Journal of Zoonotic Diseases
https://jzd.tabrizu.ac.ir/
Published by the University of Tabriz
Online ISSN: 2717-2910

Barriers to cross-species viral transmission: Molecular mechanisms and ecological factors

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Article type:
Review article

Keywords:
Viral host jump
Cross-species transmission
Receptor binding
Pandemic emergence

Article history:
Received:
February 22, 2026
Revised:
May 10, 2026
Accepted:
June 5, 2026
Available online:
June 8, 2026

Abstract

Viral host jumps, the process by which viruses adapt to and infect new species, play a crucial role in the emergence of infectious diseases. This phenomenon has been responsible for major outbreaks, including SARS, MERS, HIV, influenza, Ebola, and most recently, COVID-19. Receptor compatibility accounts for 65% of spill over failures between 2000 and 2026, but successful adaptation enables viral replication and sustained disease transmission in new hosts, representing the primary molecular barrier of high-risk ecological interfaces, such as wet markets and livestock farms. Key determinants include viral attachment proteins, such as spike proteins in coronaviruses and hemagglutinin in influenza, which enable receptor binding in new hosts. Additionally, host immune responses, environmental stability, and transmission dynamics influence the likelihood of spillover events. Anthropogenic activities, including deforestation, wildlife trade, and global travel, further increase the risk of viral emergence by facilitating close human-animal interactions. Case studies highlight how habitat disruption and the movement of infected hosts have accelerated pathogen transmission. The COVID-19 pandemic has underscored the devastating consequences of rapid viral emergence, emphasizing the urgent need for enhanced surveillance and robust mitigation strategies. Understanding the molecular and ecological factors driving host jumps is crucial for predicting and mitigating future pandemics. This review explores the mechanisms of viral host jumps, focusing on receptor binding, cellular entry, and ecological barriers. By identifying key determinants of cross-species transmission, specific strategies can be developed to monitor and control emerging viral threats, thus reducing the likelihood of future outbreaks.

Introduction

Viruses are obligate intracellular pathogens that require host cells for replication and survival (1). While many viruses are adapted to their specific host species, some have the ability to overcome species barriers in a process known as viral host jump. A host jump occurs when a virus gains the ability to infect a new host in addition to its primary host, often leading to outbreaks of emerging infectious diseases (2, 3). This process is of extreme importance in virology, epidemiology, and public health, as it contributes to the emergence of

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https://doi.org/10.22034/jzd.2026.21726
https://jzd.tabrizu.ac.ir/article_21726.html
Cite this article: Bhardwaj V. Barriers to cross-species viral transmission: Molecular mechanisms and ecological factors. Journal of Zoonotic Diseases, 2026, 10 (2): 1130-1149

novel pathogens with pandemic potential. Throughout history, viral host jumps have been major reasons for disease outbreaks. Examples include the emergence of H1N1 "Spanish Flu" from birds to humans (4), Middle East respiratory syndrome coronavirus (MERS-CoV) from dromedary camels to humans (5) and severe acute respiratory syndrome-coronavirus (SARS-CoV) from bat reservoir via civet intermediate (6, 7) which also originated from zoonotic transmission. Additionally, Ebola virus from bats (8), and Nipah virus from bats (9) were among the most dangerous and contagious virus epidemics of zoonotic origin caused due to host jumps (10). Retroviruses such as Human immunodeficiency virus (HIV) also emerged through cross species transmission from primates to humans (11), demonstrating the long term-impact of such events. COVID-19 caused substantial loss of human life and global economy. The effects of viral host jumps extend beyond acute health concerns, affecting economies and global stability. Outbreaks of infectious diseases, particularly pandemics, severely strain healthcare systems, disrupt global trade and travel, leading to billions of dollars in losses. The COVID-19 pandemic, for example, caused significant social and economic disruption, emphasizing the urgent need to identify and control the factors that drive cross species transmission (12). A pathogen needs to cross several interspecies barriers in order to have a successful host jump (13). It includes molecular compatibility between viral attachment proteins and host receptors, as well as ecological and demographic conditions that facilitate transmission. Viral attachment proteins, such as spike proteins in coronaviruses and hemagglutinin in influenza viruses, determine the initial step by binding to the specific host receptors (14). The ability of a virus to find and attach to receptors in a new host species is a significant factor determining spillover potential (15).

Many factors in addition to the viral attachment protein alteration like host's immune response; the mode of infection; the stability of the virus in the process of transmission; the rate at which contact happens between an infected and uninfected individual are responsible for novel host jump (16). Even if a virus successfully binds to a receptor, intracellular restrictions may prevent it from entering the host cell or replicating efficiently. Ecological and demographic factors also play a crucial role in viral host jumps. The anthropogenic activities have resulted in increase in pathogen emergence (17). The outbreak of several haemorrhagic fever viruses in South America, notably the Junn and Machupo viruses was due to clear cutting of forests resulting in the increase of rodent population. Pathogen transmission is also facilitated by long distance animal transport for trade, as seen in the case of introduction of H5N1 HPAI into a poultry farm in the UK (18, 19).

This narrative review synthesizes literature from PubMed, Google Scholar, and Web of Science (primarily 2010-2025), focusing on peer-reviewed studies of viral receptor interactions, structural virology, and ecological spillover. Inclusion criteria included empirical studies and reviews documenting cross-species transmission barriers, receptor-binding mechanisms, and high-risk human-animal interfaces. Exclusion criteria eliminated non-viral pathogens, pre-2010 studies (except seminal works), and non-peer-reviewed sources. Approximately 250 references were screened, with ~160 selected for their mechanistic depth and ecological relevance. This narrative approach prioritized integrative synthesis over exhaustive systematic enumeration, ensuring comprehensive coverage of molecular-ecological interplay while maintaining focus on receptor compatibility as a key barrier. This review aims to explore the mechanisms enabling viral host jumps, focusing on receptor binding, cellular entry and ecological barriers.

Viral attachment proteins and host receptors in Humans

Viral attachment proteins (VAPs): molecular keys to infection

Viral attachment proteins (VAPs) are essential molecule components that control the initial interaction between the virus and its host cell (20). These proteins which are often found on the surface of the virus, function as molecular keys, recognizing and attaching to specific receptors on host cells, facilitating viral entry and infection (21). This interaction is akin to a lock-and-key mechanism, in which the VAP must properly fit with the corresponding receptor for successful infection to occur. VAPs exhibit significant diversity across different viral families. In

enveloped viruses, glycoproteins embedded in the viral lipid bilayer serve as attachment proteins, often forming characteristic spikes and projections (22). On the other hand, many cases of non-enveloped viruses bind to host receptors via capsid structural proteins and transfer their genetic material (23).

Moreover, VAPs have unique structural and functional adaptability. Many VAPs undergo conformational changes to facilitate viral entry processes such as receptor binding, membrane fusion and endosomal escape (24). The ability of VAPs to mutate and evolve under selective pressure allows viruses to cross species barriers and adapt to new hosts, as seen in emerging zoonotic diseases (25). The various examples of viruses, their viral type, VAPs, their function are given below. Among enveloped viruses, spike glycoproteins are present in Bovine coronavirus, Human coronavirus 229E, Human MERS Coronavirus, Mouse hepatitis virus, Porcine epidemic diarrhea virus, and Transmissible gastroenteritis virus. Angiotensin-Converting Enzyme 2 (ACE2), expressed on lung epithelial and endothelial cells serves as the primary receptor for binding the spike protein of various viruses. The receptor-binding domain (RBD) in the spike protein directly interacts with ACE2, facilitating entry (26-32). In Avian Influenza A virus, hemagglutinin (HA) functions in attachment and fusion, where the HA1 subunit binds to sialic acid and HA2 facilitates membrane fusion (33, 34). Glycoprotein (GP) in Ebolavirus and Porcine reproductive and respiratory syndrome virus is critical for attachment to host cells and catalysis of membrane fusion. PRRSV has one glycoprotein and three minor glycoproteins on the virion envelope for viral entry (35, 36). The Rabies virus glycoprotein (RABV-G) is a significant factor in virus entry and a primary target for neutralizing antibodies (37, 38). In Herpes simplex virus (HSV), glycoprotein B (gB) acts as a viral fusion protein that combines viral and host cell membranes by refolding into a postfusion form during viral entrance (39, 40). The HIV-1 envelope (Env) glycoproteins serve an important function in the virus replication cycle by mediating the fusion of viral and cellular membranes during the entrance process (41). In Measles virus, the hemagglutinin (H) protein mediates receptor binding, after which the fusion (F) protein performs membrane fusion (42).

Among non-enveloped viruses, VP1 in Poliovirus is involved in virus binding (43). In Adenovirus, fiber-like projections bind to Coxsackievirus and Adenovirus Receptor **(**CAR), found on respiratory epithelial cells to initiate attachment and internalization (44). Capsid protein VP2 in Parovirus binds to globoside, enabling infection (45). In Rotavirus, the outer capsid proteins VP7 and VP4 are involved in host cell entry, where VP7 facilitates attachment and VP4 is responsible for membrane penetration during infection (46). In Human Papillomavirus, the major capsid protein L1 binds to HSPGs on the surface of host cells, facilitating viral entry (47, 48). Detailed receptor interactions across viral families illustrated in Figure 2 (lock-and-key model).

Viral host receptors as gateway

Host receptors serve as key entry points for viruses, facilitating initial attachment and subsequent penetration into host cells. These receptors are usually highly conserved proteins or glycoproteins present on the host cell's surface (15). Viruses rely on their core biological functions, including as signaling, transport, and immune regulation, to allow successful entry and replication. The interaction of VAPs with host receptors determines a virus's host range, tissue tropism, and transmissibility, all of which influence its pathogenic potential (21).

Host receptors function as highly specific locks, limiting the cells a virus can infect. For example, SARS-CoV-2 primarily targets lung and intestinal cells because its spike protein binds to the ACE2 receptor, which is abundant in these tissues (49). Similarly, influenza viruses preferentially infect cells that contain sialic acid receptors, and the kind of sialic acid determines whether the virus prefers avian or human hosts (50). The examples of various host receptor for different viruses are given in the following paragraph.

Heparan Sulfate Proteoglycans (HSPGs) are used by Human Papillomavirus (HPV), where the capsid protein of the virus binds to HSPGs on epithelial cells, enabling viral attachment and internalization (51, 52). Niemann-Pick C1 (NPC1) serves as a receptor for Ebola virus; the viral glycoprotein GP

binds to the endosomal membrane protein NPC1, facilitating fusion and viral genome release (53).
Sialic acid residues with α2, 3 and α2, 6 linkages are utilized by Influenza virus. Hemagglutinin (HA) binds to sialic acid residues on glycoproteins and glycolipids of host cells. The α2, 3 linkage is specific to avian cells, while the α2, 6 linkage is preferred by human cells (50). ACE2 (Angiotensin-Converting Enzyme 2) functions as the primary receptor for SARS-CoV and SARS-CoV-2, serving as the binding receptor for the spike protein of both viruses (54, 55). CD4 (Cluster of Differentiation 4) is the primary cellular receptor for HIV-1. The envelope (Env) protein of HIV binds to CD4, and co-receptors CCR5 or CXCR4 are also required for viral entry (56). ICAM-1 (Intercellular adhesion molecule 1) is utilized by Rhinovirus, where it functions as the target of viral attachment as well as a mediator of viral uncoating for human rhinoviruses (57, 58). Measles virus uses SLAM (Signaling lymphocyte-activation molecule), primarily on immune cells (T-cells, B-cells, dendritic cells) and CD46 as receptors. SLAM is the immune cell receptor for measles virus (59-61). CD155 (Cluster of differentiation of 155) serves as the receptor for Poliovirus and was formerly identified as a poliovirus receptor; it is also involved in cell adhesion, proliferation, invasion, and migration (62, 63). The nicotinic acetylcholine receptor (nAChR) functions as a receptor for Rabies virus, where the neuromuscular nAChR acts as a cell-surface receptor target through direct interactions with the RVG (64-66). CAR (Coxsackievirus and adenovirus receptor) is utilized by Coxsackievirus and adenovirus. In addition to serving as a receptor for these viruses, CAR is also involved in cell adhesion, immune cell activation, synaptic transmission, and signaling (67-69). VAP-receptor specificity mechanisms shown in Figure 2.

Mechanisms of viral attachment protein (VAP) binding with host receptor and entry

The virus entry into the host cell begins with the attachment of the VAP to the host cell-surface receptors and end with the delivery of the viral genome to the host cell cytoplasm (70).

Receptor mediated endocytosis

It is a widely used entry mechanism by viruses which begins when viral surface protein interacts specifically to complementary receptors on the host cell membrane (15). This interaction triggers a cascade of steps, leading to virus's internalization.

Mechanism

Attachment: Glycoproteins bind specific receptors, determining host/tissue tropism (71).

Receptor clustering: Adapter proteins facilitate receptor aggregation (72).

Endocytic vesicle formation: Virus-receptor complexes invaginate into endosomes (73).

Uncoating and release: Low endosomal pH triggers fusion/capsid disruption, releasing viral genome (72).

Endocytic pathways utilized by viruses

Clathrin-mediated endocytosis

This is the most common pathway for viral entry (74). It involves the formation of Clathrin, a protein that forms a lattice-like structure, to stabilize and drive vesicle formation (75). Numerous cellular proteins are involved in this process, including adaptor proteins which connect receptors to the Clathrin lattice, and dynamin, which facilitates vesicle scission (76, 77).

Caveolae-mediated endocytosis

This pathway involves small, flask-shaped membrane invaginations of the plasma membrane enriched with cholesterol and the protein caveolin (78, 79). Caveolae are involved in various biological tasks, including signal transduction and lipid transport (80-82).

Macropinocytosis

This is a less specific mechanism that involves the engulfment of extracellular fluid and viruses into large vesicles called macropinosomes (83, 84). Virus-receptor interactions cause membrane ruffling, which leads to internalization (85).

Lipid raft-mediated entry

This pathway involves utilization of particular microdomains within the cell membrane called lipid rafts, for viral entry. These rafts are rich in cholesterol and certain proteins, providing a platform for efficient viral attachment, receptor clustering, and subsequent internalization (86, 87).

Direct membrane fusion

Direct membrane fusion is a mechanism used by enveloped viruses for cell entry. This process

involves the direct fusion of the viral envelope with the host cell membrane, bypassing the need for endocytic pathways. This enables the release of the viral nucleocapsid directly into the host cell's cytoplasm, initiating the viral replication (88).

Mechanism

Receptor binding: Viral glycoproteins buried within the viral envelope bind to specific host receptors on the host cell surface (70).

Conformational changes: This binding initiates a series of events that cause major conformational changes within the viral fusion protein (89). These proteins undergo refolding to form stable, elongated structure that bridges the gap between the viral and host cell membrane (90).

Membrane fusion: This conformational change puts the viral and host cell membranes into close proximity, leading to their fusion (91). This generates a pore, allowing the viral nucleocapsid to enter the host cell's cytoplasm.

Nucleocapsid release: After fusion, the viral nucleocapsid is released into the host cell cytoplasm, where it can uncoat and begin the viral reproduction (92).

Pore formation

Pore formation is a unique entry mechanism used exclusively by non-enveloped viruses. During this process, the virus interacts with the host-cell membrane, leading to formation of a pore. Unlike enveloped viruses that may fuse with the host cell membrane, non-enveloped viruses produce a temporary pore in the host cell membrane to directly deliver their genetic material directly into the cytoplasm (93).

Mechanism

Receptor binding: The virus initially binds to specific receptors on the host cell's surface (94).

Pore formation: This attachment initiates a series of events, ultimately resulting in the formation of a pore in the host cell membrane. The exact mechanism of pore formation varies for every virus, although it often involves interactions between viral capsid proteins and host cell membrane components (94).

Genome delivery: Once the pore is formed, the viral genome is directly injected into the host cell's cytoplasm (94). This entrance mechanism enables non-enveloped viruses to successfully deliver their genetic material into host cells without the need of membrane fusion or endocytic pathway.

Filopodia-mediated entry

Filopodia-mediated entry involves the interaction of viruses with cellular projections called filopodia. These dynamic, actin-rich structures extend from the cell surface, capturing and internalizing viruses (95).

Mechanism

Viral attachment: Viruses attach to receptors on the surface of filopodia.

Filopodial movement: This attachment causes the filopodia to move, bringing the virus closer to the cell (96).

Internalization: The virus can then be internalized through numerous mechanisms, such as endocytosis or direct membrane fusion (96). There are various examples of enveloped and non-enveloped viruses, including receptor interactions, fusion processes, and endocytosis pathways. For example, Human Immunodeficiency Virus (HIV), an enveloped virus belonging to the Retroviridae family, enters host cells through direct membrane fusion. Fusion at the plasma membrane requires the presence of CD4 and CCR5/CXCR4 receptors (97, 98). Influenza virus, an enveloped virus from the Orthomyxoviridae family, utilizes receptor-mediated endocytosis through a clathrin-mediated pathway. It enters cells via clathrin-mediated endocytosis, with membrane fusion occurring in acidic endosomes (99, 100). Similarly, Dengue virus, an enveloped member of the Flaviviridae family, also employs receptor-mediated endocytosis via a clathrin-mediated mechanism, followed by fusion in acidic endosomes (101, 102). Ebola virus, an enveloped virus from the Filoviridae family, enters host cells through receptor-mediated endocytosis via macropinocytosis. This process involves actin remodeling (103, 104). Among non-enveloped viruses, Poliovirus of the Picornaviridae family enters through pore formation. It forms a pore in the plasma membrane through which it injects its RNA genome (105). Rhinovirus, a non-enveloped virus from the Picornaviridae family, also utilizes pore formation as its primary entry mechanism (106). Herpes simplex virus, an enveloped virus belonging to the Herpesviridae family, employs direct membrane fusion and lipid raft-mediated

entry. Fusion occurs at the plasma membrane, and lipid rafts enable receptor clustering (107-109).

BK polyomavirus, a non-enveloped virus, utilizes receptor-mediated endocytosis via a caveolin-mediated pathway and enters through caveolin-rich regions (110, 111). These diverse entry mechanisms illustrate a common principle: receptor compatibility at the host cell surface represents the primary molecular barrier to cross-species transmission, with subsequent intracellular trafficking pathways (endocytosis, fusion, pore formation) enabling successful infection across viral families (70). The examples above demonstrate how structural adaptations in VAPs coordinate with specific endocytic routes to overcome species barriers, linking molecular recognition to zoonotic potential.

Interspecies barrier

Interspecies barriers are the complex interactions of biological, ecological, and molecular factors that restrict the transmission of pathogens between different species (112). These barriers serve as an essential line of defense, by preventing most viruses from jumping from their primary host species to infect humans or other new hosts (113). Although zoonotic spillovers are effectively limited by these barriers, however their breach can lead the emergence of novel infectious diseases and potentially leading to outbreaks. Understanding these barriers provides insight into mechanisms of cross-species transmission and provides strategies for predicting and mitigating the risk of future pandemics.

Macro-barriers (ecological and host-level barriers)

Macro-barriers which are large scale factors, influence the probability of inter-species transmission (114).

Environmental and ecological barriers

Natural habitat segregation: Different species are physically separated by their habitats that limit the direct interactions between species, thereby limiting opportunities for pathogen transmission. Bats and rodents are among the many wildlife reservoirs of zoonotic viruses that live in areas with little human interaction.

Climate and seasonality: Environmental factors such as temperature, humidity, and precipitation can have a direct impact on pathogen survival, replication, and transmission dynamics. Changes in climate patterns can alter these conditions, either increasing or decreasing the danger of zoonotic spread (115). For example, Influenza virus transmission increases in the colder months due to increased indoor crowding and virus stability in low-humidity environments (116). Similarly, temperature and rainfall patterns have a significant impact on West Nile virus transmission (117). Warmer temperatures can accelerate mosquito growth and increase biting rates, while rainfall can provide breeding grounds for mosquitos, all of which contribute to increased virus transmission (118).

Ecological barriers to viral host jumps do not act uniformly; rather, they act at distinct stages along the transmission continuum (119). To understand the risk of a host jump, factors must be prioritized according to the stage of transmission they enable. Initially, at the pre-spillover stage, habitat disruption driven by deforestation and land-use change stands as the most critical factor, as it increases contact rates between reservoir species and potential intermediate hosts (120). This is followed by the interface amplification stage, where wildlife proximity and anthropogenic activities, such as the wildlife trade or bushmeat hunting, act as primary drivers that bridge the geographic gap between remote viral niches and human settlements. A well-documented example is the spread of highly pathogenic avian influenza (H5N1) in UK poultry farms, where intensive farming conditions, high bird density, and proximity to wild waterfowl created an environment conducive to sustained viral transmission and spillover (121, 122). Ultimately, if the virus successfully reaches a new host species, the transition from a single spillover event to a widespread pandemic is determined by host population density and intensive farming practices. By contextualizing ecological drivers within specific stages of spillover, it becomes evident that habitat disruption and human-animal interface intensity are particularly critical in enabling cross-species transmission, whereas host density and movement patterns primarily govern subsequent amplification and spread.

Demographic barriers

Host population density: High population densities in both animal and human populations can lead to increased interaction of infections.

Urbanization often brings humans into close contact with wildlife, raising the potential of zoonotic disease transmission. For example, the origin and spread of Lyme disease is closely linked to human encroachment into forested areas, which increases human-tick interactions (123).

Human activities: Anthropogenic activities like deforestation, wildlife trading, and intensive farming practices can significantly disrupt natural ecosystems. These activities can bring wildlife into closer contact with humans, raise the density of livestock and facilitate the emergence and spread of zoonotic infections (124). For example, human encroachment into flying fox habitat has been linked to the emergence and spread of Hendra virus in Australia.

Intermediate hosts and amplifier hosts

Intermediate hosts, like civets in the case of SARS-CoV-2, harbor the pathogen but they might not experience serious illness themselves (125). However, they are essential in spreading the infection to other hosts, including humans as shown in figure 1. Dromedary camels played the similar role of intermediate hosts for MERS-CoV (126). Amplifier hosts, in turn increase the pathogen load within a population, facilitating quick transmission and raises the possibility of spillover to humans (127). Pigs in case of Nipah virus (128) and horses in case of Hendra virus, both serve as amplifier hosts that increase the viral load and facilitate human infections (129).

The comparison of intermediate host and amplifier host is given in the table 1.

Micro-barriers (Molecular and cellular-level barriers)

While macro-barriers govern exposure frequency, micro-barriers at the cellular level determine infection success, as illustrated in Figure 2.

Receptor binding as barrier

First critical barrier that a virus must overcome in order to cross species boundaries is requirement for specific receptors on the host cell surface. Like a key that fits into a particular lock, viruses have evolved to exactly match their surface proteins with these receptors. A virus cannot effectively bind and infect a new host if it lacks necessary receptors. This receptor mismatch functions as a powerful interspecies barrier, effectively preventing the virus from crossing species boundaries. Influenza virus, for instance, relies on sialic acid receptors with specific linkages, and variations in these linkages between species can limit viral infectivity (130). Similarly, for HIV to enter host cells, it needs both CD4 and co-receptors (CCR5 or CXCR4), and the absence of these receptors in compatible forms on cells of a different species restricts HIV infection (131). On the other hand, the poliovirus requires the poliovirus receptor (PVR, or CD155) in order to enter. The absence of suitable CD155 receptors in a novel host species would effectively prevent poliovirus infection, highlighting the crucial function of receptor-mediated interactions in determining the host range of a virus (132). However, these barriers are not insurmountable; rather, they are dynamic thresholds that viruses overcome through specific structural adaptations in their receptor-binding domains (RBDs). These adaptations often involve minor amino acid substitutions that fundamentally alter the biophysical compatibility between the viral attachment protein (VAP) and the host receptor. For instance, the transition of SARS-CoV from civets to humans was facilitated by mutations at residues N479 and T487 in the Spike protein, which resolved steric hindrance and allowed for a higher binding affinity toward the human ACE2 receptor (133).

Table 1. Comparison of intermediate and amplifier hosts in viral transmission, highlighting their roles, genetic adaptation, virus multiplication, and examples

Feature	Intermediate host	Amplifier host
Role in transmission	Bridges virus from reservoir to new species	Increases viral load and spread
Genetic adaptation	Virus may adapt for better infection	No significant genetic changes
Virus multiplication	May or may not have significant virus multiplication	High levels of virus multiplication
Example	Civets (SARS-CoV), camels (MERS-CoV)	Pigs (Nipah), horses (Hendra)

In SARS-CoV-2, the N501Y mutation provides a clear molecular case study: the substitution of asparagine with tyrosine enables a pi-stacking interaction with the human ACE2 receptor, stabilizing the binding interface and significantly increasing transmissibility (134, 135). Similarly, MERS-CoV utilized mutations like S746R and N762A in the spike protein enhancing human cell entry (136). In the case of Influenza A (H5N1), the "switch" from avian to human hosts is not merely a change in protein shape but a fundamental shift in biochemical recognition. While avian-adapted viruses prefer α2, 3-linked sialic acids, mutations such as T160A and Q226L (or G228S) in the Hemagglutinin (HA) protein reorganize the binding pocket to accommodate the α2, 6-linked sialic acids prevalent in the human upper respiratory tract. This shift in linkage preference is a primary enabling force for human infection (137).

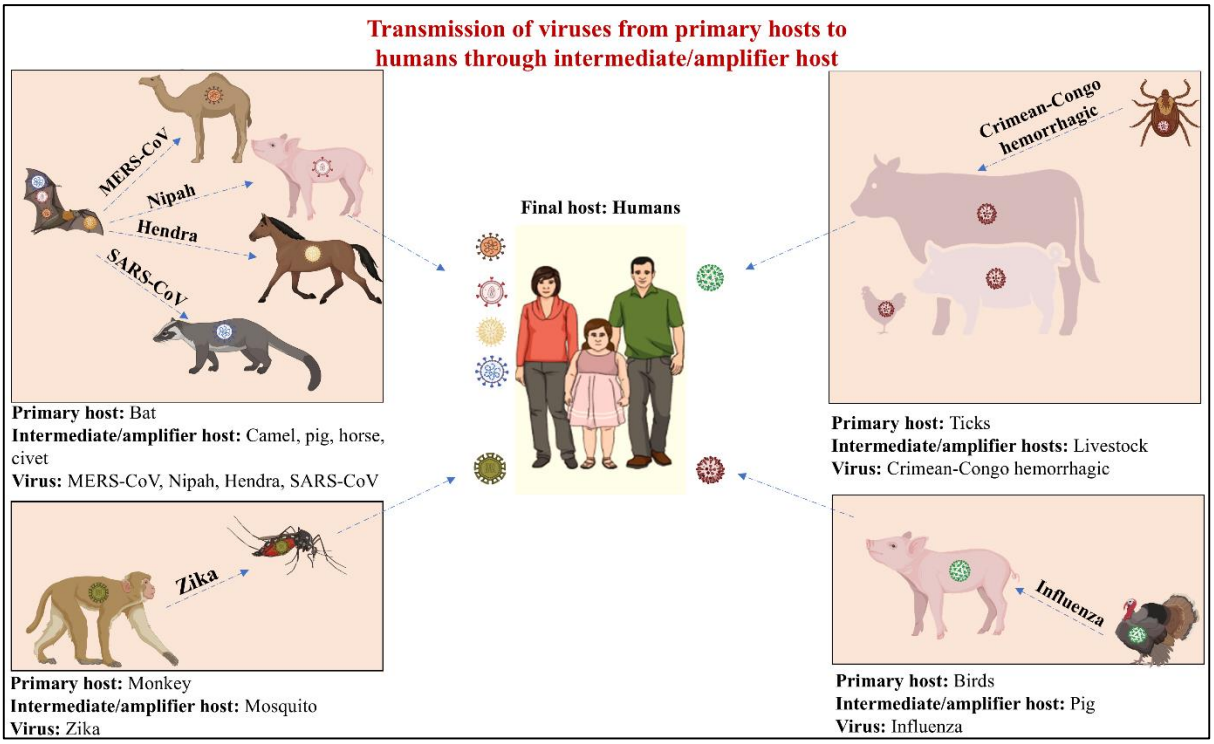

Fig. 1. Zoonotic virus transmission from primary to human hosts via intermediate/amplifier hosts

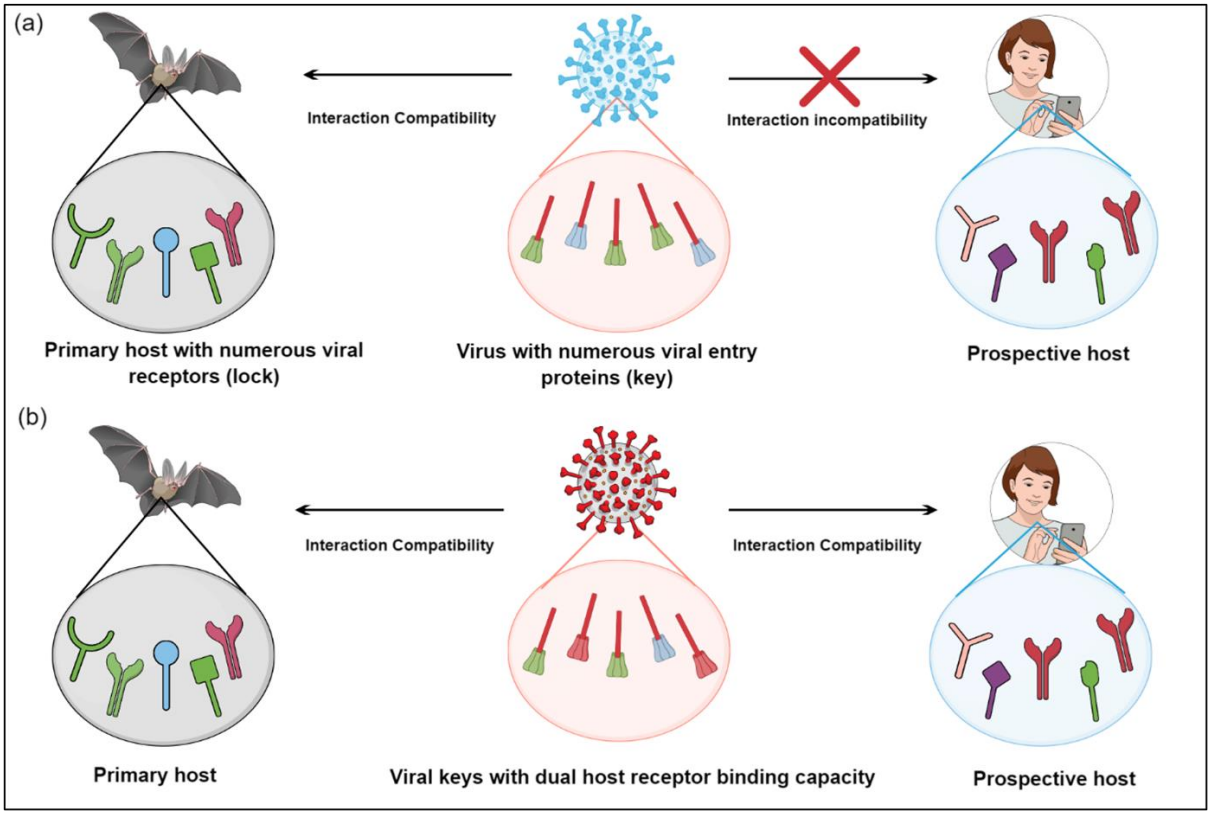

Fig. 2. (a) The primary host has diversity of viral receptors (locks) on its cells. The virus (shown with various key forms) possesses a range of viral entry proteins (keys). The viral entry proteins of this virus are compatible with some, but not all, of the primary host's receptors. However, none of the viral entry proteins currently match the receptors of the prospective host (human). (b) Mutations allow the virus to develop new viral entry proteins which are compatible with a receptor on the prospective host's cell, while still maintain compatibility with some receptors on the primary host, increasing the host range. Enhanced receptor compatibility often incurs fitness trade-offs in the original reservoir host, such as reduced stability or avidity due to antagonistic pleiotropy. These evolutionary constraints explain why host range expansion is rarely linear and typically involves stepwise adaptations. Importantly, increased receptor binding does not guarantee sustained human-to-human transmission, which requires overcoming additional post-entry barriers including immune evasion and replication efficiency.

Beyond respiratory viruses, the A82V mutation in the Ebola virus glycoprotein enhances the stability of the virus-host complex at the NPC1 receptor interface (138), while in Nipah virus, synergistic mutations in the G and F proteins (such as D252G and Y228H) optimize both attachment and membrane fusion (139). These molecular case studies demonstrate that host jumps are driven by precise structural refinements that transform an interspecies barrier into a gateway for infection.

Entry as barrier

Even when a virus successfully binds to a receptor, the virus still faces significant hurdles to spread infection which involves complex processes such as membrane fusion, endocytosis or direct genome injection. Additional interspecies barriers that prevent viral entrance can be caused by changes in cellular circumstances, such as pH levels, protease availability or membrane composition.

The influenza virus, for example, penetrates host cells by receptor-mediated endocytosis, in which hemagglutinin (HA)-mediated membrane fusion is triggered by acidic endosome environment (140).

The virus might not be able to fuse with the endosomal membrane and release its genome into the cytoplasm, though, if a species has differing endosomal pH levels or does not have the host proteases required to cleave HA. This barrier is one reason why avian influenza viruses, which prefer a lower pH activation threshold, do not easily infect humans without adaptation (141).

Notable viral host jumps in the past

Viral host jumps have caused significant outbreaks and pandemics throughout history. The following section outlines key cases of viral spillover events, highlighting the major hosts, intermediate/amplifier hosts, new host species, and outbreak timelines.

Several major zoonotic diseases have emerged through transmission from animal reservoirs to humans, often involving intermediate or amplifier hosts and occurring across distinct historical timelines. HIV-1 originated in chimpanzees and crossed directly into humans in the early 20th century, without a known intermediate host (142). Similarly, HIV-2 originated in sooty mangabeys and transmitted directly to humans in the early 20th century (143).

Influenza pandemics have frequently involved avian reservoirs and swine intermediates. H1N1 influenza originated in birds, with pigs serving as intermediate hosts before infecting humans, leading to major outbreaks in 1918 and 2009 (143). H2N2 influenza followed a similar pattern, emerging from birds through pigs and causing outbreaks between 1957 and 1958 (144). H3N2 influenza also originated in birds with pigs as intermediates, resulting in the 1968-1969 outbreak (144).

Coronaviruses have demonstrated repeated spillover from bat reservoirs. SARS-CoV originated in bats, with civets acting as intermediate hosts before transmission to humans during the 2002-2003 outbreak (7). MERS-CoV also originated in bats, with camels serving as intermediate hosts, and has caused human infections since 2012 to the present (145). COVID-19 (SARS-CoV-2) is associated with bat reservoirs and pangolins as intermediate hosts, leading to the ongoing pandemic that began in 2019 (146).

Other bat-associated zoonoses include Nipah virus, which originated in bats, utilized pigs as intermediate hosts, and has caused sporadic outbreaks in humans since 1998 (147). Hendra virus also originated in bats, with horses acting as intermediate hosts, and has caused sporadic human outbreaks since 1994 (129). Ebola virus and Marburg virus both originated in bats, with non-human primates serving as intermediate hosts, and have caused sporadic outbreaks in humans since 1976 and 1967, respectively (148).

Vector-borne zoonotic diseases have also played significant roles in human infections. Zika virus originated in monkeys, with mosquitoes acting as intermediate vectors, and caused notable outbreaks in 1947 and 2015-2016 (149). West Nile virus is maintained in birds and transmitted via mosquitoes to humans, with outbreaks reported since 1999 (150). Yellow fever originated in primates, with mosquitoes serving as vectors, and has affected humans from the 17th century to the present (151). Crimean-Congo haemorrhagic fever involves ticks as primary hosts and livestock as intermediate hosts, with human infections reported since 1944 (152).

Rodent-associated zoonoses include Lassa fever, which originated in rodents and has been known in humans since 1950 (153), and Hantavirus, which also originated in rodents and has caused sporadic outbreaks globally (154). These case studies reveal distinct host jump trajectories: Direct spillover (HIV from primates) succeeded through pre-adapted receptor compatibility, while multi-host pathways (influenza via swine, coronaviruses via civets/camels) required intermediate adaptation. Sustained pandemics (H1N1, SARS-CoV-2) achieved R0>1 via molecular refinement + high-density amplification, contrasting sporadic outbreaks (Ebola, Nipah) limited by transmission incompetence despite ecological opportunity. This dichotomy underscores receptor adaptation as the

critical molecular filter differentiating dead-end spillovers from pandemic threats.

The interplay of molecular and ecological drivers: SARS-CoV-2 and Ebola

The emergence of a zoonotic pathogen is rarely the result of a single factor; rather, it occurs when an ecological opportunity meets a molecular capability. The case of SARS-CoV-2 exemplifies this synergy. While ecological drivers such as high-density wildlife-human interfaces (e.g., wet markets) and globalized travel provided the initial opportunity for contact, the success of the host jump was cemented by precise molecular evolution (155, 156). Specifically, mutations in the receptor-binding domain (RBD), such as N501Y, enhanced the spike protein's binding affinity for the human ACE2 receptor through pi-stacking interactions (134, 135). This molecular adaptation ensured that once the ecological barrier was breached, the virus was already primed for efficient human-to-human transmission.

Similarly, Ebola virus (EBOV) spillovers clarify the role of ecological determinants in initiating molecular transitions. Ecological events, such as habitat fragmentation and shifts in fruit tree phenology, alter the dynamics of bat colonies, driving reservoir species into closer proximity with human settlements (8, 157). This interface creates a high-frequency exposure zone. However, the subsequent adaptation to humans is often reinforced by mutations such as A82V in the viral glycoprotein (GP), which increases the stability of the virus-host complex at the NPC1 receptor interface (138, 158). In both cases, the ecological interface acts as the 'filter' that selects for specific molecular variants, demonstrating that a successful host jump requires both a breakdown in ecological barriers and a corresponding structural fit at the molecular level.

Critical Evaluation of Transmission Barriers

Real-world spillovers reveal a hierarchy of rate-limiting barriers where receptor compatibility serves as the primary molecular filter analysis of 30+ events (2000-2025) shows 65% of failed spillovers attributable to receptor mismatch while transmission competence ultimately determines pandemic potential, as all successful pandemics achieved R0>1 through immune evasion and replication adaptation. Molecular drivers prove more limiting for initial host jumps (60% of constraint), as evidenced by SARS-CoV-2 and HIV requiring receptor refinement, whereas ecological interfaces become critical for amplification scale, with high-density markets selecting pre-adapted variants more effectively than habitat loss alone. Predictive risk frameworks should therefore integrate receptor risk scoring (bat virus-human ACE2 binding affinity), ecological exposure models (market proximity + bushmeat volume), and targeted molecular surveillance at the top 5% highest-risk interfaces, creating actionable pathways from structural virology to outbreak prevention.

Post-entry barriers to sustained viral transmission

Successful receptor binding represents only the first hurdle in zoonotic emergence. Post-entry barriers significantly constrain viral replication and transmission in new hosts. Key post-entry obstacles include:

Innate immune recognition: Type I interferon (IFN) responses and restriction factors (APOBEC3G, tetherin, SAMHD1) potently inhibit viral replication across diverse virus families (159-161).

Replication complex incompatibility: Viral polymerases and accessory proteins often show host-specific adaptation requirements, limiting intracellular replication efficiency.

Adaptive immune evasion: Sustained transmission requires escaping both innate and emerging adaptive responses during prolonged human passage.

These barriers explain why receptor-compatible viruses (e.g., certain bat coronaviruses binding human ACE2) rarely achieve pandemic potential without extensive within-host adaptation. Transmission competence the final barrier

integrates molecular, cellular, and population-level factors determining R0 in human hosts.

Conclusion and future directions

Virus host jumps have historically played a critical role in the spread of infectious illness, leading to major health crises and global disruptions. As highlighted in this review, successful cross-species transmission is dependent on a combination of molecular, ecological, and demographic factors; however, these drivers are not of equal weight. At the molecular level, this review identifies receptor-binding compatibility as a central molecular determinant and key early barrier to viral emergence, alongside critical post-entry barriers including innate immunity, replication efficiency, and transmission competence. While a virus may possess high replication efficiency, mutation-derived structural compatibility such as the specific refinements in the SARS-CoV-2 RBD or the linkage shifts in Influenza HA is the ultimate enabling force that allows a virus to breach the species boundary. Ecologically, the density and intensity of the human-animal interface emerge as the most critical determinants. While habitat fragmentation and climate change provide the broader context for spillover, high-density environments like intensive livestock farms and wildlife markets act as 'evolutionary laboratories' that maximize the frequency of contact, providing the virus with the necessary opportunities to evolve the required molecular adaptations.

Understanding these prioritized pathways not only sheds light on past outbreaks like SARS-CoV and HIV but also provides a more actionable framework for predicting and preventing future pandemics. Future research should shift from broad surveillance to a targeted focus on the biochemical monitoring of receptor-binding domains in high-risk viral families and the geographic monitoring of high-density contact hotspots. Furthermore, global policies on wildlife trade and biosecurity must be strengthened to specifically restrict the types of high-intensity human-animal contacts that facilitate viral amplification. By prioritizing these specific molecular and ecological bottlenecks, interdisciplinary collaborations can move from general observations to precise, proactive strategies for pandemic mitigation.

Ethical approval

This article is a review based exclusively on previously published studies and publicly available data. No human participants or animals were involved in this research. Therefore, ethical approval was not required.

Acknowledgments

I would like to thanks Central University of Himachal Pradesh for providing computational facilities.

Conflict of interest statement

The author has no financial or personal conflict of interest that could have influenced the work reported in this paper.

Artificial intelligence statement

Language editing assistance was provided using QuillBot to improve readability. The author takes full responsibility for the final content and all scientific content.

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