

Emergence of Influenza A

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Goal

To investigate the ecological and evolutionary factors contributing to the emergence of influenza A viruses in different species of hosts.

Background and motivation

Many infectious diseases emerge by increasing their host range; that is, they cause one or more outbreaks in a new host population. The probability of an emergence event is influenced by ecological and evolutionary factors. Disentangling the relative contribution of each factor has important consequences for disease management, including gauging the risk of spillovers, predicting the severity of outbreaks, and controlling virulence. Many analyses infer the conditions for emergence from an ecological framework, such as SIR models for multispecies communities (e.g. Dobson & Foufopoulos 2001), or by using evolutionary optimization models (e.g. Parker et al. 2003). Thus, they implicitly assume either no or very rapid adaptation to changing ecological conditions. Other studies have shown, however, that these kinds of assumptions can lead to substantial underestimates of disease burden (Koelle et al. 2005).

These assumptions are also unlikely to lead to sufficient descriptions of parasites that, like influenza A viruses, evolve rapidly but not instantaneously in variable host communities. In aquatic birds, their natural reservoir, influenza A viruses achieve high transmissibility with negligible fitness costs: they are considered “optimally adapted” and in evolutionary stasis (Ito & Kawaoka 1998). Their dynamics in poultry, swine, and humans are more complicated (Webster et al. 1992; Webby & Webster 2001). Though the molecular determinants of host range, transmissibility, and virulence are incompletely known (Baigent & McCauley 2003), a major determinant of a virus’s ability to infect a host cell is its receptor preference. The intestinal cells of aquatic birds have sialic acid receptors linked to galactose units in an $\alpha 2,3$ conformation, and humans have these receptors in an $\alpha 2,6$ conformation. Viruses in each population show a strong preference for their host’s receptor type. The cells of chickens and pigs have receptors in both conformations, allowing them to be infected by viruses adapted to ducks and humans (Scholtissek et al. 1998; Gambaryan et al. 2002a; Gambaryan et al. 2002b). Thus, chickens and pigs may serve as key intermediate hosts by allowing reassortment between antigenically novel subtypes from the natural reservoir and subtypes that have adapted to replication and transmission in other hosts. These reassortment events have preceded the emergence of most pandemic influenza viruses, which escape host immunity through acquisition of foreign surface proteins (Webster & Hulse 2004).

There is evidence of frequent transmission of influenza viruses between different species, especially in farms and markets in Asia (Banks et al. 2000; Lin et al. 2000; Peiris et al. 2001; Bridges et al. 2002; Liu et al. 2003a) and in commercial poultry and swine operations in Europe and North America (Castrucci et al. 1993; Claas et al.

1994; Olsen et al. 2002; Enserink 2004). These settings provide distinct interspecific transmission opportunities, which are shaped by host population dynamics, the mode of transmission, host immunity, seasonal migration, and vaccination history. The fitness of an invading strain with a particular receptor preference is thus highly contingent on local ecology. An analytic and quantitative framework to study the interplay of these ecological processes with fundamental evolutionary adaptations could be useful in understanding the long-term dynamics of influenza viruses and other zoonotic RNA viruses (Cleaveland et al. 2001; Webster & Hulse 2004).

Research questions

The primary focus of this research is to compare the expected conditions for emergence in different hosts between (1) a simple multihost SIR model of influenza's ecology; (2) an adaptive dynamics model for one subtype, constrained by the tradeoff in receptor preference; and (3) an adaptive dynamics model allowing reassortment among multiple subtypes under the same constraints in receptor preference. Secondary questions to be asked of all models include:

- How does each species contribute to the probability of outbreaks in other species? In a purely ecological model, this question amounts to investigating the ecological force of infection. In an adaptive dynamics simulation, this ecological force of infection is mediated by the extent and direction of adaptation in each host species (for models with one subtype) and the contribution of each species to reassortment events, i.e., by subtype donation or supplying cells where reassortments occur (for models with multiple subtypes).
- How does the strength of the tradeoff between preference for one receptor and probability of infecting cells with other receptors affect results?

Examining the sensitivity of the above dynamics to herd size and vaccination practices could also yield important insights to disease management. Another trait potentially worth investigating is virulence (Baigent & McCauley 2003).

Methods and work plan

I will first explore predictions for emergence by modeling influenza's ecology without evolution, using ordinary differential equations to represent dynamics on rural farms and markets in south-eastern China. The initial model will consider five host classes: wild waterfowl, domesticated free-roaming ducks, chickens, pigs, and humans. Intraspecific transmission will follow a SIS model for waterfowl, including ducks, and SIRS for other classes. For hosts with permanent immunity to a particular strain, such as humans, the R-to-S transition implicitly approximates antigenic drift as a gradual decay of immunity. The model will include parameters for rates of intraspecific transmission (β_{ii}), birth, death, recovery, decay of immunity; and static host-specific parameters such as innate susceptibility, infectiousness, and disease-induced mortality. The interspecific transmission rate β_{ij} is the number of contacts that an infected individual of species j has with susceptible individuals of species i per unit time, multiplied by the probability that contact results in infection. The probability that contact results in infection depends on receptor compatibility, host-specific susceptibility, host-specific infectiousness, and the mode of transmission. Most of these parameters will be estimated with data from farms and markets in southeastern China and multihost challenge experiments (Alexander et al. 1986; Kida et al. 1994; Alexander 2000; Gambaryan et al. 2002a; Bulaga et al. 2003; Liu et al. 2003b; Cheng

et al. 2004). This model will yield a preliminary measure of outbreak probability (measured by R_0) and forces of infection. These values are given by the dominant eigenvalue and summed rows and columns of the modified “Who Acquires Infection from Whom” transmission matrix (Dieckmann et al. 1990).

To explore the ecological and evolutionary dynamics in tandem, I will develop an individual-based simulation that allows the transmission rates β_{ii} and β_{ij} to change as a function of evolving receptor preference. Preference for a receptor type can be described as a continuous quantitative phenotypic trait with minimal genetic variance, following the hypothesis that viral preference evolves along a “spectrum” of $\alpha_{2,3}$ and $\alpha_{2,6}$ receptor types in hosts (Gambaryan et al. 2002a). Preference for cells with one receptor type necessarily involves a decreased ability to infect cells with other receptor types, thereby constraining trait space and host range. This model will use an exact stochastic approach for the SIR and evolutionary components (Gillespie 1976). The effects of ecological parameters on the frequency and size of outbreaks in different host species will be explored. The individual-based setup of the model may also require extrapolation of results to larger population sizes.

In modeling multiple subtypes, each strain will be described by one of 16 forms of hemagglutinin, one of nine forms of neuraminidase, and its receptor preference. Reassortment events occur stochastically in hosts infected with multiple subtypes. The model will track individual hosts’ immunity to particular hemagglutinin and neuraminidase antigens. Outbreaks occur following appearance of new subtypes (i.e., hemagglutinin-neuraminidase combinations) in a host population, provided R_0 exceeds unity. Particular attention will be paid to the sensitivity of the results to tradeoff strength and rates of reassortment, interspecific contact, and immune decay, which are the least understood aspects of influenza’s ecology and evolution. The model can be extended to consider cross-immunity between subtypes, e.g. H9N2 and H5N1 in poultry.

To the extent feasible and time permitting, I will also explore simplifications of these models. Retaining essential stochastic processes, such as interspecific contact, reassortment, and possibly the evolution of receptor preference, while treating population dynamics deterministically might recover key results of the individual-based, wholly stochastic approach.

Relevance and link to ADN’s research plan

This research addresses central questions in virulence management (Dieckmann et al. 2002), which is one of ADN's research foci.

Expected output and publications

This work is intended for publication as a jointly authored research article in a scientific journal. It will also be included in research presented for my preliminary examinations and dissertation.

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