

Original Contribution

Viral Host Jumps: Moving toward a Predictive Framework

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Abstract: In order to predict pathogen emergence, we must distinguish between emergence phenomena that occur via different processes. Focusing on the appearance of viral pathogens in new host species, I outline a framework that uses specific molecular characteristics to rank virus families by their expected a priori ability to complete each of three steps in the emergence process (encounter, infection, and propagation). I then discuss the degree to which the patterns expected, based solely on molecular-level structural characteristics, agree with observations regarding the ability of animal viruses to infect humans. This approach yields predictions consistent with empirical observations regarding the ability of specific viral families to infect novel host species but highlights the need for consideration of other factors, such as the ecology of host interactions and the determinants of cellular susceptibility and permissivity to specific virus groups, when trying to predict the frequency with which a virus will encounter a novel host species or the probability of propagation within a novel host species once infection has occurred.

Keywords: emerging diseases, emerging viruses, host jumps, zoonoses

CHALLENGE OF EMERGING PATHOGENS

Emerging infectious diseases present challenges to the scientist and layperson alike (Morse, 1993; Burke, 1998; Daszak et al., 2000; Cleaveland et al., 2001; Dobson and Foufopoulos, 2001; Taylor et al., 2001). These infections of wildlife, domestic animals, and humans seem to be increasing and more problematic every year. The cause of the recent increase in scientific and public interest in emerging infections is probably twofold. On the one hand, technological advances in detection methods and in global communications allow us to be increasingly aware of emergence events as they occur (Garnett and Holmes, 1996). Many pathogens, including West Nile virus, monkeypox virus, and H5N1 highly path-

ogenic avian influenza (HPAI) virus have attracted widespread media attention. Online news sources provide gripping, up-to-the-minute accounts of outbreaks occurring in locations that their primary audience may not even be able to identify on a map, such as the multimedia presentations produced by BBC News in 2005 of a Marburg virus outbreak in Angola (Phillips, 2005).

On the other hand, anthropogenic activities have increased the actual frequency of pathogen emergence. Habitat modification brings previously separated populations into contact and disrupts natural mechanisms regulating population dynamics. For example, increases in rodent populations due to clear-cutting of forested areas for the planting of food crops (particularly corn) is thought to have been responsible for outbreaks of several hemorrhagic fever viruses in South America, including Junin and Machupo viruses (Buchmeier et al., 2001). Barriers limiting

pathogen transmission are altered as we change the landscape and increase global transportation, providing unprecedented opportunities for transmission to new populations and species (Schrag and Weiner, 1995; Smith et al., 2007). These changes have implications not only for human health but for wildlife conservation and domestic animal health. Long-distance animal transport, both intentional (for agriculture or the pet trade) and unintentional, facilitates pathogen introduction (Daszak et al., 2001). For example, illegal bird transport is the suspected source of the recent introduction of H5N1 HPAI into a poultry farm in the UK (ProMED-mail, 2007abc), and accidental transportation of mosquitoes aboard aircraft is thought to pose the highest risk for the introduction of West Nile virus into Hawaii and the Galapagos Islands (Kilpatrick et al., 2004, 2006).

Considering the broad public and scientific interest in infectious disease emergence, surprisingly little work has been done to quantitatively describe broad-scale patterns of emergence in light of pathogen characteristics. Much work on emerging infections has focused on specific emergence events, trying to determine when, where, and how a particular pathogen entered a new host population. The emergence of human immunodeficiency virus (HIV), for example, has been well-studied on both ecological and molecular levels. Strong evidence suggests that the bushmeat trade in West Africa has facilitated repeated retrovirus transmission events from wild primates into humans (Wolfe et al., 2004), and independent introductions of HIV-1 subgroups (M, N, O) from chimpanzees (*Pan troglodytes*) and HIV-2 subtypes (A, B) from sooty mangabeys (*Cercocebus atys*) are believed to be responsible for the ongoing HIV/AIDS pandemic (Sharp et al., 2001). In order to predict (rather than reconstruct) pathogen emergence, however, it is necessary to extend the domain of inquiry beyond the focus on a single disease. Specific ecological processes and pathogen characteristics must affect the probability of emergence, and until these factors are recognized we will have little predictive power.

Burke has suggested that the high “evolvability” of RNA viruses facilitates host jumps (Burke, 1998). Such evolvability is derived from a combination of high replication error rates and the ability to reassort and recombine. Although he makes no attempt to quantitatively determine the relative frequency of emergence for different types of pathogens, Burke claims that recent pandemics in humans and wildlife have mostly been caused by RNA viruses, citing multiple examples (influenza A, HIV-1, enteroviruses 70

and 71, human T-cell lymphoma virus, three paramyxoviruses, porcine respiratory coronavirus, and a calicivirus that causes hemorrhagic disease in rabbits). He goes on to predict that future global pandemics will be caused by groups of viruses that have caused major epidemics in humans or animals and that have high intrinsic evolvability; however, this approach does not allow for identification of viral groups with high emergence potential that have not produced large epidemics to date. In particular, if undiscovered virus families exist that have a high potential for emergence—whether in humans or in animals—a priori identification of this potential may facilitate preparedness for and rapid response to emergence events.

A more quantitative approach was taken by three studies published in a special issue of *Philosophical Transactions of the Royal Society of London* in 2001. The first two of these studies (Cleaveland et al., 2001; Taylor et al., 2001) used a broad-scale literature search to construct a database of known infectious diseases of humans and domestic animals and to classify these diseases as emerging or not. The authors were then able to describe general patterns related to emergence status. They found that viruses are significantly more likely to be classified as emerging than are bacteria, fungi, helminths, or protozoa and that the ability to infect multiple host species is a significant risk factor for emergence in humans and domestic livestock. A recent update of the work on human pathogens has confirmed these findings with a larger dataset (Woolhouse and Gowtage-Sequeria, 2005). A similar approach was taken by Dobson and Foufopoulos (2001), who surveyed emerging infectious diseases of wildlife based on ProMED reports over a 2-year period. Emerging pathogens of wildlife were also found to be primarily viral.

The results of these studies suggest that further examination of the molecular characteristics that determine viral emergence will go a long way toward being able to predict pathogen emergence. To develop a predictive framework, however, we must distinguish between the different phenomena that the term “emergence” commonly encompasses. These include the appearance of a pathogen in a new host species (Woolhouse, 2002; Antia et al., 2003; Fenton and Pedersen, 2005; Woolhouse et al., 2005), the appearance of a pathogen in a new population of an established host species (or new geographic region) (Lederberg et al., 1992; Cleaveland et al., 2001; Taylor et al., 2001; Smolinski et al., 2003; Smith et al., 2007), the appearance of an antimicrobial-resistant variant of a pathogen within an established host population (Lederberg

et al., 1992; Smolinski et al., 2003), and a change in the immunological interaction between a pathogen and an established host population (Smolinski et al., 2003). Different mechanisms drive each of these phenomena; therefore, the ability to predict each type of emergence will require different approaches.

I focus on the appearance of viral pathogens in novel host species. I first describe the process by which this type of emergence occurs and then ask the question of whether specific molecular characteristics can be expected a priori to affect the crucial steps in this process. This approach allows for the generation of testable hypotheses regarding the emergence potential of specific viral groups. I outline these hypotheses and then determine whether expectations based on the molecular characteristics discussed correspond to observed broad-scale patterns. Agreement with observed patterns may suggest that the molecular characteristics explored will yield substantial predictive power and a useful framework for ranking virus groups in terms of emergence potential. Inconsistencies between the patterns expected based on molecular characteristics alone and observed patterns highlight specific parts of the emergence process as highly dependent on host–host or host–virus interactions and less dependent on molecular characteristics of the viruses themselves. A glossary is provided to clarify the use of terms that may be unfamiliar to the reader or that are used inconsistently within the current emerging infectious disease literature.

REQUIREMENTS FOR VIRAL HOST JUMPS

A virus is an obligate intracellular parasite that relies on the molecular machinery of its host for reproduction. All viruses comprise genetic material (RNA or DNA) and a protein coat. Virus particles (virions) of many species also contain host-derived lipids and carbohydrates. To reproduce, a virus must encounter a host organism and make its way to the site of replication within a host cell that is both susceptible and permissive. The virus then makes new copies of itself, which requires transcription of the genome to produce mRNA, protein synthesis, genome replication, and packaging. New virions must exit the cell to infect new host cells and, potentially, new host organisms. To persist, emerging viruses must be able to perform all of these steps within their new host species (Webby et al., 2004).

Host jumps, or cross-species transmission events that result in the successful infection of a potential host species,

may encounter barriers at any step in this life-cycle. Molecular characteristics of the virus itself are expected to play a large role in determining both whether a host jump occurs and the probability of transmission between individuals of a new host species. Host jumps will be considered to occur as a three-step process (Woolhouse et al., 2005):

1. encounter between a virion and a potential host species,
2. infection, or replication within an individual of a novel host species, and
3. propagation, or transmission of infection from one individual of the new host species to another.

Encountering a Novel Host Species

The probability that, and frequency with which, a potential new host will encounter a virus circulating in another species may be determined by the nature of interaction between current and potential hosts, by the frequency, duration, and distribution of viral shedding in the current host population, and by the virion's subsequent stability in the environment. Ecological interactions between current and potential host species can be divided into four categories:

1. those involving contact with bodily fluids,
2. those involving direct contact between individuals but not contact with bodily fluid,
3. those involving contact with a shared resource, and
4. those involving spatial overlap.

Interactions involving between-species contact with bodily fluid, such as predation, seem most likely to facilitate host jumps. Slaughter and consumption of bush-meat, for example, is responsible for the transmission of multiple retroviruses from wild primates to humans (Wolfe et al., 2004), lending evidence to the idea that host jumps are likely to occur as the result of trophic interactions. Shared vectors are also known to mediate transmission of viral infections between species, as occurs when Japanese encephalitis virus is transmitted between waterfowl (particularly herons), pigs, and people (Endy and Nisalak, 2002). Because predators have direct contact with their prey, they are likely to be exposed to any infections that their prey harbor, regardless of the site of excretion or transmission route, whereas a shared vector will only facilitate cross-species transmission of pathogens with high viremia.

Frequent direct contact, such as commensal relationships between humans and domestic carnivores, is the

second most likely type of interaction to lead to the encounter of virions shed by other host species. Encounter will be high for infections transmitted via respiratory secretions, urine, feces, or skin lesions (such as an infectious rash). Depending on the nature of the commensal relationship, viral shedding in saliva may also lead to frequent encounter, either directly (as a result of licking or biting) or via a fomite (such as a pet's toy). Virions found exclusively in the semen, milk, and blood, on the other hand, will have a low probability of transmission between commensal species.

Encounter may also occur between species competing for a shared resource. While competition rarely involves direct contact between individuals of different species, dissemination of virus particles through respiratory secretions, urine, or feces may be concentrated around a shared resource. Under these circumstances—as with fomite transmission between commensal species—the stability of the virion in the environment is likely to be important in determining the probability of encounter between an infectious virus particle and a potential host species. Similarly, transmission between species that overlap only in their spatial distribution may occur when virus particles are resistant to degradation but may be less frequent than in the case where current and potential host species compete for a particular resource.

Figure 1 summarizes the expected interaction between the ecological relationships of current and potential host species and the frequency of encounter. Because direct contact with infectious fluids implies encounter, ecological considerations will dominate the encounter process for the majority of source and recipient host pairs. Molecular considerations will be most important when there is no direct contact or shared vector between current and potential hosts. In such cases, the frequency with which a potential new host encounters infectious virus particles will depend on virion stability in the environment. Two main properties of the virion are likely to influence the rate of inactivation: whether the virus particle requires an envelope for entry into the host cell and the arrangement of structural proteins within the virion. Though the relative rates of inactivation of different virus species depend on specific environmental conditions (such as temperature and relative humidity), requiring an envelope for successful cellular infection may generally decrease the ability of a virus to survive outside a host, since the phospholipid membrane will be sensitive to desiccation, ultraviolet radiation, changes in pH, and ozone toxicity (Cox, 1989). Thus, the

ability to enter host cells without an envelope is expected to increase emergence potential. Similarly, isometric and complex structural arrangements contain many contacts between proteins relative to their helical counterparts. These arrangements are therefore more stable against physical damage, reducing the rate of inactivation and increasing expected frequency of encounter.

Infecting a Novel Host Species

Once a virion encounters an individual of a potential host species, the probability it will be able to replicate depends on the specificity of infection and the ability to generate genetic diversity. Viruses preadapted for emergence are likely to enter cells via highly conserved receptors (Woolhouse, 2002), to have generalized immune evasion strategies that modulate the host's innate immune response (Webby et al., 2004), and to have the potential for rapid evolution (Burke, 1997, 1998). Since the receptors that mediate host-cell entry are not generally known, grouping viruses by the level of taxonomic conservation of the receptors required for cell entry remains an important goal for the future. Similarly, while interference with host immunity has been demonstrated for several emerging viruses (Webby et al., 2004), the ability of other viruses to modulate the innate immune response has been largely unexplored.

The site of replication within a cell may also influence infection specificity. Entry into the nucleus provides an additional barrier to successful replication not present for viruses that replicate in the cytoplasm. Replication in the nucleus may therefore increase specificity and decrease potential for infection of novel host species.

Finally, the generation of genetic diversity increases the probability of infecting a potential host species by increasing the genetic state-space covered by the virus population and therefore the chance that some virus particles will successfully infect a novel host and reproduce (Burke, 1998; Webby et al., 2004). Although successful invaders may make up a tiny fraction of the population within the source host species, natural selection will increase the abundance of these variants within an infected individual of the new host species. The ability to generate genetic diversity depends primarily on the replication error rate and the potential for exchange of genomic material between genetically distinct virus particles during cellular coinfection (Burke, 1998).

While many authors (Burke, 1997, 1998; Cleaveland et al., 2001; Woolhouse et al., 2005) suggest that RNA

Respiratory secretions	Dark	Dark	Medium	Medium	Light
Urine/feces	Dark	Dark	Medium	Medium	Light
Skin lesions	Dark	Dark	Medium	Medium	Light
Saliva	Dark	Dark	Medium	Medium	Light
Semen/milk	Light	Light	Light	Light	Light
Blood	Dark	Light	Light	Light	Dark
	Predator	Commensal	Competitor	Cohabitant	Shared vector

Figure 1. The expected interaction between the ecological relationships of current and potential host species and the frequency of viral encounter. The darkest boxes represent interactions where the frequency of encounter is likely to be high, the lightest boxes represent interactions where encounter is expected to occur at very low frequency, and medium boxes represent interactions where the frequency of encounter will be highly dependent on the stability of the infectious virion in the environment, as described in the text. For all ecological relationships between species, the actual frequency of encounter via different transmission routes will depend on the exact nature of the relationship.

viruses are more likely to emerge than DNA viruses because of their high replication error rates, it may be more useful to focus on the primary reason for the difference in error rates: the availability of proofreading mechanisms during genome replication. Although host proofreading mechanisms are used when replication relies on a host-derived polymerase, most viruses that encode their own polymerase (except large DNA viruses; King et al., 1997; Huang et al., 1999; Willer et al., 2001) lack error correction and therefore have relatively high replication error rates.

Additionally, the exchange of genetic material between closely related viruses is facilitated by two processes during cellular coinfection:

1. recombination (exchange of genetic information during replication, usually via template switching), and
2. reassortment (copackaging of genome segments from genetically distinct parent virions).

Packaging multiple genome copies facilitates the recombination process (Lederberg et al., 1992; Burke, 1997); however, additional mechanisms that may promote viral recombination are poorly understood. Reassortment requires only that the viral genome be divided into distinct segments (analogous to eukaryotic chromosomes) and that cellular coinfection occurs in nature.

Propagating within a Novel Host Species

The probability of transmission between individuals of a new host species is of interest in addition to the probability of infection of a novel species (May et al., 2001). Evolutionary potential to increase spread between individuals of the new host, however, should rely on the virus's ability to produce genetic diversity, similar to the ability to infect and reproduce in a new host species (Schrag and Weiner, 1995). As demonstrated by Antia and colleagues, even a small increase in the basic reproductive number of a pathogen within a new host species can substantially increase the probability that the pathogen will eventually evolve the ability to propagate at a sufficient level to produce an epidemic within the new host species (Antia et al., 2003).

Substantial evidence suggests that rapid adaptation of plant and animal populations to a novel environment is more likely to occur through limited gene flow between related (but significantly diverged) populations than through point mutation (Lewontin and Birch, 1966; Reiseberg et al., 2003). If this holds for virus populations, recombination and reassortment may be the primary evolutionary factors permitting adaptation to propagation within a new host species; however, several virus species well known for their ability to propagate within a novel host species demonstrate that

substantial genetic change is not necessary for adaptation to propagation in all cases. SARS coronavirus, for example, appears to have adapted to transmission between humans through a series of point mutations in multiple genes (Holmes, 2005). Several mutations in the receptor-binding domain of the SARS coronavirus glycoprotein that increased binding affinity to human ACE2 (the receptor for entry into the cell) are well documented and appear to have been especially important (The Chinese SARS Molecular Epidemiology Consortium, 2004; Li et al., 2005).

EXPECTED VERSUS OBSERVED PATTERNS

Table 1 groups mammalian virus families according to each of the molecular traits discussed above for which data are available. Mammalian viruses are used for the purposes of illustration because they are particularly well studied and because mammals represent many of the source and recipient host species of primary interest (e.g., humans, domestic livestock, and domestic carnivores). A rough assessment of expected emergence potential is made by assigning scores for encounter, infection, and propagation potential, which are given and described further in Table 2. The score indicates how many traits a virus group possesses that are expected to increase success in that step, based on two standard reference texts (van Regenmortel et al., 2000; Tidona and Darai, 2001). Thus, virus families can be ranked based on molecular characteristics alone in order of the a priori expectation that they will be able to complete a particular emergence step.

Encountering a Novel Host Species

Complex or isometric protein arrangement and the absence of an envelope are expected to increase encounter when there is no direct contact between current and potential host species. Virus families with both of these characteristics provide some examples of host-jumping viruses; however, the absence of these characteristics clearly does not prohibit cross-species virus transmission. The Orthomyxoviridae, Coronaviridae, Filoviridae, Paramyxoviridae, and Rhabdoviridae all have encounter scores of 0/2 but provide a plethora of examples of host-jumping virus species: the influenzaviruses, SARS coronavirus, Ebola and Marburg viruses, Hendra and Nipah viruses, and rabies virus, respectively. Assuming the traits of interest are good indicators of a virion's susceptibility to environmental stresses, stability in the environment does not seem to be a

necessary prerequisite for cross-species transmission, probably because many hosts interact in a way that permit direct viral transmission, as noted earlier.

Infecting a Novel Host Species

In order to assess how well expected patterns of cross-species infection match observed patterns, it is necessary to consider infection within a context where encounter is expected to occur. When we consider the probability that a virus population will be able to reproduce within a potential host that has close contact with a current host, the characteristics in the left-hand columns of Table 1 dominate emergence potential. Reassortment or recombination, low replication fidelity (i.e., lack of proofreading), and the ability to complete replication within the cytoplasm are all expected to increase cross-species infection potential. Using these three criteria to rank mammalian virus families in terms of expected infection potential indicates that three families present the highest risk: Arenaviridae, which comprises multiple viral species transmitted from rodents to commensal humans, including those responsible for Lassa fever and four South American hemorrhagic fevers; Bunyaviridae, which includes the hantaviruses, similarly transmitted from rodents to humans; and Reoviridae, of which 9 of the 18 species that circulate among rodents and livestock are known to infect humans (Tidona and Darai, 2001).

In addition, nearly all high-profile viral zoonoses have at least two of the three characteristics expected to promote infection of a novel host species, including HIV-like viruses (Retroviridae), influenza viruses (Orthomyxoviridae), rabies virus (Rhabdoviridae), Ebola and Marburg viruses (Filoviridae), Hendra and Nipah viruses (Paramyxoviridae), and SARS coronavirus (Coronaviridae) (Tidona and Darai, 2001). One exception is monkeypox virus (Poxviridae), which replicates in the cytoplasm but has high replication fidelity and, according to the simple genome-packaging division used here, little recombination/reassortment potential. It is worth noting that recombination of Poxviridae species has been demonstrated in laboratory experiments (see, for example, Yao and Evans, 2001). Thus, rather than implying that recombination/reassortment potential is not an important contributor to infection of novel host species, this exception may indicate that the simple molecular traits considered here are insufficient to capture the full range of recombination mechanisms available to host-jumping viruses. Of the mammal viruses lacking all three traits associated with infection of a novel host (genome reassortment

Table 1. Mammalian Virus Families Grouped According to Factors that are Expected to be Important Determinants of the Potential for Emergence in a Novel Host Species (Compiled from van Regenmortel et al., 2000; Tidona and Darai, 2001)

Recombination/reassortment potential ^a	Replication fidelity ^b	Site of replication ^c	Envelope ^d	Protein arrangement ^e	Virus family	
Multiple copies, single segment	Viral polymerase, no proofreading	Nucleus	+	Complex	Retroviridae	
Single copy, multiple segments	Viral polymerase, no proofreading	Cytoplasm	-	Isometric	Reoviridae	
			+	Helical	Arenaviridae Bunyaviridae	
Single copy, single segment	Viral polymerase, no proofreading	Nucleus	+	Helical	Orthomyxoviridae	
			-	Isometric	Astroviridae Caliciviridae Picornaviridae	
		Cytoplasm	+	Helical	Rhabdoviridae Coronaviridae Filoviridae Paramyxoviridae	
			-	Isometric	Arteriviridae Flaviviridae Togaviridae	
			+	Isometric	Bornaviridae Hepadnaviridae	
		Nucleus	Viral polymerase, viral proofreading	- ^f	Complex	Poxviridae
				+	Isometric	Asfarviridae ^g
				-	Isometric	Adenoviridae
				+	Isometric	Herpesviridae
				-	Isometric	Circoviridae Papillomaviridae Parvoviridae Polyomaviridae
Single copy, single segment	Host polymerase, host proofreading	Nucleus	-	Isometric		

^aRecombination potential is determined by the number of copies of the genome that are packaged in a virus particle (although other, unknown factors also facilitate recombination); reassortment potential is determined by the number of genome segments (single versus multiple). High recombination or reassortment potential is expected to increase potential for both infection and propagation.

^bReplication fidelity is determined by the origin of the polymerase (host or viral) and the associated proofreading activities. Virus groups that rely on a host polymerase for replication are subject to host proofreading mechanisms and have high replication fidelity. Most virus groups that encode their own polymerase have no proofreading and therefore low replication fidelity; however, polymerases encoded by members of the Poxviridae, Adenoviridae, and Herpesviridae are known to have 3' to 5' exonuclease activity (King et al., 1997; Huang et al., 1999; Willer et al., 2001), which is the primary type of error correction expected to affect viral replication fidelity. Viruses in these groups are therefore expected to have high replication fidelity. Low replication fidelity is expected to promote the generation of genetic diversity and therefore increase potential for infection and propagation.

^cThe site of replication is considered to be the cytoplasm if all steps in the replication cycle take place within the cytoplasm of the infected cell; the site of replication is denoted as the nucleus if any step in the replication cycle (e.g., genome replication or transcription into mRNA) requires nuclear entry. The ability to complete replication within the cytoplasm is expected to increase relative infection potential, as nuclear entry provides an additional barrier to replication.

^dThe presence (+) or absence (-) of a lipid envelope will affect the stability of a virion in the environment.

^eThe arrangement of structural proteins within the virion is denoted as isometric, helical, or complex. Isometric and complex arrangements are more structurally stable than helical ones due to the larger number of protein contacts.

^fVirions of some genera of the Poxviridae are enveloped upon exiting the cell; however, an intact envelope is not required for the virus particle to remain infectious (Tidona and Darai, 2001).

^gThe lone member of the family Asfarviridae, African Swine Fever virus, encodes a viral polymerase responsible for genome replication (Fauquet et al., 2005). No studies were found in Web of Science searches that examined whether the viral polymerase has 3' to 5' exonuclease activity; however, the other families of large DNA viruses do encode polymerases with known proofreading activity (King et al., 1997; Huang et al., 1999; Willer et al., 2001) and it is assumed here that the polymerase encoded by African Swine Fever virus has undocumented exonuclease activity.

Table 2. Encounter, Infection, and Propagation Scores for Mammalian Virus Families, Determined from Table 1

Virus family ^a	Encounter ^b	Infection ^c	Propagation ^d
Reoviridae	2/2	3/3	2/2
Retroviridae	2/2	2/3	2/2
Astroviridae	2/2	2/3	1/2
Caliciviridae	2/2	2/3	1/2
Picornaviridae	2/2	2/3	1/2
Poxviridae	2/2	1/3	0/2
Adenoviridae	2/2	0/3	0/2
Circoviridae	2/2	0/3	0/2
Papillomaviridae	2/2	0/3	0/2
Parvoviridae	2/2	0/3	0/2
Polyomaviridae	2/2	0/3	0/2
Arenaviridae	1/2	3/3	2/2
Bunyaviridae	1/2	3/3	2/2
Arteriviridae	1/2	2/3	1/2
Flaviviridae	1/2	2/3	1/2
Togaviridae	1/2	2/3	1/2
Bornaviridae	1/2	1/3	1/2
Hepadnaviridae	1/2	1/3	1/2
Asfarviridae	1/2	1/3	0/2
Herpesviridae	1/2	0/3	0/2
Orthomyxoviridae	0/2	2/3	2/2
Coronaviridae	0/2	2/3	1/2
Filoviridae	0/2	2/3	1/2
Paramyxoviridae	0/2	2/3	1/2
Rhabdoviridae	0/2	2/3	1/2

^aFamilies are sorted in order of decreasing encounter score, then decreasing infection score, and finally decreasing propagation score.

^bThe encounter score denotes the number of characteristics a group has that are expected to increase exposure frequency when the current and potential hosts have little or no interaction. Characteristics that increase encounter will be those that increase the stability of a virion in the environment: being infectious without a lipid envelope and having an isometric or complex virion.

^cThe infection score denotes the number of characteristics a group has that are expected to increase the ability to infect a novel host species: high recombination/reassortment potential, low replication fidelity, and an ability to complete replication within the cytoplasm.

^dThe propagation score denotes the number of characteristics a group has that are expected to increase propagation: high recombination/reassortment potential and low replication fidelity.

or recombination, error-prone replication, and ability to replicate in the cytoplasm), none is known to infect humans, regardless of close association between humans and the animal host. Though rough, these three criteria appear to yield good predictive power regarding which viruses will be able to infect and replicate within novel host species.

Propagating within a Novel Host Species

Finally, the probability that a viral epidemic will occur via transmission within the new host species is of interest. Table 1 accounts only for the role of generation of genetic

diversity in propagation. Drawing from examples of mammal viruses that jump to humans, it becomes clear that other factors must be important determinants of propagation. While HIV (Retroviridae) and influenza (Orthomyxoviridae) propagate well in human populations, as predicted, members of the Arenaviridae and Bunyaviridae are rarely transmitted from person to person, despite having both characteristics expected to be associated with high chances of propagation.

As with encounter, molecular characteristics of the viruses themselves do not appear to provide an a priori indication of a viral group's ability to propagate within a

novel host species. Host ecology and host–virus interactions rather than general molecular characteristics appear to determine propagation potential.

FURTHER STEPS TOWARD A PREDICTIVE FRAMEWORK

The approach taken so far has shown that the ability to infect a novel host species depends heavily on molecular traits of the virus, independent of host ecology and details of the host–virus interaction; however, the approach has also highlighted the need to understand the ecology of interactions between species when considering expectations of encounter and the ecology of within-species interactions when considering expectations of propagation. Host–virus interactions occurring primarily at the molecular level may also play a large role in determining encounter and propagation, and the next steps in developing a predictive framework will examine these issues more closely.

Encountering a Novel Host: Host Ecology and Host–Virus Interactions

Stability in the environment does not appear to limit the step of pathogen encounter for most host-jumping viruses. This is not surprising in light of the expected roles of host–host and host–virus interactions in determining encounter, which are outlined above and depicted in Figure 1. Determining whether the proposed interactions work as predicted will be extremely difficult. In fact, observation of encounter independent of infection may be impossible, whether in the field, in the laboratory, or using a synthetic database approach. One useful approach may be to look within a particular category of ecological relationships and at potential source–potential recipient host pairs. The relative frequency of different sites of excretion of viruses infecting the source host could then be compared to the relative frequency of different sites of excretion of viruses transmitted from the source host to the recipient host. Databases used for previous analyses of emerging infections in livestock, domestic carnivores, and humans (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse and Gowtage-Sequeria, 2005) could be combined with data on the site of excretion as a first step in quantifying the interactions between ecological relationships, site of viral excretion, and risk of encounter.

While this approach will measure infection rather than addressing encounter directly, infection implies that

encounter and factors that affect infection directly, such as the molecular traits discussed here, can be controlled for in the analysis. Consistent patterns of shedding in the source host across host pairs with a particular type of ecological relationship will indicate that viruses shed through particular sites of excretion are more likely to be encountered than others. As ecological relationships between species change, knowledge of these patterns will provide an indication of the risk of encounter with viral species harbored by a newly contacted host species. In the pet trade, for example, where species that are isolated in nature live in artificial, commensal-like conditions, sometimes at high densities, the expectations laid out in Figure 1 suggest that viruses shed via respiratory secretions, urine, feces, or skin lesions—or those shed in the saliva if animals are kept in close enough quarters for biting to occur—are likely to be transmitted between species. This type of change in ecological relationships was responsible for the emergence of monkeypox virus in the US in 2003, as African rodents were brought into contact with prairie dogs, which then transmitted the virus to humans (Guarner et al., 2004). Practical application of this type of analysis is likely to be case-specific: the approach may be useful when evaluating threats in a specific situation, such as when interested in risks to a particular endangered wildlife species (specific recipient host) or when interested in risks associated with introduction of a particular species of animal into the wildlife pet trade or wild animal markets (specific source host).

Propagating within a Novel Host Species: Host–Virus Interactions

The ability of some pathogens to propagate within novel host species has highlighted both our economic vulnerability to previously unknown pathogens and weaknesses in our current medical and veterinary infrastructure (and in communication between these entities; see Kahn, 2006, for a recent discussion). Much epidemiological theory has been devoted to understanding the effect of within-species host interactions on the invasion and persistence of infectious diseases in novel host populations (Anderson and May, 1991). Understanding molecular-level determinants of propagation potential is also an important goal, however difficult it may be.

Factors determining a virus's ability to propagate appear to depend heavily the distribution of susceptible and permissive cells within the host. Malaysian Nipah virus, for

example, infects lung tissue of domestic pigs, causing severe respiratory symptoms that easily disseminate virus particles (Hooper et al., 2001). Humans living and working near infected pigs can also become infected; however, very few virions are able to replicate in human lung tissue. Instead, virions replicate in cerebral tissue, producing an encephalitis (Hooper et al., 2001). Replication in the brain does not promote propagation, and transmission between humans does not occur. A variant of Nipah virus found in Bangladesh, on the other hand, replicates in human lung tissue, causes respiratory disease, and can propagate within the human population (Hsu et al., 2004). Even differences in tissue tropism within a given organ system may affect propagation potential. One hypothesis as to why H5N1 HPAI has so far failed to produce large chains of human-to-human transmission is that its viral attachment is concentrated in the lower respiratory tract, whereas access to the upper respiratory tract is insufficient to produce large amounts of aerosolized virus (van Riel et al., 2006).

Some ability to generate genetic diversity may be necessary for significant transmission within a novel host species (Antia et al., 2003), as was seen with SARS (Holmes, 2005); however, a more accurate assessment of propagation potential requires a detailed understanding of the determinants of cellular susceptibility and permissivity. Large-scale characterization of receptors used for cellular entry and of the distribution of these receptors within humans, domestic animals, and wildlife could provide an invaluable tool in predicting specific interactions between viruses and potential hosts. While this task may seem daunting, host-jumping viruses often gain cellular entry via membrane proteins conserved between source and recipient host groups (Woolhouse, 2002). Thus, characterization and distribution studies should target potential receptor proteins that are conserved among and between vertebrate lineages to maximize the practical benefit of this type of basic research.

SUMMARY AND CONCLUSIONS

Knowledge of the factors that increase a pathogen's ability to jump to, and propagate in, a new host will be invaluable in the effort to prevent, prepare for, and predict viral threats to human and animal health. We currently have a good general understanding of the three steps required for a host jump to occur: encounter is heavily dependent on ecological relationships between species and often requires

close contact between a recipient host and the site of viral excretion in the source host; infection depends on a viral species' evolutionary potential and the barriers to replication that it must overcome in a new host cell, which in turn are tied to specific, conserved viral molecular characteristics; and propagation may be facilitated by a viral species' evolutionary potential but also relies on conservation of underlying mechanisms of cellular entry and other determinants of tissue tropism.

The next step toward being able to predict viral host jumps between species of interest is to quantify our understanding of the determinants of encounter and infection and thereby develop indicators of risk from a given viral group. Virus groups for which the risk of encounter and infection is substantial, particularly those with inherently high evolvability, should be prioritized for receptor characterization, and those found to rely on broadly-conserved receptors should be considered at high risk for emergence. Researchers interested in characterizing the risk to a particular target species, such as humans, domestic animals, or endangered wildlife, may then be advised to determine the distribution of receptors—and any other determinants of susceptibility and permissivity that can be characterized—within the species of interest.

GLOSSARY

Current/established host. A species supporting active viral infection.

Dissemination. The distribution of infectious virus particles in the environment.

Emergence. The appearance (or reappearance) of an infection in a new host population or species, or a change in interaction between host and pathogen due to pathogen evolution or changes in host immunity. Host jumps (see below) are the primary type of emergence discussed here.

Emergence potential. The probability that a given virus population will be able to infect and reproduce in a potential host species.

Encounter. Contact between an infectious virus particle and a species other than its source host species.

Envelope. The host-derived lipoprotein membrane that surrounds the protein core of some virus particles. Most enveloped virions require an intact membrane for receptor binding and entry into the host cell.

Host jump. A cross-species transmission event that results in the successful infection of the potential host species.

Infection. The entry and replication of a virus particle in an individual, referring here to infection of an individual of a new host species.

New/novel host. A species that has acquired a viral infection as the result of a host jump.

Permissive cell. A cell in which a virus particle can replicate.

Potential host. A species that does not currently support active viral infection.

Propagation. Transmission of an infection between individuals of a single host species, usually referring to transmission within the new host species.

Reassortment. The packaging of genome segments from genetically distinct parent virions in a coinfecting cell.

Receptor. The site on the outer membrane of a cell to which a virion binds for cellular entry.

Recipient host. A host species, or individual of a host species, that has acquired an infection as the result of a host jump.

Recombination. The exchange of genetic information between closely-related virus particles during replication in a coinfecting cell, usually via template switching.

Source host. A current host species, or individual of a current host species, that produces virus particles actually or potentially able to infect a potential host species.

Susceptible cell. A cell that permits viral entry.

Tissue tropism. The affinity of a virus particle for cells of susceptible and permissive tissues.

Zoonosis. An animal infection that can be transmitted to and replicate in humans.

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