Convalescent Serum Therapy as Rapid Advance Treatment for Ebola in West Africa

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Abstract

The 2014 public health crisis in Guinea, Liberia, and Sierra Leone has brought Ebola Viral Disease (EVD) to everyone's attention. Discovered in 1976, this deadly disease infrequently struck in remote areas of Africa. This article will critically review the literature and describe the pathobiology, transmission, signs and symptoms, diagnosis, treatment, and prevention of EVDwhich, was predicted by the Centers for Disease Control to potentially infect 1.4 million persons in Liberia and Sierra Leone by January 2015 ("Questions and Answers", 2014). Thankfully this worst case scenario did not occur and we may be experiencing natural burn out of the outbreak along with the results of aggressive education and supportive treatment as in Sierra Leone. There is no established treatment for EVD despite successes in non-human models. The WHO endorsed Convalescent Blood Products ("Potential for use of…," 2014) after it showed promise in Democratic Republic of Congo. In 2014, American Ebola patients recovered after receiving Convalescent Serum Therapy (CST) with experimental therapies like Zmapp, TKM-Ebola, and Brincidofovir. We may have missed the window of opportunity to establish the efficacy of these potential therapies, which may have unprecedented implications for health status, healthcare infrastructure development in the future, and the economic viability of the sub-region for decades to come. Additionally, an endemic area will pose a threat to the rest of the world as a potential incubator/exporter of this dangerous viral illness.

Keywords: *Ebola virus disease, convalescent serum therapy, convalescent blood products, rapid advance treatment, super-spreaders, cultural burial practices, personal protective equipment, survivability, susceptibility, hemorrhagic fever, Ebola prevention and treatment implementation plan, Hastings Ebola Cocktail.*

Introduction

Ebola Virus Disease (EVD) is a viral hemorrhagic fever caused by the Ebola virus (EBOV) (Breman et al., 1978). During the latest unprecedented outbreak in Sierra Leone, Liberia, and Guinea, initial mortality rates reached between 55 and 70%, with no well-established treatments yet found for EVD. While numerous in vitro systems and animal models have led to effective treatments in non-human primate models, no in vitro systems have been

systematically tested in humans nor are expected to be available to impact the current epidemic (Ansari, 2014).

The main purpose of this review is to present an argument for the usefulness of Convalescent Serum Therapy (CST) as a Rapid Advance Treatment (RAT), both to reduce mortality rates and also to gain the psychological advantage as more transmission determent strategies are deployed beyond the standard Quarantine, Isolation, and Case Finding public health tools. We will review CST and compare it to other experimental and routine therapies that were touted at the start of the epidemic in West Africa about 12 months ago (2014) but have since been unavailable to diminish morbidity and mortality (Ansari, 2014).

We will start by reviewing EVD demographics, biology, pathophysiology, clinical presentation, diagnosis, and predilection for the immune system. The review will also identify individuals who are most at risk, EVD's transmission mechanisms, and available methods for prevention of transmission. The article will also discuss benefits of surveillance, early warning, the fear of endemic EVD, and how these factors influence the socio-developmental trajectory of the West African sub-region.

Ebola Virus Disease and Human Development

The West African Ebola epidemic's short-term socioeconomic impact and long-term effect on human development will take some time to fully realize. It is clear, however, based on the scale of the current outbreak, that the economies of the most affected countries, Sierra Leone, Liberia, and Guinea, will bear the aftermath of this epidemic for a long time to come. The World Bank Group recently completed forecasts of economic impacts on the three most affected countries and on the West African region (2014). These conservative forecasts focus on core economic activity but do not account for long-term impacts generated by mortality, failure to treat other health conditions due to aversion behavior and lack of supply capacity, school closings and dropouts, and other shocks to livelihood. Nonetheless, in the short term, this forecast estimates the forgone output for these three countries to be approximately US$359 million in 2013 prices: 2.1 percentage points (pp) drop in gross domestic product (GDP) for Guinea, 3.4 pp drop in GDP for Liberia, and 3.3 pp drop in GDP for Sierra Leone. These very significant numbers represent a drop of anywhere from a third to half of economic growth rates for these countries (World Bank Group, 2015).

The long-term outlook is assumed since it is unclear whether the epidemic can be completely extinguished (the "zero cases" scenario) or whether it will ultimately stabilize in an endemic low-intensity mode. These two scenarios bear very dire prospects for long-term development in the affected countries. With a combined GDP of $13.1 billion in 2013, the worst-case impact predictions forecast over $9 billion in loss, even if the disease is rapidly contained (Holtz, 2014). According to the World Bank 2014 Ebola economic report, which considers both "low Ebola" and "high Ebola" scenarios, the long-term impact on development could be crippling to countries already devastated by war and entrenched poverty.

Ultimately the effect of this epidemic on quality of life is just as important as the direct effects on the economies of these countries and of the region. The economic effects, whether bearing directly on economic activity or indirectly on development, will negatively manifest in human quality of life, including the people's health status. By focusing on the human impact, we can better galvanize action that is relevant both for Ebola outbreaks as well as post-Ebola recovery. Therapies that cost-effectively improve survivability, such as CST, are particularly important in this respect. In the post-Ebola era, it will be of particular importance to establish empowering grassroots community health systems on a community-by-community basis.

Etiology of Ebola Virus Disease

EVD is a viral hemorrhagic fever that can be abrupt, severe, and fatal in humans. It also infects non-human primates like monkeys, gorillas, and chimpanzees. The Ebola virus is part of the family Filovirida and genus Ebolavirus. Its molecular structure is that of an enveloped, negative sense Ribonucleic acid (RNA), 1200 nanometers long, that codes for several proteins that function in its life cycle and aid in its pathogenesis (Ansari, 2014). EVD was first isolated during an outbreak in 1976 in the Democratic Republic of Congo (DRC), near the Ebola River. Outbreaks have been relatively sporadic and short-lived, killing virtually all who are infected and burning out quickly. In fact, there was a minor outbreak in DRC concurrent with, but separate and distinct from, the West African outbreak (Maganga et al., 2014).

To date, five subspecies of Ebola virus have been described: the Zaire, Sudan, Tai Forest, Bundibugyo, and Reston viruses. Reston has not caused clinical disease in humans and was isolated in infected cynomolgous monkeys from the Philippines (Ansari, 2014). Ebola's natural reservoir is not yet known with any certainty. It is thought to reside in the fruit bat or some form of zoonotic illness (Leroy et al., 2005). This raises the interesting question of whether EVD is transmitted by wild game, known locally as "bush meat," that is consumed in some of the affected areas ("Facts about Bushmeat and Ebola," 2014).

It is not yet known how the EVD arrived in West Africa. The most common hypothesis is that patient zero, a young boy in Guinea who has since died along with his entire family, contracted the virus through direct contact with an infected animal (Funk & Piot, 2014). However, this hypothesis has not been historically substantiated. EVD invades human tissues and cells by entering through breaks in the skin and mucus membranes when a person is exposed to body fluids from an infected individual. Person-to-person transmission of EVD occurs via contact with an infected person's blood or secretions, including urine, saliva, feces, vomitus, and semen. Also, exposure to objects like needles that are contaminated with infected secretions can cause transmission by needle-sticks, whether inadvertent as in the case of healthcare and laboratory workers, or by needle and syringe re-use as the result of improper sterilization techniques (Breman & Piot, 1976). Poor barrier protective practices in health care settings can also result in EVD contraction. This includes not adequately wearing Personal Protective Equipment (PPE) like masks, gowns, or gloves, and improper disposal of contaminated instruments.

Although EVD's pathobiology is not well understood, it is known that the virus disables the immune system, "allowing for the uncontrolled replication of Ebolaviruses" (Ansari, 2015). The initial symptoms presentation complex may include fever (>38.6 C or 101.5 F), headache, joint aches, muscle aches, weakness, diarrhea, vomiting, abdominal pain, and anorexia. In fact, this initial symptom complex is almost identical in two geographically distinct cohorts of patients, one in Hastings, Sierra Leone who presented with fatigue, anorexia, fever, vomiting, nausea, diarrhea, muscle pains, joint pains, and headaches (Ansumana et al., 2014), and one in Boende Town, DRC who presented with fatigue, anorexia, fever, vomiting, nausea, diarrhea, muscle pains, and headaches (Maganga et al., 2014).

While the extremes of the incubation period last from two to twenty-one days, a typical incubation period lasts eight to ten days. Early symptoms are usually the ones typified above, but can also include unexplained bleeding or bruising, rash, conjunctival injection, hiccups, cough, sore throat, chest pain, dyspnea, dysphagia, and life-threatening hemorrhage. Many of these also tend to be late complications. Early diagnosis is difficult because symptoms are non-specific, which presents a significant challenge, as potentially life-saving hospital supportive treatment does not usually occur until later in disease progression. Best practices include immediate isolation of patients who present early symptoms and are at risk for EVD and notification of public health professionals for immediate point of care testing in the field (Ebola Diagnosis, 2015). Early supportive treatment such as treatment with Intravenous fluids (IVF), maintenance of oxygenation and blood pressure, and treatment of other infections, increases the chance of survival as has been demonstrated during this epidemic (Ansumana, et al., 2015).

Culturally distinct burial practices that include touching the remains of a loved one may have contributed significantly to spread of the disease and have emerged as a distinct risk factor for disease transmission and increased prevalence in affected communities (Ebola Situation Report, 2015). Both the Central African and West African regions share this distinct risk factor for transmission of the virus (Maganga et al., 2014). It has been reported that 60% of EVD transmission cases in Guinea were linked to funerals that involve close contact with corpses (Chan, 2014). More medical anthropology research will need to be undertaken to understand the actual mechanism and implications of this hypothesis. There is no current understanding or general agreement on what these so-called cultural burial practices involve.

As expected, family, friends, health care personnel, and aides are at greatest risk as they perform direct patient care and clean up infected bodily fluids. Other stakeholders most concerned about the effects of this disease include people living in epidemic areas, international staff working and living in affected areas, airline personnel, travelers, staff of Governmental and Non-Governmental Agencies (NGOs) such as the Red Cross and Médecins Sans Frontières (MSF), and international agencies like the United Nations and the World Health Organization (WHO). Current thinking and published literature on susceptibility and survivability are primarily based in the study of basic science on molecular genetic analysis of so-called transcriptomes and kinomes (Ansari, 2014). These are genetic epitopes that are thought to naturally expose Ebola victims to either improved or weakened survival rates There is anecdotal

indication that sociopolitical and community factors, including but not limited to poor community health infrastructure and poor governance that cannot completely prevent at-risk burial practices, also expose certain groups of people to greater risk (Ebola Situation Report, 2015).

Convalescent Serum Therapy in Ebola Patient Management

Given the dearth of therapies available to treat this devastating viral illness, the World Health Organization (WHO) has released a position statement supporting the use of Convalescent Blood products (CBP) to treat EVD in this outbreak (Blood Regulators Network, 2014). There is evidence to suggest a significant mortality benefit with the use of convalescent whole blood, which was first described in the Kikwit, DRC outbreak in 1995, when a seven out of eight survival benefit was demonstrated in a small study. However, the epidemic ended before a well-designed clinical trial could begin (Muyembe-Tafum et al., 1999). Convalescent serum is defined as a blood product devoid of red blood cells and clotting factors that contains Immunoglobulins IgM and IgG obtained from someone who has recuperated from a particular infection, in this case EVD. Convalescent serum therapy is the use of this serum to treat a person with the same disease. Several studies on CST treatment methodology are well established in the treatment of other viral hemorrhagic fevers such as Junin virus hemorrhagic fever in Argentina (Erina et al., 2008; Maiztegui, & De Damilano, 1979). Lassa passive immune therapy was also used successfully in five well-documented cases in Nigeria in 1970, in which four out of five patients recovered and only one was considered to have had an adverse reaction (Monath & Casals, 1975). Pooled convalescent serum therapy was implemented in the treatment of Lassa fever in Lofa County, Liberia in 1986; early data showed some benefit but unfortunately the trial was terminated prematurely due to an armed insurgency at the time (Frame, 1990). In addition, other small cohorts of patients treated in other studies using convalescent serum showed improvement that was attributed to the serum (Frame & Verbrugge, 1984; Leifer et al., 1970). According to media reports, convalescent blood product (CBP) has been used in 11 recorded cases in the Western hemisphere during the current EVD outbreak (Yahoo Finance, 2014). All of these patients recovered without adverse outcomes in the short term. However, they also received other experimental therapies alongside CBP like Zmapp, TKM-Ebola, and Brincidofovir; thus the dispositive factor in their recovery remains unclear.

Given these positive examples of CBP use, we will perform a comparative review of the use of CBP versus other experimental and routine therapies, and then comment on the potential usefulness of CBP in future potential epidemics in the region and how CBP might impact healthcare infrastructure development and economic independence and viability for decades to come. Multiple candidates have been proposed and are under examination for the treatment of Ebola. These candidates fall largely into the categories of blood therapies, drug therapies, and vaccines (Table 1). Unfortunately, none of these candidate therapies have been deployed in the affected countries to the extent necessary to make a difference in the current epidemic. No doubt the reasons for this unfortunate situation will be under debate in the literature and lay press for years to come.

As Table 1 illustrates, blood therapies appear to be the most accessible, affordable, and easy to deploy by the affected countries independent of external aid. In contrast, drug therapies and vaccines are out of reach for these resource-strapped countries, at least for the near future.

Table 1
Treatment Options for Ebola Virus Disease (EVD)

Treatment Type	Overview
Blood Therapies	Blood trials were successfully used in the Kikwit, DRC outbreak with reduction of case fatality rate (CFR) from 80% to 12.5%, but only in 8 patients. Limited whole blood trials in Sierra Leone also anecdotally reported 12.5% CFR with whole blood use (Samba A., 2015). Serum treatments are standard in Argentina for treatment of the Junin virus or Argentine hemorrhagic fever (AHF), reducing mortality rates to less than 1% when administered within a week of infection (Singh & Ruzek, 2014).
	• Natural and affordable resource, thus less costly to the community • Reduced complexity in donor-to-recipient compatibility and donors can donate up to twice each week • Requires considerable logistical expertise to avoid mislabeling and mismatching and to ensure proper storage
Drug Therapies	Drug therapies include the commonly known drug Zmapp, which was used to treat missionaries Kent Brantly and Nancy Writebol. Other similar drugs include Zmab and Favipiravir.
	• High research and production costs may not be affordable for most in poor countries. • Require cold storage, another challenge for these countries
Vaccines	These will require lots of testing before approval. Also, vaccines can be challenging to develop when breakouts do not last long enough for large-scale tests to be conducted.
Other: "Hastings Ebola Cocktail" (HEC)	The Hastings Ebola Cocktail was used to treat 518 patients, resulting in 24% CFR. It is a widely available and affordable cocktail of IV fluids, antibiotics, antimalarial and nutritional supplements developed by Sierra Leonean physicians. The protocol involves a large number of components, thus unavailability of any constituent may undermine the integrity and potency of the entire protocol.

Therefore, it would be appropriate for these countries to devise an Ebola Prevention and Treatment Implementation Plan (EPTIP) that administers blood therapies as a significant plan of action, in conjunction with the prevention, containment, and modification of traditional burial practices.

Due to the highly contagious nature of the disease, EVD patients, and often their family members, are quarantined, while healthcare workers are required to wear personal protective equipment (Brodwin, 2014). Other safety precautions include limiting the analysis of EVD patients' blood in clinical care non-virus isolation methods like reverse transcriptase polymerase chain reaction (RT-PCR), antigen-capture enzyme-linked immunoabsorbent assay (ELISA), and IgM ELISA, coupled with inactivation techniques done in mobile laboratory Point of Care Testing (POCT) under appropriate biosafety conditions (Towner et al., 2004). Given the initial efficacy in the use of these techniques to limit spread and thus total mortality, some experts argue that more attention should be focused on primary prevention, early detection, and containment techniques, over design and discovery of direct treatment modalities that are currently unavailable and may or may not prove to be effective in the long term. While this may have been a successful strategy in limiting total mortality of the disease during small-scale epidemics in remote Central African regions that were already isolated (Maganga et al., 2014), it has not been systematically applied in the West African epidemic where mortality rates have remained high ("Ebola Situation Report," 2015). CST could significantly help in large-scale epidemics like the one in the West African sub-region, where robust cross-border mixing of populations, significant urbanization, and the relative ease of travel to urban areas make the quick isolation and quarantine of Ebola patients far more challenging. CST, in conjunction with" an infection control method, has been recommended in the treatment of viral hemorrhagic fevers (Ippolito et al., 2012).

Susceptibility and Survivability

Analysis of the rate of spread of the epidemic is based on an estimation of the basic reproduction number (R_0), which is the average number of secondary cases that arise when one primary case is introduced into an uninfected population. When R_0 is greater than 1, infection may spread in the population, and the rate of spread increases with increasingly high values of R_0. After the early phase of exponential growth in case numbers, once infection has become established, the number of people still at risk declines, so the reproduction number falls from its maximum value of R_0 to a smaller, net reproduction number, R_t. When R_t falls below 1, infection cannot be sustained. Estimates of R_0 and R_t help in evaluating the magnitude of the effort required to control the disease, the way in which transmission rates have fluctuated through time, and the effectiveness of control measures as they are implemented (WHO Ebola Response Team, 2014). The detailed dynamics of Ebola, like any other infectious disease, can be investigated through the use of Transmission Network Analysis to understand the actual mechanisms of spread. Particularly important is the role of a small percentage of super-spreaders who account for an unusually high percentage of disease transmissions (Smith, 2015; Yu-Hsiang et al., 2014).

The case of one herbal healer who reportedly infected over 800—with over 360 of those dying—illustrates the super-spreader phenomenon in the West African Ebola epidemic of 2014 (Menezes, 2014). Through analysis of these super-spreaders, a stronger, more effective response to the disease could have been launched earlier. Analyses have revealed that unsafe burial practices and contact with infectious individuals without adequate personal protective gear are likely cataclysmic mechanisms of Ebola spread. The main driver of communal susceptibility, from a policy perspective, is early reporting and effective quarantine actions, coupled with adequate treatment by the affected communities. A related study of the efficacy of CST or Immune Serum Treatment of Junín virus-infected marmosets was found to reduce mortality from 100% to 25% (Avila, 1987).

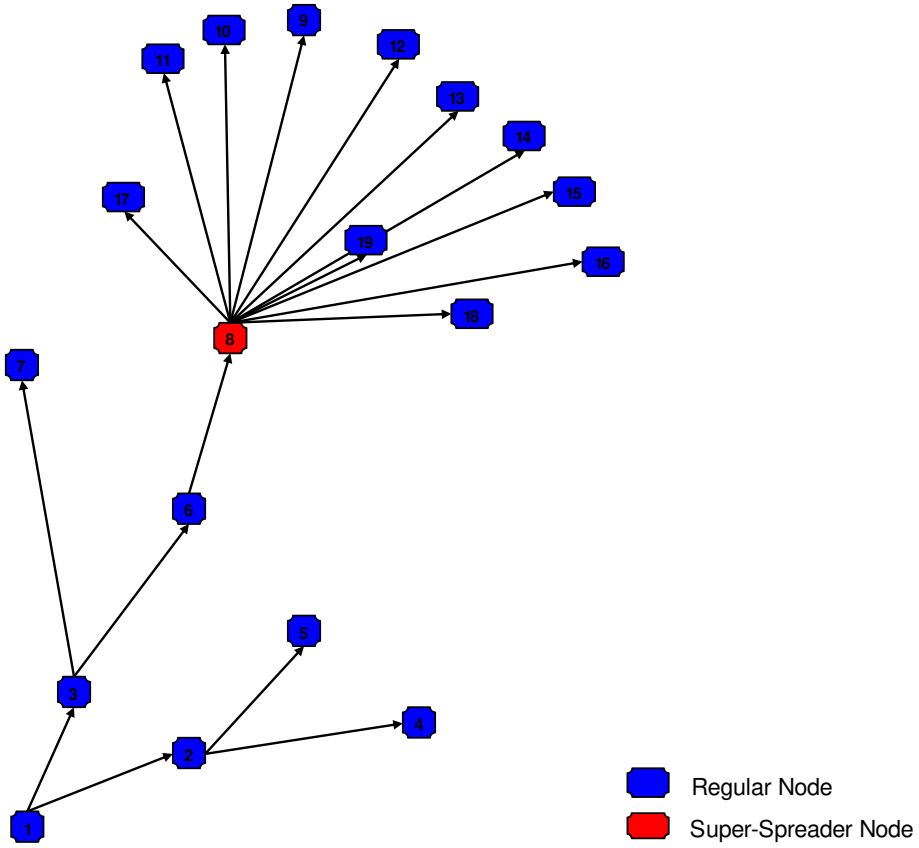

Figure 1. Epidemic Transmission Network Simulation illustrating the super-spreader phenomenon

We must integrate lessons learned from the current Ebola outbreak into a long-term epidemic vigilance system, not only to prevent and treat Ebola, but also to treat and prevent a wide range of communicable diseases that may emerge in the future. Above all, we want to emphasize the role that poverty and mistrust of governmental authority have played in deterring quarantine orders, contact tracing, and public health education. Without the voluntary community support and compliance that we have seen during this Ebola outbreak, governmental quarantine edicts can have

little to no influence in combating the spread of any communicable disease and such edicts may hamper attempts to reduce susceptibility and spread. Instead, governance should create an environment of community empowerment and shared sacrifice. A sense of common destiny underpins community consent to the challenging measures that are necessary to protect an entire community and ensure that future outbreaks are more easily controlled.

Analysis of the epidemic spread in West Africa also offers lessons for cross-border epidemic control. Ebola spread from Guinea and then into Liberia and Sierra Leone has followed a somewhat expected trend. Further spread into Nigeria, Mali, and even Senegal is unsurprising. However, the case of Ivory Coast, a country that shares a border with Liberia's Nimba County and yet reports zero cases of Ebola, is quite significant (Reuters, 2014). Two likely reasons for the difference are effective border vigilance and quick and thorough education of Ivory Coast's population to the risks and precautions of the Ebola threat. That said, the significance of Ivory Coast experiencing "traditional" Ebola versus the more recent West African variety is unknown. The devastating speed of the 2014 Ebola spread emphasizes the need for better cross-border cooperation and vigilance in the detection and containment of likely future outbreaks. Most of the border communities have long and deep historical ties that have been disrupted to varying degrees by colonial borders and more recently by war. These cross-border ties must be revitalized so that they become the basis for early warning communication systems.

Air transportation has also served as a medium for the Ebola spread, as was the case in the transmission of Ebola into Nigeria and the United States. The challenge with air travel is the size, complexity, and volume of the people flow and transportation network. Many airports are already bogged down with security checks for outbound flights; additional measures for inbound flights may prove to be too challenging to handle. Low cost, unobtrusive, and long-range temperature monitoring devices such as those deployed in Chinese airports in the wake of the SARS outbreak are one potential strategy for West African airports.

While it is difficult to estimate the economic impact of the Ebola outbreak on the most affected countries, there is no doubt that impact on economic activity has been significant, with schools closures and severe restrictions on travel and commerce. While the goal of "getting to zero," as the slogan of a Sierra Leone public health campaign proclaims, is ideal, realistic planning must also consider the possibility that certain areas may control the virus but never quite eliminate it. In the scenario of locally endemic Ebola outbreaks, societal adjustments would create a state of permanent vigilance, which would then create severe socioeconomic impact, resulting in yet another blow to development in these countries. The threat of an EVD flare-up would not only affect the countries themselves, but also put all of the countries in the region, as well as outside the region, at risk. This nightmare scenario would call for a truly international response, requiring mutual cooperation with the affected countries and communities still in the lead. From the consideration of survivability, there is still no definitive cure for Ebola, but CST, when serum from survivors is transfused into current sufferers, has shown some promise.

In light of this challenging situation, CST seems to be an obvious low-cost and high impact approach, especially for resource-strapped countries in West Africa. CST can serve as an ideal

Rapid Advance Therapy (RAT) to quickly quell resurgent EVD in impoverished hotspots in the future. The extraction, storage, and transfusion of serum is now a basic medical procedure that can be safely administered practically anywhere in the world, and it does not rely on complex and expensive technologies or pharmaceutical products. The areas in West Africa most affected by the Ebola epidemic, particularly Sierra Leone and Liberia, are now just recovering from resource wars that have wreaked serious havoc on the fabric of these communities.

Even without considering that many of these communities are war-torn, there are the perennial problems of medical personnel and supply shortages and chronic underfunding of the health systems in these countries. These facts were manifest in the ineffectual and delayed responses to Ebola in Sierra Leone, Liberia, and Guinea. The conclusion therefore is that, in light of the governance vacuum from the capital cities of the region, local communities are now required to develop and implement grassroots community health programs to prioritize and use available resources at their disposal for addressing urgent needs of the people.

CST Supply and Community Integration

The advantage of CST lies in the fact that people who have survived the disease are gifted with curative powers. The blood plasma or serum preparation process involves spinning a tube of fresh blood containing an anticoagulant in a centrifuge until the blood cells separate and fall to the bottom of the tube. The blood plasma is then poured or drawn off. Plasma donation can be safely done much more often, up to three times a week, in contrast to whole blood donation that typically requires an eight-week period between donations.

Fortunately, CST can be designed, developed, maintained, owned, and controlled by the poor communities independently, as opposed to the more expensive therapies that require a large financial and technical infrastructure to deploy. In a multi-faceted grassroots Ebola response program, it is imperative that we integrate Ebola survivors into the medical care system as community groups to donate plasma for CST for current Ebola sufferers. In such a bottom-up structure, the engendered reciprocity and trust will likely contribute significantly to the strengthening of the community fabric in communities that have been plagued by entrenched poverty, poor health, poor governance, and deep mistrust of their governments as well as the international community.

Conclusion

We believe therefore that CST should be developed as a Rapid Advance Therapy (RAT) to quickly quell resurgent EVD in impoverished hotspots around the world, given that CST is the only therapy that can be designed, developed, maintained, owned, and controlled by resource-strapped countries. This is because convalescent serum can be considered as a natural resource and is accessible through survivor engagement and support, setup and maintenance of plasma banks, in-depth training of personnel, and standard aggressive hospital treatment, all of which can be accomplished within the resource structures of impoverished countries.

Conversely, other experimental EVD therapies are still not fully tested and are too expensive, requiring massive financial investments, capital expenditures for basic research facilities and support infrastructure, and expertise unavailable to these impoverished countries, leaving them dependent on wealthy international donor groups.

A strong containment strategy couples CST Rapid Advance Therapy (RAT) with early EVD outbreak detection and prevention, which is dependent on a grassroots health infrastructure. In the absence of this containment strategy, the future for sustained socioeconomic development in the West African region is bleak. This recognition is tied to the idea of "getting to zero", but is punctuated by a nightmare scenario of not quite "getting to zero", creating economic chaos and "lost decades" to come and a perpetually "contaminated" region that diaspora and expatriate tourist elements might flee from.

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