Abstract: Emerging viral diseases are often the product of a host shift, where a pathogen jumps from its original host into a novel species. Phylogenetic studies show that host shifts are a frequent event in the evolution of most pathogens, but why pathogens successfully jump between some host species but not others is only just becoming clear. The susceptibility of potential new hosts can vary enormously, with close relatives of the natural host typically being the most susceptible. Often, pathogens must adapt to successfully infect a novel host, for example by evolving to use different cell surface receptors, to escape the immune response, or to ensure they are transmitted by the new host. In viruses there are often limited molecular solutions to achieve this, and the same sequence changes are often seen each time a virus infects a particular host. These changes may come at a cost to other aspects of the pathogen’s fitness, and this may sometimes prevent host shifts from occurring. Here we examine how these evolutionary factors affect patterns of host shifts and disease emergence.

Introduction

Emerging infectious diseases affecting humans, wildlife, and agriculture are often the result of a pathogen jumping from its original host into a novel host species. This can take the form of spillover events that result in dead end infections or short stuttering transmission chains, or a host shift with successful infection and sustained transmission in the new host (Box 1). Host shifts have resulted in multiple human pandemics, such as HIV from chimps [1] and the H1N1 “Spanish flu” from birds [2], which have both killed tens of millions of people. Other important human pathogens have originated from other host species, including Plasmodium falciparum [3], SARS coronavirus [4], Hendra and Nipah viruses [5], and the measles virus [6]. Past host shifts can be detected when the phylogenies of hosts and their pathogens are different (phylogenetic incongruence—Box 1). This is very common, with a survey of the published literature finding 93% of studies comparing host and pathogen phylogenies showed evidence of host shifts [7], and there are relatively few cases where the pathogen phylogeny mirrors that of its host completely [8].

Here we examine the evolutionary factors that affect a pathogen’s ability to infect a novel host and then discuss how the ability of a pathogen to adapt to be transmitted efficiently by a novel host can allow its long-term persistence. Following a host shift, selection will favour mutations that allow a pathogen to (a) enter a host cell with greater efficiency and (b) “fine tune” or optimise their fitness in the new host, for example by better utilising cellular machinery, enhancing immune avoidance, optimising virulence, and maximising transmission potential. Our focus is on viruses, owing to a wealth of recent studies, and because RNA viruses are the most likely group of pathogens to jump between hosts, possibly because of their ability to rapidly adapt to new hosts [9–12]. While we focus on genetics in this review, behaviour and ecological processes are clearly a hugely important factor in determining whether a novel host is exposed to a novel pathogen, and whether onward transmission occurs [10,13–15].

Variation in Susceptibility across the Host Phylogeny

The susceptibility of potential hosts varies enormously, and an important predictor of susceptibility is how closely related a novel host is to a pathogen’s natural host (Figure 1A). This “phylogenetic distance effect” has been repeatedly found using experimental cross infections in all major pathogen groups, including studies of fruit flies and viruses [16], plants and fungi [17,18], beetles and Spiroplasma bacteria [19], insects and Wolbachia [20], and fruit flies and nematodes [21]. This is presumably because close relatives of the natural host offer a similar environment to that which the pathogen is adapted to. This is likely to be especially important for pathogens because of the myriad of molecular interactions pathogens have with their hosts to infect cells, utilise resources, and avoid or suppress the host immune response.

Reconstructions of host shifts in nature have confirmed that pathogens are more likely to shift between closely related species. By reconstructing the phylogeny of rabies viruses isolated from various species of bat in North America, it has been possible to look at the patterns of cross species transmission in the wild. The rate of cross species transmission was greatest for closely related species [22] whether looking at spillover events (recent infections that might not persist long-term) or host shifts that successfully became established [13]. Similarly, viruses and other parasites of mammals are most likely to be shared by more closely related hosts [10,23,24,25,26]. Additionally, the phylogenies of hantaviruses and their rodent and insectivore hosts show evidence for host switching, with data suggestive of preferential shifts between closely related species [27]. However, within these examples there...
are cases of pathogens transferring successfully over great phylogenetic distances [28,29].

Closely related species may also have similar levels of susceptibility, regardless of their distance from the pathogen’s natural host (Figure 1B) [16], which we call the “phylogenetic clade effect.” Such effects could be due to certain host clades having lost or gained immune or cellular components that affect susceptibility to a given pathogen [30]. This may mean that the host phylogeny is a patchwork of clades with varying levels of susceptibility, with clades of susceptible hosts scattered across the tree, sometimes in taxa distantly related to the pathogen’s natural host. This has been demonstrated in experimental cross infections of fruit flies and sigma viruses [16], where after accounting for distance from the viruses’ natural hosts, the effect of the host phylogeny explained almost all of the remaining variation in viral load. If this pattern is common, it may explain cases where viruses and other pathogens recurrently shift between distantly related taxa, such as transmission of influenza viruses among birds, pigs, and humans [2], or human to bovid transmission of Staphylococcus aureus [31], although host ecology likely also plays a role in these instances.

The strength of these effects of the host phylogeny varies between pathogen groups, with RNA viruses and pathogens that already have a broad host range being particularly prone to jumping between distantly related species [10,12,32].

At the molecular level, the availability of suitable cell surface receptors to allow viruses to enter cells may be a cause of phylogenetic effects on host shifts. For example, the ability of an avian influenza virus to infect a host is initially, at least partly, determined by the presence and within-host distribution of α2,3-linked host sialic acid (SA) receptors [33].

The Importance of Viral Entry

Some pathogens may already be pre-adapted to a novel host, but specific mutations are often required to enhance a pathogen’s fitness in the new host if it is to establish successfully. A diversity of traits may change to adapt the pathogen to its new host, such as the efficiency of replication, and avoidance or suppression of host immunity, but the binding of host cell receptors is commonly especially important.

In bacteriophage (viruses of bacteria), mutations that enhance a virus’ ability to bind to host cells are important in determining a virus’ ability to infect a host. One mechanism is spontaneous mutations, which typically change host range by altering amino acid sequences in host-binding proteins, including tail fibres and capsid proteins [34,35]. Similarly, experimentally evolved phage selected to infect previously resistant bacterial genotypes or different bacterial lineages also acquire mutations in genes encoding host-binding proteins [36–38].

In vertebrates, the importance of receptors is supported by an analysis of 64 human viruses, which found that those with the broadest host range used receptors whose amino acid sequences are the most conserved [39]. Furthermore, changes in the ability to bind host cells can also be essential for host shifts by viruses of vertebrates. This is the case for the influenza virus, which binds to sialic acid receptors, of which there are two basic types (SAα-2,3- and SAα-2,6-Gal-terminated saccharides) [33]. Avian influenza viruses bind SAα-2,3 receptors in the respiratory
and gastrointestinal tracts of birds. Conversely, human seasonal influenza viruses predominantly bind to SA\(\alpha\)-2,6 receptors in the upper respiratory tract of humans. However, humans possess SA\(\alpha\)-2,3-sialic acid receptors in the lower respiratory tract. Though it is relatively difficult for influenza viruses to get into and out of the lower respiratory tract, avian influenza viruses do occasionally infect humans. Such infections typically result in severe disease with little or no secondary transmission. Successful adaptation to humans requires mutations to the SA receptor binding site in the hemagglutinin gene that allow the virus to utilise SA\(\alpha\)-2,6 receptors and thus increase the potential for efficient transmission between humans [33]. A related example of the importance of changes in receptor binding is the switch of parvoviruses from cats to dogs, which was due to two mutations in the viral capsid gene that allow it to bind the canine transferrin receptor [40].

### Table 1. Factors that evolutionary theory predicts will affect the likelihood that the correct set of mutations will arise to adapt a pathogen to a new host.

| Trait                        | Factors favouring a host shift                                                                                                                                 |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number of mutations required | The fewer mutations required to adapt to a new host, the more likely it is that they will all occur                                                              |
| Epistasis and mutation order | If mutations have to occur in particular combinations to confer high fitness, then the chances of adaptation may be reduced |
| Mutational target size       | If many different sites in the genome can be mutated to adapt to a new host, then the correct mutations are more likely to occur                                |
| Trade-offs                   | If mutations reduce other components of a pathogen’s fitness, such as replication in alternative hosts, they may be less likely to spread in the pathogen population. |
| Mutation rate                | High per nucleotide mutation rates increase the chance of specific mutations occurring, but can also slow rates of adaptation as many mutations are deleterious   |
| Recombination rate           | Genetic exchange, such as the exchange of plasmids, homologous recombination, and the reassortment of viral genomes, can allow the acquisition of adaptations to new hosts |
| Effective population size \(\left(N_e\right)\) | Natural selection is more effective when the effective population size is large, and large \(N_e\) populations generally have more standing genetic variation, which can accelerate adaptation |
| Generation time              | Short generation times can increase rates of adaptation                                                                                                       |

Such theoretical predictions as listed above have been shown to be important for adaptation per se [87], and these population genetic parameters will also be important in determining the ability of a pathogen to adapt to a novel host. doi:10.1371/journal.ppat.1004395.001

### Figure 2. Examples of parallel adaptations following host shifts.

(A) Parallel genetic changes in five replicate lines of Hibiscus chlorotic ring spot virus. The white boxes represent the viral genome, and the coloured blocks represent mutations. The virus naturally infects Hibiscus plants, but following five passages in an alternate host, *Chenopodium quinoa* the same eight mutations repeatedly occur [57]. (B) Parallel genetic changes in codon 30 of the gag gene (Met to Arg) following three independent transfers of SIVcpz into humans [59]. When a chimp was subsequently infected with HIV-1, the residue reverted back to Met. The coloured blocks represent either a Met (yellow) or Arg (blue) at codon position 30 in the HIV gag gene. (C) Parallel changes in protein function following independent transfers of SIVs from chimpanzees (HIV-1) and sooty mangabeys (HIV-2) into humans. SIV Nef protein does not antagonise tetherin in humans, and so other HIV proteins have evolved the ability to antagonise tetherin [64]. The exception to this is HIV-1 group O viruses, which do not appear to have evolved anti-tetherin activity. In HIV-1 group N viruses the evolution of anti-tetherin activity in Vpu may have come at a cost, as Vpu no longer degrades CD4 receptors to aid the release of viral particles [61]. The coloured gene names in the schematic represent the gene that provides the anti-tetherin function in that host and viral lineage. doi:10.1371/journal.ppat.1004395.g002
Mutating to Adapt to Novel Hosts

If pathogens need to adapt for a host shift to be successful, then the risk of a host shift will depend on the likelihood that the necessary set of mutations can accumulate in the newly infected host (Table 1). If specific new mutations are essential for survival in a novel host, high mutation rates may be especially advantageous [41]. Accordingly, the high mutation rate of RNA viruses may explain why they host shift more frequently than other pathogens [12]. However, most mutations will be deleterious or lethal [42,43], so the chances of a host shift will be maximised at an intermediate mutation rate [41,44] (although it has been shown in a plant virus that the fraction of mutations that are deleterious can be reduced in a novel host [45]). How close the mutation rate of different pathogen groups is to this optimum for host shifting is unclear, so it is uncertain whether high mutation rates can explain why RNA viruses frequently jump between species.

The probability of a host shift will also depend on the number of mutations required to adapt to novel hosts. At one extreme, a single mutation allowed Venezuelan equine encephalitis virus to replicate efficiently in horses when it switched from rodents in the early 1990s [46]. Similarly, single mutations can underlie the expansion of the host range of RNA phages [47]. In contrast, five amino acid changes are predicted to be required for some Avian A/H5N1 influenza viruses to acquire the ability to be transmitted between ferrets [48]. If multiple mutations are required to successfully host shift, their availability can impose a constraint on host range evolution. This is illustrated by experiments on a DNA phage of Pseudomonas fluorescens [36]. The phage rapidly evolved to infect certain host genotypes but never adapted to others. The successful shifts were associated with one to three mutations in genes affecting host binding, whilst more mutations were required to infect the other hosts (these could be acquired through a process of coevolution; see below).

If multiple mutations are required, then the number of ways that the mutations might be fixed is important; are mutations adaptive in all genetic backgrounds, or does fitness epistasis require that they fix simultaneously or in a particular order? There

Figure 3. Examples of how patterns of host shifts can affect the distribution of pathogens across the host phylogeny. Each column shows the presence of a different pathogen, with a coloured circle representing the presence of that pathogen. In panel A, pathogens preferentially shift between closely related hosts, while in B closely related host species have similar levels of susceptibility to infection, regardless of the source of the pathogen (with two increases in host resistance occurring at the asterisks on the host phylogeny). Both processes result in closely related host species harbouring similar pathogens, and in some host clades harbouring more pathogen species. However, in A, but not B, host species with more close relatives tend to have more pathogens. For example, the phylogenetically isolated species at the bottom of the tree is not infected by any of the three pathogens in A, but is in B.

doi:10.1371/journal.ppat.1004395.g003
shifted phages back onto the ancestral host and observe reversion experiments that “rewind the evolutionary tape” by adapting host-phage, where host adaptation can be highly parallel, such that the host shifts by reducing the supply of adaptive mutations. This may act as a significant constraint on (i.e., the more parallel changes observed, the smaller the may be limited molecular solutions to infecting a new host species [35]. A number of other studies in plants have found parallel mutations occurring, often after only a few passages on the novel host [54–57]. Experimental studies finding parallel mutations often enforce transmission and so bypass the critical barrier of successful transmission in the new host. Therefore, looking at the mutations that occur in chains of natural transmission is an important future direction, as, for example, the size of the mutational target may be different for cell entry compared to transmission [56].

Host shifts into humans have also involved parallel mutations (Figure 2B). In HIV-1, codon 30 of the gag gene has independently undergone the same change in all three human lineages of the virus that transferred from chimps [1]. This change increases viral replication rate in human cells [59], and when a chimp was infected with HIV-1 it reverted to the residue seen in SIVcpz [59]. Similarly, five parallel mutations have been observed in two independent epidemics of SARs coronavirus following the shift from palm civets to humans [60].

Parallel phenotypic changes may sometimes have different solutions at the molecular level. This has occurred in different HIV lineages that shifted into humans from other primates (Figure 2C). HIV-1 group M, which is responsible for the global pandemic, arose following a host shift by the chimpanzee virus SIVcpz [1]. In both human and chimpanzee cells a restriction factor called tetherin can prevent the release of viral particles from infected cells [61]. In chimps, the SIVcpz protein Nef has anti-tetherin activity, but this is ineffective in humans due to a deletion in the cytoplasmic tail of tetherin that is targeted by Nef. Instead, in HIV-1 group M, the Vpu protein has evolved to perform the same function [61]. This was paralleled in HIV-2, which originates from sooty mangabeys (Figure 2C). The sooty mangabey virus also uses Nef as a tetherin antagonist and again this is ineffective in humans, but in this case the function has been acquired by the Env protein [HIV-2 lacks the Vpu protein] [61].

In cases where mutational targets are small and multiple mutations are required, several factors may help overcome mutational constraint and allow host shifts to occur. For example, the ability of avian influenza to establish infections in the eyes and lower respiratory tract of humans [33] may give time and sufficient population size for the mutations that facilitate efficient human-to-human transmission to arise. In laboratory studies of interactions between DNA phage and bacteria, it has been found that reciprocal coevolution allows phage to build up broad host ranges through the stepwise accumulation of multiple mutations in genes associated with host binding [36]. Additionally pathogens may circulate in host populations at low levels before becoming a detectable outbreak, and this may provide time for the pathogen to evolve adaptations to optimise its fitness in the novel host [62].

have been several outbreaks of Chikungunya virus linked to the virus shifting from being predominantly vectored by the mosquito Aedes aegypti to Aedes albopictus. A single amino acid change adapts the virus to the new vector [49], but despite A. albopictus being common in Asia, this mutation did not occur for 60 years, and when it did, it was in a Chikungunya virus lineage of African origin. Here, the host shift mutation had no effect in the genetic background of the Asian strains, due to an epistatic interaction with a single amino acid difference elsewhere in the genome [49].

The likelihood that the mutations required to adapt to a novel host will occur also depend on the size of the mutational target in the pathogen—the number of different potential changes in the pathogen genome that adapt it to the new host. In some viruses it is common to see the same parallel mutations occurring each time a virus adapts to a particular host species [50,51], suggesting there may be limited molecular solutions to infecting a new host species (i.e., the more parallel changes observed, the smaller the mutational target). This may act as a significant constraint on host shifts by reducing the supply of adaptive mutations.

The size of the mutational target has been most studied in phage, where host adaptation can be highly parallel, such that the same mutations become fixed in independent replicate populations [51,52]. The importance of these mutations is illustrated by experiments that “rewind the evolutionary tape” by adapting host-shifted phages back onto the ancestral host and observe reversion mutations restoring the sequence back to the ancestral state [38]. When 40 host range mutants of ph16 phage were isolated, it was found that there were 17 unique mutations underlying this shift [35]. Furthermore, it was estimated that 56 different mutations in the phage genome have the potential to adapt it to the novel host [35]. Therefore, despite some parallelism, in this case the size of the mutational target is significant, but the possible number of combinations is large, so genetic constraints on this host shift are relatively weak.

Parallel evolution at the molecular level is also common in experiments using viruses of eukaryotes (Figure 2A). When vesicular stomatitis virus is evolved in human or dog cells, parallel mutations tend to occur within the same cell type [50]. Similarly in plants, experimental evolution of Tobacco etch potyvirus on four host species found that parallel mutations only occurred when viruses were passaged in the same host species [33]. A number of other studies have found parallel mutations occurring, often after only a few passages on the novel host [54–57]. Experimental studies finding parallel mutations often enforce transmission and so bypass the critical barrier of successful transmission in the new host. Therefore, looking at the mutations that occur in chains of natural transmission is an important future direction, as, for example, the size of the mutational target may be different for cell entry compared to transmission [56].

Host shifts into humans have also involved parallel mutations (Figure 2B). In HIV-1, codon 30 of the gag gene has independently undergone the same change in all three human lineages of the virus that transferred from chimps [1]. This change increases viral replication rate in human cells [59], and when a chimp was infected with HIV-1 it reverted to the residue seen in SIVcpz [59]. Similarly, five parallel mutations have been observed in two independent epidemics of SARs coronavirus following the shift from palm civets to humans [60].

Parallel phenotypic changes may sometimes have different solutions at the molecular level. This has occurred in different HIV lineages that shifted into humans from other primates (Figure 2C). HIV-1 group M, which is responsible for the global pandemic, arose following a host shift by the chimpanzee virus SIVcpz [1]. In both human and chimpanzee cells a restriction factor called tetherin can prevent the release of viral particles from infected cells [61]. In chimps, the SIVcpz protein Nef has anti-tetherin activity, but this is ineffective in humans due to a deletion in the cytoplasmic tail of tetherin that is targeted by Nef. Instead, in HIV-1 group M, the Vpu protein has evolved to perform the same function [61]. This was paralleled in HIV-2, which originates from sooty mangabeys (Figure 2C). The sooty mangabey virus also uses Nef as a tetherin antagonist and again this is ineffective in humans, but in this case the function has been acquired by the Env protein [HIV-2 lacks the Vpu protein] [61].

In cases where mutational targets are small and multiple mutations are required, several factors may help overcome mutational constraint and allow host shifts to occur. For example, the ability of avian influenza to establish infections in the eyes and lower respiratory tract of humans [33] may give time and sufficient population size for the mutations that facilitate efficient human-to-human transmission to arise. In laboratory studies of interactions between DNA phage and bacteria, it has been found that reciprocal coevolution allows phage to build up broad host ranges through the stepwise accumulation of multiple mutations in genes associated with host binding [36]. Additionally pathogens may circulate in host populations at low levels before becoming a detectable outbreak, and this may provide time for the pathogen to evolve adaptations to optimise its fitness in the novel host [62].
Trade-offs

Adapting to a new host may have deleterious effects on other pathogen traits, and such trade-offs may reduce the chances of a host shift occurring. A possible example of this is seen in the shift of HIV-1 from chimpanzees to humans. HIV-1 group M and HIV-1 group N have independently shifted from chimpanzees to humans [1], and in both cases the Vpu protein has evolved to antagonise the restriction factor tetherin (see above). Vpu also binds and degrades CD4 receptors in SIV to aid the release of viral particles [63], but this function has been lost in group N viruses, possibly as a pleiotropic consequence of the protein gaining anti-tetherin activity [64]. It has been speculated that this may explain why HIV group N has remained a rare pathogen in Africa, while HIV group M—where the ability to degrade CD4 was retained—has become a pandemic [64].

A common trade-off of adapting to novel hosts is that performance on the original host is reduced. For example, host range mutations in the P5 protein of the RNA phage phi6 generally reduce growth on the ancestral host, although rare, cost-free mutations do exist [35,65]. Observations of similar effects in other phage suggest that this may be a general property of phage host range expansion [38,66]. Similar patterns have been observed following virus adaptation to different cell culture types [67,68], plant species [54,55], and animal species [69]. For example, in a host switch of parvoviruses from cats to dogs, the virus responsible for the initial outbreak in dogs (CPV-2) lost the ability to infect cats, although this was later regained [40].

Once a pathogen has infected a new host, the long-term success of the host shift can be independent of reduced performance in the original host if the pathogen does not require transmission to and from the original host for survival. However, trade-offs between performance in the two hosts can prevent adaptation to a new host if the pathogen is transmitted back to the original host at a high rate. For example, a vector borne pathogen may be unlikely to shift from a common mosquito species to a rare one as it will normally end up back in the original mosquito vector. In contrast, directly transmitted pathogens like influenza may be able to establish a continuous transmission chain in the new host, so reduced performance on the original host is not important.

Another important trade-off in the novel host may be between virulence (the harm a pathogen does to a host) and the transmission potential of the pathogen. A number of theoretical and empirical studies have demonstrated that an intermediate level of virulence is often optimal to maximise transmission [70–74]. However, following a host shift, a pathogen may produce maladaptive levels of virulence as the novel host-parasite association has not been under direct selection. For example, when the myxoma virus from South American Sylvilagus rabbits was transferred to European rabbits (Oryctolagus cuniculus), initial case mortality rates were as high as 99.8% in Australia. The rapid mortality is thought to have reduced the window of time that rabbits were able to transmit the virus, and as a consequence virulence rapidly dropped to case mortality rates of ~90% due to the spread of attenuated virus strains [75,76]. There appear to be large mutational targets to evolve changes in virulence in the myxoma virus (a DNA virus with a large 162 kb genome), with no mutations common to specific virulence grades [77]. Failure to evolve lower levels of virulence may explain the stuttering chains of transmission seen in some spillover events [78,79]; however, it is difficult to disentangle whether the low rates of transmission are due to maladaptive levels of virulence or from human intervention.

Perspectives

One aim of studying host shifts is to predict future disease emergence, but it is unclear whether this will ever be possible with an accuracy that makes it practically useful [80]. While we have rules of thumb as to which groups of pathogens are most likely to host shift, and which donor species they are likely to come from [32], there will always be exceptions. This means that predicting disease emergence by fine scale surveillance of potential donor species and the individuals they are most likely to infect is a hugely difficult task [81]. The observation that specific mutations are often required in host shifts has led to studies looking at whether these mutations can be predicted in advance. For H5N1 avian influenza viruses, mammalian transmissible forms have been evolved in laboratory settings, and identified mutations may be markers for potential epidemics [82–84]. However, even in this exceptionally well-studied case, predictive power remains low and highly system specific.

While we increasingly understand the genetic details that underlie host shifts, there are still important questions unanswered. The literature is overwhelmingly skewed towards viruses, but do bacterial and eukaryotic parasites have similar properties? Under what conditions do trade-offs between performance on the original and new host prevent host shifts from happening? Do the mutations involved in host shifts originate as de novo mutations in the new host or come from standing variation in the original host? What determines the size of the mutational target, and does this depend on what the barrier to a host shift is? For example, mutational targets seem to be small for relatively simple traits like changes in receptor use, but may be larger for complex traits like virulence and transmissibility.

One little-explored consequence of host shifts is how they affect the distribution of pathogens across host species [85]. The number and type of pathogens infecting a host is partly a result of past “acquisitions” following host shifts (Box 2), and new theory is showing how our understanding of host shifts can allow us to understand the composition of pathogen communities [24,86], but these ideas remain largely untested.

Finding tractable methods to monitor emerging diseases presents a significant challenge for the future. Studying the genetics of host shifts has the potential to uncover the evolutionary processes that pathogens undergo when they find themselves in a novel host, and may allow us to begin to address this challenge.

Acknowledgments

Thanks to three anonymous reviewers for useful comments that improved the manuscript.

References

1. Sharp PM, Hahn BH (2010) The evolution of HIV-1 and the origin of AIDS. Philos Trans R Soc Lond B Biol Sci 365: 2407–2419.
2. Webby RJ, Webster RG (2001) Emergence of influenza A viruses. Philos Trans R Soc Lond B Biol Sci 356: 1817–1828.
3. Liu WM, Li YY, Learn GH, Rudicell RS, Robertson JD, et al. (2010) Origin of the human malaria parasite Plasmodium falciparum in gorillas. Nature 467: 420–426.
4. Li WD, Shi ZL, Yu M, Ren WZ, Smith C, et al. (2005) Bats are natural reservoirs of SARS-like coronaviruses. Science 310: 676–679.
5. Chua KB, Bellini WJ, Rota PA, Harcourt BH, Tamain A, et al. (2000) Nipah virus: a recently emergent deadly paramyxovirus. Science 288: 1432–1435.
6. Funse Y, Suzuki A, Oshitani H (2010) Origin of measles virus: divergence from rinderpest virus between the 11th and 12th centuries. Virol J 7: 52.
33. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, et al. (2006) Avian flu: Novel swine-origin 2009 A(H1N1) influenza virus causes mild illness among jet passengers. Proc Natl Acad Sci U S A 103: 1165-1168.

31. Weinert LA, Welch JJ, Suchard MA, Lemey P, Rambaut A, et al. (2012) Evolutionary history of pandemic influenza A/H1N1 in 2009. Proc Natl Acad Sci U S A 109: 12324.

30. Salazar-Jaramillo L, Paspati A, van de Zande L, Vermeulen CJ, Schwander T, et al. (2014) Evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

28. Li JL, Cornman RS, Evans JD, Pettis JS, Zhao Y, et al. (2014) Systemic spread of avian influenza virus in ferrets: Evidence for host adaptation. PLoS Pathog 10: e1004395.

27. Ramsden C, Holmes EC, Charleston MA (2009) Hantavirus evolution in relation to its rodent and insectivore hosts: no evidence for codivergence. Mol Phylogenet Evol 50: 174–187.

26. Hadfield JD, Krasnov BR, Poulin R, Nakagawa S (2014) A Tale of Two landscapes. Proc Natl Acad Sci U S A 111: 6970–6975.

25. Huang S, Bininda-Emonds ORP, Stephens PR, Gittleman JL, Altizer S (2013) Exceptional convergent evolution in a virus. PLoS Pathog 9: e1003260.

24. Waxman D, Weinert LA, Welch JJ (2014) Inferring host range dynamics from phylogenetic patterns in viral diversity and epidemiology of species jumps. Trends Ecol Evol 29: 1297–1298.

23. Cooper N, Griffin R, Franz M, Omotayo M, Nunn CL, et al. (2012) Phylogenetic landscapes: Comparative Analyses of Ecological Interactions. Am Nat 183: 65–74.

21. Perlman SJ, Jaenike J (2003) Infection success in novel hosts: An experimental epidemiology of species jumps by Staphylococcus aureus reduces HIV-1 infectivity by blocking Env incorporation in a Nef- and Vpu-dependent manner. J Virol 78: 7834–7840.

19. Tinsley MC, Majerus MEN (2007) Small steps or giant leaps for male-killers? Evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

17. de Vienne DM, Refregier G, Lopez-Villavicencio M, Tellier A, Hood ME, et al. (2012) Emergence of Generalist Pathogens. Am Nat 177: 44–53.

16. Pedersen AB, Davies TJ (2009) Cross-species pathogen transmission and disease emergence in primates. Ecol Lett 6: 496–508.

15. Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, et al. (2010) Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature 468: 647–652.

14. Longobd H, Hadfield JD, Webster CL, Obbard DJ, Jiggins FM (2011) Host phylogeny constrains viral persistence and replication in novel hosts. PLoS Pathog 7: e1002290.

13. Faria NR, Suchard MA, Rambaut A, Streicker DG, Lemey P (2013) Molecular dating of human-to-bovid host jumps by Staphylococcus aureus reduces HIV-1 infectivity by blocking Env incorporation in a Nef- and Vpu-dependent manner. J Virol 78: 7834–7840.

12. de Vienne DM, Hadfield ME, Giraud T (2009) Phylogenetic determinants of potential host shifts in fungal pathogens. J Ecol 22: 2532–2541.

11. Taylor LH, Latham SM, Woolhouse ME (2001) Risk factors for human disease emergence. Philos Trans R Soc Lond B Biol Sci 356: 991–999.

10. Davies TJ, Dobson AB (2008) Phylogeny and geographic prediction pathogen community similarity in wild primates and human. Proc Biol Sci 275: 1495–1701.

9. Cleaveland S, Laurenson MK, Taylor LH (2001) Diseases of humans and their domestic animals: pathogen characteristics, host range and the risk of emergence. Philos Trans R Soc Lond B Biol Sci 356: 991–999.

8. Sharp PM, Simmonds P (2011) Evaluating the evidence for virus/host co-adaptation.Curr Opin Virol 1: 346–441.

7. de Vienne DM, Hadfield ME, Giraud T (2009) Phylogenetic determinants of potential host shifts in fungal pathogens. J Ecol 22: 2532–2541.

6. Ramsden C, Holmes EC, Charleston MA (2009) Hantavirus evolution in relation to its rodent and insectivore hosts: no evidence for codivergence. Mol Phylogenet Evol: 6: 273–289.

5. Wallis CM, Stone AL, Sherman DJ, Damsteegt VD, Gildow FE, et al. (2007) Tracking the evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

4. Wallis CM, Stone AL, Sherman DJ, Damsteegt VD, Gildow FE, et al. (2007) Tracking the evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

3. Wallis CM, Stone AL, Sherman DJ, Damsteegt VD, Gildow FE, et al. (2007) Tracking the evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

2. Wallis CM, Stone AL, Sherman DJ, Damsteegt VD, Gildow FE, et al. (2007) Tracking the evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.

1. Wallis CM, Stone AL, Sherman DJ, Damsteegt VD, Gildow FE, et al. (2007) Tracking the evolution of a cellular immune response in Drosophila: a multihost experimental evolution of Rabies Virus in Bats. Science 329: 676–679.
71. Jensen KH, Little TJ, Sloopy A, Ebert D (2006) Empirical support for optimal virulence in a castrating parasite. PLoS Biol 4: e197.

72. Ebert D, Bull JJ (2008) The evolution and expression of virulence. In: Stearns SC, Koella JC, editors. Evolution in Health and Disease. 2nd ed. Oxford: Oxford University Press. pp. 153–167.

73. de Roode JC, Yates AJ, Alitzer S (2008) Virulence-transmission trade-offs and population divergence in virulence in a naturally occurring butterfly parasite. Proc Natl Acad Sci U S A 105: 7489–7494.

74. Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP (2007) Variation in HIV-1 set-point viral load: Epidemiological analysis and an evolutionary hypothesis. Proc Natl Acad Sci U S A 104: 17441–17446.

75. Kerr PJ (2012) Myxomatosis in Australia and Europe: a model for emerging infectious diseases. Antiviral Res 93: 387–415.

76. Fenner F, Ratcliffe FN (1965) Myxomatosis. Cambridge: Cambridge University press.

77. Kerr PJ, Ghedin E, DePasse JV, Fitch A, Cattadori IM, et al. (2012) Evolutionary history and attenuation of myxoma virus on two continents. PLoS Pathog 8: e1002950.

78. Lo MK, Lowe L, Hummel KB, Sazzad HM, Garley ES, et al. (2012) Characterization of Nipah virus from outbreaks in Bangladesh, 2008–2010. Emerg Infect Dis 18: 248–255.

79. Leroy EM, Rouquet P, Formenty P, Souquiere S, Kilbourne A, et al. (2004) Multiple Ebola virus transmission events and rapid decline of central African wildlife. Science 303: 387–390.

80. Holmes EC (2013) What can we predict about viral evolution and emergence? Curr Opin Virol 3: 100–104.

81. Wolfe ND, Dunavan CP, Diamond J (2007) Origins of major human infectious diseases. Nature 447: 279–283.

82. Imai M, Watanabe T, Hatta M, Das SC, Otsuka M, et al. (2012) Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature 486: 420–426.

83. Herfst S, Schrauwen EJA, Limster M, Chatzinikola S, de Wit E, et al. (2012) Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets. Science 336: 1534–1541.

84. Russell CA, Fonville JM, Brown AE, Burke DF, Smith DL, et al. (2012) The potential for respiratory droplet-transmissible A/H5N1 influenza virus to evolve in a mammalian host. Science 336: 1541–1547.

85. Engelstadter J, Hurst GD (2006) The dynamics of parasite incidence across host species. Evol Ecol 20: 603–616.

86. Cuthill IH, Charleston MA (2013) A Simple Model Explains the Dynamics of Preferential Host Switching among Mammal RNA Viruses. Evolution 67: 980–990.

87. Smith JM (1976) What determines the rate of evolution? Am Nat 110: 331–338.

88. MacArthur RH, Wilson EO (1967) The theory of island biogeography. Princeton: Princeton University Press.

89. Joy JB, Crespi BJ (2012) Island phytophagy: explaining the remarkable diversity of plant-feeding insects. Proc Biol Sci 279: 3250–3255.