

Interdisciplinary approaches to understanding disease emergence: The past, present, and future drivers of Nipah virus emergence

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Emerging infectious diseases (EIDs) pose a significant threat to human health, economic stability, and biodiversity. Despite this, the mechanisms underlying disease emergence are still not fully understood, and control measures rely heavily on mitigating the impact of EIDs after they have emerged. Here, we highlight the emergence of a zoonotic *Henipavirus*, Nipah virus, to demonstrate the interdisciplinary and macroecological approaches necessary to understand EID emergence. Previous work suggests that Nipah virus emerged due to the interaction of the wildlife reservoir (*Pteropus* spp. fruit bats) with intensively managed livestock. The emergence of this and other henipaviruses involves interactions among a suite of anthropogenic environmental changes, socioeconomic factors, and changes in demography that overlay and interact with the distribution of these pathogens in their wildlife reservoirs. Here, we demonstrate how ecological niche modeling may be used to investigate the potential role of a changing climate on the future risk for *Henipavirus* emergence. We show that the distribution of *Henipavirus* reservoirs, and therefore henipaviruses, will likely change under climate change scenarios, a fundamental precondition for disease emergence in humans. We assess the variation among climate models to estimate where *Henipavirus* host distribution is most likely to expand, contract, or remain stable, presenting new risks for human health. We conclude that there is substantial potential to use this modeling framework to explore the distribution of wildlife hosts under a changing climate. These approaches may directly inform current and future management and surveillance strategies aiming to improve pathogen detection and, ultimately, reduce emergence risk.

Emerging infectious diseases (EIDs) are a major threat to global public health (1). Here, we define an EID according to Jones et al. (2) and include all infectious diseases (i.e., caused by prions, viruses, bacteria, or eukaryotic pathogens) that have recently (within the past 60 y) (i) expanded their geographic range [e.g., West Nile virus (WNV)], (ii) infected humans for the first time [e.g., severe acute respiratory syndrome (SARS) coronavirus], (iii) evolved into new strains (e.g., triple reassortant influenza A/H1N1), or (iv) increased their pathogenicity (e.g., hantavirus pulmonary syndrome). Diseases that have affected humans historically but have recently increased in incidence or in the size of their outbreaks are also considered emerging. The impact of EIDs varies from those causing relatively few cases and little mortality to those that spread over continental areas or globally (e.g., Chikungunya virus, SARS) and those that cause significant mortality (e.g., drug-resistant tuberculosis, HIV/AIDS). With increasing dependence on international networks of travel and trade for our globalized economy, EIDs that spread through these networks may have a high economic impact (e.g., SARS, highly pathogenic avian influenza (3)). For these reasons, efforts to understand the causes of EIDs and to predict their future emergence have become part of a global strategy for addressing this public health threat (4). Previous analyses suggest that demographic and anthropogenic environmental changes are

the key underlying causes or “drivers” of disease emergence (5–7). These include ecological, political, and socioeconomic drivers, such as climate change, urbanization, international travel and trade, land use change and agricultural intensification, and breakdown of public health measures. The anthropogenic nature of EID drivers suggests that strategies to influence anthropogenic activities directly may minimize emergence or spread. For example, prevention strategies might influence agricultural development (e.g., better sanitation in backyard poultry production), social behavior (e.g., improving hygiene or hunting practices), or demographic changes (e.g., patterns of human travel, trade, and migration). It is therefore useful to identify the underlying causes of EIDs as part of a broad strategy to prevent their emergence.

Interdisciplinary Studies of EID Drivers

Studies of the underlying causes of disease emergence might assist in forecasting or predicting future emergence of novel pathogens (8–11). However, these studies require interdisciplinary efforts (12) and significant time, and are inherently difficult and costly. One reason for this is that drivers of disease emergence usually represent multidecadal temporal shifts in the underlying environmental or demographic state. For example, WNV was first identified in the New World in 1999, in Queens, New York, adjacent to two international airports (13), and analyses suggest that air travel is the most significant risk for future spread (14). It is therefore reasonable to hypothesize that WNV emerged in the Americas due to increasing air travel during the 20th century (15). However, to test this, and to deduce when critical thresholds of travel necessary for successful invasion occurred, would require multidecadal data. These would include data on the expansion of air travel networks and routes, on the capacity of airplanes to transport mosquitoes, on the prevalence of pathogens in vectors at all source countries, and on the capacity of vectors in the target country to carry these pathogens, among others. Similarly, it has been hypothesized that the pathogen responsible for pandemic AIDS (HIV-1) was first introduced into humans through the hunting and butchering of chimpanzees (16). There is substantial molecular evidence for this, including the genetic similarity of

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simian immunodeficiency virus from chimpanzees (SIV_{CZ}) pointing to initial spillover events during the early 20th century (17). However, to test this hypothesis, and to identify why HIV/AIDS emerged in people as a pandemic in the 20th century despite many thousands of years of primate hunting in the region, would require data on trends in bush-meat hunting, butchering, and consumption in Central and West Africa during the past 150 y. It would also require data on the sociological and demographic changes in the region that lead to expanding human-to-human transmission (18). A range of theories on what would turn an SIV spillover event into stuttering chains of transmission and, ultimately, a pandemic have been proposed, including vaccine production (19), historically high incidence of genitourinary disease (20), and travel and trade (19). Data on each of these would also be required. Thus, understanding disease emergence is inherently a multidisciplinary challenge.

Uncovering the Underlying Drivers of Nipah Virus Emergence

The complex interdisciplinary nature of disease emergence can be highlighted by the emergence of Nipah virus (NiV), a zoonotic paramyxovirus lethal to humans. NiV first emerged in Malaysia in 1998 during an outbreak that caused more than 100 human deaths (21). This paramyxovirus has fruit bat (*Pteropus* spp.) reservoirs, and the virus was first transmitted to domestic pigs, in which it caused respiratory pathology and allowed transmission to people via droplets. The initial spillover of NiV occurred on a pig farm in which fruit trees were planted next to pigsties as a source of additional revenue and to increase shade, and it is thought that these trees attracted fruit bats. However, given that pigs have been produced in Malaysia for many decades, it has remained unclear until recently why NiV first spilled over to people in the late 1990s. It was proposed that burning of forest fires in Sumatra, linked to anthropogenic deforestation during an El Niño southern oscillation (ENSO) event, forced bat migration from Sumatra to Peninsular Malaysia and introduced the virus into the index farm region (22). Sumatran forest fires have been linked previously to coral die-offs (23), and they cause regular haze events in the dry season in Peninsular Malaysia, which were particularly intense during late 1997. To test this hypothesis, the earliest known cases of human NiV cases were identified and found to have occurred on the index farm months before the ENSO-driven haze events (24). The pattern of infection in fruit bats was examined over a 5-y period, and it was shown that NiV antibodies were widespread, suggesting that the virus was regularly transmitted among bats and that NiV was not newly introduced (24). In addition, satellite telemetry showed regular bat movement between Sumatra and Peninsular Malaysia (25), suggesting that the range distribution of the bat host, and therefore NiV, as we argue below, historically included Peninsular Malaysia.

Significant evidence now exists for an alternative hypothesis that changes to the production of livestock drove the emergence of NiV (24). To test this, multidecadal data on pig and mango production from the Food and Agricultural Organization and the Malaysian Ministry of Agriculture and detailed data from the index farm on pig production before the outbreak were examined. Mathematical modeling of NiV transmission dynamics within the index farm showed that the initial introduction of NiV would have led to a large and rapid epizootic, increased pig mortality, and herd immunity, driving the virus extinct within 1–2 mo. The history of the first five human cases in 1997 is consistent with this evidence. However, human cases continued for over 18 mo, culminating in a full-scale outbreak. The model suggests that NiV must have been reintroduced into the pig population to persist for this period. Such reintroductions are plausible, given that field surveys identified a fruit bat colony within 10 km of the index farm (24). It appears that the initial introduction of NiV created a “priming” effect that allowed a secondary introduction to persist in what was then a partially immune population. As pigs born after the initial event gradually lost their maternal

antibodies, they became susceptible and allowed NiV persistence for periods similar to those observed at the index farm. The emergence of NiV in Malaysia was thus the product of two drivers. First, agricultural intensification, in the form of increased commercial pig production and patterns of dual-use agriculture, created a pathway for the repeated transmission of NiV from fruit bat reservoirs to pigs. Second, the initial spillover primed the pig population for persistence of the pathogen on reintroduction, in turn, leading to increased transmission among pigs and to humans. Once infected pigs were sold outside the region, the opportunities for greater human exposure, infection, and disease followed.

This case study illustrates the difficulty in testing complex hypotheses on disease emergence. It required empirical approaches at different scales, from the laboratory to the field, and multidecadal data on hypothesized drivers of emergence, or proxies for unavailable data. The study used mathematical modeling as a framework for these empirical data to be used to test key hypotheses. Importantly, it required commitment of resources to multidisciplinary teams for several years.

This type of case study has value not just in understanding why a specific disease emerged but in providing a pathway to predict and prevent future disease emergence. To push the science of disease emergence forward, novel approaches to data collection, analysis, and collaboration are required. In particular, studies will need to use a causal inference approach to test complex interactions, tipping points, and multiple drivers, and not just simple hypotheses of single causation (26). Although mathematical modeling is often critical to testing complex hypotheses, most approaches involve making basic assumptions about host and pathogen dynamics, how environmental changes affect these, and how host ranges are directly coupled to pathogen occurrence. Studies to elucidate the rules governing these assumptions may significantly improve modeling strategies. Because disease emergence occurs over multiyear or multidecadal periods, archival samples have proven valuable in some studies (27, 28). These would need to be collected systematically and in large enough numbers to give statistical power to identify the presence or absence of diseases, particularly for those found at low prevalence. In addition, samples collected for disease studies often need specific preservation for diagnostic testing. Finally, understanding disease emergence requires collaboration across the biological, physical, and social sciences (29, 30). Drivers of disease emergence are often directly related to anthropogenic change; therefore, studies that analyze how changes in socioeconomic factors alter pathogen dynamics will be particularly useful for understanding past disease risk and predicting future disease risk. This approach has been used successfully to analyze how travel and trade drive the risk of disease spread (14, 31–33), but it has not yet been applied extensively to understand disease emergence.

Climate Change as a Potential Driver of Disease Emergence

The NiV case study demonstrates how understanding the causes of disease emergence requires analysis of long-term historical datasets of host and pathogen dynamics and of the hypothesized anthropogenic drivers. Climate change has been hypothesized as an underlying driver of disease emergence in a number of cases, including directly transmitted pathogens (e.g., hantavirus, Ebola virus, NiV) and vector-borne or water-borne diseases, such as malaria, dengue, and cholera (12, 34–38). Examining linkages between climate change and biological phenomena is difficult, and requires historical time-series data that do not usually exist for emerging diseases. In some cases, these data are easily acquired. For example, colonial studies of malaria cases have been used to test whether emergence of malaria is influenced by climate change (39, 40), climate variability (41), drug resistance (42), or other factors associated with socioeconomic development (43). However, discerning causation from correlation has proven difficult. Models of malaria distribution at larger spatial and temporal scales suggest that, globally, malaria has receded

Table 1. Examples of published studies with applications of ENM to pathogen distribution

Pathogen/disease/species	Pathogen type	Scale	Algorithm	Validation	Time	Ref.
<i>Vibrio cholerae</i>	Free-living bacterium	Central California	Mantel	Bootstrap	Current	(97)
<i>Yersinia pestis</i>	Vector-borne bacterium	Western Usambara Mountains of Tanzania	GARP	Jackknife	Current	(98)
H5N1 avian influenza	Directly transmitted virus	India, Bangladesh, Nepal, and Pakistan	GARP	Actual outbreak locations	Current	(99)
Coccidiomycosis	Fungus with environmental spores	Southern California, Arizona, and Sonora	GARP	Available epidemiological data	Current	(100)
<i>Bacillus anthracis</i>	Bacterium with environmental spores	United States	GARP	AUC	Current	(101)
<i>Triatoma brasiliensis</i>	Vector-borne protozoan	Northeastern Brazil	GARP	Points sample from test data	Current	(102)
<i>Campylobacter jejuni</i>	Enteric bacterium	100 km ² around Cheshire, United Kingdom	GAM, UPGMA	Simulation data from the null model	Current	(103)
Range of parasites	Microparasites (e.g., viruses, bacteria, protozoa), macroparasites (helminths), and ectoparasites (arthropods)	North America	Correlations	N/A	Current	(104)
Bat-related pathogens	N/A	South America	MaxEnt	Jackknife, ROC, AUC	Current	(105)
West Nile encephalitis	Vector-borne virus, <i>Culex pipiens</i>	Illinois, Indiana, and Ohio	GARP	Independent datasets	Current	(106)
Chagas, <i>Trypanosoma cruzi</i>	Vector-borne protozoan	South America	NODF	Bootstrap	Current	(107)
H5N1	Directly transmitted virus	West Africa	GARP	Binomial probabilities	Current	(108)
Filoviruses	Directly transmitted virus	Africa	GARP	N/A	Current	(55)
Chagas, <i>Trypanosoma cruzi</i>	Vector-borne protozoan	Mexico	GARP	None	Current	(56)
Leishmaniasis	Vector-borne protozoan	North America	MaxEnt	AUC	Future	(95)
Leishmaniasis	Vector-borne protozoan, <i>Lutzomyia</i>	South America	GARP	Bootstrap	Future	(109)
Leishmaniasis	Vector-borne protozoan	Spain	Negative binomial regression	Independent dataset	Future	(110)
Malaria	Vector-borne protozoan	Africa	GARP	Independent dataset	Future	(46)
Dengue	Vector-borne virus	Mexico	GARP	Actual case data	Past	(111)

Scales of studies varied from state or county levels (e.g., Illinois; Cheshire, United Kingdom) to continental scales (e.g., Africa). Few studies focused on the effects of climate change on the distribution of directly transmitted pathogens, focusing instead on vector-borne or free-living pathogens. A combination of key words was used to search the International Statistical Institute Web of Science: (environmental niche model* OR ecological niche model* OR species distribution model* OR predictive habitat distribution model* OR climate envelope model* and disease* OR pathogen*); nearly 73% of ENM studies referred to vectors or an environmental reservoir (vector* OR environ* reservoir* OR environ*), whereas only 27% of studies referenced a directly transmitted pathogen without vectors or an environmental reservoir [host*NOT (vector* OR environ* reservoir* OR environ*)]. AUC, area under the curve; GAM, Generalized Additive Model; GARP, Genetic Algorithm for Rule-set Production; N/A, Not Applicable; NODF, Nestedness overlap and decreasing fills; ROC, receiver operating characteristic; UPGMA, Unweighted Pair Group Method with Arithmetic Mean.

over the past century (44, 45), and this recession is most significantly due to the success of public health interventions rather than climate change (44).

These studies all rely on analyses of historical data on disease occurrence. However, the link between climate change and disease may be better investigated using predictive models that aim to forecast future disease emergence risk under climate change scenarios. This approach has been adopted for vectors of some diseases [e.g., malaria (*Anopheles gambiae*) (46)] and those with an environmental reservoir [e.g., *Bacillus anthracis* (47)]. Vectors often have a strong link to climate due to their requirement of water bodies for reproduction, as well as the direct impact of temperature changes on their growth rates, biting rates, and population expansion. However, a recent analysis of one of the most comprehensive databases of EIDs currently available in the literature showed that only 22.7% (76 of 335) of EID events identified from 1940 to 2006 were vector-borne, with 77.3% (259 of 335) being directly transmitted. Thus, applying climate models to directly transmitted pathogens may provide a useful strategy

to predict future emergence risk. For directly transmitted pathogens, climate change may affect the distribution of a pathogen's reservoir host (e.g., mice for hantavirus, frugivorous bats for Ebola virus) or the host's food source (e.g., grasses for hantavirus reservoirs, fruiting trees for Ebola virus reservoirs). Thus, assuming that pathogen and wildlife host distributions are linked, predictive models may provide an improved understanding of potential climate change impacts on the distribution of directly transmitted EIDs.

Correlative Ecological Niche Modeling as a Tool for Studying Disease Emergence Under Climate Change

Ecological niche modeling (ENM) is a widely used tool to investigate the potential distributions of species under scenarios of environmental change. This technique employs a range of different algorithms [generalized linear model, generalized additive model, genetic algorithm for rule-set production, and MaxEnt; reviewed in (48)] to estimate the relationships between point-locality data, such as museum collection records or field observations

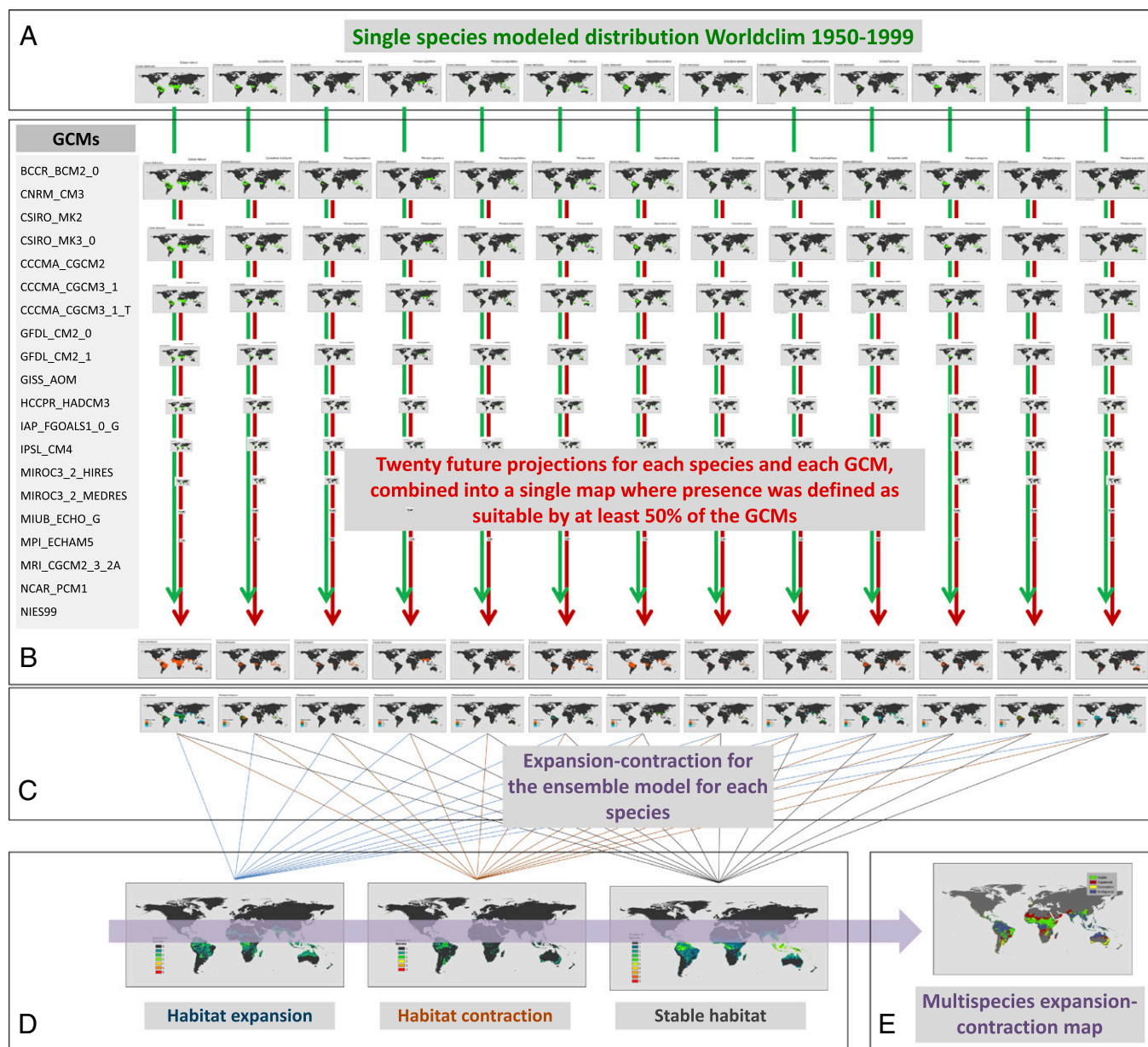


Fig. 1. Conceptual model of our methods. (A) Models of a single species' current bioclimate, based on Worldclim. (B) Projected future suitable bioclimate based on 20 downscaled GCMs, where presence was defined as suitable by at least 50% of the GCMs. (C) Expansion/contraction maps based on the subtraction of the present from the future multi-GCM predictions. (D) All 13 species expansion/contraction maps were combined into three composite maps that show habitat expansion, contraction, and stability. (E) Synthetic map across GCMs and species that shows habitat expansion, contraction, and stability.

of species' occurrences, and spatial information on factors that constrain species distributions (e.g., climate, vegetation, other biophysical attributes). This correlative method can use the realized niche as represented by occurrence records to help characterize the ecological or fundamental niche of the species (49). The relationships derived can then be used for extrapolating species distributions into different geographic regions or under different climates (50, 51). This technique is now used widely in the fields of ecology, evolutionary biology, conservation biology, agricultural science, and public health (52). However, like any statistical modeling approach, ENM requires careful consideration of inputs (e.g., reliability and representativeness of occurrence records; sampling bias; quality of plausible spatial drivers, such as environmental layers) and model assumptions (e.g., what is being modeled, equilibrium assumptions, implicit inclusion of

species interactions, extrapolation beyond the training region) to ensure that results are biologically plausible.

ENM was first used to make ecological predictions of the distribution of wildlife species from occurrence data. This has been applied to some wildlife diseases (53) and is increasingly used to estimate the current distribution of human pathogens [e.g., monkeypox (54)] based on climate, other environmental parameters, and reported human cases of infection (55, 56). These studies show how correlative models may also be used to guide the collection of new information to improve predictions iteratively. Nevertheless, in the case of monkeypox, one unresolved question relates to the role of the as yet unidentified monkeypox virus reservoir (assumed to be wildlife, with one confirmed positive record from a squirrel) and its relationship with human cases of disease.

(46, 47, 95, 96). Usually, neither scientists nor managers know if similar results would be produced if the target species were modeled under a different set of data choices. This level of uncertainty often prevents the application of the results of ecological forecast models to public health decision making and risk assessment. Here, we have demonstrated a statistically rigorous ensemble-modeling approach focused on the potential for climate change to shift the host range and on the likely occurrence (or lack thereof) of reservoir species able to support transmission for the particular case study of henipaviruses.

In conclusion, we propose that strategies to deal with EIDs proactively will require, along with continued public health investment, increased focus on (i) identifying the driving mechanisms that underpin the emergence of each new EID and (ii) predictive modeling of how these drivers will promote or shape future EID emergence potential and/or risk. These approaches are inherently multidisciplinary, and they are still in the early stages of their development as disciplines. The former requires extensive ecological studies that examine long-term trends in

environmental factors and how changes to these affect disease ecology within reservoir hosts, vectors, and people. The latter requires large datasets on environmental and ecological factors, as well as on pathogen and host distributions. As the discipline of emerging disease ecology develops, the challenge will become one of how to insert these approaches more widely into the toolbox available to agencies to predict and prevent pandemics.

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