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MUTATIONAL DYNAMICS AND EVOLUTION OF ZONOTIC RNA VIRUSES IN NATURAL RESERVOIRS

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Abstract

The emergence of zoonotic RNA viruses poses a critical threat to global public health, with approximately 75% of new infectious diseases originating from animal reservoirs. While global evolutionary trends are well-documented, the intersection of viral mutational dynamics and regional ecological factors - particularly in Central Asia remains insufficiently integrated, hindering effective biosafety surveillance. This review follows the PRISMA guidelines, synthesizing molecular-genetic data from PubMed, Web of Science, and Scopus to analyze the mutational plasticity of RNA viruses and their circulation in natural reservoirs. Our analysis characterizes the molecular drivers of interspecies barriers and demonstrates that Kazakhstan's unique biogeographic landscape acts as a catalyst for region-specific viral evolution. We conclude that integrating «One Health» frameworks with metagenomic surveillance is essential to mitigate future zoonotic risks in the region.

Keywords: RNA viruses; mutational dynamics; zoonosis; natural reservoir; spillover.

ТАБИҒИ РЕЗЕРВУАРЛАРДАҒЫ ЗООНОЗДЫҚ РНҚ-ВИРУСТАРЫНЫҢ МУТАЦИЯЛЫҚ ДИНАМИКАСЫ МЕН ЭВОЛЮЦИЯСЫ

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Аңдатпа

Зоонозды РНҚ вирустарының пайда болуы жаһандық қоғамдық денсаулық сақтау жүйесіне елеулі қауіп төндіреді, оның ішінде жаңа инфекциялық аурулардың шамамен 75%-ы жануарлар резервуарларынан бастау алады. Жаһандық эволюциялық үрдістер жақсы зерттелгенімен, вирустың мутациялық динамикасы мен өңірлік экологиялық факторлардың (әсіресе Орталық Азияда) өзара байланысы жеткілікті түрде толықтырылмаған, бұл биоқауіпсіздік саласындағы тиімді эпидемиологиялық қадағалауға кедергі келтіреді. Бұл шолу PRISMA нұсқауларына сәйкес дайындалған және РНҚ вирустарының мутациялық икемділігі мен табиғи резервуарлардағы циркуляциясын талдау үшін PubMed, Web of Science және Scopus деректер базаларынан алынған молекулалық-генетикалық мәліметтерді жинақтайды. Біздің талдауымыз түр аралық кедергілерді жеңудің молекулалық факторларын сипаттайды және Қазақстанның ерекше биогеографиялық ландшафты өңірлік деңгейдегі вирустар эволюциясының катализаторы ретінде қызмет ететінін көрсетеді. Біз аймақтағы болашақ зоонозды қауіптерді азайту үшін «Біртұтас денсаулық» (One Health) тұжырымдамасын метагеномдық мониторингпен интеграциялау қажет деген қорытындыға келдік.

Кілт сөздер: РНҚ-вирустары, мутациялық динамика, зооноз, табиғи резервуар, тұраралық ауысу.

**МУТАЦИОННАЯ ДИНАМИКА И ЭВОЛЮЦИЯ ЗООНОЗНЫХ РНК-ВИРУСОВ
В ПРИРОДНЫХ РЕЗЕРВУАРАХ****Икрамкулова Ф.Р.^{1*}, Мәлік А.М.², Абдулжанова М.А.², Кирпиченко В.В.¹,
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Возникновение зоонозных РНК-вирусов представляет критическую угрозу для глобального общественного здравоохранения, при этом около 75% новых инфекционных заболеваний имеют природные резервуары. В то время как глобальные эволюционные тренды хорошо изучены, взаимосвязь между мутационной динамикой вирусов и региональными экологическими факторами (особенно в Центральной Азии) остается недостаточно проработанной, что затрудняет эффективный эпиднадзор в области биобезопасности. Данный обзор составлен согласно руководству PRISMA и объединяет молекулярно-генетические данные из баз PubMed, Web of Science и Scopus для анализа мутационной пластичности РНК-вирусов и их циркуляции в природных резервуарах. Наш анализ характеризует молекулярные факторы преодоления межвидовых барьеров и демонстрирует, что уникальный биогеографический ландшафт Казахстана выступает катализатором регионально-специфичной эволюции вирусов. Мы приходим к выводу, что интеграция концепции «Единого здоровья» (One Health) с метагеномным мониторингом является необходимой мерой для снижения будущих зоонозных рисков в регионе.

Ключевые слова: РНК-вирусы; мутационная динамика; зооноз; природный резервуар; межвидовой переход.

Introduction

The emergence and spread of new viral diseases (emerging infections) represent a critical threat to global public health and the economic stability of nations. Human history has been punctuated by viral outbreaks that reached pandemic scales, and it is now well-established that approximately 75% of these emerging infectious diseases in humans are zoonoses [1, 2, 3, 4].

Within the global scientific context, RNA viruses - including families such as *Orthomyxoviridae*, *Coronaviridae*, *Retroviridae*, and *Filoviridae* are the primary drivers of these threats. Their evolution is inextricably linked to their high mutational capabilities during circulation in natural reservoirs [5]. While high mutation rates (10^{-4} to 10^{-6} substitutions per site per cycle) and quasispecies dynamics are recognized as the foundation of this adaptation, global surveillance often struggles to predict the specific timing and location of spillover events [6, 7, 8, 9].

Despite extensive research on these mechanisms, a significant research gap remains: while global evolutionary trends are well-documented, the intersection between global mutational trajectories and regional ecological factors-particularly in complex biogeographic zones like Central Asia is insufficiently integrated. Scientific literature often treats global viral trends and regional epizootic data as separate entities, failing to unify them under a comprehensive «One Health» framework. Consequently, we lack a granular understanding of how regional biodiversity, such as that found in the unique ecosystems of Kazakhstan - a cross-continental corridor for migratory birds, tick vectors, and reservoir mammals acts as a catalyst for region-specific evolutionary trajectories [5, 10, 11].

This review addresses these gaps by synthesizing current knowledge on the molecular basis of RNA virus mutational dynamics with the ecological realities of natural reservoirs. The

novelty of this work lies in the correlation between regional biodiversity data and the specific evolutionary plasticities of RNA viruses in Central Asia. The primary objective of this study is to characterize the molecular drivers of interspecies barriers and to map evolutionary risks specific to the regional landscape of Kazakhstan, thereby providing a foundational basis for improved regional biosafety and epidemiological surveillance.

Materials and methods of research

Study design and search strategy

The methodological framework of this study is based on a systematic analytical review conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Relevant literature was identified and selected through comprehensive searches of international bibliometric databases, including PubMed, Web of Science, and Scopus. The search strategy focused on key markers of mutational dynamics, such as RNA-dependent RNA polymerase fidelity, nucleotide substitution rates, and proofreading mechanisms, utilizing search queries combining terms related to zoonotic RNA viruses, mutational dynamics, natural reservoirs, and spillover events.

Inclusion and exclusion criteria

The selection of literature was governed by strict inclusion and exclusion criteria. The study included peer-reviewed publications providing molecular-genetic, phylogenetic, or epizootological data on zoonotic RNA viruses, with a particular focus on virus-host interactions, evolutionary clustering, and regional epidemiology. Conversely, non-peer-reviewed literature, articles lacking primary molecular-genetic evidence, and duplicate reports were excluded from the analysis to ensure the scientific rigor of the review.

Data synthesis and selection process

In addition to classical review methodology, published molecular-genetic and phylogenetic studies were comparatively analyzed using data from international genetic repositories, including GenBank and GISAID. Particular attention was paid to viral genetic lineages, nucleotide substitutions, and evolutionary clustering associated with zoonotic pathogens circulating in natural reservoirs. To support the theoretical analysis of interspecies barrier crossing, data from the ZOVER (Zoonotic Virus Database) were interpreted to facilitate a comparative assessment of global evolutionary trends and regional ecological specificities. Finally, the epidemiological situation in the Republic of Kazakhstan was assessed through a systematic analysis of published epizootic monitoring data, molecular epidemiology studies, and phylogenetic investigations of viral isolates circulating within the region.

Results

Mutations, defined as stable changes in the nucleotide sequence of the genome, play a central role in the evolution of RNA viruses. Under conditions of selective pressure from the host and the environment, it is mutagenesis that provides viruses with the genetic plasticity necessary for adaptation and survival [12].

Underlying this plasticity is the low fidelity of the RNA-dependent RNA polymerase enzyme, which catalyzes viral genome synthesis. Unlike the DNA polymerases of cellular organisms, most viral RdRps lack 3'-5' exonuclease activity, i.e., a proofreading mechanism. An exception is found in RNA viruses with large genomes, such as coronaviruses, in which a proofreading enzyme has been identified; this reduces their mutation rate compared to other RNA viruses, although it remains high. Consequently, errors arising during replication are fixed in the progeny genome [13, 14].

The molecular basis of RNA virus plasticity is rooted in the architecture and catalytic kinetics of the RNA-dependent RNA polymerase (RdRp). In most RNA viruses, the RdRp lacks

3'-5' exonuclease activity, resulting in a high error rate during replication. However, the evolutionary trajectory of these viruses is significantly shaped by the interplay between intrinsic replication fidelity and host-imposed selective pressures. For instance, in Coronaviridae, the presence of the nsp14-ExoN proofreading complex allows for the maintenance of larger genome sizes and higher replication fidelity compared to Paramyxoviridae or Orthomyxoviridae.

Mutational processes in natural reservoirs are further driven by the host's immune environment, which acts as a filter for viral variants. In bats, for example, the unique interferon-signaling pathways may exert distinct selective pressures, favoring the emergence of 'quasispecies clouds' that are pre-adapted for zoonotic transmission. These quasispecies facilitate rapid adaptation, as the presence of diverse variants within a single infection allows for the immediate selection of phenotypes capable of binding to human cell surface receptors, such as ACE2 or sialic acid-containing glycoproteins, thereby bridging the interspecies barrier [15, 16, 17].

Table 1. Comparative molecular and evolutionary characteristics of selected zoonotic RNA virus families

Viral Family	Genome Type	Proofreading Mechanism	Primary Evolutionary Driver	Zoonotic Strategy
<i>Coronaviridae</i>	(+)ssRNA	nsp14-ExoN (Present)	Recombination & Drift	Broad receptor tropism
<i>Orthomyxoviridae</i>	(-)ssRNA (segmented)	Absent	Reassortment	Antigenic shift
<i>Paramyxoviridae</i>	(-)ssRNA	Absent	Rapid mutational drift	High cell-entry efficiency
<i>Nairoviridae</i>	(-)ssRNA (segmented)	Absent	Host-vector adaptation	Vector-borne transmission

The high replication rate of RNA viruses exponentially increases the cumulative effect of mutagenesis. Within a short period, viral populations undergo numerous replication cycles, leading to the rapid accumulation of genetic diversity.

Mutation frequency and character also depend on host factors; body temperature, cellular metabolic intensity, and, in particular, the immune response create potent selective pressure. The impact of the immune system or antiviral drugs facilitates the selection of viral variants that have acquired mutations allowing them to evade immune surveillance or develop drug resistance.

The rate of mutation accumulation differs among RNA virus families. For example, the substitution rate in Influenza A virus and Ebola virus is estimated at approximately 10^{-4} substitutions/site/year, whereas in SARS-CoV-2 this value is lower ($\sim 10^{-6}$ - 10^{-5}), which is associated with the proofreading activity of the nsp14-ExoN complex. Despite the lower mutation rate, coronaviruses retain a high adaptive potential due to extensive circulation within host populations and selective pressure exerted by the host immune system [18, 19].

From a molecular perspective, point substitutions are the most common, divided into transitions (purine $\leftrightarrow$ purine; pyrimidine $\leftrightarrow$ pyrimidine) and transversions (purine $\leftrightarrow$ pyrimidine). More significant structural genomic rearrangements can cause deletions, insertions, and recombinations [20, 21].

Most mutations are neutral or deleterious and are rapidly eliminated from the population. However, epidemiological significance is attached to mutations that confer adaptive advantages: increased transmissibility, resistance to immune response, or the ability to bind to new host receptors. Such mutations can drastically alter the epidemic potential of a virus.

High mutation levels result in the existence of RNA viruses as "quasispecies" - heterogeneous populations consisting of multiple genetically distinct but related genomes. This quasispecies structure provides the population with high adaptability. Processes of competition, selection of the fittest variants, and genetic drift constantly occur within it [8, 22]. It is also noted that single-stranded RNA viruses generally mutate faster than double-stranded viruses [14].

Mechanisms of crossing the species barrier

A zoonotic spillover, or the transmission of a virus from an animal reservoir to a human, is a critical event in the evolution of emerging infections. Many factors influence this process: intrinsic host and pathogen traits, their ecosystem, phylogenetic proximity, and external environmental conditions. However, simple co-habitation of humans with infected reservoir species does not appear to be a sufficient condition. Despite extensive human contact with wildlife and immense viral diversity, instances leading to successful human-to-human transmission remain rare, indicating the complexity of interspecies transitions [23, 24].

Any zoonotic pathogen causing disease in humans already possesses, to a certain degree, the ability to cross one or more barriers: interspecies (animal-to-human), intrahuman (dissemination within the organism), and interhuman (human-to-human) [23, 25, 26]. To firmly establish itself in a population and maintain sustained transmission chains, the pathogen must successfully overcome all three barriers.

The key molecular event for crossing the first, interspecies barrier is receptor binding and cell entry. The spatial structure of the viral surface protein must ensure high-affinity binding to receptors on the cell membrane of the new host. The emergence of such properties is typically the result of the accumulation of spontaneous mutations in the viral genome while still within the reservoir host population [27].

Upon successful entry, the virus faces the second, intrahuman barrier - the need to replicate and disseminate effectively. A decisive factor here is the specific tissues or organs where replication occurs. This is determined by cell susceptibility, host immune defense features, and local conditions such as temperature and pH. The site of replication may coincide with the entry point, but some pathogens form secondary foci that do not always match the sites from which the pathogen exits the body [28].

Finally, to cross the third, interhuman barrier, the virus must not only replicate but also acquire the ability for efficient and stable transmission between humans. To achieve this, it must acquire additional adaptive mutations. These mutations must optimize replication in tissues responsible for transmission, enhance resistance to innate and adaptive immunity, and ensure virion stability in the environment [27].

The evolution of SARS-CoV-2 serves as a clear illustration of this multistep process. Phylogenetic analysis points to its origin from viruses circulating in bats, likely involving an intermediate host. At the stage of interspecies transmission, a key role was played by mutations in the receptor-binding domain of the S-protein, which ensured high-efficiency binding to the human ACE2 receptor. Subsequent mutations arising within the human population were fixed and contributed to increased transmissibility and immune evasion - that is, the successful crossing of the third barrier [29, 30].

In contrast, the avian influenza H5N1 virus demonstrates high pathogenicity for humans but an extremely limited capacity for transmission. Molecular barriers, particularly suboptimal receptor binding (preference for α -2,3-sialic acids in the lower respiratory tract rather than α -2,6-sialic acids in the upper tract), limit its epidemic potential. Nevertheless, the risk remains that H5N1 could acquire this capacity through mutational drift or reassortment.

Comparison of SARS-CoV-2 and H5N1 demonstrates that the success of interspecies transmission is determined not only by viral pathogenicity, but also by the degree of adaptation to host receptor systems and mechanisms of human-to-human transmission. In this context, viral mutational dynamics acquire critical importance as a key factor influencing pandemic potential.

The rabies virus, like other RNA viruses, mutates constantly due to errors by its RNA polymerase. However, its key proteins responsible for entering nerve cells must maintain a strictly defined shape; therefore, most mutations in these regions are «weeded out» (negative selection), creating an illusion of viral stability [31].

Natural reservoirs as a platform for viral evolution

The relationship between wildlife and emerging diseases is key to understanding global public health threats. Zoonoses - infections transmitted to humans from vertebrate animals - account for up to 75% of all new infectious diseases. These include HIV, Ebola, highly pathogenic influenza viruses, and coronaviruses [29].

Natural reservoirs are a crucial link in the circulation of these viruses. These are animal species in whose populations the virus can persist for long periods, often without causing overt clinical signs of disease. The reservoir host creates a stable ecological niche in which the virus not only survives but actively evolves, undergoing replication, mutation, recombination, and - in the case of segmented viruses like influenza - reassortment.

The role of natural reservoirs is specific. Bats (order Chiroptera) are recognized reservoirs for many coronavirus strains, as well as filoviruses (Ebola, Marburg) and rhabdoviruses. Among the threats associated with bats, a prominent position is occupied by the Nipah virus (NiV), a highly pathogenic paramyxovirus whose primary natural reservoir is fruit bats of the genus *Pteropus*. According to studies by Ang et al. (2018) and Aditi et al. (2019), NiV is characterized by a critically high case-fatality rate (ranging from 40% to 100%) and the ability to infect a broad spectrum of tissues by binding to highly conserved ephrin-B2 and -B3 receptors. Transmission to humans occurs both directly through products contaminated with bat excretions and indirectly via intermediate hosts, such as pigs, highlighting the complex circulation pathways of the pathogen within the ecosystem [32, 33].

Features of their immune system allow them to carry viruses without developing disease, facilitating long-term circulation and pathogen diversification [28]. Rodents (order Rodentia) serve as reservoirs for hantaviruses and arenaviruses (Lassa virus). Wild waterfowl (order Anseriformes) are the primary natural reservoir for influenza A viruses, ensuring their global spread and genetic renewal during seasonal migrations. Transmission can occur directly from avian reservoirs or indirectly via the infection of other mammalian species, which then become sources of human infection [34, 35]. Additionally, wild and domestic animals such as raccoons, foxes, wolves, dogs, and cats serve as reservoirs for the rabies virus, a cause for concern by the WOA [36].

Thus, natural reservoirs function as dynamic biological platforms, providing viruses with conditions to generate genetic diversity and adapt, which ultimately increases the probability of a cross-species jump.

Regional aspects of zoonotic virus circulation: the example of Kazakhstan

Due to its geographical location and diverse natural zones (mountain ecosystems, steppes, and deserts), Kazakhstan represents a region with a high risk for the circulation and evolution of zoonotic RNA viruses. The biogeographic diversity, combined with the presence of vast populations of wild animals, rodents, bats, and arthropod vectors (ticks, mosquitoes), creates optimal conditions for maintaining natural foci of infections. Of particular importance is Kazakhstan's location at the intersection of major migratory bird routes across Central Eurasia, which facilitates the continuous introduction and genetic renewal of circulating viral lineages. Combined with the diversity of climatic zones, this creates favorable conditions for sustained viral circulation and the emergence of locally adapted pathogen variants.

Under these conditions, viruses persist for extended periods within resident populations of reservoir animals. Data analysis, particularly from the ZOVER, confirms the region's epidemiological significance [37]. According to these data, 177 zoonotic viruses isolated from flies, rodents, bats, and ticks have been registered in Kazakhstan (figure 1).

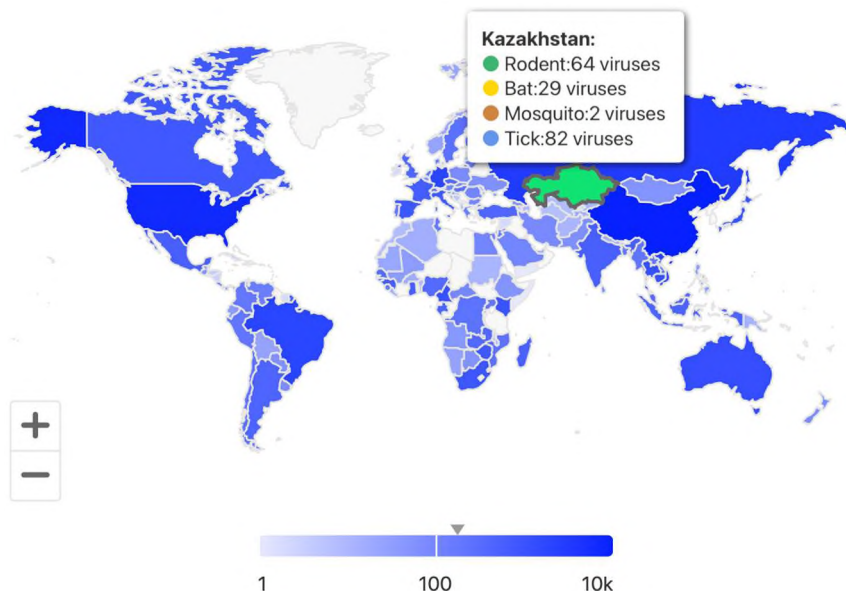


Figure 1. Comparative analysis of viruses identified in different hosts presented in the ZOVER database

The dominant reservoirs for these pathogens are ticks (associated with 82 viruses) and rodents (64 viruses). This indicates the high epidemiological significance of arboviruses transmitted by arthropods and viruses associated with rodents. The absolute majority of pathogens identified in the region are RNA viruses, which aligns with global trends (table 2). Such diversity and the active circulation of viruses in local ecosystems create prerequisites for mutational events and potential zoonotic spillovers, warranting the development of epidemiological surveillance systems in wildlife populations.

Table 2. Classification of viruses detected in different hosts (according to ZOVER data)

Genome type	Virus Families
ssRNA positive-strand viruses	<i>Caliciviridae, Astroviridae, Picornaviridae, Flaviviridae</i>
ssRNA negative-strand viruses	<i>Nairoviridae, Rhabdoviridae, Paramyxoviridae, Pneumoviridae, Orthomyxoviridae, Peribunyaviridae</i>
dsDNA viruses	<i>Poxviridae, Adenoviridae, Polyomaviridae, Orthoherpesviridae</i>
ssDNA viruses	<i>Genomoviridae, Anelloviridae, Circoviridae</i>
dsRNA viruses	<i>Sedoreoviridae</i>
DNA reverse transcribing viruses	<i>Hepadnaviridae</i>

This statistically confirmed epidemiological significance is most clearly manifested in the circulation of specific RNA viruses of high medical importance belonging to families that dominate the regional tick virome (figure 1).

The most pronounced epidemiological threat is posed by the circulation of arboviruses. In the desert and steppe ecosystems of the south (Kyzylorda, Turkistan, and Jambyl regions), endemic foci of the Crimean-Congo hemorrhagic fever virus (fam. *Nairoviridae*) are actively maintained. Here, the virus circulates in populations of the tick *Hyalomma asiaticum*, and its "Asia-1" and "Asia-2" genotypes consistently cause outbreaks among the human population [38]. Conversely, in the forest and mountain ecosystems of the east and north (Almaty region, Altai), foci of tick-borne encephalitis of the family *Flaviviridae* are formed. In these landscapes, the virus is maintained by a different reservoir - ticks of the genus *Ixodes* [39]. Furthermore, recent metagenomic studies confirm that the region is a "hotspot" for emerging viruses, identifying new pathogens from the family *Phenuiviridae* in ticks [40, 41].

Of particular note are studies of the bat virome in the cave complexes of Southern Kazakhstan. Molecular screening conducted in bat populations, specifically *Myotis blythii* and *Rhinolophus ferrumequinum*, revealed the circulation of new lineages of coronaviruses belonging to the genus *Alphacoronavirus*. Although the identified strains are phylogenetically distinct from SARS-CoV-2, the very presence of active circulation and high genetic diversity of coronaviruses in local bat populations confirms the region's role as a significant natural reservoir with the potential for interspecies transmission [10].

While the influenza virus circulates primarily in the reservoir of migratory birds, the rabies virus displays a distinct epizootic pattern linked to terrestrial mammals. According to local studies, an analysis of 989 foci registered in Kazakhstan between 2012 and 2021 revealed a clear separation of the infection into two dominant reservoir cycles: the anthropurgic cycle, most pronounced in the densely populated southern regions (Turkistan, Jambyl regions), where the virus actively circulates in domestic carnivore populations (192 cases); and the natural cycle, which dominates in the western region, where the maximum number of cases was recorded in wild predators [11].

Thus, the example of Kazakhstan clearly illustrates how various types of natural reservoirs - ticks, wild birds, and wild carnivores - combined with distinct strategies of mutational dynamics, form a complex and constantly evolving landscape of zoonotic threats.

Phylogenetic and molecular-genetic aspects of the circulation of zoonotic RNA viruses

Modern methods of molecular epidemiology and phylogenetic analysis make it possible to trace the origin, evolution, and spread of zoonotic RNA viruses through comparative analysis of nucleotide sequences available in international databases such as GenBank and GISAID.

According to published phylogenetic studies of SARS-CoV-2, viral variants circulating in Kazakhstan belonged to several genetic lineages, including B.1.1, B.1.1.7, and AY.122. Molecular-genetic analyses of whole-genome sequences revealed numerous nonsynonymous mutations in the ORF1ab, S, and ORF8 genes of Kazakhstani isolates, some of which were associated with altered functional properties of the virus. Published phylogenetic analyses of sequences deposited in the GenBank database demonstrated close genetic relatedness between Kazakhstani isolates and strains previously identified in Germany, Mexico, and other regions of Eurasia, indicating multiple routes of viral introduction and active circulation of diverse genetic lineages within the region [42].

Published phylogenetic data on SARS-related bat coronaviruses indicate the existence of several independent evolutionary lineages associated with recombination events involving the spike protein and ORF8 genes. The lineages most closely related to SARS-CoV-2 exhibit high nucleotide identity within the RdRp region; however, they differ in the structure of the receptor-binding domain, highlighting the important role of recombination in coronavirus evolution and in the emergence of novel variants capable of interspecies transmission [43].

For Crimean-Congo hemorrhagic fever virus (CCHFV) circulating in the southern regions of Kazakhstan, published phylogenetic analyses of the S and L genome segments demonstrated that local isolates belonged to the Asia-1 and Asia-2 genotypes. Kazakhstani strains showed a high degree of genetic similarity to strains identified in Uzbekistan, Turkmenistan, and China (92.1-98.4% nucleotide identity), confirming the existence of transboundary viral circulation across Central Asia. Furthermore, the identification of multiple genetic clusters indicates the simultaneous circulation of distinct evolutionary variants of the virus within populations of *Hyalomma* ticks [44, 45].

Molecular-genetic investigations of bat coronaviruses detected in Kazakhstan also confirmed the circulation of representatives of the genus Alpha-CoV. According to published analyses of the RdRp gene, the identified sequences formed distinct evolutionary branches within alphacoronaviruses, suggesting considerable reservoir diversity of coronaviruses within the natural ecosystems of the region [46].

Despite the growing accumulation of molecular-genetic data, the phylogenetic structure of zoonotic viruses circulating in Central Asia remains only fragmentarily characterized, limiting the ability to fully reconstruct their evolutionary pathways and patterns of interregional dissemination.

Thus, published phylogenetic evidence and comparative analyses of sequences from international genetic databases confirm the high genetic variability of zoonotic RNA viruses circulating in the natural reservoirs of Kazakhstan and neighboring territories. This underscores the need to expand regional genomic surveillance and integrate molecular epidemiological approaches into biological security systems.

Discussion

Evolutionary strategies and molecular plasticity

Our results demonstrate that the evolution of zoonotic RNA viruses is governed by distinct molecular strategies rather than a singular mutational path. The contrast between the conservative evolution of the rabies virus, driven by negative selection on its surface proteins, and the high plasticity of *coronaviruses*, supported by the nsp14-ExoN proofreading complex, highlights the diversity of adaptive mechanisms. While high mutation rates in families such as Paramyxoviridae and Orthomyxoviridae facilitate rapid antigenic variation, coronaviruses utilize a combination of moderate mutagenesis and efficient recombination. This indicates that assessing the pandemic potential of RNA viruses requires a family-specific approach, where

the presence or absence of proofreading mechanisms serves as a key predictor of adaptive capacity.

Regional ecological dynamics in Central Asia

The data presented for Kazakhstan identify this region as a critical interface for viral evolution. The presence of distinct reservoir cycles such as the anthroponotic and natural rabies cycles and the high diversity of tick-borne arboviruses in the south and east illustrate how ecological heterogeneity promotes the persistence of multiple genetic lineages. Our synthesis suggests that the role of Kazakhstan as a transboundary corridor is not merely geographical; it is a biological «hotspot» where migratory routes intersect with diverse resident mammal and vector populations. This convergence creates optimal conditions for the reassortment of segmented viruses and the recombination of non-segmented strains, potentially accelerating the emergence of novel variants.

Interpretation of phylogenetic findings

Published phylogenetic data for SARS-CoV-2 and CCHFV in Kazakhstan provide strong evidence for transboundary viral circulation. The high genetic similarity (92.1-98.4%) between regional CCHFV isolates and strains identified in neighboring Central Asian countries confirms that these viruses evolve within a shared ecological space. However, identified genetic clusters also reveal independent local trajectories within *Hyalomma* tick populations. This duality suggests that while viral spread is constant across the region, local ecosystems exert significant selective pressure, driving the formation of region-specific variants that may differ from global strains in virulence or transmissibility.

Implications for biosafety and integrated surveillance

The fragmented nature of current molecular data in Central Asia limits our understanding of viral evolution. We argue that epidemiological surveillance must shift from reactive clinical reporting to continuous genomic monitoring of natural reservoirs. Adopting a «One Health» framework integrating clinical records with metagenomic screening of vectors and wildlife is essential. Furthermore, our findings suggest that future antiviral development should focus on highly conserved regions of viral proteins, such as the RdRp complex, which are less prone to the rapid antigenic drift seen in surface glycoproteins.

Conclusion

The evolutionary dynamics of RNA viruses, coupled with their persistence in diverse natural reservoirs, pose an escalating threat to global public health. The inherent genetic plasticity of these viruses enables them to adapt rapidly, cross interspecies barriers, and evade host immune responses. In this context, natural reservoirs function as «evolutionary incubators» that facilitate constant viral diversification. Furthermore, anthropogenic activities such as climate change and land-use expansion continue to erode the boundaries between wildlife and human populations, significantly increasing the risk of zoonotic spillovers.

Addressing the threat of future pandemics requires a shift toward an interdisciplinary «One Health» framework. This approach must prioritize the integration of molecular research into viral evolution with continuous genomic surveillance. To improve the precision of these efforts, we recommend the implementation of modern diagnostic tools such as environmental DNA (eDNA) metabarcoding, which allows for the non-invasive identification of reservoir species in zoonotic hotspots. Ultimately, the development of universal vaccines and antiviral therapeutics targeting highly conserved viral proteins remains a crucial strategy to bolster global preparedness against current and emerging zoonotic threats.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used artificial intelligence tools (ChatGPT, Gemini) to assist with English language editing and translation in the Introduction and Discussion sections. All scientific interpretations, data collection, and statistical analyses were performed entirely by the authors. The AI tools were not used for data collection or analysis. The authors reviewed and verified all content, and take full responsibility for the originality and content of this publication.

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