

INFECTIOUS DISEASE

Emerging Viral Diseases: Confronting Threats with New Technologies

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Emerging viral diseases pose ongoing health threats, particularly in an era of globalization; however, new biomedical research technologies such as genome sequencing and structure-based vaccine and drug design have improved our ability to respond to viral threats.

INTRODUCTION

Emerging viral diseases have threatened humanity throughout history. Specific aspects of modernization such as rapid air transit, as well as demographic trends including urbanization, have accelerated both the emergence and spread of viruses. As stated in the 1992 Institute of Medicine report on Emerging Infections, "... in the context of infectious diseases, there is nowhere in the world from which we are remote and no one from whom we are disconnected" (1). Fortunately, the aspects of modernization that help to drive pathogen emergence can also propel scientific innovation, and recent important scientific advances have transformed our ability to address the challenge of emerging viruses. From advanced genomic sequencing to new methods in structural biology, we now have an increasingly sophisticated toolkit with which to facilitate the detection and possible control of emerging viral diseases. Still, current outbreaks of viral diseases such as chikungunya fever in the Americas, Ebola virus disease in West Africa, and human infections with avian influenza viruses (together with the ever-present threat of another pandemic caused by a new influenza virus) serve as powerful reminders of our ongoing vulnerability to emerging viral pathogens. These events underscore the need for concerted efforts to develop and implement new interventions while continuing to invest in proven public health measures. These events also remind us of the lack of incentives for the development and marketing of new interventions that target diseases predominantly affecting poor countries. This situation persists despite some recent successes with new partnerships and other efforts to spur development of vaccines and drugs to control "neglected" diseases (2).

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and the Middle East respiratory syndrome coronavirus (MERS-CoV) represent only a subset of viral diseases, yet they often capture public attention because of their ability (in many cases) to spread rapidly and the potential of some to cause high morbidity and mortality.

CATEGORIES OF EMERGING VIRUSES

When considering the threat posed by emerging viruses, it is useful to divide them into three categories: newly emerging viruses, reemerging viruses (Fig. 1), and viruses deliberately spread by bioterrorists (5). Each represents a particular challenge for biomedical researchers and public health practitioners. Of note, most emerging viral diseases in each of these categories are RNA viruses, which generally have higher mutation rates than do DNA viruses, in part because viral RNA polymerases lack the proofreading ability of DNA polymerases. The mutability of RNA viruses is among the reasons why it has proven difficult to make effective vaccines against these pathogens, which may quickly adapt to escape vaccine-induced population immunity. Newly

Infectious diseases account for ~20% of global mortality, with viral diseases causing about one third of these deaths (3). Individuals in resource-poor settings tend to suffer disproportionate morbidity from viral diseases because of poor sanitation and baseline nutritional status, as well as limited access to health services. These challenges have been tragically demonstrated by the ongoing Ebola outbreak in West Africa, where public health interventions are hampered by a lack of primary health infrastructure (4). Emerging viruses such as Ebola, H5N1 and H7N9 avian influenza viruses,

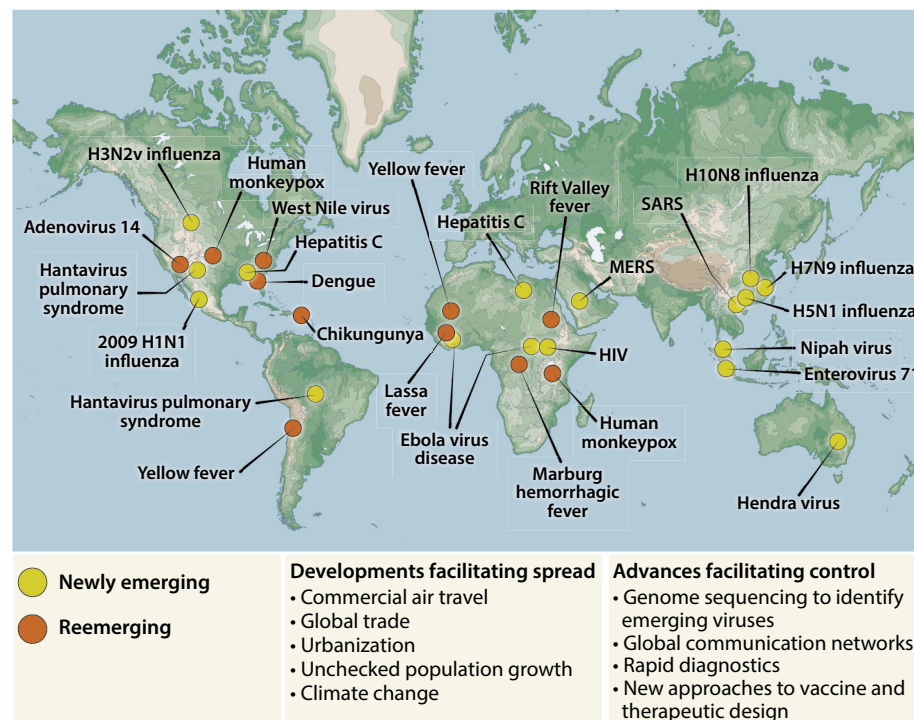


Fig. 1. Mapping emerging viral diseases. Shown are examples of sites where diseases caused by newly emerging viruses (those not known to have infected humans before, or not previously recognized as human pathogens; yellow) and reemerging viruses (those increasing in incidence, emerging in new locations or exhibiting enhanced pathogenicity; orange) have appeared. (Bottom) Listed are modern developments that facilitate virus emergence, such as commercial air travel and urbanization, and research advances that are helping to control emerging viruses, including genomic sequencing, rapid diagnostics, and new approaches to vaccine and therapeutic design.

emerging viruses are “new” in the sense that they are not known to have previously infected or caused disease in humans. The human immunodeficiency virus (HIV), first isolated in 1983 (although phylogenetic analyses indicate that it emerged in humans decades beforehand), is perhaps the most infamous virus in this category. Reemerging viruses are those that were recognized previously but have adapted to become major health threats or have appeared in previously unafflicted geographic locations. For example, the incidence of dengue fever, caused by four closely related dengue viruses and carried by *Aedes* mosquitoes, has risen as urbanization has created new breeding grounds for the insects (due to crowding, poor sanitation, and standing water) and as the mosquitoes have become dispersed geographically by humans and have adapted to new human-created ecological niches, such as discarded rubber tires. Recent data suggest that the global burden of norovirus gastroenteritis is far greater than previously appreciated (6); moreover, there has been an increase in outbreak activity as new strains emerge. Meanwhile, large outbreaks of hepatitis E virus, the leading cause of acute hepatitis, affect countries around the world, most notably in East and South Asia (7). Pathogens deliberately released into the human population—agents of bioterror—are still mainly a theoretical threat. However, the anthrax attacks of 2001 in the United States demonstrated the potential danger that deliberately emergent infections pose. Among the most concerning threats in the realm of potential bioweapons are hemorrhagic fever viruses such as Marburg virus and viruses that target livestock, such as those causing foot-and-mouth disease (8).

NEW TECHNOLOGIES TO DEFEAT VIRAL DISEASES

The threat of emerging viruses has been magnified by globalization and other realities of modernization, such as widespread and rapid human movement; at the same time, scientific advances have greatly bolstered our ability to defend against these pathogens (Table 1). For example, viruses and the mechanisms by which they cause disease can now be quickly characterized through rapid genomic sequencing, proteomics, epigenomics, and other tools. Genomics technology is also being applied diagnostically, enhancing the ability to detect viruses at the point of care and to track their spread within human populations (9,

Table 1. Modern technologies that address the challenges of emerging viral infections.

Technology	Application to emerging viral infections
Genomic sequencing	Identification of new agents (such as SARS-CoV and MERS-CoV); evaluation of strain diversity (HIV, MERS-CoV)
Rapid diagnostics	Real-time reverse transcription-PCR for Ebola virus; distinguishing bacterial versus viral causes of certain acute respiratory illness
Structural biology	Vaccine design for influenza, HIV, respiratory syncytial virus; therapeutics design for HIV, HCV
New vaccine platforms	Viral vectors for Ebola virus, Marburg virus, HIV; virus-like particles for chikungunya virus; nanoparticle platforms for influenza virus immunogens

10). Advances in structural biology, including x-ray crystallography and cryo-electron microscopy, have allowed investigators to characterize the conformations of viral proteins in detail. An improved understanding of host-pathogen interactions and viral protein function have led to more rational drug designs, resulting in important therapeutic advances against HIV and hepatitis C virus (HCV). In addition, new platforms for vaccine design, such as nanoparticles and virus-like particles, have opened avenues for vaccine development. Together, these technologies form a robust armamentarium to meet the challenges of emerging viral diseases (Table 1).

The use of rapid genomic sequencing for pathogen identification was put to the test with the emergence of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003, a global outbreak that reached nearly 40 countries and caused more than 8000 infections and close to 800 deaths. The virus apparently originated from an unsuspected enzootic reservoir involving bats and, secondarily, civet cats, with eventual emergence of a similar viral strain in humans. International air travel spread the virus across continents, leading to an outbreak in Canada that left 43 dead and thousands in isolation (11). It was the application of rapid genomic sequencing that allowed researchers to identify the causative agent of the disease in 2003. Nineteen months later, a vaccine was tested in phase I human trials (12). Fortunately, traditional public health measures such as isolation of infected patients and exposed contacts interrupted the spread of the virus, and further vaccine development has not been aggressively pursued. Nonetheless, the scientific response to the threat was efficient and effective. When the MERS-CoV appeared in 2012, the SARS experience proved instructive, and rapid genomic sequencing was again applied to identify the causative

agent and trace its origins. Once again, bats were considered to be a possible reservoir of the virus, but in this case there was secondary circulation of the MERS-CoV in dromedary camels, a domestic animal in close proximity to many human cases and therefore a suspected source of transmission to humans. Complete genome sequences of MERS-CoV isolates obtained from Saudi Arabian dromedary camels were shown to be nearly identical to 43 sequences obtained from humans treated in Saudi Arabia and other countries (13). Additionally, serological and sequence-based evidence of exposure to the virus was detected in dromedary camels across the Middle East and Africa and in serum samples dating back to 1992 (14). Ongoing genomic studies include the surveillance of animal coronaviruses in order to better understand the circulation and evolution of the MERS-CoV and to identify which mutations might facilitate transmission to or between humans. To date, MERS-CoV continues to spread, although improved infection control practices appear to have curtailed transmission within healthcare facilities (15). Health officials are remaining vigilant, particularly during the Hajj and Umra pilgrimages to Saudi Arabia.

ADVANCES IN VIRAL DISEASE DIAGNOSIS

Whereas genomic sequencing has facilitated identification of viruses, other advances are helping to diagnose viral illnesses. Specifically, polymerase chain reaction (PCR), the nucleic acid amplification technology initially developed in 1983, is now more rapid and less cumbersome, allowing for deployment in outbreaks, even in resource-poor settings. PCR technology can be particularly useful in situations of diagnostic uncertainty, a difficulty encountered in hemorrhagic fever outbreaks, such as the ongoing Ebola virus disease outbreak in West Africa. Symptoms of Ebola infection begin with an

influenza-like illness and gastrointestinal complaints. Hemorrhagic manifestations, when they occur, may appear late in the course of disease. The nonspecific symptomatology creates diagnostic uncertainty that complicates disease control. Therefore, rapid accurate diagnostics are essential. Real-time reverse transcription PCR, a quantitative RNA-based technology, has been developed and deployed in outbreaks, including Ebola virus disease outbreaks in Africa (16). The ability to diagnose infection within hours has been invaluable in disease control, facilitating both case identification and contact tracing (17).

Rapid diagnostics also have proved important for more common pathogens, including respiratory viruses such as respiratory syncytial virus and parainfluenza viruses. The ability to detect a virus at the point of care or to distinguish bacterial from viral etiologies of illnesses can be extremely helpful in determining isolation requirements and treatment options. For example, diagnosis of a primary or secondary bacterial respiratory tract infection would allow prompt administration of antibacterial agents. Conversely, ruling out bacteria as a likely cause of a respiratory infection spares the patient unnecessary antibiotics, avoiding side effects and the overuse of antimicrobials that has contributed to widespread bacterial resistance. As just one example, investigators have developed a reverse transcription-PCR-based blood test to distinguish certain viral from bacterial etiologies of respiratory infection; early testing demonstrated 90% accuracy (18). The test detects a specific host genetic pattern expressed in response to a viral infection; this or similar tools could prove useful in the emergency room or in primary care settings.

VACCINES AGAINST EMERGING VIRUSES

Although rapid diagnostics can be used to detect and control disease outbreaks, vaccine-based prevention is often the optimal long-term public health strategy. Here too, research advances have greatly improved responses to emerging viruses. In the past century, vaccinology has relied on the recapitulation of one of nature's infection models: If infection with a pathogen produces lifelong protection, then administration—for example, by injection—of an inactivated or attenuated whole pathogen or a component thereof could induce a similar immune response. However, when natural infection

produces weaker responses—whether because of viral strain diversity, rapid mutation, masking of epitopes by glycosylation, or viral infection of cells that are poorly accessible to the systemic immune system—new approaches must be applied. Diverse vaccine platforms, ranging from viral vectors expressing the genes coding for relevant viral proteins to nanoparticles that markedly enhance immunogenicity, offer new ways to present antigens to the host immune system.

The promise of these technologies is exemplified by their recent application to influenza virus. Influenza viruses evade the immune system through mutation and resulting strain diversity, predominantly reflected by mutations in the “head” region of its attachment protein, hemagglutinin. The virus may also obscure its most conserved epitopes, those on the “stem” of hemagglutinin. Small variations in the viral genome produced by antigenic drift (cumulative minor mutations) allow the virus to escape population immunity derived from natural infections and vaccinations. Such drift contributes to the 3000 to 49,000 cases of influenza each year in the United States. Antigenic variation in influenza viruses results not only from mutational drift but also from intra-subtype and subtype reassortment. Hemagglutinin subtype reassortment has been referred to as a “shift” and can lead to a pandemic, a constant threat to global health.

To overcome these challenges, scientists are pursuing improved influenza virus vaccines. For example, investigators have arrayed whole influenza hemagglutinin molecules on ferritin nanoparticles. Such nanoparticles are able to display a large amount of antigen on a concentrated surface. Experiments in mice and ferrets have demonstrated higher antibody titers than those of traditional vaccination platforms (19). Additional studies using the stem portion of hemagglutinin on a nanoparticle could provide broad viral strain protection, one of a number of potential strategies to produce a “universal influenza vaccine.” A universal influenza vaccine with durable protection would ideally obviate the need for annual influenza vaccinations and, more importantly, would protect against future pandemic strains. In all likelihood, deployment of a truly universal flu vaccine is years away. However, in the interim, vaccines with broader specificity (for example, protecting against all H1 or all influenza A strains) may be closer at hand and could provide broader protection against pandemic spread.

Virus-like particles have been assessed in preclinical and clinical studies in the search for improved vaccines for influenza viruses and many other viruses. Virus-like particles are multiprotein structures that mimic the organization and conformation of native viruses but lack viral genes (20). Licensed virus-like particle vaccines have helped to reduce the burden of hepatitis B virus infection and human papillomavirus infection, and candidate virus-like particle vaccines for noroviruses, respiratory syncytial virus, chikungunya virus and other pathogens have entered clinical trials. In this regard, recent results from a trial of a virus-like particle-based chikungunya virus vaccine are promising. Chikungunya viruses, historically carried by *Aedes aegypti* mosquitoes, circulate broadly in Africa and Asia, causing a debilitating arthritis, but only rare fatalities (21). Different strains of the chikungunya virus have recently spread independently from Africa to Europe and from Asia to the Americas, where the Asian strain has quickly reached at least 27 countries, causing more than 500,000 infections as of 4 August 2014 (22). A virus-like particle chikungunya vaccine, recently developed and tested in phase I human trials, induces a robust immune response considered predictive of protection (23). Discussions of larger human trials are under way.

Various vaccine platforms have been applied to HIV; however, recent advances in HIV vaccinology have drawn on an improved understanding of the relationship between viral structure and host-pathogen interactions. In addition to its mutational capability, HIV possesses both a highly glycosylated envelope and conformational plasticity of its envelope trimer. These complexities help to explain the challenge in developing a vaccine that elicits antibodies that protect against HIV infection. In fact, in response to natural HIV infection, only 20% of individuals develop broadly neutralizing antibodies, and this occurs after 2 to 3 years of viremia, suggesting the need for prolonged and continual stimulation of the HIV-specific B-cell repertoire in order to elicit such a response. At present, five conserved regions of the HIV envelope have been identified as the targets for broadly neutralizing antibodies. One study in an acutely infected individual traced the mutation of the virus under immune system pressure and the responsive somatic hypermutation of B cells that eventually drove the production of high-affinity, broadly reactive

antibodies (24). Building on these insights, structural biologists have used x-ray crystallography and cryo-electron microscopy to define the precise conformation of broadly neutralizing antibodies bound to their specific viral epitopes (25). Once the epitopes have been characterized, the next challenge is to convert these epitopes into a series of immunogens that will induce in an iterative fashion a broader and higher-affinity antibody response.

The design of immunogens to elicit broadly neutralizing antibodies in HIV-uninfected individuals is a major goal of HIV vaccine research development. The passive infusion of such antibodies may also have a role in HIV prevention; studies of lentiviral infection in nonhuman primates have shown that passive infusion of antibodies can prevent infection (26). The infusion of “designer” antibodies also has been pursued as a therapy for HIV and other infections, including Ebola virus disease. In this regard, a “cocktail” of humanized mouse antibodies that had shown promise in nonhuman primates was administered to several individuals who became infected with Ebola virus in West Africa during the ongoing Ebola outbreak. Although clinical improvement was reported in some patients, further experience and clinical trials with this therapeutic will be needed before its safety and efficacy can be determined. Similarly, human studies of passive immunotherapy for HIV are needed before the potential role for these modalities can be assessed.

ANTIVIRAL DESIGN AND DEVELOPMENT

Although investigators are actively pursuing the use of immunotherapy and preventive vaccines for HIV, there are more than 35 million people living with HIV infection around the world. Importantly, precise understanding of the HIV replication cycle and structure-based drug design have led to the development of effective drug therapies, including inhibitors of the viral reverse transcriptase, protease, and integrase enzymes. The protease enzyme cleaves the viral precursor polyproteins, creating all of the viral proteins that are necessary to form mature, infectious HIV virions (27). Scientists have built on this understanding, identifying the specific sites in the viral polyproteins where proteolytic cleavage occurs. This provided chemists the opportunity to build inhibitors crystallized with the HIV protease, showing with atomic precision how the active site of

the protein functions. From this work, other viral inhibitors were designed that bound to the HIV protease tightly, blocked access to the active cleavage site, and had the necessary chemical properties to be safe and effective drugs. Further improvements in protease-inhibitor design take advantage of structure-based computer techniques to optimize inhibitor binding and improve the chemical properties of the drugs. For example, inhibitors were designed with reduced hydrophobicity, which decreases their crystallization in tissues, thus avoiding side effects such as pancreatitis and nephrolithiasis (28). Using all of these methods, protease inhibitors were created and optimized, making these agents an important component of today’s effective combination antiretroviral therapy. Similar approaches have been used in the development of the highly effective integrase inhibitors for HIV. After HIV entry and conversion of the viral RNA by reverse transcriptase into a double-stranded DNA molecule, HIV genomic material is transported into the nucleus and then integrated into the host cell by the HIV integrase enzyme. Integrase inhibitors, the most recent class of antiretroviral agents to be introduced into clinical practice, prevent this critical step in HIV replication. The drugs have proven effective in clinical practice and now are included in first-line antiretroviral treatment of HIV-infected individuals. Their discovery stemmed from an understanding of the complex mechanisms of HIV integration and the subsequent development of an appropriate assay to identify the first potential leads for rational design of these antivirals (29).

Development of medications for another important virus, HCV, proceeded along a somewhat different route from that of HIV. Knowledge of viral pathogenesis and new drug-screening technologies were key to developing powerful new HCV antivirals. HCV, one of several suspected but undiscovered viruses once referred to as non-A, non-B hepatitis viruses, was identified in 1989 by using an expression cloning technique that generated a library of complementary DNA from the plasma of infected individuals (30). This represented one of the first times that genomic material was used to identify an unknown human pathogen, an advance that has been replicated for other viruses, such as the Kaposi sarcoma herpes virus (human herpesvirus 8) in 1994 (31) and human metapneumovirus in 2001 (32). Between 130 million and 150 million

people have chronic HCV infection globally, and ~350,000 to 500,000 people die from its complications annually (33). Until very recently, standard-of-care therapy for the disease was a two-drug regimen of pegylated interferon and ribavirin, both of which have substantial toxicities. During a typical 48-week regimen, an individual faces possible influenza-like symptoms and psychiatric side effects caused by interferon, as well as cytopenias that can be caused by either drug. Efficacy of this drug combination is highly variable, ranging from 40 to 80% depending on virus genotype, stage of disease, and co-infection with HIV. Moreover, a range of contraindications including chronic renal insufficiency precludes treatment in over 50% of patients (34). Today, direct-acting antiviral agents are becoming available, including inhibitors of the HCV polymerase, protease, and nonstructural protein 5A (NS5A), improving efficacy and shortening treatment duration. Some regimens now exclude interferon, minimizing toxicity.

The development of some of these direct-acting antiviral agents was based on the use of new cell-culture systems that elucidated the viral replication cycle and allowed rapid screening for enzymes that are crucial for HCV RNA synthesis and protein production (35). Specifically, replicating units called “replicons” containing HCV genes encoding these enzymes were constructed and introduced into cultured cells; candidate inhibitors were selected for their ability to specifically inhibit HCV RNA synthesis or for proteolytic cleavage of target protein substrates (depending on the drug class). The most promising compounds were further evaluated in animal models and subsequently tested in human clinical trials (35). Thus, an understanding of pathogenesis, combined with genomic and cell-culture technologies, allowed for the transformative development of effective, rapid cures for HCV infection.

The rapid rise in the number of emerging viral pathogens underscores the need to develop “broad spectrum” antivirals that target common components of multiple viruses, rather than the classic “one bug/one drug” approach. Among many examples is favipiravir (T-705), an inhibitor of RNA polymerase currently being assessed in clinical trials as an influenza therapeutic, which also blocks the replication of many other RNA viruses, including certain alphaviruses, arenaviruses, hantaviruses, flavivi-

ruses, enteroviruses, and respiratory syncytial virus (36). Another broad-spectrum antiviral approach—double-stranded RNA (dsRNA) activated caspase oligomerizer (DRACO)—selectively induces apoptosis in cells containing viral dsRNA. DRACOs have been created that are nontoxic in numerous mammalian cells and show inhibitory activity against 15 different viruses in vitro and against diverse viruses in small-animal models (37). UV4 is an investigational antiviral drug with potential as a treatment for influenza and dengue fever, with possible applications for viral hemorrhagic fevers, smallpox, and hepatitis. The drug is derived from a class of compounds known as iminosugars that includes drugs approved for other indications, such as for diabetes and Gaucher disease. Iminosugars competitively inhibit the glycoprotein-processing enzymes, α -glucosidases I and II (38). BCX4430, a broad-spectrum nucleoside analog, has activity against more than 20 RNA viruses in nine different taxonomic families, including togaviruses, bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses, flaviviruses, and filoviruses (such as Ebola virus) (39). A phase I clinical trial of this compound as an Ebola virus therapeutic is planned for 2015. Another approach that holds potential for the treatment of many viral diseases, including filoviruses and other hemorrhagic fever viruses, is RNA interference, a naturally occurring mechanism for the inhibition of protein expression. Small interfering RNA (siRNA) drugs against viruses are based on the mRNA sequences of the target viral proteins. A siRNA therapeutic can be created relatively quickly compared with the time usually required to screen and synthesize antiviral candidates. Successful delivery of siRNAs to desired cellular targets requires that they be protected from degradation in the bloodstream so as to promote cellular uptake; this may be achieved by methods such as lipid encapsulation. In this regard, a research team recently demonstrated that a lipid-encapsulated siRNA treatment completely protected nonhuman primates against the most lethal strain of Marburg virus, even when treatment began 72 hours after infection (40). A related therapeutic for Ebola virus currently is in clinical development.

In summary, although emerging viral infections will continue to pose a threat to human survival, advances in scientific technology have expanded our ability to prepare and respond. From rapid identification of

new viruses to prevention with vaccination and treatment with effective therapeutics, biomedical research has continued to supply tools to meet the perpetual threat of emerging viral pathogens. Despite these advances, complacency is not an option. Emerging and reemerging viral infections will remain a perpetual global health challenge; thus, we must stay at the cutting edge of scientific discovery, working energetically to develop new tools to combat the ever-changing threats they pose.

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