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VIRAL HEMORRHAGIC FEVERS

These outbreaks illustrate the high price exacted by introducing modern medicine . . . without due attention to good medical practice.

— S. P. Fisher-Hoch et al. "Review of Cases of Nosocomial Lassa Fever in Nigeria" (1995)

Only the wealthiest African patrons of allopathic medicine can afford to have personal physicians. The rest visit overburdened and understaffed health institutions, usually only when they are very young, pregnant, or severely ill. Patients do not necessarily visit the same institution each time, so that whatever facets of their medical history are documented tend to be fragmented, and prescribers have very little opportunity for patient follow-up. Prescribers rarely express concerns about the difficulties inherent in charting patients' progress, however. For the most part, they simply do not have the time or resources to do so.[1] Typically, the health system processes patients visiting overburdened health institutions as if they were faceless components on an assembly line. The final step before the patient is released is taken at a dispensing counter.

Each patient eventually leaves the health institution with bottles, plastic packets, or envelopes of medicine in hand. He or she is regarded as "treated" irrespective of whether cure is assured, likely, or even possible. In response, patients often view the health care system as an impersonal institution rather than a cooperative service rendered by different professionals. Drugs are frequently unaffordable outside of government-funded or publicly subsidized hospitals, so the simple desire for palliative medicine is enough to motivate clinic visits. Private practitioners, too, earn more by marking up medicines than by charging consulting fees. Obtaining medicines has become a principal objective of seeking health care. A cure—or, better still, a positive state of health[2]—is a much more distant goal; patients are often unlikely to think that the institution is even invested in achieving it. Prescribers, for their part, cannot feel guilty about failures from

whose consequences they are detached, or of which they are unaware; the inadequacy of any treatments offered is not their responsibility. For all these reasons, lack of diagnostic technology is pervasive, condoned, and almost entirely unrecognized, at least when infections are acquired outside the hospital.

Portrait of a Hospital

In 1990 Sir Mobolaji Bank-Anthony, OBE, a Nigerian philanthropist, donated a maternity wing, Ayinke House, to Ikeja General Hospital in Lagos.[3] The hospital, then owned and managed by the Lagos state government, served the urban poor but also functioned as a secondary center that accepted referrals from private institutions and community clinics. At the time Ayinke House was completed, I was one of several National Youth Service Corps members, recent graduates whom Nigerian law requires to serve the country for a year before embarking on independent careers. The National Youth Service Corps guarantees recent graduates work experience and provides the underserved in Nigeria with health workers, teachers, and administrators. Lagos state government hospitals serve the least affluent patients, in one of the world's largest cities, with very limited resources. Over two-thirds of the medical and pharmacy staff at Ikeja General were interns, residents-in-training, or Corps members. In 1990–91,[4] Ikeja General Hospital had about half a dozen physician corps members, one graduate nurse, four pharmacists, one dentist, and one physiotherapist. Conspicuously absent from our contingent were medical laboratory technicians. Most of the hundreds of biological scientists in our Youth Corps camp served as school teachers. The Youth Corps members added to a workforce of several dozen nurses, about six pharmacists and pharmacy attendants, and about sixty doctors, almost half of whom were interns. Most of the staff moonlighted at private institutions in order to make a living. The general hospital did have a lab, but it was very small and only occasionally functional.

On the day that the ribbon at the gate of Ayinke House was cut, I stood with other hospital staff along the road to the building to wave to the motorcade of dignitaries. A precious half hour of nonemergency service had been sacrificed for the biggest event that Ikeja General had seen in many years. Hospital expansions and upgrades are few and far between in Nigeria. The new building's stark whiteness was almost blinding against the dull green backdrop of the rest of the hospital. The maternity wing was only the second two-story building on the entire campus. A week later, dispensing in the shiny pharmacy for the first time, I realized that Ayinke had served up even more than we had anticipated. Water flowed from sparkling taps, a generator supplied electricity whenever the main supply

failed, tiled surfaces could be wiped clean, and the medicine cupboards were latched and rodent-proof. The very idea of rodents in Ayinke was preposterous.

Just a week before, I had been working at the Old Pharmacy, where things were not as fancy, and, despite our best efforts, the occasional rat scuttled across the floor.[5] Usually I sat on a hard, high stool at an outpatient counter, which had peeling green paint, dispensing medicines through a small window. When the electricity supply was interrupted, I leaned out of the window to catch the light and kept my feet off the floor. Angry-looking patients and their guardians watched me suspiciously, sliding toward my window on what looked, from my vantage point, like endlessly long wooden benches. After my first week, I learned that they were not angry at me, just exhausted. By the time they reached the pharmacy, they had been waiting for three to eight hours, which included less than ten minutes of contact time with all the health professionals combined. With the exception of inpatients, tuberculosis patients, and pediatric patients, who had separate pharmacy facilities, every one of several hundred patients each day had their prescriptions filled, or converted to shopping lists, at this counter. At any given time, there were at most two pharmacists or pharmacy attendants on outpatient dispensing duty at the Old Pharmacy counter.

While hundreds of outpatients poured into the clinic each day, the staff also cared for critically ill patients admitted to the wards. The pharmacy unit had other staff dedicated to inpatients, but whenever we were even more understaffed than usual I had to close the window for an hour or so to take medicines to the wards. These clinical pharmacy rounds were a welcome change from the monotony and pressure of counting out tablets, mostly antimalarials, to patients on an unending line and dictating instructions in my broken Yoruba. I felt relieved to be able to stretch my legs without being plagued by guilt about leaving an endless line of tired patients. On my occasional trips through the tightly packed wards, I was accompanied by a student or intern, whose major responsibilities included running back and forth between the pharmacy and the ward to bring in intravenous fluids that could not fit on our tiny cart and ensuring that the three-and-a-half wheeled contraption did not overturn. As I walked by the patients, their relatives, who were typically camped outside the wards, said hello through the windows. Since we were constantly fighting shortages, I dispensed what few medicines were available and translated unfilled prescriptions into shopping lists for patients' guardians to procure the rest elsewhere.

Our inventory of cheap generics and vetted donations did cover the most heavily prescribed medicines, but there were still some essential drugs that were only sometimes, or never, in stock. We were perpetually short of surgical disposals, and only rarely did we have a stock of gloves for surgical procedures. In the early 1990s, everyone had heard of AIDS, but no one thought it had reached Nigeria. We were

aware that other diseases lurked in the hospital and took some precautions to protect ourselves and our clients. Staff that wore lab coats procured their own. Patients were asked to procure gloves for their own procedures and were even given their doctor's size, but every now and then a doctor would work without gloves in an emergency or to save a poor patient some money. At the pharmacy, we staff members bought our own soap, disinfectant, and, on occasion, kegs of water.

No one was ever turned away from Ikeja General Hospital. For the many patients for whom the heavily subsidized hospital services were still out of reach, fees could be waived by completing "Pauper" forms. Considering the vast numbers of patients who pushed through its gates each day and the meager resources allocated to their care, Ikeja General Hospital was remarkably clean and efficiently run. Working in the conurbation of Lagos, where medical and allied practitioners are not scarce, I did not face the challenges that classmates of mine posted to more remote areas had to endure. There, a hospital might have only one doctor and no nurses, so the pharmacist was forced to give injections, stitch cuts, and even attend births if the doctor happened to be otherwise engaged. We had postgraduate medical residents, certified midwives, and a handful of consultant specialists. The hospital was chronically understaffed and overcrowded, but it offered better care than many private institutions.

Through my experience at Ikeja General Hospital, I later became acutely aware of how easily infectious pathogens might travel from one patient to another and to hospital staff during an outbreak. We had no untrained practitioners and easily avoided needle sharing and grossly unsafe surgical practices, but in most wards at Ikeja General we could not implement infection control at a standard necessary to contain highly virulent and transmissible pathogens. Reaching these standards routinely and reliably was attainable in parts of the new Ayinke wing, but the older buildings, which were more representative of urban public hospitals in Nigeria, lacked a reliable water supply, surgical disposables, or enough staff. Patient beds were too close together, and relatives walked in and out of the wards bringing essential supplies that had to be procured from outside.

Many patients admitted to hospital wards in sub-Saharan Africa come with a nonspecific fever. Most of them recover, even if they are still undiagnosed when they leave. If their illness is caused by malaria parasites or blood-borne bacteria, precautions taken in well-run institutions such as Ikeja General are sufficient to protect medical staff and other patients from becoming infected. In the uncommon event that a more easily transmitted pathogen is responsible, however, proper infection control is essential, particularly if the unexpected agent cannot be identified. Hospital-based outbreaks of viral hemorrhagic fever result from conditions in which infection control is desirable but difficult. This situation has repeatedly been highlighted in reports describing hemorrhagic fever outbreaks

in Africa, in spite of the growing emphasis on infection control. Viral hemorrhagic fever outbreaks are promoted by the prevalent mode of medical practice in which etiology is only of interest when a cure fails, and not always even then. Because of the challenges associated with infection control and patient diagnosis, in typical African hemorrhagic fever epidemics the death toll is high and the spread throughout the hospital has already begun before the cause of the outbreak is known or even suspected.

Allopathic medical institutions are only one of several options available to the sick African. Indigenous practitioners and unsanctioned providers also can be consulted; they often cost less and are closer to the patient, which are significant benefits. Although hospitals are greatly revered, especially for their surgical proficiency, they are also viewed with some suspicion and fear.[6] When an unusual infectious disease appears, it is difficult to tell whether the bad turn of events is inevitable or a consequence of treatment. If an illness is acquired within a hospital, however, the finger of blame can be pointed directly at the institution. The blinders that obscure the otherwise inconspicuous deficiencies of allopathic medicine are removed when death is linked to the hospital.

During a 2005 Marburg outbreak in Uige, Angola, in which almost four hundred people were infected and about 88 percent died, a local pastor explained to personnel from Médecins Sans Frontières and WHO why people were fleeing the hospital: "They say that Marburg is in the hospital; that there is a large reservoir of blood there; and that anyone who approaches it dies."[7] Just as London's John Snow was able to link cholera to the Broad Street Pump in the nineteenth century, even though he had no idea that a bacterium caused the disease, deductive epidemiology was all the people of Uige needed to link Marburg hemorrhagic fever to their hospital. In 2007, a Ugandan primary health center was attacked by locals who blamed it for an Ebola outbreak and chased five potentially infected patients, who were at the time under quarantine, from the hospital. In the same outbreak, patients were reported to have fled from the hospital to use indigenous therapies.[8] In those uncommon but significant instances when iatrogenic illness leaps out of control, patients as well as health care workers flee hospitals. Infection control remains far from optimal in many places, but at least an understanding of its importance exists within health-professional circles. Diagnostic insufficiency has yet to achieve this basic level of appreciation.

Viral Portraits

The best known African viral hemorrhagic fevers are yellow fever, Marburg, and Ebola.[9] Yellow fever is an ancient viral disease whose etiology and mosquito vector

were discovered in the early twentieth century.[10] Patients suffer from a high fever, headache, and bleeding in the skin. They often become jaundiced by the third day, resulting in the yellowness of the eyes that gives the disease its name. Yellow fever originated in tropical Africa but was transported to the Americas, where it rapidly became endemic in every locale inhabited by *Aedes aegypti* mosquitoes. It killed thousands of people, usually in the summer months. Mosquito control is one option for intervening in transmission but, as with many other mosquito-borne diseases, had limited success outside the United States.[11] Yellow fever deterred the construction of the Panama Canal. This disease, along with malaria, led to West Africa being labeled "the White man's grave." Intensive global research on yellow fever was vital to serve the goals of empire and was stimulated by its major architects. The causative virus, vector, and life cycle were worked out principally by researchers in the Americas. Successful control of yellow fever came largely through the development of an effective vaccine, 17D, an attenuated variety of a strain obtained from a Ghanaian patient, through research at early colonial laboratories in West Africa.[12] A monkey reservoir exists in rain forests of Africa and South America, and the *Aedes aegypti* mosquito continues to inhabit these parts of the world. For these reasons, yellow fever cannot be eradicated, and occasional outbreaks still occur in South America and Africa.

In contrast to yellow fever, which has been known for centuries, Ebola and Marburg hemorrhagic fevers are postcolonial or "emerging" infectious diseases. Both are caused by filoviruses, tiny, threadlike microbes capable of killing up to 90 percent of the humans they infect. Ebola and Marburg viruses look remarkably alike but have very different surface proteins. This means that infection caused by one will not protect against subsequent infection by the other, although known outbreaks have been few and none have overlapped. As yet, there is no protective vaccine for either disease. Outbreaks of Ebola and other African hemorrhagic viruses have been the subject of moving nonfiction chronicles.[13] Fear of these diseases is rooted in the knowledge that there is neither a cure nor a vaccine and that their mortality rates, which range between 50 percent and 90 percent, are among the highest for any known illness. Intense terror emanates from the painful and grisly suffering of infected patients. The disease follows a terrible course, after days or weeks of fever:

> The victim soon suffers profuse breaks in small blood vessels, causing blood to ooze from the skin, mouth and rectum. Internally, blood flows into the pleural cavity where the lungs are located, into the pericardial cavity surrounding the heart, into the abdomen, and into organs like the liver, kidney, heart and spleen, and lungs. Eventually, this uncontrolled bleeding causes prostration and death.[14]

Ironically, the efforts of relatives and health care providers to care for the sufferers of Ebola and Marburg hemorrhagic fevers are especially dangerous because these activities often foster transmission. The high rate of person-to-person transmission via infected body fluids is well documented, but the disease is not always identified until it is too late to prevent outbreaks in health care settings.

Filoviral threads often settle in the shape of a question mark, taunting scientists at the other end of the microscope by posing numerous questions. Where did Marburg and Ebola come from? How do the viruses spread? Where do they live between outbreaks? Some have supposed that Ebola virus has always been hidden in the forests of central Africa, thriving and circulating in a less susceptible or symptom-free host population. This school of thought contends that contact between the reservoir and humans or susceptible apes (gorillas and chimpanzees) is normally an unlikely event but has increased because of habitat disturbance or climate change. Another school proposes that Ebola is a new virus that did not exist anywhere before its sudden emergence the 1970s. That hypothesis is supported by the genetic similarity among viruses from outbreaks between 1976 and 2004, but this could also mean that the virus is under evolutionary pressure that does not support change.[15]

Almost as enigmatic as the origin of these filoviruses is their normal habitat. Viruses cannot exist on their own; they need a living host that can support them until they can be transmitted. Humans and primates succumb to infection too rapidly to transmit the virus to many other individuals; these diseases' rapid transmissibility and high case-fatality rates imply that we are merely incidental hosts.[16] As there is a holding period between epidemics when no one shows signs of disease, a reservoir that can transmit the virus without being killed by it must exist somewhere.[17] When a reservoir is unknown or uncertain, it is impossible to predict the advent of epidemics or to prevent and control them. It took over thirty years to identify the bat species that are the Ebola and Marburg reservoirs.

The Ugly Picture: Viruses in Hospitals

In 1995, Dustin Hoffman and Renee Russo starred in a movie called *Outbreak,* a thriller about the fictional Motaba virus that was transported from Africa to the United States via an infected monkey. In this cinematic scenario, scientists dressed in space-age suits used the latest technology to protect America against the dread disease. This somewhat absurd fictional account can be viewed as an exaggeration of an outbreak that occurred in Reston, Virginia, when an Ebola outbreak occurred in a research institute's monkey colony.[18] In contrast to outbreaks that occur in Africa, the actual and fictional United States outbreaks did

not lack high-tech facilities to protect scientists and health-care workers and make sure diagnoses were accurate and treatment prompt and efficient.

All the principal Ebola outbreaks and most Marburg outbreaks have occurred on the African continent, except for a few relatively unremarkable laboratory outbreaks in Western countries.[19] Marburg was identified in 1967 during one such laboratory outbreak in Germany. There were sporadic cases of this disease in southern Africa and Kenya in the 1970s and 1980s, but the first outbreak caused by the virus was documented in 1998, in the Democratic Republic of Congo (formerly known as Zaire). In 2005, the largest known Marburg outbreak erupted in Angola.

Ebola outbreaks were first recorded in Yambuku, Zaire, and across the border in Maridi, Western Equatoria, Sudan, in 1976.[20] The first human case, called the "index" case, came from the forest to the Yambuku Catholic Mission Hospital, a facility managed by devoted but unsupervised Belgian nuns. The hospital was popular "because it maintained a good supply of medicines"[21] but the staff's limited medical training meant that they did not appreciate the importance of aseptic procedures and infection control. In an attempt to stretch scarce resources and serve more patients, they used a sparse stock of injection paraphernalia—five syringes in all. These were sterilized by boiling just once a day, so that almost every patient in the hospital had a near 100 percent risk of infection once the index case was admitted.[22] Before long, the virus was transmitted from patients to nurses. By the end of the outbreak, most of the hospital staff, including all the health-worker nuns, had died.

The concurrent Sudanese Maridi outbreak, by contrast, featured multiple cases of community-acquired hemorrhagic fever associated with a cotton factory, followed by some hospital amplification. Patients who were stricken by the mysterious disease were taken to the district-level hospital in Maridi. Early in the epidemic, a telegraph message was sent to the central medical services in Khartoum, and WHO was notified. A team headed by Dr. Ali Idris, Sudan's director general of epidemiology, and including public health specialists, epidemiologists, and laboratory scientists, as well as doctors and nurses, was immediately dispatched to Maridi.[23] A third of the health care employees at the hospital—seventy-six of 230 staff—became infected; forty-one eventually died, and most of the rest fled.

Even though the etiologic agent of the infection was unknown to science at the time, Dr. Idris was especially prescient in requiring that barrier precautions be taken very seriously by every member of this team. A strict quarantine was instituted, and all specimens were collected and handed aseptically so that the epidemic was confined to Maridi and containment was relatively rapid.[24] An important observation in the 1976 outbreaks was that, for reasons unknown, hospital-acquired infections appeared to be more lethal than community-acquired Ebola hemorrhagic fever.[25] Hemorrhagic viruses have greater reach today than at any

other time in history because of very recent medical advances; Western medicine must ensure that it protects patients and practitioners from these deadly agents by detecting outbreaks early, before they spread in the hospital.

Why are tests necessary in order to ascertain that infection control must be heightened around a patient bleeding from all orifices? Because patients infected with Ebola or Marburg viruses do not begin to bleed early in the course of infection. They present with high fever and nonspecific malaise indistinguishable from malaria, typhoid, and other severe blood-borne diseases. By the time the patient shows definitive signs of hemorrhagic fever, his or her prognosis is poor. Even more important, the patient is likely to have been admitted to a hospital and to have shared accommodations, health care staff, and, far too often, infectious milieu with a roomful of other severely ill patients.

In 1995, an Ebola epidemic occurred in Kikwit, Zaire, a city of between two hundred thousand to six hundred thousand people. The deadly disease made its impromptu appearance at a resource-poor hospital, but the epidemiological investigation of the Kikwit outbreak was superior to most investigations in Africa. Communications had improved considerably since the 1976 Maridi and Yambuku outbreaks. Although several weeks went by before the outbreak was known to the world, the Kikwit Ebola epidemic offered more opportunities for epidemiologic investigations, and even for some preliminary inquiries into disease reservoirs.[26] In an exemplary case study in epidemiological sleuthing, the index case, a charcoal pit worker, was identified even though he had died months before the international investigation team arrived. Later in the outbreak, an international team was commissioned to propose and implement interventions and to perform epidemiological investigations. However, clinical care for most of the dying patients was furnished by volunteer Zairian doctors and nurses, who came in from the capital, Kinshasa, after the staff at Kikwit's hospital had either died of the disease or fled from it.

In addition to caring for the dying, local doctors conducted a high-risk clinical experiment that may well have succeeded. At the tail end of the epidemic, a nurse who had cared for infected patients became feverish. Clinical diagnosis in the context of the epidemic strongly suggested that she had contracted Ebola hemorrhagic fever. Since the death rate was then about 80 percent, her colleagues were devastated and acutely aware of their own vulnerability. Their helplessness to do anything to change the clinical course of the deadly disease in someone who had battled it alongside them sunk home and motivated them to handle her case aggressively.

The Zairian clinical team decided to transfuse the nurse with blood from a recovering patient. The idea was that the patient would have protective antibodies against Ebola virus in his or her blood that could offer some protection to the newly infected nurse. During the first Ebola outbreak, in Yambuku, a variation of

this procedure was tried on two patients but very little information was available to judge the value of this therapy.[27] The principle has been used to treat other infections for which there is no cure, such as Lassa fever, but in those cases the source blood is screened for blood-borne pathogens and, as in Yambuku two decades before, the therapeutic antibodies are purified away from whole blood. The Kikwit hospital did not have the facilities for either of these safety protocols but, if the procedure were to work at all, the patient needed to receive the antibodies immediately.

The few patients who survived Ebola hemorrhagic fever were still quarantined at the hospital because the virus remains in body fluids for several weeks after recovery. The clinicians had a decent pool of convalescent patients and found a compatible donor. The blood was screened for HIV, but not for hepatitis and other blood-borne viruses. Although the hospital typically transfused malaria patients with severe anemia, it lacked the facilities necessary for more complete screening. For these and other reasons, the international scientific team strongly disapproved of transfusion. Not only was there little evidence to support this radical approach to treatment, there was real risk of doing harm. Indeed, well into one of the largest Ebola outbreaks of all time, and two decades after the virus had been discovered and characterized, there was still no way to confirm that the nurse had Ebola.[28] It was likely that she had the disease, but it was impossible to rule out malaria, typhoid, or some other infection. If the nurse had something else, transfusion with blood from a convalescent Ebola patient could infect this already ill patient with the deadly virus. The Zairian medical crew and its nurse-patient weighed the pros and cons and eventually chose to go forward with the transfusion against the advice of the international scientific team. They were probably slightly desensitized to the dangers; they had performed risky transfusions in the past, although perhaps none as risky as this.

The transfused nurse and seven of the eight patients who were treated similarly recovered. Had the team stumbled upon an effective treatment for Ebola? The entire episode deserved to be aired in the pages of a prestigious medical journal, but, as one witness observed, there was no way to know whether the therapy had worked or not. Without laboratory backup for this key experiment, which cannot be replicated because of ethical considerations, it is impossible to tell whether the patients who recovered at the tail end of the epidemic were cured by the transfusion therapy, had a different type of Ebola infection, or never had Ebola at all.

Contracting the Ebola virus might not be the worst thing that could happen to a person during an outbreak. Anyone who came down with a curable infection, whether with malaria, bacteremia, or enteric fever, was likely to be housed with Ebola patients with similar signs and symptoms and could then be infected with an incurable disease. These ill patients would probably be hypersusceptible

to Ebola infection. In the most likely scenario, neither these patients nor their caregivers would ever know that the disease was acquired after, and not before, admission to hospital.

Compared to malaria, typhoid, and many other fever-causing diseases, Ebola hemorrhagic fever is uncommon, so some may argue that routine diagnosis for the disease is not cost effective. The lack of a cure also could be put forward as an argument against investing in Ebola-specific diagnostics. However, experts insist that early diagnosis allows for tailored supportive care that reduces mortality, and the evidence from treated cases supports this position. When an epidemic is occurring, rapid and precise diagnostics are essential to contain it.[29] At the inception of an epidemic, routine use of diagnostic protocols that are rigorous enough to rule out common infections would hasten the identification of a new outbreak. Certain populations should be targeted for more rapid and rigorous routine diagnostic protocols. For example, many of the people who have been sickened by Ebola and Marburg viruses are health workers on the front line in battles against the unknown. Health workers in Africa are too few to serve their populations and very expensive to train. From a purely economic standpoint, it makes sense to ensure that these skilled professionals are protected from on-the-job infection and that they receive the most effective care when they fall ill, particularly when hospital transmission is suspected. Even though health workers are not more "valuable" than other people in the community, their exposure to infectious microorganisms is greater because they are in contact with so many ill patients, and their illness could serve as red flags for hemorrhagic virus outbreaks. Health workers are also in a position to spread any diseases that they carry, so diagnosing them rapidly and precisely is an important way to contain hospital outbreaks.

The need for a simple but reliable test that can be used during an Ebola epidemic, or to screen high-risk subpopulations, has long been appreciated in scientific circles. Toward the end of the 1976 Yambuku Ebola outbreak, WHO commissioned a scientific team to conduct fieldwork and define the syndrome caused by the deadly new virus. The scientists were obliged to use hastily assembled and improvised equipment, but still prioritized the development of a diagnostic test to differentiate people infected with the new virus from those with fever of other etiology. Within two weeks of their arrival at Kinshasa, the team devised an immunofluorescence-based field test. The test was used to estimate the scale of the epidemic, as well as to identify people who had previously been exposed to the virus who could provide antisera to treat the newly infected. Unfortunately, the hastily developed test was insufficiently sensitive; its use had to be discontinued, and no replacement test was developed. Twenty years later, diagnostic testing was unavailable in the Kikwit epidemic, even to validate or at least safeguard experimental therapy.[30]

The gold standard for identifying any causative microbe in an infection is amplification of live organisms to detectable levels in a test tube, a technique known as culture. Routine detection of the Ebola virus by culture is out of the question; it is simply too dangerous to amplify the virus to necessary levels outside a Biosafety Level 4 containment facility. Level 4 represents the highest biosafety level and is used to protect scientists and technicians working with deadly pathogens, including Ebola virus. Level 4 labs are hermetically sealed off from the outside environment. Like the actors in *Outbreak,* technicians wear impervious space suits and work with samples in chambers that suck out potentially infected air. In the absence of these and other safety features present in a Biosafety Level 4 lab, surrogate methods that do not require viral amplification must be used for diagnosis.

The best available technology for routine filovirus diagnosis is probably a reverse transcriptase-PCR (RT-PCR) test, which measures viral load, in which portions of viral genetic material are amplified for detection.[31] Amplifying sections of viral genetic material in this way is safe and reliable and can be conducted in ordinary clinical laboratories. The absence of alternatives before the RT-PCR technique became routine is one explanation for the lack of progress in this essential area. In 2004, an RT-PCR test for Ebola was described in a paper authored by Ebola specialists, who are aware of the poor results from the earlier immunofluorescence assay.[32]

RT-PCR is a promising approach, particularly as viral load determinations for HIV, using the same method, are increasingly sought in Africa. Facilities and resources that are being developed for this purpose could be adapted for use with filoviruses. Presently, the dearth of molecular facilities in African hospitals presents a major roadblock to routine use of RT-PCR tests: most HIV-positive patients cannot yet access viral load testing. In the absence of suitable facilities to detect the virus itself (or viral nucleic acid) in blood specimens, surrogate serological or immunological diagnostic tests for filoviruses are theoretically possible but are rarely applied because of challenges associated with making them sensitive enough. Many patients do not develop antibody levels sufficient to be reliably detected until they are close to death or recovery. Patients who have previously been infected by the same or a similar organism have high antibody levels, resulting in false positives.

Gulu Learned Little from Kikwit

It is not enough merely to develop diagnostic tests; they must be deployed at the point of need. The Kikwit outbreak, during which 245 of 317 documented

infected patients died,[33] was highly publicized and has featured prominently in the scientific literature. One epidemiologist, reviewing recent advances in laboratory testing, commented that the power and speed of modern diagnostics "is spectacularly demonstrated by the rapid response" to this outbreak: "glycoprotein sequences from the Kikwit strains were obtained within 48 hours of the virus arriving at the CDC in Atlanta."[34] A key point that this epidemiologist appears to overlook is that the epidemic's index case died four months before the CDC's evaluation and one month after about one hundred health workers were felled by the disease. Although the technology required for the rapid confirmation of Ebola existed outside Africa, the "ability to isolate and identify quickly new pathogens" was not called in until the epidemic was approaching its fifth month (table 1).[35]

Uganda documented its first Ebola hemorrhagic fever epidemic in 2000. By that time, Ebola virus had been known for a quarter of a century, longer than HIV. Following the extensively televised 1995 Kikwit outbreak, the virus was routinely featured in U.S. undergraduate microbiology classes, and the U.S. Public Broadcasting Service (PBS) had prepared curricular resources about Ebola epidemics for high schools.[36] In spite of extensive human experience with the virus, at least 425 people ultimately contracted the disease in and around Gulu, Uganda, and roughly half of them died. As with the previous human Ebola epidemics in Africa, the identification of the disease was delayed by misdiagnosis of early cases. Although Ebola was no longer an unknown virus, the delay from the appearance of the first patient until a diagnosis of Ebola hemorrhagic fever was made was an astonishing *six weeks*.[37]

Table 1. Kikwit Ebola outbreak of 1995

KEY EVENT	APPROXIMATE NUMBER OF NEW CASES SINCE PREVIOUS EVENT
January 13: Death of index case	4 in 12 days
April 10–14: Identification of first cases among health personnel	33 in 90 days
April 27–29: Emergency message sent to health authorities; lab technician dispatched	89 in 14 days
May 1–3: Preliminary lab findings and clinical signs establish a diagnosis of viral hemorrhagic fever	141 in 3 days
May 4–5: First blood specimens sent to CDC; first antiepidemic measures taken	38 in 7 days
May 9: Specimens arrive at CDC	
May 10: Results of serological and RT-PCR tests confirming Ebola hemorrhagic fever conveyed to Kikwit	
June 30: No more new cases reported	100 in 50 days

Until a definitive Ebola diagnosis was pronounced, patients with hemorrhagic fever were variously diagnosed and treated as if they had malaria or typhoid fever by indigenous as well as allopathic health providers. Patients and their contacts were not isolated or quarantined, and the disease spread with ease. The situation was not helped by the fact that this was Uganda's first Ebola outbreak. That outbreaks of Ebola and other viral hemorrhagic diseases frequently occur in nearby Congo and Sudan, and that circulating Ebola antibodies had previously been found in eastern Ugandan residents, was not sufficient warning for the nation's health system.[38] During the 1976 Sudanese outbreak, patients at Maridi hospital were treated for malaria during their first week of illness and for typhoid fever during their second. By the third week, when patients began to hemorrhage and die, it became clear that this infection was caused by an unusual, as yet unidentified pathogen.[39] Twenty-four years later, by which time the Medline database of biomedical literature had indexed almost five hundred scientific and medical publications on Ebola, infected Ugandans met a similar fate.

The World Health Organization and the U.S. Centers for Disease Control (CDC), the principal international agencies that respond to outbreaks, recommend that viral hemorrhagic fever isolation protocols begin only *after* patients do not respond to therapy for malaria and typhoid.[40] In a typical African health care setting, following this course can result in a delay of over two weeks. In situations where drug quality is not assured and resistance has been documented, the delay could be longer, as physicians sequentially experiment with different therapies. If Ebola, by then a well-characterized virus, could not be identified in Uganda in 2000 because of its local novelty, the failure to rapidly rule out malaria and bacterial infections, which could have been done by the simple laboratory tests that are needed to manage those conditions, extended the period of ignorance and the opportunity for the infection to spread. Ebola virus was eventually confirmed through laboratory tests performed in South Africa. An internationally assisted field lab, surveillance, and containment strategies were established within a week of this confirmation, and the epidemic waned shortly thereafter.[41] The rapid demise of both the Gulu and the Kikwit outbreaks following diagnosis demonstrates that, in spite of its transmissibility and high mortality rate, Ebola is controllable once detected. In contrast to viral hemorrhagic fevers elsewhere, the repeated failure to identify and quarantine patients infected with Ebola and other African hemorrhagic viruses precipitates alarming, oversized outbreaks that perpetuate the stereotype of Africa as the infectious continent.

In 2000, it took only six days to confirm Ebola in Uganda once viral hemorrhagic fever was suspected. This time span was acceptable, allowing for unfamiliarity of Ebola in the locality and the need to ship samples to a specialist laboratory in another country. The lag time that was responsible for massive

amplification of the epidemic elapsed before Ebola was suspected and might have been shortened if an early warning system had been available:

> By and large, once an outbreak has been recognised by the public health authorities there are well-tried processes and procedures that come into play that serve to contain further spread of the infection and limit additional cases of the disease. This was shown spectacularly in the case of the SARS outbreak, in which not only was the disease controlled but the novel causative agent was identified, both within a few months. But as Lamunu and colleagues [in their 2000 chronicle of the Uganda Ebola outbreak] make clear, the most difficult aspect of the outbreak control is the initial recognition of the disease: diagnosis depends on the astute health-care worker who notices an unusual clinical picture, or more usually, an unexpected cluster of cases.[42]

Severe acute respiratory syndrome (SARS) was rapidly identified as a new disease in 2003 because other respiratory infections were ruled out with considerable help from laboratory and radiological diagnostics in Asia and North America.[43] The same conclusions might have been reached had testing been delayed, but the effect of such a delay would almost certainly have been catastrophic. The vision of an "astute" African health care worker who is responsible for recognizing a potential Ebola outbreak is bound to be clouded by numerous cases of malaria, typhoid, and other infectious diseases that continue to flow in whether or not an epidemic of viral hemorrhagic disease is under way. Jerome Groopman, who has studied physicians' decision-making behavior, notes that "availability heuristics" are among the most common causes of medical error[44]: simply put, a diagnostician is less likely to come to the correct diagnosis when he or she sees a test case in the midst of many "detractor" cases that present with similar symptoms but have other causes.

Kikyo health center in Bundibugyo district was at the epicenter of Uganda's most recent Ebola outbreak, which raged from August 2007 until early January 2008. Kikyo health center has no doctors, and its nurses treat about 850 malaria cases a month, in addition to patients with dysentery and meningitis. Between August and November 2007, patients sickened by what was later discovered to be a new subtype of Ebola did not bleed as Ebola patients typically do. Concerned by the high mortality rate, but oblivious to the fact that the outbreak was caused by a deadly virus, health workers without adequate protective clothing tended the patients and collected infectious specimens for shipment to the CDC. One experienced clinical diagnostician was convinced that the outbreak was typhoid fever. His guess was wrong: he contracted Ebola, and five more health workers—including almost all of the staff in this small health center—were sickened by

the disease before a diagnosis was made. This outbreak was caused by a new strain of Ebola, a fact that has been blamed for diagnostic delay. However, it has been observed that the disease may have been circulating before the first diagnosed case, and, although the CDC was unable to identify the causative agent within twenty-four hours, as in other recent outbreaks, Ebola was identified within three days of receipt of specimens. Testing began earlier than in the 1995 Kikwit and 2000 Gulu outbreaks, but it did not begin early enough to prevent 149 infections and thirty-seven deaths.[45]

A patient infected with even the better known strains of Ebola or Marburg initially presents with a fever, general malaise, and perhaps some diarrhea. That the patient does not have malaria, typhoid, or some other fever might only become apparent when internal organs begin to dissolve and blood starts to trickle from bodily orifices, by which time it is too late to intervene in a way that might change the course of this infection or protect others from exposure. The high prevalence of pathogens that produce similar early symptoms means that even the best clinical surveillance will detect that something is amiss only when the number of deaths spikes, by which time the outbreak will be well under way. It was the high mortality among clusters of patients that led doctors to suspect that both the 2000 and 2007 Uganda epidemics were caused by filoviruses. Clinicians working without laboratory support noticed that something was amiss before Ebola was confirmed, but not early enough to block its rapid dissemination.

Surveillance for viral diseases with epidemic potential is today of global interest, with increasing focus on influenza viruses with pandemic potential, including those that can infect birds as well as humans, the avian influenza strains. In a sense, the existing "warning system" for much more lethal viral hemorrhagic fevers in Africa is analogous to that for avian influenza, with the notable exception that a human, rather than a bird, die-off indicates an epidemic. Even if the health system did not routinely test for Ebola, a spike in the number of patients with febrile illnesses that could not be attributed to malaria or other endemic diseases could form the basis of a more effective and acceptable early warning system. Early warning systems are valuable for rare yet deadly infectious diseases, as well as for newly emergent diseases. We know enough to predict that the next emergent pathogen will most likely be an RNA virus with a broad range of hosts and will probably appear in a part of the world where human beings are being pushed to interact with unfamiliar animal species because of ecological and/or demographic change.[46] These risk factors are very likely to converge in Africa, where a new Ebola subtype emerged in 2007.[47] Preparedness for new diseases and new forms of known diseases requires, at the very least, strong surveillance systems for existing endemic infections.

Without proactive containment of a hemorrhagic virus, the hospital, which should be central to managing a disease outbreak, becomes the focus of an epidemic and is disengaged from the community as potential cases avoid treatment and quarantine. Patients with severe malaria or bacterial bloodstream infections do not need to be placed in isolation (and the cost of doing so would be prohibitive for most African hospitals), but it is imperative that patients with hemorrhagic fevers be identified early and isolated. Health workers also need to use strict protective protocols when collecting and handling body fluids, including those required for testing. Where tests are routinely performed, these precautions are normal protocol. In cases where blood, stool, and urine are almost never collected, a directive to collect laboratory specimens in a suspected outbreak could have lethal consequences.[48]

In Western countries, the risk of hospital transmission is low. When one patient who exported Lassa fever to the United States died before a diagnosis was made, no hospital staff members were infected because routine infection control procedures were sufficient to prevent nosocomial spread of most highly virulent and transmissible agents, and health workers were familiar with protocols for specimen collection and handling. A similar course of events unfolded more recently in Europe and South Africa.[49] There are considerable, ongoing efforts to improve infection control around the world, but prevailing conditions in most African hospitals are not sufficient to prevent the initial spread of a virulent pathogen. However, African hospitals can step up infection control to stem an epidemic when one is identified. Of the approximately one hundred cases of Ebola reported among health workers at one Kikwit hospital, only one infection occurred after the etiologic agent had been named and barrier precautions had been taken by health workers. Burial practices in the community can also be temporarily modified in the event of an outbreak.[50] Unless these measures are put in place in the very early stages of an Ebola epidemic, rapid spread and high mortality will almost inevitably ensue.

Some have proposed that Western notions of contagion and the need for isolation cannot always be applied in the context of many African cultures.[51] Through patient care, sharing household utensils, and ritual instruments, but most importantly during the intricate preparations employed by some peoples prior to the burial of the dead, Ebola and similar pathogens can be rapidly disseminated through a community. Although these risk factors have been associated with the epidemic spread of hemorrhagic viruses, it has been repeatedly demonstrated that, with reasonable justification, African societies will modify customs to preserve life and health. "Ignorance" is often blamed for public health failures where the word is taken to mean the lack of public health education. In truth, ignorance arises from the failure to convey the necessary information or

justifications to promote behavioral change. Too often, the outcome of an epidemic itself is the only source of information that people have. Investigators of the 1976 Yambuku Ebola outbreak were pleased to find that villagers were voluntarily enacting an effective quarantine and burying corpses away from communities.[52] In Kikwit, almost twenty years later, appropriately protected workers were permitted to perform potentially risky burial rites. Refusal to comply with potentially lifesaving public health orders can often be traced to mistrust of the Western health care delivery system.[53] Providing clear messages following precise diagnoses is one way to build trust.

After the 2000 Gulu Ebola epidemic, viral hemorrhagic diseases were added to Uganda's list of notifiable diseases,[54] and local health workers attended a one-day course on Ebola prevention and containment. Although both responses were essential and commendable,[55] it is not clear how primary health care workers can be expected to delineate future viral hemorrhagic fevers from malaria and other endemic diseases. In spite of the obvious benefits that could result from stronger laboratory support, modifications to the Gulu hospital after the outbreak focused on the development of isolation facilities: "A new purpose-built 28-bedded room and one single room isolation unit was put up. The medical ward was extended to allow more space per patient. Although there was no significant change in the laboratory aspects, the originally suspended laboratory activities during the Ebola outbreak returned to normal a few months after containment."[56]

The filovirus knowledge base has yet to generate a vaccine or cure, but we know what is needed to contain an Ebola epidemic: "barrier-nursing techniques, health education efforts, and rapid identification of cases."[57] Gulu has everything in place to isolate future Ebola cases, but no practical way to identify them. A late-arriving field lab staffed by the CDC offered on-site diagnostic testing, the first time that these facilities were available in an Ebola outbreak.[58] But there, as in Kikwit five years earlier, the internationally supported field lab was dismantled after the epidemic. Just as the 1995 Kikwit experience did little to inform events at Gulu in 2000, very few lessons learned from the 2000 epidemic were applied to the Ebola outbreak in rural Bundibugyo in 2007, where all that was received was a few years' worth of disposable protective supplies.[59]

Doctors at the Mercy of Lassa Virus

A Nigerian physician contracted a deadly infection while working in the village of Jalingo in Taraba state, northern Nigeria. On February 6, 2007, the doctor was admitted to a national hospital in the country's capital, Abuja, with a fever.[60] In a manner that is atypical for Nigeria, malaria and viral hepatitis were ruled out

by testing, so a bacterial infection was the most likely diagnosis. By February 15, it became clear that the antibiotics he was receiving were not addressing his illness. He suffered renal failure and received kidney dialysis. Four days later, he was flown to South Africa, where Lassa fever, a viral hemorrhagic disease that is less well known but just as ghastly as Ebola, was diagnosed by RT-PCR and serology. He was immediately isolated and given appropriate supportive therapy. This physician was lucky on several counts. He managed to evade the almost routine prodrome of antimalarial therapy, which could have delayed his diagnosis. He was flown to a medical center that could diagnose, manage, and contain his infection. Many other West African doctors have not been so fortunate. The deaths of at least five physicians and seven nurses infected by undiagnosed patients in Nigeria and Sierra Leone have been chronicled in the medical literature;[61] many more deaths may be undocumented.

The genetic information in the core of Lassa virus, like that in Ebola and Marburg, is carried by single-stranded RNA, rather than the double-stranded DNA that carries the code in humans and other higher organisms. But the resemblance ends there. Lassa virus is an arenavirus having a granular, more compact appearance than the threadlike filoviruses.[62] The outer proteins of filoviruses and arenaviruses are completely different, so cross-immunity cannot occur. Lassa fever was first described by Jeanette Troup and her co-workers in 1970.[63] Troup, a missionary doctor in the Jos highlands of Nigeria, tended patients with what was then an unknown disease marked by fever and terminal bleeding. She investigated and documented the outbreak, but became infected and eventually died. The index case in that epidemic is believed to have come from the village of Lassa, which lies between Jos and Nigeria's border with Cameroon. Through contact with this patient, a missionary nurse became ill and eventually died in a Jos hospital. Health and laboratory workers associated with early definition of the virus and the disease in Africa and the United States contracted the deadly condition, and very few of them survived.[64] Lassa fever developed a lasting reputation for its "proclivity for killing doctors and nurses."[65]

Since the Nigerian outbreaks of 1969, most Lassa fever outbreaks have occurred in West Africa. Lassa fever is more prevalent than either Ebola or Marburg disease: a tentative estimate suggests that over three hundred thousand cases and five thousand deaths can be attributed to this disease across West Africa each year.[66] Like many "emerging" infectious diseases, Lassa fever existed long before humans noticed and named it. Lassa fever viruses from Sierra Leone and Nigeria are considerably divergent, supporting the idea that Lassa is an ancient disease. Eight unconnected Lassa fever cases or outbreaks were reported in the five years that followed its initial description. Sporadic cases and even outbreaks of the disease probably occurred before 1969 but were missed or misdiagnosed.[67]

Epidemiologic data collected in the two decades following the discovery of Lassa fever virus, including European studies showing antibodies to Lassa virus in the blood of returned expatriates, demonstrates that the pathogen is endemic in Nigeria, Sierra Leone, Guinea, and Liberia. (The use of returned travelers to estimate disease endemicity in Africa and other parts of the world has been likened to estimating the girth of a hippopotamus from its eyes as they peer above the water.[68]) The primary Lassa virus reservoir, the brown mastomys rat (*Mastomys natalensis*), is known, so human contacts with it can be controlled. It proved easier to identify the reservoir of Lassa than of Ebola because circumstantial evidence associating *Mastomys* with humans and the disease made the rodent a likely candidate for testing. This success, however, owes much to research conducted on the ground in endemic areas by African as well as visiting scientists. Many of these scientists were based at a viral research center of excellence, at Nigeria's University of Ibadan, where laboratory capacity has declined since the 1970s.

The first documented Lassa fever outbreak was amplified in a hospital; staff became infected while conducting autopsies, rather than through poor infection control. As with Ebola, hospital outbreaks of Lassa fever continue to occur, although available evidence suggests that they are typically less extensive and less likely to be overtly caused by medical procedures.[69] In a particularly ghastly instance, injections were identified as a risk factor for infection in two 1989 nosocomial outbreaks in eastern Nigeria, suggesting that needles were being reused. The poor quality of facilities, sterilizing equipment, record keeping, and auxiliary staff supports this inference. Retrospective analysis revealed that patients from one hospital who received the same injected drug from the same nurse on the same day were more likely to die of Lassa fever. Until every one of the medical staff and patients had either been infected by Lassa fever virus or fled the premises, Lassa fever was not diagnosed. The physicians never thought to refer their intractable patients to specialists, but treated them with antibacterial and antimalarial drugs, as well as fever reducers, for up to two weeks, largely administering the drugs through shared needles. When the doctors themselves fell ill, they were referred to the University of Nigeria Teaching Hospital. Lassa fever was suspected, but only confirmed posthumously in all three cases. A team of experts that investigated the outbreak months later concluded that it "mirrored the 1995 outbreak of Ebola hemorrhagic fever in Zaire, where introduction of the virus into a poorly run hospital led to several generations of infections."[70] Patients in such atrociously run institutions fare particularly badly when their diagnoses are unknown.

Lassa fever is clinically indistinguishable from Ebola or Marburg disease. However, the arenavirus Lassa appears to be restricted to West Africa, while

filoviruses are more common in central and southern Africa. The real diagnostic challenge is that, particularly in the early stages, all three diseases share signs and symptoms with almost thirty other serious infectious conditions.[71] Outside a confirmed outbreak, a Lassa fever diagnosis is most commonly made in a patient with prolonged fever that does not respond to antimicrobial therapy. Drug resistance is becoming more commonplace among bacteria and malaria parasites, so using the patient as a diagnostic test tube in this manner becomes more and more unreliable over time. Lassa fever can kill within ten to fourteen days after symptoms start, so two courses of serial chemotherapy are sufficient to bring an undiagnosed patient precariously close to the grave.

Today, despite advances in treatment, 15 percent or more of Lassa fever patients that visit a health institution are likely to die, and mortality rates in facilities that lack diagnostic technology can exceed 50 percent. In southern Nigeria, a populous endemic epicenter for Lassa fever, investigation of epidemics in 2009 revealed that only two facilities were equipped to diagnose the disease.[72] Ribavirin, an antiviral drug, or convalescent sera from previously infected patients increase a patient's chance of survival by 90 percent if administered within six days of the onset of the disease. A Sierra Leone study found that "delays between onset and admission resulted in most patients not receiving ribavirin within the critical first six days," and a similar problem was noted at the Irrua Specialist Teaching Hospital, a Lassa fever treatment center in Nigeria.[73] West African hospitals cannot afford to administer ribavirin just in case: it has nasty side effects, including severe anemia, is complicated to administer, and an unsubsidized course cost about US$1,000 in 2007, twenty times the per capita expenditure on health care.[74] Diagnostic delay reduces the odds of a patient's survival and increases the possibility that the disease will be spread before it is identified.

Kenema Government Hospital, in Sierra Leone's third-largest city, is the world's center for Lassa fever treatment and has served as a site for clinical research on the disease for over thirty years. Diagnostic support and quality of care have fluctuated considerably during this period. In its early days, investigators from the CDC used the hospital as an outpost to study the epidemiology and ecology of Lassa fever virus, providing the baseline information that frames much of what is known about the disease. At that time, Lassa and other African hemorrhagic viruses may have been of interest not only because of scientific curiosity directed at a new and deadly disease but because of their potential as biological weapons.[75] Interest in Lassa fever research in both United States and Soviet scientific circles declined after the end of the cold war, diminishing the research and diagnostic capabilities at Kenema Government Hospital.[76] Retrospective laboratory confirmation of clinical diagnoses remained available until services at Kenema were severely disrupted by armed conflict in Sierra Leone.

Retrospective laboratory data has been important for understanding the epidemiology of and in highlighting a recent decline in the accuracy of clinical diagnosis of the disease. In the 1980s, clinical diagnosis of Lassa fever in highly endemic areas was estimated to have a high predictive value.[77] Prior to 1998, between six and seven of every ten presumptive Lassa fever cases were subsequently confirmed by laboratory tests. By 2000, the figure had dropped to about five in ten, suggesting that "apparent changes in infection patterns must be interpreted with caution." As Lassa fever can account for up to 15 percent of hospitalizations among adult patients in endemic areas,[78] diagnostic errors are not trivial. Unfortunately, laboratory diagnosis, which would resolve the uncertainties, is rarely used to enhance individual patient care in West Africa. A precise diagnosis is more likely to be obtained in South Africa, Europe, or North America than in places where the disease is endemic.

Compared to many other diseases endemic to West Africa, Lassa fever is still relatively uncommon, and few health workers are trained to diagnose, treat, and contain the disease. Until recently, Dr. Aniru S. Conteh was a principal occupant of that vital niche. The Sierra Leone–born, Nigeria-trained Lassa fever specialist was a well-placed authority in the Lassa fever field for a quarter of a century. On April, 4, 2004, the sixty-one-year-old physician died after a brief illness with fever, diarrhea, renal failure, and bleeding. Conteh had contracted an infection from a patient following a needle-stick injury. Presumptive Lassa fever was diagnosed, but the antiviral drugs and supportive care he received did not save him.

Dr. Conteh had spent most of his career battling to save the lives of hundreds who had the misfortune to be infected by the Lassa fever virus.[79] His clinical research and treatment advances contributed greatly to an 80 percent reduction in mortality from the disease by 2000. Indeed, this devoted physician's work was so profoundly admired and widely respected by the communities he served that his hospital was deliberately spared during multiple attacks on the city by anti-government forces. It is shocking to learn that in order to confirm the presence of Lassa fever virus in the blood of Dr. Conteh, and the patient who infected him, specimens had to be sent from Sierra Leone to the National Institute for Communicable Diseases in South Africa, from the undisputed center of Lassa fever to a country where this infection never occurs naturally. Three years later, a Nigerian doctor was flown to South Africa to have his Lassa fever diagnosed and treated, placing numerous people involved in his evacuation and care at risk.[80]

Why is it that Lassa fever and its reservoir, first documented in Nigeria, where the disease remains endemic, cannot be identified at the national hospital in that country nearly forty years later? Why was the Nigerian hospital unable to detect an endemic virus, even though the same hospital was equipped to successfully implement the complicated procedure of kidney dialysis? Why is it that even

though Nigeria probably has the most cases of Lassa fever in the world each year, in 2009 almost all cases defied diagnosis because only two laboratories had the necessary capacity? Why was the laboratory capacity to diagnose the disease not an integral part of Dr. Conteh's 2004 Lassa fever ward at Kenema Government Hospital in Sierra Leone? Conteh and his collaborators at the CDC had coauthored a study published in the *Journal of Clinical Microbiology* that focused specifically on the development of a diagnostic test for Lassa fever.[81] Why were effective diagnostic facilities unavailable at the station where they were most needed four years later?

Dr. Conteh is remembered for his dedication and resilience in fighting this deadly disease in the face of violent conflict, funding challenges, the changing priorities of international collaborators and donors, and limited facilities. His death engendered many concerns for the future. Obituaries published in leading medical journals lamented the loss of this key base for treating Lassa fever patients and the near impossibility of replacing a scientist-physician who pursued research and clinical care conjointly—and did so on African soil.[82] Patients voted with their feet and paid with their lives. The number of patients admitted to Kenema's Lassa fever ward declined from 321 in 2004 to nineteen in the first half of 2007. The same period saw a rise in the proportion of fatal cases from 25 percent in 2004 to 58 percent in 2007.

Finally, three Lassa fever–endemic countries, in a consortium that included virologists from Tulane University, the U.S. Army Medical Research Institute of Infectious Diseases, and the WHO, established the Mano River Union Lassa Fever Network, with a primary objective of increasing laboratory capacity in the "Mano River Countries" of Guinea, Liberia, and Sierra Leone. The first priority has been to replace the essentially derelict Lassa fever treatment and research facilities, which shut down when Conteh died. It took a couple of years to build the requisite Biosafety Level 3 Kenema lab and longer to equip it, but by the end of 2007 the consortium was able to announce that the lab was functioning and that comparable facilities were planned for Guinea and Liberia.[83] This development offers much promise, even though some of its impetus comes from biosecurity, rather than public health concerns.

Many physicians in Africa are highly skilled diagnosticians whose clinical guesses are often, but not always, right. They cure many patients but could address the illnesses of very many more if they were not handicapped in ways that could be resolved by simple tests. These tests are often described as impractical but, in fact, are both essential and feasible. Patients in endemic areas bear the brunt of this handicap and, in some cases, know it. A survey of "knowledge, attitudes and practice" conducted by the British charity Merlin, a principal supporter of Dr. Conteh's Lassa fever work at Kenema Government Hospital, reveals

that laypeople in Sierra Leone are well informed about the risks posed by the disease and the need for more rigorous diagnosis. Patients, sufficiently aware of diagnostic imprecision, used the term "guessing" to describe the prevalent mode of diagnosis.[84] One patient group pleaded for a lab: "We are begging for a Lab, so we can go there for a proper check up . . . so we can be serious and fast to know which is the sickness, instead of giving blind treatment to people."[85]

Even people without medical training are aware that the most pivotal roles that a hospital could play are early and precise laboratory diagnosis and the administration of antiviral or supportive care in a safe environment. These services are never available outside of allopathic medicine and should be available within any scientific medical care system worthy of the name. Although emphasis is frequently on therapeutics, two complementary areas of deficiency loom large: diagnostics and infection control. Instead of meeting the charge to diagnose, contain, and manage disease, African hospitals have too often served to amplify epidemics, unwittingly mediating person-to-person transfer via diagnostic imprecision and suboptimal infection control. Infections acquired in this manner are more likely to be fatal than those acquired in the wild, and their impact detracts from the many more patients that hospitals bring to health.

Bringing the Diagnosis Home

In the last three months of 1984, a hospital in the small Brazilian town of Promissão admitted about two dozen children with conjunctivitis, high fevers, intestinal disturbances, and purple skin from bleeding capillaries. Many of the children died within twenty-four hours of reaching the hospital. Promissão hospital, and then the state of São Paulo, ruled out meningococcal meningitis and a number of other known diseases that have similar clinical presentation. By the time the U.S. CDC was called in to assist in investigating the strange epidemic of "Brazilian Purpuric Fever," it was clear that this was a new disease and that it was very likely caused by an unfamiliar strain of bacteria: *Haemophilus influenzae* biogroup aegyptius, which was isolated and identified from some patients. Presumptive identification of this bacterium prompted use of antibacterials to treat the strange syndrome, ultimately saving some patients' lives. Continuing research in Brazil and at the CDC confirmed this bacterium as the cause of the new disease, and, within three years, a rapid diagnostic test for the disease was deployed. The test was used to chart the epidemiology of the new pathogen inside and outside Brazil over the next twelve years.[86]

In contrast to Brazilian purpuric fever, diagnostic expertise for African hemorrhagic viral fevers has until very recently been based almost exclusively at

locations that are far away from the places where they are endemic. Rather than augmenting local efforts and providing specialized technologies for confirming unusual or new diagnoses, Western centers of excellence are providing primary and secondary level care support for African patients. The prevailing model has been one in which outbreaks of hemorrhagic fever are identified after a considerable delay, and then experts in space suits are flown to the scene, where they work from laboratories housed in tents. Although these personnel provide valuable expertise and selfless service, their arrival is often accompanied by demoralization of local health workers, who have been struggling for weeks or months to contain an unidentified epidemic at great personal risk. Sometimes international experts even work independently, neglecting to communicate with local personnel, even though the two groups have the same goals.[87] Time and time again, field laboratories are set up to manage outbreaks and to procure specimens for distant laboratories, only to be dismantled when the epidemic wanes. Ebola and Marburg are localized in central and southern Africa, and Lassa fever is endemic to West Africa, so diagnostic and research facilities should be centered in these regions. Having laboratory capacity on the spot is the only way to mount continuous surveillance and recognize outbreaks early. Moreover, functional laboratories in endemic areas are better placed to provide testing with appropriate quality assurance, which is difficult to ensure in emergency outbreak labs or for small numbers of hurriedly shipped specimens.

A more useful and responsive diagnostic strategy would have frontline medical and laboratory personnel in local laboratories appropriately trained to recognize African viral hemorrhagic disease, respond to sporadic infections, and contain outbreaks quickly. The need to ship dangerous strains and specimens, as well as infected patients, would be reduced. The safety of local health workers, and their confidence in the health systems that employ them, would be better assured. Transmission patterns and reservoirs would be much more rapidly and effectively studied. Despite these obvious advantages, it was not until 2001 that an epidemiologic surveillance system for hemorrhagic fevers was set up to cover Congo and Gabon.[88] The network's mandate was to identify potential human and primate Ebola cases, relying on local hunters to report carcasses of suspected infected animals. Between the inception of this surveillance network and 2003, five human outbreaks of Ebola were reported, and in all but one of these index cases had likely contact with infected primates. The initial network has successfully predicted high-risk periods for human outbreaks from the occurrence and density of primate infections. The centers were also bases for recent research pointing to bats as reservoirs for Ebola and Marburg.[89] The surveillance enterprise has placed much-needed diagnostic and protective infrastructure on the ground, ensuring that it is available where and when outbreaks occur.

A 2004 Ebola outbreak in southern Sudan had a considerably better trajectory than earlier outbreaks because preliminary identification at a Kenyan lab hastened the confirmation of the epidemic. Community-based social mobilization and education began immediately, and no more than seventeen cases, seven deaths, and four generations of transmission were documented by the end of the outbreak. Diagnostics were unfortunately not available in the field, but the regional lab was still able to reduce the time from initial case presentation to diagnosis to less than a month, even in a remote area.[90] The laboratory development initiatives of the Mano River Union Lassa Fever Network may offer similar promise for Lassa fever diagnosis in Guinea, Liberia, and Sierra Leone. These projects need to be nurtured and used as a template for clinical laboratory development elsewhere on the continent. For example, the urgent need for diagnostic support to manage and control Lassa fever and other hemorrhagic infections is yet to be addressed in other endemic countries, including Nigeria, where the most virulent strains of the virus are believed to exist.[91] Similarly, not every country at risk of Ebola or Marburg outbreaks can identify hemorrhagic fevers caused by those viruses.

Africans are moving deeper into forests, and improved travel networks mean that an individual can move from the heart of the forest to a city with international connections in just a few hours. Contact with wildlife and the risk of contracting and spreading Lassa, Ebola, Marburg, and as yet unknown zoonotic infections will continue to rise. Repeated nosocomial outbreaks demonstrate that modern hospitals are sites where critically ill patients and their caregivers may face heightened risks of infection by blood-borne viruses when housed with infected but undiagnosed patients. At the time when yellow fever was a major scourge in Africa, three of the seven major yellow fever labs were located on the continent.[92] Even though the science of virology was only emerging at the time and a number of research roadblocks had to be surmounted, the vector was identified, and a vaccine was produced. Repeated flying in of space-suited superheroes equipped with mobile temporary laboratories is not a rational way to manage or learn from epidemics caused by emergent viruses. Floundering health workers and hospital amplification engender a justifiable lack of confidence in local health systems and are detrimental to containing the damage caused by these epidemics. The services of international expert teams are likely to be required in future large epidemics, irrespective of any diagnostic development, but sole dependence on this slap-dash protocol is not wise. In addition to time delays, considerable risk is associated with intercontinental transport of infected specimens harboring as-yet unidentified and possibly lethal viruses. Although the best scientific research is a global achievement, it is essential to focus diagnostic support and research in countries where the diseases occur in nature.