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COUNTERMEASURES AGAINST VIRAL HEMORRHAGIC FEVERS

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COUNTERMEASURES AGAINST VIRAL HEMORRHAGIC FEVERS

by

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CAPSTONE

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Dedication

This is dedicated to my little sister, Dr. Billie-Jo Grant. I could not have done this without your advice, courage, and daily pep talks. You inspire me.

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COUNTERMEASURES AGAINST VIRAL HEMORRHAGIC FEVERS

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Introduction

"Knowledge is power as we deal with bioterrorism." –Senator Bill Frist, M.D.

Viral hemorrhagic fevers (VHFs) are a group of viruses from four different virus families that are characterized by coagulation abnormalities with often fatal outcomes. VHFs can cause both internal and external bleeding. The virus families include: *Filoviridae*, *Arenaviridae*, *Bunyaviridae,* and *Flaviviridae.* All these viruses are enveloped and contain a single-stranded RNA genome. However, the viruses differ in their pathogenesis, transmissibility, natural host, and geographical distribution.

VHFs usually begin presentation with marked fever, fatigue, dizziness, nausea, vomiting, abdominal pain, muscle aches, loss of strength, and exhaustion. Patients can also experience bleeding under the skin, internal organs, and/or from other orifices

(mouth, eyes, or ears). Finally, patients can progress into shock, neurological involvement, coma, delirium, seizures, renal failure and even death.

The route of transmission of VHFs depends on the agent. Some VHFs are spread by close contact with infected animals or humans, while others are spread by insects. The main reservoirs can range from rodents to arthropods. Some of the vectors include: the multimammate rat, cotton rat, house mouse, deer mouse, ticks, and mosquitoes. Ebola, Marburg, Lassa, and Crimean-Congo viruses are known to spread from person to person contact. However, airborne transmission of VHFs is thought to be very rare (CDC, 1988, Baron RC, 1983). Transmission is more likely to happen late in infection when patients experience vomiting, diarrhea, shock, and hemorrhage, occurring with high levels of virus present in bodily fluids. Nosocomial transmission can occur through unprotected contact with infectious body fluids, contaminated medical equipment or supplies, or an accidental needle stick. Infections can be significantly reduced with proper hand washing, safe sharp handling, and isolation precautions. Several outbreaks of Ebola have been attributed to improper personal protective precautions or contaminated needles.

This capstone determined the countermeasures available against VHFs in clinical trials, the vaccines tested in non-human primates, the therapeutics tested in non-human primates as well as treatment strategies tested in humans.

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Chapter 1: Introduction

Significance

More than 20 different viruses can cause viral hemorrhagic fever manifestations. Although the viruses differ in size and replication patterns, the basic pathogenesis mechanism is septic shock. Viral hemorrhagic fevers (VHFs) can be separated into two categories: either those that are susceptible to a broad-spectrum anti-viral drug, Ribavirin (Virazole®) or those that are not. Crimean-Congo hemorrhagic fever, Lassa virus, and the South American hemorrhagic fevers have shown some benefit to treatment with Ribavirin.

Despite the number of VHFs and their high rates or mortality, Yellow fever is the only VHF that has a licensed effective vaccine available in the United States. Other VHFs have vaccines that are licensed in other countries or in development but these vaccines are not readily available to the public. For many VHFs, supportive care is the only treatment. Basic supportive care should maintain blood pressure, intravascular volume, organ perfusion, and should give antibiotics to combat secondary infections (Bray and Mahanty, 2003). For example, supportive care for patients with a suspected filovirus infection, includes: pain management, maintenance of proper blood volume levels, and electrolyte balance (Martini et al., 1968).

Due to the lack of VHF countermeasures and high mortality rate, the concern of bioterrorism is a threat for our society. Several VHFs have been weaponized in other countries. In 1992, Ken Alibek, who defected from the Soviet Union, reported that the

Russians had blended Ebola and Smallpox in their offensive weapons program along with weaponization of other VHFs (Alibek and Handelman, 1999). Members of the Japanese terrorist group Aum Shinrkyo even traveled to Zaire in attempt to isolate Ebola (Falkenrath, 1998). Incidents like these increase the need for researching and developing vaccines for VHFs.

The most likely form of intentional release of VHFs would be small aerosols. Signs of an intentional release include temporal or geographic clustering of illness. One example of geographic clustering is people who attend the same public event and/or present with the same clinical symptoms (NEVCO, 2007). Unusual age distribution for common disease is another indicator of a bioterrorism attack. Epidemic causes can include: ecological changes, agriculture development, changes in human demographics or behavior, international travel, commerce, technology industry, microbial adaptation and change, and breakdown in public health measures and deficiencies in public health infrastructure (Morse, 1999).

Table 1: Recommended therapy with intravenous or oral ribavirin of persons who have been exposed to an aerosolized HF virus in a bioterror attack (Borio et al., 2002).

	Contained Casualty Setting	Mass Casualty Setting
Adults	Loading dose of 30 mg/kg IV, followed by 16 mg/kg IV every 6 hours for 4 days, followed by 8 mg/kg IV every 8 hours for 6 days	Loading dose of 2000 mg orally once, followed by 1200 mg/d orally (if weight over 75 kg) or 1000 mg/d orally (if weight under 75 kg) for 10 days
Children	Same as for adults	Loading dose 30 mg/kg orally once, followed by 15 mg/kg per day orally divided into 2 doses for 10 days

Table 2: Advantages and disadvantages of different vaccine strategies.

Type of Vaccine	Advantages	Disadvantages
Live attenuated vaccines	-Highly Immunogenic -Don't require boosters	-May revert to virulence
Inactivated vaccines	-Safe	-Need to be manufactured in biocontainment Multiple immunizations required
VLPs	-Non-replicating	-Expensive to produce -Multiple immunizations required
DNA vaccines	-Safe	- Poor immunogenicity -Multiple immunizations required
Recombinant vaccines	-Multi-route delivery	-Preexisting immunity -Large dose required -Reassortments

VHFs present a host of methodological challenges for researchers. For these exotic agents, where clinical trials are not feasible or ethical, the FDA has devised an "animal rule" where testing in established animal models could be sufficient for licensure (Roberts et al., 2008). Although numerous therapeutics and vaccines have shown to be effective in non-human primates and other animal models these countermeasures must progress through phase I and II clinical trials (Bausch et al., 2008). Thus, human testing may include workers in high containment laboratories or outbreak response teams. Knowing the available countermeasures against VHFs is only the first step in responding to a potential attack and planning should also include logistics of distribution and manufacturing in different geographical regions.

This capstone will review the different vaccines and therapeutics available in clinical testing, as well as countermeasures that are in the advanced development.

Chapter 2: Methods

Potential therapeutics and vaccine candidates for VHFs were found through a search of clinicaltrials.gov, which returned seventy-four results when the keywords "hemorrhagic viral fever" were entered. Numerous results were the same drug with clinical trials being performed in different locations. Several studies were removed from the analysis because they dealt with dengue, Japanese encephalitis, malaria, or lymphoma. The search also revealed countermeasures that are in clinicaltrials.gov. Ribavirin, a DNA nucleoside analogue, has been in phase II trials for several different agents including Crimean Congo hemorrhagic fever, hemorrhagic fever with renal syndrome (HHRS), and Lassa virus. Several DNA plasmid vaccines have gone through phase I trials and are now in phase 1B trials for Ebola and Marburg. A phosphorodiamidate morpholino antisense oligomer, AVI-6002 and AVI-6003, were tested as a single administration post-exposure prophylaxis against Ebola and Marburg.

A search of Pubmed for "viral hemorrhagic fever vaccine" returned 1274 results and "viral hemorrhagic fever therapeutics" returned 1078 results. Studies were excluded that discussed dengue, Japanese encephalitis, or other non-VHF diseases. Review papers were used to find other references that could lead into more insight into countermeasures. Papers that only dealt with basic mechanisms, pathogenesis, *in vitro* testing or animal testing in rodents were also removed. The focus of this review is non-human primates and human studies only.

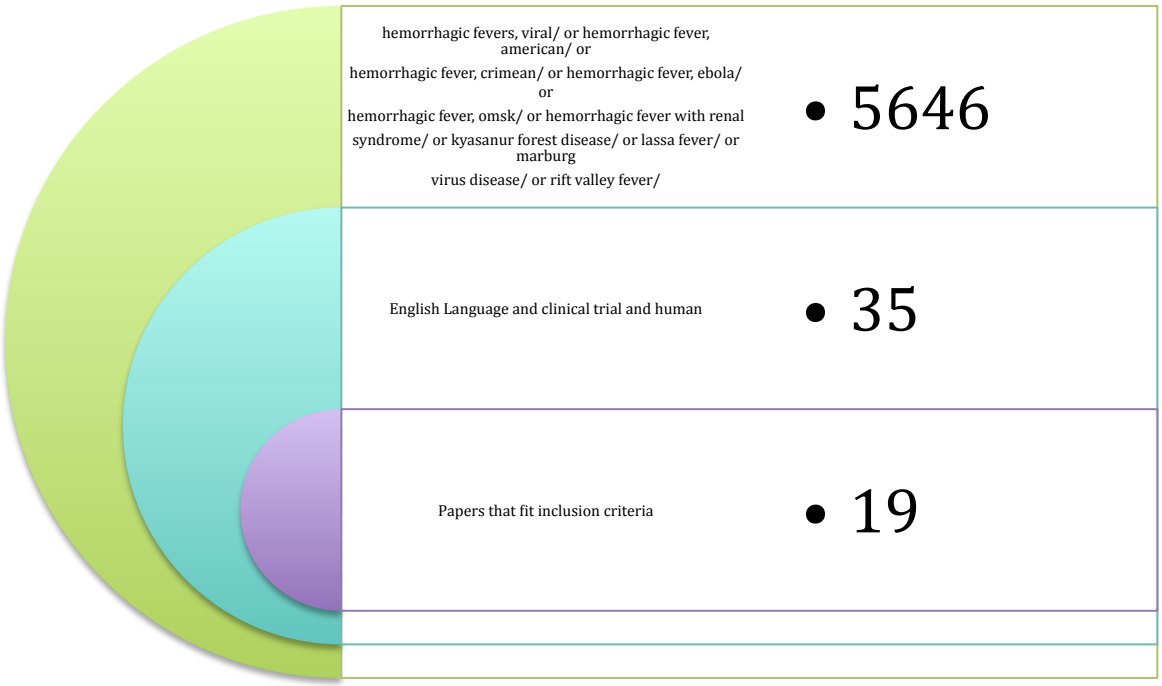

Figure 1: Ovid Medline search criteria and results for human clinical trials of viral hemorrhagic fever in the English language.

An Ovid medline search of "hemorrhagic fevers, viral/ or hemorrhagic fever, american/ or hemorrhagic fever, crimean/ or hemorrhagic fever, ebola/ or hemorrhagic fever, omsk/ or hemorrhagic fever with renal syndrome/ or kyasanur forest disease/ or lassa fever/ or marburg virus disease/ or rift valley fever/" limiting clinical trial publications that were published in English and included human subjects. This search was performed on January 19, 2012 and returned 33 results. Clinical trials looking at seroprevalence, diagnosis, disease pathogenesis, or non-medical interventions were excluded from the search. Furthermore, several papers were removed because they were nonclinical studies performed in non-primate animals. Nineteen papers remained for review of human clinical trials for viral hemorrhagic fever.

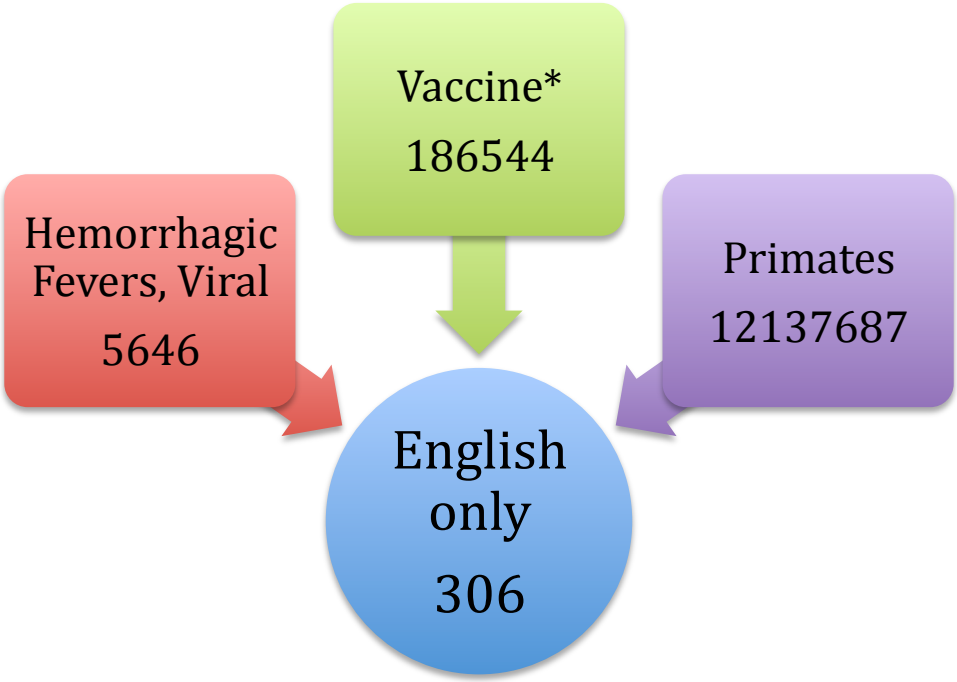

Figure 2: Ovid Medline search results of non-human primate vaccine experiments with viral hemorrhagic fevers.

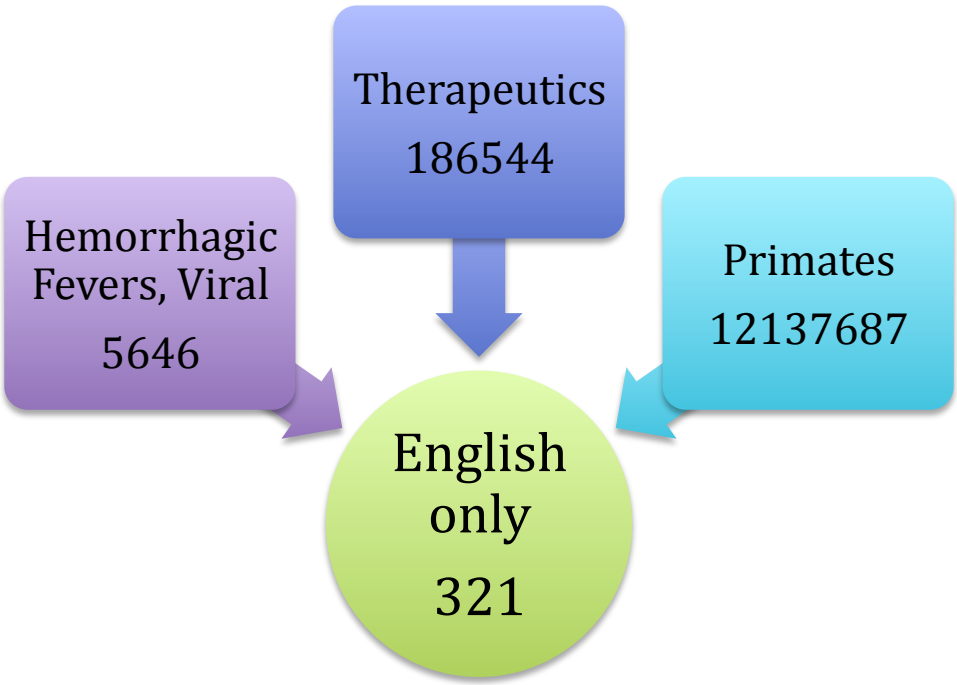

Figure 3: Ovid Medline search results of non-human primate therapeutic experiments with viral hemorrhagic fevers.

The above viral hemorrhagic fever terms were combined with "primate" along with therapeutics or "vaccine*" searches and limited to English articles. This search returned 304 results for vaccine searches and 318 for therapeutics. The following articles were manually excluded: tested the countermeasure in rodents only, case study reports, review articles, focused on pathogenesis, outbreak reports, epidemiology, patient management, or seroprevalence.

Chapter 3: Viral Hemorrhagic Vaccine and Countermeasures

Arenaviruses

The *Arenaviridae* family is separated into Old World and New World arenaviruses. The Old World human pathogens include Lassa and Lymphocytic chiromenegitis virus (LMCV) while the New World arenavirses include the South American hemorrhagic fever viruses. The arenaviruses have a single-stranded ambisense bipartite genome. The South American hemorrhagic fever viruses are responsible for Argentine, Bolivian, Venezuelan, and Brazilian hemorrhagic fever caused by Junin, Machupo, Guanarito, and Sabia viruses respectively. Several newly emerging arenaviruses include Chapare virus which was isolated in Bolivia and Lujo virus which was isolated in South Africa.

The emergence of some of the South American arenaviruses is thought to be influenced by human interaction with the environment. Agricultural workers are naturally exposed to these arenaviruses during the reaping of corn but their exposure has increased over time. For example, the 1940s clearing of the Argentinean pampas and heavy herbicide use to control the native fauna to plant corn caused the natural predators to disappear and an explosion of the local field mouse, *Calomys musculinus* (Grifo, 1999). Starting in 1958 cases of Argentine hemorrhagic fever (AHF) dramatically increased. Similarly, in the 1950s, jungles in Bolivia were cleared to grow corn and vegetables, an excellent source of food for *Calomys* and village cats were killed by excessive DTT use

(Grifo, 1999). These conditions lead to a Bolivian hemorrhagic fever (BHF) outbreak that killed 20% of the villagers.

AHF is one of the few VHFs that has a vaccine that is licensed outside the United States. Candid#1, a live attenuated vaccine, has been used against AHF and has proven to be effective in Argentinean populations with few adverse effects (Enria et al., 2010). Candid#1 had an investigational new drug (IND) status in the United States but is licensed and produced in Argentina (Maiztegui et al., 1998). Immune response studies to Candid#1 vaccination in 330 human volunteers showed that two years after vaccination there was lasting neutralizing antibodies and previous infection with the Old World areanvirus lymphocytic choriomeningitis virus (LCMV) did not alter the immune response (Ambrosio et al., 2006)

AHF is also one of the only VHFs where clinical trials have been performed in humans evaluating therapeutic options. Although treatment of AHF with convalescent serum has been shown to be effective in a randomized controlled human trial in Argentina, it was associated with a late neurologic syndrome (LNS) in up to 10% of people treated (Maiztegui, 1979). The only approved treatment for arenavirus infection in the US is 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, Ribavirin, a nucleoside analog that has been shown effective as an antiviral against a number of diseases (Parker, 2005). Non-human primate testing using rhesus macaques showed that clinical disease can be prevented if ribavirin is given at the time of challenge whereas it only results in a delay of time to death if treatment is begun at six-days post infection (McKee et al., 1988). Ribavirin has also shown to be beneficial for treatment of Bolivian hemorrhagic fever in nonhuman primates (Stephen, 1980). Ribavirin has been used to treat several

patients including a laboratory exposure to Sabia virus (Kilgore et al., 1997, Barry et al., 1995). Some evidence indicates that convalescent serum may be beneficial in Bolivian hemorrhagic fever treatment when it was used during an epidemic (Stinebaugh, 1966). Ribavirin has also been shown to be effective at treatment of AHF and Bolivian hemorrhagic fever if given to patients early in the course of the disease (Kilgore et al., 1997, Weissenbacher et al., 1987). In addition, a single laboratory case of Sabia was treated with Ribavirin but it is unclear if this affected the disease course (Barry et al., 1995). Overall, South American hemorrhagic fevers have several treatment options and a licensed vaccine for Junin virus is available in the endemic area.

Changing the human interaction with the environment also caused the emergence of another arenavirus, Lassa. Urbanization favoring rodent hosts lead to increased exposure to Lassa virus in Sub-Saharan west African (Senegal to Central African Republic) homes, where Lassa virus is endemic. Human-to-human transmission occurs through direct contact with infected blood and other body fluids or aerosolized virus. Lassa virus has been shown to be extremely infectious when aerosolized as a small particle in animals (Stephenson, 1984). Transmission can also occur through contaminated needles/syringes (Fisher-Hoch, 2005).

Several vaccine approaches have been shown to be effective in animal models but there is no approved vaccine. Lassa virus-like particles (VLPs) have been created using plasmid to transfect cells and is immunogenic in mice (Branco et al., 2010), but further testing is needed to determine if the VLPs are efficacious in non-human primates. Although several vaccine approaches have been attempted for Lassa virus they have not progressed to clinical evaluation. Table 1 illustrates the advantages and disadvantages of

different vaccine strategies.

Ribavirin has been effective against Lassa virus in non-human primates as well as reducing morbidity and mortality in humans (Stephen, 1979, McCormick et al., 1986). However, some adverse side effects have been reported such as an episode of rigors in a clinical trial performed in rural west Africa (Fisher-Hoch et al., 1992). Treatment with convalescent serum was effective after a researcher was exposed (Leifer, 1970). Immune serum has also been efficacious in non-human primates that was treated a short time after exposure to Lassa virus (Jahrling, 1984). Nonetheless even though convalescent serum has been shown to be effective at treatment of Lassa fever virus it is not the standard treatment in West Africa (Jahrling, 1985). A broad spectrum arenavirus entry inhibitor, ST-193 (Larson et al., 2008), was found to enhance survival of guinea pigs infected with Lassa virus (Cashman et al., 2011). Several promising therapies are available for Lassa virus but the evidence of effectiveness in humans is not as advanced as that for AHF. Ribavirin seems to be the standard of care for Lassa with the recommended dosing outlined in Table 2.

Several broad spectrum therapeutics and vaccines have been proposed for arenavirus prevention and management. A broad spectrum vaccine is capable of producing T cell responses against seven different pathogenic arenaviruses when HLA transgenic mice were immunized with recombinant vaccinia viruses expressing different arenavirus protein identified through HLA- restricted cytotoxic T cell responses (Kotturi et al., 2009). A phosphatidylserine targeting antibody, bavituximab, was shown to protect guinea pigs infected with a virus used to model Lassa virus infection, Pichinde (Soares et al., 2008). This therapeutic was funded by the Defense Threat Reduction Agency (DTRA) for further investigation with New World arenaviruses.

Bunyaviruses

Crimean-Congo hemorrhagic fever (CCHF) is in the family *Bunyaviridae* and is a single-stranded, negative sense RNA virus with a tripartite genome. The disease spreads by ticks or bodily fluids of infected domestic animals. CCHF occurs across Asia and down the length of Africa. CCHF primarily infects antigen-presenting cells (macrophages and dendritic cells). Once patients become infected with CCHF virus, symptoms includes headache, malaise, myalgia, and fever (Ergonul, 2008) that can progress to conjunctival injection, erythema, flushed face, and disseminated intravascular coagulation (DIC). Cutaneous hemorrhage and ecchymoses are unique to CCHF. Diagnosis is usually performed soon after illness with the detection of virus by RT-PCR.

There are no licensed vaccines available in the United States to protect persons against CCHF. CCHF vaccines have been in development for decades. In the 1970s a formaldehyde and heat inactivated vaccine was produced using brain tissue from mice and it was shown to efficacious in animals and no adverse effects in humans (Tkachenko, 1970, Vasilenko, 1976). The inactivated vaccine produced low levels of neutralizing antibodies but no studies were published showing the efficacy of the vaccine in humans. The Bulgarians used a CCHF vaccine to dramatically decrease the incidence of cases over a 22-year period (Christova , 2009, Papa et al., 2010). The vaccination course includes doses given on day zero and 30, and one-year following by booster doses every five years (Todorov, 2001). The Bulgarian vaccine is not licensed for use in the US despite the success shown through several different studies.

Prophylaxis against CCHF should include oral ribavirin administration and monitoring for symptoms. Once symptoms of CCHF develop ribavirin should be administered intravenously in combination with supportive therapy to prevent shock and management of coagulation defects (Ergonul, 2008). The CDC guidelines for CCHF prophylaxis recommends oral ribavirin dose for adults that have a high likelihood of being exposed is shown in Table 2 (CDC, 1988). Whether administering ribavirin is efficacious is unclear. A review article summarized the literature on ribavirin efficacy with CCHF since 1985 and discusses the historical comparisons and randomized and non-randomized clinical trials (Keshtkar-Jahromi et al., 2011). The authors suggest the evidence about the effectiveness of ribavirin is contradictory. For instance, a prospective randomized cohort study of 136 cases of CCHF in the Eastern Black Sea region found that there were no positive effects of ribavirin on clinical or laboratory findings (Koksal et al., 2009). On the other hand, a study in Iran determined the efficacy of oral ribavirin treatment to be 80% with confirmed cases of CCHF (Mardani et al., 2003). The review also shows that anti-CCHF immunoglobulin might be effective as a treatment for the disease. With intramuscular injections of convalescent serum once- or twice-a-day for up to four-days following the onset of hemorrhagic symptoms, no significant difference between untreated matched patients could be demonstrated, suggesting that IgG may not be effective (Martinenko, 1970). Ribavirin is the only therapeutic available for the treatment of CCHF but the exact benefit of the drug in CCHF cases is unknown.

Rift Valley fever virus (RVFV) occurs naturally in livestock in Kenya and sub-Saharan countries is spread by *Culex* and *Aedes* mosquitoes. The 1977 building of the Aswan Dam in Egypt caused a shift in the transmission cycle to humans causing 100,000 to become ill with the virus, killing 1,000 people. Besides the building of dams,

agriculture, irrigation, and the change in virulence/pathogenicity of the virus caused emergence (Morse, 1999). RVFV is a negative-sense RNA virus with a tripartitite genome consisting of a small (S), medium (M), and large (L) RNA segments in the genus *Phlebovirus*. RVFV can be transmitted through a variety of different routes including mosquito bite, exposure to viremic bodily fluids from humans or animals, ingestion, or airborne.

Several different vaccine approaches have been undertaken to prevent RVFV. The Smithburn strain was serially passaged in mouse brains to produce a live attenuated vaccine against RVFV and was used in the 1950s in South Africa (Smithburn et al., 1948). In the 1970s over 500 patients were vaccinated with NDBR 103, a formalin inactivated cell-culture vaccine derived from the RVFV Entebbe strain, but it showed some side effects during a clinical trial (Niklasson, 1982). Two different RVFV vaccines have progressed to clinical trials in humans, including an inactivated vaccine and a live attenuated vaccine. TSI-GSD-200, a formalin inactivated RVFV vaccine, is administered in three doses as an IND at United States Army Medical Research Institute of Infectious Disease (USAMRIID) (Pittman, 1999). Vaccinees have been followed for 19 years showing 90% of persons seroconverted during the primary three doses and over 99% showed neutralizing antibodies after the booster vaccination was given (Rusnak et al., 2011). A study in laboratory staff and students showed three doses of TSI-GSD 200 was needed to create a antibody titers that would correlate with protection (Frank-Peterside, 2000) A capripoxvirus recombinant vaccine expressing the glycoproteins of RVFV protected mice and sheep against virulent RVFV challenge (Soi et al., 2010). RVFV VLPs were created utilizing the viral glycoproteins and a subunit RVFV vaccine (ectodomain of Gn) were able to protect mice against RVFV lethal challenge (de Boer et

al., 2010). VLPs with RVFV glycoproteins and nucleocapsid were shown to partially protect mice and rats against lethal RVFV challenge (Mandell et al., 2009). A nonreplicating adenovirus containing the RVFV glycoproteins induced a humoral immune response that protected mice, with either preexisting adenovirus immunity or with no immunity to the vector virus, against lethal challenge with RVFV ZH501 (Holman et al., 2009). Ideally, authorities should be able to differentiate between naturally infected and vaccinated animals (DIVA) to ensure an epidemic is not occurring (Bouloy and Flick, 2009, McElroy et al., 2009). Strain ZH548 that was passed 12-times in the presence of 5-fluouracil, a mutagen, resulted in the introduction of 25 nucleotide changes and 11 amino acid substitutions (Caplen et al., 1985). This MP-12 live attenuated vaccine was shown to be immunogenic in ruminants (Morrill et al., 1991, Morrill et al., 1997b, Morrill et al., 1997a). MP-12 was shown to have no adverse effects when administered to rhesus macaques by a variety of different routes (intranasal, oral, or aerosol) (Morrill and Peters, 2011a) and MP-12 administered by the intramuscular route protected rhesus macaques against intravenous and aerosol challenge for up to 6-years after vaccination (Morrill and Peters, 2011b). A second live attenuated vaccine candidate, clone 13, was derived via plaque purification and contains a large deletion in the NSs gene and has been shown to be safe and efficacious in sheep (Muller et al., 1995, Dungu et al., 2010). A reverse genetics system has been created and has been used to create different vaccine candidates derived from MP-12 and clone 13 (Bird et al., 2008, Bouloy and Flick, 2009, Ikegami et al., 2006). In addition, a number of candidate subunit vaccines have been produced using the glycoproteins of RVFV using different viral backbones: adenovirus (Holman et al., 2009), alphavirus (Gorchakov et al., 2007, Heise et al., 2009), Newcastle disease virus (Kortekaas et al., 2010), the poxvirus lumpy skin disease (Wallace and Viljoen, 2005, Wallace et al., 2006) and empty vectors to make

VLPs (de Boer et al., 2010, Habjan et al., 2009, Liu et al., 2008, Naslund et al., 2009). Candidate RVFV DNA vaccines require several vaccinations by a gene gun to achieve induction of a protective immune response (Naslund et al., 2009, Spik et al., 2006, Wallace et al., 2006). Numerous different vaccine approaches have been attempted to combat RVFV. The live attenuated vaccine (MP-12) and formalin-inactivated vaccines that have progressed in human testing are the most promising. MP-12 only requires one vaccination and induces rapid immunity. However, there is not a licensed vaccine for RVFV approved for human use in the US.

Studies have shown that ribavirin is effective at protecting rodents and macaques and inhibiting viral replication *in vitro* (Canonico et al., 1984). However, a placebo controlled clinical trial with ribavirin in Saudi Arabia was stopped when patients treated with ribavirin had an increase incidence of encephalitis (Al-Hazmi et al., 2003). Type I interferon was shown to be effective as a prophylaxis or post-exposure therapy against RVFV (Morrill, 1990). Immune plasma was also shown to be effective in non-human primates infected with RVFV (Peters, 1986). Although there are several different potential therapies available, Ribavirin is the standard treatment for RVFV infection.

Hemorrhagic fever with renal syndrome (HFRS), also known as Korean hemorrhagic fever, and can be caused by a variety of different hantaviruses including Hantaan, Dobrava, Saaremaa, Seoul, and Puumala. Like arenaivurses, hantaviruses are spread by the aerosolized excreta from infected rodents.

A randomized, double-blind, prospective, concurrent, placebo-controlled clinical trial of patients with HFRS in China showed patients administered intravenous ribavirin

were significantly less likely to enter the oliguric phase of the disease compared to placebo treated controls (Huggins et al., 1991). Another double-blind clinical trial showed viral replication could be terminated with treatment of ribavirin as shown by virus isolation, immunofluorescence assay and ELISA (Yang et al., 1991). Although over thirty years of research has been performed on hantavirus there is still no safe, licensed and effective vaccine in the US. There are three different inactivated vaccines produced from suckling mouse brains, hamster kidney cells, and gerbil kidney cells made in Asia.

Filoviruses

The virus family that has the most notoriety among VHFs is the filoviruses, containing the nonsegmented negative stranded RNA viruses Marburg and Ebola. Ebola virus encroached into the United States by the importation of infected monkeys. Asiatic monkeys in a Reston, Virginia Primate Quarantine Facility died from an aerosolizable form of the Ebola virus that was non-pathogenic in humans (Rollin et al., 1999). The first filovirus outbreak occurred in 1967 in Marburg, Germany and Belgrade, Yugoslavia when African Green monkeys infected with Marburg were imported. Subsequently, two Ebola outbreaks in Zaire and Sudan took place in 1976 (Bres, 1978). The first appearance of Ebola in West Africa was on the Ivory Coast in 1994. Several more Ebola outbreaks have followed in Kikwit, Zaire, Gulu, and Uganda. Native animals in Africa and the Philippines have been documented to carry Ebola and Marburg viruses.

Human-to-human transmission occurs from direct body contact with infected body fluid (sweat, saliva, and semen). Outbreaks in Africa have been linked to bats plus contaminated syringes and needles. Ebola Reston is non-pathogenic in humans but

airborne transmission occurred during the Virginia primate facility outbreak. Filoviruses are not known to be particularly stable in the aerosol form. However, the Soviets stabilized Marburg by incorporating additives into the virus formulation (Frist, 2002).

The incubation period of Ebola can range from a few days to three-weeks. The disease begins with a high fever, myalgia, headache, stomach pain, malaise, and bloody diaherra. Patients can then experience chest pain, shock and death. The mortality rate ranges from 50-90%. Marburg incubation period is five to ten days and the disease starts with fever, chills, headache, fatigue, and rash. Later symptoms include jaundice, inflammation of the pancreas, severe weight loss, confusion, shock, liver failure, and death. Though a slightly lower mortality rate than Ebola, 25-75% of patients succumb to Marburg.

Standard treatments for filoviruses include fluids with electrolytes, maintenance of oxygen levels, blood transfusion when needed, and treatment of complicating infections. Isolating patients is critical and taking the necessary precautions including proper use of personal protective equipment. For Marburg virus a number of different approaches have been used in an attempt to prevent secondary infection. Marburg patients have been treated with antibiotics, electrolytes, albumin, antipyretics, and coagulation factors (Martini and Siegert, 1971). Although the results are positive with human treatment, the number of patients is too small to justify any changes in standards of care.

Basic science has revealed that the main protective antigen of filoviruses is the surface glycoprotein. The majority of vaccine strategies employ the expression of this

protein as a strategy to create protective immunity. Several different vaccine strategies have been investigated including recombinant vaccines, vaccines that can replicate, and those that are replication deficient.

One vaccine approach used to combat filoviruses is using adenovirus recombinant vaccines. A prime-boost regimen involving a DNA prime and a boost with an adenovirus vaccine containing Ebola virus protein protected non-human primates (Geisbert et al., 2002). However, problems with the adenovirus vaccine approach include the extended period needed to create protection and with pre-existing immunity to adenoviruses (Geisbert et al., 2011). Pre-existing immunity is a particular challenge among the majority of African population previously exposed to human adenoviruses (Ad5) (Geisbert et al., 2010a). This problem was circumnavigated by using a different adenovirus serotype, Ad35 and Ad26, for the backbone of the Ebola virus vaccine (Geisbert et al., 2011). A phase I clinical trial has being performed in healthy human adults using the Ebola adenovirus serotype 5 vector vaccine (Ebola-rAd5) and was shown to be both immunogenic and safe in humans (Ledgerwood et al., 2010). An adenovirus vector vaccine combination, CAdVax, containing glycoproteins of ebola virus (Zaire and Sudan) protected nonhuman primates against lethal challenge by the aerosol route (Pratt et al., 2010). Overall, adenovirus vaccine strategies appear to be effective at protecting non-human primates and are safe and immunogenic in humans.

Besides the adenovirus recombinant approach, several other viruses have been used as vehicles to carry the immunogenic antigen of filoviruses and create protection. A vector vaccine using human parainfluenza virus type 3 (HPIV3) expressing the glycoprotein of Ebola virus protected non-human primates against lethal virus challenge

(Bukreyev et al., 2007). One problem with the parainfluenza vaccine approach is preexisting immunity to the parainfluenza virus. Monkeys with previous exposure to HPIV3 had significantly less antibodies specific to the Ebola glycoprotein as well as Ebola neutralizing antibodies compared to monkeys that were not previous exposed to HPIV3 (Bukreyev et al., 2010). However, after a booster vaccination with the glycoprotein HPIV3 vector, the titers of antibodies between non-human primates that have been previously exposed to HPIV3 and those who were naïve were not significantly different (Bukreyev et al., 2010). Another recombinant vaccine approach uses Newcastle virus with the glycoprotein of Ebola Zaire, which was shown to create neutralizing antibodies against Ebola virus in rhesus monkeys (DiNapoli et al., 2010).

Another recombinant vaccine was constructed using vesicular stomatitis virus (VSV). Recombinant VSV filovirus vaccines have been shown to protect 100% of monkeys with a single dose and show no-crossprotection to related filoviruses (Hensley et al., 2005). One advantage of recombinant VSV with Ebola glycoprotein has been shown to be protective with administration through a variety of different routes (oral, intranasal, and intramuscular) in immunocompetent and immunocompromised non-human primates (Geisbert et al., 2008). The recombinant VSV vaccine has even been shown to be somewhat effective as a prophylaxis, protecting 50% of non-human primates 30-minutes after challenge (Feldmann et al., 2007). A single dose of blended recombinant vesicular stomatitis virus (VSV) expressing filovirus glycoprotein (Ebola Zaire, Ebola Sudan, or Marburg) was shown to be protective against Ebola Zaire, Ebola Sudan, and Ebola Cote d'Ivoire, in cynomolgus monkeys (Geisbert et al., 2009). The recombinant vaccine could have the potential to protect against all filoviruses.

A DNA vaccine against Ebola was shown to be immunogenic and safe in phase I clinical trials (Martin et al., 2006). DNA vaccines have several advantages over recombinant adenoviruses vaccines because there are no pre-existing immunity problems and DNA vaccines are safer in immunocompromised individuals. DNA plasmid vaccines against Ebola virus were shown to be safe and immunogenic in randomized, placebo-controlled, double-blinded, and dose escalation Phase I clinical trial (Martin et al., 2006).

Virus like particles (VLPs) is another vaccine strategy that is being investigated as a possible protection approach against filoviruses. Three doses of VLPs with the glycoprotein, nucleocapsid and VP40 of Ebola Zaire protected non-human primates against lethal challenge and any clinical symptoms of disease (Warfield et al., 2007). A VSV recombinant virus with the Ebola Zaire glycoprotein given prophylaxis through a variety of different routes (intranasally, orally, or intramuscularly) can protect non-human primates against Ebola Zaire by eliciting a humoral and cellular immune response (Qiu et al., 2009).

Several therapeutics have been tested in animals including monoclonal antibodies (Parren et al., 2002), siRNA (Geisbert et al., 2006), tissue factor inhibitors (Geisbert et al., 2003a), and a phosphorodiamidate morpholino oligomer (PMO) (Enterlein et al., 2006). KZ52, a human neutralizing monoclonal antibody, was shown to completely protect guinea pigs (Parren et al., 2002) but failed to protect non-human primates against lethal challenge with Ebola virus (Oswald et al., 2007). siRNA treatment given to guinea pigs showed complete protection (Geisbert et al., 2006) while treatment to non-human primates every other day lead to partial protection, and daily treatment of siRNA in monkeys lead to complete protection against Ebola Zaire (Geisbert et al., 2010b). A PMO

against Ebola Zaire lead to complete protection in mice and partial protection in guinea pigs and non-human primates (Warfield et al., 2006). Other inhibitors and small molecules have showed to be effective in vitro and in small animals but have not been tested in non-human primates (Bray and Paragas, 2002).

Immune serum and monoclonal antibodies are effective treatment of rodents and nonhuman primates infected with filoviruses (Jahrling et al., 1999, Jahrling et al., 2007). siRNA directed against VP24, VP35, and L proteins of Ebola Zaire strain was shown to be protective in non-human primates when administered following challenge with Ebola (Geisbert et al., 2010c). PMOs directed against VP24 and VP35 of Ebola and Marburg virus can protect rhesus macaques if the therapeutic is initiated soon after infection (Warren et al., 2010b). There is evidence that blood or immune plasma from convalescent donors can be effective at treatment of patients but more studies need to undertaken (Emond et al., 1977, Mupapa et al., 1999). Equine IgG was shown not to protect cynomolgus monkeys against Ebola Zaire strain even with different treatment strategies (Jahrling et al., 1999). Treatment with activated protein C was shown to extend the mean time to death in rhesus monkeys (Hensley et al., 2007).

Several therapies are available to attempt to counter the effects by coagulations defects that occur during viral hemorrhagic fever infection. A recombinant nematode anticoagulant protein C2 (rNAPC2) is in phase II trials in humans and has shown to be effective at protecting macaques against lethal Ebola virus challenge when administered by subcutaneous infection (Geisbert et al., 2003b). rNAPC2 acts through the extrinsic coagulation pathway by interaction with factor VIIa and tissue factor. A recombinant human activated protein C, Xigris®, has shown to be effective in macaques against lethal

dose of Ebola virus when administered intravenously within 30-minutes of exposure (Hensley et al., 2007). FGI-103, a small molecule inhibitor, was shown to have antiviral effects against Ebola (Zaire and Sudan) and Marburg (Ci67 and Ravn) *in vitro* as well as protect mice when delivered 24-hours after challenge intraperitoneally at a dose of 10 mg/kg (Warren et al., 2010a).

Flaviviruses

Yellow fever virus (YFV) emergence in West Africa was mainly due to rainforest encroachment. The principle sylvatic transmission cycle in the jungle is monkey-to-monkey transmission by *Aedes africanus*. Logging and other agricultural persuits caused humans to enter into the sylvatic cycle. Once in an urban environment the disease is transmitted by *A. aegypti*. In South America and the Caribbean the mosquito is a *Heamogogous* species. YFV is known to be quite stable in the aerosol form.

A live attenuated vaccine exists against YFV, 17D, which is required for travelers to South America and Africa (Monath, 2001). 17D is a licensed vaccine in the United States. However, serious adverse effects (SAE) are found in a small number of vaccinees (approximately 4-8 per million doses administered) including: hypersensitivity reactions as well as either viscerotropic or neurotropic syndromes (Domingo and Niedrig, 2009). These are correlated with increasing age and immunosuppression. A cell culture inactivate vaccine, XRX-001 purified whole-virus inactivated by β-propiolactone, was administered to humans in a double-blind, placebo-controlled study of two different doses (0.48 μg or 4.8 μg) producing neutralizing antibodies in 100% of the high dose group (Monath et al., 2011).

Chapter 4: Discussion

This capstone demonstrates that many different vaccine and therapeutic options for VHFs have not only been tested *in vitro* but in small animals and non-human primate animal models. This literature review should be of interest to scientists, clinicians, biological safety committees, policy makers, and the general public. From Table 3 we can see there are a number of vaccines and therapeutics that have undergone phase I and phase II clinical trial testing for these exotic diseases. There has been an explosion of possible vaccines and therapeutics that are being researched to prevent and treat filoviruses.

Table 1: Vaccines and countermeasures available against viral hemorrhagic fevers in clinical trials in the United States.[1]

Study Name	Countermeasure Name	Type	Phase	Agent
Treatment of VHFs with iv Ribavirin in Military Facilities	Ribavirin IV	DNA nucleoside analogue	Phase II	CCHF; Lassa
Ribavirin for Hemorrhagic Fever with Renal Syndrome in Germany	Ribavirin IV	DNA nucleoside analogue	Phase II	HHRS
Experimental Vaccine Prevention of Ebola Virus Infection	VRC-EBOADV018-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola
Experimental Ebola Vaccine Trial	VRC-EBODNA012-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola
Ebola and Marburg Virus Vaccines	VRC-EBODNA023-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola

Ebola and Marburg Virus Vaccines	VRC-MARDNA025-00-VP	DNA Plasmid Vaccine	Phase I Complete	Marburg
Ribavirin for Hemorrhagic Fever with Renal Syndrome	Ribavirin IV	DNA nucleoside analogue	Phase II	HHRS
Safety Study of Single Administration Post-exposure Prophylaxis Treatment for Marburg Virus	AVI-6003	PMO	Phase I	Marburg
Safety Study of Single Administration Post-exposure Prophylaxis Treatment for Ebola Virus	AVI_6002	PMO	Phase I	Ebola
Safety and Immunogenicity Study of Rift Valley Fever Vaccine, Inactivated	TSI-GSD 200	Inactivated Dried Vaccine	Phase II	RVFV
Evaluating an Ebola and a Marburg Vaccine in Uganda	VRC-EBODNA023-00-VP	DNA Plasmid Vaccine	Phase IB	Ebola
Evaluating an Ebola and a Marburg Vaccine in Uganda	VRC-MARDNA025-00-VP	DNA Plasmid Vaccine	Phase IB	Marburg
Safety/Immunogenicity/ Genetic Drift of MP-12 Rift Valley Fever Vaccine	RVF MP-12	Live-attenuated RVF Vaccine	Phase II Complete	RVFV

[1] Data collected from Clinicaltrials.gov website

Personnel working with VHFs are potentially at high risk for infection. Most of the VHFs detailed in this report require high or maximum containment laboratories (BSL-3 or BSL-4). Some Environmental Health and Safety offices of the laboratories handling these pathogens require reporting of any fever, work absence, or possible exposure to be reported to a group of experts that can convene to make a decision about possible treatments.

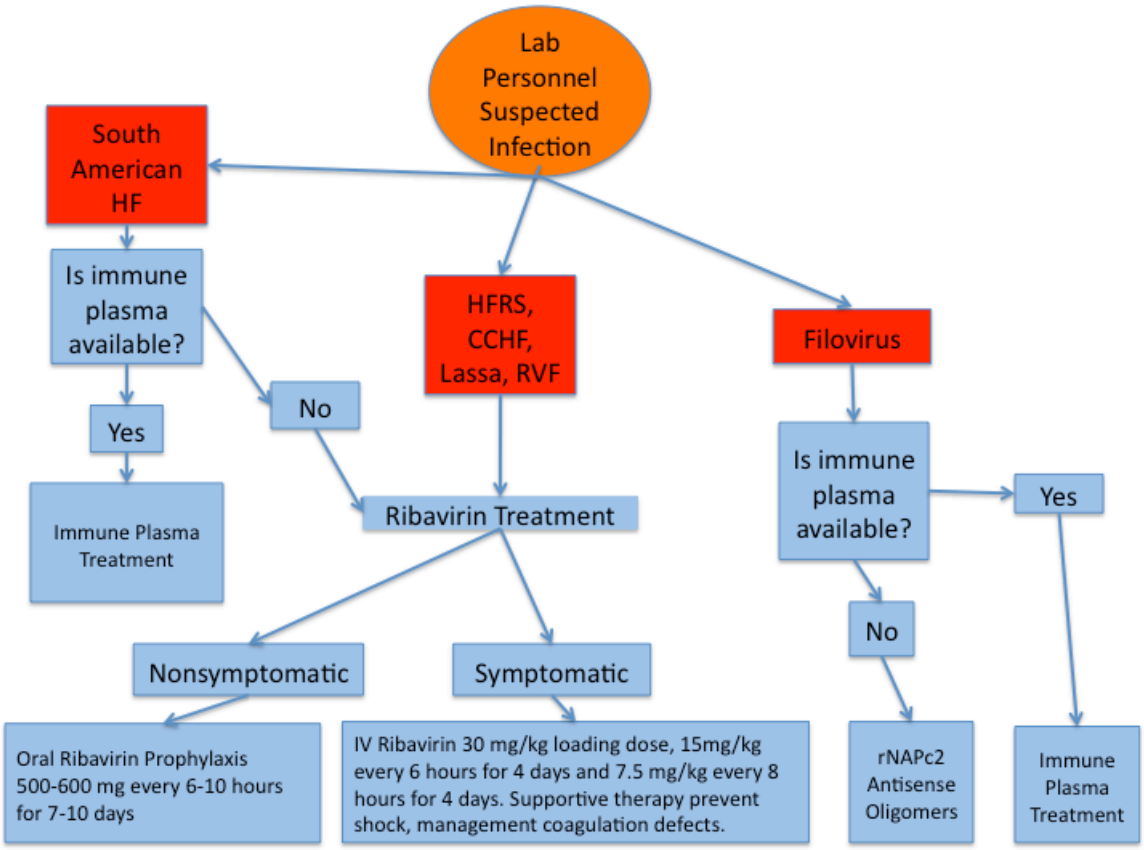

Figure 4: Decision tree for treatment of laboratory personnel with suspected infection.

Suspected cases of VHFs are defined as a patient that has a fever over 101ºF (38.3ºC) for less than three weeks and two of the following symptoms: hemorrhagic rash, episatxis, hematemesis, hemoptysis, blood in stool or petechiae. Suspected cases of VHFs are reportable immediately to local and state health departments and the CDC (404) 639-1511 during working hours and (404) 639-2888 during other times (CDC, 1995). In addition, contact should be made with the FBI field office, local police, hospital epidemiologist [or an infection control professional] and emergency medical service in the area. The epidemiologist will notify clinical laboratories, clinicians, and public health authorities regarding increased precautions to be taken in the suspected

case of VHFs. Personal protection equipments (PPE) should be implemented immediately for VHF specific barrier precautions for suspected cases. This PPE should include double gloves, impervious gowns, eye protection, shoe/leg coverings, face shield, and respiratory protection based on access. Diagnostic samples are sent to the CDC as soon as possible. Risk factors for contracting VHFs include traveling to a country that has had a recent outbreak, direct contact with potential infected bodily fluids, or working a facility that handles VHFs. The most important step in fast and effective response is the recognition of the possibility of an attack and communication to the correct personnel. Infection-control professionals (ICP) should look for changing patterns or clusters of infections and ensure that the correct authorities are informed (CDC, 2001). Several epidemiological features hint at a bioterrorism attack including patients from a single locality, differences in indoor and outdoor incidences rates, an epidemic curve that rises and falls quickly, and a dramatic increase in incidence in a short amount of time. In actuality, any cases of VHFs in the US should be suspected a bioterrorism attack if specific exposure or travel is not explanatory. Figure 5 illustrates the countermeasure decision tree that should occur when there is a suspected VHF case in the United States. In addition to the treatment of the infection individuals there should also be surveillance of high-risk individuals that had any contact with the patient. The medical surveillance can stop after there is confirmed diagnosis of a non-VHF or after 21 days without fever. If a VHF is suspected for secondary cases then it should follow the same decision tree for treatment.

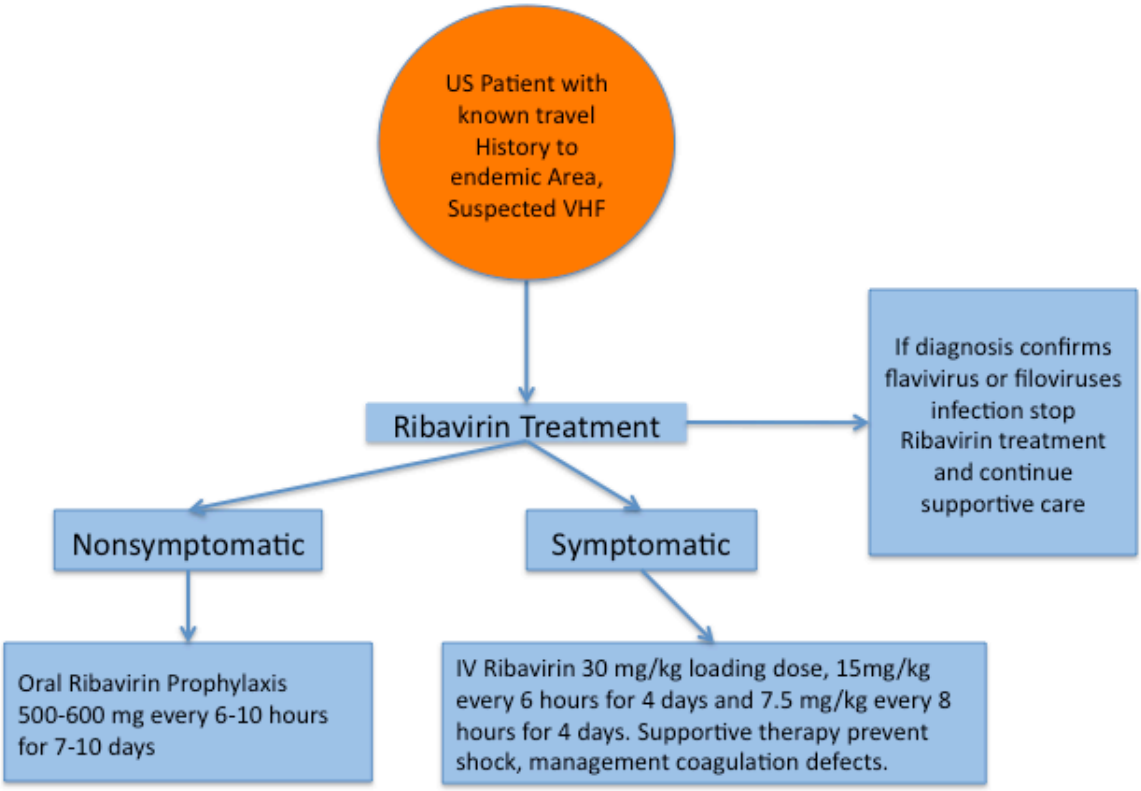

Figure 5: Decision tree for US Patient with known travel history to endemic area suspected VHF case.

Many different studies have been performed with nonhuman primates for vaccine development. A list of studies performed on non-human primates is presented in Appendix 1. Table 4 shows a number of studies performed recently with non-human primates looking at options for filovirus vaccination. The animals were vaccinated through a variety of different routes and doses. From the literature, many advantages and disadvantages to different vaccine strategies can be derived. One of the most effective strategies that provides cross protection to other filoviruses is a prime-boost regimen involving a DNA prime followed by a recombinant adenovirus booster.

The therapeutic arena is not as promising as the vaccine field. Fewer studies have been performed in nonhuman primates on therapeutics and the human trials were not properly controlled due to the sporadic cases and ethical concerns. Whether the different therapies, described in Table 5, are actually efficacious in humans remains unclear. Two of the best examples of therapies that have been proven to be effective are convalescent immune plasma in the treatment of AHF and Ribavirin in CCHF and Lassa. However, these therapies have severe consequences including late neurological syndrome in 10% of AHF patients treated with immune plasma and Ribavirin itself is a very toxic substance. The next issue is cost. Ribavirin is expensive and is in relatively short supply. Immune plasma from patients that have survived AHF is even shorter supply with the dramatic decrease in cases since the vaccine is being produced in Argentina. The clinics in Argentina are running low on immune plasma for naturally occurring cases and do not have the infrastructure or the number of donors needed for an epidemic or intentional release. In conclusion, there is a need for more therapeutic options for treatment of VHFs that have been shown to be safe in humans.

There are several strengths and limitations to consider in this literature review. A strong point is the extensive searching of several databases to ensure the list of countermeasures was comprehensive. By limiting the search to papers published in English it may have excluded countermeasures experiments/clinical trials that were published only in another language.

The number of new VHF prevention technologies has significantly increased in recent years as shown by the large number of experiments performed in non-human primates (Table 4 and Table 5). Challenges will now exist in expanding promising

countermeasures into phase I clinical trials and addressing the plausibility of large scale production in the case of an emergency. Constant evaluation of the clinical trials and review of recent literature ensures that information is available in the time of accidental infection or crisis.

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Glossary

BHF: Bolivian hemorrhagic fever

AHF: Argentine hemorrhagic fever

CCHF: Crimean-Congo hemorrhagic fever

DTT: Dithiothreitol

IM: Intramuscular

DNA: Deoxyribonucleic acid

VHF: Viral hemorrhagic fever

FDA: Food and Drug Administration

HFRS: Hemorrhagic fever with renal syndrome

LCMV: Lymphocytic choriomeningitis virus

IND: Investigational New Drug

CDC: Centers for Disease Control

HPIV3: Human parainfluenza virus 3

USAMRIID: U.S. Army Medical Research Institute of Infectious Diseases

DIC: Disseminated Intravascular Coagulation

YFV: Yellow fever virus

VEEV: Venezuelan equine encephalitis virus

VLPs: virus like particles

IV: intravenous

HF: hemorrhagic fever

HLA: human leukocyte antigen

RT-PCR: Reverse transcription polymerase chain reaction

RVFV: Rift Valley fever virus

DTRA: Defense Threat Reduction Agency

RNA: Ribonucleic acid

MP-12: live attenuated vaccine for Rift Valley fever virus

VSV: Vesicular stomatitis Indiana virus

siRNA: Small interfering RNA

IgG: Immunoglobulin G

BSL: Biological safety level

PMO: phosphorodiamidate morpholino oligo

DIVA: Differentiate between naturally infected and vaccinated animals

Appendix 1

Table 2: Studies of vaccines performed in nonhuman primates.

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
VSVΔG/SEBOVGP, VSVΔG/ZEBOVGP, and VSVΔG/MARVGP	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^7$ PFU	4 weeks	IM	Ebola Cote d'Ivoire	1000 PFU	IM	Geisbert et al, 2009
VSVΔG/SEBOVGP, VSVΔG/ZEBOVGP, and VSVΔG/MARVGP	VSV Recombinant Vaccine	cynomolgus monkeys	2/2	1		$1x10^7$ PFU	4 weeks	IM	Ebola Sudan	1000 PFU	IM	Geisbert et al, 2009
VSVΔG/SEBOVGP, VSVΔG/ZEBOVGP, and VSVΔG/MARVGP	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^7$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2009
VSVΔG/SEBOVGP, VSVΔG/ZEBOVGP, and VSVΔG/MARVGP	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	2	0, 14 days	$1x10^7$ PFU	35 days	IM	Ebola Sudan then Marburg Musoke	1000 PFU	IM	Geisbert et al, 2009
VSVΔG/SEBOVGP, VSVΔG/ZEBOVGP, and VSVΔG/MARVGP	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^7$ PFU	4 weeks	IM	Marburg Musoke	1000 PFU	IM	Geisbert et al, 2009
VSVΔG/ZEBOVGP	VSV Recombinant Vaccine	Cynomolgus macaques	1/1	1		$1x10^7$ PFU	4 weeks	IM	Ebola Sudan	1000 PFU	IM	Geisbert et al, 2009
VEEV replicon GP (Musoke)	Alphavirus Replicon	cynomolgus monkeys	3/3	3	0, 28, 56 Days	$1x10^7$ FFU	91 days	IM	Marburg Musoke	8000 PFU	SC	Hevey et al, 1998
VEEV replicon GP (Musoke)+NP(Musoke)	Alphavirus Replicon	cynomolgus monkeys	3/3	3	0, 28, 56 Days	$1x10^7$ FFU	91 days	IM	Marburg Musoke	8000 PFU	SC	Hevey et al, 1998
VEEV replicon NP (Musoke)	Alphavirus Replicon	cynomolgus monkeys	2/3	3	0, 28, 56 Days	$1x10^7$ FFU	91 days	IM	Marburg Musoke	8000 PFU	SC	Hevey et al, 1998
VEEV replicon GP (Musoke)	Alphavirus Replicon	cynomolgus monkeys	0/3	3		$1x10^7$ PFU		IM	Marburg Ravn	1000 PFU	IM	Hevey et al, 2001
VEEV replicon GP (Musoke)+NP(Muso	Alphavirus Replicon	cynomolgus monkeys	0/3	3		$1x10^7$ PFU		IM	Marburg Ravn	1000 PFU	IM	Hevey et al, 2001

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
ke)												
DNA plasmid GP (Musoke)	DNA Plasmid	cynomolgus monkeys	4/6	3		20 ug	12 weeks	IP (8 sites on abdomen)	Marburg Musoke	1000 PFU	SC	Riemenschneider et al, 2003
DNA plasmid GP (Angola)	DNA Plasmid	cynomolgus monkeys	4/4	4	0, 4, 8, 23 weeks	4 mg	26 weeks	IM	Marburg Angola	1000 PFU	IM	Geisbert et al, 2010
DNA prime [Ad5 boost GP (Angola)]	DNA Prime and Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	3 (1)	0, 4, 8, 20 weeks	4 mg ($1x10^{11}$ PFU)	26 weeks	IM	Marburg Angola	1000 PFU	IM	Geisbert et al, 2010
Ad5 GP (Angola)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{11}$ PFU	4 weeks	IM	Marburg Angola	1000 PFU	IM	Geisbert et al, 2010
Ad5 GP(Zaire)+NP(Zaire) +GP(Sudan)+GP(Ci67)+GP(Ravn)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	5/5	2	0, 63 days	$1x10^{10}$ PFU	105 days	IM	Marburg Musoke	1000 PFU	IM	Swenson et al, 2008
Ad5 GP(Zaire)+NP(Zaire) +GP(Sudan)+GP(Ci67)+GP(Ravn)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	5/5	2	0, 63 days	$1x10^{10}$ PFU	106 days	IM	Ebola Zaire	1000 PFU	IM	Swenson et al, 2008
VSV GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{7}$ PFU	28 days	IM	Marburg Musoke	1000 PFU	IM	Jones et al, 2005
VSV GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	1/1	1		$1x10^{7}$ PFU	28 days	IM	Marburg Musoke	1000 PFU	IM	Daddario-DiCaprio et al, 2006
VSV GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{7}$ PFU	28 days	IM	Marburg Ravn	1000 PFU	IM	Daddario-DiCaprio et al, 2006
VSV GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{7}$ PFU	28 days	IM	Marburg Angola	1000 PFU	IM	Daddario-DiCaprio et al, 2006
VSV GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	4/4	1		$2x10^{7}$ PFU	28 days	IM	Marburg Musoke	1000 PFU	Aerosol Exposure	Geisbert et al, 2008
VSVΔG/ZEBOVGP	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$2x10^{7}$ PFU	28 days	IM	Ebola Zaire	1000 PFU	Aerosol Exposure	Geisbert et al, 2008
VSV GP(Zaire)+GP(Sudan)+GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$3x10^{7}$ PFU	4 weeks	IM	Marburg Musoke	1000 PFU	IM	Geisbert et al, 2009

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
VSV GP(Zaire)+GP(Sudan)+GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$3x10^7$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2009
VSV GP(Zaire)+GP(Sudan)+GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	2/2	1		$3x10^7$ PFU	4 weeks	IM	Ebola Sudan	1000 PFU	IM	Geisbert et al, 2009
VSV GP(Zaire)+GP(Sudan)+GP(Musoke)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$3x10^7$ PFU	4 weeks	IM	Ebola Ivory Coast	1000 PFU	IM	Geisbert et al, 2009
VSV GP(Zaire)	VSV Recombinant Vaccine	cynomolgus monkeys	0/1	1		$1x10^7$ PFU	4 weeks	IM	Ebola Sudan	1000 PFU	IM	Geisbert et al, 2009
VSV GP(Zaire)+GP(Sudan)+GP(Musoke)	VSV Recombinant Vaccine	rhesus macaques	3/3	1		$3x10^7$ PFU	4 weeks	IM	Ebola Sudan	1000 PFU	IM	Geisbert et al, 2009
VLP GP(Musoke)+NP(Musoke)+VP40(Musoke)	Virus-like Particle	cynomolgus monkeys	3/3	3	0, 42, 84 days	1 mg	4 weeks after last vaccination	IM	Marburg Musoke	1000 PFU	SC	Swenson et al, 2008
VLP GP(Musoke)+NP(Musoke)+VP40(Musoke)	Virus-like Particle	cynomolgus monkeys	3/3	3	0, 42, 84 days	1 mg	4 weeks after last vaccination	IM	Marburg Ci67	1000 PFU	SC	Swenson et al, 2008
VLP GP(Musoke)+NP(Musoke)+VP40(Musoke)	Virus-like Particle	cynomolgus monkeys	3/3	3	0, 42, 84 days	1 mg	4 weeks after last vaccination	IM	Marburg Ravn	1000 PFU	SC	Swenson et al, 2008
Vaccinia GP(Zaire)	Poxvirus Recombinant Vaccine	cynomolgus monkeys	0/3	3	0, 28, 53 days	$1x10^7$ PFU	98 days	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2002
VEEV replicon GP(Zaire)	Alphavirus Replicon	cynomolgus monkeys	0/3	3	0, 28, 56 Days	$1x10^7$ FFU	99 days	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2002
VEEV replicon NP(Zaire)	Alphavirus Replicon	cynomolgus monkeys	0/3	3	0, 28, 56 Days	$1x10^7$ FFU	99 days	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2002
VEEV replicon GP(Zaire)+NP(Zaire)	Alphavirus Replicon	cynomolgus monkeys	0/3	3	0, 28, 56 Days	$1x10^7$ FFU	99days	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2002
DNA prime: GP(Zaire)+GP(Sudan)+GP(Ivory Coast)+NP(Zaire) [Ad5 GP(Zaire)]	DNA Prime and Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	3 (1)	0, 2 8 weeks	4 mg ($1x10^{10}$ PFU)	32 weeks	IM	Ebola Zaire	8 PFU	IM	Sullivan et al, 2000
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	1		$2x10^{12}$ PFU	4 weeks	IM	Ebola Zaire	10 PFU	IM	Sullivan et al, 2003

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	2		$2x10^{12}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2003
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{12}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{11}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	6/6	1		$1x10^{10}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GP(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	0/3	1		$1x10^{9}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GPΔTM(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	2/3	1		$1x10^{12}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GPΔTM(Zaire)+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	1/3	1		$1x10^{11}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad 5 GP (Zaire) E71D+GP(Sudan) E71D+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	1/3	1		$1x10^{10}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad 5 GP (Zaire) E71D+GP(Sudan) E71D	Adenovirus Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{10}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad 5 GP (Zaire) E71D+NP(Zaire)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	2/3	1		$1x10^{10}$ PFU	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Sullivan et al, 2006
Ad5 GP(Zaire)+NP(Zaire) +GP(Sudan)+GP(Ci67)+GP(Ravn)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	5/5	2	0, 120 days	$2x10^{10}$ PFU	162 days	IM	Ebola Sudan	1000 PFU	IM	Pratt et al, 2010
Ad5 GP(Zaire)+NP(Zaire) +GP(Sudan)+GP(Ci67)+GP(Ravn)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	5/5	2	0, 65 days	$2x10^{10}$ PFU	106 days	IM	Ebola Zaire	1000 PFU	IM	Pratt et al, 2010
Ad GP(Zaire)+NP(Zaire) +GP(Sudan)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{10}$ PFU	28 days	IM	Ebola Zaire	1000 PFU	Aerosol	Pratt et al, 2010
Ad GP(Zaire)+NP(Zaire)	Adenovirus Recombinant	cynomolgus monkeys	2/3	1		$1x10^{10}$ PFU	28 days	IM	Ebola Sudan	1000 PFU	Aerosol	Pratt et al, 2010

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
+GP(Sudan)	Vaccine											
Ad GP(Zaire)+NP(Zaire) +GP(Sudan)	Adenovirus Recombinant Vaccine	cynomolgus monkeys	3/3	2		$1x10^{10}$ PFU	28 days	IM	Ebola Sudan	1000 PFU	Aerosol	Pratt et al, 2010
VSV GP(Zaire)	VSV Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{7}$ PFU	28 days	IM	Ebola Zaire	1000 PFU	IM	Jones et al, 2005
VSV GP(Zaire)	VSV Recombinant Vaccine	cynomolgus monkeys	3/3	1		$1x10^{7}$ PFU	28 days	IM	Ebola Zaire	1000 PFU	Aerosol	Geisbert et al, 2008
VSV GP(Zaire)	VSV Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{7}$ PFU	28 days	Oral	Ebola Zaire	1000 PFU	IM	Qiu et al, 2009
VSV GP(Zaire)	VSV Recombinant Vaccine	cynomolgus monkeys	4/4	1		$1x10^{7}$ PFU	28 days	IN	Ebola Zaire	1000 PFU	IM	Qiu et al, 2009
HPIV3 GP(Zaire)	Human parainfluenza virue type 3 vector vaccine	rhesus macaques	4/4	1		$4x10^{6}$ TCID50	28 days	IN and IT	Ebola Zaire	1000 TCID50	IP	Bukreyev et al, 2007
HPIV3 GP(Zaire)	Human parainfluenza virue type 3 vector vaccine	rhesus macaques	2/3	1		$2x10^{7}$ PFU	67 days	IN and IT	Ebola Zaire	1000 PFU	IP	Bukreyev et al, 2007
HPIV3 GP(Zaire)+NP(Zaire)	Human parainfluenza virue type 3 vector vaccine	rhesus macaques	1/2	1		$4x10^{6}$ TCID50	28 days	IN and IT	Ebola Zaire	1000 TCID50	IP	Bukreyev et al, 2007
HPIV3 GP(Zaire)	Human parainfluenza virue type 3 vector vaccine	rhesus macaques	3/3	2	0 and 28 days	$2x10^{7}$ PFU	67 days	IN and IT	Ebola Zaire	1000 PFU	IP	Bukreyev et al, 2007
VLP GP(Zaire)+NP(Zaire) +VP40(Zaire)	Virus-like Particle	cynomolgus monkeys	5/5	3	0, 42, 84 days	250 ug	112 days	IM	Ebola Zaire	1000 PFU	IM	Warfield et al, 2007
RVFV MP-12	Live atteuated vaccine	rhesus macaques	4/4	1		$1x10^{4}$ PFU	56 days	Aerosol	RVFV ZH501	$1x10^{5}$ PFU	Aerosol	Morrill et al, 2011
RVFV MP-12	Live atteuated vaccine	rhesus macaques	4/4	1		$5x10^{4}$ PFU	56 days	Oral	RVFV ZH501	$1x10^{5}$ PFU	Aerosol	Morrill et al, 2011
RVFV MP-12	Live atteuated vaccine	rhesus macaques	4/4	1		$6x10^{3}$ PFU	126 days	IM	RVFV ZH501	$3x10^{6}$ PFU	IV	Morrill et al, 2011
RVFV MP-12	Live atteuated vaccine	rhesus macaques	5/5	1		$6x10^{3}$ PFU	178 days	IM	RVFV ZH501	$1x10^{5}$ PFU	Aerosol	Morrill et al, 2011
RVFV MP-12	Live atteuated vaccine	rhesus macaques	2/2	1		$6x10^{3}$ PFU	6 years	IM	RVFV ZH501	$1x10^{5}$ PFU	Aerosol	Morrill et al, 2011
ML29	Mopeia Reassortant	Marmosets	6/6	1		$1x10^{3}$ PFU	30 days	SC	Lassa Josiah	1000 PFU	SC	Lukashevich et al, 2008

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
	Vaccine											
V-LSG1 Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	0/2	1		$1x10^9$ PFU	116 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSG2 Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	0/2	1		$1x10^9$ PFU	116 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSN Vaccinia NP(Lassa)	Replication Competent Vaccinia Virus	cynomolgus macaques (M. fascicularis)	0/4	1		$1x10^9$ PFU	70-254 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSN Vaccinia NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	3/7	1		$1x10^9$ PFU	62-354 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSG2 Vaccinia GPC (Lassa)	Replication Competent Vaccinia Virus	cynomolgus macaques (M. fascicularis)	2/3	1		$1x10^9$ PFU	274-700 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSG2 Vaccinia GPC (Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	4/4	1		$1x10^9$ PFU	36-270 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
V-LSG1+V-LSG2 Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	2/2	1		$1x10^9$ PFU	82-86 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	2/2	1		$1x10^9$ PFU	354 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	cynomolgus macaques (M. fascicularis)	3/4	1		$1x10^9$ PFU	189-488 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
Vaccinia GPC (Lassa)+NP(Lassa)	Replication Competent Vaccinia Virus	rhesus macaques	2/2	1		$1x10^9$ PFU	82-86 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
Mopeia Virus	Live atteuated vaccine	rhesus macaques	2/2	1		$1x10^9$ PFU	36 days	ID	Lassa Josiah	1000 PFU	SC	Fisher-Hoch et al., 2000
VSV GPC (Lassa)	Replication Competent VSV vector	cynomolgus monkeys	4/4	1		$2x10^7$ PFU	28 days	IM	Lassa Josiah	10000 PFU	IM	Geisbert et al., 2005
Ad26 GP (Zaire)	Adenovirus Recombinant Vaccine	Cynomolgus macaques	0/4	1		10^{10} particle units (PU)	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011
Ad26 GP (Zaire)	Adenovirus Recombinant	Cynomolgus macaques	2/4	1		10^{11} particle	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011

Vaccine	Type of Vaccine	Animal	Survivors/ Total	# Doses	Dosing Schedule	Vaccine Amount	Time Before Challenge	Route of Vaccination	Challenge Virus	Challenge Dose	Challenge Route	References
	Vaccine					units (PU)						
Ad26 GP (Zaire)	Adenovirus Recombinant Vaccine	Cynomolgus macaques	3/4	1		10^{12} particle units (PU)	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011
Ad35 GP (Zaire)	Adenovirus Recombinant Vaccine	Cynomolgus macaques	0/3	1		10^{10} particle units (PU)	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011
Ad35 GP (Zaire)	Adenovirus Recombinant Vaccine	Cynomolgus macaques	0/3	1		10^{11} particle units (PU)	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011
Ad26 GP (Zaire)+Ad35 GP (Zaire)	Adenovirus Recombinant Vaccine	Cynomolgus macaques	4/4	1		10^{11} particle units (PU)	4 weeks	IM	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2011
VSVΔG/ZEBOVGP	VSV Recombinant Vaccine	rhesus macaques	4/8	1		$2x10^{7}$ particles	20-30 minutes after	IM	Ebola Zaire	1000 PFU	IM	Feldmann et al., 2007
DNA GP(Zaire), GP(Ivory Coast), GP(Sudan), and NP(Zaire)	DNA Vaccine	cynomolgus macaques (*M. fascicularis*)	4/4	3		1mg each	32 weeks	IM (2) and Bioinjector (1)	Ebola Zaire	6 PFU	IM	Sullivan et al., 2000
DNA Plasmid and rAd5 GP(Zaire) and GP(Sudan)	DNA Plasmid and Adenovirus Recombinant Vaccine	cynomolgus macaques (M. fascicularis)	8/8	3(1)	0, 4, 8, 14 (67) weeks	2 mg each (10^{11} PU)	74 weeks	IM (3) and IM	Ebola Bundibugyo	1000 TCID50	IM	Hensley et al, 2010
Candid#1	Live atteuated vaccine	rhesus macaques	20/20	1		16 to 127,000 PFU	3 months		Junin P3790	$4x10^{4}$ PFU		McKee et al, 1992

Appendix 2

Table 3: Different therapeutics tested in non-human primates

Therapeutic	Type	Animal	Survivors/Total	# Doses	Therapy Amount	Time Dose	Route of Therapy	Challenge Virus	Challenge Dose	Challenge Route	References
PMO-Plus (NP+VP24)	Phosphorodiamidate morpholino oligomers	rhesus macaque	2/4	Daily	12.5-25 mg	2 days before to 9 days after	SC, IP, IM	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	rhesus macaque	5/8	10-14 Doses Daily	40 mg/kg	30-60 minutes	IP, SC	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	rhesus macaque	0/4	Daily for 14 days	40 mg/kg	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	rhesus macaque	3/5	Daily for 14 days	40 mg/kg	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	rhesus macaque	3/5	Daily for 14 days	28 mg/kg	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	rhesus macaque	1/5	Daily for 14 days	16 mg/kg	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	rhesus macaque	0/5	Daily for 14 days	4 mg/kg	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	5/5	Daily for 14 days	30 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	3/5	Daily for 14 days	15 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	3/5	Daily for 14 days	7.5 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6002	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	0/4	Daily for 14 days	30 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	4/4	Daily for 14 days	40 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	3/3	Daily for 14 days	30 mg/kg	30-60 minutes	IP, SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	3/3	Daily for 14 days	40 mg/kg	30-60 minutes	SC	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
AVI-6003	Phosphorodiamidate morpholino oligomers	cynomolgus monkeys	3/3	Daily for 14 days	40 mg/kg	30-60 minutes	IV	Marburg Musoke	1000 PFU	SC	Warren et al., 2010
VSV GP (Marburg)	VSV Recombinant Vaccine	rhesus macaque	6/6	1	2x107 PFU	20-30 minutes	IM	Marburg Musoke	1000 PFU	IM	Geisbert et al, 2010
VSV GP (Marburg)	VSV Recombinant Vaccine	rhesus macaque	5/6	1	2x107 PFU	24 hours (after)	IM	Marburg Musoke	1000 PFU	IM	Geisbert et al, 2010

Therapeutic	Type	Animal	Survivors/Total	# Doses	Therapy Amount	Time Dose	Route of Therapy	Challenge Virus	Challenge Dose	Challenge Route	References
VSV GP (Marburg)	VSV Recombinant Vaccine	rhesus macaque	2/6	1	2x107 PFU	48 hours (After)	IM	Marburg Musoke	1000 PFU	IM	Geisbert et al, 2010
rNAPc2	TF/factor VIIa inhibitor	rhesus macaque	1/3	Daily	30 ug/kg	10 minutes (after)	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2007
rNAPc2	TF/factor VIIa inhibitor	rhesus macaque	4/6	Daily	30 ug/kg	24 hours (after)	SC	Ebola Zaire	1000 PFU	IM	Geisbert et al., 2007
KZ52	Monoclonal Antibody	rhesus macaque	0/4	2	50 mg/kg	1 day (before) and 4 days (after)	IV	Ebola Zaire	1000 PFU	IM	Oswald et al, 2007
siRNA against Ebola Zaire	siRNA	rhesus macaque	2/3	3	2 mg/kg	1, 3, 5 day	IV	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2010
siRNA against Ebola Zaire	siRNA	rhesus macaque	4/4	6	2 mg/kg	1, 2, 3, 4, 5, 6 Day	IV	Ebola Zaire	1000 PFU	IM	Geisbert et al, 2010
Ebola IgG	Equine IgG	cynomolgus monkeys	0/6	1	6 ml IgG	0 day	IM	Ebola Zaire	1000 PFU	IM	Jahrling et al, 1999
Ebola IgG	Equine IgG	cynomolgus monkeys	1/3	2	6 ml IgG	0 day and 5 day	IM	Ebola Zaire	1000 PFU	IM	Jahrling et al, 1999
Ebola IgG	Equine IgG	cynomolgus monkeys	0/3	1	6 ml IgG	2 days before	IM	Ebola Zaire	1000 PFU	IM	Jahrling et al, 1999
rhAPC	Activated Protein C	rhesus macaque	2/11	Continuous for 7 days	2 mg/m2/h	30-60 minutes	IV	Ebola Zaire	1000 PFU	IM	Hensley et al, 2007

Appendix 3

Table 4: Therapeutics and vaccines in clinical trials.

Study Name	Countermeasure Name	Type	Phase	Agent
Treatment of VHFs with iv Ribavirin in Military Facilities	Ribavirin IV	DNA *nucleoside analogue*	Phase II	CCHF; Lassa
Ribavirin for Hemorrhagic Fever with Renal Syndrome in Germany	Ribavirin IV	DNA *nucleoside analogue*	Phase II	HHRS
Experimental Vaccine Prevention of Ebola Virus Infection	VRC-EBOADV018-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola
Experimental Ebola Vaccine Trial	VRC-EBODNA012-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola
Ebola and Marburg Virus Vaccines	VRC-EBODNA023-00-VP	DNA Plasmid Vaccine	Phase I Complete	Ebola
Ebola and Marburg Virus Vaccines	VRC-MARDNA025-00-VP	DNA Plasmid Vaccine	Phase I Complete	Marburg
Ribavirin for Hemorrhagic Fever with Renal Syndrome	Ribavirin IV	DNA *nucleoside analogue*	Phase II	HHRS
Safety Study of Single Administration Post-exposure Prophylaxis Treatment for Marburg Virus	AVI-6003	Phosphorodiamidate morpholino antisense oligomer	Phase I	Marburg
Safety Study of Single Administration Post-exposure Prophylaxis Treatment for Ebola Virus	AVI_6002	Phosphorodiamidate morpholino antisense oligomer	Phase I	Ebola
Safety and Immunogenicity Study	TSI-GSD 200	Inactivated	Phase II	RVFV

Study Name	Countermeasure Name	Type	Phase	Agent
of Rift Valley Fever Vaccine, Inactivated		Dried Vaccine		
Evaluating an Ebola and a Marburg Vaccine in Uganda	VRC-EBODNA023-00-VP	DNA Plasmid Vaccine	Phase IB	Ebola
Evaluating an Ebola and a Marburg Vaccine in Uganda	VRC-MARDNA025-00-VP	DNA Plasmid Vaccine	Phase IB	Marburg
Safety/Immunogenicity/Genetic Drift of MP-12 Rift Valley Fever Vaccine	RVF MP-12	Live-attenuated RVF Vaccine	Phase II Complete	RVFV

Appendix 4

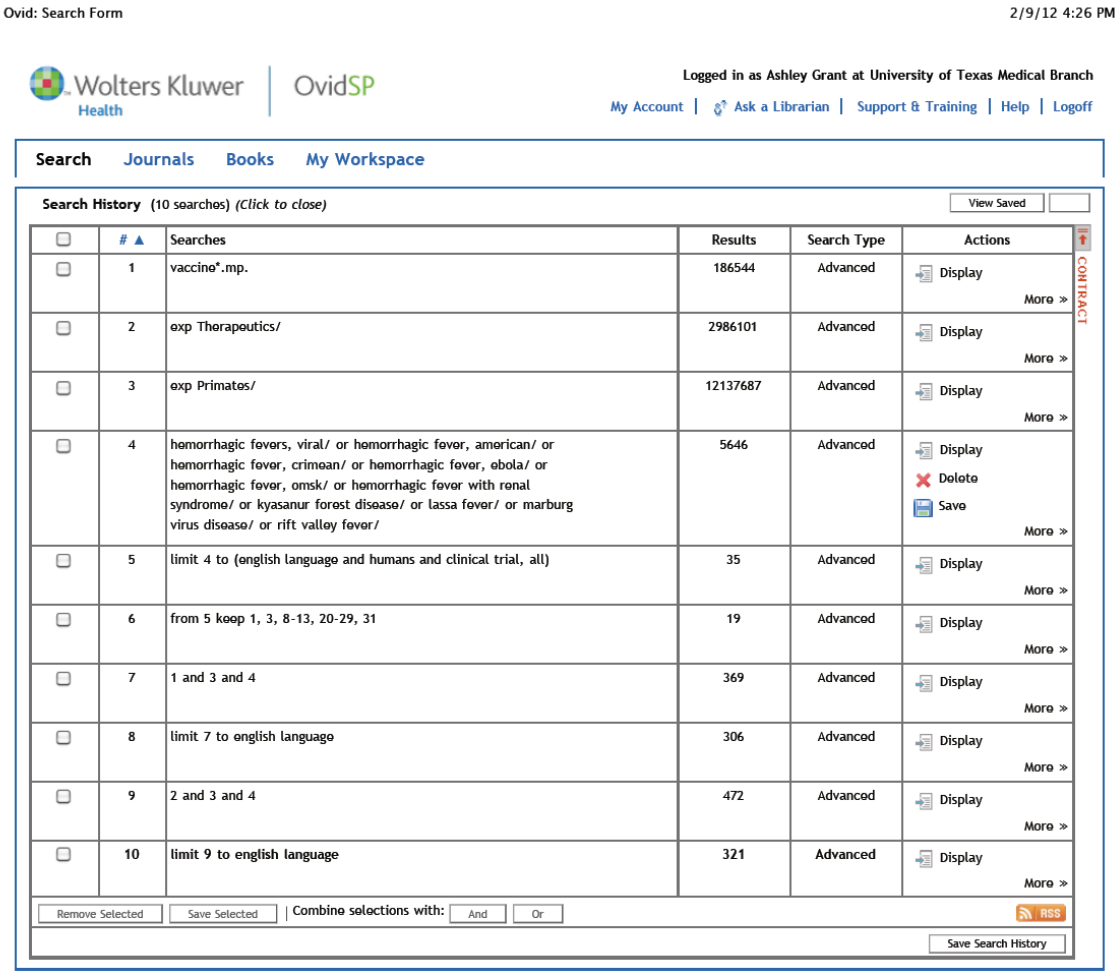
Table 5: Therapeutics tested in humans.

Therapeutic	Type	Survivors/Total	# Doses	Therapy Amount	Time before Challenge	Inclusion Criteria	Route of Therapy	Disease	References
Human convalescent serum	Immune Plasma	90/91	1	500 mL	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	3/7		Less than 1000 TU/kg	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	27/30		More Than 1000 TU/kg	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	24/26		1000-1999 TU/kg	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	46/49		2000-2999 TU/kg	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	908/913		3000-3999 TU/kg	Within 8 Days of onset			AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma	40/61		500 mL	After eight days of onset			AHF	Enria et al. 1994
Ribavirin	Nucleoside Analog	7/8		34 mg/kg Loading Dose, 17 mg/kg every 6 h for 4 days, and 8 mg/kg every 8h for following 6 days			IN	AHF	Enria et al. 1994
Human convalescent serum	Immune Plasma							Marburg	Martini et al., 1971
Prednisone	Supress Inflammatory Response								Martini et al., 1971
Human Blood Donation	Convalencent Blood (IgG EBO +)	4/5	1	150-450 mL	4-15 days after onset		IV	Ebola	Mupapa et al., 1999
Ribavirin	Nucleoside Analog	19/20			Within 6 days onset fever	AST>150 IU	IV	Lassa	McCormick et al., 1986
Ribavirin	Nucleoside Analog	32/43			7 or more days onset fever	AST>150 IU	IV	Lassa	McCormick et al., 1986
Ribavirin	Nucleoside Analog	10/11			Within 6 days onset fever	Viremia>103.6 TCID50/mL	IV	Lassa	McCormick et al., 1986
Ribavirin	Nucleoside	10/19			7 or more days	Viremia>103.	IV	Lassa	McCormick et al.,

Therapeutic	Type	Survivors/Total	# Doses	Therapy Amount	Time before Challenge	Inclusion Criteria	Route of Therapy	Disease	References
	Analog				onset fever	6 TCID50/mL			1986
Ribavirin	Nucleoside Analog	1/1		30 mg/kg Loading Dose, 15 mg/kg every 6 h for 4 days, and 7.5 mg/kg every 8h for following 6 days	Immediately after exposure		IV	Sabia	Barry et al., 1995

Appendix 5

Figure 6: Ovid medline search results.



Vita

Ashley Marie Grant was born in San Luis Obispo, California on November 19, 1983 to Mary Ann and Clayton Grant. Ashley graduated with honors from Arroyo Grande high school located in Arroyo Grande, California in 2002. After high school, she pursued a bachelor's of science degree in Pasadena, California at the California Institute of Technology, which was awarded in May 2006. Ashley enrolled in the Ph.D./MPH program at the University of Texas Medical Branch and moved to Galveston, Texas in August of 2007.

During her time at UTMB, Ashley was involved in many student leadership roles of several committees including (but not limited to) the center for career development, co-director for the National Student Research Forum, experimental pathology graduate student organization president, communications coordinator for the public health organization, and the experimental pathology representative for the graduate student organization. Ashley has also been involved in teaching first year medical and clinical laboratory science students through the teaching in pathology course. She taught a course in cellular biology for the Early Medical School Admissions Program and the Minorities Careers Diversity Program. She has been a Benchtop Tutorials Bromberg Scholar mentoring three different high school students in the lab. She is also a mentor in the Pre-Medical Allied Health Academic Achievement and Retention Program. While at UTMB, Ashley has also gained membership in several professional societies including the American Society of Virology, American Society of Microbiology, and American Association for the Advancement of Science.

Ashley does not have a permanent address, but can be contacted through her permanent email address, ashleymariegrant@gmail.com.

Education

Bachelors of Science, May 2006, California Institute of Technology, Pasadena, California

Publications

1. Balaban R.S., Batts S. A., **Grant, A. M**., et al (2011)"Finding novel ways to use imaging methods to improve the treatment of disease" See the future with imaging science. The National Academics Press, Washington, D.C. pp. 79-83.

2. **A. Grant**, E. Sbrana, V. Popov, M. Wakabayashi, K. Schlunegger, B. Freidmark, A. Brideau-Andersen, C. Peters. (2010) "Binding of phosphatidylserine targeting antibodies to Junin virions and infected cells". *Lupus* **19** (4). pp. 510.

Presentations at Scientific Meetings:

1. **A. Grant**, E. Sbrana, V. Popov, M. Wakabayashi, K. Schlunegger, B. Freidmark, A. Brideau-Andersen, C. Peters. 2011. *Evaluation of Phosphatidylserine Targeting Antibodies as a Potential Treatment for Argentine Hemorrhagic Fever*. Chemical and Biological Defense Meeting, Las Vegas, Nevada. [Poster Presentation]

2. **A. Grant**, E. Sbrana, V. Popov, M. Wakabayashi, K. Schlunegger, B. Freidmark, A. Brideau-Andersen, C. Peters. 2010. *Detection of phosphadtiylserine on Junin virions and Junin infected cells.* Negative Strand Virus Meeting, Brugges, Belgium. [Poster Presentation]

3. **A. Grant**, E. Sbrana, V. Popov, M. Wakabayashi, K. Schlunegger, B. Freidmark, A. Brideau-Andersen, C. Peters. 2010. *Binding of phosphatidylserine targeting antibodies to Junin virions and infected cells.* International Congress on Antiphospholipid Antibodies, Galveston, Texas. [Poster Presentation]

4. **A. Grant**, E. Sbrana, V. Popov, M. Wakabayashi, K. Schlunegger, B. Freidmark, A. Brideau-Andersen, C. Peters. 2010. *Presence of Phosphatidylserine on Junin virions and Junin virus-infected cells.* Sealy Center for Structural Biology Symposium, Galveston, Texas. [Poster Presentation]

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This Capstone was typed by Ashley Marie Grant.