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Background. In 1976, the first cases of Ebola virus disease in northern Democratic Republic of the Congo (then referred to as Zaire) were reported. This article addresses who was responsible for recognizing the disease; recovering, identifying, and naming the virus; and describing the epidemic. Key scientific approaches used in 1976 and their relevance to the 3-country (Guinea, Sierra Leone, and Liberia) West African epidemic during 2013–2016 are presented.

Methods. Field and laboratory investigations started soon after notification, in mid-September 1976, and included virus cell culture, electron microscopy (EM), immunofluorescence antibody (IFA) testing of sera, case tracing, containment, and epidemiological surveys. In 2013–2016, medical care and public health work were delayed for months until the Ebola virus disease epidemic was officially declared an emergency by World Health Organization, but research in pathogenesis, clinical presentation, including sequelae, treatment, and prevention, has increased more recently.

Results. Filoviruses were cultured and observed by EM in Antwerp, Belgium (Institute of Tropical Medicine); Porton Down, United Kingdom (Microbiological Research Establishment); and Atlanta, Georgia (Centers for Disease Control and Prevention). In Atlanta, serological testing identified a new virus. The 1976 outbreak (280 deaths among 318 cases) stopped in <11 weeks, and basic clinical and epidemiological features were defined. The recent massive epidemic during 2013–2016 (11 310 deaths among 28 616 cases) has virtually stopped after >2 years. Transmission indices (R0) are higher in all 3 countries than in 1976.

Conclusions. An international commission working harmoniously in laboratories and with local communities was essential for rapid success in 1976. Control and understanding of the recent West African outbreak were delayed because of late recognition and because authorities were overwhelmed by many patients and poor community involvement. Despite obstacles, research was a priority in 1976 and recently.


In late August 1976, patients with a hemorrhagic fever syndrome presented to the rural Yambuku Mission Hospital (YMH) in northwest Democratic Republic of the Congo (DRC; then referred to as Zaire); Congolese medical staff responded and ruled out the provisional diagnosis of malaria, typhoid, or yellow fever. Expert assistance was requested by the government from several countries in October 1976 by the minister of health. The International Commission for the Investigation and Control of Ebola Hemorrhagic Fever in Zaire reported their findings in 1978 [1]. With the recent massive epidemic of Ebola virus disease in Guinea, Sierra Leone, and Liberia, there has been focus on lessons from the first outbreak [2]. There have been many questions raised by the scientific and lay communities and misattributions, ascribing credit for “discovery” of Ebola. This article is written to (1) state for the record who was responsible for recognizing the new disease, for recovering, identifying, and naming Ebola virus, and for describing and controlling the epidemic in Yambuku, which spread into Kinshasa; and (2) to show the relevance of the 1976 outbreak to the 2013–2016 epidemic.

OUTBREAK ONSET AND DISCOVERY

On 22 August 1976, the 42-year-old headmaster of the Yambuku Mission School, a resident of Yandongi Village, Bumba Zone, Equateur Region, returned from a 2-week driving excursion to...
northern Zaire; along the route, he purchased antelope and smoked monkey meat. He presented on 26 August to the outpatient clinic of the 120-bed YMH with chills and fever and was treated for malaria with injections of chloroquine and an antipyretic by the chief medical assistant at YMH, with apparent relief. The patient’s fever diminished initially but after 1 week returned with severe headache, muscle pain, nausea, abdominal complaints, and intestinal bleeding. He died on 6 September with a hemorrhagic syndrome of unknown cause. On 28 August 1976, an adult male was hospitalized on the medical ward at YMH with “epistaxis, dysentery, and fever,” recorded in the hospital register. This patient remained for 2 days and left without follow-up; he was unknown in the nearby village of Yandongi, listed as his residence.

Several patients coming to YMH with a variety of conditions, including pregnancy, were given vitamins and other medicines by injection; injections were a routine practice favored by patients and medical staff. Five glass syringes and metal needles used at the outpatient department, inpatient medicine wards, and prenatal and village outreach clinics were used repeatedly without sterilization and only occasionally were rinsed. In early September, several dozen patients who had received injections at YMH developed a similar febrile hemorrhagic syndrome and died in about 1 week, as did many of their contacts [1].

INITIAL NATIONAL RESPONSE TO THE “MYSTERY DISEASE OF YAMBUKU”

The first national alert and response to the growing outbreak came from Ngoy Mushola, the chief medical officer of the Bumba Zone, who came to Yambuku during 15–19 September 1976. His report to Kinshasa was the first to describe the “mystery” disease manifesting fever, headache, abdominal pain, and bleeding; from 5 to 22 September, Ngoy reported 30 cases and 22 deaths, and patients were fleeing the hospital. Later studies showed that >120 cases had occurred during this time, over half of which were tied to injections [1].

On 23 September, a national team led by Jean-Jacques Muyembé-Tamfun, a microbiologist, and Colonel Omombo, an epidemiologist, was sent from Kinshasa to Yambuku by the Belgian Fonds Médical Tropical (FOMETRO), DRC; Gerard Raffier, chief of the French Medical Mission; and Dr Krubwa of the National University of Zaire visited Bumba and Yambuku by military helicopter from 4–9 October. Blood samples were taken from 2 persons whom they judged to have recovered from the clinical disease. The team advised the Commissaire du Zaire, Ipoya Olonga, that Bumba Zone (275 000 persons) be put under strict quarantine and YMH be closed. The advice was accepted, stopping commercial airplane landings, movement in and out of villages, and prohibiting riverboats from docking along the Zaire River. Ultimately, 13 of 17 YMH staff (76%) became ill with the disease, and 11 (80%) died.

VIRUS ISOLATION AND IDENTIFICATION

On 28 September 1976, just prior to her death, a blood specimen was again collected from the sick nun from Yambuku by Jacques Courtelle, a Belgian physician working at Ngaliema Hospital in Kinshasa. He reported that she had a 5-day febrile, hemorrhagic illness, possibly yellow fever. The sample arrived in a broken vial at the Institute of Tropical Medicine (ITM; Antwerp, Belgium) on 29 September, followed by a postmortem liver specimen a day later. These specimens were inoculated into Vero cells and analyzed by Guido van der Groen, René Delgadillo, and Peter Piot in the microbiology department directed by Stefaan Pattyn [3]; a cytopathic effect was observed. When a Marburg-like virus was observed by electron microscopist Wim Jacob, the World Health Organization (WHO; Geneva, Switzerland) was notified: the ITM team was told by Paul Brès of the WHO to send all specimens immediately to the International AIDS Research Establishment (MRE; Porton Down, United Kingdom), arriving on 5 October. Some materials were forwarded to the Centers for Disease Control and Prevention (CDC; Atlanta, Georgia), arriving on 11 October and 13 October; both laboratories had maximum containment for highly pathogenic viruses. The ITM retained some specimens in Antwerp [3]. At the MRE, Ernest Bowen, Graham Lloyd, William Harris, Geoff Platt, Arthur Baskerville, and Ethelwald Vella did the analyses. In Kinshasa, Gerard Raffier sent the blood samples taken from convalescent patients and others to Pierre Sureau at the Pasteur Institute (Paris, France). As Pasteur likewise lacked a maximum containment unit, Sureau was urged by Brès to ship all specimens immediately to the CDC (P. Sureau, Une nouvelle fièvre hémorragique virale Africaine: l’épidémie de Yambuku, Zaire, 1976: la découverte du virus Ebola; Carnet de Route, unpublished memoir).

Inoculation into animals and cell lines occurred in all 3 laboratories, and virus was grown (Table 1). Filoviruses particles, resembling Marburg virus, were seen by negative contrast electron microscopy (EM) of Vero cell culture supernatant of blood and by thin-section EM [4–6].
Using the remaining drops of convalescent serum squeezed from a black cotton mass in a broken test tube received from Sureau, a new etiologic agent was identified in the Special Pathogens Branch, CDC, by Patricia Webb, James Lange, and Karl Johnson. Patricia Webb showed that serum from 1 convalescent DRC patient did not cross-react with an archived Marburg virus in a 2-way immunofluorescence antibody (IFA) test; sera from the convalescent DRC patient and from Marburg patients were tested against viruses from a DRC patient and a Marburg virus, and a positive reaction occurred only between DRC sera and DRC virus and between Marburg sera and archived Marburg viruses (Table 2) [1, 4]. The iconic EM pictures of the new virus were taken by Alyne Harrison and Fred Murphy (Figure 1) at the CDC. Harrison performed many of the thin-section EM examinations of fixed liver specimens from DRC patients, and Murphy took the negative-contrast EM photos.

Biosafety precautions in Antwerp and Paris were those taken on an open bench, without a hood or laminar flow system. Laboratory coats, gloves, absorbent covering on the bench, and hypochlorite solution for disinfection were used. Special concern in Antwerp was avoiding contamination of cell cultures. In Paris, upon opening a thermos arriving from Kinshasa, 1 test tube broke, and the contents were transferred to another vacutainer. After being informed by the WHO to send the materials to the CDC, all Paris specimens were packaged in accordance with instructions received by Pasteur for shipping specimens containing Lassa fever virus.

**POSSIBLE SUDANESE ORIGIN**

Shortly after being notified of the outbreak in Zaire, in late September, the WHO reported that a similar outbreak of hemorrhagic fever was occurring in southern Sudan [7]. A national investigation later determined that on 27 June 1976, patients with a hemorrhagic illness started dying in Nzara, Western Equatorial Province. The outbreak spread to the neighboring town of Maridi on 6 August. National public health authorities were first notified of the epidemic on 26 September, after which they visited Maridi, where 30 patients with the syndrome were hospitalized and specimens were collected. Upon returning to Khartoum on 29 September 1976, the WHO was notified, and the specimens were forwarded to the MRE.

As it was reported that palm oil and other commerce traveled along northern DRC routes to neighboring countries, including Sudan, the initial hypothesis of the Zaire team was that the

<table>
<thead>
<tr>
<th>Year of Illness/Virus</th>
<th>Serum Origin/Country</th>
<th>Time After Onset/Patient(s)</th>
<th>Viral Antigen</th>
</tr>
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<tbody>
<tr>
<td>1967/Marburg virus</td>
<td>Germany</td>
<td>5 mo</td>
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<td></td>
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<td>5 mo</td>
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<tr>
<td>1975/Marburg virus</td>
<td>South Africa</td>
<td>1 mo</td>
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<td></td>
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<td>4 mo</td>
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<tr>
<td>1976/Ebola virus</td>
<td>Sudan</td>
<td>12 d</td>
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<tr>
<td>1976/Ebola virus</td>
<td>&quot;Convalescent&quot;, 1 mo</td>
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epidemics were connected. Epidemiologists Joseph McCormick of the CDC and Simon van Nieuwenhove of FOMETRO were airlifted to northeastern Zaire in late October to follow highly degraded, virtually impassable routes; question local authorities; seek cases; collect samples from patients and those who had possibly recovered; and review medical records. The McCormick team crossed 25 km into Sudan, visiting Nzara. Following 3 weeks of travel, no link between the Sudan and Zaire outbreaks was found. Notable was that persons afflicted in Nzara worked in a cotton factory in which many bats were hanging from the rafters. Because civil war was occurring in Sudan, the Sudan WHO investigative team could not access the outbreak area until after the Zaire team visit.

It was later determined that Ebola Sudan virus causing the Sudan outbreak was different serologically from Ebola Zaire [8]. While the Zaire and Sudan presentations were marked by almost universal fever, headache, abdominal pain, diarrhea, nausea and vomiting, bleeding, oral lesions, and conjunctivitis, the main differences involved the case-fatality rates, with values of 88% (280 deaths/318 cases) in Zaire and 53% (151 deaths/284 cases) in Sudan, and the high frequency of chest pain (83%) and cough (49%) in Sudan [1, 7].

DESCRIPTION AND CONTROL OF THE EPIDEMIC

The most comprehensive description of the 318 patients afflicted was based on standardized recording by interviewing patients’ families, convalescents, members of the mission, and the Bumba administrative community, with the help of interpreters fluent in Lingala and Budza, and by reviewing hospital records by teams under the direction of Joel Breman of the CDC. Margarethe Isaacson of the South African Institute of Medical Research, Pierre Sureau, Peter Piot, J. M. Mbuyi and V. Kintoki of the DRC, and David Heymann of the CDC also recorded clinical and epidemiological information that was incorporated into the final International Commission report and individual presentations at a conference held in Antwerp in 1978 [1, 9–12]. Control measures, initiated by Commissaire Ilongo, national authorities, and Jean-François Ruppol in Bumba Zone, were strengthened by the guidance of the International Commission in Kinshasa and nationally, which had experience in the eradication of smallpox and surveillance for monkeypox [13]; in particular, isolation of patients and rapid burial were accepted by the community. Successful restricting of movement of Ngaliema Hospital staff in Kinshasa for 3 weeks occurred [14].

Studies were performed in accordance with Zaire clinical practices, considering the acute nature of the epidemic.

PLASMAPHERESIS AND PLASMA USE

NAMING OF EBOLA VIRUS

The Ebola river is 250 km in length and part of the Congo River network, about 60 km from Yambuku and not in the area of the epidemic. During the 1976 field investigations, Karl Johnson, the International Commission scientific director, suggested the name “Ebola” virus to ensure that the Yambuku community was not stigmatized. The name is a distortion of the local Ngbandi name Legbala, meaning “white water” or “pure water,” although there is some disagreement [17]. The name Ebola was accepted by International Commission members in Kinshasa. At a meeting in London in 1977 to discuss the first 2 outbreaks, the name Ebola was accepted after some debate.

RELEVANCE OF THE 1976 OUTBREAK TO THE 2013–2016 EPIDEMIC

Key to diagnosis in 1976 was the relatively quick recognition of a severe, possibly new, disease by national authorities. International notification and specimen provision occurred within 5 weeks from onset of the first cases; this did not occur in the 2013–2016 epidemic, in which the delay was >3 months (Table 3). In 1976, one laboratory (the CDC) could identify a new agent using reagents archived from previous Marburg virus outbreaks. The CDC assessed the presence of viremia in 8 patients and analyzed serial viremia levels in one patient, using Vero cell culture [1, 4]; all these patients died.

One serologic diagnostic test, the IFA, was used in the field in 1976 to identify infected individuals who had recovered. Once the cell culture fixed slides were available, the turnaround for IFA testing was generally ≤1 hour; this required separation of the plasma or serum, incubation of the slide with the serum, and reading in an immunofluorescence microscope. Results were available in the field promptly because survivors and potential candidates for plasmapheresis needed to be assessed carefully. The IFA test was later found to lack specificity as compared to enzyme-linked immunosorbent assay, which has been used more extensively since the 1990s [18]. In the 2013–2016 epidemic, 44 diagnostic laboratories working in 3 countries used reverse transcription–polymerase chain reaction giving qualitative results [19].

The serological results in 1976 showed 38 positive individuals, several of whom had very few signs and symptoms [1, 9]. This indicated that Ebola may have been present in the area before the outbreak. Serum specimens with antibodies to Ebola virus are being reported from West Africa in specimens collected for Lassa fever and other studies [20, 21]. Nosocomial transmission and susceptibility of healthcare staff have been the hallmarks of virtually all filovirus outbreaks, particularly in the DRC [22]. While injections have not been reported as a transmission vehicle in the West African outbreak, contaminated injections, as occurred in 1976, remain a constant danger.

The 21-day maximum incubation period for individuals and the 42-day period for quarantine of populations exposed to Ebola, determined in 1976, remain in wide use. Importation into Kinshasa by plane occurred in 1976, and one secondarily infected health worker was moving freely in the city for at least 48 hours; yet, no urban transmission occurred as in West Africa in large numbers. The low overall secondary attack rate in
families in Yambuku of 5.6% and decreasing transmission rates by generation of spread indicated the disease had limited transmission potential, except in special circumstances (Table 4).

However, a recent calculation of the person-to-person basic reproduction rate ($R_0$) during the intensifying and dangerous early course of the 1976 outbreak was 1.34, with a 3% chance that ≥1000 cases could have occurred if control measures were delayed [23]. Calculations of $R_0$ occurring during the first 9 months in West African outbreaks have ranged from 1.71 for Guinea, 1.83 for Liberia, and 2.02 for Sierra Leone [24]. Other calculations for past outbreaks have been more variable [25].

While the efficacy of immunotherapy (and other treatments) for Ebola remain unknown, this avenue of research is underway in West Africa; a trial in Guinea did not find improvement with convalescent plasma [26]. Community involvement was crucial to success for understanding and controlling the 1976 outbreak. Factors causing the more extensive and explosive spread in 2013–2016 need elaboration. Regrettably, in 2013–2016 many rural and urban populations were uncooperative with national and international authorities. Much more medical, sociological, and behavioral research is needed to understand the recent community constraints leading to epidemic prolongation and disruption of medical and administrative services [27].

To rule out other diseases, suspected febrile Ebola patients in 1976 were treated for malaria, enteric and respiratory disease, and other conditions by national clinicians. In the recently established Ebola treatment units, malaria prophylaxis and treatment were provided; some Ebola treatment units also treated bacterial infections with antibiotics. As the epidemic progressed, the national health services were overwhelmed by suspected Ebola patients, and malaria diagnostic assays and treatments were reduced greatly, resulting in thousands of excess deaths from malaria [28].

### DISCUSSION

In an epidemic situation, research should be well defined and begin as soon as feasible in accordance with national and institutional approvals. Patient management can be an area of research requiring standardized protocols and careful record keeping. During an acute outbreak, patient care and biosafety have priority. Studies of drugs and vaccines are a particular challenge in a crisis situation, where there is pressure to use...
all modalities available, proven or not; thus, randomized trials are particularly difficult to do.

While not proven, it is highly likely that the adult patient with “epistaxis, dysentery, and fever” was the first 1976 Ebola patient. No other patient with a hemorrhagic syndrome had been admitted to the YMH in the previous 8 months. Regrettably, no outpatient records were available despite >1000 visits occurring monthly. In 1976, there were no reports of bat ingestion, and no sick animal contact was reported at the interviews and animal captures in 1976 and 1979. The index case in Guinea in the recent outbreak is alleged by many early media reports to have been playing under a tree laden with bats, but the connection between the tree and disease has never been proven.

National health officials and resident Belgian and French physicians were the first to see and assess patients in Yambuku. The Antwerp ITM team was the first to receive specimens and recover what they called a “Marburg-like virus,” as did the MRE. However, it was the CDC laboratory that identified and recognized a new hitherto unknown virus that fulfilled the criteria for discovery of a new virus [29]. Because of the lack of information about the nature and evolution of the disease, the remoteness of Yambuku (1100 km from Kinshasa), the concern with patients being treated in Kinshasa, and the lack of early contact tracing, with rumors of similar disease outbreaks elsewhere in the country, the distribution curve and course of the outbreak were unclear initially to the International Commission. In time, the International Commission found that the outbreak was waning (Figure 2). This was undoubtedly due to the isolation of the affected Yambuku community, effective control measures in Bumba Zone and Kinshasa, and relatively low transmission potential.

Ebola is a contact disease, with blood and other virus-laden body fluids the source of person-to-person transmission. Hospital closure, isolation of patients, culturally sensitive rapid burial, and community cooperation and quarantine were initiated early in the Yambuku area. These public health measures were not implemented initially in West Africa. As the veritable tsunami of patients overwhelmed the health and administrative systems, the first efforts were understandably to treat the sick—and only later to focus on public health containment. Many groups have assessed the West Africa outbreak and advised prediction and prevention strategies, rather than only detection and response, important as both approaches may be [27, 30].

Figure 2. Cases and key events during Ebola hemorrhagic fever outbreak, equatorial region, Democratic Republic of the Congo (formerly referred to as Zaire), by time of onset, 26 August 1976–30 January 1977. Abbreviations: CAR, Central African Republic; CDC, Centers for Disease Control and Prevention.
True viral load has almost never been measured serially in patients in any Ebola outbreak. Viral RNA copies are not infectious: we need data on how long, how much, and where infectious virus is present, with clinical correlations. Ebola RNA copies in semen and the eye have been found recently, and the importance of these findings, particularly in regard to sexual and prolonged transmission of Ebola, is being defined. Virus in testes is undoubtedly a major factor in the recent (2016) cluster of cases occurring in the forest area of Guinea and extending into Liberia [31].

Notwithstanding the trepidation in dealing with a new pathogen of very high virulence causing widespread panic and confusion, there was an exciting sense of discovery and camaraderie among team members of the 1976 International Commission. Zaire team members wanted to describe first the key clinical and epidemiological features of the disease and any links to the Sudan outbreak. Why the 2 events occurred almost simultaneously remains an unexplained coincidence.

Fruit bats are now incriminated as probable reservoirs for filoviruses, and Ebola virus genome and antibodies have been found in bat and rodent species in East and West Africa [32–34]. Marburg virus has been isolated from bats in parts of Africa [35–37]. A recent survey of human exposure to animals in the DRC shows that contact with bats occurs much less often than with rodents, duikers, and nonhuman primates [38]. There is now some evidence from serologic surveys that African populations are exposed to Ebola virus and Marburg virus during interepidemic periods [20, 21]. If this finding is verified elsewhere, one can conclude, as we did in Zaire, that the filoviruses in Africa are enzootic and epizootic within the so-called filovirus triangle [39, 40]; more-extensive preparations are needed to detect and manage future outbreaks promptly. Severely ill febrile patients, particularly with hemorrhagic manifestations, should be screened for Ebola virus and other pathogens; such conditions are often misdiagnosed and result in nosocomial amplification and community spread. Primary prevention through strengthened prediction models, detection, response, control mechanisms, and international cooperation and coordination are essential for all countries in Africa and elsewhere where Ebola virus and new and reemergent pathogens are sure to surface again.

Notes

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