Ebola Virus Disease from the Beginning: Science and Shock
Locations of Outbreaks of Ebola Hemorrhagic Fever, Sudan and DR Congo (Zaire), 1976
Unfixed diagnostic specimen from Vero cell passage: sodium phosphotungstate x 90,000
(Fred Murphy)
Villages on the Bumba to Yambuku Road, DR Congo (Zaire), October 1976

Goals: Determine

- Limits
- Active disease
- Convalescents
- Local needs

Photo: J. Breman
Hospital Staff: 17
- EHF 13
- Died 11

From CDC slide set, 1977
Patient with Ebola Hemorrhagic Fever, Bumba Zone, Equateur Province, DR Congo (Zaire), October 1976

Pierre Sureau (France) and patient, 1976

Photo: J. Breman
Patient with Ebola Hemorrhagic Fever, Bumba Zone, Equateur Province, DR Congo (Zaire), October 1976

Photo: J. Breman
Patient with Ebola Hemorrhagic Fever, Bumba Zone, Equateur Province, DR Congo (Zaire), October 1976

Photo: J. Breman
Conjunctival injection and later conjunctival hemorrhages

PHOTOS TAKEN IN UGANDA 2000 ON EBOLA PATIENTS
Case Definitions

Ebola Hemorrhagic Fever, DRC (Zaire), 1976

**Probable case** – living in endemic area who died:
  After $\geq 1$ day with two or more of
  - Headache, fever, abdominal pain, nausea/vomiting, bleeding
  Within preceding 3 weeks:
    -Received an injection or had contact with a probable or proven case

**Proven case** – Ebola virus:
  - Isolated, or shown by electron microscopy
  - Or, IFA titer $\geq 1:64$ within 3 weeks of syndrome onset

**Infection**
  - IFA titer $\geq 1:64$
  - No illness from August 30 to November 15
Fig. 2. Routes followed by the surveillance teams. The numbers identify the teams.
Investigations of EHF Cases in Villages, Equateur Province, DR Congo (Zaire), October-December 1976

Photo: J. Breman

Dr. M. Mbuyi & Nurse Sukato interviewing mourning family member
Active Surveillance for EHF Cases, Equateur Province, DR Congo (Zaire), November-December 1976

Photo: J. Breman
### Cases/Deaths, Ebola Hemorrhagic Fever in Sudan and DRC (Zaire), 1976

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Deaths/Cases</th>
<th>Case-fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>Sudan</td>
<td>150/284</td>
<td>53%</td>
</tr>
<tr>
<td>1976</td>
<td>Zaire</td>
<td>280/318</td>
<td>88%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Death (n = 178-231)</th>
<th>Recovered (n = 9-34)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>Fever</td>
<td>98%</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>96</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>81</td>
<td>6</td>
</tr>
<tr>
<td>Sore throat</td>
<td>79</td>
<td>6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>79</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Arthritis</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79</td>
<td>5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>78</td>
<td>4</td>
</tr>
<tr>
<td>Oral lesions</td>
<td>74</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>65</td>
<td>4</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>58</td>
<td>5</td>
</tr>
<tr>
<td>Cough</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Abortion</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other (including rash)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* IFA = ≥ 1:64.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Male</th>
<th>Female</th>
<th>Total (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns and &lt;12 months</td>
<td>10</td>
<td>14</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>1 – 14</td>
<td>18</td>
<td>22</td>
<td>40 (13%)</td>
</tr>
<tr>
<td>15 – 29</td>
<td>31</td>
<td>60</td>
<td>91 (29%)</td>
</tr>
<tr>
<td>30 – 49</td>
<td>57</td>
<td>52</td>
<td>109 (34%)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>23</td>
<td>26</td>
<td>49 (15%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>3</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Number of Cases of Ebola Hemorrhagic Fever in the Equator Region, by Day of Onset and Probable Type of Transmission, 1976

Probable Type of Transmission
- **Person to Person**
- **Both**
- **Syringe**

Time of Onset of Ebola Hemorrhagic Fever by Transmission Type  
(after initial contact with source)  
DR Congo (Zaire), 1976

### Factors Associated with Person-to-Person Spread of EHF, DR Congo (Zaire), 1976

<table>
<thead>
<tr>
<th>Risk</th>
<th>Case (% Yes) (n = 104-126)</th>
<th>Controls (% Yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Family (74-98)</td>
</tr>
<tr>
<td>Touched case</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Cared for case</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Slept in room</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>Prepared cadaver</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Attended funeral</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Aided in delivery of newborn</td>
<td><strong>18</strong>*</td>
<td>10</td>
</tr>
</tbody>
</table>

* < 0.05
### Distribution of Number of Cases in Villages
### Ebola Hemorrhagic Fever, DRC, (Zaire), 1976

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Number of Villages</th>
<th>% of total Villages</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>2 – 5</td>
<td>18</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>6 – 9</td>
<td>12</td>
<td>22</td>
<td>85</td>
</tr>
<tr>
<td>10 – 14</td>
<td>4</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>15 – 19</td>
<td>1</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>20 – 29</td>
<td>1</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>&gt;30</td>
<td>2</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>55</strong></td>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

## Family Contact Attack Rates of Ebola Virus Disease by Generation of Illness, Democratic Republic of Congo, 1976

<table>
<thead>
<tr>
<th>Generation</th>
<th>Number</th>
<th>Exposures</th>
<th>Cases</th>
<th>Attack Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (injection)</td>
<td>61</td>
<td>498</td>
<td>38</td>
<td>7.6</td>
</tr>
<tr>
<td>2 (person-to-person)</td>
<td>62</td>
<td>459</td>
<td>20</td>
<td>4.4</td>
</tr>
<tr>
<td>3 (person-to-person)</td>
<td>18</td>
<td>117</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>4 (person-to-person)</td>
<td>5</td>
<td>29</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>1,103</td>
<td>62</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Delivered fetus or was caregiving spouse 27.0
Laboratory in Yambuku, DR Congo (Zaire), 1976

Guido van der Groen (Belgium)
Plasmapheresis in Yambuku, DR Congo, 1976

Denis Courtois (France), Margaretha Isaacson (RSA) and convalescent patient, 1976

Photo: J. Breman
Ebola Hemorrhagic Fever, DRC (Zaire) Major Findings, 1976

■ Clinical
  - Manifestations
  - Incubation period
  - Plasmapheresis of convalescents

■ Epidemiology
  - Geographic extent
  - Persons at risk
  - Mode of transmission

■ Control
  - Area quarantine
  - Surveillance
  - Identify, isolate patients
  - Rule out other diseases

■ Laboratory
  - Basic lab tests
  - IFA for Ebola
  - Virus culture: 8 patients

■ Ecological studies
Ebola Hemorrhagic Fever, DRC (Zaire)

Major Unknowns, Unsolved, 1976

- Animal reservoir
- Transmission to humans
- Treatment
- Vaccine
- Extent globally
Virus in Zaire Epidemic Named for Ebola River

KINSHASA, Zaire, Nov. 30 (Agence France-Presse) — The virus responsible for the recent epidemic of green monkey fever that claimed several hundred lives will be known as the Ebola Virus, after a river in the north, the Health Ministry announced today.

A statement said no direct link had been established between the virus that struck at Yambuku and the Marburg strain, which caused a similar epidemic in the Sudan earlier this year.
Summary Lessons from the Ebola 1976 Outbreak

A. Administrative

1. Leadership
2. Organization
3. Transparency
4. Communications
5. Partnerships
6. Coordination
7. Logistics
8. Transport (mobility)
9. Quarantine (selective)
10. Isolation
Summary Lessons from the Ebola 1976 Outbreak (cont’d)

B. Science: Clinical and Control

1. Case definitions
2. Standardized data collection
3. Local care Ebola patients, selective referral
4. Medical care of affected community
5. Trained medical/nursing volunteers
6. Repeated village searches
7. Proper personal protection
8. Laboratory in field
9. Ecological studies

C. Monitoring and Incentives for Team

1. Strict personal monitoring
2. Equal treatment of all
3. Evacuation plan
4. Group publications
5. Selective compensation
6. Recognition
Top Local Population and Investigative Team
Ebola, Zaire, 1976
Spectrum of Emotion and Activity

Emotion

High

Confidence
Uncertainty
Anger
Celebration

Terror

Fear

Sorrow

Understanding

Comfort

Activity

People fleeing
Commission formed
Chaos
Rapid Surveillance
Patient management
Field Investigations
Active case detection
Plasmapheresis

Low

Information Sharing

High

Anxiety

J. Breman, 50th EIS Anniversary, CDC, 2001
Ebola Virus
Haemorrhagic Fever

S.R. Pattyn editor

Elsevier/North-Holland

“Bill Close’s EBOLA is an eloquent, gripping, and beautiful account of the real doctors, nurses, and victims who lived and died during that harrowing nightmare.”

—Richard Preston
Author of The Hot Zone

William T. Close, M.D.
A Documentary Novel of Its First Explosion in Zaire by a Doctor who was there

EBOLA
Ebola Hemorrhagic Fever, Kikwit, Zaire, 1995

315 cases
77% case fatality rate

32% of cases in health care staff
16% secondary attack rate
45% attack rate in care-giving spouses
Ebola Virus
Marburg Virus
Both

Ebola: The Virus and the Disease

Guest Editors:
C. J. Peters and James W. LeDuc
# Ebola virus epidemiology and ecology

<table>
<thead>
<tr>
<th>Ebola outbreaks, year</th>
<th>Country</th>
<th>Nb Cases</th>
<th>Nb deaths</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yambuku, 1976</td>
<td>DR Congo</td>
<td>318</td>
<td>280</td>
<td>Unknown</td>
</tr>
<tr>
<td>Maridi, 1976</td>
<td>Sudan</td>
<td>284</td>
<td>151</td>
<td>Coton facory, insectivorous bats</td>
</tr>
<tr>
<td>Tandala, 1977</td>
<td>DR Congo</td>
<td>1</td>
<td>1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Nzara, 1979</td>
<td>Sudan</td>
<td>34</td>
<td>22</td>
<td>Unknown</td>
</tr>
<tr>
<td>Côte d’ Ivoire 1994</td>
<td>Côte d’ Ivoire</td>
<td>1</td>
<td>0</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mekouka 1994</td>
<td>Gabon</td>
<td>52</td>
<td>31</td>
<td>Chimpanzee</td>
</tr>
<tr>
<td>Kikwit 1995</td>
<td>DR Congo</td>
<td>315</td>
<td>254</td>
<td>Chimpanzee, Gorilla</td>
</tr>
<tr>
<td>Mayibout 1996</td>
<td>Gabon</td>
<td>33</td>
<td>23</td>
<td>Unknown</td>
</tr>
<tr>
<td>Boué 1996</td>
<td>Gabon</td>
<td>60</td>
<td>45</td>
<td>Chimpanzee</td>
</tr>
<tr>
<td>Gulu 2001</td>
<td>Uganda</td>
<td>425</td>
<td>224</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mekambo 2001=2</td>
<td>Gabon</td>
<td>65</td>
<td>53</td>
<td>Gorilla, chimpanzee, duiker</td>
</tr>
<tr>
<td>Mbomo Kellé 2001=2</td>
<td>Congo</td>
<td>59</td>
<td>44</td>
<td>Gorilla, chimpanzee, monkey</td>
</tr>
<tr>
<td>Kellé 2003</td>
<td>Congo</td>
<td>143</td>
<td>128</td>
<td>Gorilla, duiker</td>
</tr>
<tr>
<td>Mbandza Mbomo 2003</td>
<td>Congo</td>
<td>35</td>
<td>29</td>
<td>Monkey, duiker</td>
</tr>
<tr>
<td>Yambio 2004</td>
<td>Sudan</td>
<td>17</td>
<td>7</td>
<td>Unknown</td>
</tr>
<tr>
<td>Etumbi 2005</td>
<td>Congo</td>
<td>12</td>
<td>10</td>
<td>Unknown, wildlife?</td>
</tr>
<tr>
<td>Mweka 2007</td>
<td>DR Congo</td>
<td>264</td>
<td>185</td>
<td>Unknown, bats?</td>
</tr>
<tr>
<td>Bundibugyo 2007</td>
<td>Uganda</td>
<td>149</td>
<td>37</td>
<td>Unknown, bats?</td>
</tr>
<tr>
<td>Kaluamba 2008</td>
<td>DR Congo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isiro 2012</td>
<td>DR Congo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afrique de l’Ouest,2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: J. J. Muyembe
Ebola Virology

- Filovirus family

- Species and average fatality in the genus *Ebolavirus*
  - Bundibugyo – ~30%
  - Zaire – 50-90%
  - Reston – animal disease
  - Sudan – ~50%
  - Taï Forest – 1 non-fatal human case

EM of Ebola virus particles (green) attached to Vero cell (blue). NIAID
Ebola Transmission Cycle

Enzootic cycle

Epizootic cycle

Fruit bats putative reservoir; evidence inconclusive
Ebola Virus Disease in West Africa March–July 2014

State of the Outbreak: March 2014

State of the Outbreak: July 2014

Source: E Ervin, CDC, WHO
2014 Ebola Outbreak in West Africa - Outbreak Distribution Map
Ebola Virus Disease in West Africa by Country, 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>4,200</td>
<td>1,519</td>
</tr>
<tr>
<td>Liberia</td>
<td>4,262</td>
<td>2,484</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>3,410</td>
<td>1,200</td>
</tr>
</tbody>
</table>

Total cases: 9,216
Total deaths: 4,555

Source: New York Times, WHO
Ebola Diagnostic Challenges

- PCR detects virus near symptom onset
- Antibody response lags behind viremia

Source: Adapted from A. Sall
AS Fauci/NIAID
Pipeline of Therapeutics

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Treatment</th>
<th>How it Works</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZMapp</td>
<td>Antibody cocktail binds to and inactivates virus</td>
<td>Protects monkeys</td>
</tr>
<tr>
<td></td>
<td>TKM-Ebola</td>
<td>Small-interfering RNA</td>
<td>Phase I human trials ongoing</td>
</tr>
<tr>
<td></td>
<td>BCX4430</td>
<td>Nucleoside analogue RNA polymerase inhibitor</td>
<td>Protects monkeys infected with Marburg virus</td>
</tr>
<tr>
<td></td>
<td>Brincidofovir</td>
<td>Small molecule, viral polymerase inhibitor, broad antiviral</td>
<td>In vitro activity against filoviruses. Late-stage clinical trial data for other viruses.</td>
</tr>
<tr>
<td></td>
<td>Favipiravir</td>
<td>RNA polymerase inhibitor; broad antiviral</td>
<td>Protects mice with Ebola. Licensed for pandemic flu in Japan.</td>
</tr>
</tbody>
</table>

Source: Adapted from Nature News, Sept 2, 2014
International Commission for the Investigation and Control of Ebola Hemorrhagic Fever
Democratic Republic of the Congo (Zaire), 1976-77

Collaborators

Belgium
Democratic Republic of the Congo (Zaire)
Canada
France
South Africa
United States
World Health Organization
Ebola Hemorrhagic Fever Team in Yambuku, DR Congo (Zaire), 1976

Left to Right: Back Row: Del Conn (obscured), Michael White, Karl Johnson, Guido van der Groen, Sister Mariette; Middle Row: G. Dujeu, Denis Courtois, Sister Marcella, Peter Piot, Stefan Pattyn, M. Miatudila; Front Row: Unidentified, Joel Breman
October 30, 2014

Perspective

Ebola Then and Now

Joel G. Breman, M.D., D.T.P.H., and Karl M. Johnson, M.D.


In October 1976, the government of Zaire (now the Democratic Republic of Congo [DRC]) asked what was then the U.S. Center for Disease Control, where we worked, to join an international group of scientists in elucidating and controlling an outbreak of an unusually lethal hemorrhagic fever. Just before we arrived in Zaire, our laboratory had used virologic and immunologic tests to identify the cause as a new filovirus, and we brought electron micrographs of the agent. In Zaire, we became, respectively, the chief of surveillance, epidemiology, and control and the scientific director of the International Commission for the Investigation and Control of Ebola Hemorrhagic Fever in Zaire.
Ebola in Africa: The Multidisciplinary Investigative Team

- Leadership linking control & research
- Clinical
- Pathogenesis
- Microbiology
- Molecular genetics
- Epidemiology
- Microbiology
- Immunology
- Anthropology
- Health education
- Wildlife disease
- Veterinary medicine
- Ecology
- Modeling
- Remote sensing
- GPS
- Information technology
FILOVIRUSES ARE THE MOST VIRULENT AGENTS OF AVHF IN DRC.

Ebola river near Yambuku catholic mission.
CARRIED AWAY  Straw-colored fruit bats, *Eidolon helvum* (shown), and other bat species may have carried Ebola virus from Central Africa to West Africa, where the virus is now causing the largest-ever epidemic of the disease.
Ebola Outbreaks 1976 to Present Day

- 1976 Sudan: 284 cases, 151 deaths
- 1976 Zaire: 318 cases, 280 deaths
- 1995 Zaire: 315 cases, 250 deaths
- 1996 Gabon
- 2000 Uganda: 425 cases, 187 deaths
- 2001 The Republic of the Congo
- 2003 The Republic of the Congo
- 2007 DRC*: 264 cases, 187 deaths
- 2007 Uganda
- 2012 DRC
- 2014 Guinea, Liberia, Nigeria, Senegal and Sierra Leone: 9,216 cases, 4,555 deaths
- 2014 DRC

*Democratic Republic of the Congo

- Number of cases
- Number of deaths

Ebola Virus Pathogenesis

1. Bodily fluids
2. Mucosal splash
3. Rents in skin
4. Small lesion
5. Infected macrophage
6. Cytokine release
7. Cell apoptosis
8. Vascular leakage and disrupted hemostasis
9. Systemic inflammatory response syndrome

Source: Adapted from H Feldmann and TW Geisbert. Lancet 377 (9768), 2011.