"Viral host range: what evolution teaches us about spillover and host-viral interactions of zoonotic viruses"

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The onset of SARS-CoV2 brought to light an urgent need to advance our understanding of how zoonotic viruses are spread and the relationship between the host and the virus. (Katsnelson, 2020) In Spring 2020, the COVID-19 outbreak marked a spillover from bats to civets, then onto humans. (Sparrer, McKenzie N et al., 2023) In retrospect, the molecular pathways that facilitated these jumps likely contain less-explored, more complex evolutionary roots.

During my time studying viruses at Stanford, I became deeply intrigued by the complex dynamics of host-virus interactions. Among the many questions these relationships raise, one in particular captured my attention: Why do some viruses, like Polio, exhibit a near-exclusive preference for humans, while others, such as Ebola, Influenza A, and Mpox, infect a wide range of hosts? This motivated my pursuit of understanding the origins of host specificity and how viruses adapt to specific ecological niches.

Gustavo Fermin described in his article Host Range, Host–Virus Interactions, and Virus Transmission "Where there is life, there are viruses" (Fermin G, 2018) These ancient entities have coexisted with cellular organisms since the dawn of life, forging intricate relationships with hosts across the three domains of life: Eukarya, Archaea, and Bacteria. Over millennia, viruses have evolved to form diverse strategies to interact with their hosts. Some, like influenza A from the Orthomyxoviridae family, are 'generalists,' capable of infecting a wide range of species. Others, such as dengue, mumps, and polio, are 'specialists,' often limited to humans as their sole mammalian host. Yet the question of whether generalist or specialist viruses hold a greater evolutionary advantage remains a topic of ongoing scientific debate.

From a theoretical standpoint, evolution often accelerates in narrower niches, potentially favoring specialist viruses. By focusing on a limited number of hosts, specialist viruses may evolve more rapidly and efficiently. In contrast, the ability of generalist viruses to infect a broader range of hosts can potentially increase their overall fitness and adaptability. (Fermin G, 2018) For example, studies of secretomes—a set of proteins secreted into the extracellular environment—reveal a general enrichment of primitive amino acids and intrinsically disordered regions in generalist prokaryote pathogens. (Blanco, Luz P et al., 2018) This trait may explain why generalist prokaryotes exhibit higher levels of molecular interaction through

their secretomes compared to specialists, potentially conferring a greater evolutionary advantage (Blanco, Luz P et al., 2018).

Host-virus compatibility is another key determinant of evolutionary advantage, critically influencing viral attachment, entry, and replication. During attachment, a virus's host specificity is often governed by its ability to bind to specific host cell surface proteins. For example, human-adapted influenza viruses use haemagglutinin (HA) to bind to α2–6-linked sialic acid (SA), a bulky cis-form sugar attached to glycoproteins on cell surfaces (Long, Jason S., et al., 2018). In contrast, avian-adapted HA targets the thinner, straighter trans-form of the same sugar, α2–3-linked SA (Long, Jason S., et al., 2018). Furthermore, influenza neuraminidase (NA), another viral surface protein, undergoes species-specific adaptation by aligning with the host's SA, matching its length to ensure efficient cleavage during the final replication stage. As such, even subtle molecular differences across species can impact viral compatibility, shaping a virus's ability to infect and replicate.

In the co-evolutionary "dance" between viruses and their hosts, host restriction factors—cellular proteins that interfere with the viral replication cycle—play a crucial role in determining a virus's host range. In fact, these factors are often more accurate predictors than phylogenetic relatedness or sequence similarities. (Rothenburg, Stefan et. al., 2020) in an evolutionary arms race, host restriction factor antiviral protein kinase R (PKR, eIF2aK2) attempt to outpace the evolution of virus antagonists, molecules which helps viruses evade the host's immune defense. (Rothenburg, Stefan et. al., 2020) In response, viruses evolved a substantial arsenal of inhibitors targeting multiple steps of the PKR pathways, illustrating the dynamic evolutionary forces on restriction factors that shape viral host range and pathogenicity.

However, the highly specific adaptations viruses develop to their hosts over the course of evolution pose significant challenges for researchers attempting to establish reliable animal models for viruses like human immunodeficiency virus (HIV) and dengue. For instance, non-human primates, such as macaques, encode at least five different restriction factors and have a significantly expanded major histocompatibility complex (MHC I), a protein responsible for flagging infected cells for immune destruction. (Warren CJ, 2019) These factors make macaques more resistant to HIV infection and less suitable as models for studying human diseases (Warren CJ, 2019). In fact, successful viral infection—indicated by an increase in viral titer—has only been achieved when macaques were genetically modified to lack key immune pathways or to express specific human receptors (Warren CJ, 2019). Such differences highlight the complex evolutionary dynamics that allow viruses to persist in animal reservoirs, a key factor in cross-species transmission.

Yet examining these immune-robust animals specifies can provide valuable insights into the differences that allow certain viruses to persist harmlessly in their hosts. Bats, for example, harbor a wide range of viruses, such as Nipah and Ebola, that are highly lethal to humans but relatively benign in their winged carriers. A compelling theory, known as the "flight as fever" hypothesis, suggests that the intense energy demands of flight, which elevate the bat's body temperature, mimic the effects of fever and may help

control infections (Zhang, Guojie, et al., 2013). In addition to this, bats have undergone unique evolutionary adaptations, such as positive selection for c-REL—a gene critical to DNA damage response—and the loss of the PYHIN gene family, which is involved in microbial DNA sensing and inflammasome formation. These adaptations shape the bat's innate immune system, regulating inflammatory responses and enhancing their capacity to serve as viral reservoirs. (Zhang, Guojie, et al., 2013)

Despite these discoveries, many questions remain: What are the long-term consequences for animals sustaining infections or serving as viral reservoirs? How do these viruses affect their hosts' genes or physiology over time? In the context of long-COVID, these questions have become even more pressing, highlighting the need for deeper exploration into the lasting impacts of viral persistence.

In these ongoing discussions, I often return to the concept of "viral chatter," a term Nathan Wolfe uses to describe viruses as persistent visitors, constantly probing for potential hosts. Through the long process of co-evolution, viruses have integrated numerous genes into our genome—some harmful, but others beneficial, playing crucial roles in development.

This reminds us that viral proteins are not static; they continuously evolve, experiencing shifts that lead to both gains and losses of function, which influence their ability to thrive in specific hosts. Amid this viral chatter, it is crucial to continue exploring our complex relationship with viruses, as this co-evolution has profound implications for our biology, health, and future responses to viral threats.

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