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SPECIAL ARTICLE

Emerging and Re-Emerging Infectious Diseases: Review of General Contributing Factors and of West Nile Virus

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Smallpox, eliminated from the world as a naturally occurring disease, now is touted as a weapon of mass destruction. The incidence of tuberculosis (TB), once on the downward slope, has been on the increase. In the early 1990s, plague reemerged in India, killing 54 persons, a number quite small in comparison with the thousands who die daily from malaria and TB but sufficient to alarm the medical community.[1] Subsequently, in 1999, West Nile encephalitis emerged in New York, sparking a new emergency. Other diseases thought to be under control or even eliminated are reemerging; certain diseases previously considered to be strictly zoonotic are appearing in people in different parts of the world; diseases that are new or that once were unrecognized, such as severe respiratory syndrome (SARS), have appeared with alarming ferocity; and many antibiotics are losing their effectiveness as a result of resistance that has been acquired by different organisms. This emergence of new and reemergence of old infectious diseases have become a major global problem.[2-4] Although the numerous concerns that these and other factors present are far beyond the scope of this publication, the next several issues of *Seminars* will present a series of special articles devoted to this subject, beginning in this issue with a review of the threat to human and social security and various factors that contribute to the situation. One particularly recent threat, West Nile virus (WNV), will be considered in this issue

Renewed Emphasis on Emerging Infectious Diseases

When, in the 1960s, most of the deadly diseases such as smallpox, poliomyelitis, and acute rheumatic fever were eliminated or reduced in frequency by vaccines or antibiotics, then Surgeon General William H. Stewart announced that the time had come for researchers to turn their attention from infectious diseases to chronic ailments such as cancer and heart disease. This "comfort zone" was shattered in the 1980s with the emergence of new diseases and the reemergence of those once considered historic.[5] Since then, numerous efforts have been made to investigate the extent of the situation and to consider measures to contain or combat it.

In 1992, Drs. Joshua Lederberg and Robert Shope reported on the conclusions of a committee convened by the Institute of Medicine of the United States to investigate the emerging microbial threats to health.[6] Results of the 18-month study included the identification of a large number of microbes (bacteria, rickettsiae, chlamydiae, viruses, parasites, fungi) that either were known to be pathogenic or were recognized as being new human pathogens. The committee also identified various contributing factors, such as human behavior, travel and mass movements of individuals, civil unrest and wars, and, especially, genomic changes and adaptations. Since that time, a plethora of publications have described the various considerations involved in emerging or reemerging infectious diseases.

In 1998, the Centers for Disease Control and Prevention presented to the United States Senate a statement, based on cooperation with the working group on domestic and international surveillance for possible bioterrorism, providing for public health leadership to strengthen public health readiness to address bioterrorism.[7] Among the measures included in the statement was the acknowledgment of a need for training public health professionals in preparing for and responding to emerging and reemerging infectious diseases and a request that public health professionals be involved in planning for public health emergencies and be considered full partners with sufficient autonomy to protect the public's health.[8]

In April 2002, the fifth annual Conference on New and Re-Emerging Infectious Diseases was held at the College of Veterinary Medicine, University of Illinois at Urbana-Cham-

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paign, where eight speakers addressed recent infectious diseases, bioweapons, cholera and multidrug-resistant tuberculosis, and re-emerging parasitic diseases.[9] Other ongoing measures include the work of the World Health Organization's Global Outbreak Alert and Response Network. Subsequent to the outbreak of SARS coronavirus (SARS-CoV), the Institute of Medicine (IOM) noted the existence of associations among various emerging diseases, emphasizing that microbial threats endanger public health across the globe and demand the urgent need for better strategies and tools to tackle infectious diseases. The IOM outlined several factors contributing to microbial spread, which officials at IOM, Centers for Disease Control and Prevention, the World Health Organization, and other health agencies are attempting to halt by limiting antimicrobial use, by pouring money into global health funds, by establishing international surveillance networks and, in severe instances, by limiting travel.[10]

Threats to Human and Social Stability

The emergence of these diseases and the resistance that is developing against various antibiotics have numerous psychological, sociological, and political implications. These three aspects are the underlying subject of an analysis provided by Brower and Chalk. Using the psychological theories of Blatz,[11] these authors delineate the effects of transnational spread of emerging infectious diseases as they threaten human security, defined as "the quality of life of the people of a society or polity. Anything which degrades their quality of life—demographic pressures, diminished access to or stock of resources, and so on—is a security threat."[12] Human security is seen to differ in three ways from the traditional concept of security: (1) the individual rather than the state is the main agent of analysis; (2) the emphasis is on unstructured chaos and turmoil as the chief challenge to global stability rather than on structured, militarized interstate violence; and (3) the potential for individual/communitarian cooperation is based on cooperation that achieves the good of all rather than on interactions in which one party "wins" at the expense of the other(s).[13] The threat to this concept of human security is depicted by Browers and Chalk in six specific aspects, as reviewed below.[13]

First, of course, is the toll on human life and the accompanying societal implications. Disease kills—and in doing so, it poses an even greater threat than that caused by war: acquired immunodeficiency syndrome (AIDS) alone is expected to account for the deaths of more than 80 million people by the year 2011, TB accounts for 3 million deaths (including 1 million children) annually, and "a staggering 1500 people die each hour from infectious ailments, the vast bulk of which are caused by just six groups of disease: human immunodeficiency virus (HIV)/AIDS, malaria, measles, pneumonia, TB, and dysentery and other gastrointestinal disorders."[14]

Second, unchecked disease can undermine public confidence in the custodial function of the state, perhaps even undermining the ability of the state to function and placing acute pressure on first responders and medical personnel that increases the responsibility of an already-stressed government to respond adequately. Two examples of this concern can be provided. The threat of the anthrax attacks in the United States in the fall of 2001 was accompanied by a lack of coordination at the federal level, which led to a loss of confidence among some citizens, particularly postal workers. Additionally, other responses were misguided (eg, the purchase by the general public of Cipro® [Bayer, West Haven, CT] the antibiotic approved for treating anthrax, in large numbers). Another example was provided by the severe food poisoning epidemic caused by *Escherichia coli* 0157 that occurred in Japan in 1996, when the perceived inability of the Tokyo government to initiate an appropriate response led to widespread public criticism of an administration that already was reeling from the effects of the previous year's Kobe earthquake.

A third concern with regard to public security is the adverse economic effect, especially evident in the fiscal burden that has been posed by the HIV/AIDS epidemic, health care for which is projected to cost in excess of $500 million USD in South Africa by the year 2009.[15] If the projected trend, which indicates that South and Southeast Asia will surpass Africa in terms of infections by the year 2010, continues, countries with fragile economies and public health infrastructures could experience demographic upheaval and wide destabilization, including the possible reduction of the general gross domestic product by as much as 20 percent.[16]

The negative impact that disease can have on a social order of the state, its function, and psyche poses the fourth effect. One example of this effect can be seen in the distortion, resulting from AIDS, of the wantok system of Papua, New Guinea, which formalizes reciprocal responsibilities that ensure that those who encounter hard times receive care from extended family members. Another example is the reaction in the Gulu district of Uganda, where the outbreak of Ebola in late 2000 led to a complete withdrawal of the populace from the outside world, such that common societal interactions and functions were reduced to a bare minimum. Adverse psychological as well as societal consequences have been associated with the emotional stress suffered during times of such withdrawal, continual subjection to poor sanitary conditions, and outbreaks of diseases.[17]

The spread of infectious diseases can pose a fifth threat as a catalyst for regional instability, as seen already in the military, demographic, and fiscal effects of the AIDS crisis in Africa. Epidemics can galvanize mass population flows across borders, thereby fostering economic problems and creating a widespread volatility that can develop quickly into heightened tension both within and between countries.

A sixth effect is one that has become increasingly important in the past decade: the threat of infectious diseases being used as weapons of biowarfare and bioterrorism. These concerns have been exacerbated by recent events: (1) the anthrax attacks that occurred in the fall of 2001, (2) discoveries of Iraq's biowarfare efforts after the Persian Gulf war, (3) revelations made by Boris Yeltsin and Ken Alibek concerning the extent of the former Soviet Union's biowarfare program, (4) Aum Shinrikyo's apparent attempt to acquire and disseminate biological agents both before and after its 1995 sarin nerve gas attack on Tokyo, and (5) indications that terrorists groups such as Osama bin Laden's al-Qaeda network are interested in developing such bioterrorist capabilities.

In addition to the aforementioned considerations of the impact of infectious diseases is the vicious cycle of the socioeconomic impact that epidemics of infectious diseases create. The costs of outbreaks can be staggering and can compromise or even retard economic development processes, particularly in developing countries. One result is the diminished size of the workforce when an epidemic occurs. Particularly in developing countries, productivity hampered by a handicapped workforce can have a seriously adverse effect on the national economy. As has occurred especially with HIV/AIDS, the incidence of new cases disproportionately affects developing countries, in which 90 percent of such cases are found. Because HIV/AIDS affects primarily individuals in their prime economic productive years, the consequences to the local, regional, and national economies can be devastating.[3] Also, because this population is in its child-bearing years, the socioeconomic consequences include a huge number of children and adolescents who are left orphans when the parents succumb to AIDS, leaving the responsibility of their children's care to extended family members, many of whom already are ill themselves or unable to bear the burden psychologically or financially. Beyond the strain on the family is the social consequence of adolescents and even children resorting to prostitution as a means of survival, thereby increasing their risks of acquiring and/or transmitting HIV and other infectious diseases.

Each of these effects, as described by the authors, indicates the far-reaching implications that the situation presents in addition to the challenges confronting physicians, other health care providers, and researchers as they seek to find solutions to contain diseases and to treat patients in light of increasing resistance to antibiotics.

Factors Contributing to Emergence/Reemergence of Infectious Diseases

Many factors have been identified as being major contributors to the scope and spread of infectious diseases in the United States and worldwide. They are complex and diverse, involving increased travel, trade, and migration; a growing number of new or more virulent, common organisms; changes in agricultural practices; more promiscuous drug and sex practices; increased and often indiscriminate use of antibiotics; use and donation of blood products; climatic changes; and tainted water supplies.

Increased Travel, Trade, and Migration

Global travel has grown considerably during the past half century: from 25 million in 1950 to 500 million in 1993, with estimates of 1 billion by the year 2010.[18] With the increases in travel and travel time between most parts of the world being less than 36 hours, individuals are at increased risk of contracting unusual illnesses from passengers who harbor organisms that may not incubate and emerge until after those persons return home. Indeed, the increased numbers of persons traveling worldwide has the potential to cause a domino-type effect in spreading old, new, and re-emerging infectious diseases.[13,19] In addition to transmitting diseases while in flight or after arriving at their destinations, infected individuals can transmit diseases while on an extended trip, such as on a ship, as seen with recent outbreaks on cruise liners.

Similarly, increased animal and food trade has affected the microbial threat, a result of the small number of samples tested by the Food Safety and Inspection Services and the lack of comprehensive inspections performed by the United States Department of Agriculture's Animal and Plant Health Inspection Service on US livestock because of lack of resources. Also, agricultural practices have changed considerably with the advent of new technologies, which allow farmers to breed animals in close proximity to one another but provide an ideal setting for the transmission of viral and bacterial agents. The rapid transport of animals from one locale to another provides yet another means for transferring infectious disease across the country, with little ability to track the geographic spread of infections, especially those that are zoonotic. Importation of food products adds additional threat of exposure to a variety of diseases when nonhygienic food production, preparation, and handling practices in the countries of origin introduced pathogens into other countries, including the United States.[13]

During the past 2 decades, the increase in migration and movement of populations also have resulted in the disappearance of national boundaries as far as the transmission of diseases is concerned.[20] In the United States, more than 1 million immigrants and refugees enter annually, often bringing with them a burden of disease. This concern is especially true for the 3 to 4 million undocumented aliens who enter illegally and do not undergo the required medical screening that is required for legal immigrants. Exacerbating the problem is that many of these same individuals do not have access to adequate health care once they enter the United States and, thereby, become reservoirs for various diseases, posing extensive public health threats.[21]

In other instances, internal displacement of individuals due to conflict, war, and natural disasters has facilitated the transmission of microbes, as has the increased poverty, poor sanitation, and inadequate nutrition that often accompany these incidents. In 1990, the number of displaced persons worldwide was estimated to be 30 million. When individuals are displaced, they often must resort to using temporary living quarters such as refugee camps and temporary shelters, both of which are harbingers of diseases and share the risk factors associated with other ideal environments for emerging infectious diseases and re-emerging infectious diseases: crowding, limited access to medical care, lack of clean water and food, and inadequate barriers for disease-carrying agents.[22] A prime example is the migration of 500,000 to 800,000 Rwandan refugees into Zaire in 1994. In this incident, cholera and *Shigella dysenteriae* type 1 swept through the refugee camp, killing almost 50,000 refugees during the first month of their displacement.[22]

Economic hardships also have contributed to the migration from rural to urban areas, allowing diseases that once were relatively isolated to reach larger populations, especially those in slum areas, which serve as breeding grounds for physical diseases and social ills such as drug abuse and prostitution.[22]

Sexual Practices and Intravenous Drug Use

Sexual practices have become more permissive in recent years, as has intravenous drug use, with the result that sexually transmitted diseases have shown an enormous increase since the 1960s, demonstrated most notably with the HIV/AIDS epidemic.

Sharing needles for drug intervention has been a primary means of transmission of HIV as well as numerous other blood-borne infections. This means of transmission is exacerbated by indiscriminate sexual practices, including multiple partners, failure to use protection, and anal sex. Estimates suggest that since the advent of the HIV/AIDS epidemic, injection drug use has accounted directly or indirectly for more than one-third (36%) of cases of AIDS in the United States. Nearly 20,000 (32%) of the 60,000+ new cases of AIDS reported in 1997 were associated with injection drug use. This means of transmission has been shown to have a greater impact on women than on men, with 61 percent of cases among women since 1981 being attributed to injection drug use or with having sex with partners who inject drugs, compared with 31 percent of cases among men.[22]

The use of noninjection drugs also contributes to the transmission of emerging infectious diseases and re-emerging infectious diseases, particularly HIV/AIDS, as use of such substances as crack cocaine often leads to users trading sex for drugs or money or engaging in other risky sexual practices.

Use of Antibiotics and Other Medical Contributors

During the past several decades, the effectiveness of antimicrobial drugs, the essential weapons in combating numerous infectious diseases, especially TB, acute respiratory infections, sexually transmitted diseases, nosocomial infections, malaria, and tropical diseases, has been compromised.[3] Among the most alarming of the resistant microbes are strains of *Staphylococcus aureus*, which are the cause of resistant, nosocomial infections that result in approximately 14,000 deaths annually.

One of the many factors contributing to the diminished effectiveness of antibiotics is the ability of organisms to quickly adapt to new environments and to replicate with mutated drug-resistant genes. Because of the frequent use of antibiotics and the close proximity of affected patients, hospitals and other medical facilities provide an ideal environment for this particular form of development and spread of antimicrobial resistance.

Misuse and overuse of antibiotics also have created a venue for the emergence of diseases that once were thought conquered but now are caused by highly resistant organisms.[23,24] The culprits involved in this means of development of resistance include failure of patients to complete drug regimens; incorrect or indiscriminate use of antibiotics, especially for viral or other infections for which antibiotics are not effective; self-medication; poor access to drugs, which also may contribute to poor compliance by patients who want to "save" medications once symptoms indicate that a disease has been cured; and inadequate training of medical personnel.

Paradoxically, the improvements that have been made in treatments for immunocompromised patients (eg, those with HIV/AIDS, organ transplants, cancer treated with chemotherapy) have lengthened their life expectancies, but in the course of doing so have created populations that are more vulnerable to acquisition of other infectious diseases. Another paradox is that the effectiveness of immunizations has led a generation of individuals who were not witnesses to the devastating effects of many diseases; they, in turn, balk at having their children vaccinated because of the slight risks associated with vaccines—risks that once were considered minimal in comparison with the successes achieved by vaccines but now appear to be more substantial in comparison with the few actual incidents of illnesses. Children who are unvaccinated not only may be vulnerable to acquiring diseases themselves but also may represent a threat to other vulnerable populations such as the very young and the elderly; these children also may serve as hosts for infections that are asymptomatic but are potentially lethal to especially vulnerable individuals such as those who are immunocompromised.

Demographic and Other Contributors

Changing weather patterns also impact the distribution of infectious pathogenic agents because they increase vector populations that spread disease to human hosts.[25] Although not as prevalent, the presence of tainted water supplies, which are screened for only representative bacteria, and the aging infrastructures have undermined the ability of investigators to ensure that all contaminants are removed sufficiently to protect the public from disease.

Changes in land usage also play an important role in transmission of emerging infectious diseases and re-emerging infectious diseases. Human alterations of local, regional, or global ecosystems have influenced the risks associated with many infectious diseases. For instance, dams created in the tropics and subtropics to store water for irrigation and hydroelectric power have introduced water-borne diseases such as schistosomiasis to communities where they did not exist previously.[22] Increased deforestation and expansion of irrigation have disturbed the habitations of many disease-carrying vectors, leading to increases in exposures of individuals to diseases and introductions of previously rare infections into society.[3]

Increased urbanization and the associated risk factors of crowding, poor sanitation, and poverty also contribute to the emergence of infectious diseases. With increased densities of populations, especially in countries that do not have adequate sewage systems, safe drinking water, and/or medical or housing facilities, microbes have an ideal environment in which to propagate. As "megacities," those with populations of a million or more, continue to develop and grow—with estimates that by 2010, 50 percent of the world's population will be living in urban areas[22]–overcrowding threatens to become an increasingly vicious foe in the battle against emerging infectious diseases and re-emerging ones.

Specific Diseases: WNV

Late in August 1999, a cluster of unusual meningoencephalitis cases in the northern part of the Borough of Queens, New York City, coincided with an unexplained increased incidence of deaths among birds, including crows and blue jays, in and around the Bronx Zoo. Although the clinical cases initially were thought to be St. Louis encephalitis (SLE), the agent eventually was identified as WNV. The cases in New York represented the first identification of infection with this virus in the Western hemisphere.[26,27] The 1999 outbreak involved infection in thousands of individuals, 59 of whom had severe cases of meningoencephalitis, seven of which were fatal.[28] By the end of 2002, all but four of the lower continental states had reported cases of WNV, the number of which totaled more than 3500.[29] This incident was not, however, the first outbreak of West Nile fever. It had surfaced in 1996 to 1997 in and near Bucharest, Romania, with more than 500 clinical cases reported and a fatality rate of 10 percent.[30,31] During 2002, 3,389 cases of illness associated with WNV were reported from 37 states in the United States and the District of Columbia, and human cases also were reported in Canada, the Caribbean, and Mexico.[26] In 2003, the first case of WNV infection imported into Europe, that of an 82-year-old man who on August 26, 2002, arrived in France from Atlanta, Georgia, with chills and fever, was reported.[32] In a 4-year span, infection with WNV evolved from a seemingly sporadic epidemic in a very circumscribed area to a disease endemic throughout North America.[26] Because of the rapid spread of the virus, physicians should be aware of the symptoms of infection with WNV and consider it in the differential diagnosis of encephalitis and viral meningitis, especially during the summer months and among older patients and those with muscle weakness.

Biology of WNV

WNV is a member of the Japanese encephalitis antigenic complex of the genus *Flavivirus*, family *Flaviridae*. Like other flaviviruses, WNV is a small, single-stranded, positive-sense RNA virus.[33] The genome has 11,000 nucleotides that are wrapped in a nucleocapsid, surrounded by a lipid membrane. A glycoprotein envelope may be responsible for mediating viral entry into cells, tissue tropism, and host range. Although serologic cross-reactions exist between WNV and SLE virus, SLE virus does not cause avian infection.[26] Six viral subtypes that represent two principal lineages have been proposed; one of them includes strains that have been associated with neurologic infections in humans.[34] Natural infections have been found in a wide variety of birds and mammals. Most notable among these infections have been encephalitis outbreaks in horses; mild febrile illness with myopathy in dogs; and widespread epornitic episodes of fatal disseminated viscerotropic and neurotropic infection in North American crows, cranes, geese, and various passerines, columbiformes, and raptors.[35]

Strains from different geographic regions have been differentiated antigenically and genetically, and they have been correlated in a novel application of cluster analysis to patterns of human virulence. Strains found in the United States are related genetically most closely to strains that circulated as early as 1997 in Israel, where they were implicated in human outbreaks and epornitic diseases involving principally geese and cranes.[35]

Transmission

All the known members of this complex are transmitted principally in an avian-*Culex* mosquito cycle. The virus has been isolated from more than 40 species of mosquitoes, primarily bird-feeding ones, mostly of the genus *Culex* and include *Culex univittatus* in Africa; *Cules modestus* and *Culex pipiens* in the Middle East, Europe, and North America; *Culex tritaeniorhychnus* and *Culex vishnui* complex mosquitoes in Asia; and the kunjin viral subtype *Culex annulirostris* in Australia.[35] In the United States, the wide range of avian species that may be involved in the transmission and amplification of WNV includes at least 75 varieties, most commonly crows and members of the jay family, but unlike typical arboviral transmission cycles, many of these avian species die of the infection, perhaps reflecting the exotic relationship of the virus to domestic hosts. Humans and other animals are thought to be dead-end hosts.

Transmission also has been reported between birds and their mites or ticks, thereby providing one means for overwintering. Another means, the most likely one to occur in the United States, is migrating birds that are responsible for transferring the virus over long distances.[35] Because the level of viremia is low and of short duration, human-to-mosquito-to-human transmission is less likely to occur.[26]

Although means by which the virus is introduced into the United States remains unknown, the record-breaking high temperatures and drought in New York that summer may have contributed to a receptive environment for the virus because *C. pipiens*, the virus' principal mosquito vector, is more abundant during hot dry years, when normally clean water sources become concentrated and polluted, thereby favoring the mosquito's larval stages.[35]

Clinical Manifestations

The spectrum of illness associated with WNV infection has not expanded beyond meningoencephalitis. Three major clinical categories of WNV infection have been reported:

asymptomatic infection, West Nile fever, and meningoencephalitis.[26] WNV commonly manifests as a subclinical infection, with an incubation period of 1 to 6 days. A West Nile fever, in which the patient experiences an abrupt onset of fever, headache, muscle aches, conjunctivitis, pharyngitis, gastrointestinal symptoms, chills, malaise, arthralgia, and myalgia, developed in approximately 20 percent of patients during the 1999 epidemic.[33] Headache often is severe and may be accompanied by ocular pain. Most patients experience grippe symptoms. A morbilliform rash affecting the trunk and extremities manifests in approximately 20 to 50 percent of cases, most frequently children.[26,35] Lymphadenopathy may be prominent, and arthralgias have been noted in some outbreaks. Defervescence usually occurs within 5 days and, as with dengue, it may be followed by a recrudescence of fever and symptoms in some cases.[35] Poor prognostic factors include presence of profound weakness, deep coma, failure to produce specific anti-WNV IgM antibody, immunosuppressive treatment, and coexisting conditions such as hypertension or diabetes.

Laboratory Diagnosis

WNV can be isolated from blood taken early in the illness; it also has been isolated at autopsy from the cerebrospinal fluid (CSF) and liver biopsy specimens, brain, and other organs. Generally, vero cells and continuous mosquito cell lines are used. Intracerebral inoculation of suckling mice is a sensitive system that has been used in reference laboratories to isolate the virus. Direct detection of viral genomic sequences from CSF is highly sensitive. Detection of virus-specific IgM in serum is presumptive evidence of recent infection, and the presence of IgM in the CSF confirms that the patient has had recent infection. Confirmation also can be established by demonstrating four-fold or greater changes in antibody titer by hemaglutination, complement fixation, immunofluorescence, or neutralization. The most specific is neutralization antibody assay, which in most cases must be performed to establish the diagnosis.

Differential Diagnosis

Uncomplicated cases of WNV cannot be distinguished clinically from dengue and other febrile illnesses with nonspecific symptoms. The diagnosis should be suspected in patients who have illnesses featuring hepatitis or encephalitis. In the United States, SLE also must be excluded.[26]

Complications

The most common complication of WNV is meningoencephalitis, which has been associated with advanced age (patients older than 70 years) or immunosuppression. The overall mortality rate for meningoencephalitis has ranged from 4 to 14 percent, with rates generally being higher among the elderly.[26] Neurologic signs may manifest initially, or they may develop after the initial "flue-like" prodrome. Neurologic infection also may result in aseptic meningitis, an encephalitis syndrome including changes in mental status, cranial nerve and bulbar palsies, motor weakness, abnormal reflexes, and myelitis. Optic neuritis and polyradiculitis and plyneuropathy with elements of axonal degeneration have been reported, as have generalized weakness that resembles that of Guillain-Barré syndrome and polio-like flaccid paralysis that appears to result from cell damage of the anterior horn. Persistent weakness, memory loss, and movement disorders, may develop in as many as 30 percent of survivors.[26] The case fatality rate in neurologic cases is 10 percent. Other complications include myocarditis, pancreatitis, and fatal hepatitis. Peripheral leudopenia and lymphocytosis are common findings.[35]

Treatment and Prevention

At present, no effective treatment exists for WNV infection. Interferon alfa and ribavirin have demonstrated in vitro activity against WNV, but neither has shown any real benefit.[36] A formalin-inactivated whole virus vaccine has been licensed for horses, and DNA vaccines coding for the structural WNV proteins also have been assessed for veterinary use and have been found to be protective in mice, horses, and birds. Live attenuated yellow fever WNV chimeric vaccines have been shown to be successful in animals and are undergoing human trials.[35,36] Prevention includes personal protection such as avoiding outdoor activity during the crepuscular periods and applying mosquito repellents containing 10 to 30 percent DEET (*N*,*N*-diethyl-m-toluamide) to clothing and exposed skin.[26,35]

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