

---

# LET'S START WITH A CASE



# Case Presentation

- 22 yo U.S. Army Active Duty male deployed to Afghanistan west of Kandahar presents with fever (102.5° F), headache, fatigue, chills, abdominal pain with non-bloody diarrhea (SEP 8, 2009)
  - Symptoms progressing over the previous 4 days
- Initially told he had a “gastroenteritis” at local clinic
  - Treated with Cipro and immodium
  - 48 hour quarters
- Returned the following day (SEP 9):
  - Symptoms worsening, now with nausea/vomiting and lethargy
  - Told he may have a “viral syndrome”
  - Referred to Kandahar for observation



# Case Presentation

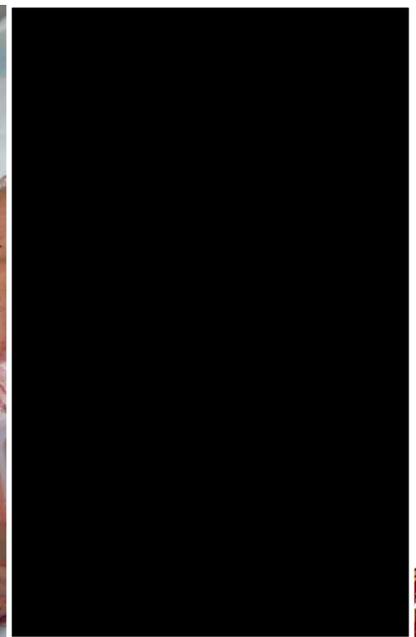
- Progressively worsened over the next several hours
  - Lethargy lead to somnolence
  - Bloody diarrhea and bleeding gums
  - Shortness of breath → intubated
  - Anemic, low platelets, developing organ failure
- Evacuated to LRMC with presumed diagnosis of pneumonia with septic shock (antibiotics started)



# Case Presentation

- Upon arrival at the Landstuhl Regional Medical Center, he is found to be bleeding EVERYWHERE
  - Petechiae everywhere
  - Large ecchymotic lesions at IV sites
  - Extremely sick
- He requires emergent bronchoscopy for bleeding
- The ICU staff raises the concern for viral hemorrhagic fever





# Case Presentation

- Co-located with Afghan army
- Potential exposures
  - Numerous outdoor activities to include sleeping outside
  - Recent tick exposures
    - Patient and battle buddy both with recent bites within a week of illness onset
    - This was a common occurrence (bragging rights)
  - Exposure to goat blood and undercooked goat meat



# AFGHANISTAN



---

This is not a case of Ebola...



# Case Presentation

- Blood sent to the Bernard Nocht Institute (BNI) in Hamburg within hours of admission
- Blood run overnight
  - SEP 10: PCR and IGM **POSITIVE** for CCHF
  - Infectious diseases consulted just prior to test results
- Within ~12 hours of diagnosis, treatment with oral ribavirin thru feeding tube
  - Dose given to match the standard IV dose
- Emergency IND approval for IV ribavirin from the FDA
- IV ribavirin started 12 hours after oral treatment (48 hours of hospitalization)



# Case Presentation

- Renal and hepatic dialysis started
- Patient appeared to be improving
  
- However:
- SEP 14
  - Patient had a asystolic/PEA arrest
  - Declared brain dead
    - At time of death, viral load had declined and antibodies present
    - Cerebral edema on CT





# Viral Hemorrhagic Fevers

---

Kris Paolino, MD  
Chief, Clinical Trials Center  
Walter Reed Army Institute of Research  
Sept 2014



UNCLASSIFIED

---

Thanks to:

COL Mark Kortepeter, MD, MPH



---

# **Will Cover Some Steps to Avoid....**



# The "Slammer"



BSL-4  
CONTAINMENT SUITE

MAJ Muckerman OIC



SECURE AREA



CONTAINMENT SUITE CHECK LIST

ITEM	STATUS
DEFIBRILLATOR	
BATTERIES	
WASTE CONTAINER	
PAPER	
TRASH CART	
CRASH CART	
PORTABLE	
PORTABLE	
ICE TANK	
PSU	
CHARGE	
RESERVE	

AUTHORIZED  
PERSONNEL

# United State Army Medical Research Institute of Infectious Diseases (USAMRIID)





1995 Kikwit Zaire ZEBOV Outbreak

Courtesy of Don Noah

# Outline

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





DUSTIN  
HOFFMAN

RENE  
RUSSO

MORGAN  
FREEMAN

This animal carries  
a deadly virus...  
and the greatest  
medical crisis in the world  
is about to happen.

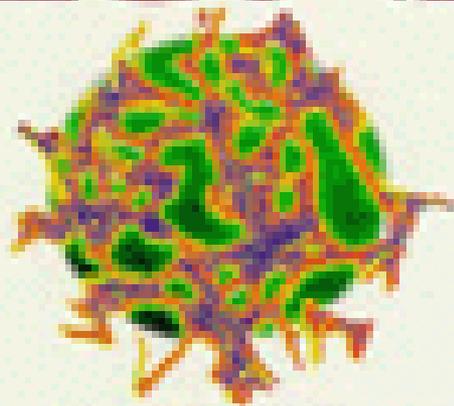


# OUTBREAK

Try to remain calm.

#1  
NEW YORK TIMES BESTSELLER

# THE HOT ZONE



A TERRIFYING TRUE STORY  
RICHARD PRESTON



# 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



# 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

- Variety of presentations
- **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	Thrombocytopenia	Leucocyte count	Rash	Icterus	Renal Disease	Pulmonary Disease	Tremor, Dysarthria	Encephalopathy	Deafness	Eye Lesions
<b>ARENNAVIRIDAE</b>											
South American HF	+++	+++	UUU	0	0	0	+	+++	++	0	0
Lassa fever	+/S	+	0	++	0	0	+	+	+/S	++	0
<b>BUNYAVIRIDAE</b>											
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
<b>FILOVIRIDAE</b>											
Marburg and Ebola HF	++	+++		+++	++	0	+	0	++	+	Uveitis Retina?
<b>FLAVIVIRIDAE</b>											
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

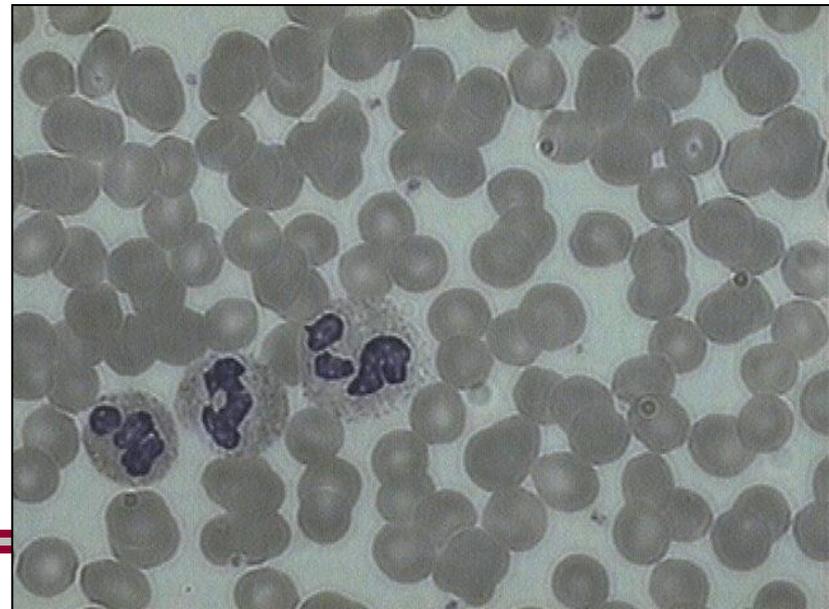
- ∩ occasionally or mildly increased
- ∩∩ commonly increased, may be marked
- ∩∩∩ characteristically increased and usually marked

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

# Overview of VHFs

- **Lab Abnormalities**

- Leukopenia
  - Lassa with leukocytosis (WBC inc.)
- Anemia
- Hemoconcentration
- Thrombocytopenia
- Elevated liver enzymes
- May have renal dysfunction
- Coagulation abnormalities



# Overview of VHF

- **Lab Abnormalities**

- Coagulation abnormalities

- Prolonged bleeding time
    - Prothrombin time
    - Activated PTT
    - ↑ fibrin degradation (i.e. increased D-dimer)
    - ↓ fibrinogen

- Urinalysis

- Proteinuria
    - Hematuria
    - Oliguria
    - Azotemia



# 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<sub>s</sub>

- **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

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

# The “Deadly” VHFs

<b>VIRUS</b>	<b>Mortality Rate</b>
<b>Ebola Zaire</b>	<b>75-90%</b>
<b>Marburg</b>	<b>25-90%</b>
<b>Lassa Lujo</b>	<b>15-20% of hospitalized 80%</b>
<b>CCHF</b>	<b>3-70% (typically 20-30%)</b>
<b>Rift Valley fever</b>	<b>50% of patients with hemorrhagic form</b>

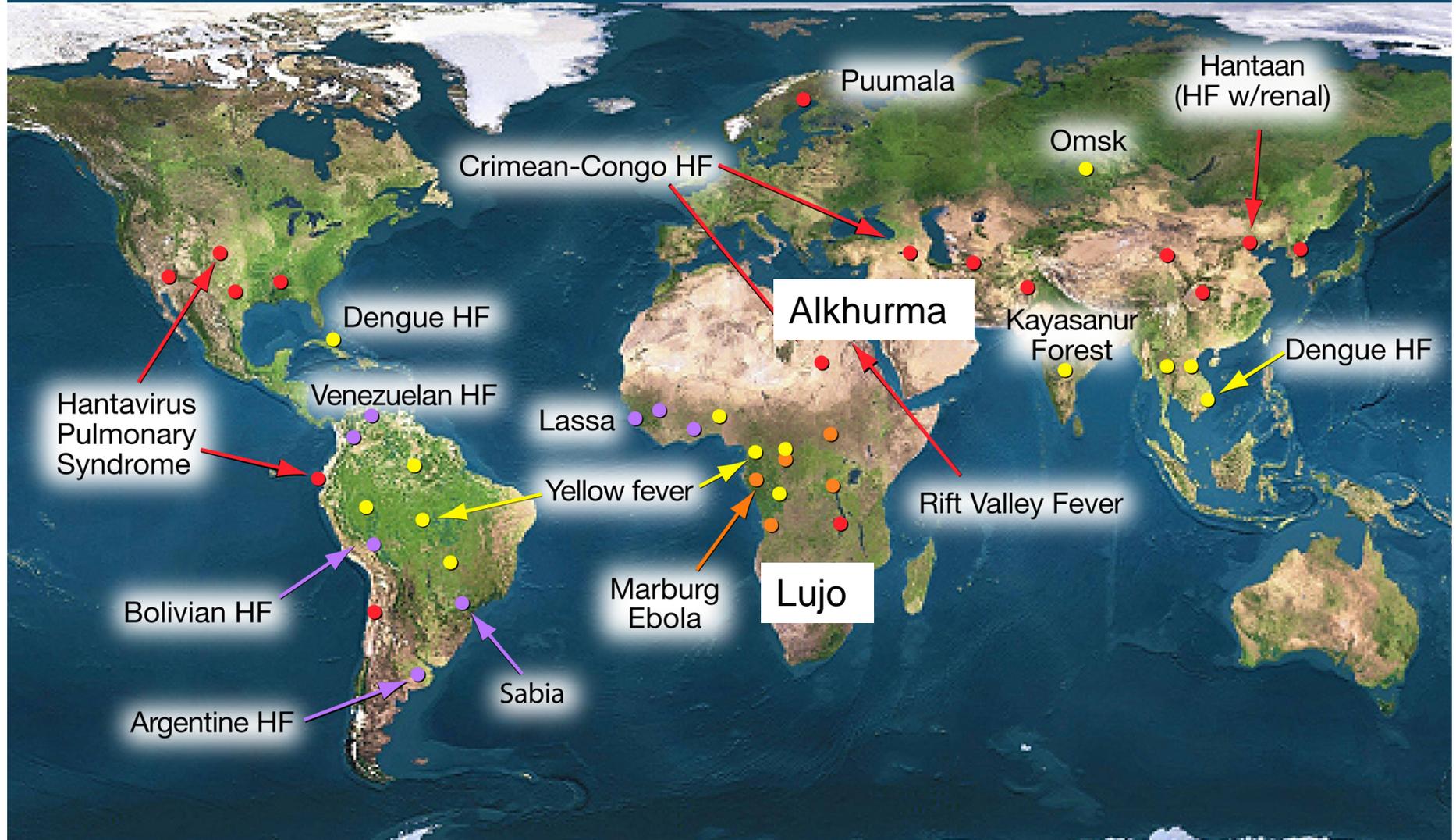


# Overview of VHF's

- **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,<sup>1</sup> Rakhee Palekar,<sup>2,3</sup> Peter Kim,<sup>1</sup> David Blythe,<sup>2</sup>  
Olivier de Senarclens,<sup>1</sup> Katherine Feldman,<sup>2</sup> Eileen C. Farnon,<sup>4</sup>  
Pierre E. Rollin,<sup>4</sup> Cesar G. Albariño,<sup>4</sup> Stuart T. Nichol,<sup>4</sup>  
and Margo Smith<sup>1</sup>**

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

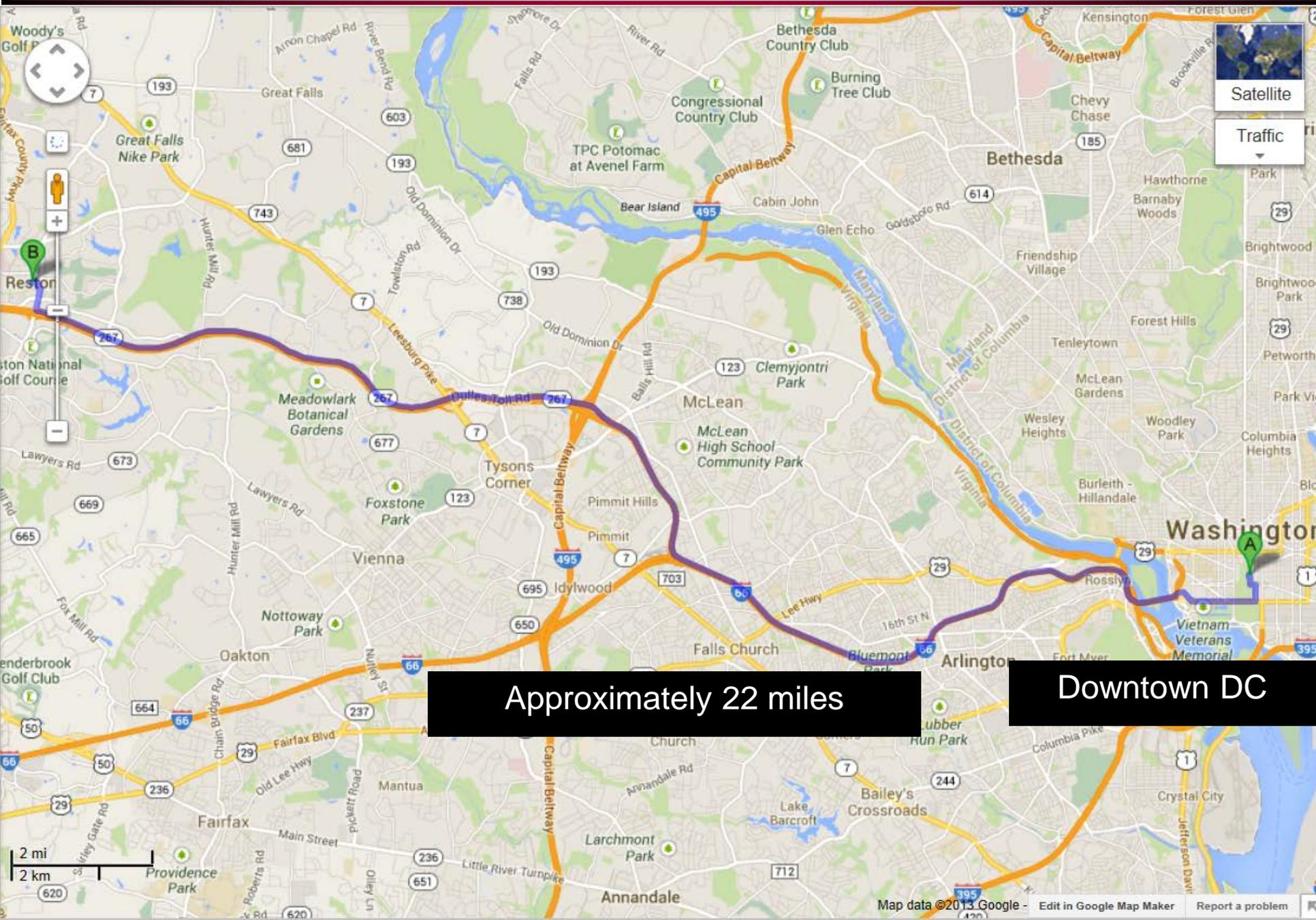
# Overview of VHF's

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

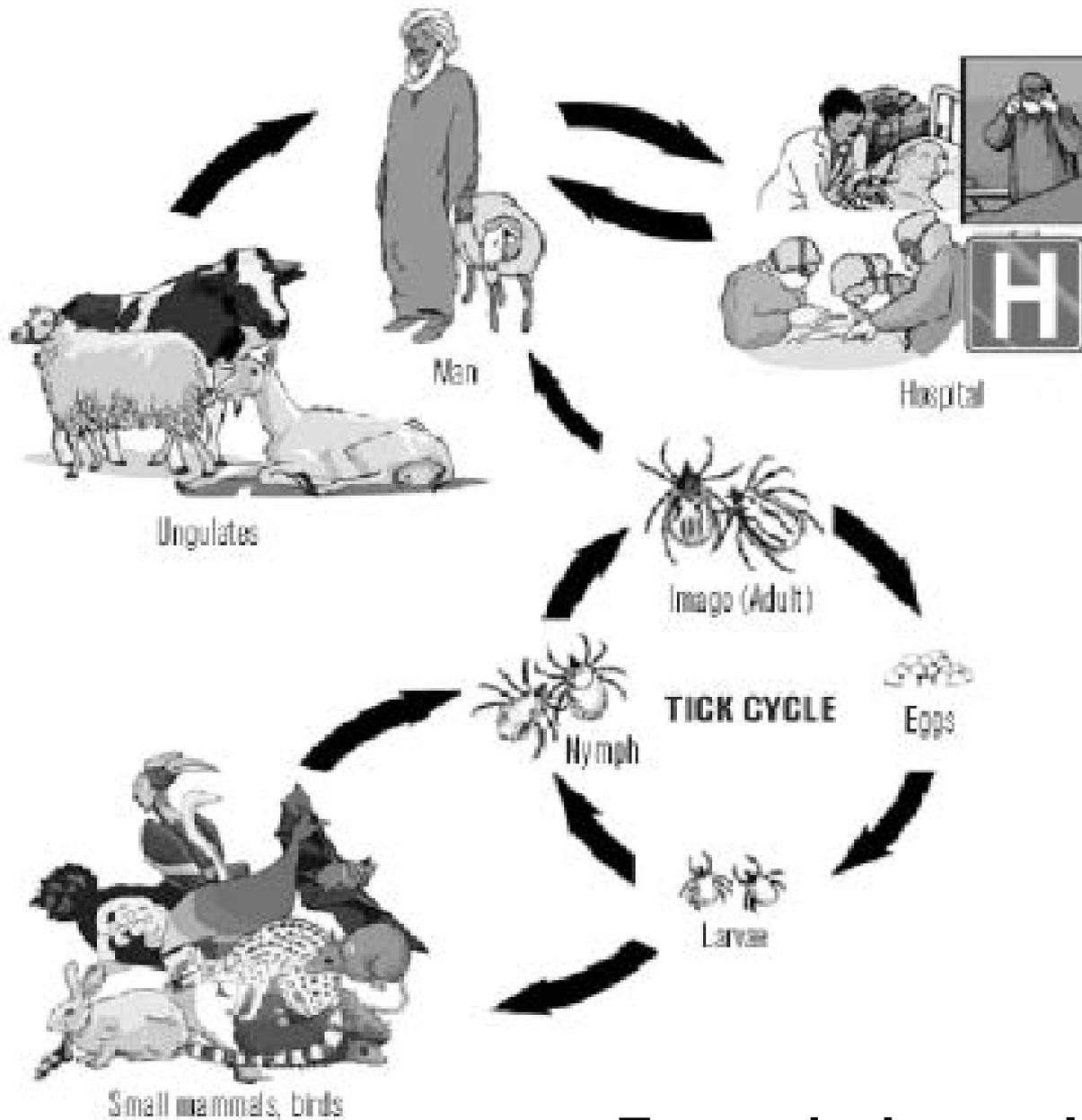
Marburg hemorrhagic fever (MHF) is a rare, viral hemorrhagic fever (VHF); the causative agent is an RNA virus in the family *Filoviridae*, and growing evidence demonstrates that fruit bats are the natural reservoir of Marburg virus (MARV) (1,2). On January 9, 2008, an infectious disease physician notified 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.

# Overview of VHF

## How are VHF 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)





**Transmission cycle of CCHF**



# 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?

### Human to Human?

Only dengue and yellow fever virus have adapted to efficient “human-to-human” transmission (via mosquitoes).

Typical story for nosocomial transmission:

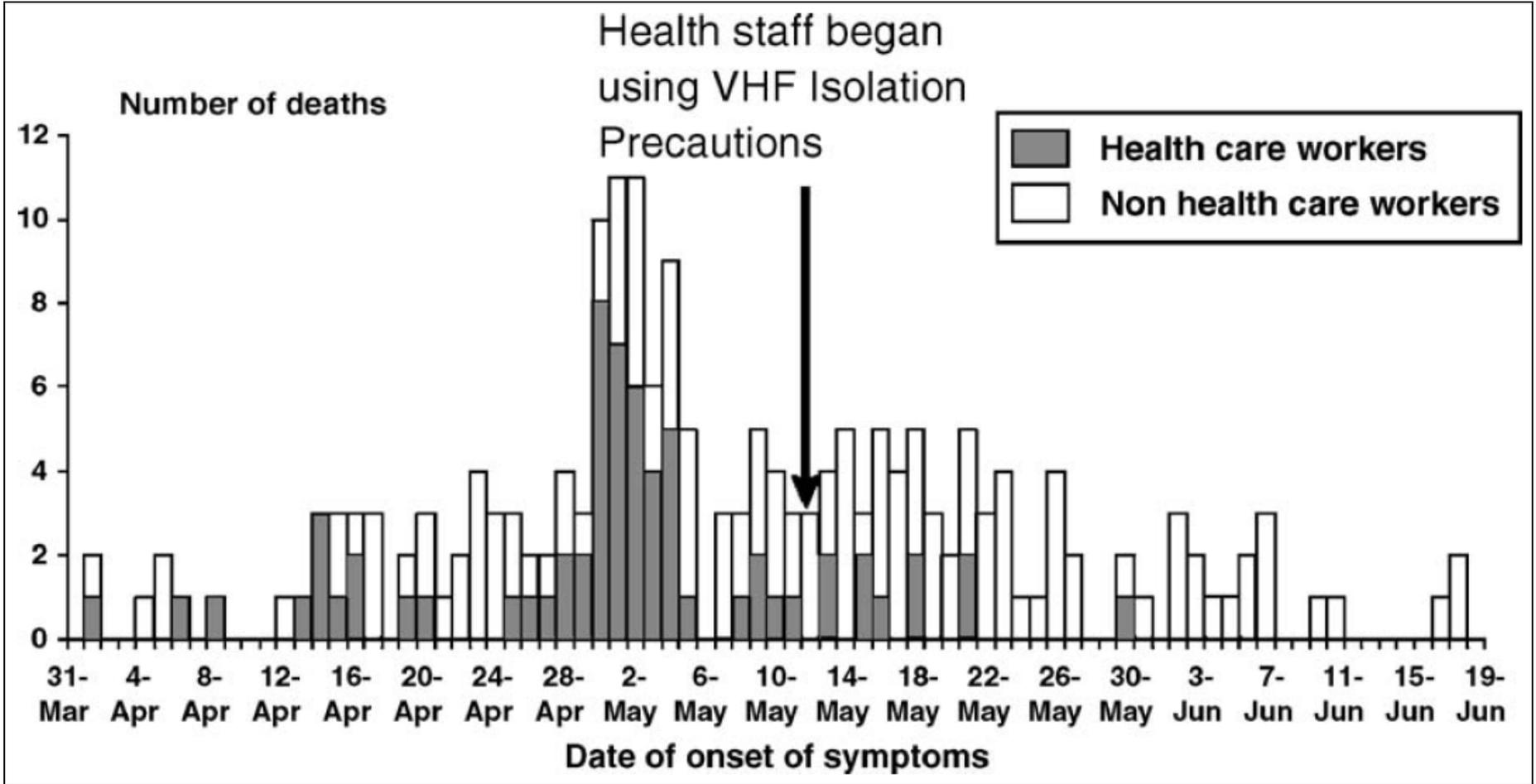
- Patient Zero enters the health care facility
- VHF is not recognized or infection control not followed
- Unrecognized spread from blood/body fluid contact
- Health care personnel among the victims
- Victims carry infection to the community
- Close family members and those doing burial rites infected

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 VHFs

## How are VHFs 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 VHFs 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



## Distribution of Junin



Figure 1: Worldwide distribution of CCHF virus

## Distribution of RVF



Antiviral Res 2008:132-39.

# Overview of VHF

## • Treatment

- **Early Supportive Care (the foundation of treatment)**
  - Careful management of fluid and electrolytes
  - 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

- 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 (ahem....contact USAMRIID or LRMC through ID consult)

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
- Junin Candid 1 – ARGENTINE HF
  - Live, attenuated
  - Safe and efficacious
  - Protects monkeys against Bolivian HF
  - **NOT AVAILABLE IN THE UNITED STATES**



# Prevention / Control:

## None Licensed in the U.S.

- Rift Valley Fever
  - Formalin-inactivated
    - safe but requires 3 shots, intermittent booster
    - limited supply
  - Live, attenuated MP-12
    - Phase II testing
- Ebola
  - Adenovirus (Ad3) vectored +/- DNA prime
  - Vesicular Stomatitis Virus (VSV) vectored
  - 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 VHF

- **Prevention**

- BACK TO THE INITIAL CASE PRESENTATION...

- 18 HCPs identified as being **HIGH** risk exposures
- Offered oral ribavirin post-exposure prophylaxis
- 2 individuals had more significant symptoms to meds

**Both were found to have developed antibodies to the CCHF virus**

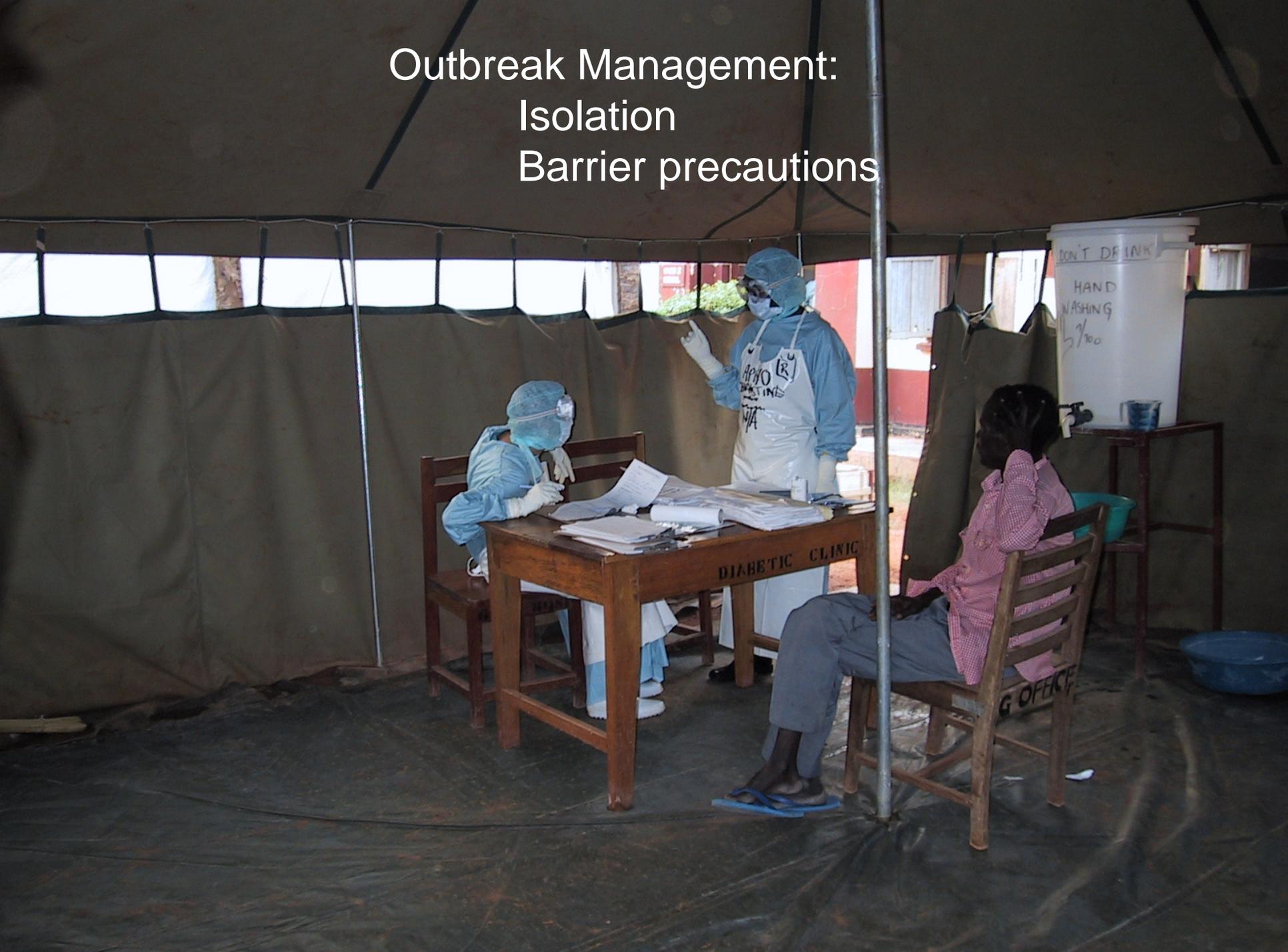


# Overview of VHF

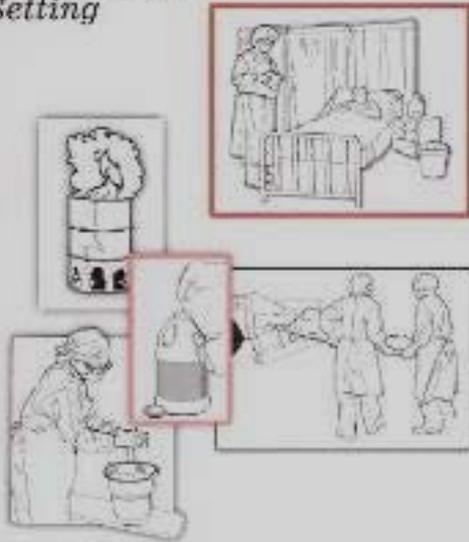
- CDC Recommendations - when to go “hot”
  - Standard Precautions in initial assessments
  - Private room upon initial hospitalization
    - “Barrier precautions” – including face shields, surgical masks, eye protection within 3 feet of patient (double glove, impermeable gown)
      - Have your VHF “battle 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



# 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.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
  - Be prepared to intensify Standard Precautions and include VHF isolation precautions
  - 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

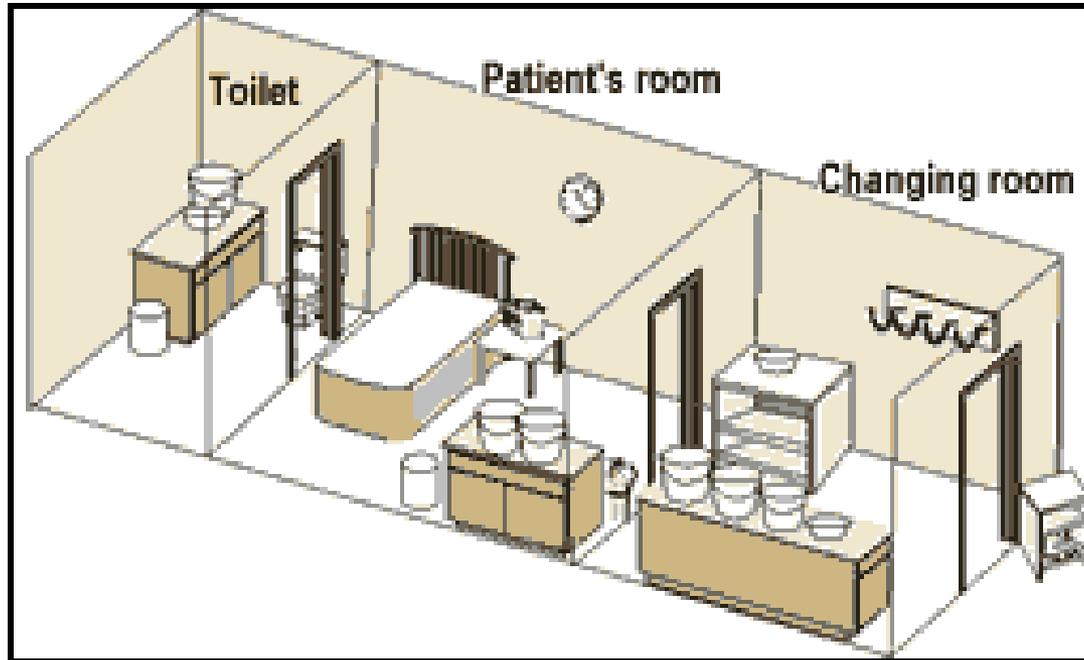


# Overview of VHFs

- 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

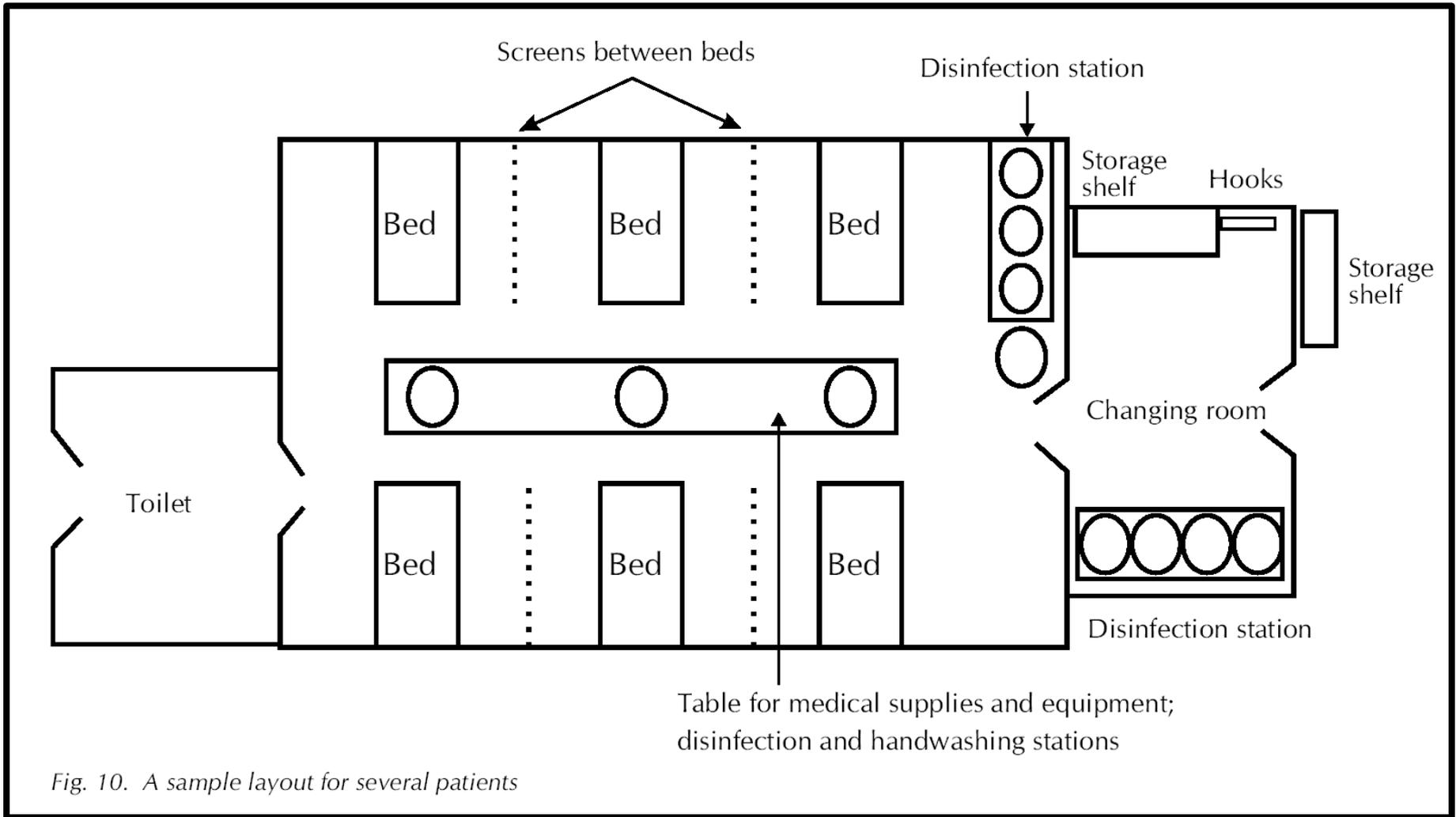


Fig. 10. A sample layout for several patients





**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

[Recommend](#) [Tweet](#) [Share](#)

*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.

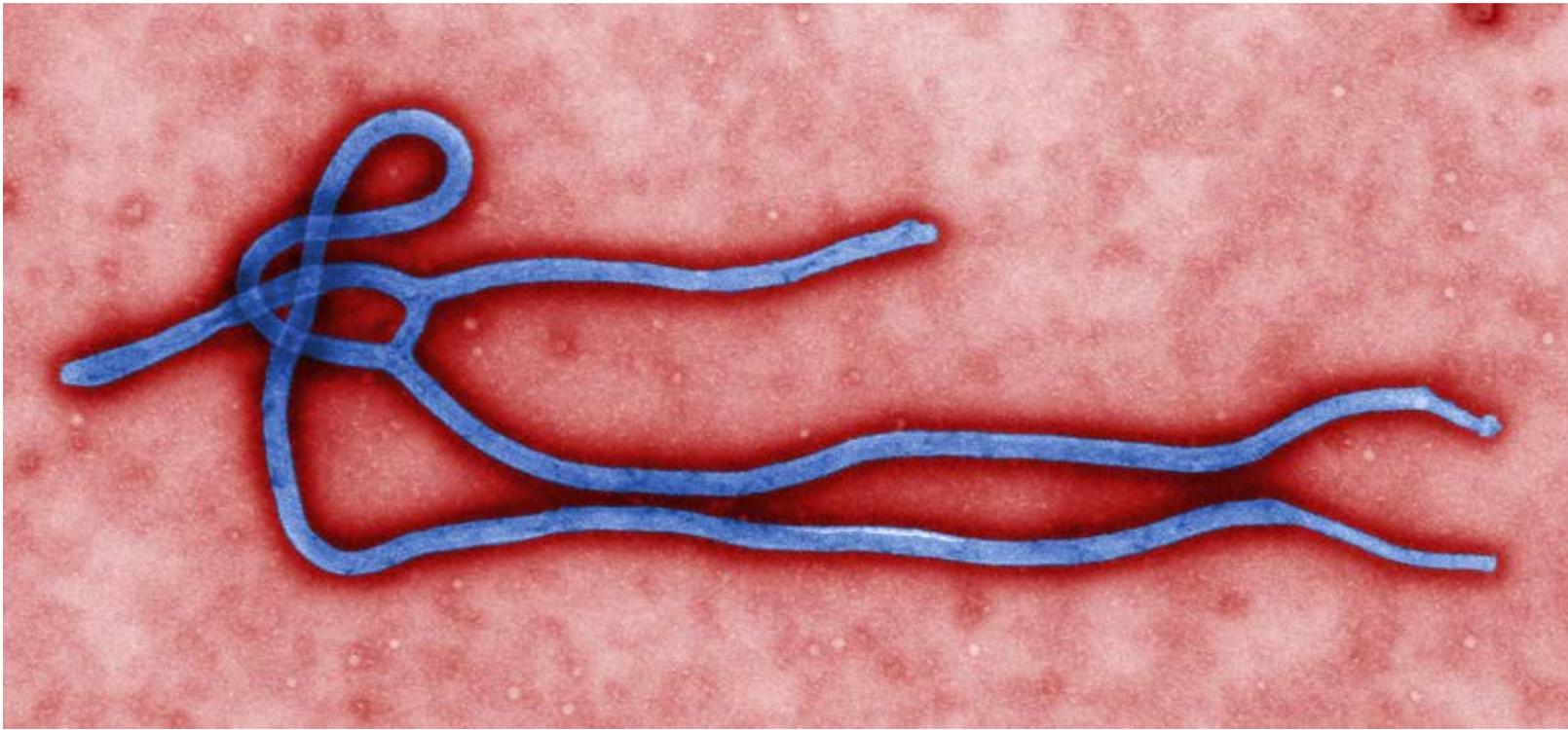
Participants intending to take this course should be currently licensed by a recognized professional agency to provide clinical care in some jurisdiction (e.g., hold a medical license to provide care in a state in the United States) and have recent relevant experience providing direct care to patients. 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 VHFs

- 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 (up to 3 weeks)



# Ebola

- Current Outbreak
  - Affecting Sierra Leone, Liberia, Guinea, Nigeria with recent spread to Senegal
  - A record number of cases
    - Cases = 5357 (2630 deaths; 49% CFR) as of 18 SEP 2014
      - This has more than **doubled** in the past month
  - The current situation is far from stable



# 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 AK<sup>1</sup>, 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)
    - 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

- 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
    - Tested in humans in a phase 1 study (2006)
    - Uses 3 different plasmids encoding proteins against Ebola
    - 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**



# 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

[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

- Vaccines

- VSV vaccines
  - VSV

**Phase I clinical trial scheduled for Oct 2014 at WRAIR**

- » 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



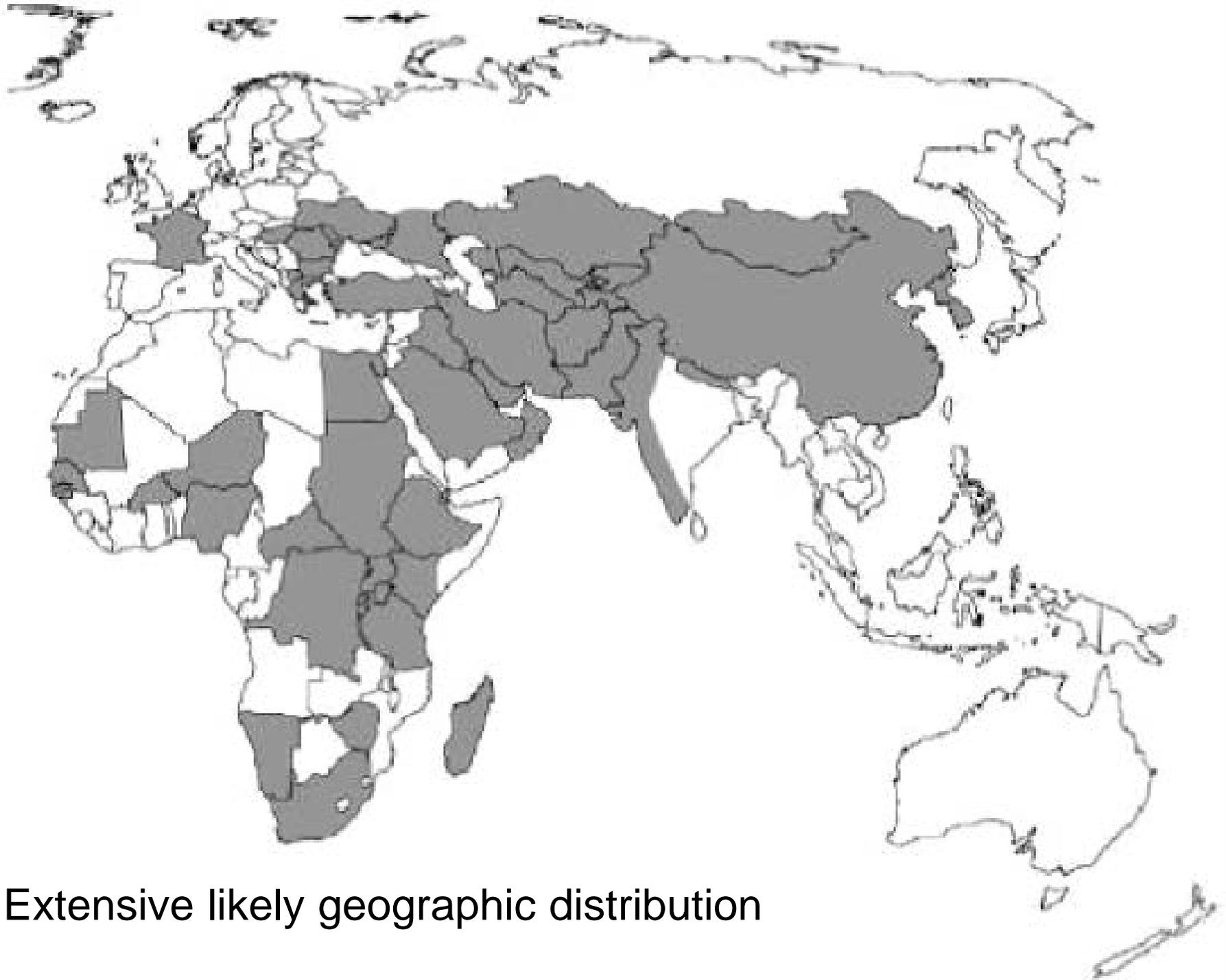
# CRIMEAN-CONGO HEMORRHAGIC FEVER



# Crimean-Congo Hemorrhagic Fever

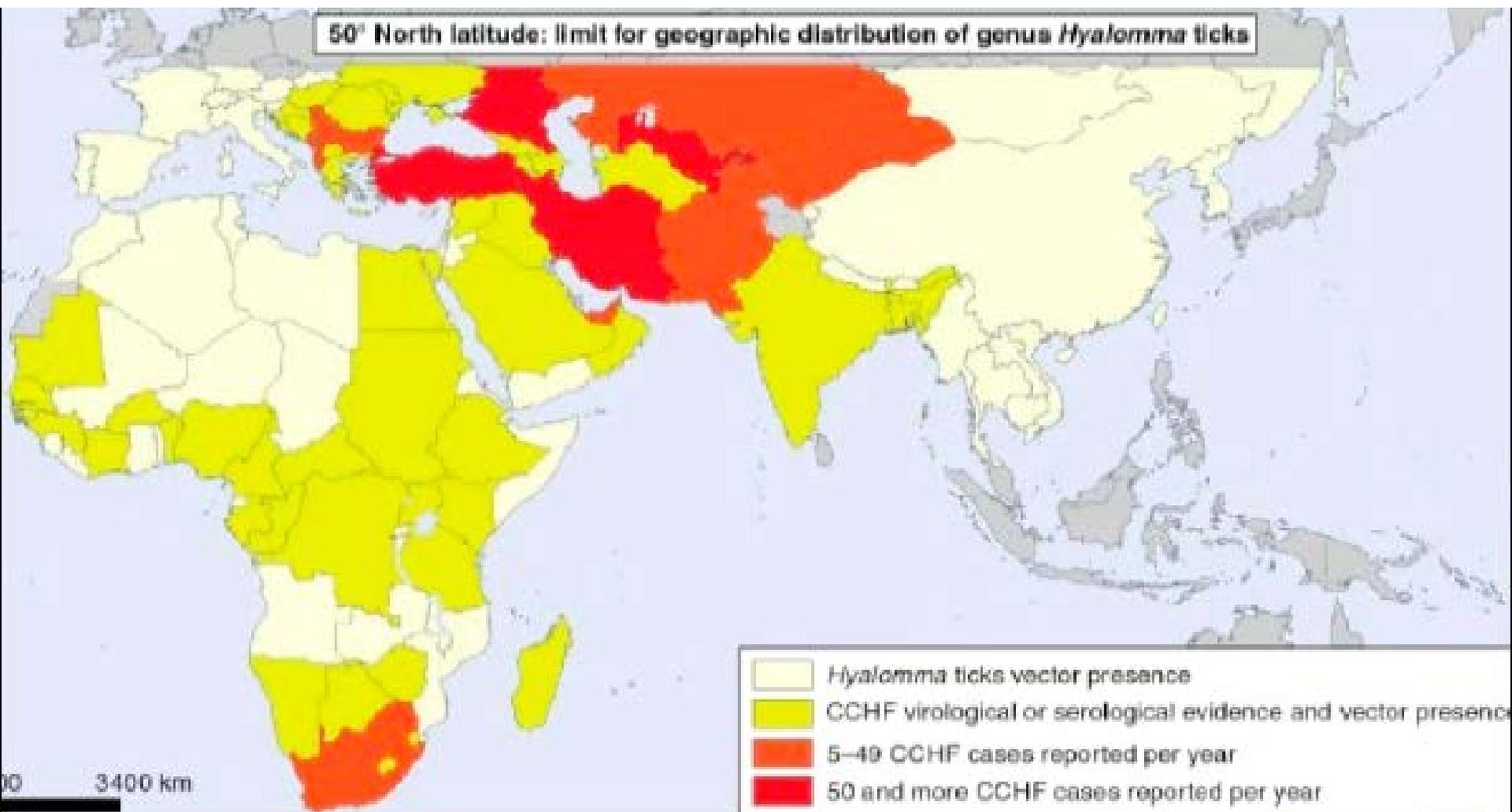
- Geographic regions
  - 12<sup>th</sup> Century: Tajikistan
    - HF syndrome: blood in urine, rectum, gums, vomit
  - 1944-45: First clinical description
    - Soviets (N=200, CFR = 10%) assisting peasants in Crimea
  - 1956: febrile patient in Belgian Congo
  - Common antigenic structure: Crimea &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

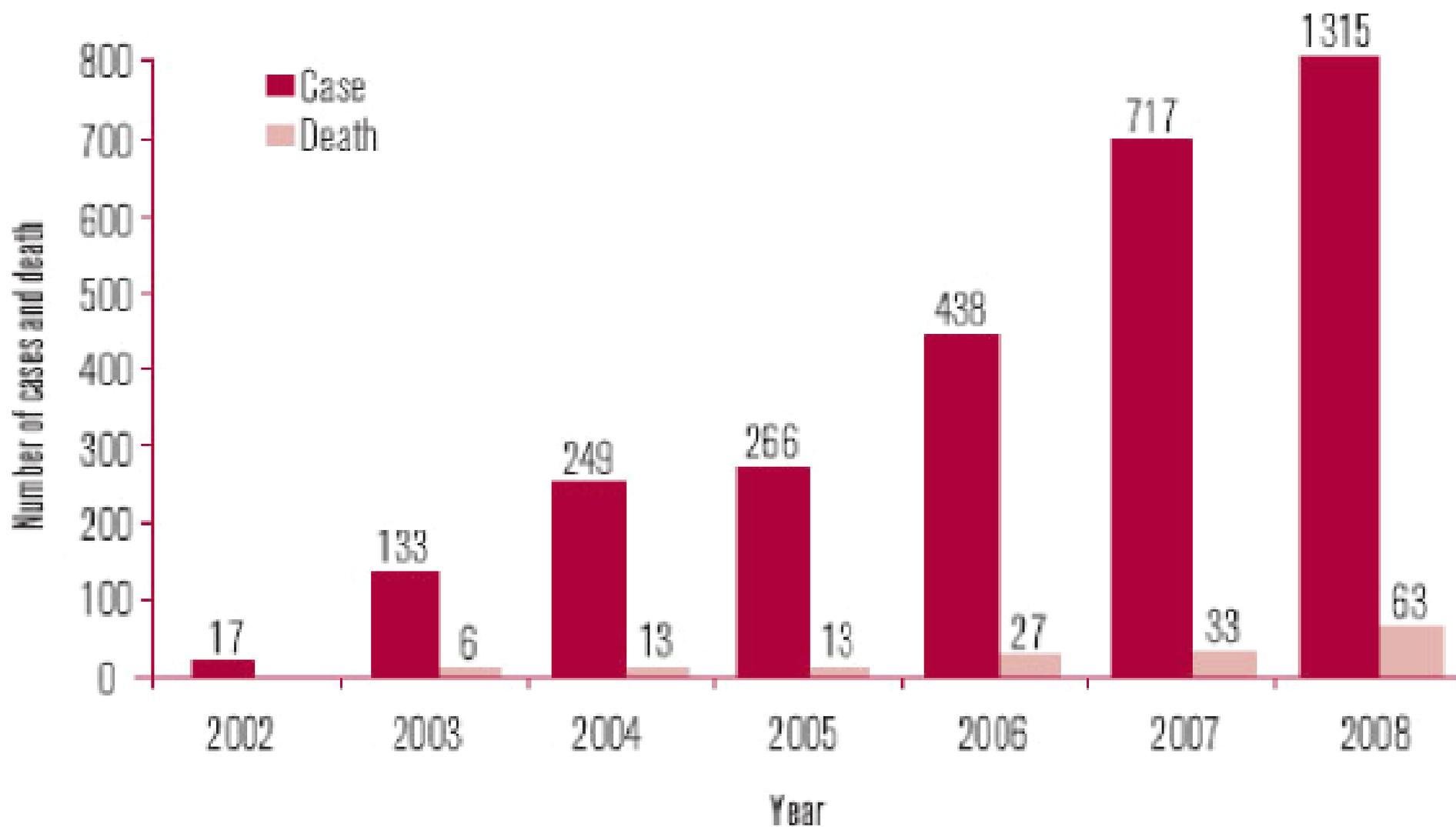
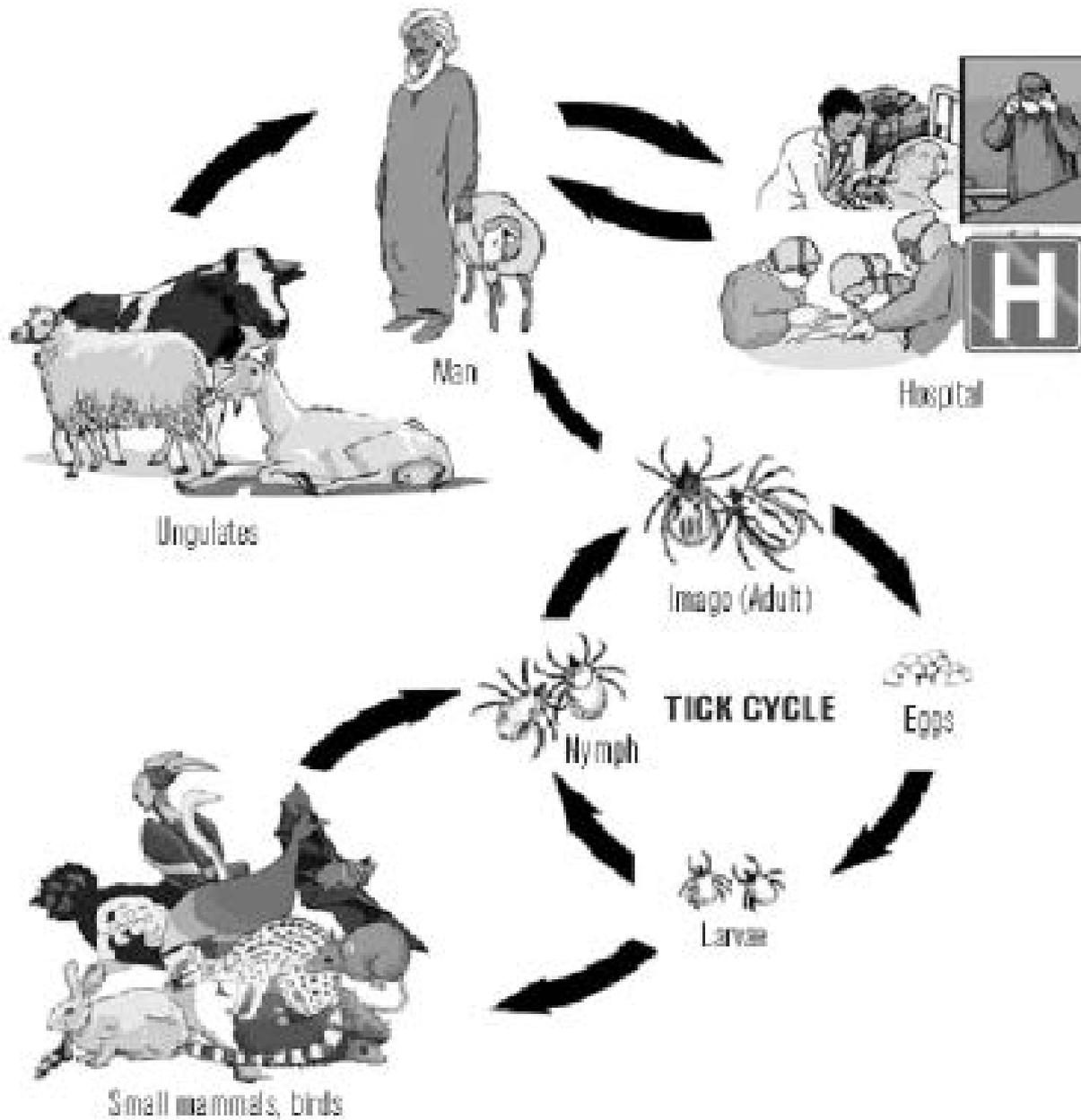


Figure 5. Number of Crimean-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008.<sup>32</sup>

# 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
<b>Platelet count, <math>\times 10^3</math> platelets/mm<sup>3</sup></b>	
>150	0
150-50	1
49-20	2
<20	3
<b>aPTT, sec</b>	
$\leq 34$	0
35-45	1
46-59	2
>60	3
<b>Fibrinogen level, mg/dL</b>	
$\geq 180$	0
179-160	1
159-120	2
<120	3
<b>Bleeding</b>	
No	0
Petechia	1
Ecchymosis	2
Bleeding	3
<b>Somnolence</b>	
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

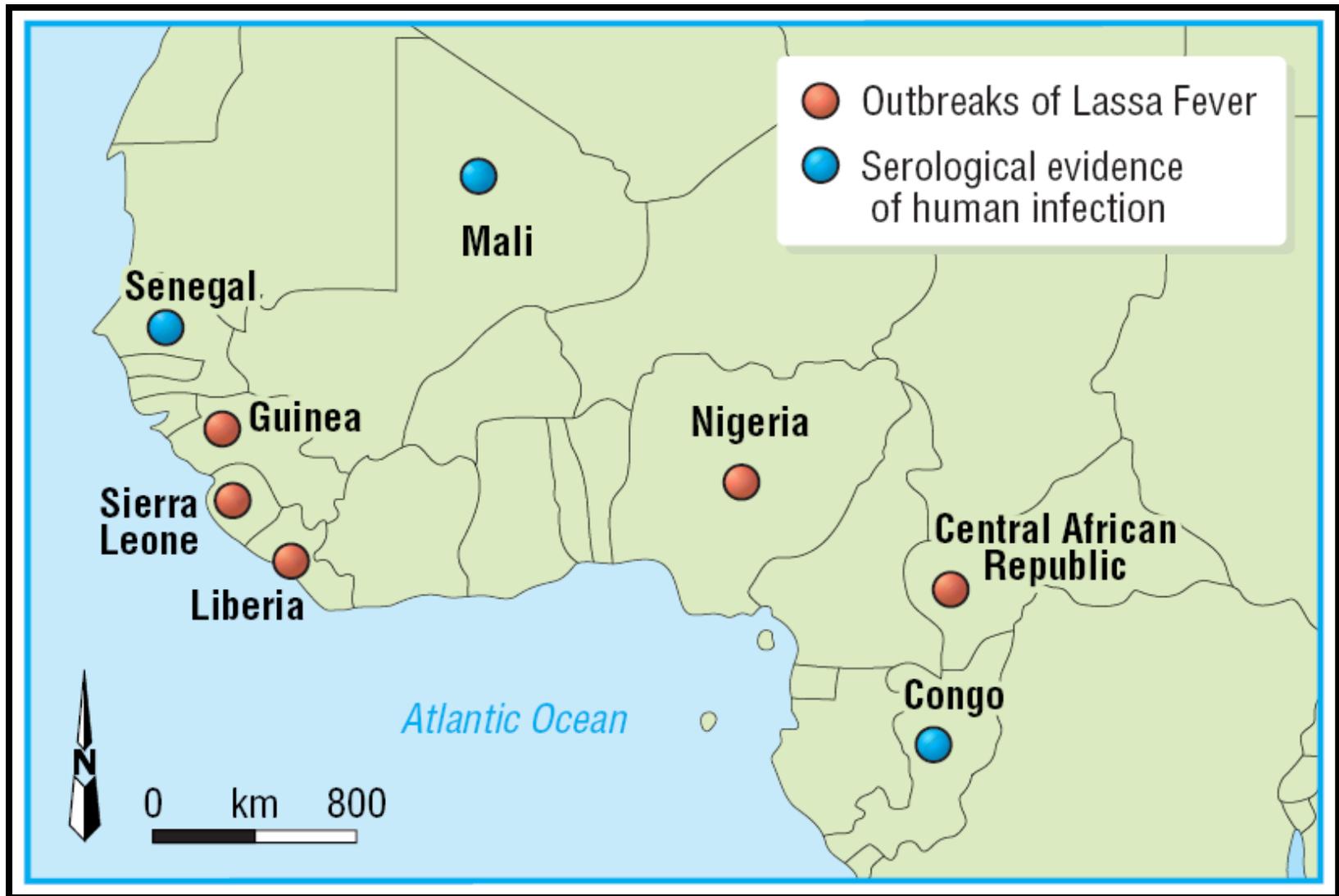


# Lassa

- 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

<b>Clinical stages of severe Lassa fever (adapted from McCarthy 2002<sup>15</sup>)</b>	
<b>Stage</b>	<b>Symptoms</b>
<b>1</b> (days 1-3)	General weakness and malaise. High fever, >39°C, constant with peaks of 40-41°C
<b>2</b> (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
<b>3</b> (after 7 days)	Oedema of the face and neck Convulsions Mucosal bleeding (mouth, nose, eyes) Internal bleeding Encephalopathy with confusion or disorientation
<b>4</b> (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

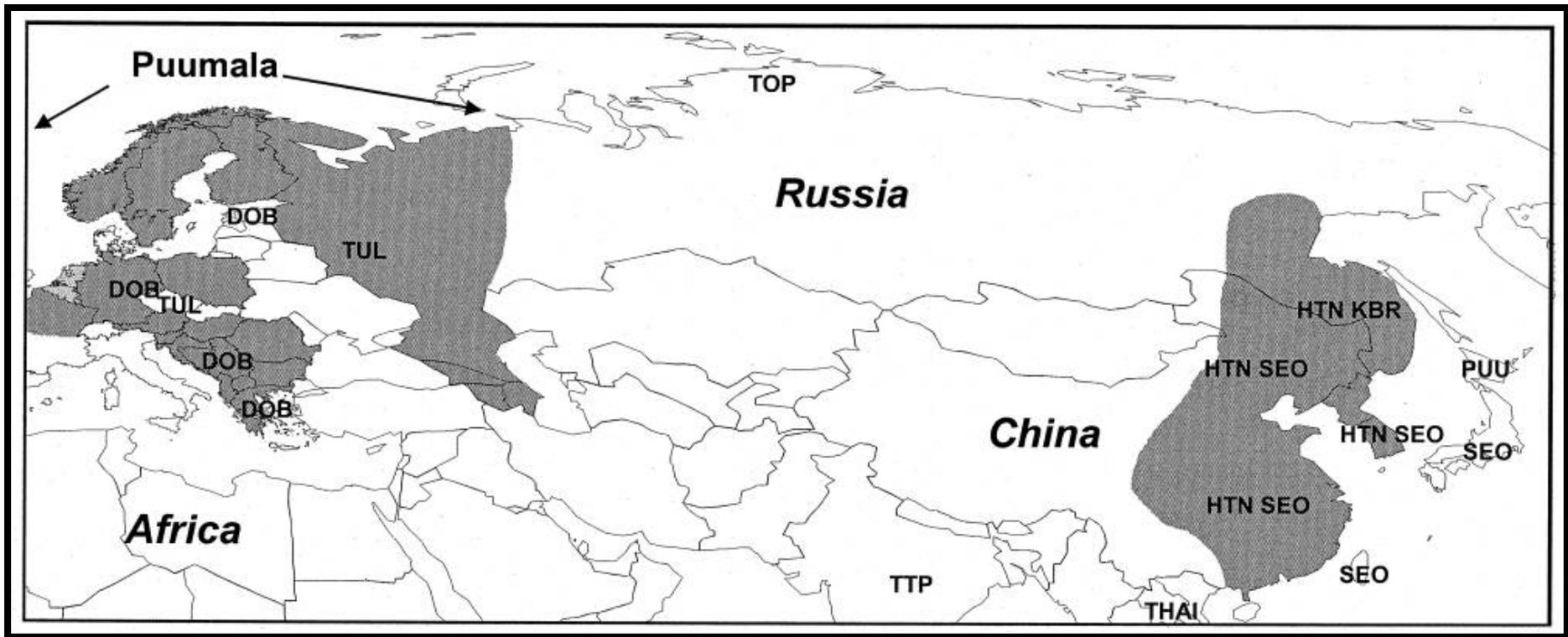
MMWR Feb 19, 1988/37(6);87-90,95-6



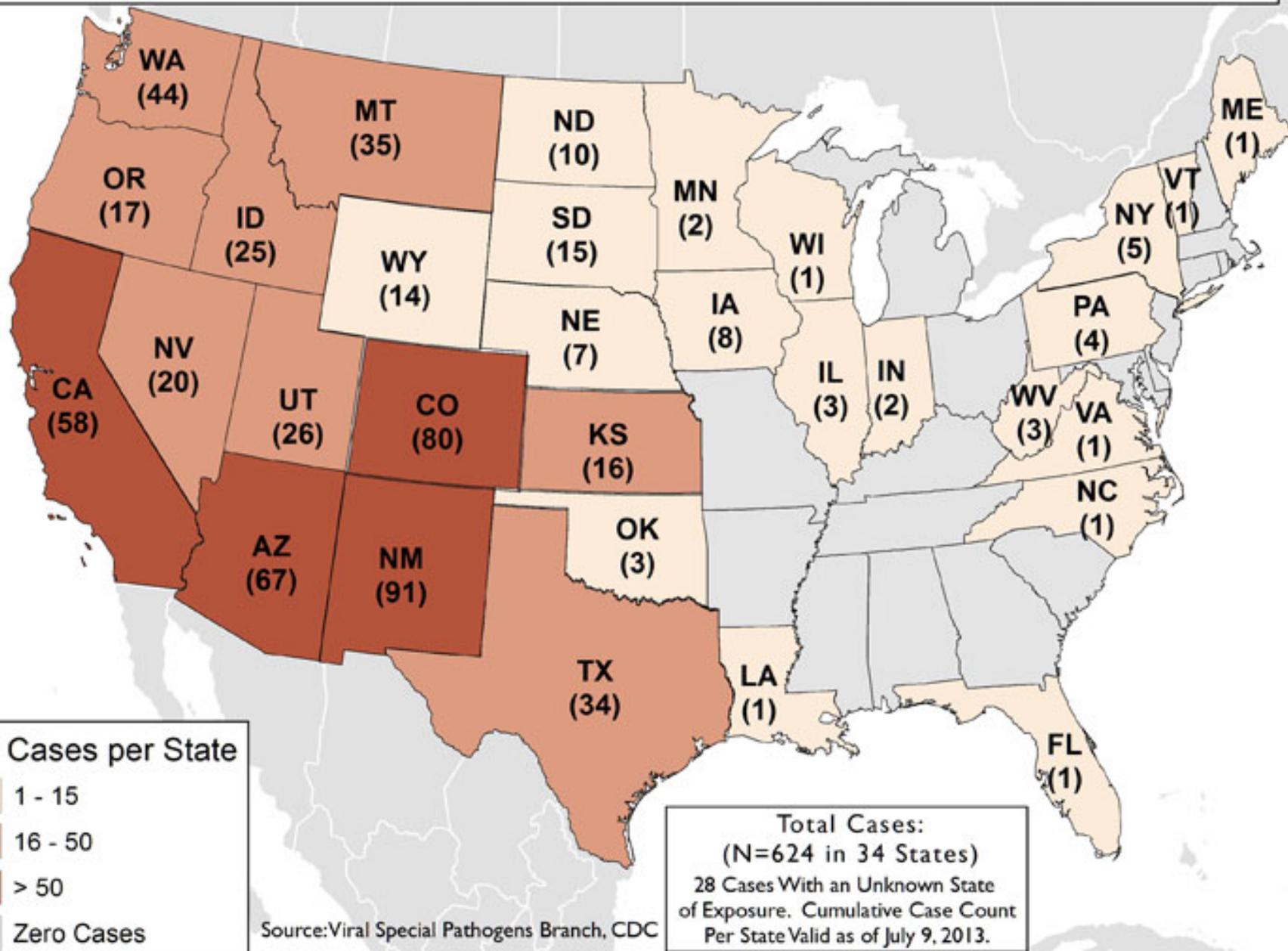
# Hantaviruses

- 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 VHF's 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)
- 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



# 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



# 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?

