# **Conservation Medicine and a New Agenda for Emerging Diseases**

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ABSTRACT: The last three decades have seen an alarming number of highprofile outbreaks of new viruses and other pathogens, many of them emerging from wildlife. Recent outbreaks of SARS, avian influenza, and others highlight emerging zoonotic diseases as one of the key threats to global health. Similar emerging diseases have been reported in wildlife populations, resulting in mass mortalities, population declines, and even extinctions. In this paper, we highlight three examples of emerging pathogens: Nipah and Hendra virus, which emerged in Malaysia and Australia in the 1990s respectively, with recent outbreaks caused by similar viruses in India in 2000 and Bangladesh in 2004; West Nile virus, which emerged in the New World in 1999; and amphibian chytridiomycosis, which has emerged globally as a threat to amphibian populations and a major cause of amphibian population declines. We discuss a new, conservation medicine approach to emerging diseases that integrates veterinary, medical, ecologic, and other sciences in interdisciplinary teams. These teams investigate the causes of emergence, analyze the underlying drivers, and attempt to define common rules governing emergence for human, wildlife, and plant EIDs. The ultimate goal is a risk analysis that allows us to predict future emergence of known and unknown pathogens.

KEYWORDS: conservation medicine; emerging diseases; zoonotic pathogens; Nipah virus; Hendra virus; West Nile virus; chytridiomycosis

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### INTRODUCTION

Emerging infectious diseases (EIDs) have become recognized as one of the most significant threats to public health over the last 30 years.<sup>1,2</sup> Emerging diseases are those that have recently: expanded in geographic range; moved from one host species to another; increased in impact or severity; undergone a change in pathogenesis; or are caused by recently evolved pathogens (see refs. 2–5 for more definitions). Some EIDs affect relatively few people, but represent a particular threat due to their high case fatality rates and lack of a vaccine or effective therapy (e.g., Ebola virus hemorrhagic fever, Nipah virus encephalitis, Lassa fever). Others (e.g., HIV/AIDS and pandemic influenza) have caused pandemics and are responsible for significant morbidity and mortality. These examples are all zoonotic and part of the 75% of human EIDs that are caused by zoonotic pathogens (those transmitted between animals and humans).<sup>6</sup> Combating these is a key goal of public health efforts nationally and globally which is hindered by the large pool of unknown agents that are yet to emerge.<sup>7</sup> Outbreaks of new zoonotic agents occur almost annually, with serious health and economic consequences. For example, SARS coronavirus caused over 700 deaths and \$50 billion loss to the global economy in 2003 and appears to have wildlife origins.<sup>8,9</sup> Recently, a number of authors have started to widen the scope of EID research. Using the criteria that define EIDs affecting humans, they have identified emerging diseases of marine and terrestrial wildlife, domestic animals and plants.<sup>3,10–14</sup>

Emerging infectious diseases of humans, wildlife, and plants are linked by two common characteristics. First, by definition they are in a process of flux, either rising in incidence, expanding in host or geographic range, or changing in pathogenicity, virulence, or some other factor. Second, these changes are almost always driven by some type of large-scale anthropogenic environmental change (e.g., deforestation, agricultural encroachment, urban sprawl) or change in human population structure (e.g., increased density linked to urbanization) or behavior (e.g., increasing drug use, changes in medical practice, agricultural intensification, international trade).<sup>2–5,7,15,16</sup> These drivers often act via complex pathways that are poorly understood so that predicting the emergence of new pathogens or the spread of introduced pathogens is difficult. Furthermore, a series of anthropogenic changes that have only recently been linked to loss of biodiversity, and this has been linked to heightened Lyme disease risk in the northeastern US.<sup>17–19</sup>

Research in emerging diseases is beginning to address the fundamental rules that govern emergence. Predictive models based on climate analyses have been used for vector-borne diseases,<sup>20,21</sup> and papers have modeled host-pathogen dynamics with pathogen evolution to analyze the process of emergence.<sup>22,23</sup> However, theoretical approaches appear to be far ahead of experimental or field research. For example, few studies have analyzed the links between viral dynamics in wildlife and the environmental changes that have led to the emergence of new EIDs. Second, although the emergence of novel zoonotic agents is an important threat to public health, few studies are attempting to identify unknown agents that have the potential to emerge in the human population. In the following case studies, we demonstrate a novel approach to emerging diseases that consists of forming interdisciplinary teams to examine the underlying causes of emergence (for amphibian chytridiomycosis),

develop risk analyses that enable prevention and control measures (for West Nile virus) and examine the likelihood that novel zoonotic pathogens from a newly discovered viral genus will emerge (Nipah virus). Each of these research approaches involves multidisciplinary teams of veterinarians, medical workers, public health researchers, ecologists, conservation biologists, and others.

## AMPHIBIAN CHYTRIDIOMYCOSIS

Amphibian population declines have occurred globally over the last two decades and have become a major conservation issue.<sup>24</sup> Although many of these are attributable to habitat loss, others have remained enigmatic until recently. In particular, amphibian declines in montane regions of the USA, Central and South America, and Australia were reported throughout the 1990s.<sup>25–29</sup> Hypotheses on the cause of these declines included pollution, increases in UV-B irradiation, unknown environmental "stressors," and climate change. However, these declines had occurred in areas outside the sphere of normal anthropogenic environmental changes: protected parks or remote montane forests with minimal human activity.<sup>26,30,31</sup> A breakthrough occurred in 1996, when amphibian carcasses were collected in the Tablelands National Park, Queensland, Australia. Just prior to this, a debate had begun in the literature over whether the pattern of amphibian declines in Australia resembled that which would be caused by a virulent pathogen.<sup>32,33</sup> Veterinary pathologists and parasitologists examined carcasses from Tablelands and other areas of Australia and determined that the cause of death was a previously unknown fungal pathogen that parasitized keratinaceous cells of the epidermis. Carcasses collected from Panama in 1997 were examined by the same group, and similar findings were reported. The new disease, amphibian chytridiomycosis, was proposed as the cause of mass mortalities related to population declines in tropical montane Australia and Central America.<sup>34</sup>

Since its description, chytridiomycosis has been reported as the cause of mass mortalities and population declines in North America,<sup>35</sup> Europe,<sup>36</sup> and New Zealand<sup>37</sup> and has been linked to at least one extinction.<sup>38</sup> The causative agent has now been described as Batrachochytrium dendrobatidis and Koch's postulates fulfilled.<sup>39,40</sup> Chytridiomycosis has been labeled as an emerging disease owing to its recent expansion in range and the likelihood that its impact has increased in recent years.<sup>38,41</sup> Because of the high profile of amphibian population declines, a number of research groups have begun to work towards understanding the life history, ecology, and impact of this pathogen. Notably, a group of over 20 researchers formed a collaborative group soon after the discovery of chytridiomycosis and have been working as a multidisciplinary team from 1999 onwards. This group has been funded by two National Science Foundation Integrated Research Challenges in Environmental Biology awards, a relatively new program (http://lsvl.la.asu.edu/irceb/ amphibians/). Research has followed similar approaches to those used to study human EIDs.<sup>42</sup> The team has used a combination of molecular techniques, with experimental infections, experimental microbiology, outbreak investigations, and the formation of a global isolate collection to investigate the underlying environmental changes that are driving emergence and to map and understand its spread and impact. The collaborative group includes Australian and American ecologists, veterinarians, mycologists, parasitologists, pathologists, mathematical modelers, and conservation biologists. The results of their research include evidence that *B. den-drobatidis* is a recently emerged pathogen, with little variation in DNA sequence between isolates.<sup>43</sup> This and the finding of the pathogen in amphibians traded internationally for food, as pets, or for conservation purposes implicates anthropogenic introduction as a leading candidate for the cause of emergence.<sup>38</sup> Evidence from outbreak investigations, experimental infection studies, and ecologic studies suggests that the bullfrog (*Rana catesbeiana*) may be an efficient carrier of the pathogen and involved in its spread in some areas.<sup>44–46</sup>

### WEST NILE VIRUS

Since its first appearance in North America in 1999, West Nile virus (WNV) has spread across the continent and into Central America. It has infected more than 14,000 people and caused over 500 deaths, with the number of cases more than doubling in each of the last 3 years.<sup>47</sup> In addition, hundreds of thousands of birds of over 200 different species have died from WNV infection.<sup>48</sup> As a result, WNV has become a serious health and conservation concern both in places where it is established and in areas where it may soon spread such as Hawaii and South America.

Under the broad umbrella of research programs led by the New York State Department of Health, the Centers for Disease Control and Prevention, and others, the ecology of WNV in the new world is being studied through a combination of laboratory, field, and remote sensing approaches by teams of ecologists, climatologists, epidemiologists, and vector control personnel. Lab studies have provided data on the pathology and host competence of different bird species.<sup>49</sup> Similarly, new studies are underway to test mosquitoes and other vectors for their ability to transmit WNV after feeding on an infective host.<sup>50</sup> This information is combined with field data collected through arbovirus surveillance activities on patterns of infection of WNV in the field.<sup>51-53</sup> This enables the determination of which hosts and vectors are most important in amplifying the disease and transmitting it to accidental hosts, including humans. Finally, climatologists study the links between patterns of spatial variation in temperature, rainfall and vegetation and vector densities, dead birds infected with WNV, and human infections.<sup>54,55</sup> This multidisciplinary collaboration will lead to a broader understanding of the drivers of disease emergence than would be possible by any single group.

Understanding WNV emergence is extremely important to predict and prevent serious impacts on many threatened and endangered bird species. A recent study has shown that the impact of WNV on American crows in New York City was a 90%+ reduction of their population.<sup>56</sup> WNV has already led to significant declines in populations of some threatened species,<sup>48</sup> and its spread to Hawaii would almost certainly result in species extinctions of Hawaii's native avifauna that are naïve to vector-borne pathogens.<sup>57</sup> The most prudent approach to preventing extinction due to WNV is to prevent it from establishing wherever possible<sup>58</sup> and to minimize other threats to species that may be susceptible to this pathogen.

### NIPAH AND HENDRA VIRUS

In 1994, the first of a new genus of paramyxoviruses emerged in Australia.<sup>59,60</sup> Hendra virus, a zoonotic pathogen carried by Australian flying foxes (*Pteropus* spp.), was responsible for a fatal outbreak that killed 14 race horses and 2 humans. Five years later, a massive outbreak of a porcine respiratory disease in Malaysia caused the death of 105 pig farm or abbatoir workers and led to the discovery of a novel virus closely related to Hendra, called Nipah virus. Nipah virus, a febrile viral encephalitis in humans, had a 40% mortality rate in the Malaysian outbreak. Two species of pteropodid bat appear to act as the reservoir for this virus and one of these, *Pteropus hypomelanus*, has yielded a new Rubulavirus.<sup>61,62</sup>

A multinational collaborative group of scientists is currently studying the ecology of both Nipah and Hendra viruses to understand what factors caused their emergence (www.henipavirus.org). This group is using field studies of pteropodid bat serology and virus isolation, laboratory studies of virus transmission, and satellite telemetry of bat migration patterns to understand the dynamics of both viruses temporally and spatially in bat populations. In addition, the role of climate, deforestation, and other anthropogenic landscape changes in altering these dynamics is being investigated. For Nipah virus, mathematical models of viral dynamics are being used to predict the threshold density and management practices that would allow future emergence. These models will be parameterized with field and experimental data to further refine predictive capacity.

The experience with Hendra virus (HeV) emergence in Australia has shown that understanding the ecology of wildlife reservoirs can be integral to understanding the epidemiology of emerging infectious diseases. Field, experimental, and molecular investigations of HeV indicate that it is an endemic fruit bat virus that has probably co-evolved with its pteropid hosts.<sup>63–65</sup> Molecular epidemiology and sequencing have shown a rather conservative genetic past and, as such, the virus has not undergone major mutational changes prior to emergence.<sup>66</sup> Furthermore, the concurrent appearance of several other bat-associated viruses implies that changes in the ecology of fruit bats, as opposed to evolution of the pathogen itself, more than likely caused HeV to spill over into new hosts.

Bat biologists have noted changes in the ecology of pteropid bats in the regions where HeV outbreaks have occurred. Two of the three northeastern Australian flying fox species have experienced recent shifts in their ecologic ranges (P. Birt and L. Hall, personal communication). Extensive land clearing, which may have been exacerbated by climate change, has dramatically reduced fruit bat feeding resources,<sup>67–69</sup> bringing bats into closer association with human settlements. It is hypothesized that increased contact opportunities between fruit bats, domestic animals, and humans has led to the current HeV outbreaks. Understanding how land use change may be affecting the distributional ecology of fruit bats (using remote sensing and geographic information systems) is key to understanding the emergence of this disease. Finally, it is not clear which bat species are most important for determining disease risk to domestic animals and humans. Field data have shown us that there are different HeV dynamics in the various species of Australian pteropid bats (Field, personal communication). It is possible that some species act as maintenance hosts, whereas others act as temporary or "spillover" hosts. Mathematical modelers,

bat ecologists, veterinary epidemiologists, and virologists are collaborating to determine which bat species maintain the virus in nature.

One hypothesis to emerge from recent work on henipaviruses is that henipaviruses es have co-evolved with pteropodid hosts within which they naturally circulate. Pteropus species are common to all the outbreak sites of henipaviruses. To examine the broader risk of future henipavirus emergence, we will be testing pteropodid bats for the presence or absence of henipaviruses and other novel, potentially zoonotic pathogens throughout major portions of their range. Pteropodids have a relatively ancient lineage (between 43 mya and 60 mya), a wide distribution, and a high degree of endemicity.<sup>70–72</sup> We predict a substantial diversity within the Henipavirus clade with a corresponding diversity of virulence and transmission potential within humans. The development of predictive models and assessment of viral biodiversity may therefore become a new predictive tool for the next unknown zoonotic pathogen of this group.

# CONSERVATION MEDICINE AND A NEW AGENDA FOR PUBLIC HEALTH AND CONSERVATION

These three examples demonstrate a new approach to investigating EIDs. All three involve multidisciplinary groups of scientists studying the ecology of an EID and testing hypotheses on the environmental changes that caused its emergence or on the primary factors that influence its transmission dynamics. They include a component of modeling, with the data from field studies and pathological and microbiological investigations providing data to parameterize these models. The underlying aim of these projects is to provide information that can be used to predict and control the emergence or spread of the disease or to predict future emergence of related pathogens. These studies enhance classic epidemiology by involving an array of medical, veterinary, health, and ecologic scientists and others in a dialog between model building, parameterization, and further refinement of models. The teams are brought together at the beginning of the study and actively collaborate throughout. Finally, the goals of improving public health and wildlife conservation are interchangeable and merge throughout all three studies.

These projects are examples of a newly evolving multidisciplinary approach, known as conservation medicine, that examines the ecologic determinants of disease. Better methods in data analysis, data synthesis, and field monitoring in the health and ecologic sciences are vividly demonstrating the connection between disease and environmental degradation. Many infectious and noninfectious diseases have ecologic drivers. From the climate change facilitated spread of dengue fever to the increased incidence of basal cell carcinoma due to ozone depletion, there is greater understanding of the ecologic aspects of the health and environment linkage. The field of conservation medicine has emerged as an integrative research and applied approach, bridging the health and ecologic sciences.<sup>73–80</sup>

The aim of conservation medicine is ultimately to develop a solution-oriented, practice-based approach in addressing health problems derived from environmental change. This builds upon existing knowledge frameworks in wildlife health, public health, epidemiology, ecology, conservation biology, and veterinary science. By working at a larger scale of perspective, conservation medicine provides context for more specialized disciplines to interact in a more effective manner. In this way, conservation medicine employs some of E.O. Wilson's concepts of "Consilience" by bringing together disciplines long separated by time and tradition.<sup>81</sup>

As with many emerging fields of multidisciplinary study, conservation medicine can be considered an evolving "work in progress." That much said, clear concepts are coming into focus that can provide a compass for others attempting to follow a similar path or pursue parallel methods. In the foregoing three cases, four "I"s can be identified that serve as guiding elements within conservation medicine: (1) Interdisciplinary interaction, the ability of individual researchers to understand how other disciplines work with their own to advance knowledge; (2) Individual collaboration, the formation of collaborative research teams of individuals from different disciplines; (3) Institutional cooperation, the building of institutional linkage and formal partnerships (consortia) to work in this collaborative way; and (4) Investigative innovation, the development by researchers of new approaches to doing integrated science. The acceptance of these concepts is challenged by well-known social barriers such as entrenched individual or institutional domains. Many times, just understanding the language of a discipline, whether existing or new, is a barrier unto itself.

For veterinarians as an example, this new way of investigating EIDs is an ideal opportunity to use the skills of their profession. Veterinarians work on both human and wildlife diseases and have a unique comparative perspective to bring to investigating zoonoses. Conservation medicine fieldwork is enhanced by an understanding of pathology. For example, the pathogen causing amphibian chytridiomycosis (*B. dendrobatidis*) is often highly prevalent in bullfrogs. This can be misinterpreted without pathological investigations that rapidly can indicate the very mild nature of lesions.<sup>45</sup> However, the dominance of domestic animal studies and the lack of population-scale focus of most veterinary curricula are a hindrance. Similarly, the lack of focus on disease ecology in most biology or ecology undergraduate programs or textbooks creates a complementary knowledge gap in these disciplines. With growing funding and interest in the study of human and wildlife EID ecology, there will likely be a dramatically increased demand for veterinarians, ecologists, modelers, and others who understand these integrated concepts.

Stories of the emergence of such viral diseases as Nipah, Hendra, and West Nile virus and the fungal disease, amphibian chytridiomycosis, demonstrate a new understanding of a pattern linking ecologic degradation and disease outcomes. At one level, the nature of this health concern is obvious but, unfortunately, only recently are these disease issues being recognized and addressed through more rigorous scientific examination. Conservation medicine builds upon the advances of knowledge in the health and ecologic sciences, so that future researchers do not remain oblivious to these obvious connections.

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