

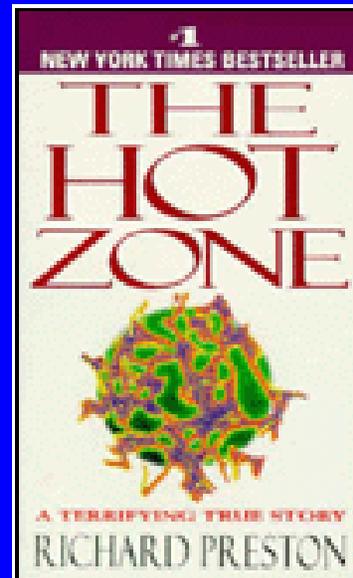
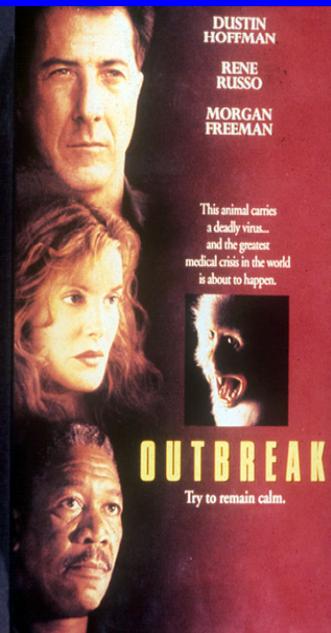
# Hemorrhagic Fever Viruses

Mark Kortepeter, MD, MPH

Colonel, US Army Medical Corps

Deputy Director, Infectious Disease  
Clinical Research Program

Uniformed Services University





# Viral Hemorrhagic Fevers

**Mark Kortepeter, COL, MC**  
**Director, IDCPRP**

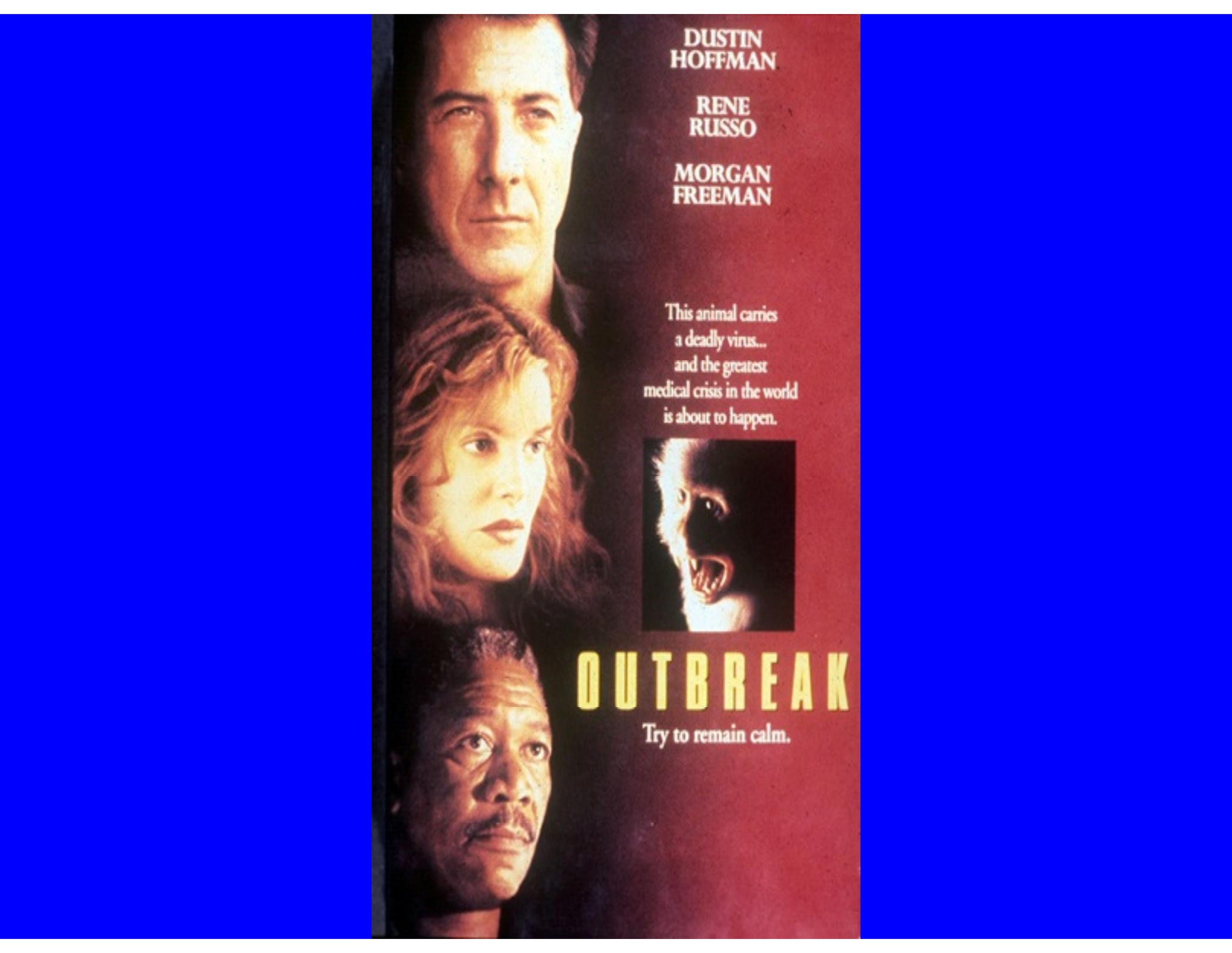
Modified from original lectures by LTCs Tom Larsen, Ed Stevens, COL Keith Steele, & DTRA lecture (MAJ Steve Thomas).

# Disclaimer

- The views expressed in this presentation are those of the speaker and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

# Film Clip





**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.

# METRO

SUNDAY, OCTOBER 2, 2005



BY ROCKY CAROTTI — THE WASHINGTON POST

Tom Geisbert, center, and his team — Joan Geisbert, left, Katie Daddario, Lisa Hensley and Elizabeth Fritz — worked for years at the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, trying to develop an Ebola vaccine. In 2003, they succeeded.

## Ebola's Dogged Enemies

*Team of Fort Detrick Scientists Labored for Years to Develop Vaccine*

By NELSON HERNANDEZ  
Washington Post Staff Writer

By Day 3, Tom Geisbert knew the monkeys were going to die. He could see it in their faces as he entered the monkey room in Suite AA-4, wearing the china-blue plastic space-suit that serves as a uniform for the scientists of Fort Detrick's U.S. Army Medical Research Institute of Infectious Diseases when they are working with the world's most vicious viruses.



Ebola is covered in spikes that attack the

...utes later, he pulled the sedated primate from its cage. He drew blood: The white blood cell count was plummeting. The vaccine for a disease more lethal than smallpox was failing. It was a bad day in the fight against Ebola.

It would take four more years of such days before Geisbert and his team would make a breakthrough that could save lives by offering protection from an epidemic or a bioterrorism attack.

Each day, Geisbert steeled himself to witness the ravages of the virus.

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By MATTHEW M  
Washington Post St

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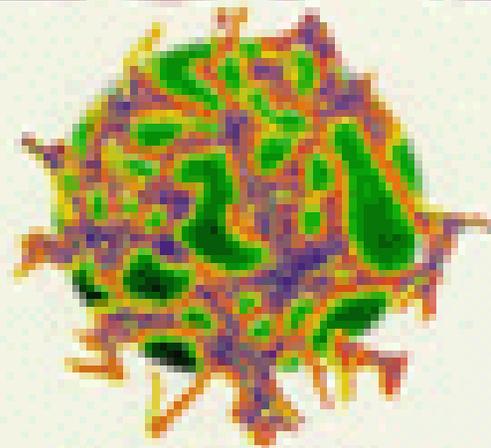
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NEW YORK TIMES BESTSELLER

# THE HOT ZONE



A TERRIFYING TRUE STORY

RICHARD PRESTON

# USAMRIID: A Unique National Resource



# Fort Detrick offers inside look at 'slammer'

 [E-Mail This Article](#)

by **Robert Schroeder**  
*Staff Writer*

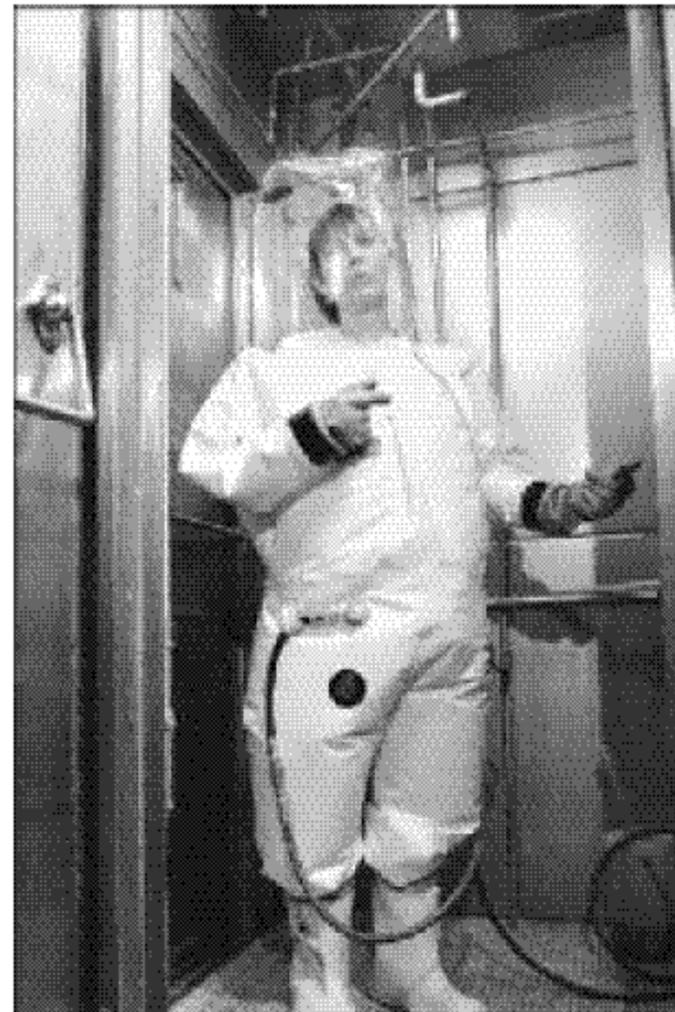
THE GAZETTE

Mar. 18, 2004

In official parlance, the room is called the BSL-4 Patient Isolation Suite.

Unofficially, it's called "the slammer."

Located at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Frederick's sprawling Fort Detrick, "the slammer" is made up of two, 180-square-foot patient care rooms and a 300-square-foot treatment room. It was here that a USAMRIID scientist who recently was feared to be exposed to a weakened form of the Ebola virus was housed for 21 days between Feb. 12 and March 3.



# Case Presentation

- U.S. Army Active Duty Native American (50%) enlisted male in his early 20s
- Co-located with Afgan army at an Afgan Army base
- Staying in old Afgan army dorms
  - Occasionally slept outside
- Afganis periodically brought in game, but he never participated in the killing
- Patient and roommate both with recent tick bites (pulled off with tweezers) within a week of illness onset
  - A common occurrence with bragging rights

# Pre-Hospital Course

- Patient presented to the local clinic
  - Fever, headache, fatigue, chills, but no rash
  - Initial Dx: “viral syndrome”
- A couple days later unimproved
  - Referred to the clinic at Kandahar
  - 4 day history of nausea/vomiting
  - Develops lethargy, bloody diarrhea, bleeding gums, shortness of breath requiring intubation
  - Treated for presumptive pneumonia
    - Concern about possible septic shock
    - Elevated LFTs, thrombocytopenia
  - Air evacuated to LRMC
    - Considered less ill than other patient on medevac flight.

# Pre-Hospital Course

- En route, began oozing blood from IV sites and old puncture sites
- Arrived at Landstuhl RMC ~5 days after onset of illness (Friday evening)
- Upon arrival, appeared very ill:
  - Oozing blood
  - Blood coming from ET tube
  - Required emergent assistance

# Hospital Course

- Emergent bronchoscopy
  - Required suction of significant amounts of blood
  - Urgent transfusions of clotting factors, FFP, cryoprecipitate, and red blood cells
  - Appeared to stabilize
  - Required paralysis on the ventilator.

# A bit of Serendipity

- ~1 week prior - patient with coumadin overdose
  - Consideration of CCHF in differential Dx
  - Contact established with the Bernard Nocht Institute (BNI) in Hamburg
- Within hours of arrival, blood sent to the BNI
- Blood run overnight
  - Saturday morning: PCR and IGM + for CCHF
  - ID consulted Saturday morning ~1 hour before Diagnosis
    - ID staff was returning from TDY in Hungary

# Treatment

- 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 (USAMRIID as intermediary)
  - CDC's protocol used, but emergency approval required:
    - Patient's renal failure (uncertain dosage adjustment needed)
    - Inability to obtain consent.
- IV ribavirin obtained from a European manufacturer
  - Begun ~12 hours after oral treatment (48 hours of hospitalization)

# Hospital Course

- Saturday
  - Remained intubated with respiratory failure, ARDS
  - Developed renal and hepatic failure (AST/ALT >500)
  - On/off pressors
  - Dialysis begun
  - IV ribavirin
- Waxing/ waning periods of bleeding
  - Each time, treated aggressively and improved
- Bronchoscopy x 3
- Sunday
  - Due to impending hepatic failure, MARS unit ordered

# Hospital Course

- Monday
  - MARs unit running
  - Dialysis continued
  - Patient appeared to have stabilized
    - Off pressors with improving LFTs
- Tues/Weds
  - Patient had a couple asystolic/PVA arrests
  - Sedation was lightened up
    - No reflexes or movement
    - Pupils fixed and dilated
  - Declared brain dead (~ 9-10 days after illness onset/5 days after arrival)
    - At time of death, viral load declined and serology increased

Will Cover Some Steps to  
Avoid....



# The "Slammer"

BSL-4  
CONTAINMENT SUITE



MAJ Muckerman OIC

SECURE AREA

AUTHORIZED  
PERSONNEL

CONTAINMENT SUITE CHECK LIST

DEFIBRILLATOR CHARGED DELIVERABLE	BATTERIES INSTALLED AND	ENG. PAPER ON	PACER CHECKED	CRASH CART EXP. DATE	PORTABLE WATER	PORTABLE WATER	DETAILED CHANGE



1995 Kikwit Zaire ZEBOV Outbreak  
Courtesy of Don Noah

# Outline

- VHF in general
- Epidemiology
- Clinical aspects
- Diagnosis
- Preventive measures
- Treatment

# Definition

- **Viral hemorrhagic fever (VHF):**
  - Acute, febrile, multisystemic illness characterized by malaise, myalgia, prostration, and bleeding diathesis
  - Caused by lipid-enveloped, single-stranded, RNA viruses
- Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF.

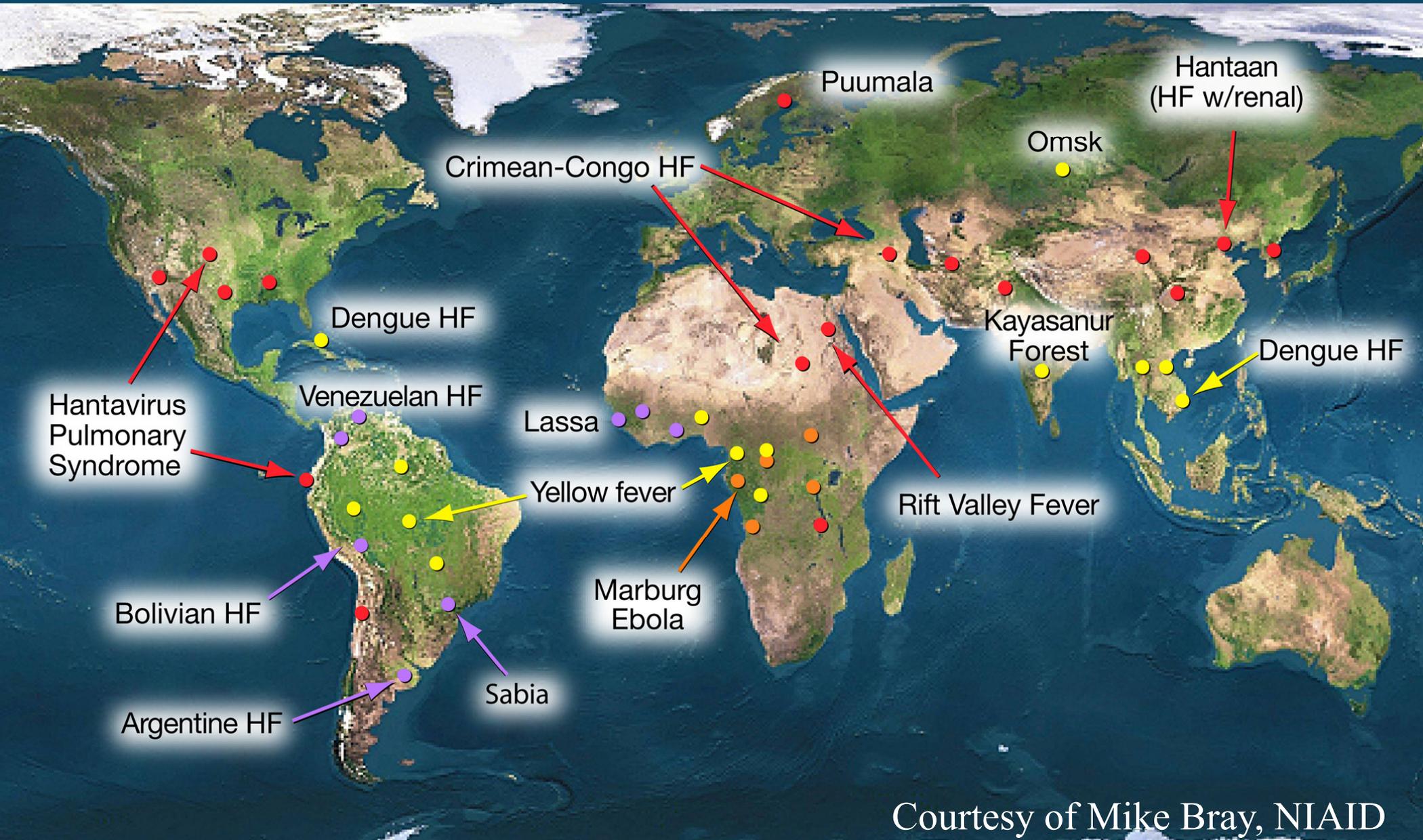
<http://0->

[www.cdc.gov/mill1.sjlibrary.org/ncidod/dvrd/spb/mnpages/dispages/vhf.htm](http://www.cdc.gov/mill1.sjlibrary.org/ncidod/dvrd/spb/mnpages/dispages/vhf.htm)

# Step 1

Know What's There and  
How You Can Get It

# Viral Hemorrhagic Fever



Courtesy of Mike Bray, NIAID

- Filoviruses
- Flaviviruses
- Bunyaviruses
- Arenaviruses

# Overview of Etiologic Agents of VHFs

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

# Overview of Epidemiology of HFVs

Disease (virus)	Distribution	Natural Host/ Vector	Other Sources	Incubation (days)
<u>Filoviruses</u>				
Ebola HF	Africa, Philippines (ER)	Bats?	Nosocomial, etc.	2-21
Marburg HF	Africa	Bats?	Nosocomial, etc.	5-10
<u>Arenaviruses</u>				
Lassa fever	Africa	Rodent	Nosocomial, etc.	5-16
Argentine HF ( <i>Junin</i> )	South America	Rodent	Nosocomial	7-14
Bolivian HF ( <i>Machupo</i> )	South America	Rodent	Nosocomial	9-15
Venezuelan HF ( <i>Guanarito</i> )	South America	Rodent	Nosocomial	7-14
Brazilian HF ( <i>Sabia</i> )	South America	Rodent	Nosocomial	7-14
<u>Bunyaviruses</u>				
CCHF	Europe, Asia, Africa	Tick	Animal slaughter	3-12
Rift Valley fever	Africa	Mosquito	Animal slaughter	2-6
HFRS/HPS ( <i>Bunyaviridae</i> )	World-wide	Rodent		9-35
<u>Flaviviruses</u>				
Omsk HF	Soviet Union	Tick		2-9
Kyasanur forest disease	India	Tick		2-9
Dengue HF	Asia, Americas, Africa	Mosquito	Nosocomial	3-15
Yellow fever	Africa, tropical America	Mosquito		3-6

# How are VHF's spread?

- In NHPs – possible airborne transmission between cages 3 meters apart
  - Lung tissue with documented virus
- In NHPs and GPs: infective via airborne, conjunctival, oral exposure
- Viremia – 3-5 ds (inoculated, 10-50 pfus)
  - 1D prior or simultaneous with clinical illness (D4-5)
  - Virus recovered from nares, pharynx, conjunctivae, anus (ds 7-10)(limited numbers)

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.

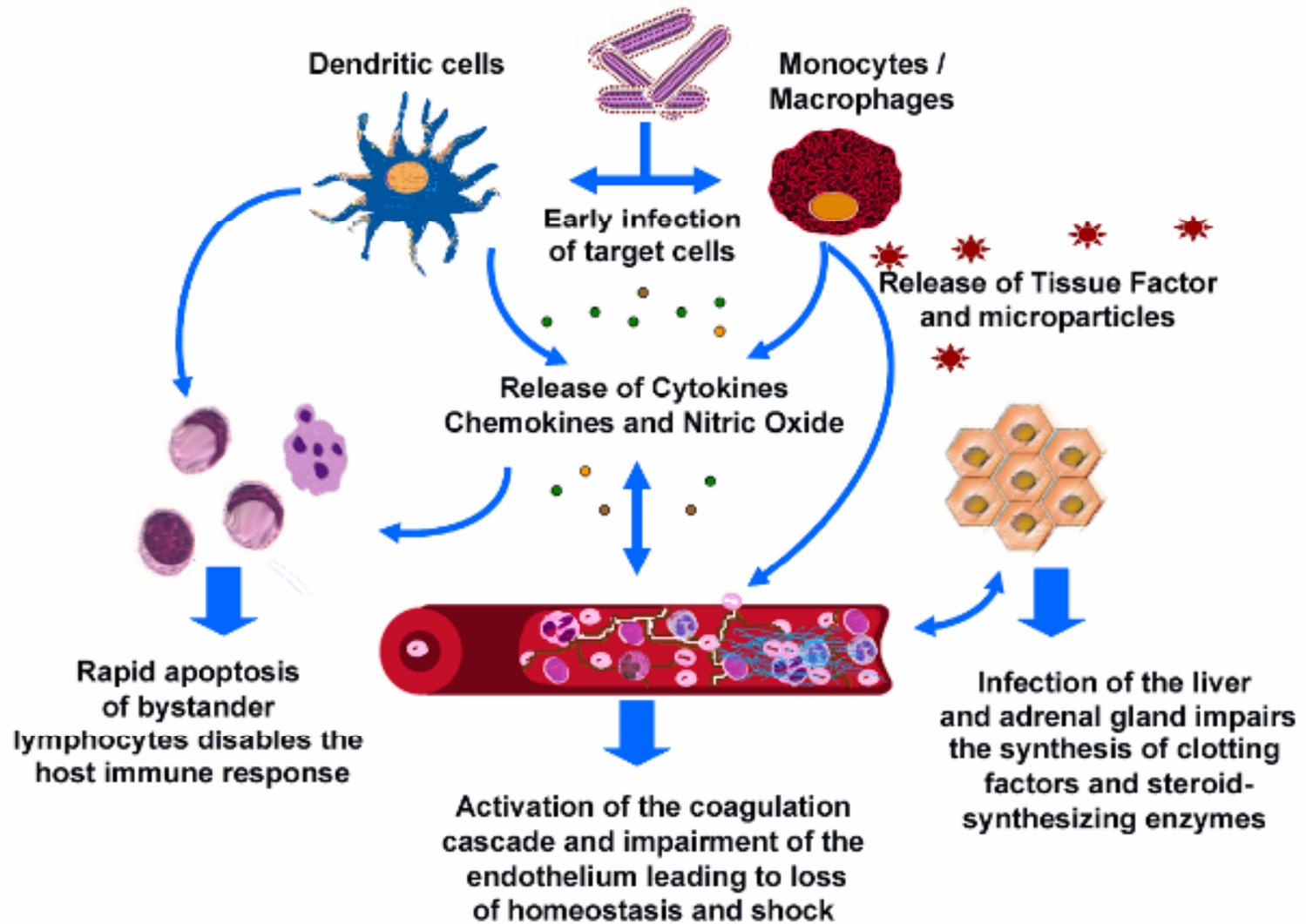
# How are VHFs Spread Person to Person?

- Human cases usually during patient care without appropriate barrier precautions
  - Contact with blood/tissue/body fluids
  - Includes re-use of syringes/needles
- Epidemiologically, VHFs not readily transmitted person-to-person by airborne route
  - A possibility in only rare circumstances
- Highest risk in later stages, when having vomiting, diarrhea, shock, hemorrhage
- Not reported during incubation period (before fever)

## Step 2

Know What They Can  
Do

# Model of Filoviral Pathogenesis in Primates



# VHF: Spectrum of Clinical Presentations

- Variety of presentations
- Prodrome
  - High fever, Headache, Malaise, Arthralgias, Myalgias
  - Nausea, Abdominal pain, Nonbloody diarrhea
- Early signs
  - Fever, ↓ BP, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
  - Flushing, Skin Rash
- Late
  - Hemorrhagic diathesis, Petechiae, Mucous membrane
  - Conj. hemorrhage, Hematuria, Hematemesis, Melena
- Major Manifestations
  - DIC, Circulatory Shock, CNS dysfunction

# Marburg Infection Human



Maculopapular rash

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

# **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.

# Argentine Hemorrhagic Fever (Junin virus – New World Arenavirus )



Gingival hemorrhage

# 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.

# Clinical Features - VHF

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

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

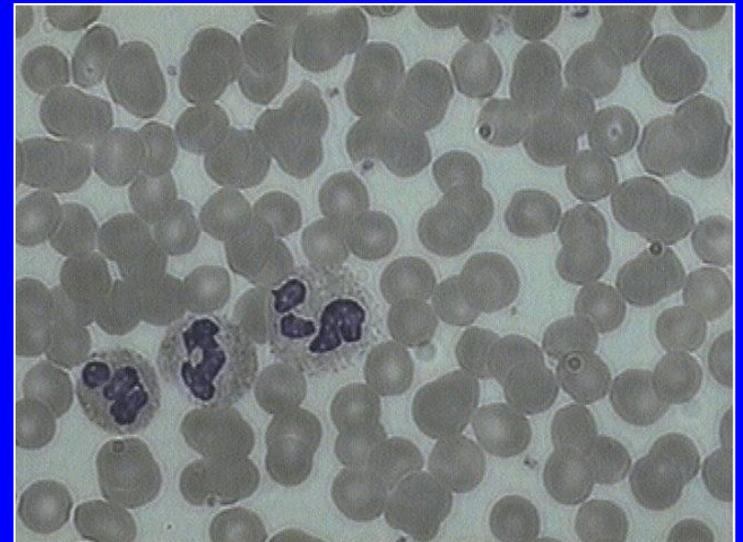
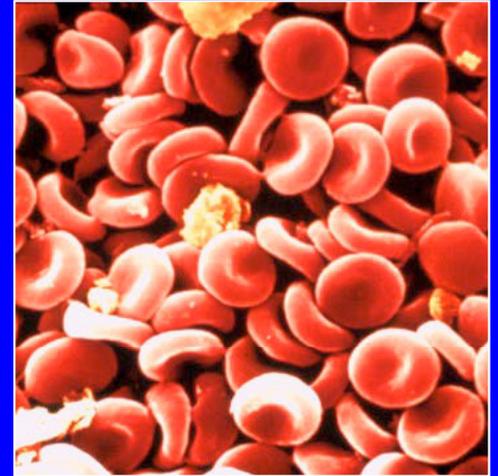
S characteristic, seen in severe cases

∩ 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)

# VHF: Spectrum of Laboratory Abnormalities

- Leukopenia
  - Lassa with leukocytosis
- Anemia
- Hemoconcentration
- Thrombocytopenia
- Elevated liver enzymes



# VHF: Spectrum of Laboratory Abnormalities

- Coagulation abnormalities
  - Prolonged bleeding time
  - Prothrombin time
  - Activated PTT
  - ↑ fibrin degradation
  - ↓ fibrinogen
- Urinalysis
  - Proteinuria
  - Hematuria
  - Oliguria
  - Azotemia

# The “Deadly” VHF

---

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

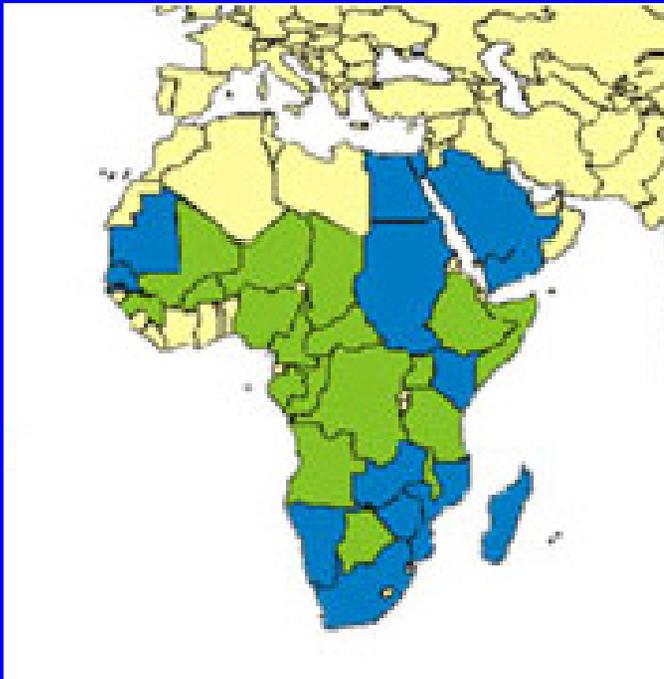
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# Step 3

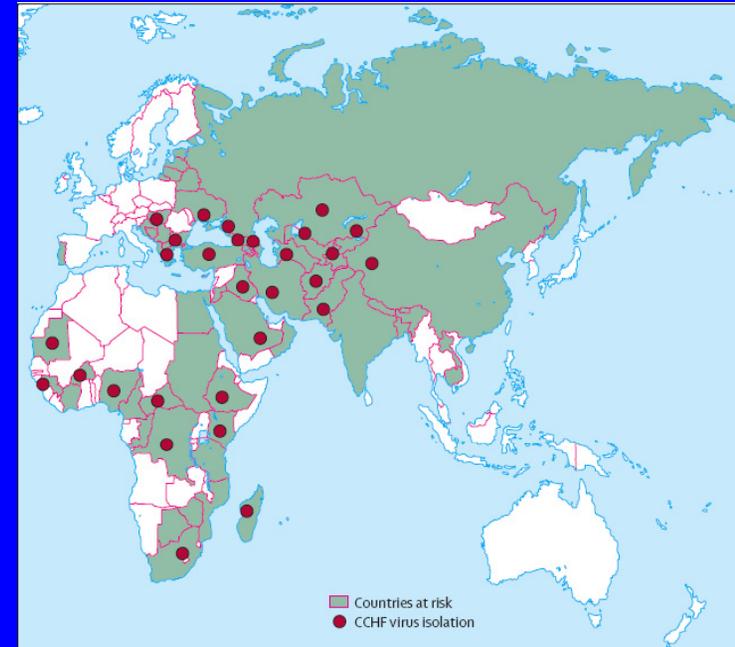
Know What Else to  
Consider and how to  
Diagnose

# Differential Diagnosis

## Distribution of RVF



## Distribution of CCHF



## Distribution of Malaria

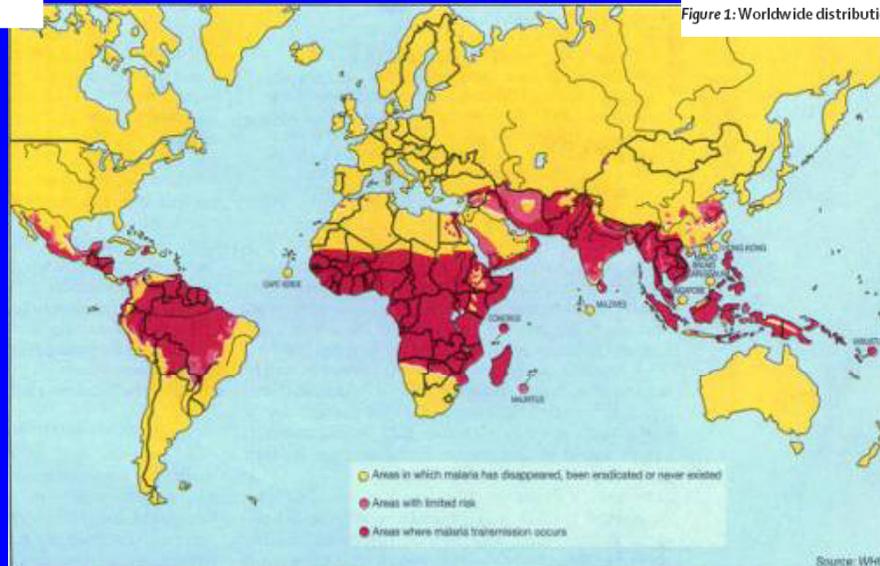


Figure 1: Worldwide distribution of CCHF virus

# Distribution of CCHF

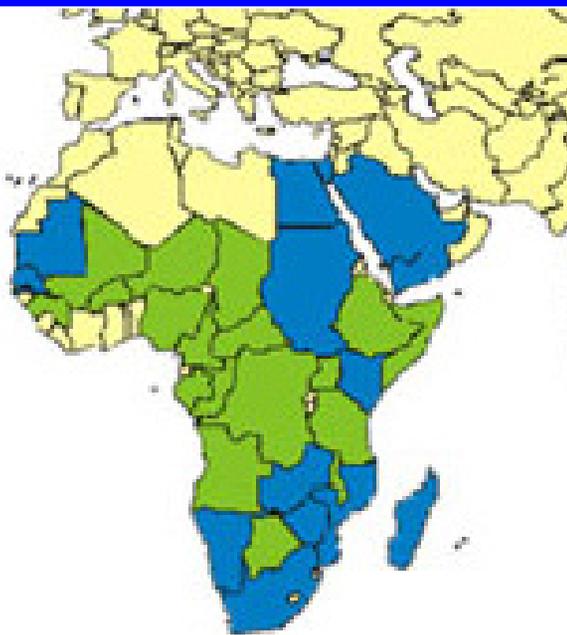


Figure 1: Worldwide distribution of CCHF virus

# Distribution of Junin



# Distribution of RVF



# Differential Diagnosis of VHF

**Clinical presentation:** Febrile, hemorrhage/purpura, thrombocytopenia, CNS signs, elevated , leukopenia, thrombocytopenia, DIC, multisystemic / multi-organ failure

- **Protozoal**

- Malaria

- **Bacterial**

- Typhoid fever
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*) & other rickettsioses
- Leptospirosis
- Meningococci
- Q fever (*Coxiella burnetti*)
- Plague

- **Viral**

- Influenza
- Viral meningitis / encephalitis (e.g. henipaviruses)
- HIV / co-infection
- Hemorrhagic smallpox

- **Other**

- Vasculitis, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), heat stroke

# Diagnosis - Clinical Pathology

- Thrombocytopenia or abnormal platelet function
- Leukopenia (exception is Lassa, which has a leukocytosis)
- Some patients have anemia
- Most have elevated liver enzymes (ALT / AST)
- Bilirubin is elevated in RVF and YF
- Prothrombin time, activated partial thromboplastin time (APTT) and bleeding time are prolonged
- Some have disseminated intravascular coagulation (DIC); those that have DIC have elevated d-dimers (FDP's) and decreased fibrinogen

# **Diagnosis**

## **Laboratory Confirmation**

- **Gold Standard - Virus isolation from blood, serum or tissue biopsy**
  - BSL-4 Lab
- **Electron microscopy**
- **Reverse transcription - polymerase chain reaction (RT-PCR)**
  - Increasingly important tool

# Diagnosis

## Laboratory Confirmation

- Rapid ELISA techniques most easily employed
  - Antigen capture detection
  - IgM (test of choice for Hantaviridae, yellow fever, & Dengue) or IgG antibody capture
- Serology on paired sera
- Immunohistochemistry (IHC) & in situ hybridization (ISH) of infected tissues
  - Formalin-fixed tissue
  - CDC has developed a skin biopsy procedure for detection of EBOV using IHC

# Step 4

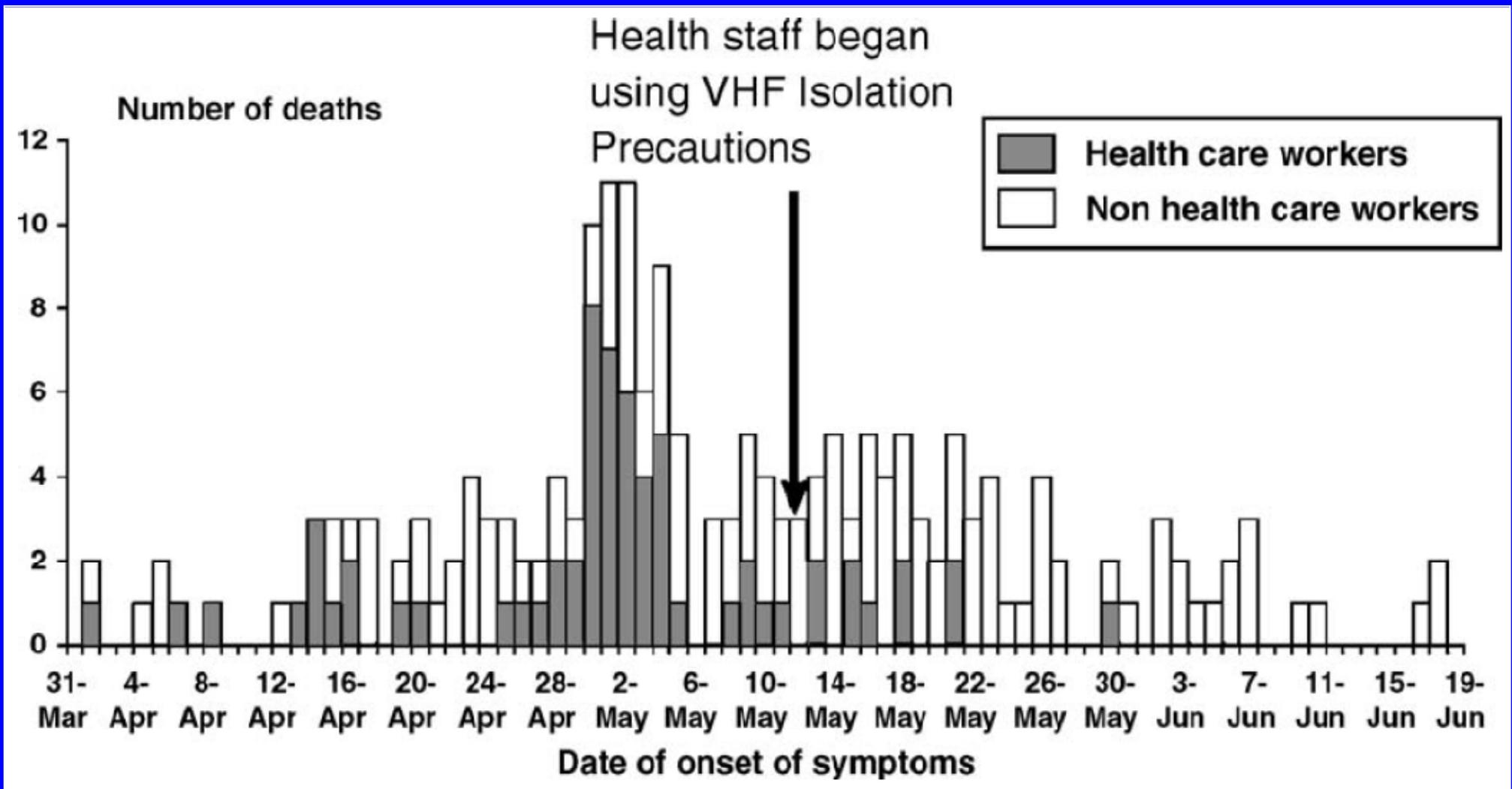
Know How To Protect  
Yourself and Others

# VHF Spread Summary – lack of spread

- 1967 – Marburg – no airborne transmission
- 1975 – 2 pts, Marburg in S. Africa
  - 1/35 HCWs infected when barrier precautions not used
- 1979 – 34 pts, Ebola in Southern Sudan
  - 29 cases – direct contact
  - 0 cases of 103 who had no direct contact
- 1994 – 1 pt, Ebola
  - 1/70 contacts infected (no airborne precautions)
- 1996 – 2 pts, Ebola
  - 0/300 contacts infected

# VHF Spread Summary – evidence of spread

- 1995 – 316 infected with Ebola in DRC
  - 3 HCPs infected after barrier precautions
    - 1 – non-adherent
    - 1 – needlestick
    - 1 – uncertain - ? Rubbed eyes with glove
  - No household non-physical contacts infected
- 2000 – 224 deaths, Ebola in Uganda
  - **14/22 (64%) infected after infx control**
  - Uncertain why this happened
  - Couldn't rule out airborne transmission
- Conclusion:
  - Preponderance of evidence: Can't r/o airborne transmission, but appears to be a minor mode if it exists
  - Transmission rarely, if ever occurs prior to onset of signs/symptoms



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.

# Prevention / Control

- YELLOW FEVER
  - Licensed 17D vaccine, highly efficacious
  - Recent 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

# Prevention / Control

- RIFT VALLEY FEVER
  - Formalin-inactivated
    - safe but requires 3 shots, intermittent booster
    - limited supply
  - Live, attenuated MP-12
    - Phase II testing
- Ebola
  - Adenovirus vectored +/- DNA prime
  - VEE replicons
  - VSV vectored
  - Virus-like particles (VLP)
- Marburg
  - Recent NHP study at RIID: 100% survival following challenge w/ lethal dose of MBGV and then post-exposure treatment w/ recombinant VSV-GP Marburg vaccine

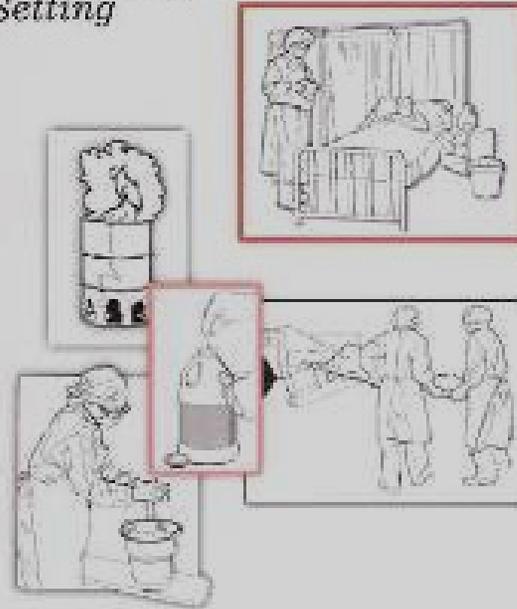
# CDC Recommendations when to go “hot”

- Standard Precautions in initial assessments
- Private room upon initial hospitalization
  - Barrier precautions – including face shields, surgical masks, eye protection within 3 feet of patient
  - 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

MMWR  
1988;37(S-3):1-16.

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

*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

CDC

[www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm](http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm)

# Standard Precautions for All Patients

- Identify a minimum level of Standard Precautions and use for all patients
- Establish routine handwashing practices
- Establish safe handling and disposal of used needles and syringes
- 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

# Use VHF Isolation Precautions

- Isolate the patient
- Wear protective clothing
  - Scrub suit, gown, apron, two pairs of gloves, mask, headcover, eyewear, rubber boots
- Clean/disinfect spills, waste, and reusable safety equipment
- Clean/disinfect soiled linens and laundry safely
- Use safe disposal methods for non-reusable supplies and infectious waste
- Provide information about the risk of VHF transmission to healthcare staff
- Provide information to families and the community about VHF prevention and care of patients



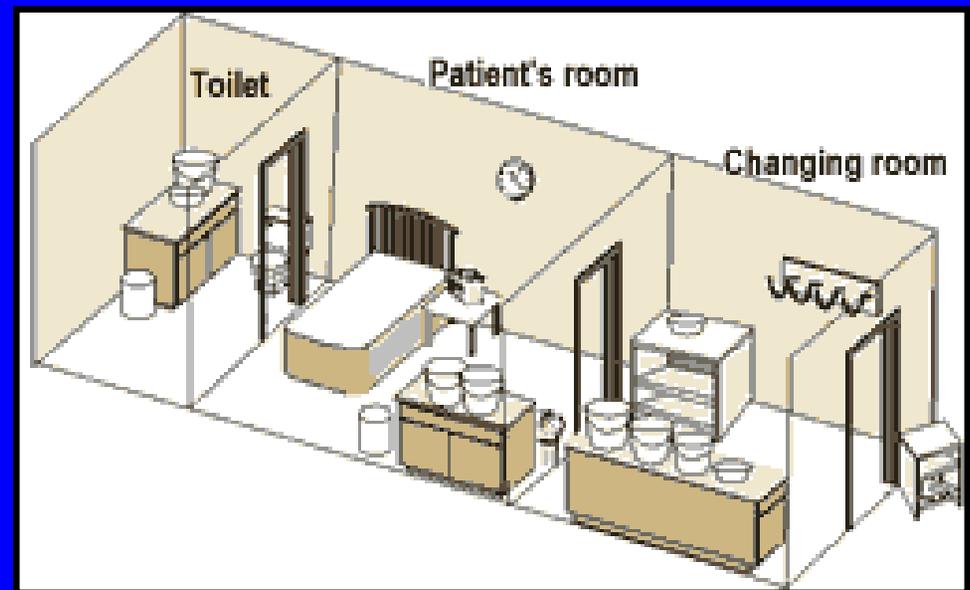
1995 Kikwit Zaire ZEBOV Outbreak  
Courtesy of Don Noah

# Selection Site for Isolation Area (if isolation area not available)

- Single room with adjoining toilet or latrine
- 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

# Infection Control

- **Single room with adjoining anteroom as only entrance**
  - Changing area/protective equipment
  - Disinfection solutions
    - 0.5% sodium hypochlorite, 2% glutaraldehyde, phenolic disinfectants (0.5%-3.0%), soaps and detergents
  - Hand washing stations
  - Chemical toilets



# Other Isolation Precautions

- Limit health facility staff and visitors in the patient's room
  - Develop and post an “authorized” list for entry
  - Provide a guard with the list
- Limit use of invasive procedures and reduce injectable medicines



# Medical Management

## First Aid for Exposures

- Anticipate in advance – be prepared
- Wash / irrigate wound or site immediately
  - within 5 minutes of exposure
- Mucous membrane (eye, mouth, nose)
  - continuous irrigation with rapidly flowing water or sterile saline for > 15 minutes
- Skin
  - scrub for at least 15 minutes while copiously soaking the wound with soap or detergent solution
    - fresh Dakin's solution (0.5% hypochlorite)

# 3 Levels of Risk

- 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  $\geq 101$

# 3 Levels of Risk

- 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  $\geq 101$

# Step 5

Know What To Do for  
Yourself or Others

# Medical Management

## The foundation of treatment is supportive care

- Hemodynamic resuscitation & monitoring
- Careful management of fluid and electrolytes, blood pressure, and circulatory volume
  - Use of colloid
  - Hemodialysis or hemofiltration as needed
    - Esp. HFERS patients
- Vasopressors and cardiotoxic drugs (some cases do not respond to i.v. fluids)
- Cautious sedation and analgesia

# Medical Management

- DIC may be important in some VHF's (RVF, CCHF, filoviruses)
- Coagulation studies and clinical judgment as guide
  - Replacement of coagulation factors / cofactors
  - Platelet transfusions
- No aspirin, NSAIDs, anticoagulant therapies, or IM injections

# Medical Management

## Antiviral Therapy

- Ribavirin
  - Investigational drug, compassionate use
  - Contraindicated in pregnancy
  - Arenaviridae (Lassa, AHF, BHF)
  - Bunyaviridae (HFRS, RVF, CCHF)
  - No utility for Filoviridae or Flaviviridae
- Immune (convalescent) plasma
  - Arenaviridae (AHF & BHF; ?Lassa)
  - Passive immunoprophylaxis post-exposure?
  - Experimental studies in animals have not proven efficacy against filovirus infection

# Medical Management For Arenavirus & Bunyavirus

- Ribavirin Treatment
  - 30 mg/kg IV single loading dose
  - 16 mg/kg IV q 6 hr for 4 days
  - 8 mg/kg IV q 8hr for 6 days
- Prophylaxis
  - 500 mg PO q 6 hr for 7 days

Note: Parenteral and oral Ribavirin 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

# No licensed treatments for filoviruses

- Neutralizing human monoclonal antibodies
  - Effective as pre and immediate (1 h) postexposure prophylaxis in guinea pigs (failed at 6 h postchallenge)
- Equine IgG ineffective for monkeys (D0)
  - Delay in viremia, but still died
  - Second dose on day 5 no added benefit

JID 1999;179(Suppl1):S224-34

J Virol 2002;76:6408-12

Lancet 2003;362:1953-58.

# Potential Options - Ebola

- No consensus on utility of use of immune convalescent plasma
  - Most case reports
  - No readily available, safe source
- Humans – limited data with blood transfusion from convalescent patients from Kikwit– 7/8 survive with Ebola c/w case fatality rate of 80%
  - Survivors received better supportive care
  - Late in the epidemic, ?decreased virulence

JID 1999;179(Suppl1):S18-23

JAMA 2002;287(18):2391-2405.

# Medical Management of Hemorrhagic Syndrome

## Potential of Activated Protein C (Xigris®)

- VHF's grouped by syndrome they produce – not by agent: Activated protein C (rhAPC / Xigris®) targets the syndrome.
- rhAPC labeled for use in syndrome, not as a specific antiviral chemotherapeutic. rhAPC has no anti-EBOV activity *in vitro*.
- Serves as an exogenous source of activated protein C. Has anti-thrombotic, pro-fibrinolytic, and anti-inflammatory effects.
- DIC a common manifestation in several VHF's, especially filoviridae; rapid and significant depletion of endogenous protein C during disease.
- Significant declines in protein C levels also reported in patients with Argentine hemorrhagic fever.
- Recent study at RIID: rhAPC (Xigris®) had beneficial effects in most NHPs (including survival in 2) challenged w/ lethal dose of ZEBOV.

# Medical Management of Hemorrhagic Syndrome

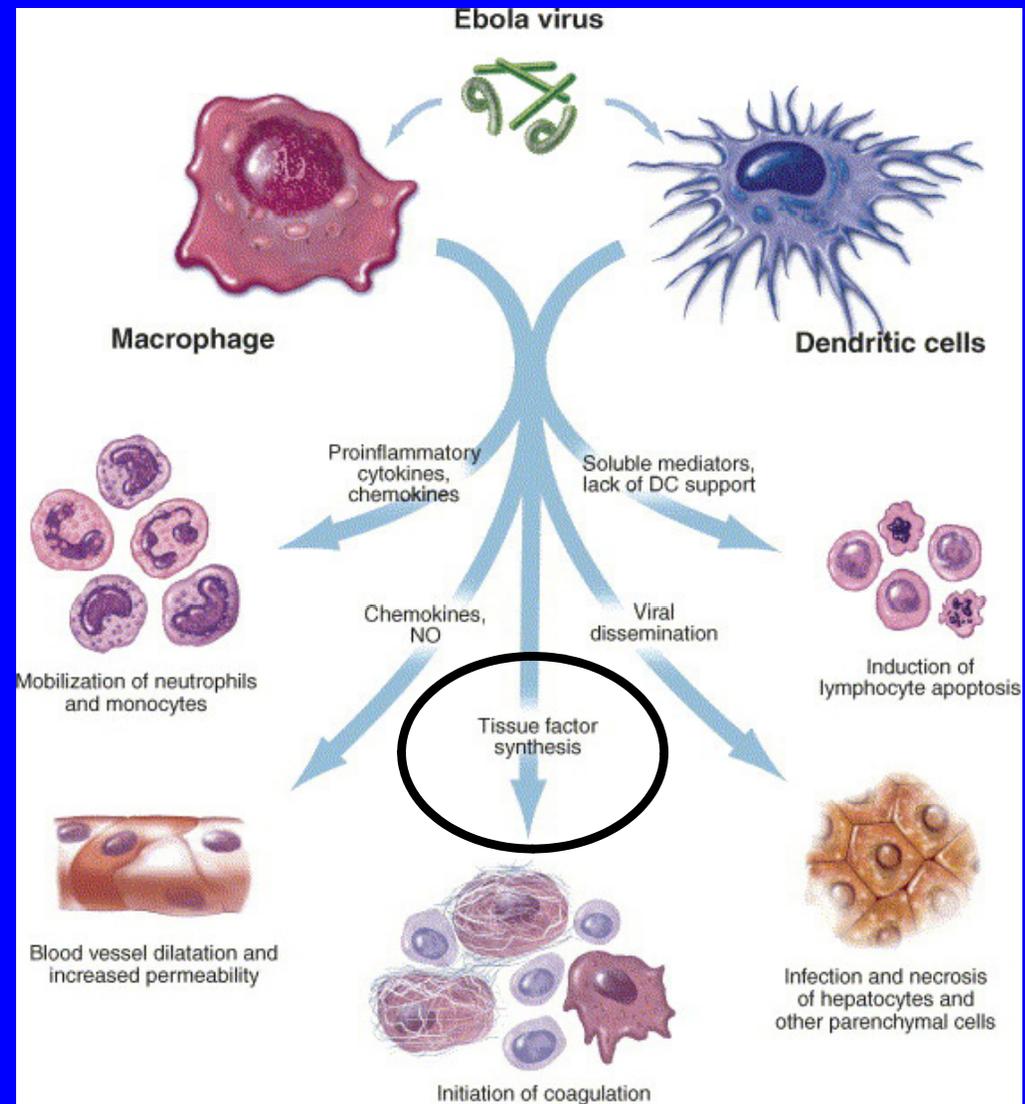
## Potential of Xigris®

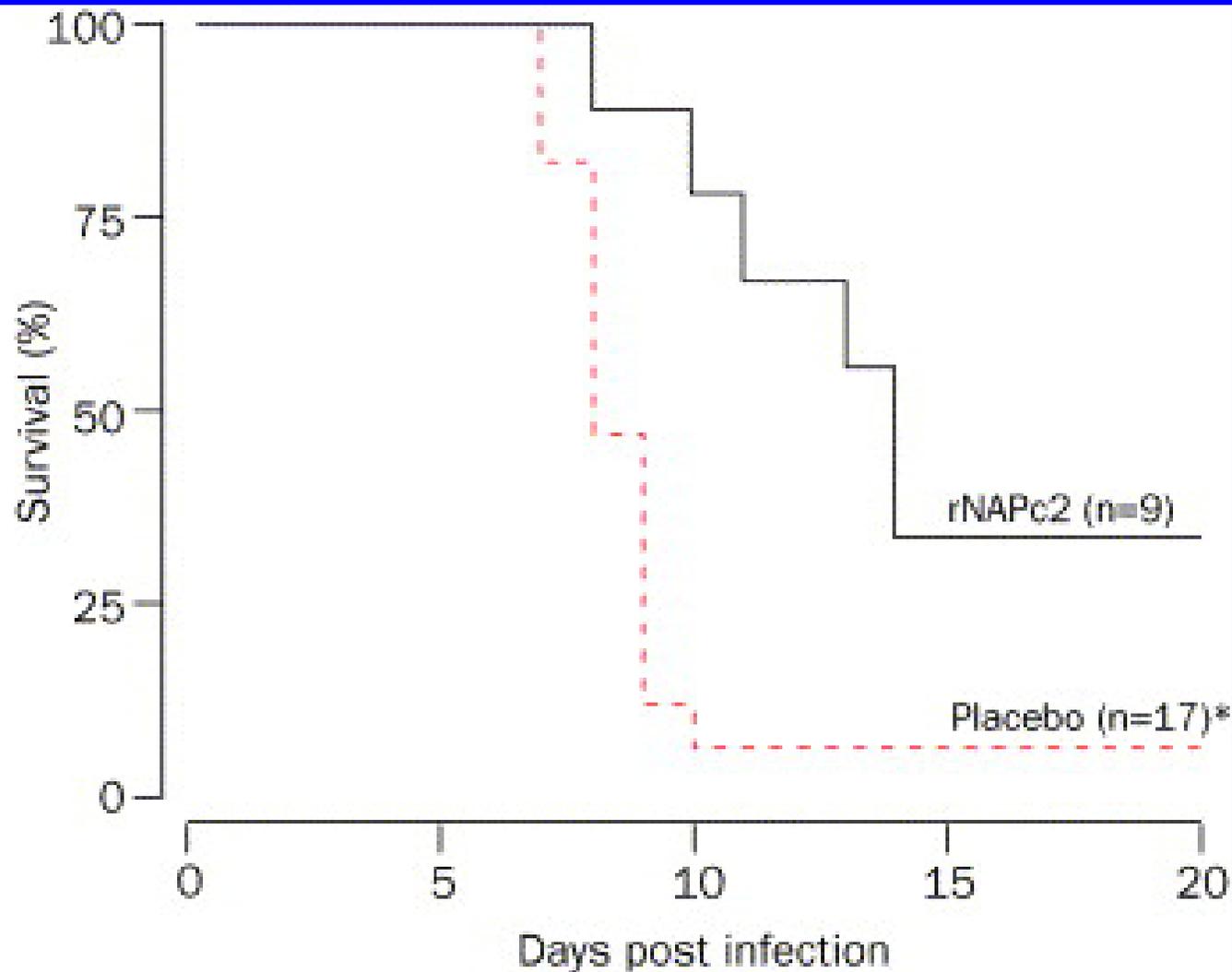
- Approved Xigris dose in humans for severe sepsis is 24  $\mu\text{g}/\text{kg}/\text{hr}$  for 96 hrs. Highest NOAEL\* (No Observed Adverse Event Level) from toxicology studies in monkeys and in phase 1 studies is 48  $\mu\text{g}/\text{kg}/\text{hr}$ .
- Disadvantages of Xigris: Administered by continuous I.V. infusion, short high-life, expensive, and potential for development of immune antibodies against recombinant product (patient becomes refractory to drug treatment after prolonged therapy).
- Not the “magic bullet”, but one possible component in combination therapy protocols for various VHF.

## 🕒 Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/tissue factor: a study in rhesus monkeys

Thomas W Geisbert, Lisa E Hensley, Peter B Jahrling, Tom Larsen, Joan B Geisbert, Jason Paragas, Howard A Young, Terry M Fredeking, William E Rote, George P Vlasuk

- Ebola virus induces overexpression of the pro-coagulant tissue factor in primate monocytes and macrophages
- Inhibition of the tissue-factor pathway could ameliorate the effects of Ebola hemorrhagic fever





33% (3/9) survival rate in each treatment group (injection of rNAPc2 either 10 min or 24 hr post lethal Ebola exposure)

All but 1/17 control animal died

Number at risk		0	5	10	15	20
rNAPc2	9	9	7	3	3	3
Placebo	17	17	1	1	1	1

# Gene-Specific Countermeasures against Ebola Virus Based on Antisense Phosphorodiamidate Morpholino Oligomers

Kelly L. Warfield<sup>1</sup>✉, Dana L. Swenson<sup>1</sup>✉, Gene G. Olinger<sup>1</sup>, Donald K. Nichols<sup>1</sup>, William D. Pratt<sup>1</sup>, Robert Blouch<sup>2</sup>, David A. Stein<sup>2</sup>, M. Javad Aman<sup>1</sup>, Patrick L. Iversen<sup>2</sup>, Sina Bavari<sup>1\*</sup>

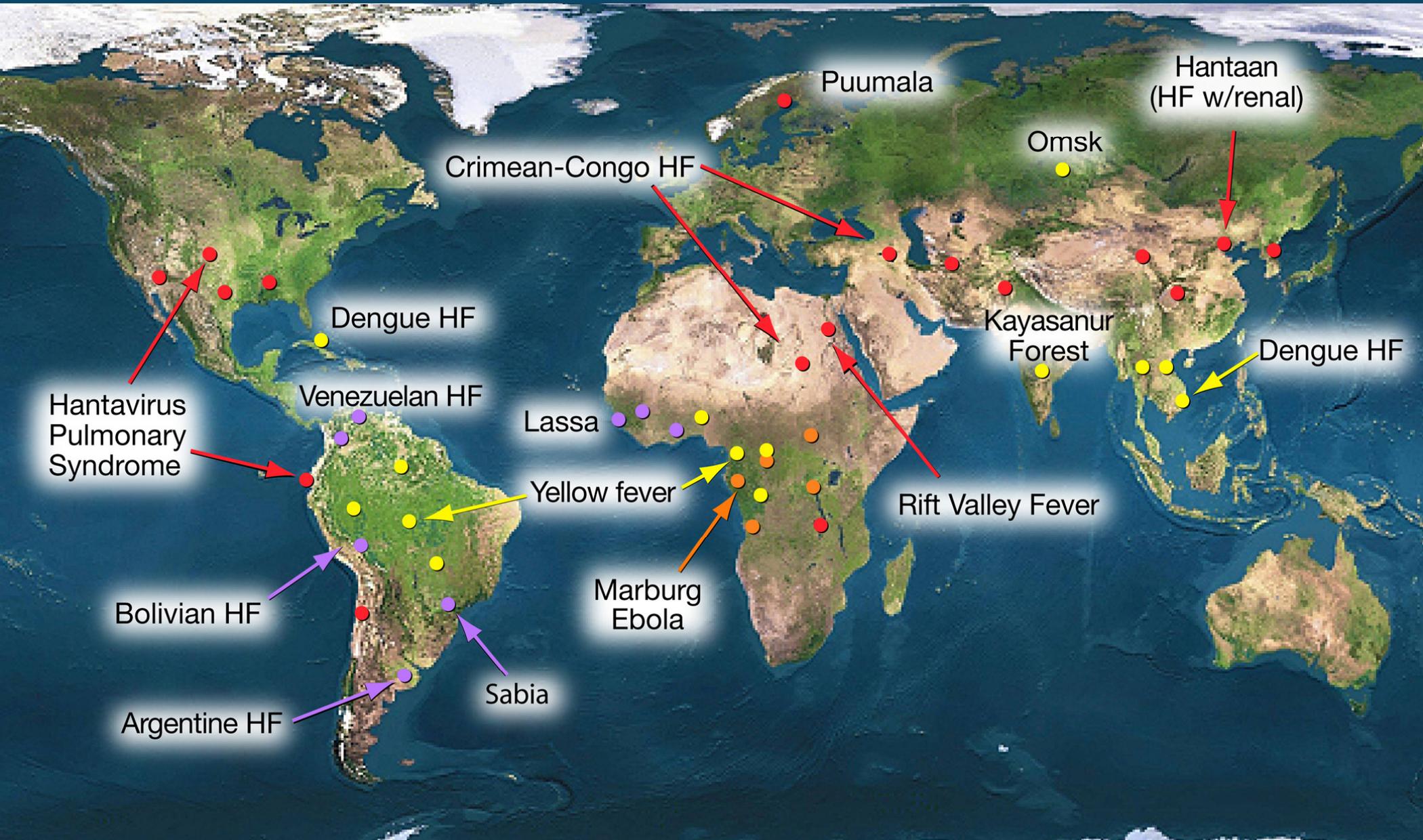
<sup>1</sup> US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, United States of America, <sup>2</sup> AVI BioPharma, Corvallis, Oregon, United States of America

- Goal: forming PMO: mRNA duplex
  - Blocks translation of viral mRNA and inhibiting viral replication
- Mice fully protected at 500  $\mu$ g, with dose response at lower doses
- Guinea pigs with best response at 96 hr postchallenge (vs 24 hr before or after)
- Nonhuman primates – 3/4 survive after combination of oligomers used (VP24, VP35, L) (one dies of bacterial infection)

PLoS Pathogens  
2006;2(1):0005-0013.

Don't Forget...

# Viral Hemorrhagic Fever



● Filoviruses

● Flaviviruses

● Bunyaviruses

● Arenaviruses

# 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

# 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* (especially 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

# Final Thoughts

- Maintain an index of suspicion
- BYOP (Bring your own PPE):
  - Masks, gowns, gloves, goggles, caps
- Have an exit strategy
- Don't let anyone use a non-sterile needle on you
- Rodent/bat control
- Get WHO guidelines

# Questions?

