8 | EBOLA VIRUS

8.1 | Disease agent

- Ebola virus (EBOV)

8.2 | Disease agent characteristics

- Family: *Filoviridae*; Genus: *Ebolavirus*.
- Six species are recognized
  - Bombali Ebolavirus.
  - Bundibugyo Ebolavirus.
  - Reston Ebolavirus.
    - This is a pathogen in nonhuman primates, primarily in the Philippines, but causes asymptomatic infection in humans.
  - Sudan Ebolavirus.
  - Tai Forest Ebolavirus.
  - Zaire Ebolavirus.
- Virion morphology and size: Enveloped, helical, cross-striated nucleocapsid, filamentous or pleomorphic virions that are flexible with extensive branching, 80 nm in diameter and 970–1200 nm in length.
- Nucleic acid: Linear, negative-sense, single-stranded RNA, ~18,900 kb in length.
- Physicochemical properties: Stable at room temperature and can resist desiccation for up to 5 days; inactivated at 60°C for 30 min; infectivity greatly reduced or destroyed by UV light and gamma irradiation, lipid solvents, β-propiolactone, formaldehyde, sodium hypochlorite (bleach), and phenolic disinfectants.

8.3 | Disease name

- Ebola virus hemorrhagic fever

8.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Very low; however, there are reasonable scientific grounds demonstrating that viremia is a feature of infection with these agents. Asymptomatic viremia has been neither well studied nor sought aggressively, so there are few or no data to make a critical assessment of risk.
- Public perception and/or regulatory concern regarding blood safety: Very low/Absent
- Public concern regarding disease agent: High

8.5 | Background

- Emerging infection clinically affecting humans and nonhuman primates.
- Filovirus epidemics have originated from Africa and apparently from a single source in the Philippines.
- First recognized in 1976 when two unrelated epidemics occurred in northern Zaire, now the Democratic Republic of the Congo (DRC) and southern Sudan (and named after the Ebola River that runs through the center of the DRC and home to fruit bats which are thought to carry the virus). Subsequent sporadic outbreaks have occurred in Central Africa with frequent occurrences in Gabon and DRC since 2000. In the last two decades, this virus has caused the death of nearly 20,000 people.
- In 1989–1991, another Ebola subtype was discovered in Reston, Virginia, among dying cynomolgus monkeys imported from the Philippines that infected four animal caretakers who remained clinically well. Episodes with the Reston strain occurred in Italy in 1992 and in the United States in 1996. From 2013 to 2016, an unprecedented outbreak occurred in West Africa (Guinea, Liberia, and Sierra Leone) with more than 28,000 cases and more than 11,000 deaths. Subsequent smaller outbreaks have occurred in the DRC (2021–22) and in Uganda (2022–2023).
- Classified among the highest priority for bioterrorism agents by the CDC (Category A).

8.6 | Common human exposure routes

- Virus is found in blood or other human tissues of sick or deceased patients and enters the host through mucosal membranes or abrasions/tears of the skin or by parenteral introduction in most recognized human infections.
- Unsafe needle injections.
- Contact with sick or dead monkeys.
- One theory is via fruit bats that may shed virus in their feces contaminating fruits and leaves that may be consumed.

8.7 | Likelihood of secondary transmission

- Prominent features of the large Ebola epidemics were secondary nosocomial, parenteral, and contact spread associated with inadequate sterilization of equipment, unsafe injection practices, and lack of basic (barrier) infection control techniques.
- In addition to high viral titers in blood, the skin of patients is extensively contaminated. This probably

accounts for the risk to those participating in traditional preparation of the cadaver and burial traditions.
- Interhuman spread of Ebola virus in the African epidemics has been very extensive among medical staff, often resulting in closure of hospitals and clinics. In Kikwit in 1995, up to 30% of physicians and 10% of nurses were affected, with high case-fatality rates.
- Transmission to household contacts has ranged between 3% and 17% and was associated with close contact with sick patients and their body fluids.
- Epidemics subsided with use of properly sterilized equipment, closure of hospitals, education of the populace, institution of barrier precautions and, most recently, ring vaccination of at-risk contacts.

8.8 | At-risk populations

- Outbreaks in endemic areas and secondary infections among susceptible populations
- A threat as a bioterrorist weapon for populations not previously considered being at risk

8.9 | Vector and reservoir involved

- Despite substantial work, no filovirus vector (e.g., mosquitoes, ticks, or fleas) has been identified.
- Human and nonhuman primates are susceptible to EBOV infections.
- Recent work suggests that ape-to-ape transmission may be responsible for epizootic waves of this disease, but the fruit bat may also act as a reservoir for this virus.

8.10 | Blood phase

- High-titer viremia (exceeding 10^6 PFU/mL) is present during acute illness (from 2 to 21 days in Kikwit, DRC outbreak in 1995).
- Prolonged presence of viral RNA in semen and vaginal fluids (>100 days) has been demonstrated in a limited number of patients and may be responsible for late transmissions.
- Asymptomatic viremia has not been described or rigorously pursued.

8.11 | Survival/persistence in blood products

- Unknown

8.12 | Transmission by blood transfusion

- Never reported.
- Nosocomial secondary spread is strongly associated with parenteral risks, suggesting that blood from ill patients is infectious.

8.13 | Cases/frequency in population

- Outbreaks are unpredictable, occurring primarily in central Africa.
- The Reston strain initially appeared in Reston, VA in association with an outbreak of hemorrhagic fever with high mortality occurring in cynomolgus macaques imported to the US from the Philippines. Four animal caretakers seroconverted but had no overt disease. Similar outbreaks subsequently have occurred in cynomolgus monkeys in Europe and the US with no clinical illness in humans.

8.14 | Incubation period

- 2–21 days (mean, 4–10 days)

8.15 | Likelihood of clinical disease

Asymptomatic infection in humans is believed to be uncommon considering that only a small percentage of the clinically unaffected population in epidemic communities has antibodies detected by IgG EIA suggesting that, with the exception of the Ebola Reston virus species, the clinical attack rate is very high.

8.16 | Primary disease symptoms

- Abrupt onset of fever and chills with myalgia, malaise, and headache sometimes accompanied by an erythematous, maculopapular rash around day 5 that is prominent on the trunk followed by desquamation in survivors. Multisystem involvement follows that includes prostration; nausea, vomiting, abdominal pain, diarrhea and pancreatitis; chest pain, cough, and pharyngitis; vascular and neurologic manifestations.
- Central nervous system involvement is often manifested by somnolence, delirium, or coma. Wasting becomes evident later, and bleeding manifestations, such as petechiae and hemorrhages occur in half or more of the patients.

- During the second week, the patient defervesces and improves markedly or dies in shock with multiorgan dysfunction, often accompanied by disseminated intravascular coagulation, anuria, and liver failure.
- Convalescence may be protracted and accompanied by arthralgia, orchitis, recurrent hepatitis, transverse myelitis, psychosocial disturbances, or uveitis.

8.17 | Severity of clinical disease

- See mortality

8.18 | Mortality

- ≈80% mortality reported in 1995 following a Zaire virus species outbreak in Kikwit (DRC). Mortality appears to be lower (53% CFR) with the Sudan virus species.

8.19 | Chronic carriage

- Viremia accompanies the acute stage and disappears about the time of defervescence in survivors during the second week of illness following detection of specific antibody.
- Viral nucleic acid may persist in some tissues for months, with infectious virus persisting in some immune-privileged sites such as CNS, semen, placenta, and eyes.

8.20 | Treatment available/efficacious

- The 2013–2016 outbreak spawned assessment of numerous treatments (especially small molecule antivirals and monoclonal antibodies) and vaccines. Ring vaccination has shown promise for controlling outbreaks. The efficacy of antiviral therapies remains under investigation.
  - Two monoclonal antibody preparations have received FDA approval for treatment of EBOV-Zaire.
- EBOV convalescent plasma (with unknown neutralization titers) did not result in clinically significant benefit during the West Africa epidemic.

8.21 | Agent-specific screening question(s)

- When there are no current outbreaks with widespread transmission, FDA 2017 guidance recommends providing donor information materials requiring self-deferral for a history of EBOV infection or disease. Specific questions regarding EBOV infection or potential exposure are additionally required when there is widespread transmission occurring in one or more countries.
- Geographic deferrals for malaria would exclude at-risk populations from endemic sub-Saharan Africa.
- Under circumstances of a bioterrorism threat, the need for, and potential effectiveness of, specific donor screening questions would need to be addressed.

8.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Virus culture, antigen detection, immunohistochemistry, and NAT are applicable to diverse body fluids and/or tissues, in addition to IgG and IgM antibody serology and electron microscopy. These diagnostic tools have all proved feasible for diagnostic and epidemiologic studies in various settings for Ebola.
  - Virus isolation requires BSL-4 facilities.

8.23 | Currently recommended donor deferral period

- 2017 FDA guidance recommends indefinite deferral of individuals with a history of EBOV infection or disease, and an 8-week deferral after potential exposures including residence in or travel to a country with widespread transmission of EBOV; close contact with a person diagnosed with or being investigated for EBOV; sexual contact with an individual known to have recovered from EBOV; other potential exposure to a person with EBOV. If one or more countries are classified as having widespread transmission of EBOV, specific donor questioning is required.
- The indefinite deferral after infection reflects concerns about chronic infection in "sanctuary" sites.
- The deferral interval for malaria (now a minimum of 3 months) is expected to be longer than what might be recommended for donors from Ebola endemic areas in Africa who may have been exposed.

8.24 | Impact on blood availability

- In the absence of widespread transmission outside of Africa, little impact is expected on blood availability in the United States.
- In the case of a bioterrorism threat, impact of a local deferral could be significant.

- Laboratory test(s) available: Not applicable

8.25 | Impact on blood safety

- Assuming that EBOV is transfusion transmissible, it is reasonable to speculate that deferral for a risk of infection will provide some margin of safety. However, the high clinical penetrance and the abrupt onset of symptoms following infection make it unlikely that many infected patients would donate blood.
- Laboratory test(s) available: Not applicable.

8.26 | Leukoreduction efficacy

- Data do not exist; however, the observation of virions in electron micrographs of cell-free serum and the cellular tropism of the virus for endothelial cells and hepatocytes suggests that leukoreduction would not be effective.

8.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in removal of enveloped viruses.

8.28 | Other prevention measures

- A Zaire EBOV-specific vaccine was used successfully as ring vaccination in a cluster randomized trial in Guinea during the West Africa epidemic, but strain-specific vaccines are not available for the other 5 species at this time and cross protection has not been demonstrated. The vaccine used in Guinea has received FDA approval.
- Using properly disinfected equipment and educating health care workers and other care givers about universal precautions are mandatory.

8.29 | Other comments

- BSL-4 biocontainment level

SUGGESTED READING

1. Chepurnov AA, Bakulina LF, Dadaeva AA, Ustinova EN, Chepurnova TS, Baker JR Jr. Inactivation of Ebola virus with a surfactant nanoemulsion. Acta Tropica. 2003;87:315–20.
2. European Centre for Disease Prevention and Control. Risk of Ebola virus transmission through donated blood and other substances of human origin. https://www.ecdc.europa.eu/en/all-topics-z/ebola-virus-disease/facts/risk-ebola-virus-transmission-through-donated-blood-and
3. Feldmann H, Sprecher A, Geisbert TW. Ebola. N Engl J Med. 2020;382:1832–42.
4. Gao Y, Zhao Y, Guyatt G, Fowler R, Kojan R, Ge L, et al. Effects of therapies for Ebola virus disease: a systematic review and network meta-analysis. Lancet Microbe. 2022;3:e683–92.
5. Geisbert TW. Marburg and Ebola virus hemorrhagic fevers. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 9th ed. Philadelphia (PA): Elsevier; 2020. ch. 164. p. 2138–42.e2.
6. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017;389:505–18.
7. International Committee on Taxonomy of Viruses. Current ICTV Taxonomy Release. 2021 https://ictv.global/taxonomy. Accessed 9 Mar 2023
8. Jacob ST, Crozier I, Fischer WA 2nd, Hewlett A, Kraft CS, Vega MA, et al. Ebola virus disease. Nat Rev Dis Primers. 2020;6(1):13. https://doi.org/10.1038/s41572-020-0147-3
9. Kuhn JH, Amarasinghe GK, Perry DL. Filoviridae. In: Howley PM, Knipe DM, Whelan S, editors. Fields virology: emerging viruses. 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2020. p. 449–503.
10. Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, et al. Fruit bats as reservoirs of Ebola virus. Nature. 2005;438:575–6.
11. Peters CJ, LeDuc JW. An introduction to Ebola: the virus and the disease. J Infect Dis. 1999;179(Suppl 1):ix–xvi.
12. Rodriguez LL, DeRoo A, Guimard Y, Trappier SG, Sanchez A, Bressler D, et al. Persistence and genetic stability of Ebolavirus during the outbreak in Kikwit, Democratic Republic of the Congo,1995. J Infect Dis. 1999;179(Suppl 1):S170–6.
13. Thorson AE, Deen GF, Bernstein KT, Liu WJ, Yamba F, Habib N, et al. Persistence of Ebola virus in semen among Ebola virus disease survivors in Sierra Leone: a cohort study of frequency, duration, and risk factors. PLoS Med. 2021;18(2):e1003273. https://doi.org/10.1371/journal.pmed.1003273
14. US Food and Drug Administration. Recommendations for assessment of blood donor eligibility, donor deferral and blood product management in response to ebola virus. 2017 Guidance for industry. https://www.fda.gov/media/94902/download
15. US Food and Drug Administration. FDA approves first treatment for ebola virus. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-ebola-virus. Accessed 24 Feb 2023
16. US Food and Drug Administration. First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health. Accessed 23 Feb 2023