fortune Journals

Review Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH
ISSN: 2572-5017

Common Challenges to the Development of Novel Antivirals to Tackle Re-emerging Infections of Pandemic Potential

Yu Wu MD[1#], Shuo Hu MBA[2#], Feng Liu MD[3*]

Abstract

Herpesviruses, HIV, Ebola virus, influenza viruses and flaviviruses like dengue virus (DENV) continue to pose a global threat due to their capacity for rapid genetic evolution. As the molecular arms race escalates, technology-driven antiviral discovery is central to modern preparedness. Emerging innovations now complement traditional direct-acting antivirals that target virus-encoded proteins and broad-spectrum agents that modulate shared viral and host pathways. High-throughput screening platforms, AI-enabled drug discovery engines, and computational protein–ligand modeling are also accelerating the identification of antiviral agents at an unprecedented speed. Drug repurposing, supported by machine learning-driven prediction of off-target antiviral activity is now a strategy in outbreak settings where clinical trial windows are compressed. Beyond small molecules, programmable RNA therapeutics, CRISPR-based antivirals, engineered peptide inhibitors, and monoclonal/bi-specific antibodies are redefining therapy. Despite these advances, significant challenges remain. Viral diversity means that resistance can emerge rapidly, meaning broad-spectrum activity without compromising safety remains challenging. These issues are beginning to be addressed through genomic surveillance networks, integrated clinical trial platforms, and globally coordinated research ecosystems. To strengthen global health resilience, future antiviral programs will require expanded investment in next-generation technologies, automation-assisted drug discovery pipelines, and scalable manufacturing/stockpiling systems. This review uses four exemplar viruses namely herpesviruses, DENV, Ebola virus, and influenza virus to outline common technological challenges and highlight the innovative strategies shaping the next era of antiviral development.

Keywords: Antiviral drug development; Direct-acting antivirals (DAAs); Broad-spectrum antivirals; Drug repurposing; RNA-based therapies; Biologics; Emerging viruses; Pandemic preparedness; Genomic surveillance; Clinical trial infrastructure; Global health collaboration

Introduction

Virus infections continue to emerge and evolve at an alarming rate [1]. They have huge capacity to cause widespread morbidity and mortality, exemplified by their high levels of transmissibility, zoonotic reservoirs, and ability to genetically adapt to therapy (Figure 1). All of which pose challenges to traditional containment and therapeutic strategies [2].

The discovery of effective antiviral interventions is central to mitigating the imminent threat of a global pandemic. The most effective antiviral drugs have focussed on virus-specific processes, resulting in agents with a potent but narrow-spectrums of activity and vulnerability to resistance [3]. Recent advances

Affiliation:
[1]Department of Clinical Laboratory and Blood Transfusion, Chinese People's Liberation Army Joint Logistic Support Force 908 Hospital, Nanchang, Jiangxi, 330002, China

[2]Department of Innovation and Development, Shanghai SPSENS Technology Co., Ltd., Shanghai 200131, China

[3]Department of Scientific Research, Beijing Fresta Technologies Co, Ltd., Beijing 100176, China

***Corresponding author:**
Feng Liu, Department of Scientific Research, Beijing Fresta Technologies Co, Ltd., Beijing 100176, China.

[#]The authors contributed equally to this study.

Citation: Yu Wu, Shuo Hu, Feng Liu. Common Challenges to the Development of Novel Antivirals to Tackle Re-emerging Infections of Pandemic Potential. Archives of Clinical and Biomedical Research. 10 (2026): 99-107.

Received: February 26, 2026
Accepted: March 03, 2026
Published: March 11, 2026

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

Pandemic Threat	Representative Viruses	Why?	Current treatment options	Key gaps / limitations
Coronaviruses	SARS-CoV-2, SARS-CoV-1, MERS-CoV	Risk of zoonotic spillover, respiratory transmission; rapid evolution	**Direct-acting antiviral** (e.g. remdesivir, nirmatrelvir/ritonavir, molnupiravir); **monoclonal antibodies** (variant-dependent); supportive care	AntiVirus resistance risk; loss of mAb efficacy; no broad-spectrum coronavirus drugs
Influenza viruses	Seasonal influenza A/B; avian H5N1, H7N9	Antigenic drift (segmented genomes); avian reservoirs	**Neuraminidase inhibitors** (oseltamivir, zanamivir); **polymerase inhibitors** (baloxavir); vaccines (strain-matched)	Resistance; small therapeutic window; vaccine production for emerging pandemic
Filoviruses	EBOV, Sudan EBOV, Marburg Virus	High fatality rates; zoonotic outbreaks	**Monoclonal antibodies** (e.g. mAb114, REGN-EB3 for Ebola); supportive care	Limited drugs availability; no broad-spectrum filovirus antivirus
Paramyxoviruses	Nipah Virus, Hendra Virus, measles Virus	Bat reservoirs; high mortality; poor global immunity	No approved antiviral; **supportive care**; ribavirin; mAbs under development	No antiviral; limited clinical trial data; poor pandemic readiness

Figure 1: Current and largest know threats of a global pandemic. Exemplar Viruses related to those discussed in this review are highlighted.

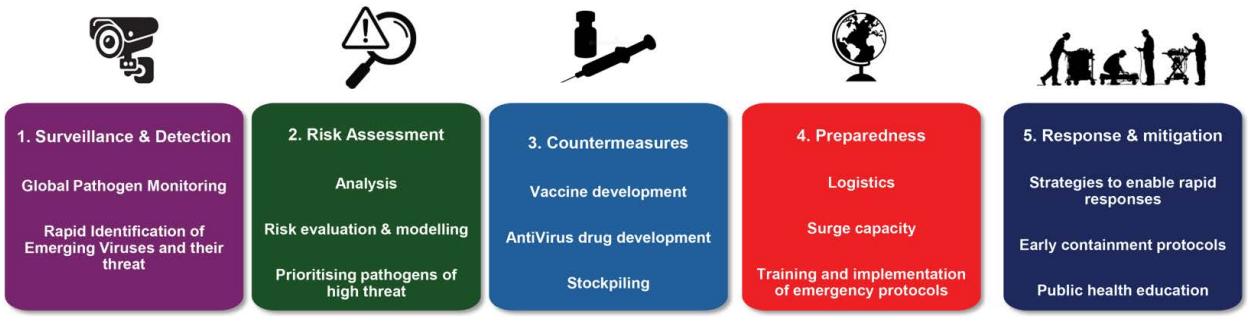

Figure 2: Key stages of Global pandemic preparedness. These encompass effective surveillance and detection, accurate risk assessment to guide planning strategies, stockpiling of antiviral agents, preparation of health systems for larger patient numbers and clear and effective delivery of health care programs.

in molecular techniques, structural biology approaches (crystallography and CryoEM), and computational drug design, have enabled more targeted strategies to combatting virus infections [4]. Herein, we use four exemplar viruses (Herpeviruses, DENV, Ebola virus and influenza virus) to discuss current problems, areas of promise and the next stages required for effective antiviral drug development.

Significant challenges remain for antiviral drug development. High mutation rates in viruses, the complexity of host-virus interactions, and the balance between safety and efficacy underscore the importance of a multi-pronged approach. The unpredictability of viral emergence means that world-class genomic surveillance is needed, combined with rapid risk assessment and health system prepardness (outlined in Figure 2). This combined with global collaboration and scalable treatment/response platforms represents the most effective route to effective drug development [5].

In this review, we discuss current strategies in antiviral development for exemplar viruses (Herpesviruses, DENV, Ebola virus and Influenza virus), highlight key scientific and logistical challenges that remain with their treatment, and provide pan-viral recommendations for strengthening pandemic preparedness through collaborative research and drug discovery innovation.

Virus

Herpesviruses

Herpesviruses are a large family of enveloped, double-stranded DNA viruses with complex lifecycles (Figure 3). This includes persistence in hosts [6]. Importantly, Herpesviruses are considered a re-emerging pathogen due to the increase in prevalence of factors that trigger their reactivation from a latent (resting) to lytic (active) state [7]. Up to nine virus genotypes are known to infect humans. These include Alphaherpesvirinae (HSV-1, HSV-2, VZV), Betaherpesvirinae (CMV, HHV-6/7), and Gammaherpesvirinae (EBV, HHV-8) [8]. HSV-1 currently infects ~65% of individuals under 50; HSV-2 infects ~13% of adults aged 15–49 [9]. Both are epidemiologically correlated [10]. Regarding diseases spectrum, HSV-1 and HSV-2 are associated with genital lesions, cold sores, keratitis and

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

encephalitis. This can be fatal in neonates [11]. VZV is associated with varicella (chickenpox) and reactivation as shingles, frequently with postherpetic neuralgia [12,13]. EBV and HHV-8 lead to Burkitt lymphoma (fast growing high grade non-Hodgkin lymphoma), nasopharyngeal carcinoma and Kaposi's sarcoma [14]. HCMV in healthy adults shows limited symptoms but can cause congenital defects in immunocompromised patients [15]. Most infections are asymptomatic but virus shedding can still occur which facilitates transmission. During the lytic phase, virus replication occurs in epithelial cells resulting in virion production. During the latent phase, viruses persist but with restricted gene expression. Reactivation (and its associated disease pathology), can occur at any time [16].

Current diagnostics include RT-PCR of blood, cerebrospinal fluid, and mucocutaneous swabs. Multiplexed platforms that detect HSV-1, HSV-2, VZV, CMV, and EBV are also available [17]. Triplex and multiplex PCR panels also show utility for cases where the clinical presentation overlaps among HSV, VZV, and related viruses, allowing tailored antiviral therapy and infection-control [18].

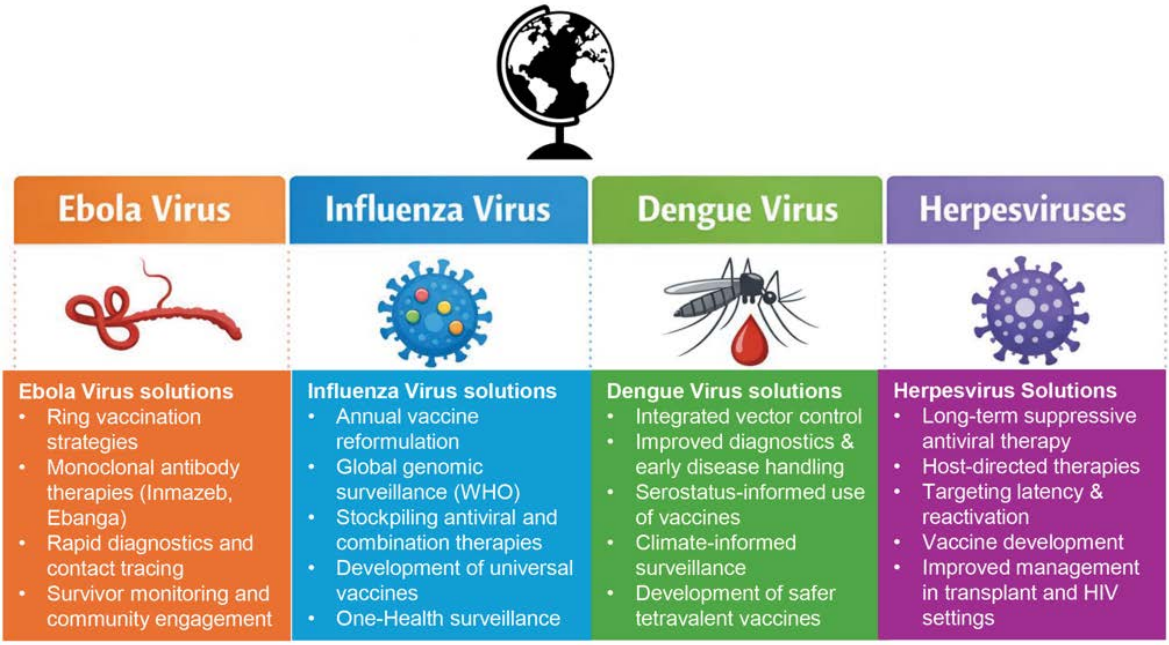

Figure 3: Summary of the proposed therapeutic solutions for Ebola Virus, Influenza Virus, Dengue Virus and Herpesviruses.

Current treatment regimens and emerging antiviral resistance

Standard antiviral regimens for herpesvirus include (but are not limited to) the nucleoside analogues acyclovir, valacyclovir (prodrug of acyclovir), and famciclovir [19]. Helicase-primase inhibitors including pritelivir can disrupt the unwinding/priming process crucial for HSV replication and are showing promise as a potential therapeutic. Whilst all improve symptoms, they fail to clear persistent and latent infections. A major problem is the emergence of resistant strains. These are common in immunocompromised populations, particularly transplant recipients, HIV-positive patients and those undergoing extended treatment/therapy. Resistance primarily maps to both DNA polymerases and/or virus encoded kinases [20], exerting structural changes that reduce drug efficacy. Ongoing public health concerns due to virus-associated stigma and increased HIV risk, particularly with genital herpes also remain significant hurdles for successful antiviral campaigns [21].

Limitation of treatments and gaps in current approaches

Treatment limitations, latency, resistance, and the lack of an effective vaccine underscore the complexity of treating herpesvirus infections [22]. Acyclovir targets the DNA polymerase but face resistance issues as a monotherapy. Recent structural studies have begun to add important information into the 3D design of novel antiviral agents. Approaches of interest include knowledge of the assembly pathway (scaffold proteins and procapsid intermediates) that may be amenable to disruption with small molecules; the heterogeneity in capsid structures which may limit pan-viral approaches, glycoprotein structures that can reveal druggable opportunities to perturb virus-host cell engagement and fusion and high-resolution structures of the helicase-primase complex (UL52, UL8) that continue to shed light on the mechanisms controlling the initiation of replication [23].

Research into vaccine development has been extensive and prolonged, but with limited success due to failures in

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

clinical trials. Current advances in this area focus on the induction of polyfunctional antibody responses, enhancing T-cell immunity and the delivery of antiviral agents via AAV approaches (Figure 4). The next stages for anti-herpesvirus therapies should aim to target both latency and resistance. This can be supported by further clinical trials for more effective prophylactic and therapeutic vaccines, increased epidemiological surveillance to track evolving transmission trends and high-risk demographics and a specific focus on patient genetics and at-risk individuals, most notably on resistant infections in immunocompromised and neonatal populations.

Dengue Virus

Dengue virus (DENV) is a single-stranded, +ve-sense RNA virus in the Flaviviridae family. It circulates as 4 serotypes (DENV-1 to DENV-4) that are transmitted by Aedes aegypti and Aedes albopictus mosquitoes (Figure 3). These vectors drive is emergence due to a complex interplay of climate change, urbanization, and increased global travel that has extended their global habitat and ability to transmit disease. DENV is endemic in ≥ 100 countries with a total of ~390 million infections occurring annually, causing a massive disease burden [24]. The virus is the major cause of Dengue fever, typically presenting as fever, headache and myalgia [25]. DENV causes haemorrhagic fever and dengue shock syndrome in severe cases, both of which can be fatal. A continual problem is DENV-mediated antibody-dependent enhancement, caused by previous infections with another DENV serotype that leads to more severe disease upon the second round of infection with another serotype [26]. The economic impact of DENV is also significant due to high rates of hospitalization and a loss of productivity due to DENV-mediated illness in endemic regions [27].

DENV lacks an effective vaccine. Dengvaxia was licensed but its use is limited to seropositive individuals as the risk of severe disease is high in seronegative recipients [25]. Cross-serotype immunity also remains a significant hurdle to DENV treatment. The picture for antivirals is similarly limited. Current patient management in DENV infected individuals involves hydration and monitoring [28]. Antivirals can be administered but often from an experimental standpoint. Mosnodenvir is an exemplar of a drug that shows some promise, but is not effective enough for widespread treatment [29]. Human challenge studies have reported a dose-dependent reduction in infection rates of ~60% with accompanying decreases in circulating DENV RNA [24]. Its mechanism of action involves inhibition of the viral NS3–NS4B interaction that is essential for virus replication. Diagnosis and rapid treatment also remains an issue as early symptoms present as febrile illness. Scalable and deployable diagnostics that accurately detect DENV infection remain lacking in many endemic regions. Current diagnostics include a combination of RT-PCR, NS1 detection, and serological assays for IgM/IgG antibodies. The selected test can vary dependent on the stage of infection [30]. During acute infection (up to 10 days), DENV RNA is detectable in the serum and NS1 can be identified via ELISA. At later stages of infection, IgM and IgG antibodies increase and their detection forms part of the diagnostic arm. Cross-reactivity with other flaviviruses can however complicate interpretation. Multiplexed platforms, biosensors and NGS all represent emerging technologies that offer hope for early detection during any future outbreak [31].

Approach	Primary target	Strengths	Limitations
Entry inhibitors	Virus attachment or fusion	Prevent infection at first step; high potential for prophylaxis	Often Virus-specific; resistance via receptor or envelope mutations
Polymerase inhibitors	Virus RNA or DNA polymerase	Target enzymes conserved across viruses; wide applicability	Resistance mutations; potential host toxicity (mitochondrial effects)
Protease inhibitors	Virus proteases	High potency; well-validated class	Resistance can emerge; drug–drug interactions
Cap formation / transcription inhibitors	Virus RNA capping or transcription machinery	Highly conserved targets	Few approved drugs; selectivity challenges
Assembly & release inhibitors	Virion maturation or egress	Limit virus spread	Narrow treatment window; resistance reported
Host-targeted antivirals	Host factors required for Virus lifecycle	High resistance barrier	Toxicity risk; host pathway redundancy
Immunomodulators	Host immune response	Broad effects; adjunctive use	Variable efficacy; inflammatory side effects
Monoclonal antibodies	Virus surface antigens	Highly specificity and scalable rapidly	Antigenic drift; IV/SC delivery
RNA-modalities	Virus RNA	Programmable and can be retargeted	Delivery challenges; innate immune activation
CRISPR	Virus RNA or DNA	Precise targeting	Delivery and safety not yet mature
Combination therapy	Multiple Virus/host targets	Low likelihood of resistance	Increased complexity; cost

Figure 4: Advantages and limitations of current and emerging antiviral drug strategies.

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

The next stages for DENV includes the advancement of NS3 protease and NS5 polymerase targeting therapeutics, by analogy to the success of these approaches for other flaviviruses (Figure 4). Combination therapy involving pairing host-targeted therapies with DAAs would also offer hope for resistance and improve outcomes. Exemplars include UV-4B (32), endosome acidification (chloroquine), and intracellular lipids (lovastatin, prednisolone).

Broad-Spectrum antivirals that target conserved processes of flavivirus replication such as fusion inhibitors and glycan-binding molecules also offer attractive treatment options. RNA-based therapeutics including oligonucleotides that target DENV genomes are also emerging, however these require improvements in delivery systems (nanoparticles and lipids) to ensure stability and tissue targeting. Immune pathway modulators and the use of cyclophilins to target the host factors required for DENV replication also offer hope for combination approaches.

Remaining challenges for DENV

- Safety and mitigating ADE mitigation.
- Rapid diagnostics for timely therapeutic intervention.
- Global collaboration: Clinical trials, surveillance, and further focus on resistant infections in immunocompromised and neonatal populations.

Influenza virus

Influenza viruses remain the most persistent global pandemic threat due to the high prevalence of zoonotic reservoirs, high mutation rates, and capacity for rapid global transmission (Figure 3) [33,34].

Pandemic preparedness for influenza relies on vaccine readiness and antiviral stockpiling. The WHO plays a central role in monitoring circulating strains in both humans and animals, enabling early detection of those with pandemic potential (35). Surveillance is complemented by preparedness at a national level.

Despite advances in both the treatment of control of Influenza virus, preparedness remains challenging due to limited manufacture of vaccines, antigenic shift, and low access to antiviral countermeasures [34]. This highlights the importance of non-vaccine interventions as first-line tools in pandemic response (Figure 4).

Current antiviral strategies include Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir) that inhibit viral assembly and release. All have been used to combat seasonal and pandemic influenza cases [36]. If administered early after infection, all can reduce disease severity, but resistance has emerged, most notably for seasonal H1N1 [37].

Polymerase-targeting antivirals have expanded the treatment landscape. These include Baloxavir marboxil, a cap-dependent endonuclease inhibitor that targets PA and effectively reduces viral loads [38]. Resistance-associated PA substitutions are however emerging [39]. Current priorities are for pan-spectrum antivirals that retain activity across influenza subtypes. The Influenza RDRP is highly conserved across strains, making it an attractive target for next-generation nucleoside and non-nucleoside inhibitors [40]. Pan-strain activity is desirable as it can provide protection against antigenic drift and shift compared with virion targeted agents.

As for DENV, combination therapy has also been explored. Whilst clinical studies combining baloxavir with NAIs have failed to show improvements for severe influenza, this remains an approach of interest for patients with high viral loads and resistant strains [41]. Vaccination remains the main method for influenza prevention, but their production early in a pandemic is challenging. Stockpiling a range of antiviral agents all with novel mechanisms of action to widen efficacy and reduce the likelihood of the emergence of resistance remains a key strategic priority [34,42].

Current influenza virus diagnostics rely on rapid influenza diagnostic tests (RIDTs), molecular assays and RT-PCR. RIDTs can detect influenza A and B as a fast point-of-care diagnostic. Sensitivity and false negatives remain common issues. Emerging platforms such as the cobas® Liat multiplex PCR assay can simultaneously detect influenza A, influenza B, SARS-CoV-2, and RSV. Microfluidic assays that detect viral proteins at zeptomolar concentrations can further enhance early detection and hold promise for point-of-care influenza diagnostics [43].

Rapid clinical trial networks to evaluate therapeutics during outbreaks and global equity frameworks for access to antivirals and vaccines early in a pandemic remain the key approaches for Influenza virus. Together, these aim to build a resilient and flexible antiviral arsenal of drugs and vaccines capable of mitigating the impact of future influenza pandemics.

Ebola Virus

Ebola virus (EBOV) part of the Filoviridae family, genus Ebolavirus, is a non-segmented, negative-sense RNA virus for which six species are known; namely Zaire ebolavirus (lethal), Sudan ebolavirus, Bundibugyo ebolavirus, Taï Forest ebolavirus, Reston ebolavirus, and Bombali ebolavirus [44]. It is spread through direct contact with blood, or contaminated surfaces [45]. Key reservoirs include fruit bats. Clinically, EBOV causes severe haemorrhagic fever leading to multi-organ failure and high rates of death (Figure 3). This can be as high as a 90% fatality rate for some outbreaks [46]. Challenges with EBOV include outbreaks frequently occurring in resource-limited settings that makes containment

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

challenging. Current treatments include cocktails of monoclonal antibodies (Ebanga and Inmazeb), but these are expensive and access is limited [47]. Remdesivir has shown some efficacy (though limited) in clinical trials. Regarding vaccine development, rVSV-ZEBOV is effective but cold-chain issues present a logistical challenge with coverage during outbreaks remaining sporadic. Delayed detection due to outbreaks in remote locations and the lack of rapid, point-of-care diagnostics are further issues. Current diagnostics include RT-PCR as the gold standard due to its ability to detect viral RNA within the first few days of infection [48]. The Xpert Ebola Test and FilmArray Biothreat-E can inform infection status within 2 hours, supporting rapid clinical decision in the advent of an outbreak. Lateral flow antigen assays are increasingly used for point-of-care screening and can detect EBOV proteins within 15–30 minutes, though their sensitivity is lower than PCR. Serological assays to detect IgM/IgG antibodies can be complementary for surveillance and are detectable approximately 7 days post-symptom onset. Used together, these diagnostics provide a layered strategy for outbreak control, but RT-PCR remains essential for definitive diagnosis [49].

Socioeconomic and cultural factors including a lack of trust in healthcare systems and cultural burial practices that enhance virus spread also hinder containment. Emerging political instability and conflict zones are now further complicating EBOV response efforts [50].

Other issues include virus persistent virus in survivors (immune-privileged sites such as the eyes and testes and genetic variability that can affect vaccine and therapeutic efficacy.

Broad-Spectrum Antivirals and their Associated Challenges

Production of Synthetic Carbohydrate Receptors

Synthetic Carbohydrate Receptors bind to viral surface glycans and can block virus entry and replication, including SARS-CoV-1/2, MERS, Nipah, Hendra and Ebola viruses. In recent *in vivo* studies, mouse models of COVID-19 showed ~90% survival with a single-dose of Synthetic Carbohydrate Receptor treatment.

Virus Polymerase Inhibitors (DNA and RNA viruses)

Broad-acting antiviral agents that target viral RNA-dependent RNA polymerases (RdRp) and viral DNA polymerases remain a therapeutic strategy to combat numerous viral infections. Polymerases offer an attractive broad acting target as they are highly conserved across viral families and are essential for viral genome replication. They are also sufficiently distinct from host polymerases that therapeutics can be selective, thereby avoiding host toxicity [51].

For RNA viruses, including human respiratory syncytial virus (RSV), influenza virus, and coronaviruses, the RdRp is central to virus replication. Due to the structural conservation of the catalytic core, inhibitors of RdRps often show cross-family activity, making them candidates for broad-spectrum antiviral development [51,52]

Examples include Nucleoside and non-nucleoside inhibitors such as remdesivir, favipiravir, ribavirin, and baloxavir marboxil, all of which inhibit viral RNA synthesis through chain termination, delayed termination, or disruption of polymerase complex assembly [40,53]. All show antiviral activity against RSV, influenza A and B viruses, and multiple coronaviruses, including SARS-CoV-2 and MERS-CoV [40,53].

An additional feature that make RdRp inhibitors attractive antiviral targets are their ability to evade immune-based interventions, highlighting their use in pandemic preparedness and as a front line therapeutic to limit virus spread in the face of a potential outbreak [54]. Structural and mechanistic studies further demonstrate that both active-site and allosteric RdRp inhibitors can suppress replication across phylogenetically diverse RNA viruses [52].

Viral DNA polymerases are similarly well-validated antiviral targets for DNA viruses and contain conserved catalytic motifs that support targeted development of inhibitors with a broad range of activity [52].

Non-Nucleoside and nucleoside analogues show efficacy against a range of DNA viruses through targeting the DNA polymerase, most notably in immunocompromised populations for which resistance is a common theme [42]. Recent structural enablement of viral polymerases (CyroEM approaches most notably) have provided mechanistic insight into polymerase inhibition and resistance mechanisms. It is hoped that this information can inform the design of next-generation broad-acting therapies [55].

Viral polymerases offers multiple strategic advantages for therapies including their broad-spectrum antiviral coverage, low levels of resistance and utility as combination therapies. Polymerase complexes in RNA viruses cap their mRNAs to enhance translation and evade host innate immune sensors. The inhibition of viral MTases prevents both translational efficiency and immune masking, impacting virus fitness and highlighting the attractiveness of this approach. Structural studies have shown for coronaviruses nsp14 and nsp16 (both MTases) perform the latter stages of capping, using S-adenosyl-L-methionine (SAM) as the methyl donor. Nsp10 acts as an essential co-factor for nsp16 and can modulate nsp14 activity, highlighting further potential for druggability. For Ebola virus, the L protein possesses capping and MTase domains with emerging high-resolution structural information revealing a series of novel features for replication competence and immune escape.

Yu Wu MD, et al., Arch Clin Biomed Res 2026
DOI:10.26502/acbr.50170513

RNA-Based Therapies & Biologics

RNA-based therapies and biologics are attractive as they can be programmed against novel sequences, can act intra- and extracellularly and can modulate host defences. As priorities shift towards platforms that can be adapted across pathogens, they may be central to anti- pandemic strategies [56].

Neutralizing mAbs engage viruses to prevent attachment/ fusion and can recruit Fc-mediated effector functions. These hold value as post-exposure prophylaxis and early treatment regimens, particularly for those who are immunocompromised and respond poorly to vaccines [42,57]. For EBOV, a randomized PALM trial showed that survival could be enhanced with mAb114 and REGN-EB3, establishing mAbs as life-saving therapy in high-risk areas [58]. A key limitation of antibody therapies is antigenic drift, highlighting the need for cocktails, careful and conserved epitope selection, and Fc-engineering for improved functionality [57].

Small interfering RNAs and CRISPR-based Approaches

siRNAs harness endogenous RNA interference to degrade target viral RNAs with sequence precision. A key advantage is their ability to be rapidly re-designed against conserved virus regions [42,59]. Although approved for non-infectious indications, RNAi use for viruses is limited [56]. The major obstacle is delivery to the site of infection whilst evading immune sensing. Advances in delivery mechanisms (lipid nanoparticles, conjugates, and chemical modifications) offer hope for improved tolerability and pharmacology [56].

RNA-targeting CRISPR systems can be programmed to directly cleave viral RNA genomes even in the face of virus mutation and evolution [60]. This can enable rapid retargeting to new viral variants and/or latent reservoirs, a major problem with current HIV therapeutics. Challenges however remain, including targeted *in vivo* delivery, stability, and limiting off-targets effects. All encompass active areas of research [60].

Summary of Challenges and Future Outlook

The ability of viruses to adapt and evolve often outpaces a single-target antiviral therapeutic. The variability is driven by high mutation rates due to error-prone polymerases, large viral population sizes and reservoirs that “bounce back” following treatment and selective pressure under treatment. Numerous examples of this evolution are evident, including influenza (NA inhibitors), HIV monotherapies, HCV and SARS-CoV-2 monoclonal antibodies. For all examples, resistance-associated mutations have arisen within months of widespread useage.

Resistance can be mitigated through structure-based drug design and combination regimens that targets variable virus processes. The ability to identify conserved catalytic or allosteric domains that impose high fitness costs on resistance mutations, e.g. polymerase and cap-methyltransferases for RNA viruses, offer a therapeutic avenue for pan-viral approaches [61]. HIV is an example of successful combination therapy whereby the likelihood of virus escape is minimised through synergistic or additive antiviral agents (6, 41). This combined with host-directed agents likely offers the most rationale path to the maintenance of clinical efficacy against evolving and newly emerging pathogens.

Acknowledgments: None.

Funding: None.

Conflicts of Interest: None.

Highlights:

- We highlight a roadmap of the current challenges with antiviral drug discovery.
- We discuss current shared approaches, novel and emerging strategies.
- We provide recommendations to strengthen global health resilience.

References

1. Morens DM, Folkers GK, Fauci AS. The challenge of emerging and re-emerging infectious diseases. Nature 430 (2004): 242-249.
2. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. Nature 451 (2008): 990-993.
3. Fauci AS, Morens DM. The perpetual challenge of infectious diseases. The New England Journal of Medicine 366 (2012): 454-461.
4. Swathi K, Nikitha B, Chandrakala B, et al. Repurposing antiviral drugs on recently emerged viral infections: A review article. Materials Today Proceedings (2021).
5. Beishuizen BHH, Stein ML, Buis JS, et al. A systematic literature review on public health and healthcare resources for pandemic preparedness planning. BMC Public Health 24 (2024): 3114.
6. De Clercq E, Field HJ. Antiviral prodrugs - the development of successful prodrug strategies for antiviral chemotherapy. British Journal of Pharmacology 147 (2006): 1-11.
7. Costa BKD, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. Jornal de Pediatria 96 (2020): 12-19.
8. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet 357 (2001): 1513-1518.

9. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. Antimicrobial Agents and Chemotherapy 55 (2011): 459-472.
10. Looker KJ, Elmes JAR, Gottlieb SL, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. The Lancet Infectious Diseases 17 (2017): 1303-1316.
11. Field HJ, Vere Hodge RA. Recent developments in anti-herpesvirus drugs. British Medical Bulletin 106 (2013): 213-249.
12. Tang J, Amin MA, Campian JL. Past, Present, and Future of Viral Vector Vaccine Platforms: A Comprehensive Review. Vaccines 13 (2025).
13. Andrei G, Snoeck R. Advances in the treatment of varicella-zoster virus infections. Advances in Pharmacology 67 (2013): 107-168.
14. Biron KK. Antiviral drugs for cytomegalovirus diseases. Antiviral Research 71 (2006): 154-163.
15. Gerna G, Lilleri D. Human cytomegalovirus (HCMV) infection/re-infection: development of a protective HCMV vaccine. The New Microbiologica 42 (2019): 1-20.
16. Prichard MN, Kern ER. The search for new therapies for human cytomegalovirus infections. Virus Research 157 (2011): 212-221.
17. Luzius T, Jeske SD, Baer J, et al. A Multiplex Polymerase Chain Reaction Assay for the Detection of Herpes Simplex Virus, Cytomegalovirus, and Varicella-Zoster Virus in Cerebrospinal Fluid. Microorganisms 13 (2025).
18. Kalhor R, Noorbazargan H, Kalhor H, et al. Design and Development of a Multiplex Real-Time PCR Method for the Detection of Herpes Family Viruses in Transplant Patients. Iranian Journal of Microbiology (Year): 1-8.
19. Shang Z, Li X. Human cytomegalovirus: pathogenesis, prevention, and treatment. Molecular Biomedicine 5 (2024): 61.
20. Tognarelli EI, Palomino TF, Corrales N, et al. Herpes Simplex Virus Evasion of Early Host Antiviral Responses. Frontiers in Cellular and Infection Microbiology 9 (2019): 127.
21. Chakrabarty A, Anderson NJ, Beutner R, et al. Valacyclovir for the management of herpes viral infections. Skin Therapy Letter 10 (2005): 1-4.
22. Beyar-Katz O, Bitterman R, Zuckerman T, et al. Anti-herpesvirus prophylaxis, pre-emptive treatment or no treatment in adults undergoing allogeneic transplant for haematological disease: systematic review and meta-analysis. Clinical Microbiology and Infection 26 (2020): 189-198.
23. Connolly SA, Jardetzky TS, Longnecker R. The structural basis of herpesvirus entry. Nature Reviews Microbiology 19 (2021): 110-121.
24. Paz-Bailey G, Adams LE, Deen J, et al. Dengue. Lancet 403 (2024): 667-682.
25. Malavige GN, Ogg GS. Molecular mechanisms in the pathogenesis of dengue infections. Trends in Molecular Medicine 30 (2024): 484-498.
26. Kalimuddin S, Chia PY, Low JG, et al. Dengue and severe dengue. Clinical Microbiology Reviews 38 (2025): e0024424.
27. Yong YK, Wong WF, Vignesh R, et al. Dengue Infection - Recent Advances in Disease Pathogenesis in the Era of COVID-19. Frontiers in Immunology 13 (2022): 889196.
28. Salles TS, da Encarnação Sá-Guimarães T, de Alvarenga ESL, et al. History, epidemiology and diagnostics of dengue in the American and Brazilian contexts: a review. Parasites & Vectors 11 (2018): 264.
29. Durbin AP, Van Wesenbeeck L, Pierce KK, et al. Daily Mosnodenvir as Dengue Prophylaxis in a Controlled Human Infection Model. The New England Journal of Medicine 393 (2025): 2107-2118.
30. CDC. Clinical Testing Guidance for Dengue. Centers for Disease Control and Prevention (2025).
31. WHO. Laboratory testing for dengue virus: Interim guidance. World Health Organization (2025).
32. Plummer E, Buck MD, Sanchez M, et al. Dengue Virus Evolution under a Host-Targeted Antiviral. Journal of Virology 89 (2015): 5592-5601.
33. Taubenberger JK, Morens DM. The pathology of influenza virus infections. Annual Review of Pathology 3 (2008): 499-522.
34. Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. Nature Reviews Disease Primers 4 (2018): 3.
35. WHO. Global Influenza Surveillance and Response System (GISRS). World Health Organization (2017).
36. Moscona A. Neuraminidase inhibitors for influenza. The New England Journal of Medicine 353 (2005): 1363-1373.
37. Meijer A, Lackenby A, Hungnes O, et al. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007-08 season. Emerging Infectious Diseases 15 (2009): 552-560.
38. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. The New England Journal of Medicine 379 (2018): 913-923.

39. Uehara T, Hayden FG, Kawaguchi K, et al. Treatment-Emergent Influenza Variant Viruses With Reduced Baloxavir Susceptibility: Impact on Clinical and Virologic Outcomes in Uncomplicated Influenza. The Journal of Infectious Diseases 221 (2020): 346-355.

40. Li J, Jin Y, Wang Y, et al. New Developments in Influenza Polymerase Inhibitors. The Journal of Infectious Diseases 232 (2025): S227-S242.

41. Govorkova EA, Baranovich T, Seiler P, et al. Antiviral resistance among highly pathogenic influenza A (H5N1) viruses isolated worldwide in 2002-2012 shows need for continued monitoring. Antiviral Research 98 (2013): 297-304.

42. Karim M, Lo CW, Einav S. Preparing for the next viral threat with broad-spectrum antivirals. The Journal of Clinical Investigation 133 (2023).

43. de Lima LF, Pradela-Filho LA, Estrela PFN, et al. High throughput influenza A virus detection by isothermal amplification in sequential-injection paper-based microfluidics. Biosensors and Bioelectronics 294 (2026): 118249.

44. El Ayoubi LW, Mahmoud O, Zakhour J, et al. Recent advances in the treatment of Ebola disease: A brief overview. PLoS Pathogens 20 (2024): e1012038.

45. Bodmer BS, Hoenen T, Wendt L. Molecular insights into the Ebola virus life cycle. Nature Microbiology 9 (2024): 1417-1426.

46. Ndayambaje M, Yadufashije C, Habyarimana T, et al. Molecular characterization of Ebola virus, immune response, and therapeutic challenges: a narrative review. 25 (2024).

47. Almeida-Pinto F, Pinto R, Rocha J. Navigating the Complex Landscape of Ebola Infection Treatment: A Review of Emerging Pharmacological Approaches. Infectious Diseases and Therapy 13 (2024): 21-55.

48. Mukadi-Bamuleka D, Bulabula-Penge J, Jacobs BKM, et al. Head-to-head comparison of diagnostic accuracy of four Ebola virus disease rapid diagnostic tests versus GeneXpert® in eastern Democratic Republic of the Congo outbreaks: a prospective observational study. EBioMedicine 91 (2023): 104568.

49. Dagens AB, Rojek A, Sigfrid L, et al. The diagnostic accuracy of rapid diagnostic tests for Ebola virus disease: a systematic review. Clinical Microbiology and Infection 29 (2023): 171-181.

50. Asare Fenteng E, Ossei PPS, Ayibor WG, et al. Beyond survival: unraveling the dynamics of Ebola virus resurgence in Sub-Saharan Africa and the remarkable journey of survivors. Frontiers in Virology 3 (2023): 1227314.

51. Luong QXT, Hoang PT, Ho PT, et al. Potential Broad-Spectrum Antiviral Agents: A Key Arsenal Against Newly Emerging and Reemerging Respiratory RNA Viruses. International Journal of Molecular Sciences 26 (2025).

52. Peng S, Wang H, Wang Z, et al. Progression of Antiviral Agents Targeting Viral Polymerases. Molecules 27 (2022).

53. Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. The Journal of Biological Chemistry 295 (2020): 6785-6797.

54. Adalja A, Inglesby T. Broad-Spectrum Antiviral Agents: A Crucial Pandemic Tool. Expert Review of Anti-Infective Therapy 17 (2019): 467-470.

55. Kumari R, Sharma SD, Kumar A, et al. Antiviral Approaches against Influenza Virus. Clinical Microbiology Reviews 36 (2023): e0004022.

56. Mitchell MJ, Billingsley MM, Haley RM, et al. Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery 20 (2021): 101-124.

57. Corti D, Lanzavecchia A. Broadly neutralizing antiviral antibodies. Annual Review of Immunology 31 (2013): 705-742.

58. Mulangu S, Dodd LE, Davey RT Jr, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. The New England Journal of Medicine 381 (2019): 2293-2303.

59. Kang H, Ga YJ, Kim SH, et al. Small interfering RNA (siRNA)-based therapeutic applications against viruses: principles, potential, and challenges. Journal of Biomedical Science 30 (2023): 88.

60. Pacesa M, Nickel L, Schellhaas C, et al. One-shot design of functional protein binders with BindCraft. Nature 646 (2025): 483-492.

61. Kumar D, Ison MG, Mira JP, et al. Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial. The Lancet Infectious Diseases 22 (2022): 718-730.

Citation: Yu Wu, Shuo Hu, Feng Liu. Common Challenges to the Development of Novel Antivirals to Tackle Re-emerging Infections of Pandemic Potential. Archives of Clinical and Biomedical Research. 10 (2026): 99-107.