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Ebola Virus as a Potential Bio-Weapon: A Fantasy or a Possibility?

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ABSTRACT

In addition to the devastations created by the Ebola epidemic of 2014, the rumors about the misuse of Ebola virus as a potential bio-weapon have already put fear among the common masses. The aim of this review was to find the evidences, from the medical literature, against and in support of the potential of Ebola virus to be used as a bio-weapon. The factors which oppose this possibility were seen to be: lack of epidemiological evidence of aerosol infectivity of Ebola, slow spread, availability of rapid diagnostic methods, and difficulty of access to nonhuman hosts and bio safety laboratories as well as environmental instability of Ebola virus. On the other hand, increased morbidity and mortality of Ebola virus disease, its spread by interpersonal contact, evidence of aerosol spread in Non-human Primates and possibility of the same in humans by harmful mutation of any Ebola strain, and lack of effective vaccines/drugs raise this possibility. We have also suggested some public health measures to be taken beforehand in order to deal with such a global emergency if it ever occurs.

Keywords: *Ebola, Biowarfare, Bioweapon, Bioterrorism, Ebola Bomb, Ebola Virus Disease*

INTRODUCTION

Ebola Virus Disease (EVD) or simply, Ebola is a type of viral hemorrhagic fever caused by 5 subtypes of Ebola virus (family filoviridae) [15] The hosts include chimpanzees, gorillas, bats and infected humans [2]. It is usually transmitted by direct contact with body fluids and/or infectious blood [16]. Its pathogenesis starts with the up

regulation of tissue factor and disseminated intravascular coagulation, thus, leading to bleeding manifestations [2]. The clinical involvement is usually multisystem and finally leads to death [2]. The diagnostic methods commonly used are ELISA, RT-PCR, Indirect fluorescent antibody test (only acute cases) and skin biopsies (post-mortem diagnosis) [17][2]. Currently, there is no effective vaccine or FDA-approved treatment for Ebola Virus Disease [12]. Conservative management leads to recovery only in less number of cases and the recovered cases are neither proved to have lifelong immunity against other species of Ebola virus nor are they free from long term complications [8]. Here, we describe in detail whether it is possible that the Ebola virus could be misused by terrorists or governmental organizations and if it is so, what should be our priorities of bio-defense at this stage.

METHODS

We searched PubMed database extensively using the terms (Ebola) combined separately with the terms (Biowarfare), (Bioweapon) and (Bioterrorism). The filter for publication dates was kept as "01-Jan-1976 to 26-Nov-2014". The following numbers of papers were obtained using these Boolean search terms:

(Ebola) AND (Biowarfare) = 50

(Ebola) AND (Bioweapon) = 01

(Ebola) AND (Bioterrorism) = 63

Out of these 114 papers, 34 were found to be duplicate copies of each other. Thus, a total of 80 papers were reviewed.

RESULTS

There is an ongoing conflict of views amongst various scientists over the possibility of Ebola virus to be used as a bio-warfare agent [28]. On one hand, we have workers who are supporting this possibility and exaggerating the fact that Ebola virus has been labeled as CDC Category A Bioterrorism agent, NIAID Category A priority agents, Select agents & Biosafety level 4 pathogens [1]. On the other hand, questions are being raised on this possibility on account of the lack of its evidence-based aerosol infectivity in humans, environmental instability and a highly difficult and dangerous process required to weaponize it.

Ebola bomb as a fantasy

1. Aerosol infectivity

Various epidemiologic studies done to gather information on air borne spread of Ebola virus (from infected humans to healthy humans) have failed to reveal any considerable evidence [10]. The reason has been attributed to the fact that Ebola virus-affected humans generate insufficient amounts of infectious aerosols. Thus, with very low amount of these aerosols generated, there is almost no threat posed to the people around them [2].

2. Spread is slow

A study was published in 2004 about the reproductive rate of Ebola virus [4]. It was estimated that compared to Spanish flu, it has a lower reproductive rate and its generation interval is comparatively longer. Ebola was also seen to have a reproductive rate much lower than that of

the measles, the fastest spreading disease in the history of mankind. Hence, even if a bioterrorism attack occurs, there is much opportunity for controlling the spread.

3. Rapid diagnostic capability

Even if somehow an attempt of bioterrorism attack with strains of Ebola occurs, there are a many sensitive and specific diagnostic techniques available. ELISA [5] and RT-PCR [6] are two such techniques which give quick results. Thus, these make the detection of Ebola virus easy and hence, the attack can be made unsuccessful by taking proper precautions, supportive management and mass treatment at the earliest possible time.

4. Obtaining Non-human hosts

The Non-human hosts of Ebola virus are usually wild fruit bats, Chimpanzees and also duikers (African antelopes) [2]. It would be quite difficult to obtain them for virus extraction for the purpose of making an Ebola bio-weapon. There is high risk that in this process, the persons obtaining the infected animal or extracting virus from them, may catch the disease apart from the fact that dealing with wild animals proves to be very difficult.

5. Laboratory for weaponizing and dealing with Ebola

There are only around two dozen Biosafety Level 4 laboratories in the world as per the Federation of American Scientists [7]. The access to these laboratories by terrorists is highly improbable. Besides, constructing such a laboratory is both important (as Ebola is a Biosafety Level 4 pathogen) [1] and at the same time impossible for the bioterrorists, as it needs a large amount of tested equipments and experienced workers in the field of infectious diseases.

6. Not capable of enduring environmental conditions

Ebola is a not a robust pathogen as far as environmental conditions are concerned. Even if an attack of bioterrorism occurs, the climatic conditions are almost always unfavorable for its existence. It only persists in blood at room temperature for weeks. Also, the virus is highly sensitive to lipid solvents, detergents, acidity and heat and can stay on surfaces for around 24 hours. [2]

Ebola bomb as a possibility:

1. Morbidity and mortality rates are very high

This is one of the important characteristics of bioterrorism Category A pathogens. As on November 26, 2014, the CDC has recorded a total case count 15,319 and a death count of 5,444 in the countries of Guinea, Liberia and Sierra Leone [8] during the 2014 Ebola epidemic, the largest in history [8]. Figure 1 and Figure 2.

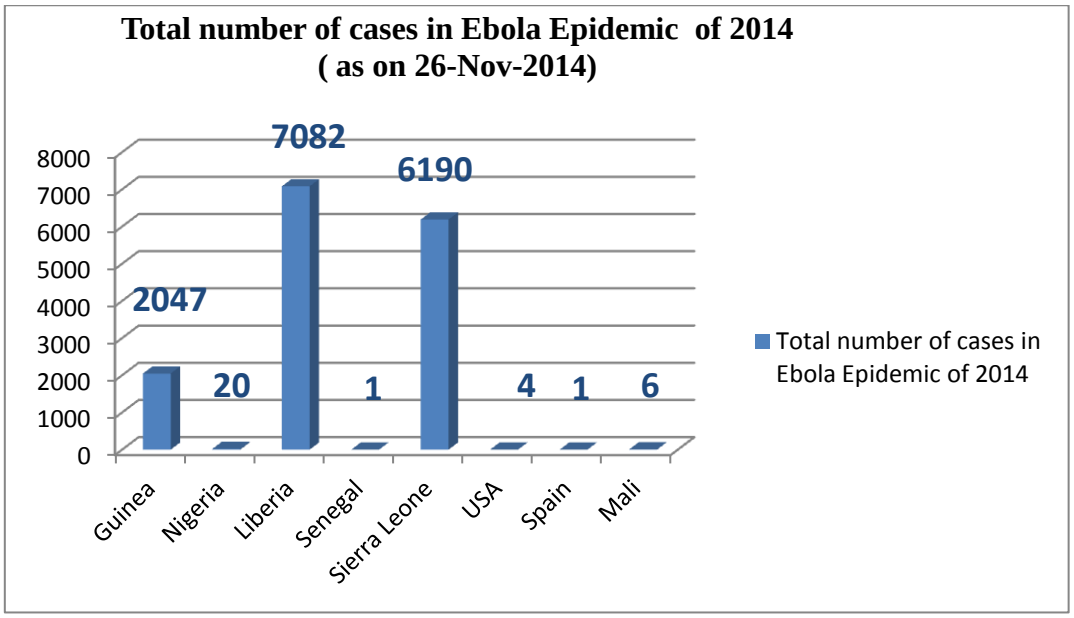

Figure 1: Total number of cases in Ebola Epidemic of 2014 as on 26-Nov-2014

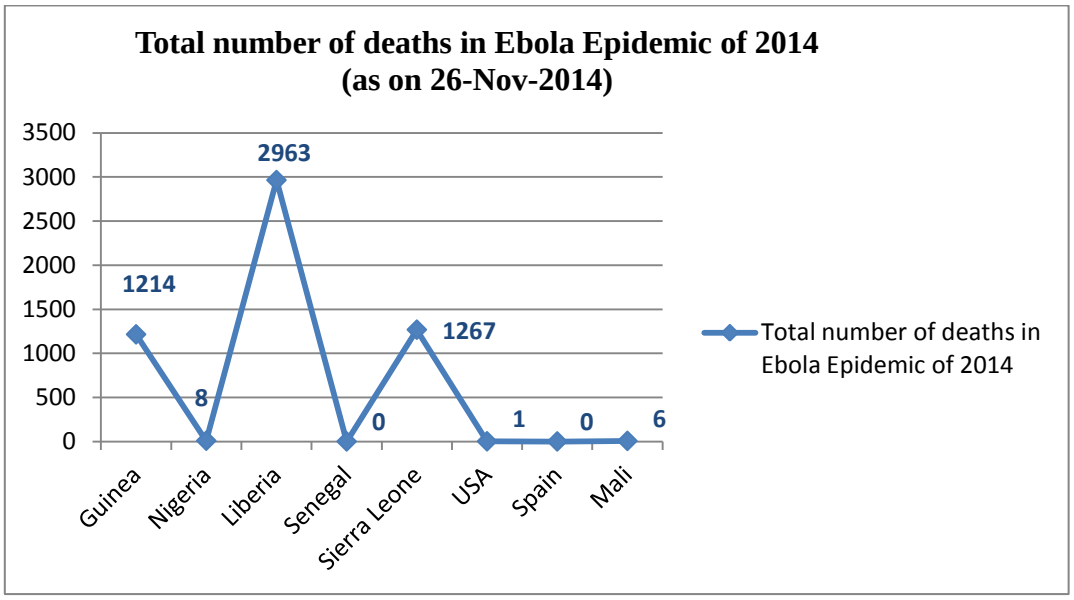

Figure 2: Total number of deaths in Ebola Epidemic of 2014 as on 26-Nov-2014

2. Spread by interpersonal contact occurs

If somehow a bioterrorism attack of Ebola virus happens over a highly populated area, it is extremely contagious by person to person contact, which includes bodily fluids, needles and syringes [8]. So, it not only risks the lives of family members and caretakers, but also puts at stake the health of physicians and nurses treating the patients [2].

3. Possibility of aerosol spread

Jaax N et al conducted a study (published in LANCET in 1995), which proved the aerosol transmission of Ebola virus to two control Rhesus monkeys (*Macaca mulatta*) kept in the same room as Ebola inoculated monkeys [9]. Another study on Rhesus macaques by Twenhafel NA et al in 2013 proved the aerosol transmission in them by exposing them to infectious aerosols artificially

created within a Bio-safety Level 4 laboratory [10]. Thus, there is a possibility of widespread aerosol infection following an attack with Ebola virus bomb. Another aspect of aerosol transmission is the mutation of its subtype, the Ebola-Reston (EBO-R) virus. Although it causes only subclinical infection in humans, it has the potential for generating highly infectious aerosols [11]. So, if a strain of Reston virus is mutated, a dangerous bio-weapon is likely to fall in the wrong hands for humanity to perish.

4. Universally available effective vaccine is lacking

There is currently no FDA- approved vaccine or antiviral drug available for Ebola virus disease [12]. This is the most dreadful fact, because this way, the bioterrorism attack is expected to have a long lasting and drastic outcome. It is not clear, whether the people who have recovered from Ebola with supportive treatment, are immune for life or are still likely to get infected with other species of this virus [8]. Furthermore, the recovered patients have developed long term complications [8]. As a bio-warfare agent, Ebola has a potential of increasing the fatalities and decreasing the quality of life of people. Another fact which cannot be ignored here is that Ebola virus can be misused by the government of any country, as a mark of dominance like the nuclear weapons, if workers of such a country secretly develop vaccines and treatment for its own people.

5. Potential for causing panic among people

The Ebola epidemic of 2014 has already created much panic among the people because of the dreadful images of bleeding from every orifice, long-term complications, increasing amounts of deaths in West Africa and lack of FDA-approved or effective treatment modalities. The perceived notion of Ebola virus to be used as a bioterrorism agent is highly frightening for common masses [13, 47].

6. Virus availability and production feasibility

The Virus can be isolated from any secretions from the live host, such as urine [10]. It is possible to synthesize Ebola from in silico sequences diffused over the internet [14]. So, the accessibility from the high security laboratories could be overlooked in this era of rapid progression of knowledge. Another threat is posed by the creation of 2nd generation bio-weapons by mutating the already available strains of Ebola [14]. Furthermore, there is a possibility of de-novo synthesis of Ebola virus strains by molecular breeding [14]. Hence, these factors raise the possibility of manufacture of Ebola-bomb by terrorists and governmental organizations.

7. Traditional burial practices

Ebola virus transmission is also known to occur through the contact with infected cadavers and during the traditional burial practices in Africa during the Ebola epidemic [2]. Since the death toll rises in an Ebola outbreak and the people cannot shun this tradition, the possibility of the mean Ebola-Bomb being effective raises.

8. Process of weaponization is easy

Apart from the access to Biosafety Level 4 laboratories, there is no need of too many

technological resources for the manufacture of Ebola biowarfare agents and these appear to be accessible to terrorists or governments, due to easy use, low cost and widespread knowledge of research on Ebola in the scientific literature [14].

DISCUSSION

Ebola virus is a single stranded RNA virus belonging to the family Filoviridae. There are 5 species (named after the original sites of recognition) of Ebola virus: *Côte d'Ivoire (Tai Forest) ebolavirus, Bundibugyo ebolavirus, Zaire ebolavirus, Sudan ebolavirus* and *Reston ebolavirus* [16] This virus was first observed in 1976 when it caused simultaneous epidemics in Sudan (50% mortality rate) and Zaire (90% mortality rate) [2]. Besides the infected humans, the hosts include non-human primates like chimpanzees, gorillas and fruit bats [2]. Its transmission is said to occur through contact with bodily fluids of infected patients [16]. It spreads through infected needles and syringes and is present in semen for up to 3 months, according to latest CDC report, in recovered patients, hence sexual spread can occur [8]. Touching the infected cadavers also lead to spread of disease [2].

The pathogenesis is said to be incited with the up regulation of tissue factor and disseminated intravascular coagulation [2]. It involves almost every organ as it replicates in all cell types. The pro-inflammatory cytokines released have their contribution in raising the severity of the illness. There occurs liver necrosis and interstitial pneumonitis. Cerebral glial nodules are also formed [2]. As research on Ebola virus has accelerated, it has been increasingly found that these viruses make use of a combination of already familiar and apparently newer ways to disturb our immune system. Ebola virus and other members of filoviridae have thus provided a new lens for examining the immune system itself [42].

After around 7 days of catching the virus (incubation period 2-21 days), patient becomes febrile with severe headache [16]. The patient also develops muscle pains, malaise, nausea, vomiting, chest pain, diarrhoea, prostration with depressed mentation . Rash is seen after about 7 days of illness which desquamates soon. Bleeding may be just mucosal/into the skin but overt bleeding is not uncommon as the virus colonizes blood vessels and causes them to become porous. Finally, the fever breaks in 10-12 days of conservative treatment and recovery may occur. Hepatomegaly, Conjunctival injection, uveitis and orchitis may also be seen [2][16].

ELISA is very sensitive and sturdy method of diagnosis of Ebola virus infection [17]. RT-PCR is useful in a quarantine/geographic spread and if additional sensitivity is needed in some cases, it provides the same [18, 41]. Indirect Fluorescent Antibody test may be required in acute cases only [2]. The post mortem diagnosis is based on the skin biopsies of the cadavers [2].

There is no licensed and effective treatment or vaccine for the Ebola virus to the current date. [12]. Supportive treatment aims at the proper treatment of shock and prevention of secondary infections [19]. Although the passive immunization for this virus was a little bit successful in the year 2012, it was only possible after more than 15 long years of failed attempts which lead to skepticism regarding the potential benefit of such approach [29].There is

ongoing research in the development of anti-viral drugs like inhibitors of tissue factor and activated protein C which have proven effective in Rhesus monkeys [20]. Others include the inhibitors of cell entry, monoclonal antibodies and Antisense oligomers [21, 22, 45, 46]. The first study dealing with the topical immunization through respiratory tract against Ebola virus was published in 2007. Thus, this was the first attempt at achieving prevention of a viral hemorrhagic fever infection in a primate model through topical route [43]. There is however no specific prophylactic agent against this virus [49].

In the field of vaccine development, Inactivated whole virion, Venezuelan equine encephalitis virus replicons, Adenovirus-vectored-Ebola glycoprotein gene, DNA vaccines, Human Para Influenza Virus 3 based vaccine, Vesicular Stomatitis Virus based Ebola vaccine and Virus like particles are gaining some fame yet not considerably effective in humans [16, 34, 39, 40]. A VSV-based Ebola vaccine was successfully used in 2010 to manage a potential laboratory exposure and can be used in the control of secondary transmission during the naturally occurring outbreaks or any sort of deliberate release. [37, 44]. Favipiravir or T-705 which was recently reported to give 100% protection against the aerosolized Ebola virus E718, has a great likelihood of getting licensed for use against the influenza in the near future. It could also be used with a new indication for the filovirus infection like that of Ebolavirus [30].

Since an ideal bio-defense vaccine should be able to elicit protective immune responses in 1-3 doses. It should be unaffected by pre-existing immunity to any of the vaccine components. Besides, it should be amenable to combination and multi-agent formulation. It also needs to be safe for all the populations and the environment. DNA vaccines for Ebola virus can potentially meet almost all of these requirements [38].

In one study, chloroquine, was found to protect mice against Ebola virus challenge when introduced in them in vivo. It is also known for its property of disrupting entry and replication of two or more viruses in vitro [31]. In other study, Filovirus GP Fc fusion proteins were claimed to be safe, efficacious and simply cost effective vaccine against Filovirus infection for human use [32]. Another study revealed superb potential for a plant-expressed Ebola Immune Complex as a human vaccine [33]. For patients that are already infected but before the onset of symptoms, a post exposure prophylaxis strategy against Ebola virus that includes both active as well as passive immunization similar to human rabies treatment could be considered [35]. Post-exposure protection is not only important in outbreak and biodefense settings, but also in the clinical and laboratory settings in case an accidental exposure occurs [36].

The bio-weapons have been prepared in the past from the various dreadful pathogens like Anthrax [23], which is also a CDC Category A agent like Ebola virus [24][1]. However, unlike Anthrax, Ebola is environmentally less stable [2]. Although, there is no clear-cut historical record of Ebola virus being used as a bio-weapon, except the fact that the former Soviet Union is reported to have evaluated Ebola virus as a weapon in the past [48].

The pathogens have been mutated in the past to create useful/dangerous strains and they are even

likely to mutate in their natural state [25]. There is a chance that a species of Ebola virus mutates [26] and in such a way that it becomes highly contagious in aerosol form. On the positive side, there is also a chance that it loses its potential to cause a clinical disease. However, we cannot risk human lives based on a mere chance of mutations and we do have to take into consideration the possibility of dangerous mutation and/or its misuse as a deadly bio-weapon. The Ebola virus epidemics can be halted by the process of patient isolation and instituting standard control of infection and barrier nursing procedures [50]. Thus, following measures are suggested:

1. Use of Rapid diagnostic methods for Ebola virus detection in an outbreak (which fortunately are available).
2. Hasten the research work for pre-exposure prophylaxis and vaccine development.
3. Post exposure vaccines and medications.
4. Effective supportive treatment that would decrease the morbidity and development of complications.
5. Universal precautions while handling the patient (as hospitals have been responsible for increasing the severity of epidemics in past)
6. Effective and reliable antiviral drugs against Ebola virus which would decrease the morbidity and mortality.
7. Use of HVAC filters in large public buildings for detection of Ebola virus in case of a bioterrorism attack [27].

Hence, it is clear that we need more resources for research, materials and manpower in order to tackle this global menace.

CONCLUSIONS AND OUTLOOK

A lot of questions have been raised against the possibility of an Ebola-bomb. However, the lack of treatment of Ebola, possibility of aerosol spread and increased morbidity and mortality along with other factors raise the likelihood of the devastation that would be caused by such an attack of bioterrorism. The question that arises is: Do we have the necessary precautionary and treatment strategies to deal with such a devastating global emergency? We should plan the effective universal precautions that would prevent the nosocomial spread of Ebola. The development of proper vaccines and life-saving anti-viral drugs should really be paced up. Finally, the governments and their departments of bio-defense should not overlook such a globally disastrous possible issue which could wipe the mankind off the surface of the planet in less than a year.

List of abbreviations

FDA = Food and Drug Administration

ELISA = Enzyme Linked Immuno Sorbent Assay

RT-PCR = Reverse Transcriptase Polymerase Chain Reaction

CDC = Centers for Disease Control and Prevention

NIAID = National Institute of Allergy And Infectious Diseases

DNA= deoxyribonucleic Acid

HVAC = Heating, Ventilating and Air conditioning

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