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REVIEW ARTICLE

EBOLA VIRUS DISEASE: A DISEASE WITH NO SPECIFIC CURE

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ABSTRACT

Ebola virus disease is an infectious virus-based disease that spreads through human-to-human contacts. The first human case was found in 1967, in Germany, the patient was a scientist working in a lab with monkeys that were imported from the Uganda region. The first outbreak of this disease was found in 1976 in the Africa region near the Ebola River, Republic of Congo. Major symptoms of this disease are normal "flu-like" in its primary stage such as fever, coughing, headache, and diarrhea. As the disease progresses the symptoms get worsen. The treatment options for this disease are very limited. Many vaccines are found to be effective against the Ebola virus disease such as the chad3 vaccine, rVSV-ZEBOV vaccine, MVA-BN-Filoã vaccine, ERVEBO vaccine, there are many treatment options therapies such as Janssen Ebola prevention vaccine therapy, combination therapy (2014), EBANGA treatment, etc. Recently in 2019 US-FDA has approved another vaccine as the treatment option for Ebola virus disease. The basic supportive care system Is also found to be very helpful in the treatment of the disease. Some medications are still under investigation for their effectiveness against the Ebola virus such as Remdesivir, Favipiravir, Quinacrine, Tilorone. Some studies were done to compare the effectiveness of newly found drugs against Ebola virus disease which were known as PALM studies. Here In this review, we are going to look at all the possible treatment options and vaccines that are effective against Ebola virus disease.

Keywords: Ebola virus disease, Treatment options, Vaccines, Medications, Supportive care

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INTRODUCTION

Ebola is a human-to-human transmitted viral disease that was recognized as Ebola virus disease when the outbreak of this viral infection took place near the Ebola River in 1976 in the Republic of Congo. Afterward many outbreaks have been reported but the most severe one was between 2013- 2016 and it was a major outbreak that originated from the middle Africa region affecting many countries in the West Africa region[1]. In 1976 the underlying reason for the outbreak was found to be the use of the contaminated syringe in the hospitals.[2] This disease is fatal with a mortality rate varying from 50% to 90% in different regions of affected population areas.[3] This disease is mainly caused by the "**Ebola virus**" Which is a negatively charged single-stranded RNA virus belonging to order- *mononegaviral* and family *filoviridae* and genus *ebolavirus* [4]. This disease can infect all ages from the elderly to infants and adults as well.[5]

The family of *filovir*idae includes mainly genera such as Ebolavirus, Marburgvirus, Striavirus, Dianlovirus, and Thamnovirus. There are mainly 5 species of Ebola virus that have been identified till now: Bundibugyo Ebolavirus, Reston Ebolavirus, Sudan Ebolavirus, Tai Forest Ebolavirus, Zaire Ebolavirus.[6] Among these 5 species major 3 species are associated with human-to-human transmitted Ebola virus disease: Bundibugyo Ebolavirus and Sudan Ebolavirus (South Sudan and Uganda), Zaire Ebolavirus (Republic of Congo and Gabon). The highest infections in humans are seen by the Zaire Ebolavirus (80%) followed by Sudan Ebolavirus (50%) and Bundibugyo Ebolavirus (25%) [7]. EBOLA (EBOV) and MARBURG (MARV) are the viruses of the *filoviridae* family.

EBOV virus is said to be more dangerous and lethal than HIV virus. It is noted that these 2 viruses produce hemorrhagic fever and death within few days of their entry into host cells. Within the range of 60-90% deaths of infected persons.[8] in 1989, in the USA another species of Ebola virus was found which was named as *Reston ebolavirus* after it was found in Reston, Virginia, USA.[9] after that outbreak the major outbreak of REBOV was seen in 2008-2009 in the Philippines.[10]

Ebola virus disease shows the major symptoms as high fever, headache, vomiting, anorexia, diarrhea, unexplained bleeding from the eyes, nose, gut and gums. This disease is regarded as endemic in some areas of central Africa.[11]. Many vaccines and treatment options have been developed till now. Vaccines such as chad3, MVA-BN-Filoã, rVSV-ZEBOV has been found among these rVSV-ZEBOV is found to be most effective till now which was found in 2016.[3] Many treatment options are found and approved to date such as combination therapy of 3 drugs was approved in 2014 by USFDA and another EBANGA treatment was approved recently in 2020 by USFDA. There are

many studies are going on such as PALM 2019 and 2020 which focus on the comparison of different potentially useful drugs.

In April 2019 Remdesivir prodrug was under investigation for its potential use in Ebola virus disease treatment. The major mechanism to be thought behind this drug is said to be the inhibition of the Ebola virus RNA-dependent RNA- polymerase.[12] There are majorly 2 types of immune system parts involved in response to controlling viral replication: innate and adaptive immune system. The innate system response to EBOV is done in the manner of "cytokines storm" as various pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, CCl_2, CCl_3, and CCl_4.[13] the interactors for Nucleoproteins; RUVBL1 and RUVBL2 play a role in transcription/replication of the virus and these also affect the minigenome activity.[14] In 2002 Japan found a drug favipiravir which was an anti-viral drug against the influenza virus but it has been now found to be a potential treatment option for Ebola virus disease as well.[15]

HISTORY OF EBOLA VIRUS DISEASE

In 1967 the first case of the illness was recorded in a laboratory in Germany. Then ultimately 37 people were found to be infected and from which 9 people died. The virus to be responsible for this was found to be from the *filoviridae* family.[16]

The first laboratory worker, Porton down accidentally got infected by the virus when he mistakenly pricked himself with an infected syringe.[17] After 9 years of this incident Ebola virus disease first major outbreak was noted in the Democratic Republic of Congo (DRC) and Sudan in 1976.[18] In that outbreak 284 cases were recorded in Sudan while 318 cases were recorded in DRC. As the outbreak happened near the Ebola River in DRC this disease was named as Ebola virus disease.[19] And 2 species were acknowledged from this outbreak were: EBOV-Zaire and EBOV-Sudan. [11]

The outbreak of 1976 in DRC started when a 42 years old male Yambuku appeared at the clinical outpatient ward at YMH, Zaire (DRC). The virus already spread to many people who have been in close contact with him due to which 13 of YMH staff became infected and 11 of them died.[20]

In 1989, another species of Ebola virus was found after an outbreak was observed in cynomolgus macaques in Reston, Virginia, USA. This was seen in a primate facility care center, where the new species *Reston ebolavirus* (REBOV) was found.[9] the major non-human primate outbreak of this virus was also seen in the same year of 1989. And as the scientist tried to find the main origin of this outbreak it was found to be Philippines.[10]

To this date, there are major more than 20 outbreaks have been reported since the first outbreak in 1976. During the outbreak in 2014, there was panic and fear in people

that this disease can spread to other countries like North America and Europe.[21] As the number of cases was rising worldwide WHO on 8th august 2014 declared Ebola endemic as public health emergency of international concerns.[8] During the 2014-16 outbreak there were almost 30,000 people infected with the EBOLA virus in the West Africa region and the mortality rate reached 70% initially.[22]

The outbreaks from 2014 to 2021 are recorded in major areas as below: 2014-2016 west Africa; 2017 BAS-Uele and DRC; 2018 Equateur and DRC; 2018-2020 North Kivu/Ituri and DRC; 2020 Equateur and DRC; 2021 North Kivu and DRC.[23] Based on the severity of the virus infection and the mortality rate of the disease this virus can also be misused as bioweapon.[24]

The data in the chart (Fig 1) below shows the number of cases and number of deaths observed in each year in the regions of Africa due to the outbreaks of Ebola virus disease.

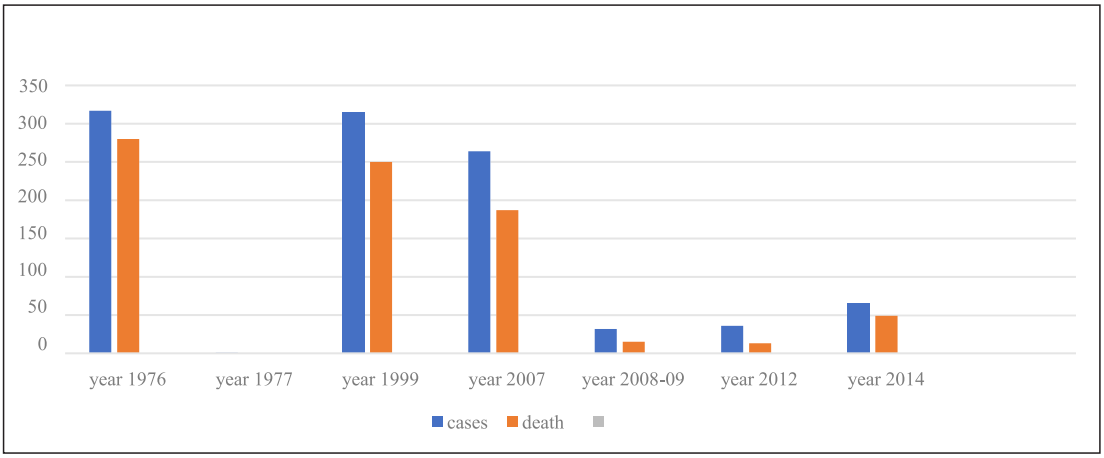

Fig 1: chart of ratio of cases observed each year in Africa region and number of deaths observed

Structure of the virus

Ebola virus structure is mainly a single strand negatively charged ssRNA genome. The main part of the structure of the Ebola virus is the glycoprotein (GP)envelop that is encoded by the 4th gene in the viral genome. This GP is responsible for the entry of the virus into a host cell. There are 2 subunits defined in the GP membrane which are the GP1 andGP2. GP1 associates with the cell membrane receptors while the GP2 facilitates the entry of the virus into the cell cytoplasm [25].

The Ebola virus virions are naturally 80-90 nm in diameter, 19-kb, and 14000nm in long [26,27]. Ebola virus is composed of 7 genes that code at least 10 proteins from 3' head to 5' end which is essential for virus

integrity and its functioning and its work. These 10 proteins are: Nucleoprotein {NP}; Viral protein 35 {VP35}; Viral protein 40 {VP40}; viral protein 24 {VP24}; viral protein 30 {VP30}; soluble glycol protein {SGP}; glycol protein {GP}; small soluble glycol protein {ssGP}; "-peptide; and RNA-dependent viral polymerase (L)[28].

Many types of glycoproteins are present on the cell surface. The VSV (vesicular stomatitis virus) has been used in one study to know about the replication and assembly of RNA viruses that are enveloped. In the study, the VSV virus was used as recombinant containing GRP gene, and thus it is not infectious until the envelope is provided which contains the protein which is responsible for the binding of receptor and fusion of membrane.[29]

The secreted GP is a non-residual 364-residue encoding protein present in all the ebolavirus GP. It is not known till now what role dose sGP plays in the infection but during the infection by EBOV high amount of sGP is observed in patient blood. The pre-sGP undergoes proteolytic cleavage by furin Prost-transitionally which gives a yield of mature sGP and a small, nonstructural peptide "-peptide which is heavy O-glycosylated and it is also a secreted protein. The major difference between GP and sGP is that they both have different C- terminals which is a result of the insertion of extra adenosine nucleotide in 20% of the transcription process. GP and sGP have similar N-terminals. The final GP is a trimer while the starting sGP is a dimer. Due to the difference in GP in various stands of proteins, there is more difference in their infection as well e.g., ZEBOV GP causes destruction of endothelial cells in monkeys and humans both, while the REBOV GP causes cytotoxicity in only monkeys. It is observed that the music-like domain is highly responsible for the cytotoxicity caused by GP.It is still not clear how the EBOV enters the host cells but it is believed that the host cell entry mechanism is through receptor-mediated endocytosis mechanism.[30]

It is confirmed in many studies that there are specific interactions of host-pathogen in the EBOV virus lifecycle. To date, the known host interaction partners to EBOV virus proteins are VP30, VP35, VP40, GP1, GP2 and VP24. The studies also confirmed that the host proteins RBBP6 compete with nucleoprotein for binding with VP30 to inhibit the EBOV virus RNA synthesis. Nucleoproteins are playing a major role in transcription and capsid assembly. The major nucleoprotein-host interaction impactor protein is Hsp70 which is a chaperone protein that binds to and impacts nucleoprotein stability.

The structural similarity of all 5 species is very distant and it is also fascinating to know that the 2 most dangerous species Sudan ebolavirus and Zaire ebolavirus are the most distant in case of structural similarities.[32] The structure of the virus is shown in the figure below (fig 2,3).

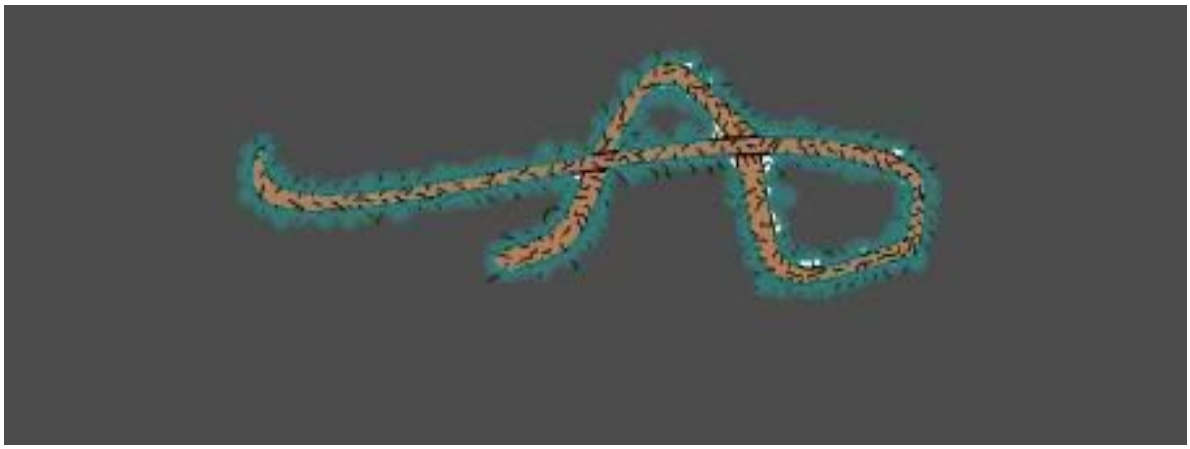

Fig 2: Structure of Ebola virus under microscope

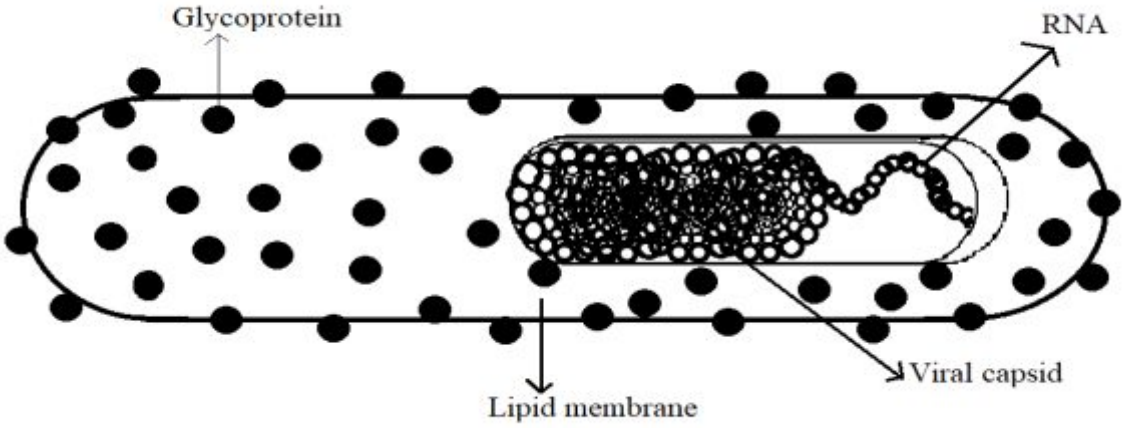

Fig 3: Structure of Ebola virus with RNA, Lipid membrane, Viral capsid, Glycoprotein

Transmission of the virus through different pathways

The human genome sequence of 5% of patients of all the population infected showed the record of spread in the country. The main entry point into a human body is through the mucous membranes such as the eye, nose and mouth[5]. Ebola virus disease is known to be an animal to human disease. Natural hosts of the Ebola virus are thought to be the fruit bats belonging to the family of *pteropodidae.*[7] The infection spreads when a healthy human being comes in contact with any blood or body fluid secreted from an infected animal or bat.[33]

After the entry of the Ebola virus into the human body, it spreads into the body through first striking the macrophages, monocytes, and the dendritic cells, then it goes into the lymph nodes where the replication of the virus starts and then

before the onset of symptoms the virus begins to spread and it immediately starts to infect a variety of cells such as hepatocytes, adrenocortical cells, endothelial cells, fibroblast, and many others.[5]

Then after the first infection, the secondary transmission seen here is direct or indirect human-to-human contact either by blood or any other body secretions contacts.[19] The virus has been detected to be present in human breast milk, saliva, semen and blood. Studies have also reported that airborne transmission is possible between the pigs and other primates but further transmission through the air is not reported after that and one of the reasons being concluded is the lack of virus in the human lungs and other parts of the body giving no chances of transmission. The pigs with EVD are having a high concentration of virus in their respiratory tract than in their bloodstream so they can transmit the disease through droplet form in the air [27].

It is seen that the EBOV virus can remain present in some human sites such as the brain, testis, and eyes which are known as immune privilege sites since they can protect the virus from rejection by host animals or humans [34]. Infectious EVOB virus has been observed in breast milk, semen, blood, saliva, urine, tears, skin, amniotic fluid, stool and CSF From 1976 to 2014 there were 65 EBOV GP has been collected from isolates which showed that the temporal evaluation of EBOV is mostly due to neutral genetic drift [35] It is observed that non-human primates show more close conditions to human infections than the animal models (in immunocompetent mice, Syrian hamsters, domesticated hamsters). Viral pathogenesis data has been largely studied by experiments on the wild-type EBOV predominant in the crab-eating macaques and rhesus monkey[35]. After the 1976 outbreak in DRC and Sudan, it was said that the EBOV-Zaire virus is autochthonic and pestilent within the so-called Zaire virus triangle.[20]

In the 2014 outbreak, the major seen mode of transmission was the nosocomial transmission. This transmission is the one that was responsible for disease progression in the population of healthcare workers. In west Africa in 2014 outbreak of majorly 665 cases was reported due to the nosocomial transmission from which 375 deaths occurred.[36]

A study in Texas biomedical research institute shows that one of the mechanisms of entry of the Ebola virus into host cells is “Autophagy” which means the self-eating mechanism of the cell. This is observed that the cell enters the host cell through a process called “micropinocytosis”. So basically, the process of this entry of the Ebola virus into the cell starts when the plasma membrane ruffles over the virus attached to the cell surface, and then this plasma membrane forms a vesicle over the virus. And then this vesicle is enclosed with virion being inside it and then it gets internalized into the cell.[37]

Transmission of immunization infection is a hypothetical chance. Even after 14 days of vaccination Antibody of infectious RNA has been identified in the body fluids of the person. The time period of shedding isn't known, but the sample after 28 days of vaccination tested negative for the presence of a virus. The antibody of infectious RNA has been recognized in secretions from the skin that showed up after vaccination.[19]

There is a comfortable mathematical model has been adopted for predicting the spread of the Ebola virus. This system is known as the SIRDP model which governs the problem. This system was developed after the 2014 major outbreak in the West Africa region.[38]

During a recent outbreak in 2019 in the West Africa region, it was observed that there was an increase in transmission of disease due to violent incidents that took place as people were angry as the number of cases were rising and thus, they were attacking the hospitals and the isolation ward where Ebola virus disease patients were kept.[39]

SIGNS AND SYMPTOMS OF EVD

Symptoms of this disease are seen after the incubation period of 2-21 days.[5] The major symptoms observed in the current 2021-outbreak are a severe decrease in neutrophile count and an increase in liver enzyme and hematological changes (leukopenia and lymphopenia). It is observed in disease pathophysiology studies that the recovery from this disease is majorly dependent on the immune response against the virus.[40]

In children, the symptoms are hard to be identified as in children the symptoms are more common and undifferentiated from other disease symptoms. It is seen that in some cases the major symptom of fever is also not present in children.[18]

The symptoms of this disease are normal at the first stage 'flu like' (headache, coughing, weakness) and then as the disease progresses it becomes more severe (internal and external bleedings, rhinorrhea) which makes this disease more and more unidentified at the initial stage and when it gets identified it has already reached to a bigger stage.[41] After the onset of the disease, the most common symptoms prevalent at 5 -7 days period are fever with anorexia, asthenia, and maculopapular rash. In the last stage of disease, the death of a patient occurs due to shock, hemorrhage, and multi-organ failure conditions [42].

It is observed that this disease mainly starts with rather unidentified symptoms such as fever, myalgia, and arthralgia [43]. It is also observed that not all patients in the 2014 outbreak showed hemorrhagic symptoms.[36]

TREATMENT OPTIONS FOR EBOLA VIRUS DISEASE

VACCINE

The first vaccine was made of the whole virus deactivated by formalin, heat and

radiations and it was ineffective to all humans and animals.[41]

For future treatment development, an inhibitor of viral cell entry will be a better option. As in a study done, it has revealed that immunity transfer by transfusing the blood of survival of Ebola virus disease to a patient suffering from Ebola virus disease is not much of help and not always effective.[41] Till 2016 there were no specially licensed or approved vaccines or antiviral treatment approved by U.S.FDA. China, Russia and European regions have approved 3 EBOV vaccines.

1. The chad3-EBO non-replicating vaccine vector based on the chimpanzee adenovirus type 3 (chad3)

2. The heterologous prime-boost Ebola vaccine regimen based on recombinant adenovirus type 26 vector (Ad26.ZEBOV) priming followed by boosting with modified vaccinia Ankara vector (MVA-BN- Filoã)

3. The recombinant Vesicular Stomatitis Virus (VSV) vector-based Ebola vaccine (rVSV-ZEBOV) [44].

In 2016 most promising and most effective treatment was by rVSV-ZEBOV which is a vesicular stomatitis virus-based vaccine.[45] But this vaccine was approved to be used in emergency conditions only. Till 30 November 2019 total of 274,871 individuals were vaccinated with this vaccine between the clinical trials and emergencies within the DRC region [43].

Although many vaccines have been designed for the treatment and just a year ago USA-FDA in December 2019 has approved another vaccine called ERVEBO for the prevention of disease caused by the *Zaire ebolavirus* in 18 years old or older than that. But this vaccine is only useful in infection by *Zaire ebolavirus* and not against any other infection caused by other species of Ebola virus[46].

INTRODUCTION TO MECHANISM AND BASICS OF VACCINES

rVSV-ZEBOV VACCINE

In the response mechanism of this vaccine both innate and adaptive immune systems take part. Yet the mechanism of contribution from these responses in the protective action after primary exposure for the short or long term is still unknown.[47]

After the intravenous introduction of a lethal dose of ZEBOV, monkeys were vaccinated with rVSV-ZEBOV showed cerebral and humoral immune responses with no evidence of virus replication. The rVSV-ZEBOV was observed to be present in synovial fluid and skin tissues have confirmed viral replication in the peripheral tissues [44].

During the phase 1 trial, the serological investigation showed that EBOV-GP specific IgG antibody responses were detected in almost all participants, with significantly high EBOV specific IgG concentrations in high-dose treatments. It has also been recently shown that ZEBOV-

specific circulating follicular T helper cells (ctfh) correlate with antibody titers and with the Tfh17 subset [44].

Many MVA vectors initiated a strong innate immune response in human monocytes cell lines with the production of interferon β, proinflammatory cytokines, and chemokines. In the rVSV-ZEBOV vaccine, VSV GP has been substituted by the GP from EBOV Kikwit-96 variants, having pathogenicity of the VSV and enabling infection of cells and replication using the EBOV GP. Chad3-EBO-Z also encodes the EBOV GP in the monovalent or bivalent form, and its impregnability and susceptibility have been tested in many human clinical trials[26].

As of April 2019 WHO stated that the rVSV-ZEBOV vaccine in total 97.5% effective. To check the duration of effectiveness of this vaccine rodent models were also used and the result showed that this vaccine is quite effective for a long time after first dosing.[48]

ERVEBO VACCINE

The ERVEBO vaccine is given in a dose of 1ml intramuscularly only. It is to be given in a non-dominant arm in the hastate area of the arm.[49]The adverse events occurrence rate after the administration of ERVEBO is relatively low and the events noted till now are basic systemic adverse effects such as headache, nausea, abnormal sweating, rash, and muscle/joint pain. This vaccine is contraindicated in patients who has a history of anaphylaxis type hypersensitivity reactions.[46]

This vaccine works on the immune system response of person. The vaccine contains proteins of the virus. When this vaccine is injected to the person it activates the immune system and triggers a response against the virus protein, thus when after receiving the vaccine person comes in contact with the disease virus it will not affect the person. There was study done for the clinical development program in which open-label and placebo control groups were observed for the adverse effects' occurrence. The results of this study are given below:

Study group	Major injection site adverse effect observed (% of the population)	The major systemic adverse effect observed (% of the population)
Open-label trial group	Swelling (12%) redness (17%) Pain at injection site (70%)	Joint pain (18%) Vascular lesions (2%) Arthritis (5%) Rash (4%)
Placebo control group	Pain at site of inj ection (3 4.0%), redness/swelling (2%)	Headache (37%), Fever (34%), Muscle pain (33%), Nausea (8%), Rash (4%), Sweating (3%)

JANSSEN EBOLA PREVENTION VACCINE THERAPY

In May 2020, Zabdeno and Mvabea 2 component vaccine authorization were recommended by the European medicine agency. This vaccine is given in 2 parts when given to the patient; first Zabdeno is given and after 8 weeks Mvabea is given, both are given intramuscularly. In times of an outbreak situation when immediate action is needed this 2 dose vaccine is not much of use.[50] this vaccine therapy is known as Janssen Ebola prevention vaccine therapy.[51] This Janssen therapy was found by Johnson and Johnson's Janssen division. The Zabdeno vaccine is a monovalent vaccine while the Mvabea vaccine is a multivalent vaccine. The major component of Zabdeno vaccine is Zaire ebolavirus Mayinga variant GP. This variant stimulates the immune response and it is expressed locally.

Clinical studies were done to check the safety and immunology of the vaccines and these vaccines were observed to be well-tolerated and un-harmful to healthy volunteers. There were no such serious adverse effects observed in the patients who received both the doses and only a minor headache was observed. The Mvabea vaccine is designed to provide immunity against the Sudan virus, Ebola virus, Marburg virus, and the Tai Forest virus. [51] These studies also showed that the 1st dose of Ad26.ZEBOV induced more robust initial antibody binding and cell response than the 2nd dose of MVA-BN-Filo vaccine.[52]

The Zabdeno vaccine is mainly designed to provide active specific immunity against the Ebola virus and this vaccine is based on the Ad26 vector expressing the Ebola virus mayinga variant's glycoprotein. [51]

DNA BASED VACCINE

Vaccination by plasmid DNA delivery is very practical and advantageous for the future development of a more effective and safe vaccine based on the Ebola virus DNA vaccine concept. A study on 21 healthy participants showed that 3- plasmid DNA candidate Ebola virus vaccine is secure and well accepted.[24]

A study was conducted in Africa in which the immunogenicity and safety of two DNA-based vaccines were checked: first encoding Zaire and Sudan ebolavirus glycoprotein and second encoding Marburg virus glycoprotein. This study showed that both these vaccines were well accepted and gave antigen-specific antibody-mediated and cellular immune responses.[53]

The DNA vaccines were designed from Zaire ebolavirus and Sudan ebolavirus transmembrane-deleted glycoproteins with viral nucleoproteins. In 2006 during the first clinical trials of these types of vaccines, the vaccine was given by intramuscular injection but as time changes and technologies have advanced now this vaccine is given by a novel biojector 2000

needle-free injection management system.[43] A study has shown that the protective efficacy and immunogenicity of DNA based vaccines can be enhanced and improved by the use of Nanoplasmid vectors.[54]

DRUG THERAPIES

COMBINATION THERAPY OF ATOLTIVIMAB, MAFTIVIMAB AND ODESIVIMAB-EBGN

In October 2014 U.S.FDA approved a mixture of 3 monoclonal antibodies atoltivimab, maftivimab, and odesivimab-ebgn. This mixture mainly targets the glycol protein present in the virus which facilitates the virus entry into the cell by binding to the cell membrane receptor. The mixture binds with this glycoprotein and inhibits its activity and thus inhibits the entry of the virus into the host cell. [43]

Atoltivimab, maftivimab, and odesivimab-ebgn together is a combination used to treat infection of Zaire ebolavirus and this is a mixture of Zaire ebolavirus glycoprotein-directed human monoclonal antibodies used in adult and juvenile or infant patients, including neonates given birth by a mother who is RT-PCR positive for infection. This combination is of Zaire ebolavirus glycoprotein (GP) directed recombinant human IgG1 human monoclonal antibodies of similar structure.[55]

The potential for this combination to repress replication of a live vaccine virus indicated for avoidance of *Zaire ebolavirus* infection and conceivably decrease the efficacy of the vaccine, avoid the simultaneous administration of a live vaccine during treatment with this combination. The time difference between vaccination after the initiation of the combinational therapy should be in according to current vaccination guidelines.[55]

This combination is an infusion. It is given one time by a healthcare provider straight into the vein (intravenous imbuement). The amount of the drug combination to be administered is calculated by the patient's weight. It may cause serious side effects including severe and life-threatening allergic reactions during and after the infusion. The most commonly observed adverse effects of this are body temperature rise, chills, rapid heartbeats with heavy breathing, and puke.[56]

EBANGA TREATMENT

In 2020 December U.S. FDA has approved a monoclonal antibody named "EBANGA" for treatment of Ebola virus disease caused by the *Zaire Ebola virus* strain.[57]

EBANGA is also known as ansuvimab. The major side effects associated with the use of this monoclonal antibody are: fever, tachycardia, tachypnoea, hypoxia, chills, hypotension, vomiting and diarrhea.[58] It binds to a certain part of the EBOV virus and prevents it from entering into any host cells. The major mechanism of its effect is by inhibiting receptor binding and thus it inhibits the virus entry into the host cells.[59]

EBANGA is a human monoclonal antibody directed by Zaire ebolavirus glycoprotein for treatment against Ebola virus disease caused by Zaire ebolavirus. But this can only be used in adults and pediatric patients as geriatric use data have not been supported yet.[57]

PALM STUDIES

After the 2018 outbreak in the West Africa region WHO decided to start and research and development department for research on Ebola virus disease treatment options.[60]

The PALM studies compared 4 drug options which were possibly the most effective ones for the treatment of Ebola virus disease: ZMapp, Remdesivir, MAB114, and REGN-EB3. At the end of the study, it was found that both MAB114 and REGN-EB3 are more effective in comparison to ZMapp drugs and they have superiority in case of mortality rates than ZMapp and Remdesivir both. Here Remdesivir is a nucleotide analog RNA polymerase inhibitor, MAB114 is a single human monoclonal antibody derived from EBOLA survivor while REGN-EB3 is a mixture of 3 IgG1 monoclonal antibodies.[61]

In June 2020 another study called PALM studies were randomized control trials of 3 investigational agents which are under investigation compared with the control group including patients of EVD (infected with the filoviridae: ebolavirus) treated with ZMapp drugs. ZMapp is comprised of 3 chimerical monoclonal antibodies under development for EVD.[62]

The safety and efficacy of ERVEBO in people younger than 18 years old have not been done yet. For the development of treatment and prevention against Ebola virus disease, the year 2019 was seen to be very useful as many treatment options and vaccines were approved by U.S. FDA. [63]

A study was also done to identify some antibodies which might be useful in giving protective action. These antibodies mAbs were isolated from the survivors of Ebola virus disease. There were 2 antibodies mab110 and mab114 were the most potent and gave the most neutralizing effect and has shown ADDC (antibody-dependent cell-mediated cytotoxicity) activity as well.[64]

OTHER MEDICATIONS

In 2016, one small novel molecule GS-5734 was found which was effective against many different strains of the Ebola virus and it was investigated in rhesus monkey species and has an effective antiviral activity. This drug is an adenosine analog monophosphoramidate prodrug and it showed inhibition of virus replication in many human cell types such as human endothelial cells and primary macrophages[65].

The molecule GS-5734 was later named “Remdesivir”. The clinical data of the efficacy and safety of Remdesivir were generated in 2016 by studies done using rhesus monkeys. Remdesivir acts by inhibition of virus replication by interference with RNA polymerase.[66]

Currently there are 7 clinical trials involving Remdesivir which are ongoing and registered under clinicaltrial.gov.[60]

One of the most advanced technologically manufactured treatment options for Ebola virus disease was done in 2019 when isolated lectin from banana was engineered into H84T banlec molecule which was found to be very effective against EBOV virus in cell cultures. This molecule was found to be very much effective against the strain which was responsible for the 2013-2016 outbreak of the Makona strain.[67]

A mechanical-based study identified a potent antiprotozoal drug "quinacrine" to might be useful against the Ebola virus disease. The basic mechanism of this drug is that it enters the cells and cell organelles and rises the pH which interferes with the cathepsin B activity which is important for Ebola virus entry into the host cell. Thus, it is safe to say that this medication works by inhibiting virus entry into the host cells.[68]

Some data shows that quinacrine showed good effectiveness in studies as an anti-viral agent against dengue and zika virus. Quinacrine is used in salt form as quinacrine hydrochloride. As a small-molecule inhibitor of the Ebola virus "Tilorone" was acknowledged by the Bayesian machine learning model. It is the most potent one of all the tested drugs. It is also proven to be effective in-vitro against the Ebola virus.[69]

SUPPORTIVE CARE SYSTEM

Once the disease is confirmed, the patient is required to be hospitalized in an isolation ward and closely monitored and the supportive care is started. Supportive care includes fluid resuscitation, electrolyte and glucose monitoring, correction and treatment of possible co-infections.[70]

When GIT problems arise during Ebola virus disease, the highly oral bioavailable drugs will be of less use thus use of supportive care systems will be playing a major role in monitoring and treatment of the patient with these complications.[6] In five Ebola treatment units (ETU) a retrospective cohort study was conducted on Ebola virus disease patients to check the effect of multivitamins supplements as supportive care during treatment of Ebola virus disease patients. The result from these studies showing low facility-based mortality in patients suggested that multivitamin supplements should be used as supportive care during the treatment of Ebola virus disease treatment.[71]

As a part of the supportive care If the patient suffers from high fluid loss it may result in hypovolemia; so, to prevent such an event patient should be provided with oral rehydration solutions, and if required anti-diarrheal and anti-emetic should also be given.[3]

In a study, it was also seen that antimicrobials used in the supportive care systems have reduced mortality due to

bacterial infection associated with Ebola virus disease. And for this purpose, antibiotic therapy is also said to be useful as a supportive care treatment option. Broad-spectrum antibiotics to be used in this therapy.[72]

After the 2014-2016 outbreak clinicians found that basic supportive care is very helpful in controlling the mortality rate of Ebola virus disease. Analgesic therapy recommendation was made in a guideline that follows GRADE methodology. According to this therapy option, analgesics should be used for the patient having high abdominal pain and parenteral opioid therapy can also be given in some cases.[71]

CONCLUSION

Based on the available studies it can be concluded that the vaccines are more effective then the drug treatment options which are available. Based on clinical trials data and results of different triala it is concluded that rVSV-ZEBOV and the Janssen therapy are most promising and effective options for Ebola virus disease treatment. The functioning of glycoprotein must be evaluated in further studies as it may give a potential new theory of binding and fusion of the Ebola virus into the host cell from which a target can be generated to formulate aa medicine or therapy which can inhibit the entry of the Ebola virus into the host cell. Multi-organ failures are associated with Ebola virus disease progression for which the supportive care system with advanced machines and technology might be useful for better treatment. DNA-based vaccines should be considered as potential candidates for Ebola virus disease treatment. Clinical trials should be done for the efficacy and safety of the use of the drug quinacrine in Ebola virus disease treatment.

REFERENCES

(1) Rojek A, Horby P, Dunning J. Insights from clinical research completed during the west Africa Ebola virus disease epidemic. *Lancet Infect Dis*. 2017;17(9):e280-e292. doi:10.1016/S1473-3099(17)30234-7

(2) Chowdhury S, Chakraborty P pratim. Universal health coverage There is more to it than meets the eye.*J Fam Med Prim Care*. 2017;6(2):169-170. doi:10.4103/jfmpc.jfmpc

(3) Dhama K, Malik YS. Advances in Designing and Developing vaccines , Drugs , and Therapies to Counter ebola virus. 2018;9(August). doi:10.3389/fimmu.2018.01803

(4) Zawilińska B, Kosz-Vnenchak M. General introduction into the Ebola virus biology and disease. *Folia Med Cracov*. 2014;54(3):57-65.

(5) Kiiza P, Mullin S, Teo K, Adhikari NKJ, Fowler RA. Treatment of Ebola-related critical illness. *Intensive Care Med*. 2020;46(2):285-297. doi:10.1007/s00134-020-05949-z

(6) Hoenen T. Therapeutic strategies to target the Ebola virus life cycle. *Nat Rev Microbiol*. 2019;17(October):593-606. doi:10.1038/s41579-019-0233-2

(7) Malvy D, McElroy AK, de Clerck H, Günther S, van Griensven J. Ebola virus disease. *Lancet*. 2019;393(10174):936-948. doi:10.1016/S0140-6736(18)33132-5

(8) Marcinkiewicz J, Bryniarski K, Nazimek K. Ebola haemorrhagic fever virus: pathogenesis, immune responses, potential prevention. *Folia Med Cracov*. 2014;54(3):39-48.

(9) Demetria C, Smith I, Tan T, et al. in Cynomolgus Monkeys ,. 2018;24(7):1285-1291.

(10) Miranda MEG, Miranda NLJ. Reston Ebolavirus in humans and animals in the Philippines: A review. *J Infect Dis*. 2011;204(SUPPL. 3):757-760. doi:10.1093/infdis/jir296

(11) Kimura H, Tsukagoshi H, Ryo A, et al. Ebola virus disease: a literature review. *J Coast Life Med*. 2015;3(2):85-90. doi:10.12980/jclm.3.201514j93

(12) Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses*. 2019;11(4):1-16. doi:10.3390/v11040326

(13) Colavita F, Biava M, Castilletti C, et al. Inflammatory and humoral immune response during ebola virus infection in survivor and fatal cases occurred in sierra leone during the 2014–2016 outbreak in west Africa. *Viruses*. 2019;11(4). doi:10.3390/v11040373

(14) Morwitzer MJ, Tritsch SR, Cazares LH, et al. Cellular Interactors of the Ebola Virus Nucleoprotein. Published online 2019.

(15) Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. *Antiviral Res*. 2014;105(1):17-21. doi:10.1016/j.antiviral.2014.02.014

(16) Murray MJ. Ebola Virus Disease: A Review of Its Past and Present. *Anesth Analg*. 2015;121(3):798-809. doi:10.1213/ANE.0000000000000866

(17) Emond RTD, Evans B, Bowen TW, Lloyd G. PAPERS AND ORIGINALS A case of Ebola virus infection. *Br Med J*. 1977;2(August):541-544.

(18) Dixit D, Masumbuko Claude K, Kjaldgaard L, Hawkes MT. Review of Ebola virus disease in children–how far have we come? *Paediatr Int Child Health*. 2021;41(1):12-27. doi:10.1080/20469047.2020.1805260

(19) Simpson DIH, Zuckerman AJ. Marburg and Ebola: Viruses in search of a relation. *Nature*. 1977;266(5599):217-218. doi:10.1038/266217a0

(20) Breman JG, Heymann DL, Lloyd G, et al. Discovery and Description of Ebola Zaire Virus in 1976 and Relevance to the West African Epidemic during 2013-2016. *J Infect Dis*. 2016;214(Suppl 3):S93-S101. doi:10.1093/infdis/jiw207

(21) Watle SV, Norheim G, Røttingen JA. Ebola vaccines – Where are we? *Hum Vaccines Immunother*. 2016;12(10):2700-2703. doi:10.1080/21645515.2016.1217372

(22) Lamontagne F, Clément C, Kojan R, Godin M, Kabuni P, Fowler RA. The evolution of supportive care for Ebola virus disease. *Lancet*. 2019;393(10172):620-621. doi:10.1016/S0140-6736(19)30242-9

(23) 6c5b28318fe7bc41e03b9585b52c651c6a7463e3 @ www.who.int. https://www.who.int/health-topics/ebola/#tab=tab_1

(24) Martin JE, Sullivan NJ, Enama ME, et al. A DNA Vaccine for Ebola Virus Is Safe and Immunogenic in a Phase I Clinical Trial —“ †. 2006;13(11):1267-1277. doi:10.1128/CVI.00162-06

(25) Marzi A, Wegele A, Pöhlmann S. Modulation of virion incorporation of Ebolavirus glycoprotein: Effects on attachment, cellular entry and neutralization. *Virology*. 2006;352(2):345-356. doi:10.1016/j.virol.2006.04.038

(26) Proteins VP. crossm Distinct Immunogenicity and Efficacy of Poxvirus-Based Vaccine Candidates against Ebola Virus Expressing GP and. 2018;92(11):1-30.

(27) Wiwanitkit V. Ebola virus disease. *J Chinese Med Assoc*. 2015;78(4):264. doi:10.1016/j.jcma.2015.03.003

(28) Yu DS, Weng TH, Wu XX, et al. The lifecycle of the Ebola virus in host cells. *Oncotarget*. 2017;8(33):55750-55759. doi:10.18632/oncotarget.18498

(29) Takada A, Robison C, Goto H, et al. A system for functional analysis of Ebola virus glycoprotein. *Proc Natl Acad Sci U S A*. 1997;94(26):14764-14769. doi:10.1073/pnas.94.26.14764

(30) Lee JE, Saphire EO. Ebolavirus glycoprotein structure and mechanism of entry. *Future Virol*. 2009;4(6):621-635. doi:10.2217/fvl.09.56

(31) Batra J, Hultquist JF, Liu D, et al. regulator of Ebola virus replication. 2019;175(7):1917-1930. doi:10.1016/j.cell.2018.08.044.Protein

(32) Nyakatura EK, Frei JC, Lai JR. Chemical and Structural Aspects of Ebola Virus Entry Inhibitors. *ACS Infect Dis*. 2015;1(1):42-52. doi:10.1021/id500025n

(33) World Health Organization. Fact sheet: Ebola virus disease. Published online 2015:1-5. http://www.who.int/mediacentre/factsheets/fs103/en/

(34) Boon S Den, Marston BJ, Nyenswah TG, et al. with Transmission from Survivors. 2019;25(2).

(35) Jacob ST, Crozier I, Fischer WA, et al. *Ebola Virus Disease*. Springer US; 2016. doi:10.1038/s41572-020-0147-3

(36) Shears P, O'Dempsey TJD. Ebola virus disease in Africa: Epidemiology and nosocomial transmission. *J Hosp Infect*. 2015;90(1):1-9. doi:10.1016/j.jhin.2015.01.002

(37) 799c3d75f4ec7f046153ce57a6247f27c3a5004e @ www.txbiomed.org. https://www.txbiomed.org/news-press/news-releases/new-research-pinpoints-pathways-ebola-virus-uses-to-enter-cells/

(38) Nazir A, Ahmed N, Khan U, Mohyud-Din ST, Nisar KS, Khan I. An advanced version of a conformable mathematical model of Ebola virus disease in Africa. *Alexandria Eng J*. 2020;59(5):3261-3268. doi:10.1016/j.aej.2020.08.050

(39) Wannier SR, Worden L, Ho NA, et al. Estimating the impact of violent events on transmission in Ebola virus disease outbreak , Democratic Republic of the Congo , 2018 – 2019. 2019;28(January). doi:10.1016/j.epidem.2019.100353

(40) Tests A. Persistent Immune Responses after Ebola Virus Infection. 2013;649:492-493. doi:10.1056/NEJMc1300266

(41) Wager MGT and JFS. úWàV„v9eØSNIH Public Access. *Bone*. 2011;23(1):1-7. doi:10.1007/s40259-013- 0046-1.Emerging

(42) Goeijenbier M, van Kampen JJA, Reusken CBEM, Koopmans MPG, van Gorp ECM. Ebola virus disease: A review on epidemiology, symptoms, treatment and pathogenesis. *Neth J Med*. 2014;72(9):442-448.

(43) Matz KM, Marzi A, Feldmann H. Ebola vaccine trials: progress in vaccine safety and immunogenicity.*Expert Rev Vaccines*. 2019;18(12):1229-1242. doi:10.1080/14760584.2019.1698952

(44) Medaglini D, Siegrist C. ScienceDirect Immunomonitoring of human responses to the rVSV-ZEBOV Ebola vaccine. *Curr Opin*

Virol. 2017;23:88-94. doi:10.1016/j.coviro.2017.03.008

(45) Metzger WG, Vivas-Martínez S. Questionable efficacy of the rVSV-ZEBOV Ebola vaccine. *Lancet*. 2018;391(10125):1021. doi:10.1016/S0140-6736(18)30560-9

(46) News V. Merck Announces FDA Approval for ERVEBO ® (Ebola Zaire Vaccine , Live) Action Represents Another Milestone for the Global Partnership Against Ebola. Published online 2020.

(47) Medaglini D, Santoro F, Siegrist CA. Correlates of vaccine-induced protective immunity against Ebola virus disease. *Semin Immunol*. 2018;39(June):65-72. doi:10.1016/j.smim.2018.07.003

(48) Suder E, Furuyama W, Feldmann H, Marzi A, de Wit E. The vesicular stomatitis virus-based Ebola virus vaccine: From concept to clinical trials. *Hum Vaccines Immunother*. 2018;14(9):2107-2113. doi:10.1080/21645515.2018.1473698

(49) INDICATIONS AND USAGE ERVEBO ® is indicated for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older . 1 . 1 Limitations of Use The duration of protection conferred by ERVEBO is unknown. ERVEBO does not protec. Published online 2019:1-8.

(50) WHO. Ebola-Virus-Disease @ Www.Who.Int. Published online 2020. http://www.who.int/en/news-room/fact-sheets/detail/ebola-virus-disease

(51) zabdeno-mvabea-ebola-vaccine @ www.precisionvaccinations.com. https://www.precisionvaccinations.com/vaccines/zabdeno-mvabea-ebola-vaccine

(52) Anywaine Z, Whitworth H, Kaleebu P, et al. Safety and Immunogenicity of a 2-Dose Heterologous Vaccination Regimen with Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data from a Phase 1 Randomized Clinical Trial in Uganda and Tanzania. *J Infect Dis*. 2019;220(1):46-56. doi:10.1093/infdis/jiz070

(53) Kibuuka H, Berkowitz NM, Millard M, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: A phase 1b, randomised, double-blind, placebo-controlled clinical trial. *Lancet*. 2015;385(9977):1545-1554. doi:10.1016/S0140-6736(14)62385-0

(54) Suschak JJ, Dupuy LC, Shoemaker CJ, et al. Nanoplasmid Vectors Co-expressing Innate Immune Agonists Enhance DNA Vaccines for Venezuelan Equine Encephalitis Virus and Ebola Virus. *Mol Ther*

Methods Clin Dev. 2020;17(June):810-821. doi:10.1016/j.omtm.2020.04.009

(55) inmazeb-drug @ www.rxlist.com. https://www.rxlist.com/inmazeb-drug.htm

(56) drug-trials-snapshots-inmazeb @ www.fda.gov. https://www.fda.gov/drugs/drug-approvals-and- databases/drug-trials-snapshots-inmazeb

(57) 29a5a4ddc77b34ae5b4d33ed988d61923c4436a2 @ www.clinicaltrialsarena.com. https://www.clinicaltrialsarena.com/projects/ebanga-ansuvimab-zykl/

(58) 58. Lee A. Ansuvimab: First Approval. *Drugs*. 2021;81(5):595-598. doi:10.1007/s40265-021-01483-4

(59) 278a6874e747f69e9f0e6576ac4f5326fa4b802d @ www.europeanpharmaceuticalreview.com. https://www.europeanpharmaceuticalreview.com/news/138368/fda-approves-ebanga-ansuvimab- zykl-for-the-treatment-of-ebola/

(60) Pardo J, Shukla AM, Chamarthi G, Gupte A. The journey of remdesivir: From Ebola to COVID-19. *Drugs Context*. 2020;9:1-9. doi:10.7573/DIC.2020-4-14

(61) Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*. 2019;381(24):2293-2303. doi:10.1056/nejmoa1910993

(62) Ramanathan K, Antognini D, Combes A, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- research that is available on the COVID-19 resource centre - including this for unrestricted research re- use a. 2020;(January):19-21.

(63) Levine MM. Edi t or i a l s Monoclonal Antibody Therapy for Ebola Virus Disease. Published online 2019. doi:10.1056/NEJMe1915350

(64) Corti D, Misasi J, Mulangu S, et al. Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody. *Science (80-)*. 2016;351(6279):1339-1342. doi:10.1126/science.aad5224

(65) Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 2016;531(7594):381-385. doi:10.1038/nature17180

(66) Nili A, Farbod A, Neishabouri A, Mozafarihashjin M, Tavakolpour S, Mahmoudi H. Remdesivir/ : A

beacon of hope from Ebola virus disease to. 2020;(May):1-13. doi:10.1002/rmv.2133

(67) Dyall J, Evans L, King SR, et al. Inhibition of Ebola Virus by a Molecularly Engineered Banana Lectin. Published online 2019:1-20.

(68) Quinacrine R, Infection V, Vivo I. crossm. 2019;(June):1-8.

(69) Harutyunyan A, Mcfarlane C, Green CE, Madrid B. crossm Efficacy of Tilorone Dihydrochloride against Ebola Virus Infection. 2018;62(2):1-13.

(70) WHO. *Optimized Supportive Care for Ebola Virus Disease - CLINICAL MANAGEMENT STANDARD OPERATING PROCEDURES*.; 2019. https://apps.who.int/iris/bitstream/handle/10665/325000/9789241515894-eng.pdf?sequence=1

(71) Lamontagne F, Fowler RA, Adhikari NK, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet*. 2018;391(10121):700-708. doi:10.1016/S0140-6736(17)31795-6

(72) Savini H, Ficko C, Simon F. Post-exposure prophylaxis in Ebola virus disease: don't forget the psychological factors. *Lancet Infect Dis*. 2018;18(4):378. doi:10.1016/S1473-3099(18)30131-2