CASE HISTORY: EBOLA HEMORRHAGIC FEVER IN ZAIRE, 1995

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Summary

An outbreak of Ebola hemorrhagic fever (EHF) began in the winter of 1995 in the city of Kikwit in Zaire (now the Democratic Republic of the Congo), but was not recognized until May, when serum samples were sent for diagnosis to the U.S. Centers for Disease Control and Prevention. There is no known drug treatment or vaccine for EHF, which is caused by a filovirus that is transmitted through contact with bodily fluids. By April, poorly equipped and understaffed hospitals in Kikwit and the nearby town of Mosango had become the foci for infection.

The World Health Organization assisted the Government of Zaire by coordinating a response that included sending scientists and relief workers from Belgium, France, Sweden, South Africa, and the United States to Zaire. The number of new cases dropped after the international team supplied hospital staff with protective clothing and disposable syringes. Actively finding cases, and the dissemination of health information to the local population apparently contributed to lessening the spread of disease outside of the hospital.

The outbreak affected 315 people, and had a fatality rate of 81%. Nearly every case was traced back to an infected family member, friend, or health worker who had been in direct contact with the index patient, or who had experienced a needle stab or undergone surgery. Although the index case of the outbreak was identified, the source of his infection (presumed to be an animal or insect) was not found.

During the year and a half after the outbreak ended, international projects were initiated to support ongoing EHF surveillance and to help maintain infection control practices at hospitals in the area. However, these efforts were interrupted by the civil war that is still in progress. If an outbreak of EHF occurred today in the Democratic Republic of the Congo, it might go undetected for a long period of time, either running its course unnoticed, or spreading until it could not be ignored.

Part I: A Chronological Account

An outbreak of Ebola hemorrhagic fever (EHF), a severe and often fatal viral disease,

was reported in the city of Kikwit in Zaire (now the Democratic Republic of the Congo (DRC)) in May 1995. Partly because the disease was so little known and so highly dangerous, and partly because the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), and other international partners assisted in the disease investigation, the outbreak received worldwide attention.

1. Detection

On Saturday, May 6, 1995, physicians stationed at the US and Belgian embassies in Zaire were contacted by an American doctor employed by the Chevron Company in Kinshasa, who passed reports of an unidentified, fever-causing, fatal illness in the town of Kikwit, about 250 miles from Kinshasa. Some of the victims were Italian nuns from Kikwit General Hospital. The American doctor also contacted an epidemiologist at CDC's Special Pathogens Branch in Atlanta.

According to the rumors that reached Kinshasa, hundreds or thousands of people were affected. In addition to fever and chills, the victims experienced severe headaches, weakness, and back pain, followed within a few days by abdominal pain, vomiting, and diarrhea, with blood in both vomitus and stool. A medical professor at the University of Kinshasa reported that he had observed similar symptoms during the outbreak of EHF in northern Zaire in 1976. As Kikwit is a densely populated city of about 200 000 people, that lies relatively close to Kinshasa and Brazzaville, an outbreak of EHF in Kikwit had the potential to grow into a national or international disaster.

After speaking with the doctor at Chevron, a physician at the Belgian embassy contacted Zairian health authorities and arranged for blood samples from hospitals in the area to be hand-carried to the Prince Leopold Institute of Tropical Medicine and Hygiene in Antwerp. Scientists at the Institute had helped identify Ebola virus as the causative agent of the 1976 outbreak.

However, the Institute in Antwerp no longer maintained the type of biocontainment equipment required to work safely with live Ebola virus, as the laboratory that had diagnosed EHF in the 1970s was now focused on AIDS research. The head of the Special Pathogens Branch (SPB) of CDC's National Center for Infectious Disease (NCID) spoke with a scientist from the Institute and arranged for the samples to be sent by overnight carrier from Antwerp to Atlanta. The samples arrived on Monday, May 8.

2. Diagnosis

Scientists at SPB tested the samples for evidence of infection with hemorrhagic fever viruses, such as Ebola and Crimean-Congo, using enzyme-linked immunoabsorbant assays (ELISAs) to detect viral antigens and virus-specific antibodies. On May 9, within nine hours of receiving the specimens, the laboratory found evidence of either ongoing or recent Ebola virus infection in all 14 patients tested. The results of additional assays to detect acute infection, including viral isolation and RNA analysis (see section 4.0), were consistent with the diagnosis of EHF.

These cases apparently represented infections in hospital patients, physicians, nurses,

and other hospital workers, including two Italian nuns from Kikwit General Hospital and from a hospital in the nearby town of Mosango, where one of the Kikwit nuns had been sent for care.

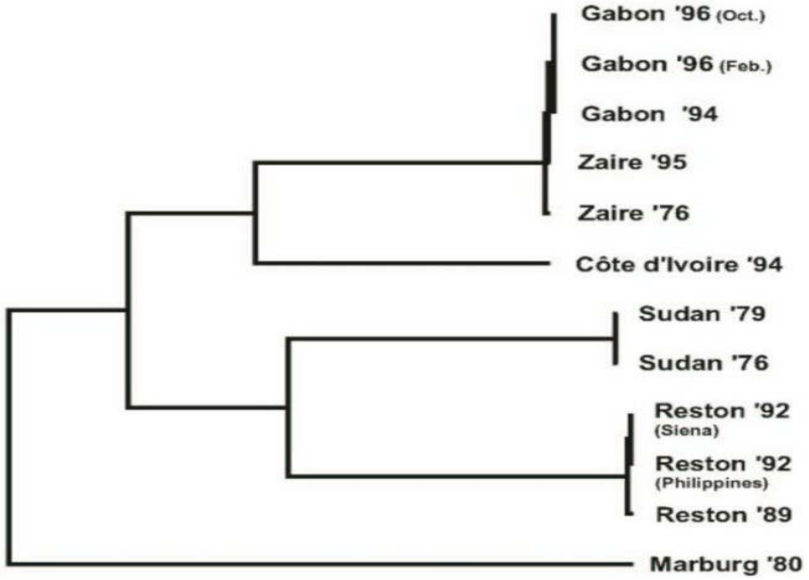
3. Background on Filoviral Diseases

There is no known drug treatment or vaccine for EHF, which is transmitted to humans from an unknown natural reservoir, as well as person-to-person through contact with infected bodily fluids, causing a fatal illness in 50-90 percent of its victims. It is caused by a filovirus, an RNA virus that resembles a long filament or thread when viewed under the electron microscope. Two filoviruses are known to be pathogenic in humans: Marburg and Ebola.

3.1 Marburg virus.

The first filoviral pathogen was identified in 1967, in Marburg, Germany, when laboratory technicians at the Behringwerke and the Paul Ehrlich Institute were exposed to infected tissues from vervet monkeys imported from Uganda. Twenty-five technicians and six of their contacts, in Marburg and Frankfurt, Germany, and Belgrade, Yugoslavia, fell ill. Seven people died. As a result of the 1967 outbreak, several countries instituted a 31-day quarantine for imported monkeys. Since then, only a few cases have been reported. In 1975, a man who had travelled in Zimbabwe fell ill with Marburg hemorrhagic fever in Johannesburg, South Africa, and infected two other people (see Section 3.2). Three additional cases of Marburg were identified in Kenya during the 1980s, two in 1980 (see Section 13.2), and one in 1987.

3.2 Ebola virus.



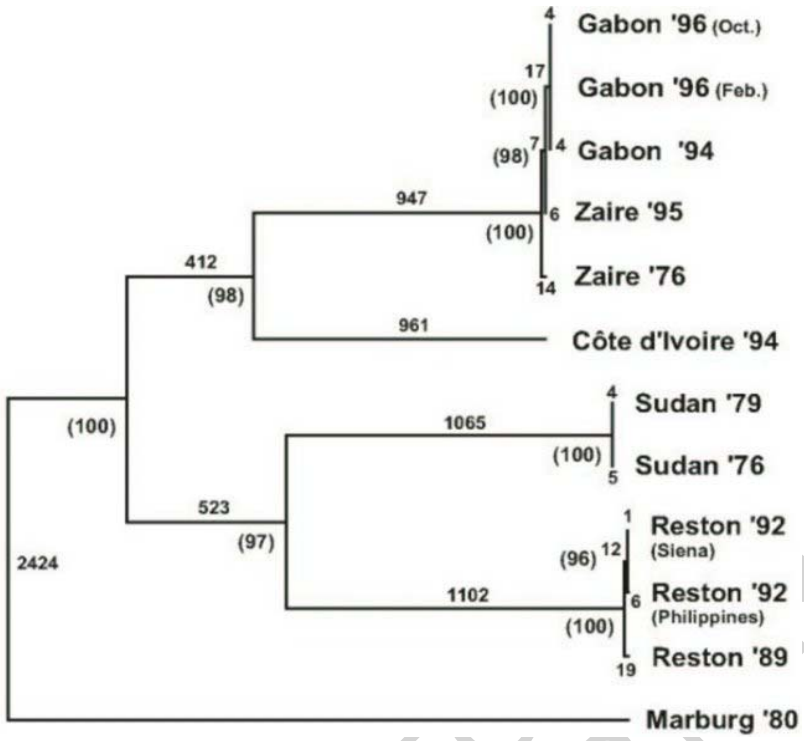


Figure 1. Phylogenetic tree showing the evolutionary relationship of Ebola viruses. Courtesy of A. Sanchez, Centers for Disease Control and Prevention; derived from: Georges-Courbot MC, Sanchez A, Lu CY, *et al.* (1997) Isolation and phylogenetic characterization of Ebola viruses causing different outbreaks in Gabon. *Emerg Infect Dis* **3**, 59-62.

Four subtypes of Ebola virus have been identified: Ebola-Zaire, Ebola-Sudan, Ebola-Cote d'Ivoire, and Ebola-Reston (see Figure 1). Ebola-Sudan and Ebola-Zaire were first isolated in 1976, following outbreaks that occurred concurrently in those two countries. In Zaire, the 1976 outbreak was centered around the small rural village of Yambuku, near the Ebola River, about 1000 kilometers north of Kikwit. In the Sudan, the outbreak occurred in the town of Maridi in a southern grasslands province. Over a two month period, Ebola-Zaire infected 318 patients, with a fatality rate of 88%, and Ebola-Sudan infected 284 people, with a fatality rate of 53%. A second, smaller outbreak of Ebola-Sudan occurred in 1979, in the same village in which it appeared in 1976. It infected about 34 people and killed two thirds of them.

No other instances of EHF (aside from a laboratory infection in the United Kingdom caused by a needle-stick) were recognized until 1994, when a Swiss researcher in Cote d'Ivoire contracted the disease while performing a necropsy on a wild chimpanzee found dead in the Tai National Forest. She was evacuated to a Swiss hospital and survived. Subtype Ebola-Cote d'Ivoire was isolated from a sample of her blood. In 1996, two EHF outbreaks occurred in different provinces of Gabon, affecting about 54 people and killing about 35. The source of these outbreaks was traced to contact with chimpanzee cadavers. As indicated in Figure 1, the isolates obtained during the outbreaks in Gabon are variants of Ebola-Zaire. Another outbreak may have occurred in Gabon two years earlier, in 1994, but was thought at the time to be yellow fever.

3.2.1 Ebola-Reston.

Ten years ago, in 1989, a simian Ebola outbreak occurred in the United States, among macaques from the Philippines that were housed in an animal quarantine facility in Reston, Virginia. Between 1990 and 1996, five additional shipments of Philippine monkeys (four to the United States and one to Italy) were associated with simian outbreaks of Ebola-Reston.

Unlike Marburg virus and the other Ebola subtypes, Ebola-Reston apparently does not cause illness in humans. Of four people in the United States and three in the Philippines who were infected (as indicated by positive serology tests), none had symptoms, although live virus was isolated from one of the U.S. cases. However, too few people were exposed to conclude with certainty that Reston virus never causes human disease.

4. Genetic characterization of the 1995 isolate of Ebola virus.

Scientists at SPB also tested the Kikwit blood samples for Ebola-specific RNA, both to confirm the diagnosis (see section 2.0) and to learn how the Kikwit Ebola strain was related to other known Ebola isolates.

The blood samples were tested by the reverse transcriptase - polymerase chain reaction (RT-PCR) method, using two sets of DNA probes. The first set was designed to detect all known filoviruses. It had been developed at CDC earlier in the year, using sequence data on the conserved portions of the polymerase genes of the 1976 Zaire and Sudan isolates, the 1967 Marburg isolate, and the 1989 Reston isolate. The second set, which was designed to detect all strains of Ebola virus, had been developed in 1994, using data on the glycoprotein genes of the two 1976 isolates and the 1994 Cote d'Ivoire isolate. Amplified gene fragments of predicted sizes were detected in blood samples from 12 of the 14 patients from Kikwit and Mosango.

Identical copies of a 528-base-pair glycoprotein gene fragment were generated from four different blood samples. The glycoprotein gene fragment differed from the equivalent fragment in the 1976 Yambuku isolate by only 4 base pairs: less than 1%. A 350-base-pair polymerase gene fragment was amplified from the same four patients and found to be identical to the equivalent sequence in the Yambuku isolate. The researchers concluded that the same viral subtype was responsible for the 1995 and 1976 outbreaks of Ebola fever in Zaire. Further confirmation was obtained three days later, when the complete sequence of the glycoprotein genes from the Kikwit and Yambuku isolates were compared and found to be 98.5% identical.

5. Mobilization of an International Outbreak Response

On May 10, 1995, CDC relayed the diagnosis of Ebola hemorrhagic fever to the US Embassy in Kinshasa and to the WHO in Geneva, both of whom notified the Zairian Ministry of Health. On the following day, the Government of Zaire quarantined the Kikwit area and closed the road leading from Kinshasa to Bandundu Province, where Kikwit is located. The U.S. Embassy declared the outbreak a disaster, and the Office of Foreign Disaster Assistance of the U.S. Agency for International Development

(OFDA/USAID) authorized the payment of $25,000 to local non-governmental organizations for the purchase and transport of disposable protective clothing, plasma, body bags, and essential medicines and supplies. Although air as well as road traffic was restricted, the Government of Zaire allowed the Mission Aviation Fellowship (MAF) to fly medical supplies and personnel (including a team from *Medicins Sans Frontiers* (see section 6.1) into the area.

Through the U.S. Embassy, the Government of Zaire requested that CDC send an investigative team to Kikwit. At the same time, WHO asked CDC (which supports a WHO Collaborating Centre for Virus Reference and Research on Special Pathogens) to join its team of outbreak consultants.

Other WHO consultants included representatives of the Pasteur Institute in Paris, the National Institute of Virology (NIV) in Sandringham, South Africa, and the Institute of Tropical Medicine in Antwerp. To oversee the international effort in Kikwit, the WHO established the International Committee on Scientific and Technical Coordination, under the chairmanship of Dr. Jean-Jacques Muyembe-Tamfum of the University of Kinshasa. The Committees charge was to ensure administrative, technical, and scientific coordination of the international team in Kikwit.

A CDC team from SPB arrived in Kinshasa on May 11, joining scientists from Paris, Sandringham, and Antwerp. In deference to a request from the WHO, the primary CDC team was limited to three people. It included Dr. Pierre Rollin, a French-born physician and epidemiologist who had extensive field experience in Africa; Dr. Ali Khan, a physician and graduate of CDCs Epidemiology Intelligence Service, who had extensive field experience in North America; and Dr. Phillipe Calain, a Swiss physician and virologist who was completing a postdoctoral fellowship in molecular biology at CDC. Dr. Rollin had participated in the 1989 investigation of the simian filovirus outbreak in Reston, Virginia.

The CDC team arrived at Kikwit General Hospital on May 12, accompanied by the hospitals medical director, by a representative of the Institut Pasteur, and by an army doctor working with the Zairian Red Cross.

6. Providing Medical Care to EHF Patients

The primary mission of Dr. Khan was to establish disease surveillance, determine transmission factors, and implement measures to help control the outbreak. The primary mission of Dr. Rollin and Dr. Calain was to gather clinical information and laboratory data on EHF. However, it quickly became clear that the most urgent need at Kikwit Hospital was to provide care for the patients. The hospital was in extreme disarray. People lay dead in beds and on floors. There was extensive contamination by blood, vomit, and excrement; needles and syringes lay underfoot. There was no electricity, lighting, or running water. There was no latrine.

Most of the staff and the patients had fled the 350-bed hospital, leaving about 20 critically ill patients. The people who had left could be spreading EHF outside the hospital. Two of the 15 Italian nuns who administered hospital activities or worked in

the surgical ward were sick, and one had died. Three doctors were also ill. One was recovering at home, and two were in the hospital ward. One would die a few days later. Only three nurses and one ward attendant, or orderly, remained, and they had been working without rest for several days, unsupervised and unprotected.

The director of Kikwit General and the CDC physicians recruited two more nurses and one more orderly. One nurse of the "old" team kept working until the next morning, when a third volunteer nurse joined them. Thus, for the first week, the hospital was staffed by a rotating team of only three nurses and one ward attendant. On May 12, wearing a plastic gown, glasses, boots, and gloves, Dr. Calain and the two volunteer nurses entered the hospital to help colleagues from *Medecins Sans Frontieres* (MSF) provide medical care and remove dead bodies from the wards.

For the first day, Dr. Rollin remained outside to carry medical supplies and protective gear to the door of the hospital. Meanwhile, Dr. Khan began to work with Dr. David Heymann of WHO/Geneva to set up surveillance systems (see section 8.0).

6.1 Medicins Sans Frontieres

A team from MSFs Belgian branch, which maintains a permanent office in Kinshasa, had arrived in Kikwit on May 11. It assessed the situation and set about the task of reestablishing a working hospital. The MSF team was led by a physician, Dr. Barbara Kerstiens, and included two sanitary engineers, one of whom could speak the local language. Well-prepared and well-equipped, they set about rehabilitating the hospital by installing a water tank and a waste disposal system, providing an electric generator, and supplying sterile water filters. They also distributed protective equipment to the hospital staff and to other relief workers.

6.2 The Zairian Red Cross

The Zairian Red Cross was already in action when MSF and CDC arrived. Red Cross volunteers went through the town of Kikwit to bury corpses and to bring sick people to the hospital. As the volunteers lacked protective clothing, gloves, and masks, this was dangerous work; six Red Cross volunteers became infected with Ebola virus and died. Just before the international workers appeared in Kikwit, the Red Cross had recruited Colonel Dr. Nsukami Zaki from the Zairian Army, one of the only functional government entities in Zaire. Dr. Zaki took charge of organizing the work of the Red Cross volunteers. He procured a truck for carrying the dead to burial and a bulldozer for digging graves.

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