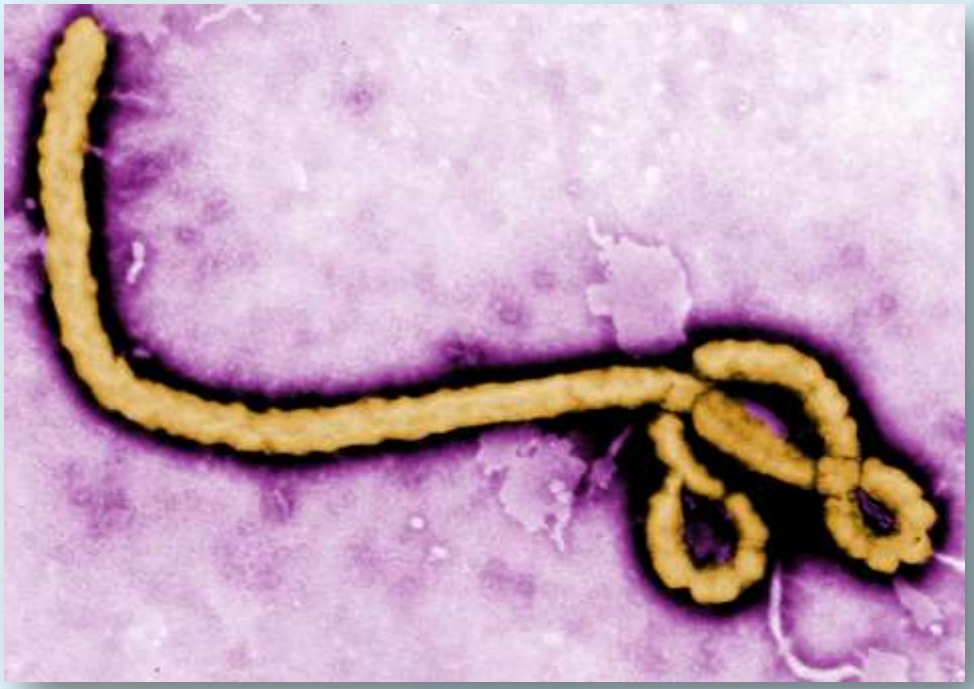
Ebola Virus Disease



CDC Slides for U.S. Healthcare Workers*

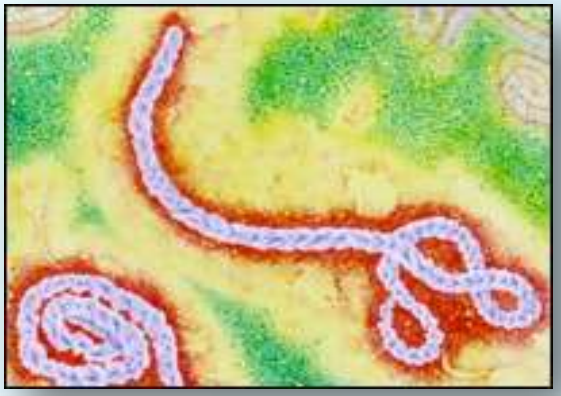
January 9, 2015

Presentation is current through January 9, 2015 and will be updated every Friday by 5pm. For the most up-to-date information, please visit www.cdc.gov/ebola.

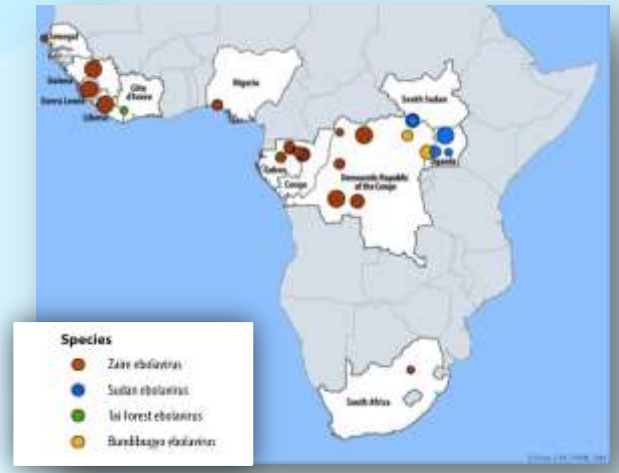
*Presentation contains materials from CDC, MSF, and WHO

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

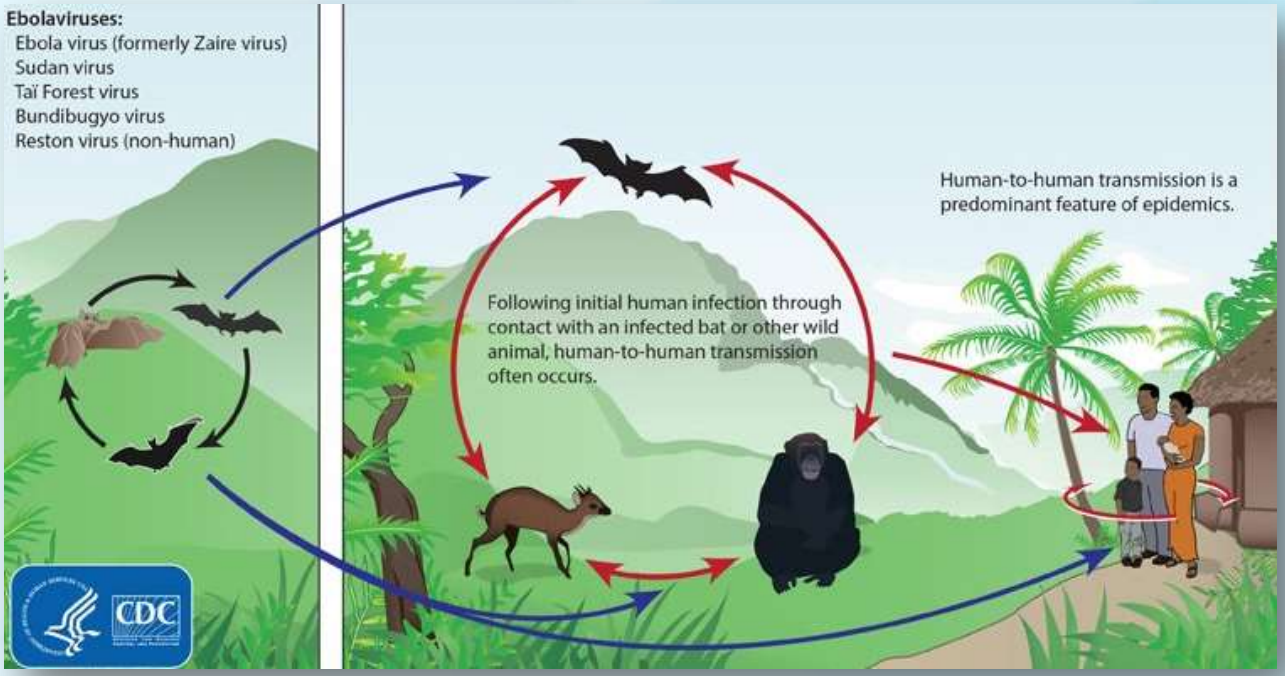
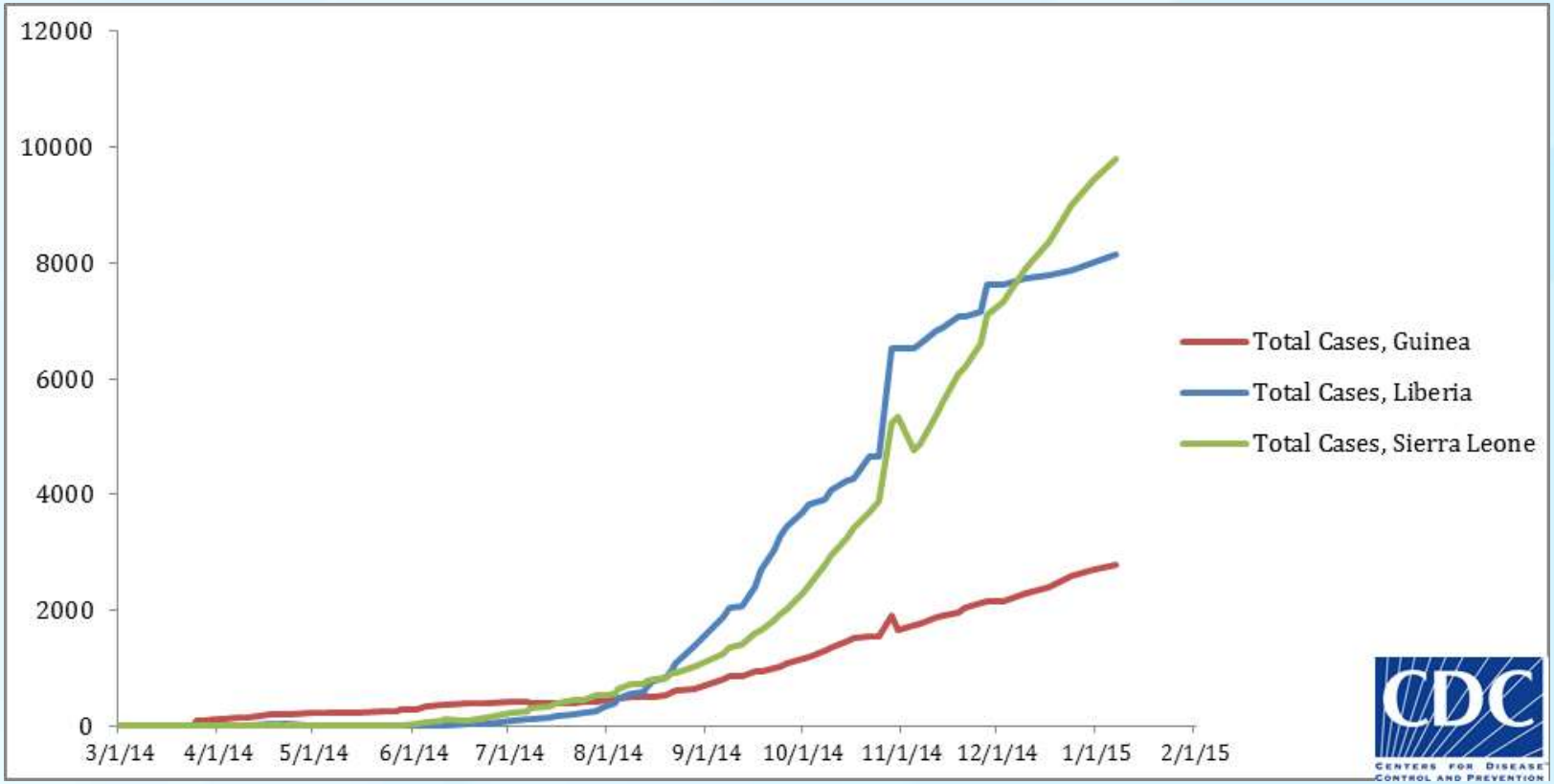


Figure. Ebola virus disease (EVD) cumulative incidence* — West Africa, January 7, 2015

* Cumulative number of reported EVD cases to WHO

2014 Ebola Outbreak
Reported Cases in Guinea, Liberia, and Sierra Leone



This graph shows the cumulative reported cases in Guinea, Liberia, and Sierra Leone provided in WHO situation reports beginning on March 25, 2014 through the most recent situation report on January 7, 2015.

EVD Cases and Deaths*

	Reporting Date	Total Cases	Confirmed Cases	Total Deaths
Guinea	7 Jan 15	2,793	2,493	1,797
Liberia	6 Jan 15	8,263	3,123	3,515
Sierra Leone	6 Jan 15	10,030	7,759	2,977
Mali	23 Nov 14	8	7	6
United Kingdom	29 Dec 14	1	1	0
Nigeria**	15 Oct 14	20	19	8
Spain**	27 Oct 14	1	1	0
Senegal**	15 Oct 14	1	1	0
United States**	24 Oct 14	4	4	1
TOTAL		**21,121**	**13,408**	**8,304**

Updated case counts available at http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html.

*Reported by WHO using data from Ministries of Health

**The outbreaks of EVD in Senegal, Nigeria, Spain, and the United States have ended.

EVD Cases (United States)

- 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, recovered and released from Bellevue Hospital in New York City November 11.

Information on U.S. EVD cases available at http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html.

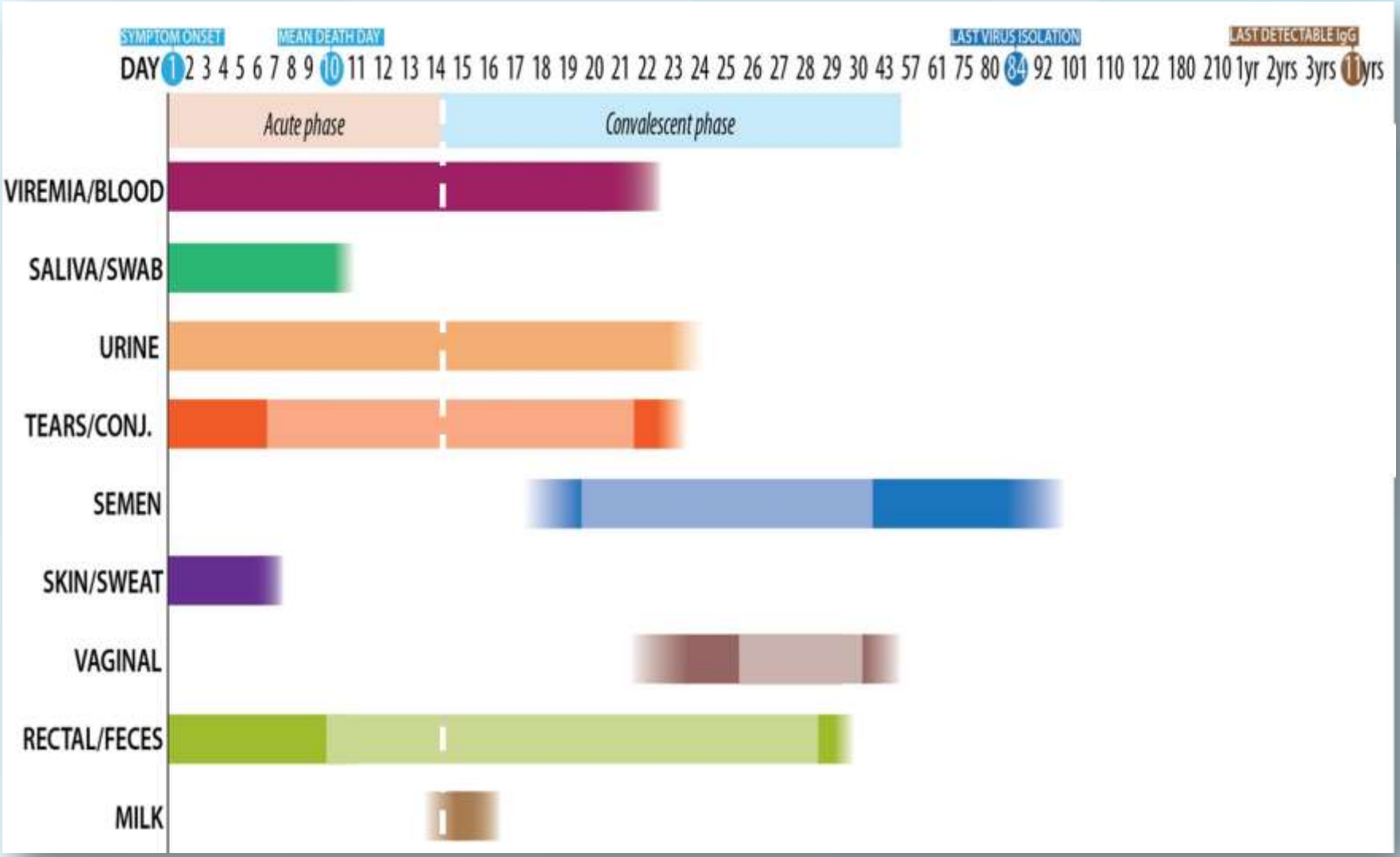
EVD Cases (United States)

- During this outbreak, five health workers and one journalist have been infected with Ebola virus while in West Africa and transported to hospitals in the United States. Five of these patients have recovered.
  - One of the health workers died on November 17 after being transported from Sierra Leone to Nebraska Medical Center.

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



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 exposure to blood or body fluids of a person with Ebola while the person was symptomatic

OR

Exposure to the blood or body fluids (including but not limited to feces, saliva, sweat, urine, vomit, and semen) of a person with Ebola while the person was symptomatic without appropriate personal protective equipment (PPE)

OR

Processing blood or body fluids from an Ebola patient without appropriate PPE or standard biosafety precautions

OR

Direct contact with a dead body without appropriate PPE in a country with widespread transmission or cases in urban areas with uncertain control measures

OR

Having lived in the immediate household and provided direct care to a person with Ebola while the person was symptomatic

SOME RISK EXPOSURE

In countries with widespread transmission or cases in urban areas with uncertain control measures:

- Direct contact while using appropriate PPE with a person with Ebola while the person was symptomatic or with the person's body fluids
- Any direct patient care in other healthcare settings

OR

Close contact in households, healthcare facilities, or community settings with a person with Ebola while the person was symptomatic

- Close contact is defined as being for a prolonged period of time while not wearing appropriate PPE within approximately 3 feet (1 meter) of a person with Ebola while the person was symptomatic

**CDC Website to check current affected areas: www.cdc.gov/vhf/ebola

EVD Risk Assessment (continued)

LOW (but not zero) RISK EXPOSURE

Having been in a country with widespread transmission or cases in urban areas with uncertain control measures within the past 21 days and having no known exposures

OR

Having brief direct contact (e.g. shaking hands) while not wearing appropriate PPE, with a person with Ebola while the person was in the stage of disease

OR

Brief proximity, such as being in the same room for a brief period of time, with a person with Ebola while the person was symptomatic

OR

In countries without widespread transmission or cases in urban settings with uncertain control measures: direct contact while using appropriate PPE with a person with Ebola while the person was symptomatic or with the person's body fluids

OR

Traveled on an aircraft with a person with Ebola while the person was symptomatic

NO IDENTIFIABLE RISK EXPOSURE

Contact with an asymptomatic person who had contact with person with Ebola

OR

Contact with a person with Ebola before the person developed symptoms

OR

Having been more than 21 days previously in a country with widespread transmission or cases in urban areas with uncertain control measures

OR

Having been in a country with Ebola cases, but without widespread transmission or cases in urban settings with uncertain control measures, and not having any other exposures as defined above

OR

Having remained on or in the immediate vicinity of an aircraft or ship during the entire time that the conveyance was present in a country with widespread transmission or cases in urban areas with uncertain control measures and having had no direct contact with anyone from the community

**CDC Website to check current affected areas: 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

Lancet. Mar 5, 2011; 377(9768): 849–862.

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

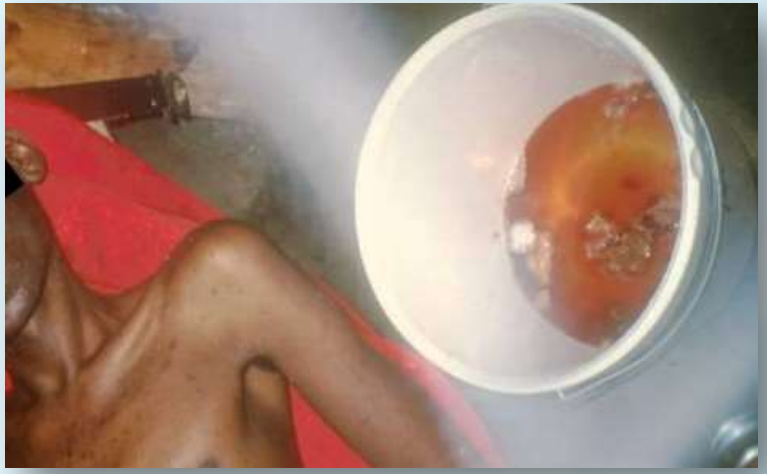
Clinical Manifestations by Organ System in West African Ebola Outbreak

Organ System	Clinical Manifestation
General	Fever (87%), fatigue (76%), arthralgia (39%), myalgia (39%)
Neurological	Headache (53%), confusion (13%), eye pain (8%), coma (6%)
Cardiovascular	Chest pain (37%),
Pulmonary	Cough (30%), dyspnea (23%), sore throat (22%), hiccups (11%)
Gastrointestinal	Vomiting (68%), diarrhea (66%), anorexia (65%), abdominal pain (44%), dysphagia (33%), jaundice (10%)
Hematological	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%)
Integumentary	Conjunctivitis (21%), rash (6%)

WHO Ebola Response team. *NEJM*. 2014

Examples of Hemorrhagic Signs

Hematemesis



Gingival bleeding

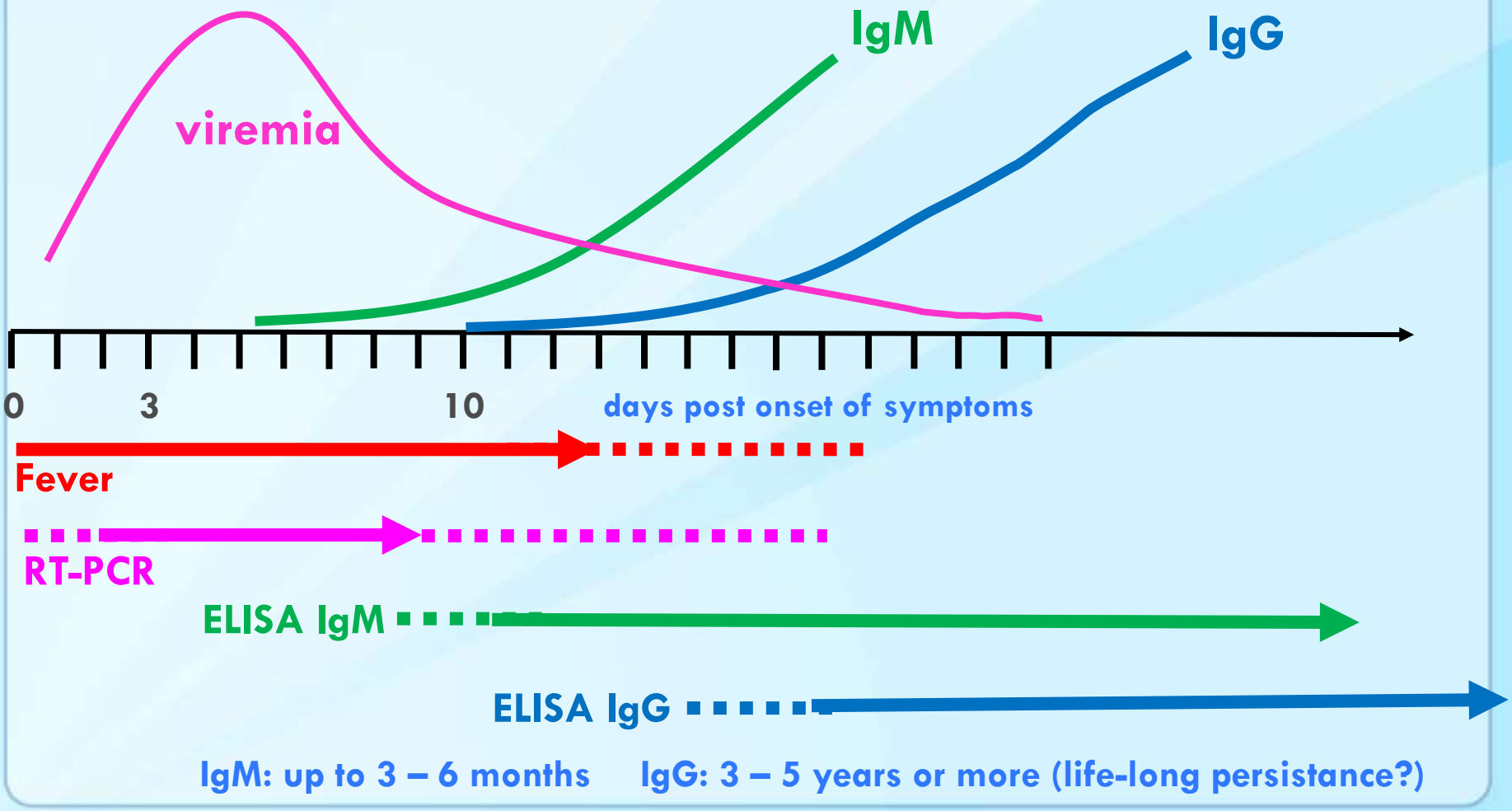
Bleeding at IV Site

Laboratory Findings

- Thrombocytopenia (50,000–100,000/μL range)
- Leukopenia followed by neutrophilia
- Transaminase elevation: elevation serum aspartate amino-transferase (AST) > alanine transferase (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



IgM: up to 3 – 6 months IgG: 3 – 5 years or more (life-long persistance?)

Ebola Virus Diagnosis

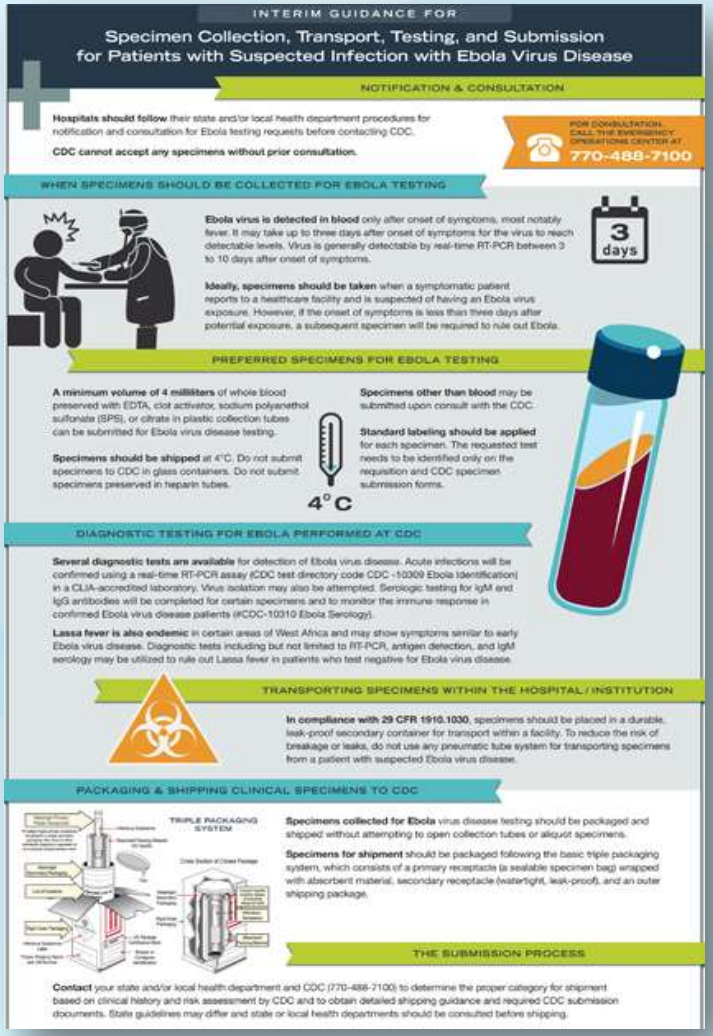
- Real Time PCR (RT-PCR)
  - Used to diagnose acute infection
  - More sensitive than antigen detection ELISA
  - Identification of specific viral genetic fragments
  - Performed in select CLIA-certified laboratories
- RT-PCR sample collection
  - Volume: minimum volume of 4mL whole blood
  - Plastic 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

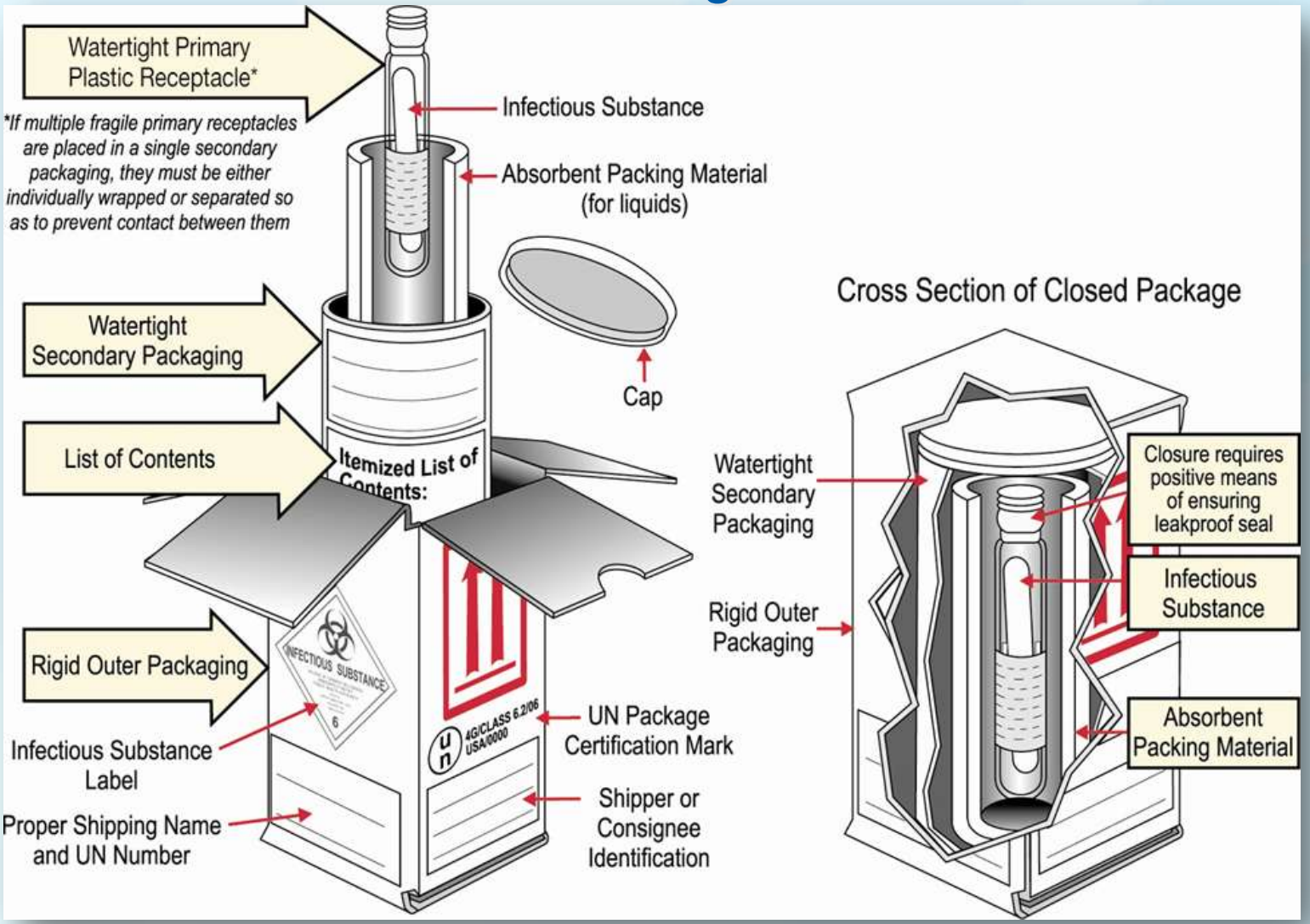
Laboratories

- 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



Information available at: http://www.cdc.gov/vhf/ebola/hcp/interim-guidance-specimen-collection-submission-patients-suspected-infection-ebola.html

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 ≥3 days before the negative result
  - EVD is unlikely → 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 ≥72 hours after onset of symptoms
  - Keep in isolation as a suspected case until a repeat RT-PCR ≥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

Reference: Fowler RA et al. *Am J Respir Crit Care Med*. 2014

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 – three chimeric human-mouse monoclonal antibodies
      - Tekmira – lipid nanoparticle small interfering RNA
      - Favipiravir – oral RNA-dependent RNA polymerase inhibitor
  - Vaccines – in clinical trials
    - Chimpanzee-derived adenovirus with an Ebola virus gene inserted
    - Attenuated vesicular stomatitis virus with an Ebola virus gene inserted

References: [1]Huggins, JW et al. *Rev Infect Dis* 1989; [2]Jarhling, P et al. *JI*D 2007; [3]Mupapa, K et al. *JID* 1999 S18; [4]Olinger, GG et al. *PNAS* 2012; [5]Dye, JM et al. *PNAS* 2012; [6]Qiu, X et al. *Sci Transl Med* 2013; [7]Qiu, X et al. *Nature* 2014; [8]Geisbert, TW et al. *JID* 2007; [9]Geisbert, TW et al. *Lancet* 2010; [10]Kobinger, GP et al. *Virology* 2006; [11]Wang, D et al. *J Virol* 2006; [12]Geisbert, TW et al. *JID* 2011; [13]Gunther et al. *JID* 2011; [14]Oestereich, L et al. Antiviral Res. 2014.

Patient Recovery

- Case-fatality rate between 50-70% 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

References: [1]WHO Ebola Response Team. *NEJM* 2014; [2]Feldman H & Geisbert TW. *Lancet* 2011; [3]Ksiazek TG et al. *JID* 1999; [4]Sanchez A et al. *J Virol* 2004; [5]Sobarzo A et al. *NEJM* 2013; and [6]Rowe AK et al. *JID* 1999.

Practical Considerations for Evaluating Patients for EVD in the United States

- CDC encourages all U.S. healthcare providers to
  - Ask patients with Ebola-like symptoms about travel to West Africa or contact with individuals with confirmed EVD 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
    - Available at http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf The checklist for evaluation of a patient being evaluated for EVD
    - Available at http://www.cdc.gov/vhf/ebola/pdf/checklist-patients-evaluated-us-evd.pdf

EVD Algorithm for Evaluation of the Returned Traveler

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

NO

Report asymptomatic patients with high- or low-risk exposures (see below) in the past 21 days to the health department

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

**CDC Website to check current affected areas: www.cdc.gov/vhf/ebola
Algorithm available at http://www.cdc.gov/vhf/ebola/pdf/ebola-algorithm.pdf
Checklist available at http://www.cdc.gov/vhf/ebola/pdf/checklist-patients-evaluated-us-evd.pdf

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

RISK LEVEL	PUBLIC HEALTH ACTION		
	Monitoring	**Restricted Public Activities**	**Restricted Travel**
HIGH risk	Direct Active Monitoring	Yes	Yes
SOME risk	Direct Active Monitoring	Case-by-case assessment	Case-by-case assessment
LOW risk	Active Monitoring for some; Direct Active Monitoring for others	No	No
NO risk	No	No	No

www.cdc.gov/vhf/ebola/hcp/monitoring-and-movement-of-persons-with-exposure.html

EVD Summary

- 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.atsdr.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.