Ebola: research during outbreaks in Africa and Asia, a historical perspective
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 Edmond missionnaire à Yambuku
avant à Kinshasa 19 oct. 1976

Sœur Romana missionnaire à Yambuku
avant à Yambuku 2 oct. 1976

Sœur Myriam missionnaire à Yambuku
avant à Kinshasa 26 sept. 1976

Sœur Beata missionnaire à Yambuku
avant à Yambuku 19 sept. 1976

Sékou mou akaló bomoi buwa ye mpa ya bandène, nsa ak yío bálingo waka (Yoh. 15:13): 
Kristo ak childhood mpa yó lela la lela ka konde.
Sanyangé ba báu bámel: Sr. Srata, Sr. Mynam, Sr. Ramana na Sr. Edmonda liñændi; bamekili Kristu, 
Lóo ba yía lela yínó bomoi buwa bámel. Ut tía bóloungu tinkópki mbómbi na Kristu na báu lela 
bómbi liñændi tele báu na naa.
Fúko bóloungu buwa bóloungu rólo lela tinkópki mbómbi liñændi tele báu na naa. Bóu bámel 
bómbi lela bóloungu bóloungu mpa. Mba bóloungu yía lela, Kristo ak childhood bóloungu bóloungu lela, bamekili Kristu.

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VRÖÖM AANDENKEN AAN
Pater Germain LOOTENS
Missionaris van Ghent
geboren te St.-Kruis-Brugge op 30 oktober 1919, 
priester gewijd op 16 augustus 1935,
naar Zaire verrezen op 14 augustus 1956, 
overleden te Yambuku op 2 oktober 1976 
als slachtoffer van een zware epidemic.
Ngaliema Hospital, Kinshasa, DRC
Filoform virus, electron micrograph, 1976

Source: CDC
Patient record, outpatient department, Yambuku Hospital, DRC, August 1976
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

- Animal source suspected

- Unknown potential to reappear – one time emergence vs. periodic re-emergence
Mission Hospital, Tandala Zaire (DRC), 1977

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>
</tr>
<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

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>No. of contacts tested/no. with titers $\geqslant 1:64$ (%)</th>
<th>No. of controls tested/no. with titers $\geqslant 1:64$ (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–14</td>
<td>61/4 (7)</td>
<td>43/2 (5)</td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>13/2 (15)</td>
<td>10/0</td>
<td></td>
</tr>
<tr>
<td>$\geqslant$20</td>
<td>114/22 (19)</td>
<td>84/0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>188/28 (15)</td>
<td>137/2 (&lt;1)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Source: WHO
Risk assessment, Ebola haemorrhagic fever, 1977

- 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*

- Animal source suspected

- Unknown potential to reappear – one time emergence vs. periodic re-emergence: *re-emergence occurs*
Kikwit General Hospital, Zaire, 1995
Nursing sisters, Kikwit General Hospital, Zaire, 1995
Ebola Haemorrhagic Fever by mode of transmission, Kikwit Zaire, 1995

- **Non health care workers**
- **Health care workers**

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 environmental decontamination
Tai Forest, Cote d’Ivoire, 1992
Chimpanzee die off, Tai Forest sociology research project area, 1992 - 1994
Ebola Haemorrhagic Fever, Mayibout Gabon, 1996

- 19 index cases: found and butchered freshly dead chimpanzee
- 18 family members/health workers infected
- Minimal nosocomial 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

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 an animal reservoir, Ebola Haemorrhagic Fever, 1976 - 1996

Random collection:
Markets, nets, traps

Baka (Pygmy) hunters
The search for a reservoir in nature, Ebola Haemorrhagic Fever, 1996

Source:: Emerging Infectious Diseases
The search for a reservoir in nature, Ebola Haemorrhagic Fever, 2001 - 2003

Brief Communications

Fruit bats as reservoirs of Ebola virus

Eric M. Leroy1,2, Brice Kumulungui3, Xavier Pourrut4,5, Pierre Rouquet6, Alexandre Hassanin7, Philippe Yaba1, André Délicat8, Janusz T. Paweska9, Jean-Paul Gonzalez2 and Robert Swanepoel2

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.

1. Centre International de Recherches Médicales de Franceville, BP 760 Franceville, Gabon
2. Muséum National d’Histoire Naturelle, UMR 5202, Paris 75005, France
3. National Institute for Communicable Diseases, Special Pathogens Unit, Private Bag X4, Sandringham 2131, South Africa
4. Institut de Recherche pour le Développement, UR138, Mahidol University at Salaya, Salaya Road 33110, Thailand
5. Institut de Recherches pour le Développement, UR138, Centre International de Recherches Médicales de Franceville, BP 760 Franceville, Gabon

Correspondence to: Eric M. Leroy Email: eric.leroy@ird.fr
Risk assessment, Ebola haemorrhagic fever, 1995

- 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

- 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
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

Lymph node germinal center stained for PRRSV antigens

Lung tissue stained for PRRSV antigens
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</td>
<td>Backyard pig farmer</td>
<td>Metro Manial and Bulacan farm</td>
</tr>
<tr>
<td></td>
<td>Close contact and care for sick pigs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collection and use of boar semen</td>
<td></td>
</tr>
<tr>
<td>Mr DZ</td>
<td>Farm worker</td>
<td>Bulacan farm</td>
</tr>
<tr>
<td></td>
<td>Close contact and care of sick pigs</td>
<td></td>
</tr>
<tr>
<td>Mr SB</td>
<td>Farm worker</td>
<td>Bulacan farm</td>
</tr>
<tr>
<td></td>
<td>Close contact and care of sick pigs</td>
<td></td>
</tr>
<tr>
<td>Mr WZ</td>
<td>Farm worker</td>
<td>Pangasinan farm</td>
</tr>
<tr>
<td></td>
<td>Close contact and care of sick pigs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collection of boar semen</td>
<td></td>
</tr>
<tr>
<td>Mr JD</td>
<td>Slaughterhouse worker</td>
<td>Pangasinan – backyard farms</td>
</tr>
<tr>
<td></td>
<td>Slaughtered on average 4 pigs(day)</td>
<td></td>
</tr>
<tr>
<td>Mr Y</td>
<td>Slaughterhouse worker</td>
<td>Nueva Ejica -commercial farms</td>
</tr>
<tr>
<td></td>
<td>Slaughtered pigs daily</td>
<td>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 outbreaks, West Africa, 2014

Total deaths per region:
- 0
- 1-10
- 11-50
- 51-100
- 101-250
- 251-500
- 501+

Source: WHO data published 5 November 2014
Ebola outbreak, Ikanamongo, DRC, 2014

- Cases: 66
- Deaths: 49 (74%)
- Health workers: 8
- Duration: August-October
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
Clinical trials: WHO consensus on need and ethics

- Maintaining electrolyte balance: early oral rehydration/parenteral
Ebola: where and how well-managed fluid balance may make a difference
Clinical trials: WHO consensus on need and ethics
- Maintaining electrolyte balance: early oral rehydration/parenteral
- Convalescent plasma or blood: treatment and/or post-exposure prophylaxis
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.¹

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.² Infection spread rapidly among the local people, particularly within the hospitals. There was an appallingly high death rate—30-80% in the Sudan² 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.³⁻⁴ The name Ebola was given to the prototype strain.

Case report

On the 5 November 1976 one of the investigators at the Micro-
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

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

The medical charity Medecins Sans Frontieres, 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 treatment

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

February 2015
**Ebola antibody preparations, 2015**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>trials</th>
<th>comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG/IgM from convalescent patients</td>
<td>Case series</td>
<td>7/8 patients survived. Received t/f &gt;10/7, 1 death t/f-ed @ D4</td>
<td>Mupapa et al JID 1999</td>
</tr>
<tr>
<td>Purified IgG</td>
<td>Nil.</td>
<td>From NH-primates.48 hrs protection post infection (100%)</td>
<td>Dye et al. Proc Nat Acad Sc 2012</td>
</tr>
<tr>
<td>Cocktail of 3x monoclonal antibodies</td>
<td>nil</td>
<td>100% effective at 24 hrs 50% @ 48 hrs</td>
<td>Qui et al Sci transl Med 2012</td>
</tr>
<tr>
<td>Above combined with adenovirus vectored interferon-alpha</td>
<td>nil</td>
<td>72 hrs post infection 75-100% NH-primates</td>
<td>Qui et al Transl Med 2012</td>
</tr>
<tr>
<td>Cocktail of 3x humanised monoclonal a.b (MB-003)Z-Mapp</td>
<td>Cases</td>
<td>Protection 100% @ 1 hr, 67% @24/48 hrs. 43% survival at 120 hrs post infection + development of viraemia and fever</td>
<td>Olinger et al Proc Nat Acad Sc USA 2012 Pettitt et al Sci Transl Med 2013</td>
</tr>
</tbody>
</table>
Clinical trials: WHO consensus on need and ethics

- Maintaining electrolyte balance: early oral rehydration/parenteral
- Convalescent plasma or blood: treatment and/or post-exposure prophylaxis
- Antivirals: sequential or comparative trial methodologies
## Ebola candidate antiviral products, 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>trials</th>
<th>comment</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCX4430</td>
<td>Adenosine analogue (PO/IM). Incorporation into viral RNA → chain termination</td>
<td>nil</td>
<td>100% protection of NH-primates at 48 hrs post infection (Marburg v).</td>
<td>Warren et al. Nature 2014</td>
</tr>
<tr>
<td>TKM-Ebola Tekmira</td>
<td>Small interfering RNA cocktail against VP24, VP35, and L prot. Encapsulated in stable nucleic acid lipid particles (SNALP)</td>
<td>Case Phase I-suspended (partial lift by FDA)</td>
<td>IV prep. 100% protection 30 mins post exposure to ebola in NH-primates</td>
<td>Geisbert et al Lancet 2003</td>
</tr>
<tr>
<td>PMOs AVI-6002</td>
<td>Phosphorodiamidate morpholino oligomers</td>
<td>Phase I PEP</td>
<td>62.5% protection within 30 mins</td>
<td>Warren et al Nature med 2010</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Pyrazine carboxamide deriative. Selective inhibition of viral RNA dep RNA polymerase</td>
<td>Cases Phase III (U.S) Licensed in Japan for flu.</td>
<td>Rapid viral clearance, used up to day 6 post infection- mice. European cases</td>
<td>Oestereich et al. Antiviral research 2014</td>
</tr>
<tr>
<td>Brincidofovir CMX001</td>
<td>Nucleotide analogue</td>
<td>Cases Phase 2</td>
<td>Broad spectrum antiviral. Developed for CMV, BK viruses. Now trialing on Ebola</td>
<td>Florescu et al. expert rev anti therapy 2014</td>
</tr>
</tbody>
</table>
Clinical trials: WHO consensus on need and ethics

- Maintaining electrolyte balance: early oral rehydration/parenteral
- Convalescent plasma or blood: treatment and/or post-exposure prophylaxis
- Antivirals: sequential or comparative trial methodologies
- Vaccines: health workers, patient transport, burial teams and other select populations (ring vaccination for outbreak control?)
Experimental Medicine in a Time of Ebola

The only way to discover whether new interventions are effective is to test them during an epidemic.

A virologist carrying out mouse experiments in a lab in Hamburg five years ago accidently pricked her finger. The syringe contained the Zaire Ebola virus, the same strain wreaking havoc today in Guinea, Liberia and Sierra Leone. This is no approved treatment or vaccine for Ebola, or even one that has passed the first phase of safety trials in human volunteers. Yet unlike those exposed to Ebola in West Africa recently, the Hamburg virologist was quickly offered an experimental vaccine.

This vaccine hadn’t yet been tested on humans, but it had been shown to offer primestime protection against Ebola infections. For the virologist, it wasn’t a good option, but it was the only one available in the face of a virus with an extremely high mortality rate. She chose to take the vaccine.

We expect it is a risk we would take if one of us was exposed to Ebola. The Hamburg researcher didn’t feel ill. It is unclear exactly how the virus worked, or indeed whether she was ever infected. What is important is that immediate access to an experimental vaccine allowed her to try something with the potential to protect her.

It is highly likely that if Ebola were now spreading in Western countries, public-health authorities would give at-risk patients access to experimental drugs or vaccines. Indeed, there are reports that two U.S. relief workers infected with Ebola in Liberia have been offered experimental therapies, which they have accepted.

There are antiviral drugs, monoclonal antibodies and vaccines under study that have shown varying degrees of effectiveness in animals that have been infected with or exposed to the Ebola virus. Medical agencies in rich countries affected by Ebola would begin discussions with companies and labs developing these products and then make rapid decisions about which of them might be appropriate for compassionate use.

The African countries where the current outbreak of Ebola are occurring should have the same opportunity. African governments should be allowed to make informed decisions about whether or not to use these products, for example to protect and treat health-care workers who run especially high risks of infection.

The World Health Organization could assist African countries with developing
Randomised controlled trials for Ebola: practical and ethical issues

A fast-track initiative for evaluating investigational drug was launched in September, 2014. But although the question of whether unknown treatments should be offered at all is now settled, the question of how they should be designed and tested is not. Still at issue is whether such treatments should be made available only in the context of randomised controlled trials (RCTs) in which patients receive either a new intervention and conventional care, or conventional care alone or with a placebo.

Advocates of this RCT approach state that is the only approach that should be considered. We disagree.

While we concur that RCTs provide robust evidence, and support their use where this is ethical and practical, we do not believe that either consideration is likely to be satisfied in the context of this epidemic. The priority must be to generate data about effectiveness and safety as swiftly as possible, so that the most useful new treatments can be identified for rapid deployment. Alternative trial designs have the potential to do this more quickly, and with greater dose and ethnic acceptability.

The first objection to RCTs in which investigational drugs plus conventional care are compared purely with conventional care is ethical. Such randomisation is ethical when there is equipoise—when there is genuine uncertainty about whether an untried treatment has benefits or risks that exceed those of conventional care. equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high. This is precisely the problem with Ebola: current conventional care does not much affect clinical outcomes and mortality is as high as 90% when conventional care means such a high probability of death, it is problematic to trust on randomizing patients to it when the intervention arm holds out at least the possibility of benefit. Ethical arguments are not the same for all levels of risk.

No-one hopes that western medical workers offered an experimental drug, and other investigational products were randomised to receive the drug or conventional care plus a placebo. None of us would consent to be randomised in such circumstances. In cancers with a poor prognosis for which there are no good treatments, evidence from studies without a control group can be accepted as sufficient for deployment, and even for licensing by regulators, with future analysis following later. There is no need for risks to
Ebola outbreak, Ikanamongo, DRC, 2014

- Cases: 66
- Deaths: 49 (74%)
- Health workers: 8
- Duration: August-October
- Cases: 66
- Deaths: 49 (74%)
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