems (due to poor nutrition and chronic diseases such as HIV/AIDS) are likely to ensure ongoing opportunities for AMR EIDs. Contamination of communities, water, soil and wildlife with large numbers of AMR organisms also impedes the control of emerging pathogens. Inadvertent selection of vectorcidal resistance and the creation of new niches for vectors or environmentally sourced microbes (such as urban wetlands or the translocation to air-conditioning systems of

pond-dwelling Legionella and their symbiotic amoeba) are simple reminders of the extent to which we can drive disease emergence through change in human environments.

In a general sense, continued change in the environment and its micro- and macroorganisms will result in continued change in infectious disease. Although many disease mechanisms are relatively specific and difficult to use for generalised predictions, existing research is suggesting approaches to mitigating risk. For example, some cross-species movement and mutations of the influenza virus may be limited by avoiding the proximity of intensive pig and poultry farms, human population centres and wetlands of importance to (internationally) migrating wildfowl. Proper treatment of biological waste and its containment may also control the movement of antibiotic resistance by migratory waterfowl from contaminated wetlands (Cole et al., 2005). Risk of Hendra virus infection diminishes with reduced spatial overlap of horses with flying foxes (McFarlane et al., 2011). Even in the absence of a unified understanding of the role of ecological change in disease emergence, there is the opportunity to research, cost and communicate adaptive management strategies for safer microbial environments.

Conclusion

Concurrent, accelerated socioecological change may account for a significant component of the rise in EIDs observed globally and locally. Assessing these associations is impeded by an uneven research effort across countries of different wealth and history of ecological disruption. A series of transdisciplinary studies has explored the relationships between land use, biotic change and EIDs in the Australasian region. Zoonoses, particularly those of wild mammalian origin, are the largest group of EIDs. Organisms with antimicrobial resistance and those of environmental origin are also major causes of disease. Synanthropic wild mammals dominate as hosts of zoonotic EIDs in the Australasian–Asian regions. In the Australian context, we have explored temporally sequenced and biologically plausible relationships between land-use change and EIDs, particularly those of environmental and wildlife origins. However, patterns observed at a landscape scale may not be important at a smaller scale (and vice versa). By progressively exploring and mapping key relationships, we are building a better understanding of how change in complex systems drives infectious disease emergence, and how we can use this information to mitigate risk.

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This text is taken from *Health of People, Places And Planet: Reflections based on Tony McMichael's four decades of contribution to epidemiological understanding*, edited by Colin D. Butler, Jane Dixon and Anthony G. Capon, published 2015 by ANU Press, The Australian National University, Canberra, Australia.