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Effects of life history and ecology on virus evolutionary potential

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ABSTRACT

The life history traits of viruses pose many consequences for viral population structure. In turn, population structure may influence the evolutionary trajectory of a virus. Here we review factors that affect the evolutionary potential of viruses, including rates of mutation and recombination, bottlenecks, selection pressure, and ecological factors such as the requirement for hosts and vectors. Mutation, while supplying a pool of raw genetic material, also results in the generation of numerous unfit mutants. The infection of multiple host species may expand a virus' ecological niche, although it may come at a cost to genetic diversity. Vector-borne viruses often experience a diminished frequency of positive selection and exhibit little diversity, and resistance against vector-borne viruses may thus be more durable than against non-vectored viruses. Evidence indicates that adaptation to a vector is more evolutionarily difficult than adaptation to a host. Overall, a better understanding of how various factors influence viral dynamics in both plant and animal pathosystems will lead to more effective anti-viral treatments and countermeasures.

1. Introduction

Viruses face environmental and ecological challenges related to replication in hosts and transmission between hosts. Successful viral pathogens must be able to evade the host immune response, replicate effectively, and transmit progeny to novel hosts without the benefit of any complex cellular machinery. Viruses reproduce asexually and although recombination, present in viruses as in cellular organisms, is a driver of genetic diversity, mutation is thought to play a greater role in generating diversity in viruses than in cellular life (Lynch, 2010). Additionally, many viruses rely on vector species, often arthropods, to find and colonize new hosts.

Viruses display a diversity of life histories, from the way they are transmitted (vector-borne, direct), the molecules that store genetic information (RNA, DNA), and the type of host (animal, plant, bacteria). Each trait has benefits and constraints that manifest in the structure and evolutionary potential of the virus. Studies have explored 'evolutionary potential' of pathogens (Geoghegan et al., 2016; McDonald and Linde, 2002; Obbard and Dudas, 2014), a phrase often used to describe the ability of an organism to adapt to new environments. Evolutionary potential can also be placed in the context of the Red Queen Hypothesis (Van Valen, 1973, 1974), whereby species must constantly evolve to avoid extinction in shifting environments. Viral life history traits can affect evolution by altering both population structure and adaptive potential.

In this review, we outline the various ways in which virus life history traits and ecology affect population dynamics and evolutionary potential. We examine traits including mutation and recombination rates, bottlenecks, selection pressure, host range, and transmission mode. Upon considering these processes, we suggest that virus management will be improved through a deeper understanding of the links between virus life history, population dynamics, and evolution.

2. Sources of viral diversity

2.1. High mutation rates create both evolutionary opportunity and constraint

Compared to cellular organisms, viruses possess high mutation rates. Mutation rates are expressed as the probability of mutation in a single base per replicative event, μ. Multiplying μ by the size of the genome gives the per-genome mutation rate, U. For multicellular eukaryotes, values for μ typically range from 10^{-8} to 10^{-11}, and U from 0.2 to 1, although values of U as high as 3 have been reported for some human populations (Nishant et al., 2009). Values of μ are similar for bacteria, but values for U are much smaller due to their smaller genomes, ranging from 0.002 to 0.005 (Barrick and Lenski, 2013). In viruses, however, mutation rates often range from 10^{-4} to 10^{-6}, with

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Table 1
Average number of individuals initiating infections from viruses exhibiting different structures and life histories.

Virus (Reference)	Avg # of individuals initiating infection	Persistence in vector	Structure	Genome segmentation	Inoculation
Cauliflower mosaic virus (Monsion et al., 2008)	300	Non-persistent	dsDNA	Monopartite	Mechanical
Potato virus Y (Moury et al., 2007)	0.5 to 3.2	Persistent	ssRNA	Monopartite	Vector
Cucumber mosaic virus (Betancourt et al., 2008)	1 to 2	Non-persistent	ssRNA	Tripartite	Vector

associated U values $> = 1$ (Peck and Lauring, 2018; Sanjuán et al., 2010).

Viral mutation rates are strongly correlated with the nucleic acid backbone. The Baltimore classification (Baltimore, 1971) separates viruses into 7 groups based on molecular structure and provides an effective tool for deducing viral mutation rates (Table 1). Because DNA-dependent polymerases are less error-prone than RNA-dependent polymerases (Flint et al., 2009), DNA-based viruses mutate much slower, on the order of 10^{-6} to 10^{-8} mutations per base per replication (Sanjuán et al., 2010). Additionally, single-stranded viral pathogens mutate faster than double-stranded viral pathogens (dsDNA; Duffy et al., 2008). Retroviruses, which are RNA-based and encode intermediate DNA for incorporation into the host's genome, were initially thought to have lower mutation rates than other RNA viruses (Drake et al., 1998; Mansky, 1998). However, recent evidence suggests that mutation rates are not significantly different among RNA viruses, regardless of whether or not they produce DNA intermediates (Sanjuán et al., 2010).

The adaptive value of high mutation rates has been debated. In static environments, adapted pathogens will possess traits for high fitness, and mutations are generally deleterious (Hughes and Hughes, 2007; Sasaki and Nowak, 2003). Conversely, fluctuating environments, such as an immune system that adapts to destroy a pathogen, may favor more mutationally-active pathogens (Kamp et al., 2002; Wichman et al., 2005). Consequently, high mutation rates, typical of viruses, may be a function of the dynamic environments they persist in. Indeed, studies have revealed dramatic decreases in the fitness of poliovirus (Pfeiffer and Kirkegaard, 2005) and chikungunya virus (Coffey and Vignuzzi, 2011) when fidelity of RNA-dependent polymerases was artificially increased, indicating that lower mutation rates likely deprive viruses of adaptive potential.

Despite its hypothesized adaptive advantage, high viral mutation rates have severe costs. Because viral genomes are small, virally-encoded proteins must be multi-functional (Fang and Snijder, 2010; Lu and Gong, 2013), and mutations can thus impair multiple processes, creating a cascade of deleterious effects. Moreover, since RNA viruses possess a genomic mutation rate of $U \approx 1$, most lineages will possess at least one deleterious mutation that will be selected against, slowing the colonization of a potential host. Indeed, empirical evidence indicates that the high mutation rate of RNA viruses places them on the brink of extinction. For instance, Holland et al. (1990) found that only a 3-fold increase in mutation rates caused the local collapse of vesicular stomatitis virus, leading them to suggest that mutation rates above $\mu = 10^{-4}$ are unstable and will lead to extinction. Similarly, a 10-fold increase in the mutation rate of poliovirus led to a 1000-fold decrease in virus titer (Crotty et al., 2001). These observations support the hypothesis that viral evolution favors the highest mutation rate that does not cause complete loss of viability (Summers and Litwin, 2006). This discovery has led to a number of anti-viral pharmaceutical therapies in humans. For instance, 3′-azido-3′-deoxythymidine (AZT), the first commercial drug approved by the FDA for the treatment of human immunodeficiency virus-1 (HIV-1), works in part by inducing a 7-fold increase in the mutation rate of HIV-1 (Mansky and Bernard, 2000).

High mutation rates may also constrain the size of viral genomes because larger genomes have a higher probability of containing a deleterious mutation (Bull et al., 2007; Holmes, 2003a). Eigen (1971) proposed a universal "error threshold" that is a function of both mutation rate and genome size, predicting that viral genome size would evolve toward a value defined by the reciprocal of the mutation rate to reflect the overall production of unfit mutants. As the genome size and mutation rates of more viruses have become known, the existence of this error threshold has received additional support (Sanjuán and Domingo-Calap, 2016; Sanjuán et al., 2010).

An alternate hypothesis challenges the adaptive value of high mutation rates. Rather than providing an evolutionary advantage, high mutation rates may simply reflect faster replication modes, which are error-prone (Baer et al., 2007). Modelling indicates that selection favors fast modes of replication (Regoes et al., 2013), and poor fidelity is a typical consequence (Belshaw et al., 2008). However, escaping the host immune system, a key reason a high mutation rate might be advantageous, is not always important for viruses since many are transmitted to new hosts without ever overcoming host defenses (Bonhoeffer and Sniegowski, 2002). If high mutation rates were adaptations to intense selection pressure from the host immune system, viruses subject to weak immune selection, such as GB virus type C (Maidana-Geret et al., 2009), would be expected to have lower mutation rates. However, viruses under weak immune pressure do not seem to possess mutation rates lower than those under strong immune pressure (Holmes, 2009).

The small genome sizes necessitated by high mutation rates also mean opportunities for gene duplication are rare (Holmes, 2009). Gene duplication is a key component of evolutionary potential in high-level organisms, since it generates redundant gene copies upon which mutations may potentially create novel versions without disrupting ancestral functions (Hughes, 1994; Lynch and Conery, 2000; Ohno et al., 1968). In contrast, the small genomes of error-prone RNA viruses might provide few opportunities for mutation to create new versions of a gene without compromised function. The comparatively large genomes of dsDNA viruses, such as human cytomegalovirus, can often endure multiple deletions without undergoing fitness losses (Dunn et al., 2003). This indicates the existence of multiple loci where mutation and selection can act to produce new viral properties without reducing replicative ability. Despite the noted theoretical constraints on gene duplication in RNA viruses, however, evidence of gene duplication-mediated evolution exists in several RNA virus families, including Potyviridae (Valli et al., 2007), Pneumoviridae (Eshaghi et al., 2012), and Closteroviridae (Boyko et al., 1992). Whether viral gene duplication, and associated production of adaptive variants, is constrained by small genome size thus remains an open question.

Additionally, relatively low mutation rates may generate a satisfactory number of adaptive mutants, given large viral population sizes and relatively short generation times. For instance, the generation time of HIV-1 is estimated at 1–2 days (Rodrigo et al., 1999), and its total population size in an infected individual may exceed 10^8 (Brown, 1997a,b; Haase et al., 1996). Consequently, the probability that any specific mutational variant arises over the course of a long-term chronic infection approaches 1, even at relatively low mutation rates (Hughes, 1994). Thus, for the purpose of producing adaptive viral variants, high mutation rates may be unnecessary, since viruses are not mutation limited throughout much of their evolutionary history.

2.2. Generation of novel isolates through recombination

Virions of the same or different species may incidentally swap portions of their genome during replication, a process known as viral

recombination. Recombination rates seem to be positively correlated with mutation rates (Hahn, 2008; Tromas et al., 2014), presenting viruses with additional capacity to produce novel and potentially adaptive genotypes. However, in populations at equilibrium in a static environment, most recombinant events produce genotypes with low fitness that are eliminated by purifying selection (Feldman et al., 1980; Monjane et al., 2014). Because unfit recombinant mutants exist transiently and are difficult to detect, evidence on total recombination rates is scant. However, per nucleotide recombination rates of 10^{-4} to 10^{-8} have been estimated for a number of viruses (Simon-Lonere and Holmes, 2011). This wide range reflects the many factors that influence recombination frequency, including the relatedness of viral species and the degree of homology between potentially-recombinant sequences (Han and Worobey, 2011; Simon-Lonere and Holmes, 2011).

Recent evidence suggests that recombination is a major source of new, emergent viruses (Anthony et al., 2017; Holmes, 2009; Miras et al., 2014). Recombination allows a virus to quickly develop new phenotypes in a novel environment, such as insect transmissibility, via the acquisition of novel coding sequences from sympatrically occurring strains (Perry and Francki, 1992). Some viral taxa show enhanced levels of recombinant activity, including the economically important plant virus families Potyviridae (Chare and Holmes, 2006), Geminiviridae (Padidam et al., 1999), and Bromoviridae (Codoñer and Elena, 2008). Many emergent plant viruses of economic importance are found in these groups; in east Africa, for instance, a recombinant form of two native geminiviruses virtually wiped out local production of cassava, an important food staple, in the 1990s (Deng et al., 1997).

Viruses infecting animals also show adaptive ability stemming from recombination events (McMahon et al., 2016). Superinfection with HIV-1, where an HIV-positive patient is infected with an additional HIV strain through a secondary contact event, has resulted in recombinant HIV strains exhibiting advanced virulence (Fang et al., 2004; Smith et al., 2004) that cause advanced viremia and loss of immune or pharmacological control (Streeck et al., 2008). In communities where HIV transmission is more prevalent, and secondary infection is common, 40–50% of HIV strains may show recombinant activity (Billings et al., 2015; Dowling et al., 2002). Other epidemics, such as a 2008 outbreak of hand, foot, and mouth disease in China, have been also been attributed to a recombinant form of the HEV71 virus (Zhang et al., 2010). Thus, while recombination events are typically deleterious, they may also enable viruses to make large evolutionary leaps.

3. Virus population structure: determinants and evolutionary implications

Although high mutation and recombination rates create an enormous potential for genetic diversity, populations of viruses paradoxically often show a remarkably low level of diversity. The effective population size of HIV-1, for instance, is 10^4 or lower (Brown, 1997a,b; Kouyos et al., 2002; Rodrigo et al., 1999). Such small effective population sizes of viruses may likely constrain evolutionary potential. However, small effective population sizes may reflect two primary processes: transmission bottlenecks and intense purifying selection.

3.1. Bottlenecks constantly reduce population diversity

Life history events create opportunities for a virus to experience severe bottlenecks, with transmission considered the most important. Studies show that viral infections are often initiated by as few as one individual virion (Betancourt et al., 2008; Gutiérrez et al., 2012; Moury et al., 2007), though bottleneck size may be modulated by the infection intensity of the source host (Gutiérrez et al., 2012). The very nature of viral population dynamics likely strongly depresses effective population size below the census population size (Kalinowski and Waples, 2002). In turn, because only a single virion can initiate infections, founder effects may lead to coalescence of alleles in a population, such that most genetic diversity is distributed among viral populations (i.e., populations have high F_{ST}) (Ayllón et al., 1999). Vertical transmission (parent to progeny) may impose similar bottlenecks. In HIV, considerable bottlenecks occur during mother-to-child transmission (Russell et al., 2011) that are similar to those seen during horizontal transmission (Edwards et al., 2006). Similarly, seed-borne plant viruses experience major bottlenecks during vertical transmission (Fabre et al., 2014), and bacteriophages can be highly constrained by bottlenecks imposed by bacterial host diversity (Common and Westra, 2019).

Virus transmission and dispersal in hosts may also impose severe bottlenecks. Miyashita and Kishino (2010) estimated that only 5–6 viral genomes initiate infection during intra-plant cell to cell transmission, and long-term infection of a perennial plant leads to extreme differentiation of viral sub-populations found in different plant locations (Jridi et al., 2006). Similarly, Li and Roossinck (2004) infected plants with 12 clones of cucumber mosaic virus and monitored their movement. Although all 12 clones were recovered from inoculated leaves, fewer clones were recovered as sampling moved away from the point of inoculation. Moreover, the distribution of the recovered clones did not follow a discernable pattern, indicating that their dispersal was random rather than the result of specific adaptations in particular clones (Li and Roossinck, 2004).

3.2. Role of vectors in bottlenecks

Inoculation of viruses in hosts via a vector may cause additional demographic bottlenecks that reduce genetic diversity (Lequime et al., 2016). While it is unclear if bottleneck intensities are elevated in vector-borne viruses, requiring a vector creates possible bottlenecks, because a virus must be acquired and inoculated by a vector, while a mechanically transmitted virus only needs to be inoculated (Fig. 1). Attempts to quantify the number of viral particles ingested by vectors at acquisition have varied, ranging from 10-4,000 for a plant-hosted potyvirus (Pirone and Thornbury, 1988). This indicates potential for bottlenecks during vectors acquisition is likely, but also variable. Given that intra-plant virus populations are often heterogeneous (Jridi et al., 2006; Li and Roossinck, 2004), the location where a vector feeds on a host could also be important (Gutiérrez et al., 2013) since different viral

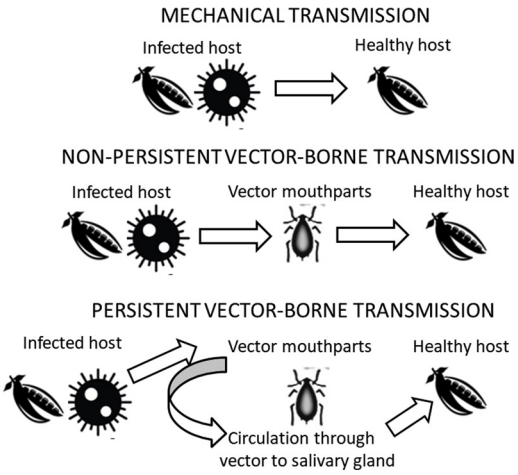

Fig. 1. Potential effects of transmission mode on bottlenecks and genetic diversity of viruses. Shown are three common types of transmission for plant viruses between infected and healthy hosts, where arrows indicate potential bottlenecks. In mechanical transmission, viruses are transmitted directly and there is only one bottleneck. In non-persistent vector-borne transmission, virions bind to vector mouthparts, creating one potential bottleneck, and not all virions may be transmitted, creating a second potential bottleneck. In persistent vector-borne transmission bottlenecks may occur during acquisition by the vector, during circulation from vector mouthparts through the blood to the salivary glands, and during transmission.

isolates may be encountered by the vector in different host parts. Evidence from cucumber mosaic virus indicates that bottlenecks in vector-borne viruses occur primarily at inoculation rather than acquisition, which would downplay the importance of vector feeding behavior (Ali et al., 2006). However, a study of Venezuelan equine encephalitis virus found intense bottlenecks (1–2 virions) as the virus migrated from the vector midgut to the salivary glands (Forrester et al., 2012), which suggests bottlenecks are not limited to vector acquisition and transmission but can occur during movement within the vector (Fig. 1).

Evidence of bottleneck intensities during vector- and non-vector-borne transmission is scant, as are studies measuring the number of virions initiating infection. Moreover, efforts to relate bottleneck size to transmission mode are confounded by genome segmentation and the nucleic acid backbone structure (Table 1). Further complicating the picture is that some studies have attained founder numbers for vector-borne viruses using mechanical inoculation (Monsion et al., 2008), which may produce different bottleneck sizes than a vector. However, studies that have measured the severity of bottlenecks created when a virus was inoculated mechanically and by a vector found no difference (Gutiérrez et al., 2012; Simmons et al., 2012). These experiments were carried out over a short timeframe and relatively few passages, however, and more studies are needed to understand the relationship between transmission mode and bottleneck intensity.

3.3. Fitness loss due to Muller's ratchet

The combination of high mutation rates and bottlenecks leaves viruses prone to the gradual accumulation of deleterious mutations. In finite populations, substantial declines in viral fitness may occur – a phenomenon known as Muller's ratchet (Muller, 1964) Because a high proportion of virions in a given virus population will contain one or more mutations, the random sampling of individuals during bottlenecks may not include the most fit genotypes, causing the minimum number of mutations per virion to increase. This "click" of Muller's ratchet is irreversible unless countered by alternative processes. If bottlenecks are extreme and frequent, the less fit forms of a virus may even be fixed stochastically in small populations, causing the overall viral population fitness to markedly diminish. This phenomenon was first observed in a bacteriophage by Chao (1990) and has since been seen in other bacteriophages (de la Pena et al., 2000) and in several animal viruses (Duarte et al., 1992; Escarmís et al., 1996).

Several mechanisms may alleviate the effects of Muller's ratchet. For instance, a virus weakened by successive small bottlenecks quickly recovers fitness when the passage size is increased (Clarke et al., 1993). Additionally, highly mutated and unfit viral isolates often gain fitness with each bottleneck, regardless of passage size (Elena et al., 1998). This occurs because while a virus grows less fit as deleterious mutations accumulate, a higher proportion of mutations will be beneficial by reverting the virus to the fitter wild-type variant. In a metaphorical sense, viruses at the bottom of the fitness ladder can only go up as long as they do not fall off (i.e., go extinct). Additionally, complementation, whereby one virion uses gene products synthesized by others, can reduce the effects of deleterious mutations and dampen the effects of Muller's ratchet (Froissart et al., 2004). Complementation could underlie the evolution of multi-component virus species complexes such as pea enation mosaic virus, a virus complex consisting of a mutually-dependent Umbravirus and Enamovirus (Demler et al., 1996). Additionally, high mutation and recombination rates, such as in RNA viruses, could create genomes without deleterious mutations, preventing ratchet-like reductions in population fitness (Tromas et al., 2014).

Nearly all studies demonstrating Muller's ratchet have been conducted on animal viruses. However, circumstantial evidence from natural environments indicates it may play a major role in plant virus evolution. In Australia, the introduced plant *Nicotiana glauca* hosted co-infections of tobacco mosaic virus (TMV) and tobacco mild green mosaic virus (TMGMV) before 1950, but only TMGMV after 1950. Nucleotide analysis from preserved specimens revealed that while the diversity of TMGMV remained stable over time, mutations gradually accumulated in various TMV isolates. Likewise, experimental co-infections of TMV and TMGMV revealed that TMV titers were only 10% as high as those found in single infections, while the titer of TMGMV was unchanged. The authors hypothesized that perhaps TMGMV invaded Australian *N. glauca* plants later and gradually outcompeted TMV by reducing its within-host populations to levels that were more susceptible to the incapacitating effects of Muller's ratchet (Fraile et al., 1997).

3.4. Evidence of strong purifying selection

Viruses experience intense purifying selection, which may explain the often high similarity between allopatric populations experiencing similar environments. Since viral proteins often are multi-functional (Fang and Snijder, 2010; Lu and Gong, 2013), most mutations trigger multiple harmful effects and are quickly purged. Purifying selection may thus counter Muller's ratchet by limiting the persistence of unfit mutants, decreasing the odds they will survive random sampling during bottlenecks. Theory predicts that a high mutation rate, coupled with frequent transmission bottlenecks in neutral environments, would drive within-host homogeneity but generate between-host differentiation (Ayllón et al., 1999). The fact that numerous plant (Vives et al., 2002) and animal (Holmes, 2003a; Jerzak et al., 2005) viruses exhibit low inter-population diversity, even for globally-distributed viruses, is indicative of strong purifying selection on viral genomes.

Some parts of the viral genome, such as the region coding for the coat protein (Altschuh et al., 1987) and the origin of replication (Argüello-Astorga et al., 1994), are critical to virus fitness and show extreme conservation across different strains. Moreover, secondary structure is a vital component of virus fitness (Hofacker et al., 2004), and changes to the secondary structure of the nucleic acid chain may impose costs related to virus survival. Saito et al. (1990) hypothesized that the secondary structure of a virus may be related to its ability to fit inside a coat protein, and subsequent studies have confirmed higher rates of conservation among genomic loci associated with potential stem-loop structures (Honda et al., 1999; Simmonds and Smith, 1999) and helices (Tycowski et al., 2012). This makes the identification of truly "neutral" sites within the genome difficult, since even a non-coding, non-regulatory sequence could experience strong selection based on the changes in secondary structure a mutation would produce. Consequently, many molecular estimates of viral divergence may be suspect, since they tend to predict much earlier divergence times than historical or epidemiological records indicate (Wertheim and Pond, 2011).

Although the general trend certainly points to intense purifying selection, recent research, aided by advances in high-throughput sequencing, has indicated that differentiation among virus populations may be more common than previously thought. For example, grapevine leafroll-associated virus 1 has three clades correlating with geography (Alabi et al., 2011), and high-throughput analyses of HIV-1 has revealed a complex population structure characterized by bottlenecks and positive selection (Dong et al., 2011; Hemelaar, 2012). The diversity of Ebola virus is strongly correlated with geographical and temporal outbreaks (Gire et al., 2014), and a comprehensive analysis of dengue virus (Parameswaran et al., 2012) revealed a higher degree of differentiation than initial estimates (Holmes, 2003b). Consequently, while inter-population diversity may generally be lower for viruses than sexual multicellular organisms, the degree of genetic differentiation between viral populations is extremely context dependent.

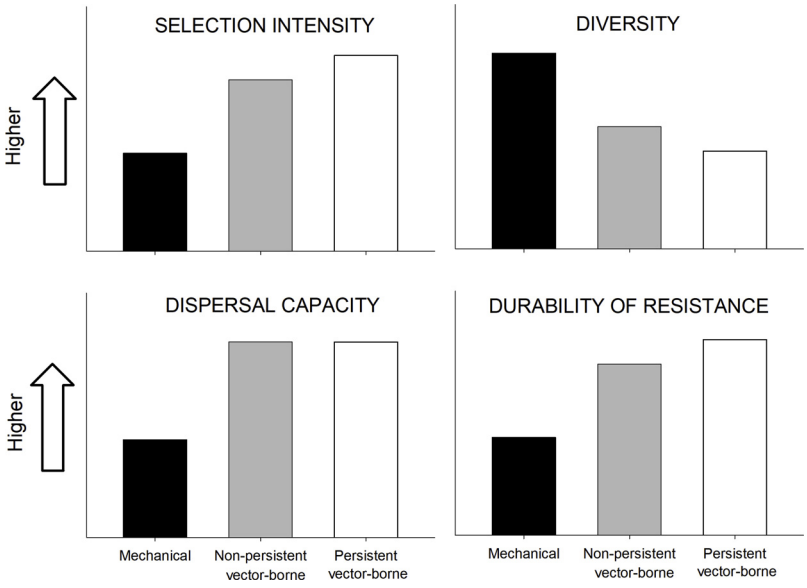

Fig. 2. Hypothesized effects of transmission mode on the selection pressure against viruses, the diversity of viruses, the dispersal capacity of viruses, and the durability of resistance against viruses. Mechanically-transmitted viruses have relatively weak selection, high diversity, low dispersal, and low durability of resistance, while vector-borne viruses have strong selection, low diversity, high diversity, and high durability of resistance. Persistent vector-borne viruses (both circulative and propagative sub-types) are expected to have increased selection and bottlenecks compared to non-vector borne viruses, which increases selection pressure, decreases diversity, and increased resistance durability.

4. Does viral adaptation to hosts or vectors come with an evolutionary cost?

4.1. Host identity and diversity can influence viral evolution

While viral defenses are ubiquitous across many taxa (Koonin and Dolja, 2013), plant immune systems lack specialized immune cells used by animals to neutralize viruses. This led to the hypothesis that the frequency of positive selection may be higher in animal viruses, which must overcome a dynamic immune system where somatic selection causes intense fluctuating selection (Desbiez et al., 2011). In contrast, observed ratios of nonsynonymous and synonymous substitution rates (dN/dS) are lower in vector-borne animal compared to plant viruses (Chare and Holmes, 2004; Woelk and Holmes, 2002). This may indicate more intense purifying selection in animal viruses, though this effect could be more attributable to differences in vectors than in hosts (Chare and Holmes, 2004). In a separate study, dN/dS did not vary among viruses from insects, vertebrates, or plant hosts (Obbard and Dudas, 2014), such that the direction and magnitude of selection pressure was consistent across host types. However, since dN/dS can poorly reflect molecular evolution when strong positive selection results in a complete selective sweep of a population (Kryazhimskiy and Plotkin, 2008), positive selection in adaptive animal immune systems may not manifest in examinations of dN/dS (Obbard and Dudas, 2014).

Many viruses infect multiple divergent hosts, which may also affect evolutionary potential. Since a host-switching virus must be adapted to two different immune environments, viruses relying upon alternating hosts likely experience a fitness trade-off where fitness on one host is reduced to achieve viability on a second (Whitlock, 1996). However, empirical evidence has not supported such a tradeoff. For instance, when isolated to one cell line, vesicular stomatitis virus (VSV) quickly gained fitness in the host cell line but lost fitness on alternate cell lines. Similar results have been shown for bacteriophages, which adapt quickly to divergent host populations (Forde et al., 2004; Morgan et al., 2005). However, when the virus was cycled between cell lines (hamster, dog, human), viral fitness on all cell lines equalled the fitness of specialist strains (Turner and Elena, 2000), indicating that a "jack-of-all-trades" is not necessarily a "master of none" (Whitlock, 1996). Other studies similarly did not find a fitness cost of host generalism in animal (Novella et al., 1999; Smith-Tsurkan et al., 2010) or plant (Elena, 2017) viruses. However, evidence suggests that host-switching may inhibit the evolution of viral escape variants that are resistant to immune responses. Immuno-resistant strains of simian immunodeficiency virus (SIV) revert to susceptibility when transferred to novel hosts (Friedrich et al., 2004), suggesting that frequent host-switching may prevent the selection of host-resistant alleles if those alleles do not confer a fitness advantage in the alternate host.

4.2. Vector transmission imposes strong purifying selection and decreases viral diversity

Consequences of transmission mode (direct vs. vector-borne) for evolutionary potential has received considerable attention. In vectors, viruses can be persistent and propagative, infecting and replicating within hosts, persistent and circulative, infecting but not replicating in hosts, or non-persistent, attaching to vector mouthparts but not infecting the vector's body. Since vectors of both types of persistent viruses (circulative and propagative) become infected, an argument could be made that they are secondary hosts rather than vectors. However, while some vectors infected with persistent viruses suffer fitness costs, such as alphavirus-infected mosquitos (Lambrechts and Scott, 2009), other groups, such as plant-pathogenic rhabdoviruses (Ammar et al., 2009), seem to have little impact on vectors. Consequently, persistent viruses exhibit a wide range of pathogenicity within their arthropod vectors, complicating accurate classification of arthropod intermediates as hosts or vectors. For purposes of simplicity, this review maintains the classical nomenclature and refers to infected arthropods as vectors, even for persistent viruses.

While there does not seem to be a fitness tradeoff associated with vector utilization, as in host-switching, there may be a cost to diversity, and dN/dS values are often significantly lower in vector- than non-vector-borne viruses (Chare and Holmes, 2004; Jenkins et al., 2002; Woelk and Holmes, 2002) (Fig. 2). When an arbovirus passages through one cell line it quickly loses fitness on the alternate host but acquires more mutations. Alternatively, when the same virus is cycled between vector or host cells, it maintains fitness on both cell lines but exhibits relatively little diversity (Coffey and Vignuzzi, 2011; Weaver et al., 1999). Low diversity in vector-borne viruses may also be a result of strong purifying selection (Fig. 2). Values of dN/dS in dengue virus, for instance, are lower in inter- than in intra-host populations (Holmes, 2003b), and mutations accumulate slower in mosquito than human cells (Vasilakis et al., 2009) (Fig. 2).

Selection pressure on capsid genes does not vary with the number of plant families infected by a virus, indicating that infection of multiple hosts does not impose a strong evolutionary constraint (Chare and Holmes, 2004). In contrast, non-persistent and persistent circulative

viruses are constrained to single arthropod families for transmission (Power, 2000), and viruses as a whole appear to be limited to a single transmission mode (Chare and Holmes, 2004). This supports the hypothesis that viruses are more vector- than host-limited. Capsid diversity is relatively high in non-vector-borne viruses such as prune dwarf virus (Kalinowska et al., 2014), indicative of weaker purifying selection. However, if there seems to be a general trend of stronger viral selection in vectors than in hosts, a counterexample exists with West Nile virus (WNV), which experiences weak purifying selection and high diversity in its mosquito vector but strong purifying selection and low diversity in its avian host (Ciota et al., 2007a, b; Jerzak et al., 2005). Thus, empirical evidence indicates that vector adaptation imposes a severe cap on the evolutionary potential of vector-borne viruses.

The transmission mode of a vector-borne virus may impact selection pressure (Fig. 2). Viral transmission mode is often categorized as persistent or non-persistent, depending on the length of time a vector remains infectious (Hogenhout et al., 2008; Pirone and Harris, 1977). Non-persistent viruses are often referred to as “stylet-borne”, because they attach to vector mouthparts and are acquired and transmitted rapidly, but the vector can become non-infectious after transmitting the pathogen (Hogenhout et al., 2008). In contrast, persistent viruses must circulate through the vector’s blood and reach the salivary glands before the vector becomes infectious (Hogenhout et al., 2008); vectors of persistent viruses also remain infectious through their death. Persistent viruses are further sub-divided in two groups: circulative and propagative. Persistent circulative viruses travel through the vector’s blood to the salivary glands but do not replicate within the vector, whereas persistent propagative viruses replicate within the vector (Gray and Banerjee, 1999; Hogenhout et al., 2008).

Even though persistent circulative viruses do not replicate within the vector, adaptation to vector species is extremely important due to molecular binding interactions that occur between viral capsid proteins and proteins on the vector’s stylet or gut (Gray and Banerjee, 1999; Perry et al., 1998). A meta-analysis of the selective forces acting on plant virus capsid proteins (Chare and Holmes, 2004) revealed that vector-borne viruses experienced stronger purifying selection despite being primarily constituted of persistent circulative viruses, which indicates that vector adaptation a major selective force for viruses that do not replicate in vectors (Fig. 2). Indeed, while persistent circulative viruses are restricted to single arthropod families for transmission (Power, 2000), persistent propagative viruses such as vesicular stomatitis virus are compatible with vectors from many arthropod families (Comer et al., 1991; Drolet et al., 2005; Mead et al., 1999). Hence, persistent circulative viruses may not be more evolutionarily flexible.

5. Implications for disease and resistance management

For centuries, humans have used biotechnology and selective breeding to develop anti-viral drugs, disease-resistant plants, and antimicrobial disinfectants (Brooks, 1928; Hutt, 1958; Renis and Buthala, 1965). Some viruses overcome countermeasures (Davies and Davies, 2010; Onstad, 2013; Powles and Yu, 2010), while others do not, and geneticists have sought to determine why through the lens of evolutionary potential. Weak purifying selection may be a predictor of a plant virus’ ability to break host resistance (Janzac et al., 2009) (Fig. 2). Biological agents with low potential for developing resistance have low rates of gene flow, small effective population sizes, and low mutation rates (Harrison, 2002; McDonald and Linde, 2002). These factors limit the gene pool potentially generating advantageous mutants and therefore constrain the evolutionary potential of virus populations (Fig. 2).

5.1. The consequences of being vector-borne

Reliance on a vector for transmission imposes limitations on virus population structure that can affect whether it overcomes host immunity, develops drug resistance, or spills over into an alternate host. Since vector-borne viruses often have low diversity and strong purifying selection (Chare and Holmes, 2004; Holmes, 2003a; Woelk and Holmes, 2002), they are evolutionarily constrained compared to non-vector-borne viruses (Fig. 2). For example, resistance in lettuce mosaic virus, which has aphid- and seed-borne strains, has only been observed in seed-borne strains, indicating that the strong purifying selection inherent to vector transmission may prevent the emergence of resistant vector-borne isolates (Krause-Sakate et al., 2002). Moreover, potato virus X, a pathogen known for its ability to overcome resistant hosts, is also non-vector-borne (Moreira et al., 1980). Because non-vector-borne plant viruses are relatively few, and resistance-breaking is rare, it is difficult to discern if non-vector-borne viruses are truly more capable of overcoming resistance. However, the higher rates of positive selection in non-vector-borne viruses, coupled with these observations, suggest this may be the case (Fig. 2).

Vector-borne viruses may also be less likely to jump from animal to human hosts, which is known as pathogen spillover (Power and Mitchell, 2004). Directly transmitted pathogens may be more likely to jump from animals to humans, because they do not have vector bottlenecks that constrain diversity (Woolhouse et al., 2005). Modelling approaches (Geoghegan et al., 2016) have predicted that pathogens under strong purifying selection, such as vector-borne viruses, will have few mutant virions in the transmission dose, such that the odds of a mutated virus infecting humans from a non-human host may be low (Geoghegan et al., 2016). Independent of genetics, ecological factors may increase the likelihood of a vector-borne virus spilling over into human populations (Kreuder Johnson et al., 2015), since vectors increase dispersal and diminish the need for human hosts to come into direct contact with animals (Fig. 2). Parsing out the individual impacts of population structure and ecology as they relate to vector-borne transmission would considerably boost our understanding of the factors driving spillover events.

5.2. Are plant viruses less likely to break resistance than other plant pathogens?

Even before the molecular mechanisms underlying host resistance and resistance-breaking pathogens were known, researchers noted that crop resistance to viruses seemed more durable than to fungal or bacterial pathogens (Harrison, 1981). Examples of plant viruses overcoming host resistance are rare (Miras et al., 2014), and resistance-breaking genotypes often appear but do not proliferate (García-Arenal and McDonald, 2003). Reliance on vectors may explain this relative lack of resistance, given that the diversity of vector-borne viruses is constrained by purifying selection, and most plant viruses are vector-borne. An alternative explanation lies in an examination of the mechanism by which plant viruses overcome resistance, which is often mutation of the effector protein. Since evolution of completely novel effector proteins is unlikely, immune escape is accomplished through mutation of existing effectors, which often results in a less virulent virus. Cellular pathogens, such as bacteria and fungi, can make copies of effector proteins that can then mutate without compromising the function of the original (Kobayashi et al., 2014).

5.3. Stability of resistant populations

Because of the multifunctional role of viral genomes, adaptive genotypes produced through mutation or recombination are likely to be less fit in non-resistant hosts. Resistance-breaking strains of plant viruses (Harrison, 2002; Jenner et al., 2002) and drug-resistant animal viruses (Hughes and Andersson, 2015) are often less fit than wild-type strains. In turn, these mutant strains are often outcompeted by wild-type isolates in the absence of selection (Jenner et al., 2002). Given the fitness costs often imposed by adaptation to resistance genes or drugs, and the intrinsically high viral mutation rate, treatment-resistant phenotypes may be selected against in the absence of treatment. For

doctors, this presents a tantalizing solution to the problem of drug-resistant viruses, since it would mean that resistant viruses could revert to susceptibility and become treatable with time. Although susceptibility reversion has been documented in multiple organisms including insects (Parrella and Trumble, 1989), bacteria (Meka et al., 2004; Villa et al., 2013), mites (Beers et al., 1998), and helminth worms (Leathwick et al., 2015), there has not been a documented example of a human virus reverting to susceptibility on a scale that would influence treatment. Resistance alleles do not always pose fitness costs (Gassmann et al., 2009), and long periods of time may pass before small fitness differences drive a complete selective sweep. Still, the partial or complete reversion of a resistant virus population to susceptibility has been demonstrated experimentally (Cane et al., 1999; Gandhi et al., 2003), so the potential exists for such a phenomenon, even if it has not yet been observed outside of laboratory settings.

6. Conclusion: Virus life history and ecology affect evolutionary potential

Viruses have evolved various life histories that affect viral reproduction, adaptation, and epidemiology. The use of an RNA backbone and single-stranded structure results in higher mutation rates than DNA-based or double-stranded viruses; this means that while RNA viruses may be more adaptable, they are also constrained to a smaller genome and must tolerate a large proportion of their population existing as unfit mutants. Constant transmission bottlenecks mean that stochastic processes, such as the random loss of genotypes, have the potential to play a large role in virus evolution, and the relative intensities of these bottlenecks could be influenced by the structure of the virus and its mode of transmission. Vectors present additional opportunities and constraints, and vector-borne viruses tend to have lower rates of positive selection. As a result, it appears that overcoming host resistance may be unlikely for vector-borne viruses compared to other pathogens, meaning that countermeasures targeting vector-borne viruses may be relatively durable. Although recent advances in population genetics have allowed us to develop a rough framework of evolution for plant and animal viruses, research should focus on delineating the consequences of specific life histories on evolutionary potential of viruses and other pathogens.

Declarations of interest

None.

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