The emergence of Ebola Hemorrhagic Fever: from Central Africa to West Africa
Yambuku Mission Hospital, DRC (Zaire), 1976
Yambuku Mission, DRC, 1970s

Nurses, Yambuku Mission Hospital

Maternity, Yambuku Mission Hospital
Deceased health workers, Yambuku Mission Hospital, DRC, 1976

Sœur Beata
missionnaire à Yambuku
avril 1976

Sœur Myriam
missionnaire à Yambuku
avril 1976

Sœur Romana
missionnaire à Yambuku
avril 1976

Sœur Edmonda
missionnaire à Yambuku
avril 1976

VROÔM AANENKEN AAN
Pater Germain Lootens
Missionaris van Schout
geboren te St.-Kruis-Brugge op 30 oktober 1910,
priester gewijd op 16 augustus 1935,
overleden te Yambuku op 2 oktober 1976
niet slachtoffer van een zware epidemie.
Ngaliema Hospital, Kinshasa, DRC
Filoform virus, electron micrograph, 1976

Source: CDC
<table>
<thead>
<tr>
<th>Date</th>
<th>Name</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/4/76</td>
<td>123456</td>
<td>34</td>
<td>Malaria</td>
<td>Quinine</td>
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<tr>
<td>28/4/76</td>
<td>789012</td>
<td>45</td>
<td>Typhoid</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>28/4/76</td>
<td>345678</td>
<td>56</td>
<td>TB</td>
<td>Isolation</td>
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</tbody>
</table>

*Note: All patient records are anonymized for privacy.*
Animal market, near Yambuku, DRC
Hospital Implements, Yambuku, 1976
Ebola Haemorrhagic Fever by mode of transmission, Yambuku DRC, 1976

Source: CDC

Cases: 318
Deaths: 280 (88%)
Risk assessment, Ebola haemorrhagic fever, 1976

- Two highly lethal outbreaks simultaneously
  - Zaire (Yambuku) 280/318
  - Sudan (Maridi) 151/284

- Transmitted by blood, secretions, excretions of patients – epidemiology not consistent with airborne infection

- Nosocomial transmission drove outbreaks into health workers and through them to community

- Outbreak ended spontaneously as communities learned how to prevent

- Animal source suspected

- Unknown potential to reappear – one time emergence vs. periodic re-emergence
1 clinical case/died
1 contact (sister) fit possible case definition/survived
1 historical probable clinical case/recovered, 1972
## Ebola haemorrhagic fever surveillance, Zaire, 1981–1985: antibody in reported possible, probable and clinical cases

<table>
<thead>
<tr>
<th>Case definition</th>
<th>1981 (n = 0)</th>
<th>1982 (n = 4)</th>
<th>1983 (n = 36)</th>
<th>1984 (n = 27)</th>
<th>1985 (n = 31)</th>
<th>1981–1985 (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Clinical</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Probable</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>21</td>
</tr>
</tbody>
</table>

**NOTE.** \(n\) = no. of surveillance reports investigated.

Source: WHO
Risk assessment, Ebola haemorrhagic fever, 1985

- Two highly lethal outbreaks simultaneously
  - Zaire (Yambuku) 280/318
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Kikwit General Hospital, Zaire, 1995
Nursing sisters, Kikwit General Hospital, Zaire, 1995
Ebola Haemorrhagic Fever by mode of transmission, Kikwit Zaire, 1995

315 cases
250 (80%) deaths

Source: WHO/CDC
Contact with patients and funeral practices transmit in communities

Kikwit 1995
Ebola outbreaks can be stopped

- Patient identification, isolation and protection of health workers/infection control
- Surveillance/contact tracing and fever surveillance with rapid diagnosis and isolation
- Community understanding with safe patient and body transport systems, safe burial and household/environmental decontamination
The search for an animal reservoir, Ebola Haemorrhagic Fever, 1976 - 1990

Random collection,
Outbreak sites:
Markets, nets, traps

Pygmy ethnic groups, Congo Basin
Pygmies hunters, Congo Basin
Tai Forest, Cote d’Ivoire, 1992
Clinical course, Ebola virus infection, patient presumably infected during necropsy of infected chimpanzee

Ebola Haemorrhagic Fever, Mayibout Gabon, 1996

- 19 index cases: found and butchered freshly dead chimpanzee
- 18 family members/health workers infected
- Minimal onwards transmission
- 21/37 (70%) fatal
Two highly lethal outbreaks simultaneously
- Zaire (Yambuku) 280/318
- Sudan (Maridi) 151/284

Transmitted by blood, secretions, excretions of patients – epidemiology not consistent with airborne infection

Nosocomial transmission drove outbreaks into health workers and through them to community: outbreaks can be prevented

Outbreak ended spontaneously as communities learned how to prevent

Animal source suspected: link to non-human primates confirmed

Unknown potential to reappear – one time emergence vs. periodic re-emergence: re-emergence occurs
The search for a reservoir in nature, Ebola Haemorrhagic Fever, 1996

Source:: Emerging Infectious Diseases
Brief Communications

Fruit bats as reservoirs of Ebola virus

Eric M. Leroy1,2, Brice Kurunlungu3, Xavier Pourrut4,5, Pierre Rouquet6, Alexandre Hassanin7, Philippe Yaba8, André Délitala9, Janusz T. Pawska10, Jean-Paul Gonzalez11 and Robert Swanepoel12

The first recorded human outbreak of Ebola virus was in 1976, but the wild reservoir of this virus is still unknown1. Here we test for Ebola in more than a thousand small vertebrates that were collected during Ebola outbreaks in humans and great apes between 2001 and 2003 in Gabon and the Republic of the Congo. We find evidence of asymptomatic infection by Ebola virus in three species of fruit bat, indicating that these animals may be acting as a reservoir for this deadly virus.

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Correspondence to: Eric M. Leroy1 Email: eric.leroy@ird.fr
Ebola emergence: current hypotheses
Risk assessment, Ebola haemorrhagic fever, 2003

- Two highly lethal outbreaks simultaneously
  - Zaire (Yambuku) 280/318
  - Sudan (Maridi) 151/284

- Transmitted by blood, secretions, excretions of patients – epidemiology not consistent with airborne infection

- Nosocomial transmission drove outbreaks into health workers and through them to community: outbreaks can be prevented

- Outbreak ended spontaneously as communities learned how to prevent

- Animal source suspected: link to non-human primates confirmed: fruit bats may play a role in transmission

- Unknown potential to reappear – one time emergence vs. periodic re-emergence: re-emergence occurs
Ebola Reston Virus, 1989 – 1990, USA and Philippines

- Animal quarantine facility, monkeys imported from Philippines - highly lethal outbreak
  - 4 asymptomatic human infections

- Primate facility in Philippines - highly lethal outbreak
  - 3 asymptomatic human infections
Philippines, Porcine Reproductive and Respiratory Syndrome, July 2007 – June 2008

[Map showing Philippine Provincial Boundaries with marked outbreaks]
Swine tissue specimens and cell culture specimens, Philippines, 2007-2008

Lymph node capsule stained for EBV

Lymph node germinal center stained for PRRSV antigens

Lung tissue stained for PRRSV antigens

Swine tissue specimens and cell culture specimens, Philippines, 2007-2008
Ebola and Ebola Reston Virus, 1976 - 2008

Source: CDC

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Risk exposure</th>
<th>Location of likely exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr X  Backyard pig farmer</td>
<td>Close contact and care for sick pigs Collection and use of boar semen</td>
<td>Metro Manial and Bulacan farm</td>
</tr>
<tr>
<td>Mr DZ Farm worker</td>
<td>Close contact and care of sick pigs</td>
<td>Bulacan farm</td>
</tr>
<tr>
<td>Mr SB Farm worker</td>
<td>Close contact and care of sick pigs</td>
<td>Bulacan farm</td>
</tr>
<tr>
<td>Mr WZ Farm worker</td>
<td>Close contact and care of sick pigs Collection of boar semen</td>
<td>Pangasinan farm</td>
</tr>
<tr>
<td>Mr JD Slaughterhouse worker</td>
<td>Slaughtered on average 4 pigs(day)</td>
<td>Pangasinan – backyard farms</td>
</tr>
<tr>
<td>Mr Y Slaughterhouse worker</td>
<td>Slaughtered pigs daily</td>
<td>Nueva Ejica -commercial farms Bulacan – backyard farms</td>
</tr>
</tbody>
</table>

Source: CDC
Risk assessment: testing the hypothesis of bat to pig transmission of Ebola Reston, 2008

- Bats present in fruit trees (banana, palm trees, guava) in farm and in the vicinity
- 71 bats (5 species) tested: all negative
  - Cynopterus brachyotis
  - Eonycteris spelaea
  - Ptenochirus jagori
  - Rousettus amplexicaudatus
  - Scotophilus kuhili

Source: CDC
Risk assessment: Ebola Reston virus in pigs at slaughter (n = 70), 2008

- 19/70 (27%) PCR positive for Ebola Reston Virus in blood specimens
- 19 PCR positive pigs not reported as overtly ill at time of slaughter
- Organs investigated:
  - 13/19 spleen samples tested PCR positive
  - 12/19 lung samples tested PCR positive

Source: CDC
Risk assessment, Ebola Reston virus, Philippines, 2008

- Swine infected, some remain asymptomatic
- Humans at risk but infections asymptomatic
- Bats possible source of infection – not yet confirmed
- Precautionary measures to eliminate exposure may be warranted
Ebola outbreaks and virus strains, 1976 - 2013

Ebola, 1976 - 2014

Source: CDC, WHO
Ebola outbreaks, West Africa, 2014

Map showing the spread of Ebola in West Africa with a graph showing the number of cases over epidemiologic weeks for Guinea, Sierra Leone, and Liberia. The graph includes data from WHO, published 5 November.
Ebola outbreak, Ikanamongo, DRC, 2014

- Cases: 66
- Deaths: 49 (74%)
- Health workers: 8
- Duration: August-October
Ebola, new cases as of mid-February, 2015

23874 cases (839 HCW)
9,800 deaths

Source: WHO
So what’s next?

- Contain the outbreak with innovation on the three strategies shown to have worked in the past (and in the DRC outbreak that began in August 2014 and was fully contained three months later)
  - Patient identification, isolation and protection of health workers/infection control
  - Surveillance/contact tracing and fever surveillance with rapid diagnosis and isolation
  - Community understanding with safe patient and body transport systems, and household/ environmental decontamination
Clinical research

- Maintaining electrolyte balance: early oral rehydration/parenteral replacement and maintenance
- Convalescent plasma or blood: treatment and/or post-exposure prophylaxis
- Point of care diagnostic tests: adequate sensitivity/specificity
- Antivirals: sequential or comparative trial methodologies
- Vaccines: outbreak control and primary prevention in Ebola belt health workers
A case of Ebola virus infection

R T D EMOND, BRANDON EVANS, E T W BOWEN, G LLOYD

British Medical Journal, 1977, 2, 541-544

Summary

In November 1976 an investigator at the Microbiological Research Establishment accidentally inoculated himself while processing material from patients in Africa who had been suffering from a haemorrhagic fever of unknown cause. He developed an illness closely resembling Marburg disease, and a virus was isolated from his blood that resembled Marburg virus but was distinct serologically. The course of the illness was mild and may have been modified by treatment with human interferon and convalescent serum. Convalescence was protracted; there was evidence of bone-marrow depression and virus was excreted in low titre for some weeks. Recovery was complete. Infection was contained by barrier-nursing techniques using a negative-pressure plastic isolator and infection did not spread to attendant staff or to the community.

Admitted to hospital in South Africa having recently travelled extensively in Rhodesia. This patient was found to have Marburg disease and infection spread to his travelling companion and to a nurse. The original patient died but the other two survived. The source of the infection was not determined. Just over a year later, in July to November 1976, a serious outbreak of haemorrhagic fever occurred in the Western Equatoria province of the Sudan and the adjacent Equateur Region of Zaire. Infection spread rapidly among the local people, particularly within the hospitals. There was an appallingly high death rate—30-80% in the Sudan and 89% in Zaire. In view of the severity of this outbreak specimens were sent to high-security laboratories in England, Belgium, and the United States of America for identification of the agent responsible. All three laboratories isolated a virus that resembled Marburg virus morphologically but was serologically distinct. The name Ebola was given to the prototype strain.
Convalescent blood transfusion, Kikwit 1995

Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients

Members of the International Humanitarian Ebola Task Force and the World Health Organization

Between 18 and 22 June 1995, 8 patients in Kikwit, Democratic Republic of the Congo, who met the case definition used in Kikwit for Ebola (EE) hemorrhagic fever, were transfused with blood donated by 2 convalescent patients. The donated blood contained IgG Ebola antibodies but no Ebola antigen. Ebola antigen was detected in all the transfusions recipients just before transfusion. The 8 transfused patients had clinical symptoms similar to those of other Ebola patients seen during the epidemic. All were transfused with Ebola-positive 4 convalescent with hemorrhagic manifestations, and 2 became convalescent at their disease progressed. Only 1 transfused patient (E 1.1) died; this number is significantly lower than the overall case fatality rate (60% of the 80 patients in Kikwit and than the case for other Ebola epidemics. The reason for this low fatality rate remains to be understood. The transfused patients did not develop detectable than those in the initial phase of the epidemics. These should be made to prevent for a more thorough evaluation of passive immune therapy during an new Ebola epidemic.
WHO Blood Regulators Network (BRN)

……if possible, the WHO Blood Regulators Network recommends that scientific studies on the feasibility and medical effectiveness for collection and use of convalescent plasma or serum be explored through clinical trials.

1.1 Overview

The periodicity and extent of filovirus outbreaks in Africa have increased significantly since the initial identification of these viruses in the mid-1960s. Addressing the threat of filovirus outbreaks has become an urgent global public health priority. Vaccines and antiviral therapies are under development but currently they are not approved by regulatory authorities. Recent work has shown that immune therapies based on anti-filovirus glycoprotein (GP) monoclonal antibodies (mAbs) and convalescent monkey immunoglobulin preparations are effective in the filovirus rodent and monkey lethal challenge models. Cocktails of anti-filovirus GP mAbs against different species of filoviruses produced in plants are currently under development. The efficacy of the
Clinical trials, convalescent plasma, Guinea

Ebola outbreak: MSF to start West Africa clinical trials

By Tulip Mazumdar
Global health reporter

The rate of transmission of Ebola remains high, the WHO says.

Clinical trials are to try and find an effective treatment for Ebola patients and to start in West Africa next month.

The medical charity, Doctors Without Borders, which has been helping lead the fight against the virus, says three of its treatment centres will host three separate research projects.

One trial involves using the blood of recovered Ebola patients to treat sick people in the Guinean capital, Conacry.

Two antiviral drugs will be trialled in Guinea and an unconfirmed vaccine.

Ebola outbreak

Robots to the rescue?

Ebola’s undertakers

Are cases levelling off?

The basics
Some of the lessons learned

- Initial response to emerging infection outbreaks must be rapid and robust
- Emphasis from start must be on three strategies that stop transmission and support patients – no one strategy should dominate at the expense of the others
- Health workers are at great risk of emerging infections, and serve as an inadvertent link to family/community transmission
- Functioning strong public health, and health systems with basic infection control, can prevent amplification of transmission and provide best possible care to patients: international agreements must be followed (IHR)
- Methods and tools for field monitoring electrolyte balance in patients infected with BSL-4 organisms, and + for collecting and using convalescent plasma must developed and be in place
- Phase one trials in humans must be undertaken as soon as safety and efficacy of products is determined in animal models
- Approved and funded clinical trial protocols, including stockpiles of investigational products, must be in place; and advance agreements with governments and national ethics committees and regulatory agencies must be agreed in advance in areas at risk of transmission