Research & Reviews: Journal of Medical and Health Sciences

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

Review: Yellow Fever

Endalu Mulatu[1]* and Abdi Feyisa[2]

[1]Bedelle College of Agriculture and Forestry, Metu University, Bedelle, Ethiopia

[2]Alage Agricultural Technical Vocational Educational Training College, Alage, Ethiopia

Review Article

Received date: 17/05/2018

Accepted date: 18/08/2018

Published date: 25/08/2018

*For Correspondence:

Endalu Mulatu, Bedelle College of Agriculture and Forestry, Metu University, Bedelle, Ethiopia, Tel: +251-961-916-608;

Email: indexbest2010@gmail.com

Keywords: *Aedes aegypti*, Clinical disease, Prognosis, Transmissions, Yellow fever, Yellow fever virus

ABSTRACT

Yellow fever is a viral hemorrhagic a vector-borne disease that transmitted by the bite of infected *Aedes aegypti* mosquito which affects and poses a serious problem to humans and non-human primates in tropical areas of Africa and South America. The yellow fever-causing virus was RNA virus that belongs to the genus *Flavivirus*. Numerous factors are responsible for the emergence/ reemergence of the disease to occur. Thus includes that migration of susceptible vector habitat individuals, increased urbanization and travel. There are 3 transmission cycles for yellow fever: sylvatic (jungle), intermediate (Savannah), and urban. Yellow fever virus incubates in the body for 3 to 6 days and develops asymptomatic to severe clinical signs such as muscle pain with a prominent backache, headache, loss of appetite and nausea or vomiting, jaundice dark urine and abdominal pain, kidney and liver failure. The disease can be diagnosed by enzyme-linked immune-sorbent assay, polymerase chain reaction. There is no specific treatments have been found to benefit patients with yellow fever. Whenever possible, yellow fever patients should be hospitalized for supportive care and close observation. The majority of individuals will develop asymptomatic or have mild disease with complete recovery and severe form of the disease will end up in death. Yellow fever can be prevented by massive vaccination and vector control. In areas where the disease is endemic, all population should be vaccinated against the disease.

INTRODUCTION

In the past few years, emergent disease episodes were amplified and most of the diseases have zoonotic importance or species-jumping infectious agents [1]. They have major consequences for public and veterinary health and economic productivity across the globe and account for an estimated 60% of emerging human pathogens. Many of them cause severe and potentially fatal illness in humans and are a cause of serious epidemics and pandemics [2].

Numerous factors were identified for the emergence of zoonotic diseases. Among thus factors, Environmental changes, human and animal demography, pathogen changes and changes in farming practice are a few of them that lead to the occurrence of newly emerging or reemerging zoonotic diseases. Additionally, Social and cultural factors such as food habits and religious beliefs play a role in zoonotic disease emergence [3].

Yellow fever is the disease that currently re-emerging and poses serious harm in Africa, South America, and Central America, with an annual estimate of serious cases 84,000 to 170,000 and about 29,000 to 60,000 deaths. Yellow fever outbreak is spread to North America and Europe and cause disrupted economies, development and in some cases decimated populations in 17th to 19th centuries [4].

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

Yellow fever disease is a viral hemorrhagic fever with high mortality that is transmitted by mosquitoes. Factors that were related to the recurrence of yellow fever in South America included relatively low vaccine coverage in areas where outbreaks of the disease occurred, migration of susceptible individuals to forested regions where the disease is transmitted, and increasing urbanization of the disease. Some reports also revealed that unvaccinated travelers were also serving as a potential source of infection for the Yellow fever to a different part of the world [5-7].

REVIEW OF LITERATURE

History and overview of yellow fever

The Yellow fever is an ancient human disease that poses a serious problem before the causative agent of the disease was not identified. In early history, yellow fever was misunderstood by other fever causing diseases. Any documentation of the disease before the 1700's was inaccurate for two reasons: The confusion of the disease with other diseases having the same symptom and lack of knowledge about the disease [8].

Yellow fever is a well-known disease having public health importance in Africa, south and Central America the Caribbean and Mexico but it also affects the southern latitudes of the United States. The disease named as yellow fever from the fact that the disease typically causes the mucous membrane to be yellowish as well as producing a fever to victims. It is acute hemorrhagic viral disease gained from the bite of female mosquitoes. Primates and mosquitoes (the *Aedes* and *haemogogus* species) are known for being the host for the disease. Currently, the disease was known by different names as "yellow jack" (short form of a yellow jacket), yellow plague, yellow Rainer, bronze john, dock fever, ship fever, strangers fever, American plague [9].

The disease is most likely originated in African and spread to Latin America during the slave trade in the 16th century. Yellow fever was reported accurately in the Yucatan, Mexico, in 1648, when many people affected with a condition that best matches yellow fever. It was believed that the disease made its way to Mexico from the Bahamas after people reported a similar disease that spread throughout the Caribbean islands. Nowadays, the disease is endemic to 31 countries in Sub-Saharan Africa in which 508 million people are estimated to be at risk and 13 Latin America countries with 400 million people at risk. Although the disease has never been reported in Asia, the region has remained at risk due to increasingly favorable conditions and the disease can occur anywhere virtually through imported cases [9,10].

The first trail to identify yellow fever was made in 1881 by Cuban scientist Carlos Finlay. This was done for investigation of a large number of deaths at the lower of Mississippi valley in 1879 due to yellow fever. As the belief of Finlay, mosquitos of the tropical regions were a vector for transmission of the disease through its bite. He concluded this without experimental investigations because these types of mosquitoes were prevalent in areas where the disease is prevalent. Later, in 1898 during the Spanish-American war which took place in Cuba and Puerto more soldiers were dying because of yellow fever than war-related injuries this condition forced them to find the cause of yellow fever. The surgeon general of the United States assembled the group of medical researchers to find the cause of yellow fever. The group was led by army surgeon Walter Reed.

Reed team evaluated many ideas about the disease spread, including Carlos Finlay Hypothesis. Reed's team conducted an experiment using military volunteers. They have first tested whether the disease was spread through direct contact by having volunteers sleep on bedding and clothing from yellow fever patients. The volunteers were kept in a vector proof room. This experiment showed that yellow fever was not transmitted by contact because no one developed the disease from the experimental group. Another experiment was done by exposing a group of volunteers to mosquitoes that were fed on people infected with yellow fever and the volunteers developed the disease, supporting the idea that it was spread by mosquitoes bite.

In 1927 virology studies was made to identify the causative agent of yellow fever from Ghanaian patient named Asibi, and Asibi Yellow fever virus strain is isolated. This virus strain is highly virulent and still widely used by scientists today [11]. Later, in 1937 a 17D live-attenuated vaccine strain produced from Asibi strain yellow fever virus by Max Theiler and his colleagues [11,12]. Low vaccine coverage in areas where outbreaks of the disease occurred, migration of susceptible individuals to forested regions where the disease is transmitted and increasing urbanization will result in re-emergence of yellow fever.

Report of Brazilian Ministry of Health revealed that From December 2016 to 22 February, 2017. Brazil has affected by yellow fever outbreak, with 1345 suspected cases, of which 295 have been confirmed, and 215 deaths. According to the report, the majority of victims were male individuals living in the rural areas, in the economically active segment of the population, which have not been previously vaccinated.

The risk of widely spread of emerging and vector-borne infections have become increased with increasing volumes of air travel. This risk is particularly acute in the Asia-Pacific region, where systems for yellow fever surveillance and detection are largely untested, and yellow fever vaccination is limited to travelers. At early December of 2015, in Angola

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

large populations of urban areas were affected with the outbreak of yellow fever which caused more than 7334 suspected cases and subsequently spread to the Democratic Republic of Congo, causing 961 confirmed cases and 137 deaths. In addition, causes related to travel from those countries were noted in nonendemic areas such as China, raising concern about the international spread of disease **(Figure 1)** [13,14].

Figure 1. Yellow fever endemic zones across the globe.

Cause of yellow fever

The yellow fever disease is caused by virus genus *flavivirus* which belongs to a family of viruses called Flaviviridae. This family naming is from the Latin word flavus, which means "yellow". *Flaviviruses* primarily cause disease in humans and cattle. However, these viruses can live in a variety of insects and mammals.

The family Flaviviridae classified into three genera (*Flavivirus*, *Pestivirus*, and *Hepacivirus*), the members of which, although similar in genomic organization and physicochemical properties, are genetically distinct and biologically quite different. The genus *Flavivirus* contains at least 70 viruses; and most of the have veterinary importance, including Japanese encephalitis, West Nile, louping ill, and Wesselsbron viruses. Among the members of this genus 30 of them are arthropod borne human pathogens, the causative agents of diseases varying from fevers with a rash to life-threatening hemorrhagic fevers to encephalitis to hepatic necrosis. Out of members of this genus; the four dengue viruses, West Nile virus, Japanese encephalitis virus, and several tick-borne encephalitis viruses rank among the most important human viral pathogens. The genus *Pestivirus* contains important veterinary pathogens, including bovine viral diarrhea virus, border disease virus of sheep, and classical swine fever virus. The genus *Hepacivirus* contains only the human pathogens, hepatitis C and the inappropriately named hepatitis G viruses. Yellow fever virus, the prototype of the genus *Flavivirus*, was discovered in the course of investigating epidemic yellow fever and that it was transmitted by the mosquito, *Aedes aegypti* [15].

The genome yellow fever virus consists of a linear positive sense, single stranded RNA. Its RNA is made up of 11,000 nucleotides. The yellow fever virus genome primarily programs for capsomere and attachment proteins. Because it is an RNA virus, a replication protein is also part of the genome to help the virus replication. Yellow fever is an enveloped virus with a spherical capsid. Attached to the genome is a nucleocapsid. The virus is 40 to 50 nanometers in diameter. Its nucleocapsid has a box like a shape and is 25 to 30 nanometers in diameter. The capsomere proteins are uniform and interlock to form the capsid. Nucleocapsid proteins intertwine with the RNA genome, forming a geometric pattern that fits snuggly into the capsid. Protein spikes that serve as attachment proteins are inserted onto the outer surface of the envelope.

Virus replication in the mosquito's body starts after three days and first reproduces in cells of mosquito's digestive system and fat cells. Then it moves to the nervous system, salivary glands, and reproductive system. *Aedes* mosquitoes have a rapid life cycle. They can develop into young adult mosquitoes two weeks after the eggs are laid in water. The virus is spread to a human or monkey when the virus escapes with saliva and enters the host's body during the mosquito bite. Yellow fever viruses are also passed from a mosquito to its offspring through the mosquito eggs, giving rise to mosquitoes containing the virus at birth [8].

Transmission

Ethical Yellow fever virus is transmitted to people primarily through the bite of infected *Aedes* or *Haemagogus* species mosquitoes. Mosquitoes acquire the virus by feeding on infected primates (human or non-human) and then can transmit

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

the virus to other primates (human or non-human). People infected with yellow fever virus are infectious to mosquitoes (referred to as being "viremic") shortly before the onset of fever and up to 5 days after onset [16].

Yellow fever virus has three transmission cycles: Jungle (sylvatic), Intermediate (Savannah), and Urban. In its jungle habitat, yellow fever virus is maintained in a mosquito–monkey–mosquito cycle [15]. The jungle (sylvatic) cycle involves transmission of the virus between non-human primates (eg: Monkeys) and mosquito species found in the forest canopy. In tropical rainforests, monkeys, which are the primary reservoirs of yellow fever and occasionally humans working or traveling in the forest are bitten by infected mosquitoes and develop yellow fever. In Africa, an intermediate (savannah) cycle exists that involves the transmission of the virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from monkey to human or from human to human via mosquitoes [16].

The urban cycle involves transmission of the virus between humans and urban mosquitoes, primarily *Aedes aegypti*. The virus is usually brought to the urban setting by who had infected in the Jungle or Savannah [16]. Large epidemics occur when infected people introduce the virus into heavily populated areas with high mosquito density and where most people have little or no immunity, due to lack of vaccination **(Figure 2)**.

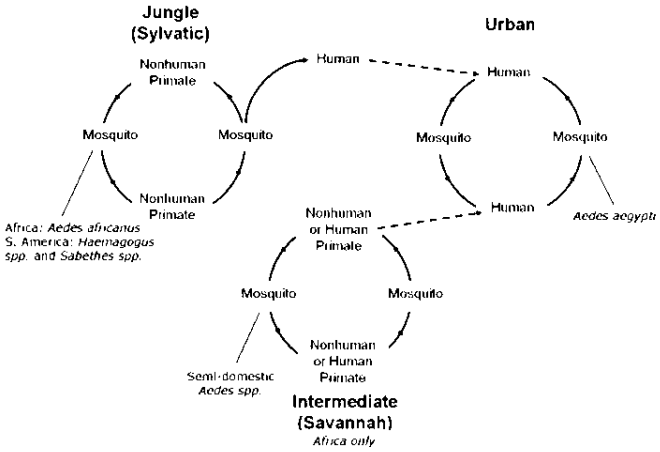

Figure 2. Transmission cycle of Yellow Fever Virus.

CLINICAL DISEASE

Upon, initial exposure to the bite with an infected mosquito the incubation period of yellow fever starts. It usually takes three to six days for the yellow fever virus to replicate a large enough number of viral particles to produce disease. There are usually no signs or symptoms of the disease observed during the incubation period. The incubation period leads to the infection or invasion stage. This lasts for two to five days after the end of the incubation period. The viruses are now reproducing rapidly and traveling throughout the body [8].

During its classical stage, the human disease begins abruptly with fever, headache, myalgia, and nausea and redness of the eyes [15]. These signs and symptoms can take one to three days. Other signs and symptoms appear in severe cases, including constipation, dizziness, irritability, restlessness, stomach distress, decreased urination, vomiting, and weakness. Children may exhibit seizures. The most extreme cases of yellow fever produce black vomit and the breakage of blood vessels throughout the body (hemorrhaging). This is sometimes seen as bleeding from the gums and nose. The black color of the vomit is due to decayed blood [8]. A remission stage follows the infection stage, usually five days after the end of the incubation period. The remission stage is indicated by a decrease in the disease signs and symptoms. It makes the patient believe that the body has fought off the disease and that he or she is getting better. This stage can last five hours to several days. Some people recover entirely from yellow fever at this stage. The intoxication stage is characterized by fever, jaundice, and bleeding from the nose, rectum, and vagina. Vomiting begins again, as does the slowing of the heart rate that was typical in the infection stage. The virus is now doing great damage throughout the body systems and kills cells of the kidneys, liver, and lungs. Organ failure can occur at this stage. Approximately 50% of people who progress to this stage die 7–10 days after onset, with progressive hepatic and renal failure, shock, delirium, and convulsions occurred at this stage [15].

DIAGNOSIS

Yellow fever Special laboratory should be implanted for effective diagnosis of the disease. According to World Health Organization recommendation, every country at risk of yellow fever outbreaks/endemic should have at least one national laboratory for diagnosis of the disease and in addition to this organization provides training programs to help medical staff and public health officials perform and understand the test results. These tests, called diagnostic tests, look for

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

direct evidence of the virus in the body. The viral genome, viral attachment proteins called antigens, and immune system proteins called antibodies will be measured by diagnostic tests made. Beside with other microscopic examination of the infected body, samples can be used to confirm yellow fever.

The viral genetic material is tested by collecting blood or tissue samples from the patient. The viral genome is found in very low concentrations in the body even in heavy infections, so a procedure called a polymerase chain reaction (PCR) is performed to make multiple copies of the viral RNA. A special modification of the PCR reaction called RNA amplification is performed because PCR was developed to multiply DNA. The RNA is then analyzed using a procedure called electrophoresis, by which molecules can be separated according to size and electrical charge as a means of identification. This technique is good for distinguishing between the different types of yellow fever viruses. The other diagnostic testing uses immunohistochemistry to identify the virus or antibodies. Immunohistochemistry is a chemical procedure that uses antibodies to detect the presence of disease organisms. The most common tests used in the detection of yellow fever virus is enzyme-linked immunosorbent assay (ELISA) and microsphere-based immunoassay (MIA). Both techniques use antibodies glued to a substrate to isolate and detect particular types of proteins. The antibodies used in ELISA and MIA stick specifically to yellow fever attachment proteins and antibodies against the yellow fever virus. The tests look for the presence of an antibody called immunoglobin G (IgG). Other types of tests serological examinations use blood cells and immune system components called complements to detect viral proteins or antibodies. Both tests have methods of detecting whether the viral proteins or antibodies are sticking to the test chemicals. The histopathological examination is also used for detection of yellow fever. Clinical testing for yellow fever can take several days, meaning that the disease can progress and worsen before the results are confirmed (Figure 3) [17,18].

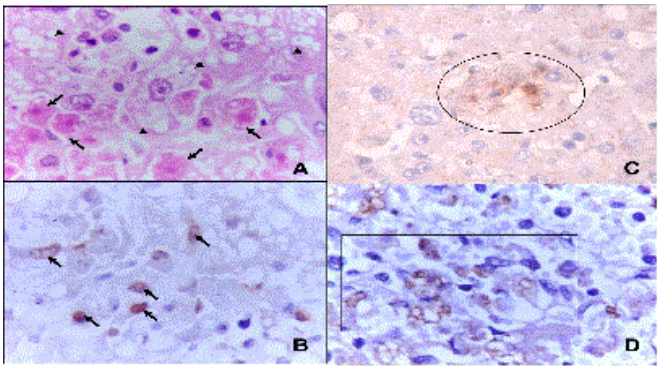

Figure 3. Human liver in fatal Yellow fever. (A) Councilman bodies (arrows) and steatosis (arrowheads) stained by hematoxylin and eosin, (B) Immunohistochemical staining showing hepatocytes in apoptosis (arrows) which correspond to Councilman bodies in A, (C) Apoptotic hepatocytes expressing FAS/APO-1 (circle) by immunohistochemical assay, (D) Immunohistochemical assay showing TGF-_ expressed in hepatocytes (rectangle).

ONE HEALTH APPROACH IN CONTROL AND TREATMENT

Data Yellow fever has no antiviral drug treatment. Supportive care is given in which patient become comfortable and reduces anybody damage caused by the disease. The typical supportive care includes giving plenty of water to make up for fluids lost during vomiting. Oxygen is also provided to make up for the gas exchange lost by the damaged lungs. Medications may be administered to regulate the blood pressure and the heart rate. Patients with severe yellow fever may need blood and kidney dialysis. Some patients need transfusions of blood liquids to replace proteins that improve blood clotting and healing of damage from hemorrhaging.

All stakeholders should cooperate on zoonotic disease spread between animals, humans and the environment and monitor and prevent major outbreaks [19].

PREVENTION AND VACCINES

A Vaccination is the main strategy in which yellow fever is effectively prevented in areas where the disease is epidemic [20] which provide high levels of protection, with seroconversion rates of 95%. The 17D Live attenuated vaccine strain is used and a single vaccination dose will be enough to provide long-term immunity [21,22].

Several vaccination strategies are used to protect against outbreaks: routine infant immunization; mass vaccination campaigns designed to increase coverage in countries at risk; and vaccination of travelers going to yellow fever endemic areas. A mass vaccination campaign is the most effective public health strategy to control yellow fever outbreaks [20].

Some reports verified that the yellow fever vaccine will result in serious contraindications such as the attack on the liver, the kidneys or on the nervous system, which will result in hospitalization, about 0.4-0.8 per 1,00,000 people

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

vaccinated. Peoples which have immune suppression disease like HIV/AIDS with less than 200/mm^3 CD4 cell count, individuals with age of greater than 60 years old and who have a thymus disorder should be given the vaccine after a careful risk-benefit analysis. Vaccination for yellow fever is not allowed for infants aged less than 9 months, pregnant women, and people with severe allergies to egg protein.

Vector control is another way in which the disease is controlled. The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites and water storage containers and other places where standing water collects. In addition to this reduction of mosquito population by using insecticides and larvicides in areas with high mosquito density is a way in which yellow fever vector can be controlled [20].

PROGNOSIS

The majority of diseased individuals will be asymptomatic or have a mild form with complete recovery. In the symptomatic course of the disease victim, individuals may recover but, weakness and fatigue may last for several months. Severe form disease, up to 20–50% will end with death. Those who recover from yellow fever generally have lasting immunity against subsequent infection.

CONCLUSION

Yellow fever is a viral hemorrhagic disease which is transmitted by mosquitoes. The disease is endemic in most African and South American countries. In countries with high risk of the disease, there should be a vaccination against yellow fever and control vector of the disease. Occasionally travelers who visit yellow fever endemic countries may bring the disease to countries free from yellow fever. In order to prevent such importation of the disease, many countries require proof of vaccination against yellow fever before they will issue a visa, particularly if travelers come from, or have visited the yellow fever endemic area.

REFERENCES

1. Frederick AM. Emerging infectious diseases. CDC. 1998;4.
2. Quan L, et al. Major emerging and re-emerging zoonoses in China: A matter of global health and socioeconomic development for 1.3 billion. Int J Infect Dis. 2014;25:65-72.
3. http://www.who.int/zoonoses/emerging_zoonoses/en/
4. http://www.who.int/en/news-room/fact-sheets/detail/yellow-fever
5. Elizabeth DB. Yellow Fever: Epidemiology and Prevention. Clin Infect Dis. 2007;44:850-856.
6. Luciano ZG. Yellow fever outbreak in Brazil. Braz J Infect Dis. 2017;21:123-124.
7. Sean W, et al. Yellow fever cases in Asia: Primed for an epidemic. Int J Infect Dis. 2016;48:98-103.
8. Brain RS, et al. Deadly Diseases and Epidemics: Yellow fever. 2010.
9. Kotar SL, et al. Yellow Fever: A World Wide History. 2017.
10. Jordi R, et al. Is the re-emergence of yellow fever a new global public health threat. Med Clin. 2016;147:492-494.
11. Christina LG, et al. Yellow Fever: A Reemerging Threat. Clin Lab Med. 2010;30:237-260.
12. Emile F, et al. Advances and controversies in yellow fever vaccination. Ther Adv Vacc. 2013;1:144-152.
13. Catharine IP, et al. Yellow Fever: Once Again on the Radar Screen in the Americas. N Engl J Med. 2018;376:1397-1399.
14. Moritz UGK, et al. Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015-16: A modelling study. Lancet Infect Dis. 2017;17:330-338.
15. James MN, et al. Fenner's Veterinary Virology. Elsevier Inc. 2011;4.
16. https://www.cdc.gov/yellowfever/transmission/index.html
17. Monath TP, et al. Yellow fever. J Clin Vir. 2015;64:160-173.
18. https://www.cdc.gov/yellowfever/healthcareproviders/healthcareproviders-diagnostic.html
19. Eskild P. Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential. Int J Infect Dis. 2016;47:5-9.

e-ISSN: e-ISSN:2319-9865
p-ISSN: p-ISSN:2322-0104

20. https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-outbreak-yellow-fever-angola-24-march-2016

21. Weiten RW, et al. A Single 17D Yellow Fever Vaccination Provides Lifelong Immunity: Characterization of Yellow Fever Specific Neutralizing Antibody and T-Cell Responses after Vaccination. Plos One. 2016;11:1-18.

22. Alan MW, et al. T-Cell Mediated Immunity towards Yellow Fever Virus and Useful Animal Models. Viruses. 2017;9:14.