

# Avian Influenza (H5N1) and the Evolutionary and Social Ecology of Infectious Disease Emergence

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## INTRODUCTION

The recent ascendance of the H5N1 subtype of avian influenza (AI) as the world's most prominent emerging disease threat presents an opportunity to examine the determinants of infectious disease emergence, particularly because H5N1's perceived epidemic potential has not been realized. Although social and ecological conditions may seem highly conducive to an AI epidemic in humans, adaptations necessary for efficient human–human transmission have not yet occurred. What are the ecological conditions that increase the probability of emergence? How does an increase in cross-species exposure affect the probability of an evolutionary host switch by H5N1? Can the higher order drivers of change in these conditions be studied to help understand and ultimately manage the risk of infectious disease emergence? Although there exists a large literature on the threat of an AI epidemic, this article aims to synthesize epidemiological, evolutionary, social, and ecologic perspectives into an integrative assessment of the factors influencing infectious disease emergence.

Disease emergence, broadly defined as an increase in the incidence of human cases of a disease (Lederberg et al., 1992), implies an increase in transmission rates, either arising from a change in host contact dynamics (e.g., West Nile Virus ongoing emergence in North America due to introduction and local mosquito feeding behavior; Weaver and Barrett, 2004; Kilpatrick et al., 2006) and/or a change in the pathogen (e.g., changes in host specificity of the equine encephalitic viruses, reviewed in Weaver and Barrett, 2004; host switching in HIV-1, Sharp et al., 1995; reassortment in influenza A, Scholtissek et al., 1978; Parrish and Kawaoka, 2005; dengue epidemic potential, Bennett et al., 2003).

While traditional biomedical and epidemiological research can elucidate proximate causes and circumstances leading to disease emergence—*a posteriori*—H5N1 exemplifies the challenge to determining *a priori* disease emergence risk. Causal explanations do not always translate directly into predictive power (Casti, 1991). However, integrating the best practices of disciplines which embody both prediction and explanation offers a possible solution. The combined perspectives of evolutionary ecology and social ecology can provide a basis for associating qualitative levels of risk with quantifiable factors from pathogen

mutation rate to patterns of land use change. Evolutionary ecology focuses on how interaction between phenotype and environment generates differences in Darwinian fitness among different phenotypes (Pianka, 2000). For example, an evolutionary ecological focus on life-history trade-offs that maximize pathogen transmission and determine optimal levels of virulence renders it particularly relevant to infectious disease epidemiology (Galvani and Slatkin, 2003). Social ecology focuses on the social, institutional, and cultural contexts of human–environment relationships of particular relevance to public health, the behavioral sciences, and medicine (McLaren and Hawe, 2005). When integrated with systems thinking, it is often described in terms of the “social–ecological systems perspective” whose potential for understanding infectious disease emergence has been suggested elsewhere (Wilcox and Colwell, 2005).

The emergence of different infectious diseases has been attributed alternately to changes in ecological conditions affecting transmission dynamics with or without accompanying adaptive evolution in, say, host specificity, of the pathogen. Traditionally, epidemiologists describe disease emergence in terms of the standard epidemiological measure “basic reproductive rate” ( $R_0$ ) of a pathogen (the number of infections per infected individual in a completely immunologically naive population) and “critical host threshold density” ( $N_t$ , the population size for which a pathogen ( $R_0 \geq 1$ ) can persist (Anderson and May, 1986; Anderson et al., 1992; Grenfell et al., 2004). More recently, it has been recognized that ecological factors which increase transmission also increase ongoing opportunities for adaptive evolution in the pathogen (Antia et al., 2003; Woolhouse et al., 2005), can increase  $R_0$  and, thus, affect the probability of disease emergence or reemergence. In enzootics, such as H5N1, where the ecological conditions appear to be in place for emergence, yet barriers to cross-species transmission exist, we must combine both the social–ecological context and evolutionary potential (mutation, genetic drift, recombination, and adaptation due to natural selection) of the pathogen to begin to quantify the risk of emergence.

Furthermore, as members of complex and dynamic natural host communities (a “coupled human–natural system”), humans are exposed to infectious diseases from each other or other animals. This process depends on social and ecological factors such as regional environmental change or cultural practices affecting landscapes, communities, through to population density (Morse, 1993; Daszak et al., 2000, 2001; Smolinski et al., 2003; Morens et al.,

2004; Weiss and McMichael, 2004; Wilcox and Colwell, 2005; Wilcox and Gubler, 2005). These factors, in turn, interact with host–pathogen biology via evolutionary ecological processes to contribute to emergence of novel (or reemergence of familiar) pathogens and diseases.

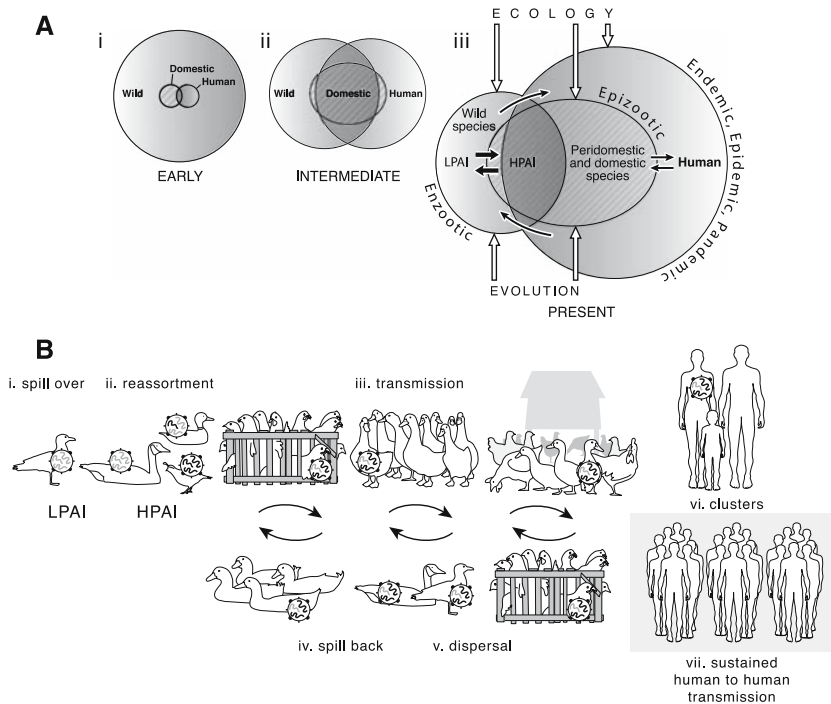
## UNCERTAINTY AND THE CAUSAL CHAIN OF EMERGENCE

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The causal chain of emergence for H5N1 influenza A, or any enzootic pathogen, consists of a series of events that may potentially lead to a pandemic, where each key factor has sources of uncertainty in the largely stochastic nature of exposure, infection, and transmission, and in a lack of empirical data. Epidemic or pandemic disease emergence in a novel host species, here referred to as the recipient for cross-species infection by spill-over from a donor host species, involves four phases: 1) initial exposure of the potential hosts; 2) subsequent cross-species infection (e.g., determined by degree of host specificity); 3) onward transmission of the novel pathogen within the focal population, where  $R_0 > 1$  (Antia et al., 2003; Woolhouse et al., 2005; Kuiken et al., 2006); and 4) spread of disease between host populations (Anderson and May, 1986). Although these phases are related to the epidemiological phases listed by Anderson and May (1986)—invasion (phase 2), persistence (phase 3), and spread (phase 4 between populations)—they did not include an accounting of the ongoing exposure process that drives the initial stages of crossing the species barrier.

Several ecological factors concomitantly affect the exposure rates of hosts (phase 1) and the evolutionary likelihood of a host switch (phases 2 and 3) via changes to pathogen  $R_0$ . Increasing human population density directly increases  $R_0$  and as density exceeds a threshold ( $N_t$ ),  $R_0$  becomes greater than 1 and pathogen invasion and persistence is facilitated (Anderson et al., 1992). Ecological factors that increase the physical proximity of potential donor or reservoir species and potential novel recipient species, although not truly separable from changes in density, increase the possibility of cross-species exposure and infection as well as the subsequent spread of a disease within (phase 3) and between different host populations (phase 4, the recipient “metapopulation”; Arino and van den Driessche, 2003).

Anthropogenic environmental change can dramatically affect host density and contact rate modifying all phases of disease emergence. For example, changes in bird breeding,



**Figure 1.** Emergence of highly pathogenic avian influenza (HPAI) H5N1 in SE Asia and subsequent worldwide spread. Schematic representation of spatiotemporal overlap between wild reservoir species, peri-domestic and domestic species, and humans affecting AI emergence in humans. Degree of overlap is hypothesized to be positively correlated to potential for exposure between species. Open arrows represent external forcers of ecological or evolutionary change, solid arrows represent cross-species transmission of a pathogen from a donor reservoir (e.g., wild waterfowl) or donor host that is experiencing a recent zoonotic (e.g., free-grazing ducks). **A:** Temporal change in the relative overlap between species: (i) early human history where small populations of humans and their human-associated species existed in a matrix dominated by wild species; (ii) an generalized intermediate stage where human

populations and their associated domestic animal species have an increased overlap with wild species worldwide; and (iii) the current situation where humans and associated domestic animals dominate many landscapes worldwide. **B:** Specific events leading to exposure and infection of H5N1: i) spill-over of low pathogenic avian influenza (LPAI) variants from wild to domesticated avian species; ii) reassortment of different strains among species increases pathogenicity; iii) onward transmission of HPAI in wet-markets and continued transmission, including iv) spill-back to wild avian species, and v) dispersal and movement across the metapopulation, between species associated with domiciles, wet-markets, free-grazing on rice paddies, and migrants leading to sporadic human infections, vi) clusters, and potential for vii) sustained human-to-human transmission in SE Asia, Asia, Europe, and Africa (as of June 2006).

migratory or wintering habits in response to habitat modification, may affect the probability of cross-species transmission of avian influenza (both spill-over and spill-back, Fig. 1) by increasing the overlap between wild bird species or more importantly between wild species and peri-domestic species (Olsen et al., 2006). Successful onward transmission of highly pathogenic strains of AI appear to only occur in dense populations of domestic recipient avian species (e.g., ducks) in very crowded conditions (e.g., wet-markets, factory farms, and large free-grazing flocks; Gilbert et al., 2006). Conditions that may be exacerbated by changes in other physical factors in the environment including long-term changes in climate, associated rainfall patterns and temperature change affecting the environ-

mental persistence of AI, host ecology, etc. (Olsen et al., 2006).

Many zoonoses, because they are host-specific to some degree, characteristically have a low cross-species reproductive rate ( $R_0$  donor–recipient), with an even lower effective recipient–recipient  $R_0$  (Antia et al., 2003) in the absence of ecological or evolutionary changes. Increases in recipient–recipient  $R_0$  to  $> 1$  can arise either “coincidentally” or due to evolution in the donor host for specificity. Even if  $R_0$  remains below unity, ecological factors such as increased recipient host density may lead to more onward stochastic transmission events, and slightly longer chains of transmission, thus providing the opportunity for a pathogen to evolve an  $R_0 > 1$  (Antia et al., 2003). In addition, the

“effective population size” for H5N1, at any one time is a function of the infected host density for each species weighted by the specific  $R_0$  values for within and between species transmission. There are a number of evolutionary implications resulting from larger effective host population size and other ecological factors that increase the likelihood of disease emergence. For example, inflated population sizes/densities due to habitat loss for wild host species and agricultural practices leading to crowding and mixing of both wild and domestic hosts results in increased genetic diversity of the pathogen population, increased opportunities for reassortment, and longer chains of transmission (higher instantaneous  $R_0$ ) (Antia et al., 2003; Chen et al., 2004; Gilbert et al., 2006; Holmes et al., 2005; Kuiken et al., 2006; Mills et al., 2006; Olsen et al., 2006).

The ecological factors that increase exposure/contact rate and the length of stochastic chains of transmission can also increase the probability of adaptive evolution in the pathogen. Although to emerge as a significant cause of morbidity and mortality, infectious diseases need not necessarily undergo adaptation, it is the missing link in the emergence of AI. Some of the evolutionary changes in H5N1 in specificity, replication efficiency, and/or immune evasion, necessary for efficient ongoing human–human transmission and pandemic emergence, are occurring and are sensitive to ecologic dynamics. Because of the organization of its genome, influenza experiences evolutionary change both in the form of point mutations and the exchange of whole gene segments between subtypes. The low-pathogenicity influenza strains currently circulating among humans undergo small evolutionary changes (such as nonsynonymous point mutations leading to “antigenic drift”), 1% or less every year (Webster et al., 1992). However, the last two major influenza outbreaks in humans have been caused by reassortment between flu viruses (or “antigenic shift”; Scholtissek et al., 1978; Murphy et al., 1982; Kawaoka et al., 1989; Lindstrom et al., 2004; Holmes et al., 2005); and probably the 1918 epidemic as well (Antonovics et al., 2006; Gibbs and Gibbs, 2006; but see Taubenberger et al., 2005, for opposite view). Several amino acid substitutions and/or reassortments have occurred in structural and nonstructural genes that affect H5N1 host specificity, replication efficiency, and virulence in bird hosts (Naffakh et al., 2000; Hatta et al., 2001; Chen et al., 2004; Li et al., 2004; Zambon, 2004; Beigel et al., 2005; Olsen et al., 2006; Stevens et al., 2006). Since the outbreak of highly pathogenic avian influenza (HPAI), evolving in domestic fowl (Olsen et al., 2006) and leading

to the first human case in Hong Kong in 1997 (Beigel et al., 2005), H5N1 has crossed avian species barriers and produce onward (within several domestic avian species) recipient–recipient transmission and spread across the old world. These evolutionary events apparently have not yet produced a variant capable of sustained human-to-human transmission, although some strains show modified cell-surface receptor binding affinity within donor species that could coincidentally lead to increased  $R_0$  in humans (Li et al., 2004). The multiple routes by which HPAI H5N1 could evolve into a strain that easily infects humans lends uncertainty to the estimation of its likelihood. However, the fixation rate of mutations beneficial to viral fitness, the underlying genetic diversity of AI populations and the likelihood of reassortment to produce novel strains increases with population size, interspecific host interactions, and other ecological factors (Table 1, Fig 1). These types of evolutionary dynamics, or phylodynamics, in concert with epidemiologic factors have been documented in a range of emergent pathogens (Grenfell et al., 2004).

## SCALING UP: LINKING MICRO-SCALE TRANSMISSION AND MACRO-SCALE FACTORS

Ecological factors at the meso- and macro-scale drive emergence from donor to recipient host species by influencing ecological and evolutionary opportunities for cross-species transmission. Although the individual ecological and evolutionary events leading to emergence of a novel zoonosis are stochastic in nature, understanding the influence of external social ecological drivers on overall exposure to novel pathogens is potentially more tractable. For example, in many parts of the world, as in Southeast Asia, traditional methods such as multi-species livestock husbandry at the family level, are being replaced by industrial, mass-production-oriented operations, similar to western countries in the 1950s, and can pose significant environmental health risks (e.g., Mallin and Cahoon, 2003) due to increases in livestock pools and thus opportunities for disease transmission. Simultaneously, rapid urban and peri-urban development in such countries is often unplanned (Wing-Shing and Him Chung, 2002; Montgomery et al., 2004), accompanied by more refuse, standing water, and animals in and around the home, and has been correlated with environmental health risks (e.g., Graham et al., 2004). With respect to H5N1, expansion at the urban fringe places a larger proportion of the human population in

**Table 1.** Social Economic Factors That Are Correlated With Land-Use Change and Hypothesized Implications for EIDs<sup>a</sup>

Factor	Examples	Speed of change	Mechanisms by which they might affect EID	Synergistic effects on the evolutionary ecology of EID
Resource scarcity causing pressure of production on resources	Natural population growth and division of land parcels, changes in labor availability, loss of land productivity	Slow	Increased population density, increased poverty, landlessness, hunger	Synergistic increase in $R_0$ , chains of transmission, and evolutionary potential
Changing opportunities created by markets	Spontaneous migration Increases in agricultural commercialization, road construction, market prices	Fast		
Outside policy intervention	Changes in global trade conditions Economic development programs, frontier development for geopolitical purposes Government instability	Fast	Decrease in biodiversity, intensification of few crops, increased transportation speeds, increased urbanization	Synergistic increase in spatio-temporal overlap and exposure between species, decrease in barriers to disease spread
Loss of adaptive capacity and increased vulnerability	Economic development programs, frontier development for geopolitical purposes Creeping household debts, breakdown of social networks, dependence on external assistance, social discrimination	Slow	Increased population density, decreased biodiversity, increased transportation speeds	All of the above synergies; increased chains of transmission, intra- and inter-specific contact rates, and evolution
Changes in social organization, in resource access, and in attitudes	Government instability Creeping household debts, breakdown of social networks, dependence on external assistance, social discrimination Internal conflicts, illness (HIV) Changes in institutions, growth of urban aspirations, breakdown of family Loss of entitlements to environmental resources	Fast	Increased poverty, landlessness, hunger	All of the above synergies; decreased immunocompetence
		Fast	Urbanization, breakdown of social networks	Increased mixing/contact at larger spatial scales; decreased isolation at local scales; increase in $R_0$ and length of chains of transmission

<sup>a</sup>This table is based on Lambin et al. 2003, and used with permission from the Annual Review of Environment and Resources, Volume 28 ©2003 by Annual Reviews.

contact with formerly dispersed farm environments that include potentially infected poultry and swine populations. Such urban–rural interfaces have been hotspots of other infectious diseases such as leishmaniasis (Oliveira et al., 2004).

Expanding “fronts” of human settlement, intensified agriculture, conversion of land use from rural to urban-industrial, and societal/cultural changes from government stability to family structure (Lambin et al., 2003) can increase the risk of EIDs (Table 1). Ecotonal-level changes resulting from large-scale land-use conversion from wetlands to rice-cultivation or dryland forests to farming are also associated with disease emergence (Despommier et al., 2006). The increasing movement of humans and animals enabled by modernized transportation systems both locally from village to town and city, as well as internationally through cheap and easily accessible air travel has further increased the spatial and temporal scope of human exposure to people and livestock infected with HPAI and other infectious diseases and could well increase subsequent spread of H5N1 to novel hosts as it did in the SARS epidemic (Kan et al., 2005).

Thus, the spatial and temporal patterns of social ecological changes that increase the potential for overlap of wild reservoir hosts (the donor species), human-associated species, and humans (the recipient species), may be amenable to analysis even in the absence of specific pathogen identification. For example, trends in changing human demographics, land use, and densities and distributions of known domestic and peri-domestic host species characteristic of particular geographic areas are relatively predictable within a short historical time frame (Kaimowitz and Angelsen, 1998; Lambin et al., 2003) and can be measured with geospatial information systems (including maps and satellite information), census data, and agricultural, trade and policy analyses, to predict geographic hotspots of disease emergence.

## TRANSDISCIPLINARY FRAMEWORK FOR UNDERSTANDING EMERGING INFECTIOUS DISEASES

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Linking the largely, stochastically driven, evolutionary dynamics of potential EIDs with the more deterministic, larger-scale changes in human ecology via the mechanism of host population size and interspecific interactions, points the way toward understanding the risk of a zoonosis

becoming the next pandemic. An interaction between individual donor species, their pathogens, and a novel recipient host must occur for novel disease emergence to occur. Numerous ecological factors affecting the potential transmission arena, from denser host populations to increased interactions among donor and recipient host species, interact with evolutionary changes to increase the risk that pathogens such as H5N1 will emerge as a major threat to human health. Opportunities for evolutionary change increase with donor species population size leading to larger variation in the pool of pathogen strains, increased fixation of mutants with enhanced viral fitness as well as increased probability of recombination/reassortment. Although the evolutionary route by which pathogens such as H5N1 may change into efficient highly transmissible, human-to-human forms is unpredictable, knowledge of these evolutionary ecological mechanisms and the affects of specific social ecological factors is largely understood. Combining data on human population density, avian–human exposure, avian disease clusters, avian host population density, movements of wild and domestic species (and their by-products), and their spatio-temporal distributions in a given geographic area could form the basis for estimates of probable hot-spots of human infection.

We have, so far, ignored population health status and any human genetic variation that could affect susceptibility, which ultimately may be a critical factor in disease emergence. This may be considered to include acquired or native immunity to a pathogen, although human immunocompetence varies with the health of an individual in spite of immune status. This is highlighted by the recent cluster of seven cases of H5N1 AI with definite human-to-human transmission within a single family in North Sumatra, Indonesia, where nonfamily members were also similarly exposed but never infected (Normile, 2006; WHO, 2006a, b). This suggests the hypothesis that the family had either a shared genetic, behavioral, and/or environmental circumstance that predisposed them to human-to-human infection. Although this stochastic emergence event did not lead to ongoing transmission on a larger scale, it suggests the importance of human genetic, behavioral, or environmental heterogeneity and, thus, could be a harbinger of future case clusters in which lengthened chains of transmission among uniquely susceptible persons may allow the virus to undergo evolutionary change necessary to drive  $R_0 > 1$  in the general population.

More generally, it is likely that population health status, including infectious disease or parasite load, is intimately

related to the same social ecological factors associated with rapidly changing land use and livelihood patterns. The very places and populations in which the emergence and resurgence of infectious diseases are first noticed are often where there is rapid and generally unplanned economic development and intensification of human activities. These typically are the same places where sharp disparities in human health emerge, which could also impact the evolution of  $R_0$ .

## CONCLUSION: RISK OF EMERGENCE OF INFECTIOUS DISEASES

Risk assessment in a human health context is defined as the systematic, scientific characterization of potential adverse effects of human or ecological exposures to hazardous agents or activities (NRC, 1983). The paradigm in vogue suggests a four-step approach to risk assessment: hazard identification, exposure assessment, dose-response analysis, and risk characterization (Goldstein, 2005). The knowledge in each step is combined to represent a cause-and-effect chain from the prevalence and concentration of the hazardous agent to the probability and magnitude of health effects. In risk assessment, risk consists of both the probability and impact of disease. In this way, risk reduction can be achieved in either dimension—by reducing the probability of disease or by reducing its severity.

However, risk characterization involving living hazards such as emergent pathogens is problematical because of the discussed uncertainties in ecological and evolutionary systems. This makes the three data-driven steps, hazard identification, exposure assessment, and dose-response analysis not only subject to the increased difficulty of measurement (epistemic error) but also to inherent stochasticity (aleatory error; Hilborn and Mangel, 1997). Thus, the challenge of understanding the risk of disease emergence (and thus quantifying the risk of exposure, infection, and transmission) is how to integrate knowledge and methods of ecology and evolutionary biology dealing with stochastic processes, at and below the organismal level, with an understanding of social and ecological processes at the level of landscapes, ecosystems regions, and ultimately, globally (Wilcox and Colwell, 2005).

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