

Medical virology

Ebola virus

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1- History of the disease

The first time the disease appeared was in August 1976 .¹ Patient zero was a school teacher who had been touring along the Ebola River just days before he was identified with what become known as the Ebola virus .²

There are four kinds of Ebola virus: Ebola- Ivory Coast, Ebola-Reston, Ebola-Sudan, and Ebola-Zaire. Ebola-Reston is the only kind that has been found in the United States. In 1989, monkeys that were brought to Reston, Virginia, had the disease they got very sick and died none of the people who worked with the monkeys got sick.³

The first appear of the virus in Saudi Arabia it was in 2014 It confirmed, this would be the first Ebola-related death outside Africa in an outbreak that has killed more than 900 people this year.

The 40-year-old man recently visited Sierra Leone, one of four countries in the outbreak.

October 5, 2014 Saudi Arabia issued a travel ban on citizens of Liberia, Guinea and Sierra Leone as what it called a “precautionary measure,” saying the risk of Ebola infection is too high for travelers from those countries to be allowed entry now.

But still there was cases of the virus in hajj more than 250 cases.⁴

1-2. Introduction of the virus

What is Ebola?

The name of the Ebola virus originates from the Ebola River in the and Congo and it is –RNA virus.¹

1-3. The distribution of this disease.⁵

1-4. Epidemiology 1976.

The first known outbreak of EVD was identified only after the fact, occurring between June and November 1976 it was in Zaire (Democratic Republic of the Congo - DRC) the Ebola subtype Zaire virus the Reported number of human cases 318 the Reported number (%) of deaths among cases 280 (88%) the Situation Occurred in Yambuku and surrounding area. Disease was spread by close personal contact and by use of contaminated needles and syringes in hospitals/clinics. This outbreak was the first recognition of the disease.

March 2014-Present

In Multiple countries the causes Ebola virus Reported number of human cases 28652 Reported number (%) of deaths among cases 11325.⁶

Outbreaks Chronology: Ebola Virus Disease⁷

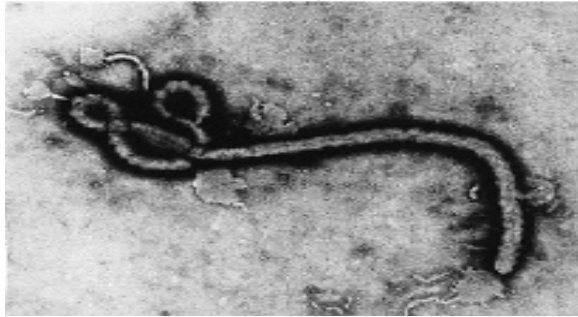
2- Classification of virus :

2-1. Order: *Mononegavirales*.

2-2. Family: *Filoviridae*.

2-3. Genus: *Ebola*.⁸

3- Structure and genome :



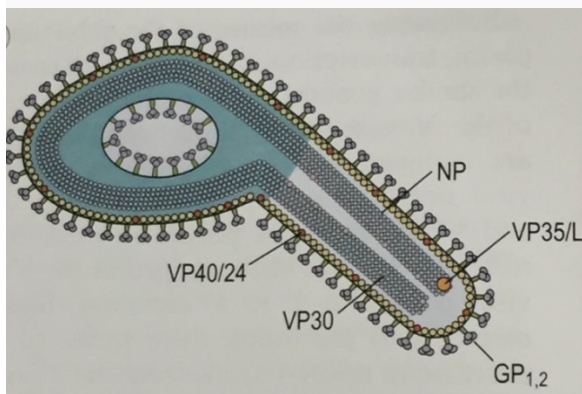
Electron micrograph of famous filamentous morphology of the Ebola virus. ¹¹

Ebola is an elongated filamentous virus, which can vary between 800 - 1000 nm in length, and can reach up to 14000 nm long (due to concatamerization) with a uniform diameter of 80 nm. It contains a helical nucleocapsid (with a central axis), 20 - 30 nm in diameter, and is enveloped by a helical capsid, 40 - 50 nm in diameter, with 5 nm cross-striations. The pleomorphic viral fragment may take on several distinct shapes (e.g., in the shape of a "6", a "U", or a circle), and are contained within a lipid membrane. Each virion contains a single-strand of non-segmented, negative-sense viral genomic RNA.⁹

4. Protein (virulence factors):

4-1. Structural proteins:

Their genomes encode the same set of seven genes in the same order, namely nucleoprotein (NP), viral structural protein 35 (VP35), VP40, glycoprotein (GP), VP30, VP24, and RNA-dependent RNA polymerase (L).⁸



In all filoviruses the full-length GP is further proteolytically cleaved to form two heavily glycosylated subunits, GP1 and GP2, which together form the surface spikes seen by electron microscopy. The GP2 is a transmembrane protein and bears a fusion site, and has been shown to modify permeability of the plasma membrane. The GP1 is involved in viral attachment and entry, the latter associated with critical conserved sequences. During entry and assembly and budding, viral proteins including GP1 have been shown to associate with lipid rafts on the cell surface, and released viruses, including virus-like particles (VLPs), incorporate raft-associated host molecules.

The VP30, VP35, NP and L proteins are necessary and sufficient for in vitro replication. VP30 is a nucleocapsid-associated transcription factor which interacts directly with viral RNA, and is thought to be associated with the nascent molecule.

VP35 is capable of targeting several pathways of antiviral interferon systems. It is an RNA-binding protein which acts as an interferon antagonist. It works by blocking the activation of interferon regulatory factor 3 which is responsible for facilitating interferon-associated gene expression. VP35 has further been shown to block the host miRNA responsible for RNA silencing. This silencing is part of the host innate antiviral activity, and is analogous to the activity of the HIV-Tat protein. It has also been shown to be capable of blocking α -interferon-induced antiviral activities and inhibition of the β -interferon promoter.

NP is associated with the nucleocapsid, serving as a scaffold and binding with VP40 is important for its incorporation into the virion during assembly.

The L protein is the RNA-directed RNA polymerase.

The VP24 protein, an abundant but poorly glycosylated protein, is believed to be a secondary matrix protein. It is associated with assembly and budding, and appears to localize to the plasma membrane and the perinuclear region. It has been shown to be capable of budding from mammalian cells as lipid-bound VLPs. There is some evidence in a mouse model that VP24 and NP are associated with virulence and may also interfere with the host cell antiviral interferon response.¹⁰

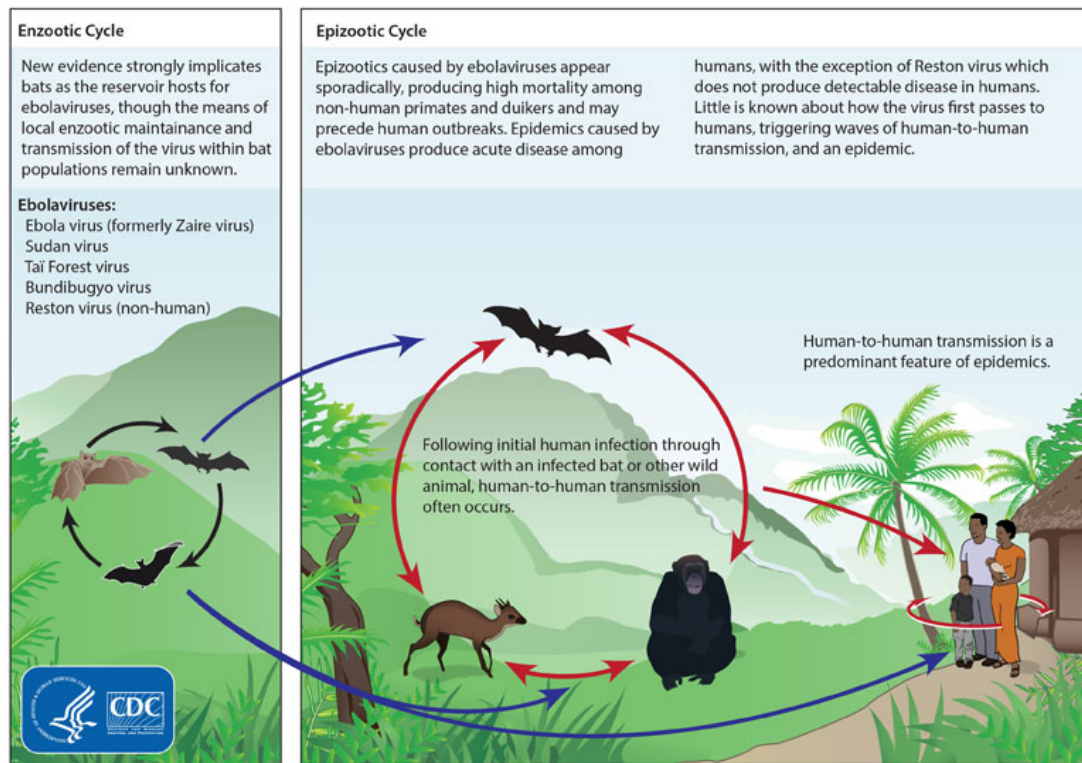
4-2. Non- Structural proteins:

sGP is produced in relatively large amounts in Ebola virus infection and might remove neutralizing antibodies from the circulation. This would require similarities in the antigenicity of sGP and GP that might be reflected in immunogenicity.¹¹

5- Transmission:

the way in which the virus first appears in a human at the start of an outbreak is unknown. However, scientists believe that the first patient becomes infected through contact with an infected animal.¹² Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rainforest. Ebola then spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids¹³ of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. Health-care workers have frequently been infected while treating patients with suspected or

confirmed EVD. This has occurred through close contact with patients when infection control precautions are not strictly practiced. People remain infectious as long as their blood contains the virus.¹⁴



6- Penetration and the target organ

Everyone knows that Ebola kills, but what exactly does it do. Once it gets in the body, the virus attaches itself to the surface of the cells by glycoprotein and the NP-C1 cholesterol transporter facilitates the fusion of the virus with endosomes and lysosomes and allows the virus to escape into the cytoplasm. Then it invades them, replicates, and causes the cells to explode, sending infectious particles flying. From there, Ebola overpowers the immune system. It uses the very cells that are meant to fight infection to travel to other parts of the body, including the liver, spleen, kidneys, and brain. It attacks almost every organ and tissue. The particle explosion also sets off an overwhelming inflammatory reaction. That's what causes the sudden flu-like symptoms that are the first signs of Ebola.¹⁵ Inside the blood vessels, the virus causes abnormal clotting and bleeding at the same time. Bleeding into the skin causes a red rash that appears all over. With the ability to clot normally destroyed, bleeding occurs internally as well as from the eyes, ears, and nose. This whole cascade of events causes the organs to fail. The loss of blood, along with organ failure, is what makes Ebola so deadly. The infection moves fast and it can kill in 1 to 2 weeks. In the current outbreak, 60% of the people who caught the virus have died. Many more could likely be saved with better access to medical care.¹⁶

7- REPLICATION

7-1. Host immune system attack:

ebola is single-stranded RNA is enveloped by a helical capsid. Each virion contains a target of the virus are the monocytes and the macrophages of the host immune system. Most of these host immune system attack processes involve the virus' structural proteins. One such mechanism is called the antibody-dependent enhancement (ADE) wherein the host antibodies (Abs), facilitate or enhance the virus's attachment to the host cells increasing infection in these cells. Abs bind to the glycoprotein (GP) spikes of the virus, and the C1q component of the complement system binds to the Ab-GP complex. The C1q component enhances the Ab-GP complex to bind to C1q ligands on the host cell surface thus increasing the interaction of the virus with its receptor on the host cell surface. This way, the GP spikes on the virus use the host immune system (Abs and the complement components) to enhance its attachment to the target cells: the primary mRNA transcript of the GP gene encodes the soluble sGP which is speculated to have an anti-inflammatory role during infection which further enhances the virus' escape from host immune system response. the viral proteins disrupt different components of the immune system to attach to the host cell for subsequent entry.

7-2. Virus entry into the host cell:

The exact mechanism by which the Ebola virus enters host cells remains poorly understood. One general mechanism to infect host cells for most enveloped viruses including the Ebola virus is endocytosis. Research indicates that the virus utilizes a lipid-dependent, non-clathrin and dynamin-independent endocytic pathway of entry. Macropinocytosis is the most likely mechanism employed by the Ebola virus. This process involves outward extensions of the plasma membrane formed by actin polymerization, which can fold back upon themselves. The exact mechanism by which the virus induces macropinocytosis is not understood. It is speculated that interactions between GP and host cell surface receptors can trigger macropinocytosis to initiate viral entry.

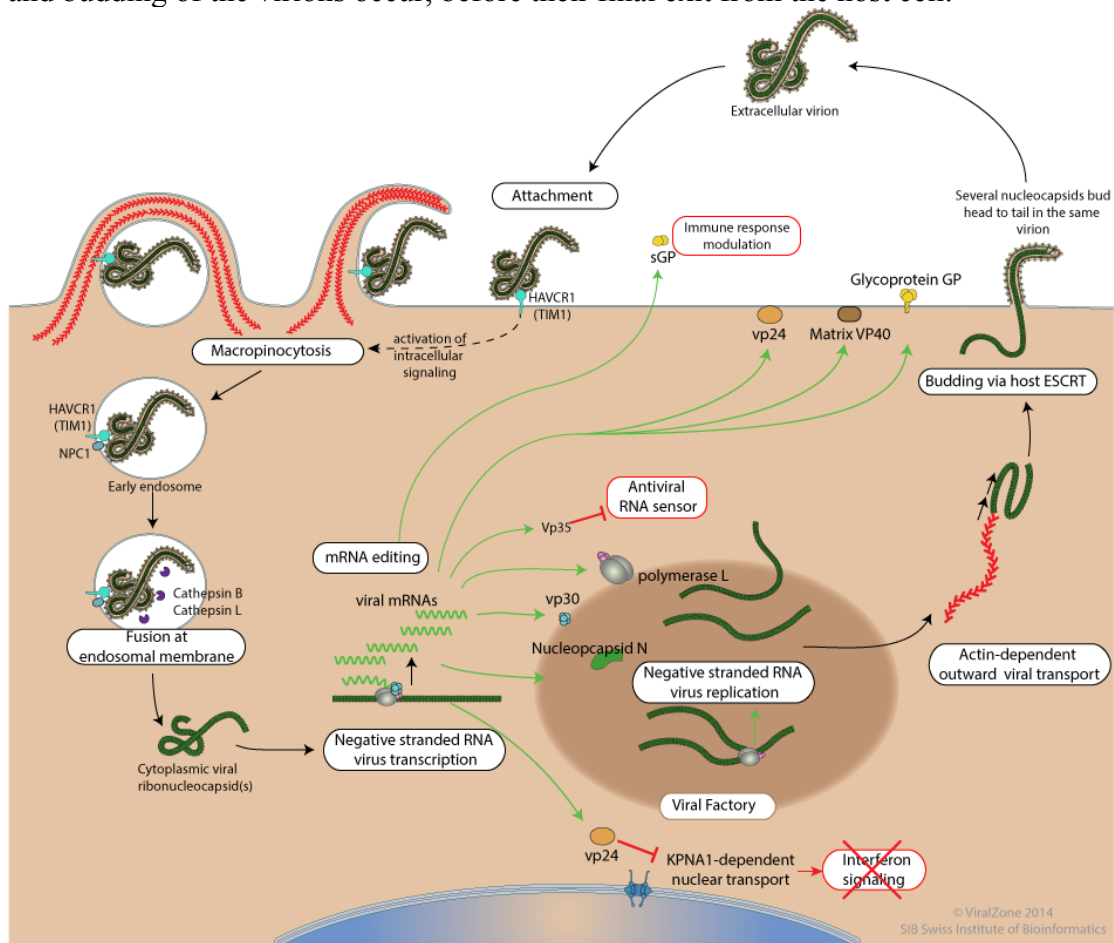
7-3. Virus replication:

Once inside the host cell, the virus initiates transcription in cytoplasm at the leader end of the genome with the binding of the polymerase complex. VP30 is an important transcription activation factor for viral genome transcription, while VP24 is an inhibitor to this process. The exact mechanism of VP24-dependent transcription termination is not fully understood, but it seems to be important for converting the virus from its transcriptional or replication active form to one that is geared for virion assembly and exit from host cell.

7-4. Virus budding and exit from host cell:

Following replication, the cell loses its connection with other cells as well as attachment to its substrate. Meanwhile, the newly synthesized genomes are packaged into new buds or virions and egresses from the host cell surface with the help of the matrix protein VP40. VP40 interacts with ubiquitin ligase Nedd4 which is a part of human ubiquitination enzyme pathway and links multiple copies of ubiquitin molecules to VP40. VP40 itself is transported to the host cell plasma membrane. Then in the plasma membrane, the virus moves through lipid rafts where the final assembly

and budding of the virions occur, before their final exit from the host cell.¹³



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8-Assembly and egression

Ebolavirus is responsible for highly lethal hemorrhagic fever. Like all viruses, it must reproduce its various components and assemble them in cells in order to reproduce infectious virions and perpetuate itself.¹⁸ Ebola triggers a system-wide inflammation and fever and can also damage many types of tissues in the body, either by prompting immune cells such as macrophages to release inflammatory molecules or by direct damage: invading the cells and consuming them from within. But the consequences are especially profound in the liver, where Ebola wipes out cells required to produce coagulation proteins and other important components of plasma. Damaged cells in the gastrointestinal tract lead to diarrhea that often puts patients at risk of dehydration. And in the adrenal gland, the virus cripples the cells that make steroids to regulate blood pressure and causes circulatory failure that can starve organs of oxygen¹⁹. The EBOV VP40 matrix proteins play a central role in virion assembly and little is known about nucleocapsid assembly of this virus in infected cells. We report here that three viral proteins are necessary and sufficient for formation of Ebola virus particles and that intracellular posttranslational modification regulates this process²⁰ and there is egress, such that independent expression of VP40 leads to the production and egress of virus-like particles that accurately mimic budding of infectious virus. Late budding domains of eVP40 recruit host proteins that are important for efficient virus egress and spread²¹.

9- Symptoms

The incubation period, that is, the time interval from infection with the virus to onset of symptoms is 2 to 21 days. Humans are not infectious until they develop symptoms. First symptoms are the sudden onset of fever fatigue, muscle pain, headache and sore throat. This is followed by vomiting, diarrhea, rash, symptoms of impaired kidney and liver function, and in some cases, both internal and external bleeding (e.g. oozing from the gums, blood in the stools). Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes.²²

10- DIAGNOSIS

As filovirus outbreaks occur sporadically, typically in isolated regions of Africa, initial diagnosis is usually based on clinical symptoms. It is quite likely that single cases of filovirus infection are misdiagnosed as the symptoms can be similar to other diseases, such as malaria or hemorrhagic measles. When possible, international reference laboratories should be involved in sample collection, storage and transport, especially when potential cases occur in non-endemic countries

10-1. Genome detection Currently the most frequently used method to identify filovirus infections is RT-PCR on blood samples Nucleic acid be detected in blood as early as 3 days post-onset of symptoms. Most laboratories favour RT-PCR (real-time polymerase chain reaction is a laboratory technique of molecular biology based on the polymerase chain reaction (PCR). It monitors the amplification of a targeted DNA molecule during the PCR)

because of its sensitivity, specificity on and rapidity. It has been successfully implemented in the mobile laboratory setting and has proven accurate on- and effective in both Ebola and Marburg hemorrhagic fever outbreaks. Due to the seriousness of a positive test for filoviruses, the diagnosis of index cases or of single imported cases should not be solely based on a single assay. Confirmation by an independent assay and/or laboratory should always be attempted

10-2. Antigen detection Viral antigen detection is performed using ELISA based methods. Typically this is performed to confirm results from RT-PCR. Classically, antigen detection was performed on formalin-fixed tissue samples by immunofluorescence assay (IFA)

10-3. Serology: Antibodies Are the AG-binding Proteins present on B cell(memory cell) membranes & Secreted by plasma cells, also called Immunoglobulins.

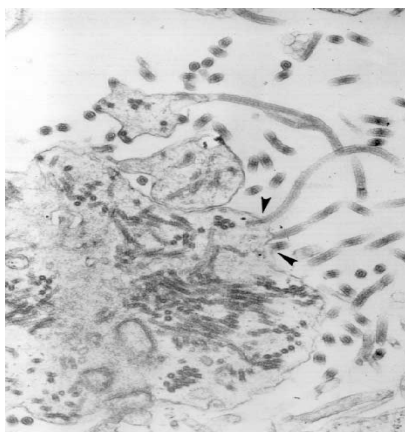
Antibody detection can be performed by ELISA based methods on both acute Immunoglobulin M and convalescent Immunoglobulin G serum. These assays are typically used to confirm diagnosis and for surveillance efforts.

10.4-Virus Isolation Filoviruses can be isolated from blood and tissue samples by cell

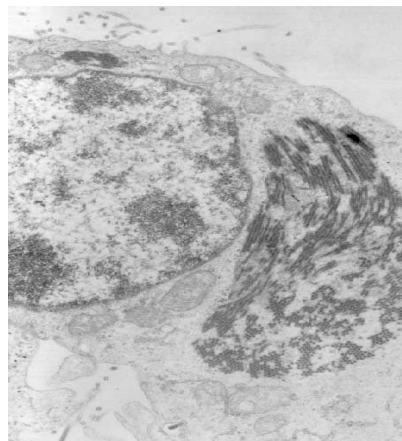
culture, typically on Vero cells (A lineage of cells used in cell cultures and isolated from kidney epithelial cells of the African green monkey (*Cercopithecus aethiops*)). These viruses are considered category A agents and require biosafety level 4 for virus isolation.²³

11- cytopathic effect

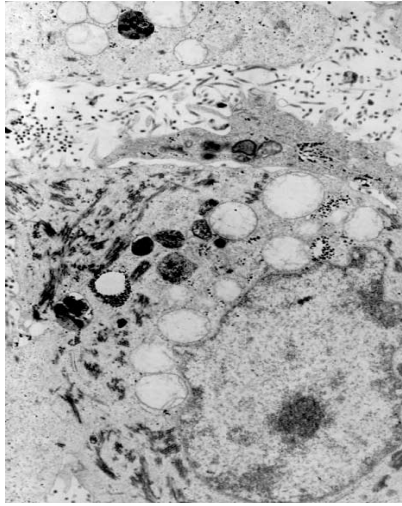
The cytopathic change in tissues and in cultured cells infected with Ebola virus is striking, especially because cells are not arrested in late stages of the common terminal pathway of cytonecrosis. The progression of cell destruction has been shown to be similar in cell culture (for example, in an Ebola virus-infected Vero cell harvest series) and in vivo (for example, in monkey liver; 7). Infection processes, of course, form a continuum, but for convenience 4 stages can be distinguished. In the first stage of infection, virus particle budding and inclusion body formation occurs without apparent effect upon the morphologic appearance of cell organelles. Large amounts of virus are formed in this stage (Figures 1,2). In the second stage of infection virus particle budding and inclusion body formation continue in cells with dilated endoplasmic reticulum, beginning intracytoplasmic vesiculation, and mitochondrial damage (loss of cristae and swelling) (Figures 3,4,5). In the third stage of infection, virus production ceases as the breakdown of cytoplasmic organelles and associated endophagocytosis (lysosomal response) continues. In this stage there is a change in cytoplasmic and nuclear density -- the alternate pathways to cell death appear as condensation or rarification. In the fourth stage of infection, destruction of membrane systems, including the nuclear and plasma membranes, reduces cells to debris (Figures 6,7). The progression of infection to this last stage is extreme with the virus. In Ebola virus-infected Vero cells (A lineage of cells used in cell cultures and isolated from kidney epithelial cells of the African green monkey (*Cercopithecus aethiops*)), the progression of infection in individual cells is rapid; between 48 and 96 hours post infection, when more and more cells are still becoming infected; there is no shift in the proportion of cells observed in late versus early stages of infection, and there is no build-up of intact dead cells as would be the case with most other viral infections.²⁴



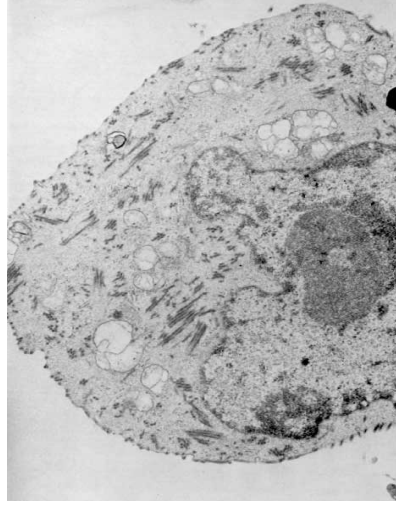
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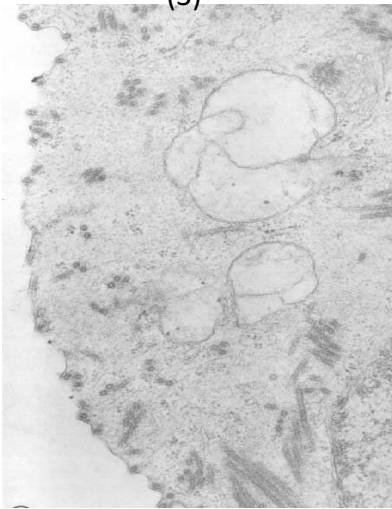
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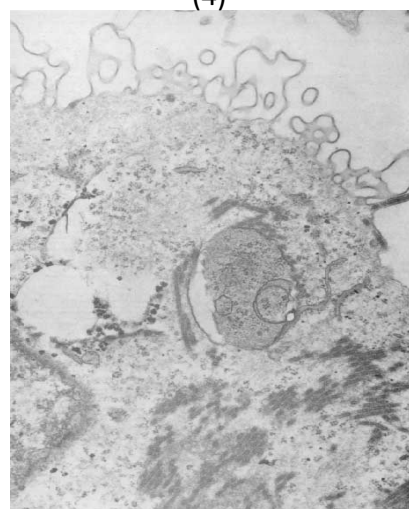
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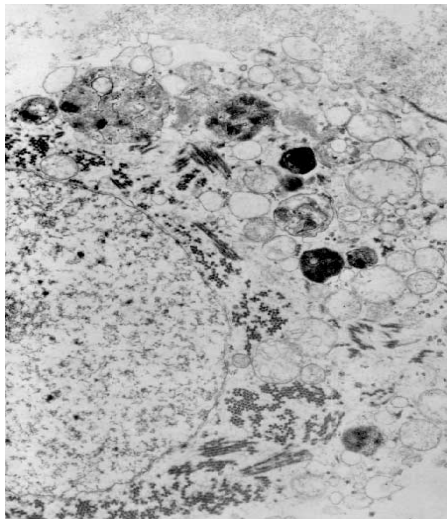
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12- prevention and control

Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilisation. Community engagement is key to successfully controlling outbreaks. Raising awareness of risk factors for Ebola infection and protective measures that individuals can take is an effective way to reduce human transmission. Risk reduction messaging should focus on several factors:

- Reducing the risk of wildlife-to-human transmission from contact with infected fruit bats or monkeys/apes and the consumption of their raw meat. Animals should be handled with gloves and other appropriate protective clothing. Animal products (blood and meat) should be thoroughly cooked before consumption.
- Reducing the risk of human-to-human transmission from direct or close contact with people with Ebola symptoms, particularly with their bodily fluids. Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home. Regular hand washing is required after visiting patients in hospital, as well as after taking care of patients at home.
- Reducing the risk of possible sexual transmission, based on further analysis of ongoing research and consideration by the WHO Advisory Group on the Ebola Virus Disease Response, WHO recommends that male survivors of Ebola virus disease practice safe sex and hygiene for 12 months from onset of symptoms or until their semen tests negative twice for Ebola virus. Contact with body fluids should be avoided and washing with soap and water is recommended. WHO does not recommend isolation of male or female convalescent patients whose blood has been tested negative for Ebola virus.
- Outbreak containment measures, including prompt and safe burial of the dead, identifying people who may have been in contact with someone infected with Ebola and monitoring their health for 21 days, the importance of separating the healthy from the sick to prevent further spread, and the importance of good hygiene and maintaining a clean environment.²⁵

13- Treatment:

13-1. Vaccines & Medication :

No FDA-approved vaccine or medicine (e.g., antiviral drug) is available for Ebola.

Symptoms of Ebola and complications are treated as they appear. The following basic interventions, when used early, can significantly improve the chances of survival:

- Providing intravenous fluids (IV) and balancing electrolytes (body salts).
- Maintaining oxygen status and blood pressure.
- Treating other infections if they occur.

Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness.

Recovery from Ebola depends on good supportive care and the patient's immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years, possibly longer. It is not known if people who recover are immune for life or if they can become infected with a different species of Ebola. Some people who have recovered from Ebola have developed long-term complications, such as joint and vision problems.

Even after recovery, Ebola might be found in some body fluids, including semen. The time it takes for Ebola to leave the semen is different for each man. For some men who survived Ebola, the virus left their semen in three months. For other men, the virus did not leave their semen for more than nine months. Based on the results from limited studies conducted to date, it appears that the amount of virus decreases over time and eventually leaves the semen.²⁶

14- Host Immune Defense:

Once the virus enters the body, it targets several types of immune cells that represent the first line of defense against invasion. It infects dendritic cells, which normally display signals of an infection on their surfaces to activate T lymphocytes—the white blood cells that could destroy other infected cells before the virus replicates further. With defective dendritic cells failing to give the right signal, the T cells don't respond to infection, and neither do the antibodies that depend on them for activation. The virus can start replicating immediately and very quickly.

Ebola, like many viruses, works in part by inhibiting interferon—a type of molecule that cells use to hinder further viral reproduction. In a new studies published , researchers found of Ebola's proteins VP24, VP40, VP30 and VP35, binds to and blocks a transport protein on the surface of immune cells that plays an important role in the interferon pathwa.²⁷

15- Genetics (Gene Mutation):

Ebola virus (EBOV) is an enveloped nonsegmented negative-stranded RNA virus that belongs to the family Filoviridae in the order Mononegavirales. Negatively contrasted EBOV particles contain an electron-dense central core formed by the ribonucleoprotein (RNP) complex, which is surrounded by a lipid envelope derived from the host cell plasma membrane. RNP complexes consist of genomic RNA and the viral structural proteins VP30, VP35, nucleoprotein (NP), and polymerase (L) protein. It was recently demonstrated that the NP, VP35, VP30, and L proteins are the minimal requirements for the efficient transcription and RNA replication of an EBOV minigenome . Three other proteins (VP40, glycoprotein [GP], and VP24) are membrane-associated. Except for GP, which is encoded in two frames and expressed through transcriptional editing , all EBOV proteins are encoded in single reading frames . Mature surface GP_{1,2} is a complex of the subunits GP1 (140 kDa) and GP2

(26 kDa) that are linked by a disulfide bond. Cleavage of precursor GP occurs during intracellular transport by subtilisin-like endoproteases, most likely furin . A nonstructural small glycoprotein sGP is expressed from nonedited GP mRNA and efficiently secreted from infected cells as a homodimer in antiparallel orientation . Mature sGP is also proteolytically cleaved by furin, and cleavage results in the release of a short carboxyl-terminal glycopeptide (D-peptide) into the culture medium.²⁸ A study of some of the earliest Ebola cases in Sierra Leone reveals more than 300 genetic changes in the virus as it has leapt from person to person. These rapid changes could blunt the effectiveness of diagnostic tests and experimental treatments now in development. The studies shows changes in the glycoprotein, the surface protein that binds the virus to human cells, allowing it to start replicating in its human host.²⁹

16- End of Ebola transmission in Guinea and Liberia

June 2016 -- WHO declares the end of Ebola virus transmission in the Republic of Guinea and in Liberia. Forty-two days have passed since the last person confirmed to have Ebola virus disease tested negative for the second time. Guinea and Liberia now enter a 90-day period of heightened surveillance to ensure that any new cases are identified quickly before they can spread to other people.³⁰

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