REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Ebola Virus Disease: A Perspective for the United States

Miguel G. Madariaga, MD, MSc

Infectious Diseases, Naples Community Hospital, Naples, Fla.

ABSTRACT

Ebola virus caused an epidemic of unprecedented extension in West Africa. There was concern that the outbreak would not be controlled for a prolonged period of time. Two cases of infected returning travelers have been reported in the US. One of the cases has been associated with secondary transmission and other infected subjects have been repatriated for treatment. This article reviews the etiology, pathogenesis, transmission, clinical manifestations, diagnosis, treatment, and prevention of the disease with emphasis on the identification and management in the US.

 • *The American Journal of Medicine (2015) 128, 682-691*

KEYWORDS: Diagnosis; Ebola; Filovirus; Prevention; Treatment

The recent repatriation of several health care workers affected with Ebola virus disease to the US and the arrival of an infected traveler from Liberia and an infected health aid worker from Guinea have galvanized the interest in a disease that is ravaging West Africa. This article summarizes current knowledge and perspectives on Ebola, and pretends to be a primer for clinicians working in the US.

ETIOLOGY

The Ebola virus, named after a tributary of the River Congo, belongs to the family *Filoviridae*. *Filoviridae* is a family of long filamentous viruses that include 3 genera: *Cuevavirus*, *Marburgvirus*, and *Ebolavirus*. The last 2 are pathogenic in humans.

There are 5 species in the genus *Ebolavirus*: Taï Forest (previously known as Ivory Coast), Sudan, Zaire, Reston, and Bundibugyo.[1] Sudan and Zaire are the species associated with higher lethality. Reston seems to cause asymptomatic disease in Asia. The species *zaire* is causing the current epidemic in West Africa.

Funding: None.

Conflict of Interest: None.

Authorship: The author is solely responsible for the content of this manuscript.

Requests for reprints should be addressed to Miguel G. Madariaga, MD, MSc, Naples Community Hospital, 800 Goodlette Road, Suite 370, Naples, FL 34102.

E-mail address: mmadariaga@nchmd.org

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2015.01.035

The Ebola virus genome contains a nonsegmented, single-stranded linear RNA molecule of negative polarity. The full viral sequence of the genome based on isolates from previous outbreaks is available online.[2] The RNA genome is wrapped around proteins NP, VP35, VP30, and L. Surrounding the nucleocapsid there is a lipid envelope with embedded glycoproteins. Between the outer envelope and the nucleocapsid there are additional viral proteins VP40 and VP24. The **Table** shows the function of each protein and **Figure 1** shows the structure of the virus.

PATHOGENESIS

Although previous studies using modified Ebola virus have suggested clathrin-mediated endocytosis or caveolin-mediated endocytosis as the entry mechanism into the cell, experiments with the wild virus showed macropinocytosis, a form of endocytosis associated with cell surface ruffling, as the primarily internalization process via interaction of viral glycoproteins and cell surface receptors.[3]

Once inside the cell, the viral polymerase complex proceeds along the ribonucleoprotein initiating the transcription. It is likely that VP24 holds the ribonucleoprotein in a condensed state, preventing the complex from proceeding along the template. On the other hand, VP30 has the opposite effect, favoring the viral genome transcription.[4]

The viral polymerase complex has 2 functions: transcribing the negative single-stranded genome into monocistronic pieces of positive mRNA and replicating the

positive-stranded mRNA to synthesize the viral progeny genome.

Recently, it has been reported that VP40 has a crucial role in viral replication. Contrary to the biology dogma that a gene encodes a single protein with a unique tridimensional shape, it seems VP40 can assume 3 different shapes: one while the virus travels through the infected cells, at the time of transcription (serving as a regulator), and as an important component of the liner structure in the newly formed virions, thus helping with the budding and release of the viruses from the cell.[5]

After entering the body via small lesions in the skin or mucous membranes, the virus targets monocyte/macrophages and dendritic cells. Interaction of the virus with the immune system may actually be detrimental by triggering an antibody-dependent enhancement of the Ebola virus infection: complexes formed by virus, antibodies, and C1 may actually promote endocytosis of the organism, and may potentially explain the virulence of certain strains.[6]

After acquisition, the infection spreads via the lymphatic vessels to regional lymph nodes and from there, causes viremia infecting the spleen, liver, and adrenal glands (**Figure 2**).

CLINICAL SIGNIFICANCE

- Ebola virus disease (EVD) is transmitted by direct contact of infected fluids with skin lesions or mucous membranes.
- EVD is highly contagious, but stringent use of personal protective equipment, contact follow-up, and infection control measures can contain outbreaks.
- EVD carries high mortality, mainly due to delayed care and inefficient foreign health systems.
- There are no vaccines or specific treatment for Ebola virus, however, supportive treatment is of upmost importance.

Macrophages and dendritic cells play a key role in the pathogenesis of Ebola virus infection by secreting cytokines, chemokines, and other immune mediators. The consequences of the release of those substances include: mobilization of neutrophils and monocytes, which, in turn, contribute to a spiraling "inflammatory storm," lymphocyte apoptosis, necrosis of hepatocytes, endothelial damage, and coagulopathy, eventually leading into septic shock and disseminated intravascular coagulation.[7]

Very limited information is available on the tissue pathology of Ebola virus; similar to infections caused by Marburg virus, extensive liver necrosis with large intracytoplasmatic eosinophilic inclusion bodies seems to be the most common postmortem finding.

EPIDEMIOLOGY

There is evidence that bats serve as a reservoir for Ebola virus. The initial evidence came from epidemiological observation of cases of Marburg virus infection associated with mining. Subsequently, antibodies against Ebola virus have been detected in several fruit bat species from Africa and Asia, however, only a Marburg virus has ever been isolated from a bat (*Rosettus aegyptiacus*). Laboratory experiments have

Table Protein Components of the Ebola Virus and Their Function

Protein	Location	Function
L	Wrapped around viral RNA	Caps and polyadenylates mRNAs
NP	Wrapped around viral RNA	Needed for the formation of the nucleocapsids
VP24	Between the outer envelope and the nucleocapsid	Reduces transcription and replication of the virus genome by direct association with the ribonucleoprotein complex
VP30	Wrapped around viral RNA	Essential activator of viral transcription
VP35	Wrapped around viral RNA	Blocks the virus-induced phosphorylation and activation of interferon regulatory factor 3, a transcription factor critical for the induction of alpha/beta interferon expression
VP40	Between the outer envelope and the nucleocapsid	Multipurpose protein that regulates transcription and serves as a component of the liner structure in newly formed virions

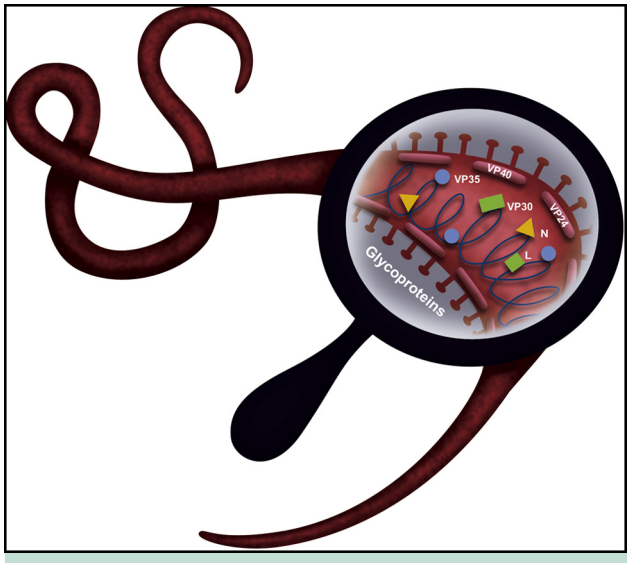

Figure 1 Structure of the Ebola virus. The negative single stranded RNA of the Ebola virus is wrapped around proteins NP, VP35, VP30, and L. Additional proteins VP40 and VP24 lie between the nucleocapsid and the lipid. Glycoproteins spike from the envelope.

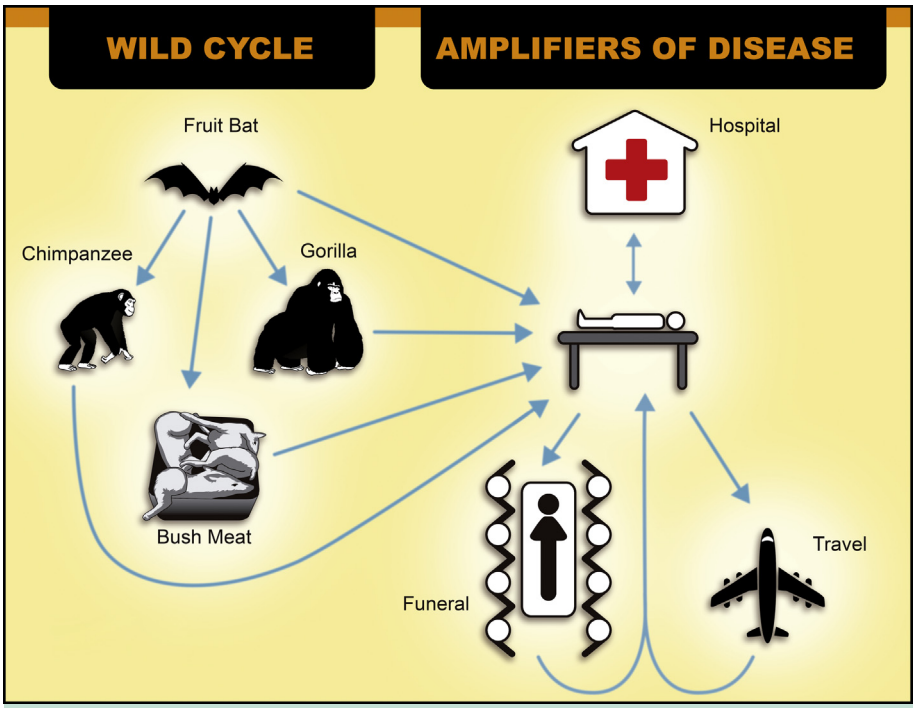

Figure 2 The wild cycle and amplifiers of Ebola virus disease transmission. Fruit bats are the likely reservoir of the disease. In the wild, chimpanzees, gorillas, and potentially other mammals (including so called "bush meat") may become accidentally infected. Outbreaks in humans start by contact with an infected animal. The disease spreads in humans from direct contact. Unrestricted travel, attendance to extended funerals, and stay at hospitals with lack of infection control plans or personal protective equipment amplifies the outbreak.

been able to replicate the Ebola virus in different species of bats and lead to seroconversion without causing disease.[8]

Primates and other mammals are likely accidental hosts of the virus rather than true reservoirs. Devastating epizootics in Central Africa (particularly in the Democratic Republic of Congo or DRC) have caused a substantial decline in the population of gorillas and chimpanzees in that area.[9] Unfortunately, trade and handling of "bush meat" (meat of wild animals including hoofed animals, primates, rodents, and occasionally, bats) is common in poor areas of Africa, despite being considered illegal, and have likely triggered human outbreaks (**Figure 3**).

The first outbreak of Ebola virus disease was reported in 1976 in Yambuku, Zaire (now DRC). The origin of the outbreak was unknown. The Zaire strain caused 318 cases with a mortality of 88%. Reuse of disposable needles and syringes without sterilization was rampant during this outbreak.[10] Around the same time, another outbreak caused disease in Sudan. The Sudan strain affected 151 people, but the mortality rate was 53%. Health care personnel were heavily affected, as no proper barrier precautions were used.[11] Since 1976, episodic cases and frank outbreaks have occurred predominantly in the DRC, Gabon, Sudan, and Uganda. In general, once proper infection control measures have been established, further transmission has ceased. The largest outbreak of Ebola, before the current one, occurred in 3 districts of Uganda in 2000-2001, causing disease in 425 people, with a mortality of 53%. Close contact with corpses during elaborate funerals and lack of adequate personal protective measures explained the extension of the outbreak.[12] The Reston strain of Ebola virus has been introduced on 3 different occasions in 1989, 1990, and 1996 in the US, via monkeys imported from Asia. Four humans developed antibodies but did not experience any type of symptoms.[13]

The largest outbreak of Ebola in history started in Meliandou, prefecture of Guéckédou in Guinea. Initially, a 2-year-old child was affected in December 2013; the source was unclear. A health care worker spread the disease to neighboring districts. By March 2014, a disease characterized by fever, severe diarrhea, vomiting, and fatality rate of 71% was recognized by the Ministry of Health, and soon thereafter, a new strain of Ebola was recognized as the cause.[14] Since then the disease has disseminated to Liberia and Sierra Leone, with the highest number of cases reported from Liberia. None of these countries had reported cases before 2014, except for a single nonlethal case of a researcher who performed a necropsy on a chimpanzee in the Thai Forest area.[15] As of November 2, 2014, the total number of suspected Ebola virus disease cases was 13,015, with 4808 deaths. The total number of confirmed cases was 7965.[16] These counts do not include a high number of patients who distrust the local health care system and who may die or survive without being accounted for. The basic

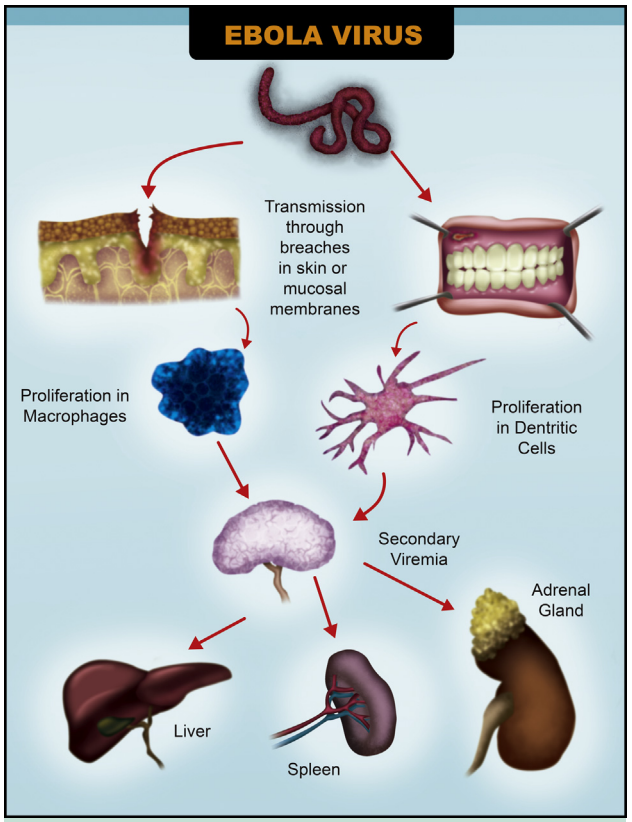

Figure 3 Life cycle of the Ebola virus in humans. After entering the body via small lesions in the skin or mucous membranes, the virus targets monocyte/macrophages and dendritic cells. The infection then spreads via the lymphatic vessels to regional lymph nodes and from there causes secondary viremia infecting the spleen, liver, and adrenal glands.

reproduction number (or number of secondary cases caused by a primary one) has been calculated at 1.71 (95% confidence interval [CI], 1.44-2.01) in Guinea, 1.83 (95% CI, 1.72-1.94) in Liberia, and 2.20 (95% CI, 1.79-2.26) in Sierra Leone. These numbers are similar to the ones reported for previous outbreaks, and—in conjunction with similar clinical presentation and not above-average lethality (around 70%)—suggest that the extent of the current epidemics is not due to virulence or intrinsic factors related to the virus, but rather to inability of the health system to arrest the spread of disease.[17] An extremely weak and deficient health care system, a highly mobile population with noncontrolled and porous borders, overcrowding in congested cities, ceremonial customs including close contact with corpses during funerals, and mistrust of and lack of confidence in the local authorities are causing the relentless progression of the outbreak. The World Health Organization estimates that the case count may continue to climb and warns about the disease becoming endemic in West Africa.[18]

Important lessons for infection control could be obtained from experiences in neighboring countries. A single case imported into Senegal from Guinea was rapidly contained in the hospital. Sixty-seven contacts of the patient were followed and released after 21 days of follow-up, with no subsequent transmission.[19] Similarly, an ill traveler from Liberia arrived to Lagos, Nigeria on July 20, 2014, originating an outbreak that caused 19 laboratory-confirmed cases and 891 contacts. With optimal health response, the outbreak was contained by the beginning of October 2014.[20]

Recently, a nurse's aide became infected with Ebola in Spain after treating an infected missionary. Additional people may have also been secondarily affected. Breaches in the use of personal protective equipment (PPE) and lack of a containment plan and exposure follow-up seem to have occurred.[21]

A handful of US health care workers infected with Ebola have been repatriated and treated at 2 of the 4 biocontainment units in the country (total number of biocontainment beds in the US is 19); on September 30, 2014, the first travel-associated case of Ebola was reported in the US.[22] The patient eventually became the single lethal case in the US. Two health care workers who attended the traveler also were infected, but recovered fully. The secondary transmission triggered the Centers for Disease Control and Prevention (CDC) to change their recommendations on the use of PPE. It seems unlikely that any epidemic of vast proportion will ensue in the US.

In parallel with the devastating epidemic in West Africa, a new outbreak caused by a different Zaire strain of Ebola virus has been reported in the DRC, causing a dozen cases.

TRANSMISSION

Ebola virus is transmitted by direct contact of infected fluids with small skin lesions or with mucous membranes. Blood and other body fluids including urine, saliva, feces, and vomit are considered infectious.[23] The virus can survive in breast milk and semen even after recovery from the disease, and there are reports of disease transmission to partners or children from convalescing individuals.

There is no firm evidence that fomites can transmit the disease, however, caution is recommended. The virus seems to be sensitive to ultraviolent radiation, but 3%-10% of viable viruses were present in the only study that tested dried inoculums.[24] It is expected that with daily cleaning and disinfection as routinely performed in US hospitals, the virus will not survive for more than 24 hours in the environment.[23]

In Africa, hospitals have served as amplifiers of the outbreak as a consequence of lack of PPE and secondary to poor infection control measurements, including reuse of needles and equipment and inadequate sterilization techniques. Enhanced infection control procedures as recommended by the CDC or organizations such as Doctors without Borders should rapidly contain the transmission of the virus.[25]

There is no evidence of airborne transmission or transmission via mosquito or arthropod bites.

Although the disease is not considered water-borne or food-borne, handling of bush meat is an important risk

factor in Africa,[26] as hunters may be exposed to cutaneous injuries, and all handlers could get in contact with animal blood or other fluids. There is no evidence that cats or dogs transmit the disease (although pets of infected patients have been euthanized in Spain and in the US).

In Africa, funerals are major events that can last for days and require bathing, cleaning, dressing, and kissing the body of the deceased, increasing exponentially the risk of acquiring the disease. The CDC has issued specific guidance for the safe handling of Ebola virus-infected corpses in US hospitals and mortuaries[27] (**Figure 3**).

CLINICAL MANIFESTATIONS

Ebola virus disease has an incubation period of about 8-10 days. The incubation period is never longer than 21 days.

The clinical presentation is quite unspecific. In travelers, particular attention should be given to rule out malaria, typhoid fever, traveler's diarrhea, and yellow fever, which are more common diagnoses.

The disease usually has a sudden onset characterized by fever, headache, myalgias, arthralgias of the large joints, and cervical and lower back pain. Two or 3 days after, gastrointestinal manifestations ensue, including abdominal pain, nausea, vomiting, and diarrhea. Watery material is eliminated initially, but blood can appear later in the vomitus or the stool. Patients have poor appetite and may lose weight fast. A characteristic expressionless face, described sometimes as "ghost-like," has been reported. Severe sore throat, dysphagia, and oral ulcers have been more common in previous outbreaks. Some experts believe sore throat is a manifestation associated with poor prognosis. Chest pain, shortness of breath, and cough are relatively uncommon. Severe neurologic manifestations including confusion and frank encephalitis can occur late in the course.[28] During the current outbreak in West Africa, the most common manifestations reported included: fever (87.1%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%), diarrhea (65.6%), headache (53.4%), and abdominal pain (44.3%).[17]

A macular or maculopapular skin rash may appear on the fifth to seventh day of the disease. The rash may be difficult to detect in individuals with dark skin. The rash may precede hemorrhagic manifestations. Survivors usually have extensive skin desquamation.[29]

Contrary to popular belief, hemorrhages occur in only 18% of cases.[17] The most common source of bleeding is gastrointestinal (hematemesis and melena), however, hemorrhagic conjunctivitis, bleeding ulcerations in the mouth and lips, gingival bleeding, epistaxis, ear bleeding, hematuria, and postpartum hemorrhages have also been reported.[29]

In terminal cases, patients develop disseminated intravascular coagulation, septic shock, and multi-organ failure.

Ebola virus disease has a more aggressive course in pregnant females, and the mortality rate has been up to 95% in previous outbreaks. Abortion and placenta previa are common occurrences.[30]

Laboratory findings in Ebola are unspecific and include marked leukopenia with lymphopenia, sometimes followed by leukocytosis, moderate thrombocytopenia, severe transaminitis, and hyperamylasemia.[31] Proteinuria is an almost universal finding. In fact, during the first outbreak of Ebola in 1976, the only test obtained (due to the lack of resources) was a dipstick for detection of protein in the urine.[28] Hypokalemia and lactic acidosis are common markers of severe dehydration.[32] Prolonged prothrombin time and partial thromboplastin time, diminished fibrinogen, and elevated degradation of fibrinogen products can be seen in cases of disseminated intravascular coagulation.[31]

Clinical laboratories in the US can handle samples safely from patients infected with Ebola virus if they adhere to the standards proposed by the Occupational Safety and Health Administration.[33] Ideally, samples should be handled in a certified Class II biosafety cabinet or Plexiglas splash guard. Personnel should wear PPE similar to that described in the section on prevention. Ideally, a point-of-care small laboratory with dedicated equipment should handle the samples of an infected patient.

DIAGNOSIS

An Ebola case should be suspected when clinical manifestations and epidemiological risk factors are suggestive:

- Fever of 38.6°C, unexplained bleeding, severe headache, myalgias, and gastrointestinal manifestations (vomiting, abdominal pain, and diarrhea).
- Skin, mucosal, or percutaneous exposure to body fluids or blood of patient infected with Ebola; living in the same household and providing care to an infected patient or direct contact with a corpse suspected to be infected with Ebola. Other contacts that potentially may be of risk include handling of bush meat; household contact without using appropriate PPE (for individuals not living in the same household); and, in countries with high transmission, direct contact with patients even while using PPE. Brief contact with patients (eg, handshaking) or brief proximity with a patient (being in the same room or traveling on the same aircraft) and staying in a country with high transmission within the last 21 days is associated with a very low but not nil risk.[34]

Laboratory confirmation of Ebola can be achieved by measuring viral components or the immune response of the host:[35]

- Detection of antigen by enzyme-linked immunosorbent assay and real-time polymerase chain reaction (PCR) are both sensitive and can be done in a short period of time, although they require specialized equipment. Viral RNA is usually detectable by PCR between 3 and 10 days after the onset of symptoms. Less commonly used methods to detect viral antigens include: cultures, electron microscopy, fluorescence assay, and immunohistochemistry.

- Detection of antibodies is commonly done using enzyme-linked immunosorbent assay. Less commonly used methods include: indirect immunofluorescence assay and Western blot.

In the US, suspicious cases should be reported to the local Public Health Department or the Emergency Operations center at CDC (phone: 770-488-7100).

If the CDC agrees to testing, at least 4 mL of whole blood in an EDTA tube should be shipped using a triple package including a sealable bag wrapped with absorbent material, a secondary leak-proof container, and a rigid outer container. The material should be frozen or shipped at 2°C-8°C. The CDC testing includes real-time PCR and immunoglobulin M and immunoglobulin G antibodies.[36]

Many patients infected with Ebola virus may also have concomitant malaria infection, so a peripheral smear should be analyzed for that purpose. Blood cultures and other studies for associated bacterial infections also are indicated.

Because of the threat to public health, Ebola virus is considered a "select agent." By Federal regulations, if a case is confirmed, all clinical specimens will have to be destroyed, decontaminated, or transferred to specified facilities within 7 days.[37]

TREATMENT

If a returned traveler fits into one of the exposure categories as summarized above, the patient should be isolated as described in the section on prevention.[38] The hospital infection control program, an infectious disease consultant, and a critical care consultant should be contacted, as well as other appropriate staff. The disease needs to be reported to the health department immediately. Although the few cases of Ebola in the US have been treated in biocontainment units, all hospitals should be prepared to provide initial care to patients with Ebola virus disease.[25]

There is no specific treatment for Ebola available at this time. Supportive treatment is key for affected patients. The high mortality during outbreaks may be due in part to delay in seeking medical attention and lack of aggressive support care.[32]

Vigorous and immediate correction of volume depletion is of utmost importance, as well as management of electrolyte misbalances and correction of acid base defects. Use of vasopressors, oxygen supplements, pain control, and appropriate nutrition also are important. Broad-spectrum antibiotics may be indicated if bacterial superinfection is presumed. Treatment of malaria should be considered also, if coexisting.[32,39]

ZMapp is a combination of 3 humanized monoclonal antibodies produced transgenically by using the *Nicotiana benthamiana* plant. The antibodies are directed against the Ebola glycoprotein, and they were able to reverse advanced disease in 100% of 18 rhesus macaques infected 5 days before the administration of the drug. All animals had full recovery despite having significant abnormalities, including elevated liver enzymes, high fever, and mucosal hemorrhages.[40] The drug also has been used in 7 people based on compassionate use. Five of the treated survived, but the role the medication had in their recovery is unclear. No Phase 1 clinical trials have been started yet and the manufacturer will be unable to produce significant amounts of the drug in the foreseeable future.

A combination of modified small interfering RNAs (RNAi) formulated in stable nucleic acid-lipid particles targeting the virus polymerase and viral proteins VP24 and VP35 protected 66% of rhesus monkeys and 100% of macaques exposed experimentally to Zaire Ebola virus.[41] In March 2014, the manufacturing company Tekmira (Burnaby, BC, Canada) was given a fast track designation to develop this RNAi therapeutic product under the name TKM-Ebola. In May 2014 a Phase I clinical trial was completed in healthy subjects, and in November 2014 the US Department of Defense acquired 500 courses of the experimental treatment. No evidence of the efficacy or safety of this product is available yet.[42]

Brincidofovir, an oral nucleotide analogue with broad antiviral effect in vitro, has been approved by the US Food and Drug Administration as an experimental drug for emergency use, and it has been used in 2 patients in the US, but the clinical efficacy of the drug is unknown.[43]

The World Health Organization (WHO) has recommended the use of whole blood or serum from convalescent patients. WHO has provided guidelines for the use of this experimental treatment, but the effectiveness and safety of the procedure are unknown.[44]

Amiodarone, dronedarone, and verapamil have been shown to inhibit the cell entry of filovirus to the cell in vitro.[45] Immunomodulators such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blocker have been proposed in a well-publicized article in the lay press, but no proof of their usefulness exists.[46] Several medications used in preclinical studies have not been included in this review.

Unscrupulous merchants have been offering fraudulent treatments for Ebola online.[47]

INFECTION CONTROL AND PREVENTION

In Africa, individuals can decrease the risk of infection with Ebola virus by averting contact with blood or body fluids from infected people, avoiding attendance of funerals of infected people, refraining from handling "bush meat," avoiding attendance to hospitals with infected patients, and by careful hand washing and hygiene.

In the US, the most important step to prevent dissemination of the disease is prompt recognition of cases. People who have a history of exposure but who are asymptomatic should be monitored daily for 21 days after the exposure by public health authorities (direct active monitoring). They should record their temperature at least twice a day and report to the authorities if any fever or symptoms suggestive of Ebola disease develop. During the 21 days following

exposure, exposed people should report any travel plans and avoid use of public transportation unless explicitly approved to do so by the public health authority (controlled movement). People should also refrain from congregating in public places or attending work unless authorized.[48]

As it is expected that some patients may need to be repatriated or transported by air flights, specific guidelines on air medical transport have been issued by the CDC.[49]

All patients with history of moderate or high exposure and fever or other suggestive symptoms should be placed in a private room immediately. If the patient is identified in the ambulatory setting, the local Public Health Department should be contacted immediately to make arrangements for transportation to a designated hospital. In the meantime, contact with the patient should be performed only if essential and using appropriate PPE.[50] If the patient is identified in the emergency department, both the Hospital Infection Prevention Department and the local Public Health Department should be contacted.[51] The patient should be placed in a private room with a bathroom and with the door to the hallway closed. Standard, contact, and droplet precautions (all of which include proper hand washing) need to be immediately established. No visitors should be allowed.[25,51]

The use of PPE is paramount for protection of health care workers. The recommendations for specific PPE to be worn have evolved rapidly in the US after secondary cases were described in relation to the first traveler case reported. Current emphasis includes the following:[52]

- PPE should not leave exposed any piece of skin.
- The process of putting on and removing PPE (donning and doffing) requires meticulous attention and training. Health care workers need to demonstrate competence of this skill and should not take care of potentially infected patients until strict protocol is completed.
- Close observation of donning and doffing by a trained individual is of fundamental importance to prevent any breach of protocol. Ideally, the observation should continue while health care workers perform their duties in the room via glass walls or cameras.

In the ambulatory setting and while preparing the patient for transportation, health care workers should wear, at a minimum, an impermeable gown, a surgical mask, a face shield, and 2 pairs of gloves.

After admission, the patient should be placed in a private room and precautions should be instituted as stated previously. Staff taking care of the sick individual must remove their clothes and wear hospital scrubs and shoe wear. On top of those garments, staff must use the following equipment:[52]

- Powered Air Purifying Respirator (known as PAPR) or N95 mask. PAPR is a device equipped with a face piece, hood or helmet, breathing tube, canister, cartridge, filter, canister with filter or cartridge with filter, and a powered blower. N95 mask is a filtering face piece respirator commonly used for tuberculosis isolation. It must be noted that Ebola is not airborne transmitted, however, the use of these respiratory devices is expected to prevent transmission in cases of aerosol-generating procedures.
- Disposable fluid-resistant gown or a coverall without integrated hood. The gown should extend at least to the mid-calf. A coverall is sometimes called a Tyvek, which is actually a specific brand name.
- Two or 3 pairs of disposable nitrile examination gloves with extended cuffs.
- Disposable fluid-resistant boot or shoe covers.
- Disposable fluid-resistant apron (to be used if patients have vomiting or diarrhea).

The donning and doffing should be done in 2 separate rooms contiguous to the patient room. Both procedures should be observed by trained individuals wearing less stringent PPE (similar to the one described for the ambulatory setting plus shoe covers). Donning and doffing take a prolonged time to be performed appropriately and require follow-up of strict sequential steps to prevent contamination.[53,54] It cannot be expected that untrained individuals will be able to perform appropriately with short notice. Doffing is the highest risk event for contamination and requires particular care.

Alcohol-based hand rub use before, after, and during donning and doffing, as well as frequently during patient care, is an essential component of infection prevention.

The number of health care workers in contact with the patient should be limited as much as possible; nonessential consultants may be able to provide advice "at the door" without entering the room. A log should be kept of people entering the room.

Use of needles or sharps in patient care should be limited to the minimum possible, and aerosol-generating procedures should be avoided. Other safe practices that prevent health care transmission include limiting touching of body fluids or patients' skin, avoiding facial self-touching, preventing sharps injuries, and frequently disinfecting room surfaces even if not visibly contaminated. Ideally, disposable dedicated equipment should be used. If the equipment is nondedicated or nondisposable, it should be cleaned and disinfected appropriately.[52] If dialysis is required, guidelines for its use are available.[55]

If health care personnel get exposed to blood or body secretions, they should stop their task immediately, irrigate the skin or mucosal surfaces profusely with water, contact the occupational health department for postexposure management of HIV and hepatitis, and be monitored for the development of fever and other symptoms suggestive of Ebola infection, as suggested at the beginning of this section.[56]

Environmental service staff should also wear PPE. For disinfection purposes, Environmental Protection Agency-approved products with ability to destroy nonenveloped viruses should be used. Only mattresses and pillows with fluid-resistant covering should be used. All contaminated linen and textiles should be discarded. All contaminated

material needs to be handled as category A infection substances in accordance with the US Department of Transportation Hazardous Material Regulations.[57,58]

All hospitals should have a preparedness plan for dealing with cases of Ebola, including education about the disease, documentation of proper triage questions (travel history, symptoms), availability of PPE, establishment of appropriate internal and external channels of communication, and specific guidelines for infection control and environmental protection.[59]

There are no vaccines available for the prevention of Ebola, however, 2 candidate vaccines are undergoing clinical trials:[60]

- cAd3-ZEBOV, a vaccine based on a chimpanzee adenovirus type 3 genetically modified to express glycoproteins from the Zaire and Sudan strains, produced collaboratively by the US National Institutes of Health and GlaxoSmithKline (Brentford, UK).
- VSV-EBOV, a vaccine based on the vesicular stomatitis virus, genetically engineered to express Ebola glycoproteins, produced by the Canadian National Microbiology Laboratory and licensed by NewLink Genetics Corporation based in Iowa.

There are several other candidate vaccines in preclinical stage and they have not been included in this review.

PROGNOSIS

The lethality rates of previous Ebola outbreaks have ranged between 16% and 92% (mortality of 100% has occurred among single case outbreaks). The lethality rate of the current outbreak among hospitalized patients was 64%, and among health care workers, between 56% and 80%. Significant risk factors for death included age older than 45 years, higher number of general symptoms at presentation, and presence of hemorrhagic symptoms.[17]

Patients who survive Ebola infection have a long and torpid convalescence. At 6 months of follow-up, patients can still report arthralgias, myalgias, abdominal pain, extreme fatigue, and anorexia; and even at 21 months, 70% of them can be in poor general health and unable to work.[61]

MORAL DILEMMAS

There are several ethical and moral dilemmas that the current outbreak of Ebola has disclosed. Many of them are beyond the scope of this article but will be mentioned briefly here.

Health care workers need to balance their fear of acquiring the disease vs their moral obligation to provide help to affected patients. Proper use of PPE may significantly decrease the risk of acquiring the disease.[62] Anecdotal evidence from the early years of the HIV epidemics and from cholera outbreaks in South America suggest that self-selected volunteers with scientific curiosity and clear sense of their role as health care workers may be best qualified to deal with emergent diseases.

The cultural milieu where the outbreak is occurring requires a tactful approach. Forbidding of elaborated funerary rituals, prohibiting visits to the sick, or even interacting with the health care system may be a completely foreign experience for some of the affected patients. Mistrust of the health care system and governmental organizations may be rampant in West Africa; as a consequence, people may avoid contact with the health care workers or even confront them. Education and community participation are extremely important to curtail the outbreak.[63]

Experimental drugs and vaccines should not be administered based on "compassionate use," rather, rigorous protocols should be established for the scientific testing of yet-unproven treatments. Safety testing and informed consent before their use are mandatory.[64]

Control of the current epidemic requires a global response that should include deploying of mobile laboratories, establishment of a network of field hospitals, and air bridges to transport personnel and equipment to West Africa. Massive allocation of assets and careful logistic planning is necessary to succeed.[65]

BIOTERRORISM USE

Ebola and other hemorrhagic fever viruses are classified as bioterrorism agents type A because they can disseminate from person to person and cause high mortality and social disruption. Recognition of a biological attack may be difficult in the absence of classic risk factors, however, the absence of prominent respiratory symptoms may be helpful to differentiate it from other type A agents such as plague or tularemia.[66] Although a theoretical concern, the chances of the virus being actually used for bioterrorism purposes are almost nil. Noncareful handling of the virus most likely will cause severe illness and death of the attackers.

ACKNOWLEDGMENT

I would like to thank David Leyva for outstanding support with the medical illustrations embedded in this article.

References

1. Kuhn JH, Becker S, Ebihara H, et al. Proposal for a revised taxonomy of the family *Filoviridae*: classification, names of taxa and viruses, and virus abbreviations. *Arch Virol*. 2010;155(12):2083-2103.
2. UCSC Genome Informatics Group. UCSC Ebola genome portal. Available at: https://genome.ucsc.edu/ebolaPortal/. Accessed October 11, 2014.
3. Saeed MF, Kolokoltsov AA, Albrecht T, Davey RA. Cellular entry of Ebola virus involves uptake by a macropinocytosis-like mechanism and subsequent trafficking through early and late endosomes. *PLoS Pathog*. 2010;6(9):e1001110.
4. Watt A, Moukambi F, Banadyga L, et al. A novel life cycle modeling system for Ebola virus shows a genome length-dependent role of VP24 in virus infectivity. *J Virol*. 2014;88(18):10511-10524.
5. Bornholdt ZA, Noda T, Abelson DM, et al. Structural rearrangement of Ebola virus VP40 begets multiple functions in the virus life cycle. *Cell*. 2013;154(4):763-774.

6. Takada A, Feldmann H, Ksiazek TG, Kawaoka Y. Antibody-dependent enhancement of Ebola virus infection. *J Virol*. 2003;77(13):7539-7544.
7. Bray M, Geisbert TW. Ebola virus: the role of macrophages and dendritic cells in the pathogenesis of Ebola hemorrhagic fever. *Int J Biochem Cell Biol*. 2005;37(8):1560-1566.
8. Olival KJ, Hayman DT. Filoviruses in bats: current knowledge and future directions. *Viruses*. 2014;6(4):1759-1788.
9. Leroy EM, Telfer P, Kumulungui B, et al. A serological survey of Ebola virus infection in central African nonhuman primates. *J Infect Dis*. 2004;190(11):1895-1899.
10. World Health Organization. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ*. 1978;56(2):271-293.
11. World Health Organization. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. *Bull World Health Organ*. 1978;56(2):247-270.
12. Okware SI, Omaswa FG, Zaramba S, et al. An outbreak of Ebola in Uganda. *Trop Med Int Health*. 2002;7(12):1068-1075.
13. Centers for Disease Control and Prevention (CDC). Outbreaks chronology: Ebola virus disease. Available at: http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html. Accessed November 6, 2014.
14. Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea. *N Engl J Med*. 2014;371(15):1418-1425.
15. Feldmann H. Ebola—a growing threat? *N Engl J Med*. 2014;371(15):1375-1378.
16. Centers for Disease Control and Prevention (CDC). 2014 Ebola outbreak in West Africa—case counts. Available at: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html. Accessed November 6, 2014.
17. WHO Ebola Response Team. Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. *N Engl J Med*. 2014;371(16):1481-1495.
18. Farrar JJ, Piot P. The Ebola emergency—immediate action, ongoing strategy. *N Engl J Med*. 2014;371(16):1545-1546.
19. Mirkovic K, Thwing J, Diack PA. Importation and containment of Ebola virus disease—Senegal, August-September 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(39):873-874.
20. Shuaib F, Gunnala R, Musa EO, et al. Ebola virus disease outbreak—Nigeria, July-September 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(39):867-872.
21. Ohlheiser A. *Spanish hospital workers protest Ebola safety measures as more people enter isolation*. Washington, DC: Washington Post; October 10, 2014.
22. McCarthy M. Ebola is diagnosed in traveler to US. *BMJ*. 2014;349:g5980.
23. Centers for Disease Control and Prevention (CDC). Ebola virus disease—transmission. Available at: http://www.cdc.gov/vhf/ebola/transmission/. Accessed November 6, 2014.
24. Sagripanti JL, Lytle CD. Sensitivity to ultraviolet radiation of Lassa, vaccinia, and Ebola viruses dried on surfaces. *Arch Virol*. 2011;156(3):489-494.
25. Centers for Disease Control and Prevention (CDC). Safe management of patients with Ebola virus disease (EVD) in US hospitals. Available at: http://www.cdc.gov/vhf/ebola/hcp/patient-management-us-hospitals.html. Accessed November 6, 2014.
26. Mitman G. Ebola in a stew of fear. *N Engl J Med*. 2014;371(19):1763-1765.
27. Centers for Disease Control and Prevention (CDC). Guidance for safe handling of human remains of Ebola patients in U.S. hospitals and mortuaries. Available at: http://www.cdc.gov/vhf/ebola/hcp/guidance-safe-handling-human-remains-ebola-patients-us-hospitals-mortuaries.html. Accessed November 6, 2014.
28. Pattyn SR, ed. *Ebola Virus Haemorrhagic Fever. Proceedings of an International Colloquium on Ebola Virus Infection and Other Haemorrhagic Fevers*. Amsterdam: Elsevier/North Holland Biomedical Press; 1978.
29. Sureau PH. Firsthand clinical observations of hemorrhagic manifestations in Ebola hemorrhagic fever in Zaire. *Rev Infect Dis*. 1989;11(Suppl 4):S790-S793.
30. Mupapa K, Mukundu W, Bwaka MA, et al. Ebola hemorrhagic fever and pregnancy. *J Infect Dis*. 1999;179(Suppl 1):S11-S12.
31. Centers for Disease Control and Prevention (CDC). Ebola virus disease information for clinicians in U.S. healthcare settings. Available at: http://www.cdc.gov/vhf/ebola/hcp/clinician-information-us-healthcare-settings.html. Accessed November 6, 2014.
32. Fowler RA, Fletcher T, Fischer WA 2nd, et al. Caring for critically ill patients with Ebola virus disease. Perspectives from West Africa. *Am J Respir Crit Care Med*. 2014;190(7):733-737.
33. Occupational Safety and Health Administration (OSHA). Laboratory safety guidance. Available at: https://www.osha.gov/Publications/laboratory/OSHA3404laboratory-safety-guidance.pdf. Accessed November 7, 2014.
34. Centers for Disease Control and Prevention (CDC). Case definition for Ebola virus disease (EVD). Available at: http://www.cdc.gov/vhf/ebola/hcp/case-definition.html. Accessed November 7, 2014.
35. Wang YP, Zhang XE, Wei HP. Laboratory detection and diagnosis of filoviruses. *Virol Sin*. 2011;26(2):73-80.
36. Centers for Disease Control and Prevention (CDC). Ebola virus disease—diagnosis. Available at: http://www.cdc.gov/vhf/ebola/diagnosis/. Accessed November 7, 2014.
37. Centers for Disease Control and Prevention (CDC). Interim guidance regarding compliance with select agent regulations for laboratories handling patient specimens that are known or suspected to contain Ebola virus. Available at: http://www.cdc.gov/vhf/ebola/hcp/select-agent-regulations.html. Accessed November 7, 2014.
38. Centers for Disease Control and Prevention (CDC). Ebola virus disease—algorithm for evaluation of the returned traveler. Available at: http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf. Accessed November 7, 2014.
39. Centers for Disease Control and Prevention (CDC). Ebola virus disease—treatment. Available at: http://www.cdc.gov/vhf/ebola/treatment/index.html. Accessed November 6, 2014.
40. Qiu X, Wong G, Audet J, et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature*. 2014;514(7520):47-53.
41. Geisbert TW, Lee AC, Robbins M, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof of concept study. *Lancet*. 2010;375(9729):1896-1905.
42. Tekmira. TKM-Ebola. Available at: http://www.tekmira.com/pipeline/tkm.ebola.php. Accessed November 7, 2014.
43. Chimerix, Inc. Chimerix announces emergency investigational new drug applications for brincidofovir authorized by FDA for patients with Ebola virus disease. Available at: http://ir.chimerix.com/releasedetail.cfm?ReleaseID=874647. Accessed November 7, 2014.
44. World Health Organization. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. Available at: http://apps.who.int/iris/bitstream/10665/135591/1/WHO_HIS_SDS_2014.8_eng.pdf?ua=1. Accessed November 7, 2014.
45. Gehring G, Rohrmann K, Atenchong N, et al. The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry. *J Antimicrob Chemother*. 2014;69(8):2123-2131.
46. Fedson DS. A practical treatment for patients with Ebola virus disease. *J Infect Dis*. 2015;211(4):661-662.
47. US Food and Drug Administration. FDA warns consumers about fraudulent Ebola treatment products. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm410086.htmcdcd. Accessed October 11, 2014.
48. Centers for Disease Control and Prevention (CDC). Infection prevention and control recommendations for hospitalized patients with known or suspected Ebola virus disease in U.S. hospitals. Available at: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html. Accessed November 7, 2014.
49. Centers for Disease Control and Prevention (CDC). Guidance on air medical transport for patients with Ebola virus disease. Available at: http://www.cdc.gov/vhf/ebola/hcp/guidance-air-medical-transport-patients.html. Accessed November 7, 2014.
50. Centers for Disease Control and Prevention (CDC). Available at: http://www.cdc.gov/vhf/ebola/pdf/ambulatory-care-evaluation-of-patients-with-possible-ebola.pdf. Accessed November 7, 2014.

51. Centers for Disease Control and Prevention (CDC. Identify, isolate, inform: emergency department evaluation and management for patients who present with possible Ebola virus disease. Available at: http://www.cdc.gov/vhf/ebola/pdf/ed-algorithm-management-patients-possible-ebola.pdf. Accessed November 7, 2014.
52. Centers for Disease Control and Prevention (CDC). Guidance on personal protective equipment to be used by healthcare workers during management of patients with Ebola virus disease in U.S. hospitals, including procedures for putting on (donning) and removing (doffing). Available at: http://www.cdc.gov/vhf/ebola/healthcare-us/ppe/guidance.html. Accessed November 8, 2014.
53. Centers for Disease Control and Prevention (CDC). Ebola: personal protective equipment (PPE) donning and doffing procedures. Available at: http://www.cdc.gov/vhf/ebola/hcp/ppetraining/index.html. Accessed November 8, 2014.
54. Srinivasan A, Christensen B, Smith BA. Ebola: donning and doffing of personal protective equipment (PPE). Available at: www.medscape.com/viewarticle/833907. Accessed November 8, 2014.
55. Centers for Disease Control and Prevention (CDC). Recommendations for safely performing acute hemodialysis in patients with Ebola virus disease in U.S. hospitals. Available at: http://www.cdc.gov/vhf/ebola/hcp/guidance-dialysis.html. Accessed November 8, 2014.
56. Centers for Disease Control and Prevention (CDC). Infection prevention and control recommendations for hospitalized patients with known or suspected Ebola virus disease in U.S. hospitals. Available at: http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html. Accessed November 8, 2014.
57. Centers for Disease Control and Prevention (CDC). Interim guidance for environmental infection control in hospitals for Ebola virus. Available at: http://www.cdc.gov/vhf/ebola/hcp/environmental-infection-control-in-hospitals.html. Accessed November 8, 2014.
58. US Department of Transportation. Federal hazardous materials transportation law. Available at: http://phmsa.dot.gov/hazmat/guidance. Accessed October 11, 2014.
59. Centers for Disease Control and Prevention (CDC). Detailed hospital checklist for Ebola preparedness. Available at: http://www.cdc.gov/vhf/ebola/pdf/hospital-checklist-ebola-preparedness.pdf. Accessed November 8, 2014.
60. National Institutes of Health (NIH). NIH begins early human clinical trial of VSV Ebola vaccine. Available at: http://www.nih.gov/news/health/oct2014/niaid-22.htm. Accessed November 8, 2014.
61. Rowe AK, Bertolli J, Khan AS, et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis*. 1999;179(Suppl 1):S28-S35.
62. Yakubu A, Folayan MO, Sani-Gwarzo N, Nguku P, Peterson K, Brown B. The Ebola outbreak in Western Africa: ethical obligations for care. *J Med Ethics*. 2014. pii: medethics-2014-102434. http://dx.doi.org/10.1136/medethics-2014-102434. [Epub ahead of print].
63. Hewlett B, Hewlett BL. *Ebola, Culture and Politics: The Anthropology of an Emerging Disease (Case Studies on Contemporary Social Issues)*. 1st ed. San Francisco: Cengage Learning; 2007.
64. Farrar J, Heymann D, Piot P. *Experimental medicine in a time of Ebola*. New York, NY: The Wall Street Journal; August 6, 2014.
65. Liu J. Doctors without borders. United Nations special briefing on Ebola. Available at: http://www.doctorswithoutborders.org/news-stories/speechopen-letter/united-nations-special-briefing-ebola. Accessed October 11, 2014.
66. Borio L, Inglesby T, Peters CJ, et al. Working Group on Civilian Biodefense. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287(18):2391-2405.