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ScienceDirect
Antiviral Research 78 (2008) 1–8
Antiviral Research
www.elsevier.com/locate/antiviral

Review

Highly pathogenic RNA viral infections: Challenges for antiviral research

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Received 6 November 2007; accepted 13 December 2007

Abstract

A number of RNA viruses can cause severe disease when transmitted to humans from an animal reservoir. One of them, the recently emerged H5N1 subtype of influenza A virus, has caused several hundred cases of severe disease when transferred directly from domestic poultry. This or another avian subtype could potentially evolve to a form more transmissible by the respiratory route or reassort with a circulating strain to initiate a pandemic. Other zoonotic RNA viruses cause sporadic single cases or outbreaks of hemorrhagic fever or encephalitis that spread inefficiently from person-to-person, and thus remain confined to the geographic range of the maintenance host. RNA viral infections of farm animals, such as foot and mouth disease and classical swine fever, also pose a major threat to human well-being through economic loss and impaired nutrition. Only a few licensed antiviral drugs are available to prevent or treat these conditions. Medications that inhibit the replication of influenza virus might be used in an epidemic both to treat severe disease and to block the spread of infection. The guanosine analog ribavirin has been used to treat a few types of hemorrhagic fever, but there is no specific therapy for the others, or for any type of RNA viral encephalitis. The quest for new antivirals is being supported by government programs and new collaborative research networks. Major efforts will be required to identify active compounds, test their efficacy in laboratory animals, obtain approval for human use and develop rapid diagnostic methods that can identify patients early enough in the disease course for treatment to be of benefit.

Keywords: Viral hemorrhagic fever; Viral encephalitis; Arbovirus; Influenza; H5N1 influenza; Filovirus; Flavivirus; Yellow fever; Lassa fever; Lassa virus; Ebola hemorrhagic fever; Marburg hemorrhagic fever; Junin virus; Argentine hemorrhagic fever; Hantavirus; Hantavirus pulmonary syndrome; Crimean-Congo hemorrhagic fever; Arenavirus; Bunyavirus; Alphavirus; Japanese encephalitis; Zoonosis; Antiviral therapy; Antiviral drug; Emerging infectious diseases; Livestock diseases; Foot-and-mouth disease; Biodefense

Contents

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0166-3542/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.antiviral.2007.12.007

1. Introduction

This special issue of *Antiviral Research* reviews current approaches to the treatment of highly pathogenic RNA viral infections and efforts to develop new therapies. In contrast to less virulent agents such as the rhinoviruses, which persist through continuous person-to-person transmission, the RNA viruses discussed in this issue are maintained in animals, and can cause severe illness with high case fatality rates or significant residual disability when transferred to humans. This introductory article reviews the problem of RNA viral zoonoses and briefly examines each of the diseases covered in this issue. Two additional introductory papers discuss licensed and experimental therapies: that by Leyssen et al. focuses on nucleoside analogs and other "small molecules," while that by Spurgers et al. reviews sequence-based therapies using antisense molecules and siRNA (Leyssen et al., 2008; Spurgers et al., 2008).

Diseases caused by nine RNA viruses from six different families have been chosen as the subjects of articles in this special issue (Table 1). They can be divided into three groups. The first consists of illness caused by influenza virus. Various viral subtypes produce sporadic cases of conjunctivitis or respiratory disease in humans when transferred directly from infected birds, but also have the proven capacity to evolve into highly transmissible agents that spread by the airborne route to cause global epidemics. Current concern focuses on the H5N1 virus, which was first recognized as a highly virulent pathogen of domestic poultry and humans in Hong Kong in 1997 and re-emerged in Southeast Asia in 2003. The second group consists of more than 30 different types of severe hemorrhagic fever or encephalitis caused by zoonotic RNA viruses. In contrast to influenza virus, the causative agents discussed in this review have so far proven incapable of sustained human-to-human transmission, causing only single cases or small outbreaks of illness within the regions occupied by their maintenance hosts or arthropod vectors. However, they still impose a significant burden on public health resources, through a frequent requirement for prolonged hospitalization, high case fatality rates and the danger some of them pose to health care workers. Many have the potential to be used as bioterror weapons. The third group of pathogens consists of RNA viruses that infect farm animals, causing major financial losses and impairing the nutrition of people dependent on them for food. As in the case of some hemorrhagic fever and encephalitis viruses, certain livestock pathogens could also be used in terrorist attacks against the agricultural industry.

2. Potential for new drug development

Specific therapies exist for only a few of the diseases discussed in this issue. The most effort has gone into developing drugs for influenza, probably because the prospect of treating millions of people in a global epidemic has encouraged pharmaceutical companies to undertake the necessary research and development efforts. RNA viral encephalitis and hemorrhagic fever have received much less attention, in part because the diseases occur predominantly in underdeveloped countries that lack the infrastructure for clinical trials and the resources to pay for expensive medications. Only a single licensed drug, ribavirin, is in use against any of these infections; its efficacy against a few types of viral hemorrhagic fever has been reported only in observational studies.

Surprisingly, even though RNA viral infections of livestock have cost the industrialized countries many billions of dollars in lost trade over the past decade, little effort has been made to develop antivirals against these diseases, and none are in veterinary use. As discussed by Goris et al. (2008), the focused use of antiviral therapy could be a useful control measure in outbreaks of foot-and-mouth disease and other conditions, supplementing or replacing such costly and inefficient strategies as emergency vaccination and mass slaughter.

Fortunately, the absence of approved therapies does not mean that no compounds inhibit highly pathogenic RNA viruses. As reviewed in this issue, a considerable number of substances show good activity *in vitro*, and some have been protective in the large number of laboratory animal models that are now being used to assess drug efficacy (Gowen and Holbrook, 2008; Holbrook and Gowen, 2008; Leyssen et al., 2008; Spurgers et al., 2008). The number of candidate medications will increase as new technology and sources of financial support become available. As described here, a variety of US government resources have been made available to aid in this effort, and new multinational research networks are providing a wealth of data on viral structural proteins, replication mechanisms and potential drug targets (Coutard et al., 2008; Greenstone et al., 2008; Kuhn and Canard, 2008). Procedural innovations such as the US Food and Drug Administration's recently promulgated "Animal Rule" are also helping to smooth the path for drug development (Roberts et al., 2008).

3. Developing new therapies—and finding the patients

Because RNA viral zoonoses cannot be eradicated, countermeasures will always be needed to prevent and treat them. Some diseases will increase in incidence over coming decades,

Table 1
RNA viruses that cause severe illness in humans or economically important disease in livestock and are the subject of articles in a this issue of *Antiviral Research*

Family	Virus	Disease	Host, vector	Current therapy
Arenaviridae	Junin	Argentine HF	Rodents, none	Immune globulin
	Lassa	Lassa fever	Multimammate mouse, none	Ribavirin
Bunyaviridae	Crimean-Congo HF	Crimean-Congo HF	Numerous wild and domestic mammals, ticks	Ribavirin
	New World hantaviruses	Hantavirus pulmonary syndrome	Rodents, none	None
Filoviridae	Ebola, Marburg virus	Ebola, Marburg HF	Unknown	None
Flaviviridae	Japanese encephalitis virus	Japanese encephalitis	Wild birds, pigs, mosquitoes	None
	Yellow fever virus	Yellow fever	Wild primates, mosquitoes	None
Orthomyxoviridae	Influenza A viruses	Pandemic, seasonal and avian influenza	Waterfowl, none	M2 ion channel blockers, neuraminidase inhibitors
Picornaviridae	Foot-and-mouth disease virus	Foot-and-mouth disease	Hoofed animals, none	None

All of these agents have single-stranded genomes; the flaviviruses and picornaviruses are positive-sense, the others negative-sense. HF: hemorrhagic fever.

as expanding populations, failure of vector control, the effects of global warming on vector distribution and other factors increase the contact rate between humans and sources of infection. Others will become less prevalent, as changes in human behavior reduce exposure to the causative agents and vaccines are introduced or more widely applied. Although vaccination would of course be the simplest strategy for dealing with these threats, complete success would require continuous universal immunization across the entire regions where the agents persist in their maintenance hosts—an unlikely prospect, given limited public health resources.

Even if safe and effective medications are developed in the laboratory, it will often prove challenging to use them in ways that benefit patients. Antiviral therapy is more effective, the sooner it is begun in the course of infection, but the early initiation of specific treatment is particularly difficult for the diseases discussed in this issue. Because the transmission event (mosquito bite, exposure to aerosolized animal excretions, etc.) by which infection is acquired usually passes unnoticed; the incubation period is measured in days to weeks; and the initial signs and symptoms are nonspecific, an RNA viral zoonosis is rarely diagnosed before the patient is severely ill. By that time, intense inflammatory responses and tissue damage may dominate the clinical picture, and attempts to block viral replication may have little impact on the further course of illness.

The challenge of early diagnosis and treatment of highly pathogenic RNA viral infections is illustrated by recent efforts to assess the therapeutic efficacy of ribavirin in hantavirus pulmonary syndrome (HPS). Providing treatment is started early, ribavirin is beneficial for Old World hantaviral infections, and would therefore be expected to be of value for HPS. However, because patients with New World hantaviral infections were usually in incipient respiratory failure by the time their disease was recognized and ribavirin was begun, no effect was observed (Mertz et al., 2004). The message is clear: the success of antiviral therapy for highly pathogenic RNA viral infections is linked to the development of rapid diagnostic techniques that can identify patients early enough for treatment to be of benefit.

4. Influenza: zoonotic and epidemic disease

Influenza A viruses asymptomatically infect the gastrointestinal tracts of wild waterfowl. A large number of viral subtypes exist, each with one of 16 different hemaglutinin and 9 different neuraminidase molecules on the virion surface. In contrast to other diseases discussed in this issue, influenza virus infection of humans occurs in two forms that differ markedly in their epidemiology. The first is a zoonotic illness that occurs when virus is transferred directly from birds, usually during outbreaks of illness in domestic poultry; its nature depends on the viral subtype, and possibly on the dose and route of infection. Several subtypes, including H7N7 and H7N2, have caused outbreaks of severe disease in chickens and conjunctivitis or mild respiratory illness in workers exposed to them. The recently emerged H5N1 subtype, however, is an unusual pathogen that lethally infects a wide range of animals, including various species of wild and domestic birds, small and large felines, mice, ferrets and nonhuman primates. The virus has now been carried halfway round the world from its origin in Southeast Asia, but so far it has fortunately shown a very limited capacity to spread from person-to-person. The fatality rate among more than 300 confirmed human cases has exceeded 50%.

The second, more familiar form of influenza virus infection is caused by those subtypes that have acquired the capacity for efficient human-to-human transmission, spread through the population to cause global epidemics, then continued to circulate and return to cause outbreaks of respiratory infection. During the past century, the pandemic subtypes have consisted in turn of the H1N1, H2N2 and H3N2 viruses. The occurrence of repeated outbreaks of seasonal influenza in the same population caused by the same viral subtype is explained by the accumulation of mutations in the HA and NA genes, which causes sufficient antigenic "drift" to permit re-infection. Zoonotic and epidemic forms of influenza virus infection are of course not independent, since each circulating agent is descended from a virus that was once transferred from an animal host to a human being.

What enables influenza virus to "jump" from the gastrointestinal tracts of wild waterfowl to cause worldwide epidemics of respiratory illness? One essential characteristic is the agent's capacity to replicate in human respiratory epithelium, providing the basis for airborne transmission. The second feature that makes periodic pandemics inevitable is the multipartite viral genome, which makes possible the sudden appearance of new antigenic variants to which the entire human population lacks immunity. These "shifts" occur when one host is infected by both a zoonotic and an epidemic influenza subtype, as reassortment of viral genes within a simultaneously infected cell generates viruses with unprecedented combinations of replicative enzymes and surface antigens. Although it is widely assumed that the occurrence of severe H5N1 infections herald its emergence as the next pandemic subtype, either through "drift" towards ever-greater transmissability or reassortment with a currently circulating seasonal virus, other avian HAs, such as H7 or H9, could also be transferred to a seasonal virus. Only time will tell.

If an antigenically novel and highly infectious form of influenza virus does arise, modern civilization could inadvertently aid its dissemination by providing huge, densely populated cities to serve as "culture flasks" and rapid transportation systems to speed its worldwide spread. At the same time, however, a multinational network of scientists and clinicians is working to keep that from happening, by tracking infected birds and carrying out intensive surveillance to detect human disease. Because vaccines against a newly emergent virus will take months to produce and deliver, initial control strategies could include the use of antiviral prophylaxis and therapy to create a "wall of resistance" around an emerging focus, using dosing regimens chosen to discourage the appearance of drug-resistant mutants. In this issue, Beigel and Bray review antivirals now in use to treat influenza and other approaches "in the pipeline," and in a second paper, Higgs et al. describe the creation of a new clinical research network in Southeast Asia that could play a number of roles in responding to the emergence of a new pandemic virus, including the evaluation of new treatment regimens (Beigel and Bray, 2008; Higgs et al., 2008).

5. Viral hemorrhagic fever

In spite of frequent opportunities for cross-species transmission, only a small fraction of viruses that infect animals also cause disease in humans. Many factors presumably contribute to the rarity of viral zoonoses: the absence of suitable receptors on human cells, a lack of intracellular co-factors for replication or the inability of an invading virus to block the innate immune defenses of its new host. For RNA viruses, which generate double-stranded intermediates during their replication, the ability to suppress human type I interferon responses may be an essential requirement for successful cross-species transmission (Bray, 2005). Perhaps because they have not co-evolved with humans, those viruses that manage to cross the species barrier tend to cause severe disease with high case fatality rates, but spread inefficiently from person-to-person.

The 15–20 different types of hemorrhagic fever appear to share a similar pathogenesis, in which macrophages and dendritic cells, rather than acting as barriers to an invading pathogen, instead serve as the principal sites of viral replication, permitting the rapid spread of infection (Bray, 2005; Bray and Geisbert, 2005; Geisbert and Jahrling, 2004). Because these cell types are ubiquitous in mucous membranes, the dermis and other tissues, infection can be initiated by any route, including inoculation, ingestion and inhalation. The release of large quantities of proinflammatory mediators from these infected cells results in a procoagulant state and increased vascular permeability, leading to hemorrhage, intravascular volume depletion and circulatory collapse. The similarity of this syndrome to septic shock is leading to the experimental use of sepsis therapies for viral hemorrhagic fever (Bray and Mahanty, 2003; Hensley et al., 2007).

5.1. Lassa fever

Of all the types of viral hemorrhagic fever, Lassa may be the most amenable to the development of effective antiviral therapy. Most importantly, patients are comparatively easy to find, as the disease occurs year-round in a zone of West Africa where residents are exposed to excretions of the rodent host, the multimammate mouse. In Sierra Leone, the incidence of Lassa fever has been high enough to justify the creation of a dedicated ward at Kenema Hospital. As Dr. Khan, the ward chief, and his colleagues describe in this issue, continuing improvements in the unit's capacity for diagnosis and patient care are making pathogenesis studies and drug trials at Kenema a practical possibility (Khan et al., 2008).

Ribavirin was proven two decades ago to be beneficial in nonhuman primates infected with Lassa virus (Jahrling et al., 1980), but only a single published study has shown evidence of benefit in humans, when McCormick et al. (1986) reported that severely ill patients treated with intravenous ribavirin had a better outcome than an earlier series who received no specific therapy. A short-term goal for researchers would be to establish a standard, minimally toxic but beneficial regimen of ribavirin for LF that could be used to establish biological markers of protective activity and employed as a benchmark for testing new drugs. As for other diseases discussed in this issue, the development of simple point-of-care diagnostic methods could play a critical role in improving the treatment of LF by enabling patients to be identified early in the course of illness.

5.2. Yellow fever

Even though mosquito control was proven more than a century ago to prevent the spread of yellow fever, and a highly effective single-dose vaccine has been in use since the 1930s, the World Health Organization estimates that up to 200,000 cases of the disease still occur each year, resulting in thousands of deaths. The causative agent is maintained in wild primates in rain forest regions of South America and Africa, where mosquito transmission results in sporadic infections among local residents. Epidemic disease is seen only in Africa, when heavy rainfall is followed by an increase in vector density.

An effective treatment could obviously help to reduce mortality during a recognized yellow fever outbreak, but finding and treating sporadic cases of the disease would be a major challenge. As discussed by Monath in this issue, endemic yellow fever is difficult to recognize against the background of more common tropical infections, since it begins as a nonspecific febrile syndrome, and only a minority of patients proceed to the severe hepatitis and jaundice that gave the disease its name (Monath, 2008). Ribavirin and some other drugs have been protective in rodent models, but none has prevented illness in laboratory primates or been tested for efficacy in humans. The ideal yellow fever drug would have broad-spectrum activity against other flaviviral infections, such as dengue, that occur in wealthy countries, so as to provide a financial stimulus for drug development. Determining whether flaviviruses share conserved drug targets is therefore a focus of current research.

5.3. Argentine hemorrhagic fever

The present situation for Argentine hemorrhagic fever (AHF) might be seen as a golden future for many RNA viral zoonoses: targeted vaccination in the endemic zone has markedly diminished its incidence, and the fatality rate among remaining cases has been reduced through treatment with immune globulin from convalescent patients. Only sporadic infections in unvaccinated individuals continue to occur. Unfortunately, as Enria and colleagues report in this issue, success in preventing AHF now threatens the ability to treat it, by diminishing the number of potential plasma donors (Enria et al., 2008).

The therapy itself is also less than ideal. Even though highly effective in preventing death, treatment with immune globulin is frequently followed by the development of a delayed viral encephalitis, with its own set of health consequences. As noted by Enria et al., ribavirin has been used to a limited extent to treat AHF, and the same syndrome of delayed encephalitis was also seen. The mechanism by which treatment of a systemic infection facilitates viral invasion of the central nervous system remains unexplained, but is clearly worthy of study; the findings could improve our understanding of diseases such as Rift Valley fever, in which late encephalitis is a feature of the untreated illness. Fortunately, the work of Argentine scientists over the past three decades has established a solid basis for studying this phenomenon and a standard of therapeutic success against which new treatments can be tested.

5.4. Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) presents an especially difficult challenge for antiviral drug development. Even though a large number of cases occur each year across an area reaching from western China to South Africa, their unpredictable appearance and wide dispersion have hindered the systematic study of the disease. At the same time, the failure of CCHF virus to cause illness in any of its maintenance hosts or in laboratory animals other than suckling mice has hampered efforts to test new drugs, and may prove a significant barrier to developing new therapies (Nalca and Whitehouse, 2007). The continued effort to create an animal model of CCHF, perhaps in a less commonly used species of nonhuman primate, is clearly a worthwhile endeavor.

As described by Ergonul (2008), progress is being made in understanding the pathogenesis of CCHF and improving its therapy. Isolates of CCHF virus from across its entire geographic range are sensitive to ribavirin, and uncontrolled studies suggest that early initiation of treatment can improve the outcome of illness. As in the case of Lassa fever, an appropriate short-term goal for clinical research would be to supplement these reports with a body of systematically collected data on the response of CCHF patients with various degrees of severity and stages of infection to a standard regimen of ribavirin, that could be used as a benchmark for assessing new therapies. Such an effort would benefit from the development of rapid diagnostic methods and the creation of a research network among hospitals accustomed to treating CCHF patients. The large number of cases now being diagnosed in Turkey could make this a practical possibility (Vatansever et al., 2007).

5.5. Hantavirus pulmonary syndrome

Although newly discovered, hantavirus pulmonary syndrome (HPS) is not a new disease. Sporadic cases have presumably occurred for millenia, whenever residents of the New World came into close contact with the excretions of infected rodents, but the disease went undetected until 1995, when an “el Niño” event led to heavy rains, an expanded food supply for mice and a cluster of cases of rapidly progressive respiratory failure in the American southwest. HPS is acquired by inhaling infectious material, but in contrast to influenza, it does not represent an infection of the epithelial lining of the respiratory tract. Instead, it is considered to be a variant of viral hemorrhagic fever, in which intense inflammatory responses are manifested principally through increased vascular permeability in the lungs.

As Jonsson et al. discuss in this issue, even though ribavirin inhibits hantaviral replication *in vitro* and is beneficial for treating Old World forms of hantaviral disease, it did not show an effect against HPS in a placebo-controlled trial, probably because patients who received the drug were already severely ill by the time their disease was recognized (Jonsson et al., 2008; Mertz et al., 2004). Until methods are developed for identifying patients during the short prodromal phase of illness, when inhibition of viral replication would presumably be beneficial, antiviral therapy may be most useful for protecting close contacts of patients infected with the Andes virus, which has been transmitted from person-to-person in a number of cases.

5.6. Filoviral hemorrhagic fever

Marburg and Ebola hemorrhagic fever present the greatest challenge to the development of new antiviral therapies for highly pathogenic RNA viral infections. The basic problem can be summarized by noting the striking contrast between the high-tech containment laboratories in which these diseases are studied and the impoverished locations in central Africa where they occur (Bray and Murphy, 2007). The past decade

has seen impressive progress in developing experimental forms of prophylaxis and therapy that protect nonhuman primates against otherwise lethal Marburg and Ebola virus infections. Five different vaccine approaches have given solid protection, and one is even effective when administered after virus challenge (Daddario-DiCaprio et al., 2006). In addition, several types of treatment have prevented fatal illness in macaques when initiated early in the incubation period, suggesting that they would benefit persons infected with a filovirus who have not yet become ill (Bausch et al., 2008). At the same time, however, limited resources at the sites of African outbreaks has precluded providing victims with any type of advanced medical care, often making it impossible even to administer intravenous fluids, and case fatality rates continue to be as high as they were in the 1970s.

In this issue, Bausch et al. (2008) discuss how discoveries in the laboratory could be transferred to a field setting, and how a clinical trial might be performed in a location that lacks a constant electrical power supply, let alone a modern hospital and laboratory. Until the complex preparations have been made for the introduction of new vaccines and therapies into Africa, the first group to benefit from them will probably be the laboratory workers who developed them. The occurrence in the past few years of a fatal case of Ebola hemorrhagic fever in a Russian researcher and a "near miss" in a US investigator make it clear that effective pre- and postexposure prophylaxis for Marburg and Ebola hemorrhagic fever should be a top priority, especially as the number of high-containment laboratories continues to increase (Akinfeeva et al., 2005). Members of international response teams will also benefit.

6. RNA viral encephalitis

The various forms of arboviral encephalitis are among the few RNA viral zoonoses that occur both in "third world" countries and in economically developed regions, wherever humans co-exist with an appropriate arthropod vector and reservoir host. Even the richest nations, however, have made little progress in developing specific treatments for these diseases, in part because no methods have yet been devised to identify patients before they develop neurologic abnormalities, indicating that viral replication in the brain is already well under way.

RNA encephalitis viruses induce systemic inflammation, but in a milder form than the agents of hemorrhagic fever. Most persons infected by these pathogens develop only a nonspecific flu-like illness, but in a small percentage of cases (which varies with the individual agent) virus crosses the endothelial lining of the cerebrovascular system and infects the brain. Current therapeutic approaches are limited to efforts to reduce the resultant brain swelling and prevent permanent neurologic deficits and death. Although a number of drugs strongly inhibit the replication of encephalitis viruses *in vitro*, they are generally ineffective in animal models, because they fail to cross the "blood–brain barrier," an evolutionary adaptation of the cerebrovascular endothelium that protects the central nervous system against the entry of noxious substances. An important goal of research is to identify natural transvascular transport mechanisms, including those utilized by the encephalitis viruses themselve, and exploit them to deliver therapeutic molecules to the brain (Kumar et al., 2007, Pardridge, 2007).

6.1. Japanese encephalitis

As described by Gould et al. (2008), Japanese encephalitis (JE) virus imposes the greatest public health burden of all types of RNA viral encephalitis, infecting thousands of persons each year across a huge region of Asia, with a high toll of death or irreparable neurologic damage. Even as a number of countries have reduced the incidence of JE within their borders by developing their own vaccines, its geographic range has continued to expand (Mackenzie et al., 2004).

Because universal vaccination in all endemic countries appears an unlikely prospect, antiviral therapy could make an important contribution to reducing the public health impact of JE. Even a small decrease in death and lifelong disability would justify the expense of drug development. Good animal models are available, and an (unfortunately unsuccessful) test of interferon-α 2a therapy in Viet Nam has demonstrated that a sufficient number of cases can be recognized on a clinical basis in some locations for a double-blinded clinical trial to be performed (Solomon et al., 2003). As noted, the major challenge for developing effective therapy for JE and other types of RNA viral encephalitis may not lie in logistics, but in devising methods of diagnosing infections early and administering drugs that can cross the blood–brain barrier.

7. Protecting livestock against the spread of pathogenic RNA viruses

Discussions of antiviral therapy invariably focus on human illness, but it should be recognized that infections of farm animals also threaten human well-being. Disease outbreaks can occur when a virus is transferred from a wild animal reservoir, as in the case of Rift Valley fever, or when an agent is accidentally transported from a country where a disease is prevalent to another from which, 7 has been eliminated, as has often been seen for foot-and-mouth disease. Either form of introduction can result in the death or forced slaughter of thousands of animals.

Just as much thought is now being given to how antiviral medications could be used to help slow the spread of influenza among humans, it is worth considering how drugs could be used in similar fashion to block disease transmission in the setting of a livestock outbreak. As discussed by Goris et al. (2008), improved surveillance and the development of rapid diagnostic tests could make targeted treatment a reasonable strategy in situations where vaccination is impractical or ineffective and mass slaughter is the only alternative. Considering the vast sums that are lost whenever foot-and-mouth disease virus turns up in previously disease-free areas, investment in research on antiviral prophylaxis and therapy would be money well spent.

8. Vaccines and antiviral therapy

Because it is better to prevent a disease than treat it, vaccines are an essential weapon in the fight against highly pathogenic

RNA viruses. For a number of diseases discussed in this issue, such as Argentine hemorrhagic fever, yellow fever and Japanese encephalitis, there is abundant evidence that vaccines now in use can markedly reduce the incidence of disease when delivered to the appropriate population. Lassa fever is a reasonable next target, as the disease is confined to a relatively small area of West Africa where field trials of vaccine safety and efficacy could be performed.

Vaccination as a major control strategy is more problematic, however, for diseases such as Crimean-Congo hemorrhagic fever or hantavirus pulmonary syndrome, which occur sporadically and unpredictably across huge geographic regions. Although effective products could probably be developed, a very large number of people would have to be immunized for each case of disease prevented. Even when population-wide vaccination is not feasible or affordable, however, vaccines could still play an important role by protecting laboratory researchers who study these pathogens and health care workers who risk their lives to treat the victims of an epidemic. Fast-acting vaccines, such as those that protect nonhuman primates when administered soon after a lethal dose of Marburg or Ebola virus, would be especially useful, since they could be used as "drugs" to treat persons accidentally exposed to a pathogen (Daddario-DiCaprio et al., 2006).

9. Conclusion

The effort to develop effective therapies for highly pathogenic RNA viral infections is one of the most challenging in public health. Its success will require intensive research at multiple levels, from basic studies of the causative agents and their replication mechanisms through medicinal chemistry, efficacy testing in animals, epidemiologic surveys, the development of improved diagnostic methods and the performance of clinical trials. An essential requirement for the success of this enterprise is a system of rapid and efficient communication to enable scientists to share their findings and connect the investigator in the biocontainment laboratory to the doctor at the patient's bedside. If this special issue of *Antiviral Research* helps to develop and strengthen such a worldwide network, it will have achieved its purpose.

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