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Review article *Medical research*

Ebola - A review of threatening epidemic

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ABSTRACT

Ebola, which is widely spreading epidemic, has to be considered seriously to wipe it off completely from all corners of the world. The present study helps us to augment the awareness and knowledge to healthcare providers and to strengthen the standard precautions for prophylaxis and implementation of health care facilities at all the stages. There is no risk of transmission of this disease during the incubation period. Thus, the information flourished here helps us to overview the causes, symptoms, risk factors, etc. and also the necessary precautions, diagnosis in time, treatment and safety measures to be taken to eradicate Ebola virus completely from the roots.

Keywords: Ebola, Epidemic, Augment, Incubation.

INTRODUCTION

Ebola hemorrhagic fever is severe, fatal disease that affects human and few primate species. This epidemic has been at a wide spread all over the world and it was first identified in 1976. The origin of this outbreak is currently unknown [1].

The disease is caused by Ebola virus, which was named after a river in Congo in Africa where it was first recognized. This virus belongs to the family of RNA virus called Filoviridae. There are five identified subspecies of the virus. They are:

1) Ebola virus (Zaire Ebola virus)
2) Sudan virus (Sudan Ebola virus)
3) Tai Forest virus (Tai Forest Ebola virus)
4) Bundibugyo virus (Bundibugyo Ebola virus)
5) Reston virus (Reston Ebola virus).

The four among five different viruses are those which affect the human beings whereas the Reston Ebola virus affects the primates but not the humans.

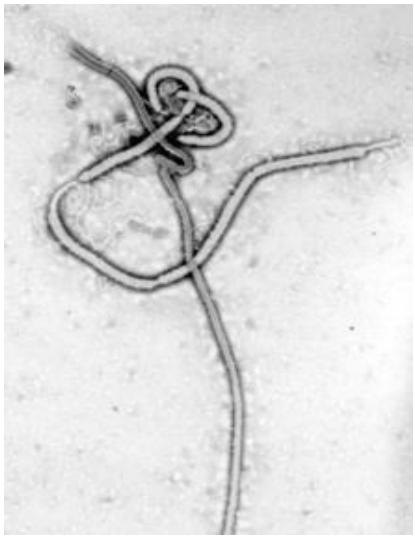


Figure 1: Structure of Ebola virus

Ebola is rare and very deadly virus. Since the first outbreak in 1976, these viruses have infected thousands of people and killed roughly around 60 percent of them. Symptoms occur in a very little fraction of time and leads to death. Ebola is more inimical to humans perhaps any known virus on the Earth, even rabies and HIV-1 are not as fast as Ebola to attack and damage the human body[2].

Key facts

- Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever is a severe, often fatal illness in humans.
- The case fatality rate of EVD outbreak is up to 90%.
- EVD outbreaks occur primarily in remote villages in Central and West Africa, near tropical rainforests.
- The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.
- Fruit bats of the Pteropodidae family are considered to be the natural host of the Ebola virus[3].
- Severely ill patients require intensive supportive care. No licensed specific treatment or vaccine is available till date.

Ebola virus characteristics

- Stable at room temperature and has resistance for desiccation.
- Inactivated at 60 0C for 30min.
- Infectivity greatly reduced/destroyed by UV-light and ɣ-irradiation, lipid solvents,β-propiolactone, formaldehyde, sodium hypochlorite & phenolic disinfectants[4].
- Freezing/refrigeration will not inactivate Ebola virus.
- Widely emerging and spreading infections.

Symptoms

- The incubation period of the disease is 2-21 days. The onset of illness is sudden which includes symptoms like fever, headache, joint and muscle aches, sore throat and weakness followed by minor symptoms diarrhea, vomiting, stomach pain, rash, red eyes, hiccups and internal & external bleeding will be experienced in very few of the patients[5].
- Chills with myalgia, malaise.
- Prostration, nausea, vomiting, abdominal pain, diarrhea, pancreatitis, chest pain, cough, pharyngitis.
- Around the onset of epidemic of Ebola disease, of day 5, patients develop a maculopapular rash that is prominent on the trunk followed by desquamation in survivors.
- During second week, may cause shock or multi organ dysfunction.
- People will be infectious as long as their blood and secretions contain the virus. Ebola virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory.

Routes of infection

- Skin / mucous membrane when is in contact with virus/ sick patients is main cause for human infections.
- Use of unsafe needle injections.
- Other routes involve nosocomial, parenteral due to inadequate sterilization of equipment and lack of infection control techniques.

Risk factors

- Health care workers have frequently been infected while treating patients with suspected or confirmed Ebola Virus Disease. This occurred through close contact with patients when infection control precautions were not strictly practiced.
- Due to international travel, this epidemic is at a widespread.
- Health care workers can become infected through close contact with infected patients / contaminated hospital materials and medical waste. The risk for infection can be significantly reduced through appropriate use of infection and individual control precautions, adequate and strict barrier nursing procedures [6,7].
- Has had physical contact with the case during illness, at funeral or when touched his/ her blood or body fluids during the illness.

Pathogenesis

- Ebola Zaire seems to be highly virulent identified first in 1976.
- In Central and West Africa, Ebola virus, a member of filovirus group has caused sporadic out breaks of lethal hemorrhagic disease for which no effective vaccine /antiviral treatment is currently available.
- Ebola Reston, which is isolated from cynomolgus monkeys, is less pathogenic in non-human primates [9] and no lethal effect in humans.
- Few like genetically engineered vaccine (DNA, plasmids and viral vectors expressing, Ebola virus proteins) and passive transfer of neutralizing antibodies can be employed for control of Ebola virus disease.
- The glycoprotein and the interaction of some viral proteins with the immune system play an important role in determining the pathophysiology of the Ebola virus.
- Ebola virus glycoprotein plays an important role in pathogenesis; fourth gene from third end of Ebola virus genomes encodes two glycoproteins [8,10]**.**
- Among the two encoded glycoproteins, one is the envelopeglycoprotein,which is responsible for receptor binding and fusion of host cells[11,12]and second one being non-structural secretory glycoprotein(sGP) which is secreted from infected cells[13,14]
- Glycoprotein, expressed by transcriptional editing, resulting in the addition of an extra adenosine in the coding region of the molecule)**.**
- Glycoprotein and secretory glycoprotein share approximately 300 amino-terminal amino acids, but contain an additional 380 and 70 of carboxy terminal amino acids.

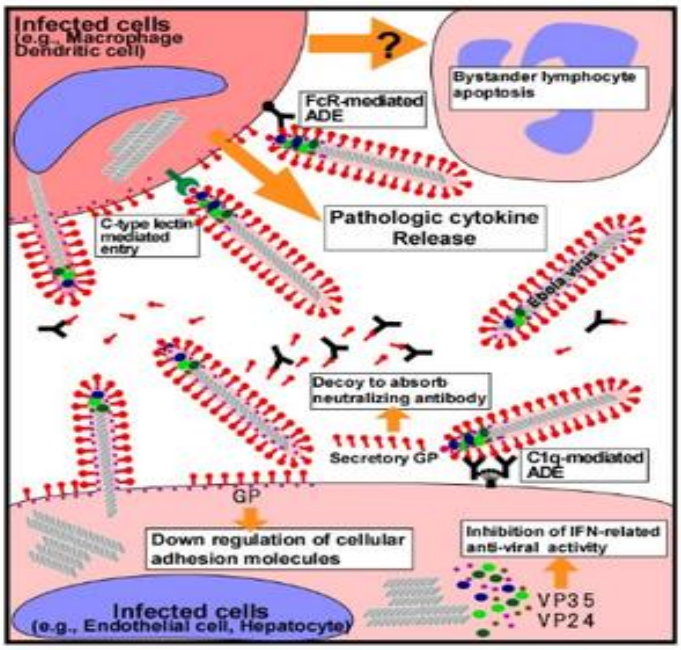


Figure 2: Ebola virus pathogenesis and host immunity

The pathophysiology of Ebola virus includes the following steps

a. Glycoprotein Cleavage
b. Glycoprotein Toxicity
c. s Glycoprotein (s GP)
d. interaction with immune system
e. VP35 as an interferon antagonist
f. Immuunosupression
g. Hemorrhage and disseminated intravascular coagulation (DIC)
h. Effect of VP40.

Glycoprotein Cleavage

- Cleavage activation of membrane glycoproteins by proteases is prerequisite for fusion between viral envelope and membrane of host cell in most of the enveloped viruses.
- The Ebola glycoprotein like surface glycoprotein which are similar to those of hemagglutinins(HA) as in Avian Influenza can be cleaved by cellular proteases, furin and PC6[15-17]. This cleavage enables virus to replicate in various cells, which leads to systemic infection and increased mortality.
- Ebola Zaire glycoprotein which is cleaved by furin and all other filoviruses contain a recognition site for furin and PC6 in their glycoprotein[18].In recent years, a recombinant Ebola virus has been generated with no furin recognition motif at glycoprotein cleavage site, using a reverse genetics system. Even the attenuated Ebola virus mutants in cell culture, underwent multiple cycles of replication in cell culture. Thus, it is suggested that cleavage activation is not essential for the glycoprotein of Ebola virus in the cell cultures. So it is important to investigate the role of glycoprotein cleavage in replication and pathogenesis of recombinant viruses with altered glycoproteins in animal models.

Gylcoprotein Toxicity

- Glycoproteins produce cytotoxicity. Glycoprotein expression induces cell rounding and detachment by down regulation of cell surface expression of integrins[20]. These effects also observed when glycoprotein was expressed in endothelial cells of primates, which are targets for filoviruses both in vivo and in-vitro [21-24].
- The Zaire Ebola virus glycoprotein expression induced cytopathic effect include increase permeability in endothelial cells of both human and non-human primates, where as the other subtype-Reston glycoprotein induced same effects only in endothelial cells of non-human primates[24].
- Glycoprotein is viral determinate of endothelial cell toxicity in human Ebola infection[24].

- The endothelial cell dysfunction owing to virus infection explains the hemorrhagic manifestations of filovirus infection[21].
- The Ebola virus glycoprotein binds to epithelial cells more efficiently than to endothelial cells [19]and the cell rounding and detachment were also observed in expressing cells of epithelial cell-binding glycoprotein[20,23,24].
- Thus, disruption of cell function by glycoprotein expression in other organs is required for lethal outcome of disease, for studying the disease in depth and for knowing the hidden facts of the spreading epidemic.

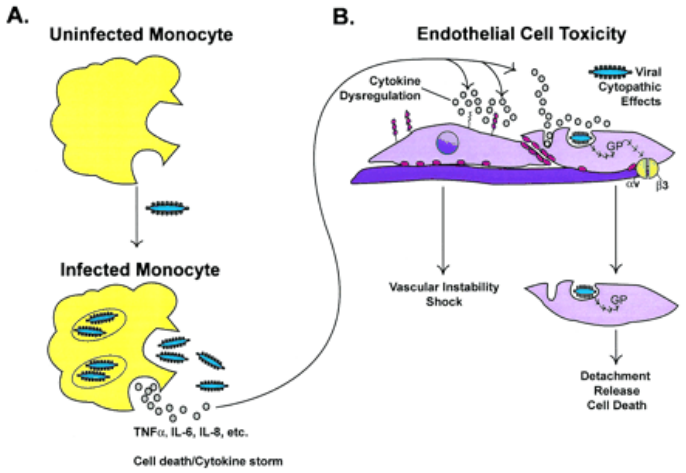


Figure 3: Pictogram representing Glycoprotein Toxicity

s Glycoprotein (sGP)

- sGylcoprotein also detected in blood of infected patients in increased concentration but its action is yet to be determined in specific.
- sGlycoprotein's might serve to evade immune responses and therefore plays a key role in pathogenesis of Ebola.
- These sGP's bind to human neutrophils via FC-gamma receptors III (CD16b), which is involved in intracellular singling to activate neutrophils via lateral membrane interaction with complement receptor type 3 (CR3) [23,26].
- This states that early neutrophil activation is inhibited through interference with normal physical interaction between CD16b and CR3.
- This potential function of sGP as the protein can bind to neutrophils via the FC portion of anti sGP rabbit antibodies used in binding assays[27].
- Recently by using reverse genetic system[28]a recombinant Ebola virus has been generated and this does not produce sGP.
- This express high amount of glycoprotein and that gets accumulated in endoplasmic reticulum, results in greater cytotoxicity when compared to wild-virus types. Thus, glycoprotein induced cytotoxicity is controlled by transcriptional editing.

Interaction with immune system

- Immune system is greatly affected by the Ebola virus infection. The Ebola infected patients lose their ability in producing adequate immune responses and thus leads to the infection of mononuclear phagocyte and fibroblastic reticular systems[28,29] as fibroblastic reticular cell networks associated with lymph nodes serve to maximize immune responses.
- Thus, infection of these cells my disrupt antigen attack and cytokinine production, leads to inadequate immunity as in HIV Infection, circulating monocytesand macrophages transmit the virus to other tissues[30].
- In Ebola affected patients, failure of early activation of T-cells,subsequent impaired humoral responses, antibody and cytokinine responses followed by apoptosis of blood

leukocytes, thus associated with fatal outcome of disease[31].

- The state of Lymphopenia-severe damage to lymphoid tissues such as spleen, lymph nodes and bone marrow seen in patients and infected monkeys[32-35].
- By contrast, massive upregulation ofcytokines,such as interferons (IFN), interleukin (IL)-2, IL-10 and tumour necrosis factor-α (TNF-α) owing to abnormal macrophage activation induced by viral infection, links to the onset of disease[36].
- However, cytokinine responses vary among infected patients, it is not clear whether specific cytokinine profiles are associated with outcome of infection[31,35,36].

VP35 as an interferon antagonist

- Recent data [38]indicates that Ebola virus VP35 protein, which plays an essential role in viral RNA synthesis, acts as type-IIFN antagonist. The production of an IFN antagonist might contribute to the pathogenecity of Ebola virus. Thus, comparing the IFN- inhibiting potency of VP35 among Ebola virus strains with different virulence capacities[40].

Immunosuppression

- The amino acids sequence at the amino terminus of GP suppresses human lymphocyte mitogen-stimulated proliferation invitro[39].
- Ebola virus infection also suppresses induction of major histocompatibility complex (MHC) class I family of genes (IL-6, IFN-regulatory factor-1 and intercellular adhesion molecule-1) in human umbilical vein endothelial cells[41-43].
- Such inhibition of immunomodulatory gene responsiveness plays a role in immunosuppression seen in patients with Ebola virus infection.

Hemorrhage and disseminated intravascular coagulation(DIC)

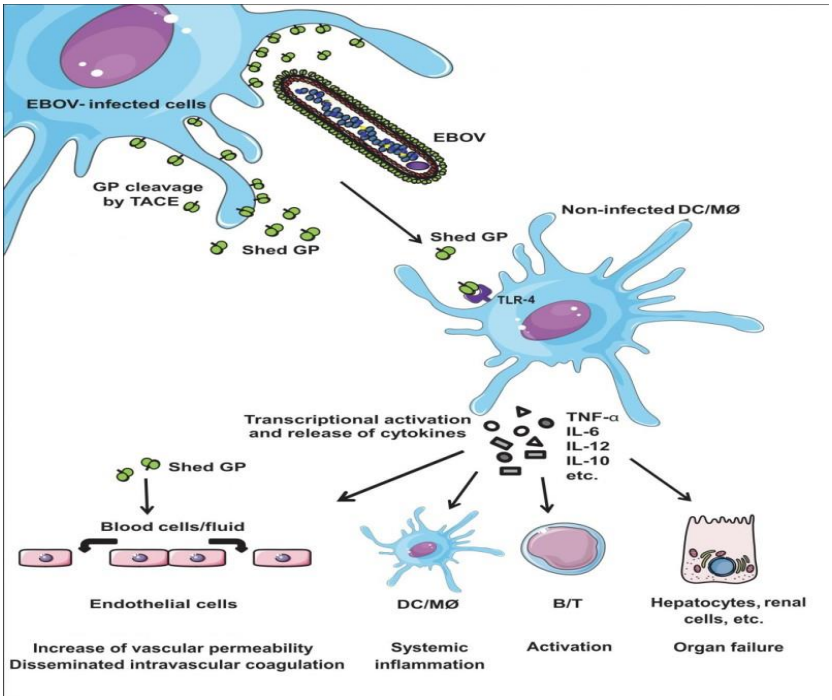


Figure 4: Disseminated Intravascular Coagulation (DIC)

- Hemorrhage and DIC are vital components of Ebola virus infection. Rapid release of many vasoactive agents, including cytokines, chemokines, histamines and peroxidases from virus infected monocytes and endothelial cells could evoke a shock syndrome associated with DIC [29,31].
- During the filovirus infection**30**, the elevated levels of TNF-α followed by an increase of endothelial permeability seem to play an

important role in the induction of circulatory shock.

- Damage of other organs, like liver might cause DIC by thrombi in multiple organs.
- The platelet-derived agents triggered by damaged endothelial cells might also contribute to shock.
- The relation of DIC to the pathogenesis of Ebola virus is unclear; the characteristic hemorrhagic manifestation might be directly attributed to this coagulation defect.

Effect of VP40

- Viral protein 40 (VP40), the putative matrix protein of filoviruses, is also cytotoxic.VP40 can induce particle formation when expressed in mammalian cells and this process most likely requires cellular WW-domain containing proteins that interact with the amino-terminal proline rich region (PPXY-motif, where X=any amino acid) of VP40[42].
- Recent demonstrations reveal that, VP40 can interact with a ubiquitin ligase through interaction between the PPXY motif of VP40 and the WW-domain of the cellular protein[43].
- Eventhough, it is involved in budding of filoviruses, as ubiquitin and ubiquitinated proteins in cellular processes including endocytosis / exocytosis[44].
- Revealing few facts regarding the pathogenesis of Ebola,led to the development of passive immunization techniques and vaccines which led to the fore step of remarkable implementations in the field of medical researchin the treatment of such terrific diseases like Ebola.

DEVELOPMENT OF PASSIVE IMMUNIZATION AND VACCINES FOR EBOLA VIRUS INFECTION

Prophylaxis

- No vaccine or effective therapy is currently available for Ebola virus infections, which is one among the filovirus infections.
- Since, GP is the only viral surface protein known and is responsible for virus entry[11], this must be important target of neutralizing antibodies.
- The experimental studies of passive transfer of immunity from hyper immune animal sera in mice, guinea pigs and monkeys has been evaluated, but the results were found inconsistent.
- Blood transfusions from patients has been tested during Kit wit outbreak of Ebola hemorrhagic fever in 1995[45].
- Due to lack of controls, these studies also do not produce acceptable results.
- Recent studies show that the serum from mice subcutaneously infected with live Ebola virus protected recipient mice from challenge with lethal doses of virus[46] whether virus-induced immune factors other than antibodies(Eg: cytokines) affect the efficacy of such treatment remains unclear.

Infectivity – Enhancing antibodies

- Antisera produced by DNA immunization with a plasmid encoding Ebola Zaire GP enhanced the infectivity of VSV pseudotyped with GP, whereas antisera to GP of Ebola Reston shows weaker enhancement compared to Ebola Zaire[48].Ability to produce monoclonal antibodies that specificallyenhance the infectivity of virus of Zaire GP verifies existence of infectivity enhancing epitopes on Zaire GP-molecule
- Lack of this antibody-dependent infectivity enhancement is the reason for reduced virulence of Ebola Reston.
- Development of Ebola virus vaccines with discovery of infectivity enhancing antibodies to GP and use of passive prophylaxis / treatment with Ebola GP antibodies.
- Passive prophylaxis with GP antiserum might not be optimal approach in fighting with Ebola infact, neutralizing antibodies might serve the case[52].

Vaccine

- Recently, immunization of guinea pigs, monkeys, mice with plasmids, adenoviral vectors expressing GP / NP conferred protective immunity, by inducing cytotoxic T-cell responses[49-52].
- An epitope associated with recruitment of mouse cytotoxic T-cells was identified in

nucleoprotein molecule of Ebola virus recently[53].

- Many attempts were being to develop effective vaccines / medicines to fight against this wide spread epidemic.
- This can be achieved by aiming to activate the specific T-cell response as well as inducing neutralizing antibody response.
- Basing on different types of Ebola virus, a multivalent vaccine might be needed. There is also difficulty in generating cross-reacting neutralizing antibodies among all subtypes of Ebola virus.
- The antigenic difference must be considered for both passive prophylaxis and vaccination.

Genetic engineering of ebola virus

- The nucleoprotein, VP35 and-30 and RNA polymerase were required for RNA replication and transcription[54].
- By use of Reverse Genetic System which allows the generation of infectious Ebola virus from cloned cDNA is now available[28].These reveal the underlying facts regarding the pathogenesis of the Ebola virus, since the manipulation of viral genes and proteins can be made as desired.
- Thus, it also helps to clarify many issues pending about role of GP cleavage and cytotoxicity and also functions of sGP and VP35 in pathogenesis of Ebola virus infection.
- By Reverse Genetics System, it is also possible to generate live-attenuated Ebola vaccines and also facilitates screening of antiviral drugs that helps in inhibiting the filovirus replication and thus finally eradication of such dangerous infections.

Prevention

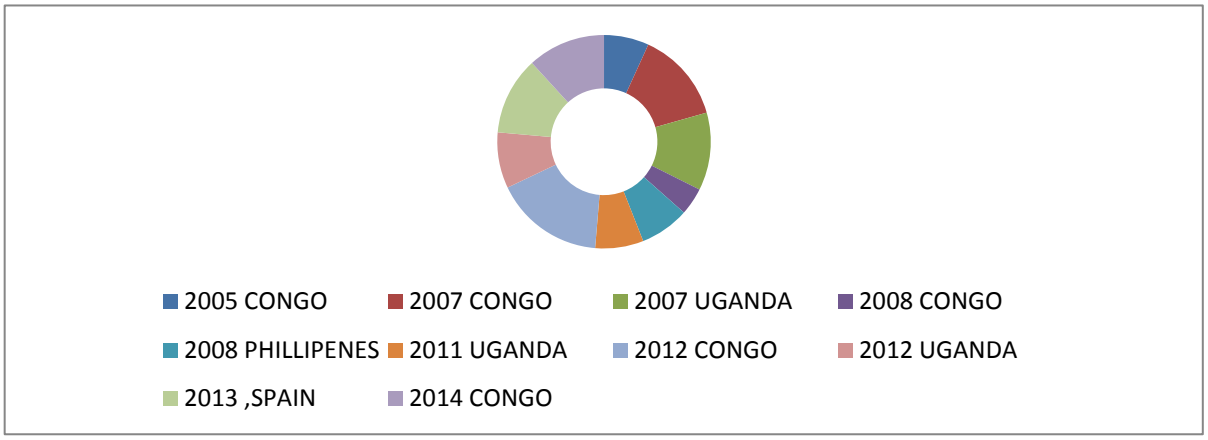
Prevention stands as a challenge, since the cause of how people are getting infected by the virus is yet unknown. There are few primary prevention measures. They include:

- Health care workers must be able to recognize a case of Ebola and employ barrier nursing techniques(USCDCP).
    - Wearing of protective clothing (masks, gloves, gowns, goggles)
    - Use of infection- control measures(complete equipment sterilization and routine use of disinfectant).
    - Isolation of Ebola hemorrhagic fever patients from contact with other persons.
- Avoid contact with blood and secretions of an infected patient.
- If patient with Ebola virus disease dies, it is equally important to prevent the direct contact with body of the deceased patient.

Diagnosis

- Ag-capture ELISA technique, IgM ELISA, Polymer Chain Reaction (PCR), Virus Isolation techniques, etc[56].
- If patient died of Ebola Virus Disease, autopsy is contraindicated.
- The confirmation of Ebola virus infection can only be performed in patients who have already developed symptoms [57].
- The confirmation is not possible during the incubation period.
- Samples from patients are an extreme biohazard risk; testing should be conducted under maximum biological containment conditions [58].
- Forty percent of infections included in the current tally occurred within the past three weeks, according to the WHO. And the virus has mutated during the outbreak, which could hinder diagnosis and treatment of the disease, according to scientists who genetically sequenced the virus in scores of victims.

Fatality Rate/Statistics of the cases of Ebola since 1976 to 2014 (WHO 201404-01)



YEAR	COUNTRY	EBOLA VIRUS SPECIES	HUMAN CASES	HUMAN DEATHS	CASE FATALITY RATE
2014	Democratic Republic of the Congo	EBOV	70	42	UNDETERMNED
	Liberia Sierra Leone	EBOV	13,703	4,922	7%
2013	Guinea, Nigeria, United States, Mali, Senegal Spain				
2012	Uganda	SUDV	24	17	71%
2012	Democratic Republic of Congo	Bundibugyo	57	29	51%
2012	Democratic Republic of the Congo	BDBV	77	36	47%
2011	Uganda	Sudan	1	1	100%
2008	Philippines	RESTV	6	0	N/A
2008	Democratic Republic of Congo	Zaire	32	14	44%
2008–2009	Democratic Republic of the Congo	EBOV	32	14	45%
2007–2008	Uganda	BDBV	149	37	25%
2007–2008	Uganda	BDBV	149	37	25%
2007	Democratic Republic of Congo	Zaire	264	187	71%
2007	Democratic Republic of Congo	Zaire	264	187	71%
2005	Congo	Zaire	12	10	83%
2004	Sudan	SUDV	17	7	41%
2004	Russia	EBOV	1	1	N/A
2003 (Nov-Dec)	Congo	Zaire	35	29	83%
2003	Republic of the Congo	EBOV	35	29	83%
2001-2002	Congo	Zaire	59	44	75%
2001-2002	Gabon	Zaire	65	53	82%
2000	Uganda	SUDV	425	224	53%
1996	Gabon	EBOV	37	21	57%
1996	South Africa (ex-Gabon)	Zaire	1	1	100%

1996 (Jul-Dec)	Gabon	Zaire	60	45	75%
1996 (Jan-Apr)	Gabon	Zaire	31	21	68%
1996–1997	Gabon	EBOV	60	45	75%
1996	South Africa	EBOV	2	1	N/A
1996	United States	RESTV	0	0	N/A
1996	Philippines	RESTV	0	0	N/A
1996	Russia	EBOV	1	1	N/A
1995	Democratic Republic of Congo	Zaire	315	254	81%
1995	Zaire	EBOV	315	254	81%
1994	Gabon	EBOV	52	31	60%
1994	Cote d'Ivoire	Taï Forest	1	0	0%
1992	Italy	RESTV	0	0	N/A
1990	United States	RESTV	4[note 3]	0	N/A
1989–1990	Philippines	RESTV	3[note 2]	0	N/A
1989	United States	RESTV	0	0	N/A
1979	Sudan	SUDV	34	22	65%
1977	Zaire	EBOV	1	1	100%
1976	Sudan	SUDV	284	151	53%
1976	Zaire	EBOV	318	280	88%
1976	United Kingdom	SUDV or EBOV	1	0	N/A

TREATMENT

There is no specific anti-viral drug or **Vaccine** for the treatment of this Ebola virus disease. But to the present context, the **supportive therapy has been in use**, which includes the balancing of the body fluids and electrolytes, maintaining the oxygen and blood pressure of the patients[60].

- Several vaccines are being tested, but **none are available for clinical use till 2015**.
- New drug therapies are being evaluated.
- DNA vaccines, adenovirus-based vaccines, and VSIV-based vaccines have entered clinical trials[61,62].
- The vaccine called rVSV-ZEBOV was studies in a trial involving 11841 people in guninea during 2015. Among the 5837 people who received the vaccine, no Ebola cases were recorded 10 days or more after vaccination.

ASPECTS

- Recently, WHO said that it is ethical to provide experimental drugs and vaccines for Ebola, but that there's also a "moral duty" to conduct clinical trials of these experimental drugs and vaccines to determine whether they are safe and effective.
- Also, a new study states that the Ebola virus is mutating rapidly, which could make it more transmissible reduce the effectiveness of drugs and vaccines.
- ZMapp is one of the drug used for Ebola so far. This is a combination of three, antibodies, proteins that bind and neutralize Ebola virus. ZMapp was developed by a biotech firm (Mapp Biopharmaceutical, Inc.).
- Few years ago, this company and National Institute Of Health and the Defence Threat Reduction Agency were decided to develop a treatment for Ebola virus infection. This drug consists of an anti-Ebola antibody made up of part mouse and part human antibody**(R).**
- But ZMapp has not yet been confirmed in clinical trials. It is also expensive to make and in short supply.
- Other treatments include TKM-Ebola, AVI-7537, favipiravir, selective estrogen receptor modulators like clomiphene and toremifene, BCX-4430 and ST-383.
- Other recent technologies like RNA interference are also employed.

- There might be less chances of mass vaccination of general population, but the WHO has not ruled it out.
- WHO says it is getting daily proposals for potential medicine, yet many trials did not produce effective results against the virus.
- **Two potential drugs tested**
  - Brincidofovir
  - Favipiravir
- The primary results of these drugs came in February 2015.
- The latest data from 26 December reveals that Ebola has infected more than 19,000 people in Guinea, Liberia and Sierra Leone with atleast 7,600 deaths.**(R)**
- Other drug FX06 proved out with better results in Sierra Leone.
- Scientists have found 53 existing drugs that may prevent Ebola virus from entering human cells.
- Major drugs of Ebola class include several cancer drugs, antihistamines and antibiotics.
- Among most effective at keeping the virus out of human cells were found to be microtubule inhibitors used to treat cancer.
- Other categories include estrogen receptor modulators used against cancer and serotonin reuptake inhibitors used to treat depression.

CONCLUSION

Many animal models [9,26,63]are employed to evaluate the virulence of Ebola virus, the host responses and the immunization reports have provided many insights into pathogenesis of Ebola. The information regarding the glycoproteins, interactions of other viral proteins with immune system, all these made important contributions to know study the pathology of infection. Recently, Reverse Genetics approach would lead us in further study of Ebola virus and thus helps us in developing effective vaccines and medicines or anti-virals. With all these weapons in hand we would be able to combat the Ebola virus disease.To raise awareness and knowledge of health care providers and to strengthen the implementation of standard precautions for infection prevention and control in health care facilities at all levels.No risk of transmission during incubation period and so this epidemic needed utmost care to prevent from dangerous loss. The people or public should be well educated regarding the epidemic and even the slightest suspicion that an individual might be infected by Ebola virus which must be reported to public health authorities and followed by the International Health Regulations (IHR)[65].There is also a need for environmental infection control-diligent environmental cleaning and disinfection and safe handling of potentially contaminated material is paramount, as blood, sweat, emesis, feces and other body secretions represent potentially infectious materials. By following certain measures, such epidemics can be prevented and also completely wiped off from the roots of their existence.

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