Matryoshka Dolls of Virus Evolution: the Internal Forces That Shape Viral Fate

Running title: Matryoshka Dolls of Virus Evolution

John Yin

Department of Chemical and Biological Engineering, Wisconsin Institute for Discovery

University of Wisconsin-Madison, 330 N. Orchard Street, Madison, WI 53715 USA

john.yin@wisc.edu

Abstract

Viral evolution unfolds across nested layers of adaptation, much like a set of Matryoshka dolls. The outermost, well-studied layer involves interactions between viruses and their hosts—where immune evasion, cross-species transmission, and long-term coevolution drive viral diversification. Yet, hidden within this framework is an often-overlooked inner layer: the coevolution of viruses with their own molecular parasites, defective interfering (DI) particles and defective viral genomes (DVGs). These molecular parasites exploit viral replication machinery, reshaping infection dynamics and imposing selective pressures that influence viral fitness, transmission, and persistence. This perspective synthesizes evidence from experimental evolution, mathematical modeling, and molecular virology to propose a more integrated view of viral evolution. By framing host-virus interactions and virus-DI particle dynamics within a unified evolutionary framework, we highlight the underappreciated role of DI particles as evolutionary players, not just aberrant byproducts. Recognizing these internal layers of viral evolution may inform the development of antiviral strategies and broader questions in host-pathogen coevolution.

Word total: 3170

Introduction

Viruses continuously adapt to dynamic host environments, evolving across multiple timescales. Within individual hosts, high mutation rates and replication efficiencies enable rapid adaptation to immune pressures (Steinhauer and Holland 1987; Drake and Holland 1999; Marques et al. 2024). Over months to years, cross-species transmission events create evolutionary bottlenecks that select for variants capable of infecting new hosts (Taubenberger and Kash 2010; Singh and Yi 2021). On even longer timescales, a continuous arms race unfolds: viral adaptations drive host immune countermeasures, which in turn shape further viral diversification (Hoffmann et al. 2015; Tenthorey et al. 2022).

This perspective frames these processes as nested “Matryoshka dolls,” highlighting both established and hidden layers of viral evolution (**Figure 1**). The more conspicuous “outer doll” encompasses host immune evasion, drug resistance, and host switching, classically inferred from genetic changes and selection signatures. Nestled inside lies an often-overlooked “inner doll”: viruses co-evolving with their own molecular parasites, classically known as defective interfering particles (Huang and Baltimore 1977) and more recently as defective viral genomes (Brennan and Sun 2024). We view such particles and genomes as parasites that prey on productive virus infection. From this perspective, theories that have been developed to understand the coevolution of hosts and their parasites may be both challenged and enriched.

The External Doll: Viral Evolution over Time and Across Hosts

The “external doll” represents the most readily observed and better-studied layer of viral evolution. It encompasses mutations, recombinations, and selective sweeps identifiable through genome sequencing, functional assays, and comparative analyses. These events lead to shifts

in receptor binding, immune evasion, and species adaptation—features central to our current grasp of how viruses establish infections, spread and persist.

Short-term evolution: rapid adaptation and immune evasion. Within a single infected host, viral populations are in constant flux, shaped by selection pressures that favor mutants capable of evading immune recognition. RNA viruses, in particular, exhibit astonishing adaptability due to their high mutation rates and error-prone replication mechanisms (Domingo and Perales 2019). Influenza viruses exemplify antigenic drift, where mutations in the hemagglutinin (HA) protein accumulate under immune selection, allowing evasion of pre-existing immunity (Bush et al. 1999). These antigenic changes fuel seasonal influenza epidemics and necessitate frequent vaccine updates (Hensley et al. 2009).

A similar evolutionary trajectory is observed in HIV-1, where continuous within-host selection drives viral escape from both neutralizing antibodies and cytotoxic T lymphocyte responses. As soon as the immune system mounts a targeted attack against a particular viral epitope, new mutants emerge that weaken or entirely evade immune recognition (Borrow et al. 1997; Richman et al. 2003). This relentless cycle of immune pressure and viral adaptation explains why HIV-1 is so difficult to control and why, even within a single patient, the virus can diversify into a complex quasi-species (Mansky and Temin 1995).

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, further illustrates these principles on a population scale. As global immunity increased through infection and vaccination, new variants of concern emerged, each carrying mutations that confer enhanced transmissibility and immune evasion (Harvey et al. 2021). The rapid rise of Omicron, which carried multiple spike protein mutations that diminished neutralization by existing antibodies, exemplifies the strong selection pressures shaping viral evolution in real time (Cele et al. 2022).

The forces driving short-term viral evolution are relatively well understood: high mutation rates generate genetic diversity, while immune-driven selection favors variants that can escape recognition. However, viral evolution is not confined to single hosts or isolated epidemics. In some cases, a virus may face an even greater evolutionary challenge—the transition to an entirely new host species.

Host switching: evolutionary bottlenecks and adaptation to new hosts. Few events in viral evolution are as consequential as a successful host switch. When a virus jumps from one species to another, it must overcome multiple biological barriers, including differences in cell entry receptors, host immune defenses, and replication machinery (Parrish et al. 2008; Longdon et al. 2014). Most spillover events fail, but when adaptation occurs, the consequences can be profound, leading to the emergence of new viral diseases in humans and reshaping viral evolution in the long term.

Influenza viruses provide a textbook example of host switching and viral emergence. The segmented nature of the influenza genome allows for reassortment when multiple strains infect the same host, a process that can generate entirely new viral subtypes with pandemic potential (Koçer et al. 2013). Historical influenza pandemics—including the 1918 H1N1 virus and the more recent 2009 H1N1 pandemic strain—originated from reassortment events that facilitated viral adaptation to human transmission (Nelson et al. 2008).

Similarly, SARS-CoV-2 emerged after a likely zoonotic jump from animal reservoirs, possibly bats or intermediate hosts, requiring genetic changes in its spike protein to efficiently bind human ACE2 receptors (Starr et al. 2020). Early in the pandemic, rapid evolutionary adaptations fine-tuned the virus for efficient human-to-human transmission, highlighting the powerful selection pressures at play following host switching events (Carabelli et al. 2023).

HIV-1, too, exemplifies the impact of host switching on viral evolution. The virus arose through multiple independent cross-species transmission events from nonhuman primates, each introducing distinct viral lineages into the human population (Sharp and Hahn 2011). These transmission events required substantial genetic adaptation, particularly in viral accessory proteins that counteract human immune restriction factors (Sheehy et al. 2003; Neil et al. 2008). The ability of HIV-1 to adapt to human-specific antiviral defenses, such as tetherin and APOBEC3, underscores the intense evolutionary bottlenecks viruses face when adapting to new hosts.

Long-term coevolution: shaping viral genomes and host immune defenses. At the broadest evolutionary scale, viruses and their hosts are engaged in an ancient arms race, with each side continuously adapting in response to the other. This long-term coevolution has left indelible marks on both viral and host genomes, revealing the deep evolutionary imprint of past infections (Emerman and Malik 2010; Kaján et al. 2020).

One of the most striking examples of this interplay is the evolution of innate immune sensors, such as RIG-I, MDA5, and Toll-like receptors. These pattern recognition receptors detect viral nucleic acids and initiate antiviral responses, yet viruses have evolved countermeasures to suppress or evade these defenses (Eisenächer et al. 2007; Loo and Gale 2011). Influenza virus encodes the NS1 protein, which inhibits host interferon signaling (Ji et al. 2021), while HIV-1 deploys Vpu to degrade tetherin, a host protein that restricts viral budding (Neil et al. 2008). The continuous back-and-forth between viral evasion strategies and host immune defenses underscores the dynamic nature of virus-host coevolution (Duggal and Emerman 2012; Kmiec and Kirchhoff 2024).

Beyond individual immune genes, remnants of ancient viral infections can be found embedded within host genomes. Endogenous retroviruses (ERVs), the remnants of past retroviral

infections, now make up a significant fraction of mammalian DNA (Feschotte and Gilbert 2012). While many of these sequences are inactive, some have been co-opted for essential host functions, including immune regulation and placental development (Dunlap et al. 2006; Katzourakis and Gifford 2010).

While external selection pressures—immune evasion, host switching, and long-term coevolution—have shaped viral evolution in profound ways, they do not tell the whole story. Within viral populations, an obscured layer of evolution is unfolding, one that does not fit neatly into the traditional framework of adaptive selection.

The Internal Doll: Molecular Parasites as Evolutionary Players

Long regarded as evolutionary byproducts, defective interfering (DI) particles and their associated defective viral genomes (DVGs) may play a significant role in virus evolution. These molecular parasites hijack the replication machinery of co-infected cells, outcompeting wild-type viruses and altering infection dynamics (Huang and Baltimore 1970; Bhat et al. 2022). DI particles carry and deliver truncated genomes that lack the functions needed for independent replication yet retain their ability to replicate and package into virus-like particles in the presence of functional helper viruses. Moreover, their defective virus genomes or DVGs are prevalent in natural and clinical virus isolates, they can trigger protective host immune responses, and the absence or presence of DVGs has been associated with more or less severe disease (Vignuzzi and López 2019; Bhat et al. 2022; Brennan and Sun 2024). To frame how DVGs may contribute to viral evolution we focus on a single feature of their multifaceted nature: their ability as molecular parasites to prey on productively infected hosts.

Pathogen-host coevolution. More than 50 years ago, Van Valen introduced the Red Queen Hypothesis, arguing that species must evolve continuously just to maintain their relative fitness in response to coevolving adversaries (Van Valen 1973). Unlike traditional views of evolution as

progress toward a static optimum, Van Valen's model suggests that the biotic environment, shaped by interactions with competitors, predators, and pathogens, creates ever-changing selection pressures. In short, species face constant evolutionary pressure where their survival depends not only on their own adaptations but also on how their competitors, predators, and pathogens evolve. So the survival of a species depends on how well it adapts compared to its co-evolving counterparts. As one species gains an advantage, others must evolve to counter it. The hypothesis predicts that evolutionary rates remain relatively constant over time because adaptation never stops; molecular evolution in pathogens and hosts reflects this continuous struggle.

Building on Van Valen's foundation, Alfaro has formulated a mathematical model of pathogen-host coevolution, showing how host and pathogen populations can engage in perpetual chases in phenotypic space (Alfaro et al. 2025). Their model exhibits two key features: (i) a perpetual ams race, where hosts and pathogens follow trajectories, with each mutation met by a counter-mutation, and (ii) cyclical evolution, where some systems exhibit oscillatory dynamics; evolutionary traits fluctuate in predictable cycles, akin to classic predator-prey relationships.

While the Red Queen Hypothesis explains why evolution is an ongoing race, May and Anderson explored the specific trade-offs that shape pathogen evolution, integrating epidemiological dynamics with population genetics (May and Anderson 1983). Their study employed mathematical modeling to challenge the widely held assumption that pathogens inevitably evolve toward reduced virulence (Burnet and White 1972; Holmes 1982). They found that pathogen virulence does not necessarily decline over time; instead, the evolutionary success of a pathogen depends on the balance between virulence (how much harm it causes) and transmissibility (how efficiently it spreads). If a pathogen spreads before killing its host, high virulence can be advantageous. Further, host-pathogen interactions drive genetic diversity;

pathogens apply strong selection pressure, so host populations must maintain diverse resistance alleles, preventing their complete extinction. Finally, multiple evolutionary trajectories exist. Some pathogens evolve toward lower virulence, allowing hosts to survive longer and spread the infection. But others evolve greater virulence, maximizing short-term transmission before the host dies. More broadly, the **m**athematical models of May and Anderson showed that the evolution of pathogens depends on their basic reproductive number (R_0), which depends on host susceptibility, pathogen adaptation, and environmental factors. This work laid the foundation for modern models of infectious disease evolution, helping predict how diseases like influenza or COVID-19 might change over time.

Microbial arms races. Bacteria and their viral predators, bacteriophages, provide a well-characterized model of pathogen-host coevolution (Chao et al. 1977; Bohannan and Lenski 1997). Mathematical models demonstrate that as bacteria evolve resistance, phages counter-adapt, fueling an ongoing arms race that drives genetic diversity and ecosystem complexity, even in stable environments (Weitz et al. 2005). Their modeling has shown how coevolution generates genetic diversity; even in stable environments, the ongoing arms race leads to the emergence of multiple bacterial and phage strains, increasing the ecosystem complexity. Moreover, bacteria-phage interactions involve gradual evolutionary changes, where bacteria modify their surface receptors, and phages adapt their tail fibers to regain infectivity; in short, mechanisms of coevolution do not support a simple “one mutation cancels the other” scenario. Finally, the work predicts the coexistence of multiple pathogen and host strains. Instead of a single dominant genotype, coevolution leads to a diverse ecosystem of bacterial and viral strains, each adapting to different infection strategies.

Viruses and their defective interfering variants. While host-pathogen interactions are often framed in terms of the coevolutionary arms race between viruses and their hosts, an equally

intricate evolutionary struggle may be unfolding at the molecular level within viral populations themselves. Many viruses do not evolve in isolation but instead interact dynamically with their DI particles or DVGs (defective viral genomes), molecular parasites that arise spontaneously through replication errors. This layer of coevolution challenges more established views of viral adaptation, revealing that evolutionary success for a virus is not simply about outpacing host defenses but also about managing internal parasites that can divert resources and disrupt replication.

Phage Φ6 and its DI particles. Experimental evolution studies with RNA bacteriophage Φ6 demonstrated that viral populations can be shaped by game-theoretic principles akin to the "prisoner's dilemma," where viral variants competing within the same host cell evolve either cooperative or selfish replication strategies (Turner and Chao 1999). At high multiplicities of infection (MOI), where multiple phages infect the same cell, defective phage variants—DI particles—can emerge. These variants exploit the replication machinery of fully functional phages while contributing little to their own encapsidation, thereby gaining an advantage at the expense of their productive counterparts. The evolutionary dynamics of these interactions are frequency-dependent: at low frequencies, defectors can spread, but as they become dominant, they reduce the overall fitness of the viral population, illustrating an evolutionary tension between cooperation and defection (Turner and Chao 2003).

Vesicular stomatitis virus and Its DI particles. DI particles also play a significant role in the evolution of vesicular stomatitis virus (VSV), an RNA virus widely used as a model for studying viral replication and evolution. DI particles of VSV are truncated viral genomes that retain sequences necessary for replication but lack essential coding regions, rendering them incapable of independent propagation. These particles emerge most frequently in high-MOI conditions, where they compete with full-length VSV genomes for replication machinery, often suppressing

wild-type virus production (DePolo et al. 1987). A striking feature of VSV evolution is its ability to co-evolve with DI particles over extended passages. Experimental studies have shown that as DI particles increase in frequency, the wild-type virus responds by selecting for mutants resistant to DI interference. This resistance can arise through mutations in viral polymerase proteins or other genomic regions that reduce DI particle replication efficiency (Giachetti and Holland 1988). The process is cyclic: new DI particles emerge with altered interference properties, triggering further adaptations in the wild-type virus, leading to an ongoing evolutionary interplay between helper viruses and their defective counterparts (DePolo et al. 1987). These findings appear to align with the cyclic evolution observed in computational models of pathogen-host coevolution (Alfaro et al. 2025). Moreover, they highlight the potential for DI particles to act as evolutionary constraints on virus replication, shaping long-term viral population dynamics.

Therapeutic interfering particles. Beyond natural examples of virus-DI particle coevolution, efforts have long sought to harness defective viral genomes for therapeutic applications (Doyle and Holland 1973; Dimmock and Easton 2014; Baltes et al. 2017; Chaturvedi et al. 2021; Xiao et al. 2021; Pitchai et al. 2024). Inspired by the principles of DI particle interference, researchers have explored the possibility of engineering therapeutic interfering particles (TIPs) that can selectively suppress pathogenic viruses while maintaining long-term stability within a host population (Metzger et al. 2011).

HIV presents an especially compelling case for TIP-based interventions. Given the high mutation rate and immune evasion capabilities of HIV, conventional antiviral strategies struggle with the emergence of resistant strains. TIPs, however, exploit the same replication pathways as HIV, competing for packaging and transmission resources while lacking the ability to cause disease. Recent work in nonhuman primates has demonstrated that engineered TIPs can establish stable, long-term presence in infected hosts, suppressing HIV replication and delaying

disease progression (Pitchai et al. 2024). By maintaining an evolutionary arms race with HIV, TIPs may offer a novel therapeutic approach that resists viral escape and reduces overall transmission potential. Mathematical modeling suggests that TIPs could exert strong selective pressure on HIV populations, favoring variants with reduced fitness and lowering overall viral loads in infected individuals. Unlike conventional antivirals, which necessitate ongoing treatment and risk resistance, TIPs may persist as stable molecular parasites, co-evolving with HIV to sustain long-term suppression (Pitchai et al. 2024).

Pathogen-host interactions: the external and internal layers. As highlighted in **Table 1**, the relationships between DI particles and viruses mirror, but also significantly diverge from, the classic virus-host interaction paradigm. A defining feature of DI particles is their ability to replicate at rates comparable to, or even exceeding, their parental virus (Thompson and Yin 2010; Timm et al. 2014). This is a striking contrast to the virus-host relationship, where viral replication is orders of magnitude more productive than host cell division (Jin and Yin 2021). The comparable generation times of DI particles and viruses lead to a dynamic interplay where DI particles can rapidly amplify within an infection cycle, often outcompeting the virus for essential replication and packaging resources (Akpinar et al. 2016; Baltes et al. 2017).

A key distinction between DI particles and viruses lies in their emergence. Unlike viruses, which arise independently of host growth, DI particles are obligate byproducts of viral replication. Their defective genomes originate from replication errors, internal deletions, or recombination events within the viral genome, leading to defective yet highly competitive entities (Lazzarini et al. 1981; Aguilar Rangel et al. 2023). This dependence on viral replication sets up a unique evolutionary dependency, where DI particles can only persist in the presence of a replicating virus but can dominate when conditions favor their proliferation.

The mutation rate of DI particles will likely be comparable to that of their parental virus, ensuring rapid evolutionary adaptation. This aligns with the high spontaneous mutation rates observed in RNA viruses, which approach the theoretical upper limit for viability (Drake 1993; Drake and Holland 1999). However, the evolutionary potential of DI particles extends beyond that of intact viruses due to their unique selection pressures. While viruses primarily evolve through incremental genetic changes optimizing their fitness within a host environment, DI particles operate under a different evolutionary regime: tuning interference with the parental virus and under selection for their own persistence. This drives extensive genome innovation, as DI particles accumulate insertions and deletions at rates shaped by the error-prone nature of their replication machinery (Aguilar Rangel et al. 2023). Such innovations in DI genomes include more efficient replication signals, enhanced packaging efficiency, and altered interactions with host immune responses, in multiple cases mediated by novel DVG-encoded proteins (Patel and Elliott 1992; Boergeling et al. 2015; Imamichi et al. 2016; Girgis et al. 2022; Ghorbani et al. 2023; Ranum et al. 2024). This ability of DI particles to explore a vast mutational landscape underscores their potential for rapid functional diversification making them formidable modulators of viral population dynamics.

Table 1. Hosts of Virus and DI particle pathogens

Feature	Virus vs. Host	DI Particle vs. Virus
Generation Time	**Virus << Host** (viruses replicate much faster than their hosts).	**DI Particle ≈ Virus** (DI particles replicate at comparable or faster rates than the virus).
Emergence	**Virus ≠ Byproduct of Host Growth** (viruses do not arise as a byproduct of host growth).	**DI Particle = Byproduct of Virus Growth** (DI particles arise as byproducts of virus growth).
Mutation Rate	**Virus >> Host** (viruses mutate much faster than their hosts).	**DI Particle ≈ Virus** (DI particles mutate at similar rates as their virus).
Evolutionary Potential	**Virus (Large)** (virus evolution alters gene functions).	**DI Particle (Astronomical)** (DI genomes can innovate new functions).

Conclusion. The "Matryoshka Dolls" framework unifies external viral adaptations with the underappreciated role of DI particles in shaping evolution. Recognizing these nested layers may inspire next-generation antiviral strategies and deepen our understanding of viral evolution in dynamic host environments.

Acknowledgements

I am grateful for support by the US National Science Foundation (DMS-2151959, MCB-2029281 and CBET- 2030750), the National Institutes of Health (R01DK133605) and the University of Wisconsin-Madison: Chemical and Biological Engineering, Wisconsin Institute for Discovery, the Office of the Vice-Chancellor for Research, and the Wisconsin Alumni Research Foundation. Thanks to Nan (Yifang) Jiang, Chung-Hui Hsu, and Shiv Muthupandiyan for helpful discussions.

References

Aguilar Rangel M, Dolan PT, Taguwa S, Xiao Y, Andino R, Frydman J. 2023. High-resolution mapping reveals the mechanism and contribution of genome insertions and deletions to RNA virus evolution. Proc Natl Acad Sci U S A. 120(31):e2304667120.

Akpinar F, Inankur B, Yin J. 2016. Spatial-Temporal Patterns of Viral Amplification and Interference Initiated by a Single Infected Cell. J Virol. 90(16):7552–7566.

Alfaro M, Lavigne F, Roques L. 2025. A host-pathogen coevolution model, Part I: Run straight for your life. Nonlinear Anal Real World Appl. 84(104305):104305.

Baltes A, Akpinar F, Inankur B, Yin J. 2017. Inhibition of infection spread by co-transmitted defective interfering particles. PLoS One. 12(9):e0184029.

Bhat T, Cao A, Yin J. 2022. Virus-like Particles: Measures and Biological Functions. Viruses. 14(2). doi:10.3390/v14020383. http://dx.doi.org/10.3390/v14020383.

Boergeling Y, Rozhdestvensky TS, Schmolke M, Resa-Infante P, Robeck T, Randau G, Wolff T,

Gabriel G, Brosius J, Ludwig S. 2015. Evidence for a novel mechanism of influenza virus-induced type I interferon expression by a defective RNA-encoded protein. PLoS Pathog. 11(5):e1004924.

Bohannan BJM, Lenski RE. 1997. Effect of resource enrichment on a chemostat community of bacteria and bacteriophage. Ecology. 78(8):2303–2315.

Borrow P, Lewicki H, Wei X, Horwitz MS, Peffer N, Meyers H, Nelson JA, Gairin JE, Hahn BH, Oldstone MBA, et al. 1997. Antiviral pressure exerted by HIV-l-specific cytotoxic T lymphocytes (CTLs) during primary infection demonstrated by rapid selection of CTL escape virus. Nat Med. 3(2):205–211.

Brennan JW, Sun Y. 2024. Defective viral genomes: advances in understanding their generation, function, and impact on infection outcomes. MBio. https://journals.asm.org/doi/abs/10.1128/mbio.00692-24.

Burnet M, White DO. 1972. Natural history of infectious disease. 4th ed. Cambridge, England: Cambridge University Press.

Bush RM, Bender CA, Subbarao K, Cox NJ, Fitch WM. 1999. Predicting the evolution of human influenza A. Science. 286(5446):1921–1925.

Carabelli AM, Peacock TP, Thorne LG, Harvey WT, Hughes J, COVID-19 Genomics UK Consortium, Peacock SJ, Barclay WS, de Silva TI, Towers GJ, et al. 2023. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol. 21(3):162–177.

Cele S, Jackson L, Khoury DS, Khan K, Moyo-Gwete T, Tegally H, San JE, Cromer D, Scheepers C, Amoako DG, et al. 2022. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. Nature. 602(7898):654–656.

Chao L, Levin BR, Stewart FM. 1977. A complex community in a simple habitat: An experimental study with bacteria and phage. Ecology. 58(2):369–378.

Chaturvedi S, Vasen G, Pablo M, Chen X, Beutler N, Kumar A, Tanner E, Illouz S, Rahgoshay D, Burnett J, et al. 2021. Identification of a therapeutic interfering particle—A single-dose SARS-CoV-2 antiviral intervention with a high barrier to resistance. Cell. 184(25):6022–6036. e18.

DePolo NJ, Giachetti C, Holland JJ. 1987. Continuing coevolution of virus and defective interfering particles and of viral genome sequences during undiluted passages: virus mutants exhibiting nearly complete resistance to formerly dominant defective interfering particles. J Virol. 61(2):454–464.

Dimmock NJ, Easton AJ. 2014. Defective interfering influenza virus RNAs: time to reevaluate their clinical potential as broad-spectrum antivirals? J Virol. 88(10):5217–5227.

Domingo E, Perales C. 2019. Viral quasispecies. PLoS Genet. 15(10):e1008271.

Doyle M, Holland JJ. 1973. Prophylaxis and immunization in mice by use of virus-free defective T particles to protect against intracerebral infection by vesicular stomatitis virus. Proc Natl Acad Sci U S A. 70(7):2105–2108.

Drake JW. 1993. Rates of spontaneous mutation among RNA viruses. Proc Natl Acad Sci U S

A. 90(9):4171–4175.

Drake JW, Holland JJ. 1999. Mutation rates among RNA viruses. Proc Natl Acad Sci U S A. 96(24):13910–13913.

Duggal NK, Emerman M. 2012. Evolutionary conflicts between viruses and restriction factors shape immunity. Nat Rev Immunol. 12(10):687–695.

Dunlap KA, Palmarini M, Varela M, Burghardt RC, Hayashi K, Farmer JL, Spencer TE. 2006. Endogenous retroviruses regulate periimplantation placental growth and differentiation. Proc Natl Acad Sci U S A. 103(39):14390–14395.

Eisenächer K, Steinberg C, Reindl W, Krug A. 2007. The role of viral nucleic acid recognition in dendritic cells for innate and adaptive antiviral immunity. Immunobiology. 212(9-10):701–714.

Emerman M, Malik HS. 2010. Paleovirology--modern consequences of ancient viruses. PLoS Biol. 8(2):e1000301.

Feschotte C, Gilbert C. 2012. Endogenous viruses: insights into viral evolution and impact on host biology. Nat Rev Genet. 13(4):283–296.

Ghorbani A, Ngunjiri JM, Rendon G, Brooke CB, Kenney SP, Lee C-W. 2023. Diversity and complexity of internally deleted viral genomes in influenza A virus subpopulations with enhanced interferon-inducing phenotypes. Viruses. 15(10):2107.

Giachetti C, Holland JJ. 1988. Altered replicase specificity is responsible for resistance to defective interfering particle interference of an Sdi- mutant of vesicular stomatitis virus. J Virol. 62(10):3614–3621.

Girgis S, Xu Z, Oikonomopoulos S, Fedorova AD, Tchesnokov EP, Gordon CJ, Schmeing TM, Götte M, Sonenberg N, Baranov PV, et al. 2022. Evolution of naturally arising SARS-CoV-2 defective interfering particles. Commun Biol. 5(1):1140.

Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, Ludden C, Reeve R, Rambaut A, Peacock SJ. 2021. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 19(7):409–424.

Hensley SE, Das SR, Bailey AL, Schmidt LM, Hickman HD, Jayaraman A, Viswanathan K, Raman R, Sasisekharan R, Bennink JR, et al. 2009. Hemagglutinin receptor binding avidity drives influenza A virus antigenic drift. Science. 326(5953):734–736.

Hoffmann H-H, Schneider WM, Rice CM. 2015. Interferons and viruses: an evolutionary arms race of molecular interactions. Trends Immunol. 36(3):124–138.

Holmes JC. 1982. Impact of infectious disease agents on the population growth and geographical distribution of animals. In: Population Biology of Infectious Diseases. Berlin, Heidelberg: Springer Berlin Heidelberg. p. 37–51.

Huang AS, Baltimore D. 1970. Defective viral particles and viral disease processes. Nature. 226(5243):325–327.

Huang AS, Baltimore D. 1977. Defective interfering animal viruses. In: Fraenkel-Conrat H, Wagner RR, editors. Comprehensive Virology. New York: Plenum Press. p. 73–116.

Imamichi H, Dewar RL, Adelsberger JW, Rehm CA, O'Doherty U, Paxinos EE, Fauci AS, Lane HC. 2016. Defective HIV-1 proviruses produce novel protein-coding RNA species in HIV-infected patients on combination antiretroviral therapy. Proc Natl Acad Sci U S A. 113(31):8783–8788.

Jin T, Yin J. 2021. Patterns of virus growth across the diversity of life. Integr Biol. 13(2):44–59.

Ji Z-X, Wang X-Q, Liu X-F. 2021. NS1: A key protein in the "game" between influenza A virus and host in innate immunity. Front Cell Infect Microbiol. 11:670177.

Kaján GL, Doszpoly A, Tarján ZL, Vidovszky MZ, Papp T. 2020. Virus-host coevolution with a focus on animal and human DNA viruses. J Mol Evol. 88(1):41–56.

Katzourakis A, Gifford RJ. 2010. Endogenous viral elements in animal genomes. PLoS Genet. 6(11):e1001191.

Kmiec D, Kirchhoff F. 2024. Antiviral factors and their counteraction by HIV-1: many uncovered and more to be discovered. J Mol Cell Biol. 16(2). doi:10.1093/jmcb/mjae005. http://dx.doi.org/10.1093/jmcb/mjae005.

Koçer ZA, Jones JC, Webster RG. 2013. Emergence of influenza viruses and crossing the species barrier. Microbiol Spectr. 1(2). doi:10.1128/microbiolspec.OH-0010-2012. http://dx.doi.org/10.1128/microbiolspec.OH-0010-2012.

Lazzarini RA, Keene JD, Schubert M. 1981. The origins of defective interfering particles of the negative-strand RNA viruses. Cell. 26(2 Pt 2):145–154.

Longdon B, Brockhurst MA, Russell CA, Welch JJ, Jiggins FM. 2014. The evolution and genetics of virus host shifts. PLoS Pathog. 10(11):e1004395.

Loo Y-M, Gale M Jr. 2011. Immune signaling by RIG-I-like receptors. Immunity. 34(5):680–692.

Mansky LM, Temin HM. 1995. Lower In Vivo Mutation Rate of Human Immunodeficiency Virus Type 1 than that Predicted from the Fidelity of Purified Reverse Transcriptase. J Virol. 69(8):5087–5094.

Marques AD, Graham-Wooten J, Fitzgerald AS, Sobel Leonard A, Cook EJ, Everett JK, Rodino KG, Moncla LH, Kelly BJ, Collman RG, et al. 2024. SARS-CoV-2 evolution during prolonged infection in immunocompromised patients. MBio. 15(3):e0011024.

May RM, Anderson RM. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. Proc R Soc Lond B Biol Sci. 219(1216):281–313.

Metzger VT, Lloyd-Smith JO, Weinberger LS. 2011. Autonomous targeting of infectious superspreaders using engineered transmissible therapies. PLoS Comput Biol. 7(3):e1002015.

Neil SJD, Zang T, Bieniasz PD. 2008. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. Nature. 451(7177):425–430.

Nelson MI, Viboud C, Simonsen L, Bennett RT, Griesemer SB, St George K, Taylor J, Spiro DJ, Sengamalay NA, Ghedin E, et al. 2008. Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918. PLoS Pathog. 4(2):e1000012.

Parrish CR, Holmes EC, Morens DM, Park E-C, Burke DS, Calisher CH, Laughlin CA, Saif LJ, Daszak P. 2008. Cross-species virus transmission and the emergence of new epidemic diseases. Microbiol Mol Biol Rev. 72(3):457–470.

Patel AH, Elliott RM. 1992. Characterization of Bunyamwera virus defective interfering particles. J Gen Virol. 73 (Pt 2)(2):389–396.

Pitchai FNN, Tanner EJ, Khetan N, Vasen G, Levrel C, Kumar AJ, Pandey S, Ordonez T, Barnette P, Spencer D, et al. 2024. Engineered deletions of HIV replicate conditionally to reduce disease in nonhuman primates. Science. 385(6709):eadn5866.

Ranum JN, Ledwith MP, Alnaji FG, Diefenbacher M, Orton R, Sloan E, Güereca M, Feltman EM, Smollett K, da Silva Filipe A, et al. 2024. Cryptic proteins translated from deletion-containing viral genomes dramatically expand the influenza virus proteome. Nucleic Acids Res. 52(6):3199–3212.

Richman DD, Wrin T, Little SJ, Petropoulos CJ. 2003. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci U S A. 100(7):4144–4149.

Sharp PM, Hahn BH. 2011. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med. 1(1):a006841.

Sheehy AM, Gaddis NC, Malim MH. 2003. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. Nat Med. 9(11):1404–1407.

Singh D, Yi SV. 2021. On the origin and evolution of SARS-CoV-2. Experimental & Molecular Medicine. 53(4):537–547. doi:10.1038/s12276-021-00604-z. http://dx.doi.org/10.1038/s12276-021-00604-z.

Starr TN, Greaney AJ, Hilton SK, Ellis D, Crawford KHD, Dingens AS, Navarro MJ, Bowen JE, Tortorici MA, Walls AC, et al. 2020. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. Cell. 182(5):1295–1310.e20.

Steinhauer DA, Holland JJ. 1987. Rapid Evolution of RNA Viruses. Ann RevMicrobiol. 41:409–433.

Taubenberger JK, Kash JC. 2010. Influenza virus evolution, host adaptation, and pandemic formation. Cell Host Microbe. 7(6):440–451.

Tenthorey JL, Emerman M, Malik HS. 2022. Evolutionary landscapes of host-virus arms races. Annu Rev Immunol. 40(1):271–294.

Thompson KA, Yin J. 2010. Population dynamics of an RNA virus and its defective interfering particles in passage cultures. Virol J. 7:257.

Timm C, Akpinar F, Yin J. 2014. Quantitative characterization of defective virus emergence by deep sequencing. J Virol. 88(5):2623–2632.

Turner PE, Chao L. 1999. Prisoner’s dilemma in an RNA virus. Nature. 398(6726):441–443.

Turner PE, Chao L. 2003. Escape from Prisoner’s Dilemma in RNA phage phi6. Am Nat. 161(3):497–505.

Van Valen L. 1973. A New Evolutionary Law. Evolutionary Theory. 1:1–30.

Vignuzzi M, López CB. 2019. Defective viral genomes are key drivers of the virus–host interaction. Nature Microbiology. 4(7):1075–1087.

Weitz JS, Hartman H, Levin SA. 2005. Coevolutionary arms races between bacteria and bacteriophage. Proc Natl Acad Sci U S A. 102(27):9535–9540.

Xiao Y, Lidsky PV, Shirogane Y, Aviner R, Wu C-T, Li W, Zheng W, Talbot D, Catching A, Doitsh G, et al. 2021. A defective viral genome strategy elicits broad protective immunity against respiratory viruses. Cell. 184(25):6037–6051. e14.