



Viral Hemorrhagic Fevers

Kris Paolino, MD
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UNCLASSIFIED



Thanks to:

COL Mark Kortepeter, MD, MPH

COL Art Lyons, MD

COL Clinton Murray, MD

LTC Rose Ressler, DO



Outline

- VHF – Overview of Syndrome
- Selected Pathogens:
 - Ebola
 - Crimean-Congo Hemorrhagic Fever
 - Lassa Fever
 - Hantaviruses
- Emerging Threats



Definition

- **Viral hemorrhagic fever (VHF):**
 - **Fever**
 - **Malaise**
 - **Myalgia**
 - **Prostration**
 - **Bleeding diathesis**
 - **Severe multi-organ failure**
 - **Enveloped, single-stranded, RNA viruses**
- Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF



Overview of VHFs

• Clinical Presentation

– Prodrome

- High fever, Headache, Malaise, Arthralgias, Myalgias
- Nausea, Abdominal pain, Non-bloody diarrhea

– Early signs

- Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
- Flushing, Skin Rash

– Late

- ↓ BP, Hemorrhagic diathesis, Petechiae, Mucous membrane
- Conj. hemorrhage, Hematuria, Hematemesis, Melena

– Severe Manifestations

- DIC, Circulatory Shock, CNS dysfunction, Death
- Mortality rates can be as high as 90%+



Overview of VHFs

DISEASE	Hemorrhage	Thrombocyto-penia	Leucocyte count	Rash	Icterus	Renal Disease	Pulmonary Disease	Tremor, Dysarthria	Encephalo-pathy	Deafness	Eye Lesions
ARENAVIRIDAE											
South American HF	+++	+++	UUU	0	0	0	+	+++	++	0	0
Lassa fever	+/S	+	0	++	0	0	+	+	+/S	++	0
BUNYAVIRIDAE											
Rift Valley fever	+++	+++		0	++	+		0	E	0	Retina
Crimean Congo HF	+++	+++	UU/∅	0	++	0	+	0	+	0	0
HFRS	+++	+++	∅∅∅	0	0	+++	+	0	+	0	0
HPS	+	++	∅∅	0	0	+	+++	0	+	0	0
FILOVIRIDAE											
Marburg and Ebola HF	++	+++		+++	++	0	+	0	++	+	Uveitis Retina?
FLAVIVIRIDAE											
Yellow fever	+++	++	0/UU	0	+++	++	+	0	++	0	0
DHF/DSS	++	+++	∅∅	+++	+	0	+	0	+	0	0
KFD/OHF	++	++	UU	0	0	0	++	0	E	0	Retina

Courtesy of Drs. Zaki & Peters

- + occasional or mild
- ++ commonly seen, may be severe
- +++ characteristic and usually marked

S characteristic, seen in severe cases

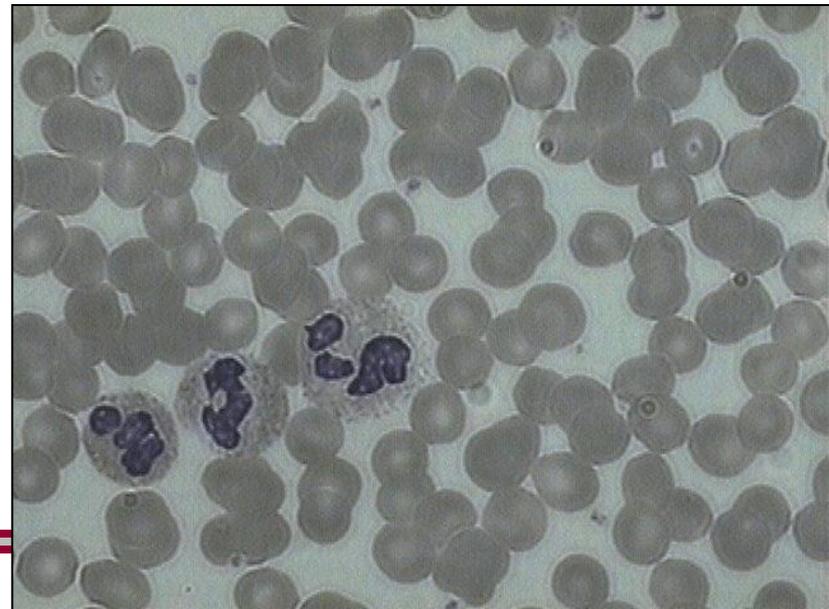
- ∅ occasionally or mildly increased
- ∅∅ commonly increased, may be marked
- ∅∅∅ characteristically increased and usually marked

E Develop true encephalitis but either after HF (KFD, Omsk) or in other patients (RVF)

Overview of VHF

- **Lab Abnormalities**

- Leukopenia
- Hemoconcentration (early) → Anemia
- Thrombocytopenia
- Elevated liver enzymes
- May have renal dysfunction
- Coagulation abnormalities
 - Prolonged bleeding time
 - Prothrombin time
 - Activated PTT
 - ↑ D-dimer
 - ↓ fibrinogen



Overview of VHF's

- **Lab Abnormalities and Disease Presentations**
 - These are not hard and fast rules.
 - There will be overlap with many of these infections





Bolivian Hemorrhagic Fever (Machupo virus – New World Arenavirus)



Conjunctival injection & subconjunctival hemorrhage

Ref: Current Science/Current Medicine (Peters CJ, Zaki SR, Rollin PE). Viral hemorrhagic fevers. In: Fekety R, vol ed. Atlas of Infectious Diseases, p10.1-10.26, Volume VIII, 1997.





CCHF



Left arm. Ecchymosis, diffuse, severe.
(1 week after clinical onset)

Photo credit: Robert Swaneopoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.





CCHF





BOLIVIAN HEMORRHAGIC FEVER (MACHUPO)



**KOREAN
HEMORRHAGIC
FEVER (HANTAAN)**





CCHF



Marburg Infection Human



Maculopapular rash

Photo credit: Martini GA, Knauff HG, Schmidt HA, et. al. *Ger Med Mon.* 1968:13:457-470.



Overview of VHF_s

- **General Summary of What is Known...**
 - Pathogens
 - Geographic distribution
 - Animal hosts and vectors
 - Nosocomial and occupational risks
 - Estimated incubation periods



Overview of Etiologic Agents of VHFs

Family	Genus	Species
<i>Filoviridae</i>	<i>Ebolavirus</i> <i>Marburgvirus</i>	Zaire, Sudan, Ivory Coast, Bundibugyo, Reston Lake Victoria marburgvirus
<i>Arenaviridae</i>	<i>Arenavirus</i>	Lassa, Lujo (“Old World”) Junin, Machupo, Guanarito, Sabia, (“New World”)
<i>Bunyaviridae</i>	<i>Nairovirus</i> <i>Phlebovirus</i> <i>Hantavirus</i>	Crimean-Congo hemorrhagic fever Rift Valley fever Hantaan, Seoul, Puumala, Dobrava, Sin Nombre
<i>Flaviviridae</i>	<i>Flavivirus</i>	Omsk HF Kyasanur forest disease (including Alkhurma) Dengue Yellow fever



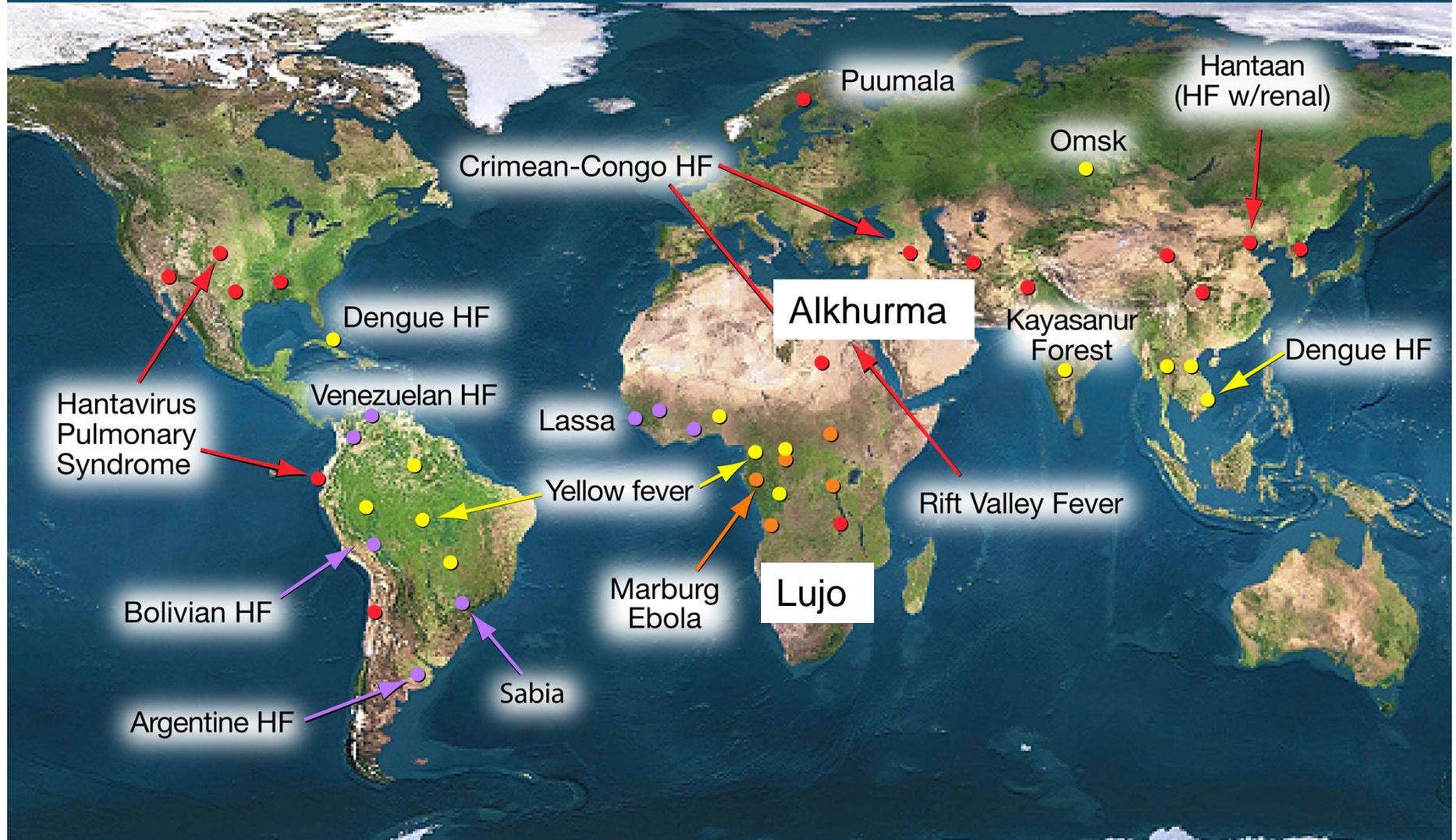
Disease (Virus)	Distribution	Host/Vector	Other risks	Incubation	CFR
Ebola	Africa, Philippines (ER)	Bats/Pigs?	Nosocomial	2-21	25 - 88% (~67%)
Marburg	Africa	Bats?	Nosocomial	5-10	82%
Lassa (and Lujo)	Africa (Western)	Rodent	Nococomial	5-16	15-80%
Junin	Argentina	Rodent	Nococomial	7-14	10-30%
Machupo	Bolivia	Rodent	Nococomial	9-15	5-30%
Guanarito	Venezuela	Rodent	Nococomial	7-14	23%
Sabia	Brazil	Rodent	Nococomial	7-14	1 of 3
Crimean-Congo	Europe, Asia, Africa	Tick, herding animals, birds?	Nosocomial, slaughterhouse	3-12	3 - 70% (~20-30%)
Rift Valley Fever	Africa	Mosquito	slaughterhouse	2-6	1 - 50%
Hantaviruses	Worldwide	Rodent	Nosocomial (Andes virus)	9-35	1-15% (~50% HPS)
Omsk	Soviet Union	Tick		2-9	0.3-5%
Kyasanur	India	Tick		2-9	3-5%
Alkhumra	Middle East	Tick (Camels?)	Butchers	2-9	~30%
Yellow Fever	Africa, Americas	Mosquito		3-6	20-50%

Overview of VHF's

- **Geography of VHF**



Viral Hemorrhagic Fever



● Filoviruses ● Flaviviruses ● Bunyaviruses ● Arenaviruses

Courtesy of Mike Bray, NIAID

Domestically Acquired Seoul Virus Causing Hemorrhagic Fever with Renal Syndrome—Maryland, 2008

**Christian Woods,¹ Rakhee Palekar,^{2,3} Peter Kim,¹ David Blythe,²
Olivier de Senarclens,¹ Katherine Feldman,² Eileen C. Farnon,⁴
Pierre E. Rollin,⁴ Cesar G. Albariño,⁴ Stuart T. Nichol,⁴
and Margo Smith¹**

¹Washington Hospital Center, Washington, DC; ²Maryland Department of Health and Mental Hygiene, Baltimore, Maryland; ³Epidemic Intelligence Service, Office of Workforce and Career Development, and ⁴Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

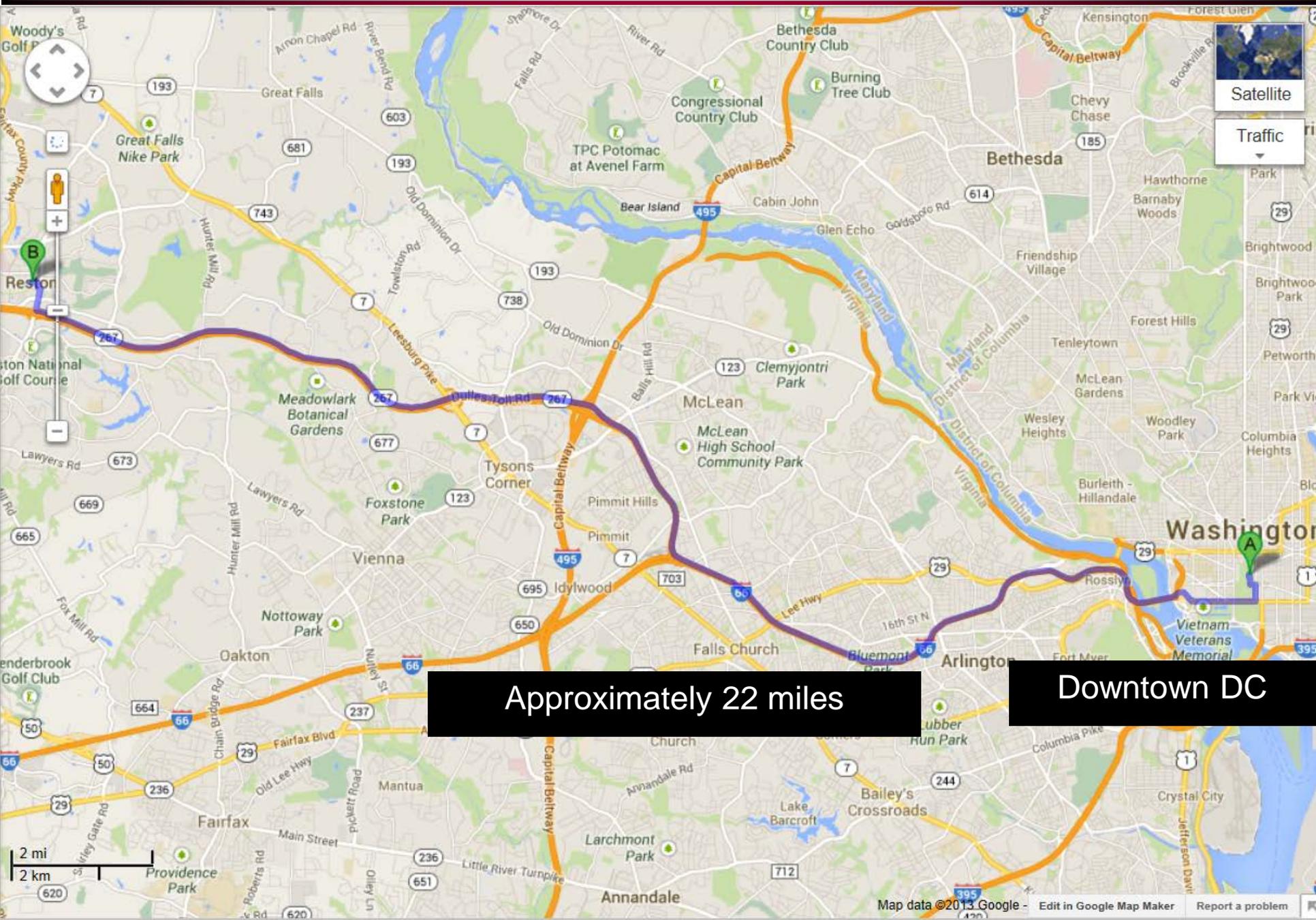
Overview of VHF's

Why do we even care?

Most of these infections are not where near the United States. Why should the U.S. use resources and risk personnel?



Ebola Reston



Approximately 22 miles

Downtown DC



Imported Case of Marburg Hemorrhagic Fever --- Colorado, 2008

Marburg hemorrhagic fever (MHF) is a rare, viral hemorrhagic fever (VHF); the causative agent is an RNA virus in the family *Filoviridae*, and growing evidence demonstrates that fruit bats are the natural reservoir of Marburg virus (MARV) (1,2). On January 9, 2008, an infectious disease physician notified the Colorado Department of Public Health and Environment (CDPHE) of a case of unexplained febrile illness requiring hospitalization in a woman who had returned from travel in Uganda. Testing of early convalescent serum demonstrated no evidence of infection with agents that cause tropical febrile illnesses, including VHF. Six months later, in July 2008, the patient requested repeat testing after she learned of the death from MHF of a Dutch tourist who had visited the same bat-roosting cave as the patient, the Python Cave in Queen Elizabeth National Park, Uganda (3). The convalescent serologic testing revealed evidence of prior infection with MARV, and MARV RNA was detected in the archived early convalescent serum. A public health investigation did not identify illness consistent with secondary MHF transmission among her contacts, and no serologic evidence of infection was detected among the six tested of her eight tour companions. The patient might have acquired MARV infection through exposure to bat secretions or excretions while visiting the Python Cave. Travelers should be aware of the risk for acquiring MHF in caves or mines inhabited by bats in endemic areas in sub-Saharan Africa. Health-care providers should consider VHF among travelers returning from endemic areas who experience unexplained febrile illness.

Minnesota Lassa fever case is first in US since 2010

Filed Under: [Lassa](#); [VHF](#)

[Robert Roos](#) | News Editor | [CIDRAP News](#) | Apr 04, 2014

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A Minnesota man who recently returned from a trip to West Africa is being treated for the viral disease Lassa fever, marking the first US case since 2010, Minnesota and federal officials announced today.

The man is hospitalized in stable condition and is recovering, the Minnesota Department of Health (MDH) and the Centers for Disease Control and Prevention (CDC) said in statements. They said the disease does not spread through casual contact, but they are working to identify and notify airline passengers and others who may have had contact with the patient.

In West Africa, Lassa virus is carried by rodents and spreads to humans through contact with rodent urine or droppings, the health agencies said. In rare cases it can spread from person to person through direct contact with a sick person's blood or bodily fluids, through mucous membranes, or through sexual contact. cases of Lassa fever and 5,000 deaths each year.



CDC / C. S. Goldsmith

Micrograph shows Lassa fever virus, which is rare in the United States but causes 100,000 to 300,000 illnesses annually in West Africa.

Potential of VHF's for Weaponization

- PRO

- Many demonstrated as infectious by aerosol transmission
 - Exception is Dengue
- Potentially high morbidity and mortality
- Replicate well in cell culture
 - Exception are viruses in *Bunyaviridae* (e.g. CCHF)
- Capability to overwhelm medical resources
- Frightening effects of illness / terror value

- CON

- Lack of treatment or vaccine to protect user's own "troops"
 - May not be deterrent for some countries / non-state actors
- Possible entry into local vector / reservoir population
- Stabilizers must be used to enhance viability



Other Military Relevance: History of Weaponization

- Yellow fever and RVF were weaponized by the U.S. during their offensive program
- Former Soviet Union produced large quantities of Ebola, Marburg, Lassa, Junin, and Machupo
- Yellow fever may have been weaponized by North Koreans
- **The Aum Shinrikyo cult unsuccessfully tried to obtain Ebola virus to create biological weapons**
- Several studies have demonstrated ability to aerosolize Ebola, Marburg, Lassa, and some of the New World arenaviruses



Overview of VHF's

How are VHF's Spread?

- 1 - Inhaling or ingesting excretions/secretions from rodent hosts (urine, feces)
- 2 - Bite of an infected arthropod (tick, mosquito)
- 3 - Nosocomial/lab transmission – contact with human or animal blood/body fluids/tissue
- 4 - Artificially generated aerosols (biowarfare)





Overview of VHF

How are VHF spread?

Airborne?

- In monkeys, possible airborne transmission between cages 3 m
- Lung tissue, along with nares, pharynx, and conjunctiva w/virus
- Monkeys and guinea pigs able to be infected via airborne route

Arch Pathol Lab Med 1996;120: 140-5.
Int J Exp Path 1995;76:227-36.

Lancet 1995;346:1669-71.
Arch Virol 1996(suppl);11:115-134.



Overview of VHFs

How are VHFs spread?

Direct Human to Human Transmission?

Typical story for nosocomial transmission:

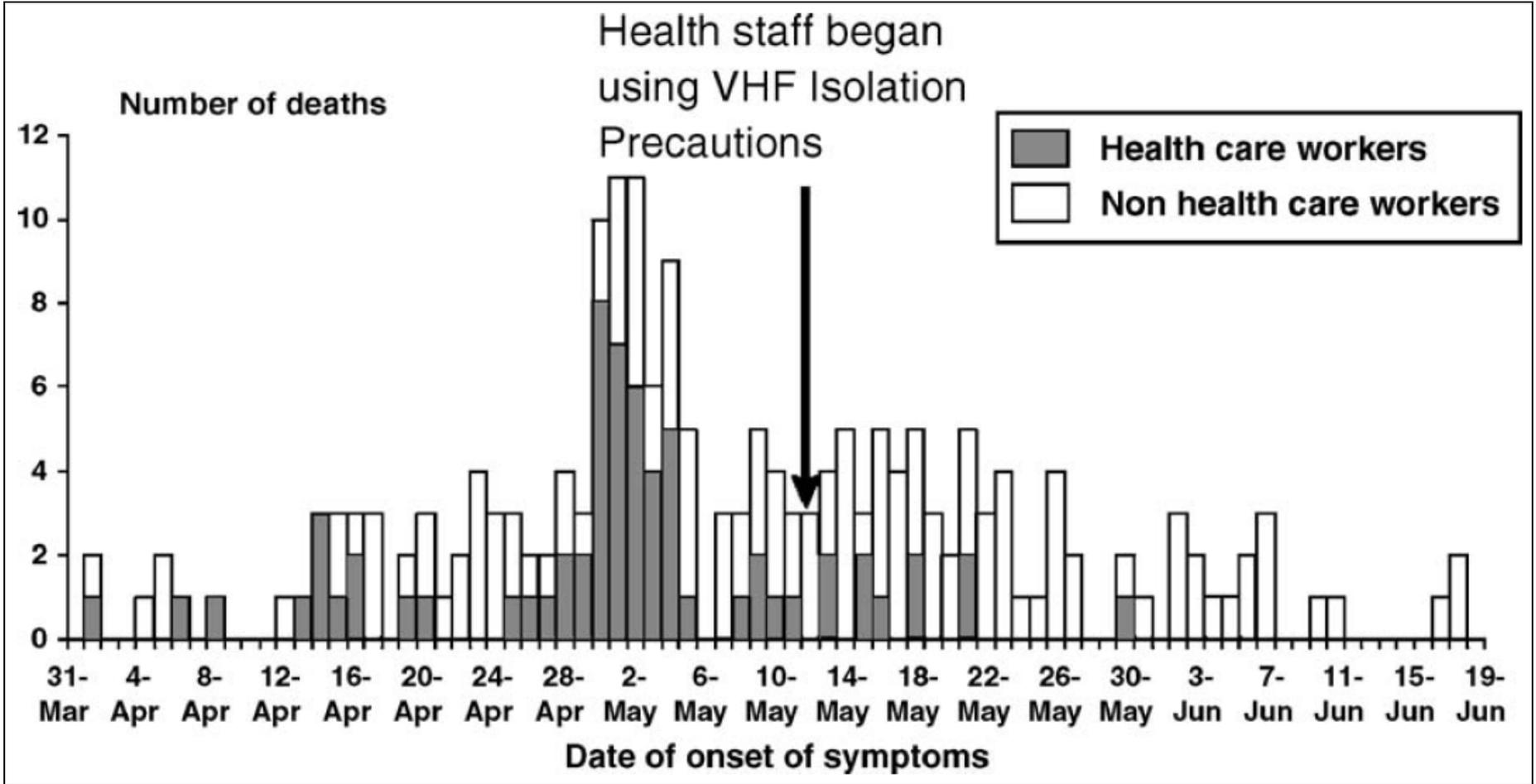
- Patient Zero enters the health care facility
- VHF is not recognized or infection control not followed
- Unrecognized spread from blood/body fluid contact
- **Health care personnel among the victims**
- Victims carry infection to the community
- Close family members and those doing burial rites infected

No **proven** human to human respiratory transmission

- A possibility in rare circumstances, in later stages of disease

MMWR 1995;44(25):475-79.





Number of infected health care workers declined after barrier nursing practices were begun during the Ebola HF outbreak in Kikwit, DRC, 1995.

Critical Care Clinics (2005) 21:765-783.



Overview of VHF

How are VHF spread?

Nosocomial

Filoviruses – **Ebola** and **Marburg**

Arenaviruses – **Lassa**, Junin/Machupo (rare)

Bunyaviruses – **CCHF**, Andes virus (a cause of HPS)

Flaviviruses – Dengue (rare – from blood splash)

Lassa – most common imported VHF
(if dengue not included)

Transmission of VHF rarely if ever occur prior to onset of symptoms



Overview of VHFs

Differential Diagnosis

- Malaria
- Typhoid fever (*Salmonella*)
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
- Other rickettsioses
- Leptospirosis
- Meningococci
- Q fever (*Coxiella burnetii*)
- Plague
- Influenza
- Viral meningitis / encephalitis
 - Herpesviruses
- HIV / co-infection
- Hemorrhagic smallpox
- Vasculitis (i.e. autoimmune diseases)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Hemophagocytic syndrome

Clinical presentation: Fever, hemorrhage/purpura, thrombocytopenia, CNS signs, elevated LFTs, leukopenia, thrombocytopenia, DIC, multisystem / multi-organ failure



Overview of VHFs

This stuff is all great, but in reality you may not have readily available basic labs let alone PCR capabilities

• Diagnosis

- **High index of suspicion (know what is in your AO)**
- Lab findings
 - Thrombocytopenia , low WBC, anemia, transaminitis, increased bilirubin, prolonged PT, PTT, increased D-dimer, decreased fibrinogen
- Virus isolation (Gold Standard, but requires BSL-4 Lab)
- Electron microscopy
- Reverse transcription - polymerase chain reaction (RT-PCR)
- Rapid ELISA techniques (most easily employed)
- Immunohistochemistry (IHC) & in situ hybridization (ISH) of infected tissues



Overview of VHF

• Treatment

- **Early Supportive Care (the foundation of treatment)**
 - Careful management of fluid and electrolytes (PICC line early)
 - Blood transfusions as needed (whole blood if available)
 - Hemodialysis as needed
 - Vasopressors and cardiotoxic drugs (some do not respond to fluids)
 - Monitor for signs of hypotension and shock
 - Cautious sedation and analgesia
 - Watch for secondary infections (add broad spectrum antibiotics, malaria RDTs vs. empiric treatment)
- Treatment of Disseminated Intravascular Coagulation (DIC)
 - Coagulation studies and clinical judgment as guide
 - Replacement of coagulation factors / cofactors
 - Platelet transfusions
 - **No aspirin, NSAIDs, anticoagulant therapies, or IM injections**
 - Use acetaminophen for pain or fevers



Overview of VHF

• Treatment

– Ribavirin

- Investigational drug, compassionate use
- **Contraindicated in pregnancy**
- Arenaviridae (Lassa, Junin, Sabia, Lujo)
- Bunyaviridae (Hantaan, CCHF) – *not* RVF
- NO UTILITY FOR FILOVIRUSES OR FLAVIVIRUSES

– Monoclonal antibodies (experimental)

– Immune (convalescent) plasma

- Arenaviridae (Junin, Machupo; ?Lassa)
- Passive immunoprophylaxis post-exposure?
- Experimental studies in animals have not proven efficacy against filovirus infection
- NOT READILY AVAILABLE



Overview of VHF_s

- Ribavirin Treatment

- 30 mg/kg IV single loading dose
- 15 mg/kg IV q 6 hr for 4 days
- 7.5 mg/kg IV q 8hr for 6 days

Risks:

- Upset stomach
- Reversible hemolytic anemia
- Arrhythmias
- Teratogenic

- Ribavirin Post-Exposure Prophylaxis

- 500 mg PO q 6 hr for 7 days
- 35 mg/kg x 1, then 15 mg/kg Q8hrs x10 days (WHO)

Note: Parenteral (Rx) and oral Ribavirin (PEP) are **investigational** and available only through human use protocols

Borio L, et al. *JAMA* 287(18):2391-2405, 2002

McCormick JB et al. *N Eng J Med* 314(1):20-26, 1986

Jahrling PB et al. *J Infect Dis* 141:580-589, 1980



Overview of VHF

	Contained Casualty	Mass Casualty
Adults	Same as previous slide	Load 2g po x 1, followed by 1.2g po qd divided in 2 doses (if >75kg pt), or 1g po qd in 2 doses (if pt <75kg) for 10 days
Pregnant	Same as adults	Same as adults
Children	Same as Adults, dosed according to weight	Loading dose 30mg/kg po x1, followed by 15mg/kg qd in 2 divided doses for 10 days

RIBAVIRIN TREATMENT

Prevention / Control

- **YELLOW FEVER**
 - Licensed 17D vaccine, highly efficacious
 - Live virus vaccine
 - Reports of vaccine associated deaths
 - Cannot be used in persons with egg allergy



Prevention / Control: None Licensed in the U.S.

- Ebola

- Adenovirus (Ad3) vectored +/- DNA prime
- Vesicular Stomatitis Virus (VSV) vectored
- Adenovirus (Ad26) + Modified Vaccinia Ankara filovirus vaccine
- VEE replicons
- Virus-like particles (VLP)

- Marburg

- Recent NHP study at USAMRIID: 100% survival following challenge w/ lethal dose of MBGV and then post-exposure treatment w/ recombinant VSV-GP Marburg vaccine



Overview of VHFs

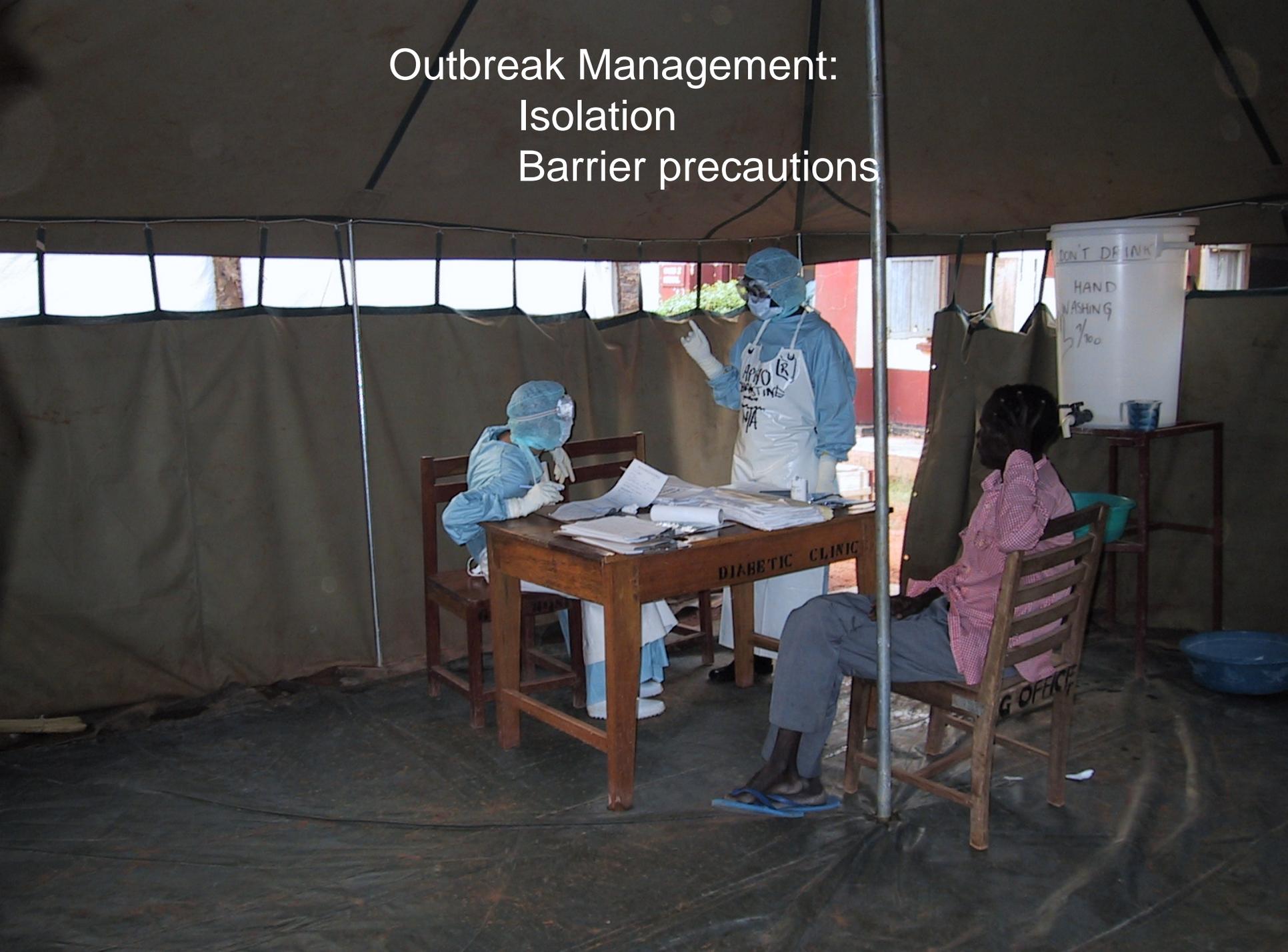
- CDC Recommendations - when to go “hot”
 - Standard Precautions in initial assessments
 - Private room upon initial hospitalization
 - “Barrier precautions” – including face shields, surgical masks, eye protection within 3 feet of patient (double glove, impermeable gown)
 - Have your VHF “battle buddy” double check you
 - Negative pressure room not required initially, but should be considered early to prevent later need for transfer
 - Airborne precautions if prominent cough, vomiting, diarrhea, hemorrhage
 - E.g. HEPA masks, negative pressure isolation

<http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html>

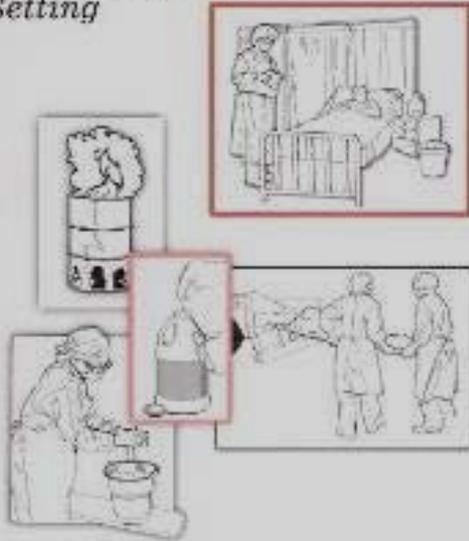
MMWR 1988;37(S-3):1-16. MMWR 1995;44(25):475-79.



Outbreak Management: Isolation Barrier precautions



*Infection Control for
Viral Haemorrhagic Fevers
in the African
Health Care
Setting*



World Health Organization



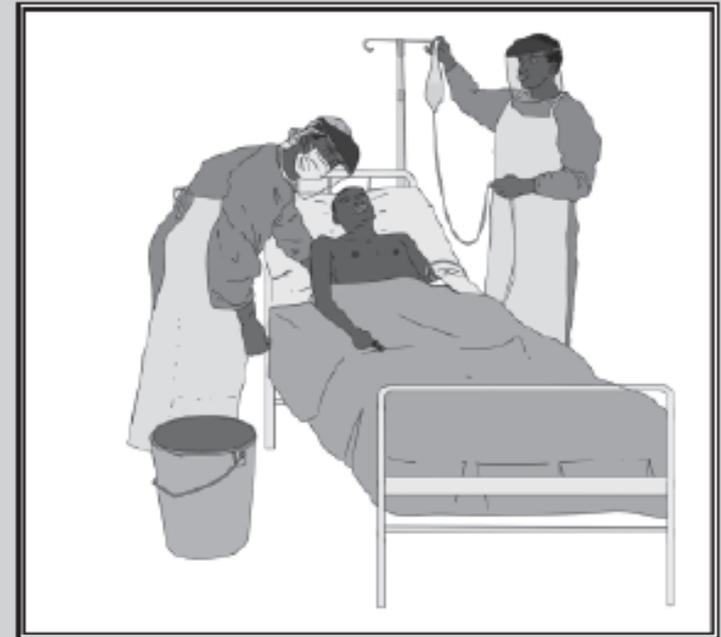
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service



Clinical Management of Patients with Viral Haemorrhagic Fever:

A Pocket Guide for the Front-line Health Worker

30 MARCH 2014



Interim emergency guidance- generic draft
for West African adaptation



World Health
Organization

www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm

<http://www.who.int/csr/resources/publications/clinical-management-patients/en/>



Overview of VHFs

- Identify a minimum level of Standard Precautions
 - Establish routine hand washing
 - Establish safe handling and disposal of used sharps
 - Minimize the use of sharps if possible
 - Identify a VHF coordinator to oversee and coordinate activities associated with VHF isolation precautions



Overview of VHFs

- Isolation Procedures
 - Isolate the patient in a pre-selected area
 - Wear protective clothing:
 - Scrub suit, gown, apron, two pairs of gloves, mask, headcover, eyewear, rubber boots
 - Clean/disinfect spills, waste, and reusable safety equipment, soiled linens, and laundry safely
 - Use safe disposal methods for non-reusable supplies and waste
 - Counsel staff about the risk of transmission
 - Limit exposure to patient (use an “authorized” list and use a guard)
 - Provide information to families and the community about VHF prevention and care of patients
 - Consider all samples **highly infectious**
 - Surgical mask for patient for any patient movement

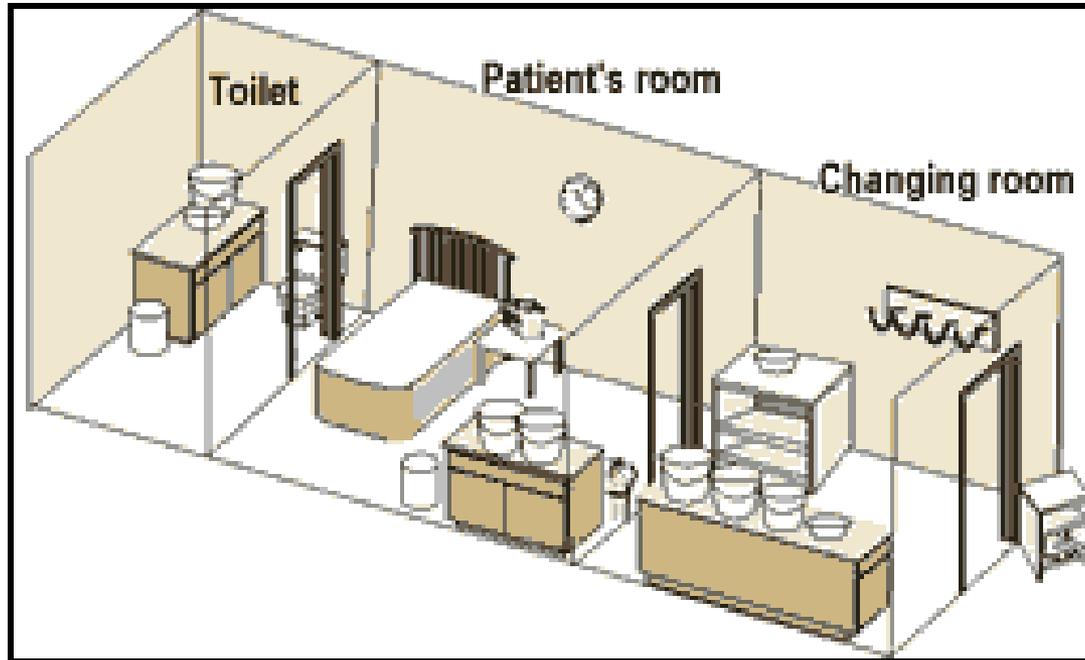


Overview of VHFs

- Isolation Area
 - Single room with adjoining toilet or latrine
 - Prefer to use chemical toilets if possible (5% sodium hypochlorite)
 - Changing area to put on PPE
 - Hand washing stations
 - Separate building or ward for VHF patients only
 - An area in a larger ward that is separate and far away from other patients
 - An uncrowded corner of a large room or hall
 - Any area that can be separated from the rest of the health facility



Overview of VHF



– Disinfection solutions

- 0.5% sodium hypochlorite (Dakin's solution)
- 2% glutaraldehyde
- Phenolic disinfectants (0.5%-3.0%)
- Soaps and detergents

Overview of VHF

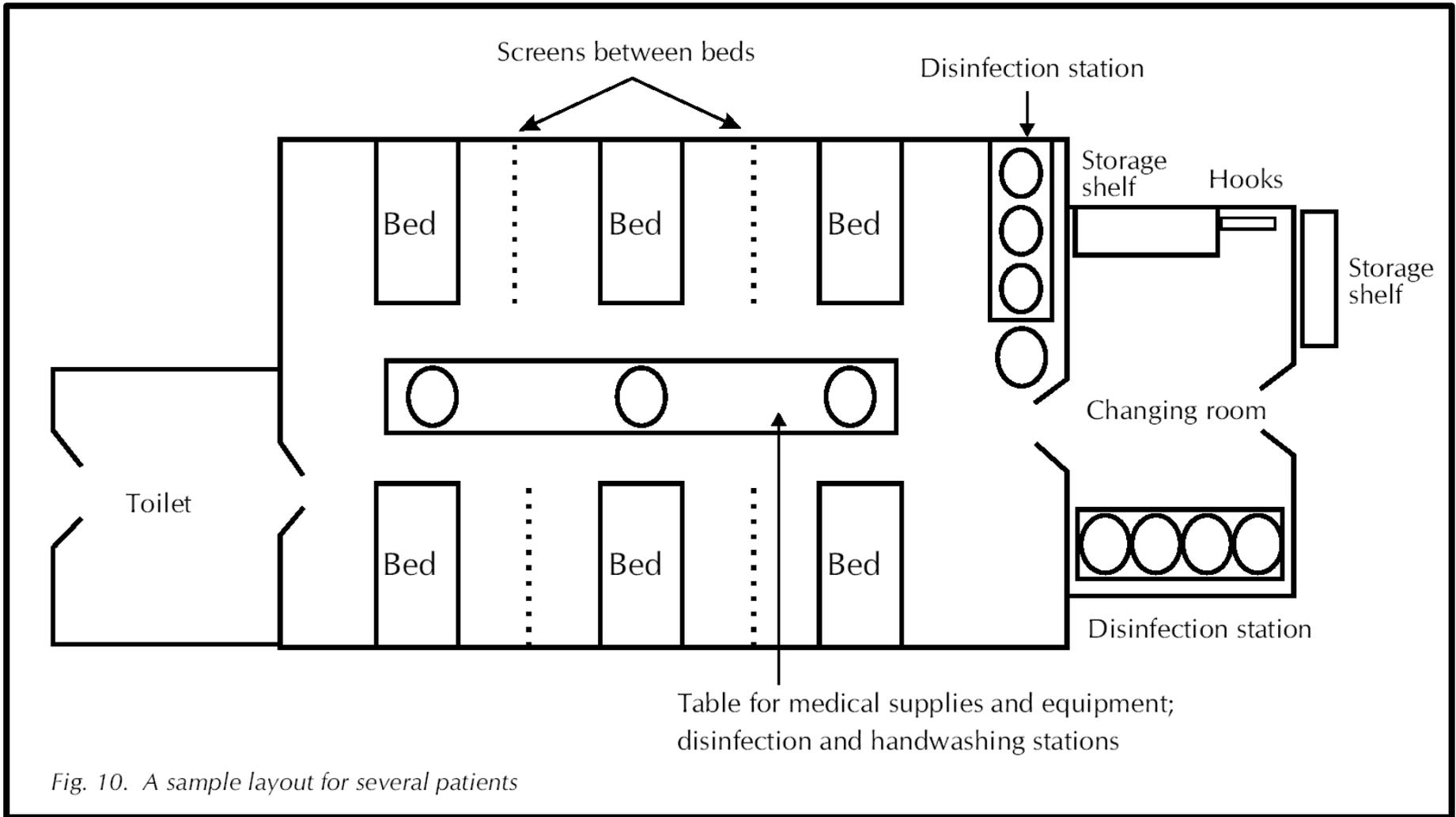


Fig. 10. A sample layout for several patients





**Identify a single lab personnel that will handle the samples
-lab testing may not be available at all**





Overview of VHF's

- First Aid for Exposures
 - Anticipate in advance – be prepared
 - Wash / irrigate wound or site immediately
 - Mucous membrane (eye, mouth, nose)
 - Continuous irrigation with rapidly flowing water or sterile saline for > 15 minutes
 - Percutaneous
 - Scrub for at least 15 minutes while copiously soaking the wound with soap or detergent solution
 - Fresh Dakin's solution (0.5% hypochlorite)



Overview of VHF

- Casual contacts:
 - Remote contact (same airplane/hotel)
 - No surveillance indicated
- Close contacts:
 - Housemates, nursing personnel, shaking hands, hugging, handling lab specimens
 - Place under surveillance when diagnosis confirmed
 - Record temperatures **twice daily** x 3 wks
 - Notify for temperature $\geq 101^{\circ}$
- High-risk:
 - Mucous membrane contact (kissing, sex) or needle stick or other penetrating injury involving blood/body fluid
 - Place under surveillance as soon as diagnosis is considered
 - Immediately isolate for temperature $\geq 101^{\circ}$

If you are dealing with something where ribavirin may be of benefit consider it as a post-exposure prophylaxis option

MMWR 1988;37:1-16



Additional Resources

Ebola (Ebola Virus Disease)

Ebola (Ebola Virus Disease)
About Ebola
2014 West Africa Outbreak +
2014 Democratic Republic of the Congo Outbreak
Outbreak List +
Signs and Symptoms
Transmission
Risk of Exposure
Prevention
Diagnosis
Treatment
Healthcare Workers -
Case Definition for Ebola Virus Disease (EVD) +

[CDC](#) > [Ebola \(Ebola Virus Disease\)](#) > [Healthcare Workers](#) > [Safety Training Course: Healthcare Workers Going to West Africa](#)

Detailed information on CDC's Safety Training Course for Healthcare Workers Going to West Africa in Response to the 2014 Ebola Outbreak

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CDC's Safety Training Course for Healthcare Workers Going West Africa in Response to the 2014 Ebola Outbreak is intended to provide the first step in training that will help prepare healthcare personnel (HCP) to provide medical care to Ebola patients in an Ebola Treatment Unit (ETU) that has been established and is staffed by MSF personnel, or in a facility that maintains MSF standards of care, or in an ETU established and staffed by WHO personnel. Further training (see below), under the direct supervision of qualified personnel in an ETU, should follow this course.

Participants should understand that providing care or conducting activities in other ETUs (e.g., a non-MSF, non-WHO Ebola treatment center or a general hospital) may not offer the same level of engineering and/or administrative infection control measures that an MSF- or WHO-ETU provides. This course may not provide sufficient training to work safely in such environments.

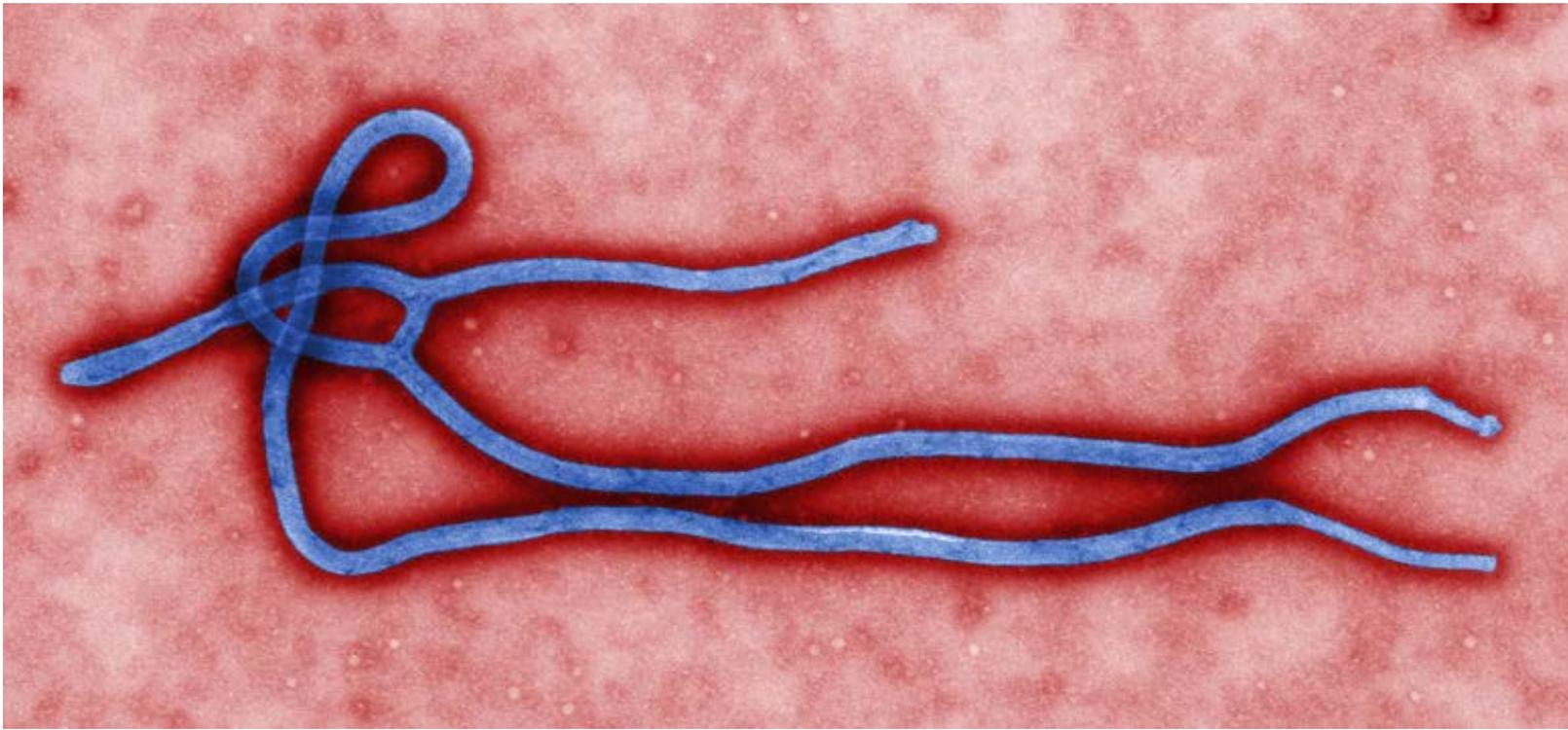
Participants intending to take this course should be currently licensed by a recognized professional agency to provide clinical care in some jurisdiction (e.g., hold a medical license to provide care in a state in the United States) and have recent relevant experience providing direct care to patients. The course is intended for licensed medical doctors (MD, DO degrees), licensed nurses (RN, BSN, LPN, etc.), and other licensed clinical care providers (e.g., paramedics, physician assistants, and other clinical providers). This course is designed to instruct practitioners on how to protect themselves from infection while providing basic clinical care to Ebola patients, and assumes clinical proficiency and familiarity with standard infection control as practiced at this time in North American healthcare facilities. This course will not provide general medical training or instruction on advanced medical topics.



Overview of VHF

- Summary for the Deploying Provider
 - Identify the potential KNOWN risks in your AO
 - Identify your unit's VHF coordinator
 - Keep track of all patient contacts
 - Identify your evac plan BEFORE you need it
 - Identify nearest medical support that can handle such patients
 - Could your patient benefit from ribavirin? Other meds?
 - Have your nearest infectious disease and prev med support on speed dial
 - If going in support of the Ebola outbreak, familiarize yourself with the WHO handbooks and OTSG Clinical Practice Guidelines (in draft form)





EBOLA



Ebola

- Filovirus (Marburg virus is related)
- Several different strains
 - Zaire, Sudan, Ivory Coast, Bundibugyo, (Reston)
- First identified in 1976
- Has become the “prototypical” VHF
 - Classic bleeding diatheses
 - High case fatality rates
 - Significant nosocomial risk
 - Incubation typically 8 – 10 days (2 days to 3 weeks)

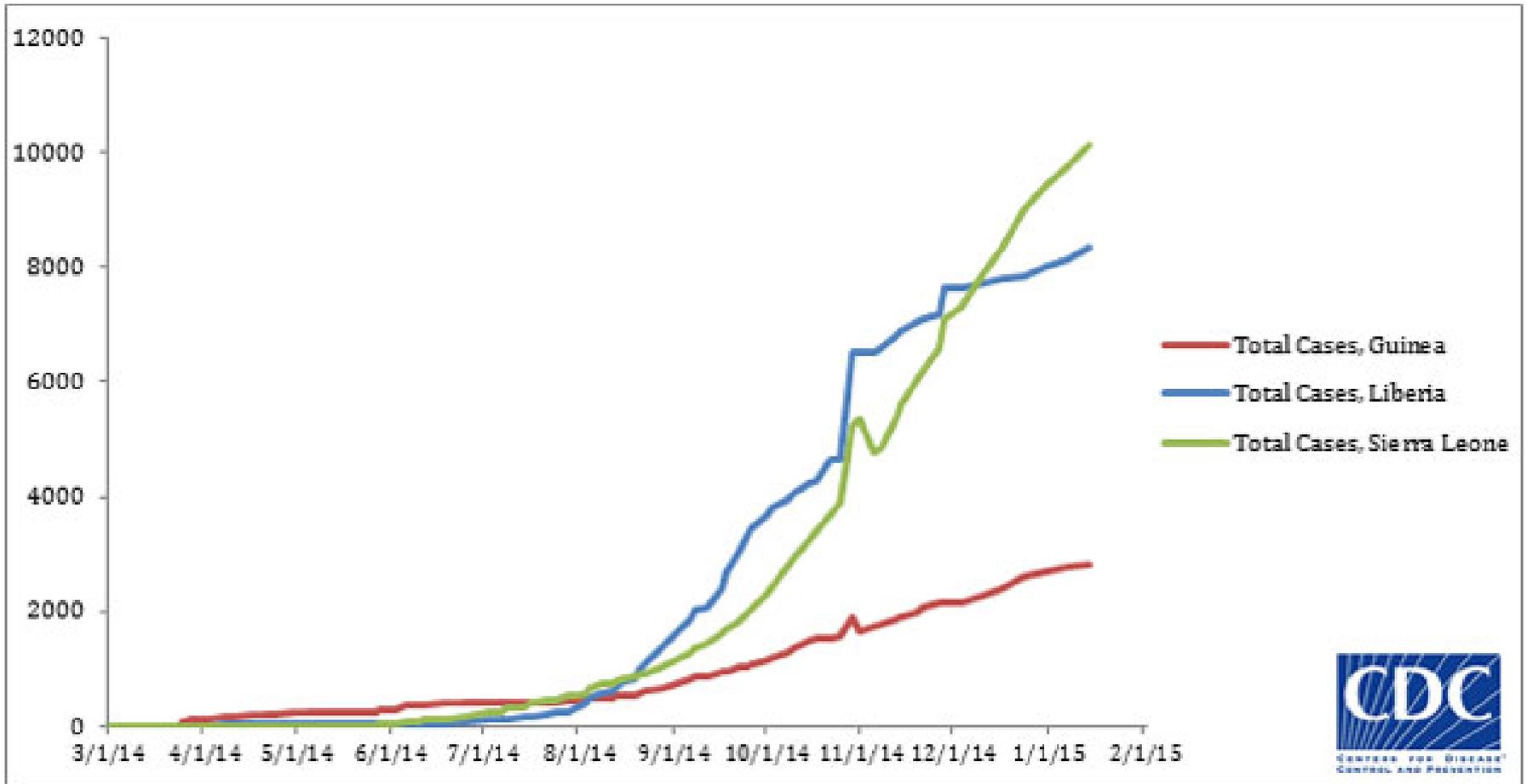


Ebola Current Outbreak (as of 16 JAN 2015)

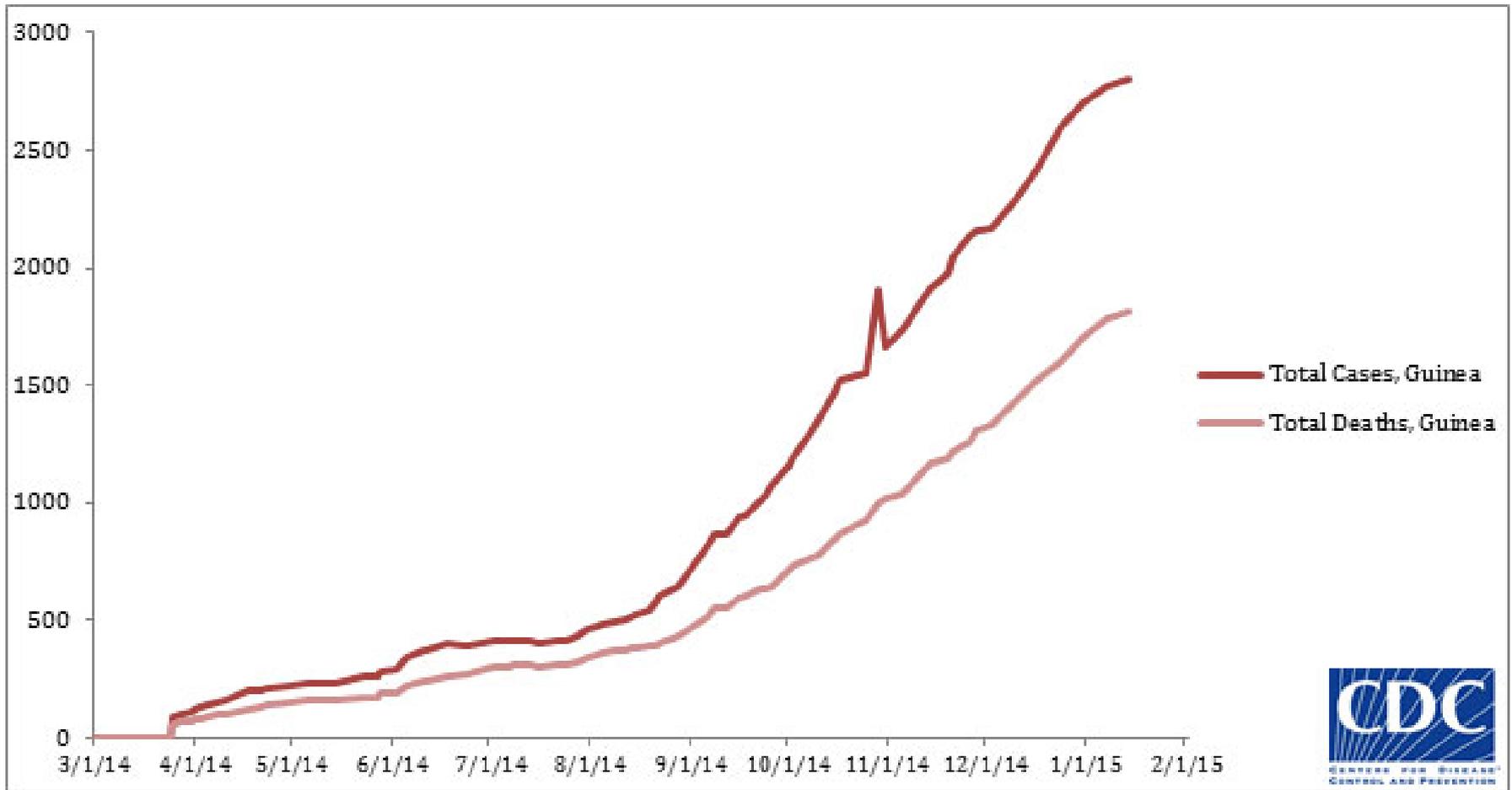
- Affecting Sierra Leone, Liberia, and Guinea, Nigeria, Senegal, United States, Spain, Mali, Scotland
- A record number of cases
 - Cases = 21,373 (8,468 deaths; 40% CFR)
- A comparison of case counts during the week ending 22 DEC 2014 to those from the week ending 11 JAN 2015
 - Guinea from 115 cases to 42 cases (-63%)
 - Liberia from 31 cases to 8 cases (-74%)
 - Sierra Leone from 337 cases to 184 cases (-45%).
 - All three countries have sufficient capacity to isolate patients and bury the dead but the under-reporting of cases and the uneven geographical distribution of beds and cases means that not all EVD cases are isolated in several areas (WHO, 14 JAN).
- The current situation is far from stable



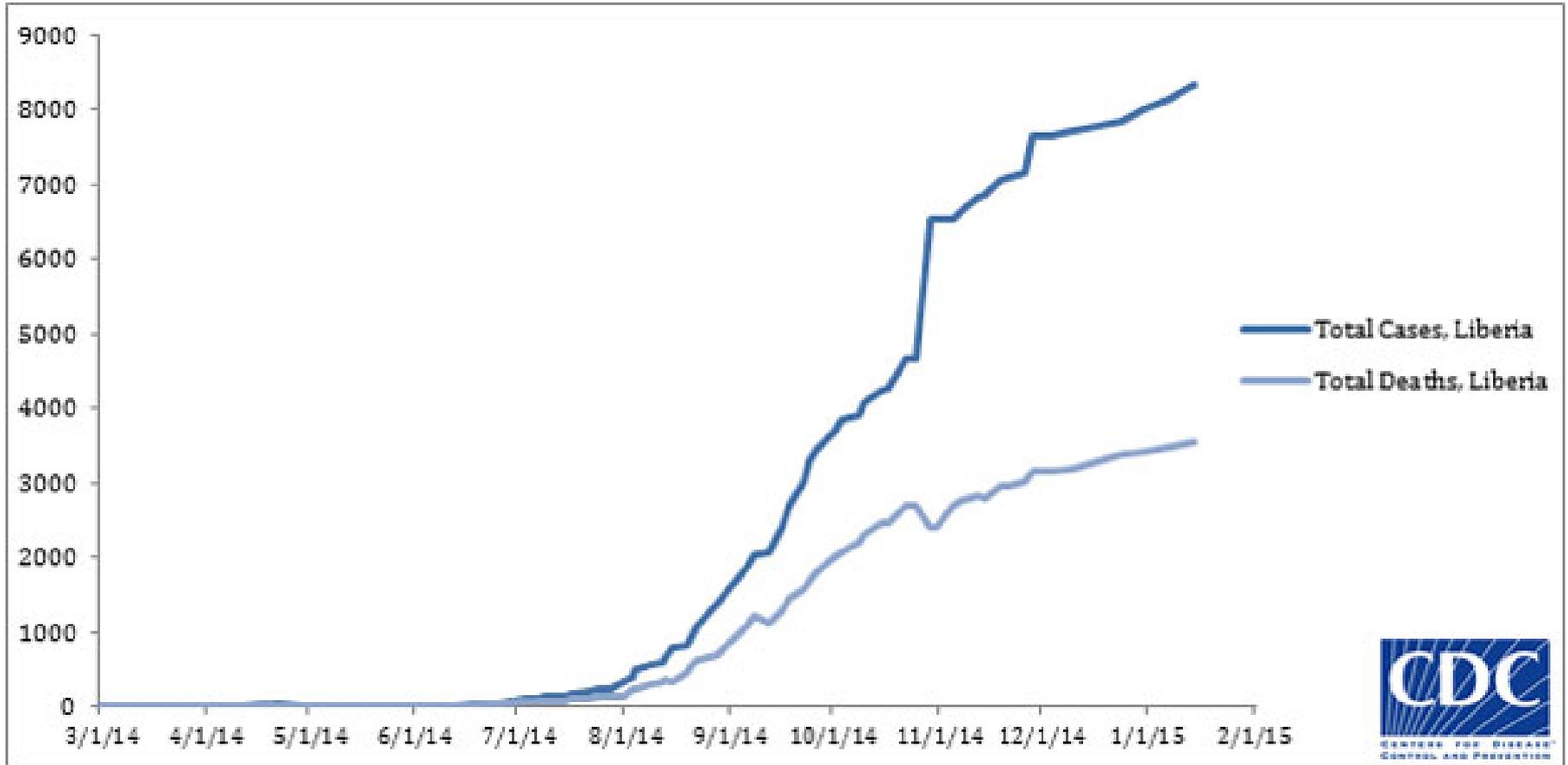
Cumulative Reported Cases



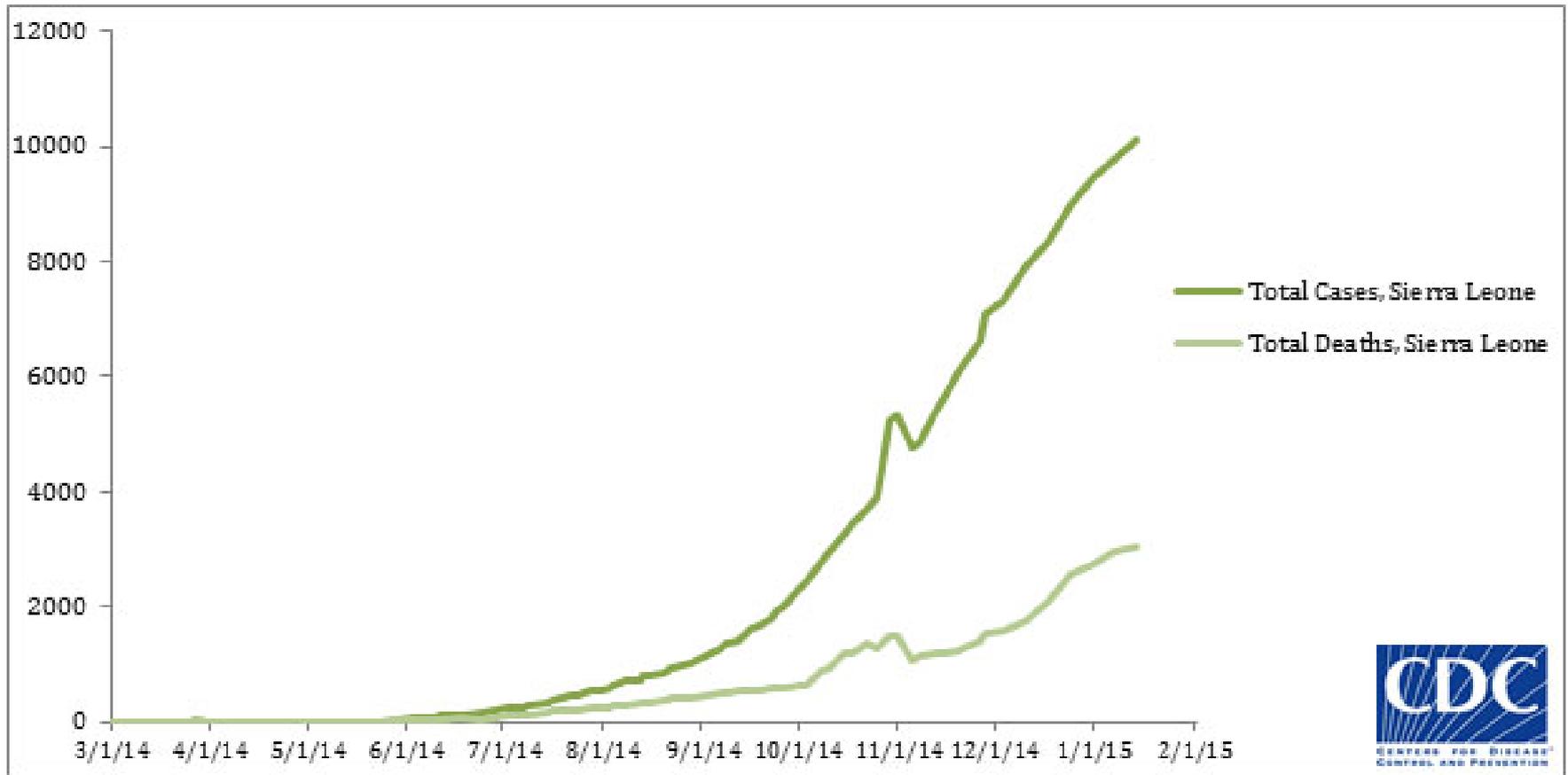
Cumulative Reported Cases: Guinea



Cumulative Reported Cases: Liberia



Cumulative Reported Cases: Sierra Leone



Ebola

- Case Definition
 - **Person Under Investigation (PUI)**
 - A person who has both consistent symptoms and risk factors as follows:
 - Clinical criteria, which includes fever of greater than 38.0 degrees Celsius or 100.4 degrees Fahrenheit, **and**
 - Additional symptoms such as severe headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; **and**
 - Risk factors within the past 21 days before the onset of symptoms
 - » Contact with blood or other body fluids or human remains of a patient known to have or suspected to have EVD;
 - » Residence in—or travel to—an area where EVD transmission is active
 - » Direct handling of bats or non-human primates from disease-endemic areas.



Ebola

- Case Definition

- **Probable Case**

- A PUI whose epidemiologic risk factors include high or low risk exposure(s)
 - **High risk exposures:**
 - Percutaneous (e.g., needle stick) or mucous membrane exposure to blood or body fluids of EVD patient
 - Direct skin contact with, or exposure to blood or body fluids of, an EVD patient without appropriate personal protective equipment (PPE)
 - Processing blood or body fluids of a confirmed EVD patient without appropriate PPE or standard biosafety precautions
 - Direct contact with a dead body without appropriate PPE in a country where an EVD outbreak is occurring*
 - Having lived in the immediate household and provided direct care to an EVD patient while the person was symptomatic



Ebola

- **Some Risk**

- In countries with widespread transmission or cases in urban areas with uncertain control measures
 - Direct contact while using appropriate PPE with a person with EVD while that person was symptomatic or with the person's body fluids
 - Any direct patient care in other healthcare settings
- Close contact in households, healthcare facilities, or community settings with a person with EVD while that 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 EVD while the person was symptomatic.



Ebola

- Case Definition

- Probable Case

- A PUI whose epidemiologic risk factors include high or low risk exposure(s)
 - Low (but not zero) risk exposures
 - Having been in a country with widespread transmission or cases in urban areas with uncertain control measures within the past 21 days and having had no known exposures.
 - Other close contact with EVD patients in health care facilities or community settings.
 - » Being within approximately 3 feet (1 meter) of an EVD patient or in the patient's room or care area for a prolonged period of time while not wearing recommended PPE and the person was symptomatic
 - » Having direct brief contact (e.g., shaking hands) with an EVD patient while not wearing recommended PPE and patient was in early stages of disease
 - » Traveled on an aircraft with a person with EVD while the person was symptomatic
 - » 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

Brief interactions, such as walking by a person or moving through a hospital, do not constitute close contact



Ebola

- **No identifiable risk (CDC)**

- Contact with an asymptomatic person who had contact with person with Ebola
- Contact with a person with Ebola before the person developed symptoms
- Having been more than 21 days previously in a country with widespread transmission or cases in urban areas with uncertain control measures
- 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
- 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.



Ebola

- Case Definition
 - **Confirmed Case**
 - A case with laboratory-confirmed diagnostic evidence of Ebola virus infection



Post-Deployment Monitoring:

Once individuals depart the Ebola outbreak area, regardless of any previous monitoring in theater, they will be monitored for 21 days IAW the following guidance:

1. **No known exposure** – Appropriately trained DoD personnel (e.g., unit leaders, healthcare personnel) will conduct a face-to-face interview to review clinical symptoms and perform a temperature check twice daily during the 21-day monitoring period. As long as individuals remain asymptomatic, they may return to work and routine daily activities with family members. During the 21-day monitoring period, no leave or Temporary Duty/Temporary Additional Duty will be authorized outside the local area to assure continued face-to-face monitoring.
2. **Regulated movement secondary to exposure risk** – All DoD personnel moved out of theater due to elevated exposure risk will be quarantined for 21 days at a DoD facility (reference DoDI 6200.03) designated to monitor for signs and symptoms and/or care for EVD patients.



Ebola

- Lessons learned from Emory University
 - EMS and transport crews need to comply with hand hygiene
 - Universal compliance with standard infection control precautions needs to be maintained
 - Proper training of how to put on and remove PPE is imperative
 - Prepare transport vehicles

Slides from Dr. Isakov – Emory University



Ebola

PPE and equipment selection



Slides from Dr. Isakov – Emory University



Ebola

Ambulance disinfection Mission recovery

- Driver compartment isolation and patient compartment barrier drapes
- Decon, disinfection of ambulance, PPE doffing and waste removal **ALL SUPERVISED**
- Surveillance (monitor for fever amongst medics)



Slides from Dr. Isakov – Emory University



Ebola

- Personal Protective Equipment
 - PPE is in short supply
 - Do not cut corners
 - Ensure your supply chain is monitoring your PPE
 - Do not reuse unless you can ensure optimal cleaning
 - PPE doesn't work unless you use it correctly
 - Training
 - Supervision when using and removing
 - Do not work if you are ill

Slides from Dr. Ribner– Emory University



Ebola

- Complications of Ebola:
 - Diarrhea
 - Loss of water and electrolytes (may be massive)
 - Dehydration- may be difficult to monitor or replace
 - Replacement with Oral Rehydration Solution or Lactated Ringers may lead to low sodium levels (hyponatremia) and low potassium levels (hypokalemia)
 - Both of the Emory patients had low potassium and one had low
 - Exacerbates hypotension

Slides from Dr. Ribner– Emory University



Ebola

- Complications of Ebola:
 - Vomiting
 - Difficult to use oral meds and hydration
 - Electrolyte management is made more difficult
 - Edema
 - Both patients at Emory gained over 20 pounds
 - IV access become difficult if not impossible
 - Early access if you can
 - Masks low intravascular volume

Slides from Dr. Ribner– Emory University



Ebola

- Complications of Ebola:
 - Low Platelets
 - Increases bleeding tendency
 - Need to replace with platelet transfusions
 - This is problematic:
 - » Can't measure platelets in many places
 - » Platelet transfusions not likely available due to storage issues
 - » Whole Blood transfusions
 - Disseminated Intravascular Coagulation
 - Worsens bleeding
 - Need plasma

Slides from Dr. Ribner– Emory University



Ebola

- Emory University patients
 - Presented like what you would expect to see here in the U.S. in a severe infection
 - Severe electrolyte abnormalities
 - Severe edema (with low protein levels)
 - Thrombocytopenia
- Early supportive care and aggressive resuscitation is key
 - Difficult if monitoring equipment is not available and resources are depleted without replacement

Slides from Dr. Ribner– Emory University



Ebola

- A question that has been raised...

J Infect Dis. 1999 Feb;179 Suppl 1:S28-35.

Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidémies à Kikwit.

Rowe AK¹, Bertolli J, Khan AS, Mukunu R, Muyembe-Tamfum JJ, Bressler D, Williams AJ, Peters CJ, Rodriguez L, Feldmann H, Nichol ST, Rollin PE, Ksiazek TG.

⊕ **Author information**

Abstract

A cohort of convalescent Ebola hemorrhagic fever (EHF) patients and their household contacts (HHCs) were studied prospectively to determine if convalescent body fluids contain Ebola virus and if secondary transmission occurs during convalescence. Twenty-nine EHF convalescents and 152 HHCs were monitored for up to 21 months. Blood specimens were obtained and symptom information was collected from convalescents and their HHCs; other body fluid specimens were also obtained from convalescents. Arthralgias and myalgia were reported significantly more often by convalescents than HHCs. Evidence of Ebola virus was detected by reverse transcription-polymerase chain reaction in semen specimens up to 91 days after disease onset; however, these and all other non-blood body fluids tested negative by virus isolation. Among 81 initially antibody negative HHCs, none became antibody positive. Blood specimens of 5 HHCs not identified as EHF patients were initially antibody positive. No direct evidence of convalescent-to-HHC transmission of EHF was found, although the semen of convalescents may be infectious. The existence of initially antibody-positive HHCs suggests that mild cases of Ebola virus infection occurred and that the full extent of the EHF epidemic was probably underestimated.

- Easy Answer = Survivors wear condoms for 3 months



Ebola

- Treatment is primarily supportive
- In the works...
 - Recombinant human monoclonal antibodies
 - Vaccines mostly in pre-clinical stage (few human studies)
 - DNA vaccines
 - Live viral vector vaccines
 - Virus-like particles vaccines
 - Medications:
 - Pyrazinecarboxamide derivative, T-705 (favipiravir)
 - Broad-spectrum nucleoside analogue (BCX4430)
 - Brincidofovir (CMX001)
 - Recombinant nematode anticoagulant protein (NAP)
 - inhibits activated factor VII-tissue factor complex



Ebola

- Recombinant Human Monoclonal Antibodies
 - MB-003 (c13C6, h13F6 and c6D8)
 - ZMAb (m1H3, m2G4 and m4G7)
 - ZMapp = MB-003 + ZMAb
 - Consists of 3 humanized monoclonal antibodies
 - Best components of the MB-003 and ZMAb products
 - Produced in tobacco plants
 - Protected all 18 NHPs when given up to 5 days after infection
 - Human experience
 - To date, 7 ebola patients have received the drug
 - 5 have survived
 - Difficult to decipher if there is a benefit in such small group

[Nature](#). 2014 Aug 29.[Epub ahead of print]



Ebola

- TKM-100802
 - Tekmira Pharmaceuticals Corporation
 - Small interfering RNAs targeting various components of the Ebola virus
 - Macaque study showed 100% protection when given after infection (30 mins, then daily for 6 days)
 - Phase 1 safety study suspended by FDA in July 2014, due to safety concerns (inflammatory, flu-like symptoms)
 - FDA recently allowed for compassionate use
 - Given to an aid worker who returned from Liberia on 5 SEP 2014
 - Also received blood transfusion from Kent Brantly



Ebola

- Pyrazinecarboxamide derivative, T-705 (Favipiravir)
 - Inhibits virus RNA polymerase
 - Broad spectrum antiviral activity against several viruses
 - » Currently in phase 3 development for influenza treatment
 - Activity against Ebolavirus noted in mouse studies
 - » 18 mice challenged with lethal aerosol exposure
 - » Treatment started 1 hour post-challenge, then BID x 14 days
 - » All control mice died 7-8 days later
 - » All mice treated with T-705 survived at 4 weeks
 - » Mice treated 6 days post infection in a separate study
 - » Treatment mice had viremia at treatment start
 - » Virus cleared in 4 days (100% survival at 21 days)
 - » No survival benefit if started at 8 days



Ebola

- Broad-spectrum nucleoside analogue (BCX4430)
 - Inhibits viral RNA polymerase through RNA chain termination
 - Prophylactic studies in mice showed 75-100% protection when given up to 96 hours after infection
 - Treatment studies in macaques up to 48 hours after infection showed 100% protection when challenged with Marburg virus
 - No human trials



Ebola

- Recombinant nematode anticoagulant protein (NAP)
 - Directly inhibits the factor VIIa/tissue factor complex
 - » Has antithrombotic potential as shown in phase II surgical trials
 - In Ebola challenge in macaques with NAP either 10 mins or 24 hours after infection
 - » 16 of 17 controls died
 - » 6 of 9 treatment animals died (33% survival vs 6%)
 - A separate Marburg study in 2007 showed less favorable outcomes

Lancet. 2003 Dec 13;362(9400):1953-8.
J Infect Dis. 2007 Nov 15;196 Suppl 2:S372-81.



Ebola

- AVI-6002
 - An experimental combination of 2 phosphorodiamidate morpholino antisense oligomers
 - Specifically target viral mRNA encoding Ebolavirus proteins
 - Found to suppress disease in infected NHPs

 - Phase 1 safety study has been completed
 - 30 healthy adults aged 18-50
 - Dose escalation study
 - Safety was equivalent to placebo groups



Ebola

- Clomiphene and Toremifene
 - Screen of Food and Drug Administration (FDA) approved drugs
 - Looked for antiviral activity against Ebolavirus
 - Identified a set of selective estrogen receptor modulators (SERMs),
 - Act as potent inhibitors of EBOV infection.
 - Anti-EBOV activity was confirmed for both in a mouse model.
 - Response appeared to be an off-target effect where the compounds interfere with a step late in viral entry
 - These compounds represent an immediately actionable class of approved drugs that can be repurposed for treatment of filovirus infections.
 - Studies have yet to be started



Ebola

- Retanizone
 - Novel vitamin A derived (retinoid) thiosemicarbazone derivative
 - Broad spectrum antiviral activity (HIV, HCV, VZV, CMV)
 - Tested against Ebola virus Zaire in lab
 - Showed some evidence of disrupting multiplication of the virus at small concentrations



Ebola

- Brincidofovir (CMX001)
 - Oral lipid-conjugated cidofovir derivative
 - Created as an anti-smallpox therapeutic
 - Excellent bioavailability
 - Activity against DNA viruses (CMV, Adenovirus, etc)
 - Activity against Ebola based on cell culture data with high inhibitory properties
 - No animal studies specifically for ebola efficacy
 - Over 1000 humans treated for other viral infections with good safety profile



Ebola

- Vaccines
 - Inactivated ebola virus
 - Virus-like particles
 - DNA vaccines
 - Recombinant viral vector vaccines
 - Adenovirus (both Ad5 and cAd3, “chimp Ad”)
 - Vesicular Stomatitis Virus (VSV)
 - Rabies virus
 - Vaccinia virus
 - CMV
 - Paramyxovirus



Ebola

- Vaccines
 - DNA vaccines
 - Phase 1 study (2006) using 3 different plasmids encoding proteins against Ebola in healthy adults 18-44 years old
 - No significant adverse effects of the vaccine
 - Appeared to be immunogenic
 - Given intramuscularly via a needle free device (Biojector 2000)
 - All subjects produced an immune response to at least one of the 3 antigens encoded by the vaccine
 - » **Specific neutralizing antibody was NOT detected**
 - **A subsequent study of Ebola and Marburg DNA vaccines recently completed, although immune response not great and did not last more than 44 weeks**

[Clin Vaccine Immunol.](#) 2006 Nov;13(11):1267-77.

Lancet 2014 Dec 22 epub ahead of print



Ebola

- Vaccines
 - Adenovirus vaccines
 - Ad 5 vectors and chimpanzee Ad3 (cAd3) vectors
 - » Phase 1 safety study of Ad5 vector vaccine shown to be safe in a dose escalation study when given intramuscularly
 - » 50% of subjects had neutralizing antibody titers against adenovirus 5 prior to study start
 - » Potentially makes the vaccine less effective
 - » Antibody response to Ebola was 64-82% for the highest dose of vaccine tested
 - cAd3 phase 1 study recently initiated at the NIH and at Oxford
 - » Shown to be safe
 - » All subjects mounted immune responses (some with T-cell response)

[Virology](#). 2006 Mar 15;346(2):394-401

Vaccine. 2010 Dec 16;29(2):304-13.

[Nat Med](#). 2014 Sep 7. [Epub ahead of print]



Ebola

Phase I clinical trial started Oct 2014 here at WRAIR now in safety follow-up

- Vaccines

- VSV vaccines

- VSV

- » In the same family as rabies virus

- » Infects cattle, horses, pigs (rare human infections)

- » Causes oral lesions in animals

- » Can cause mild, flu-like illness in humans (rare cases of encephalitis)

- Vaccine virus has the glycoprotein removed and replaced with the filovirus glycoprotein

- » Limits immunity against the vaccine virus

- » Limits the VSV pathogenicity

- » Produces antibody response against ebola

[PLoS Negl Trop Dis.](#) 2013 Dec 19;7(12):e2600

PLoS One. 2014 Apr 23;9(4):e94355.

[Vaccine.](#) 2014 Sep 29;32(43):5722-5729



Ebola

- Why don't we just test these products on the sick?
 - The story of TGN1412...
 - CD28-monoclonal antibody
 - Intended for treatment of B-cell CLL and rheumatoid arthritis
 - Tested in animals previously and noted to be safe
 - Clinical Trial (2006)
 - » First in humans study
 - » Given at a fraction of the dose found safe in animals
 - » All 6 human volunteers were hospitalized that same day
 - » Multi-organ failure
 - » Cytokine storm
 - » Prolonged hospitalization
- Bottom line: We don't know if they are safe



Summary

- VHF will start as flu-like illness and progress to organ failure (**bleeding may not be evident**)
- Have high concern for the nosocomial risk as the treating provider
- Masks, gloves, gowns, and eye protection at a minimum
- Have isolation plan, post-exposure plan, and evac plans ready
- Ribavirin may be of benefit to some (not all VHF, **NOT EBOLA**) if given **early**



Summary

- Ribavirin is an investigational drug for VHF, thus you need to use it on a research protocol
- Avoid rodents
- If you are in a remote tropical locale with little epidemiologic data, and there are cases of something that appears hemorrhagic in nature, consider the unknown
- Experimental drugs and vaccines for Ebola are working their way into human clinical trials



Final Thoughts

- Any fever in a traveler to a malaria endemic region is malaria until proven otherwise



- Any traveler with fever **AND** bleeding out of their eyeballs is VHF until proven otherwise

Questions?



Bonus Slides



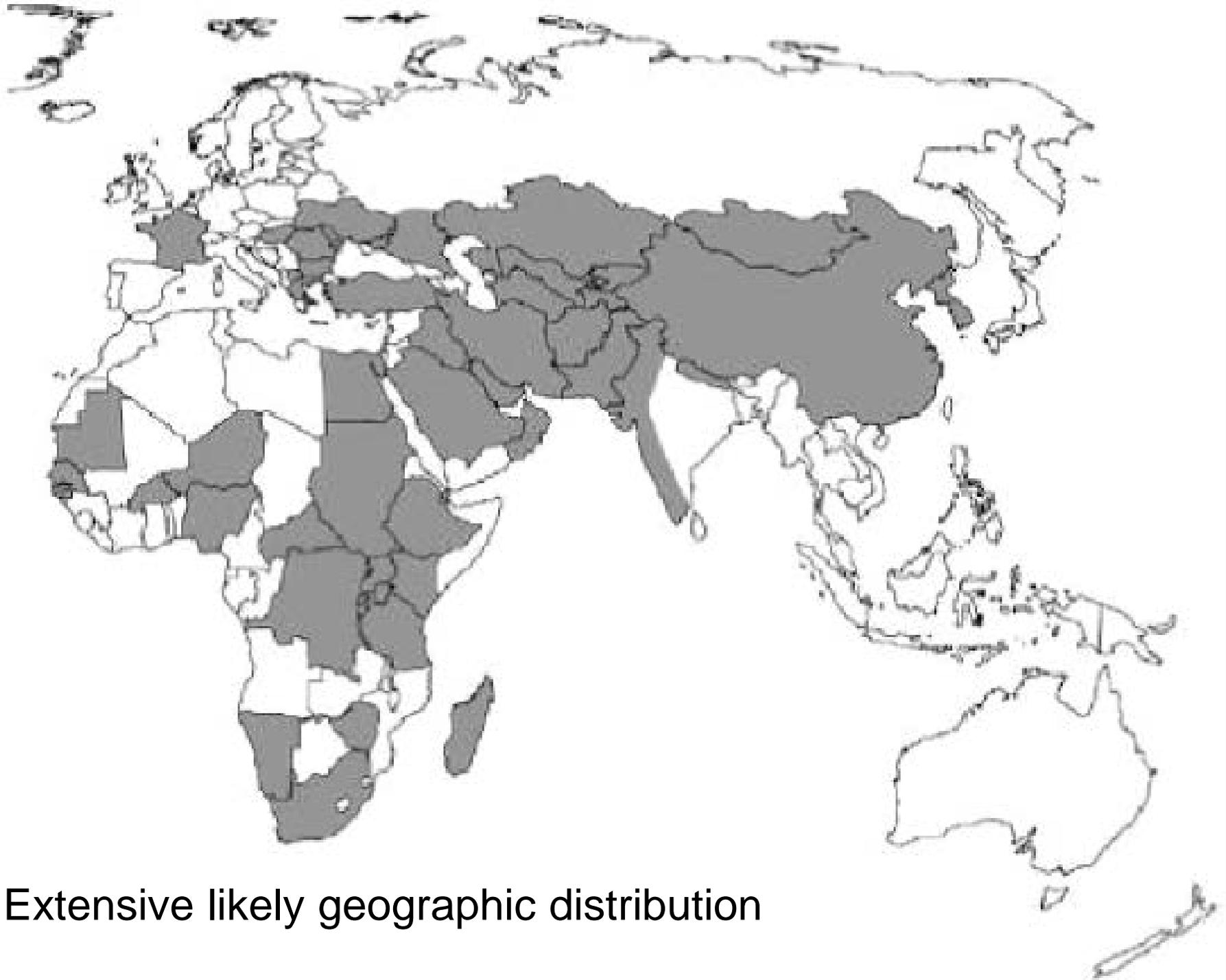
CRIMEAN-CONGO HEMORRHAGIC FEVER



Crimean-Congo Hemorrhagic Fever

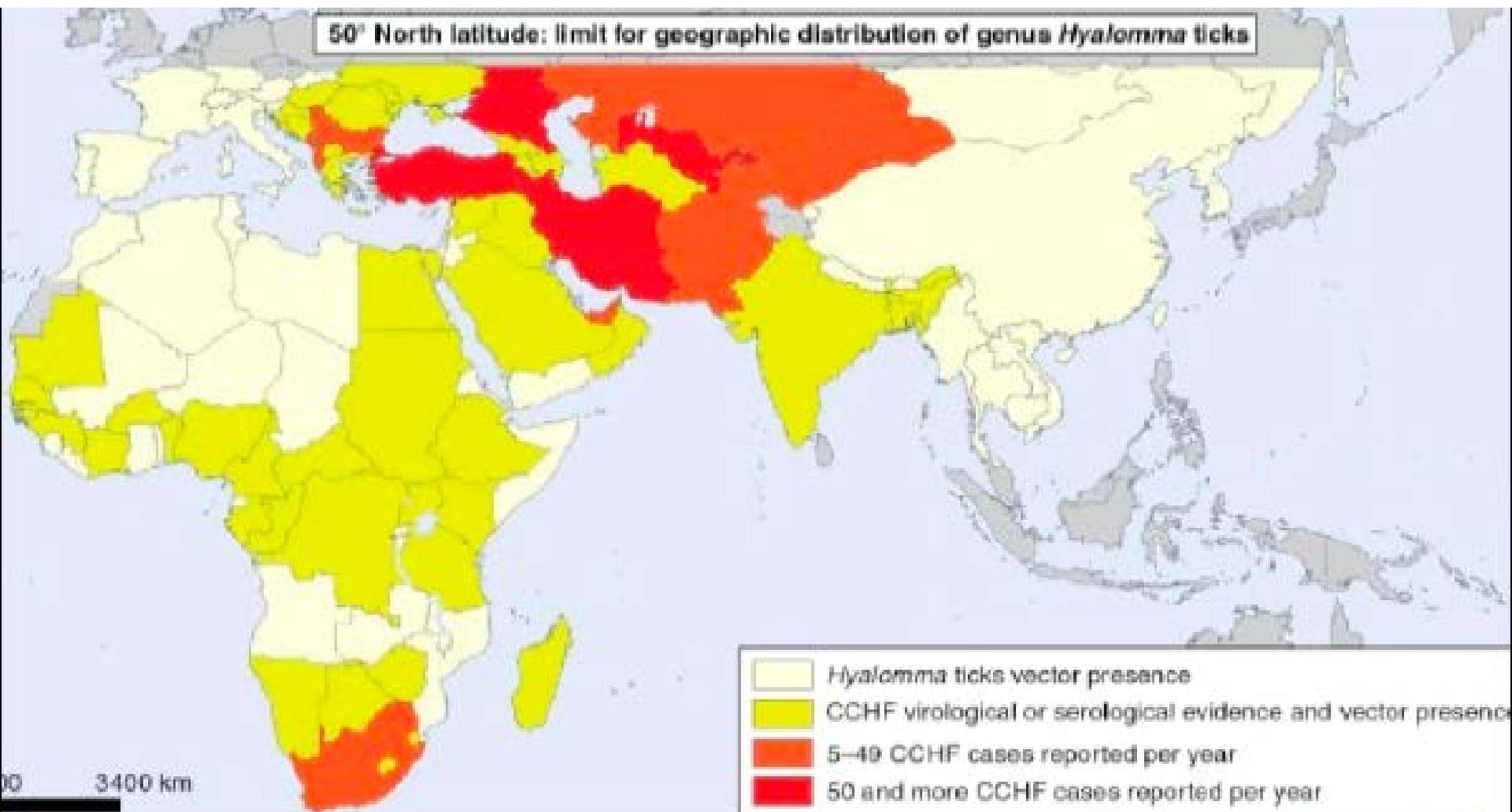
- Geographic regions
 - 12th Century: Tajikistan
 - HF syndrome: blood in urine, rectum, gums, vomit
 - 1944-45: First clinical description
 - Soviets (N=200, CFR = 10%) assisting peasants in Crimea
 - 1956: febrile patient in Belgian Congo
 - Common antigenic structure: Crimea & Congo viruses = CCHF





Extensive likely geographic distribution

50° North latitude: limit for geographic distribution of genus *Hyalomma* ticks



-  *Hyalomma* ticks vector presence
-  CCHF virological or serological evidence and vector presence
-  5–49 CCHF cases reported per year
-  50 and more CCHF cases reported per year

Medscape

CCHF

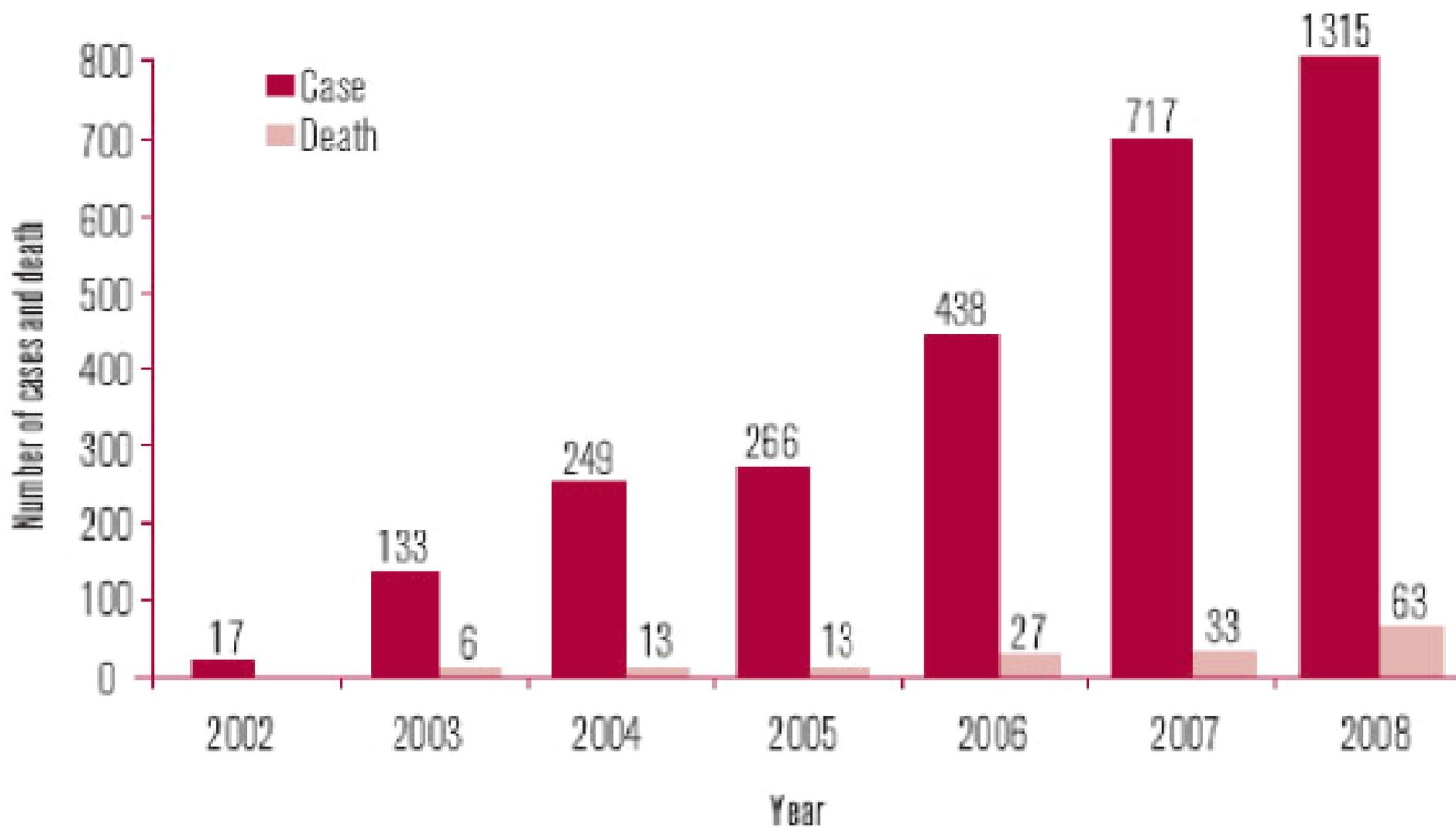
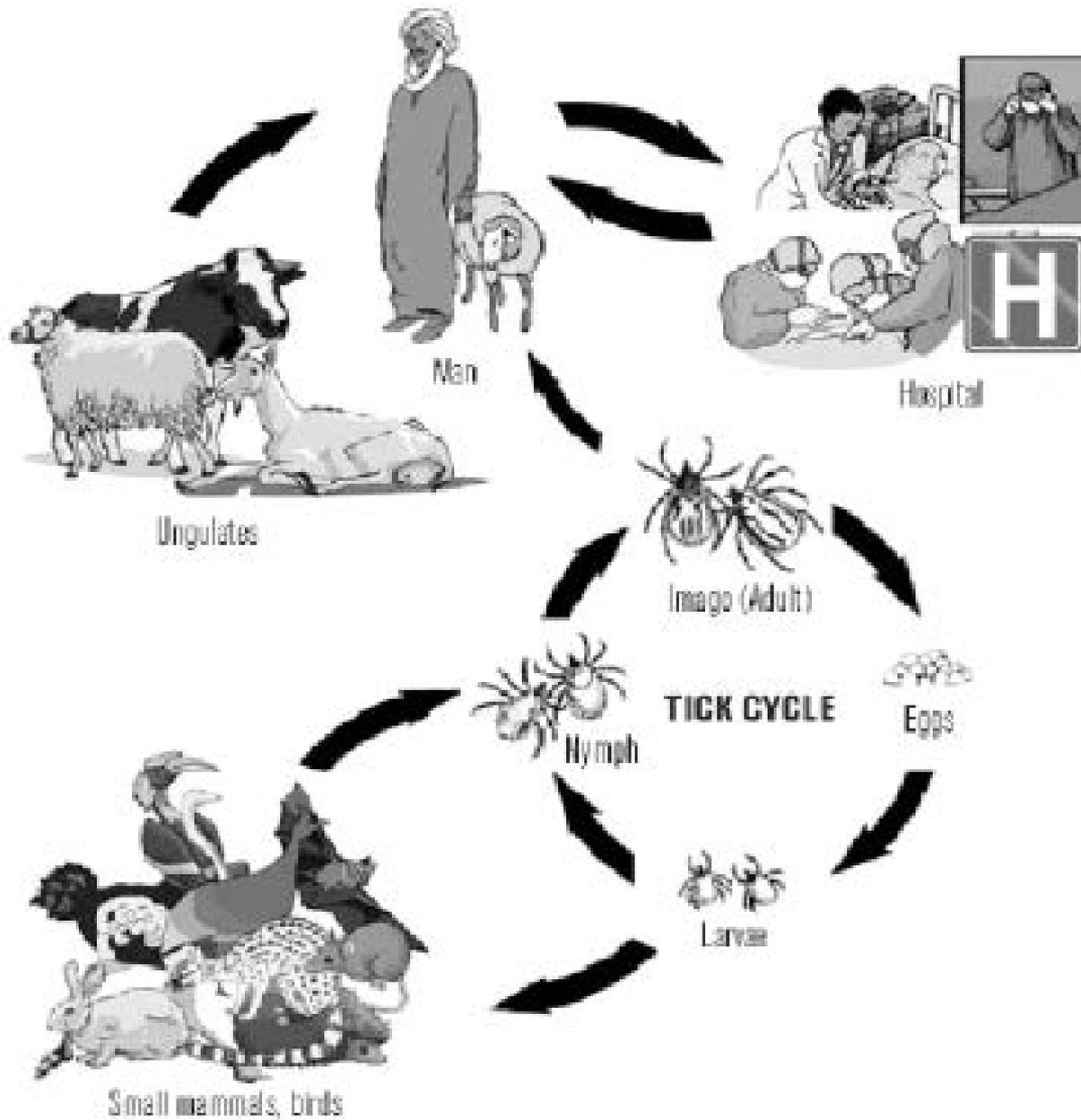


Figure 5. Number of Crimean-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008.³²

Crimean-Congo Hemorrhagic Fever

- Exposure Risks
 - Ticks (*Hyalomma* sp.) – primary vector
 - Bite (increased exposure in Spring and Summer)
 - Crushed against skin
 - Animals
 - Rabbits, small mammals and birds – reservoir
 - Hoofed mammals (ungulates) – may be infected but won't show evidence of illness
 - Contact with dead animals (farmers, slaughterhouse, undercooked meat)
 - Nosocomial risk (many HCP have died)
- Mortality Rates: 3-70% (typically 20-30%)





Crimean-Congo Hemorrhagic Fever

- Diagnosis
 - ELISA (antigen capture as well as antibody)
 - RT-PCR (blood or tissue)
 - Virus isolation
 - Immunohistochemical staining
- Some predictors for severity in literature



Crimean-Congo Hemorrhagic Fever

• Containment & Prevention

- Several reports in the literature indicating high risk of nosocomial transmission to HCPs
 - One report of a patient acquiring CCHF from being in same hospital room
- Turkish study of HCPs in setting with high number of cases showed high rates of PPE use was associated with only a 0.53% seroprevalence rate
 - The 2 HCP who seroconverted in our initial case admitted to accidental mask slippage during care where aerosolization was a high risk

[Int J Infect Dis.](#) 2013 Nov;17(11):e1046-50
IntJ Infect Dis. 2009; 13: e105-7



Crimean-Congo Hemorrhagic Fever

- Containment & Prevention
 - Ribavirin
 - High risk contacts can be considered
 - Use oral ribavirin
 - For the CCHF case from Afghanistan, it was recommended that high risk contacts take 600 mg PO twice daily for 14 days
 - Providers only took meds for 7 days in all cases, due to gastrointestinal side effects



Crimean-Congo Hemorrhagic Fever

- Treatment

- Supportive Care

- Ribavirin-CCHF controversy

- In-vitro activity against CCHF
- No randomized controlled trials
- Many case reports and case series indicating efficacy
- Several others indicate no significant benefit
- CDC does not “fully” recommend it’s use for CCHF
- WHO recommends its use for CCHF (as well as Lassa, Junin, and hantavirus with renal syndrome)
- DoD has a phase 2 open label study for ribavirin treatment of Lassa and CCHF (clinicaltrials.gov - NCT00992693)



Crimean-Congo Hemorrhagic Fever

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

SSI Parameter	Score
Platelet count, $\times 10^3$ platelets/mm ³	
>150	0
150-50	1
49-20	2
<20	3
aPTT, sec	
≤ 34	0
35-45	1
46-59	2
>60	3
Fibrinogen level, mg/dL	
≥ 180	0
179-160	1
159-120	2
<120	3
Bleeding	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
Somnolence	
No	0
Yes	1

Abbreviation: aPTT, activated partial thromboplastin time; SSI, severity scoring

- Severity Scoring Index
 - 0-2 = mild disease
 - 3-9 = moderate
 - 10-13 = severe
- Those with moderate disease had significantly better outcomes when receiving ribavirin
- Individuals with severe disease did better with corticosteroids added

CID 2013; 57:1270-4



Crimean-Congo Hemorrhagic Fever

- Treatment

- Ribavirin appears to be beneficial to overall survival in at least moderate to severe disease
- Earlier the therapy the better (within first 4 days of illness)
- Corticosteroids in severe illness in addition to ribavirin may be beneficial to survival



Crimean-Congo Hemorrhagic Fever

- Vaccine Development
 - DNA vaccine study in mice not impressive
 - Attenuated vaccinia (poxvirus) virus vector vaccine
 - Expresses the CCHF virus glycoproteins
 - Protected all mice in challenge model

[Vaccine.](#) 2006 May 22;24(21):4657-66.
[PLoS One.](#) 2014 Mar 12;9(3):e91516.





LASSA

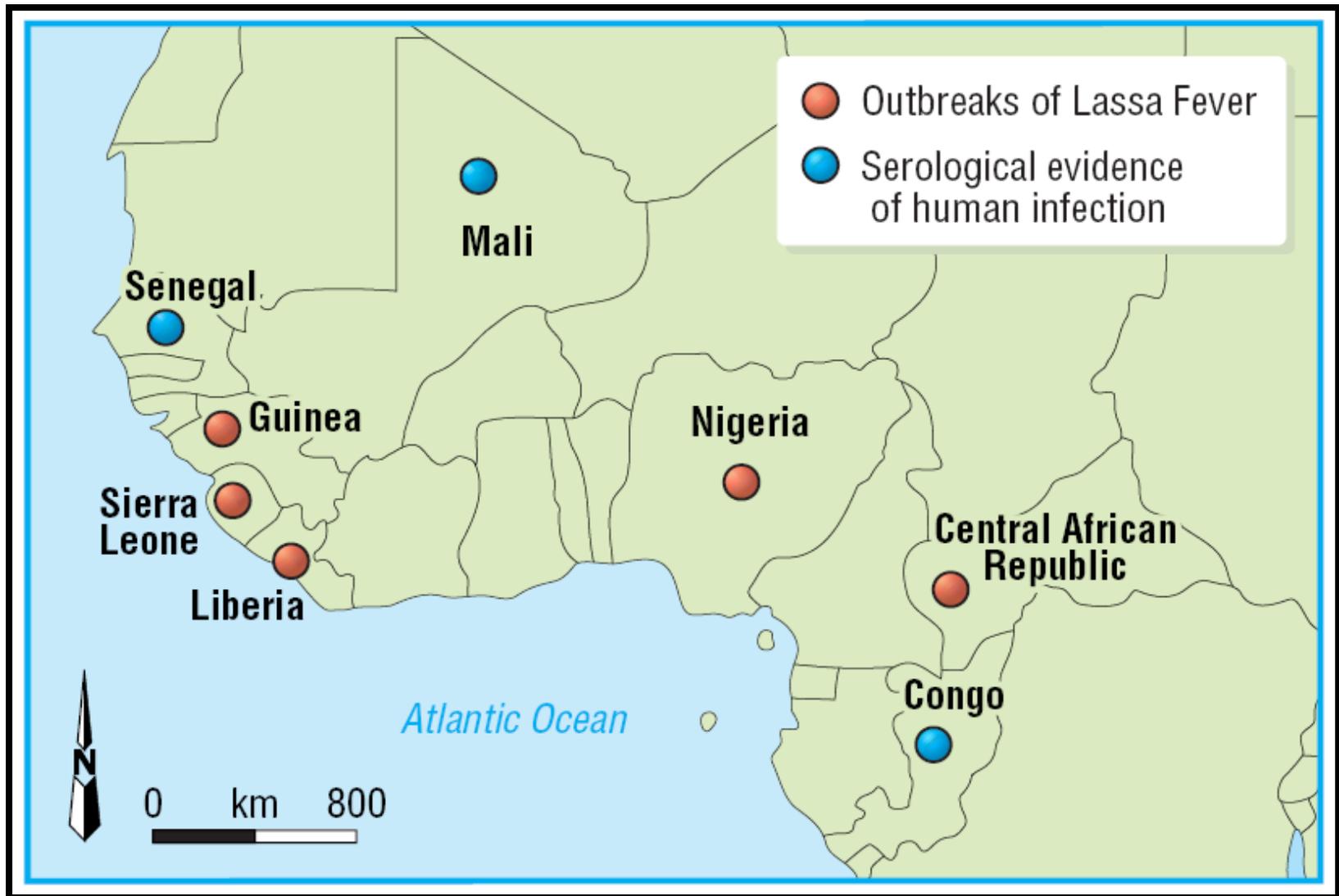


Lassa

- Geographic regions
 - *Arenavirus* first described in Nigeria in 1969 with distribution primarily in West Africa
 - Outbreaks have occurred in:
 - Central African Republic
 - Guinea
 - Liberia
 - Nigeria
 - Sierra Leone (1987)
 - 10-16% of all adult medical admissions
 - 30% of adult deaths
 - 25% of all maternal deaths
 - Serological evidence found in Democratic Republic of the Congo, Mali, and Senegal



Lassa



Lassa



- Exposure Risks

- Reservoir: *Mastomys* rodents

- Rodent-to-human:

- Inhalation of aerosolized virus from rodent urine and feces
 - Ingestion of food or materials contaminated by infected excreta
 - Catching and preparing *Mastomys* as a food source

- Human-to-human:

- Direct contact with blood, tissues, secretions or excretions
 - Needle stick or cut
 - Inhalation of aerosolized virus suspected

- Mortality Rates: 15-20% of hospitalized



Lassa

- Exposure Risks

- Nosocomial Outbreaks

- Dry season (JAN to APR)
- All age groups and both sexes

- Pregnant women and fetus at high risk

- 80% fetal death

- The Kenema Government Hospital

- January to April 2004
- 95 pediatric cases admitted
- 50% of all cases aged under 15 years
 - CFR was 30–50% in children <5
 - CFR was 71% in children <1

(WHO, Weekly Epi Record, MAR 2005)



Photo by F. Jacquerioz

Aniru Conteh
1942–2004

Dr. Conteh attempted femoral venipuncture and sustained a needlestick.



Lassa

- Diagnosis
 - Clinical diagnosis is tough
 - May present with nonspecific symptoms
 - Sore throat, swollen face and neck
 - Hemorrhagic manifestations may not be evident
 - Neurologic symptoms (hearing loss, tremors, encephalitis)
 - ELISA (antibody or antigen)
 - Viral culture (wouldn't do this unless you have BSL-4)
 - Immunohistochemical staining of tissue
 - RT-PCR



Lassa

Clinical stages of severe Lassa fever (adapted from McCarthy 2002¹⁵)	
Stage	Symptoms
1 (days 1-3)	General weakness and malaise. High fever, >39°C, constant with peaks of 40-41°C
2 (days 4-7)	Sore throat (with white exudative patches) very common Headache; back, chest, side, or abdominal pain Conjunctivitis Nausea and vomiting Diarrhoea Productive cough Proteinuria Low blood pressure (systolic <100 mm Hg) Anaemia
3 (after 7 days)	Oedema of the face and neck Convulsions Mucosal bleeding (mouth, nose, eyes) Internal bleeding Encephalopathy with confusion or disorientation
4 (after 14 days)	Coma Death



Lassa

- Containment & Prevention
 - Rodent control (food storage is key)
 - Use of VHF barrier precautions can limit or eliminate healthcare worker risks
 - Isolation of patients as discussed
 - Excreted in the urine for 3 – 9 weeks
 - Lassa vaccine
 - USAMRIID had a vaccine based on a live viral platform that protected monkeys against a lethal challenge of Lassa
 - Monkeys did not have symptoms, BUT were found to have circulating virus



Lassa

- Containment & Prevention
 - Ribavirin
 - High risk contacts can be considered
 - Needle sticks or sharp injury
 - Mucous membrane or broken skin with blood/secretions
 - Participation in emergency procedures without PPE
 - Prolonged contact in enclosed space (e.g. med evac)
 - Use oral ribavirin
 - 800 mg daily for 10 days (EID article)
 - 35 mg/kg x 1 (up to 2.5 g) then 15 mg/kg (up to 1 g) TID x 10 d

CID 2010; 15;51(12):1435-41
EID 2010; 16 (20): 2009-2011



Lassa

- Treatment
 - Supportive Care
 - Ribavirin
 - If used early (within 6 days) may significantly reduce mortality (76% to 9%)
 - If you wait to start ribavirin after 6 days, rate goes up to 47%
- WHO recommends use (CDC also promotes its use)
- DoD use via the open label study (see CCHF info above)

N Engl J Med 1986; 314:20–6.
Antiviral Res. 1994;23:23
Rev Infect Dis. 1989;11:S750





HANTAVIRUSES



Hantaviruses

- History

- 1934: First published case of HFRS
- 1951-1953
 - United Nation's troops in Korean War (near Hantaan River)
 - 3000 cases of fever + hemorrhage in 33%
- 1978: virus isolated
- 1986: US – Korean military joint field exercise
 - 14 cases of HFRS among 3,754 US Marines
 - 10 were hospitalized & 2 died (CFR = 14%)
 - Cases confirmed by serologic testing

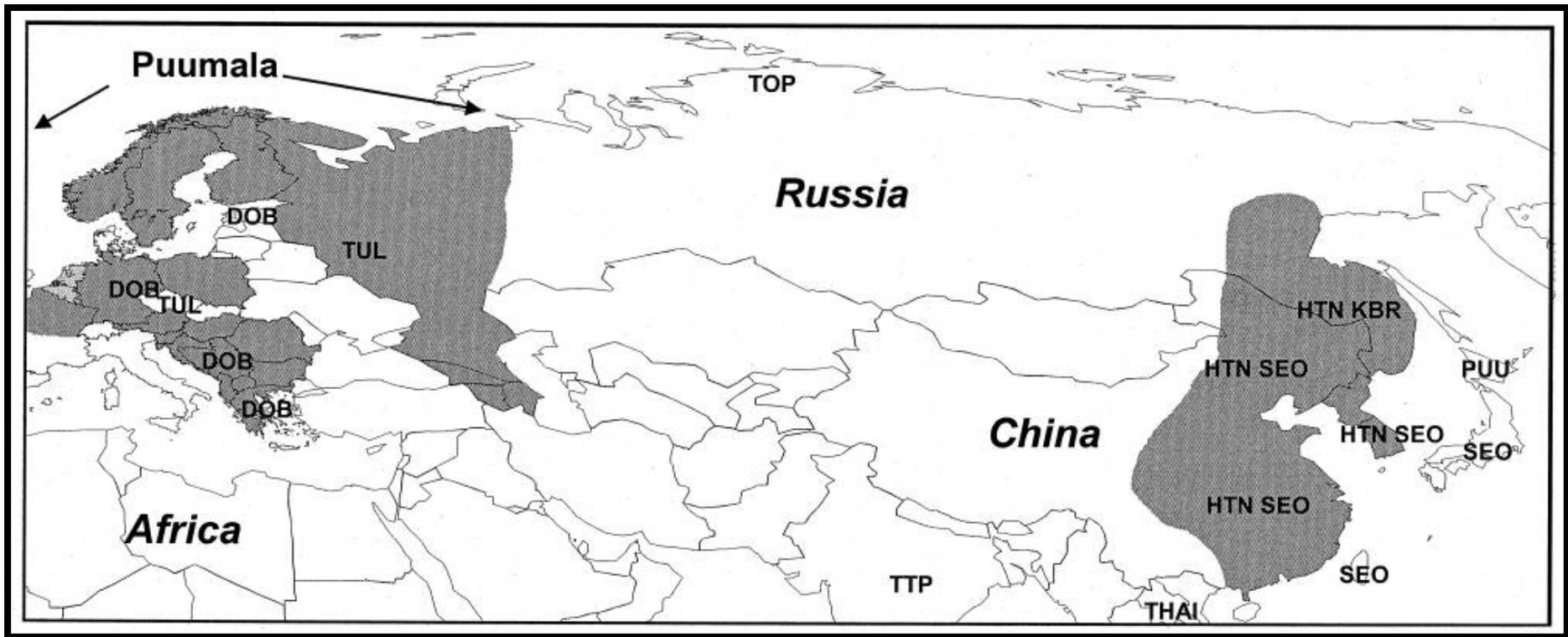
MMWR Feb 19, 1988/37(6);87-90,95-6



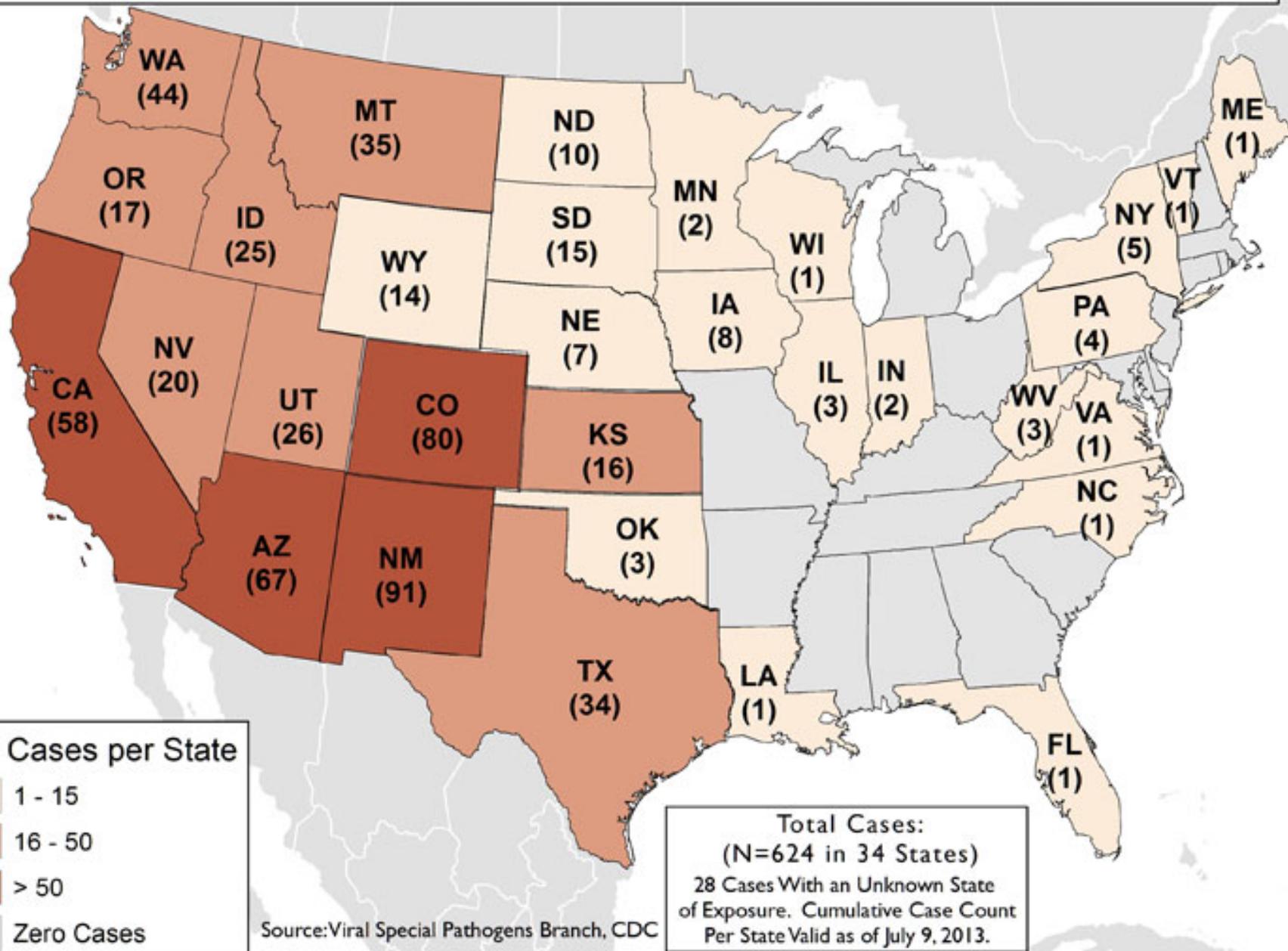
Hantaviruses

- Geographic regions
 - “Old World”:
 - Hantaan (Korea, China, Eastern Russia)
 - Dobrava (Balkans)
 - Seoul (Asia)
 - Puumala (Scandinavia, Western Russia, Europe)
 - “New World”: Sin Nombre (U.S.), Andes





Hantavirus Pulmonary Syndrome (HPS) Cases, by State of Exposure



Hantaviruses



- Exposure risks

- Rodent excreta (aerosolized)

- Reservoir

- *Apodemus agrarius* : striped field mouse (Hantaan)
- *Aedes flavicollis* : yellow necked mouse (Dobrava)
- *Clethrionomys glareolus* : bank voles (Puumala)
- *Rattus norvegicus* : rat (Seoul)

- Demographic

- Farmers, forest workers, soldiers in the field
- Opening and utilizing previously unused buildings
- 20 to 50 years in age
- Male > Female

- Human to Human (very rare, with Andes virus)



Hantaviruses

- Diagnosis
 - Presentation:
 - Hemorrhagic Fever with Renal Syndrome (Old World)
 - Incubation period may be 2-4 weeks
 - Flu-like symptoms, flushing or rash, red eyes, hemorrhagic symptoms possible
 - Acute renal failure
 - » Puumala may have a milder presentation
 - Hantavirus Pulmonary Syndrome (New World)
 - Early = nonspecific, flu-like symptoms
 - Late = severe shortness of breath and cough secondary to pulmonary edema
 - Lab diagnosis similar to other VHFs mentioned



Hantaviruses

- Containment & Prevention
 - Rodent control and maintain adequate food storage
 - No need for VHF isolation procedures
 - Vaccines are being developed
 - Recently completed a phase 1 study at WRAIR
 - Phase 2a study started in July 2014



Hantaviruses

- Treatment
 - Supportive care
 - Dialysis frequently required for “Old World”
 - Ribavirin appears to be of benefit in “Old World” cases, by decreasing mortality and improving renal morbidity
 - A double-blind, RCT of ribavirin in New World HPS did not indicate effectiveness

JID 1991;164(6):1119-27

[Antiviral Res.](#) 2009 Jan;81(1):68-76

CID 2004; 39 (9): 1307-1313.



Emerging Threats

“There are known knowns; there are things we know that we know.

There are known unknowns; that is to say, there are things that we now know we don't know.

But there are also unknown unknowns – there are things we do not know we don't know.”

DONALD RUMSFELD
United States Secretary of Defense
February 12, 2002



Be on alert for emerging infections...

- Lujo hemorrhagic fever (Zambia, South Africa)
 - 4 out of 5 patients died
 - The lone survivor received ribavirin

EID 2009; 15(10): 1598-1602
- Alkhurma hemorrhagic fever (Saudi Arabi, Egypt)
 - Case fatality rate ~30%
 - Considered to be tick born
 - Hemorrhagic fever +/- encephalitis (similar to Kyasanur Forest Disease)



Be on alert for emerging infections...

- Novel bunyaviruses (likely tick borne)
 - Severe Fever with Thrombocytopenia Syndrome virus (China)
 - Heartland virus (10 cases, 2 deaths; in Missouri, Oklahoma, and Tennessee)
 - Lone star tick may transmit this virus
- Bas-Congo Virus
 - Rhabdovirus (relative to rabies)
 - Identified in Democratic Republic of Congo in 2009
 - Rapid onset of severe disease with hemorrhage (2-3 days to death)
 - 3 cases (67% CFR) with apparent nosocomial spread



Emerging Threats

- Chapare Virus
 - Small cluster of cases occurred in rural Bolivia (2003-2004)
 - Hemorrhagic fever symptoms
 - Novel arenavirus found in 1 pt
 - 22 yo male, died on DOI 14

