DHS SCIENCE AND TECHNOLOGY

Master Question List for Ebolaviruses

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Science and Technology

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Ebolaviruses – Master Question List

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Foreword

The following Master Question List (MQL) was developed by the Department of Homeland Security Science and Technology Directorate (DHS S&T) to provide government decision makers with up-to-date information which will enable them to appropriately respond to outbreaks caused by ebolaviruses. This MQL summarizes what is known and what knowledge gaps exist to address fundamental questions such as, "What is the infectious dose?" and "How long does the virus persist in the environment?" The information provided is a succinct summary to facilitate structured and scientifically guided discussions across the federal government without burdening them with the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

Situation Overview

Ebolaviruses are zoonotic viruses (viruses that originate in animals) that cause severe and frequently fatal diseases in humans and non-human primates (NHPs). There are several species of ebolavirus, but Ebola virus (EBOV), which causes Ebola virus disease (EVD), and Sudan virus (SUDV), which causes Sudan virus disease (SVD) have been responsible for the most outbreaks. These viruses are endemic in parts of Africa, and although outbreaks have been rare and relatively small in the past, they have increased in size and frequency over the past decade. Within the past five years, multiple effective vaccines and therapeutics have become available for EVD and have had demonstrated efficacy during epidemics in Africa; and although SVD vaccines have lagged, several are now in clinical trials. The risk of an epidemic in the United States is low, and experience from the 2013-2016 West African outbreak has bolstered response capabilities.

The most recent outbreak of an ebolavirus occurred in Uganda. The Ugandan Ministry of Health confirmed an outbreak of SVD in Mubende District (western Uganda) on September 20, 2022. This was the sixth outbreak associated with ebolaviruses in Uganda. All but one has been caused by SUDV. On January 11, 2023, the Ministry of Health declared the end of the outbreak. The outbreak covered nine districts (Bunyangabu, Jinja, Kagadi, Kampala, Kassanda, Kyegegwa, Masaka, Mubende, and Wakiso) and resulted in 164 cases (142 confirmed, 22 probable) with 77 deaths. Mubende was the epicenter of the outbreak. The last confirmed case tested negative on November 29, 2022, and the last confirmed death was also on November 29, 2022; no new cases have been reported since. No confirmed cases were reported outside Uganda. Surveillance will be maintained, and neighboring countries remain on alert. A report describing the clinical progression of the index case has been released.

The cutoff date for information-gathering related to this document was 5/22/2023.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
VIRUS BACKGROUND	• The ebolaviruses are members of the family *Filoviridae*, which includes Marburg virus, another human pathogen associated with severe disease that was first discovered in 1967. • Marburg virus is covered under a separate MQL. • Filoviruses are filamentous (string-shaped) viruses with RNA genomes. • The term "Ebola virus" refers specifically to EBOV, formerly known as Ebola Zaire, while the term "ebolavirus" includes all six viruses in the genus *Ebolavirus* which are Ebola virus (EBOV), Sudan virus (SUDV), Bundibugyo virus (BDBV), Taï Forest virus (TAFV), Reston virus (RESTV) and Bombali virus (BOMV). • SUDV, BDBV and TAFV are known to cause ebolavirus disease (EVD) in humans, while RESTV and BOMV are not known to cause disease in humans. • EBOV was first isolated in 1976 during an outbreak in Zaire (now the Democratic Republic of the Congo [DRC]). • SUDV was first isolated in 1976 during an outbreak in what is now known as South Sudan.
INFECTIOUS DOSE	• The infectious dose for any ebolavirus in humans is not well established but is known to be low. • Estimates of infectious dose range from 10 to about 100 infectious particles. • The route of infection may impact the amount of virus required to cause an infection. • Mucosal and respiratory exposures generally tend to require higher doses than percutaneous exposures (i.e., exposure via injection or through a break in the skin).
TRANSMISSIBILITY	• Outbreaks are initiated by spillover events in which a human comes in contact with an infected animal, usually from hunting or other forest activities involving contact with animals. • The bushmeat trade has been implicated in transmission throughout Africa. • Transmission is typically via contact with contaminated bodily fluids of an actively symptomatic person. • Contact with mucous membranes or percutaneous exposure is required for infection. • Caregivers and those involved in handling cadavers are at the highest risk of infection. • Hospitals and clinics not using appropriate personal protective equipment (PPE) and administrative and engineering controls for care of EVD patients can be foci of new infections. • Contact with fomites (inanimate objects contaminated with infectious agents) is a low-risk mechanism of transmission in public places, but in healthcare settings, contaminated items associated with patient care and waste are a high-risk mechanism.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	• The risk of airborne transmission of EBOV by aerosol particles (small particle) during the course of a naturally occurring infection is considered to be minimal. • Large droplets generated from an infected individual (i.e., coughing, sneezing, vomiting, experiencing diarrhea) could transmit the virus to another individual in close proximity (a few feet). • Patients are normally no longer contagious after recovery, but prolonged persistent infection is known to occur (see relevant section for details). • Transmission without direct contact from confirmed cases has been observed. The mechanism of this transmission is unclear.
HOST RANGE	• Bats, and in particular three species of fruit bat (*Epomops franqueti*, *Myonycteris torquata*, and *Hypsignathus monstrosus*), are the likely reservoirs of ebolaviruses. • Bats infected with filoviruses do not develop disease. • Other mammals including non-human primates (NHPs), dogs, and pigs can be naturally infected, but are not considered reservoirs. • Habitat disruption due to human activity is increasing the frequency of contact with animals potentially infected with ebolaviruses. • Rodents are not naturally susceptible to any filovirus. Extensive adaptation of the virus in a laboratory is required to infect rodents.
INCUBATION PERIOD	• The incubation period can range from 2-21 days but is typically 3-14 days. • Incubation period may vary depending upon the route of transmission. • Percutaneous exposures (such as through a needlestick or break in the skin) have been associated with shorter incubation periods than mucosal exposures. • Outbreaks are considered to be over when two maximum incubation periods have passed without the detection of a new case (42 days). • The incubation and infectious periods for SUDV are similar to EBOV.
CLINICAL PRESENTATION	• Diseases caused by ebolaviruses present as severe febrile illnesses with abrupt onset. • Case fatality for EVD is variable, but high, ranging from 25-90%, depending upon the virus and the level of care provided. The average fatality for EVD is 66%. • Case fatality for SVD is typically lower than EVD, averaging 50%. • Symptoms include fever, malaise, exhaustion, nausea, vomiting, diarrhea, abdominal pain, sore throat, and headache. • Many patients develop a characteristic rash (known as a maculopapular rash) approximately five days after disease onset.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	• This initial cluster of symptoms resembles many tropical diseases, including yellow fever, malaria, and Lassa fever, which makes clinical diagnosis of EVD extremely difficult outside of a known outbreak and requires laboratory diagnostics to confirm. • Neurological symptoms such as delirium or coma can occur in the later stages of the disease. • Hemorrhagic (bleeding) symptoms do not always occur, and typically appear only late in the course of the disease. • Multiple organ dysfunction and hypovolemia (low blood pressure secondary to fluid loss from vomiting and diarrhea) are the most common proximal causes of death. • Hemorrhagic symptoms are more common in severe disease, but patients do not lose enough blood to progress to a life-threatening state. • Patients typically die or begin to recover within 8-12 days of disease onset. • High-quality supportive care can significantly improve outcomes. • Asymptomatic infections are estimated to occur in less than 5% of infections. • Patients are considered to be non-infectious after two sequential negative polymerase chain reaction (PCR) tests.
PERSISTENT INFECTION	• In some instances, the virus can be detected in patients for over two months after the disease resolves. • Studies of patients after the 2013-2016 West African outbreak have detected EBOV in patient semen up to 18 months after recovery, but it appears that most patients clear the virus entirely within six months. • Infections have been linked to sexual transmission of EBOV via the semen of recovered patients. • Prolonged persistence of the virus does occur. The 2021 outbreak in Guinea was linked to reactivation of a persistent infection in a patient from the 2013-2016 outbreak. • The biology of this phenomenon is poorly understood, but it is believed to be linked to long-term infection of so-called “immunologically privileged” tissues such as the testes and eyes that are not subject to surveillance by the immune system.
CLINICAL DIAGNOSIS	• Definitive diagnosis is via quantitative real-time (qRT)-PCR detection of viral RNA in a patient sample. • Patients will become PCR positive within a few days of infection. • Lateral flow antigen detection assays are available for rapid preliminary diagnosis. • Enzyme-linked immunosorbent assay (ELISA) methods for antibody detection are reliable but are not useful for early and pre-symptomatic diagnosis. • Diagnosis by viral culture should never be attempted outside of a biosafety level 4 (BSL4) laboratory.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	• Other testing methodologies are available or are in development, but are either not yet approved, or require specialized resources.
MEDICAL TREATMENT	• Although specific treatments for EVD exist, intensive supportive care remains essential to effective treatment. • Vaccines can be used as post-exposure prophylaxis (PEP) in conjunction with other therapeutics but may not be as useful in patients who have already begun to show symptoms. • Two U.S. Food and Drug Administration (FDA)-approved monoclonal antibody (mAB) treatments exist and have demonstrated efficacy in humans against EBOV. • No small molecule antiviral drug exists, though several have been tested and failed human trials despite promising results in animal studies. • No approved therapeutics for SVD exist. However, a combination therapy using remdesivir and an antibody-based treatment has shown promise in NHPs. This treatment has been made available to Ugandan health authorities by the United States.

VACCINES	• The FDA and European Medicines Agency have approved Ervebo, Merck's single-dose EBOV vaccine:
	  ○ This vaccine is highly effective with reported efficacy >95%.
	  ○ Duration of protection is not known.
	  ○ Adverse reactions are common. Nearly all recipients report some sort of adverse reaction, with some reporting more serious events.
	• The European Medicines Agency approved Zabdeno and Mvabea, Janssen/Johnson and Johnson's two-dose vaccine.
	  ○ Efficacy is slightly lower than Ervebo, but the vaccine appears to be better tolerated.
	  ○ Duration of protection is not known.
	• Ring vaccination, a strategy in which contacts of patients and subsequent contacts are vaccinated, has been used with considerable success during outbreaks to contain transmission.
	• The expense and adverse event rate associated with the vaccines may limit their use outside of outbreak control.
	• In the United States, laboratory workers, individuals who will have contact with EVD patients, and healthcare personnel at Regional Ebola and Other Special Pathogen Treatment Centers (RESPTC) and Laboratory Response Network facilities are eligible for vaccination.
	• No vaccines specific to SUDV are approved for use.
	  ○ The World Health Organization (WHO) and Ugandan Ministry of Health initiated a clinical trial in December 2022 to evaluate three vaccine candidates, which are: Sabin Vaccine Institute's ChAd3-SUDV, BiEBOV (Oxford University) and the Merck SV-SUDV vaccine.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
FORECASTING	• The risk of an EVD or SVD outbreak in the United States is considered low. • Forecasting was critical for decision support during the 2013-2016 outbreak. • Current models account for the impact of vaccines and other interventions such as contact tracing and safe burial. • Ensemble forecasts incorporating multiple diverse models outperform single-model forecasts. • Data quality and timeliness have been limiting factors for the utility of real-time modeling.
ENVIRONMENTAL STABILITY	• EBOV can remain infectious in most liquids (blood, urine, semen, wastewater) for 5-8 days. • EBOV persists on hard surfaces for up to eight days, but is less stable under high humidity/temperature, which has been shown to reduce persistence to 1-3 days. • The virus appears to be less persistent (typically less than a week) on some soft materials, such as cotton cloth.
DECONTAMINATION	• Disinfectants on the U.S. Environmental Protection Agency (EPA) Lists L or Q are recommended for use with EBOV. • Due to the extremely low infectious dose of EBOV, greater than typical inactivation efficiency is required. • Chlorine bleach is an extremely effective disinfectant. • Germicidal ultraviolet (UV) light, chlorine dioxide, and vaporized hydrogen peroxide are useful for decontamination of rooms. • The presence or absence of viral RNA should not be used as an indicator of the presence of infectious virus prior to or following decontamination, as this parameter does not equate to infectious virus. Testing methods that utilize infectivity as a readout should be used to determine efficacy. • Following contact times for decontamination when using wipes is critical, as the virus can be transferred between surfaces by inappropriately used disinfecting wipes.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	• The U.S. Centers for Disease Control and Prevention (CDC)-recommended PPE for persons caring for a patient with confirmed EVD includes single-use and disposable PPE, and respiratory protection in the form of a powered air-purifying respirator (PAPR) or National Institute for Occupational Safety and Health (NIOSH)-certified N95 respirator. • Respiratory protection is not required by CDC recommendations for caring for a patient under investigation (PUI) of EVD who is clinically stable, and not exhibiting symptoms. • Detailed instructions for the recommended procedures for donning and doffing of PPE are available from CDC. • The risk for errors and self-contamination is highest in the doffing phase. Consistent and correct use of PPE, reinforced with repeated training and practice, is key to minimizing exposure.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
	• Use of full-body PPE in Ebola treatment units (ETUs) presents a number of issues, including heat exhaustion, reduced sensory perception, and reduced dexterity. Recent tests suggest that the use of cooling clothing made with phase-changing materials can partially alleviate heat-related stresses.
GENOMICS	• EBOV is one of four members of the genus Ebolavirus (collectively known as ebolaviruses) known to cause disease in humans. • Since humans are dead-end hosts for ebolaviruses, variants associated with outbreaks do not persist in nature after the outbreak ends, and do not "spill back" into the animal reservoir of the virus. • The characteristics of the virus (e.g., virulence, efficacy of transmission) are similar among outbreaks. • EBOV evolves slowly in its animal reservoir and during recent outbreaks. Mutations associated with adaptation to humans appeared only after relatively long chains of successive human-to-human transmission. • Sequences were not publicly available for the SUDV outbreak in Uganda as of May 2023.
VIRUS IMPORTATION	• Air travel is a concern for importation of EVD from infected passengers. • Undetected importation can result in local transmission within receiving healthcare facilities if they are not adequately prepared, as observed in Dallas, Texas in 2014. • The air travel restrictions put into place during the 2013-2016 EVD epidemic were effective in preventing export of EVD from Africa but were not sufficient to entirely prevent spread. • Modeling suggests that airport screening alone may not be able to detect the majority of EVD cases. • To avoid importation, controlling the virus in the country of origin is critical. • The most effective air passenger screening occurs when applied at the embarkation airport where infected air travelers are most likely to depart. • Importation of medically evacuated EVD patients for treatment in designated healthcare facilities does not pose a significant risk of transmission within the United States.
NON-PHARMACEUTICAL INTERVENTIONS (NPI)	• Until recently, non-pharmaceutical interventions (NPIs) were the sole means of controlling EBOV outbreaks, which include contact tracing, establishment of ETUs, changes in burial practices, and isolation of infected individuals. These steps were key to stopping the 2013-2016 West African EVD epidemic. • Community support and buy-in/cooperation is critical for enhancing efficacy of NPIs.

Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
U.S. HEALTH SYSTEM CAPACITY	• Care of symptomatic EVD patients is staff- and resource-intensive. • Patients with symptomatic disease require advanced treatment in an intensive care unit (ICU) setting, and ICU beds are an extremely limited resource. • Infection control measures required to prevent hospital-acquired transmission (e.g., increased staff workload) are demanding. • The United States has the capacity to handle a certain number of imported cases (generally no more than seven at any given time) if they are identified prior to significant transmission. • Within the United States, 10 specialized RESPTC have been established, with one in each of the 10 U.S. Health and Human Services (HHS) regions; there are plans to add 2-3 more. • Early identification of EBOV clusters and rapid control via contact tracing can limit outbreak size. • Nosocomial (hospital-acquired) transmission presents a significant risk to staff and non-EVD patients when large numbers of EVD patients are treated in the same facility. • In Africa, dedicated ETUs are utilized to treat large numbers of EVD patients outside of normal hospitals, though due to the lack of advanced equipment and trained staff, patient outcomes do not match those achieved in ICUs present in Western countries. • The ability of U.S. healthcare facilities to adequately handle a large number of EVD patients is unknown, but prior experience with a single patient at a non-specialty facility suggests that most facilities are unprepared or underprepared.

Infectious Dose
How much agent will make a healthy individual ill?

What do we know?

- The infectious dose for EBOV in humans is not established. However, based upon experimental data in multiple animal models, it is likely to be extremely low, possibly fewer than 10 infectious units. The infectious dose also likely varies by route. Median lethal dose (LD_{50}) values for virus delivered via injection are typically about one log lower than LD_{50} values for mucosal (e.g., intranasal, oral) routes. Differences in animal model susceptibility likely contribute to this broad distribution.
- Multiple EBOV infection animal studies suggest that virus particle infectivity can be affected by repeated viral passages in cell culture as it alters the particle-to-plaque forming unit (PFU) ratio. Higher passages result in a lower particle-to-PFU ratio, which leads to decreased potency in a lethal macaque model. Because of testing of viral titer by plaque assay alone, two different stocks of the same virus could have the same PFU, but different levels of infectivity, causing variation in the reported lethality of the strain. Additional studies should monitor viral stocks prior to infection.[1]
    - Median tissue culture infectious dose ($TCID_{50}$) units and PFU, two measures of viral quantity commonly used in this document, may be interconverted by multiplying $TCID_{50}$ units by 0.7 to derive the PFU equivalent.
- Infectious dose determinations have not been made for SUDV, though aerosol and intramuscular challenges with 1000 PFU were lethal in cynomolgus macaques.[2-3]
- Experimental aerosol studies in marmosets with EBOV-Kikwit found 4-27 $TCID_{50}$ to be infectious with clinical signs similar to that observed in humans and other NHP models.[4]
- Aerosol and intranasal (IN) inoculation of EBOV-Makona in cynomolgus macaques found a dose of 64 PFU only 83% lethal with variability in disease onset when administered by these routes.[5] Similar studies with lower doses are needed to better understand the variability of infection.
- Additional studies in cynomolgus macaques when exposed to EBOV-Kikwit strain, by the IN route found the LD_{50} = 10 PFU[6] to 65 PFU;[7] however, lower values were not tested to determine the median infectious dose (ID_{50}). Experimentally, the clinical course seen for cynomolgus macaques when exposed intranasally more closely mimicked clinical disease seen in humans, suggesting this to be a good model for study.[6-7]
- EBOV (Kikwit variant) in cynomolgus macaques has an ID_{50} < 4.2 PFU, as animals exposed to 0.8 and 4.2 PFU by the aerosol route survived, but aerosol doses of 2, 11, and 128.3 PFU were lethal.[8]
- Cynomolgus macaques experimentally infected with EBOV-Makona at 10 PFU by the oral or conjunctival route showed low to no infection with no clinical disease; however, 100 PFU administered orally was lethal. Conversely, 100 PFU by the conjunctival route was not lethal, suggesting that both the viral titer and transmission route play a role in infection.[9]
- Rhesus macaques challenged with 1,000 $TCID_{50}$ (~700 PFU) EBOV-Makona by different routes of infection (intraesophageal [oral], intratracheal, aerosol [nebulizer], and intramuscular) had variable results on transmission. Measurements of viral load from shedding and seroconversion of animals showed that viral loads determine the transmission potential in both intramuscular and intratracheal models. Intraesophageal infection did not result in clinical disease or seroconversion. Aerosol infection resulted in subclinical infection in challenged animals, and seroconversion in naïve animals exposed to challenged animals, suggesting both transmission route and viral load impact infection.[10]
- Experimental studies in ferrets determined that a dose as low as one PFU caused infection when inoculated by the oronasal route, but not by the ocular route.[11]

- Guinea pig studies with EBOV-Makona variant not adapted to guinea pigs showed survival at a high dose of 3.5 x 10^5 PFU, but proved lethal when given a low dose of guinea pig-adapted EBOV-Makona of 3.5 PFU, suggesting they could be an appropriate animal model once the strain is adapted in that species.[12-13]
- EBOV-Zaire is lethal when inoculated into newborn BALB/c mice via intraperitoneal (IP) inoculation, but not when inoculated into adult (>8-15 day old) mice. Mouse-adapted EBOV was highly infectious and lethal in adult mice when injected via IP; the adapted virus had a LD_{50} of approximately one virion and infected mice showed symptoms mimicking those observed in NHPs with EBO-Zaire. In contrast, adult mice injected subcutaneously, intradermally, or intramuscularly with mouse-adapted EBOV did not show symptoms, even with doses as high as 10^6 PFU. While mice did not show symptoms, EBOV virions were disseminated to lymph nodes, but the mice appeared to develop a protective immune response when injected by these routes.[14]
- EBOV-Makona, when administered IP to A129 interferon α/β receptor-deficient immune-deficient mice (A129 mice), was lethal, with an extremely low ID_{50} of approximately 0.002 $TCID_{50}$ (0.0014 PFU).[15]
- Additional studies in the same A129 mice where EBOV was administered by aerosolization found significant variation in lethal dose when animals were exposed to 100 $TCID_{50}$ (70 PFU) by IP and 10 $TCID_{50}$ (7 PFU) among three strains. At this exposure dose, EBOV-Ecran was 90% lethal, EBOV-Kikwit was 70% lethal, and EBOV-Makona was 50% lethal. There were significant differences in lethality when comparing IP and aerosolized routes of infection, suggesting that dose and route play a role in disease. This model may be useful in future virulence studies when new variants are identified.[16]

What do we need to know?

- What is the human infectious dose for different routes of infection: mucus (aerosol, lung), cutaneous (skin contact), or oral (consumption through food/water)?
- Does the human infectious dose vary among different sub-populations by age, immunocompromised status, sex, or other factors?
- Does the human infectious dose vary by virus variant?

Transmissibility
How does it spread from one host to another? How easily is it spread?

What do we know?

- Ebolavirus outbreaks are initiated through a spillover event in which a human comes into contact with an animal reservoir.[17-18]
  - The index case is often a forest worker, hunter, or an individual known to have contact with wildlife.[18-22]
  - Hunting, handling, and consumption of bushmeat are potential routes of spillover.[18, 23]
- Virus is transmitted from person to person via contact with the bodily fluids of an actively symptomatic individual or cadaver. Contact with mucous membranes, breaks in skin, or percutaneous (e.g., needlestick) exposure is required.[24]
  - Potentially infectious fluids include blood, sweat, saliva, feces, urine, semen, and breast milk.[24-26]
  - Pre-symptomatic individuals cannot transmit the virus.[27]
  - EBOV can be persistent in semen and be potentially transmitted sexually several months post-infection.[28]
  - There is evidence that suggests that the route of infection has significant effects on an individual's ability to transmit the virus. NHPs infected via aerosol or mucosal routes transmitted the virus more efficiently via the mucosal route than intramuscular-challenged NHPs in a recently published study.[10]

- Caregivers and those involved in handling cadavers are at the highest risk of infection.[17, 29-32]
  - Clusters of cases tend to form within family groups due to heavy reliance on family members for care.[31]
  - Traditional funeral rites in many EBOV-endemic regions of Africa involve significant contact with the cadaver, which poses an extremely high risk of transmission, as bodily fluids of cadavers are highly infectious.[31]
  - In industrialized countries, medical examiners and those performing autopsies are at risk.[33-35]
- Hospitals and clinics without training and equipment to handle EVD cases are frequently the source of transmission.
  - Healthcare workers are at particularly high risk, and represent a large percentage of cases in large outbreaks.[29-30, 36]
  - Reuse of needles has been a significant mechanism of hospital-acquired transmission.[37]
  - Waste from patient care contaminated with bodily fluids is treated as highly infectious until sterilized.[38]
- There may be a dose-dependent relationship with disease severity, where the highest risk of infection and severe illness is associated with direct contact with patients or bodily fluids, while minimal or indirect contact (e.g., sleeping in the same room, eating the same meals) is associated with a lower likelihood of infection and decreased severity of disease.[39]
  - EVD transmission without direct contact with EVD cases has been observed, suggesting that exposure to asymptomatic or unrecognized EVD cases may be involved.[32, 39]
- Fomites are a low-risk mechanism of transmission in public places, but contaminated PPE is highly infectious.[24-25, 38, 40]
- Aerosol transmission via respiratory droplets (in the manner of SARS-CoV-2/COVID-19) does not appear to occur naturally.
  - Consensus from epidemiologic evidence is that ebolavirus aerosols do not contribute to normal transmission.[18]
  - Some animal studies have shown aerosol transmission to and between NHPs, though transmission may have been through fomite, large droplet, or cross-contamination instead of respiratory droplet transmission.[32, 41-42]
  - Aerosols generated by aerosol-generating medical procedures (intubation, patient ventilation, surgery, suctioning, surgical laser or power tools, and any methods inducing patient coughing or respiratory aerosolization) pose a transmission risk to those involved.[43]
- Large droplets of fluids generated by coughing, for example, could transmit the virus to individuals in close contact (~3 feet) with the patient.
  - Droplets would need to contain contaminated bodily fluids to be infectious.[32]
  - In one study, facial spray exposure in macaques led to no clinical symptoms, but subjects developed antibodies.[10]
- Large droplets do not remain suspended in the air,[44] meaning that only individuals in close proximity to the patient are at risk from infection via this route.
- A recently published study found that intraesophageal exposure was not infectious in macaques.[10]
- Individuals are typically no longer contagious after recovery, but prolonged persistence in patient semen and the vitreous humor of the eye is known to occur.[45]
- Patients normally remain in medical facilities until they are PCR negative for EBOV by two sequential tests.[17]

What do we need to know?

- What is the risk of transmission via droplets?

- What is the frequency of sexual transmission and other forms of atypical transmission of EBOV?
- What is the frequency of true "superspreader events" during an EBOV outbreak?

Host Range
How many species does it infect? Can it transfer from species to species?

What do we know?

- Bats, particularly fruit bats, are the likely natural reservoir of the virus.[18] Bats infected with filoviruses do not develop the disease.[46]
  - Viral RNA has been detected in the fruit bat species *Epomops franqueti*, *Myonycteris torquata*, and *Hypsignathus monstrosus*.[21]
  - Anti-EBOV antibodies have been identified in at least nine[47] species of fruit and insectivorous bats.[18, 48]
  - The geographic distribution of *E. franqueti, M. torquata* and *H. monstrosus* overlaps with nearly all of known EBOV spillover events and outbreak sites, further suggesting that these species could be part of the natural reservoir of EBOV.[47]
  - Anti-EBOV antibodies and viral RNA were reported in *Miniopterus inflatus*, an insectivorous bat in West Africa, but no further confirmation or data was provided.[49]
  - Bombali virus (BOMV), a new member of the genus *Ebolavirus*, was detected via sequencing in the insectivorous bat *Mops condylurus*, and anti-EBOV antibodies have been repeatedly isolated from this species.[50] Initial studies in humanized mice using infectious BOMV show similar behavior to the apathogenic (in humans) RESTV, suggesting that it has low pathogenic potential in humans.[51]. However, given that these animals live in close proximity with humans, it is unlikely that they are the definitive reservoir of EBOV.[50]
- Other mammals, including NHPs (apes in particular), dogs, pigs, and potentially duikers (a type of small forest antelope) can be naturally infected, but are dead-end hosts.
  - EBOV causes epizootics among great apes.[22, 52-53]
  - EBOV is readily transmitted between NHPs.[18]
  - Dogs were found to have been infected during the 2013-2016 outbreak via serosurveys, but did not appear to develop the disease.[54]
  - Pigs are susceptible and can transmit the virus to other pigs and to NHPs.[55]
  - Although frequently cited as a host species, only a single individual duiker has ever tested positive for EBOV, and then only by a single method (PCR).[52]
  - Porcupines have been suggested as potential intermediate hosts, though no infected porcupine has ever been identified.[56-57]
- Most animals are likely infected via exposure to bats (feces or urine are probable routes).[18]
  - Bat-to-human transmission has been the definitive cause of multiple Marburg virus spillover events, a closely related virus to EBOV.[18]
  - Bat-to-human transmission has been strongly suspected in at least two EBOV outbreaks, including the 2013-2016 outbreak in West Africa.[58-59]
  - NHP-to-human transmission has been suspected in the initiation of several EBOV outbreaks.[18]
- Habitat disruption via human activity has led to increased spillover risk.[60]
  - Deforestation is a particularly important factor.[60]
- Varying degrees of susceptibility have been demonstrated for several species of snake.[61-62]
  - Some snake species are susceptible following a point mutation in the receptor NPC1.[62]
  - Boid snakes (boas, pythons, and anacondas) may be susceptible to infection without adaptation of either the host or virus.[61]
- NHPs are the ideal animal model for research purposes. Ferrets are also suitable models of EVD, and do not require adaptation of the virus. Commonly used small animal models include

guinea pigs, Syrian golden hamsters, and mice, but these models require adaptation of the virus in order to produce lethal infection.[63]
  - All rodents require adaptation of the virus in order to produce a lethal infection.[63-65]
  - Rodents are generally an inadequate model of EBOV disease presentation.[13, 63-67]
  - Ferrets and NHPs offer the best approximation of human disease.[63-65]
- EBOV VP24, a minor matrix protein, appears to be a key factor in determining host range.[68-70]
  - Rodent-adapted viruses feature mutations in VP24.[69-70]
  - Structural changes in VP24 appear to be responsible for lack of disease in humans infected with RESTV, another species in the genus *Ebolavirus*.[68]

What do we need to know?

- Which species of bat(s) are the natural reservoir(s) of EBOV?
- How does the ecology of EBOV and its reservoir host(s) impact the frequency of human outbreaks?
- Do snakes or other reptiles play any role in the ecology of EBOV?
- What are the restriction factors that determine host range?

Incubation Period
How long after infection do symptoms appear? Are people infectious during this time?

What do we know?

- The generally accepted incubation period following exposure to EBOV is 2-21 days.[71]
  - Based on a literature survey, EBOV had an incubation period distribution of 5.3-12.7 days, SUDV had a distribution of 3.35-14 days, and Bundibugyo virus had a distribution of 6.3 days.[72]
  - Children appear to have shorter incubation periods, with an average of 6.9 days in children younger than one year old, and 9.8 days in children aged 10-15 years old.[73] [29]

Year	Location	Virus	Incubation Period (days)
1995	DRC	EBOV	6.2 (range 5-8)[75]
2009	DRC	EBOV	12.7[78]
2013-2016	West Africa	EBOV	9.7 (range 6-15)[80] [81-84]
1976	Sudan	SUDV	7-14[74]
2000	Uganda	SUDV	6 (range 1-16)[29]
2007	Uganda	BDBV	6.3 (range 5.2-7.3)[77]
2012	DRC	BDBV	11.3[79]

- In the 2014 EVD outbreak in West Africa, fatal cases had shorter incubation periods (7 days) than nonfatal cases (8.5 days).[84]
- Incubation periods vary depending on routes of transmission. The mean incubation period reported for all routes of transmission was 6.22 ± 1.57 days and 5.86 ± 1.42 days for percutaneous transmission specifically.[86]
  - Cynomolgus macaques exposed to aerosolized EBOV developed a fever in ~3.9 days.[87]
  - Monkeys exposed via IP injection to EBOV developed symptoms after 3-4 days,[88] which is an incubation period shorter than that of the Salisbury scientist who accidentally inoculated himself and had an incubation period of 6 days.[89]
- Estimates of the infectious period range from ~3 days to over 14 days, with most estimates being between 4-6 days.[85]
- The incubation and infectious periods for SUDV are similar to EBOV (typically 3-14 days,

range 2-21 days).[3, 74, 90]

What do we need to know?

- Are there signs or symptoms to suggest that a patient is infected prior to them becoming infectious?

Clinical Presentation
What are the signs and symptoms of an infected person?

What do we know?

- Disease caused by ebolaviruses presents as a severe febrile illness with abrupt onset.[17, 91]
- Typical symptoms include fever, malaise, prostration, nausea, vomiting, diarrhea, abdominal pain, sore throat, and headache.[17, 91-92]
  - This cluster of symptoms is typical of multiple hemorrhagic fever viruses.[91]
  - Patients lose large amounts of fluid due to vomiting and diarrhea, leading to hypovolemia and electrolyte imbalance.[17, 93]
  - Although rare, patients occasionally present with hiccups, jaundice, and photophobia.[94-95]
- Presentation makes disease caused by ebolaviruses difficult to distinguish from other common tropical diseases, such as malaria and yellow fever.[27, 91]
  - This difficulty commonly delays identification of ebolavirus outbreaks.[23]
  - Diagnosis requires laboratory testing.[17]
  - Unrecognized EVD may account for up to 8.7% of contacts, complicating contact tracing and suggesting the need for wider testing during outbreaks.[96]
- EVD-specific signs may be less prevalent in vaccinated individuals testing positive for EVD on or after day three post-symptoms, including abdominal pain, difficulty swallowing, vomiting blood, bloody stools, breathlessness and bleeding gums.[97]
- Many patients develop a maculopapular rash approximately five days after the onset of symptoms.[17, 91]
  - This rash can be difficult to observe in patients with dark skin tones.[91]
- Delirium, obtundation (drowsiness, lethargy, reduced responsiveness, etc.), and coma are typical features as the disease progresses.[27, 91]
  - Neurological manifestations may persist after infection is cleared, including memory loss, headache, cranial nerve issues, tremors, and seizures.[98]
- Liver enzymes, blood urea nitrogen, creatinine, clotting time, and d-dimers will be elevated, and fibrinogen and platelet counts are typically depressed.[91]
- Hemorrhagic manifestations appear later in the course of the disease and are more common in severe cases. Significant bleeding is rare, and patients do not die of blood loss.[17, 91]
  - Typical hemorrhagic signs include petechiae (distinct spots that appear on the skin) and ecchymoses (skin discoloration), oozing from injection sites, subconjunctival hemorrhage, and gingival bleeding.[17, 91]
- Multiple organ dysfunction and disseminated intravascular coagulation are common features of severe disease.[17, 91]
  - Liver and kidney failure are common.[93]
  - Disseminated intravascular coagulation is a result of cytokine storm induced by infection of immune cells.[93]
- Death normally occurs within 8-12 days of disease onset and is typically the result of hypovolemic shock due to non-hemorrhagic fluid loss.[17, 91, 93]
- Case fatality for EVD is variable, but high (25-90%, skewing heavily toward the upper end). High-quality medical intervention such as fluid resuscitation and advanced supportive care including dialysis significantly reduces mortality.[17, 91, 93]
  - Case fatality for SUDV tends to be lower, averaging ~55%.[99]

  - Fatality rates depend on a number of factors, including the particular variant responsible for the outbreak and patient variables such as age and general health.[17, 93]
- Asymptomatic infections are rare, but do occur at a low rate; typically between 2.6-7.5% among contacts of patients.[100] Some (11/24) asymptomatic individuals showed early and strong inflammatory responses, with viral RNA may be detectable for up to two weeks.[101]
- EBOV can be detected in clinical specimens (e.g., ocular fluid, saliva, stool, semen, breast milk, tears, nasal blood, and skin swabs).[25, 102-103]
  - EBOV RNA was detectable for 70 days in oral, nasal, ocular, urogenital, rectal, skin, and blood (pooled in the body cavity) swab samples and tissue biopsy specimens from the liver, spleen, lung, and muscle of the corpses of five cynomolgus macaques. Viable virus was detectable from the body cavity for one week after death.[33]
  - Breast milk and semen samples were found to be positive at days 15 and 40 after disease onset, respectively, when EBOV was already cleared from the blood.[25]
  - Modeling based on semen samples from 26 patients predicts (90% certainty) that 50-90% of men will clear EBOV RNA from seminal fluid at 115-294 days (respectively) post disease onset.[103]
  - Infectious EBOV was detected in a patient's aqueous humor (ocular fluid) 63 days after recovery of the disease.[102]
  - EBOV RNA could be detected for up to 33 days in vaginal, rectal, and conjunctival swabs of one patient and up to 101 days in the seminal fluid of four patients, and infectious virus was detected 82 days after disease onset in the seminal fluid of one patient.[104]
  - A Sierra Leone outbreak survivor had EBOV RNA recovered from vaginal fluid up to 36 days after symptom onset.[105]

What do we need to know?

- Is fever a useful indicator for the ability of a patient to transmit the virus? Is a patient ever able to transmit the virus after developing less noticeable symptoms, but prior to becoming febrile?
- Can individuals who remain asymptomatic throughout the course of infection transmit the virus?
- Is there a naturally immune population?
- Are there unique biomarkers that can be used for early detection of infection?

Persistent Infection
What is the biology and how does it impact outbreak response?

What do we know?

- In the 2013-2016 EVD outbreak in West Africa, it was found that the virus may persist in semen for up to two months, and possibly much longer.
  - Multiple sexually transmitted cases of EVD occurred during the outbreak.[103, 106-108]
  - "Flare ups" of local transmission may occur near the end of epidemics due to sexual transmission from recovered patients.[106-107]
- EBOV was detected in the semen of 75% of male EVD survivors from the Sierra Leone outbreak after six months, and 27% of survivors at nine months.[28, 109] 4% of a sampling of men had EBOV RNA detected at 16-18 months after recovery, though another report found a shorter duration of 9-12 months.[110-112]
  - EBOV RNA was detected in a human immunodeficiency virus (HIV)-positive man's semen over 18 months after recovery from the disease.[113]
  - EBOV RNA was found in the seminal fluid of an EVD survivor approximately 18 months after onset of disease, and was sexually transmitted between ~7-17 months after onset of symptoms.[114-115]
  - Longer persistence in semen appears to be associated with severe acute disease, as well as in older men (>35 years).[28]

  - While sexual transmission chains have been verified and linked to EBOV RNA, isolation of infectious EBOV from semen has only been reported from five EVD survivors. Infectious virus was isolated out to 70 days post-EVD onset.[116]
- Various proposed mechanisms of viral persistence in humans include "hiding" from the body's immune system in parts of the body, the virus entering a latent (non-replicating) state, defective virus genomes modulating replication, or reduced virus replication.[45]
  - Defective EBOV genomes were found in the testes of EBOV-infected NHPs. Testes are one of the human organs thought to allow persistence of the virus.[117]
  - A primate cell line was persistently infected with EBOV due to defective interfering particles (virus-like particles that cannot replicate in the absence of a functional viral genome).[118]
  - Viable EBOV was recovered from the patients' aqueous humor of the eye nine weeks after viremia was cleared. This was associated with uveitis (a serious eye inflammation) in the patient.[102]
- Reactivation of infection has been observed from persistent virus in cerebrospinal fluid.[119]
- The 2021 outbreak in Guinea appears to have occurred as a result of transmission from a patient with a reactivated persistent infection from the 2013-2016 outbreak.[120]
  - Sequencing of virus from 12 patients found extremely low levels of sequence divergence from the virus associated with the prior outbreak.[120]
  - This finding makes spillover an unlikely initiating event for this outbreak.[120]
  - This finding suggests prolonged persistent infection occurs with low levels of viral replication.[120]
- Persistent EBOV infection was detected in the ventricular system of the brain in 7 of 36 rhesus macaques post-mAb treatment after surviving EBOV infection.[121]
- In Liberia, 126 male participants all tested negative for EBOV RNA in their blood when tested 30 months after EBOV onset. One participant still tested positive for EBOV RNA in his semen.[122]

What do we need to know?

- What is the duration of persistence of virus in tissues where it can survive after clearance of systemic infection?
- What percentage of EBOV survivors with persistent detectable EBOV RNA in semen and ocular fluid, for example, are still infectious? In other words, how often does persistent PCR positivity equate to persistent infectivity?

Clinical Diagnosis
Are there tools to diagnose infected individuals and when are they effective?

What do we know?

- Clinical diagnosis can occur within a few days of infection. Various test modalities are available.[17, 92]
  - Viral Hemorrhagic Fever clinical diagnosis is considered for any patient presenting with severe acute febrile illness and evidence of vascular instability. Confirmed diagnosis requires both meeting case definition and positive laboratory tests.[93]
- qRT-PCR is the current standard diagnostic test for EBOV and is useful for rapid disease diagnosis.[17, 92, 123]
  - Multiplex PCR and oligonucleotide microarray technology have been developed that can detect and differentiate between EBOV and other hemorrhagic fever viruses.[124]
  - A systematic review of 14 studies conducted in Angola, Guinea, Liberia, and Sierra Leone from 2005-2015 indicated that q-PCR on admission was the most commonly used method for clinical diagnosis of EVD.[125]
- Lateral flow immunoassays (point-of-care, single-use) have been developed for EBOV.[126]
  - A new immunoassay targeting secreted EBOV glycoprotein (Ebola sGP Detection Kit)

provides rapid diagnosis of EVD, with a specificity of 100% and a sensitivity of 85.7%. This assay's EBOV detection limit is ~10 times lower than the seven WHO-approved *in vitro* detection tests.[127] No other lateral flow diagnostic test demonstrates as low of a detection limit for EBOV from infected NHPs.[128]
  - EBOV sGP has been detected as early as four days post-infection in NHP samples in an ELISA test.[129]
  - A new immunoassay using optical micro-ring resonators specifically targeting EBOV sGP in a sandwich ELISA rapidly detected EBOV infection with a limit of detection (LOD) of 1.00 ng/mL in 1% serum.[130]
- Antibody detection/ELISA tests have been used in EBOV diagnostics for more than 20 years, and are sensitive and specific.[17, 131]
  - Human anti-EBOV GP immunoglobulin G (IgG) ELISA developed by the Filovirus Animal Nonclinical Group is used in multiple laboratories.[132-133]
  - The ReEBOV® Antigen Rapid Test (ReEBOV RDT®) using polyclonal antibodies specific for EBOV VP40 antigen has been validated by the WHO and FDA.[134]
  - The EBOV D4 immunoassay uses M13 phage display to increase antibody sensitivity, and showed higher sensitivity than RT-PCR by detecting EBOV in IM-challenged NHPs (1000 PFU) one-day post-infection (LOD of 20 pg/mL) compared to RT-PCR and infection (PFU) assays that signified infection by day three.[128]
  - Antigen detection sensitivity declines 1-2 weeks after the onset of symptoms, making late-stage serum diagnosis less reliable.[135]
- Viral isolation followed by electron microscopy, plaque reduction neutralization testing, or immunofluorescence provides definitive diagnosis, but requires specialized resources.[17, 136]
  - An EBOV fluorescence reduction neutralization assay testing for neutralizing antibodies has been developed that requires a small sample volume with the potential of being automated.[137]
- A CRISPR-CAS13a Specific High-sensitivity Enzymatic Reporter unlocking (SHERLOCK) platform has been developed to provide field testing for EBOV in real time, but it has not been FDA-approved for detection of EBOV, though it has received an emergency use authorization for SARS-CoV-2.[138]
- The U.S. Department of Defense (DoD) has developed EBOV diagnostic assays.[139]

What do we need to know?

- How can the dissemination and availability of diagnostics and relevant training be improved?
- Do current assays lose sensitivity due to viral mutations?
- For immune- or PCR-based assays, do they cross-react or detect all EBOV isolates and species?
- Can the period between initial infection and diagnostic detection be shortened?
- Can viral RNA and antibody detection methods be validated in domestic animal species?

Medical Treatment
Are there effective treatments?

What do we know?

- Intensive supportive care remains essential for EVD treatment.[17]
  - Intensive supportive care was associated with improved survival and less time in ETUs in Sierra Leone during the 2013-2016 EBOV outbreak.[140]
  - A recently proposed remote controlled optimized pulse-pressure fluid resuscitation treatment may provide an innovative approach to providing supportive care for EVD patients in low resource settings.[141]

- Vaccines can be used as post-exposure prophylaxis (PEP) and in conjunction with other therapeutics, but may be less appropriate for use in patients who have already begun to show symptoms.[17, 142-143]
  - An EVD patient in the DRC treated with rVSV-ZEBOV recovered within 14 days. He relapsed six months later with acute EVD that led to transmission of 91 additional EVD cases.[143]
  - Rhesus monkeys vaccinated with rVSV-ZEBOV were challenged one day post-vaccination with a lethal dose of EBOV, immediately followed by treatment three days post-exposure with MIL77 (a 3-mAB cocktail), and did not become ill and all survived.[142]
- REGN-EB3 (INMAZEB, Regeneron Pharmaceuticals), a combination of three human mAbs (atoltivimab, maftivimab, and odesivimab) targeting EBOV glycoprotein, is the first FDA-approved EVD treatment.[144-145]
  - Trials of REGN-EB3 show a 28-day mortality rate 17.8% lower than for the antibody cocktail ZMapp, which was used successfully in the 2013-2016 epidemic. A 15-day median time to the first negative EBOV RT-PCR test in REGN-EB3 was observed in recipients compared to 27 days in the ZMapp group.[144]
  - A recent study of PEP used REGN-EB3 and another antibody, Mab114, to treat 23 un-vaccinated patients who were in contact with EVD patients within one day. After 14 days post-contact, none of the patients developed EVD, and all produced negative PCR tests.[146]
  - Another recent clinical study supports the improved efficacy of Mab114 and REGN-EB3 over ZMapp and the antiviral drug remdesivir.[95]
- Ebanga, a human mAb (Ansuvimab-zykl), has been approved by the FDA for the treatment of Ebola Zaire virus.[147]
  - A trial of Ebanga (mAb1114) in 2018 showed a decreased 28-day mortality rate (35.1%) and reduced time to negative RT-PCR test (16 days) when compared to ZMapp (49.7%, 27 days).
- Early treatment (with either Ebanga, Remdesivir, Mab114, and ZMapp) is effective at reducing the case fatality rate; for each day symptoms persistent prior to enrollment, patient odds of death increased by 11%. Only 19% of patients who sought treatment within one day of symptom onset died, compared to 47% of patients who sought treatment after five days of symptoms.[148-149]
- Clinical trials of antiviral drugs such as remdesivir and favipiravir have generally found limited or inconclusive evidence for efficacy.[17, 148, 150]
  - BCX4430 (a broad spectrum antiviral nucleoside analogue)[151] has also been used with inconclusive results.[152]
  - The antiviral Brincidofovir was used unsuccessfully to treat four EVD patients, who all died from EVD.[153-154]
- Plasma from EVD survivors (containing antibodies to EBOV) is frequently used as a final treatment measure, but evidence for efficacy is lacking.[155-156]
- No approved therapeutics for SVD exist. However, a combination therapy using remdesivir and MBP134, an antibody-based treatment, has shown promise in NHPs.[157]
  - The United States has provided this treatment to Uganda as part of its response to the SVD outbreak.[158]

What do we need to know?

- Can methods be developed to address the gap between successful animal trials and efficacy in humans?
- What additional non-specific treatments (i.e., supportive care measures) can be implemented to improve patient outcomes?
- Would a sufficient supply of FDA-approved therapeutics be available in the event of an outbreak in the United States?

Vaccines
Are there effective vaccines?
What do we know?

- The U.S. FDA approved Merck's Ervebo (rVSV-ZEBOV) vaccine in 2020. The European Medicines Agency licensed Ervebo in 2019 and Zabdeno and Mvabea (Ad26.ZEBOV/MVA-BN-Filo) by Janssen/Johnson & Johnson (J&J) in 2020. Adverse events remain a concern.
  - Merck's rVSV-ZEBOV/Ervebo is a live attenuated vaccine given as a single dose and is approved for use in individuals 18 years of age and older.[159] This vaccine is a vesicular stomatitis virus (VSV)-based vaccine expressing the glycoprotein of EBOV (rVSV-ZEBOV).[160]
    - Adverse events associated with Ervebo are extremely common, and include headache (37%), feverishness (34%), muscle pain (33%), fatigue (19%), joint pain (18%), nausea (8%), arthritis (5%), rash (4%) and abnormal sweating (3%).[161-162]
    - Serious side effects have also been noted, and recipients of the vaccine should be monitored for anaphylactic responses for 30 minutes after administration.[163-164] A small study identified that most immunized individuals (rVSV-EBOV) reported at least one adverse event (105/109 respondents), with an average of three adverse events per person; four (4/109 respondents) experienced serious adverse events.[165]
    - A booster dose of Ervebo may extend the duration of protection, and can be given six months or more after the initial dose.[162-166]
    - In November 2019, Merck's vaccine gained conditional approval from the European Commission and was given to hundreds of thousands of people to control the 2019 outbreak in the DRC.[160, 167] Following clinical trials to assess safety in 15,000 people, the Merck vaccine was also approved by the FDA in December 2019.[161]
    - Analyzing Merck's data from 90,000 vaccinated individuals, the efficacy is 97.5% at 10 days after vaccination.[160, 168] The duration of protection, or level of protection for immunocompromised, pregnant, or elderly (over 65 years) patients, is unknown.[163-164] Follow-up serological studies to assess the duration of immunogenicity in vaccinated individuals showed 87.2% had an antibody response after 21 days, with 95.6% of those showing antibody persistence after six months.[169]
    - While Merck's Ervebo vaccine is not licensed for use as a PEP, it has been used in ring vaccination campaigns in areas of active infection and has likely been administered to individuals with recent exposure to EBOV. The Phase III efficacy study that was conducted in these areas found no new cases of EVD 10 days after vaccination, suggesting that the vaccine was likely effective as PEP. This is consistent with nonclinical data that when Ervebo is given as PEP following infection in animal models there was partial protection.[170]
  - J&J's Ad26.ZEBOV/MVA-BN-Filo (Zabdeno/Mvabea) is given as two doses, eight weeks apart, and is approved for use in individuals that are one year and older.[159] The regimen consists of two vaccines: an adenovirus-vectored vaccine encoding the glycoprotein of EBOV followed by a booster shot with a Modified vaccinia Ankara–vectored vaccine encoding glycoproteins and a nucleoprotein from several types of ebolavirus.[160]
    - J&J's vaccine received European approval in July 2020,[171] and prequalification by the WHO in 2021[172], but is not currently FDA-approved.
    - When assessed at 21 days following the second dose, J&J's vaccine induced an antibody response in 98% of recipients, which persists for at least two years. Participants who received an additional booster after two years showed a rapid and strong response. Efficacy studies remain incomplete as the outbreak ended prior to their conclusion.[173-174]
    - An efficacy study, the first to include pregnant women, was planned in the DRC for November 2019 to February 2022 but was cut short in 2020 due to conditions not

conducive to the trial (the outbreak was poorly controlled, and the COVID-19 pandemic began during the trial). However, the participants are still being observed for immunogenicity, safety, and impact on birth outcomes in pregnant women, as well as immunogenicity of a delayed second dose.[175]

- Two additional vaccines, Ad5-EBOV (lyophilized vaccine) and GamEvac-Combi vaccine have been developed and approved for use in China and Russia, respectively. However, these are not licensed for use in other countries. Roughly 10 additional vaccines worldwide are currently in development and being tested in Phase I–III clinical trials, including vaccines being developed by GlaxoSmithKline, Mapp Biopharmaceuticals, Novavax, Gilead, Regeneron, Moderna, and others.[176]
- University of Oxford's single-dose vaccine candidate ChAdOx1 biEBOV is currently in clinical trials to test for safety and immunogenicity against both Zaire and Sudan Ebola Virus species.[177-178]

- Two studies conducted in 2018 followed participants for over 12 months to evaluate the safety and immunogenicity of three different vaccine regimens. One study included 1400 adults and the other 1401 children (1-17 years old). Vaccine regimens evaluated were: J&J's Ad26.ZEBOV followed by MVA-BN-Filo 56 days later, Merck's rVSVΔG-ZEBOV-GP followed by placebo 56 days later, and Merck's rVSVΔG-ZEBOV-GP followed by a second dose of rVSVΔG-ZEBOV-GP 56 days later. Although there was no universally accepted correlation of protection, all three regimens elicited significant antibody titers by day 14 and antibodies remained detectable for a year. All three vaccine regimens also had good safety profiles in adults as well as in children as young as one year.[179-180]
- During recent outbreaks, a "ring vaccination" strategy has been used to attempt to contain transmission.
  - During outbreaks, the single-dose Merck vaccine Ervebo was given preventatively to front-line healthcare workers, individuals exposed to a known case, and any secondary contacts.[160, 181] Of the 5,837 individuals that immediately received the vaccine, there were zero cases of infection onset after 10 days following injection. In comparison, 23 cases developed in a control group whose vaccination was delayed.[182]
  - The slower-to-immunity, two-dose J&J vaccine has been used in a role complementary to the Merck vaccine, in which it was given to occupants of villages on the outskirts of ongoing infections,[159] which targets at-risk populations, but not currently involved in an active infection.[183]
- There are challenges in ebolavirus vaccine development. Since conventional trials for efficacy would not be ethical, trials rely on the FDA "animal efficacy rule," and there are issues with safety and antibody immune response shown in humans.[184]
  - Challenges in vaccine approval result from lack of controlled clinical trials and participants, such as the J&J trials, which ended prematurely when the outbreak was contained.[173-174] There is also a lack of a commercial market for the end product, which is supplemented by government funding for development.[176]
  - Despite having a large population at risk, EVD remains a rare disease, but comes with a significant health and financial impact. The cost-benefit and population safety analysis need to be considered when developing vaccination strategies.[185]
  - Vaccine efficacy data may vary depending on region due to factors such as improper storage in areas with resources, general health and nutrition of the population in the region, prevalence of immunosuppressive conditions such as HIV, and the serological profile of a population based on prior exposure to other filoviruses in the area.[169]
- There are several studies in the early stages of developing a non-reproducing multi-epitope vaccine against EBOV.[186-188]

- The U.S. CDC recommends pre-exposure vaccination with Ervebo for the following subsets of the U.S. population that are at the highest risk for occupational exposure: adults that are18 and older who are involved in the Ebola outbreak response or patient transport, healthcare workers at designated Ebola treatment centers in the U.S., and laboratory staff working with EBOV at BSL-4 facilities.[189]
- No vaccines specific to SUDV are approved for use.
  - Three vaccine candidates have reached human trials.[190]
  - The most advanced candidate is GlaxoSmithKline's chimpanzee adenovirus (ChAd) vectored vaccine. The license for this vaccine was donated to the Sabin Vaccine Institute, which was contracted by the U.S. Biomedical Advanced Research and Development Authority to develop the vaccine. One hundred doses are currently ready for use, with 40,000 doses in bulk form awaiting completion.[190]
  - The other two candidates are another ChAd vaccine developed by the University of Oxford,[177] and the Johnson and Johnson vaccine developed for EBOV, which may offer some protection against SUDV.[190]
  - Merck produced a batch of a VSV/SUDV-GP vaccine in 2015-2016 using the same technology as Ervebo. This vaccine has not been tested in humans. 100,000 doses exist in bulk form, and Merck intends to complete them and make them available to the WHO for potential use in clinical trials in Uganda.[191]
  - Uganda's Makerere University, with Uganda's Ministry of Health and the WHO, began conducting a clinical trial in December 2022 called Solidarity Against Ebola that will evaluate three vaccine candidates against SUDV. The vaccines tested are: Sabin Vaccine Institute's ChAd3-SUDV, Oxford University/Jenner Institute/Serum Institute of India's cAdOx1 biEBOV, and Merck/IAVI's SV-SUDV.[192]

What do we need to know?

- What is the efficacy of the vaccines when used for PEP?
- What is the actual efficacy of the vaccines for pre-exposure prophylaxis?
- What is the impact and safety of vaccines on pregnant or lactating women?
- How long are the vaccines effective? What is the onset and duration of protection?
- What are the correlates and thresholds of protection? In other words, what types of vaccine-induced immune responses are responsible for preventing infection and disease, and how strong do these responses have to be?
- How often do breakthrough infections occur?
- Can the current vaccines or vaccines in development provide any protection from ebolaviruses other than EBOV, such as SUDV?
- Are there additional unknown adverse effects?
- Are there vaccine-related risks that are dependent on the various routes of exposure to EBOV?

Forecasting
How effective are models at predicting outbreak trajectories?

What do we know?

- The risk of a large EVD outbreak in the United States is considered to be low.
  - During the 2013-2016 EVD epidemic in West Africa, the U.S. was estimated to have a less than 25% chance of importing an EVD case near the peak of the epidemic, with predicted outbreak sizes resulting from a single imported case typically being fewer than 100 individuals.[193]
- Forecasting was critical during the 2013-2016 West African EVD epidemic, highlighting the potential magnitude of the unmitigated epidemic and decision support as the epidemic unfolded.

  - There are a number of different model types used to forecast EVD outbreaks and epidemics, including compartmental (e.g., Susceptible-Exposed-Infectious-Removed [SEIR]) models,[194-195] agent-based models,[196] phenomenological models,[82] network models,[197] and point process models.[198]
- A number of factors tend to improve the accuracy of EVD forecasts, including clustering of cases within households, transmission in hospitals and among healthcare workers, and transmission at funerals.
  - In the 2013-2016 EVD epidemic, assessing the potential final epidemic size in the early stages of the outbreak was difficult because the long-term effects of public health interventions and changes in human behavior were unknown.[199]
  - There was substantial variation in EBOV transmission among districts within affected countries during the 2013-2016 epidemic,[199] limiting the utility of national-level forecasts, which generally predicted large final epidemic sizes.[200] Indeed, early epidemic dynamics within countries were sub-exponential and better represented by polynomial growth terms,[201] growing more slowly than data aggregated at the national level would predict.
  - Agent-based models, where populations are represented at the individual level, were generally able to predict key features of the 2013-2016 EVD epidemic[199] such as high spatial clustering (e.g., hospitals, households, and funerals)[196] and the beneficial effect of isolation in ETUs.[80]
  - As a result of these transmission patterns (e.g., hospitals, homes, and funerals), models estimated substantial clustering of EVD cases (e.g., non-random mixing through the population).[202] This clustering can affect forecasting results, particularly for location-specific predictions of necessary resources.[202]
  - Funerals were a large initial driver of the 2013-2016 EVD epidemic, though their importance decreased over time as a result of information dissemination and mitigation measures.[203-204]
  - The 2013-2016 EVD epidemic was characterized by high levels of infection in hospitals[204] and among healthcare workers.[203]
- Forecasts now account for the impact of vaccines (e.g., ring vaccination strategies).
  - Ring vaccination has been shown to be an effective way to mitigate EVD outbreaks.[205]
  - Vaccination of healthcare workers in high-risk areas may also be an effective strategy for mitigating outbreaks.[206]
- Ensemble forecasts outperformed individual forecasts during the 2013-2016 EVD epidemic.
  - Ensemble forecasts, where several individual forecasts are combined with a statistical model,[207] often provide more accurate predictions than their constituent forecasts,[208] even for ensembles of relatively simple phenomenological models.[209]
  - EVD forecasts may benefit from a multi-model approach, whereby different model types (e.g., logistic, Richards) are fit to different time periods to enhance forecast accuracy.[210]
- Real-time EVD forecasts have been limited by timely and accurate data.
  - Forecasts reliant on fitting deterministic models (e.g., exponential growth) to cumulative data are prone to overestimate confidence in key model parameters, resulting in inaccurate forecasts that underestimate uncertainty.[211]
  - Most EVD forecasts during the 2013-2016 epidemic relied on publicly available data published by the WHO or the countries affected by the epidemic, highlighting the need for fast, accurate, and open-access publication of data.[212] The CDC Ebola modeling response team noted a lack of timely, accurate data as a key challenge to making accurate forecasts.[213]
  - It may be possible, however, to use non-traditional datasets (like the email listserv ProMed mail and the outbreak visualization tool HealthMap) to forecast short-term Ebola incidence in real time.[214]

- In the 2013-2016 EVD epidemic, forecasts that were made earlier and with longer time horizons had lower accuracy.[212]
- Complex models with more parameter inputs were not necessarily more accurate than simpler forecasting models during the 2013-2016 EVD epidemic,[208, 212] though additional model parameters are usually needed for finer-resolution forecasts.[208]
- One limitation in forecasting the 2013-2016 EVD epidemic was the initial lack of information on contact networks, which showed a high degree of clustering and superspreading that was not visible in previous, smaller EVD outbreaks.[203]

What do we need to know?

- How do forecast models effectively incorporate long-lasting maintenance of infectious virus in human fluids?
- How many imported EVD cases are necessary to spark significant outbreak risk in the United States?
- How do local and regional conflicts affect the size and duration of EVD outbreaks?
- How can EVD forecast models avoid model overfitting (a modeling error that arises from overdependence on making the model outputs fit existing data), particularly when used early in an outbreak to estimate potential growth?

Environmental Stability
How long does the agent live in the environment?

What do we know?

- EBOV maintains infectivity in whole blood and plasma after five days, even when the blood is stored at higher temperatures.[215]
  - EBOV remains infectious in liquid blood in syringe needles up to 190 days.[216]
  - EBOV in blood also remains infectious on banknotes for up to six days.[216]
- EBOV loses all infectivity in urine and semen at 37°C by 4-5 days and five days, respectively.[215]
- EBOV remains viable in wastewater for at least eight days.[217]
  - EBOV remains viable in water for three (27°C) to six (21°C) days, depending on the temperature of the water.[218]
- Aerosol stabilities of the EBOV Kitwit and Makona variants were determined, resulting in similar decay rates between 1 and 2% per minute and an approximate half-life of 43 minutes.[16]
- EBOV remains viable on some surfaces (wood, plastic, stainless steel, glass, some PPE) longer than others (cotton). EBOV remains viable potentially up to eight days on some materials such as stainless steel, and up to three weeks in liquids and on plastic and glass surfaces.[218-222]
  - At an ETU in Sierra Leone, EBOV RNA was detected on material and surfaces that was in direct contact with patients (clothing, blankets, pit latrines). No RNA was detected on chlorine tap handles and ceiling fan blades. RNA was also found in bodily fluids and visibly bloodied soaker pads.[223]
  - A 4-log inactivation of EBOV on glass (22°C, 30-40% humidity, no light) required 5.9 days.[221]
  - EBOV persisted on surfaces for 1-3 days (27°C 80% relative humidity [RH]).[220]
  - There was no difference in the stabilities of aerosolized Mayinga 1976 EBOV and Makona 2014 EBOV over three hours at 22°C and 80% RH. Both viruses remained viable, and was comparable to the stability of EBOV dried on surfaces at 27°C.[224]

What do we need to know?

- What are the best surrogates for persistence testing?
- Are surrogates used for decontamination testing also acceptable for use in persistence testing?

Decontamination
What are effective methods to inactivate the agent in the environment?

What do we know?

- Disinfectants on EPA Lists L or Q are recommended for use with EBOV.[225-226]
- Decontamination studies need to show complete eradication of infectious virus due to the low infectious dose for EBOV.
  - There have been recent modifications to $TCID_{50}$ assay methodologies to accommodate the ability to show eradication even in the presence of chemical cytotoxicity such as serial passaging.[227]
- It is critical that correct contact times for wipes are used, as improper use may result in transfer of virus between surfaces.
  - Accelerated hydrogen peroxide-impregnated wipes demonstrated secondary transfer of EBOV up to 0.5 log10 $TCID_{50}$/mL when contaminated steel surfaces were wiped for 30 seconds. Wipes containing a single quaternary ammonium compound transferred up to 0.8 log10 $TCID_{50}$/mL EBOV when wiped for five seconds, but EBOV was undetectable when wiped for 15 seconds or longer.[228]
- Chlorine disinfectants are effective and widely used for routine/daily disinfection of non-porous surfaces (floors, bedside surfaces, equipment).
  - At least 0.5% sodium hypochlorite and a contact time of at least five minutes.[219, 229-232]
  - Contact time and concentration are key for effective disinfection. Even a high concentration (1%) of sodium hypochlorite did not decontaminate EBOV-contaminated surfaces within one minute of contact time.[219]
  - Effective against EBOV variants (Mayinga, Kikwit, Makona); however, differing disinfection characteristics are observed with lower (below 0.1% sodium hypochlorite) concentrations.[230]
- Other commonly used disinfectants have shown varying effectiveness of EBOV inactivation on non-porous surfaces (e.g., stainless steel, aluminum).
  - 67-70% ethanol is effective at inactivating EBOV within 5-10 minutes.[219, 230]
  - Chloroxylenol (≥0.12%) is effective at inactivating EBOV within five minutes.[227, 233]
  - Commonly used military aircraft disinfectants showed varying effectiveness at EBOV inactivation on seat belts and aluminum surfaces.[231]
  - Povidone iodine (PVP-I) formulations (e.g., 7.5% PVP-I surgical scrub, 10% PVP-I solution, or 3.2% PVP-I and 78% alcohol solution) are >99.99% effective against EBOV at a 15-second exposure time.[234]
  - Quaternary ammonium compounds (QAC) MicroChem Plus (5%) and Forward (5%) reduced infectious EBOV by >99.99% at 15-30 seconds when mixed in liquids being tested. Efficacy of QACs was diminished if the diluted solution was stored for up to one week.[235]
- Chlorine dioxide,[236] vaporized hydrogen peroxide fumigation,[237-238] or UV germicidal irradiation[239] can be used to decontaminate medical equipment and isolation units.
  - Degree of soiling of material can reduce effectiveness of fumigation methods; prior physical cleaning is required.[239]
  - UV germicidal irradiation inactivates EBOV at an exposure level of >17 mJ/cm^2.[239] Areas with higher contamination (e.g., bathrooms, patient rooms) should be treated with higher exposures (>800 mJ/cm^2).[240]
  - The process of decontamination requires nearly one week from the time the patient exits the room to when personnel can enter without PPE.[240]
  - Decontamination with vaporized hydrogen peroxide fumigation can be completed in three working days – approximately half the time of formaldehyde decontamination procedures.[237]

- Field decontamination kits utilize chlorine dioxide and can sterilize ebolavirus-contaminated medical equipment at remote clinical sites over a 30-60-minute period.[236]
- Surrogate studies suggest that chlorine dioxide gas may not be effective at inactivating EBOV present in body fluids.[241]

- Surrogate agents are required for efficacy testing of EBOV in lower containment laboratories. Multiple surrogates are used for efficacy testing.[236-237, 241 234, 238, 242-246]
  - *Geobacillus stearothermophilus* dried onto metal disks and sealed inside Tyvek pouches[237] were used to evaluate terminal sterility of patient care areas.
  - Bacterial spores often provide the standard test assay for sterility and/or decontamination of units, primarily because spores exhibit more resistance to chemical and physical decontamination methods than EBOV.[236]
  - Bacteriophage Phi 6 may be a conservative surrogate for EBOV,[238, 242-243] but suitability may be dependent on temperature and media compositions.[247]
  - Modified vaccinia virus Ankara (MVA) was shown to be a suitable surrogate for EBOV in efficacy testing with PVP-I solutions.[234]
- Environmental sampling of viral genomic RNA should not be used to evaluate infectious virus contamination.
  - High amounts of viral RNA may remain on surfaces despite complete inactivation of infectious particles. Evaluation of effective decontamination should be determined or corroborated by quantifying infectious virus.[230]

What do we need to know?

- What are the best practices for disinfecting EBOV-contaminated porous materials (i.e., seat fabric, bedding, seatbelts)?
- What disinfection procedures should be used for equipment used during transport of EBOV-confirmed or PUI patients between treatment facilities and medical evacuation?

Personal Protective Equipment (PPE)
What PPE is effective and who should be using it?

What do we know?

- CDC's PPE guidance differentiates between confirmed EVD cases/PUIs for EVD who are clinically unstable or exhibiting bleeding, vomiting, or diarrhea,[248] and PUIs that are clinically stable and not exhibiting bleeding, vomiting, or diarrhea.[249]
  - Variations in PPE should be avoided within a specific facility.
- CDC-recommended PPE for caring for a patient with confirmed EVD[249] includes single-use, disposable PPE and respiratory protection in the form of a PAPR or NIOSH-certified N95 respirator.[250-251]
  - Single-use disposable impermeable gown or coverall, examination gloves with extended cuffs (two pair), boot covers that extend to at least mid-calf, and an apron that covers the torso to the level of mid-calf should be used over the gown or coveralls if the coverall has an exposed, unprotected zipper in front.
  - Standardized attire should be worn under PPE (e.g., scrubs and dedicated washable footwear).
- CDC-recommended PPE for caring for a PUI who is clinically stable, and not exhibiting bleeding, vomiting, or diarrhea includes single-use, disposable PPE. Respiratory protection (PAPR or N95 respirator) is not required, but a face shield should be worn.[249]
- Detailed instructions for the recommended procedures for donning and doffing of PPE are available from CDC.[249, 252]
  - A trained individual should observe donning and doffing to confirm and document that each step has been completed correctly.
  - Designated areas separate from the patient care area should be dedicated to donning or

doffing of PPE.
  - Use of a checklist and closed loop communication strategy can result in a more deliberate and mindful doffing process.[253-254]
  - It is crucial that facial and respiratory protection is removed last for safe doffing.[255]
- The risk for errors and self-contamination is highest in the doffing phase.[40, 256-259] Consistent and correct use of PPE, reinforced with repeated training and practice, is key to minimizing exposure.
  - Ambiguity is a common reason for guideline non-compliance.[253, 260]
  - Highest risks for contamination were related to hand hygiene (insufficient duration, failure to properly disinfect).[261]
  - Frequent sanitizing of gloves with an alcohol-based hand-sanitizer (or 0.5% chlorine) is recommended.[258, 262-264]
  - Reinforced training programs reduce risk.[265-269]
  - A web-based training program developed by a transdisciplinary team with expertise in infection prevention, medicine, nursing, and human factors engineering is available on the CDC website.[270]
- PPE should be available in a variety of sizes and resistant to heat, sweat, and chemicals to minimize loss of dexterity.[271]
  - The use of cooling clothing with phase-changing material under PPE reduced heat-related discomfort symptoms (head, chest, back limbs) by 9-58% and reduced skin temperature (average of 0.65°C) when working in 26°C and 32°C environments.[272]
- Redesigns in PPE (e.g., doffing tabs, rear zipper, high neck collar) can increase comfort and safety.[271, 273-275]
- Use of full-body PPE in ETUs presents a number of issues, including heat exhaustion, reduced sensory perception, reduced dexterity, and increased fluid loss.[276]
- There is no evidence of environmental contamination of nearby surfaces when bleach solution spray or wipes are used to disinfect PPE (gloves or hoods), based on testing with bacteriophage.[277]
  - Disinfection of PPE did not eliminate the surrogate virus, which supports recommendations for extremely careful, protocol-based doffing and single-use, disposable PPE.
  - Pulsed xenon UV disinfection may be useful for reducing contamination on PPE prior to doffing.[246]
  - Using a surrogate virus, >4.0 log reduction in viral titer was demonstrated on face shields and surgical gowns after a five-minute exposure at one-meter distance from the source. UV exposure to healthcare workers wearing the PPE during UV disinfection was determined to be below the recommended exposure limits.[246]

What do we need to know?

- How can PPE be improved to reduce occupational risks (e.g., heat stress, dexterity)?
- Are there improved PPE designs to allow for easier removal without touching the outside of the PPE?
- Can a standardized simulation system for training clinical workers in PPE usage for care of EVD patients be devised?

Genomics
How does the disease agent compare to previous strains?

What do we know?

- EBOV is one of four members of the genus *Ebolavirus* known to cause disease in humans.[18]
  - Others include Sudan, Bundibugyo, and Taï Forest viruses,[18] which are typically less virulent and have generally been associated with smaller outbreaks.[18]
  - Two other ebolaviruses, RESTV and BOMV, are not known to cause disease in humans.[18,

- Since humans are dead-end hosts for EBOV, variants associated with outbreaks do not persist in nature after the outbreak ends, and do not "spill back" into the animal reservoir of the virus.[18]
  - Much like avian influenza, the virus must start "from scratch" in terms of human adaptation with each outbreak.[278-279]
- Each outbreak has been associated with a new EBOV variant, though the characteristics of the virus such as virulence and efficacy of transmission are similar between outbreaks.
  - Viruses associated with the latest EBOV outbreaks are >95% identical to the virus responsible for the 1976 outbreak in Yambuku, DRC.[280]
  - Genomic differences between variants have an effect on phenotype, but is not typically large.[281-282 283]
  - A notable exception was the 2021 Guinea outbreak, which was associated with transmission from a persistently infected individual who was initially infected during the 2013-2016 outbreak.[120]
  - Persistent infection and prolonged outbreaks may facilitate adaptive evolution of the virus in a manner that could enhance human-to-human transmission.[284]
- EBOV evolves slowly in its reservoir, and during recent outbreaks, mutations associated with adaptation to humans appeared only after relatively long chains of successive human-to-human transmission.[278, 285]
  - In the case of the 2013-2016 West African outbreak, mutations linked to enhanced replication in human cells appeared only after 3-4 months of continuous human-to-human transmission.[278]
- EBOV adaptation to humans appears to involve changes in its spike glycoprotein and/or parts of its genomic replication proteins, though there is little evidence that the adaptations observed in recent outbreaks have led to dramatic increases in transmissibility or disease severity.[278-279, 281-282, 286]
  - Mutations in GP (A82V in particular), the transcriptional activator VP30, and the polymerase L have been identified in human sequencing data from the West African epidemic.[278-279, 285]
  - Mutations were reconstituted using reverse genetics systems and found to enhance viral replication.[286]
  - Animal studies have failed to find evidence for enhanced disease severity, though studies have been either underpowered or performed in inappropriate model organisms.[282]
  - *In vitro* evolution studies have also identified VP30 and L polymerase, along with the viral nucleoprotein, as potential foci of human adapting mutations. However, no *in vivo* data are available.[287]
- Sequencing and genetic studies have found that there are three distinct clades of EBOV within the species, though there is minimal-to-no direct evidence of practical differences between members of these groups.[280]
  - The variant responsible for the recent West African outbreaks is most closely related to viruses responsible for outbreaks in Central Africa in 2003-2004, 2007, and 2017.[280]
  - The variant responsible for 2018-2020 large outbreak in eastern DRC is more distantly related.[280]
- The variant responsible for the 2021 West African outbreak appears to be the same virus that was responsible for the 2013-2016 outbreak and was likely maintained via persistent infection in a human host.[288]
  - Nearly identical to viruses circulating in the same area in 2015-2016, with slower than expected sequence evolution.[288]

- Sequences were not publicly available for the 2023 SUDV outbreak in Uganda as of May 2023.

What do we need to know?

- How does the virus adapt to increased efficiency of transmission, and which parts of the genome are associated with this?
- What mutations or types of mutations should prompt concern that a new variant may exhibit enhanced transmission?
- What is the diversity of EBOV within its animal reservoir?

Virus Importation
What are the main routes of entry into the United States?

What do we know?

- Air travel is the primary concern for importation of EVD from abroad.[289]
- It is notable that during the 2013-2016 West African Ebola epidemic, most EVD cases in Sierra Leone (the country with ~50% of all Ebola cases during this outbreak) were descended from an initial introduction of Ebola from Guinea in early 2014, with additional cases re-introduced from Guinea in 2015. These cases almost certainly occurred from infected individuals crossing land borders, as has been noted for the 2018-2020 Ebola outbreak transmission from the DRC to neighboring African nations.[290]
- International travel restrictions are necessary, but not sufficient to effectively prevent global spread of EVD. A more efficient control method is to attempt to prevent the spread of disease locally during an early phase of an epidemic.[291-292]
  - Air travelers from EVD-affected West African nations were permitted to enter at five designated U.S. airports and subjected to appropriate screening beginning in October 2014.[293]
  - The effectiveness of travel restrictions was estimated to have been greatest in African and Eastern Mediterranean countries and lowest in Europe.[291]
  - Regardless of restrictions, during the 2013-2016 outbreak, EVD spread to Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom and the United States from the three affected West African nations (Guinea, Liberia, Sierra Leone).[291]
  - Instituting secondary backup evaluation safeguards (temperature checks, symptom questionnaires, etc.) for travel screening may help strengthen travel restrictions, as can improvements in molecular screening and diagnostic testing.[294-295]
- The most effective air passenger screening (such as temperature checks) occurs when applied at the embarkation airport where infected air travelers are most likely to depart. One modeling study indicated that 2.8 Ebola-infected air travelers per month departed the countries of Guinea, Liberia, and Sierra Leone during the epidemic.[296]
  - Modeling, however, suggests that airport screening is unlikely to detect a substantial proportion of EVD cases, due in part to the long incubation time of the disease.[297]
- Importation of medically evacuated patients does not pose a significant risk of transmission within the United States, but one incidental importation resulted in local transmission within a healthcare facility.[298-299]
  - Eleven people were treated for EVD in the United States during the 2013-2016 West African epidemic. No deliberately evacuated cases were associated with local transmission.[298]
  - A patient who traveled from Libera to the United States presented at a Dallas hospital, and in the course of his care, two nurses were infected.[300]
  - The public health response to a single incidental EVD case importation in the United States is extremely labor intensive for public health authorities. In 2014, a nurse who contracted EVD while caring for an EVD patient in Texas traveled from Dallas to Cleveland for four

days via commercial airlines. During this travel, the nurse came in contact with 164 individuals, with various lengths and types of direct contact exposure. As a result, all 164 contacts required active follow-up and 20 had direct active monitoring with movement restrictions during a 21-day incubation period.[299]

- Successful cross-border viral surveillance was implemented to prevent imported EVD cases in Uganda in 2019. Three EVD cases crossing into Uganda from the DRC were detected at the time of first contact with a healthcare facility and a fourth case was detected at point of entry by temperature screening.[301-302]

What do we need to know?

- How can response times be improved to implement protective measures more rapidly?
- Can an effective screening methodology be developed for inbound international travelers?
- How can monitoring be more sensitive, cost-effective, and efficient with personnel resources?

Non-Pharmaceutical Interventions (NPI)
What public health interventions are capable of limiting spread?

What do we know?

- Until recently, NPIs were the sole means of controlling EBOV outbreaks.[17, 23]
- These NPIs include contact tracing, establishment of ETUs, changes in burial practices, and isolation of infected individuals, and were key to stopping the 2013-2016 West African EVD epidemic.
  - Activation of an ETU after importation of an EVD case in Nigeria was credited with rapidly reducing local transmission and avoiding a large EVD outbreak.[303]
  - Public health interventions aimed at improving the safety of burial practices and implementing infection control in hospitals played a role in limiting person-to-person spread during the 2013-2016 EVD epidemic in West Africa.[204]
  - Contact tracing and prompt isolation of infected individuals in hospitals or treatment centers was predicted to play a significant role in the reduction of EVD spread,[304] and observational evidence suggests that effective isolation in a hospital was critical for reducing transmission.[204] Thus, the supply of hospital beds was also an important factor in limiting EVD spread,[305] with bed shortages linked to extended transmission chains.[204]
  - Contact tracing in the DRC in 2018-2020 successfully identified the majority of cases with >1 contact overall, but only identified 48% of cases with infected contacts, which may be insufficient for limiting transmission.[306]
  - Effective isolation, quarantine, contact tracing, and ring vaccination may have contributed to a reduction in the number of people at risk of contracting EVD during the 2018-2020 DRC epidemic.[307]
  - Modeling suggests that earlier interventions would have substantially reduced EVD cases during prior EVD outbreaks[308] and epidemics.[309]
  - A modeling study found that reducing the time between death and safe burial and increasing the effectiveness of case isolation were the most important NPIs in terms of reducing EVD transmission, though importance varied by country.[310]
  - An early warning, alert, and response system implemented in the DRC in 2018 showed high sensitivity (85%) and specificity (91%) when detecting possible EVD cases, with response teams investigating >180,000 alerts in less than two hours.[311]
- Community support and buy-in/cooperation is critical for enhancing efficacy of NPIs.[31]
  - During the 2013-2016 EVD epidemic in West Africa, NPIs that were instituted without the support of local communities experienced resistance,[312] potentially prolonging local outbreaks.[313]
  - Community engagement, training, and behavior changes implemented prior to top-down interventions have been credited with limiting local disease spread.[314]

- Retrospective assessment of public health strategies (e.g., hygiene programs) suggest that consistency in messaging, additional research on means of effective ways to change behavior, and additional training may increase efficacy.[315]
- Modeling suggests that increased communication of EVD risk, which may reduce individual infection likelihood, can delay outbreaks and reduce their size.[316] While education campaigns in Uganda improved the ability of individuals to correctly identify EVD symptoms and reject misinformation, they were not associated with increases in prevention practices,[317] potentially limiting their impact on spread.
- Behavioral changes on their own may have contributed to reduced spatial spread of EBOV in the 2013-2016 epidemic in Guinea, prior to the arrival of international aid and ETUs.[318]

What do we need to know?

- Given the potential for long-term maintenance of infectious virus in human fluid, are there effective NPIs that can mitigate the risk of transmission recurrence after months or years?
- How do regional conflicts affect the efficacy of NPIs?

U.S. Health System Capacity
What U.S. infrastructure exists to respond to an outbreak?

What do we know?

- Care of symptomatic EVD patients is staff- and resource-intensive.[17, 319-320]
  - Although specific treatments are available, they are adjuncts to supportive care, not replacements.[17, 319]
  - Ideal clinical outcomes require extremely low patient-to-nursing staff ratios.[319-320]
- The United States has capacity to handle expected numbers of imported cases (generally no more than seven at any given time) if they are identified prior to significant transmission.
  - Researchers created a tool to estimate the number of beds required to treat potential U.S. EVD patients and found that fewer than seven beds would be needed at any point in time, which assumes limited importation and spread similar to what was observed in developed nations during the 2013-2016 epidemic.[321]
- Within the United States, 10 specialized Regional Ebola and Other Special Pathogen Treatment Centers (RESPTCs) have been established, with one in each of the 10 HHS regions. There are three more in development as of July 2023.[322-323]
- Early identification of EBOV clusters and rapid control via contact tracing can limit outbreak size.[324]
- Patients with actively symptomatic disease require advanced treatment in an ICU setting, and ICU beds are an extremely limited resource.[17, 319-320]
  - Few U.S. ICUs are able to provide biocontainment appropriate for care of an EVD patient.[40, 320, 325]
- Patients may require artificial respiration and/or renal dialysis treatment due to multiple organ dysfunction; availability of this equipment is typically limited.[319-320, 325]
- Infection control measures required to prevent nosocomial transmission increase staff workload and are taxing.[40, 319-320, 325]
  - Staff burnout has been a serious challenge during the COVID-19 pandemic.[326]
- Nosocomial transmission presents a significant risk to staff and non-EVD patients when large numbers of EVD patients are treated in the same facility.[24-25, 29, 40, 43, 106, 319]
  - A common occurrence in Africa prior to the development of specialized ETUs and protocols.[31]
- In Africa, dedicated ETUs are used to treat large numbers of EVD patients outside of normal hospitals, though due to the lack of advanced equipment and trained staff, patient outcomes do not match those achieved in Western ICUs.[319-320]

  - Case fatality rates for patients presenting for care in Western medical facilities are below 10%,[325] which assumes a high staff-to-patient ratio, and availability of complete ICU care.[319, 325]
- The ability of U.S. healthcare facilities to adequately handle a large number of EVD patients is unknown, but prior experience with a single patient at a non-specialty facility suggests that most facilities are unprepared or underprepared.[40, 300, 320, 325]
  - Two Texas Health Presbyterian hospital staff were infected while providing care for a single imported case due to inadequate training in use of PPE and unavailability of adequate PPE.[300]
- Management of clinical and diagnostic waste associated with the care of a patient infected with an ebolavirus is extremely complex and costly due to the high hazard associated with untreated waste. This waste generally requires incineration.[38]

What do we need to know?

- Are measures taken in U.S. hospitals following the 2014 EBOV outbreak in West Africa and subsequent importation of cases to the United States sufficient to increase resilience to imported EVD cases or large numbers of EVD cases from a local outbreak?
- How many patients could be reasonably expected to require advanced care in the event of a U.S. EVD outbreak?
- Do U.S. hospitals have sufficient ICU capacity to safely treat more than a small number of EVD patients?
- How effective are hospital infection control measures in the United States, especially if an outbreak occurs that requires more isolation beds than are currently available?

Commonly Used Acronyms and Abbreviations

Acronym/Term	Definition	Description
BSL	Biosafety Level	Level of safety practices and engineering features used to contain pathogenic microorganisms in a laboratory setting
CDC	Centers for Disease Control and Prevention	N/A
DHS S&T	U.S. Department of Homeland Security Science and Technology Directorate	N/A
DoD	U.S. Department of Defense	N/A
DRC	Democratic Republic of the Congo	N/A
EBOV	Ebola Virus	N/A
ELISA	Enzyme-Linked Immunosorbent Assay	An assay used to detect the presence of antibodies to a specific protein
EPA	U.S. Environmental Protection Agency	N/A
ETU	Ebola Treatment Unit	Specialized medical facilities established to care for EVD patients during outbreak
EVD	Ebola Virus Disease	N/A
FDA	U.S. Food and Drug Administration	N/A
HIV	Human Immunodeficiency Virus	N/A
ICU	Intensive Care Unit	Medical facility capable of providing advanced care to critically ill patients
ID_{50}	Median Infectious Dose	The dose required to infect 50% of the population
Ig	Immunoglobulin	Antibodies (glycoprotein molecules produced by white blood cells)
IN	Intranasal	Route of drug or test article administration in which a substance is introduced into the nostrils
IP	Intraperitoneal	Route of drug or test article administration in which a substance is injected into the free space in the abdominal cavity
J&J	Janssen/Johnson & Johnson	Pharmaceutical company
LD_{50}	Median Lethal Dose	The dose required to cause a lethal effect in 50% of the population
LOD	Limit of Detection	The smallest amount of a virus that can be detected by a given test
MQL	Master Question List	N/A
MVA	Modified Vaccinia Virus Ankara	A vaccina virus that cannot replicate in normal cells
NGDS	Next Generation Diagnostics System	DoD diagnostic platform
NHP	Non-Human Primate	N/A
NIOSH	National Institute for Occupational Safety and Health	N/A
NPI	Non-Pharmaceutical Intervention	Infectious disease control measures reliant on items other than drugs and vaccines; includes PPE and quarantines
PAPR	Powered Air-Purifying Respirator	A type of respirator that provides high-efficiency particulate air filtered via a blower system instead of static filter cartridges as in a conventional respirator

Acronym/Term	Definition	Description
PCR	Polymerase Chain Reaction	Test used to detect the presence of specific nucleic acid sequence
PEP	Post-Exposure Prophylaxis	The use of drugs or vaccines after exposure to a pathogen, but prior to onset of symptoms to prevent or lessen severity of disease
PFU	Plaque Forming Unit	A unit representing a single infectious viral particle derived from viral quantification via plaque assay
PPE	Personal Protective Equipment	Equipment intended to protect individuals against hazardous environments
PUI	Patient Under Investigation	An individual suspected of being infected with EBOV, but who has not yet had a positive laboratory diagnostic test
PVP	Povidone Iodine	Disinfectant
qRT-PCR	Quantitative Real-Time Polymerase Chain Reaction	Version of PCR that allows for quantification of RNA copy number
ReEBOV RDT	ReEBOV® Antigen Rapid Test	A commercial test for EBOV
RESPTC	Regional Ebola and Other Special Pathogen Treatment Center	US Department of Health and Human Services accredited healthcare facilities able to treat patients infected with exotic pathogens under biocontainment conditions
RH	Relative Humidity	Water content of a body of air, as a percentage of the amount of water vapor that can be retained by the air at a specific temperature and pressure without condensation
SEIR	Susceptible-Exposed-Infectious-Removed model	A type of epidemiological model used to generate outbreak forecasts
$TCID_{50}$	Median Tissue Culture Infectious Dose	The dose necessary to infect 50% of tissue cells; used as a standard measure of infectivity (e.g., it required 10^3 $TCID_{50}$ to produce clinical signs in exposed chickens)
UV	Ultraviolet	Light with wavelength in the 100-400 nm range
VSV	Vesicular Stomatitis Virus	A virus commonly used as a vaccine platform
WHO	World Health Organization	N/A

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