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WHO recommended Guidelines for Epidemic Preparedness and Response: Ebola Haemorrhagic Fever (EHF)

World Health Organization
Emerging and other Communicable Diseases,
Surveillance and Control

WHO guidelines for epidemic preparedness and response: Ebola Haemorrhagic Fever (EHF)

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*These technical guidelines are part of a series created by the World Health Organization*s Division of Emerging and Other Communicable Diseases (EMC) as part of the Epidemic Preparedness and Response program. Their purpose is to update current knowledge on diseases with epidemic potential, to help health officials detect and control outbreaks, and, with the present document, to strengthen the capacity for emergency response to an epidemic of EHF.*

A detailed training manual on precautions against the institutional spread of Viral Haemorrhagic fevers is in preparation (Infection control of viral haemorrhagic fevers in the African health care setting). An educational video on the management of EHF cases and outbreaks, including protective measures, has also been developed by WHO/EMC and is available on request.

The guidelines, the training manual and the video are or shall be available in both English and French.

Any questions or comments concerning these guidelines or the video should be directed to Disease Surveillance and Control (DIS), Division of Emerging and Other Communicable Diseases (EMC), World Health Organization, 20 avenue Appia, CH-1211 Geneva 27 Switzerland.
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Table of Contents

Part one: Background information on the organism and the disease

Ebola virus causes the acute viral syndrome known as Ebola haemorrhagic fever (EHF). Named after a river in northern Zaire (now Congo) where it was first discovered in 1976, Ebola is morphologically related to the Marburg virus recognized in 1967, but is antigenically distinct. EHF is a severe disease, with or without haemorrhagic symptoms, characterized by person-to-person transmission through close contact with patients, dead bodies or infected body fluids. The potential for explosive nosocomial infection in health care centres with poor hygiene standards constitutes its main threat to public health. The case fatality rate of EHF is over 50%; there are no individual preventive treatments or vaccines available although supportive care, particularly proper rehydration, significantly reduces the number of deaths. The epidemic potential of EHF can be prevented through proper management in health care centres, such as rapid investigation and strict follow-up of contacts, patient isolation and the rigorous use of universal precautions.

1.1.   The organism

Ebola is a lipid-enveloped RNA virus belonging to the *Filoviridae* family of thread-like viruses. Detection of IgM antibodies and evidence of increased titres of IgG antibodies by comparison of enzyme-linked immunosorbent assay (ELISA) titres in serum specimens from acute and convalescent cases serve to support diagnosis. Confirmatory virus isolation requires a biosafety level 4 laboratory. Four strains of Ebola are known to cause human illness (Zaire, Sudan, Ivory Coast and Gabon, after the place where they were first isolated); a fifth strain, Reston, highly pathogenic for some monkey species but not for man, was isolated from quarantined cynomolgus monkeys (*Macaca fascicularis*) imported from the Philippines in 1989. Primates (humans and monkeys) are thought to be only accidental hosts. The ecology and natural reservoir of the virus are still unknown.

See Annex 1 for a historical review of Ebola outbreaks

1.2.   The disease

EHF epidemics have shown that, after an incubation period which ranges from 2 to 21 days (5-12 days in most cases), the disease begins with acute fever, diarrhea that can be bloody (referred to as "diarrhée rouge" in French-speaking Africa), and vomiting. Headache, nausea, and abdominal pain are common. Conjunctival injection, dysphagia, hiccups, and haemorrhagic symptoms such as epistaxis, gum haemorrhage, haematemesis, melaena, purpura may further develop. Some patients may also show a maculopapular rash on the trunk. Dehydration and significant wasting occur as the disease progresses. At a later stage, there is frequent involvement of the CNS, manifested by somnolence, delirium, or coma.

By the second week of illness, the patient will either markedly improve and convalesce or will have multi-organ failure and will die in shock. Autopsies show panencephalitis, cerebral oedema, and serious renal damage. The case fatality rate ranges from 50% to 90%.

The occurrence of initial cases usually coincides with the end of the rainy season. Cases may be sporadic and small outbreaks in rural areas may often go undetected. Larger outbreaks usually occur once cases have entered a health care system of low hygiene standard. Epidemiological data suggest that Ebola infection is not highly communicable and most patients do not transmit Ebola infection or infect a limited number of persons only. A few individuals play a major role in transmission, because of particularly high infectiousness (not necessarily associated with the presence of haemorrhage), or because of more frequent interactions with the community (patients of high social status with many visitors, or where many are people involved in burial ceremonies).

Without laboratory support, the clinical diagnosis of EHF may be difficult, but epidemiological elements (Ebola endemic area, high fatality rate among adults, reported haemorrhage, person-to-person transmission particularly in health care settings) should suggest Ebola infection.

See Annex 2 for clinical course and differential diagnosis

1.3.   Transmission

Physical contact with skin and mucous membranes of patients is responsible for most human transmission. Ebola is transmitted through direct contact with virus-infected body fluids such as blood, saliva, vomitus, stools and possibly sweat. Parenteral inoculation with infectious material is associated with a high infection risk and a high fatality rate. As for Marburg virus, Ebola virus has been shown to be present in the genital secretions of convalescents several weeks after illness; however, the potential for transmission of sexual contacts with a recovered case has not been determined. There is no evidence that close personal contact with a non-febrile, non symptomatic, Ebola-infected individual during incubation period or convalescence results in transmission.

Household contacts have been responsible for 3 to 17 percent of transmission and up to 5 generations of infection in the past. Previous epidemics in Africa have resulted largely from secondary spread to health care workers and family contacts caring for the ill. Reuse of needles and syringes, inadequate barrier techniques, and unhygienic practices are the major catalysts for nosocomial transmission among hospital staff and patients. Contact with the body or body fluids of the dead in customary preparation for burial is also a well known cause of infection.

The Ebola virus is not airborne, but infected droplet spray from a patient may effectively transmit the virus if it comes into contact with mucous membranes. Aerosol infectivity of Ebola *Reston* has been suggested in outbreaks among non-human primates in quarantine facilities; there is no evidence for aerosol transmission of the other Ebola viruses in man.

1.4.   Treatment

No specific treatment is available. However, many deaths during an Ebola epidemic are due to severe dehydration; management of patients should be supportive, with careful maintenance of hydration, and minimal trauma – in particular, injections and parenteral interventions must be kept to a minimum. Replacement of coagulation factors and of platelets may be of value. Experimental studies on animals involving the use of hyper-immune sera have shown no long-term protection against illness after interruption of therapy, and research has suggested that hyper-immune sera may still carry live virus.

Part two: Measures for case detection and control

2.1.   Defining a surveillance system

The purpose of epidemiological surveillance is to confirm the outbreak, to identify all cases and contact subjects, to detect patterns of epidemic spread, to estimate the potential for further spread of the disease, and to determine whether control measures are working effectively. It must be implemented promptly upon arrival to the site.

2.1.1. Definition of a case of EHF

The use of a consistent case definition (*Annex 3*) is essential in order to ensure accurate reporting. Once laboratory investigations have confirmed the diagnosis of EHF in the initial cases, the use of a clinical/epidemiological case definition is sufficient. The area to be immediately put under EHF surveillance must be clearly defined and local resources for surveillance (dispensaries, hospital, missions) identified, with appropriate training of personnel. The detection and isolation of all cases and the detection and follow-up of all contacts in the area under surveillance is essential for effective control. All categories of cases, as outlined below, must be submitted to the same management rules

In the context of a suspected epidemic, the following definitions must be considered:

Suspected (clinical) case:
Any person ill or deceased who has or had fever with acute clinical symptoms and signs of haemorrhage, such as bleeding of the gums, nose-bleeds, conjunctival injection, red spots on the body, bloody stools and/or melaena (black liquid stools), or vomiting blood (haematemesis). Documented prior contact with an EHF case is **not** required.

Probable case (with or without bleeding):
Any person (living or dead) having had contact with a clinical case of EHF and with a history of acute fever.
OR

Any person (living or dead) with a history of acute fever and three or more of the following symptoms: headache/ vomiting/nausea/ loss of appetite/ diarrhea/ intense fatigue/ abdominal pain/ general muscular or articular pain/ difficulty in swallowing/ difficulty in breathing/

hiccoughs

OR
Any unexplained death.

The distinction between a suspected case and a probable case in practice relatively unimportant as far as outbreak control is concerned.

Contact:
A person without any symptoms having had physical contact with a case or the body fluids of a case within the last three weeks. The notion of physical contact may be proven or highly suspected such as having shared the same room/bed, cared for a patient, touched body fluids, or closely participated in a burial (e.g. physical contact with the corpse).

See Annex 3 for case and contact definition of EHF in an epidemic context.

2.1.2   Monitoring and follow-up of cases and contacts

When reporting cases, no distinction should be made between suspected and probable cases. A *Case Report Form (Annex 4)* must be completed for each new case. A record of all cases must be kept separately on the main register of the health care facility, in order to have a permanent chronicle of the epidemic. Contacts must be told to report to the local health facility if they develop fever and must be observed daily, usually at home. Close surveillance of contacts must include body temperature checks at least once and, where possible, twice daily for 21 days after last exposure. In the case of a temperature above 38.5°C (101°F), the contact must be considered a new case and put in strict isolation. Households of all cases must be surveyed for possible additional cases and contacts using an *Active Surveillance Form (Annex 5)*.

The surveillance area must be monitored for a time corresponding to 2 estimated incubation periods (twice 21 days, i.e. 42 days) after the date of death or hospital discharge of the last case.

See Annex 4 for Case report form for EHF
See Annex 5 for EHF active surveillance form

2.1.3. Rumour and information management

A rumour registry must be established to record rumours of cases systematically. This should be handled by at least two persons appointed to this effect, who must be available 24 hours a day for contact with both the local community and the investigation and control teams. A room must be dedicated this activity. The rumour registry must be carefully maintained and used to provide materials for the investigation teams, and its existence must be widely advertised in the community.

An **epidemiological bulletin** must be sent daily to local health authorities and to WHO

headquarters through the WHO Country Representative by the fastest available means. This daily bulletin must include at least the following information:

C   total cumulative number of cases since the first report
C   total cumulative number of deaths since the first report
C   number of patients under treatment (on the day of reporting)
C   number of patients hospitalized (on the day of reporting)
C   number of contacts requiring follow up (on the day of reporting)
C   number of contacts under effective follow-up (on the day of reporting)
C   date of latest identified case
C   date of death or discharge of latest reported case.

When possible, the geographic distribution of cases and contacts should be provided, as well as a simple epidemic curve. Case-fatality rates, overall and age-specific attack rates *(Annex 6)* may be included to facilitate epidemiological assessment. All reported epidemiological data and information must be agreed upon daily through a meeting of key participants to the outbreak control. Figures and information should be released once a day at a stated time, preferably by one single invariable source. This helps avoid confusion, especially vis-à-vis the media.

See Annex 6 for epidemiological calculations

2.1.4. Death of suspected cases

If a suspected case of EHF dies, a post-mortem skin biopsy should be taken (*Annex 7*) and sent for laboratory confirmation. This suspected case must also be reported on the *Case Report Form* and counted in epidemiological calculations.

See Annex 7 for instructions on taking a post-mortem skin biopsy

2.2   Laboratory confirmation and findings

Laboratory confirmation of initial cases is necessary when an epidemic of EHF is suspected. Once the outbreak is confirmed, however, there is no need to collect specimens systematically from each patient, unless this can be done under perfectly safe conditions with appropriate laboratory support. The case definition based on clinical and epidemiological elements must serve as a guide for action; waiting for laboratory results is not acceptable in an epidemic control perspective.

Confirmed diagnosis is based on ELISA for Ebola specific IgG and IgM antibodies or Ebola specific antigen detection. These tests are not commercially available and must be performed in specially equipped laboratories. It is usually not feasible to establish viral diagnostic facilities under field conditions at the site of the outbreak. Specimens should therefore be collected on-site and shipped to WHO Collaborating Centres. Attempts to isolate a suspected Ebola virus must be made only in a specifically equipped laboratory with P4 biosafety level and trained personnel.

As regards case management, clinical laboratory support is essential. However, laboratory tests must not be performed unless appropriate biosafety measures can be implemented. Findings usually show lymphopenia, severe thrombocytopenia and elevation of transaminases (AST>ALT), sometimes with hyperamylasaemia.

2.3.   Collection and shipment of specimens

2.3.1. Collection

Three types of samples should be collected, if possible:

(1)   *Acute phase whole blood* obtained from a patient within 7 days of onset of illness.
(2)   *Convalescent sera* collected from patients at least 14 days after onset of illness. Paired serum samples are ideal, usually collected 7-20 days apart. There is no need to separate acute phase sera from blood clots (a procedure which may significantly increase the risk of accidental infection). The use of sealed sterile dry tubes (Vacutainer® type) is recommended. Ideally, blood samples should be kept in their original tube and stored at 4ºC to allow virus isolation. If blood samples are collected for serological or biochemical purpose only, they should be frozen. Each collected blood sample must be properly coded and dated for easy connection with the corresponding individual record of the case database. The use of labels prepared in advance for both the collection of clinical samples and case report forms is recommended.
(3)   *Post mortem specimens*. These include skin biopsy (*Annex 7)* or biopsy of other organs (e.g. liver). Strict biosafety measures must be applied during the collection of specimens.

See Annex 7 for **post-mortem** *skin biopsy collection procedures*

2.3.2. Shipment

The special procedure for shipping blood samples and other specimens (see below) must be strictly applied. In addition, the parcel must include up-to-date information about each sample, i.e. case code, symptoms or clinical diagnosis, date of specimen collection, proposed laboratory test and the name and contact information of the person responsible for the shipment. After proper packing, the specimens must be sent to a WHO Collaborating Centre for viral haemorrhagic fever *(see Annex 8)*. It is advisable that a responsible person accompany the specimens to ensure proper travel and delivery. The WHO Collaborating Centre(s) to which the specimens are addressed must be contacted before shipment for agreement, and rapidly notified of the estimated date and the conditions of arrival. Blood samples from suspected *Ebola* cases are classified as *diagnostic specimens*, code 3.6.6.4, under the Dangerous Goods Regulations of the International Air Transport Association (IATA). These are summarized in *Annex 9.*

See Annex 8 for WHO Collaborating Centres, EHF addresses and contact information
See Annex 9 for IATA recommendations and infectious substances packaging diagrams

Part three: Management of an epidemic

3.1.   Patient management

3.1.1. Transport

Upon arrival at an epidemic site, health officials must decide where to isolate and treat patients. Since the treatment of a case is labour-intensive and the patient requires significant medical attention, evacuation to a well-equipped medical centre from the patient's home or a rural primary care centre is optimal. However, transport of the patient may not be suitable and may present a hazard to drivers and attendants if the right vehicles and barrier technologies are not available. Circumstances when moving the patient is desirable include:
C   patient is at a local, poorly-equipped facility unable to isolate cases
C   local inhabitants are at an increased risk of exposure
C   transport can be undertaken in good and safe conditions
C   an isolation ward is ready to receive the case.

Transport of a case of Ebola haemorrhagic fever must be by the safest and shortest route. Barrier protection for attending staff, vehicle capacity to accommodate a stretcher, isolation of the patient, and decontamination of the vehicle after transport must be taken into account. All persons assisting with transport of cases must be trained in universal precautions.

3.1.2. Sanitation and hygiene/Nursing practices

Measures to prevent percutaneous injuries associated with the use and disposal of needles and other sharp instruments must be taken. If surgical or obstetric procedures are necessary for the patient, WHO Collaborating Centres should be consulted for appropriate precautions.

Protective Clothing
All items of protective clothing worn by caretakers and hospital staff are potentially contaminated; they must remain in the isolation area, and be disinfected or (if disposable) destroyed after use.

Hand washing
Hands must be washed after each contact with patient or contaminated materials. They must first be rinsed in disinfectant and then washed with soap and water. Disinfectant and washing facilities must be located just outside isolation rooms. If there is no sewerage system, washing water must be disposed of in latrines.

Instruments and Dressings
Each patient must have an individual thermometer labelled with the patient*s name and kept in a receptacle containing disinfectant. The stethoscope and the sleeve of the sphygmomanometre must be decontaminated between each use by rinsing them in disinfectant solution. All reusable instruments must be placed in disinfecting fluid after use.

Bed covering
The use of a plastic sheet is essential to avoid the contamination of mattresses. They must be large enough to cover the entire mattress, be waterproof, and be thoroughly disinfected after the discharge or the death of patients.

Linen
All bedding and other linen must be placed in plastic bags and removed for sterilization (soaking in disinfectant, autoclaving or boiling) before laundering.

Food
When possible, relatives should not prepare food for patients in the hospital. The hospital should make its own arrangements for food and drink supply to limit physical contacts between patients and relatives. Eating utensils must be used by individual patients only, and washed and disinfected within the isolation area. Uneaten food must be regarded as infectious and disposed of accordingly.

Charts and records
No charts, notes, or clinical records should be allowed in the isolation ward; they must be written and kept outside.

Methods of disinfection
> *Ordinary household bleach*: The virus is very sensitive to bleach solution; this kills the virus almost instantly in 1:10 bleach solution or after soaking for at least ten minutes in 1:100 bleach solution..
> *Soap and clean water*: Scrubbing with soap and water before disinfection removes infectious body fluids and other foreign matter from contaminated items. This makes bleach solutions more effective.
> *Sterilization*: Heat sterilization requires special equipment such as an autoclave or steam sterilizer. When this equipment is not working or is not available, boiling heat-resistant items in water for 20 minutes will kill VHF viruses.

Patient Isolation
Health care facilities must institute strict barrier isolation of cases in a room away from traffic, if possible. The isolation room must be in a building separate from other patient areas or a private room with strictly limited access. There must be no cross-circulation of personnel or materials from other hospital areas. Good ventilation with screened doors and windows is ideal, but fans should be avoided as they raise up dust and droplets; if available, a negative pressure room is optimal. All rooms housing patients must be identified at the entrance with biohazard warning notices. Patients must remain isolated until they have fully recovered.

Decision to remove from isolation must be made based on clinical grounds. Prior to patient release, a minimum of 7 days without fever and 21 days from onset of illness is usually required.

Biohazardous materials
The threat of infection from such material is serious, and strict procedures for body fluids and excreta must be maintained. Patient excreta, vomit, sputum, blood, and all the objects with which the patient had contact must be disinfected with bleach. Laboratory equipment used to carry out blood tests must also be disinfected. When possible, heating methods such as autoclaving, incineration, or boiling can be used to disinfect. When appropriate, serum may be heat-inactivated at 60°C (140°F) for one hour. Thorough thermal disinfection or the use of bleach is adequate; formaldehyde fumigation can be considered. Proper disposal of needles and other hospital equipment is essential.

Persons with percutaneous or mucocutaneous exposures to blood, body fluids, secretions or excretions from a patient must immediately wash the affected skin surfaces with disinfectant, followed by soap and water. Mucous membranes such as conjunctiva must be flushed with water or eyewash solution. Exposed persons must be considered as contacts and receive medical evaluation, and must be followed up for 21 days for the possible development of symptoms.

Please refer to the WHO Viral Haemorrhagic Fever (VHF) Guidelines mentioned at the beginning of the present document

3.1.3. Handling corpses

Corpses must be wrapped in sealed leakproof material (body bag). They must not be embalmed but buried (or cremated) promptly in a sealed casket. Disinfection or incineration of all dirtied belongings of the patient must be immediately performed. If this is culturally appropriate, the facility must build or obtain an on-site incinerator in order to avoid transport of biohazardous corpses.

3.1.4. Burials/Burial sites

Burial sites must be identified early on, so as to obtain permission from the local authorities, organize and facilitate transport of dead bodies. Local burial customs must be adhered to as closely as possible provided they do not conflict with good public health practices (such as the avoidance of direct physical contact with corpses or body fluids). The community must be informed that these public health practices are aimed to protect against the further spread of disease.

3.2.   Logistic support/Training of health care workers and volunteers

All persons coming into contact with suspected cases or with corpses must be trained in the proper infection control methods. They must be instructed on how to route patients from output to isolation, and on how to manage cases by way of symptomatic relief of headache,

diarrhoea, pain and dehydration.

Surveillance must be combined with health education aimed at limiting contact with patients. Those conducting epidemiological surveillance must be instructed on how to administer surveys for accurate information and how to ensure the proper information and education of, and co-operation from, case household members and the affected community. Special attention must be given to the actual perception of the outbreak by the community. In particular, specific cultural elements and local beliefs must be taken into account to ensure proper messages, confidence, and close co-operation of the community.

Part four: Planning and resource allocation

4.1.   Local and national health authorities, WHO, and other international partners

The hierarchy of responsibility that these guidelines suggest is designed to increase efficiency and maximize the resources allocated for the control of any given epidemic. The guidelines are not intended to be prescriptions but a sample framework that has proven itself in past epidemics.

4.1.1 Local health facility level

Responsibilities at this level include:
C   *Surveillance and reporting*
  C   recognize cases of Ebola haemorrhagic fever
  C   collect information on cases and contacts
  C   arrange for laboratory confirmation of initial cases
  C   immediately report all suspected/probable cases to the district/regional level
C   *Management of cases*
  C   take steps to confirm cases, as necessary
  C   administer supportive care
  C   ensure that universal precaution measures are implemented
C   *Inventory supply and logistics management*
  C   ensure availability of local resources (e.g. protective medical equipment) for outbreak control
  C   analyse needs and request additional support
C   *Public information management and public health education*
  C   release technical information on the epidemic and its control
  C   ensure accurate and thorough public awareness on epidemic.

4.1.2 District/regional/provincial level

Coordinate individual health facilities and plan macro level interventions in close cooperation with representatives of NGOs as appropriate:
C   *Surveillance, analysis of data, and investigation of suspected epidemics*

C   *Intervention planning*
   C   define high risk populations
   C   calculate supplies needed for health facilities
C   *Monitoring the course of the epidemic and the control measures*
   C   send weekly summaries of epidemic surveillance data to all local government authorities and health facilities
   C   send daily summaries to Ministry of Health, WHO, NGOs (if applicable)

4.1.3. National level

This level coordinates epidemic control measures within the entire country, and international help if appropriate, along with the WHO and with NGOs:
C   *Public information management*
C   *Notification of suspected EHF cases to the WHO*
C   *Organisation of laboratory confirmation of EHF*
C   *Convening national epidemic coordinating committee and assigning duties*
C   *Assisting in field investigations*
C   *Providing assistance in obtaining emergency supplies, technical and personnel support*
C   *Assessing and obtaining resources*
            (e.g., mobilizing and convening a "donors' meeting" to obtain support from NGOs and governments and collect funds for epidemic control.

See Annex 10 for communicable disease contacts at Headquarters and Regional Offices

4.2.   Supplies

WHO Rapid Epidemic Response kits will provide both medical and operational supplies, if necessary. These supplies are intended to cover the first three weeks of field control. A list of the supplies available is included within the kit boxes. Further inquiries regarding the availability of supplies and the coordination of available help should be directed either to the Regional Office or to WHO headquarters, Division of Emerging and Other Communicable Diseases (EMC) – Epidemic Preparedness and Response/Rapid Epidemic Response.

Annex 1: Historical review of Ebola outbreaks

Date	Place	Characteristics
1961-1962	ETHIOPIA	*retrospective*: serological evidence for concomitant Ebola/Ebola-like infection during yellow fever epidemic
1972	ZAIRE	*retrospective*: physician developed disease after performing an autopsy
1976 (June-November)	Nzara, Maridi, Tembura, and Juba towns, SUDAN	284 cases, 150 deaths (CFR 52%)
(September-October)	Yambuku, Bumba (Équateur Region) ZAIRE	318 cases, 280 deaths (CFR 88%)
(November)	Salisbury, UK	laboratory worker infected, recovered
1977 (June)	Tandala, ZAIRE	child infected and died
1979 (August)	Nzara, Yambio SUDAN	34 cases, 22 deaths (CFR 64%)
1989-1990	Reston VA, USA	*Reston* strain isolated in monkeys (*Macaca fascicularis*) imported from the Philippines; animal caretakers developed antibodies, but did not develop the disease
1992	ITALY	*Reston* strain in monkeys imported from the Philippines
1994 (November)	Taï forest, CÔTE D'IVOIRE	chimpanzee outbreak, 12/40 died; 1 autopsy worker infected, evacuated to Switzerland where she recovered
1995 (May-June)	Kikwit, ZAIRE	315 cases, 244 deaths (CFR 77%)
1996 (February-March)	Mayibout II, Makokou, Ogooué-Ivindo, GABON	37 cases, 21 deaths (CFR 57%), linked to butchering and preparation of dead chimpanzee
(April)	Alice TX, USA	*Reston* strain in monkeys imported from the Philippines
(July 1996-February 1997)	Booué, Ogooué-Ivindo, GABON	61 cases; 45 deaths (CFR 78%) – 1 case exported to South Africa, transmitted EHF to a nurse who subsequently died

Annex 2: Clinical course and differential diagnosis of EHF

Understanding the clinical picture and differential diagnosis of disease is important for the accurate detection and treatment of suspected cases.

The clinical features of EHF may vary with the Ebola strain involved. The description below refer to the clinical presentation of EHF patients observed in Zaire and Gabon.

Clinical course: Incubation period 2 to 21 days, after which:

Day 1-2: Patient presents with fever up to 39ºC, profuse sweating, malaise and prostration, frontal and temporal headache, myalgia, ocular pain, and conjunctival injection. Relative bradycardia accompanies fever. Nausea and profuse vomiting, watery diarrhea, and diffuse abdominal pain occur. Within 2 days blood may appear both in vomitus and in stools (often described as "diarrhée rouge" in French-speaking countries).

Day 3-6: Enlargement of occipital, nuchal, cervical, and axillary lymph nodes may be noticed. Sore throat with difficulty in swallowing is frequent. Soft palate may display enanthem. Dehydration is usually clinically evident at this stage.

Day 5-7: About fifty percent of patients display fulminant haemorrhagic diathesis with spontaneous epistaxis, gingival haemorrhage, gastro-intestinal and genital bleeding (female), haematuria, bleeding at injection sites. Conjunctival haemorrhage is frequent. Erythematous rash, spreading from the face and buttocks to the trunk and arms, may develop from a papular to a maculopapular lesion in 24 hours. Lesions become confluent and non-itchy.

Day 8-16: The occurrence of persistent hiccups, almost always associated with severe prognosis, is rare and of poor prognosis. Dehydration is severe in the absence of supportive care. Most deaths occur around day 12 with clinical evidence of multi-organ failure, in particular kidney and liver failure. Oedema may be present; CNS involvement, including coma, and terminal shock syndrome immediately precede death.

Among those who recover, the rash usually disappears around day 12; palmar and plantar desquamation occurs at day 14-16. Immediate sequelae may involve orchitis, recurrent hepatitis, transverse myelitis or uveitis.

Differential Diagnosis:

Shigellosis & other bacterial enteric infections:
A common initial diagnosis of EHF ("diarrhée rouge"). Presents with diarrhea, possibly bloody, accompanied by fever, nausea, and sometimes toxaemia, vomiting, cramps, and tenesmus. Stools contain blood and mucous in a typical case. A search for possible sites of bacterial infection, together with cultures and blood smears, should be made. Presence of leucocytosis distinguishes bacterial infections.

Typhoid fever:
Presents with fever, headache, rash, gastrointestinal symptoms, with lymphadenopathy, relative bradycardia, cough and leucopenia and sometimes sore throat. Therapeutic trial with chloramphenicol or tetracyclines. Blood and stool culture can demonstrate causative bacteria.

Malaria:
Presents with acute fever, headache and sometime diarrhoea (children). Blood smears must be examined for malaria parasites. Presence of parasites does NOT exclude concurrent viral infection. Antimalarial must be prescribed in an attempt at therapy.

Lassa fever:
Disease onset is usually gradual, with fever, sore throat, cough, pharyngitis, and facial oedema in the later stages. Inflammation and exudation of the pharynx and conjunctivae are common.

Yellow fever and other *Flaviviridae*:
Present with haemorrhagic complications. Epidemiological investigation may reveal a pattern of disease transmission by an insect vector. Virus isolation and serological investigation serves to distinguish these viruses. Confirmed history of previous yellow fever vaccination will rule out yellow fever.

Others:
Viral hepatitis, leptospirosis, rheumatic fever, typhus, and mononucleosis produce signs and symptoms that may be confused with *Ebola* in the early stages of infection.

NOTE:
Evidence of person-to-person transmission through close contact with patients (e.g. health care, burial ceremony) is a key pattern of EHF and, together with an abnormally high fatality rate in adults, strongly suggests the diagnosis of EHF. This is particularly true in Ebola endemic areas (i.e. African tropical rain forest).

Annex 3: Case and contact definitions for Ebola Haemorrhagic Fever

To be used for control purposes:

C   *in an epidemic context*
C   *in the absence of systematic laboratory confirmation*

SUSPECTED (OR CLINICAL) CASE*:*
Must be considered as such all persons presenting with fever and signs of haemorrhage such as:
C   bleeding of the gums
C   epistaxis
C   conjunctival injection
C   petechiae/purpura
C   bloody stools or melaena
C   haematemesis
C   other haemorrhagic signs

Proof of previous contact with a case of EHF is **not** required.

PROBABLE CASE:
Must be considered as such:
All persons, living or deceased, with:
C   contact with a case of Ebola Haemorrhagic Fever *and*
C   a history of fever, with or without bleeding

OR
All persons, living or deceased, with:
C   a history of acute fever *and*
C   3 or more of the following symptoms:
        C   headache
        C   vomiting/nausea
        C   anorexia/loss of appetite
        C   diarrhea
        C   weakness/severe fatigue
        C   abdominal pain
        C   generalized muscular or articular pain
        C   difficulty in swallowing
        C   difficulty in breathing
        C   hiccoughs

OR
Any unexplained death.

CONTACT

A person without any symptoms having had physical contact with a case or the body fluids of a case within the last three weeks.

The notion of physical contact may be proven or highly suspected such as having shared the same room/bed, cared for a patient, touched body fluids, or closely participated in a burial (e.g. physical contact with the corpse).

Annex 4: Case report form for Ebola Haemorrhagic Fever

Date .../.../...

I.   IDENTIFICATION

Name ....   Patient N° ....

Age or date of birth ....   Sex M/F   Occupation ....

Address ....   Quarter ....   Zone ....

Head of household ....   Name of father (if child) ....

Place of hospitalization ....

Date of admission ....   Date of release ....

This case was identified by (circle one):

1. Rumour   2. Death   3. Passive surveillance   4. Active surveillance

Were there any other ill persons surrounding this case?   *Yes   No*
If so, specify, and indicate symptoms
....

II.   CLINICAL CONDITION

Alive .... Dead ....   ===>Date of death.....................................

(*Date of post-mortem skin biopsy......................*)

High fever   Yes   ===> Date of onset ....   No .... Unknown ....

Contact with case of EHF   Yes...............   No .... Unknown ....
                                  Name of last contact ....
                                  Relationship ....
                                  Date of last contact ....
                                  Type of contact ....

Annex 4 (ctd) Case report form

Physician/Facility ....

Name .... *Date* ....

*Check patient*s signs/symptoms below:*

GROUP	*yes*	Signs/Symptoms	Duration/Observations
A		headache	
		vomiting/nausea	
		anorexia/loss of appetite	
		diarrhea	
		intense fatigue	
		abdominal pain	
		muscular/articular pain	
		difficulty swallowing	
		difficulty breathing	
		hiccoughs	
Signs of haemorrhage:			
B		bleeding of gums	
		conjunctival injection	
		petechiae/purpura	
		black blood in stool	
		vomiting blood	
		nose bleeds	
		other:	

Case Definition: (circle one) **Suspected**   **Probable**   **Not a case**

III. LABORATORY

Sample 1:   *Date:*   *Result:*
Sample 2:   *Date:*   *Result:*

IV. COMMENTS

Annex 5: Ebola Haemorrhagic Fever active surveillance form

Team: Date of first observation: Follow-up through:

Follow-up must last a minimum of 21 days after the date of detection of a case.

I. IDENTIFICATION

Name of case ....   Type (circle one)   Clinical   Probable

Name of head of household ....

Address:...

Quarter................................. Zone...

Number of persons in household ....

II. HOUSEHOLD COMPOSITION AND CLINICAL SITUATION

Person #	1	2	3	4	5	6	7
Surname							
Name							
Relation							
Sex							
Age							
Latest Contact							
Type of Contact							
Care							
Burial							
Physical							
Presence							

Annex 5 (ctd): EHF active surveillance form

Person # Name	1	2	3	4	5	6	7
Symptoms							
high fever							
headache							
nausea/vomiting							
low of appetite							
diarrhoea							
intense fatigue							
abdominal pain							
general pain							
difficulty swallowing							
difficulty breathing							
hiccoughs							
gingivitis							
conjunctival injection							
petechiae/purpura.							
melaena							
vomiting blood							
nosebleeds							
other							

III. OBSERVATIONS/COMMENTS

Annex 6: Epidemiological calculations

Case-fatality rate (CFR): corresponds to the percentage of cases which result in death.

(number of deaths/number of cases) x 100

Weekly attack rate: expressed as the number of cases per 100 000 people per week.

1.   *Divide 100 000 by the population of the area under study*
2.   *Multiply the result by the number of cases that occurred in a given week.*

That result is the *attack rate*, expressed as cases per 100 000 people per week.

Weekly age-specific attack rate: number of cases per 100 000 in one age-group, per week

1.   *Calculate the number of persons in the age group in the area under study*
2.   *Tally the number of cases in the age-group for the chosen time period*
3.   *Divide 100 000 by the number of persons in the age group*
4.   *Multiply the result by the number of cases in that age group*

The result is the *age-specific attack rate*, expressed as cases per 100 000 per week in a given age-group.

Annex 7: Skin biopsy on fatal cases for diagnosis of Ebola

Ebola virus can be detected in fatal cases from a skin specimen using an immunohistochemistry test developed by the CDC Molecular Pathology Unit. Skin is fixed in formalin which kills the virus. The specimen is no longer infectious once it has been placed in formalin and the outside of the vial has been decontaminated. The vial can be shipped by mail or hand carried to the lab without risk. Results are available within a week of arrival at the CDC.

CDC provides Skin Biopsy kits for the collection of skin samples in formalin. If these are available in your area, follow the simple instructions that are provided in the kit (see next page). If a kit is not available, the biopsy can still be collected and sent for diagnosis to:
Dr. Sherif Zaki
Molecular Pathology G-32
1600 Clifton Road, NE
Atlanta, GA 30329-4018

To perform the biopsy, you will need:
C   scissors
C   a vial with a screw cap
C   formalin
C   protective clothing
C   heavy duty gloves to handle the cadaver.

Instructions for collection of skin biopsy for Ebola Haemorrhagic Fever:

1.   Provide the contact address for sending the results back to you. Patient information is
        important to the diagnosis:
C   patient name
C   hospital number or number which is on vial for your reference of results
C   date of onset of illness
C   date of death
C   date of collection of biopsy
C   signs and symptoms seen and length of duration if known.

2.   Before starting, make sure you have all of the equipment you need:
C   disinfectant
C   gloves
C   heavy duty gloves
C   mask
C   gown
C   plastic apron to protect from spills
C   scissors or biopsy tool and forceps (scalpel not recommended because too risky)
C   vial with formalin (10 % buffered formalin)
C   soap and bucket of water.

3.   Prepare disinfectant and put on protective clothing. Begin the gown, next the latex gloves, then the kitchen gloves and the mask. Use a plastic apron.

4.   Take the equipment to the work site. Open the vial of formalin. Lay out your instruments (scissors and forceps).

5.   Gently turn the head of the cadaver to expose the nape of the neck. Cut a small piece of skin from the area. Any area of skin is OK, this is selected because of vascularity and lack of visible deformation to the body.

6.   Use forceps or tweezers to gently lift skin sample.

7.   Place the skin section in the formalin and close the cap tightly.

8.   Dip the closed vial in the disinfectant for 1 minute. Set aside to dry.

9.   Place the tools in the disinfectant and leave. Move the cadaver if necessary while still wearing the protective clothing. When you have finished, rinse your outer gloves in the disinfectant and remove them. Drop the gloves in the disinfectant.

10.   Wearing the inner gloves, remove all disinfected materials for cleaning or dispose of these materials in the incinerator. Disinfect the inner gloves and remove for cleaning or burn.

11.   Wash your hands with soap and water. The specimen is not infectious after it has been placed in formalin and the outside has been disinfected.

12.   Place the specimen vial in a mailing container with the patient information and send to CDC, or to the United States Embassy with instruction to send to CDC.

Annex 8: WHO Collaborating Centres, Ebola Haemorrhagic Fever
(Specimen analysis and personnel support)

Institut Pasteur
28, rue du Dr Roux
75724 Paris Cedex 15
FRANCE
Tel: (33) 1 406 13088
Fax: (33) 1 406 13151

Special Pathogens Unit
National Institute for Virology
Private Bag X4
Sandringham 2131, Zaloska 4
SOUTH AFRICA
Tel: (27) 11 882 4238
Fax: (27) 11 321 0596

Division of Pathology
Centre for Applied Microbiology and
Research
Porton Down, Salisbury
Wiltshire SP4 0JG UK
Tel: (44) 198 061 2224
Fax: (44) 198 061 2731

US Army Medical Research
Institute of Infectious Diseases
(USAMRIID)
Fort Detrick, Maryland 21702-5011
USA
Tel: (1) 301 619 4608
Fax: (1) 301 619 4625

Special Pathogens Branch
Division of Viral and Rickettsial Diseases
National Center for Infectious Diseases
Centres for Disease Control and Infection
1600 Clifton Road
Atlanta, Georgia 30333
USA
Tel: (1) 404 639 1115
Fax: (1) 404 639 1118
CDC Ebola Hotline: (800) 900 0681

Annex 9: IATA instructions and infectious substance packaging diagrams

Shipment of specimens by airfreight are subject to strict IATA regulations with regards to packaging, labelling, and transport. Specimens must be packaged in three layers:

(1) a primary water-tight container containing the specimen
(2) a second water-tight container enclosing enough absorptive material between it and the primary container to absorb all of the fluid in the specimen in case of leakage and
(3) an outer package which is intended to protect the secondary package from outside influences, such as physical damage and water while in transit.
These packages must bear the infectious substance (biohazard) label.

At least 48 hours before arrival of the shipment, a *preadvice message* must be sent to the consignee by telex or fax. This must include the following information:

Preadvice Message:
C   place of departure
C   place of arrival
C   number of boxes
C   flight arrival details (flight number/date/time)
          Avoid arrival of goods on weekends (Sat/Sun or Thu/Fri according to destination)
C   airway bill (AWB) number
C   recommended storage temperature.

To facilitate customs formalities on departure and arrival, a *proforma invoice/packing list* is necessary and must include:

Proforma Invoice/Packing List:
C   consignee*s address
C   number of cartons
C   details of contents
C   gross weight (optional)
C   value (for customs reasons, enter a symbolic value even for medical samples)
C   identifying marks
C   a short statement clarifying that the items are supplied *free of charge*.

An *Airway bill* made out by or on behalf of the shipper determines the contract for the carriage of specimens over the routes of the carrier. It must show the text: "*Diagnostic specimens-Not Restricted-Packed in Compliance with IATA Packing Instruction 650.*" It is usually completed by the airline representative or the forwarding agent.
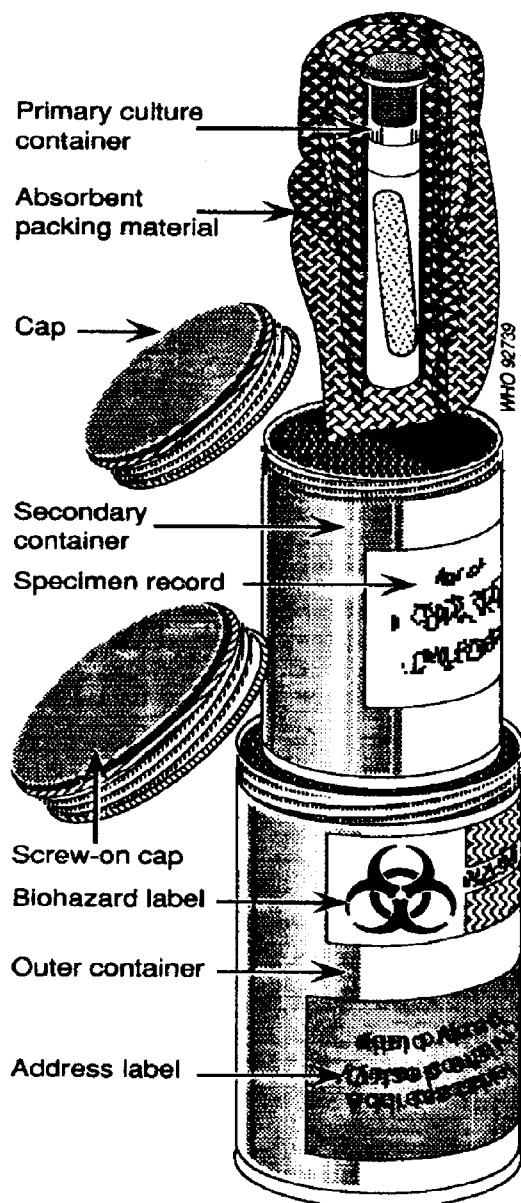
The name and telephone number of the person responsible for the shipment must be marked durably and legibly on the outside of the package. One copy of specimen data forms, letters, and other identification material must be attached to the outside of the second container. A

copy must also be sent air mail to the receiving laboratory and a third copy retained by the sender. Materials consigned in liquid nitrogen or with other protection from ambient or high temperatures must be able to withstand very low temperatures; both primary and secondary packaging must be able to withstand a pressure differential of at least 95kPa and temperatures ranges of -40° to + 50ºC.

Packaging infectious substances for shipment

Triple packaging system   *Infectious substance (BIOHAZARD) label*

Primary culture container

Absorbent packing material

Cap

Secondary container

Specimen record

Screw-on cap

Biohazard label

Outer container

Address label

INFECTIOUS SUBSTANCE

IN CASE OF DAMAGE OR LEAKAGE
IMMEDIATELY NOTIFY
PUBLIC HEALTH
AUTHORITY

Annex 10: WHO contacts at headquarters and regional offices

HEADQUARTERS
Dr. D. Heymann, Division of Emerging and Other Communicable Diseases Surveillance and Control (EMC)
Direct telephone: (41 22) 791 2660, fax (41 22) 791 4198
E-mail: HEYMANND@WHO.CH

AFRO
Dr D. Barakamfitiye, Director, Prevention and Control of Diseases (DDC)
Direct telephone: 26311 401 743, fax 263 479 1214/0146
E-mail: BARAKAMFITIYED@HTSD.COM at INET
Dr A. Ndikuyeze, Regional Adviser, Prevention and Control of Diseases (DDC),
Direct telephone: 26311-403823. E-mail: NDIKUYEZEA@SERVER.WHOAFR.ORG

AMRO
Dr S. Corber, Director, Division of Communicable Disease Prevention and Control (HCP) Direct
telephone: 001 202 974-3632, fax 001 202 974-3648 or 001 202 974-3643.
E-mail: CORBERST@PAHO.ORG
Dr G. Schmunis, Coordinator, Program of Communicable Diseases (HCP/HCT)
Direct telephone: 001 202 974-3272, fax 001 202 861-8483
E-Mail: SCHMUNIG@PAHO.ORG

EMRO
Dr M.H. Wahdan, Assistant Regional Director - Direct tel. 00 203 483 0039; fax 00 203 48 21 545. E-Mail: WAHDANM@WHO.SCI.EG
Dr B. Sadrizadeh, Director, Integrated Control of Diseases, fax 00 203 4838916
E-mail: SADRIZADEB@WHO.SCI.EG
Dr Z. Hallaj, RA/CDS, Direct telephone: 00 203 4830096 fax 00 203 4838916
E-mail : HALLAJZ@WHO.SCI.EG

EURO
Professor S. Dittman, Coordinator, Communicable Diseases and Immunization and Vaccine
programme (CDI)). Direct telephone: 0045 39 17 13 98 or 0045 39 17 14 15 (secretariat)
fax 00 45 39 17 18 51. E-mail: SDI@WHO.DK

SEARO
Acting Director, Integrated Control of Diseases (ICD) fax: 00 91 11 331 8412
Dr A.G. Andjaparidze, Regional Adviser on Communicable Diseases (CDA),
Direct telephone: 00 91 11 331 7804 to 7823 fax 00 91 11 331 8412
E-mail: ANDJA@WHO.ERNET.IN
Dr Sawat Ramaboot, Regional Epidemiologist, Division of Integrated Communicable Diseases (ICD),
Direct telephone: 00 9111 331-7804 to 00 9111 331-7823
Fax 00 9111 331-8412 and 00 9111 331-8607. E-mail: SAWAT@WHO.ERNET.IN

WPRO
Dr Shigeru Omi, Director, Disease Prevention and Control (DPC)
Direct telephone: 00 632 522-9961, fax 00632 521-1036. E-mail: OMIS@WHO.ORG.PH
Dr Kouichi Morita, Regional Adviser in Communicable Diseases, CDS(M)
Direct telephone: 00 632 522 9964, fax 00 632 521 1036
E-mail: MORITAK@WHO.ORG.PH