OUT OF AFRICA: EBOLA VIRUS

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"Plagues are as certain as death and taxes."
--Dr. Richard Krause, former Director, National Institute of Allergy and Infectious Diseases, NIH

"The history of our time will be marked by recurrent eruptions of newly discovered diseases, epidemics of diseases migrating to new areas, diseases which become important through human technologies, and diseases which spring from insects and animals to humans through manmade disruptions in local habitats."
--Dr. Jonathan Mann, Harvard AIDS Institute

INTRODUCTION

For medical practitioners and public alike, the approach of the new millennium should be a source of optimism in the marvelous advances to ensue as the secrets of the human genome are disclosed by the powerful tools of molecular biology. Unfortunately, this promise for a future of unparalleled advancement of individual health is clouded by the certainty that humankind also will need to endure relentless assaults by the microbial world largely beyond its control. Penicillin-resistant pneumococci, "flesh-eating" group A streptococci, Hanta virus, multi-drug resistant tuberculosis, Lyme disease, and, of course, AIDS, are only a few of the emerging and/or resurging pathogens which have ravaged our civilization in the latter part of the twentieth century. Today in this Grand Rounds, I am going to discuss one of the latest, but certainly not the last, in this expanding list of pathogens--Ebola virus (EBO). Though affecting many fewer persons than the above illnesses, EBO is nonetheless remarkable because of its periodic emergence from total obscurity to cause spectacular outbreaks of highly lethal viral hemorrhagic fever (VHF). It is fair to say that EBO is one of the most virulent human pathogens on the face of the earth. Nevertheless, apprehensions about this disease clearly have been fueled by the apocalyptic tone of the mass media and medical journalists' coverage of the disease (1-3).

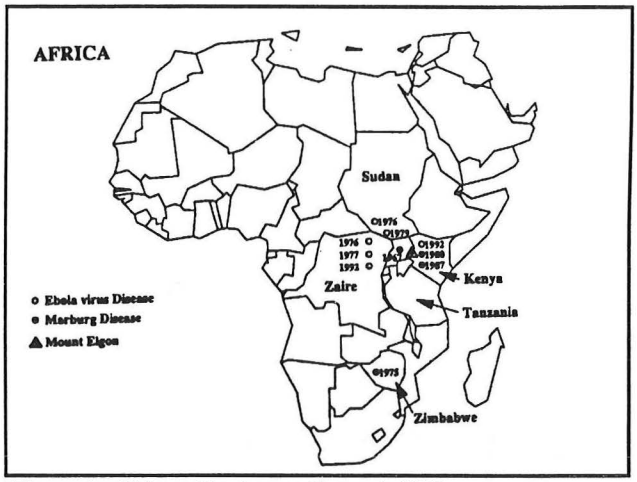


Figure 1. African filoviruses through 1992.

As shown in figure 1 and table 1, EBO and its close relative, Marburg virus (MBG), are relatively new and uncommon viral agents. With the exception of single cases in Zimbabwe and the Ivory Coast in 1975 and 1994, respectively, human disease caused by these agents either occurred or originated from a circumscribed region of central equatorial Africa (4). The discovery of these agents, now classified as filoviruses, followed an outbreak of hemorrhagic fever (HF) in Marburg, Germany and Yugoslavia among laboratory workers who processed tissues from African green (vervet) monkeys caught in Uganda. In 1976, simultaneous epidemics of a VHF in Zaire and Sudan caused more than 500 cases with about 430 deaths (4,5). EBO, which is morphologically identical but serologically and genetically distinguishable from MBG, was isolated from patients in both countries (4,5). The mystery of the origins of these viruses deepened further when in 1989 a new strain of EBO was isolated from macaques shipped to the USA, not from Africa, but from the Philippines (1,2). Our current preoccupation with EBO began on May 6 of this

Table 1
All Human Filovirus Infections Recorded in the Literature (6/1995)

Virus	Date	Place of Infection	All Cases Deaths/Total	Secondary Cases Deaths/Total	Incubation Period	Complications/ Comments
Marburg	1967	Marburg	7/31 (23%)	0/8	3-9 days	Orchitis/psychosis
Marburg	1967	Belgrade	0/2	0/1		Myocarditis
Marburg	1975	Zimbabwe	1/3	0/2	7-8 days	Uveitis
Marburg	1980	Mount Elgon, Kenya	1/2	0/1	9 days	
Marburg	1987	Mount Elgon, Kenya	1/1	0		
Marburg	1994	Sub-Saharan, Africa	0/1	0		Probable case
			10/37 (27%)	0/10 (0%)		
Ebola (Zaire)	1978	Yambuku, Zaire	280/318 (88%)		4 days	
Ebola (Zaire)	1978	England	0/1		4 days	Laboratory acquired
Ebola (Sudan)	1978	Maridi, Sudan	151/284 (53%)		7-14 days	
Ebola (Zaire)	1977-8	Tandala, Zaire	1/1			
Ebola (Sudan)	1979	Maridi, Sudan	22/34 (65%)			
Ebola (Zaire)	1980	Nzoia, Kenya	0/1			Probable case
Ebola (Ivory Coast)	1994	Tai Forest	0/1			Chimpanzee epizootic
Ebola (Zaire)*	1995	Kikwit, Zaire	164/211			
			617/850 (73%)			
Ebola (Reston)	1990	Richmond, Virginia	0/4 (0%)		N/A	All asymptomatic
Ebola (Reston)	1990	Manila, Philippines	0/12 (0%)		N/A	All asymptomatic
			0/16 (0%)			

* Based on World Health Organization Press Release 6/1/95

The hemorrhagic fever (HF) viruses, their distribution, and principal mode of transmission.

Family, virus	Disease	Distribution	Means of transmission
Arenaviridae			
Lassa	Lassa fever	West Africa	Rodent
Junin	Argentine HF	Argentina	Rodent
Machupo	Bolivian HF	Bolivia	Rodent
Bunyaviridae			
Rift Valley fever virus	Rift Valley fever	Sub-Saharan Africa	Mosquito
Crimean-Congo HF	Crimean-Congo HF	Africa, Asia, Southern USSR	Tick
Hantaan and related viruses	HF with renal syndrome	Asia, Balkans, USSR, Europe	Rodent
Filoviridae			
Marburg	Marburg HF	Sub-Saharan Africa	Unknown
Ebola	Ebola HF	Sub-Saharan Africa	Unknown
Flaviviridae			
Yellow fever	Yellow fever	Tropical Americas, sub-Saharan Africa	Mosquito
Dengue	Dengue fever, dengue HF, dengue shock syndrome	Asia, Africa, Pacific, Americas	Mosquito
Kyasanur Forest disease	Kyasanur Forest disease	India	Tick
Omsk	Omsk HF	USSR	Tick

Table 2

year when the Centers for Disease Control and the World Health Organization were asked by Zairian health officials to investigate an outbreak of VHF in Kikwit, a city of 400,000 persons located 240 miles east of Kinshasa (6). As will become clear shortly, each of these epidemics has followed a rather similar pattern: the source and index case of the virus were unknown, transmission accelerated after an unrecognized case was hospitalized, the epidemic was curtailed following the institution of modest barrier techniques (e.g., use of gowns and gloves) and exhaustive investigations into the ecology and potential reservoirs were unproductive. Thus, no information was obtained which enabled the prediction of subsequent episodes. Moreover, as recent events have shown, attempts to develop ongoing surveillance systems to recognize new cases, a major recommendation of the original WHO-sponsored investigative team, have been only partly successful.

VIRAL HEMORRHAGIC FEVERS - BACKGROUND

Before discussing EBO and MBG in depth, some background material about VHF is necessary. Generally speaking, the clinical manifestations of disease caused by these "nasty viruses" (7) range from undifferentiated febrile illnesses to capillary leak syndromes with bleeding diatheses and various types of end-organ damage (e.g., CNS, pulmonary, renal, hepatic). As shown in table 2, the VHFs are caused by 12 distinct RNA viruses grouped into four families (Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae) which are global in distribution (8). Yellow fever, the original hemorrhagic fever virus, and dengue virus date back to antiquity as public health problems. Hanta virus, which is maintained in nature by chronic infection of rodents and other small mammals, was the cause of a well publicized outbreak in the "four corners" region of the Southwestern United States in 1993. The agent responsible for that outbreak, Muerto Canyon virus, is transmitted from infected deer mice to humans. Of the remainder, Lassa virus is particularly notable because of its epidemiological similarities to EBO. Lassa, one of the so-called "nasty viruses" (7), was discovered in the late 1960s after an outbreak at a mission hospital in Jos, Nigeria (9,10). During that outbreak, several persons died who had contracted the disease nosocomially and the impression was created that lassa was a highly virulent, easily transmissible agent. Subsequent seroepidemiological studies in West Africa showed that lassa is much more common and benign than initially thought (8). Detailed epidemiological studies identified the rodent

Mastomys natalensis as the natural host of lassa virus and established that transmission from rodent to human is primarily by aerosol from infected urine (11-13). During nosocomial outbreaks, parenteral inoculation of body fluids, contact with infected body fluids, and aerosols generated by patients have all been incriminated (11). As with EBO and MBG, control of Lassa in the hospital environment can be accomplished with simple barrier nursing techniques (14). Lassa virus gained notoriety because of well-publicized infections among a virologist at the Yale Arbovirus Research Unit and, five months later, a laboratory technician who had not had direct contact with the virus (7).

HISTORY, EPIDEMIOLOGY, AND ECOLOGY

Marburg Virus ("African Green Monkey Disease"). Filoviruses made their explosive entrance onto the world stage in 1967 when a fulminant form of HF struck workers in Marburg, Germany and Belgrade, Yugoslavia who had handled body fluids and tissues of African green monkeys (*Cercopithecus aethiops*) shipped from Uganda. Considerable effort was expended in tracing the route of the monkeys to discern clues to the source(s) of the catastrophic illness. The epidemic originated from consignments of monkeys shipped from Entebbe to Frankfurt, Marburg, and Belgrade via London between late July and early September. The monkeys had been caught in the Lake Kyoga region of Uganda where they were caged individually in one of three holding stations (Fig. 2). After periods as long as two weeks, the animals then were transported in individual compartments to the central holding area in Entebbe where they also were caged singly. After a further holding period of at least three days, the monkeys were exported. Most, but not all shipments, were via London. While being held at London airport (only for several hours), the monkeys were in potential contact with a large variety of animals from many parts of the world. Excess mortality was not reported for the monkeys quarantined in Germany (15). In contrast, records from the Belgrade facility (which are said to be better than those from Marburg) were consistent with ongoing viral transmission throughout the quarantine period (Fig. 3) (16). That MBG is highly virulent for

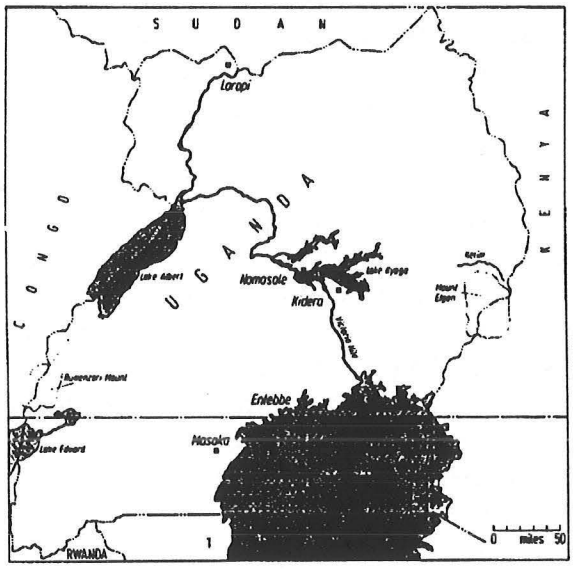


Figure 2

monkeys was subsequently demonstrated by experimental inoculation studies (17).

The human epidemic consisted of a total of 31 cases, 29 of which occurred in Marburg, during August and September of 1967. Twenty-five of the 31 (20 in Marburg, 4 in Frankfurt, 1 in Belgrade) were primary infections among individuals involved in procedures such as autopsies, trephining skulls, or handling glassware that contained cell cultures from the monkeys (15). All seven deaths were primary infections. Six secondary cases, none of which was fatal, resulted from person-to-person contact either at home or in hospital. One of the secondary cases involved the wife of a veterinarian who became ill several weeks after her husband's recovery; MBG was cultured from his seminal fluid 83 days after the onset of illness and demonstrated by immunofluorescence seven months later (18,19). The paucity of infections in Belgrade was due to the fact that experimental procedures were not performed on the monkeys. The two Yugoslavian cases involved a veterinarian who performed autopsies on dead monkeys and his wife who became infected while nursing him at home.

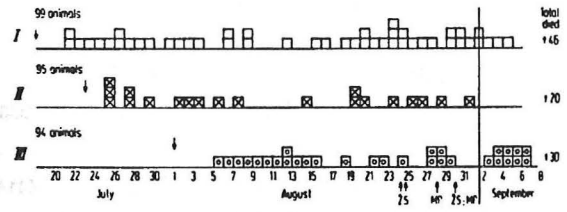
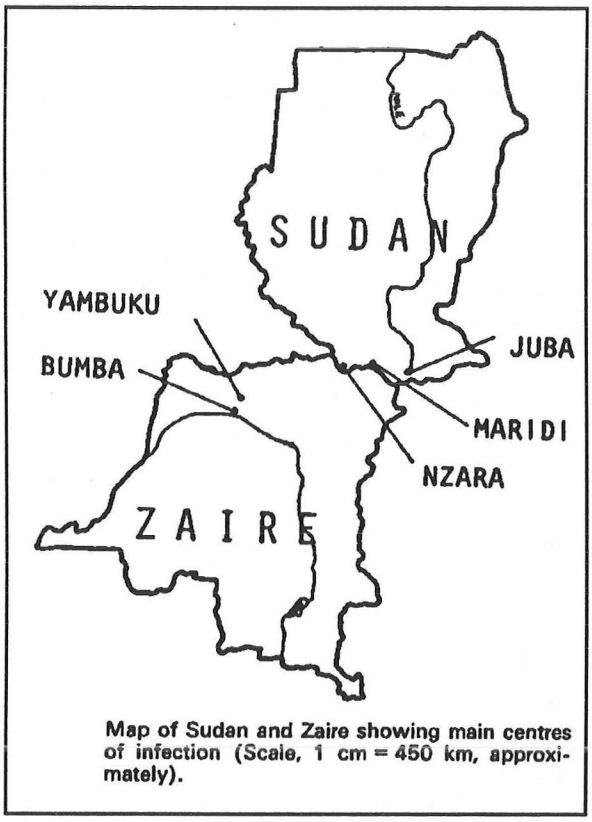


Figure 3. Monkey mortality in Belgarde, 1967

Extensive field investigations were performed in Uganda to uncover evidence of a comparable disease in monkeys and/or humans (20). Initial inquiry revealed that no unusual incidence of illness had occurred among monkey trappers or among trapped green monkeys. Using a crude antigen prepared from the livers of guinea pigs inoculated with MBG in complement fixation assays, Henderson and co-workers (20) found a progressive increase in the seropositivity rate of monkeys at the Entebbe collecting station from mid-September through October. This suggested that an infectious agent related to MBG had been circulating in primates in the Lake Kyoga area somewhat earlier. However, no viruses were recovered from monkey bloods inoculated into guinea pigs and mice. The fact that no seropositive monkeys were ill suggested that the cause of the seropositivity was not the same agent responsible for the outbreak (20). Slenczka *et al.* (21) called these serological results into question by showing that false-positive reactions were frequent using infected organs as antigen and that MBG-specific antibodies were not detectable using antigen consisting of infected Vero cells. At present, claims of naturally occurring antibodies to MBG in African primates are not generally accepted.

Since the original outbreak, there have been only four primary human MBG infections, all naturally acquired and all equally baffling (Table 1). The 1975 primary infection involved a 20 year-old Australian backpacker who contracted his

disease in Zimbabwe six days after being bitten or stung on the flank and subsequently died in Johannesburg, South Africa (22). Secondary cases occurred among his traveling companion and a South African nurse who cared for both travellers (22). Virologic and serologic studies confirmed that these infections were due to an agent virtually identical to that which caused the 1967 outbreak (22). Of particular interest, the nurse who recovered developed anterior uveitis three months after her illness; MBG was cultured from her anterior chamber (22). An exhaustive study of insects and mammals along the traveler's itinerary, made possible by photographic records and an hour-by-hour reconstruction of antecedent events by the surviving companion, failed to produce a source of infection, despite the fact that numerous potential environmental contacts were identified (23). The 1980 and 1987 primary cases, a 56 year old French engineer and a 10 year old Danish boy, respectively, occurred shortly following excursions into Kitum Cave on Mount Elgon, a major peak near the Uganda-Kenya border, which harbors enormous colonies of bats and is visited by a wide range of mammals, birds, reptiles and insects (22,24). This region in Kenya happens to be within 200-300 km from of the site from which the monkeys were shipped in 1967. The similar location of these two cases, coupled with the large time interval separating them, has fueled speculation that, despite the negative field studies, a natural host of MBG lives "within the shadow of Mount Elgon" (Fig. 1) (2). The 1980 incident also was notable for the fact that virus was recovered from seminal fluid of the secondary case, a Nairobi Hospital physician who attempted resuscitation of the dying engineer, approximately two months after the illness (24). Furthermore, although prospective studies failed to identify any other cases of Marburg Disease, they did identify three sporadic serologically confirmed cases of Ebola HF. The fourth involved a young Swedish male who contracted VHF while backpacking in subSaharan Africa. Acute phase serum samples contained particles consistent with filoviruses and he seroconverted to MBG. Exhaustive attempts to isolate virus by cell culture and guinea pig inoculation were unsuccessful (25).



Map of Sudan and Zaire showing main centres of infection (Scale, 1 cm = 450 km, approximately).

Figure 4

Ebola Sudan (26,27). After the MBG outbreak, the filoviruses attracted little attention until 1976 when nearly simultaneous outbreaks of highly lethal HF occurred in northern Zaire and southern Sudan (Fig. 4). Initially, it was felt that the causative agent must have spread from one region to the other. Extensive searching, however, failed to identify possible links between the two epidemics. The lack of established communications and trade routes between these two regions separated by 900 kilometers of rugged terrain lent additional credibility to the suggestion that these two outbreaks were unrelated. This deduction subsequently was confirmed by antigenic and molecular analyses of the viral isolates (28). Although these outbreaks share many features, they will be discussed separately.

The first cases of HF in the Sudanese outbreak were traced to three employees of a cotton factory situated near the center of Nzara township (population 20,000), located in the remote savanna of southern Sudan near the Zairian border. It was subsequently noted that the roof of the factory was heavily infested with bats. The index case was a storekeeper in the factory who became ill on June 27, 1976 with a severe febrile illness, headache, and chest pains. He developed hemorrhagic manifestations on the fifth day of illness with profuse bleeding from the nose and mouth along with bloody diarrhea. He was admitted to Nzara hospital on June 30 and died on July 6. Shortly thereafter, two of the index case's co-workers also became ill. 48 cases and 27 deaths in Nzara were related to one of these co-workers, a popular individual who was well known throughout the city and was comforted by many people before he was admitted to hospital. The disease was introduced into Maridi (population 15,000 and 128 km from Nzara), a second epicenter, when one of his contacts was hospitalized in that city. Largely because of inadequate nursing techniques and, to a lesser extent, reuse of hypodermic needles, the hospital became an efficient amplifier for dissemination of the virus throughout the town and environs for further transmission by household spread. Throughout July, September, and October, unrelated cases continued to occur among cotton factory employees who had no previous contact with sick persons, supporting the notion that the viral vector or reservoir resided within the building. In fact, a unique feature of the Nzara outbreak was that 21% of all cases lacked contact with previous cases. Eventually, a total of 284 cases were documented with 151 deaths (mortality rate of 53%).

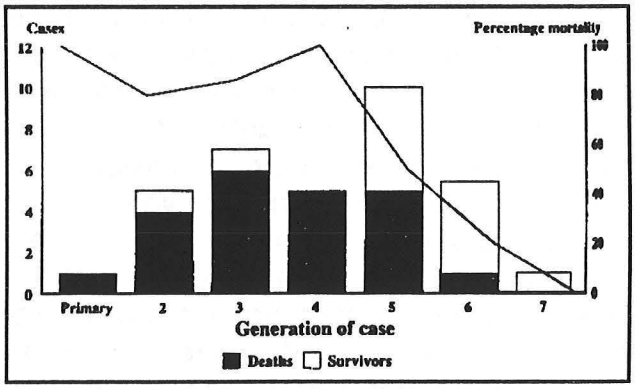


Figure 5. Mortality during successive human-to-human transmission, Sudan, 1979

Secondary attack rates were determined to be between 9% and 14%.

The notion that EBO is endemic in that region of Sudan was reinforced when the epidemic recurred in Nazara and Yambio (25 km away) during a three month period in 1979. The index case for this smaller epidemic, which eventually involved involving 34 cases and 22 fatalities, worked in the same cotton factory as the index cases for the 1976 epidemic. Unlike the earlier outbreak, this time the hospital in Nzara served as a focus for dissemination of infection to family units after the admission of the index patient. A description of the Nzara hospital explains why it served so efficiently as an amplifier of the epidemic:

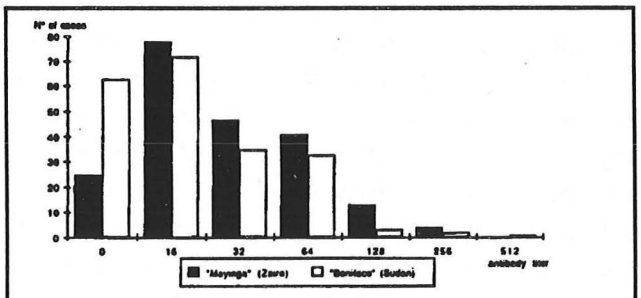
> The hospital in Nzara consists of two small concrete structures for 2 patients each, and a larger building with three 8-bed wards. Patients at the Yambio facility are accommodated in several thatched huts. There is no running water in the patient-care areas, and the hospitals have a limited supply of masks, caps, and gowns. The staff do not routinely practice barrier nursing and often do not sterilize needles, syringes, or other instruments used on the wards. Relatives of hospitalized patients provide much of the routine nursing, which includes handling emesis, excreta, and soiled clothing. (27)

As many as seven generations of transmission were identified during this one comparatively small outbreak. An interesting observation was that a reduction in case fatality occurred with succeeding generations of human-to-human transmission (Fig. 5) (27).

<u>Ebola Zaire</u> (29). The Zairian epidemic occurred in the unpopulated northwestern Bumba Zone of the Equateur Region. The epicenter of the outbreak was the Yambuku Catholic Mission, an under-equipped field hospital established by Belgian missionaries in 1935 with 120 beds, a medical staff of 17, and three Belgian nuns who served as nurse/midwives. Although the index case is not known, the epidemic appears to have begun when a 44 year-old male instructor in the Mission School presented to the outpatient clinic of Yambuku Mission Hospital in August of 1986 with a febrile illness presumed to be malaria following a motor tour of the Northern Equateur Region. He was given chloroquine by injection and his fever promptly resolved. Five days later, however, he developed high fever and was admitted several days later to the mission hospital with gastrointestinal bleeding. At least nine other cases occurred during the first week of September, all among persons who had recently been treated as outpatients at the mission hospital. Between September 1 and October 24, 318 probable and confirmed cases of HF occurred with 280 deaths, a fatality rate of 88%! Fifty five of about 250 villages in the Bumba Zone recorded cases, the majority being along roads running east and west of the mission. The single common risk factor for 85 of 288 cases for which

the mode of transmission could be determined was receipt of one or more injections at the mission hospital. Needles and syringes were in extremely short supply. The medical staff had to make do with a total of five syringes and needles for use in the outpatient department, prenatal clinic, and the inpatient wards each day. To make matters worse, the syringes were only rinsed in warm water between patients and then boiled at the end of the day. All 20 patients in whom injections was the only means of transmission died. An additional 149 persons acquired the disease following contact with patients, usually in their home villages, and 43 cases had a history of both patient contact receipt of injection within three weeks prior to onset of illness. The single most important event related to containment of the epidemic was closure of the mission hospital four weeks after the epidemic began! Extensive serological and virological studies of insects and animals in the epidemic area were negative.

In June 1977, a nine year-old girl died of EBO disease at the mission hospital in Tandala, approximately 200 km from Yambuku. No epidemic resulted, however, because a physician immediately suspected HF and instituted appropriate precautions as soon as the clinical diagnosis was made. Virus was isolated from a postmortem blood specimen inoculated into a guinea pig at the CDC approximately nine days after she died (30). Interestingly, the physician who suspected the diagnosis and obtained specimens from this patient had experienced a severe illness compatible with EBO infection in 1972 (four years prior to the large outbreak), 10 days after cutting himself with a scalpel during the performance of an autopsy on another patient thought to have had yellow fever. His serum contained an extraordinarily high antibody titer to EBO. Retrospective review of Tandala Hospital records identified other sporadic cases of presumed HF, reinforcing the impression that EBO is endemic in that region of Zaire (30).



— *Histogram of titres of 1,083 human sera randomly selected from central Africa and tested by IFA against two Ebola antigens.*

Figure 6

A number of serological surveys have been conducted to determine the prevalence of EBO and obtain clues to the habitat of its natural reservoir. These studies, which mainly employed indirect immunofluorescence with infected tissue culture cells as antigen, have shown antibody prevalences as high as 30% in persons living within the tropical rain forests of central equatorial Africa (31-33) (Fig. 6). Significant seropositivity (e.g., 1.8% in Nigeria, 4.5% in Madagascar) was reported from regions of Africa outside the areas presumed to be endemic for EBO (34,35). These findings suggest that the African filoviruses may be less pathogenic in their natural settings than is commonly thought. On the

other hand, as with MBG, the specificity of these population surveys has been called into question by finding seropositivity rates of 0.3% to 0.5% in populations far removed from regions experiencing filovirus outbreaks (e.g., Cona Indians from Central America and Alaskans) (4,30,36). Even newer methodologies such as immunoblotting do not appear to be entirely free of false-positive (37).

Ebola Reston. Conceptions regarding the geographic distribution of EBO, its geographic and host-ranges, and, perhaps, the potential for EBO outbreaks in the United States were shattered by events which transpired in 1989 and early 1990 in monkey quarantine facilities located in Reston, Virginia and Alice, Texas. The Reston episode is the subject of Richard Preston's now famous article "Crisis in the Hot Zone" which appeared in the October 26, 1992 issue of the Atlantic Monthly (1) and his current bestseller "The Hot Zone" (2). A more sober account of these events can be found in the article by Dalgard *et al.* (38) and a series of updates in MMWR (39-41). The outbreak involved a 12-room facility for quarantine of 550 feral cynomolgus monkeys (macaques, *Macaca fascicularis*) operated by Hazelton Research Products in Reston, Virginia, an affluent suburban community ten miles west of Washington, D.C. A consignment of 100 monkeys was received from Manila, the Philippines via Amsterdam on October 4, 1989 and placed in room F (Fig. 7). During the next four weeks, a progressive number of deaths among the animals was noted. An infectious cause was suspected when marked splenomegaly and scattered petechial hemorrhages in various organs were noted at necropsy. A tentative diagnosis of simian hemorrhagic fever (SHF), a disease caused by a virus nonpathogenic for humans, was made based on the clinical and histopathological findings and subsequently confirmed on November 16 by virus isolation from specimens submitted to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. (Here it should be noted that co-infection of these monkeys with SHFV, a DNA virus known to be highly virulent in nonhuman primates, and EBO complicated assessment of the true pathogenicity of the EBO strain(s) subsequently isolated). The room was depopulated on November 16 in an attempt to prevent spread of the virus to the remainder of the animals in the facility. By November 20, however, the disease animals in Room H, which held animals obtained from a different shipment from the same Filipino exporting facility

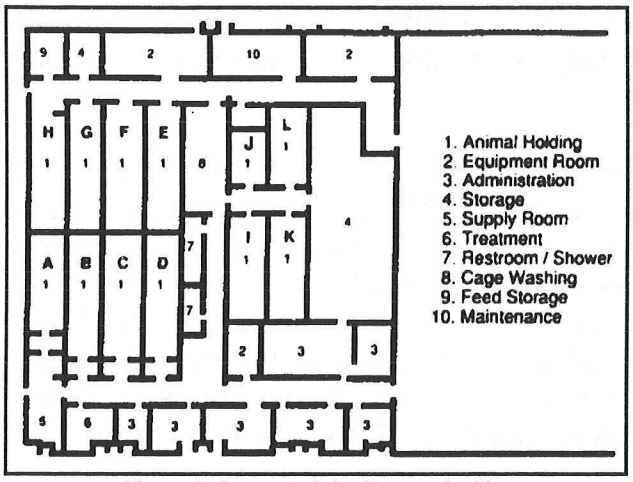


Figure 7. Layout of the Reston facility

as those housed in room F, also became sick. On November 28, the "crisis" began when USAMRIID personnel reported that there was electron microscopic, serologic, and cultural confirmation of EBO in samples submitted from Room F. Four EBO isolates and three SHFV isolates eventually were recovered from animals in room F, and one EBO isolate was recovered from an animal in room H (42). Officials from USAMRIID, the Virginia Department of Health (VDH), and the CDC quickly went into action to avert what was believed to be a potential public health threat of catastrophic proportions. Personnel in the facility were fitted with full-face respirators and required to wear Tyvek suits and gloves while in the animal rooms. Measures also were instituted to safely dispose of animal wastes and carcasses. As more animals in Room H became sick and the presence of ER also was confirmed, it was decided to depopulate this room as well. This was done by USAMRIID personnel equipped with positive pressure containment suits. Despite extraordinary measures to contain the outbreak, animals in rooms A-D became sick and a decision was made on December 4 to depopulate and then decontaminate the entire facility. This decision was partly a response to the apprehension generated by hospitalization of an animal handler earlier that same day with a viral syndrome subsequently diagnosed as influenza. In January, 1990, the decontaminated Reston facility again began receiving animals and by February had received three shipments of 100 animals, all from the same supplier in the Philippines who had supplied animals involved in the outbreak. A fourth shipment of 100 animals, also from this supplier, was sent to the Texas Primate Center (TPC), another Hazelton quarantine facility in Alice, Texas. Within a week after arrival, clinical signs identical to those of the original outbreak were observed among animals in the third Reston shipment as well as animals sent to TPC. SHF and EBO were eventually isolated at both locations. Inasmuch as there had been no contact between animals shipped to Virginia and Texas after leaving the Philippines, it became apparent that viral transmission at the export facility was involved. This subsequently was confirmed in a serological survey of monkey export facilities in the Philippines. Seropositivity rates for EBO Reston and animal mortality rates were dramatically higher in the facility which supplied animals to the Reston facility (43). Transmission of virus within this facility appeared to have been facilitated by housing animals in group cages. How the virus was introduced into the facility, however, has never been determined.

Figure 8. Transmission EM of Ebola (Zaire)

Remarkably, although seroconversions to this new strain of EBO occurred in four animal handlers with a high level of daily exposure to the animals, none of these individuals developed febrile illness! One of the animal handlers serconverted after cutting his finger while performing a necropsy on a heavily infected animal; he remained asymptomatic despite a transient viremia (42). In previous EBO epidemics, such an exposure almost certainly would have resulted in severe disease. Asymptomatic infection subsequently was reported in the Philippines in persons working in a facility that housed the source monkeys of the US outbreak (44). The Reston outbreak is not the only one associated with importation of cynomolgus monkeys. In 1992, a highly similar filovirus was isolated from monkeys imported into Italy from the same exporter that shipped Reston-infected monkeys into the United States in 1989; human infections also were not observed during that outbreak (28,45). Population-based serological surveys also support that the Reston-associated EBO has low pathogenicity for humans. Samples from 550 persons with varying levels of occupational exposure to monkeys or monkey tissues subsequently were tested for filovirus antibody. 42 or 7.6% were positive for one or more filovirus test antigens (41); two-thirds of these individuals had contact with monkeys within quarantine facilities. None of the seropositive individuals had illness consistent with HF. Surprisingly, 12 of 449 control sera (2.7%) also were positive in the same assays.

Shortly after the Reston outbreaks in early 1990, the CDC instituted a series of measures to prevent recurrent epidemics with potentially more lethal outcomes while, at the same time, providing sufficient numbers of animals to meet the needs of United States researchers (46). In March, interim new guidelines for handling nonhuman primates during transit and quarantine (40). Compliance with these guidelines became a mandatory condition for continued registration of importers; on-site inspections of all import facilities also were begun. In April, the CDC also announced the availability of a special permit procedure for the importation of cynomolgus, African green, and rhesus monkeys (47). To obtain the permit, applicants were required to submit an importation plan describing the steps that would be taken to minimize the risk for filovirus exposure of persons and animals during the entire importation and quarantine process. Serologic testing for filovirus and CDC review of results were required before release of animals from quarantine. These measures were so successful in reducing mortality among quarantined monkeys that routine testing for filovirus antibody was discontinued in October of 1991 (47).

<u>EBO Zaire 1995</u> (6,48). The index case for the present epidemic is not known but may have been a middle-aged male forest worker who became ill in December of last year. A chain of deaths occurred in households throughout January, February, and March. In a pattern all too familiar from previous outbreaks, the epidemic was

dramatically amplified when a 36 year-old hospital laboratory technician at Kikwit General Hospital had onset of fever and bloody diarrhea. On April 10, he underwent surgery at the same facility for a suspected perforated bowel and died on April 14 from a massive intra-abdominal hemorrhage. At about the same time, medical personnel who took care of this patient, either in the operating theater or in hospital wards, developed similar symptoms. One of these ill persons was transferred to Mosango Hospital (75 miles west of Kikwit) which shortly thereafter became a second epicenter of the epidemic. On May 11, blood samples from 14 acutely ill persons were positive for EBO antigen, EBO antibody, and/or viral RNA by reverse transcriptase PCR, thereby confirming that EBO was responsible for this latest VHF outbreak and deepening the mystery that surrounds these viral pathogens (6). Sequence analysis of the glycoprotein genes from the 14 isolates revealed that they were essentially identical to the virus which had caused the 1976 outbreak (A. Sanchez, CDC, personal communication). The latter part of May, the WHO declared on June 1 that the acute phase of the epidemic was over and that ongoing increases in the number of cases were largely due to retrospective identification of cases from January through March. As of that date, WHO estimated that the outbreak involved 211 confirmed or suspected cases with 164 deaths. CDC reported 296 cases with 79% mortality as of June 25 (103).

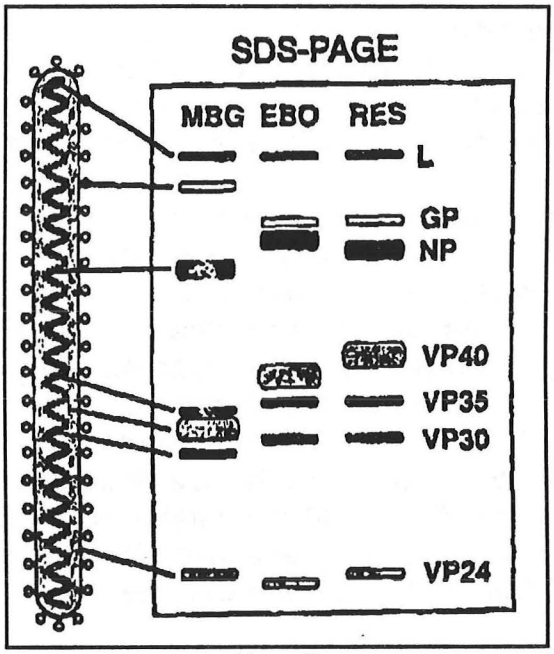


Figure 9

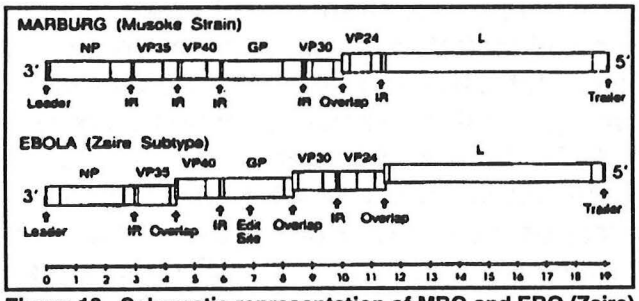


Figure 10. Schematic representation of MBG and EBO (Zaire) genomes.

<u>Ebola Ivory Coast</u>. One of the major difficulties in identifying the source of EBO is caused by the need to reconstruct critical events weeks, even months, after the beginning of an outbreak. This is compounded by the fact that index cases have not always been identified or died before detailed interviews could take place. For this reason, an outbreak of EBO among chimpanzees in the Ivory Coast may represent a potential breakthrough because it enables

investigators, for the first time, to study the illness in its natural habitat (23). Ethologists studying a troop of chimpanzees in the Tai National Park of western Ivory Coast noted two abrupt episodes of mortality in 1992 and 1994. One freshly dead chimpanzee was discovered in November, 1994 and autopsied in the field; findings were consistent with HF. A 34-year old female, one of three who autopsied the chimp, developed a dengue-like illness shortly thereafter and had to be evacuated by air to Switzerland where she eventually recovered. A new strain of EBO was isolated from her blood. Histopathological and immunocytochemical analyses of specimens from the dead chimpanzee also were consistent with EBO. The authors concluded that the chimps were dying from an EBO epizootic. The fact that the outbreak occurred at the end of the rainy season was consistent with an insect vector. They hypothesize that, as with arboviruses, an insect vector infects an intermediate host mammal in which the virus can replicate to high titers without being harmed. These investigators now plan to search the 4200 square kilometers of the Tai Forest to prove their hypothesis.

Filovirus structural proteins and their proposed functions

Designation	MW (MBG) A	MW (MBG) B	MW (EBO) A	MW (EBO) B	Encoded by gene	Proposed function
L	267.2K	180K	–	180K	7	RNA-dependent RNA polymerase: transcription and replication
GP	74.8K	170K	74.5K	125K	4	glycoprotein: forms viral spikes, mediates virus entry
NP	77.9K	96K	83.3K	104K	1	major nucleoprotein: encapsidation
VP40	31.7K	38K	35.3K	40K	3	matrix protein: membrane-associated
VP35	31.0K	32K	38.8K	35K	2	transcriptase component: P protein analogue
VP30	31.5K	28K	29.7K	30K	5	minor nucleoprotein: ribonucleoprotein-associated
VP24	28.8K	24K	28.3K	24K	6	second matrixprotein: membrane-associated

MW/A Molecular weight calculated from the deduced amino acid sequences of the open reading frames of the seven filovirus genes; *MW/B* molecular weight estimated from SDS-PAGE analysis

Table 3

VIRUS CHARACTERIZATION

Gordon Smith *et al.* (49) showed that guinea pigs became sick after inoculation with whole blood or post-mortem tissue suspensions from Marburg patients and that the agent of disease could be serially passaged in guinea pigs. Serological studies with a large number of reference antigens were negative, however, while filtration studies revealed that the agent was larger than most known viruses. In 1968, Kissling and co-workers (50) reported isolation of the "African green monkey disease agent" by inoculating blood from infected guinea pigs onto tissue culture cells. Morphologically identical, but antigenically distinct, particles were isolated from specimens associated with the 1976 Zaire and Sudan outbreaks (51-55) or were visualized by EM analysis of post-mortem tissue specimens (56). This new virus was named "Ebola" after a tributary of the Congo River close to the outbreak site in Zaire. Based upon their distinctive morphology, as well as other shared physicochemical characteristics (57-60), it was proposed that a new taxon be created to distinguish these viruses from the rhabdoviruses (to which they are related) (57). The name filoviruses ("filo" being Latin for "filament" or thread") was recommended (57) and eventually adopted. Sequence analyses of viral proteins

and, more recently, the entire viral genomes, have validated this taxonomic classification (28,61-65). Antigenic, structural, and pathogenicity studies have provided strong evidence that the Sudanese and Zairian isolates are distinct subtypes (28,66-68). It is still undetermined whether the Reston isolates are EBO subtypes or a distinct filovirus species (28).

MBG and EBO are highly pleomorphic cylindrical particles appearing as long filamentous, sometimes branches, or as "U"-shaped, "6"-shaped, or circular (torus) forms (Fig. 8). Virions vary greatly in length but have a uniform diameter of approximately 80 nm - 90 nm. The relatively uniform viral particles purified by rate zonal gradient centrifugation have an average length of 665 nm for MBG and 805 nm for EBO and are associated with peak infectivity (28). Particle cores are formed by nucleocapsid consisting of a dark central space 20 nm in diameter surrounded by a helical capsid 50 nm in diameter. Within the nucleocapsid is an axial channel of 10-15 nm. The helical nucleocapsid is surrounded by a lipid envelope derived from the host plasma membrane. Spikes of approximately 7 nm in length and spaced at about 10 nm intervals are located on the virion surface (Fig. 9).

EBO and MBG particles contain seven proteins (Table 3); as shown in fig. 9, each of the filoviruses has a characteristic polypeptide profile. Differences in mobility are most prominent for the glycoprotein (GP) and the viral structural proteins (VP) 40, 35, and 30. Four proteins are associated with the viral ribonucleocapsid complex: the nucleoprotein (NP), VP 35 and 30, and the large protein (L) (the viral RNA-dependent RNA polymerase). VP40 and VP24 are matrix proteins believed to connect the helical nucleocapsid with the viral membrane. The glycoprotein (GP) is a class I transmembrane protein which exists as a homotrimer. GP is the only glycosylated viral protein; GPs of MBG and EBO have different glycosylation patterns (64). Sequence analysis of GPs revealed that the middle portion of the protein contains the antigenically variable domains. GPs also contain a stretch of amino acids with homologous to an immunosuppressive motif found in the glycoproteins of oncogenic retroviruses (e.g., feline leukemia virus, avian reticuloendotheliosis virus) (69,70) which has been shown to inhibit cytotoxic T cell responses, monocyte chemotaxis, cytokine gene expression, and natural killer cell activity (71-75). It has been speculated that immunosuppression by the virus is responsible for the impressive lack of inflammatory

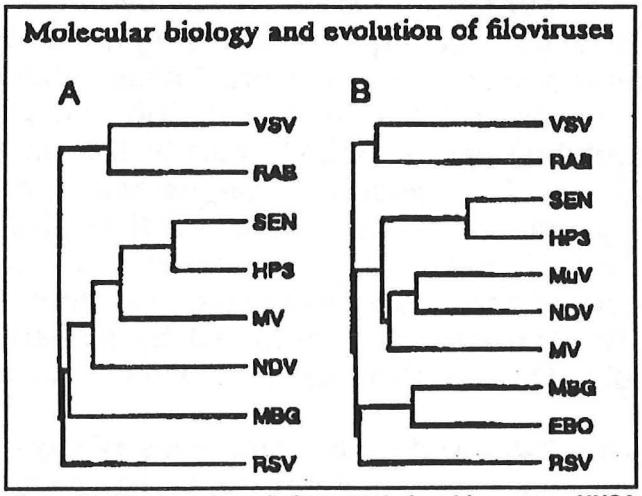


Figure 11. Proposed revolutionary relationships among NNSA RNA viruses. A. L proteins. B. Nucleoproteins

response in infected tissues. Significant homologies between filovirus GPs and envelope proteins of other nonsegmented, negative strand (NNS) RNA viruses do not exist. The functions of VP 40, 35, 30, and 24 are poorly understood. VP40 and VP24 are thought to function as matrix proteins connecting the helical nucleocapsid and the viral membrane (76).

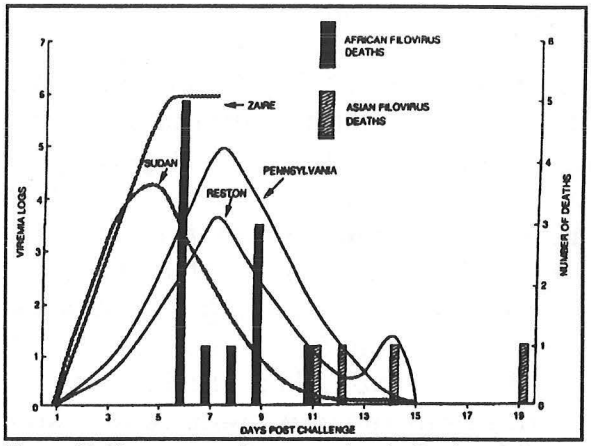


Figure 12. Mean serum titers over time in filovirus-infected rhesus monkeys

The genomes of filoviruses consist of a single, continuous strand of RNA which is noninfectious, not polyadenylated, and complementary to viral messenger RNA (that is the viral genome is negative-stranded). The genome's size, 19 kb, is larger than those of other negative strand RNA viruses (e.g., influenza A, bunyavirus, rhabdovirus, and paramyxovirus). Filovirus genes are arranged in the following order: 3'-NP-VP35-VP40-GP-VP30-VP24-L-5' (Fig. 10). EBO has three gene overlaps (VP35/VP40; GP/VP30; VP24/L), while MBG has one (VP30/VP24). Transcriptional start and termination signals are at the 3' and 5' ends, respectively. Six mRNA species have been identified from filovirus-infected cells. In vitro translation resulted in products co-migrating with the structural proteins NP, VP40, VP35, VP30, VP24, and the unglycosylated form of GP. A mRNA specific for the L protein has not been detected, presumably due to its low copy number (63,77,78).

Sequence analyses of the MBG and EBO genomes have demonstrated that filoviruses and other NNS RNA viruses (*Paramyxoviridae, Rhabdoviridae*) are genetically related and have a similar arrangement of genes according to function (3' leader-core proteins-envelope proteins-polymerase-5' leader). These genomes can be viewed as containing conserved regions at the 3' and 5' ends (which encode functionally conserved L and core proteins) and a variable part in the middle encoding the nonconserved glycoproteins. Comparisons of the deduced amino acid sequences of the L and the NP genes with those of different NNS viruses demonstrate that filoviruses are more closely related to paramyxoviruses than to rhabdoviruses. The dendrogram in figure 11 shows the evolutionary relationships between filoviruses and other NNS RNA viruses as determined by nucleotide sequence analysis of the genes encoding the L protein and the nucleoprotein.

The international teams investigating the Zaire and Sudan outbreaks recognized clinical differences between the two outbreaks, most notably the higher mortality rate among victims of the Zairian outbreak (26,29). Histopathological examination

of specimens indicated that cases from Zaire had more extensive necrotic changes and greater viral burdens (26,29,56). Cumulative experimental evidence shortly thereafter began to support the notion that biological differences exist between the Sudanese and Zairian EBO. Isolates of EBO strains from Zaire were readily obtained by primary inoculation of cell cultures, while strains from the Sudan were difficult to isolate using the same cell lines and technique (79); the poor CPE of Sudanese strains also contrasted with the marked CPE of strains from Zaire (79). Ellis and co-workers (80) found that rhesus monkeys survived inoculation with a Sudanese strain of EBO while an identical sized inoculum of a Zairian isolate was fatal. They also noted that virions were relatively difficult to find in the livers of monkeys inoculated with the Sudanese strain and included a high proportion of "aberrant" or defective forms (RNA cores without coats or coats without cores). In contrast, monkeys given the Zairian strain had great numbers of virions in liver, lung, and spleen with only rare aberrant particles (similar to humans). The propensity of Sudanese strains to produce aberrant virions could be reproduced in cell culture (81). Bowen *et al.* (52) also observed greater virulence of Zairian strains for rhesus monkeys and guinea pigs.

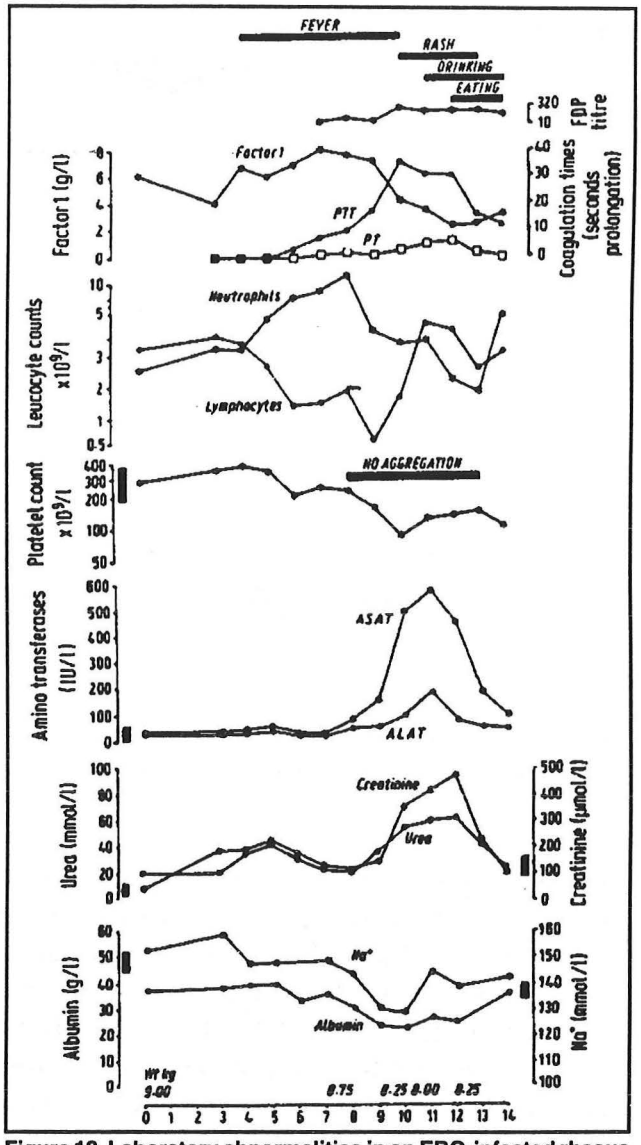


Figure 13. Laboratory abnormalities in an EBO-infected rhesus monkey

They also showed that infection with a Sudanese viral strain completely protected monkeys against re-challenge with the homologous strain but did not prevent a lethal outcome following challenge with a Zairian isolate. McCormick *et al.* (79) found that the LD_{50}s of Sudanese isolates for suckling mice were five logs lower than those of Zairian strains. Based upon their lack of pathogenicity for humans, it has been presumed that the Asian filoviruses are less virulent than their African counterparts. This was confirmed by experiments in which vervet monkeys and macaques were challenged with either African or Asian filoviruses. Compared to disease caused by African viruses, Asian filovirus disease was characterized by

lower mortality, slower development of viremia, and delayed onset of hepatocellular and hematological abnormalities (15). Nevertheless, these studies did demonstrate that the Asian filoviruses are pathogenic, even lethal, for monkeys in the absence of the SFHV infection. These experiments also emphasized the extraordinary pathogenicity of the Zairian strains (Fig. 12) (15).

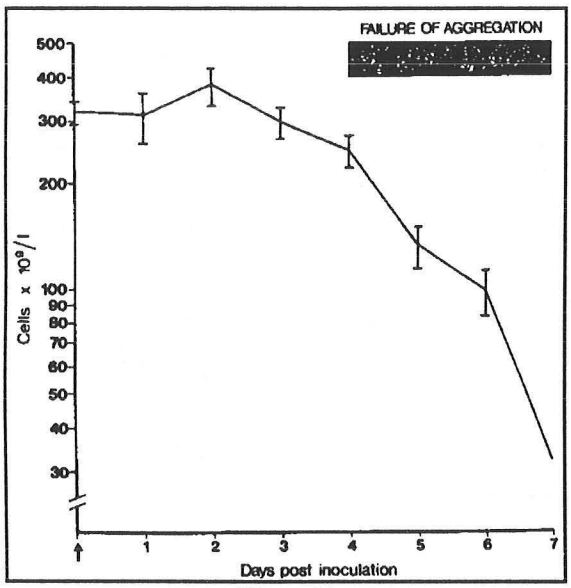


Figure 14

PATHOGENESIS AND PATHOLOGY

Soon after the discovery of filoviruses, infectivity studies confirmed the extraordinary susceptibility of monkeys to filovirus infection and established them as the animals of choice for the study of disease pathogenesis (4). In contrast, results with small animals have been less impressive. EBO (Zaire) kills guinea pigs only after it has become adapted by serial passage, while EBO (Sudan) and MBG do not (4). Only the Sudan variant was found to be lethal for suckling mice (79).

MBG Disease. Subcutaneous inoculation of either vervet or rhesus monkeys with 0.5 ml of acute-phase blood from MBG patients resulted in death within 9-10 days (17,82). Monkeys did not appear overtly sick until 1-2 days prior to death. Levels of viremia were so high that their antemortem blood remained lethal for other animals when diluted 1 x 10^{10}-fold (83,84). Uninoculated animals which had direct contact with infected monkeys also died but the course of disease was protracted (i.e, 20-36 days), consistent with a smaller inoculum. Aerosolization as a mode of transmission was ruled out by the observation that animals living in the same room but without direct contact showed no symptoms of disease (82). Within four days of infection, liver biopsies revealed diffuse intracytoplasmic eosinophilic inclusions (dense aggregates of viral tubular structures by EM), similar to Councilman bodies of yellow fever, and scattered necrotic hepatocytes (85,86). This was followed by progressive necrosis with focal hemorrhage. Diffuse necrotic changes also were observed in the spleen and lymph nodes of premorbid animals. Inflammatory cell infiltrates were noticeably absent (85,86).

EBO Disease. Vervet or rhesus monkeys inoculated intraperitoneally with 10^3-10^5 guinea-pig infectious units of EBO Zaire become febrile on the third to fifth day

after inoculation (51,87,88). Rhesus monkeys tend to develop a petechial rash on the forehead, face, limbs, and chest. Intractable hypovolemic shock, exacerbated by diarrhea, bleeding, ARDS, and central nervous system dysfunction is the cause of death. Figure 13 shows the typical progression of hematological and biochemical abnormalities (89). Hematologic abnormalities consist of lymphopenia in combination with neutrophilia (degranulated and band forms are pronounced on peripheral blood smear) (88,89). Progressive quantitative decreases in platelets also occur, but these are preceded by profound platelet dysfunction (measured by *in vitro* platelet responsiveness to ADP and collagen) (Fig. 14). Laboratory evidence of disseminated intravascular coagulation (DIC) is present as disease progresses but is usually rather modest, suggesting that DIC is neither a primary pathophysiological process nor a major cause of bleeding (Fig. 15). Hepatocellular liver enzymes become elevated (AST disproportionate to ALT), while alkaline phosphatase and bilirubin tend to remain normal (88,89). Overall, the elevations in hepatocellular enzymes are unimpressive compared to those seen in viral hepatitis. Histopathologic abnormalities are similar to but even more widespread than those observed with MBG and are consistent with the high viral titers found in many tissues (i.e., the virus is pantropic) (Table 4). Authorities have been perplexed about the cause of the devastating pathophysiologic abnormalities characteristic of fulminant HF. Schnittler and co-workers (90) showed that MBG replicates well in cultured endothelial cells and they proposed that disruption of endothelium due to viral replication deranges the vascular permeability barrier and other physiological functions of endothelium. Others have noted that severe damage to vascular endothelium is not a typical finding at autopsy even though vascular changes are widespread (5). Presently, the pathophysiologic events that

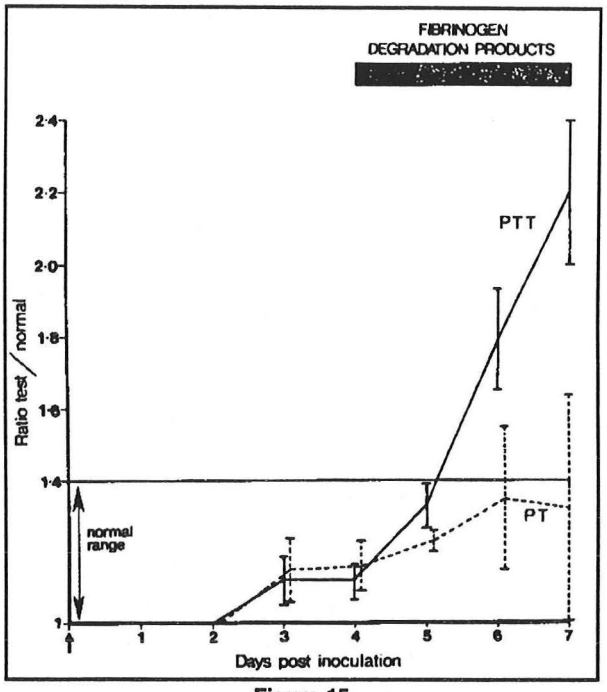


Figure 15

Titres of Ebola virus in monkey tissues expressed as Log 10 guinea-pig infectious units/ml or grams of tissues

Tissue	Rhesus 20 Killed Day 4	Rhesus 6 Killed Day 5	Rhesus 7 Killed Day 6	Vervet 3 Killed Day 6	Rhesus 12 Killed Day 8
Blood	6·0	5·5	6·5	6·5	6·5
Heart	4·5	7·5	5·0	6·0	6·5
Lungs	7·5	8	6·5	6·0	7·5
Liver	7·5	7·5	7·0	7·0	7·5
Spleen	7·5	6·5	8·0	7·5	7·5
Adrenals	5·0	7·0	7·0	5·0	7·5
Kidneys	5·0	6·5	4·0	7·0	5·5
Testes	6·5	6·5	6·0	N.D.	N.D.
Mes. Lymph Nodes	5·5	4·5	4·0	6·5	6·5
Pancreas	N.D.[a]	N.D.	N.D.	N.D.	7·5
Bile	NEG	NEG	NEG	N.D.	NEG
Feces	NEG	NEG	NEG	N.D.	N.D.
Urine	N.D.	NEG	3·5	3·5	N.D.

[a] N.D. — Not Done

Table 4

make filovirus infections of humans so devastating remain obscure. It is worth noting that essentially nothing is known about disease pathogenesis at the molecular level.

CLINICAL MANIFESTATIONS

Serological studies of contacts of confirmed EBO cases, population-based serological surveys, and the experience with Ebola Reston, suggest that the spectrum of EBO disease includes asymptomatic or mildly symptomatic disease. If one believes that population-based serological assays are specific, mild disease due to infection with cross-reactive less virulent viruses may also be relatively widespread, perhaps worldwide (91).

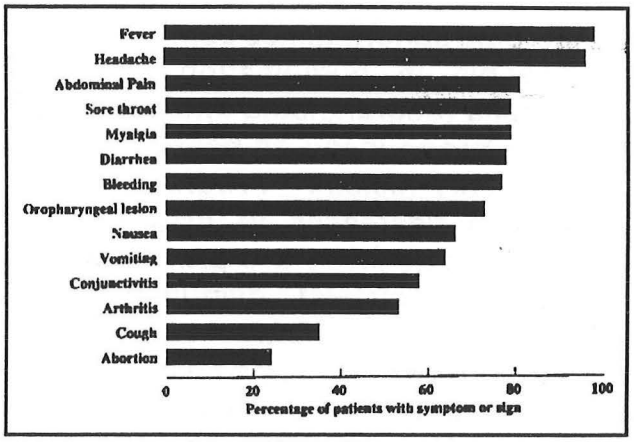


Figure 16

Severe EBO disease in humans closely parallels that in nonhuman primates (Figs. 16, 17, and Table 5). Figure 17 graphically describes the clinical course of a laboratory worker in England who accidentally inoculated himself with EBO (Zaire). Fortunately, he survived! After an incubation period of 2-21 days with an average of 7 days (the incubation period depends on inoculum size and whether the mode of transmission is by needle inoculation or person-to-person contact). The onset is abrupt with fever, severe periorbital/frontal headache, myalgia, conjunctivitis, and malaise. Nonexudative sore throat also is common but is less pronounced than the pharyngitis of Lassa fever. These prodromal symptoms are followed by gastrointestinal symptoms, crampy abdominal pain, nausea, vomiting, and watery diarrhea. Jaundice is not a feature of filovirus infection despite the fulminant hepatic involvement. Chest pain, usually pleuritic, was common in the Sudan outbreak but infrequent in Zaire (26). A papular rash may occur in some patients, especially on the trunk and back, though it may be difficult to appreciate in blacks; the rash eventually desquamates. Bleeding occurs 5-7 days into the illness and, when spontaneous, is most commonly from mucosal surfaces. Persistent bleeding at venipuncture sites also is well described. Hemorrhagic complications are a poor prognostic sign; they were noted in 77.6% of fatal cases as opposed to 17.6% of nonfatal cases (Table 5). Central nervous system involvement is manifested as disorientation, apathy ("ghost-like facies"), and occasionally frank psychosis. There are no available data

Frequency of Symptoms and Signs in Fatal and Nonfatal Ebola Infections (Zaire, 1976)

	Fatal Infections			Nonfatal Infections		
	N	*Frequency*	%	*N*	*Frequency*	%
Symptoms						
Fever	231	226	98	34	20	59
Headache	210	202	96	34	20	59
Abdominal pain	201	163	81	34	17	50
Sore throat	207	164	79	34	11	32
Myalgia	206	163	79	34	16	47
Nausea	178	117	66	30	10	33
Arthritis	193	102	53	34	13	38
Signs						
Diarrhea	228	180	79	34	15	44
Bleeding	223	174	78	34	6	18
Oral/throat lesions	208	154	74	34	9	27
Vomiting	225	146	65	34	12	35
Conjunctivitis	208	121	58	34	12	35
Cough	208	75	36	34	6	18
Abortion	73	18	25	9	1	11
Jaundice	191	10	5	34	0	0

Table 5

on the spinal fluid abnormalities characteristic of CNS involvement in EBO disease. Laboratory abnormalities parallel those observed in animal models. Death occurs from hypovolemic shock secondary to diffuse capillary leakage with or without hemorrhage.

DIAGNOSIS AND MANAGEMENT

From a purely technical standpoint, diagnosis of EBO disease is straightforward. The diagnosis of EBO HF traditionally has been made by isolating the virus or by demonstrating IgM antibody or a fourfold rise in IgG antibody in serum (4,5). Virions are profuse in body fluids and easily cultured on appropriate cell lines (e.g., Vero cells derived from African green monkey kidneys). Experience from the 1970's showed that virus often can be recovered from acute-stage specimens handled under suboptimal conditions (26,29). At this time, viral titers are so high that a rapid diagnosis can be confirmed by direct EM examination (29,92). IEM using specific antisera has been proposed as a means of confirming that observed viral particles are filoviruses (93,94). Antigen ELISA (91,93) has the obvious advantages that it obviates the need for viral culture and it can be performed on chemically inactivated sera in most hospital clinical laboratories (95,96). PCR as a nonculture-based detection method has particular appeal (97) although data on its clinical performance are lacking and it is not yet adapted for routine use in clinical laboratories. While the specificity of EBO serologies, particularly IFA, has been questioned, it is believed that they are accurate in an appropriate clinical setting (i.e., a patient from an endemic area with a compatible clinical syndrome) (36). For diagnostic purposes, the ELISA has supplanted the IFA. Seroconversion occurs on days 8-12 of illness. Serologic tests are performed with gamma-irradiated and serum samples that have been inactivated with heat or gamma irradiation. Recognition of postmortem cases is important for infection control and should be vigorously pursued. Confirmation is readily accomplished by routine transmission EM of tissues and by immunocytochemistry of fixed tissues (26,29).

Expeditious diagnosis of EBO disease has profound implications for public health as well as for the health of the individual patient. As with any rare disease, the difficulty in diagnosing EBO HF rests largely in not having the presence of mind

to think of the diagnosis. This is compounded further by the nonspecificity of its many symptoms and signs, particularly early in the disease course, and their resemblance to other far more common entities. Thus, diagnosis of EBO begins with suspicion of the diagnosis. For this reason, one cannot emphasize too strongly the importance of taking an accurate history paying particular attention to travel and exposure. The key pieces of historical information which should raise the possibility of EBO are (i) travel to a specific area of a where VHF has recently occurred with direct contact with blood or other body fluids from infected persons or (ii) exposure to recently imported nonhuman primates. The diagnosis is realistically excluded if the interval between the onset of symptoms and the last possible exposure exceeds three weeks. Even so it must be recognized that the differential diagnosis is broad and includes many other entities (e.g., malaria, typhoid, relapsing fever, leptospirosis, other hemorrhagic fevers, brucellosis, and meningococcemia) which must be vigorously sought and, perhaps, empirically treated while precautions are taken to deal with the possibility of EBO disease (98). The CDC has emphasized the importance of ruling out malaria in travelers from endemic areas and has provided explicit instructions on how to do this at minimal risk for laboratory personnel who perform the blood smears (98,99).

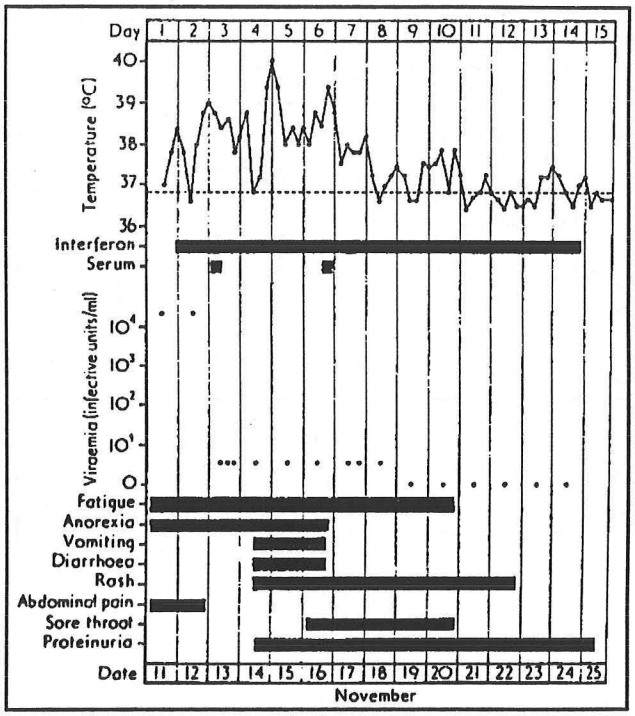


Figure 17. Clinical course of a patient with EBO (Zaire) infection.

Risk of Transmission of Ebola Virus by Degree of Person to Person Contact (Sudan, 1976 and 1979)

	1976			1979		
	Contacts	*Cases*	*%*	*Contacts*	*Cases*	*%*
Nursing care	48	39	81	60	24	40
Physical contact only	28	5	23	26	3	12
Entered room (no contact)	Not available			23	0	0

Table 6

Unfortunately, specific antiviral chemotherapeutic agents are not available. Ribavirin, the most broad-spectrum antiviral available, has no *in vitro* activity against EBO (100). Convalescent plasma and interferon have been used in isolated cases, but there is no evidence that these agents are efficacious in animal models (101). Management of the patient is entirely supportive. Heparin therapy for DIC, which

is usually mild, is generally not indicated (5).

As elegantly stated by the CDC, "the challenge of managing patients with VHF is to provide the highest quality care with the least risk of transmitting infection to health care providers" (98). Fulfillment of this injunction is possible only if care providers understand the mechanisms of viral transmission. As noted earlier, epidemiologic studies indicated that viral transmission occurs either by direct inoculation (the most efficient and deadly route of inoculation) or by direct skin or mucous membrane contact with infected body fluids (27,98). Studies in animals have shown that viral titers in urine are substantial, though below those in serum (15), and it is presumed that large numbers of virus also are excreted in stool, saliva, and tears. On the other hand, data from the Reston outbreak and more recent studies (102) suggest that airborne transmission of EBO is possible. This would most likely occur during late stage disease.

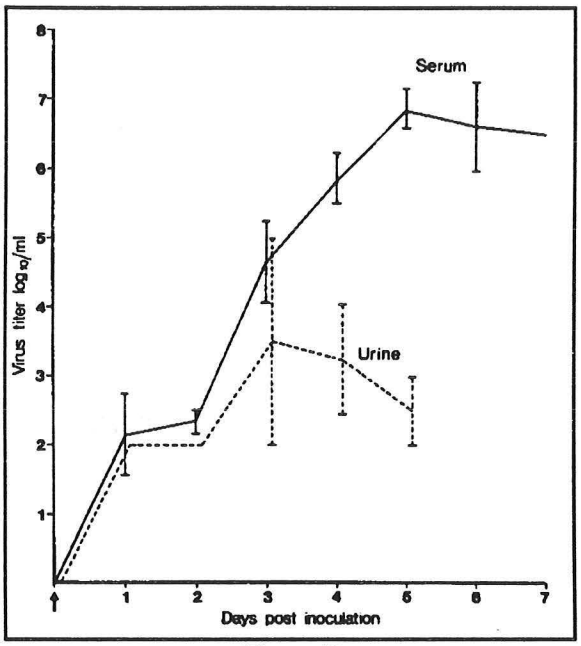


Figure 18

In 1988 the CDC published a MMWR supplement entitled "Management of patients with suspected viral hemorrhagic fever" (98); an update was recently published as well (99). These documents, which are appended to the protocol, lay out the basic principles involved in caring for patients with various viral HFs, including EBO. A second document entitled "Special Pathogen Plan for DCHD", also appended to the protocol, describes in great detail how the CDC recommendations are to be implemented in the Parkland environment. In the event that a patient is suspected of having VHF, Infection Control should be contacted immediately. They will take care of implementing all aspects of the "Special Pathogen Plan", including mobilization of appropriate support personnel. The basic principle is that patients can be safely managed using the universal precautions now routinely implemented for all blood and body fluids combined with strict barrier nursing techniques (i.e., disposable gloves, gowns, masks, shoe covers, and, when appropriate, protective eye covers). This can be accomplished by isolating a patient with suspected VHF in a single room with an adjoining anteroom serving as its only entrance (at PMH the designated rooms are in 9E or the ICU, depending on the severity of illness). Rooms at negative pressure are needed for patients with advanced disease who might be capable of transmitting virus in respiratory droplets. Blood specimens pose a particular risk to personnel.

However, specimens can be handled using universal precautions and transported by dedicated personnel to clinical laboratories. There the sera can be inactivated by chemical agents for appropriate laboratory and diagnostic tests (96,99). Specimens for viral isolation will be sent to the CDC which has the containment (P4) laboratory required for these manipulations.

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Heat-Related Deaths — Continued

temperature varies with the humidity), fans should not be used for preventing heat-related illness in areas of high humidity (5,7). Persons without home air conditioners should be assisted in taking advantage of such environments in private or in public places, such as shopping malls. Immersion in cool water (59.0 F– 61.0 F [15.0 C–16.1 C]) also can be used for maintaining acceptable body temperature.

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Update: Outbreak of Ebola Viral Hemorrhagic Fever — Zaire, 1995

As of June 25, public health authorities have identified 296 persons with viral hemorrhagic fever (VHF) attributable to documented or suspected Ebola virus infection in an outbreak in the city of Kikwit and the surrounding Bandundu region of Zaire (*1,2*). 79% of the cases have been fatal, and 90 (32%) of 283 cases in persons for whom occupation was known occurred in health-care workers. This report summarizes characteristics of persons with VHF from an initial description of cases and preliminary findings of an assessment of risk factors for transmission.

A case was defined as confirmed or suspected VHF in a resident of Kikwit or the surrounding Bandundu region identified since January 1. The median age of persons with VHF was 37 years (range: 1 month–71 years); 52% were female. Based on preliminary analysis of 66 cases for which data were available, the most frequent symptoms at onset were fever (94%), diarrhea (80%), and severe weakness (74%); other symptoms included dysphagia (41%) and hiccups (15%). Clinical signs of bleeding occurred in 38% of cases.

Potential risk factors for intrafamilial transmission were evaluated for secondary cases within households of 27 primary household cases identified through May 10. A primary household case was defined as the first case of VHF in a household; household was defined as persons who shared a cooking fire at the onset of illness in the primary household case. Among 173 household members of the 27 primary household cases, there were 28 (16%) secondary case-patients. The risk for developing VHF was higher for spouses of the primary household case-patients than for other household members (10 [45%] of 22 compared with 18 [14%] of 151; rate ratio [RR]=3.8;

Update: Ebola Virus — Continued

95% confidence interval [CI]=2.0–7.2) and for adults (aged ≥18 years) than for children (24 [30%] of 81 compared with four [4%] of 92; RR=6.7; 95% CI=2.4–18.4).

Needle sticks or surgical procedures during the 2 weeks before illness were reported for two of the 27 primary household case-patients and none of 28 secondary case-patients. Of the 28 secondary case-patients, 12 had direct contact with blood, vomitus, or stool of the ill person during hospitalization (i.e., later stages of illness), and 17 simultaneously shared the same hospital bed. Of 78 household members who had no direct physical contact with the person with the primary household case-patient during their clinical illness, none developed VHF (95% CI=0–4).

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Editorial Note: The incidence of VHF related to Ebola virus in Kikwit has diminished following the institution of interventions including 1) training of medical and relief personnel on the proper use of protective equipment, 2) initiation of aggressive case-finding; and 3) educational measures in the community (e.g., pamphlets and public announcements) (*1,2*). However, cases continue to occur, and each case has the potential to be a source for additional infections. Therefore, ongoing measures including continued intensive surveillance, training activities, and public education are necessary to contain the epidemic.

To maximize prevention and control measures, prompt laboratory diagnosis is an important component of surveillance. An enzyme-linked immunosorbent assay (ELISA) detected Ebola antigen in specimens initially submitted to CDC from 11 of 13 acutely infected persons (*1*). Ongoing testing of additional specimens will assess the utility of this ELISA as a rapid diagnostic test that could be used locally. In addition, Ebola antigen was detected in multiple formalin-fixed tissue samples (liver, lung, and skin) of seven case-patients by immunohistochemical (IHC) staining using a specific polyclonal antibody. These findings suggest that IHC staining of fixed tissue may assist in surveillance for hemorrhagic fevers in Africa and other countries. Other activities include ecologic studies to identify the natural reservoir of the virus; these studies are focusing especially on mammals, nonmammalian vertebrates, and arthropods.

Transmission associated with health-care providers and caregivers has been a prominent feature of the current and previous VHF outbreaks in Africa attributable to Lassa, Marburg, Ebola, or Crimean-Congo hemorrhagic fever viruses (*3*). In some outbreaks, transmission from patient to patient within hospitals has been associated with the reuse of unsterile needles and syringes. As in previous outbreaks, high rates of transmission in this outbreak have occurred from patients to health-care workers and to family members who provided nursing care without appropriate barrier precautions to prevent exposure to blood, other body fluids, vomitus, urine, and stool. Based on findings in this report, the risk for transmitting infection from patients appears to be highest during the later stages of illness, which is characterized by vomiting, diarrhea, shock, and often hemorrhage. However, a small number of cases of VHF in Zaire

(Continued on page 475)

Appendix: Suggested Equipment and Supplies for Anteroom Adjoining Patient's Room

- Prescribed medications (analgesics, antipyretics, antibiotics, etc.)
- Resuscitation equipment
- Material for physical examination
- Portable X-ray machine
- Electrocardiogram machine
- Intravenous equipment and supplies
- Tourniquets
- Dry gauze
- Alcohol swabs
- Needles (various sizes)
- Syringes (various sizes)
- Plastic container for disposal of needles and other sharp equipment
- Tubes for hematologic and biochemical investigations
- Blood-culture bottles
- Containers with solution for throat swabs and urine specimens (see text)
- Labels
- Marker pens
- Plastic airtight bags (various sizes)
- Plastic trash bags
- Disinfectant solutions (see text)
- Chemical toilet
- Urinals
- Nursing supplies
- Disposable linen, towels, pajamas, etc.
- Toilet articles
- Gowns, masks, surgical gloves, shoe covers, and protective eye wear for staff
- Housekeeping materials (absorbent towels for spills, etc.)

MMWR is prepared by the Centers for Disease Control, Atlanta, Georgia.

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Management of Patients with Suspected Viral Hemorrhagic Fever

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control
Center for Infectious Diseases
Division of Viral Diseases
Atlanta, Georgia 30333

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TABLE OF CONTENTS

Vol. 37 / No. S-3 MMWR

Management of Patients with Suspected Viral Hemorrhagic Fever

INTRODUCTION

The term viral hemorrhagic fever (VHF) refers to the illness associated with a number of geographically restricted viruses. This illness is characterized by fever and, in the most severe cases, shock and hemorrhage (*1*). Although a number of other febrile viral infections may produce hemorrhage, only the agents of Lassa, Marburg, Ebola, and Crimean-Congo hemorrhagic fevers are known to have caused significant outbreaks of disease with person-to-person transmission. Therefore, the following recommendations specifically address these four agents.

The increasing volume of international travel, including visits to rural areas of the tropical world, provides opportunity for the importation of these infections into countries with no endemic VHF, such as the United States. Since most physicians have little or no experience with these viruses, uncertainty often arises when VHF is a diagnostic possibility. Lassa, Marburg, and Ebola viruses are restricted to sub-Saharan Africa, and the differential diagnosis of VHF will most often be made for illness in travelers to this region. Since 1976, no imported cases of VHF have been confirmed in the United States, but every year there are approximately five to 10 suspected cases.

These guidelines review the clinical and epidemiologic features of these diseases; provide recommendations on diagnosis, investigation, and care of patients; and suggest measures to prevent secondary transmission. This document updates earlier recommendations, issued in 1983 (*2*), for the management of suspected and confirmed cases of VHF. Accumulated evidence shows that transmission of these viruses does not occur through casual contact; thus, some earlier recommendations for preventing secondary transmission have been relaxed. Similarly, therapy recommendations have taken into account recent knowledge of the effects of antiviral drugs.

Further information on investigating and managing patients with suspected VHF, collecting and shipping diagnostic specimens, and instituting control measures is available on request from the following persons at CDC in Atlanta, Georgia. For all telephone numbers, dial 404-639 + extension:

1. Epidemic Intelligence Service (EIS) Officer, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases (ext. 1344).
2. Chief, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases: Joseph B. McCormick, M.D. (ext. 3308).
3. Senior Medical Officer, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases: Susan P. Fisher-Hoch, M.D. (ext. 3308)

4. Director, Division of Viral Diseases, Center for Infectious Diseases (ext. 3574).
5. After regular office hours and on weekends, the persons named above may be contacted through the CDC duty officer (ext. 2888).

LASSA FEVER

Lassa virus, named after a small town in northeastern Nigeria, is an enveloped, single-stranded, bisegmented ribonucleic acid (RNA) virus classified in the family Arenaviridae. Its natural host is the multimammate rat *Mastomys natalensis*. This ubiquitous African rodent lives in close association with humans and is commonly found in and around houses in rural areas. The rats are infected throughout life and shed high levels of virus in their urine. Although the rodent reservoir exists across wide areas of Africa, Lassa virus appears to be restricted to the continent's western part. Closely related viruses are found in other areas, but their potential for causing human disease is poorly understood.

Lassa fever was first recognized in 1969 in northern Nigeria (*3*) when two of three nurses infected in a rural hospital died. Two persons working in a U.S. laboratory with material from the original outbreak subsequently became infected, one fatally. One person had worked with animals infected with live virus, but it is uncertain how the other person acquired the infection (*4,5*). Naturally occurring infections, often associated with subsequent nosocomial outbreaks, have been recognized in Nigeria, Sierra Leone, and Liberia (*6*). On the basis of historical information, as well as serologic testing, sporadic Lassa infection may have occurred also in Guinea, Senegal, Mali, and the Central African Republic (*6,7*). In at least 10 instances, Lassa fever has been imported into countries outside of Africa (*3,6-15*). In the United States, the last imported case occurred in 1976 (*15*). No secondary transmission from these imported infections has been documented, despite intensive surveillance of many potentially exposed people (*16*).

Under natural circumstances, infection with Lassa virus occurs through contact with *M. natalensis* or its excreta, probably within the household. Subsequent person-to-person transmission occurs, although it is difficult to distinguish epidemiologically between these two modes of infection (*17,18*). Person-to-person spread requires close personal contact or contact with blood or excreta. Careful follow-up of household and other close contacts of cases imported into western Europe and North America has not shown any evidence of secondary transmission from casual contact. Early reports of Lassa fever stressed the high infectivity of the condition and the risks of nosocomial transmission. Recent evidence shows that avoiding direct contact with infected tissue, blood, secretions, and excretions, even in poorly equipped rural African hospitals, virtually eliminates the risk of infection (*19,20*).

In areas where it is endemic, Lassa fever occurs more frequently in the dry than in the rainy season. The clinical spectrum of disease is wide, and the ratio of illness to infection is 9%-26% (*18*). After an incubation period of 1-3 weeks, illness begins insidiously, with early symptoms of fever, sore throat, weakness, and malaise (*21*). Pains in the joints and lower back, headache, and nonproductive cough commonly follow. Retrosternal or epigastric pain, vomiting, diarrhea, and abdominal discomfort are also common. Frequent physical signs include fever, exudative pharyngitis, and

conjunctival injection. Jaundice and skin rash are rare. Diffuse rales may be hear auscultating the chest, and pleural and pericardial friction rubs may sometime detected. Edema of the face and neck, conjunctival hemorrhages, mucosal bleed central cyanosis, encephalopathy, and shock characterize the most severe ca Some patients experience adult respiratory distress syndrome.

After the first week of illness, the patient begins to recover in milder cases, starts to deteriorate clinically in more serious ones. The mortality rate for pati hospitalized with Lassa fever is 15%-20% (*21*), despite higher earlier estimates prognosis is particularly poor for women in the third trimester of pregnancy, a high rate of fetal wastage occurs. Overall, the case-fatality rate is about 1%-2% (Various degrees of permanent sensorineural deafness result in nearly one-fourt the cases.

Specific diagnosis of Lassa fever can be made in three ways: by isolating the v from blood, urine, or throat washings; by demonstrating the presence of immu globulin M (IgM) antibody to Lassa virus; or by showing a fourfold rise in titer of antibody between acute- and convalescent-phase serum specimens. Antibodies measured with the indirect fluorescent antibody technique (IFA), which remains diagnostic method of choice. Nonspecific laboratory abnormalities include prot uria and elevated liver enzymes, with aspartate aminotransferase (AST) le exceeding those of alanine aminotransferase (ALT).

Adverse prognostic factors are AST elevation above 150 international units/ and high levels of viremia during hospitalization (*22,23*). Treatment is supportive may require all the modern intensive-care facilities, including renal dialysis mechanical ventilation. It is essential to pay attention to fluid and electrolyte bala maintenance of blood pressure and circulatory volume, and control of seizures

A controlled clinical trial has shown an increased survival rate for Lassa fe patients treated with ribavirin (*22*). All patients with the disease should now rec this drug. Side effects are largely restricted to reversible hemolysis. Severely patients should receive ribavirin parenterally. Lassa fever convalescent plasma not been shown to be beneficial (*22*) and currently cannot be recommend particularly when the potential for transmitting other viruses such as human imm nodeficiency virus, hepatitis B virus, and the agent(s) of non-A, non-B hepatiti considered.

Prevention of Lassa virus infection requires an understanding of the disease an modes of transmission. Persons who intend to work in areas with endemic dise should be briefed about Lassa fever (*20*). Currently, no vaccine is available for in humans.

EBOLA HEMORRHAGIC FEVER

Ebola virus is a single-stranded, unsegmented, enveloped RNA virus with characteristic filamentous structure. Classification of the virus in the new fam Filoviridae has been accepted. The virus is named after a small river in northw Zaire. It is morphologically similar to, but antigenically distinct from Marburg vir The reservoir of the virus in nature remains unknown.

Ebola hemorrhagic fever was first recognized in 1976. Two epidemics occur within a short time of each other, the first in southern Sudan (*24*) and the secon

northwest Zaire (*25*). The index case in the Sudan epidemic occurred in a worker in a cotton factory, who subsequently was the source of hospital transmission. The mortality rate among the 284 recognized cases was 53%. In the Zaire outbreak, which from the beginning centered around a hospital, 88% of the 318 affected persons died. Having close contact with a case and receiving injections at the hospital were strong risk factors for acquiring infection.

Two cases were identified elsewhere in northwest Zaire in 1977 and 1978. Retrospectively, another case was diagnosed in a physician in the same area, who cut himself while performing an autopsy in 1972 and contracted an Ebola-like illness 12 days later (*26*).

In 1979 another small outbreak occurred in the same area as the 1976 outbreak in Sudan. The index case involved a worker in the same cotton factory (*27*). The case-fatality rate was 65%. Evidence from serologic studies suggested that Ebola virus may be endemic in certain areas of Sudan and Zaire, as well as in other parts of East and Central Africa (*28*).

The mode of acquiring natural infection with Ebola virus is unknown. Secondary person-to-person transmission results from close personal contact, which, in the epidemics described above, frequently included the nursing of sick patients. Nosocomial transmission depends on contact with blood, secretions, and excretions. Transmission of infection has been documented in the case of a laboratory worker who experienced a needle-stick injury (*29*). Epidemiologic studies from Zaire and Sudan (*24,25*) do not suggest that spread occurred through casual contact or by aerosol transmission.

The incubation period ranges from 2 to 21 days; the average is approximately 1 week. In the cases resulting from a needle stick (*25,29*), the incubation period was 6 days; however, this may not characterize the natural illness. The illness-to-infection ratio for Ebola virus is unknown, but seroepidemiologic investigations suggest that mild or asymptomatic infections can occur.

The onset of illness is abrupt, and initial symptoms resemble those of an influenza-like syndrome. Fever, headache, general malaise, myalgia, joint pain, and sore throat are commonly followed by diarrhea and abdominal pain. A transient morbilliform skin rash, which subsequently desquamates, often appears at the end of the first week of illness. Other physical findings include pharyngitis, which is frequently exudative, and occasionally conjunctivitis, jaundice, and edema. After the third day of illness, hemorrhagic manifestations are common and include petechiae as well as frank bleeding, which can arise from any part of the gastrointestinal tract and from multiple other sites.

Specific diagnosis requires isolating the virus from blood or demonstrating IgM or rising IgG antibodies by IFA. Proteinuria occurs early, and elevation of liver enzymes, AST more than ALT, is typical. Experimental infections in primates have shown that neutrophilia, lymphopenia, and thrombocytopenia occur early in the illness (*30*).

Treatment is supportive and may require intensive care. Limited information exists on the efficacy of antiviral drugs or immune plasma to prevent or ameliorate Ebola hemorrhagic fever. Ribavirin shows no in vitro activity. Since the Zaire and the Sudan strains of the virus are distinct (*31*), if immune plasma is considered for therapeutic use, it must be strain specific. The dangers of transmitting other viral infections through plasma should be remembered. No vaccine exists against Ebola virus.

MARBURG HEMORRHAGIC FEVER

Marburg virus is a single-stranded, unsegmented, enveloped RNA virus that morphologically identical to, but antigenically distinct from Ebola virus. Classificati of the virus in the new family Filoviridae has been accepted. Marburg virus is nam after the town in Germany where some of the first cases were described (*32*). reservoir in nature remains unknown.

In 1967, 25 people in Europe became ill after handling material from infec African green monkeys, *Cercopithecus aethiops*, imported from Uganda (*32*). T case-fatality rate was 23% for the primary cases, but no deaths were reported for t six secondary cases.

An Australian traveler died of Marburg virus disease in South Africa in 1975, af apparently acquiring his infection in Zimbabwe (*33*). Two persons with second cases—a female companion and a nurse of the index patient—survived. The th recognized outbreak of Marburg virus disease occurred in Kenya in 1980 (*34*). French engineer contracted the infection in western Kenya, and a physician in Nairobi hospital became infected while trying to resuscitate the engineer from terminal bout of hematemesis. The physician survived. Despite extensive conta with other staff before his illness was diagnosed, the infected physician did n spread the disease further. Another case of Marburg virus disease occurred in Sou Africa in 1982, with no secondary cases identified (*35*). The most recent case Marburg virus disease occurred in Kenya in 1987; it involved a boy visiting a park the western part of the country near where the engineer had acquired the infection 1980. The boy died, but no secondary cases occurred.

The mode of acquiring natural infection with Marburg virus is unknown. Secon ary spread results from close contact with infected persons or contact with blood body secretions or excretions. In the original epidemic (*32*), the only perso primarily infected had direct contact with animal blood or tissues, without takin precautions to prevent infection. Sexual transmission apparently occurred in on instance in Germany (*32*), and virus has been isolated from seminal fluid up to months after illness (*34*). Marburg virus was also isolated from the anterior chambe of the eye in a patient who developed uveitis 2 months after the acute illness (*33*). Although the geographic distribution of Marburg virus is ill-defined, Central and Ea Africa should be considered endemic areas.

The illness-to-infection ratio is unknown but seems high for primary infections judging from experience with the original 1967 epidemic. The incubation perio ranges from 3 to 10 days, but was typically 5-7 days in the original outbreak (*32*). Th physician infected in the Nairobi hospital had a 9-day incubation period.

Clinical and laboratory features of Marburg virus disease are essentially similar t those described for Ebola virus disease. Diagnosis is confirmed by isolating the viru or demonstrating IgM or rising IgG antibodies by IFA. The treatment is the same as fo Ebola virus disease, and the same comments about antiviral drugs and the use o immune plasma apply.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Crimean-Congo hemorrhagic fever (CCHF) virus is an enveloped, single stranded RNA virus with a tripartite genome. It is classified in the family Bunyaviridae. A hemorrhagic fever that had long been recognized in Asia came to international

attention after a disease outbreak in the Crimean peninsula in 1944 and 1945 (*36*). The causative agent was later recognized to be identical to the Congo virus (*37,38*), isolated in Zaire, hence the name CCHF. Many wild and domestic animals act as reservoirs for the virus, including cattle, sheep, goats, and hares. Ixodid (hard) ticks, particularly those of the genus *Hyalomma*, act both as a reservoir and vector for CCHF virus. Ground-feeding birds may disseminate infected vectors. Twenty-seven species of ticks are known to harbor the CCHF virus (*36*).

CCHF is endemic in eastern Europe, particularly in the Soviet Union. However, it may occur in other parts of Europe, especially around the Mediterranean. CCHF has been recognized in northwest China (*39*), Central Asia, and the Indian subcontinent and may occur in the Middle East and throughout much of Africa. Humans become infected by being bitten by ticks or by crushing ticks, often while working with domestic animals or livestock. Contact with blood, secretions, or excretions of infected animals or humans may also transmit infection. In areas with endemic CCHF, the disease may occur most often in the spring or summer.

Nosocomial transmission is well described in recent reports from Pakistan (*40*), Iraq (*41*), Dubai (*42*), and South Africa (*43-48*). Available evidence, including recently unpublished experiences, suggests that blood and other body fluids are highly infectious, but simple precautions, such as barrier nursing, effectively prevent secondary transmission (*41*). Concern has been raised about two nosocomial cases in South Africa that occurred without documented evidence of direct exposure to infectious material (*43-47*). However, all other evidence rules out airborne transmission.

The incubation period for CCHF is about 2-9 days. Initial symptoms are nonspecific and sometimes occur suddenly. They include fever, headache, myalgia, arthralgia, abdominal pain, and vomiting. Sore throat, conjunctivitis, jaundice, photophobia, and various sensory and mood alterations may develop. A petechial rash is common and may precede a gross and obvious hemorrhagic diathesis, manifested by large ecchymoses, bleeding from needle-puncture sites, and hemorrhage from multiple other sources. The case-fatality rate has been estimated to range from 15% to 70% (*2*), but mild or inapparent infections occur. One study suggested an illness-to-infection ratio of 1:5 (*44*).

Diagnosis requires isolating the virus from blood during the first week of illness or detecting rising antibody titer by IFA, complement fixation, or one of several other methods. No data are available on the evaluation of IgM antibody response. Nonspecific laboratory abnormalities include progressive neutropenia, lymphopenia, thrombocytopenia, and anemia. Hyperbilirubinemia and elevated liver enzymes are common.

Treatment is supportive and may require intensive care. Ribavirin inhibits CCHF virus in vitro, but its efficacy in clinical practice remains unconfirmed. Although immune plasma has been used, its effectiveness has not been evaluated.

APPROACH TO A SUSPECTED CASE OF VHF

General Principles

The patient's travel history, symptoms, and physical signs provide the most important clues to the potential diagnosis of VHF. Under natural circumstances,

infection is most often acquired in rural areas, and for most visitors and tourist areas with endemic VHF, exposure to the causative agents is extremely unlikely. If patient has visited exclusively urban zones, a diagnosis of VHF is improbable. diagnosis is realistically excluded if the interval between the onset of symptoms the last possible exposure exceeds 3 weeks. A careful history must be taken about patient's possible exposure to ill persons or traveling companions in an area v endemic VHF.

Initial symptoms may include fever, headache, sore throat, myalgia, abdom pain, and diarrhea. Diagnosis at this stage is difficult, since these symptoms nonspecific. The differential diagnosis is wide and includes other viral infection particularly arbovirus infections – bacterial infections such as typhoid fever, rickett diseases, and parasitic infections such as malaria. Symptoms and signs suppor the diagnosis of VHF are pharyngitis and conjunctivitis, a skin rash (particularly Marburg and Ebola virus diseases), and later, hemorrhage and shock.

Two critical studies should be done for any patient who has recently returned fr the tropics and has fever; these are a blood-film examination for malaria and bl cultures. An experienced technician may need to examine several blood smear identify malarial parasites, particularly for patients who have taken prophyla antimalarial chemotherapy. When VHF is a diagnostic possibility, blood cultures m be done in a closed system. These initial specimens should be handled with the sa precautions used for samples infected with hepatitis B virus or human immunod ciency virus. An experienced technician should be briefed about the safe handlin such material. All of the patient's body fluids, secretions, and excretions must considered potentially infectious.

If clinicians feel that VHF is a likely diagnosis, they should take two immed steps: 1) isolate the patient, and 2) notify local and state health departments and C

The aim of management is to provide optimal care to the patient with the le hazard to staff. A mobile laboratory capable of performing routine laboratory test available on request from CDC (see below). Laboratory tests essential for the patie immediate care must be done by trained staff using the precautions outlined in t document. Meticulous adherence to barrier-nursing procedures and precautions prevent contact with blood or other body fluids are fundamental to the effect management of patients with possible VHF and to the protection of the staff.

ISOLATION OF PATIENTS WITH SUSPECTED AND CONFIRMED VHF

General Principles

Extensive experience in West Africa has shown that the ordinary precautions, s as those taken with blood and other body fluids from patients infected with hepat B virus or human immunodeficiency virus, combined with barrier nursing, effectiv prevent Lassa virus transmission in hospitals (*19*). Ideally, patients should be ca for at the hospital where they are first seen, since patients ill with VHF tolerate stress of transfer poorly, and a move only increases the potential for second transmission. If care at the hospital where the patient presented is not possi

transfer to another local facility is preferable to travel to a more distant center. Personnel involved in the transfer of patients with suspected VHF must follow the same precautions recommended for medical and nursing staff.

The patient should be isolated in a single room with an adjoining anteroom serving as its only entrance. The anteroom should contain supplies for routine patient care, as well as gloves, gowns, and masks for the staff. The Appendix lists suggested supplies for the anteroom. Hand-washing facilities should be available in the anteroom, as well as containers of decontaminating solutions. If possible, the patient's room should be at negative air pressure compared with the anteroom and the outside hall, and the air should not be recirculated. However, this is not absolutely required, and does not constitute a reason to transfer the patient. If a room such as described is not available, use adjacent rooms to provide safe and adequate space.

Strict barrier-nursing techniques should be enforced: all persons entering the patient's room should wear disposable gloves, gowns, masks, and shoe covers. Protective eye wear should be worn by persons dealing with disoriented or uncooperative patients or performing procedures that might involve the patient's vomiting or bleeding (for example, inserting a nasogastric tube or an intravenous or arterial line). Protective clothing should be donned and removed in the anteroom. Only essential medical and nursing personnel should enter the patient's room and anteroom. Isolation signs listing necessary precautions should be posted outside the anteroom. The patient should use a chemical toilet. All secretions, excretions, and other body fluids (other than laboratory specimens) should be treated with disinfectant solution. All material used for patients, such as disposable linen and pajamas, should be double-bagged in airtight bags. The outside bags should be sponged with disinfectant solution and later incinerated or autoclaved. Disposable items worn by staff, such as gowns, gloves, etc., should be similarly treated. Disposable items used in patient care (suction catheters, dressings, etc.) should be placed in a rigid plastic container of disinfectant solution. The outside of the container should be sponged with disinfectant, and the container should be autoclaved, incinerated, or otherwise safely discarded.

If surgery is required, surgical staff should wear protective eye wear and double gloves. Advice should be sought from CDC.

Disinfectant Solutions

Lipid-containing viruses, including the enveloped viruses, are among the most readily inactivated of all viral agents (*50*). Suitable disinfectant solutions include 0.5% sodium hypochlorite (10% aqueous solution of household bleach), as well as fresh, correctly prepared solutions of glutaraldehyde (2% or as recommended by the manufacturer) and phenolic disinfectants (0.5%-3%) (*50,51*). Soaps and detergents can also inactivate these viruses and should be used liberally.

CONFIRMATION OF THE DIAGNOSIS

General Principles

The diagnosis of VHF is confirmed by isolating the virus or by demonstrating IgM antibody or a fourfold rise in IgG antibody in serum, as described earlier. Antibody

may not appear in blood until the second week of illness. Virus is usually reco from blood, although Lassa virus may also be isolated from the throat or urine tissue collected after death may also be a rich source of virus.

Virus isolation must only be attempted in Biosafety Level 4 facilities (*52*), su are available at CDC. Serologic tests can be performed either at CDC or in the m laboratory (see below). Serologic tests for antibodies are done with gamma-irrad antigens and serum samples that have been inactivated with heat or ga irradiation.

Handling Laboratory Specimens

Collecting Specimens

Recommendations for safely collecting and transporting specimens remai changed. The essential specimens to be submitted for virus isolation are a samp venous blood, a midstream ("clean catch") specimen of urine, and a throat sw postmortem specimens are available, serum, liver, spleen, and kidney tissu desirable. The following procedures should be followed:

1. Glass containers should not be used. Disposable sharp objects, such as sc blades, also should not be handled unnecessarily after use and should be autocl or incinerated.

2. Venous blood samples must be collected with extreme care to avoid inoculation. Ten milliliters of clotted blood should be placed in a sealed pl container. Needles should not be recapped, bent, broken, removed from dispos syringes, or otherwise handled. Blood-taking equipment should be put in a plastic container filled with disinfectant solution and autoclaved or incinerated.

3. Midstream urine specimens should be collected by clean catch. Five milli of urine should be put in a plastic screw-cap container with one of the follow rabbit serum albumin diluted to a final concentration of 25%, human serum albu diluted to a 1% concentration, or bovine serum albumin at a final concentra of 10%.

4. Throat swabs should be placed in plastic screw-cap containers in 1 n sterile, phosphate-buffered neutral saline containing 25% rabbit serum, 1% hu serum albumin, or 10% bovine serum albumin.

The outside of each specimen container should be swabbed with disinfectant, a label should be attached bearing the patient's name, hospital identification, the of collection, and the nature of the suspected infection. Then, the specimens sh be double-bagged in secure, airtight and watertight bags, which have been simil labeled. Bags containing specimens should be sponged with disinfectant before t are removed from the patient's room.

Packaging and Transporting Specimens

The Office of Biosafety at CDC (ext. 3883), the persons listed in the Introductio the state health department should be contacted for instructions on packag labeling, and shipping diagnostic laboratory specimens since shipment of specim is subject to the applicable provisions of the Federal Interstate quarantine regulati (*53*). In general, the specimens should be packaged as follows:

1. Place the specimens for transport in a tightly sealed, watertight container, s as a screw-cap plastic tube or vial, and seal the cap with tape. Make sure pla

containers are resistant to temperatures as low as -80°C. If the specimen is in a glass or other unsuitable container, it should be carefully transferred using the laboratory precautions listed below.

2. Wrap the primary container in sufficient absorbent material (for example, tissue) to absorb the entire contents in case the container leaks or breaks.

3. Place the wrapped, sealed primary container in a durable, watertight screw-cap mailing tube or metal can. This secondary container should be sealed with tape. Several primary containers of specimens, each individually wrapped in absorbent material, may be placed in one secondary container, to a maximum of 50 ml of specimen material.

4. On the outside of the secondary container, attach the specimen labels and other relevant information.

5. Place the secondary container in a secure box or mailing tube addressed to one of the individuals listed in the Introduction.

6. Transport the specimen for virus isolation on dry ice.

7. Since individual commercial and noncommercial carriers or shipping services may apply different regulations for transporting biologic specimens, contact a representative of the chosen carrier beforehand to ensure that all necessary formalities are fulfilled. One person listed in the Introduction must be contacted by telephone about the specimen's nature, the method of shipment, and the expected date and time of arrival at CDC.

Exposure of Laboratory Personnel to Specimens

Laboratory tests should be kept to the minimum required for the immediate care of the patient until the mobile laboratory arrives. Critical investigations, such as examination of a blood smear for malaria and the inoculation of blood cultures, must not, however, be postponed. Laboratory staff dealing with specimens from patients who might have a VHF must take the same personal precautions as patient-care staff. Surgical gloves, gowns, shoe covers, and masks should be worn. When possible, laboratory tests should be performed in biological safety cabinets. Blood cultures should be prepared in a closed system. Every effort should be made to avoid creating an aerosol or splashing, and protective eye wear should be worn if possible. A full-face respirator with an HEPA (high efficiency particulate air) filter is an acceptable, but cumbersome alternative to masks and protective eye wear. Nonessential tests should not be performed, nor should routine automated equipment be used unless the specimen has been inactivated. Abundant supplies of disinfectant solutions should be readily available. Safe laboratory work has been done with use of these precautions for many years in VHF-endemic areas with poorly equipped hospitals.

Laboratory personnel accidentally exposed to potentially infected material (for example, through injections or cuts or abrasions on the hands) should immediately wash the infected part, apply a disinfectant solution such as hypochlorite solution, and notify the patient's physician. The person should then be considered as a high-risk contact and placed under surveillance (see below).

Accidental spills of potentially contaminated material should be liberally covered with disinfectant solution, left to soak for 30 minutes, and wiped up with absorbent material soaked in disinfectant.

CLINICAL CARE OF PATIENTS WITH SUSPECTED VHF

General Principles

The challenge of managing patients with VHF is to provide the highest qual care with the least risk of transmitting infection. Detailed discussion about ther beyond the scope of this document. Patients require close supervision, and som need modern intensive-care facilities. Since pathogenesis is not entirely under and antiviral therapy is limited, treatment is largely supportive. It is essential t careful attention to fluid and electrolyte balance. In severe cases, therapy w required for shock and blood loss. The supportive care of patients critically il VHF is the same as the conventional care provided to patients with other cau multisystem failure. Adult respiratory distress syndrome, renal failure, seizure coma may require specific interventions, such as mechanical ventilation, dialysi neurologic intensive care. If surgery is required (for example, obstetric interve it should be done.

The prognosis for patients with Lassa fever has been shown to correlate with of viremia, but not with the development of IgM or IgG antibodies (*23*). antibodies have not been shown to neutralize Lassa virus. Experimental infe with Lassa and Ebola viruses in rhesus monkeys suggest that shock results platelet and endothelial dysfunction, with subsequent leakage of fluid fro intravascular system and hemorrhage. To date, therapeutic use of hepa corticosteroids has not proven effective and is probably contraindicated.

Patients with Lassa fever should receive ribavirin (see box). For sever persons, treatment may begin while confirmation of the diagnosis is pe Ribavirin is recommended both therapeutically for patients with Lassa feve prophylactically for high-risk contacts of such patients. Its use for patients with and their high-risk contacts may be justified but is unstudied.

Treatment Regimen

Ribavirin 30 mg/kg intravenously (IV) loading dose, then 16 mg/kg IV every 6 hours for 4 days, and then 8 mg/kg IV every 8 hours for 6 days (total treatment time 10 days).

Prophylactic Regimen

Ribavirin 500 mg by mouth every 6 hours for 7 days.

Use of convalescent plasma for Lassa fever is not currently recomme Analogues of prostacyclin are being evaluated as to their efficacy in restori endothelial cell defect (*20*). Therapy can be discussed with persons listed Introduction.

Clinical experience with Ebola and Marburg virus diseases is limited, and in ual judgment must determine whether convalescent plasma or antiviral drugs s be used. Interferon and ribavirin show no in vitro effect against these agents

Ribavirin has been shown effective against some of the Bunyaviridae in vitr its use in patients with CCHF seems reasonable, although no clinical experie available.

MOBILE LABORATORY

CDC has adapted a mobile isolator that can be used as a portable laboratory to investigate cases of suspected or confirmed VHF safely (*54*). This facility can be transported immediately to any part of the United States, with an accompanying technician and physician experienced in dealing with hemorrhagic fevers. The mobile laboratory has facilities for routine hematologic and biochemical studies, as well as for basic bacteriologic and coagulation investigations. Serodiagnostic tests for VHF can be performed in this facility, but cultures for virus isolation cannot. Electrolyte measurements on inactivated serum specimens are also possible, but blood gas analysis is not. Early use of this facility is preferable to delays in investigating the suspected case because of concern about the hazards of handling specimens. Further information about the mobile laboratory and its use can be obtained from the persons listed in the Introduction.

AUTOPSY AND HANDLING OF A CORPSE

Before an autopsy is done on a patient suspected to have died from VHF, the possible risks and benefits must be carefully considered. Autopsies have been conducted safely on these patients, sometimes without prior knowledge of the diagnosis (*34*), but under some circumstances it may be wiser to forego this procedure. Limited autopsy or postmortem collection of blood and percutaneous liver biopsy material may be appropriate.

The same precautions recommended for clinicians and laboratory staff working with infected patients and specimens must be followed. Double gloves, caps and gowns, waterproof aprons, shoe covers, and protective eye wear are required. Aerosol formation must be avoided (for example, electrical cutting instruments must not be used). All solid and liquid waste should be decontaminated with disinfectant solution or by heating for 1 hour at 60°C. Liquid waste can then be washed down the drain; solid waste should be incinerated.

All unnecessary handling of the body, including embalming, should be avoided. Persons who dispose of the corpse must take the same precautions outlined for medical and laboratory staff. The corpse should be placed in an airtight bag and cremated or buried immediately.

DECONTAMINATION PROCEDURES

Disposable items, such as pipette tips, specimen containers, swabs, etc., should be placed in a container filled with disinfectant solution and incinerated. Clothes and blankets that were used by the patient should be washed in a disinfectant, such as hypochlorite solution.

Nondisposable items such as endoscopes used in patient care must be cleaned with decontaminating fluids (for example, gluteraldehyde or hypochlorite). Laboratory equipment must be treated similarly. All nondisposable materials that withstand autoclaving should be autoclaved, after they have been soaked in disinfectant solution. The patient's bed and other exposed surfaces in the hospital room, or in vehicles used to transport the patient, should be decontaminated with disinfectant solution.

IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF PATIENT CONTACTS

A contact is defined as a person who has been exposed to an infected person an infected person's secretions, excretions, or tissues within 3 weeks of the pati onset of illness. Contacts may be subdivided into three levels of risk.

1. *Casual contacts* are persons who had remote contact with the ill patient. T include persons on the same airplane, in the same hotel, etc. Since the agents of are not spread by such contact, no special surveillance is indicated.

2. *Close contacts* are persons who had more than casual contact with the pa They include persons living with the patient, nursing or serving the patient whe or she was ill, shaking hands with or hugging the patient, handling the pati laboratory specimens, etc. These contact persons should be identified by state local health departments, in collaboration with CDC, as soon as VHF is consider likely diagnosis for the index case. Once the diagnosis is confirmed, close con should be placed under surveillance. This requires these individuals to record temperatures twice daily and report any temperature of 101°F (38.3°C) or above or symptom of illness to the public health officer responsible for surveillance. Sur lance should be continued for 3 weeks after the person's last contact with the i patient.

3. *High-risk contacts* are persons who have had mucous membrane contact the patient, such as kissing or sexual intercourse, or have had a needle stick or o penetrating injury involving contact with the patient's secretions, excretions, bl tissues, or other body fluids. These individuals should be placed under surveillanc soon as VHF is considered a likely diagnosis in the index case.

Any contact who develops a temperature of 101°F (38.3°C) or higher or any o symptoms of illness should be immediately isolated and treated as a VHF pat Ribavirin should be prescribed as postexposure prophylaxis for high-risk contac patients with Lassa fever. Dosage schedules are given in the box on page Although experience is more limited, postexposure prophylaxis with ribavirin is recommended for high-risk contacts of patients with CCHF.

Convalescent patients and their contacts should be warned that some of causative agents of VHF may continue to be excreted for many weeks n semen demonstrated with Marburg (*32,34*) and Ebola (*29*) viruses, and in urine, as oc sometimes with Lassa virus (*13*). It is recommended that the persons listed in Introduction be contacted about arranging shipment to CDC of seminal fluid and u specimens from patients in the convalescent period for virus isolation. Convales patients must be meticulous about personal hygiene. While data are limited conc ing infectivity in the convalescent period, abstinence from sexual intercours advised until genital fluids have been shown to be free of the virus. If the patient engage in sexual intercourse before tests are done, the use of condoms is advi

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Update: Ebola Virus — Continued

have been reported in family members whose only contact with an infected person was in the domestic setting within a few days after onset of illness.

Updated recommendations for the management of VHFs attributable to these viruses in the United States are presented in a Notice to Readers in this issue (*4*).

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Notice to Readers

Update: Management of Patients with Suspected Viral Hemorrhagic Fever — United States

In 1988, CDC published guidelines for managing patients with suspected viral hemorrhagic fever (VHF) (*1*). Pending a comprehensive review of the 1988 guidelines, this notice provides interim recommendations that update the 1988 guidelines for healthcare settings in the United States. This update applies to four viruses that cause syndromes of VHF: Lassa, Marburg, Ebola, and Congo-Crimean hemorrhagic fever viruses; although the risk and/or mode of nosocomial transmission differs for each of these viruses, the limited data do not permit clear distinctions.

Background

In Africa, transmission of VHF has been associated with reuse of unsterile needles and syringes and with provision of patient care without appropriate barrier precautions to prevent exposure to virus-containing blood and other body fluids (including vomitus, urine, and stool). The risks associated with various body fluids have not been well defined as most caregivers who acquired infection had multiple contacts with multiple fluids. Epidemiologic studies of VHF in humans indicate that infection is not readily transmitted from person to person by the airborne route (*1,2*). Airborne transmission involving humans has never been documented and is considered a possibility only in rare instances from persons with advanced stages of disease (e.g., one patient with Lassa fever who had extensive pulmonary involvement may have transmitted infection by the airborne route) (*3*). In contrast, investigation of VHF in nonhuman primates (i.e., monkeys) has suggested possible airborne spread among these species (*4–7*). Despite uncertainties regarding the applicability to humans of data regarding airborne transmission in nonhuman primates, such information must be considered in the development of infection-control precautions because information regarding exposure and transmission in humans is limited.

The risk for person-to-person transmission of hemorrhagic fever viruses is highest during the latter stages of illness, which are characterized by vomiting, diarrhea, shock, and often hemorrhage. VHF infection has not been reported in persons whose contact with an infected patient occurred only during the incubation period (i.e., be-

Notice to Readers — Continued

fore the patient became febrile; the incubation period ranges from 2 days to 3 weeks, depending on the etiology of the VHF [*1*]). In the 1995 Zaire outbreak, some instances of Ebola virus transmission within a few days after onset of fever were reported; however, other symptoms in the source patients and the level of exposure to body fluids among these secondary cases were unknown (CDC, unpublished data, 1995). In studies involving three monkeys experimentally infected with Ebola virus (Reston strain), fever and other systemic signs of illness preceded detection of infectious virus in the pharynx by 2–4 days, in the nares by 5–10 days, in the conjunctivae by 5–6 days, and on anal swabs by 5–6 days (P. Jahrling, U.S. Army Medical Research Institute of Infectious Diseases, unpublished data, 1995).

Reporting

All suspected cases of infection with Ebola virus and other hemorrhagic fever viruses should be reported immediately to local and state health departments and to CDC (telephone [404] 639-1511; from 4:30 p.m. to 8 a.m., telephone [404] 639-2888). Specimens for virus-specific diagnostic tests should be sent to CDC as rapidly as possible according to instructions provided when contact is made. General information regarding Ebola virus infection is available through the CDC Ebola Hotline (telephone [800] 900-0681).

Recommendations

The following recommendations apply to patients who, within 3 weeks before onset of fever, have either 1) traveled in the specific local area of a country where VHF has recently occurred; 2) had direct contact with blood, other body fluids, secretions, or excretions of a person or animal with VHF; or 3) worked in a laboratory or animal facility that handles hemorrhagic fever viruses. **The likelihood of acquiring VHF is considered extremely low in persons who do not meet any of these criteria.** The cause of fever in persons who have traveled in areas where VHF is endemic is more likely to be a different infectious disease (e.g., malaria or typhoid fever); evaluation for and treatment of these other potentially serious infections should not be delayed.

1. Because most ill persons undergoing prehospital evaluation and transport are in the early stages of disease and would not be expected to have symptoms that increase the likelihood of contact with infectious body fluids (e.g., vomiting, diarrhea, or hemorrhage), universal precautions are generally sufficient (*8*). If a patient has respiratory symptoms (e.g., cough or rhinitis), face shields or surgical masks and eye protection (e.g., goggles or eyeglasses with side shields) should be worn by caregivers to prevent droplet contact (*8*). Blood, urine, feces, or vomitus, if present, should be handled as described in the following recommendations for hospitalized patients.
2. Patients in a hospital outpatient or inpatient setting should be placed in a private room. A negative pressure room is not required during the early stages of illness, but should be considered at the time of hospitalization to avoid the need for subsequent transfer of the patient. Nonessential staff and visitors should be restricted from entering the room. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure to blood and other body fluids, secretions, and excretions. All persons entering the patient's room should wear gloves and gowns to prevent contact with items or environmental surfaces that may be soiled. In addition, face shields or surgical masks and eye protection

Notice to Readers — Continued

(e.g., goggles or eyeglasses with side shields) should be worn by persons coming within approximately 3 feet of the patient to prevent contact with blood, other body fluids, secretions (including respiratory droplets), or excretions. The need for additional barriers depends on the potential for fluid contact, as determined by the procedure performed and the presence of clinical symptoms that increase the likelihood of contact with body fluids from the patient (*8*). For example, if copious amounts of blood, other body fluids, vomit, or feces are present in the environment, leg and shoe coverings also may be needed. Before entering the hallway, all protective barriers should be removed and shoes that are soiled with body fluids should be cleaned and disinfected as described below (see recommendation 6). An anteroom for putting on and removing protective barriers and for storing supplies would be useful, if available (*1*).

3. For patients with suspected VHF who have a prominent cough, vomiting, diarrhea, or hemorrhage, additional precautions are indicated to prevent possible exposure to airborne particles that may contain virus. Patients with these symptoms should be placed in a negative-pressure room (*9*). Persons entering the room should wear personal protective respirators as recommended for care of patients with active tuberculosis (high efficiency particulate air [HEPA] respirators or more protective respirators) (*9*).
4. Measures to prevent percutaneous injuries associated with the use and disposal of needles and other sharp instruments should be undertaken as outlined in recommendations for universal precautions (*8*). If surgical or obstetric procedures are necessary, the state health department and CDC's National Center for Infectious Diseases, Hospital Infections Program (telephone [404] 639-6425) and Division of Viral and Rickettsial Diseases (telephone [404] 639-1511; from 4:30 p.m. to 8 a.m., telephone [404] 639-2888) should be consulted regarding appropriate precautions for these procedures.
5. Because of the potential risks associated with handling infectious materials, laboratory testing should be the minimum necessary for diagnostic evaluation and patient care. Clinical laboratory specimens should be obtained using precautions outlined above (see recommendations 1–4 above), placed in plastic bags that are sealed, then transported in clearly labeled, durable, leakproof containers directly to the specimen handling area of the laboratory. Care should be taken not to contaminate the external surfaces of the container. Laboratory staff should be alerted to the nature of the specimens, which should remain in the custody of a designated person until testing is done. Specimens in clinical laboratories should be handled in a class II biological safety cabinet following biosafety level 3 practices (*10*). Serum used in laboratory tests should be pretreated with polyethylene glycol *p*-tert-octylphenyl ether (Triton® X-100)*; treatment with 10 µL of 10% Triton® X-100 per 1 mL of serum for 1 hour reduces the titer of hemorrhagic fever viruses in serum, although 100% efficacy in inactivating these viruses should not be assumed. Blood smears (e.g., for malaria) are not infectious after fixation in solvents. Routine procedures can be used for automated analyzers; analyzers should be disinfected as recommended by the

*Use of trade names and commercial sources is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Notice to Readers — Continued

manufacturer or with a 500 parts per million solution of sodium hypochlorite (1:100 dilution of household bleach: ¼ cup to 1 gallon water) after use. Virus isolation or cultivation must be done at biosafety level 4 (*10*). The CDC mobile isolation laboratory is no longer available (*1*).

6. Environmental surfaces or inanimate objects contaminated with blood, other body fluids, secretions, or excretions should be cleaned and disinfected using standard procedures (*8*). Disinfection can be accomplished using a U.S. Environmental Protection Agency (EPA)-registered hospital disinfectant or a 1:100 dilution of household bleach.
7. Soiled linens should be placed in clearly labeled leak-proof bags at the site of use and transported directly to the decontamination area. Linens can be decontaminated in a gravity displacement autoclave or incinerated. Alternatively, linens can be laundered using a normal hot water cycle with bleach if universal precautions to prevent exposures are precisely followed (*8*) and linens are placed directly into washing machines without sorting.
8. There is no evidence for transmission of hemorrhagic fever viruses to humans or animals through exposure to contaminated sewage; the risk of such transmission would be expected to be extremely low with sewage treatment procedures in use in the United States. As an added precaution, however, measures should be taken to eliminate or reduce the infectivity of bulk blood, suctioned fluids, secretions, and excretions before disposal. These fluids should be either autoclaved, processed in a chemical toilet, or treated with several ounces of household bleach for ≥5 minutes (e.g., in a bedpan or commode) before flushing or disposal in a drain connected to a sanitary sewer. Care should be taken to avoid splashing when disposing of these materials. Potentially infectious solid medical waste (e.g., contaminated needles, syringes, and tubing) should either be incinerated or be decontaminated by autoclaving or immersion in a suitable chemical germicide (i.e., an EPA-registered hospital disinfectant or a 1:100 dilution of household bleach), then handled according to existing local and state regulations for waste management.
9. If the patient dies, handling of the body should be minimal. The corpse should be wrapped in sealed leakproof material, not embalmed, and cremated or buried promptly in a sealed casket. If an autopsy is necessary, the state health department and CDC should be consulted regarding appropriate precautions (*1*).
10. Persons with percutaneous or mucocutaneous exposures to blood, body fluids, secretions, or excretions from a patient with suspected VHF should immediately wash the affected skin surfaces with soap and water. Application of an antiseptic solution or handwashing product may be considered also, although the efficacy of this supplemental measure is unknown. Mucous membranes (e.g., conjunctiva) should be irrigated with copious amounts of water or eyewash solution. Exposed persons should receive medical evaluation and follow-up management (*1*).

Reported by: Hospital Infections Program, Div of Viral and Rickettsial Diseases, and Div of Quarantine, National Center for Infectious Diseases; Office of the Director, National Institute for Occupational Safety and Health; Office of Health and Safety, CDC.

Notice to Readers — Continued

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Notice to Readers

Prevention 96 Conference: Prevention for All — Challenges, Opportunities, and Strategies

Prevention 96, the 13th annual national preventive medicine meeting, will be sponsored by the American College of Preventive Medicine and the Association of Teachers of Preventive Medicine in collaboration with CDC and other national health agencies in Dallas, Texas, March 23–26, 1996. The conference will explore challenges, opportunities, and strategies for preventive medicine in the health-care system. Information on registration and submission of abstracts is available from the Meetings Manager, Prevention 96, 1660 L Street, N.W., Suite 206, Washington, DC, 20036-5603; telephone (202) 466-2569.

Erratum: Vol. 44, No. SS-2

In the *CDC Surveillance Summaries*, on page 29 of the report titled "Abortion Surveillance—United States, 1991," the ninth footnote to Table 3 should read: ***>100 abortions per 1,000 women 15–44 years of age.

Erratum: Vol. 44, No. 23

In the article "Implementation of Health Initiatives During a Cease Fire—Sudan, 1995" one of the areas in Figures 1 (page 434) and 2 (page 435) was mislabeled. In Figure 1, the area labeled "Red Sea" should have been labeled Red Sea state. In Figure 2, the area labeled "Red Sea" should not have been labeled.

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DALLAS COUNTY HOSPITAL DISTRICT

SPECIAL PATHOGEN INFECTION CONTROL PLAN

Table of Contents

Developed May 19, 1995 by Special Pathogen Management Team
Approval June 21, 1995 Infection Control Committee

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DALLAS COUNTY HOSPITAL DISTRICT

SPECIAL PATHOGEN INFECTION CONTROL PLAN

POLICY: Patients suspected or diagnosed with Special Pathogens will be will be cared for in/by Dallas County Hospital District (Parkland) facilities, staff and physicians according to the elements included in this plan and procedure.

Management of special pathogens will depend upon the means of transmitting the disease to other people in accord with procedures developed by the CDC (Centers for Disease Control) (see APPENDIX VI).

The Infection Control Team will coordinate the management of patients with special pathogens. The CDC Team will prevail when on site.

Contact tracing is the responsibility of the Dallas County Health Department or the CDC; Parkland staff will cooperate and assist with the process. (see APPENDIX V).

Registering patients admitted with Special Pathogens will be managed in a special CDC account. See APPENDIX VII *to be written

PURPOSE: To contain and prevent the spread of highly transmissible organisms (special pathogens).

DEFINITIONS:

Special Pathogens are microorganisms with a high potential for serious disease, morbidity and mortality. They are presently endemic or epidemic outside the USA and could be imported into this country. They are readily transmitted by contact with blood and body fluids (Viral Hemorrhagic Fever) or by airborne means (Pneumonic plague) or by droplets from the respiratory tract (Diphtheria-pharyngeal).

Special Pathogens include (but are not limited to) organisms which cause the following diseases:

Viral Hemorrhagic Fever (eg. Lassa, Ebola, Marburg, Crimean-Congo viruses)

Pneumonic Plague

Diphtheria -pharyngeal

CRITERIA:

1. Patients who are suspected of incubating or having a Special Pathogen must immediately be isolated.
   A. Those who are very ill should be placed in Strict Isolation in the MICU in a Negative Air pressure room with an anteroom.
   B. Those who do not require intensive care: Strict Isolation on 9E.

2. Brief Description of Entry: Upon notification or diagnosis of an incoming patient/suspect case or contact, the following procedure will be used.
   The ED Supervisor will contact:
   (1) the Infection Control Team (who will activate their chain of contacts; at least 1 I.C.Nurse will go directly to the hospital.)
   (2) the MICU Charge nurse (who will prepare for Isolation in the unit)
   (3) Infectious Disease attending

3. Upon recognition of symptoms/suspicion of a Special Pathogen in-house:
   A. The Charge Nurse of the unit and/or physician making the diagnosis will alert:
      (1) Chairman Infection Control Committee/ Chief of Infectious Disease
      (2) Infectious Disease Attending and Fellow on call.
      (3) Infection Control (IC) Team member by page
      (4) Medical Director of the MICU or unit where patient assigned.
      (See Communication List APPENDIX I.)
   B. Infection Control Team responsibilities are:
      (1) Immediately communicate with the ID Chair or Attending
      (2) At least one member of the IC Team will be available to the hospital at all times (until/unless relieved by the CDC).
      (3). Assess status of the patient and determine placement in MICU or 9E.
      (4). Notify the following: Dallas County Health Dept.Epidemiologist, the Dallas County Health Department, the CDC, Administration, Security and Public Relations dept/delegate.
      (5) Request immediate verification of negative air pressure from Engineering for the room(s) selected.
      (6) Supervise the isolation of the patient.
   C. Place Patient in Strict Isolation in a Negative air pressure room with an anteroom.
   D. Caregivers should be minimized in number.
   E. Security (Department of Public Safety) responsibilities:
      (1) Provide officer(s) at Administration, the unit and/or patient's room.
      (2) Provide a secure elevator and escort for transport through the hospital.
      (3) Cordon off areas as necessary for press and to provide security for the other patients at Parkland.
      (4) Provide security for the CDC containment unit as appropriate.

   F. Communication
      (1) All communication with the media will be handled by the Public Relations Dept.
      (2) Administration will issue statement(s) for DCHD and Medical Staffs awareness.

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PROCEDURE FOR STRICT ISOLATION (SPECIAL PATHOGEN)

POLICY: Suspected or known persons who have Special Pathogens will be placed in rooms with negative air pressure and an anteroom and cared for by staff using Strict Isolation procedures.

The exact procedures will vary depending on the mode of transmission and the incubation of the disease.

DEFINITIONS:

Special Pathogens: Certain diseases which are readily transmitted, have the ability to cause outbreaks of illness, or have high morbidity and/or mortality.

Examples include:

--Diphtheria pharyngitis
--Pneumonic plague
--Viral Hemorrhagic Fever (VHF) includes Lassa, Marburg and Ebola and Crimean-congo viruses)

Strict Isolation: Procedure details are listed. Those which differ from the standard are indicated by specific disease. (See grid of diseases, incubation, requirements etc. APPENDIX IV)

Phenolic disinfectant (>0.5%): Phenexcel disinfectant (1 oz to 1 gallon of water.) Available from the Infection Control Team only. Do not use Wexcide.

Isolation tape: Special tape for labeling trash and reusable equipment. Available from Infection Control Team only.

PROCEDURE:

1. Notification: When notified in advance of the patient's arrival, the patient should be taken directly to the MICU isolation room or other designated room as determined by Infection Control Team designee.
   Avoid dwell time in the ED (Emergency Department) if possible since ED Isolation rooms do not have anterooms.

2. Begin Strict Isolation: negative air pressure required with anteroom.
   Engineering must verify negative air flow in the designated room.

3. Location for initial case(s)
   A. MICU Isolation room WITH anteroom
   B. Additional case placement will be in area(s) which profides patient support and minimizes contact with other patients/visitors.

4. Signs: Post STRICT Isolation sign (see APPENDIX II) on the outer door and door from anteroom into patient room.

5. Procedure details follow guidelines by the CDC:
   VHF: - **Management of Patients with suspected Viral Hemorrhagic Fever procedures (MMWR Vol. 37; S-3, 2/26/88** (see APPENDIX VI)
   Plague: Plague (CDC) see Ref. list APPENDIX IX
   Diphtheria: Communicable Disease in Man

6. PPE: Personal Protective Equipment -Mandatory to enter room:
   A. Gowns: Disposable. Must cover neck to knees.
   B. Masks/ Goggles
   C. Gloves
   D. Shoe covers: VHF only
   E. All barriers must be removed prior to leaving room.
   F. VHF: DCHD scrub suits are to be worn; waterproof boots will be available for use as necessary.

Note: Caps not necessary.

7. Transport plan:
   A. An RN will accompany the patient in transport until patient placed into isolation..
   B. Transporters must take gown, mask and gloves with them in case there is any secretions, contact or splatter occurring during transport.
   C. The patient should be masked if possible and taken by the most direct route to the room. If the patient is intubated and being bagged there is potential airborne contamination in the immediate vicinity.
      --Preferred route is via Basement floor to elevators by Dietary Department.
      --No other patient or persons not connected with the infected patient, permitted on the elevator at the same time.
   C. Transportation of the patient will be escorted by DPS (security).

8. Caregiver staff: Attempts should be made to minimize exposure of the staff.
   A. Nursing staff will not care for other patients the same shift.
   B. Physician contacts will be minimized.
   C. A roster of caregivers will be maintained.
   D. DCHD scrub suits will be available for wear.
   E. Diphtheria: Vaccine boosters will be given as indicated by the Dallas County Health Department.

9. Soiled Linen:
   A. All soiled linen will be double-bagged out of the room. There must be no pre-sorting of laundry prior to washing.
   B. Exception: VHF: **No linens will be laundered**. Soiled Linen (cloth and/or disposable paper linens) will be discarded into the red bag trash (Infectious Waste).

10. Excretions/Secretions will be discarded in the sewer routinely.
    A. VHF: Excretions/secretions (and bath water from cleaning up secretions/excretions) will be disinfected prior to discharge in sewer.

(1) A chemical toilet will be used for all waste prior to disposal in the sewer as follows:
(2) A portable commode with liner bag in the bucket will be used.
(Use heavy duty bags from Housekeeping Supervisor: ≥ 1.5 ml)
(3) Disinfectant* will be added in equal parts to the secretions/excretions to be disinfected for 10 minutes minimum prior to discarding in the sewer *(>0.5% phenolic Phenexcel-available from Infection Control).
(4) After 10 minutes disinfection time, the contents of the bag will be flushed down the toilet, the bag discarded into the red bag trash.

11. Bathing: In-room shower or sponge bath may be performed. Drainage water is permitted to enter sewer system.

Exception:

VHF: For clean-up of secretions/excretions, bath water should be disinfected prior to discarding as above in #10.

12. Disposable items are discarded into red-bag trash:
    A. Examples of disposables include:
        -- Dishes, utensils
        -- Blood pressure cuff and stethoscope .
    B. Exceptions:
        -- Sharps ie needles, syringes, lancets, razors, etc. will be placed into sharps disposal units. These units will be red-bagged when full or at the end of Isolation, disinfectant added as above in 10.3 for 10 minutes, labeled Isolation, removed via "double-bag technique then microwave sterilized.
        -- Thermometer (glass) (do not use electronic): discard into Sharps containers at the end of Isolation or if broken.

13. Reusable items will be disinfected and/or gas sterilized as appropriate.
    A. Infection Control will advise re disinfecting/sterilizing.
    B. Phenexcel disinfectant will be used (1 oz to 1 gallon of water).
    C. Examples of reusables include:
        --IV pole, pump
        --BP sphygmomanometer
        --Monitors and cables
        --Instruments (must be sterilized)

14. Double-bag technique:
    A. Items removed from the room will be double bagged. The gowned/gloved person inside the room places the inner bag into a second bag held by a person outside the door maintaining the outside of the outer bag free from contamination (example: Infectious Waste in red bags to be double-bagged.)
    B. If the outside of the bag touches anything from inside the room, the outside of the bag must be disinfected with Phenexcel.
    C. Place reusable Equipment (ie instruments)in regular bags (double bag system, the outer bag labeled "ISOLATION" with Isolation tape. Infection Control will advise SPD or OR regarding disinfection and/or sterilization.
    C. All bags used in any part of double-bagging must be directly laundered (no pre-sorting) or discarded into red-bag waste.

15. Visitors will utilize the Special Pathogen precautions regarding apparel. Nursing staff will advise about precautions as appropriate.
    A. All visitation will be supervised.
    B. Exception: VHF:
        (1) Visitors are limited to direct family and/or significant other.
        (2) Visitation should be limited; depends on the patient's status..
        (3) If confirmed VHF, it is necessary to restrict visitation to indirect video and telephone visitation from the anteroom (MICU).
        Note: other locations (i.e. 9E), visitation mechanisms will be set up as needed.

16. Cleaning the room:
    A. Qualified staff from Environmental Services will clean the room daily and as necessary using standard cleaning techniques. Environmental Services Management will provide supervision of cleaning procedures/process.
    B. **VHF Procedure**: Materials will remain in the room (bucket, mop, Phenexcel disinfectant). Mop heads will be discarded into red-bag trash when soiled.
    C. Terminal Cleaning:
        (1) All linens removed and laundered (including curtains).
        (2) All surfaces to be cleaned (not ceilings). Standard disinfectant used. **Exception: VHF**, use Phenexcel, available from Infection Control.
        (3) Mattress and pillow must be visually inspected and discarded if any tears in the surface coverings.
        (4) Sharps containers will be discarded (whether or not filled).
        (5) Disposable glove containers emptied (remainder discarded) and units disinfected.
        (6) Residual soaps, paper towels and toilet paper will be discarded.

14. Specimens sent to Lab will be handled with great care.
    A. Lab tests will be limited as much as possible.
    B. If Lab specimens are sent to the lab or to be sent to the CDC specific double-bagging and/or double-containerizing along with disinfection of the internal container.
    Transport to the lab must be by 1 person who directly gives it to a designated person in the lab.
    C. **See details for all lab specimens in APPENDIX IV**.

15. Post-mortem:
    A. Autopsy considered with great caution.
    B. VHF:
        (1) A waterproof shroud/body bag must be used.
        (2) No viewing of the body after placement in special body bag
        (3) The outside of the bag will be clearly labeled "Isolation."
        (4) NO embalming may occur; cremation or rapid burial necessary.
        (5) Disposal of corpse: Contact Dr. Burns, Coroner &/or DC Health Dept. before and about disposal.

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APPENDIX I

SPECIAL PATHOGEN I.C.PLAN: COMMUNICATION LIST

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Dallas County Health Dept: Tel: ..... Tel: 528-6125
(Night or day)
Charles Haley, MD, Epidemiologist ..... Infection Control
(He will notify TDH)

Infection Control Team:
James P. Luby, MD, Chairman Infection Control Committee Tel : 648-3480
Barbara Moody, Manager Infection Control: 590-8429 Ho: 247-8709 Beeper 786-8192
Laura Thurman, Infection Control Coordinator Beeper 786-8196
Patti Grant, Infection Control Coordinator Beeper 786-8185

Infectious Disease Attending: .....Tel: 648-3480
Check with Page Operator

Public Relations
Evening nights call .....Beeper 786-8333

Administration ..... Tel: 590- 8011
Administrator On Call.....Check with Page Operator for Beeper number

DPS (Security):
Shift supervisor..... Tel: 590-8496

STRICT ISOLATION - SPECIAL PATHOGENS

1. **Negative Air Pressure Room with Anteroom**

2. **To enter the room, all persons must wear:**
   - **masks/goggles**
   - **gowns**
   - **gloves**
   - **shoe covers**

   - If actively bleeding, wear D.C. H.D. scrub suits/shoe boots

3. **Hands must be washed after touching the patient or potentially contaminated articles and before taking care of another patient.**

4. **Articles contaminated with infective material must be discarded into red bag waste.**

5. **Soiled linens must be discarded into red bag waste. (including scrubs)**

6. **Reusable equipment must be disinfected with Phenexcel* (1 oz./gallon water).**

7. **Use Phenexcel* for all cleaning, mopping.**

***Infection Control Department will provide**

APPENDIX VII

SPECIAL PATHOGEN

REGISTERING / ADMITTING PROCEDURE (* to complete)

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1. A special account will be utilized for admissions meeting the Special Pathogen Criteria. It will be coded/targeted for CDC.

2. Reimbursement procedures will be detailed in this protocol; Business Services will be copied as well.

3. Elements covered for care of such patients include:
   Lab work relevant to the disease
   Basic Hospital charge for room including ICU
   Isolation costs
   Ventilator costs
   Blood transfusions (including Platelets, other blood components)

   Determine the standard of care for VHF: To what limits does medical care go?)
   Dialysis
   Cardiac monitoring
   Neurological interventions or diagnostic procedures
   Physiotherapy
   Occupational Therapy
   Respiratory Therapy
   EKG's
   Other:
   MRI
   CAT scan
   Enteral feedings
   G/J-Tube insertions
   Lab testing: what limits are there?
   Elective surgery
   Resuscitation procedures
   Autopsy fees

4. Reimbursement fees not covered in care of patients with Special Pathogens include: (to obtain list from CDC)

APPENDIX IIIA

SPECIAL PATHOGEN: DEPARTMENT SPECIFIC DETAILS

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NOTE: **Departments where patient contact does not occur presently will not contact patients with Special Pathogens.**

DEPARTMENT	CONTACT YES - X/P Possible Blank = No Contact	DETAILS OF INTERACTION WITH THE PATIENT/ROOM
Admitting		Communicate via family members and nursery
Anesthesia		
Cardiac Labs		Contact possible, not expected
COPC		Possibly in a community exposure
Dietetic		Communicate via nursing staff
Discharge		
EEG	P	Possible
EKG	P	Possible
Engineering (Maintenance)	P	Only as necessary to repair utilities. Direct supervision by Infection Control or Unit Manager.
Food Service		No patient contact. Disposable dishes, trays delivered to unit. Nothing returned to kitchen.
GI Lab	P	Possible Contact
Labor & Delivery Vaginal C-Section	P	Private Isolation Room. Use delivery bed. Use OR or bring special HEPA filter unit to L&D.
Nursery NNICU		
Nursing MICU 9E ER Other	 X X X X	 Most likely contact Most likely contact Most likely contact As Needed
OPC		
Operating Room		Use HEPA Filter
Patient Relations		Only if interpreters needed. Use closed circuit TV or telephone interaction if possible. If needed to visit room, direct supervision by IC or Unit Manager.
Pharmacy		
PM&R	P	Indirect, consultation role possible
Public Relations		Involved but not contact necessary
Radiology CT, MRI, Nuclear	P Not anticipated	None except for portble x-ray. Portable X-ray machine will be covered as much as possible prior to entry; exposed areas will be physically disinfected upon leaving the room. Phenexcel will be used.
Respiratory/Pulmonary	X	Possible contact: Ventilator Use
Safety		
Security	P	Indirect(Distant)during transport
Social Service		Preferred to communicate from outside the room. If necessary to visit in person, supervision by IC.
Volunteers		No contact with patient or room.

APPENDIX IV

SPECIAL PATHOGEN: LAB SPECIMEN HANDLING

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APPENDIX V

SPECIAL PATHOGEN: CONTACT TRACING

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1. Infection Control, Infectious Disease Physicians or Dallas County Health Dept. will work together to identify close contacts.
2. Definition of Contact: Those who:
   A. Took care of the infected person (prior to start of Isolation)
   B. Were intimately involved with the infected person prior to infectious stage or symptoms, whichever came first.(* intimate: i.e. lives with, shares room, bed, eating or drinking utensils).
   C. Determine quarantine period based on the incubation and likely exposure date.
      (1) **VHF:**
         a. Quarantine for a 3 week surveillance period. (2-21 day incubation). Take and record temperature
         b. VHF Contact: Close contacts i.e. hugging, kissing, shaking hands, handling lab specimens, performing nursing care or living with the patient.
         c. Symptoms: VHF cannot transmit until symptomatic.
            -- Temperature of $\geq$ 101 d. F., headache, malaise, vomiting or active bleeding, consider a case until it is ruled out.
         d. If symptoms appear, isolate promptly (Strict Isolation)
      (2) **Pneumonic plague:** Additional details provided by Infection Control at the time of suspicion of identification of pneumonic plague.
         a. Contacts are those living in the same household or who had face to face contact with a case.
         b. Quarantine ie place under surveillance for 7 days providing antibiotics taken by contacts.
         c. If antibiotics refused, place in Strict Isolation Quarantine for 7 days.
      3) **Diphtheria**: Additional details provided by Infection Control at the time of diphtheria suspicion/identification.
         a. Culture nose and throat. If Diphtheria cultures positive contacts must be treated with antibiotics.
         b. Quarantine for 7 days
         c. If handles food or work with children, exclude from work until proven culture negative.
4. Determine quarantine site/location:
   - A. Ensure that all contacts will be observed for symptoms of disease.
   - B Instruct caregivers (family or others) who will care for the exposed (quarantined) person in the following:
   - (1) symptoms of the disease
   - (2) practices to prevent transmission
5. A record of all Parkland identified contacts will be maintained by Infection Control and shared with the Dallas County Health Department or the CDC as appropriate.

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disease prevention news

DPN

Vol. 55, No. 12 June 12, 1995

Zaire is Hot Again - How Cool is Texas?

A laboratory technician in Kikwit, a city about 240 miles east of Zaire's capital, was hospitalized for fever and bloody diarrhea on April 4, 1995. A few days after the patient underwent surgery for a presumptive perforated bowel, hospital personnel began having similar symptoms. One of the ill employees was transferred to another hospital about 75 miles away. Personnel who cared for the transferred patient at the second hospital had onset of similar symptoms on April 20.[1]

Because Ebola virus was suspected as the cause of illness, blood samples were obtained from fourteen of the earliest suspected case-patients and shipped to the Centers for Disease Control and Prevention (CDC). All fourteen samples were positive for Ebola virus. Gene sequencing suggests that the virus responsible for this outbreak is an Ebola subtype closely related to the one that caused an outbreak in Zaire in 1976.[1] As of June 1, 211 suspected cases have been identified, and 164 (78%) of the patients have died.[2]

Background

Ebola viral hemorrhagic fever (VHF) is one of several VHFs caused by enveloped RNA viruses belonging to four families: *Filoviridae; Flaviviridae; Bunyaviridae;* and *Arenaviridae.* Ebola and Marburg viruses are rare and cause clinically indistinguishable, severe hemorrhagic fevers. Because of their filamentous appearance on electron microscopy, these viruses are classified as filoviruses in the family *Filoviridae.* Other better known hemorrhagic fevers are dengue, yellow fever, and Omsk hemorrhagic fever *(Flaviviridae);* hemorrhagic fever with renal syndrome (HFRS), Crimean-Congo hemorrhagic fever, and Rift Valley fever *(Bunyaviridae);* and Lassa and Argentine hemorrhagic fever *(Arenaviridae).*

The intermediate arthropod and rodent hosts for the viral agents of these better known VHFs have been elucidated.[3] In contrast, very little is known about the natural reservoirs for Ebola and Marburg viruses. While most viral agents of hemorrhagic fever are not transmitted person-to-person, Ebola, Marburg, and Lassa viruses are notable for their ability to be spread this way.[3,4] Additional information on transmission is provided later in this report.

The incubation period for Ebola hemorrhagic fever ranges from 2 to 21 days, with an average of 5 to 10 days. The illness is characterized by an abrupt onset of high fever, chills, and headache followed by general malaise, myalgia, joint pain, anorexia, nausea, and abdominal pain. Vomiting, watery diarrhea, pharyngitis, and chest pain often occur, and conjunctivitis is common. A maculopapular rash may appear between days 5 and 7 and is most marked on the buttocks, trunk, and outer aspects of the upper arms. Liver function is usually impaired by the second week of illness. Disseminated intravascular coagulation (DIC), a major feature of the disease, is often accompanied by gastrointestinal hemorrhage, as well as bleeding from injection sites, skin, orifices, and internal organs.[4-7]

Patients typically have thrombocytopenia, lymphopenia, elevated serum transaminases (AST > ALT), and proteinuria.[3,4] Seroconversion occurs between days 8 and 12. Currently, an IgG ELISA procedure, done at CDC, is considered the most reliable antibody test. Cultures, which should be attempted only in a biosafety level 4 (BSL4) laboratory, are positive during the acute stage of illness.[6]

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Ebola Outbreaks

Prior to 1995, three separate Ebola outbreaks occurred in Africa: in northwestern Zaire in 1976[8] and in southwestern Sudan in 1976[9] and 1979.[10] In the Zairean outbreak, 280 of 318 patients died, for a case-fatality rate of 88%. In Sudan's 1976 outbreak, 151 of 284 patients died, for a case-fatality rate of 53%.[8,9] Twenty-two of 34 (65%) patients died in the 1979 outbreak in Sudan.[10] The viruses that caused the Sudanese and Zairean outbreaks are genetically distinguishable and are referred to as the Ebola-Sudan and Ebola-Zaire subtypes.[6]

In 1989 and 1990 a new subtype, Ebola-Reston, appeared . . . in Texas.

In 1989 and 1990 a new subtype, Ebola-Reston, appeared unexpectedly in primate quarantine facilities in Virginia, Pennsylvania, and Texas. In the Virginia outbreak, graphically described in the recent best-seller *The Hot Zone*,[11] this filovirus caused a high mortality rate in quarantined macaque monkeys. All the animals in the facility were euthanitized.[12] Concurrent with the Virginia outbreak, a similar outbreak occurred in animals quarantined in Pennsylvania.[13]

On February 23, 1990 Texas Department of Health (TDH) staff were notified that macaques from the Philippines were dying at a primate quarantine facility in South Texas, and that an Ebola-like filovirus had been cultured from the liver of a dead animal.[14] On arrival in early February, 50 animals had been placed in each of two rooms in one quarantine building. In one room the outbreak was allowed to run its course; in the second, the animals were euthanitized when it became apparent that few would survive. The attack rate in the first room was 96% and the fatality rate was 87%.

The definitive means of transmission of Ebola, Marburg, and Lassa viruses have not been unequivocally established.

Transmission of Filoviruses

The definitive means of transmission of Ebola, Marburg, and Lassa viruses have not been unequivocally established. However, epidemiologic data from outbreaks of VHFs due to these viruses provide compelling evidence of certain means of spread. While person-to-person transmission of Ebola, Marburg, and Lassa viruses is well documented, exposure is most likely to occur through direct contact with infected blood, organs, or secretions (including semen). Although respiratory transmission through droplet nuclei has not been documented in patient care settings, aerosol transmission associated with close personal contact cannot be absolutely discounted.

Laboratory transmission of filoviruses was documented as early as 1967 when outbreaks of Marburg virus occurred concurrently in laboratories in Germany and Yugoslavia. In these outbreaks, 25 of 31 persons were infected through contact with tissue from African Green monkeys from Uganda. Six were infected through person-to-person transmission, and seven persons died.[4] Following these outbreaks, strict 31-day quarantines for imported monkeys were instituted in the U.S. as a precautionary measure.[13]

There were 29 secondary cases in the 1979 Ebola-Sudan outbreak. Twenty-four of the 29 case-patients had provided nursing care to other patients with Ebola, three had had non-nursing direct physical contact with patients, and the contact history for two was unknown.[10] These data suggest that a high rate of person-to-person transmission of the Ebola-Sudan virus is most likely among those who have direct physical contact with infected persons.

Four persons exposed to the monkeys in Virginia in 1989 seroconverted, but none exhibited symptoms consistent with disease.[15] In the South Texas outbreak in 1990, none of the 16 persons exposed to the animals directly or to their blood or secretions became symptomatic or seroconverted. These data suggest that, while capable of human infectivity, the Ebola-Reston virus may not cause serious human disease.

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Viral hemorrhagic fever cases with potential for person-to-person spread have been diagnosed in the U.S. only rarely. In February 1989 Lassa fever was diagnosed in a Chicagoan who had traveled to Nigeria to attend his mother's funeral. Two days after returning to Chicago the man was hospitalized for fever, headache, pharyngitis, and myalgias; he died two weeks later.[16] Sabia virus *(Arenaviridae)* was first isolated from a woman who died of a hemorrhagic fever in Brazil in 1990.[17] In August 1994, a case of Sabia virus infection was reported to the Connecticut Department of Public Health and Addiction Services. The patient was a virologist exposed to the virus during a laboratory accident.[18] No secondary cases occurred among persons exposed to the patients in either Chicago or Connecticut.[16,18] Neither of the U.S. cases of VHF have been considered autochthonous.

Recommendations

As a result of stringent safety precautions for laboratories and healthcare facilities in the U.S., the risk of contracting a VHF in this country remains extremely low. However, an estimated 130,000 U.S. citizens travel to sub-Saharan Africa each year.[19] The current outbreak of Ebola in Zaire, the imported case of Lassa fever in Chicago, the Sabia virus infection in Connecticut, and the importation of monkeys infected with Ebola-Reston virus underscore the importance of patient **travel and occupational histories.** Because foreign travel is common, and occupational exposure in this country is possible, it may be appropriate to consider "zebras at the sound of hoofbeats," even in Texas.

Patient Management Guidelines

- Consider a VHF in the differential diagnosis of an acutely ill person with fever, prostration, and a history of recent travel to an area known to be endemic or epidemic for VHFs. However, be aware that other diseases such as **malaria, invasive meningococcal disease, and typhoid fever** are much more likely to cause fever in a traveler. Persons who work with exotic animals or their tissues and persons working in viral research laboratories may also be at risk for VHFs.

Persons who work with exotic animals . . . may also be at risk for VHFs.

- Place patients with suspected VHFs in rooms not directly accessible from common area hallways, if possible. Ideally, these rooms should have an anteroom so medical staff can don appropriate barrier items before entry into the patient's room. Although respiratory transmission has never been demonstrated, placing the patient in a negative pressure room vented directly to the outside via the roof is an added precaution.

- Rigorously observe universal precautions for blood and body secretions; use gloves, gowns, shoe covers, and masks. These precautions are mandatory. If available, use full-face shields and particulate respirators approved by the National Institute for Occupational Safety and Health (NIOSH) for added protection.

- Avoid using glass items and equipment for patient care. Whenever possible, find appropriate substitute materials (e.g., plastic) for glass items. **Do not** collect blood specimens with a needle and syringe. Use glass Vacutainer® tubes only if plastic ones are not available. **Do not** recap needles! Prior to disposal, place used needles in a chemical disinfectant in a sharps container (see Environmental Infection Control on page 4).

As of June 1, 211 suspected cases have been identified, and 164 (78%) of the patients have died.

- Avoid creating aerosols during any procedure involving patient blood or body secretions.

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Collection and Management of the Patient's Specimens

- Keep manipulation of clinical specimens to a minimum.
- Prepare thick and thin smears for malaria testing only under a laminar flow hood. Use blood treated with the anticoagulant EDTA. Make the smears within 30 minutes of specimen collection and allow to dry; fix thin smears in absolute methanol.
- Dilute anticoagulated blood 1:100 (v/v) with 3% acetic acid. Keep at room temperature for 15 minutes to inactivate the virus prior to measurement of WBCs.[20]
- Heat serum at 60°C for one hour to inactivate Ebola, Marburg, or Lassa viruses for safe measurement of heat-stable substances such as electrolytes, BUN, and creatinine.[20]
- Use beta-propiolactone (BPL) to inactivate these viruses for serologic tests such as antigen-capture assays, complement assays, and serum enzyme measurements. Prepare a 10% (v/v) BPL stock solution initially at 4°C to prevent loss of the active ingredient. Add this stock solution to serum until a final concentration of 0.2% BPL is reached. Let treated serum stand at 37°C for 30 minutes.[21, 22]
- Perform virus isolation only in a BSL4 containment laboratory. Package all samples for shipment in accordance with established, triple containment guidelines[23] and send to the CDC containment facilities or the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) at Fort Detrick, Maryland.

Environmental Infection Control

Covered by a protein-lipid envelope, the VHF viruses are sensitive to many readily available chemical disinfectants, including organic solvents.

- Disinfect all contaminated objects, including patient-care items and laboratory equipment, with 0.5% sodium hypochlorite (a 1:10 dilution of household bleach), 0.5% phenol with detergent, or a quaternary ammonium compound solution. Disinfectant solutions should be compatible with the surfaces to be treated. When possible, also steam sterilize, incinerate, or boil the contaminated objects.[21]
- Prior to removal, chemically disinfect gloves that have been in direct contact with the patient's blood or secretions.
- Disassemble reusable equipment properly for cleaning and disinfection; sterilize as appropriate.
- Run autoclave cycles according to times and temperatures supplied by the manufacturer.
- Perform thorough terminal disinfection of environmental surfaces. A phenolic compound or 0.5% sodium hypochlorite is adequate; formaldehyde fumigation can be considered.[21]

Notification Procedures

Physicians in Texas who suspect that they have a patient with one of the hemorrhagic fevers should first isolate the patient, then call the TDH State Epidemiologist at (800) 252-8239 (business hours) or (512) 458-7111 (nights and weekends). TDH will promptly notify

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the appropriate health authority. If a TDH physician is not available at the above numbers, the reporting physician should call the CDC Special Pathogens Branch, Division of Viral Diseases, at (404) 639-1115 (business hours) or (404) 639-2888 (nights and week-ends).

Published Guidelines

For more in-depth information regarding the containment and management of viral hemorrhagic fever, an MMWR supplement entitled *Management of Patients with Suspected Viral Hemorrhagic Fever*[24] delineates infection control procedures for either suspected or confirmed cases. Veterinarians caring for primates suspected of having hemorrhagic fevers should review the document, *Interim Guidelines for Handling Nonhuman Primates during Transit and Quarantine* [13] and consult with the CDC Special Pathogens Branch. Veterinarians also should consult with the State Epidemiologist as well. (Phone numbers are listed above.)

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Hantavirus Pulmonary Syndrome - Third Case Confirmed in Texas

The first recognized outbreak of HPS began in May 1993 in the "Four Corners" area . . .

The Texas Department of Health recently confirmed Texas' third case of hantavirus pulmonary syndrome (HPS). The patient, a 15-year-old Hispanic male from Deaf Smith County, was seen at a local emergency room on May 17 after four days of flu-like illness accompanied by nausea, vomiting, and progressive weakness. He arrived with no measurable blood pressure, barely palpable pulses, and an axillary temperature of 97.1° F. After an hour of rehydration with Lactated Ringers, he had a temperature of 102.6° F, pulse of 96, respiratory rate of 28, and a systolic blood pressure of 82 mm Hg. His heart sounded normal; his lungs were clear, although his O_2 saturation was only in the 70s. With a preliminary diagnosis of septic shock, he was given 500 cc of 5% albumin, placed on ceftriaxone, and transferred to a tertiary care hospital.

On May 18 he was tachycardic (98-170), hypotensive (palpable at 60 mm Hg systolic, rising to 80 mm Hg systolic after two liters IV fluid), and hypoxic to the point of requiring intubation. His chest x-ray showed bilateral interstitial and alveolar infiltrates consistent with adult respiratory distress syndrome (ARDS). Approximately 850 cc of serous pleural fluid was removed from the left hemithorax.

Initial clinical laboratory results showed that his creatinine level was 1.3 mg/dL, hematocrit level was 50.6%, platelet count was 61,000/cu mm, white blood cell count was 10,500/cu mm with a left shift, and coagulation times were consistent with disseminated intravascular coagulation (DIC).

Despite aggressive therapy with intubation, hemodynamic monitoring, massive doses of pressors, and a prolonged attempt at resuscitation, the patient died approximately 24 hours after his transfer. Postmortem examination revealed "heavy lungs" consistent with severe viral pneumonitis. There were 950 cc of "brownish" pleural fluid in the right hemithorax and 300 cc in the left. Frozen lung specimens, blood obtained at autopsy, and tissues in formalin were sent for laboratory analysis to detect possible hantavirus infection. The patient's serum, tested at TDH, contained hantavirus antibody.

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