

Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2015

Contains Nonbinding Recommendations

Draft – Not for Implementation

Table of Contents

I. INTRODUCTION..... 1

II. BACKGROUND 1

III. RECOMMENDATIONS..... 3

A. Donor Educational Material and Donor History Questionnaire..... 3

B. Donor Deferral 4

C. Product Retrieval and Quarantine and Notification 6

IV. REPORTING A BIOLOGICAL PRODUCT DEVIATION (BPD)..... 7

V. CONVALESCENT PLASMA 7

VI. IMPLEMENTATION 8

VII. REFERENCES..... 9

Contains Nonbinding Recommendations

Draft – Not for Implementation

Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance document provides, you, blood establishments that collect blood and blood components for transfusion or further manufacture, including Source Plasma, with our (FDA) recommendations for assessing donor suitability, donor deferral and blood product management in the event that an outbreak of Ebola virus disease (EVD) with widespread transmission is declared in at least one country. This guidance document applies primarily to Ebola virus (species *Zaire ebolavirus*), but recommendations are expected to apply to other viruses of the Ebolavirus genus such as Sudan virus, Bundibugyo virus, and Tai Forest virus. The recommendations in section III. of the guidance document would apply to the routine collection of blood and blood components for transfusion or further manufacture, including Source Plasma. The collection of convalescent plasma from EVD survivors is addressed in section V. of the guidance document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Ebola virus is a member of the family *Filoviridae* that can cause severe hemorrhagic fever in humans and non-human primates (NHPs) with historically high morbidity and mortality rates of up to 90% (Refs. 1 and 2). However, in the 2014 outbreak in West Africa, the mortality rate has been lower, with 28,617 suspected, probable and confirmed cases and 11,314 deaths reported as

Contains Nonbinding Recommendations

Draft – Not for Implementation

of early November 2015.¹ Ebola virus is a lipid-enveloped zoonotic pathogen that, when studied in the laboratory, requires the highest level of biosafety containment (BSL-4). The Centers for Disease Control and Prevention (CDC) has classified it as a “Category A” bioterrorism agent/disease.² Ebola virus is reported to be inactivated by heating at 60°C for 60 minutes, and also following incubation at pH 2.5 (Ref. 3). Solvent detergent treatment and pathogen inactivation technologies are also known to inactivate lipid-enveloped viruses (Refs. 4 through 8).

In humans, EVD is typically characterized at onset by fever, severe headache, muscle pain and weakness, followed by diarrhea, vomiting, abdominal pain and sometimes diffuse hemorrhage (bleeding or bruising). In previous outbreaks of EVD, symptoms generally appeared within 21 days and most often within 4-10 days following infection (Refs. 9 and 10). Based on mathematical models, symptom onset later than 21 days is estimated as possible in 0.1 to 12% of cases (Refs. 10 and 11). In a retrospective study in which 500 patients diagnosed in 2014 recalled their likely source of infection, 5% reported symptom onset > 21 days (up to a maximum of 43 days) post-exposure (Ref. 10).

Viremia and virus shedding escalate rapidly after onset of symptoms and infectivity appears to correlate with severity and stage of disease. Although viremia in survivors typically resolves within 21 days of disease onset, infectious virus and viral RNA has been detected in other body components or fluids (e.g., aqueous humor, semen and vaginal fluids) for longer periods. For instance, viable Ebola virus was detected in aqueous humor obtained from the eye 14 weeks after the onset of the initial symptoms of EVD and 9 weeks after the clearance of viremia (Ref. 12). Infectious virus and viral RNA have been detected in semen up to 82 and 272 days post EVD onset, respectively (Refs. 13 through 17).³ Further, a case of sexual transmission of Ebola virus was reported in which the patient was exposed to Ebola virus through sexual contact with a survivor 179 days after likely disease onset (Refs. 18 and 19). These findings raise the theoretical possibility, which has not been documented in humans or animal models, of an intermittent low level viremia after recovery from illness. In addition, there have been isolated reports of apparently asymptomatic Ebola virus infection in individuals who had contact with Ebola patients (Ref. 18), and of antibody to Ebola virus in rural African populations reportedly unassociated with acute illness (Ref. 19). These reports raise the possibility that there may be an asymptomatic infection or mild disease in some individuals; if this condition exists, the infectivity of these individuals is uncertain but likely to be less than that of severely ill persons.

Ebola virus is transmitted from human to human by direct contact with body fluids (such as blood, urine, stool, saliva, semen, vaginal fluids or vomit) of symptomatic infected individuals. Therefore, blood and blood products from symptomatic individuals, if they were to donate, would have the potential of transmitting Ebola virus to recipients. The theoretical possibility of pre-symptomatic viremia has not been extensively investigated. If this condition exists the

¹ See CDC website: <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html>.

² See CDC website: <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

³ See also the CDC Review of Human-to-Human Transmission of Ebola Virus, <http://www.cdc.gov/vhf/ebola/transmission/human-transmission.html>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

infectivity is uncertain, but likely to be less than of symptomatic persons. Healthcare providers caring for symptomatic Ebola patients, and family and friends in close contact with symptomatic Ebola patients, are at the highest risk of becoming infected because they may come in direct contact with infected blood or other body fluids of sick patients.

III. RECOMMENDATIONS

A donor must be in good health with a normal temperature at the time of donation (21 CFR 640.3(b) and 21 CFR 640.63(b)(3)). Standard procedures that are already in place to assure that the donor feels healthy at the time of donation serve as an effective safeguard against collecting blood or blood components from a donor who seeks to donate after the onset of clinical symptoms. The following recommendations are intended to reduce the risks of collecting blood and blood components from potentially Ebola virus-infected persons during the asymptomatic incubation period before the onset of clinical symptoms, as well as from individuals with a history of Ebola virus infection or disease.

The guidance contains recommendation for updating your donor educational materials in section III.A.1. The remaining recommendations should be implemented when the CDC has classified one or more countries as having widespread transmission of Ebola virus. When there are no countries classified by CDC as having widespread transmission of Ebola virus it is appropriate to discontinue asking donors questions related to risk of Ebola virus infection or disease. (See <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html>.)

A. Donor Educational Material and Donor History Questionnaire

1. Donor Educational Material

We expect very few individuals with a history of Ebola virus infection or disease to present as blood donors. When there are no countries classified as having widespread transmission of Ebola virus, self-deferral of donors with a history of Ebola virus infection or disease should provide sufficient protection. You may update your donor educational materials to instruct donors with a history of Ebola virus infection or disease to not donate blood or blood components.

2. Donor History Questionnaire

In the event that one or more countries is designated as having widespread transmission of Ebola virus, we recommend that you update your donor history questionnaire (DHQ), including your full-length and abbreviated DHQ, and accompanying materials to incorporate the recommendations provided in this guidance.

We recommend that the updated DHQ include the following elements to assess prospective donors for risk of Ebola virus infection or disease.

Contains Nonbinding Recommendations

Draft – Not for Implementation

- a. A history of Ebola virus infection or disease.
- b. A history of residence in or travel in the past 8 weeks to a country with widespread transmission of Ebola virus disease or cases in urban areas with uncertain control measures. (See <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html>).
- c. A history of close contact in the past 8 weeks with a person confirmed to have Ebola virus infection or disease or any person under investigation (PUI) for Ebola virus infection or disease in whom diagnosis is pending. For the purposes of this guidance, close contact is defined as contact that could have resulted in direct exposure to body fluids. Individuals falling into this close contact category include healthcare workers and other persons who care for, have lived with, or have otherwise been in contact with a PUI or a person confirmed to have Ebola virus infection or disease.⁴
 - Additionally, this close contact category includes individuals with a history of sexual contact in the past 8 weeks with a person known to have recovered from EVD prior to that instance of sexual contact.
- d. A history of notification by a public health authority that he or she may have been exposed in the past 8 weeks to a person with Ebola virus disease.

We note that educational material may assist donors in assessing their risk factors for Ebola virus infection or disease as described above. Relevant information on risk factors can be found on CDC's website at <http://www.cdc.gov/vhf/ebola>.

B. Donor Deferral

1. We recommend that you defer indefinitely⁵ a donor with a history of Ebola virus infection or disease.

Note: This recommendation excludes the collection of convalescent plasma for treatment of EVD as described in section V. of this guidance.

⁴ For additional information on epidemiologic risk factors to consider when evaluating a person for exposure to Ebola virus see: <http://www.cdc.gov/vhf/ebola/exposure/risk-factors-when-evaluating-person-for-exposure.html>. We expect individuals in the "high risk," "some risk," and "low risk" categories would fall into this close contact category.

⁵ Until more data regarding the persistence of Ebola virus in survivors becomes available, we recommend you defer such donors indefinitely.

Contains Nonbinding Recommendations

Draft – Not for Implementation

2. We recommend that you defer for 8 weeks⁶ from the date of his or her departure a donor who has been a resident of or has travelled to a country with widespread transmission of Ebola virus disease or with cases in urban areas with uncertain control measures. (See <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html>.)

Note: Longer deferral periods may apply based on recommendations for deferral due to risk of malaria exposure. See FDA document entitled, “Guidance for Industry: Recommendations for Donor Questioning, Deferral, Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Malaria,” dated August 2014. <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm365191.htm>.

3. We recommend that you defer for 8 weeks⁶ after the last contact a donor who has had close contact with any PUI or confirmed to have Ebola virus infection or disease, in whom the diagnosis is pending. Individuals falling into this category include healthcare workers and other persons who care for, or have lived with, a PUI or person confirmed to have Ebola virus infection or disease.⁴
 - We recommend that you defer for 8 weeks⁶ after the last sexual contact a donor who has had sexual contact with a person known to have recovered from Ebola virus disease.⁷
4. We recommend that you defer for a period of 8 weeks after exposure⁶ a donor who has been notified by a federal, state, or local public health authority that he or she may have been exposed to a person with Ebola virus disease.

⁶ Although symptoms generally appear within 21 days of infection, we recommend an extended deferral period of 8 weeks to prevent blood and blood component collection from an individual who could be infected and have an extended incubation period. In addition, 8 weeks is consistent with the inter-donation interval for Whole Blood donations.

⁷ Until additional data regarding the length of time semen could be infectious post Ebola virus disease becomes available, we recommend that you defer for 8 weeks after the last sexual contact a donor who has had sexual contact with a person known to have recovered from Ebola virus disease.

Contains Nonbinding Recommendations

Draft – Not for Implementation

C. Product Retrieval and Quarantine and Notification

1. Blood and Blood Components Collected from Donors at Risk for Ebola Virus Infection or Disease Because of Risk Factors Related to Residency, Travel or Close Contact.
 - a. If you collected blood or blood components intended for transfusion or further manufacturing from a donor who should have been deferred for risk factors for EVD related to residency, travel, or close contact, according to the recommendations in section III.B. of this document, we recommend that you quarantine and destroy all undistributed in-date blood and blood components from that donor.
 - b. If you distributed blood or blood components intended for transfusion or further manufacture from a donor who should have been deferred for risk factors for EVD related to residency, travel or close contact according to the recommendations in section III.B. of this document, we recommend that you notify consignees to retrieve, quarantine and destroy the in-date blood and blood components collected from that donor.
 - c. We do not recommend retrieval or quarantine of plasma pooled for further manufacturing into products that are manufactured under processes that include multiple validated viral clearance steps, which have been shown to be robust in the clearance of lipid-enveloped viruses.
2. Blood and Blood Components Collected from Donors Later Determined to Have Ebola Virus Infection or Disease.

We recommend you contact FDA⁸ as soon as possible upon learning that you collected blood or blood components from a donor later determined to have Ebola virus infection or disease. In addition, blood establishments should consider the need to notify state and local public health authorities.

- a. If you collected blood or blood components within a recommended deferral period as specified in section III.B. of this document from a donor later determined to have Ebola virus infection or disease, you should promptly retrieve and quarantine the blood and blood components collected in the 8 weeks prior to disease onset and after disease onset.
 - If such blood components were transfused, we recommend that consignees notify the transfusion recipient's physician of record

⁸ Contact CBER's Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 240-402-8010. After regular business hours and on weekends, call the FDA emergency number: 1-866-300-4374 or 301-796-8240.

Contains Nonbinding Recommendations

Draft – Not for Implementation

regarding the need for notification and monitoring of the recipient for possible Ebola virus infection or disease.

- b. Manufacturers should contact FDA to discuss their conduct of an adequate risk analysis if plasma collected from a donor later determined to have Ebola virus infection or disease has been pooled for further manufacturing or manufactured into a finished product. Finished products manufactured from such plasma pools should not be released prior to completion of an adequate risk analysis demonstrating that the product will not place patients at risk of Ebola virus disease. Finished products manufactured from such plasma pools that have been released should also undergo a risk analysis.

IV. REPORTING A BIOLOGICAL PRODUCT DEVIATION (BPD)

If you have distributed blood or blood components for transfusion or further manufacture collected from a donor at risk for or known to have Ebola virus infection or disease according to section III.B. of this document, you should report a BPD as soon as possible but you must report at a date not to exceed 45 calendar days from the date you acquire the information reasonably suggesting that a reportable event has occurred (21 CFR 606.171).

If you have distributed finished products manufactured from blood or blood components collected from a donor later determined to have Ebola virus infection or disease according to section III.B. of this guidance, you should report a BPD as soon as possible but you must report at a date not to exceed 45 calendar days from the date you acquire the information reasonably suggesting that a reportable event has occurred (21 CFR 600.14).

V. CONVALESCENT PLASMA

As of the date of issuance of this guidance, there are no FDA-approved therapeutics or licensed vaccines for Ebola virus disease. Standard treatment for Ebola virus disease is limited to supportive care, which includes intravenous fluids and electrolytes, treatment of secondary infections, and pain control.

Serum and plasma therapies have been used to treat many infectious diseases, including Junin Virus, a virus that also causes hemorrhagic fever (Ref. 22). There is similar interest in whether convalescent serum or plasma collected from Ebola virus disease survivors may be an effective therapy in Ebola virus outbreaks. Neutralizing antibodies are generated during filovirus infection in humans (Ref. 23). Ebola virus-infected individuals develop humoral immune responses (Ref. 24) that include neutralizing antibodies in some survivors. In previous studies conducted using non-human primates, passive transfer of certain neutralizing monoclonal antibodies (Refs. 25 and 26) and convalescent immunoglobulin concentrate prepared from non-

Contains Nonbinding Recommendations

Draft – Not for Implementation

human primates that were vaccinated and virus challenged (Ref. 27) have resulted in protection against lethal challenge with Ebola virus. However, whole blood from Ebola virus vaccinated and challenged monkeys did not protect against Ebola virus challenge in non-human primates (Ref. 28).

Treatment of Ebola virus disease patients with convalescent human sera has been used in uncontrolled studies (Refs. 29 through 31). Based on the available scientific evidence, the World Health Organization (WHO) has developed interim guidance for national health authorities and blood transfusion services, entitled, “Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks,” dated September 2014, <http://www.who.int/csr/resources/publications/ebola/convalescent-treatment/en/>.

As noted, although this investigational treatment has not yet been proven effective, its effectiveness is biologically plausible and has been prioritized by WHO for investigation. Convalescent plasma or serum collected from donors who have recovered from Ebola virus disease is an investigational product, and controlled studies with an adequate number of patients are needed to assess safety and effectiveness. Blood establishments wishing to collect or distribute convalescent plasma intended for transfusion in the United States must submit an investigational new drug application in accordance with 21 CFR Part 312, and sponsors seeking to develop devices for this use are subject to the investigational device regulations in 21 CFR Part 812 (see 21 CFR 601.21). We encourage such sponsors to contact FDA.⁹

VI. IMPLEMENTATION

This guidance is being issued for comment purposes only. If you elect to implement the recommendations contained in this draft guidance, you may do so without prior approval of FDA.

We will provide recommendations in the final guidance to licensed establishments on reporting implementation of the recommendations contained in the guidance, including revised donor history questionnaires and accompanying materials, to FDA under 21 CFR 601.12.

⁹ Please contact the Office of Blood Research and Review, CBER in accordance with CBER SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. See <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

VII. REFERENCES

1. Feldmann, H., Jones, S., Klenk, H.D., et al., “Ebola Virus: from Discovery to Vaccine. Nature Review,” *Immunology*, 2003; 3:677-685.
2. Towner, J.S., Sealy, T.K., Khristova, M.L., et al., “Newly Discovered Ebola Virus Associated With Hemorrhagic Fever Outbreak in Uganda,” *PLoS pathogens*, 2008; 4:e1000212.
3. Mitchell, S.W., McCormick, J.B., “Physicochemical inactivation of Lassa, Ebola, and Marburg Viruses and Effect on Clinical Laboratory Analyses,” *J Clin Microbiol*, 1984; 20:486-489.
4. Horowitz, B., Bonomo, R., Prince, A.M., et al., “Solvent/Detergent-Treated Plasma: a Virus-Inactivated Substitute for Fresh Frozen Plasma,” *Blood*, 1992; 79:826-831.
5. Dichtelmuller, H., et al., “Robustness of Solvent/Detergent Treatment of Plasma Derivatives: A Data Collection from Plasma Protein Therapeutics Association Member Companies,” *Transfusion*, 2009; 49:1931-1943.
6. El-Ekiaby, M., et al., “Solvent-Detergent Filtered (S/D-F) Fresh Frozen Plasma and Cryoprecipitate Minipools Prepared in a Newly Designed Integral Disposable Processing Bag System,” *Transfusion Medicine*, 2010; 20:48-61.
7. Singh, Y., et al., “Photochemical Treatment of Plasma with Amotosalen and Long Wavelength Ultraviolet Light Inactivates Pathogens While Retaining Coagulation Function,” *Transfusion*, 2006; 46:1168-1177.
8. Lin, L., et al., “Inactivation of Viruses in Platelet Concentrates by Photochemical Treatment with Amotosalen and Long-Wavelength Ultraviolet Light,” *Transfusion*, 2005; 45:580-590.
9. Eichner, M., Dowell, S.F., Firese, N., “Incubation Period of Ebola Hemorrhagic Virus Subtype Zaire,” *Osong Public Health Res. Perspect*, 2011; 2:3-7.
10. World Health Organization Ebola Response Team. “Ebola Virus Disease in West Africa—the First 9 Months of the Epidemic and Forward Projections,” *N Engl J Med*, 2014; 371:1481-1495.
11. Haas, C.N., “On the Quarantine Period for Ebola Virus,” *PLOS Currents Outbreaks*. 2014 Oct 14, 1st ed.
12. Varkey, J.B., et al., “Persistence of Ebola Virus in Ocular Fluid during Convalescence,” *N Engl J Med*, 2015; 372: 2423-2437.

Contains Nonbinding Recommendations

Draft – Not for Implementation

13. Bausch, D.G., Towner, J.S., Dowell, S.F., et al., “Assessment of the Risk of Ebola Virus Transmission from Bodily Fluids and Fomites,” *The Journal of Infectious Diseases*, Nov 15, 2007; 196 Suppl 2:S142-147.
14. Rodriguez, L.L., De Roo, A., Guimard, Y, et al., “Persistence and Genetic Stability of Ebola Virus During the Outbreak in Kikwit, Democratic Republic of the Congo, 1995,” *The Journal of Infectious Diseases*, Feb 1999; 179 Suppl 1:S170-176.4.
15. Rowe, A.K., Bertolli, J., Khan, A.S., et al., “Clinical, Virologic, and Immunologic Follow-Up of Convalescent Ebola Hemorrhagic Fever Patients and Their Household Contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidemies a Kikwit,” *The Journal of Infectious Diseases*, Feb 1999; 179 Suppl 1:S28-35.
16. Richards, G.A., Murphy, S., Jobson, R., et al., “Unexpected Ebola virus in a Tertiary Setting: Clinical and Epidemiologic Aspects,” *Critical Care Medicine*, Jan 2000; 28(1):240-244.
17. Deen, G.F. et al. “Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors – Preliminary Report,” *N Engl J Med*, October 2015; DIO: 10.1056/NEJMoas1511410.
18. Centers for Disease Control and Prevention, “Possible Sexual Transmission of Ebola Virus – Liberia, 2015,” *Morbidity and Mortality Weekly* May 2015; 64(17): 479-481.
19. Mate, S.E. et al. “Molecular Evidence of Sexual Transmission of Ebola Virus,” *N Engl J Med*, October 2015; DIO:10.1056/NEJMoas1509773.
20. Leroy, E.M. et al., “Human Asymptomatic Ebola Infection and Strong Inflammatory Response,” *The Lancet*, 2000; 255: 2210-2215.
21. Nkoghe, D., Padilla, C., Becquart, P., et al., “Risk Factors for Zaire Ebolavirus--Specific IgG in Rural Gabonese Populations,” *J Infect Dis*, 2011; 204 Suppl 3:S768-775.
22. Maiztegui, J.I., Fernandez, N.J., de Damilano, A.J., “Efficacy of Immune Plasma in Treatment of Argentine Haemorrhagic Fever and Association between Treatment and A Late Neurological Syndrome,” *The Lancet*, 1979; 2:1216-1217.
23. Maruyama, T., Rodriguez, L.L., Jahrling, P.B., et al., “Ebola Virus Can Be Effectively Neutralized by Antibody Produced in Natural Human Infection,” *J Virol*, 1999; 73:6024-6030.
24. Bradfute, S.B., Bavari, S., “Correlates of Immunity to Filovirus Infection,” *Viruses*, 2011; 3:982-1000.

Contains Nonbinding Recommendations

Draft – Not for Implementation

25. Qiu, X., Audet, J., Wong, G., et al., “Successful Treatment of Ebola Virus-Infected Cynomolgus Macaques with Monoclonal Antibodies,” *Sci Transl Med*, 2012; 4:138ra181.
26. Olinger, G.G., Pettitt, Jr., J., Kim, D., et al., “Delayed Treatment of Ebola Virus Infection with Plant-Derived Monoclonal Antibodies Provides Protection in Rhesus Macaques,” *Proc Natl Acad Sci USA*, 2012.
27. Dye, J.M., Herbert, A.S., Kuehne, A.I., et al., “Postexposure Antibody Prophylaxis Protects Nonhuman Primates from Filovirus Disease,” *Proc Natl Acad Sci USA*, 2012; 109:5034-5039.
28. Jahrling, P.B., Geisbert, J.B., Swearingen, J.R., et al., “Ebola Hemorrhagic Fever: Evaluation of Passive Immunotherapy in Nonhuman Primates,” *J Infect Dis*, 2007; 196 Suppl 2:S400-403.
29. International Commission, “Ebola Haemorrhagic Fever in Zaire, 1976,” *Bull World Health Organ* 1978; 56:271-293.
30. Emond, R.T., Evans, B., Bowen, E.T., et al., “A Case of Ebola Virus Infection,” *Br Med J*, 1977; 2:541-544.
31. Mupapa, K., Massamba, M., Kibadi, K., et al., “Treatment of Ebola Hemorrhagic Fever with Blood Transfusions from Convalescent Patients. International Scientific and Technical Committee,” *J Infect Dis*, 1999; 179 Suppl 1:S18-23.