Ebola Virus Disease

CDC Slides for U.S. Healthcare Workers*

October 31, 2014

Presentation is current through October 31, 2014 and will be updated every Friday by 5pm. For the most up-to-date information, please visit www.cdc.gov/ebola.

*Presentation contains materials from CDC, MSF, and WHO
Ebola Virus

- Prototype Viral Hemorrhagic Fever Pathogen
  - Filovirus: enveloped, non-segmented, negative-stranded RNA virus
  - Severe disease with high case fatality
  - Absence of specific treatment or vaccine

- >20 previous Ebola and Marburg virus outbreaks

- 2014 West Africa Ebola outbreak caused by Zaire ebolavirus species (five known Ebola virus species)
Ebola Virus

- Zoonotic virus – bats the most likely reservoir, although species unknown
- Spillover event from infected wild animals (e.g., fruit bats, monkey, duiker) to humans, followed by human-human transmission
Figure. Ebola virus disease (EVD) cumulative incidence* — West Africa, October 18, 2014

* Cumulative number of reported EVD cases per 100,000 persons since December 22, 2013.

MMWR 2014;63(43):978-981
2014 Ebola Outbreak, West Africa

# EVD Cases and Deaths*

<table>
<thead>
<tr>
<th>Country</th>
<th>Reporting Date</th>
<th>Total Cases</th>
<th>Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>27 Oct 14</td>
<td>1,906</td>
<td>1,391</td>
<td>997</td>
</tr>
<tr>
<td>Liberia</td>
<td>25 Oct 14</td>
<td>6,535</td>
<td>2,515</td>
<td>2,413</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>27 Oct 14</td>
<td>5,235</td>
<td>3,700</td>
<td>1,500</td>
</tr>
<tr>
<td>Nigeria**</td>
<td>15 Oct 14</td>
<td>20</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Spain</td>
<td>27 Oct 14</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Senegal**</td>
<td>15 Oct 14</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>United States</td>
<td>24 Oct 14</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Mali</td>
<td>23 Oct 14</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>13,733</td>
<td>7,632</td>
<td>4,920</td>
</tr>
</tbody>
</table>


*Reported by WHO using data from Ministries of Health

**The outbreaks of EVD in Senegal and Nigeria were declared over on October 17 and 19, respectively.
As of October 24, 2014, EVD has been diagnosed in the United States in four people, one (the index patient) who traveled to Dallas, Texas from Liberia, two healthcare workers who cared for the index patient, and one medical aid worker who traveled to New York City from Guinea.

- **Index patient** – Symptoms developed on September 24, 2014 approximately four days after arrival, sought medical care at Texas Health Presbyterian Hospital of Dallas on September 26, was admitted to hospital on September 28, testing confirmed EVD on September 30, patient died October 8.

- **TX Healthcare Worker, Case 2** – Cared for index patient, was self-monitoring and presented to hospital reporting low-grade fever, diagnosed with EVD on October 10, recovered and released from NIH Clinical Center October 24.

- **TX Healthcare Worker, Case 3** – Cared for index patient, was self-monitoring and reported low-grade fever, diagnosed with EVD on October 15, recovered and released from Emory University Hospital in Atlanta October 28.

- **NY Medical Aid Worker, Case 4** – Worked with Ebola patients in Guinea, was self-monitoring and reported fever, diagnosed with EVD on October 24, currently in isolation at Bellevue Hospital in New York City.

As of October 31, 2014, four U.S. health workers and one journalist who were infected with Ebola virus in West Africa were transported to hospitals in the United States for care.

- All the patients have recovered and have been released from the hospital after laboratory testing confirmed that they no longer have Ebola virus in their blood.
Ebola Virus Transmission

- Virus present in high quantity in blood, body fluids, and excreta of symptomatic EVD-infected patients

- Opportunities for human-to-human transmission
  - Direct contact (through broken skin or unprotected mucous membranes) with an EVD-infected patient’s blood or body fluids
  - Sharps injury (with EVD-contaminated needle or other sharp)
  - Direct contact with the corpse of a person who died of EVD
  - Indirect contact with an EVD-infected patient’s blood or body fluids via a contaminated object (soiled linens or used utensils)

- Ebola can also be transmitted via contact with blood, fluids, or meat of an infected animal
  - Limited evidence that dogs become infected with Ebola virus
  - No reports of dogs or cats becoming sick with or transmitting Ebola
Detection of Ebola Virus in Different Human Body Fluids over Time

<table>
<thead>
<tr>
<th>Symptom Onset</th>
<th>Mean Death Day</th>
<th>Last Virus Isolation</th>
<th>Last Detectable Log</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1-10</td>
<td>Day 12-21</td>
<td>Day 30</td>
<td>Day 57</td>
</tr>
</tbody>
</table>

- **Viremia/Blood**: Acute phase to Convalescent phase
- **Saliva/Swab**: Day 4-10
- **Urine**: Day 5-15
- ** Tears/Conj.**: Day 7-10
- **Semen**: Day 10-30
- **Skin/Sweat**: Day 7-21
- **Vaginal**: Day 14-21
- **Rectal/Feces**: Day 14-21
- **Milk**: Day 7-10

- **Acute Phase**: Initially detectable
- **Convalescent Phase**: Virus detectable throughout
- **Mean Death Day**: Peak detectability
- **Last Virus Isolation**: Virus detectable for 60 days
- **Last Detectable Log**: Virus detectable for 57 days
Human-to-Human Transmission

- Infected persons are not contagious until onset of symptoms
- Infectiousness of body fluids (e.g., viral load) increases as patient becomes more ill
  - Remains from deceased infected persons are highly infectious
- Human-to-human transmission of Ebola virus via inhalation (aerosols) has not been demonstrated
EVD Risk Assessment

**HIGH-RISK EXPOSURE**
Percutaneous (e.g., needle stick) or mucous membrane contact with blood or body fluids from an Ebola patient

**OR**
Direct skin contact with, or exposure to blood or body fluids of, an Ebola patient

**OR**
Processing blood or body fluids from an Ebola patient without appropriate personal protective equipment (PPE) or biosafety precautions

**OR**
Direct contact with a dead body (including during funeral rites) in a country with wide-spread Ebola transmission** without appropriate PPE

**LOW-RISK EXPOSURE**
Household members of an Ebola patient and others who had brief direct contact (e.g., shaking hands) with an Ebola patient without appropriate PPE

**OR**
Healthcare personnel in facilities with confirmed or probable Ebola patients who have been in the care area for a prolonged period of time while not wearing recommended PPE

**NO KNOWN EXPOSURE**
Residence in or travel to a country with wide-spread Ebola transmission** without HIGH- or LOW-risk exposure

**CDC Website to check current affected areas:** [www.cdc.gov/vhf/ebola](http://www.cdc.gov/vhf/ebola)
Ebola Virus Pathogenesis

- Direct infection of tissues
- Immune dysregulation
- Hypovolemia and vascular collapse
  - Electrolyte abnormalities
  - Multi-organ failure, septic shock
- Disseminated intravascular coagulation (DIC) and coagulopathy

Early Clinical Presentation

- Acute onset; typically 8–10 days after exposure (range 2–21 days)

- Signs and symptoms
  - Initial: Fever, chills, myalgias, malaise, anorexia
  - After 5 days: GI symptoms, such as nausea, vomiting, watery diarrhea, abdominal pain
  - Other: Headache, conjunctivitis, hiccups, rash, chest pain, shortness of breath, confusion, seizures
  - Hemorrhagic symptoms in 18% of cases

- Other possible infectious causes of symptoms
  - Malaria, typhoid fever, meningococcemia, Lassa fever and other bacterial infections (e.g., pneumonia) – all very common in Africa
Clinical Features

- Nonspecific early symptoms progress to:
  - Hypovolemic shock and multi-organ failure
  - Hemorrhagic disease
  - Death

- Non-fatal cases typically improve 6–11 days after symptoms onset

- Fatal disease associated with more severe early symptoms
  - Fatality rates of 70% have been reported in rural Africa
  - Intensive care, especially early intravenous and electrolyte management, may increase the survival rate
## Clinical Manifestations by Organ System in West African Ebola Outbreak

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Fever (87%), fatigue (76%), arthralgia (39%), myalgia (39%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache (53%), confusion (13%), eye pain (8%), coma (6%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Chest pain (37%),</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Cough (30%), dyspnea (23%), sore throat (22%), hiccups (11%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Vomiting (68%), diarrhea (66%), anorexia (65%), abdominal pain (44%), dysphagia (33%), jaundice (10%)</td>
</tr>
<tr>
<td>Hematological</td>
<td>Any unexplained bleeding (18%), melena/hematochezia (6%), hematemesis (4%), vaginal bleeding (3%), gingival bleeding (2%), hemoptysis (2%), epistaxis (2%), bleeding at injection site (2%), hematuria (1%), petechiae/ecchymoses (1%)</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Conjunctivitis (21%), rash (6%)</td>
</tr>
</tbody>
</table>

Examples of Hemorrhagic Signs

Hematemesis

Gingival bleeding

Bleeding at IV Site
Laboratory Findings

- Thrombocytopenia (50,000–100,000/µL range)
- Leukopenia followed by neutrophilia
- Transaminase elevation: elevation serum aspartate aminotransferase (AST) > alanine transference (ALT)
- Electrolyte abnormalities from fluid shifts
- Coagulation: PT and PTT prolonged
- Renal: proteinuria, increased creatinine
EVD: Expected diagnostic test results over time

Critical information: Date of onset of fever/symptoms

viremia
IgM
IgG

Fever
RT-PCR
ELISA IgM
ELISA IgG

IgM: up to 3 – 6 months    IgG: 3 – 5 years or more (life-long persistence?)
Ebola Virus Diagnosis

- Real Time PCR (RT-PCR)
  - Used to diagnose acute infection
  - More sensitive than antigen detection ELISA
  - Identification of specific viral genetic fragments
  - Performed in select CLIA-certified laboratories

- RT-PCR sample collection
  - Volume: minimum volume of 4mL whole blood
  - Plastic collection tubes (not glass or heparinized tubes)
  - Whole blood preserved with EDTA is preferred
    - Whole blood preserved with sodium polyanethol sulfonate (SPS), citrate, or with clot activator is acceptable
Other Ebola Virus Diagnostics

- Virus isolation
  - Requires Biosafety Level 4 laboratory;
  - Can take several days

- Immunohistochemical staining and histopathology
  - On collected tissue or dead wild animals; localizes viral antigen

- Serologic testing for IgM and IgG antibodies (ELISA)
  - Detection of viral antibodies in specimens, such as blood, serum, or tissue suspensions
  - Monitor the immune response in confirmed EVD patients
CDC has developed interim guidance for U.S. laboratory workers and other healthcare personnel who collect or handle specimens.

This guidance includes information about the appropriate steps for collecting, transporting, and testing specimens from patients who are suspected to be infected with Ebola.

Specimens should NOT be shipped to CDC without consultation with CDC and local/state health departments.

Packaging & Shipping Clinical Specimens to CDC for Ebola Testing

http://www.cdc.gov/vhf/ebola/hcp/packaging-diagram.html
Interpreting Negative Ebola RT-PCR Result

- If symptoms started $\geq 3$ days before the negative result
  - EVD is unlikely $\rightarrow$ consider other diagnoses
  - Infection control precautions for EVD can be discontinued unless clinical suspicion for EVD persists

- If symptoms started $< 3$ days before the negative RT-PCR result
  - Interpret result with caution
  - Repeat the test at $\geq 72$ hours after onset of symptoms
  - Keep in isolation as a suspected case until a repeat RT-PCR $\geq 72$ hours after onset of symptoms is negative
Clinical Management of EVD: Supportive, but Aggressive

- Hypovolemia and sepsis physiology
  - Aggressive intravenous fluid resuscitation
  - Hemodynamic support and critical care management if necessary
- Electrolyte and acid-base abnormalities
  - Aggressive electrolyte repletion
  - Correction of acid-base derangements
- Symptomatic management of fever and gastrointestinal symptoms
  - Avoid NSAIDS
- Multisystem organ failure can develop and may require
  - Oxygenation and mechanical ventilation
  - Correction of severe coagulopathy
  - Renal replacement therapy

Investigational Therapies for EVD Patients

- No approved Ebola-specific prophylaxis or treatment
  - Ribavirin has no in-vitro or in-vivo effect on Ebola virus
  - Therapeutics in development with limited human clinical trial data
    - Convalescent serum
    - Therapeutic medications
      - Zmapp – chimeric human-mouse monoclonal antibodies
      - Tekmira – lipid nanoparticle small interfering RNA
      - Brincidofovir – oral nucleotide analogue with antiviral activity
  - Vaccines – in clinical trials
    - Chimpanzee-derived adenovirus with an Ebola virus gene inserted
    - Attenuated vesicular stomatitis virus with an Ebola virus gene inserted

Patient Recovery

- Case-fatality rate 71% in the 2014 Ebola outbreak
  - Case-fatality rate is likely much lower with access to intensive care

- Patients who survive often have signs of clinical improvement by the second week of illness
  - Associated with the development of virus-specific antibodies
  - Antibody with neutralizing activity against Ebola persists greater than 12 years after infection

- Prolonged convalescence
  - Includes arthralgia, myalgia, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months
  - Significant arthralgia and myalgia may persist for >21 months
  - Skin sloughing and hair loss has also been reported

Practical Considerations for Evaluating Patients for EVD in the United States

- CDC encourages all U.S. healthcare providers to
  - Ask patients with symptoms about a history of travel to West Africa in the 21 days before illness onset
  - Know the signs and symptoms of EVD
  - Know the initial steps to take if a diagnosis of EVD is suspected

- CDC has developed documents to facilitate these evaluations
  - The EVD algorithm for the evaluation of a returned traveler
  - The checklist for evaluation of a patient being evaluated for EVD
EVD Algorithm for Evaluation of the Returned Traveler

**CDC Website to check current affected areas:** [www.cdc.gov/vhf/ebola](http://www.cdc.gov/vhf/ebola)


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**FEVER** (subjective or ≥100.4°F or 38.0°C) or compatible Ebola symptoms* in a patient who has resided in or traveled to a country with wide-spread Ebola transmission** in the 21 days before illness onset

* headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or hemorrhage

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**YES**

1. Isolate patient in single room with a private bathroom and with the door to hallway closed
2. Implement standard, contact, and droplet precautions (gown, facemask, eye protection, and gloves)
3. Notify the hospital Infection Control Program and other appropriate staff
4. Evaluate for any risk exposures for Ebola
5. IMMEDIATELY report to the health department

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**NO**

Report asymptomatic patients with high- or low-risk exposures (see below) in the past 21 days to the health department
Interim Guidance for Monitoring and Movement of Persons with EVD Exposure

- CDC has created guidance for monitoring people exposed to Ebola virus but without symptoms

<table>
<thead>
<tr>
<th>RISK LEVEL</th>
<th>PUBLIC HEALTH ACTION</th>
<th>Monitoring</th>
<th>Restricted Public Activities</th>
<th>Restricted Travel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH risk</td>
<td>Direct Active Monitoring</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SOME risk</td>
<td>Direct Active Monitoring</td>
<td>Case-by-case assessment</td>
<td>Case-by-case assessment</td>
<td></td>
</tr>
<tr>
<td>LOW risk</td>
<td>Active Monitoring for some; Direct Active Monitoring for others</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NO risk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The 2014 Ebola outbreak in West Africa is the largest in history and has affected multiple countries.

Think Ebola: U.S. healthcare providers should be aware of clinical presentation and risk factors for EVD.

- Human-to-human transmission by direct contact:
  - No human-to-human transmission via inhalation (aerosols)
  - No transmission before symptom onset

- Early case identification, isolation, treatment and effective infection control are essential to prevent Ebola transmission.
For more information, please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.atiddr.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.