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Ebola disease: an international public health emergency

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ABSTRACT

Ebola virus disease (EVD), previously known as Ebola hemorrhagic fever, is a severe illness caused by Ebola filovirus, and is often fatal if left untreated. The first case of the current EVD was diagnosed in Guinea in March 2014, and since then it has spread to Sierra Leone, Liberia, Nigeria, and Senegal. The current review has been performed with an objective to explore the magnitude of the current Ebola virus epidemic and identify the multiple determinants that have resulted in the exponential growth of the epidemic. An extensive search of all materials related to the topic was done for almost two months (August-October) in Pubmed, Medline, World Health Organization website and Google Scholar search engines. Relevant documents, reports, recommendations, guidelines and research articles focusing on the different aspects of Ebola virus and its current outbreak, published in the period 2002-2014 were included in the review. Keywords used in the search include Ebola virus, Ebola virus disease, Ebola hemorrhagic fever, Ebola vaccine, and Ebola treatment. The current EVD epidemic has turned out to be extensive, severe, and uncontrollable because of a delayed response and ineffective public health care delivery system. In fact, multiple challenges have also been identified and thus a range of interventions have been proposed to control the epidemic. In conclusion, the 2014 epidemic of EVD has shown to the world that in absence of a strong public health care delivery system even a rare disease can risk the lives of millions of people. The crux of this epidemic is that a large scale and coordinated international response is the need of the hour to support affected and at-risk nations in intensifying their response activities and strengthening of national capacities.

1. Introduction

Ebola virus disease (EVD), previously known as Ebola hemorrhagic fever, is a severe illness caused by Ebola filovirus, and is often fatal if left untreated[1]. The first outbreak of EVD was reported in the year in 1976 in two different locations in remote villages in Central Africa-Nzara in Sudan, and Yambuku in Democratic Republic of Congo (reported in a village near the Ebola River, from which the disease takes its name)[1,2]. However, the most recent outbreak, is the largest and most complex Ebola outbreak, and is being observed in both urban and rural areas of West-Africa[1].

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The first case of the current EVD was diagnosed in Guinea in March 2014, and since then it has spread to Sierra Leone and Liberia across the border; to Nigeria by air traveler; and to Senegal by land traveler[1,3,4]. In addition, a separate, unrelated Ebola outbreak has originated in Boende, Democratic Republic of Congo in August 2014[1]. In fact, the number of cases and deaths in the current outbreak was reported by the end of September. A total of 5 833 confirmed cases and 2 833 Ebola associated deaths have been reported, which includes 355 cases and 194 deaths among health professionals-clearly exceeded the estimates of all similar previous outbreaks[1,2,5-7]. Furthermore, analysis of the recent trends suggests that the current epidemic of EVD has grown at an exponential rate since May 2014, with the number of new cases getting doubled every 20-30 days[8].

However, amidst extensive mobility and air travel in West Africa, extremely weak public health infrastructure, absence of adequate number of diagnostic and treatment centers, and limited involvement of members of community, there is a definite potential risk that EVD could reach other countries in the region and

beyond[7,8]. In addition, the case fatality rate in EVD is extremely high, almost 90% in some outbreaks (varying from 25% to 90%), and thus members of the family Filoviridae have been classified as Category A potential bioterrorism agents by the Centers for Disease Control and Prevention[9,10]. Furthermore, aftermaths in the form of social disruption, deteriorating impact on the standard medical care required for management of other common conditions, significant financial burden, sense of financial and health insecurity among community, daily hardship in the quarantine zones, riots, uncollected bodies, and emergence of myths and misconceptions have also been reported[1,4,7,8]. Owing to the presence of the above-mentioned factors, the World Health Organization (WHO) Director-General declared the current outbreak in West Africa as an international public health emergency on August 8, 2014[11,12]. Subsequent to this declaration, Heads of the involved state have declared a national emergency, activated national disaster-management mechanisms, and even established emergency treatment centers[11].

The current review has been performed with an objective to explore the magnitude of the current Ebola virus epidemic and identify the multiple determinants that have resulted in the exponential growth of the epidemic. In addition, multiple challenges have been identified and based on the same a comprehensive package of interventions have been proposed which, if implemented strategically, will reduce the burden of the disease.

2. Methods

An extensive search of all materials related to the topic was done for almost two months (August-October) in Pubmed, Medline, WHO website and Google Scholar search engines. Relevant documents, reports, recommendations, guidelines and research articles focusing on the different aspects of Ebola virus and its current outbreak, published in the period 2002-2014 were included in the review. A total of 49 studies similar to current study objectives were identified initially, of which, five were excluded on account of irrelevance to the present study because of the unavailability of the complete version of the articles. Overall 44 articles were selected based upon the suitability with the current review objectives and analyzed. Also, multiple guidelines pertaining to different aspects of the EVD were referred to explore all measures which can be implemented to reduce the magnitude of the disease. These identified articles, guidelines, and recent reports were then re-grouped into different sections namely Overview of Ebola virus (Ebola virus, Resistance, Reservoir, Transmission, Period of communicability, Pathogenesis, Clinical features, Case fatality rate, Diagnosis, Prevention and Control, Treatment); Standard case definitions; The current epidemic; Identified challenges; Lessons learnt; Comprehensive package of interventions; Implications for practice and implications for research. Keywords used in the search include Ebola virus, Ebola virus disease, Ebola hemorrhagic fever, Ebola vaccine, and Ebola treatment.

3. Ebola virus: overview

3.1. Ebola virus

According to the International Committee on Taxonomy of Viruses, Ebola virus is a non-segmented, enveloped negative-stranded ssRNA virus of the family Filoviridae (order Mononegavirales)[13]. It has a uniform diameter of 80 nm, and can form twisted filaments (has tubular nucleocapsid) of 800 to 1 400 nm in length[13]. The virus family Filoviridae comprises of three genera, namely *Cuevavirus*, *Marburgvirus*, and *Ebolavirus*. Furthermore, the genus *Ebolavirus* is classified into five species-Sudan, Zaire, Bundibugyo, Reston, and Tai Forest, of which the first three have been associated with large outbreaks in Africa, and the current outbreak has been caused by the Zaire species[1,4,14]. Over the years, Ebola virus has gradually evolved because of the multiple genomic mutations[15].

3.2. Resistance

The Ebola virus can be easily eliminated by heat, alcohol-based products, and sodium hypochlorite (bleach) or calcium hypochlorite (bleaching powder) in appropriate concentrations[16]. Thus, it is recommended to cook meat products properly and maintain hand hygiene to avoid transmission of the disease[1,17].

3.3. Reservoir

In endemic settings, Ebola virus persists in a reservoir species like apes, man, and perhaps other mammalian species[18]. During the country's long years of civil unrest, natural resources were exploited and thus ecology of the forests was altered, and fruit bats (potential natural reservoir of the virus) moved closer to human inhabitations[18,19]. From fruit bats, the virus can pass to different primate species (gorilla, chimpanzee and macaques), and from bats or apes the virus reaches humans, who develop EVD after a variable incubation period of 2-21 days[1].

3.4. Transmission

Ebola virus is transmitted to the human population through close contact with various body fluids of infected primate species or fruit bats, found ill or dead in the rainforest[1]. Subsequently, Ebola can spread from man-to-man through direct contact (*viz*. broken skin or mucous membranes) with different body fluids of infected people, and with surfaces and materials contaminated with these fluids[1,16,20]. Most of the health care professionals while treating patients acquire the infection because they do not practice universal standard precautions[1]. Burial ceremonies in which people have contact with body of the deceased persons can also play an important role in the disease transmission[21,22]. In addition, humans can acquire infection from eating food/animal products, if they are not properly cooked[17].

3.5. Period of communicability

Humans are not infectious until they develop symptoms[1]. Individuals remain infective till their body fluids (*viz*. blood, saliva, urine, breast milk, semen, *etc*.) contains the virus[1,18]. Men who have recovered from the disease should avoid unprotected sex for almost three months after recovery from the disease[1,18].

3.6. Pathogenesis

Ebola virus generally targets multiple host cells including hepatocytes, endothelial cells, macrophages, dendritic cells, *etc*[23]. Overall, alterations in the immune system play a significant role

in the fatal infection process of the virus[23]. The Ebola virus tends to eliminate lymphocytes through the so-called bystander apoptosis mechanism, and at the same time sustains useful cells (*viz*. monocytes, macrophages, dendritic cells and endothelial cells) [19]. The release of inflammatory mediators increases vascular permeability, and the viral envelope glycoprotein GP acts as a key indicator of vascular injury[24].

In fact, fatal Ebola virus infection is generally characterized by the extensive immunosuppression (resulting because of the nonspecific and the deleterious innate immune response, and minimal or nil stimulation of an antigen-specific adaptive response) [23]. Furthermore, the "cytokine storm" with immune suppression of helper and suppressor lymphocytes is the proposed mechanism for production of the terminal hemorrhagic fever[25,26].

3.7. Clinical features

After an incubation period of 2-21 days, patients generally present with nonspecific flu-like symptoms, like fever, chills, malaise, sore throat, muscle pain, and headache[1]. This is followed by vomiting, diarrhea, appearance of erythematous maculopapular rash around the fifth day of the illness, and symptoms of impaired kidney and liver function[4]. Extensive viral replication results in appearance of systemic, vascular (both internal and external bleeding), and neurologic manifestations, and necrosis of the liver, spleen, kidneys, and gonads has also been reported[4,27]. In fatal cases, death is caused by multiple system failure[1,18].

3.8. Case fatality rate

A variable extent of case fatality has been associated with different species of Ebolaviruses-Zaire (57%-90%), Sudan (41%-65%), and Bundibugyo (40%)[28]. However, Tai Forest and Reston species have not been associated with any fatal infections till date[28]. Findings of a study performed on the outbreak related data of Zaire, Sudan, and Bundibugyo Ebola species revealed that the case fatality rate was approximately 65.4%, with the highest case fatality rate for the Zaire species[10].

3.9. Diagnosis

The final confirmation of the disease can be done by only laboratory investigations[1]. For early detection of Ebola virus in suspect or probable cases, detection of viral RNA or viral antigen are the recommended tests[29]. Laboratory-confirmed cases must test positive for the presence of the Ebola virus, either by detection of virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR), and/or by detection of Ebola antigen by a specific antigen detection test, and/or by detection of Immunoglobulin M (IgM) antibodies directed against Ebola[29]. Other investigations like antibody-capture ELISA, antigen-capture detection tests, serum neutralization test, electron microscopy, virus isolation by cell culture, have also been proposed to reflect confirmation of symptoms[1,29].

In addition, blood reports suggest low white blood cell and platelet counts and elevated hepatic enzymes[18]. Furthermore, research findings of a study suggested that pediatric patients who survived had higher levels of the chemokine, normal T-cell count, and lower levels of plasminogen activator inhibitor 1, and soluble intracellular/vascular cell adhesion molecule[30].

3.10. Prevention and control

The outbreak of Ebola virus can be prevented or controlled by adoption of a wide range of interventions namely standardized case management, surveillance and contact tracing for 21 d, a good laboratory support, safe burial of the deceased, maintaining good personal hygiene and environment sanitation, and social mobilization in the form of community engagement by creating awareness among them about risk factors for Ebola infection and protective measures that individuals should take (*viz*. use of personal protective equipments while taking care of ill patients, regular hand washing, consuming thoroughly cooked food, *etc*.) to minimize human transmission[1,3,5,7,12,16-18,31]. Administration of an effective vaccine to the population at risk (like health workers, family members or others in close contact with infected people, individuals who have direct contact with the body of the deceased, *etc*.), can deliver encouraging results, nevertheless no vaccine is available currently[32,33].

3.11. Treatment

Despite of extensive research, no specific treatment (licensed antiviral drug) is available for the management of victims of Ebola virus disease[32,34]. Hence, current line of management of EVD is purely symptomatic[18]. However, positive outcome have been obtained in laboratory-infected mice for the antiviral drug favipiravir[35].

4. Standard case definitions

4.1. Confirmed case

A suspected case was diagnosed with laboratory confirmation (positive IgM antibody, positive PCR or viral isolation)[36].

4.2. Suspect case

A suspect case is any person having had contact with a clinical case and presenting with acute fever (>38 ˚C), or having had contact with a clinical case (suspect, probable or confirmed), and presenting with three or more of the symptoms (*viz.* headache, abdominal pain, generalized or articular pain, intense fatigue, difficulty in breathing, nausea or vomiting, hiccups, loss of appetite, miscarriage, diarrhea) or any person with unexplained bleeding or miscarriage, or any unexplained death[36].

4.3. Probable case

A probable case is either a suspect case that is known to have had contact with a known case (suspect, probable, or confirmed), or a patient that is, on clinical and/or epidemiological grounds, very likely to have Ebola infection[36].

4.4. Alert case

In community-based surveillance, health workers have been trained to look for alert cases (*viz*. illness with onset of fever and no response to treatment of usual causes of fever in the area, or at least one of the following signs: bleeding, bloody diarrhoea, bleeding into urine or any sudden death). On identification of an alert case (living or dead-make arrangements for a safe burial), case is reported to the surveillance team, sample is collected, case is notified to concerned health authority, and a list of contacts of the suspected case is prepared who are then followed-up for 21 d after exposure[37].

5. The current epidemic

5.1. Origin of the epidemic

Although, most of the reports suggest that first case of the current Ebola virus epidemic was diagnosed in March 2014, prior to that in December 2013, a 2-year-old boy died in the remote Guinean village of Meliandou with an illness characterized by fever, black stools, and vomiting (later on confirmed as the first case of EVD in West-Africa) [19]. In the similar context, the forest background of the affected area cannot be ruled out where people have destroyed forests as a part of civil unrest and unknowingly moved closer to the Ebola virus[18,19]. Different hypotheses have been proposed for the origin of the disease in Guinea, nevertheless no one seems to be convincing enough[38].

5.2. Why the current EVD epidemic is so extensive, so severe, and so intractable?

Multiple explanations have been provided by the WHO, the heads of the affected countries, and by the stakeholders to suggest that why a small outbreak has eventually become a public health emergency, with an enormous potential to spread across the globe.

1. Delayed response: The magnitude of previous outbreaks has not been extensive owing to the implementation of preventive and control measures at an early stage of the outbreak[2]. Adequate preparedness by the health authorities and implementation of a scientific response developed on the basis of infected individuals' movement patterns, social interactions, beliefs about disease causation and trust in authorities, could have remarkably influenced the extent of transmission[39].

2. Poverty and ineffective public health care delivery system: Three of the affected nations-Guinea, Liberia, and Sierra Leone, are among the poorest in the world, and have recently emerged from years of conflict and civil war, owing to which their public health system is incapacitated in most of the regions of the nation. In most of the settings, there are no isolation wards and existing hospitals do not having adequate infection control measures[40].

3. Human resource constraints: In contrast to the WHO recommendations for the doctor-population ratio, only 1-2 doctors are available to cater health care that needs for 0.1 million people. To further complicate the situation, most of these doctors are concentrated in urban areas. Even if the contacts of the cases are listed and traced out, not an adequate number of health care personnels are available to ensure their follow-up for the recommended period of time[40,41].

4. Lack of employment opportunities: This fact can be again linked back to the prevalent poverty in most of these settings, because of which people have to explore vocational opportunities in different areas. Most of the people migrate across the borders (hot zone) of Guinea, Liberia, and Sierra Leone, where transmission is intense and thus people continue to re-infect each other[7,40].

5. Poor community awareness: Most of the community members lack adequate knowledge about the potential risk factors and do's & don'ts for cases and their contacts. This problem is further aggravated because most of the affected people are illiterate and have never been exposed to basic education services[3,8].

6. Fear: In the absence of community enlightenment and very high fatality rates (not only among the members of the community, but even health care professionals, including doctors), a sense of fear has developed among the masses. Currently, fear remains the most difficult barrier to overcome and most of the contacts of the infected persons are not approaching health centers, but to the traditional healers for the management of their complaints. In fact, reports have even suggested that diagnosed patients have also left the treatment centers. Furthermore, owing to the fast spread of panic and rumor (faster than the virus itself), the security of national and international response teams has become questionable amidst the existing epidemic[11,12,40].

7. Rituals and traditional practices: In these areas, a long-standing practice was to involve close contact with highly infectious corpses at the time of the funeral. In fact, almost 60% of the Ebola cases have had been linked to local funeral practices. Furthermore, conclusive evidence is available to track the linkage of 3 000 Ebola cases with a single funeral[19,21].

8. Environmental attributes: Use of personal protective equipments is a must for all those involved in the care of Ebola confirmed/suspect cases or even their contacts. However, the atmosphere in the affected nations is extremely hot and thus limits the amount of time which health care professionals can spend in an isolation room[40].

9. Lack of research: Although, the first outbreak of EVD was reported almost 38 years ago, still even now no effective preventive or therapeutic control measure is available to reduce the magnitude of the problem[2,42].

5.3. Identified challenges

The previous trends of past Ebola outbreaks suggest that in the last 20 years of reported Ebola outbreaks, the number of cases never exceeded beyond few hundreds, and even the case fatality rate was low, in contrast to the 2014 EVD epidemic[2,43]. Also, the agent characteristics (*viz*. long incubation period, and cases are infectious only after the appearance of symptoms) suggest that Ebola can be easily controlled, by mere isolation of symptomatic patients and follow-up surveillance of contacts[44,45]. However, the outbreak could not be controlled owing to the identification of multiple challenges.

1. Nil/minimal laboratory diagnostic facilities and insufficient logistics support: For isolation to be effective during an Ebola outbreak, rapid identification of cases and follow-up of contacts should be done. In the absence of the diagnostic facilities, most

of the cases remain undiagnosed or misdiagnosed and thus the problem of EVD keeps on multiplying[45]. Similarly, the problem of inadequate logistic support has also come into the picture due to unnecessary travel restrictions from the neighboring nations[46].

2. Dearth of health care personnel and treatment centers: Owing to the inherent weakness in the existing health care delivery system and limited resources, the outbreak of EVD has amplified to epidemic proportions[18,44]. In most of the settings, isolation centers have already exceeded their limits and thus these potential sources of infection remain in the community to infect their contacts[8].

3. Incomplete contact tracing or follow-up: As the number of cases of the EVD has grown at an exponential rate, the crucial activity of contact tracing and follow-up has taken backstage and it is almost unfeasible in settings with limited number of health care workers[8,47].

4. Absence of trust in health authorities: A sense of fear and mistrust has evolved among the people and thus they are not attending healthcare facilities, and instead either remaining in the community or approaching traditional healers[4,7,11,12].

5. No accurate estimates: As most of the infected patients are not availing health services and thus remain unreported, it is extremely difficult to estimate the exact burden of the disease, and hence to plan and rationally allocate resources[40,48].

6. Failure to alter people behavior: In the chain of transmission of Ebola virus disease, a significant linkage has been established with funerals[4,21]. However, this is not new, similar such incidence had been reported in previous outbreaks emerging in Central Africa, nevertheless in many instances, with the help of health educators, program managers were successful to change people's behavior[14,22,49]. Similar sort of success has not been reported uniformly in all the affected areas in the current epidemic[40,42,44].

5.4. Lessons learnt

The 2014 epidemic of EVD highlights the hazards associated with world's growing socio-economic disparities, where the rich people get the best care and poor sections of society are left to die[40]. It also showed that the existence of an effective public health care delivery system is a must to be prepared to successfully counter such diseases[18,42]. Furthermore, it is extremely difficult to develop such systems after the crisis has resulted, and absence of the same clearly suggests that even a trivial condition can assume epidemic proportions[43]. In addition, it is an eye opener for not only the clinicians/researchers, but even for the policy makers/stakeholders from international welfare agencies that even after four decades (first such outbreak detected in 1976), we don't have any specific treatment or even a vaccine to control the disease[27,32,33].

In other words, this outbreak has shown to the world that one of the deadliest pathogens can easily maneuver weakness in the health care delivery system (*viz.* inadequate numbers of health care personnel, absence of isolation wards and intensive care facilities, *etc.*), and the magnitude of the disease can enormously increase if it is combined with the problem of poverty and fear at work[40,42]. At the same time, it emphasizes on the need for international support-financial support, training of health workers, provision of equipments, and laboratory support[46,50]. The scientific community can also support in controlling the EVD by development of mathematical models for quantifying the transmission in different areas, and providing short-term forecasts; assist in development of potential drugs and vaccines[12,33,34].

The experience obtained from the past EVD outbreaks revealed that disease outbreaks can be controlled without using a vaccine or drug therapy. Nevertheless, the current outbreak is unprecedented both in size and scale and thus it requires an equally appropriate response to combat the current menace of EVD[40,41]. In addition, to control the infection, authorities needed to provide leadership and build trust, and specific interventions should be put in place to ensure community participation[48].

6. Comprehensive package of interventions

A wide gamut of interventions has been recommended to reduce the magnitude of the disease and thus interrupt the chain of transmission[1,5]. As a primary line of defense, three specific interventions, namely exhaustive case and contact finding, effective response to patients and the community, and preventive interventions, have been proposed[7,8].

6.1. Exhaustive case and contact finding

Identification of all confirmed cases and their contacts is one of the most important steps in reducing the incidence of EVD cases[7]. The case load estimates and trends of the current epidemic suggest that the number of patients diagnosed has exceeded way beyond the capacity of the local public health authorities[1,2,5,6]. Thus the main challenge is to ensure rapid detection of infected persons through easily accessible diagnostic services[11]. The WHO recommends that all Ebola cases (probable and suspected) should be referred to a designated Ebola Treatment Centre (ETC) or appropriate health care establishment for confirmation of the diagnosis[24,29,51]. These laboratories are biosafety level 4 (BSL4)/BSL3 facilities, in which competent medical staff (*viz*. how to collect, store, package and ship specimens) are employed to safely collect the appropriate specimens (*viz*. whole blood/oral swabs if blood collection is not possible)[52].

In addition, all laboratory staffs and health-care professionals working in connection with EVD should wear appropriate personal protective equipments (PPE)[18,29]. In case, these workers report any symptoms (similar to case definition of EVD), they should promptly report to health authorities[36]. Furthermore, it is of prime importance to ensure safe processing of laboratory samples from suspected or confirmed EVD cases, and safe handling of dead bodies or human remains for post-mortem examination[29,52]. All confirmed cases should be notified to the WHO at the earliest to enable rational allocation of resources[40,48]. Finally, in order to reach a decision regarding discharge of an asymptomatic patient from hospital, two negative RT-PCR test results, obtained at least 48 h apart, is needed[29].

6.2. Effective response to patients and the community

The healthcare professionals should strictly adhere with the

guidelines recommended for the management of patients (*viz*. case detection, assessment of exposure, detailed clinical evaluation, samples to be collected, laboratory notification, notification of the cases to the public health authorities, isolation of the suspected/confirmed cases, management of contacts or special groups like pregnant women/breastfeeding women/children, and guidelines for use of personal protective equipments) with viral hemorrhagic fever[36,53]. Response to cases involves as follow:

1. Isolation of patients and symptomatic contacts: Isolation serves as the key intervention to interrupt the chain of transmission and thus reduce the incidence of EVD cases[1,12]. The cases and the symptomatic contacts are isolated either in a single isolation room or in designated areas separate from other patients in low resource settings[13,16,22]. All measures should be taken in order to restrict the access of clinical/family members/visitors in these isolated rooms[12]. In fact, a set of needed equipment (*viz*. personnel protective equipment) should be earmarked for these isolation rooms to avoid any undue contact[18,20].

2. Appropriate and adequate treatment: As no specific drug therapy is available for the management of the disease, all the patients of EVD are managed symptomatically[18,35]. In addition, provision of supportive therapy, especially fluid and electrolyte maintenance and treatment of bacterial super-infections, can significantly enhance the chances of survival[16,45,54]. Also, it is recommended that mere attention towards rational use of personal protective equipment by the health care workers and improved hospital infection practices can significantly improve the outcome indicators, and thus no negative air flow/special respirators are needed[18,31]. Furthermore, whole blood and plasma obtained from recovered patients have been evaluated as one of the treatment options[55].

3. Contact tracing and monitoring each contact for 21 d after exposure: The overwhelming magnitude, duration, and complexity of the current EVD outbreak have necessitated the implementation of prompt and effective evidence-based containment measures[18]. Contact tracing is defined as the identification and follow-up of individuals (as these possess an extremely high risk of acquiring and transmitting the infection), who may have come in contact with an infected person[54]. The strategy of contact tracing deserves significant importance as most of the new cases of EVD precipitates on contact with the infected individuals, and hence all potential contacts of suspect, probable and confirmed Ebola cases are systematically traced and observed for 21 d (the maximum incubation period of Ebola virus) from the last day of contact[7,12].

4. Broadly, the practice of contact tracing essentially comprises of three elements, namely, contact identification, contact listing, and follow-up[54]. In order to reduce the magnitude of the EVD, the public health authorities should build an effective system for contact tracing right at the onset of the outbreak[12,13]. Furthermore, contacts that develop illness during the period of follow-up should be immediately isolated to prevent further transmission of infection during home-based care, funeral procedures and other social activities[1,5].

5. Other measures: As it is extremely difficult to maintain strict isolation in poor resource settings and because all body fluids are infectious, the use of full-body protective clothing by medical and surveillance staff (*viz*. gloves, an impermeable gown, boots/closed shoes with overshoes, a mask, and eye protection for splashes), and maintenance of hand hygiene (*viz*. applying an alcohol-based hand rub or soap and running water for hand washing in the recommended manner), plays a key role in interrupting the chain of transmission[1,16,18,56].

6.3. Preventive interventions

Three key preventive interventions, namely infection control in health care settings, community education, and avoiding handling of bush meat and contact with bats, have been identified to prevent the EVD outbreak/epidemic. In addition, other measures have also been identified that improve the overall effectiveness of these three key interventions.

6.4. Infection control in health care settings

It is very essential to realize that the maximum risk of acquisition of infection is not from EVD confirmed patients, but from the late detection or isolation of the suspect/probable cases[16]. Laboratory diagnosis and isolation becomes really difficult as most of the symptoms with which patient presents in the early stages of the disease are nonspecific, and hence in most of the cases, many of the family members/health care workers have been already exposed, even before the EVD infection is detected[1,8,16,29]. Thus, it becomes indispensable to strengthen infection prevention and control measures in all the health-care settings-adopt standard precautions for all patients regardless of the their clinical presentation; isolation of the confirmed/suspect cases of EVD in isolation rooms; restrict the access of medical and non-medical personnel in isolation rooms; assign only trained personnel/PPE for these isolation wards; ensure the usage of PPE by health workers (*viz*. patient care-takers/who handle dead bodies-at the time of post-mortem or burial activities) and relatives (especially indicated for children); safe handling of biomedical wastes and solid linen; use disinfectants for the decontamination of surfaces and equipments; ensure safe processing of laboratory samples from suspect or confirmed patients; and prompt evaluation and management of any health professional or person exposed to any infectious body fluid[16,18,29,53,56-58].

In addition, strict adherence should be practiced by the health care workers towards the recommended guidelines for the general patient care, direct patient care (for suspected or confirmed patients with hemorrhagic fever); movement and burial of human remains; standard precautions in health-care settings; use and removal of personal protective equipments; and in performing hand hygiene[3,7,8,16]. Furthermore, health workers who are engaged in tracing contacts in the community should avoid shaking hands, maintain a distance of more than 1 m during an interview with the contacts, and always carry alcohol-based hand rub solutions[16,56].

In fact, it is even recommended to constitute a committee in the affected areas and a person should be ear-marked to coordinate the infection prevention and control activities in both hospitals and communities[59]. It has been realized that careful implementation of the infection prevention and control measures can significantly reduce or stop the transmission of the disease in the community and among health care workers[16,60].

6.5. Community education

Community engagement has remained as the key component in successfully controlling the outbreaks of EVD in the past[22,45]. Similarly, encouraging results have been obtained in the current epidemic as well. Senegal has been declared by WHO as Ebola-free and in Liberia, survivors of the disease are providing training to healthcare workers for Ebola care[39,60,61]. In fact, early involvement of the community is a crucial necessity for the success of contact tracing[54].

Conclusive evidence is available to establish an association between traditional customs/religious practices (*viz*. extensive contact at time of funeral with dead body) and occurrence of EVD outbreaks[21,62,63]. As it is a culturally sensitive issue, there is a need to develop a culturally-sensitive approach within the purview of public health programs, to modify long-standing funeral practices in the affected nations[21,62]. The proposed communication strategy tends to target the human behavior, which in turn determines the magnitude of the disease[63]. In fact, definitive evidence is available to suggest the potential role of a systematically planned communication strategy in altering the cultural practices, which are critical in outbreak control[64].

6.6. Avoid contact with reservoirs

Awareness should be created among members of the community regarding the different modes in which Ebola virus infection can be acquired[7,17]. In addition, people should be informed to avoid contact with bush meat/bats, to minimize the risk of the initial introduction of Ebola virus into humans[17,18].

6.7. Travel to affected nations

In order to prevent the spread of the life threatening disease across international borders and reduce the burden on the health care delivery systems, the WHO has developed standardized guidelines in accordance with the international best practices and standard operational procedures, for the management of suspected cases at points of entry (*viz*. a passage for international entry or exit of travelers, baggage, cargo, *etc*.)[65]. The aim is to provide early detection of potentially infected individuals, assist in implementing WHO recommendations related to Ebola management, and to prevent the international spread of the disease while allowing authorities to avoid unnecessary restrictions and delays[66,67].

The current trends and recommendation by international agencies suggest that any travel to and from Ebola-affected nation's carries low-risk (since transmission requires direct contact with body fluids of infected living or dead persons or animal, all of which are unlikely exposures for the average traveler) for acquiring EVD infection[5,7,66]. However, some precautions (*e.g.* avoid direct physical contact with anyone who is displaying the symptoms of Ebola, do not touch the body of a person who has died from Ebola, use alcohol rub/soap and water throughout the day, seek prompt medical attention if you have Ebola symptoms, alert airline personnel about a fellow traveler who has Ebola symptoms) need to be followed during the travel to ensure safety of self as well as other travelers[12,65,67]. Even though risk to travelers is minimal, contact tracing is still recommended[65,66]. Furthermore, health workers traveling to affected areas should strictly follow WHO-recommended infection control guidance to avoid acquisition of Ebola virus infection[16,18].

6.8. Role of vaccines

Although the utility of Ebola virus vaccine was questioned initially owing to the rare nature of the disease, minimal attention by pharmaceutical companies, and attributes of the vaccine (*viz*. potency, efficacy, safety, cost, *etc*.), nevertheless, administration of the vaccine appears to be the most cost-effective strategy in affected nations with weak public health care delivery system[31,33,42]. Vaccines under development include both pre-exposure and post-exposure related vaccines[12,33]. In fact, two candidate vaccines (*viz*. cAd3-ZEBOV by GlaxoSmithKline) and rVSVZEBOV (by the Public Health Agency of Canada) have been subjected to different phases of clinical trials[33,68,69]. In view of the magnitude of the EVD epidemic, the international agencies and researchers are mobilizing diverse ways to fast-track the development of these compounds[70].

6.9. Expectation from countries with no EVD cases

In nations, where no suspect/confirmed cases of Ebola have been detected till date, the concerned stakeholders should develop a systematic framework to successfully counter the sudden outbreak or epidemic[71]. This essentially requires strategies for the preparedness (*viz*. strengthening of the existing health care, capacity building, development of a network of laboratories throughout the country, mobilization of other resources, sensitization of the healthcare professionals regarding different aspects of the disease, creating awareness among the members of the society about the do's and don'ts pertaining to disease, *etc*.), response (*viz*. alert management, field investigation and field response), and periodic monitoring and evaluation to plan, implement and improve the public health strategy[72,73].

In addition, measures like the establishment of an alert system in well-defined sites (*viz*. land border crossing with already affected countries; capital cities, including at airports, seaports, and health-care facilities); creating a rapid response team trained in case definitions, reporting, and infection prevention and control measures; developing a fully equipped isolation centre with a trained staff in different aspects of the disease; and identification of a national or international WHO-recognized reference laboratory, should be taken by the public health authorities to deal with any untoward incidence[51,74]. In case, any patient is diagnosed with EVD, the health authorities should notify within 6 h to the WHO, and then implement response strategies, including daily medical follow-up of the patient's contacts for 21 d after exposure[5,13,20].

6.10. Response plan

All the above mentioned measures are direct interventions, developed on the basis of epidemiological attributes of the Ebola virus. However, Ebola virus is difficult to contain, as even if a single case is missed, or a single contact becomes ill and isn't isolated, or

a single lapse in infection control or safe burial of deceased occurs, another chain of transmission can start[7]. Thus, a clear need has been identified to develop an action plan in order to launch an Ebola response in nations with widespread transmission, to ensure prompt deployment of holistic measures in affected countries, and to strengthen preparedness of all countries to rapidly detect and respond to an Ebola exposure[73,75].

In fact, as a part of preparedness, a Regional Ebola Emergency Preparedness and Response Plan has been developed which includes specific recommendations on mobilizing and retaining sufficient human resources to implement Ebola response measures (address issues of remuneration, training, equipment, physical security, medical care, *etc*.); strategies to ensure social mobilization and involvement of communities by developing a sense of ownership among the masses; measures to allow quick access of people to a WHO-recognized Ebola diagnostic laboratory; maintain logistics support (*viz*. personal protective equipments, infection prevention and control materials); travel and trade related recommendations; establishment of a system for information management and data analysis; building a liaison with the international health agencies for the financial support; establishment of new Ebola treatment centers; facilitating research work and development of drugs/vaccines; and guidelines to ensure coordination and crisis management at different levels[5,39,46,60,71,76,77].

7. Implications for practice

In this current epidemic, each confirmed case of Ebola tends to transmit infection to two other people, which indirectly means that just a two-fold reduction in transmission will be enough to eliminate the virus[8]. Regardless of the fact that trends of the disease over six months suggested that disease was intractable, nevertheless, the number of cases has stopped increasing in countries in Guinea, Liberia and Sierra Leone, especially where the three countries have common borders[8]. Also, in response to the concerted efforts of multiple stakeholders and with active community participation, encouraging results have been obtained from a town in Guinea[78]. In fact, Senegal has been declared free of Ebola virus as 42 days have passed and no new cases have been detected from the nation[60,79].

All these instances suggest that in this epidemic, as in previous outbreaks, the disease can be controlled and provided a package of interventions like early diagnosis, good laboratory service, case management, patient isolation, contact tracing, infection control, community involvement, and safe burial, which are implemented nation-wide in a comprehensive manner[1,8,80]. Finally, the need for a strong political will be a must for preparing and implementing a comprehensive plan to ensure encouraging results.

8. Implications for research

The current EVD epidemic has highlighted the dearth of research in the field of Ebola, despite detecting its existence almost 40 years back. It is an area of major concern as even after four decades the medical practitioners don't have an answer to the disease-neither any specific antiviral drug nor any effective vaccine. There is ample scope for research in understanding the ecology of reservoir species (*viz*. their infection status and shedding mechanisms), way to disrupt the ecological cycle of Ebolavirus, underlying mechanism for lymphocyte apoptosis, and in development of a potent drug and vaccine.

9. Conclusion

The 2014 epidemic of EVD has shown to the world that in absence of a strong public health care delivery system even a rare disease can risk the lives of millions of people. The crux of this epidemic is that a large scale and coordinated international response is the need of the hour to support affected and at-risk nations in intensifying their response activities and strengthening of national capacities.

Conflict of interest statement

We declare that we have no conflict of interest.

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