European Review for Medical and Pharmacological Sciences 2015; 19: 2983-2996

# Ebola and blood transfusion: existing challenges and emerging opportunities

S. ABDULLAH[1], K. KARUNAMOORTHI[2]

[1]Laboratory Medicine Department, Faculty of Applied medical Sciences, Jazan University, Kingdom of Saudi Arabia
[2]Unit of Tropical Diseases, Division of Medical Entomology and Vector Control, Department of Environmental Health, Faculty of Public Health and Tropical Medicine, Jazan University, Kingdom of Saudi Arabia

**Abstract. – OBJECTIVE: The deadly Ebola virus has been first known to mankind since 1976. In the past decades, Ebola outbreaks has often been ignored/neglected as erupted in the rural remote/isolated areas of Africa. The recent 2013-2014 epidemic is the most wide-spread with high incidence rates, morbidity and, mortality in the Ebola history. Eventually, the World Health Organization (WHO) has declared it as a 'Public Health Concern of the International Community'. This scrutiny was conducted to initiate a serious debate on various aspects of Ebola, particularly blood transfusion as an empirical therapeutic modality.**

**METHODS: A search has been performed using the premier scientific databases, WHO documents, and English language search engines. Of 278 potential articles that were identified using a fixed set of criteria, a convenience sample of eighty-two appropriate articles was chosen for this review.**

**RESULTS: The current EBO outbreak is predominantly driven by various confounding risk-factors like: (1) frail health care system, (2) unique cultural and religious customs, (3) huge-shortage of skilled professionals, (4) no licensed therapeutic agents, (5) ill-prepared monitoring and early warning systems, and (6) strained budgets; all these have bolstered this epidemic. As lack of neither specific treatments nor reliable interventions to quickly quell this epidemic, WHO has indorsed 'blood transfusion as an empirical therapeutic modality'. Currently, several clinical trials are underway, particularly the two Ebola candidate vaccines and several antiviral drugs and it has been observed that the initial results are quite promising. However, there are several daunting ethical and practical challenges ahead to stem off this outbreak.**

**CONCLUSIONS: The Ebola-hit poverty stricken West-African countries struggle to contain the outbreak, due to lack of potent therapeutics. Consequently, blood-transfusion could serve as an ideal therapeutic modality to save millions of lives. Therefore, industrialized nations and international agencies must aid them to combat with this catastrophe. Besides, it must warrant further multi-layered interventions and interagency policies, in order to build an Ebola-free safe world in the near future.**

*Key Words:*
Ebola, Blood transfusion, Ebola virus, West African Countries, Therapuetic agents.

## Introduction

Ebola is a deadly infectious disease of humans and other primates and is often fatal. Ebola viruses (EBOV) cause a rash, reddened eyes, hiccups, substantial intravascular volume depletion and marked electrolyte abnormalities attributable to both internal and external bleeding[1]. It first emerged in a small remote village of the Democratic Republic of Congo (DRC) near the Ebola River, subsequently it's named as an 'Ebola hemorrhagic fever'[2]. Though EBOV was first identified in southern Sudan in 1976[3], but most likely occurred as early as 1972 in Tandala, DRC (formerly known as Zaire)[4].

The recent outbreak erupted in Guinea in December 2013 but soon spurted into neighboring Liberia and Sierra Leone with a reported seventy percent of the case fatality rate[5]. It is unprecedented in terms of number of cases, mortality rate and deleterious socio-economic impact. Thereupon World Health Organization (WHO) declared Ebola as a 'Public Health Emergency of International Concern' on 8th August 2014[2]. To date there is no specific preventive and curative therapeutic agent in existence, henceforth, EBOV remains to pose a serious public health threat to both civilian and military populations as bio-weapons[6].

Though, ever since the mid of 1970s there are several sporadic outbreaks reported, 2014 epidemic has broken down the entire civic society by killing thousands of people, destroying families

*Corresponding Author:* Kaliyaperumal Karunamoorthi, MD; e-mail: karunamoorthi@gmail.com

and threatening the world. It is a matter of grave concern that urges us to find a countermeasure quickly to fight against the 'common enemy' of mankind. In these perspectives, the present communication becomes more significant and pertain.

This review is an attempt to initiate serious debates on various Ebola related issues like mode of transmission, high risk-groups, symptoms, existing therapeutic modalities, particularly blood transfusions. Furthermore, it is an effort to shed some limelight on the existing practical challenges and emerging opportunities to minimize the Ebola related illness and deaths by adopting blood transfusion as one of the empirical therapeutic modalities. We strongly believe that the outcome of this scrutiny could serve as a baseline data for public health care providers and policy-makers to combat with Ebola outbreaks or epidemics effectively in the near future.

## Methods

### Data Mining: Evidence Acquisition Identification of studies

The search strategy and terms were developed collaboratively with the assistance from the information specialists. An appropriate search was performed in PubMed, Google Scholar, Web of Science, EMBASE, Scopus, World Health Organization's WHOLIS, Research gate, and Academic Premier databases in English, using the terms: "Ebola virus disease /Recent outbreak" OR "Ebola and blood transfusion", "Ebola and Public Health", "Ebola transmission", "Ebola and Human Health" ' Ebola and West Africa' and "Ebola vaccine" to include articles published without time limitations i.e., from earliest to most recent (December 2014).

Potentially relevant articles (in all languages) and websites were accessed in order to review the full-text. Besides, references cited by each relevant paper, review, and book chapters were also scrutinized to identify additional potential papers. Furthermore, the reference lists of all articles were hand-searched, and the full text of those references that appeared relevant to Ebola and blood transfusion were retrieved. The exclusion and inclusion criteria for choosing the appropriate research articles, notes and reviews were shown in Figure 1 for this narrative review, and their bibliographic details (authors, title, full source, document type and addresses) have been downloaded and maintained in a file.

## Results

The study selection process is given in Figure 1 as a flow diagram. Of 228 potentially relevant, unique citations from all literature searches, sixty-one studies met the inclusion criteria. Twenty-seven studies were empirical research studies; three were booked chapters, two of them is from conference and three involved systematic reviews and meta-analyses, with the rest twenty-six involving case reports or press releases. The majority of studies was carried out in the WHO defined African region (n=48), and the remaining studies (n=13), covers the rest of the world; the majority of them have been published later than 2012. Meta-analysis was not performed as the included studies were heterogeneous in important aspects, including: populations (different ages and settings), and study designs (cross-sectional, case-control, cohort).

### Filoviruses

Filoviruses are lager, negative stranded, non-segmented RNA viruses with a characteristic of thread like structure, henceforth the family name is *Filoviridae* (Latin *filum* = thread). Over the past decades, several natural outbreaks have been reported in the DRC, Sudan, Uganda, Angola, and Gabon[6]. Both Marburg and Ebola species are morphologically identical, but vary in length[7]. They are imposing potential threats to humans as well as non-human primates[8]. Filovirus illness is characterized by fever, myalgia, headache, and gastrointestinal symptoms, and patients may also develop a maculopapular rash. Death has often been correlated with increased viremia, convulsions, and disseminated intravascular coagulation[9].

### Ebola Virus: An Old Enemy and Recent Killer

It is an ancient one, having split off from other viruses dating back thousands of years with a relatively constant mutation rate[10]. Filoviridae includes three genera viz., Cuevavirus, Marburgvirus, and Ebola virus. EBOV is a filovirus with a 19-kb, non-segmented, negative-strand RNA genome that encodes seven viral proteins[11]. Till date, five genetically distinct subspecies have been identified, namely Zaire, Bundibugyo, Sudan, Reston and Taï Forest. However, three species [(Bundibugyo Ebola virus (Côte D'Ivoire); Zaire Ebola virus (Democratic Republic of the Congo, formerly Zaire); and Sudan

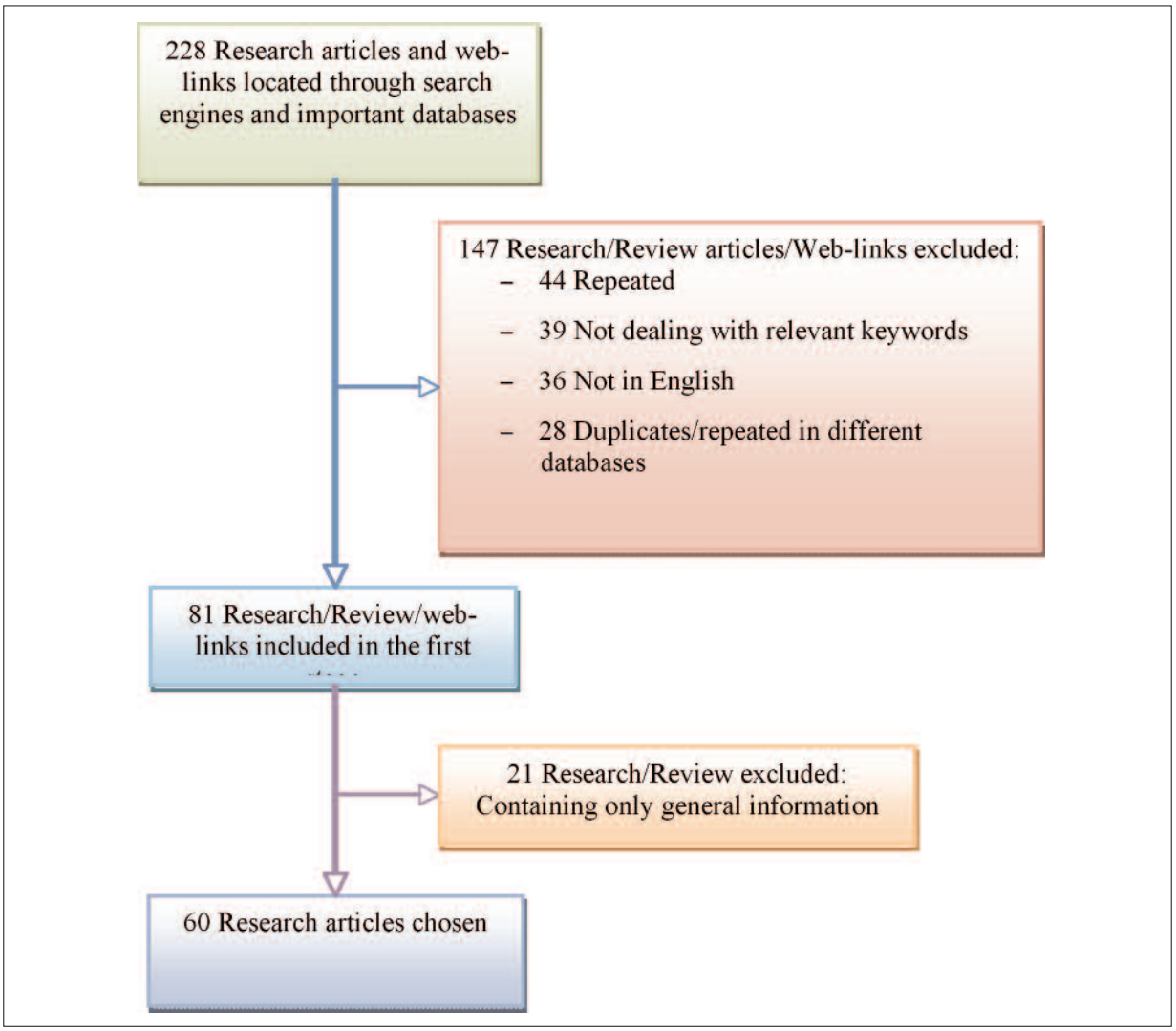


**Figure 1.** The exclusion and inclusion criteria, for choosing the appropriate research articles, notes and reviews for this narrative review.

Ebola virus (Sudan)] have been associated with larger outbreaks in Africa. The recent 2014 West African outbreak was caused by the Zaire Ebola virus (ZEBOV)[2], with a ninety percent of mortality rate[12] and it cannot further mutate and become more contagious[10].

### *Existing Ebola Virus Strains*

In 1976, the first outbreak of Ebola (Ebola-Sudan) was reported in southern Sudan and a few months later, the second Ebola virus emerged from Yambuku, Zaire, Ebola-Zaire (EBOZ). The third strain of Ebola, Ebola Reston (EBOR), was first identified in 1989 when infected monkeys were imported from the Philippines to Reston, Virginia, United States of America. The last known strain of Ebola, Ebola Cote d'Ivoire (EBO-CI) was discovered in 1994 when a female ethologist was performing a necropsy on a dead chimpanzee from the Tai Forest, Cote D'Ivoire, got accidentally infected herself during the necropsy[13].

### *The Deadly History of Ebola Outbreaks*

It is not a new disease of mankind and typically occurs as deadly outbreak in the resource-constrained tropical Sub-Saharan Africa. Since mid of 1970s to until December 2013, 1,716 confirmed cases have ever been reported[2,10]. To date, the ongoing 2014 West African Ebola outbreak is the largest, which affects many African countries viz., Guinea, Sierra Leone, Liberia, Mali, and

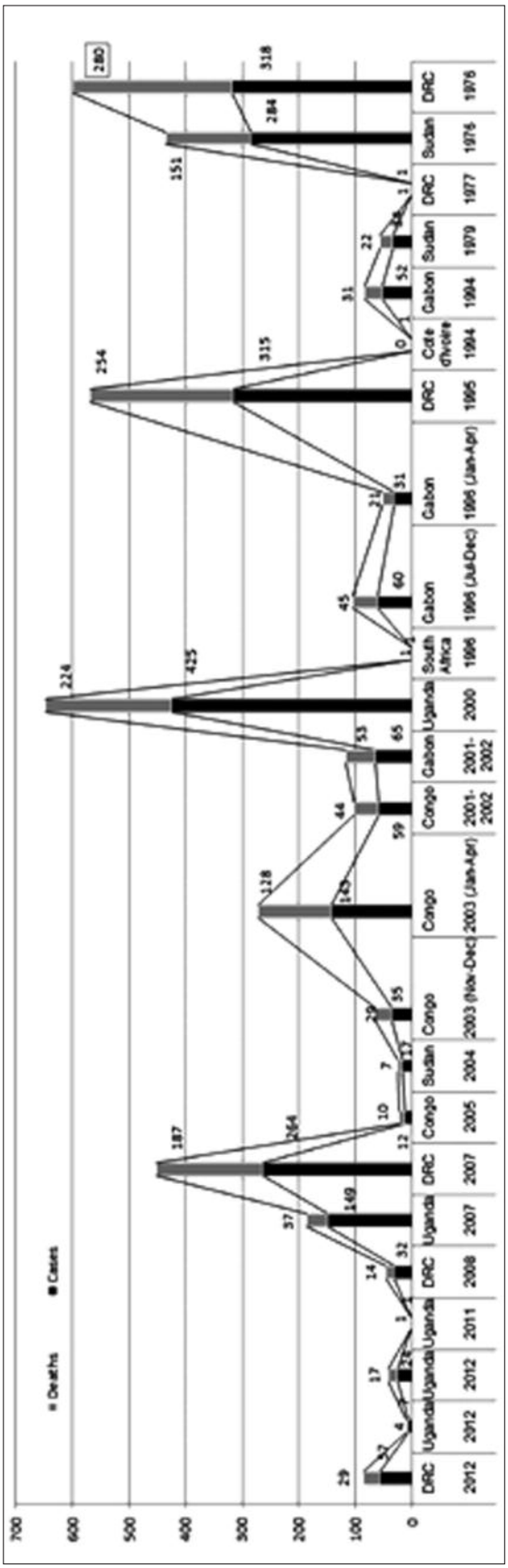


**Figure 2.** The previous Ebola virus disease outbreaks.

Nigeria. As of 7th January 2015, 20 747 suspected cases and 8235 deaths had been reported[14]. Past Ebola outbreaks have been elaborately illustrated in terms of number of cases and deaths in Figure 2[2].

### High Risk Group

Whoever in close contact with Ebola patients are at the highest risk of infection, notably healthcare providers, close family members, and friends as they have higher probabilities to be infected by blood or body fluids of patients[10]. Fortunately, Ebola survivors cannot serve as a source of infection. It spreads rapidly during outbreaks within healthcare settings and could be easily evaded by wearing appropriate personal protective equipment[10]. As of 23 October 2014, nearly 450 health care workers (HCWs) [eighty-in-Guinea; 228 in Liberia; eleven in Nigeria; 127 in Sierra Leone; one in Spain; and three in the US] are known to have been infected and a total of 244 HCWs have died during 2014 outbreak alone[15,16]. Quite a considerable number of people have acquired infection by means of attending the burial ceremonies of Ebola victims[17].

### Ebola Recent outbreak: a Public Health Emergency of International Concern Ground Zero in Guinea: the outbreak Smoulders

Currently, West Africa is experiencing the world's largest Ebola outbreak[18]. It has erupted on 6th December 2013, when a two-year-old male child Emile (the first known case of 2014 Ebola epidemic) in Meliandou village, Guéckédou Prefecture, in the Nzérékoré Region of southern Guinea got infected[19-21]. It is one of the most difficult villages to reach by road and it is a two-day drive from the national capital of Conakry, followed by a long walk through the dense rain-forest[22]. This outbreak's 'hot zone' (Meliandou) is located in a triangle-shaped forested area, where the borders of Guinea, Liberia and Sierra Leone shared. As a result of decades of civil wars and unrest, these countries has deeply been impoverished and the health infrastructures have severely been damaged[19].

### Death Toll and Morbidity

As of 7th January 2015, a total of 20 747 cases (confirmed, probable, and suspected cases of Ebola) and 8 235 deaths have been reported in five Ebola-hit countries viz., Guinea, Liberia, Mali, Sierra Leone, and the USA and in three

previously affected countries viz., Nigeria, Senegal and Spain[14]. Reported case incidence is slightly increasing in Guinea, declining in Liberia, and may still be increasing in Sierra Leone. The case fatality rate across the three most-affected countries in all reported cases with a recorded definitive outcome is seventy-six percent; in hospitalized patients the case fatality rate is sixty-one percent[23]. WHO has estimated that it may take nearly six-to-nine months to contain the ongoing outbreak and during this period of time it may likely to claim another 20,000 lives. Recent WHO (2014)[24] report indicates that cases in Liberia are under-reported. It may be due to asymptomatic infections, which have also been observed in earlier outbreaks too[25]. Ebola imposes an urgent public health threat not only to Africa but also to the rest of the world.

### Driving Forces of Recent Outbreak

Past outbreaks have flared up in the remote and isolated forested communities and these outbreaks die out, like the flare-up in the central African countries like DRC in the past few months[26]. However, the recent 2013-2014 outbreak is the largest and most complex in terms of duration, number of people affected, and geographic extent[27]. Currently, Ebola has been considered as not only as a public health emergency, but also as a 'poverty', 'infrastructure', as well as a 'educational' crisis[26]. This epidemic (2014-2015) driven by various sociological, ecological, and environmental determinants, has both directly and indirectly influenced the emergence of Ebola in the poverty pervasive West African countries.

High-risk of confounding factors (Alexander et al, 2014)[27]:

- **Free people movement** – rural-to-urban migration as well as extensive movement of people within and across borders.
- **Decades of civil war/unrest** – have severely weakened the basic and health care sector infrastructures.
- **Behavioral and cultural practices** – traditional customs/practices like burial ceremony traditions and rites.
- **Bush meat consumption** – principal mechanism of EBOV spillover from wildlife reservoirs to humans.
- **Traditional medicine and cures** – it delays the Ebola patient to access life-saving quality healthcare.

### Natural Host and Mode of Transmission

Fruit Bats (Family: *Pteropodidae*) are serving as a natural host. EBOV introduced into the human through close contact through body fluids and other secretions of infected wild-animals viz., chimpanzees, gorillas, fruit bats, monkeys, antelope and porcupines found ill or dead[5]. Once infection is established, it can be transmitted through human-to-human via direct contact with the blood, secretions, organs or other bodily fluids (including but not limited to urine, saliva, sweat, feces, vomit, breast milk, and semen) of infected human[28], and animals [fruit bats or primates (apes and monkeys)]. Human handling and consumption of contaminated bushmeat (Ebola infected animals) has been cited as a major source of transmission to human[5].

A study found that the case mortality rates highly correlate with the mode of transmission. Overall, hundred and eighty percent mortality was observed among those exposed via contaminated needles, and close-contact with infected people, respectively[29]. Aerosol transmission has also been reported but only in the laboratory settings[30] and is rare or absent in natural outbreaks[31]. The contaminated surfaces, materials (bedding, clothing), and objects (needles and syringes) could also transmit infection. Therefore, healthcare professional are at the highest risk of infection, when the transmission control protocols (TCP) are not strictly practiced[5]. People remain infectious as long as their blood and body fluids (including semen and breast milk), contain the Ebola virus[5]. There is no evidence that mosquitoes or other insects can transmit EBOV[10].

### Mode of Disease Causing Mechanism and Pathophysiology

Ebola virus kills cells, making some of them to explode. Subsequently, it wrecks the immune system, causes heavy internal hemorrhage and electrolytes abnormalities. It virtually damages every organ[32], often leading to death[31,33]. Distinguishing the symptoms of Ebola from other infectious diseases is quite a challenging task. However, it can be diagnosed by performing standard serological diagnostic tests like antibody-capture enzyme-linked immunosorbent assay (ELISA), antigen-capture detection, serum neutralization, reverse transcriptase polymerase chain reaction (RT-PCR) assay, electron microscopy and virus isolation by cell culture[5]. Since, samples are potential biohazard risks, diagnosis should be performed under highest-level of biosafety containment conditions.

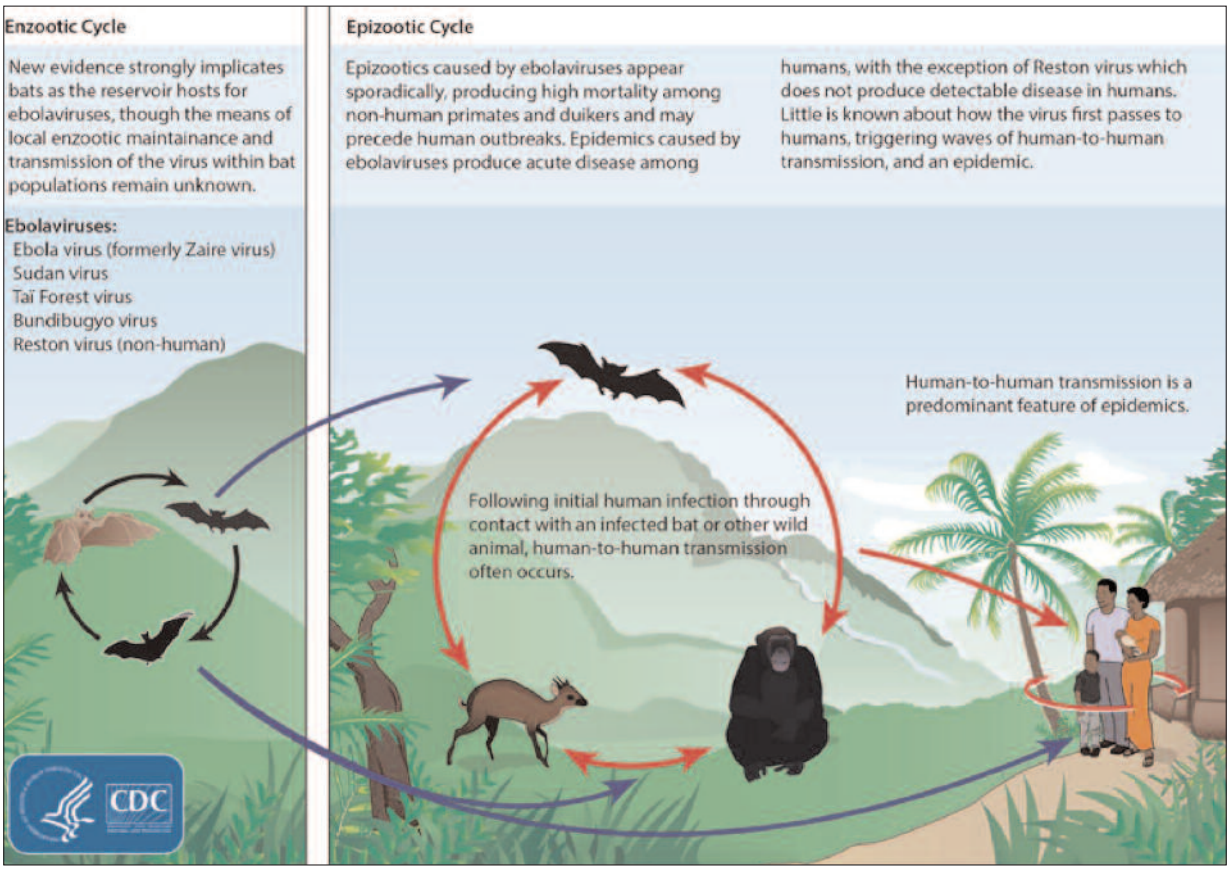


**Figure 3.** Ebola virus transmission cycle (Source: CDC 2014)10.

### *Ebola virus Infection Treatment and Management*

As there are currently no licensed vaccines or therapeutics to prevent or treat any filovirus infection, particularly Ebola[30], it has emerged as a potential global public health threat[34]. Prior EVD outbreaks have been controlled by implementation of integrated strategies like identification of cases, contact tracing, quarantine, early diagnosis, supportive care, infection control, and safe burial practices. Fortunately, the negative impact of current 2014 epidemic illustrate the importance of effective novel preventive and curative arsenal[35] to fight against the Ebola. Though to date no approved therapeutic agents exist to treat or prevent Ebola, the following therapeutic options have been administered to curb Ebola-associated illness and death (Table I).

### *Importance of Blood Transfusion to Treat EVD cases*

Due to the absence of effective vaccine and reliable drugs to neutralize the Ebola virus, the treatment or management of Ebola patients have been mainly focused on symptomatic treatments with available antiviral agents and blood transfusion[17]. Besides, early supportive care with rehydration and electrolyte correction, monitoring basic physiological functions, protein deficiencies, has often been administered to improve the survival of Ebola patients[5].

In 1995, eight Ebola patients were transfused with convalescent whole blood (CWB) and plasma (CP) of EVD survivors to treat illness in the DRC. Donated blood contained only IgG EBO antibodies and no antigen. However, antigens were detected in all the recipients just prior to the transfusion and this empirical study found that among the eight only one patient (12.5%) died. The percent of the mortality rate is significantly lower than other EBO epidemic in Congo and rest of the world[45]. The reason for the lower- mortality rate remains to be scientifically authenticated and warranted by further clinical studies to evaluate and elucidate the passive immune therapy.

In addition, currently several blood transfusion studies are underway by enrolling patients of 2014 epidemic and the preliminary results are

**Table II.** Existing therapeutic options to treat Ebola virus disease.

| S. No. | Name of the therapeutic agent | Nature | Mode of action | Remarks | Reference (s) |
|---|---|---|---|---|---|
| 1. | AVI 6002 (AVI-7537) | Drug | Blocking viral protein | It helps monkeys tosurvive from Ebola for some sixty-to-eighty percent. It has shown human tolerability in early studies. | Axtelle et al. 2012[36] |
| 2. | Hyperimmune globulin | Prepared by purifying and concentrating plasma of immunized animals or previously infected humans with high titers. | Neutralizing antibody against Ebola virus | Protective in monkeys, but are not currently available and would not be expected before mid of 2015 | Kudoyarova-Zubavichene et al. 1999[17]; Maron 2014[37] |
| 3. | KZ52 | A neutralizing human monoclonal antibody | It protects guinea pigs from lethal Ebola Zaire virus challenge | KZ52 is a promising candidate for immunoprophylaxis of Ebola virus infection | Parren et al. 2002[38] |
| 4. | Favipivavir (T-705 or Avigan) | Antiviral drug approved for influenza in Japan | Blocks the replication of many RNA viruses, particularly it inhibits the RNA-dependent RNA polymerase (RdRP) of influenza | Need to be used at much higher doses. Though the efficiency of this drug against human Ebola infection remains unclear, some positive results are emerging in animal experiments | Furuta et al. 2009[39], 2013[40] |
| 5. | Interferons | | Targeting and disabling the VP24 protein | Though they did not increase overall survival, but delay the death. Nevertheless, it remains unclear which interferon to use, when and at what dosage regimen to obtain optimal results. | Basler and Amarasinghe 2009[41] |
| 6. | BioCryst | Drug | | It needs more animal treatment data before it could be considered. | |
| 7. | ZMapp (a mixture of three antibodies) | Under development as a treatment for Ebola virus disease | Like intravenous immunoglobulin therapy, ZMapp contains neutralizing antibodies that provide passive immunity to the virus by directly and specifically reacting with it in a "lock and key" fashion. | It was first used experimentally to treat some people with Ebola virus disease during the 2014 West African Ebola outbreak, but as of August 2014 it had not yet been tested in a clinical trial to support widespread usage in humans; it is not known whether it is effective to treat the disease, nor if it is safe | Qiu et al. 2013[42]; WHO 2014g, h[43,44] |

quite promising and encouraging too[46-48]. The unprecedented attack of Ebola on world community has created a high demand of blood transfusion than ever before[2]. It remains to be considered as the best option to treat Ebola virus disease in the absence of effective therapeutic agents.

Accordingly, during the ongoing 2014 EVD outbreak, whole blood and plasma obtained from Ebola recovered patients have been prioritized for reconnaissance, as one of the empirical treatment modalities[49] for the patients with early EVD clinical symptoms and manifestations. As convalescent plasma has been successfully administered to treat various infectious diseases, this modality is biologically plausible[50] and could be efficacious too. In addition, by reviewing all the existing experimental potential therapies and vaccines, the WHO experts indicate that treating Ebola patients with blood transfusions from survivors of EVD is the top most priority[17] to save hundreds of thousands of lives.

### Ebola and Blood Transfusions Mode of Mechanism

Since the survivors of Ebola infection typically produce effective antibodies against the virus, the transfusions of their blood into a newly Ebola infected individual could save life[17]. As none of the existing/considered Ebola regimes have been adequately tested in humans, the convalescent whole-blood (CWB) and serum could serve as therapeutic agents against Ebola virus. Indeed, it has to be transfused safely with careful screening[17], or else mismatched blood type and infected blood could cause a few severe reactions that may be life-threatening too. Therefore, both WHO and public health experts debated on the pros and cons of treating Ebola patients with transfusions of whole blood and plasma of EBVD survivors[51].

In the past, CWB modality has been adopted empirically among a small group of patients, with promising results[45]. However, the use of CWB is technically more complex and demands more facilities and skills. Consequently the eventual use of CP in Guinea, Sierra Leone and the Democratic Republic of Congo will depend on the availability of technical expertise[51]. Finally, WHO (2014)[49] has issued an interim guidance to national health authorities and blood transfusion services to outline the steps required to collect CWB or CP from EVD recovered patients for transfusion to patients with early EVD, as an empirical treatment modality. It includes the following phases:

### Key phases for the Blood Transfusion Identification

The EVD recovered patients (those have been discharged from the recognized Ebola treatment centers or units) could serve as potential donors (after 28 days of discharge) for CWB/CP. It is important to note that the Ebola neutralizing antibodies are expected to be most effective when CWB/CP is sourced from the epidemic/endemic areas of active Ebola virus (EBOV) transmission. However, in circumstances where the demand is high and the system is challenged by an overwhelming number of active EVD patients, and CWB/CP could also be sourced from the places linked to the current EVD outbreak in West Africa where the outbreak has come under control[49].

### Screening/Pre-Donation Tests (WHO 2014)[49]

- Estimation of donors hemoglobin concentration
- ABO (A, B, AB and O) grouping and RhD type screening tests for blood borne infectious diseases like human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis co-infections and other locally transmitted infections like malaria, as applicable
- Titration of total Ebola neutralizing antibodies to identify the potential donor, particularly if the donor is willing to continue serving as CWB/CP source.

### Review of Pre-Donation Tests

It is one of the critical phases in empirical blood transfusion treatment. Results of the predonation tests must be carefully reviewed. Donors, those are shown negative for all TTI tests and fulfilling the remaining all other criteria should be chosen for CWD/CP donations. If the duration between predonation test and donation exceeds forty-eight h, then the routine TTI tests must be repeated[49]. A minimum period of twelve and sixteen weeks for males and females, respectively is needed for further blood donation.

### Selection of EVD Patients and Blood Sample Collection

Only EVD confirmed patients in the early stages should be selected for CWB/CP transfusion[49]. Two venous blood samples (5 mL) each must be drawned from the patient prior to transfusion; (a) one in EDTA for a plasma, while (b) another one in a plain tube (without anticoagulant) for a serum sample for the (a) ABO and

RhD blood grouping, and cross-matching and, (b) baseline viral load assay. Plain sample is used to measure the viral-load and other tests. Furthermore, prior to discharge of recovered patients, two additional five mL plain samples have to be collected to analyze the viral-load in the successive days. Residual serum of the blood samples should be stored in aliquots for retrospective antibody or any other future examinations[49].

### Selection of Convalescent Whole Blood or Plasma Units

ABO and RhD matched blood or plasma units need to be chosen for transfusion. RhD-ve units should be transfused to RhD-ve women of childbearing age (if possible). However, If the RhD group of the patient is not known or in case of non-availability of RhD specific group, blood matched only for ABO group may be used for treatment[49]:

- In order to minimize the risk associated with handling of infectious blood samples, cross matching of patients' serum and donors' red cells, can be omitted if ABO group compatible CWB/CP is selected.
- If it is not possible to test the patient's ABO group or if ABO matched CWB/CP is not available then: (1) for whole blood transfusion - group O convalescent whole blood, ideally from donors with low titer anti-A and anti-B, can be transfused; while (2) for plasma transfusion - group AB convalescent plasma separated by centrifugation should be used.
- Non ABO-matched CP could also be considered if group AB plasma is not available, but should preferably be group A or B.
- Transfusion needs to be done within twenty-four hours of CP preparation in order to obtain higher RBC concentration.

### Transfusion of Convalescent Whole Blood or Plasma

CWB/CP units should be transfused to the EVD patients by following the clinical transfusion protocols. One unit of CWB [equals is 450 mL (just under a pint)] have to be transfused for adult patients. In the absence of evidence, 400-500 mL of CP in two doses of 200-250 mL each, separated from two different WB donations, should be considered for adult patients, and whereas, in the case of pediatric CWB/CP transfusion, a dose of 10 mL/kg could be ideal based on the considerations of blood volume[49].

### Patient Monitoring

Transfused EVD patients must be closely monitored in order to assess the patient improvement in terms of clinical conditions and the concomitant decline of virus load detected in plasma[18], as well as to evaluate the effectiveness of the treatment. In addition to clinical monitoring, Ebola antibody levels and other tests are also extremely important. Besides, standard case reporting forms must also be maintained to monitor all potential interventions for EVD[49, 52].

However, a few public health experts have raised their concern regarding adopting blood transfusion as a therapeutic modality for the Ebola treatment: (1) the emergence of a black market trading of blood of EVD survivors[2], (2) risk of escalating transmission of several infectious diseases, particularly killer diseases like human immunodeficiency virus (HIV), malaria and viral hepatitis infection and, (3) other infectious diseases[46, 53]. Nevertheless, blood transfusion is one of the easily adoptable empirical therapeutic modalities with the potential to be implemented immediately on a large scale to address the current epidemic[54]. If healthcare providers strictly adopt the WHO standard protocol called 'Interim guidance to national health authorities and blood transfusion services,' it shall be one of the safest as well as suitable therapeutic modalities to save lives.

Though there is as yet no licensed treatment proven to neutralize the virus but a wide-range of blood, immunological and drug therapies are under development. At the moment, two potential Ebola candidate vaccines are undergoing for clinical and immunological evaluation[55]. One experimental drug viz., ZMapp was administered to some of the patients (including two US aid workers) and a few of them died. Therefore, there is no substantial evidence to prove that the ZMapp has saved the lives of Ebola patients or had no effect[17].

### Existing Major Challenges and Emerging Opportunities

The potentialities of Ebola fighting antibodies are not identical and it may trigger a few adverse side-effects and negative sequelae[17]. The edict, from some two-hundred public health experts and WHO scientists, was a follow-up to an earlier Ebola ethics review on October 2014 and concluded that blood transfusion would be ethical to transfuse patients experimental therapies when and if they are easily obtainable[17]: (1) possible to

recruit large number of potential donors, (2) collection and, (3) screening of any infectious diseases to potentially save Ebola patients.

### Necessity of Adequate Healthcare Professionals and Facilities

A strong health system immensely minimize a country's vulnerability to potential health risks in terms of disease outbreaks and catastrophes with a high-level of preparedness to mitigate any public health crises. Subsequently, it ensures quality healthcare for their citizens[56]. However, if health systems are ill-equipped to deal with outbreaks and natural disasters, the populations can be very much vulnerable to several infections ultimately death[57]. The Ebola hit West African countries like Guinea, Sierra Leone and Liberia have very fragile health systems, lacking human and infrastructural resources to deal with the outbreaks since they have recently emerged from decades of civil war and insurgencies[2]. The 2014 Ebola outbreak highlights how an epidemic can proliferate rapidly and pose huge problems in the absence of a strong health system[56].

When the recent Ebola outbreak erupted, the capacity of health systems in Guinea, Liberia and Sierra Leone was limited[56]. Essential health-system functions were not performing well and this hampered the development of timely response to the outbreak. Besides, there were inadequate qualified health professionals[58] as well as infrastructure, logistics, health information, surveillance, governance and also, the drug supply chains were feeble[56].

### Sharing Knowledge and Resources: a Key to Saving Lives

In the Ebola-hit countries, all the febrile individuals need to be screened for Ebola and even if they are found to be negative, they still need to be treated for Ebola. Besides, normal routine services like paediatric, antenatal, safe delivery and postnatal services should be assured while dealing with the direct and indirect effects of epidemic. Otherwise breakdown of general health services may slay more people than the epidemic[56]. In the remote rural areas the health system is virtually nonexistent or if it does, it often runs down a clinic with shortage of essential life-saving medicines and these countries must improve with their national healthcare sectors immediately.

Since these third world countries lack resources and funds to implement effective intervention strategies, appropriate long-lasting workable strategy has to be framed by bringing all potential stakeholders. It is extremely important to fight against the 'common enemy', the so called 'Ebola'. It must include various non-governmental organizations, civil society and international organizations to incentivize the national health systems, both to mitigate the direct consequences of the outbreak and ensure all essential health services being delivered[56]. It could pave the way to combat with the Ebola related illness, deaths as well as to minimize the avoidable deaths due to various other infectious diseases[56]. Besides, international donors, and agencies must assist them to bolster their health system to develop stronger disaster preparedness for the future outbreaks.

### Maximum Use of Supportive Therapy (MUST)

The purpose of the MUST is to save the lives. It includes intravenous (IV) drips to substitute the excessive fluid loss due to diarrhea and vomiting. Balancing of electrolytes such as calcium or potassium could prevent kidney and heart failure. Furthermore, nasogastric tubes for feeding and as well as diagnosis and treatment of secondary infections like malaria could be useful to minimize the Ebola related illness and deaths. In addition, MUST might reveal side-effects of new drugs that would otherwise be masked by Ebola symptoms, and it could reduce the rate of complications that might be incorrectly blamed on a drug[59].

### Integrative Approaches

Indeed interagency policies for outbreak detection and rapid response is extremely important. Besides, understanding the cultural and traditional risk factors within and between nations could be useful to develop appropriate communication strategies to generate awareness among people. In addition, the regional coordination and collaboration, particularly with governments and health ministries throughout Africa[27] could pave the way to minimize Ebola related illness and deaths. Pandey et al[60] urged the effective integrative approaches like case isolation, contact-tracing with quarantine, and sanitary funeral practices must be strictly implemented in order to contain the Ebola outbreak. It has been reported that the actual number of Ebola infection underreported as much as seventy-five percent are due to several factors and it has torn the society in the

poverty stricken countries. This has to be addressed immediately unless otherwise a single infected individual is enough to create Ebola outbreak.

### Formulation of Effective Chemotherapy

Though currently we have a few anti-viral drugs to treat several viral illnesses, there is no approved specific therapeutics to treat filovirus infections. It is a matter of deep and grave concern and pressing need to develop both preventive and curative antiviral agents against filovirus infection[6]. The experimental Ebola drug called 'ZMapp' has been administered to a limited number of Ebola victims and the results are quite promising. Notably the drug (ZMapp) has proved as a potent antiviral agent in monkeys. However, further clinical trials are yet to be conducted to demonstrate its safety and efficacy in human[27]. The WHO expert panel has considered the outlook for another seven potential Ebola drugs, but none of them has been proved of effectiveness against Ebola in humans.

### Ebola Vaccine Development and Clinical Trials

The unprecedented 2014 EVD epidemic has prompted an international response to accelerate the availability of a preventive vaccine. Two vaccine candidates viz., chimpanzee adenovirus serotype 3 (ChAD3-ZEBOV) and recombinant vesicular stomatitis virus (rVSV-ZEBOV) are currently being tested in humans. Both vaccines have shown to be safe and efficacious in animals. Further Phase 1 results are expected to emerge during December 2014 to January 2015[55].

- **Phase I clinical trials** of the cAd3-ZEBOV vaccine in healthy adults are nearing completion in the United Kingdom, United States, Mali and Switzerland, whereas, the rVSV-ZEBOV vaccine, trials are well advanced or near completion in Canada, the United States, Gabon, Germany, and Switzerland. Trials in Kenya are begin September 2014.
- **Phase II clinical trials** of the cdA3-ZEBOV will test the safety and potential to induce an immune response in larger numbers and in broader populations, particularly among children. These trials are expected to begin in Cameroon, Ghana, Mali, Nigeria and Senegal in early 2015.
- **Phase III clinical trials** are planned to start in the first quarter of 2015 in Guinea, Liberia and Sierra Leone to assess the extent to which the vaccines protect against EVD and to gauge the feasibility of full deployment.

Besides, two other vaccines – one developed by Johnson and Johnson and the other by Novavax – are in due to enter clinical trials in the very near future[55].

### Cost-free Ebola Vaccination

WHO Director-General (Dr Margaret Chan) has indicated that developing Ebola vaccine is not a profit-driven industry, as the victims are poorest people to procure vaccine. At least in the humanity ground the international stake holders and concerned authorities must initiate to develop low-cost potential vaccine and all people must be vaccinated at least in the Ebola-prone African countries. However, with the available existing resources we can substantially contain the Ebola outbreaks by generating awareness and creating supportive community.

## Conclusions

Indeed, EVD remains one of the most dreadful infectious diseases and the recent 2014 outbreak is the most devastating in terms of fatality rate in recorded Ebola history. At the moment, there is no effective curative agents to fight against our common enemy. WHO scientists and a group of key public health experts endorse the blood transfusion as an empirical modality by considering various existing therapeutic options to contain this deadliest outbreak. Nevertheless, it is one of the challenging tasks to implement in the resource-limited settings of tropical sub-Saharan Africa. Therefore, the following interventions must be adopted to address the existing major challenges effectively and immediately: (1) pinpointing the virus's source, (2) early case detection, (3) quarantine the infected people, (4) tracking and treating the Ebola patients, (5) providing supportive care, (6) free supply of personal protective equipment (PPE) in Ebola epicenters, (7) development and application of simple diagnostic tools and potent therapeutic interventions, (8) identifying and understanding the emerging viral strains through gene sequencing, (9) building a strong global health infrastructure/network, (10) generating the awareness through print and E-media (11) patients who died of Ebola should be cremated or buried promptly in a hermetically

sealed casket and, (12) community engagements through social mobilization.

Besides, presently several clinical trials are underway to assess the potentialities of various anti-viral agents and vaccines against EBOV and the preliminary results are quite encouraging. Until acquiring reliable therapeutic agents, we can adopt blood transfusion as therapeutic modality by strictly following the WHO standard protocol in order to avoid any undesirable effects. Furthermore, strong regional, national and international multilayered collaborations by bringing all the stakeholders is extremely important to address the existing challenges to build a Ebola-free healthiest society in the near future.

### Acknowledgements

The authors would like to acknowledge Ms. L. Melita for her sincere assistance in editing the manuscript. Our last but not least heartfelt thanks go to our colleagues from the Department of Environmental Health, Faculty of Public Health and Tropical Medicine, Jazan University, Kingdom of Saudi Arabia, for their kind support and cooperation.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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