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Ebola: history, treatment, and lessons from a new emerging pathogen

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“DOES IT EVER END?” That was what a neighbor said to me one evening after hearing of the Guinea Ebola outbreak in West Africa. We have watched other epidemics unfold before us, thanks to our around-the-clock media access. The HIV problem developed more quietly owing to the lack of understanding of human immunodeficiencies, social taboos, and the absence of the Internet. The full experience of watching epidemics develop is a more recent phenomenon. The first televised outbreak was the Severe Acute Respiratory Syndrome (SARS)-coronavirus (CoV) epidemic in 2003. This outbreak was clearly aided by a lack of appreciation for the ability of CoVs to cause severe disease and the escalation of global travel. Then the 2009 pandemic H1N1 influenza was predicted and occurred while an anxious public viewed. Highly pathogenic avian influenza (HPAI) seems to be on the cusp of efficient human transmission every year, first with H5N1 serotypes and now the fearsome H7N9 with its lack of pathogenicity in its preferred host, birds, thus rendering it difficult to track. Middle Eastern Respiratory Virus (MERS) CoV has emerged from its natural host, bats or camels, and is a cause for concern despite its apparent lack of efficient human-to-human transmission (40).

Now the emergence of yet another highly pathogenic virus has taken the biomedical and public imagination in its grasp. No virus has triggered fear in the general population more than the filovirus Ebolavirus. This reflects in large part its frightening fatality rates that approach 80% in some outbreak regions. Currently West Africa is dealing with an outbreak of Zaire ebolavirus that is causing extraordinary numbers of cases and deaths (1). The fear in the developed world has led to misguided proposals to lock down borders and halt global traffic. More familiarity with the natural history of Ebola virus infections, experimental investigations, and knowledge of pathogenesis can help alleviate fears (Table 1). Such knowledge can also allow us to consider possibilities that have not been widely discussed beyond a few public health experts and researchers. This editorial will focus on the aspects of Ebola virus disease that are closest to the interests of the readership of AJP-Lung, while providing perspectives and assurances that many of our family, friends, and neighbors seek from us whether we study pathogens or not.

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Phylogeny

The Zaire ebolavirus species is one of five in the Ebolavirus genus formerly called Ebola hemorrhagic fever viruses. Ebolavirus is classified in the family Filoviridae, in the order Mononegavirales of single-stranded negative-sense RNA viruses (9). Ebolavirus is made up of five known viral species, four of which (Zaire ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus, and Tai Forest ebolavirus) lead to a viral hemorrhagic fever (VHF) that is highly pathogenic and often lethal in humans. A fifth ebolavirus, Reston ebolavirus, has infected humans but has not been shown to cause disease (18). Other genera of the Filoviridae family are the Marburg marburgvirus, consisting of the two members Marburg (MARV) and Ravn (RAVV), both causing similar hemorrhagic fevers with high lethality in humans, and the genus Lloviu cuevavirus (LLOV), found in bats, with no reported infection in humans known. The five members of the Ebolavirus genus are the most highly studied of the Filoviridae, and the natural history of viral replication of filoviruses is largely known from studies of the Ebolavirus genus (Fig. 1). Filoviruses are enveloped RNA viruses that attach to host cells through glycoproteins on the viral outer membrane that appear to contain a fusion domain as well, unlike other Mononegavirales, such as respiratory syncytial virus (RSV), that encode a distinct fusion (F) protein. Following release of the genomic RNA-containing nucleocapsid from the endosome, viral replication takes place by a RNA-dependent RNA polymerase (L) encoded by the viral genome. Positive-stranded viral RNA (vRNA) species for each encoded viral protein (NP, VP35, VP40, GP/sGP, VP30, VP24, and L) are transcribed initially, followed by production of the positive-stranded full-length viral antigenomes that serve as the template for the transcription of negative-stranded viral genomes of progeny virions. Following genomic replication, the viral genomes are packaged in the nucleocapsid. They traffic to the cell membrane surface, where the envelope proteins embedded in the cell membrane await and where host envelope budding around the nucleocapsid takes place, forming nascent progeny virions that are released. Much of the detailed cell biology and replication of Ebola virus just described, such as the switch from viral transcription to viral RNA genomes or the cell entry mechanisms, are largely unknown in filoviruses but have been widely studied in a number of other negative-stranded RNA viruses such as Paramyxoviridae and pneumoviruses such as the aforementioned RSV. This large body of literature on similar viruses, while helpful, does not necessarily indicate that investigations into other less pathogenic viruses can supplant the study of Ebola virus. As an example, viruses...
of Paramyxoviridae often inhibit interferon (IFN)-mediated viral host defense but do so by distinct mechanisms within their own virus family. For this reason, we cannot rely on our working knowledge of less pathogenic viruses to fully understand Ebola virus biology.

Zoonosis

Ebola outbreaks are largely the result of zoonotic transmission from bats or primates, although the natural reservoir for Ebola virus is not yet substantiated. Transmission to humans typically comes from the preparation and consumption of bushmeat from infected animals. Bats appear to be the most likely natural reservoir, with several species of fruit bats implicated despite the lack of apparent disease (31). Nonhuman primates (NHPs) including chimpanzees appear to become infected after eating fruit tainted by the body fluids of infected fruit bats, although evidence for animal-to-animal transmission is mostly lacking. Of domesticated animals, pigs and dogs have been shown to become infected enough to elicit seroconversion in West Africa despite any apparent disease (36). The complexity of ecological studies of highly migratory animals such as fruit bats and the lack of apparent disease in most animals, primates being the exception, make tracking the virus difficult and largely rely on seroprevalence studies that have little informative value other than previous exposure. It should be noted that bats continue to be prime suspects in the zoonosis of emerging pathogens, including the CoVs SARS-CoV (24), MERS-CoV (23), the highly lethal Nipah (NiV) and Hendra (HeV) viruses, and the filovirus MARV, not to mention others. Why bats continue to be central to the transmission of new viruses into humans, either directly or through an intermediate animal, is of great debate. Clearly a better understanding of bat biology and ecology is warranted to determine whether bats are opportunistic vectors for many zoonotic viruses or whether bats are indeed preferred hosts.

History

The first known outbreak of Ebola occurred in Zaire [what is now known as the Democratic Republic of the Congo (DRC)] in 1976 (7). It was attributed to the prototype Ebola strain Zaire ebolavirus and named for the Ebola River, where the Zaire index case is thought to have contracted the virus. This outbreak produced the prototype virus upon which much of our scientific understanding is based. A similar outbreak was occurring at the same time in the Sudan, but at the time it was unclear whether the outbreaks were related. A novel virus, first thought to be the Marburg virus or malaria and then discovered to be a related yet genetically distinct filovirus, was discovered by investigators from the Zaire Ministry of Health and the US Centers for Disease Control and Prevention (CDC). It was later discovered the viruses in these outbreaks were distinct and provide two of the five ebolavirus species, Zaire ebolavirus and Sudan ebolavirus, known today. High fatality rates were observed in both outbreaks, with as much as an 88% fatality rate observed in Zaire. It is these outbreaks that have fostered much of the fear in the African communities that exists today (31). Quarantine measures and increased practice of universal precautions are thought to have contributed to quelling the outbreak. A second outbreak occurred in 1995 in the DRC, an outbreak in Uganda in 2000 (caused by the Sudan ebolavirus species), and a third outbreak in the Congo in 2003. A subsequent outbreak in Uganda in 2007 yielded the Bundibugyo ebolavirus species after confirmation that a distinct species was identified by the CDC and the World Health Organization (WHO) in Bundibugyo district in western Uganda. A second outbreak caused by the Bundibugyo ebolavirus species was identified in the Congo in 2012, infecting 57 confirmed cases with 29 fatalities. Whereas recent Ebola outbreaks may be news to the public in the West (save for a few cinematic productions), the frequent recurrence of outbreaks in Africa has created a much different atmosphere in the villages of Africans. Fears and taboos run deep in these communities, and a lack of knowledge regarding the disease and transmission often necessitates substantial education by aid workers. The recent outbreaks in Guinea have led to public distrust of government and international officials, international aid workers, and medical groups providing care in stricken villages and regions. It should be noted that Western aid workers are often seen with suspicion by locals, since there is a history of social imbalance in that, although past epidemics such as the yellow fever outbreak in the 1920s have led to numerous biomedical advances, very little benefit has been obtained by the local communities that suffer the greatest loss (31).

The Current Outbreak in West Africa

March 10, 2014, serves as the start of the chronological events in the current Ebola outbreak in West Africa, when public health officials in the villages of Guexkedou and Macenta in southern Guinea alerted the Guinea Ministry of Health officials and subsequently Medecins sans Frontieres (Doctors without Borders) regarding a cluster of mysterious diseases in eight patients in Guexkedou (with three fatalities) and several cases in Macenta including cases with fatalities of health care workers (1). Patient samples from 20 cases were analyzed by RT-PCR for filovirus-specific conserved polymerase L, glycoprotein (GP), and nucleocapsid (NP) genes and were found to be positive, whereas a panel of other likely etiologic agents such as Lassa fever and malaria was negative. Retrospective analysis of cases in Guexkedou indicates that deaths from

Table 1. Ebola overview

- Ebola disease is caused by a filovirus that leads to a viral hemorrhagic fever.
- Transmission among people typically occurs by exposure to body fluids from infected individuals.
- The incubation period is 3–14 days.
- Human-to-human transmission occurs only after the onset of symptoms.
- Currently, there are no approved vaccines or treatments.

Fig. 1. Colorized transmission electron micrograph of the Ebola virus virion. Created by Cynthia Goldsmith, CDC.
Ebola likely extend back to December 2013. Complete sequences of three Ebola virus isolates indicate a separate Ebola strain clade distinct from those viruses isolated in the DRC and Gabon, and this suggests a single introduction from a presumed animal reservoir sometime in December 2013. As of this writing, nearly 14,000 cases have been reported in Guinea, Sierra Leone, and Liberia with nearly 5,000 deaths. The current status of the outbreak can be found on the CDC website www.cdc.gov/vhf/ebola. This constitutes the largest Ebola outbreak to date. Molecular clock analysis of isolated genomes estimates that the outbreak likely progressed undetected in a number of individuals from the initial index case, thus making containment by quarantine and standard health practices unable to limit transmission. Although many lessons can hopefully be learned from this tragedy, the importance of surveillance and diagnostics of even small clusters in regions where zoonosis of deadly pathogens can occur should not be the least of them, particularly given the ease of nucleic acid-based detection approaches even in resource-poor health care environments.

**Ebola Hemorrhagic Fever in Humans**

Ebola virus infection causes a severe hemorrhagic syndrome in humans with extraordinary high fatality rates (1). I will use reports of human disease from the current Guinea outbreak to highlight this syndrome in humans, because the release of medical information in this event has been more reliable than in previous Ebola outbreaks. Ebola disease initially presents not unlike many other viral infections, i.e., nonspecific in nature and consisting of fever, malaise, and myalgia. The initial incubation period following infection can last up to 14 days, a lengthy period considering that most infections show a typical 2- to 5-day incubation period. It is this lengthy incubation period that can make transmission difficult to halt and outbreaks difficult to identify, since travel among villages in indigenous regions is common and lack of a sophisticated surveillance program or communication among local and regional health care enterprises impedes rapid dissemination of information. Following the initial symptoms, the most common symptom of a progressing disease is severe gastrointestinal illness with vomiting and diarrhea. The most common signs and symptoms reported from West Africa in descending order include fever (87%), fatigue (76%), vomiting (68%), diarrhea (66%), and loss of appetite (65%). A common sign of Ebola hemorrhagic fever, and one seen conspicuously in the earlier outbreaks, is the appearance of bleeding from mucous membranes, conjunctiva, or mouth, and profuse bleeding upon venipuncture. This sign has been much less dependable as a sign in patients of the Guinea Ebola outbreak, another reason why the most recent outbreak may have been slow to identify. Other internal signs of hemorrhage such as blood in the stools or bruising are also common to previous outbreaks but less so in West Africa. Progression of severe disease leads to hypovolemic shock, resultant metabolic disorders, and multiorgan failure that may result from systemic vascular leak and coagulopathies. Fatality rates in the Guinea Ebola outbreak have ranged from 70% in Guinea, Sierra Leone, and Liberia to 41% in Nigeria. Fatality rates in cases of individuals that have traveled to more developed parts of the globe appear to be lower, but the death of a patient in Texas highlights that the fatality rate is not simply a matter of the standard of care in developing nations vs. those in the United States or Europe (Table 2).

**The Role of the Lung in Ebola Hemorrhagic Fever Illness**

VHF is commonly associated with multiple organ systems owing to their propensity to infect either immune cells or the resident cells of the vascular system (38). Ebola VHF is associated with multiple organ systems, including the lungs, liver, and renal organs. Little information exists regarding the molecular pathogenesis of Ebola viruses specifically in the lung, owing in part to the necessity of care given to the remains of fatal cases and the fear of transmission from the remains. For this reason I will limit my discussions here to VHF of multiple etiologies and lung involvement. Five histological observations in the lung can be made of VHFs: alveolar hemorrhage, pulmonary edema, diffuse alveolar damage, interstitial pneumonitis, and, although much less common, bronchopneumonia (39). Although these pathologies can often be observed in various VHFs, none are diagnostic of or consistent with any particular etiologic cause of VHF or of VHF in general. In Ebola VHF, alveolar edema, interstitial pneumonitis, and diffuse alveolar disease can be identified in Ebola disease. Abundant viral antigen in necrotic debris in the alveolar interstitium and hyaline membranes are characteristic observations of diffuse alveolar disease. Any of these pathological features can lead to the acute respiratory distress syndrome (ARDS) that occurs at the end of life in fatal Ebola cases or to the cough that is often reported in severe infections (1). The detection of viral antigen, indicating active infection of a particular tissue, most commonly identifies alveolar macrophages and endothelial cells as being harbinger of Ebola in humans, although widespread infection of any particular cell type is not atypical. Studies in animal models have provided more information on the effect of Ebola virus infection in the lung.

**Ebola Disease in Animal Models**

Multiple animal models of Ebola infection have been utilized to varying degrees under high biocontainment practices and in regulated facilities (32). The Zaire ebolavirus has been largely used for most experimental studies, and little is known about other genera. Mice are generally not permissive of Ebola infection and are resistant to any disease save for mounting a serological response with sufficient doses (21). Mouse-adapted Ebola strains have been developed and show lethality with similar characteristics of innate immune tropism and charac-

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**Table 2. Ebola questions and answers**

- Is the ebolavirus a new virus that we have only recently discovered?
  No, numerous ebolavirus outbreaks have occurred since the discovery of the virus in 1976, primarily in Africa.
- What are the origins of the virus?
  The virus can be found in bats and nonhuman primates, but it is unclear which is the primary source, or whether another animal is the source.
- How do humans become infected?
  The virus is transmitted through contact with infected animals, either directly or indirectly through contact with contaminated materials.
- How deadly is the ebolavirus?
  Fatality rates in Africa are often 50–70% but it is unclear what the fatality rate would be in a more advanced health care setting.
tensive disease in the liver leading to coagulopathies and death (4, 5, 8). Mutations in the mouse-adapted ebolaviruses suggest that amino acid changes in proteins that antagonize IFN-induced viral host defense are important in the adaptation to permissive or lethal murine infection (3). Similar findings have been made using mouse-adapted Ebola virus in guinea pigs and Syrian hamsters, but the limited reagents available have made these models less desirable (32).

Clearly, the most utilized animal model of Ebola disease is the NHP. Rhesus macaques (Macaca mulatta), cynomolgus macaques (Macaca fascicularis), African green monkeys (AGMs) (Chlorocebus aethiops), and Hamadryas baboons (Papio hamadryas) have all been used with generally similar results. The effectiveness of NHPs as an experimental model should not be surprising, since monkeys indigenous to West Africa have been reported to be a common host or intermediary of zoonotic transmission to humans (11). NHPs infected with ebolavirus become febrile and exhibit behavior characteristic of malaise and loss of appetite generally starting about 3 days following infection (2, 4, 9, 11, 25). Disease progresses to include anorexia, dehydration from an inability to take fluids, diarrhea, and rectal bleeding. Some NHP species but not AGMs developed a petechial rash that has become characteristic of filovirus infections, although the recent Guinea outbreak in humans has not shown this rash to be a common outcome in severe cases. Viremia occurs generally around the onset of signs of disease, remains elevated throughout disease, and can reach viral loads of 10^6 pfu/ml in the blood (13, 20). Viral antigen detection occurs predominantly in the liver, spleen, and lung and to a lesser extent in other tissues. NHPs typically succumb during days 5–7. It is noteworthy that typically animal studies do not provide the level of support given to patients in a critical care setting, particularly with regard to fluid resuscitation, and these measures are clearly more difficult at the biosafety level 4 requirement for handling this pathogen. Thus some aspects of the experimental NHP model of Ebola do not completely recapitulate that observed in humans, particularly with the timing of signs of disease. For instance, the use of needles and sharps for studies of highly pathogenic organisms like Ebola is strongly curtailed in light of the seriousness of accidental exposure in this experimental setting. Nevertheless, the NHP model closely mimics the disease course and signs of infection in Ebola patients and provides a good model for the evaluation of vaccines and therapeutics.

An important distinction in the study of Ebola infection in NHPs is the disparity of responses with different Ebolavirus genera. Much of the information presented above and subsequently were studied by utilizing Zaire ebolavirus, the most widely studied Ebola virus. Interestingly, studies in rhesus macaques with Sudan ebolavirus produced much less disease and fewer fatalities (4, 9, 11). This is in conflict with five reported outbreaks of Sudan ebolavirus in Sudan or Uganda that had case fatality rates of 53% (1976), 65% (1979), 53% (2000–01), 41% (2004), and 41% (2011–13) (6). Another important distinction is the lack of human infection by Reston ebolavirus infection in humans (20). Three distinct instances of Reston ebolavirus infection in NHP colonies have occurred, including two instances in which infected NHPs were imported to animal facilities in the US (6). In all cases, NHPs developed signs of infection whereas humans exposed to the NHPs were asymptomatic yet developed a serological response. The most recent incident occurred in the Philippines in 2008, when domesticated pigs were infected (29, 30). Several farmers and slaughterhouse workers again were asymptomatic yet developed antibodies against the virus. The lack of disease in humans by Reston virus may offer an opportunity to explore underlying mechanisms of disease.

The vast majority of information regarding the hematologic and immunologic pathogenesis in Ebola infection has been gleaned from the study of infection in NHPs (13). Neutrophilia and lymphopenia are characteristics of experimental infection that have been observed in severe human infections. Lymphopenia appears to be the result of extensive lymphocyte apoptosis in the vasculature and peripheral lymphoid tissues leading to a sharp drop in CD8+ subsets, including natural killer cells, that precedes the onset of severe disease and may lead to expansion of the viremia despite a lack of evidence for ebolavirus tropism for lymphocytes. Some evidence exists for the role of monocytes, macrophages, and dendritic cells (DCs) in the release of soluble factors such as nitric oxide and cytokines such as IFN-α that may lead to the activation of lymphocyte apoptosis. In regard to the coagulopathy that is common in human Ebola disease, coagulopathies in Ebola-infected NHPs are triggered not by endothelial cytolysis of Ebola virus but by viremia-induced proinflammatory cytokine release, including IL-6, that triggers coagulation cascades that confer fibrinogenic and fibrinolytic events and diffuse intravascular coagulation and hemorrhagic shock (8, 12, 17, 38).

**Risk Factors for Transmission**

Ebola infections in humans are acquired typically through direct contact with the body fluids of symptomatic infected individuals. It is important to reiterate that although the symptoms of early infection may be similar to those of many other infections, the mucosal hemorrhage, diarrhea, and vomiting that are characteristic of sustained, severe infections are the greatest cause for alarm with regard to transmission between humans. The CDC has established risk factors for determining the exposure risk for monitoring and movement considerations often used for travel and public health actions (http://www.cdc.gov/vhf/ebola/exposure/risk-factors-when-evaluating-person-for-exposure.html). In general, individuals with direct contact to body fluids of Ebola victims (without appropriate personal protective equipment), direct contact with deceased Ebola individuals (without appropriate personal protective equipment), or living in a household with and providing care to a person with symptomatic Ebola constitute the highest risk for infection. Having contact with an individual prior to Ebola symptoms or having arrived from one of the stricken regions and not shown symptoms for 21 days would classify one as having no identifiable risk to others. “Low” and “some risk” categories are also outlined. Many myths and misconceptions exist with regard to individual risk, and efforts by our national public health experts, at times, seem to be ignored by our leadership. Unjustified actions and restrictions on travel based on fear and not sound medical practice of Ebola risk can lead to grave impositions, economic disruption, and disregard for civil liberties.
Airborne Transmission

Ebola infections are not thought to occur by aerosol transmission, and contact with body fluids, blood, or deceased individuals has been consistently reported in cases of Ebola disease. However, two reports suggest that transmission by aerosol may be possible and should be cautiously expressed to the public when our health officials seek to alleviate fear of transmission. Animal-to-animal and animal-to-human transmission is thought to occur when cynomolagus macaques were imported into a US NHP quarantine facility infected with Reston virus and became ill (19). Intercage infection of NHPs was noted in the outbreak, and in some cases the distance between cages supported the notion of aerosol droplet transmission. Viral antigen detection was heaviest in the lung, suggesting the respiratory tract as the primary site of infection and indicating that lung-resident cells, including alveolar epithelial cells, are capable of supporting Reston virus replication. Seroconversion of workers both in the exporting facility in the Philippines and in the receiving facility in the US suggest asymptomatic infections (28). No evidence of direct contact with NHPs or their body fluids could be established in several cases, and the resultant conclusion was aerosol transmission. In this scenario, both the ability to produce infectious droplets and the ability to become infected by droplet transmission would be required. Infection by aerosol can be experimentally supported as well. In an experimental setting, rhesus macaques were infected by mechanical aerosolization of Zaire ebolavirus with particles of median mass diameter ranging from 0.8 to 1.2 μm and flow rate of 16.6 l/min in a head-only exposure apparatus (21). Exposure doses of as little as 400 pfu were able to cause disease. Interstitial pneumonia centered around terminal bronchioles suggested distal lung exposure. Type I pneumocytes were observed to have inclusion bodies, indicating a permissive infection in alveolar epithelial cells. Fatal infections were a common outcome. Studies to determine whether inhaled infectious particles could be detected were not performed.

Collectively, these findings suggest that aerosol transmission is possible. A number of thoughts, though, should be considered. First, the ability to eliminate either aerosol or direct contact as a means of transmission of many pathogens and not just Ebola in humans is continually debated in public health and few examples exist where either can be fully excluded. Unfortunately, this is true of Ebola disease as well. Health care workers are likely exposed to both. Evidence of Ebola in the lung has been reported in both natural human infections and experimental infections by multiple, nonpulmonary routes of inoculation, although the viral load measured by antigen detection and the lung pathology was reported to be stronger in the experimental aerosol transmission study (21). It should be noted that any upper respiratory tract deposition would likely result in capture by the mucociliary clearance mechanisms and deposited in gastrointestinal tract, leading to a natural form of infection, since the consumption of bushmeat is thought to be the cause of zoonotic transmission of index cases in human outbreaks (31). The findings from the Reston virus outbreak in the NHP facility suggest that both release of infectious exhaled particles and the permissiveness of the respiratory tract are plausible. Clearly more investigation is needed.

Potential Treatments

Currently, no vaccines or treatments are licensed by the Food and Drug Administration for Ebola prophylaxis or intervention within the US, or by any similar global authorities. The recent widespread emergence of Ebola, the need for extraordinary biocontainment requirements, and the lack of good small animal models for evaluation all likely contribute to the dearth of interventions or preventions of disease. A few reports exist showing efficacy, primarily in NHP models of disease. IFN-β therapy has been shown to increase survival and time to death in a lethal NHP model, consistent with many other viral infection models in light of the central role of IFN-mediated mechanisms in viral host defense (35). Pegylated IFN has not been studied; however, it has shown to be successful in other viral infections such as SARS-CoV and hepatitis C virus infections (16, 26). Another approach has been the use of coagulation inhibitors to address the coagulopathy associated with Ebola VHF, Recombinant activated protein C (Xigris; Eli Lilly), approved and then removed from the market for the treatment of severe sepsis, has shown some efficacy and highlights the similarities that exist between VHF and bacterial sepsis (17). Furthermore, anticoagulation protein C2 derived from hematides that inhibits Factor VIIa/tissue factor in the coagulation cascade was able to increase survival and mean time to death and to reduce intravascular thromboemboli in Ebola-infected rhesus macaques (12). Despite some success of anticoagulation end points, the overall survival experimentally was minimal. The lack of efficacy was likely due to the inability to directly mitigate the virus. Treatment of the cardiovascular component of the disease alone may be insufficient as a therapeutic approach.

RNA interference has been investigated as well, and two approaches using small interfering RNAs (siRNA) are currently in clinical trials (www.clinicaltrials.gov, keyword: ebola). TKM-Ebola developed by Tekmira Pharmaceuticals is a formulation of pooled siRNAs targeting the viral RNA polymerase L, VP24, and VP35 proteins. When delivered at the time of exposure and on subsequent days, it increased survival and reduced plasma viral loads (14). Another siRNA compound utilizing a different formulation, called AVI-6002 and developed by Sarepta Therapeutics (formerly AVI BioPharma), targets the viral VP24 protein alone with two distinct siRNA species based on morpholino oligomer design and likewise increases survival in a lethal NHP model (18). Neither compound has yet been tested in humans.

A novel antiviral called brincidofovir (called CMX001 and developed by Chimerix), a prodrug formulation of cidofovir (Vistide, Gilead Sciences), has been proposed for use against Ebola infection and is currently under Phase I investigation in humans. Cidofovir has been shown effective against a number of DNA viruses (particularly cytomegalovirus) as a DNA polymerase inhibitor (27). The mechanism of action of brincidofovir or cidofovir against RNA viruses is only presumptively thought to be similar. In vitro studies have shown cidofovir to have antiviral activity against Ebola infection (as reported by the company in news releases); however, no studies in experimental in vivo models have been performed. It should be noted that brincidofovir was used under a compassionate use agreement for the treatment of two cases of Ebola in the US, with one case surviving while the other did not. One
can only assume that the known safety profile of brincidofovir and cidofovir for use against DNA viruses was an important factor in allowing treatment of human Ebola cases, given the lack of experimental animal studies to support their use.

The treatment that has received the most attention has been a therapeutic antibody cocktail called ZMapp. Developed by Mapp Biopharmaceutical, ZMapp is a plant-derived cocktail of chimeric, humanized-mouse monoclonal antibodies targeting the G glycoprotein and produced in Nicotiana benthamiana, a species of tobacco (34). Widely reported in the media, ZMapp was administered to two US health care workers who were transported to US after contracting Ebola in West Africa. In light of the encouraging outcomes of those cases, ZMapp has become the media-hyped cure for the Ebola outbreak. Unfortunately, only a limited number of doses were available and no systematic evaluation of ZMapp effectiveness in humans can be made. In the lethal NHP model, ZMapp has shown to have 100% protection from Zaire ebolavirus variant Kikwit infection when administered up to 6 days following infection (34). To date, this is the only therapeutic intervention that provides this level of protection when administered on subsequent days following the onset of experimental disease. It should be acknowledged that efficacy was noted when ZMapp was initiated 5 days following experimental infection, a time window that allows for treatment of suspected cases before high viral loads can hinder effective intervention. Despite the encouraging results, clinical trials of ZMapp are not pending and quantities of the drug required for such trials are awaiting production. It is unclear when further evaluation of ZMapp will continue.

Vaccines for prophylaxis against Ebola constitute the most efficient and feasible approach to mitigating Ebola outbreaks and disease globally, and evidence exists that immune mechanisms are effective at conferring protection (37). Several vaccine trials are underway (www.clinicaltrials.gov, keyword: ebola) with results pending in most cases. Two vaccines have received the most attention and utilize a carrier “backbone” approach to streamline production and increase the safety profile of the vaccine. A vaccine under development with GlaxoSmithKline in collaboration with the National Institute of Allergy and Infectious Disease utilizes a chimpanzee adenovirus backbone to express the GP glycoprotein of Zaire ebolavirus, the main target of humoral immunity against the Ebola virus (22). A similar vaccine rVSV-ZEBOV under development by the Canadian National Microbiology Laboratory also expresses the Zaire ebolavirus GP protein in a vesicular stomatitis virus (33) backbone and has been shown to be effective in cynomolgus macaques in preventing Ebola disease. Both vaccines are in Phase I safety evaluation trials in the US and Africa, and efficacy trials will be performed likely in outbreak regions with recruitment of individuals that have a high probability of exposure.

One emerging therapy that is not in the typical repertoire of clinicians’ hands is the use of serum or blood from convalescent Ebola patients (15). As both a form of passive immunization in patients exposed but not presenting disease as well as a therapeutic antibody approach in patients already ill, transfusions of serum or whole blood to individuals from surviving patients is an interesting approach akin somewhat to Jenner’s “chickenpox parties” of yesteryear to confer infection and ultimately protection in adulthood to varicella (chickenpox). Convalescent serum has been used in the US in cases in which blood typing matches between surviving and infected patients. Although emergency use of such measures may make sense in outbreak scenarios, concerns exist with rampant use of blood transfusions in settings with poor hygiene controls, and the monetizing of convalescent serum in settings where resources are poor is plausible. Hemochromatosis, alloimmunization, and transfusion shock are not uncommon adverse outcomes in sickle cell disease therapy by blood transfusion.

Conclusion

The Guinea ebolavirus epidemic is yet another outbreak with which we are becoming all too familiar. The high lethality of Ebola disease coupled with the ease of transmission during severe infection has created an anxious tension among the populace that has spread to the public health sector. Just the ease with which the Ebola has been transmitted in the US health care settings with so few cases presenting has created a very heightened sense of unease. The current Ebola epidemic has exposed numerous fissures between practice and policy in our health care settings that remind us that new pathogens bring new challenges to the ongoing struggle of coordinating the policy makers and practitioners, just as HIV has challenged us for nearly 30 years now. Furthermore, it has exposed a serious quandary in our research infrastructure: fewer resources are being funded for research of highly dangerous pathogens, but yet the need grows more urgent to quickly develop therapies and vaccines to these emerging pathogens.

At the beginning of this article, I asked you to consider the question posed by my neighbor, in passing, “Does it ever end?” The answer: Probably not. Zoonotic outbreaks and the emergence of new pathogens have occurred throughout time and will continue as nature evolves new microbes to explore novel niches. We now get to watch them unfold in front of us by a media apparatus that covets our attention.

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K.S.H. prepared figures, drafted manuscript, edited and revised manuscript, approved final version of manuscript.

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