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REVIEW ARTICLE

Anticipating the Species Jump: Surveillance for Emerging Viral Threats

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Impacts

- This review examines the future of predictive surveillance for viruses that might jump from animal hosts to infect humans. Canine parvoviruses as well as H3N2 and H1N1 influenza viruses are discussed as exemplars that suggest *what to look for* in anticipating viral species jumps.
- To answer the question of *where to look* for viral species jumps, prospects for discovering emerging viruses among wildlife, bats, rodents, vectors and occupationally exposed humans are discussed.
- The authors identify opportunities and obstacles to predict species jumps using genetic and ecological data as well as suggestions for *how to look* for species jumps.

Keywords:
Species jump; infectious disease surveillance; science policy/biology; host–pathogen interactions; disease reservoirs/virology; predictive virus surveillance

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Summary

Zoonotic disease surveillance is typically triggered after animal pathogens have already infected humans. Are there ways to identify high-risk viruses before they emerge in humans? If so, then how and where can identifications be made and by what methods? These were the fundamental questions driving a workshop to examine the future of predictive surveillance for viruses that might jump from animals to infect humans. Virologists, ecologists and computational biologists from academia, federal government and non-governmental organizations discussed opportunities as well as obstacles to the prediction of species jumps using genetic and ecological data from viruses and their hosts, vectors and reservoirs. This workshop marked an important first step towards envisioning both scientific and organizational frameworks for this future capability. Canine parvoviruses as well as seasonal H3N2 and pandemic H1N1 influenza viruses are discussed as exemplars that suggest *what to look for* in anticipating species jumps. To answer the question of *where to look*, prospects for discovering emerging viruses among wildlife, bats, rodents, arthropod vectors and occupationally exposed humans are discussed. Finally, opportunities and obstacles are identified and accompanied by suggestions for *how to look* for species jumps. Taken together, these findings constitute the beginnings of a conceptual framework for achieving a virus surveillance capability that could predict future species jumps.

Introduction

Most emerging human diseases are zoonoses, which are infections caused by pathogens of animal origin (Taylor et al., 2001). Early detection of potentially high-risk pathogens within animal hosts or vectors could enable mitigation strategies to prevent a species jump to humans, such as avoidance of high-risk areas, prophylactic drug distribution or timely mobilization of surveillance and medical resources to cope with emergent disease. However, our understanding of host–pathogen ecology and evolution is not yet sufficiently robust to allow us to recognize the patterns, processes and mechanisms that predicate species jumps. In the future, persistent surveillance in animals could detect changes in viruses that precede a species jump and allow mitigation or prevention of human infections. The prospects for predicting infectious disease outbreaks have been reviewed and discussed by several authors (Cleaveland et al., 2001; Taylor et al., 2001; Childs, 2004; Wolfe et al., 2005; Holmes and Drummond, 2007; Parrish et al., 2008; Childs and Gordon, 2009; Pulliam and Dushoff, 2009; Pepin et al., 2010). In this review, we outline a conceptual framework for achieving a virus surveillance capability that could predict future species jumps.

There are two distinct phenomena that result in human infection by zoonotic viruses: spillover events and species jumps. During a *spillover event*, humans become infected with zoonotic viruses to which they are susceptible but are rarely exposed and which do not efficiently transmit from human to human. To make a *species jump*, animal viruses undergo genetic changes that render them newly able to spread efficiently among humans. Species-jumping viruses may (or may not) have been able to cause sporadic human infections during spillover events. Conversely, viruses that have spilled over into human populations may subsequently evolve (i.e. jump) to efficiently transmit among human hosts (see Table 1 for historical examples of each).

Most zoonotic surveillance efforts are reactive, collecting incidence data from people who are already sick and seeking animal sources of pathogens that have already spread to humans. By contrast, predictive surveillance efforts aim to identify ecological conditions (e.g. climate, vegetation, land use) that precede animal and human outbreaks and can provide timely warning to human populations (Ostfeld et al., 2005; Anyamba et al., 2009). Both spillover events and species jumps have historically been revealed by public health surveillance. A limited number of surveillance efforts, such as those undertaken by the Global Viral Forecasting Initiative and the EcoHealth Alliance, attempt predictive surveillance for species jumps by seeking underlying ecological drivers. Like the viruses they target, predictive surveillance efforts are emergent, and there are numerous obstacles, both technical and organizational, that challenge their development.

Canine parvoviruses as well as seasonal H3N2 and pandemic H1N1 influenza viruses are discussed below as exemplars that suggest *what to look for* in anticipating species jumps. To answer the question of *where to look*, prospects for discovering emerging viruses among wildlife, bats, rodents, arthropod vectors and occupationally exposed humans are discussed. Finally, opportunities and obstacles are identified and accompanied by suggestions for *how to look* for species jumps. Taken together, these findings constitute the beginnings of a conceptual framework for achieving a virus surveillance capability that could predict future species jumps.

What to Look For: Virus–Host Dynamics

H3N2 evolution

Seasonal H3N2 influenza viruses are capable of evading immune recognition through continual antigenic drift of their surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), complicating long-term control of the disease by vaccination. Despite high mutation rates, the genetic diversity of HA is constrained. This limited diversity is evident in HA phylogeny, which shows high extinction rates that result partly from cross-immunity between similar strains. That is, many HA mutants go extinct because they fail to spread efficiently from host to host because of immunity in previously infected individuals. Several hypotheses have been suggested to explain how competition between closely related strains interacts with other factors to limit the observed diversity of HA and NA. One hypothesis suggests that short-term, strain-transcending immunity may limit the growth and mutation of influenza strains (Ferguson et al., 2003). Another hypothesis is that punctuated antigenic changes in HA may precipitate selective sweeps, allowing sufficiently novel mutants to outcompete related strains of the same subtype (Koelle et al., 2006). This process has been termed 'epochal evolution', as the discovery of new antigenic phenotypes depends on periods of extensive genotypic change with generally minor but occasionally dramatic effects on phenotype.

How are the patterns of seasonal influenza in humans useful to predict species jumps? Understanding the dynamics of influenza in human hosts sheds light on the potential of the human population to be infected by new strains, the probability that a spillover virus can acquire evolutionary adaptations to facilitate spread in humans and the abilities of intermediate hosts (such as chickens and pigs) to generate pandemic viruses. Seasonal influenza creates cycles of higher and lower immunity in

Table 1. Historical examples of spillover events [a] and species jumps [b]

Virus (species name)	Animal hosts*	Date	Location	Reference*
[a] Spillover events				
Marburgvirus (*Lake Victoria marburgvirus*)	Unknown[†]	1967	Marburg and Frankfurt, Germany[‡]	Martini, 1969; Towner et al., 2009
Hantavirus (*Sin Nombre virus*)	Deer mouse	1993	Four Corners area, US	Centers for Disease Control, Prevention., 1993
Monkeypox (*Monkeypox virus*)	Monkey, prairie dog, African rodents, et al.	1970	Liberia, Sierra Leone, Democratic Republic of Congo	Anon. 1971

Human-adapted virus	Animal-derived virus	Animals with confirmed infections*	Date of first detected human outbreak/case	Location	Reference*
[b] Species jumps					
SARS coronavirus	SARS-like coronavirus	Civet, raccoon dog, bat[§]	2003	Multicountry (Viet Nam, China, Singapore, Thailand, Canada)	Anon, 2003, Li et al., 2005; Guan et al., 2003
HIV-1	SIVcpz (simian immunodeficiency virus chimpanzee)	Chimpanzee	Before 1959[¶]	Leopoldville, Belgian Congo (now Kinshasa, Democratic Rep of Congo)	Zhu et al., 1998; Korber et al., 2000; Worobey et al., 2008
Influenza A subtype pdmH1N1	Influenza A subtype H1N1	Pig	2009	Northern Mexico	Anon, 2009

*The distinction between spillover events and species jumps can be blurry. Spillover events are defined here as incidental human outbreaks without sustained human-human transmission; species jumps are driven by genetic changes that enable sustained human-human transmission. Viruses that have spilled over into human populations may subsequently evolve (i.e. jump) to efficiently transmit among human hosts.

[†]Marburg viral RNA and antiviral serum antibodies were detected in Egyptian fruit bats (*Rousettus aegyptiacus*) in Uganda (Towner et al., 2009).

[‡]While these outbreaks occurred in Germany, both were caused by exposure to the same lot of green monkeys (*Chlorocebus* sp, formerly genus *Cercopithecus*) imported from Uganda.

[§]While infected animals have been detected in markets, they have not yet been detected in the wild.

[¶]Two more recent studies have narrowed this estimate to 1915–1941 (Korber et al., 2000) and 1884–1923 (Worobey et al., 2008) using phylogenetic analyses.

humans: epidemics deplete susceptibles, leaving a higher fraction of the population with protective immunity. Some of this immunity has been shown to be cross-protective against viruses of other subtypes (e.g. infection with seasonal influenza can confer partial protection to infection with H5N1). In addition, the diversity of viruses circulating in humans should in theory correlate with the potential for an emerging virus to exchange gene segments with an adapted resident virus, which could increase the emerging virus's rate of transmission. Reassortment events are commonly associated with seasonal influenza and appear to be an integral evolutionary step in pandemics. The generation of pandemic viruses through reassortment depends sensitively on dynamics in the intermediate host population, including the amount of herd immunity in non-human hosts and the dynamics of viral diversity in that host population. Compared to humans, pig populations can contain a much greater diversity of H3N2 viruses, including antigenic variants of H3 HA that have long been extinct in the human population (de Jong et al., 2007), but the rate of viral antigenic evolution in pigs is slower. As with humans, an important question is how host immunity, local climate, viral mutation and birth/death processes affect the observed patterns of influenza diversity. Understanding these basic processes should allow the long-term effects of interventions (e.g. culls, quarantines, antivirals and vaccinations) on viral evolution to be predicted and shed light on which steps (such as key mutations or contact rates between hosts) (Cobey et al., 2010) limit emergence.

H1N1 jump from swine to humans

Data collected from the 2009 H1N1 influenza pandemic may provide new insights into its tropism and virulence mechanisms. Shortly after its detection in humans, the 2009 H1N1 pandemic influenza A virus (A/H1N1pan) was determined by phylogenetic analysis to have arisen from combinations of viruses that previously infected human, swine and avian hosts (Dawood et al., 2009). Subsequent animal studies revealed host-specific differences in virulence among A/H1N1pan strains – that is,

animal species (mice, ferrets, macaques) were affected differently depending upon the strain with which they were infected (Memoli et al., 2009). These pathotype variations suggest that for a given A/H1N1pan strain, different species are more or less susceptible to infection and/or develop different immune responses that diminish or worsen outcomes of infection, leading to species-specific differences in morbidity and mortality. Despite fears, A/H1N1pan has exhibited a global mortality rate of far <1%, compared with an estimated 2.5% for 1918 pandemic influenza A virus (Taubenberger and Morens, 2006; Bautista et al., 2010). Smith et al. (2009), utilizing a Bayesian molecular clock analysis of swine-origin influenza virus (S-OIV) outbreak strains, estimated that the A/H1N1pan common ancestor emerged between August 2008 and January 2009. Additional retrospective analyses may help reveal how sentinel cases during this time frame went unnoticed. The possibility that A/H1N1pan emerged up to 8 months before detection illuminates the uncertainties, opportunities and risks accompanying the current zoonotic viral surveillance vacuum.

Parvovirus jump between cats, dogs and raccoons

Parvoviruses infect several carnivorous species, including domestic dogs and cats as well as wild foxes, mink and raccoons. While those viruses are not infectious to humans, these viruses are known to have made a species jump from cats to dogs and also to raccoons. Their small, single-stranded DNA genomes (comprised of two genes that encode four proteins) and widespread occurrence among domestic and wild carnivores make the parvoviruses particularly useful as models for understanding how species jumps occur.

In the late 1970s, canine parvovirus (strain 2, CPV-2) emerged as a new pathogen infecting dogs and spread globally within the year (Hoelzer and Parrish, 2010). That virus was clearly shown to be a descendant of a cat virus (feline panleukopenia virus, FPV) that jumped from cats to dogs within 5 years prior to its emergence. Since that time, CPV-2 has continued to evolve, and in one of those steps, it re-acquired the ability to infect cats while continuing to evolve within its canine host. Phylogenetic analyses reveal changes in amino acid residues on the surface of the viral capsid proteins. Although those are single-stranded DNA viruses, they show high levels of variation, similar to those seen for RNA viruses. Parrish et al. have shown that many of the genetic differences between CPV and FPV associated with host range variation occur in these capsid protein genes, resulting in a tropism shift that enabled the species jump from cats to dogs. They further characterized the viruses structurally and showed that they differ in their antigenicity and exhibit species-specific differences in attachment to the host cell receptor (transferrin receptor type 1) (Harbison et al., 2009). In case of the FPV-to-CPV jump, genotypic changes (likely about five mutations) gave rise to the changes in the viral capsid that enabled the new virus (CPV-2) to bind to the transferrin receptor in the canine host.

However, further research to elucidate the genotype–phenotype relationships for other viruses must be undertaken to determine how to identify viruses with altered host range properties. As many zoonotic viruses bind to animal host receptors for which orthologous receptors exist in humans, laboratory studies using pseudotyped zoonotic viruses in human cell systems may reveal genotypic and phenotypic changes that enable tropism shifts.

Where to Look: Discovering Spatial Patterns

To develop a predictive capability for detecting species jumps, it is important to consider not only what to look for but also where to look. The preceding section uses specific examples of species-jumping viruses to suggest means by which viruses adapt to new host species. However, in these and other examples, the sources of any viral samples collected for analysis are crucial for detecting informative changes.

Wildlife reservoirs of viruses

Historical reviews (Taylor et al., 2001; Brown et al., 2008a; Jones et al., 2008) of emerging infectious disease (EID) events have shown that (i) most are of zoonotic origin, (ii) among zoonotic EID events, most originated in wildlife and (iii) an estimated 10–40 new human viruses are expected to emerge by 2020. Jones et al. (2008) found that 'Wildlife host species richness [a measure of the geographic distribution of 4219 terrestrial mammalian species] is a significant predictor for the emergence of zoonotic EIDs with a wildlife origin'. When plotted on a global map, the areas at greatest risk for zoonotic pathogen emergence ('hotspots') were the equatorial tropics. (By contrast, the most intensive EID research and surveillance efforts were concentrated in temperate zone countries.) These investigators and others (Kuiken et al., 2005) suggest that surveillance efforts can be rationally focused both geographically and based on income. These data were compiled before the emergence of A/H1N1pan in 2009 in Mexico, but as more geolocated virus sample information becomes available, biogeographic relationships may be revealed and predictors identified.

Zoonotic surveillance efforts focused on hotspots, such as those undertaken by investigators from the U.S. Centers for Disease Control and Prevention (discussed below) and the Global Virus Forecasting Initiative, offer evidence

that such efforts provide information that makes predictive surveillance feasible (Wolfe et al., 2005), including discovery of a novel retrovirus in monkey and human populations (Sintasath et al., 2009; Zheng et al., 2010). The ability to make correlations between homologous viruses transferred between proximal species will be fundamental to predict species jumps.

Bats and rodents

Of the more than four thousand known mammalian species, ~50% are rodents and ~25% are bats. This rich species diversity, plus other ecological traits (high population densities and reproductive rates), suggests that surveillance efforts focused on rodents and bats could offer high value. Rodents are typically small and can be trapped in large numbers for surveillance, and they are easier to handle and less expensive to keep in laboratory settings than large animals. The ability to study viral infections in animal hosts under controlled laboratory conditions is central to understanding virus–host ecology at molecular and organismal levels, including the duration and severity of infection, immune response, tissue tropism and pathology. Laboratory-induced infections can also clarify the species that are true reservoirs among the various susceptible host species.

As with other wildlife, importation of exotic rodents can drive viral emergence. In 2003, a multistate US monkeypox outbreak was driven by exposure to prairie dogs (*Cynomys* spp.), which were infected by exposure to imported Gambian giant rats (*Cricetomys* spp.) (Centers for Disease Control, Prevention., 2003). Also, one human case was acquired from a rabbit that became infected when exposed to a prairie dog in a veterinary setting. In this case, rodents commercially captured in forested areas of southern Ghana were the sources of the US outbreak, and a 2010 study by the US CDC found that 53% of nearby human residents had been previously exposed to orthopox viruses (Reynolds et al., 2010). While the 2003 outbreak was likely a spillover event, surveillance efforts focused on the international rodent pet trade may detect such events and enable genotypic/phenotypic characterization of viruses that jump among rodent species and to humans and pets.

Arthropod vectors

Many viruses are transmitted to animals and humans from arthropod vectors. West Nile, Chikungunya and Yellow Fever viruses are examples of arthropod-borne viruses that have jumped to new mosquito species. In particular, flying insects can greatly expand viral access to bird, wildlife and human hosts. While collecting samples from wildlife is a resource-intensive endeavour, large numbers of known arthropod vectors can be collected at much lower cost, making virus surveillance in arthropods an attractive goal. Furthermore, geographic information system-based maps that layer environmental measurements (temperature, precipitation, land use) and vector/host distribution data can be used to inform rational decisions about when and where surveillance samples should be collected. This approach has been used to correlate environmental factors with competent West Nile virus vectors trapped in urban areas of the north-eastern United States (Brown et al., 2008a,b). Assembling such risk-based maps would concentrate surveillance efforts to maximize impact and minimize cost. While detecting genetic precursors to species jumps in sampled viruses is a long-term goal for which underlying knowledge is lacking, in the short-term, characterizing endemic viruses transmitted by local arthropod vector populations would provide baseline information required for future prediction. Such knowledge can be used to assess risk to human populations and drive mitigation strategies (e.g. vector control strategies).

Occupational infections

There are occupations whose members are frequently (and in some cases continually) exposed to zoonotic viruses, including veterinarians, farmers, ranchers, tanners and food processors. Immunity acquired among members of this 'front line' group, whether through symptomatic or asymptomatic infection, would alter the dynamics of infection and the spread of zoonotic pathogens. Yet, there are surprisingly few studies in the literature reporting the patterns and mechanisms of exposure, including the consequences for immunity among the occupationally exposed.

For example, exposure to swine influenza has caused elevated levels of anti-swine influenza antibody among animal workers. Olsen et al. (2002) found higher seropositivity to swine-adapted influenza viruses among swine farm employees and their families than in people with no swine contact. Myers et al. (2006) found that farm workers, veterinarians and meat-processing workers all had greatly elevated serum antibody levels for swine isolates of H1N1 and H1N2, compared with controls. Extension of serological surveys to other at-risk occupational groups could help define a baseline frequency of spillover by influenza and other zoonotic viruses.

How to Look: Envisioning a Path Forward

The following is a discussion of recurrent issues that present both opportunities and obstacles to achieve a predic-

tive virus surveillance capability, accompanied by suggestions to leverage the opportunities and overcome the obstacles.

Leveraging opportunities

While whole-genome sequence data may be ideal in the long term for maximizing information about emerging or re-emerging viruses, deep sequencing remains a relatively expensive and time-consuming method. This is especially true when considering the large number of samples that sustained surveillance efforts require. Standardized PCR assays are a quicker, less expensive alternative, but primer sets may fail to capture mutant strains or new viruses. MassTag PCR is a relatively quick and inexpensive tool that has successfully identified novel pathogens, including members of the parvovirus (Kapoor et al., 2010), rhinovirus (Lamson et al., 2006) and arenavirus (Paweska et al., 2009) families. The TIGER broadband pathogen detection system was also extremely useful in identifying the A/H1N1pan index case in the United States, which was 'untypeable' human influenza A by standard methods (Metzgar et al., 2010). Whole viral genome sequencing should expand as costs decrease and as host and vector genomes continue to be assembled. Such data should provide insights into the genomic correlates of virus–host dynamics. However, elucidating the mechanisms by which species jumps occur will further require longitudinal studies and collection of genomic data over time. In the short term, increased use of advanced PCR techniques (including MassTag and TIGER) should improve surveillance for zoonotic spillover events. In the long term, an open access repository resource, into which practitioners could deposit viral, vector or host sequence data, could be hosted to facilitate *in silico* longitudinal analyses.

Deriving predictive value from genetic sequences will require elucidation of the complex relationship between genotype, phenotype, pathotype and ecotype (Pepin et al., 2010). Over-reliance on genomic (versus phenotypic) studies will not enable prediction of which viruses will jump to new host species. Even for well-characterized viruses like HIV and influenza, it is currently challenging to determine from sequence information alone whether a given viral strain will be more or less virulent (or able to replicate) in a given host. Understanding the relationship between genotype and phenotype is one of biology's 'grand challenges' – and its elucidation will require a combination of many different and diverse approaches (Pepin et al., 2010).

Overcoming obstacles

The ability to predict species jumps is presently limited by organizational obstacles that hamper needed scientific progress. Prediction requires inputs derived from many disparate bioscience fields (virology, ecology, evolutionary and computational biology, immunology, veterinary science, wildlife biology, etc.) that have little history of collaboration or current impetus to do so. No single field can accomplish the required research, obtain the desired knowledge or develop actionable models on its own. Transdisciplinary collaboration can push experts and funding agencies outside their default zones and create opportunities for progress. However, anecdotal evidence suggests that practitioners in required fields like entomology have steadily declined, while newer fields like modelling and informatics still have too few trainees.

Currently there is no single organization or group whose mission is to achieve a future capability to predict and prevent species jumps. Future prediction capability relies on a foundation of basic science that currently exists only in fragmented programs. At the same time, there is a body of scientific experts interested in elucidating species jumps. New predictive biosurveillance supply/demand architectures could achieve real progress in this area. A transdisciplinary permanent working group could encourage and promote orthogonal approaches to key research questions, including: Can laboratory viral adaptation in animals or cell cultures be used to model species jumps? What evolutionary drivers underlie species jumps by wild-type viruses? What human host factors and polymorphisms ameliorate or exacerbate viral pathology?

'Gap-filling' research will yield synergistic benefits and further progress in diverse fields ranging from vaccine and drug development to microbial forensics to biosecurity policy. For example, holistic study of a simple virus–host system across molecular, genetic, organismal and population levels can yield insights into how viruses overcome barriers across these levels to jump hosts. Canine parvovirus infection of mammalian hosts is a candidate system, with known molecular changes that resulted in tropism shifts, sustained transmissions between animal populations and species jumps.

Furthermore, data from basic laboratory studies can support the discovery, development and testing of computational models that fuse essential biological, ecological and evolutionary phenomena. Multidisciplinary teams should organize to curate data sets, build and validate new models, improve extant models and most importantly, define data requirements for future predictive models that could be used to drive new sample collection requirements and algorithm improvements.

Finally, before species jumps can be predicted, sustained animal surveillance systems must be in place in geographies of potential emergence to support longitudinal studies. This is a challenge in a world where countries lack resources and the mandate and infrastructure for

livestock and wildlife surveillance. To that end, current spillover surveillance efforts could be leveraged. For example, plans could be made to process and share currently collected virus samples with multidisciplinary teams for longitudinal genomic analyses. To conduct predictive surveillance in the long term, practitioners must lay the groundwork for optimizing surveillance efforts in the short term to include laboratory analyses that can detect tropism shifts or other changes that may preclude species jumps.

Conclusion

The species jump mechanisms, processes and dynamics discussed here suggest that distinguishing causal predictive signatures of species jump risk will be challenging. They further suggest that biosurveillance systems tailored to recognize salient changes in viral fitness for alternative hosts could cue early warning of species jumps. The emergence of A/H1N1pan in North America highlights the uncertainties and challenges in predicting whether spillover events can lead to species jumps – yet, understanding the sources of new viruses is critical to understanding how they emerged. The extant zoonotic viral surveillance vacuum (Smith et al., 2009) relegates the power of sequence and phylogeny-based analytics to the reactive realm of outbreak reconstruction. There is an urgent need for pervasive surveillance capability at nodes of disease emergence. This surveillance regime could proactively direct tools for disease characterization, response and mitigation to flash points while localized outbreak control is still possible.

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Conflict of interest

The authors declare no conflicts of interest, financial or personal.

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