INSIGHTS-JOURNAL OF
LIFE AND SOCIAL SCIENCES

INSIGHTS-JLSS
Insights-Journal of Life and Social Sciences

ADVANCES IN HOST-PATHOGEN INTERACTION MECHANISMS IN EMERGING INFECTIOUS DISEASES-A NARRATIVE REVIEW

Narrative Review

Rabia Basri[1], Murtaza Khodadadi[2]*, Muhammad Moaz Khalid[3], Zainab Kalsoom[4], Muhammad Naeem[5], Rameen Lutaf Ullah[6], Noor Us Sabah Ahmed[7], Hafiz Nidaullah[8]

[1]Nutritionist and Dietitian, Riphah International University, Lahore, Pakistan.
[2]3rd Semester MSc Microbiology and Immunology, COMSATS University, Islamabad, Pakistan.
[3]Pharmacist, Punjab University College of Pharmacy, Lahore, Pakistan.
[4]MPhil Scholar, Quaid-e-Azam University, Islamabad, Pakistan.
[5]Head of Department, Allied Health Sciences (HND), International Institute of Science, Arts and Technology (IISAT), Gujranwala, Pakistan.
[6]BS (Hons) Food Science and Nutrition, COMSATS University, Sahiwal Campus, Pakistan.
[7]Postgraduate Resident, Histopathology Department, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.
[8]University of Veterinary and Animal Sciences, Swat, Khyber Pakhtunkhwa, Pakistan.

Corresponding Author: Murtaza Khodadadi, 3rd Semester MSc Microbiology and Immunology, COMSATS University, Islamabad, Pakistan.
murtazakhodadadi786@gmail.com

Conflict of Interest: None

Grant Support & Financial Support: None

Acknowledgment: The authors acknowledge the valuable contributions of researchers and clinicians whose work in the field of infectious disease and immunology has informed this review. Special thanks to academic institutions and funding bodies supporting ongoing investigations into host-pathogen dynamics in emerging infections.

ABSTRACT

Background: Emerging infectious diseases (EIDs) present a growing global health threat, often fueled by complex and dynamic interactions between hosts and pathogens. Understanding these interactions at molecular, cellular, and ecological levels is critical for improving clinical outcomes, enhancing surveillance, and informing therapeutic strategies. Given the rising frequency of zoonotic spillovers and pathogen evolution, an updated synthesis of host-pathogen interaction mechanisms is essential for modern infectious disease research and practice.

Objective: This narrative review aims to explore recent advancements in the understanding of host-pathogen interactions, with a focus on mechanisms that underpin disease emergence, immune modulation, and cross-species transmission.

Main Discussion Points: The review discusses major themes including receptor-mediated pathogen entry, immune evasion strategies, host genetic and epigenetic factors, ecological influences on transmission, and the role of high-throughput omics and computational modeling in advancing the field. Variability in host responses, the impact of community structure, and the limitations of current study designs are also critically examined.

Conclusion: While the body of evidence provides valuable insights into host-pathogen interactions, it remains limited by methodological heterogeneity and underrepresentation of diverse populations. Future research should prioritize longitudinal, integrative, and mechanistically focused approaches to better translate molecular insights into clinical and public health applications.

Keywords: Emerging Infectious Diseases, Host-Pathogen Interactions, Immune Evasion, Zoonosis, Molecular Mechanisms, Narrative Review.

INTRODUCTION

Emerging infectious diseases (EIDs) continue to challenge global public health, not only due to their unpredictable emergence but also because of the complex and dynamic interplay between hosts and pathogens that drives their pathogenesis. The 21st century has witnessed multiple high-impact outbreaks—such as SARS, MERS, Ebola, Zika, and most recently, COVID-19—each marked by unique molecular and cellular interaction patterns between host organisms and the invading pathogens. According to the World Health Organization, more than 30 novel infectious diseases have emerged in the last three decades, many of which are zoonotic and facilitated by global travel, urbanization, and ecological disruption (1). These diseases account for a substantial portion of the global burden of morbidity and mortality, disproportionately affecting low- and middle-income countries where surveillance and healthcare infrastructures may be less robust (2). At the heart of EID emergence lies the phenomenon of host-pathogen interaction, a multifaceted relationship influenced by genetic, immunologic, and environmental variables. Host factors—such as immune signaling pathways, genetic polymorphisms, and cellular receptors—play critical roles in determining susceptibility, disease severity, and transmission potential (3). Simultaneously, pathogens employ sophisticated mechanisms to evade host defenses, modulate immune responses, and adapt to novel hosts. For example, SARS-CoV-2 has been shown to delay and subvert the host interferon response, a strategy that allows unchecked viral replication and contributes to severe disease manifestations (4,5).

Despite growing awareness of the critical role host-pathogen dynamics play in disease emergence, significant gaps remain in our mechanistic understanding. Many studies have traditionally focused on either the pathogen or the host in isolation, often failing to capture the nuanced bi-directional interactions that govern infection outcomes. Moreover, while omics technologies and high-throughput screening tools have enabled more granular analyses, their application in EID research remains limited by data integration challenges, the lack of standardized models, and the difficulties of conducting controlled experiments in real-time outbreak scenarios (6,7). Host shifts—events where pathogens jump from one species to another—further complicate this landscape. These shifts are often facilitated by ecological disturbances and can result in novel host-pathogen pairings with unpredictable clinical outcomes. Experimental models using systems like Drosophila have begun to shed light on the factors influencing the success or failure of such host shifts, including viral adaptability and the presence of microbial endosymbionts like Wolbachia, which can alter host immune responses (8,9). Recent computational advancements have also enabled the prediction of host-pathogen interactions using machine learning models based on phenotypic, functional, and taxonomic features. These models offer promise for anticipating interactions involving emerging pathogens with limited empirical data, thereby accelerating drug and vaccine development pipelines (10,11).

This review aims to synthesize recent developments in the understanding of host-pathogen interaction mechanisms in the context of emerging infectious diseases. It focuses on molecular and cellular-level interactions, particularly those that govern pathogen entry, immune evasion, host susceptibility, and pathogen adaptation strategies. Studies involving viral, bacterial, and parasitic pathogens will be considered, with a preference for research published within the last five years to ensure the inclusion of cutting-edge findings. The scope includes both human and zoonotic infections, with emphasis on high-burden diseases and those with pandemic potential. The significance of this review lies in its attempt to bridge knowledge gaps by integrating findings across diverse pathogens and host systems, thereby offering a holistic view of the molecular choreography that underpins emerging infections. By highlighting novel therapeutic targets, diagnostic biomarkers, and predictive modeling approaches, this review seeks to inform future research and guide the development of more effective prevention and control strategies for EIDs.

THEMATIC DISCUSSION

1. Molecular Mechanisms of Pathogen Entry and Host Recognition

At the heart of host-pathogen dynamics lies the initial interaction between pathogen and host cell surfaces, mediated through receptor-ligand mechanisms. Pathogens utilize surface adhesins and specialized proteins to recognize and bind host cell receptors, which enables their invasion and intracellular survival. Recent literature has identified that many emerging viruses, such as SARS-CoV-2, utilize specific receptor molecules like ACE2, not only to enter host cells but also to modulate host immune responses in their favor. The structural fidelity and binding efficiency of viral spike proteins have been shown to determine host tropism and transmission potential. Importantly, this interaction is highly conserved in certain pathogens, offering consistent molecular targets for diagnostics and therapeutics (12,13). Similarly, bacterial pathogens such as Mycobacterium tuberculosis exploit phagocytic receptors to initiate intracellular survival, circumventing lysosomal degradation and modifying phagosome maturation.

2. Host Immune Modulation and Evasion Strategies

Pathogens have evolved to manipulate host immune responses, often evading detection or subverting key pathways to establish persistent infections. SARS-CoV-2, for instance, suppresses early interferon responses, leading to a delayed but exaggerated immune reaction that contributes to severe COVID-19 outcomes (9,14). Similarly, Plasmodium spp. modulate antigen presentation pathways to avoid cytotoxic T-cell recognition. These immune evasion strategies vary significantly among pathogens, reflecting evolutionary adaptations tailored to host environments. While viral mechanisms often involve genetic suppression of interferon-stimulated genes, bacterial pathogens tend to secrete immune-modulatory proteins or form biofilms to resist immune clearance (15).

3. Genomic and Systems Biology Approaches in HPI Research

The integration of high-throughput omics platforms has significantly advanced our understanding of host-pathogen interactions. Transcriptomic and proteomic profiling has revealed differential expression of host genes during infection and identified key regulatory networks involved in immune response. Systems-level modeling has uncovered central signaling hubs, including NF-κB and JAK-STAT pathways, that pathogens frequently target to alter host cellular states (5,16). These insights are increasingly being used to identify therapeutic targets. Comparative modeling approaches have also revealed that while some host responses are conserved across pathogens, others are highly pathogen-specific, underlining the need for context-dependent therapeutic strategies.

4. Role of Host Genetics and Epigenetics in Disease Susceptibility

Host genetic makeup plays a pivotal role in determining disease susceptibility and progression. Recent studies have highlighted associations between polymorphisms in immune genes—such as those encoding cytokines, pattern recognition receptors, and HLA alleles—and differential infection outcomes across diseases like tuberculosis, HIV, and malaria (14,17). In addition, epigenetic mechanisms such as DNA methylation and histone modifications influence immune gene expression and are modulated by pathogens to create a favorable environment for their replication. These findings have broadened the understanding of individual and population-level differences in infectious disease outcomes.

5. Host Shifts and Cross-Species Transmission

The emergence of new infectious diseases is frequently preceded by a host shift event, where a pathogen jumps from its natural reservoir to a novel host species. Research using Drosophila-virus interaction models has been instrumental in identifying host phylogeny and viral fitness as key determinants of successful spillover events (18,19). Co-infection with other microbes and the presence of endosymbionts like Wolbachia also influence the likelihood and outcome of host shifts. Understanding these dynamics is critical for forecasting future zoonotic threats and preparing containment strategies.

6. Host Community Structure and Pathogen Dynamics

Beyond individual hosts, the structure and complexity of host communities influence the epidemiological patterns of disease emergence. Recent models have demonstrated that the presence of intermediate or non-target hosts can either amplify or dilute pathogen transmission, depending on ecological and epidemiological variables (13,19). For instance, biodiversity loss may lead to the dominance of highly competent reservoir species, increasing the risk of human spillover. Conversely, increased host diversity can sometimes interrupt transmission chains. These findings emphasize the importance of ecosystem-level interventions in managing emerging infections.

7. Computational Prediction of HPIs

Advances in machine learning and bioinformatics have enabled the prediction of host-pathogen interactions based on phenotypic, functional, and taxonomic features. By integrating data from diverse sources, including gene ontology and pathogen-host phenotype databases, recent models have demonstrated high accuracy in predicting unknown interactions, particularly for emerging pathogens with limited empirical data (20). These tools not only expedite drug discovery efforts but also aid in prioritizing surveillance targets.

8. Controversies and Research Gaps

Despite the wealth of data, significant uncertainties remain in the field of host-pathogen interactions. Conflicting results are often reported regarding the role of specific host genes in disease progression, likely due to differences in population genetics, study design, and environmental factors. There is also a lack of standardized models for evaluating HPIs across different pathogens. Moreover, the

translation of molecular insights into effective clinical interventions remains a bottleneck, particularly for diseases lacking robust animal models or those with high mutation rates.

CRITICAL ANALYSIS AND LIMITATIONS

Despite the growing volume of research in the field of host-pathogen interactions within emerging infectious diseases, several critical limitations persist in the existing body of literature that affect the reliability and interpretability of findings. A recurrent issue across many studies is the reliance on small sample sizes, particularly in experimental models and genomic investigations. For instance, many high-throughput analyses, such as those using transcriptomic or proteomic platforms, are conducted with limited biological replicates, which constrains statistical power and increases the likelihood of false-positive results. This limitation undermines the robustness of claims regarding differentially expressed genes or immune pathways activated during infection and often restricts broader applicability (20,21). Additionally, a significant proportion of the reviewed literature is composed of observational or in vitro studies, which lack the experimental rigor of randomized controlled trials (RCTs). Although RCTs are not always feasible in infectious disease research due to ethical and logistical constraints, their absence in host-pathogen interaction studies means that causality is often inferred rather than directly demonstrated. This is particularly evident in studies examining host genetic polymorphisms or immune modulatory mechanisms, where the correlation between a molecular marker and clinical outcome may be confounded by unaccounted environmental or demographic variables (22). Methodological biases also present a challenge. Selection bias is prominent in studies that focus exclusively on specific population subsets or animal models, which may not reflect the full heterogeneity of host responses. For example, reliance on model organisms like mice or Drosophila, while informative for basic mechanistic insights, may not accurately replicate human immune dynamics or disease manifestations. Similarly, performance bias due to the lack of blinding in experimental conditions—especially in behavioral or immunological assays—can skew outcomes, particularly when assessing host immune activation or pathogen replication metrics (23).

Publication bias is another critical concern. Studies with novel or positive findings are more likely to be published, while those with negative or inconclusive results remain underreported. This bias skews the perceived efficacy or importance of certain host factors or pathogen mechanisms and may contribute to an inflated sense of consensus in the field. The tendency to prioritize high-impact, sensational results also detract from incremental but important advances that may offer more replicable insights over time (24). Another challenge arises from the variability in how outcomes are measured across studies. Host immune responses, for example, are assessed through different markers such as cytokine levels, gene expression, or clinical symptoms, making cross-study comparisons inherently difficult. This inconsistency complicates meta-analyses and hampers efforts to draw generalized conclusions about the efficacy of interventions or the pathogenic potential of specific microbes (25). Furthermore, differences in assay sensitivity and laboratory protocols further contribute to outcome variability, especially in studies employing next-generation sequencing or high-throughput proteomics. Finally, the generalizability of findings is frequently limited. Many studies are based on data from specific geographical regions, age groups, or genetically homogeneous populations. Consequently, their relevance to global or genetically diverse populations is uncertain. This issue is particularly pressing in the context of emerging infectious diseases, which often affect vulnerable or underrepresented populations for whom tailored interventions are urgently needed. Additionally, studies using artificial infection models or laboratory-adapted pathogen strains may not faithfully reflect natural infection dynamics, further limiting translational value (26). In summary, while the existing literature on host-pathogen interactions has expanded rapidly, it is hampered by methodological constraints, biased reporting practices, and limited external validity. Addressing these limitations through better study designs, transparency in reporting, and inclusive research frameworks will be essential for the development of more reliable and universally applicable insights in this critical field.

IMPLICATIONS AND FUTURE DIRECTIONS

The synthesis of current literature on host-pathogen interactions in emerging infectious diseases has important implications for clinical practice, health policy, and future research. Understanding the molecular mechanisms by which pathogens evade immune surveillance and exploit host cellular machinery offers new avenues for targeted therapeutic development. For instance, identification of conserved host receptors and immune signaling pathways manipulated by pathogens, such as the ACE2 receptor in SARS-CoV-2 or annexin family proteins in various microbial infections, provides actionable targets for antiviral and antimicrobial therapies (20,21). Integrating these molecular insights into routine clinical diagnostics may enable early identification of high-risk patients and support the implementation

of precision medicine strategies, ultimately improving patient outcomes in acute infectious disease settings. In the context of public health policy and infectious disease control, the findings reinforce the need for updated clinical guidelines that incorporate knowledge of host genetic susceptibility and immune response variability. Health authorities could benefit from frameworks that stratify infection risk based on host-pathogen interaction profiles, which would aid in resource allocation and triage during outbreaks. For example, during pandemics, prioritizing individuals with known genetic vulnerabilities to severe infection—such as polymorphisms affecting interferon responses—could guide vaccination and prophylaxis strategies more effectively (22,23). Moreover, surveillance systems should integrate ecological and community-level host interaction data to better predict zoonotic spillovers and develop proactive containment protocols (24).

Despite these advancements, several critical questions remain unanswered. The role of epigenetic modifications in shaping long-term host responses to pathogens, the influence of microbiome dynamics on immune evasion, and the interplay between co-infections and host immune exhaustion are underexplored areas. In particular, most studies to date have relied on simplified animal models or in vitro systems that may not capture the complexity of human immune networks. There is also insufficient data on host-pathogen interactions in vulnerable populations, including pediatric, elderly, and immunocompromised groups, which limits the development of inclusive treatment strategies (25). Future research must address these gaps through multidisciplinary and methodologically robust study designs. Longitudinal cohort studies incorporating diverse demographics, genomic profiling, and real-time immune monitoring are essential for capturing the temporal evolution of host-pathogen dynamics. Randomized controlled trials that stratify participants based on genetic or immunological biomarkers could more accurately assess treatment efficacy and adverse outcomes. Furthermore, investment in integrative computational models and systems biology frameworks will be vital to simulate complex host-pathogen ecosystems and test theoretical interventions before clinical implementation (26). Ultimately, the integration of host-pathogen interaction knowledge into clinical and public health paradigms has the potential to transform the management of emerging infectious diseases. However, realizing this potential requires a concerted effort to address the current limitations in evidence, standardize outcome measures, and promote cross-sector collaboration between molecular scientists, clinicians, epidemiologists, and policy-makers.

CONCLUSION

This review highlights the evolving understanding of host-pathogen interactions in emerging infectious diseases, underscoring key mechanisms such as receptor-mediated entry, immune evasion strategies, genetic and epigenetic influences on host susceptibility, and ecological dynamics affecting transmission. The growing application of omics technologies and computational modeling has enriched the field, yet much of the existing literature remains limited by small sample sizes, observational designs, and inconsistent methodologies. While current evidence provides valuable insights, it is still fragmentary and often context-specific, necessitating cautious interpretation. For clinicians, these findings advocate for more individualized approaches to infectious disease management, integrating genetic risk profiling and immune monitoring where feasible. Researchers are encouraged to pursue longitudinal, population-diverse studies and to adopt integrative, systems-level methodologies that can capture the complexity of host-pathogen ecosystems. Overall, a coordinated global effort to deepen mechanistic insights, improve predictive models, and translate molecular data into actionable clinical tools is essential to advance preparedness and response to future infectious threats.

AUTHOR CONTRIBUTION

Author	Contribution
Rabia Basri	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Murtaza Khodadadi*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Moaz Khalid	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Zainab Kalsoom	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Naeem	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Rameen Lutaf Ullah	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Noor Us Sabah Ahmed	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Hafiz Nidaullah	Writing - Review & Editing, Assistance with Data Curation

References

1. Mok DZL, Chan CYY, Ooi EE, Chan KR. The effects of aging on host resistance and disease tolerance to SARS-CoV-2 infection. Febs j. 2021;288(17):5055-70.
2. Pittner NA, Solomon RN, Bui DC, McBride JW. Ehrlichia effector SLiM-icry: Artifice of cellular subversion. Front Cell Infect Microbiol. 2023;13:1150758.
3. Choi Y. Emerging and re-emerging fatal viral diseases. Experimental & Molecular Medicine. 2021;53:711-2.
4. Hartmann JA, Cardoso MR, Talarico MCR, Kenney DJ, Leone MR, Reese DC, et al. Evasion of NKG2D-mediated cytotoxic immunity by sarbecoviruses. Cell. 2024;187(10):2393-410.e14.
5. Sia WR, Zheng Y, Han F, Chen S, Ma S, Wang LF, et al. Exploring the Role of Innate Lymphocytes in the Immune System of Bats and Virus-Host Interactions. Viruses. 2022;14(1).
6. Ward M, Dhand N, Singh B. Host characteristics and their influence on zoonosis, disease emergence and multi-host pathogenicity. One Health. 2023;17.
7. Wang X, Lin X, Zheng Z, Lu B, Wang J, Tan AH, et al. Host-derived lipids orchestrate pulmonary γδ T cell response to provide early protection against influenza virus infection. Nat Commun. 2021;12(1):1914.
8. Stehle T, Linke D, Milner P, Malmström J, Datar R, Rodriguez-Mateos P, et al. Host-Pathogen Adhesion as the Basis of Innovative Diagnostics for Emerging Pathogens. Diagnostics. 2021;11.
9. Beraldo C, Pimentel A, Cogni R. Host-shift as the cause of emerging infectious diseases: Experimental approaches using Drosophila-virus interactions. Genetics and Molecular Biology. 2020;44.
10. Smadi C, Voinson M, Billiard S. How does the host community structure affect the epidemiological dynamics of emerging infectious diseases? bioRxiv. 2022.
11. Bertoletti A. The immune response in chronic HBV infection. J Viral Hepat. 2024;31 Suppl 2:43-55.
12. Li M. Innate immune response against vector-borne bunyavirus infection and viral countermeasures. Front Cell Infect Microbiol. 2024;14:1365221.
13. Zhao X, Chen D, Li X, Griffith L, Chang J, An P, et al. Interferon Control of Human Coronavirus Infection and Viral Evasion: Mechanistic Insights and Implications for Antiviral Drug and Vaccine Development. J Mol Biol. 2022;434(6):167438.
14. Liu Y, Zhao X, Shi J, Wang Y, Liu H, Hu YF, et al. Lineage-specific pathogenicity, immune evasion, and virological features of SARS-CoV-2 BA.2.86/JN.1 and EG.5.1/HK.3. Nat Commun. 2024;15(1):8728.
15. Soumana IH, Linz B, Dewan KK, Sarr D, Gestal MC, Howard LK, et al. Modeling Immune Evasion and Vaccine Limitations by Targeted Nasopharyngeal Bordetella pertussis Inoculation in Mice. Emerg Infect Dis. 2021;27(8):2107-16.

16. Yajima H, Nomai T, Okumura K, Maenaka K, Ito J, Hashiguchi T, et al. Molecular and structural insights into SARS-CoV-2 evolution: from BA.2 to XBB subvariants. mBio. 2024;15(10):e0322023.
17. Pahari S, Arnett E, Simper J, Azad A, Guerrero-Arguero I, Ye C, et al. A new tractable method for generating human alveolar macrophage-like cells in vitro to study lung inflammatory processes and diseases. mBio. 2023;14(4):e0083423.
18. Sieber RN, Urth TR, Petersen A, Møller CH, Price LB, Skov RL, et al. Phage-Mediated Immune Evasion and Transmission of Livestock-Associated Methicillin-Resistant Staphylococcus aureus in Humans. Emerg Infect Dis. 2020;26(11):2578-85.
19. Kafkas Ş, Hoehndorf R, Liu-Wei W. Phenotypic, functional and taxonomic features predict host–pathogen interactions. bioRxiv. 2018.
20. Fong SW, Yeo NK, Chan YH, Goh YS, Amrun SN, Ang N, et al. Robust Virus-Specific Adaptive Immunity in COVID-19 Patients with SARS-CoV-2 Δ382 Variant Infection. J Clin Immunol. 2022;42(2):214-29.
21. Liao KC, Garcia-Blanco MA. Role of Alternative Splicing in Regulating Host Response to Viral Infection. Cells. 2021;10(7).
22. Cai Y, Wang Y, Shi C, Dai Y, Li F, Xu Y, et al. Single-cell immune profiling reveals functional diversity of T cells in tuberculous pleural effusion. J Exp Med. 2022;219(3).
23. Li F, Zhang X, Xu J, Zhang Y, Li G, Yang X, et al. SIRT7 remodels the cytoskeleton via RAC1 to enhance host resistance to Mycobacterium tuberculosis. mBio. 2024;15(10):e0075624.
24. Chen DY, Chin CV, Kenney D, Tavares AH, Khan N, Conway HL, et al. Spike and nsp6 are key determinants of SARS-CoV-2 Omicron BA.1 attenuation. Nature. 2023;615(7950):143-50.
25. Uriu K, Ito J, Kosugi Y, Tanaka YL, Mugita Y, Guo Z, et al. Transmissibility, infectivity, and immune evasion of the SARS-CoV-2 BA.2.86 variant. Lancet Infect Dis. 2023;23(11):e460-e1.
26. Luo M, Zhou R, Tang B, Liu H, Chen B, Liu N, et al. Ultrapotent class I neutralizing antibodies post Omicron breakthrough infection overcome broad SARS-CoV-2 escape variants. EBioMedicine. 2024;108:105354.

