LMU MLS Continuing Education Conference November 2014

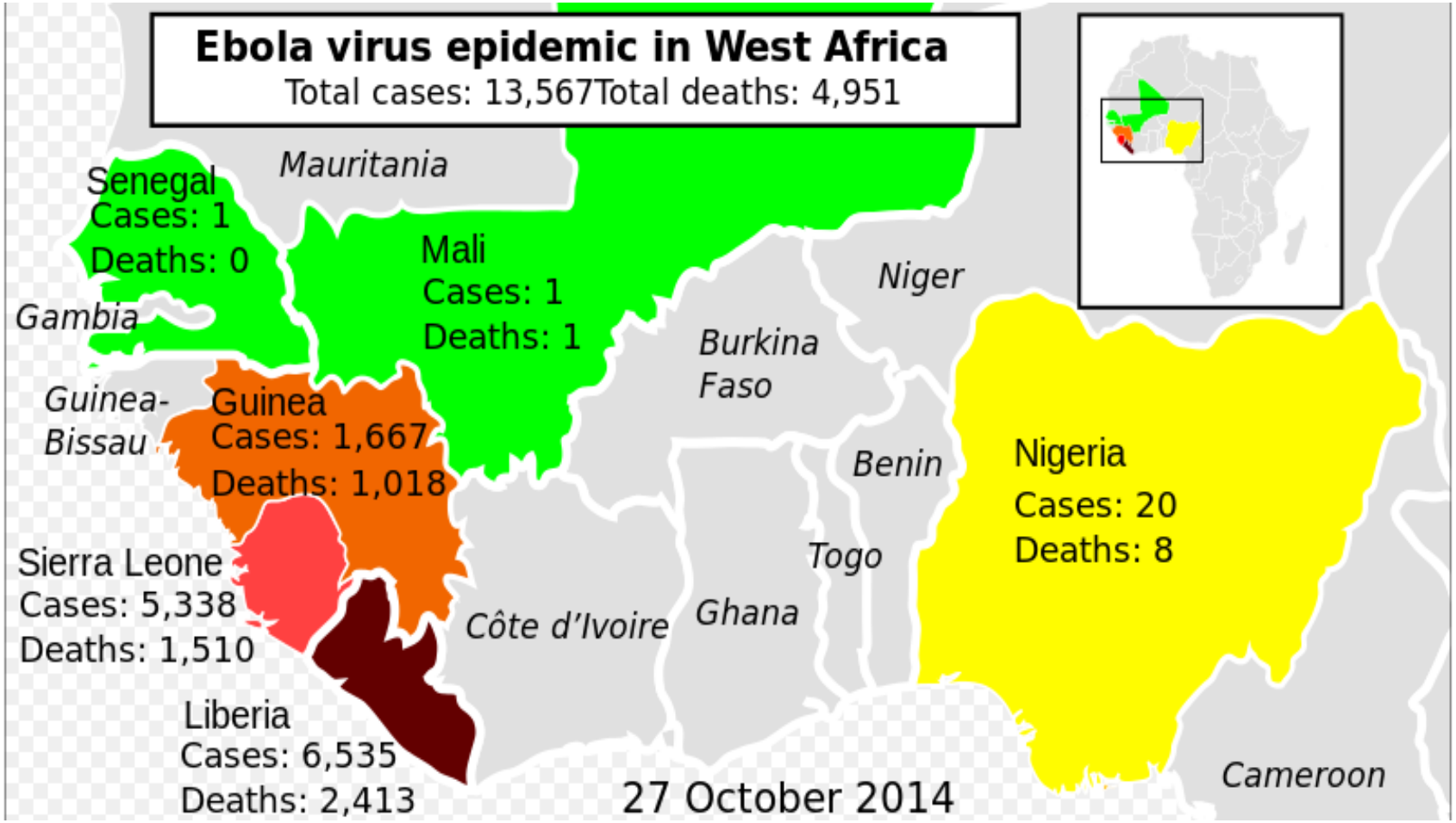
PACE Session #: 304-112-14

What Laboratorians Need to Know About the Ebola Virus Disease

Dr. Teresa Campbell, MD

Objectives

- 1) Describe the classification, structure, basic genetics and the viral proteins of the Ebola virus and understand how these viral proteins induce disease in humans (pathogenesis).
- 2) Describe the epidemiology of Ebola virus including geographic features, reservoirs, vectors, incubation period, mode of transmission, and mortality rates in humans.
- 3) Describe the clinical features of Ebola virus disease including laboratory abnormalities and laboratory diagnostic tests currently in use.
- 4) Know the current CDC recommendations for laboratory personnel.



Author	Mikael Häggström. Also updated by BrianGroen

http://commons.wikimedia.org/wiki/File:2014_ebola_virus_epidemic_in_West_Africa...

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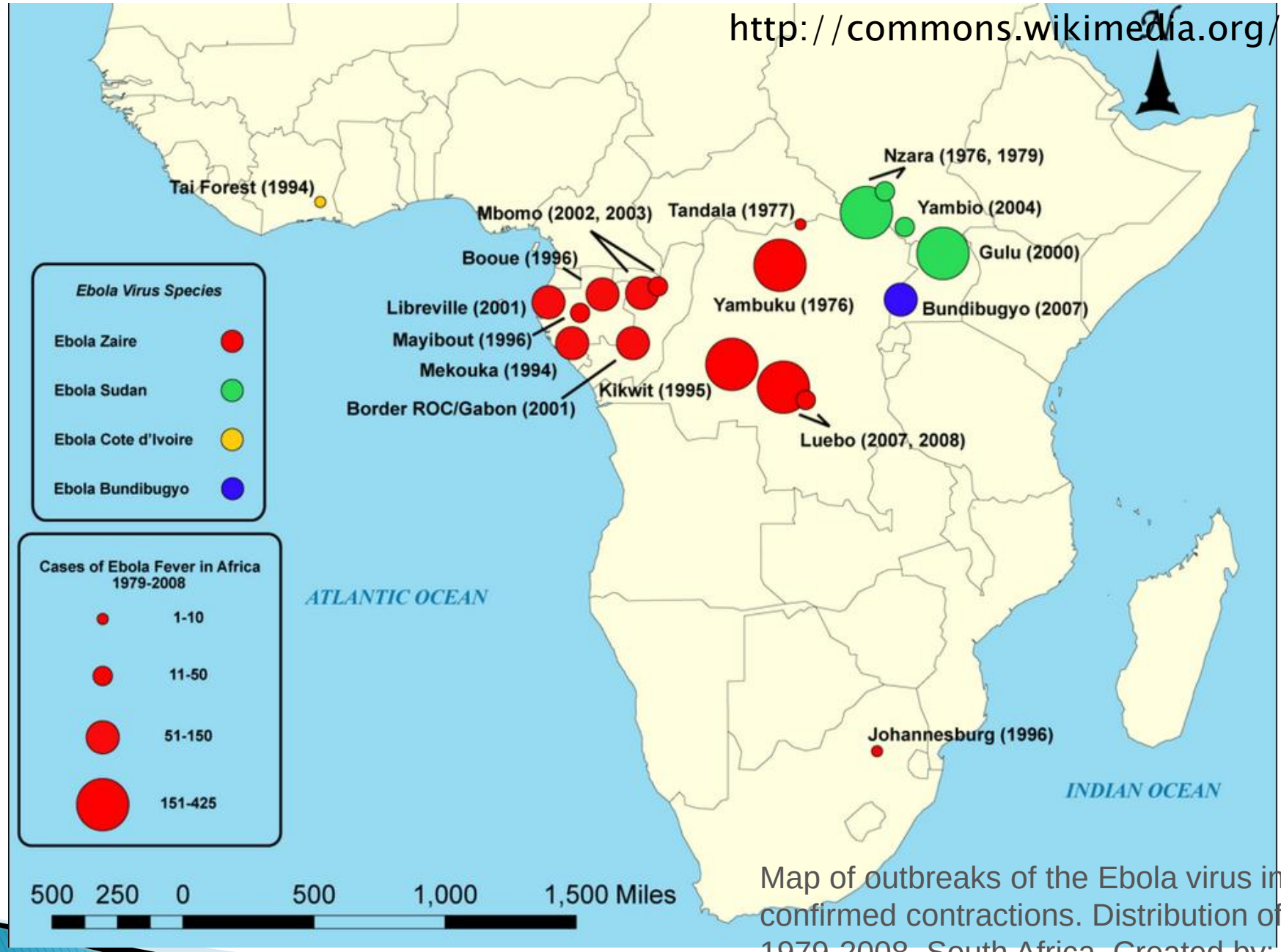


Map of outbreaks of the Ebola virus in Africa by strain and confirmed contractions. Distribution of Ebola Virus Outbreaks 1979-2008, South Africa. Created by: Zach Orecchio, University of South Florida Geography Dep.

Order: Mononegavirales

Family: Filoviridae

- Genus:Cuevavirus
  - Species: Lloviu cuevavirus (found in dead bats in Spain in 2002)

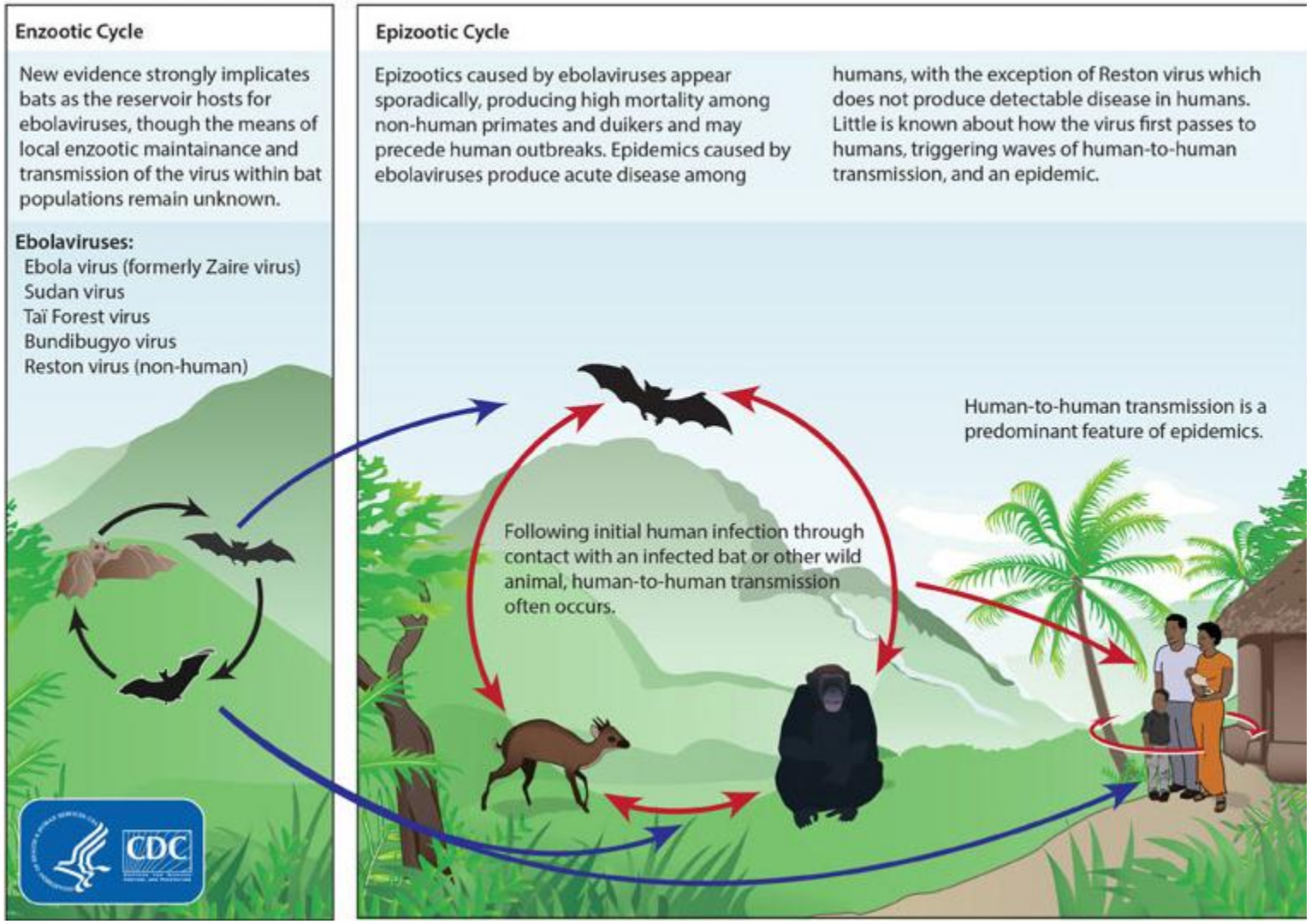
- Genus:**Ebolavirus**
  - **Species: Bundibugyo ebolavirus (first outbreak 2007)**
  - **Species: Reston ebolavirus (first outbreak 1989, asymptomatic human infection)**
  - **Species: Sudan ebolavirus (first outbreak 1970s)**
  - **Species: Tai Forest ebolavirus (formerly called Ivory Coast ebolavirus; one person infected after performing necropsy on chimpanzee found dead)**
  - **Species: Zaire ebolavirus (first outbreak 1976)**

- Genus: Marburgvirus
  - Species: Marburg marburgvirus (**first filovirus discovered in 1967, 21% mortality; other African outbreaks had 80 to 90% mortality**)

Epidemiology of filoviruses

- Case-fatality rate ranges from 50 to 90%
- Zaire Ebola is the most virulent, first recognized in 1976
  - Named Ebola after the nearby river
- Multiple outbreaks of different strains of Ebola as well as Marburg have occurred in Africa since then; usually in small villages and easily contained
- Reservoirs: possibly various species of bats
- Transmission:
  - Human exposure to or consumption of infected animals
    - Infection of chimps and gorillas is felt to have contributed to their decreasing numbers
    - Some evidence exists that dogs can be infected but no reports of sickness developing or of dog to human transmission
  - Human to human transmission via exposure to blood and body fluids; not aerosol
    - Direct contact as well as indirect contact such as through an object contaminated with infectious material
  - Has been aerosolized for biologic warfare
  - Experimental evidence of aerosol transmission in non-human primates

Ebolavirus Ecology



EbolaCycle Public Domain
CDC - http://www.cdc.gov/vhf/ebola/resources/virus-ecology.html

Current West African outbreak

- First outbreak in West Africa with most having occurred in Central Africa
  - Index case was 2 year old child in late 2013 in Guinea
  - Transmission has been person to person
  - Case-fatality rate ~70%
  - 55% of infected health care workers in Africa have died
- Also outbreak in 2014 in Democratic Republic of Congo in August 2014; genetic sequencing shows this outbreak is NOT related to the above outbreak; in October, 66 cases and 49 deaths

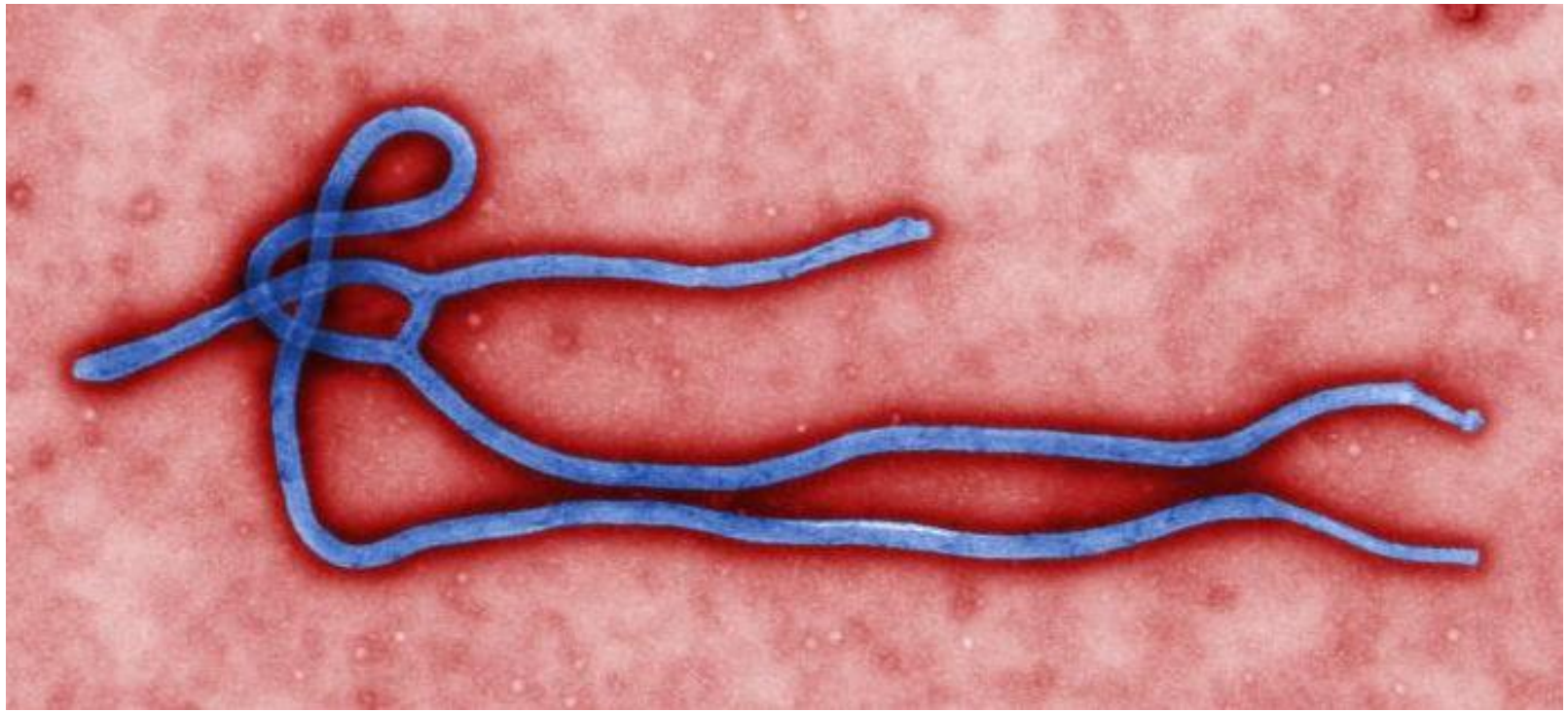
Ebolavirus

- Filoviruses have a filamentous form (filum in latin means thread-like), variable length up to 1000nm, uniform width ~80nm, usually straight but may fold on self
  - “shepherd’s crook”

- Nonsegmented negative sense single stranded RNA virus
  - Negative sense RNA must be copied into complementary sequences mRNA in order to make proteins
  - RNA-dependent RNA polymerase is in the virion already and starts transcribing the negative sense RNA into mRNA
  - Once mRNA production has started, the infected cells’ translation system is utilized to produce viral proteins
  - New virions form, bud off the cell and infect other cells.

- Virions have an envelope and a helical nucleocapsid containing RNA-dependent RNA polymerase (RDRP) and genomic RNA.

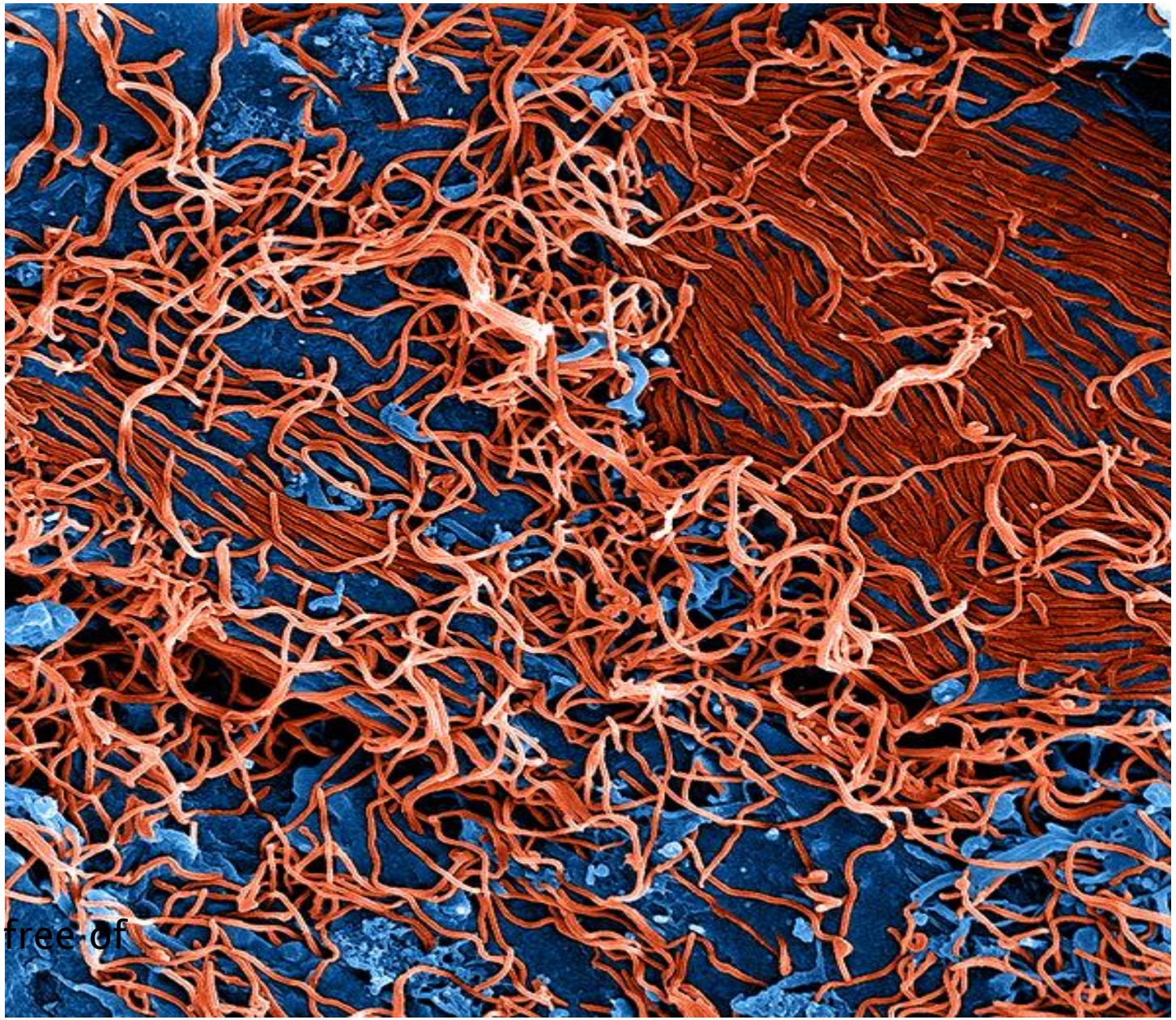
EBOLA



Created by CDC microbiologist Cynthia Goldsmith, this colorized transmission electron micrograph (TEM) revealed some of the ultrastructural morphology displayed by an Ebola virus virion. See PHIL 1832 for a black and white version of this image

CDC/ Cynthia Goldsmith
ID# 10816

Ebola virus

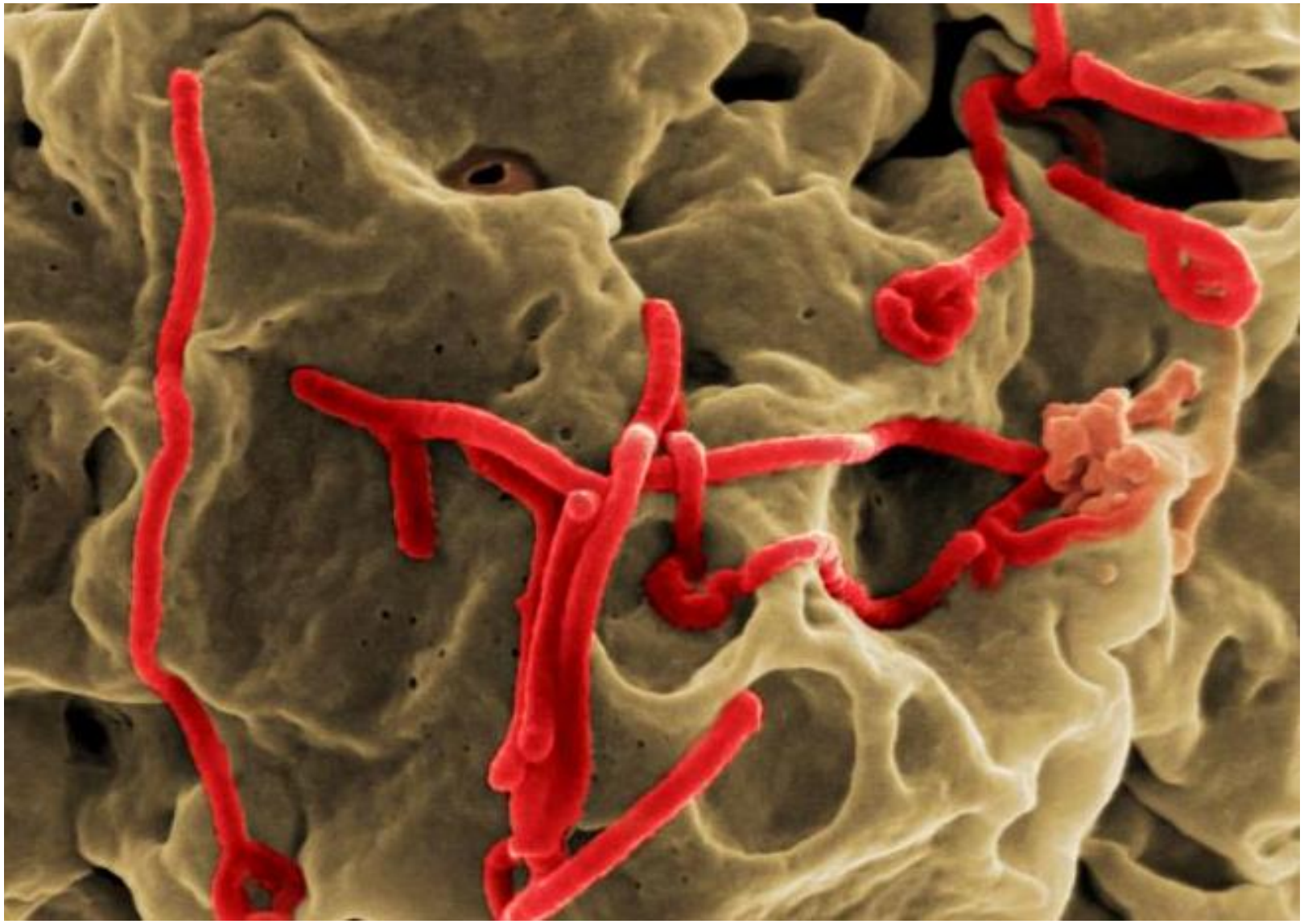


Produced by the National Institute of Allergy and Infectious Diseases (NIAID), under a magnification of 25,000X, this digitally-colorized scanning electron micrograph (SEM) depicts numerous filamentous Ebola virus particles (red) budding from a chronically-infected VERO E6 cell (blue).

Ebola virus

Produced by the National Institute of Allergy and Infectious Diseases (NIAID), under a very-high magnification, this digitally-colorized scanning electron micrograph (SEM) depicts a number of filamentous Ebola virus particles (red) that had budded from the surface of a VERO cell (brown) of the African green monkey kidney epithelial cell line.

ID#: 17777

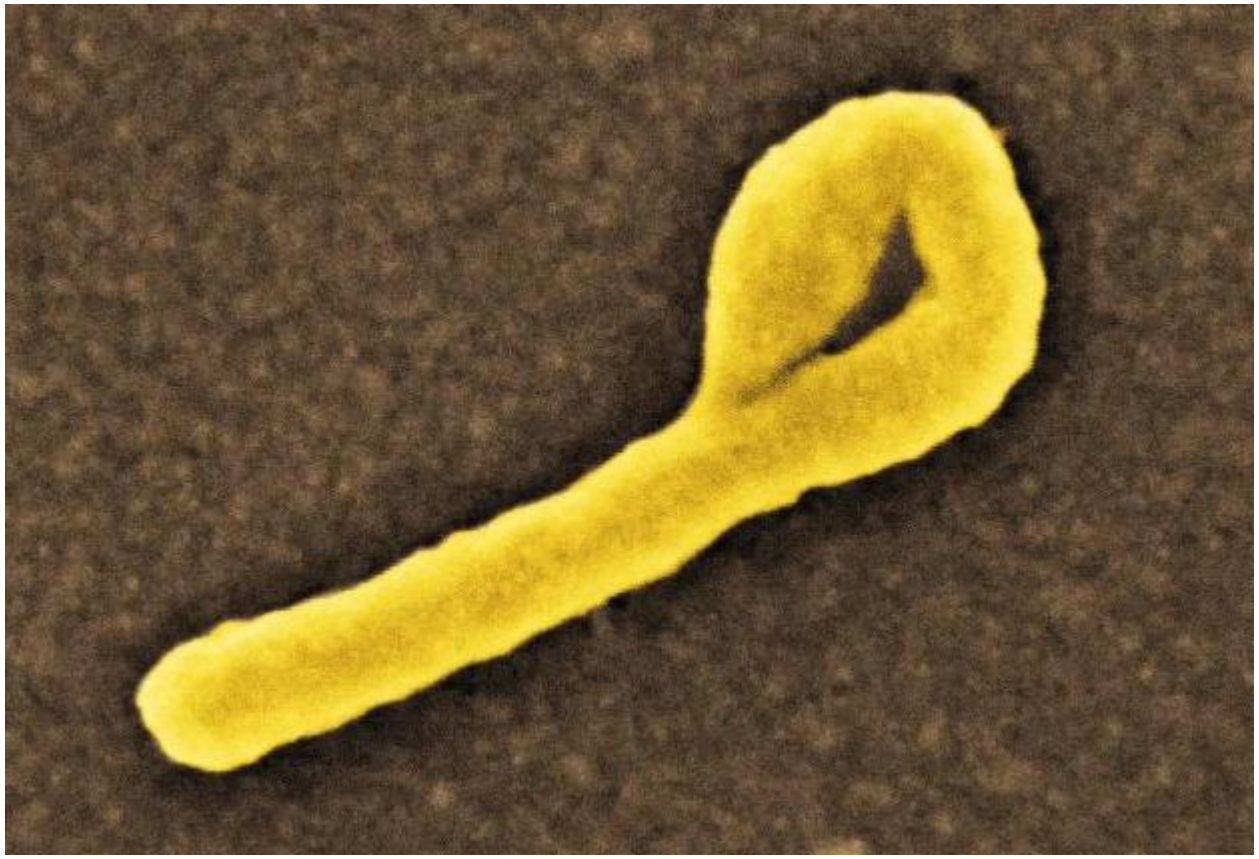


CONTENT PROVIDER: CDC/ NIAID http://phil.cdc.gov/phil/details.asp

Ebola Virus

Produced by the National Institute of Allergy and Infectious Diseases (NIAID), under a very-high magnification, this digitally-colorized scanning electron micrograph (SEM) depicts a single filamentous Ebola virus particle that had budded from the surface of a VERO cell of the African green monkey kidney epithelial cell line. ID#: 17776

CONTENT PROVIDER: CDC/ NIAID



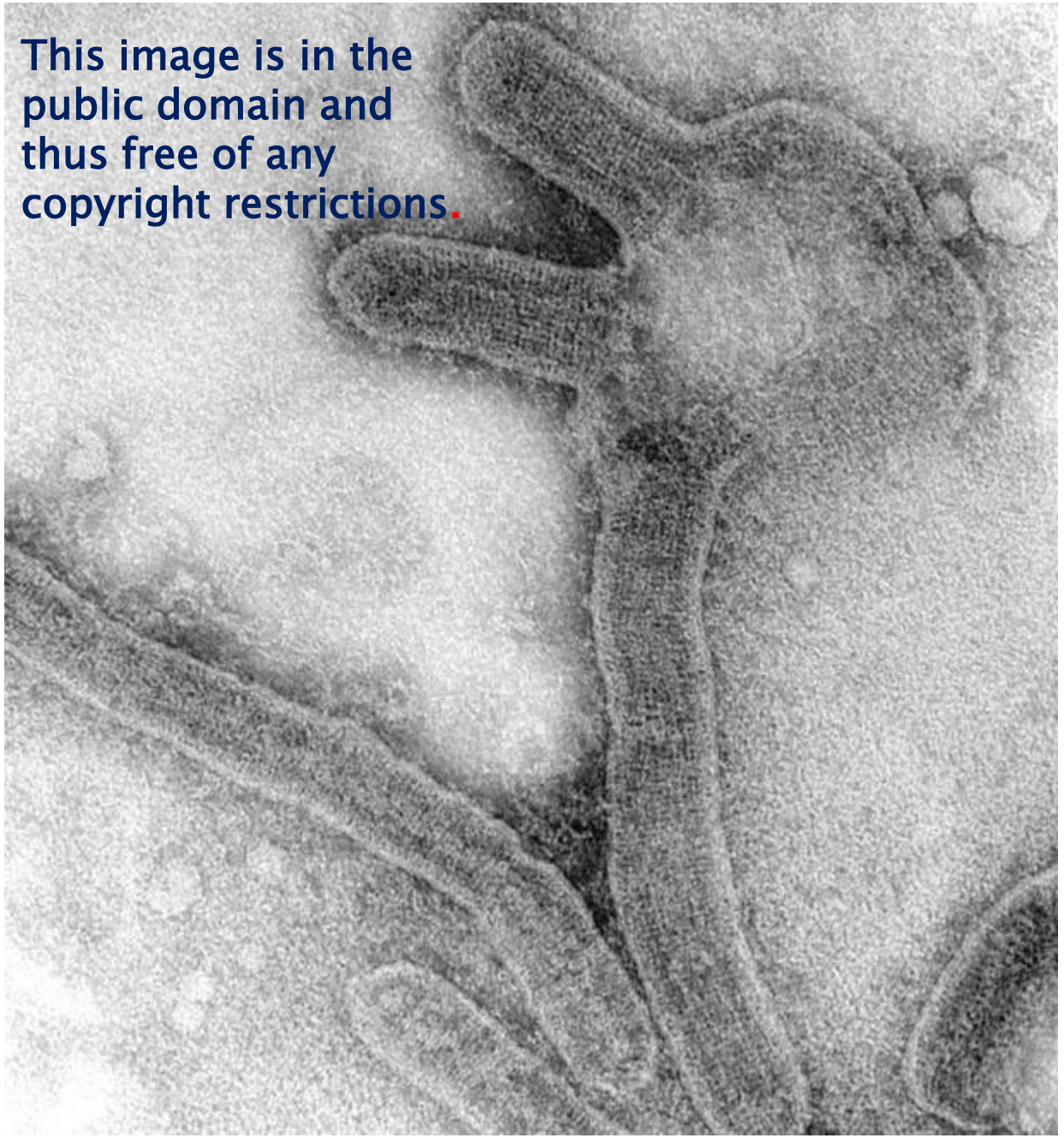
http://phil.cdc.gov/phil/details.asp

Marburg virus

This negative stained transmission electron micrograph (TEM), captured by F.A. Murphy in 1968, depicts a Marburg virus virion, which had been grown in an environment of tissue culture cells. Marburg hemorrhagic fever is a rare, severe type of hemorrhagic fever which affects both humans and non-human primates. Caused by a genetically unique zoonotic (that is, animal-borne) RNA virus of the filovirus family, its recognition led to the creation of this virus family. The four species of Ebola virus are the only other known members of the filovirus family. See PHIL 10813 for a colorized version of this image.

Providers(s): CDC/ F. A. Murphy. ID#: 7219

Marburg virus



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Providers(s): CDC/ F. A. Murphy **ID#:** 7218

Ebolavirus

- Genome consists of 7 genes encodes for
  - 7 Structural proteins: virion envelope glycoprotein (GP), nucleoprotein (NP) and inner matrix proteins, VP 30, VP35 and matrix proteins VP40 and VP24, RNA polymerase (L)

- A nonstructural small soluble secretory GP (sGP) important in pathogenesis is produced early in the infection in large quantities
  - GP gene gives rise to two proteins: transmembrane GP and sGP which does not occur in Marburg

Some possible mechanisms causing disease in Ebola virus infection

- Transmembrane GP preferentially binds to endothelial cells and macrophages allowing introduction of the virus into the cell

- Evades immune response
  - Virus infects dendritic cell which then cannot present antigen to naïve lymphocytes; decreased cytokine production early in disease and decreased T cell proliferation and lymphocyte apoptosis
  - VP 24: suppress interferon production
  - VP35: interferon antagonist
  - sGP binds CD 16b on neutrophils inhibiting activation
  - sGP may be responsible for severe lymphopenia
  - Transmembrane GP diminishes CD8 T-cell mediated cytotoxicity

- Dysregulated inflammatory response
  - Virus infected macrophages release of cytokines may result in uncontrolled inflammatory response

- Loss of vascular integrity due to loss of adhesion of infected endothelial cells

- Viral cytopathic effect: infected cells destroyed due to inhibition of cell processes, excessive viral proteins in cell, budding of viruses from cell, etc.

- Coagulopathy
  - Virus infected macrophages produce cell surface tissue factor triggering coagulation

Pathogenesis of disease

- Studies re: pathogenesis on **nonhuman** primates
- Enters body via mucous membranes, breaks in skin, parenterally
- Macrophages and dendritic cells are likely first cells infected with subsequent spread to lymph nodes, spleen, liver, thymus, adrenal glands, epithelial cells (lymphocytes are not infected)
- Rapidly spread throughout body due to interferon suppression and immune system impairment
- Results in:
  - Cellular necrosis, coagulation defects, systemic inflammatory response due to release of pro-inflammatory mediators resulting in shock, adrenal insufficiency, hypovolemia and electrolyte abnormalities, multi-organ failure, DIC (disseminated intravascular coagulation) and death

Clinical

- Incubation period: range of 2-21 days; usually 8-12 days
- Evidence does not support spread of virus by asymptomatic persons
- **Initial symptoms**: fever, chills malaise, headache, back pain
  - GI: vomiting, diarrhea, abdominal pain starting several days later
  - Rash: diffuse red rash involving face, neck, trunk, arms on days 5-7
  - Hemorrhage: may occur late in disease; ~20% have had bleeding in the most current outbreak
  - Other symptoms: hiccups, confusion, seizures, **conjunctival injection**, soft palate with dark red appearance, chest pain, short of breath, etc.
- **Most common symptoms in current outbreak** are fever, fatigue, vomiting, diarrhea and loss of appetite
- Nonfatal cases usually improve about a week after symptoms start
  - Detectable viral antibodies in second week
- Fatal cases have severe symptoms early and die between days 6 to 16,

Diagnostic Tests

- Rapid tests
  - Reverse transcriptase-polymerase chain reaction- detects specific RNA sequences
    - Viral RNA usually detectable within 3 to 10 days
    - Continued sensitivity of this test could be a problem with rapidly changing genetic sequences in the current Ebola Zaire virus
  - Viral antigen detection by enzyme-linked immunosorbent assay (ELISA)
  - Under development: POC testing giving results in less than 10 minutes
  - Must have 2 negative PCR tests separated by 48 hours before discharge
- Culture: Do only in biosafety level (BSL) 4 laboratory
- Immunohistochemical staining on tissue specimens
- Antibody detection, IgG and IgM, may be used to monitor immune response and check for past infection (IgG levels detectable up to 11 years after infection per CDC)
  - IgM becomes detectable ~10 days after symptom onset
  - IgG becomes detectable ~18 days after symptom onset

Differential Diagnosis

- Malaria
- Influenza
- Lassa hemorrhagic fever
- Meningococcemia
- Typhoid fever
- Yellow fever
- Etc.

Other Lab findings

- Leukopenia, especially decreased lymphocytes; later in disease have elevated neutrophils with immature forms
- Thrombocytopenia: 50 to 100,000 reaching a nadir day 6-8
- Elevated AST and ALT due to hepatic necrosis
- DIC in severe cases with elevated PT and PTT and elevated fibrin degradation products
- Electrolyte abnormalities
- May develop renal insufficiency

Treatment

- Supportive care: maintain hydration and electrolyte balance, nutrition
- **Experimental therapies; none approved in humans** (Ribavirin is not effective in Ebola)
  - Neutralizing antibodies:
    - Monoclonal antibodies directed against GP Human derived convalescent immune globulin
    - Equine derived hyperimmune globulins
  - Brincidofovir: inhibits DNA virus replication and was developed for CMV, small pox, adenovirus but has been found to inhibit the Ebola virus (an RNA virus)
  - siRNAs or Small interfering RNAs: cause mRNA to be broken down preventing synthesis of L polymerase, VP24 and VP35, viral proteins in Ebola
  - Favipiravir: effective against RNA viruses (being stockpiled in Japan for influenza) by inhibiting RNA-dependent RNA polymerase
  - Antisense phosphorodiamidate morpholina oligomers: synthetic DNA analogs that inhibit gene expression
- Drugs for DIC (activated protein C and nematode anticoagulant protein that inhibits activated factor VII-tissue factor complex)

Vaccines

- **In clinical trials**:
  - rVSV (recombinant vesicular stomatitis virus) in which the VSV glycoprotein gene has been replaced with the Ebola GP gene
  - NIAID/GSK Ebola vaccine (National Institute of Allergy and Infectious Diseases /GlaxoSmithKline)
    - Chimp adenovirus type 3 delivers portions of Ebola genes (Zaire and Sudan) to human cells which then produce a single Ebola protein with a subsequent immune response
- No cross reactivity of immunity between Ebola species apparently

Postinfectious sequalae

- Prolonged recovery period with weakness, difficulty gaining weight back
- “serum sickness” type symptoms due to antigen-antibody complexes
- Desquamation of skin, hair loss
- Virus may be present in semen for up to 3 months
  - One documented case of transmission via sexual contact in 1967 Marburg outbreak
- Virus may be present in breast milk after cleared from blood

Protection of Lab personnel

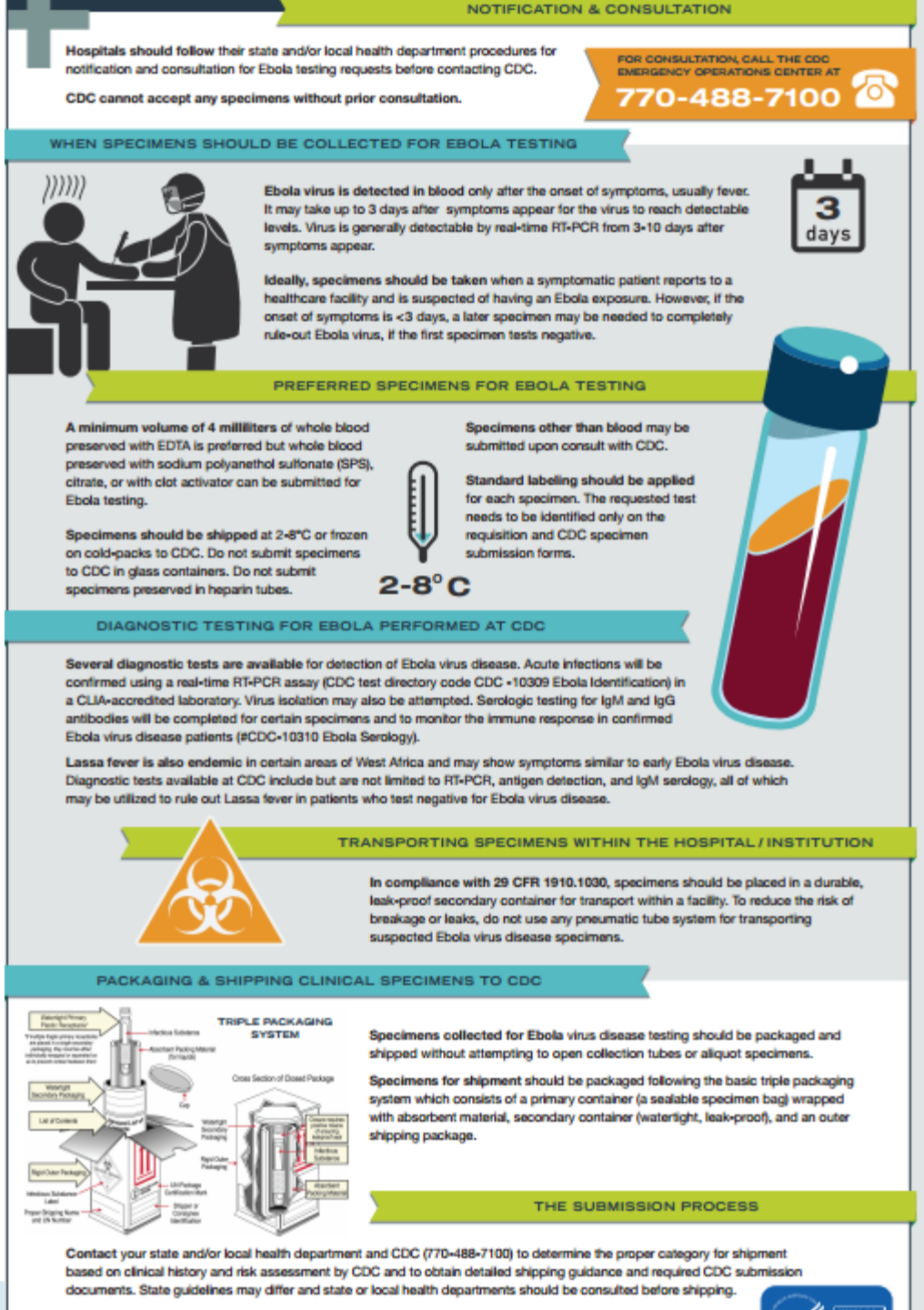
http://www.cdc.gov/vhf/ebola/hcp/interim-guidance-specimen-collection-submission-patients-suspected-infection-ebola.html

- Specimen collection: gloves, water-resistant gown, full face shield or goggles, mask http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html
- video for donning and doffing PPE http://www.medscape.com/viewarticle/833907
- Laboratory testing: As above with addition of below;
  - Certified Class II biosafety cabinet or Plexiglass splash guard
  - Use manufacturer installed safety features on lab instruments
- Use EPA-registered hospital disinfectants which are active against non-enveloped virus as specified on the label (e.g., norovirus, adenovirus, etc)
- Laboratory waste management: Any waste with a Category A infectious substance must be packaged and transported according to DOT's Hazardous Materials Regulations (HMR,49 C.F.R., Parts 171-180) prior steam sterilization or incineration is desirable prior to transport.
  - US sewer systems designed to inactivate infectious agents BUT check with your state's medical waste program for more guidance
  - Check with your waste management contractor

Specimen handling

- Specimen transportation
  - Within hospital:
    - place specimen in a leak-proof, durable second container
    - DO NOT use pneumatic tube system
- Transport to CDC: “Hospitals should follow their state and/or local health department procedures for notification and consultation for Ebola testing requests **prior** to contacting CDC.”
- “NO specimens will be accepted without prior consultation. For consultation call the EOC at 770-488-7100.”
  - Preferred specimen: whole blood EDTA plastic tube
  - Storage of specimen: store at 2-8 degrees Celsius
  - Packaging and shipping:
    - Transport at 2-8 degrees C or frozen on ice packs
    - See packing instructions

http://www.cdc.gov/vhf/ebola/pdf/ebola-lab-guidance.pdf



NOTIFICATION & CONSULTATION

Hospitals should follow their state and/or local health department procedures for notification and consultation for Ebola testing requests before contacting CDC.

CDC cannot accept any specimens without prior consultation.

FOR CONSULTATION, CALL THE CDC EMERGENCY OPERATIONS CENTER AT
770-488-7100

WHEN SPECIMENS SHOULD BE COLLECTED FOR EBOLA TESTING

Ebola virus is detected in blood only after the onset of symptoms, usually fever. It may take up to 3 days after symptoms appear for the virus to reach detectable levels. Virus is generally detectable by real-time RT-PCR from 3-10 days after symptoms appear.

3 days

Ideally, specimens should be taken when a symptomatic patient reports to a healthcare facility and is suspected of having an Ebola exposure. However, if the onset of symptoms is <3 days, a later specimen may be needed to completely rule-out Ebola virus, if the first specimen tests negative.

PREFERRED SPECIMENS FOR EBOLA TESTING

A minimum volume of 4 milliliters of whole blood preserved with EDTA is preferred but whole blood preserved with sodium polyanethol sulfonate (SPS), citrate, or with clot activator can be submitted for Ebola testing.

Specimens should be shipped at 2-8°C or frozen on cold-packs to CDC. Do not submit specimens to CDC in glass containers. Do not submit specimens preserved in heparin tubes.

2-8° C

Specimens other than blood may be submitted upon consult with CDC.

Standard labelling should be applied for each specimen. The requested test needs to be identified only on the requisition and CDC specimen submission forms.

DIAGNOSTIC TESTING FOR EBOLA PERFORMED AT CDC

Several diagnostic tests are available for detection of Ebola virus disease. Acute infections will be confirmed using a real-time RT-PCR assay (CDC test directory code CDC -10309 Ebola Identification) in a CLIA-accredited laboratory. Virus isolation may also be attempted. Serologic testing for IgM and IgG antibodies will be completed for certain specimens and to monitor the immune response in confirmed Ebola virus disease patients (#CDC-10310 Ebola Serology).

Lassa fever is also endemic in certain areas of West Africa and may show symptoms similar to early Ebola virus disease. Diagnostic tests available at CDC include but are not limited to RT-PCR, antigen detection, and IgM serology, all of which may be utilized to rule out Lassa fever in patients who test negative for Ebola virus disease.

TRANSPORTING SPECIMENS WITHIN THE HOSPITAL / INSTITUTION

In compliance with 29 CFR 1910.1030, specimens should be placed in a durable, leak-proof secondary container for transport within a facility. To reduce the risk of breakage or leaks, do not use any pneumatic tube system for transporting suspected Ebola virus disease specimens.

PACKAGING & SHIPPING CLINICAL SPECIMENS TO CDC

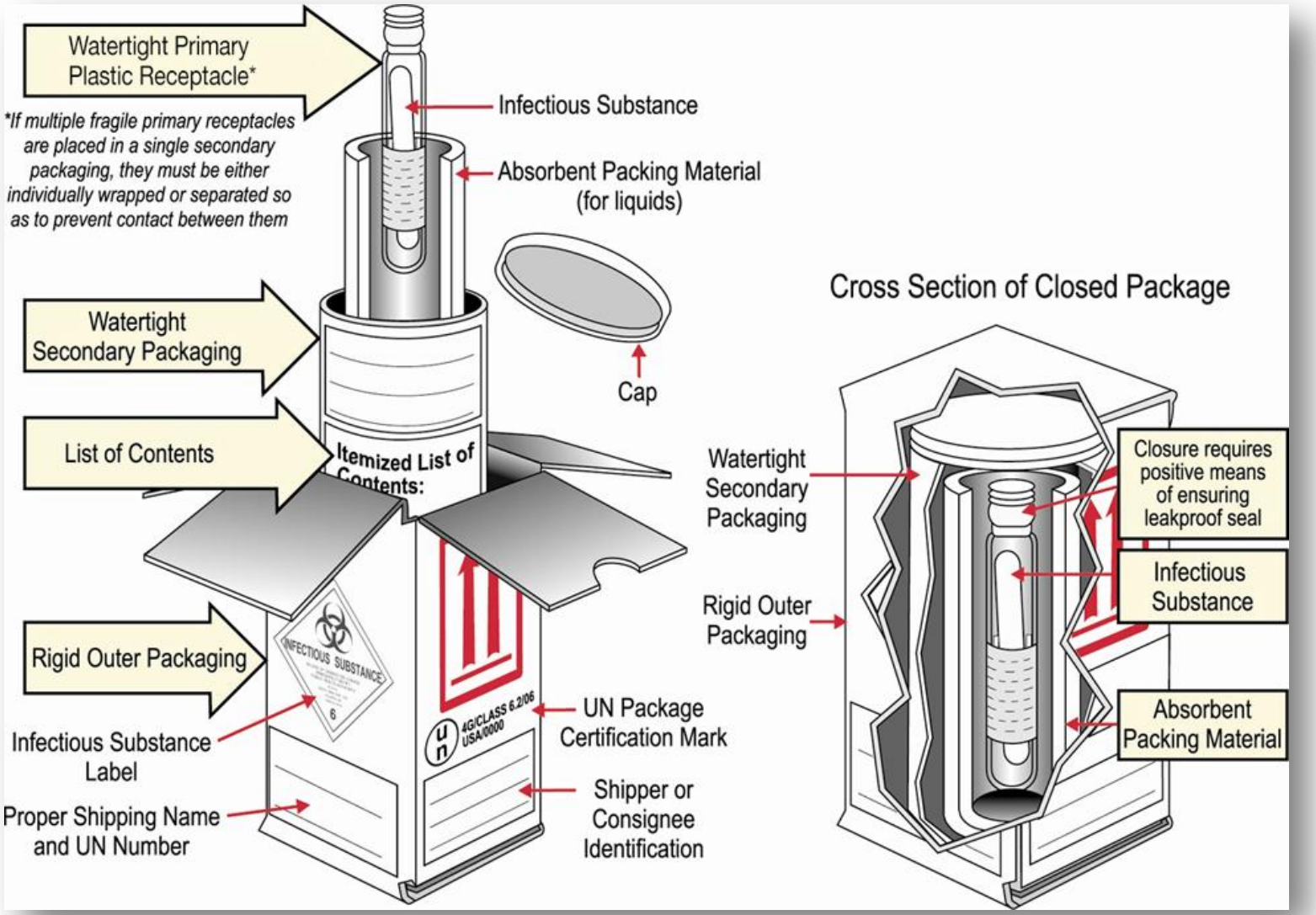
TRIPLE PACKAGING SYSTEM

Specimens collected for Ebola virus disease testing should be packaged and shipped without attempting to open collection tubes or aliquot specimens.

Specimens for shipment should be packaged following the basic triple packaging system which consists of a primary container (a sealable specimen bag) wrapped with absorbent material, secondary container (watertight, leak-proof), and an outer shipping package.

THE SUBMISSION PROCESS

Contact your state and/or local health department and CDC (770-488-7100) to determine the proper category for shipment based on clinical history and risk assessment by CDC and to obtain detailed shipping guidance and required CDC submission documents. State guidelines may differ and state or local health departments should be consulted before shipping.


Watertight Primary Plastic Receptacle*
*If multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them
Infectious Substance
Absorbent Packing Material (for liquids)
Watertight Secondary Packaging
Cap
List of Contents
Itemized List of Contents:
Rigid Outer Packaging
INFECTIOUS SUBSTANCE
6
4G/CLASS 6.2/06 USA/0000
UN Package Certification Mark
Infectious Substance Label
Proper Shipping Name and UN Number
Shipper or Consignee Identification
Cross Section of Closed Package
Watertight Secondary Packaging
Rigid Outer Packaging
Closure requires positive means of ensuring leakproof seal
Infectious Substance
Absorbent Packing Material

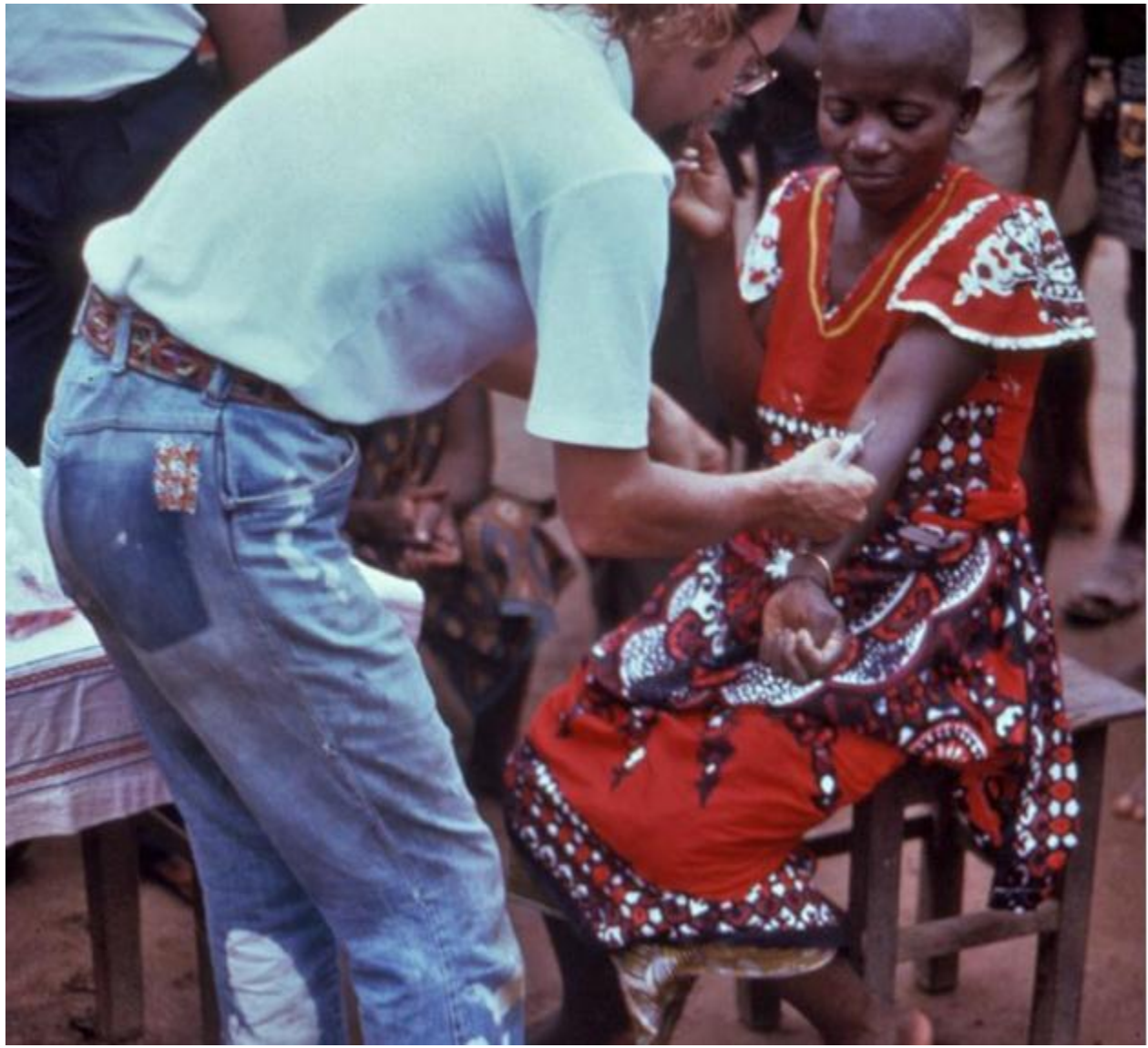
CDC

“This CDC laboratorian was shown looking through a microscope at samples collected from the field by an Ebola survey team in Zaire, 1976. The Ebola outbreak in Zaire, now known as the Democratic Republic of Congo, started in the town of Yambuku, and from there spread to surrounding areas. In Kinshasa, the country’s capital, an area hospital was sealed off during the outbreak, helping to bring the situation under control. The total number of cases in Zaire was 318 and had a mortality rate of 88%. “ Centers for Disease Control

ID#: 7200

Content Providers(s): CDC/ Dr. Lyle Conrad

“This was a member of an Ebola survey team shown as he extracted a blood sample from a resident of the town of Yambuku, Zaire during the country’s 1976 outbreak. “ Centers for Disease Control



Content Provider(s): CDC/ Dr. Lyle Conrad

ID#: 7198

Photo Credit: Joel G. Breman, M.D., D.T.P.H

“This 1976 photograph showed a field laboratorian using a centrifuge to separate blood in order to prepare plasma that was collected from patients who recovered from Ebola hemorrhagic fever (Ebola HF). "Convalescent-plasma" contains antibodies to the Ebola virus, and was often administered to Ebola patients during numerous outbreaks. Treatment with convalescent-plasma seems to help in the recovery of Ebola HF patients, but its effectiveness has not been unequivocally proven” Centers for Disease Control

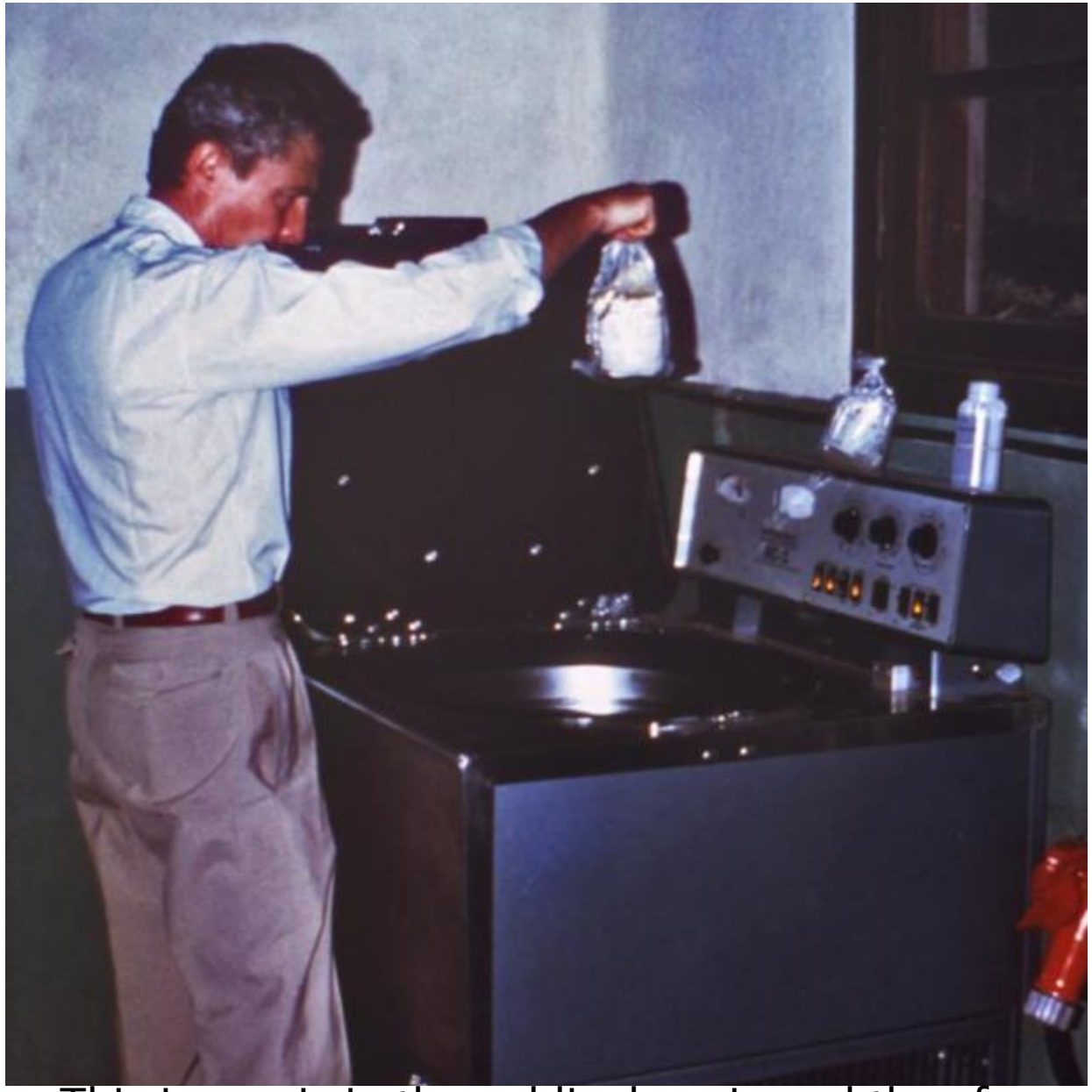
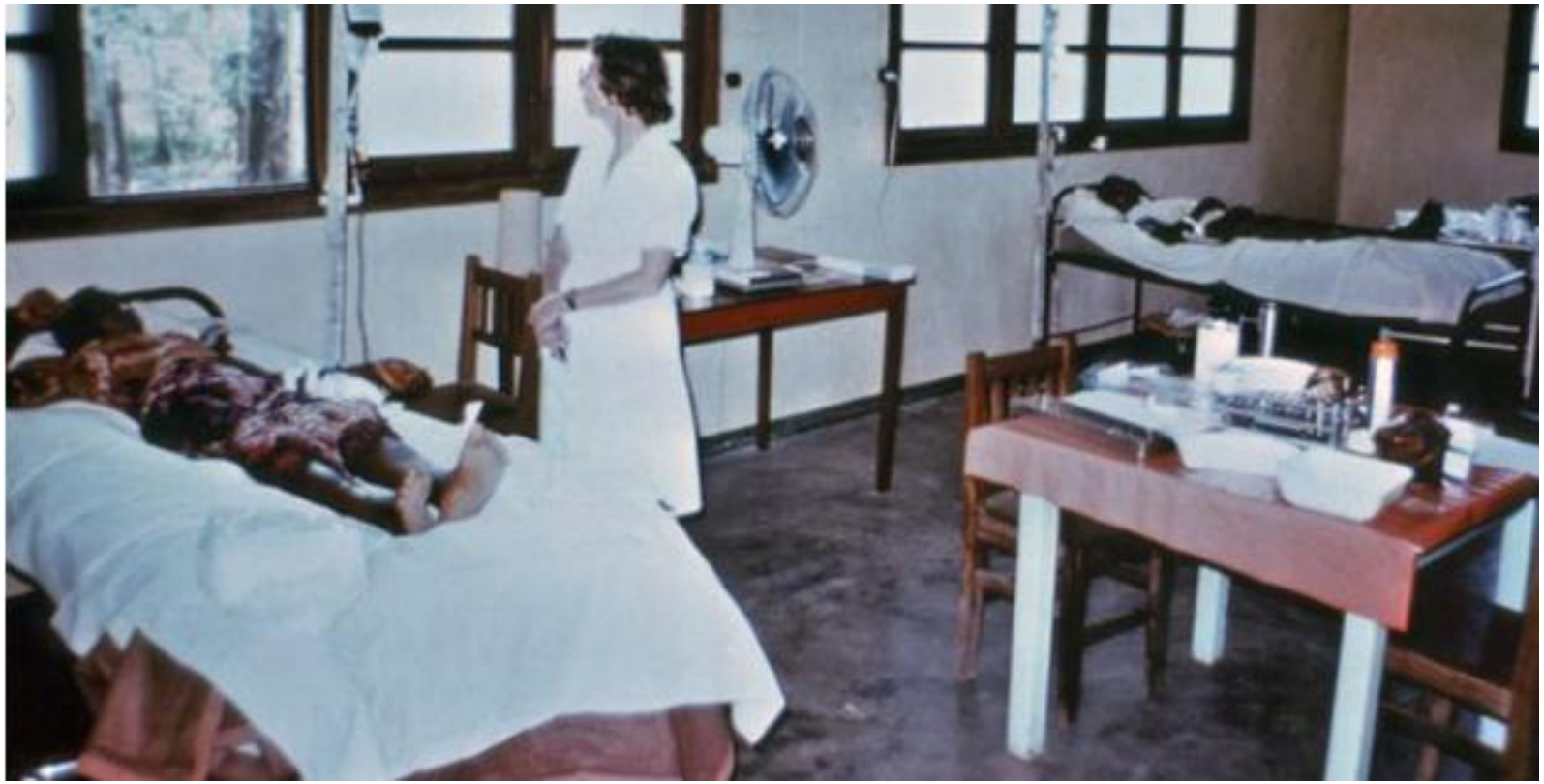


Photo Credit: Joel G. Breman, M.D., D.T.P.H

ID#: 7202

Content Provider(s): CDC/ Dr. Lyle Conrad

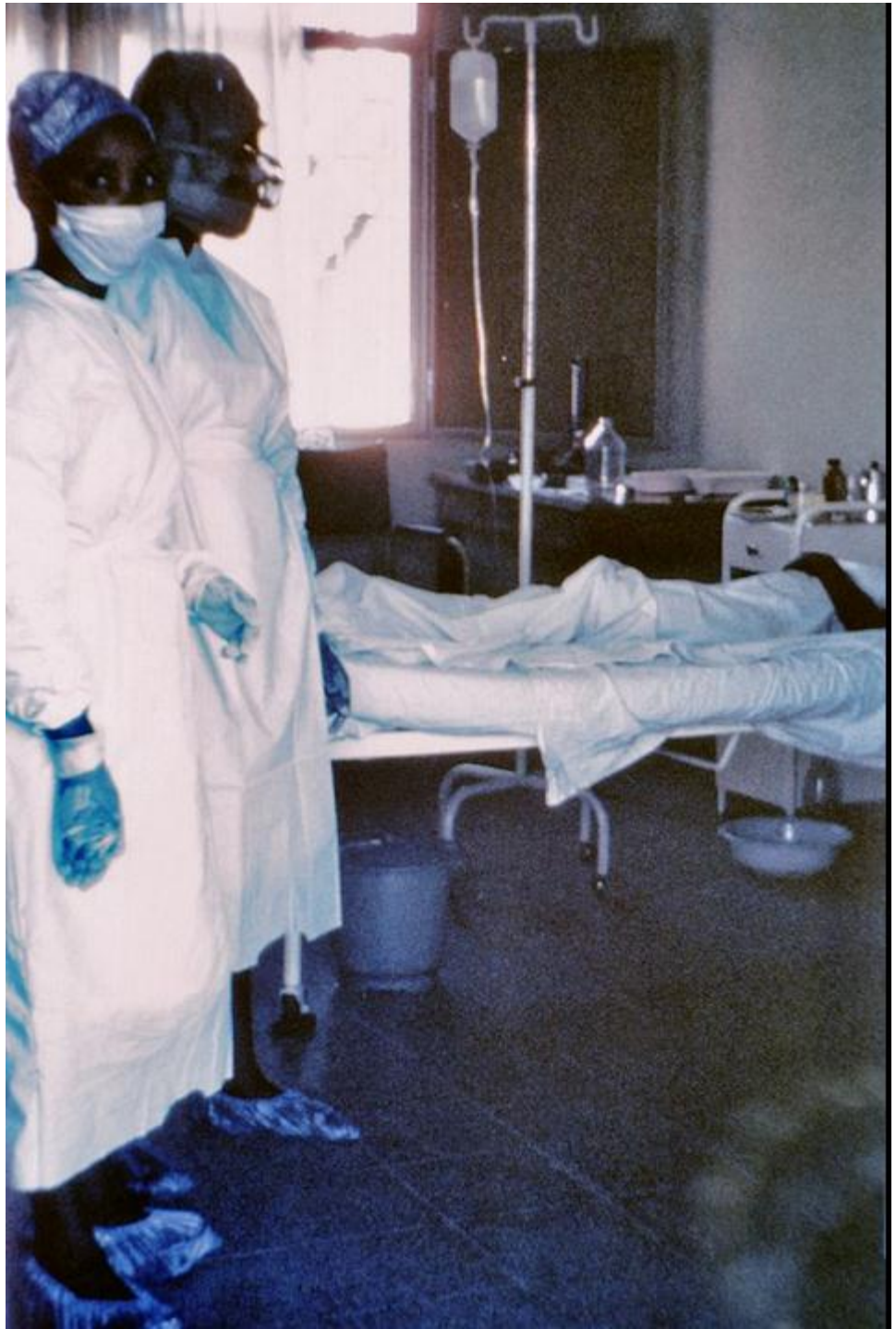


ID#: 7089

Photo Credit: Joel G. Breman, M.D., D.T.P.H.
Content Providers(s): CDC/ Dr. Lyle Conrad

"This photograph showed Dr. Margaret Isaacson as she was tending to the needs of an Ebola patient in a Yambuku, Zaire hospital theatre block that was used as a temporary ICU for Ebola patients during the country's 1976 outbreak. "

Ebola case #3 (1976)
This 1976 photograph shows two nurses standing in front of Ebola case #3, who was treated, and later died at Ngaliema Hospital, in Kinshasa, Zaire. Ebola hemorrhagic fever (Ebola HF) is a severe, often-fatal disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees) that has appeared sporadically since its initial recognition in 1976



This image was created by U.S. Army Africa, Chief Petty Officer Jerrold Diederich, and depicts U.S. Navy Lt. Jose Garcia, as he was inspecting specimen labels, and preparing for the first step in sample-processing at a Naval Medical Research Center (NMRC) mobile laboratory located on Bushrod Island, Liberia. The NMRC sent two mobile testing labs to Liberia to support Operation United Assistance (OUA). Each two-person lab is capable of testing up to 80 samples per day.

CDC/ U.S. Army Africa

Photo credit: Chief Petty Officer Jerrold Diederich/ U.S. Army Africa

ID#18118

This image was created by U.S. Army Africa, Chief Petty Officer Jerrold Diederich, and depicts U.S. Navy Lt. Jose Garcia, as he was inactivating the Ebola virus in each specimen, while wearing his personal protective equipment (PPE), which included a self-contained breathing apparatus. This step of sample processing renders the virus safe for further analysis at a Naval Medical Research Center (NMRC) mobile laboratory at Bushrod Island, Liberia. The NMRC sent two mobile testing labs to Liberia to support Operation United Assistance (OUA). Each two-person lab is capable of testing up to 80 samples per day.

CDC/ U.S. Army Africa, ID#18122

http://phil.cdc.gov/phil/details.asp

Photo credit: Chief Petty Officer Jerrold Diederich/ U.S. Army Africa

This image was created by U.S. Army Africa, Chief Petty Officer Jerrold Diederich, and depicts U.S. Navy Lt. Jose Garcia, as he was in the process of pipetting each of the patient samples into a 96 well testing plate for analysis, in order to identify the Ebola virus. Garcia works at a Naval Medical Research Center mobile laboratory located on Bushrod Island, Liberia. The NMRC sent two mobile testing labs to Liberia to support Operation United Assistance (OUA). Each two-person lab is capable of testing up to 80 samples per day

ID#18121

Photo credit: Chief Petty Officer Jerrold Diederich/ U.S. Army Africa

CDC/ U.S. Army Africa,

This image was created by U.S. Army Africa, Chief Petty Officer Jerrold Diederich, and depicts U.S. Navy Lt. Andrea McCoy in the process of extracting ribonucleic acid, known as RNA, from a patient sample at a Naval Medical Research Center (NMRC) mobile laboratory at Bushrod Island, Liberia. Extracted RNA would then be analyzed to determine if the Ebola virus was present in each respective specimen. The NMRC sent two mobile testing labs to Liberia to support Operation United Assistance (OUA). Each two-person lab is capable of testing up to 80 samples per day.

http://phil.cdc.gov/phil/details.asp

CDC/ U.S. Army Africa ID# 18124

Photo credit: Chief Petty Officer Jerrold Diederich/ U.S. Army Africa

“Depicted here in this 2007 photograph, was Centers for Disease Control microbiologist, and Special Pathogens Branch (SPB) staff member, as he was in the process of counting viral plaques within fixed monolayers of cells, which had been set atop a light box. While inside the organization’s Biosafety Level 4 (BSL-4) laboratory, this activity was taking place, thereby, enabling the laboratorian to titrate a viral stock. He was outfitted in an orange, air-tight, self-contained, positively-pressurized suit, which kept him free of possible contamination. See PHIL 10725 for another view of this activity. “ CDC

ID#10725

Content provider: CDC/ Dr. Scott Smith

“This 2007 image depicted Centers for Disease Control microbiologists as they were in the process of suiting up in order to access the interior of the organization’s Biosafety Level-4 (BSL-4) laboratory. The scientist on the left was attaching his supportive air hose, which would provide a supply of filtered, breathable air, as well as maintain positive air pressure inside his air tight orange suit. The Special Pathogens Branch works with BSL-4 viruses. These viruses are highly pathogenic and require handling in special laboratory facilities designed to contain them.”
CDC

Content providers: CDC / Dr. Scott Smith

Photo credit: James Gathany

References, page 1 of 2

- Bosio CM et al. Ebola and Marburg virus replicate in monocyte derived dendritic cells without inducing the production of cytokines and full maturation. J Infect Dis (2003) 188 (11): 1630-38. doi: 10.1086/379199
- Bray M. Epidemiology, pathogenesis and clinical manifestations of Ebola and Marburg virus disease. UpToDate. 2014. http://www.uptodate.com/contents/epidemiology-pathogenesis-and-clinical-manifestations-of-ebola-and-marburg-virus-disease.
- Bray M. Diagnosis and treatment of Ebola and Marburg virus disease. UpToDate. 2014. http://www.uptodate.com/contents/diagnosis-and-treatment-of-ebola-and-marburg-virus-disease
- Centers for Disease Control and Prevention at http://www.cdc.gov/vhf/ebola/
- Deere J, Iversen P, Geller BL. Antisense Phosphorodiamidate Morpholino Oligomer Length and Target Position Effects on Gene-Specific Inhibition in *Escherichia coli.* Antimicrob Agents Chemother. Jan 2005; 49(1): 249-255. doi: 10.1128/AAC.49.1.249-255.2005
- Feldmann H, Geisbert TW. Ebola Haemorrhagic Fever. Lancet. 2011 Mar 5;377(9768):849-62. doi: 10.1016/S0140-6736(10)60667-8
- Geisbert TW et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study.. Lancet29 May 2010; 375(9729): 1896-1905. doi:10.1016/140-6736(10)60357-1
- International Committee on Taxonomy of Viruses. Viral Taxonomy: 2013 Release. http://ictvonline.org/virusTaxonomy.asp
- King JW. Ebola virus infections. Medscape.2014. http://emedicine.medscape.com/article/216288-overview

References, page 2 of 2

- Leroy EM, Gonzalez JP, Baize S. Ebola and Marburg haemorrhagic fever viruses: major scientific advances, but a relatively minor public health threat for Africa. Clinical Microbiology and Infection; July 2011; 17 (7):964-76. doi: 10.1111/j.1469-0691.2011.03535.x
- Mahanty S, Bray M. Pathogenesis of Filoviral Haemorrhagic Fevers. Lancet Infect Dis. 2004 Aug; 4(8): 487-98. doi:10.1016/S1473-3099(04)01103-X
- Marzi A, Feldmann H, Geisbert TW, Falzarano D (2011) Vesicular Stomatitis Virus-Based Vaccines for Prophylaxis and Treatment of Filovirus Infections. J Bioterr Biodef S1:004. doi:10.4172/2157-2526.S1-004
- Morello L and Nature News Blog. Millions of Doses of Ebola Vaccine to Be Ready by End of 2015. October 27, 2014. http://www.scientificamerican.com/article/millions-of-doses-of-ebola-vaccine-to-be-ready-by-end-of-2015/
- Negredo N et al. Discovery of an Ebolavirus-Like Filovirus in Europe. PLoS Pathog. Oct 2011;7(10)e1002304. doi:10.1371/journal.ppat.1002304
- QUESTIONS AND ANSWERS Phase1 Clinical Trials of NIAID/GSK Investigational Ebola Vaccine, August 28,2014. http://www.niaid.nih.gov/news/QA/Pages/EbolaVaxQA.aspx
- Racaniello V. Treatment of Ebola virus infection with brincidofovir. Virology blog about viruses and viral disease. 9 Oct 2014. http://www.virology.ws/2014/10/09/treatment-of-ebola-virus-infection-with-brincidofovir/
- Smee DF et al. Intracellular metabolism of favipiravir (T-705) in uninfected and influenzaA (H5N1) virus-infected cells. J Antimicrob Chemother. Oct 2009; 64(4): 741-746. doi: 10.1093/jac/dkp274
- Sullivan N, Zhi-Yong Y, Nabel GJ. Ebola Virus Pathogenesis: Implications for Vaccines and Therapies. J. Virology. September 2003; 77 (18): 9733-9737. doi: 10.1128/JVI.77.18.9733-9737.2003