Viral Hemorrhagic Fevers

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

UNCLASSIFIED

Disclaimer

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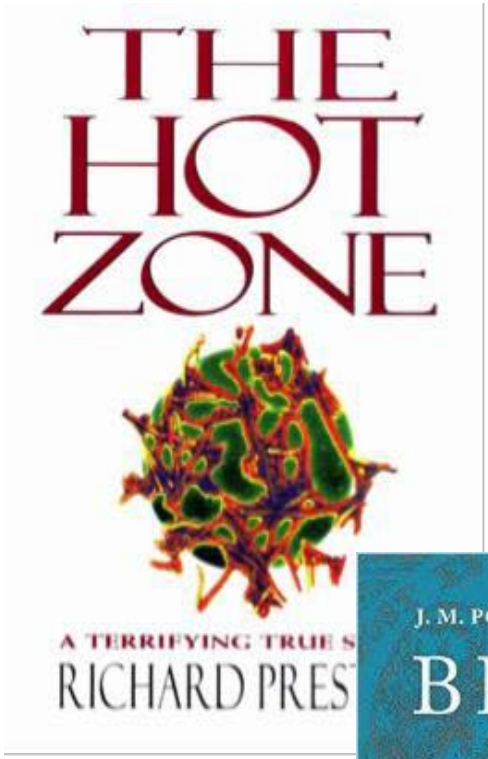
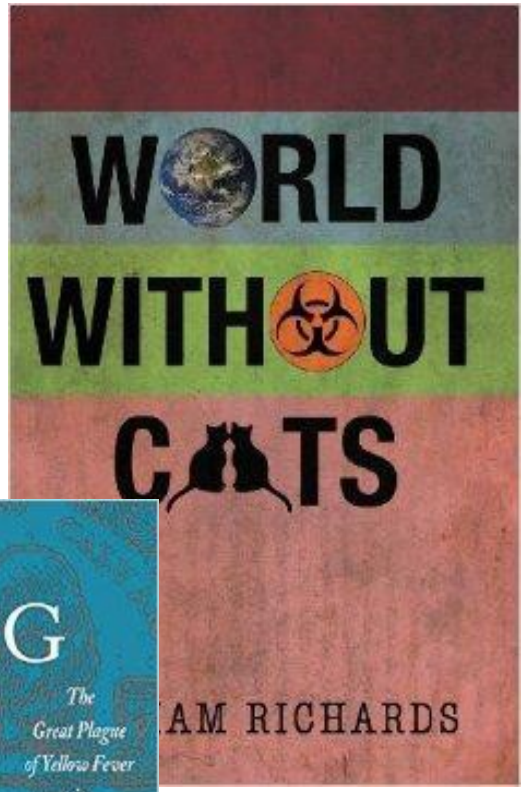
Acknowledgements

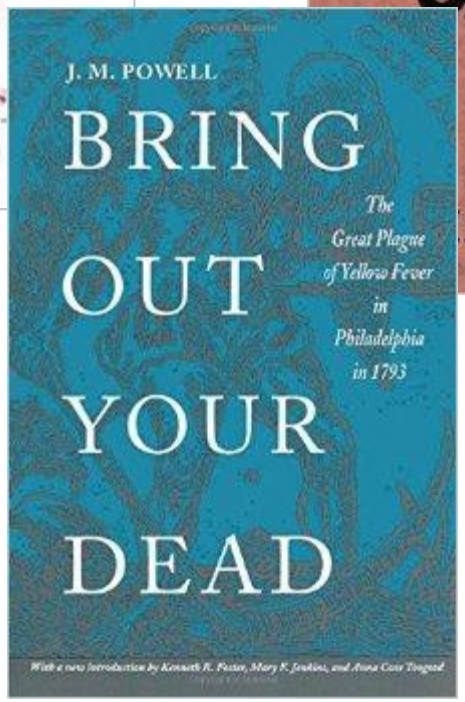
- COL Arthur Lyons
- COL Mark Kortepeter

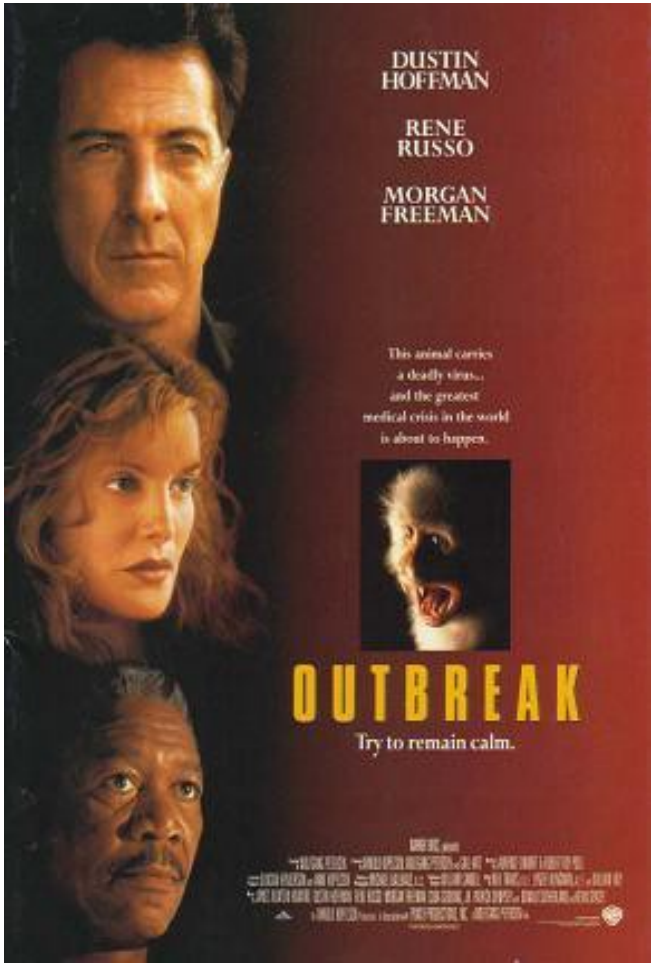
Outline

- VHFs – General Summary of What is Known…
  - Overview of syndrome
  - Geographic distribution
  - Animal hosts and vectors
  - Nosocomial and occupational risks
  - Estimated incubation periods
- Selected Pathogens (time permitting):
  - Ebola
  - Crimean-Congo Hemorrhagic Fever
  - Lassa Fever
  - Hantaviruses
- Emerging Threats (time permitting)









OUTBREAK (1995)
3 weeks on top of US box office
Grossed: $190M ($50M budget)

Will Cover Some Steps to Avoid….

Source: mirror.co.uk

The “Slammer”

BSL-4
CONTAINMENT SUITE
MAGNEHELIC
MAJ Muckerman OIC
SECURE AREA
CONTAINMENT SUITE CHECK LIST
AUTHORIZED

Source: vox.com

1995 Kikwit Zaire ZEBOV Outbreak

Source: Don Noah

Definition

- **Viral hemorrhagic fever (VHF):**
  - **Fever**
  - **Malaise**
  - **Myalgia**
  - **Prostration**
  - **<u>Bleeding diathesis</u>**
  - **Severe multi-organ failure**
  - **Enveloped, single-stranded, *<u>RNA viruses</u>***

- Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF

Overview of Etiologic Agents of VHFs

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

Family Features

- Small RNA viruses, enveloped in a fatty (lipid) coating, acid sensitive.
- Survival is dependent on an animal or insect host, called the natural reservoir; geographically restricted to the areas where their host species live. Humans are not natural reservoirs.
- All aerosol-infectious
  - Exception: dengue viruses

Family Features

- Humans are infected when they come into contact with infected hosts. However, with some viruses, after the accidental transmission from the host, humans can transmit the virus to one another.
- Human cases or outbreaks of HF occur sporadically and irregularly. The occurrence of outbreaks cannot be easily predicted.
- With a few noteworthy exceptions, there is no cure or established drug treatment for VHFs.

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	2-5	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%

Military Relevance: Weaponization

- Bioterrorism (BT)
  - Hoaxes to mass casualties
  - Small attacks may be incredibly disruptive
    - 2001 Anthrax: ADLs, Commerce, Government, $$
- VHFs are important considerations in Bioterrorism (BT) preparedness
  - Reputation from popular literature, cinema
  - Media
  - Dramatic clinical syndrome(s) produced
- Stability and infectivity of VHF viruses is sufficient (or could be enhanced) to produce effective WMD

This will be discussed in more detail in the Biothreats Lecture

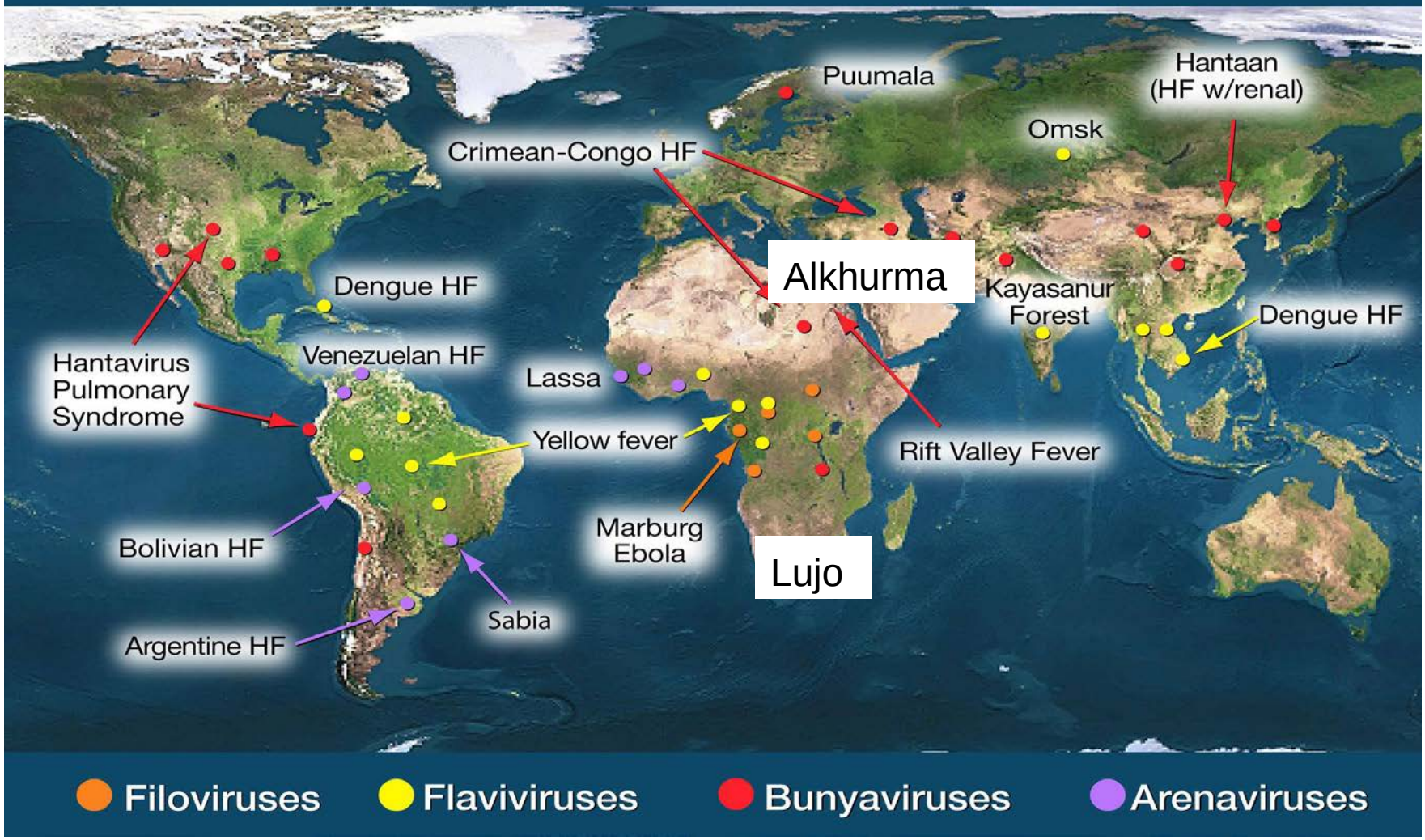
The “Deadly” VHFs

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

Overview of VHFs

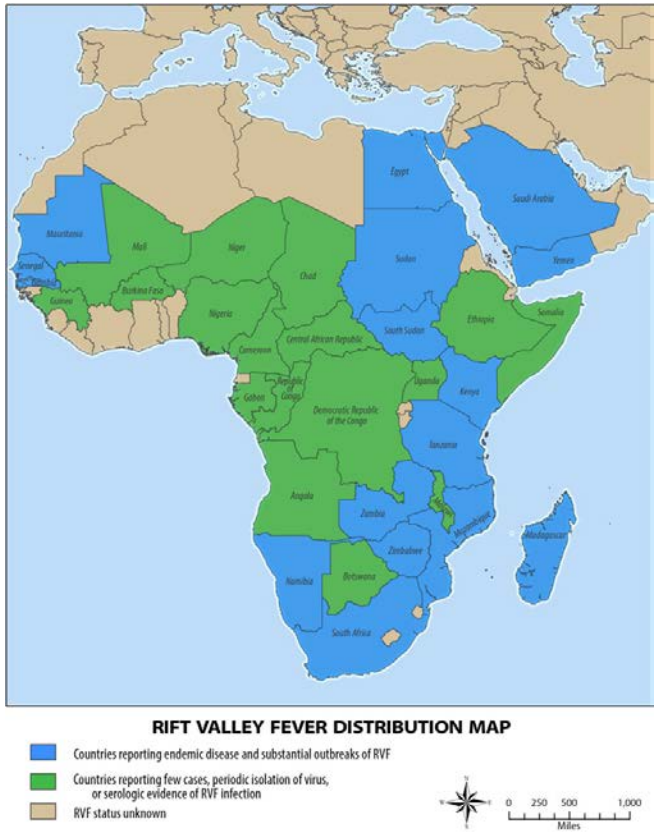
Geography of VHF

Viral Hemorrhagic Fever



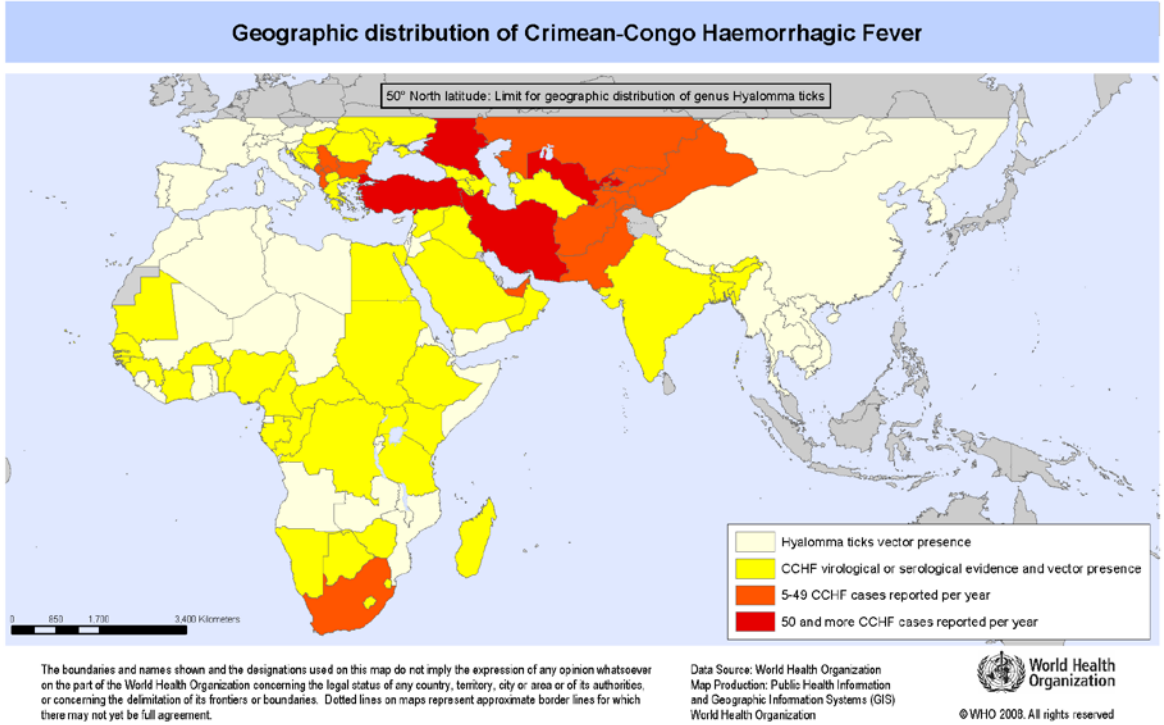
Source: Mike Bray, NIAID

Distribution of RVF



CDC © 2013

Distribution of CCHF



WHO © 2008

Distribution

- Virus and disease(s) are limited to where the host species live(s)
  - Geographically restricted: Rodent (New World arenaviruses)
  - Geographically diverse: Rodent (Hantavirus); common rat (Seoul virus)
- Occasionally, exported hosts can spread disease
  - Marburg (Germany, Yugoslavia)
- Human travelers
  - Ebola

Overview of VHFs

Why do we even care?

Most of these infections are nowhere near the United States. Why should the U.S. use resources and risk personnel?

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,[1] Eileen C. Farnon,[4] Pierre E. Rollin,[4] Cesar G. Albariño,[4] Stuart T. Nichol,[4] and Margo Smith[1]

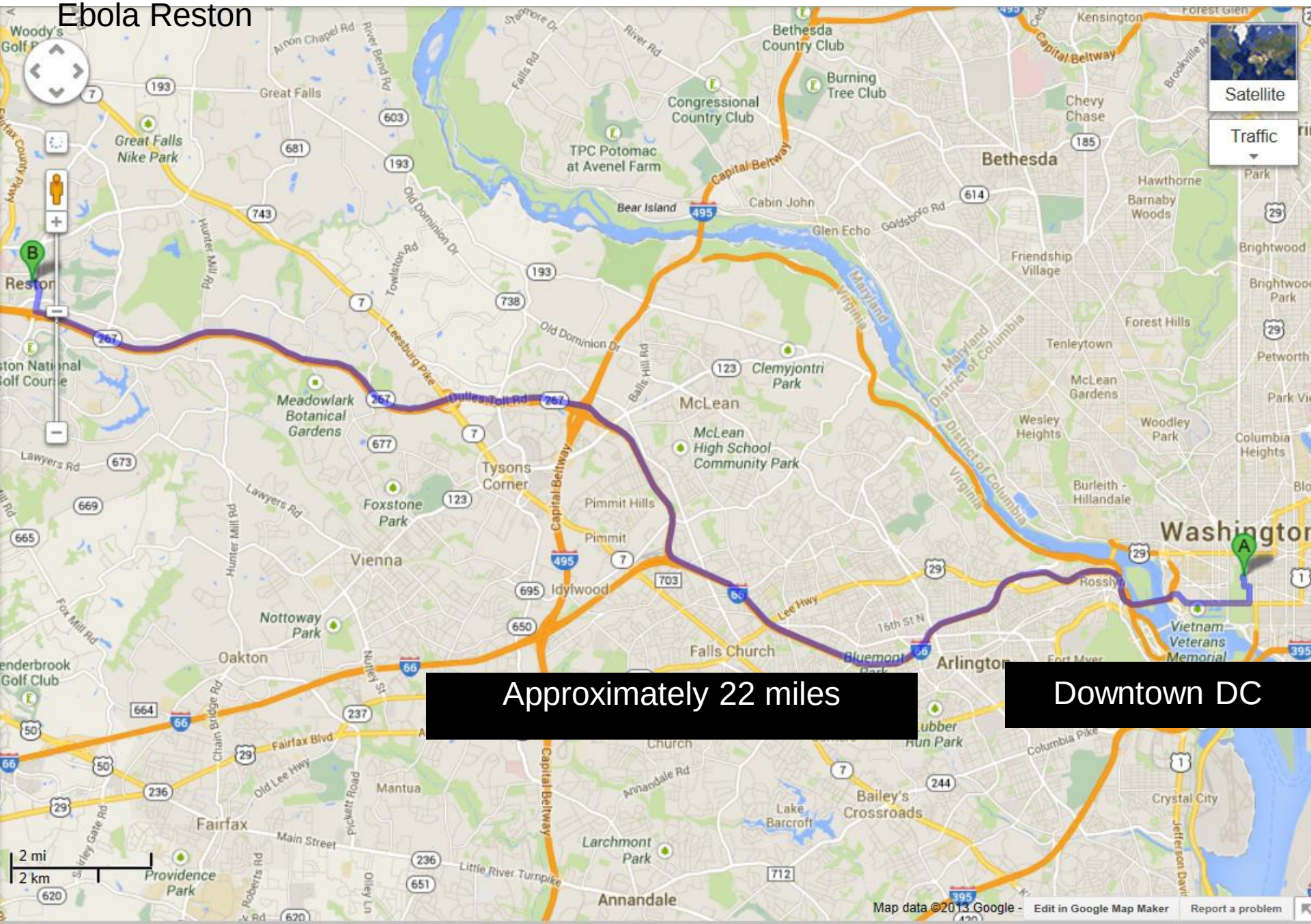
[1]Washington Hospital Center, Washington, DC; [2]Maryland Department of Health nd Mental Hygiene, Baltimore, Maryland; [3]Epidemic Intelligence Service, Office f Workforce and Career Development, and [4]Special Pathogens Branch, Division f Viral and Rickettsial Diseases, Centers for Disease Con Preventio orgia

MMWR Weekly
December 18, 2009 / 58(49);1377-1381

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.

Ebola Reston



Overview of VHFs

How are VHFs Spread?

1 - Inhaling or ingesting excretions/secretions from rodent hosts (urine, feces, saliva)

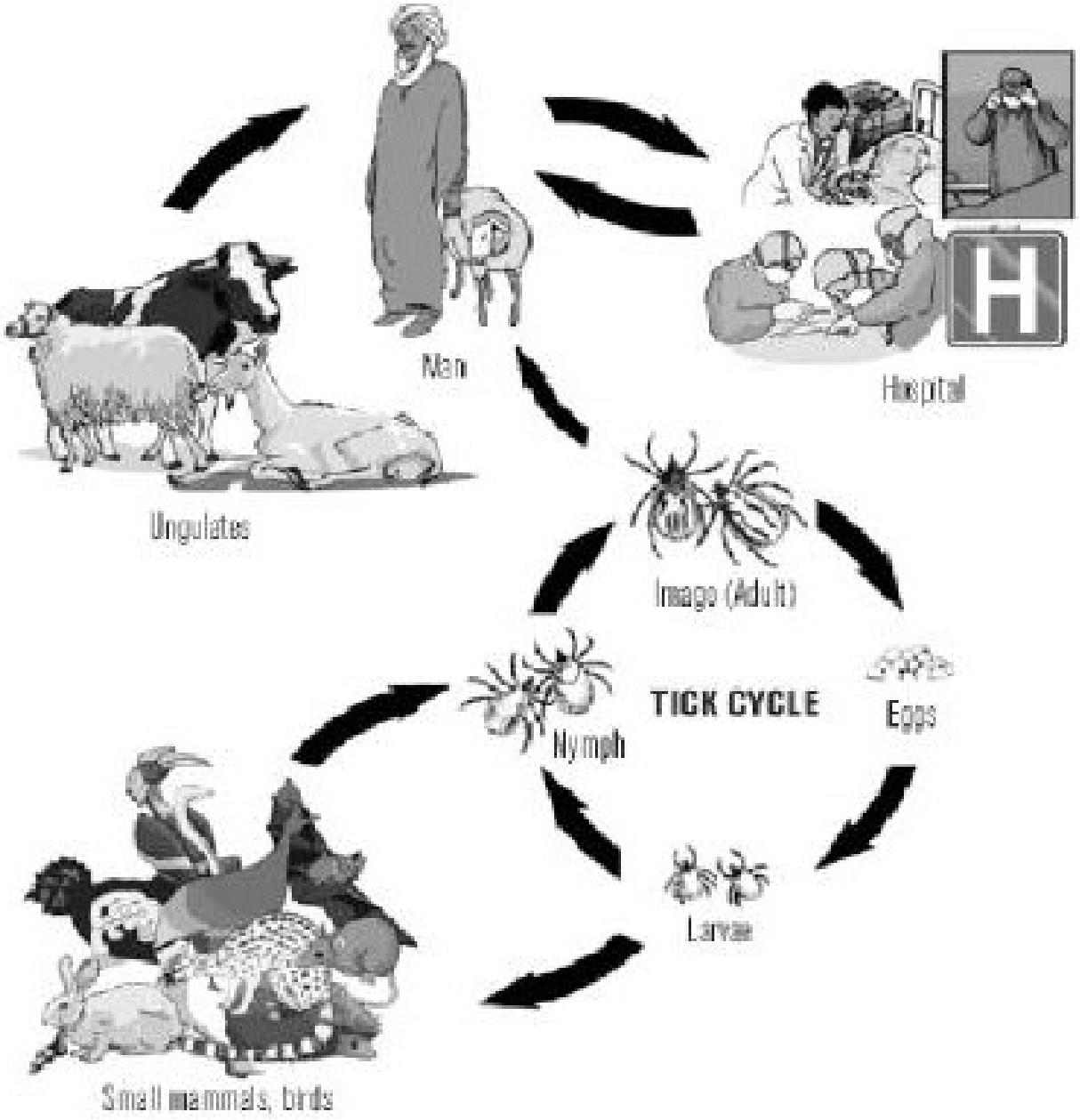
2 - Bite of an infected arthropod (tick, mosquito) or crushing infected arthropod

3 - Nosocomial/lab transmission – contact with human or animal blood/body fluids/tissue

4 - Artificially generated aerosols (biowarfare)

5- Exposure to infected animals (Care, consumption, slaughter)

Sources: independent.co.uk
Stroke-survivors.org
Mklop.com



Transmission cycle of CCHF

Overview of VHFs

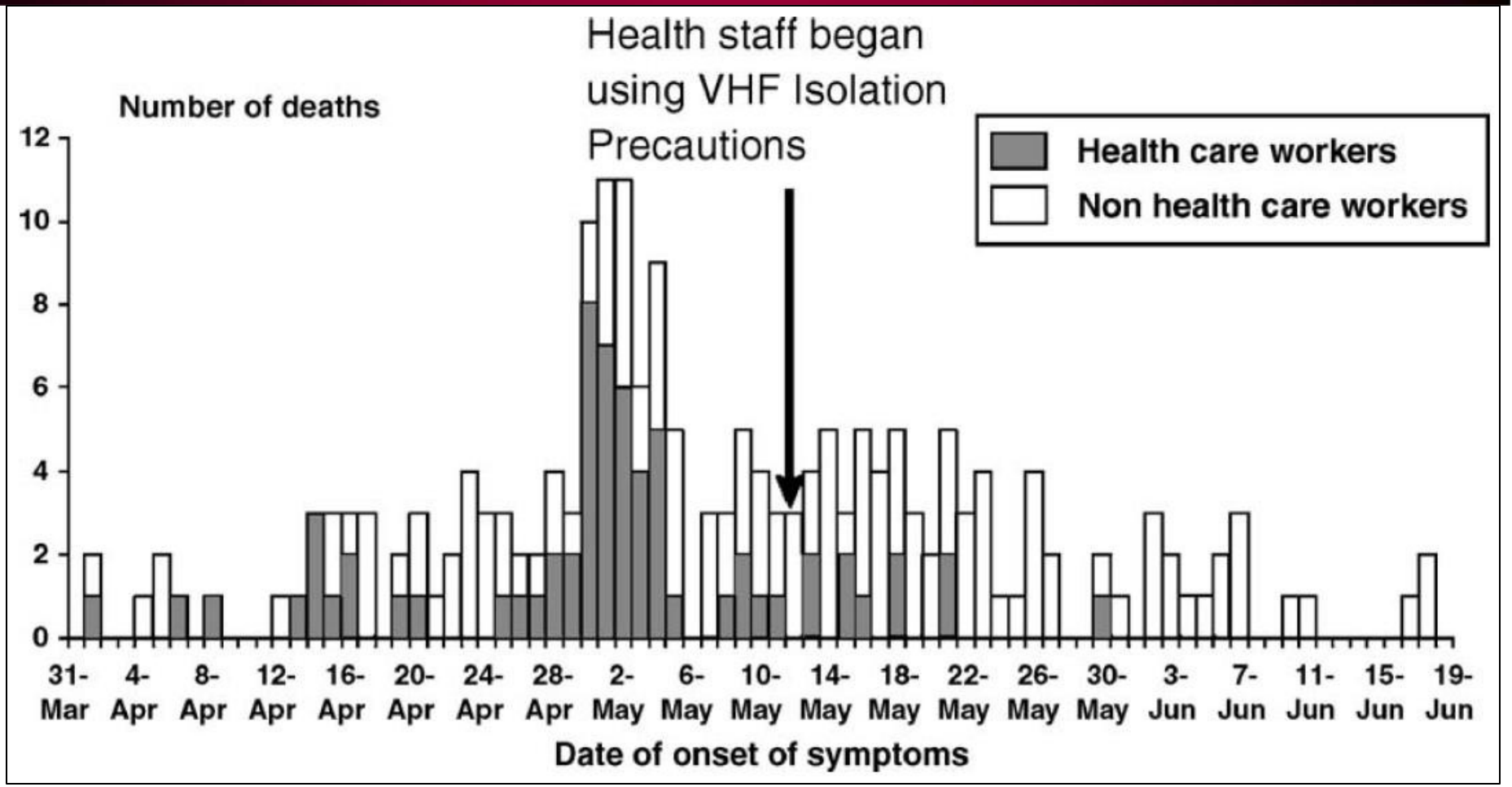
- How are VHFs spread?
  - Airborne?
    - - In monkeys, possible airborne transmission between cages 3 m
    - - Lung tissue, along with nares, pharynx, and conjunctiva w/virus
    - - Monkeys and guinea pigs able to be infected via airborne route

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

Source: 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

Pathogenesis

- Varying degrees of, singly or in combination:
  - Direct viral damage
  - Disseminated intravascular coagulation (DIC)
  - Hepatic damage
  - Vascular damage
  - Cytokine release
- Fatal cases
  - Lymphoid depletion (ex: hantavirus: immunopathology)

Overview of VHFs

- **Clinical Presentation: Nonspecific, Wide Variety**
  - **Prodrome (3-4 days)**
    - Fever, Headache, Malaise, Arthralgias, Myalgias, fatigue
    - Nausea, Abdominal pain, Non-bloody diarrhea
  - **Early signs**
    - High Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
    - Flushing, Skin Rash
    - Prostration, capillary leak (nondependent edema, effusions)
  - **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%+

Symptoms/Signs

- Hemorrhage
  - Most cases: South American hemorrhagic fevers
  - <50%: Lassa
  - Requires thrombocytopenia and capillary damage
- Shock, florid hemorrhage, extensive CNS damage
  - Poor prognosis
- Physical signs early in the course may be suggestive
  - Low BP
  - Postural hypotension
  - Petechial hemorrhage
  - Conjunctival injection common (ex: HPS)

Clinical Features of VHFs

Disease	Clinical	Therapeutic Synopsis
South American HF	Hemorrhage, dysarthria, tremor usual	Ribavirin, vaccine (limited availability)
Lassa fever	Prostration/shock/deafness: hemorrhage less so	Ribavirin
Rift Valley Fever	HF low; rapid course: DIC/hepatitis/retinal vasculitis/encephalitis	?Ribavirin Vaccine (limited availability)
Crimean Congo Hemorrhagic Fever	HF, hemorrhage, DIC	Ribavirin No vaccine
Hemorrhagic Fever with Renal Syndrome (HFRS)	Febrile prodrome, shock, renal failure, hemoconcentration	Supportive care, dialysis ?ribavirin Vax: China, Korea
Hantavirus Pulmonary Syndrome (HPS)	Similar to HFRS, but pulmonary edema vice renal failure	ICU management Ribavirin not useful

Adapted from: Peters CJ

Clinical Features of VHFs

Disease	Clinical Features	Therapeutic Synopsis
Marburg/Ebola	Weight loss/prostration, rash, hepatitis, uveitis, orchitis, arthralgias common in convalescence	Supportive Vaccine in advanced clinical development
Yellow Fever	Severe HF with jaundice	Vaccine
Dengue	Need sequential infection with heterotypic serotypes	Supportive care Vaccines in clinical development
Tick-Borne Flavivirus	Biphasic: fever, thrombocytopenia, hemorrhage, followed by neurologic signs	No specific therapy or vaccine

Adapted from: Peters CJ

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	+++	+++	⇓⇓⇓	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	+++	+++	⇓⇓/⇑	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/⇓⇓	0	+++	++	+	0	++	0	0
DHF/DSS	++	+++	⇑⇑	+++	+	0	+	0	+	0	0
KFD/OHF	++	++	⇓⇓	0	0	0	++	0	E	0	Retina

Courtesy of Drs. Zaki & Peters

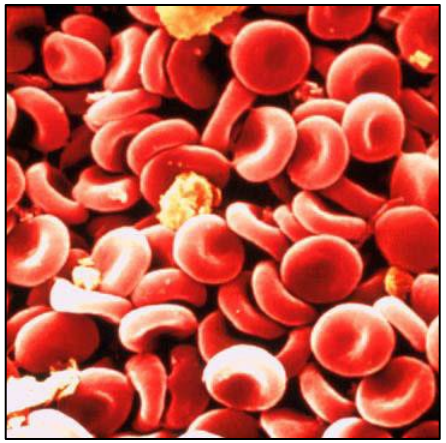
\+ occasional or mild
++ commonly seen, may be severe
+++ characteristic and usually marked

S characteristic, seen in severe cases

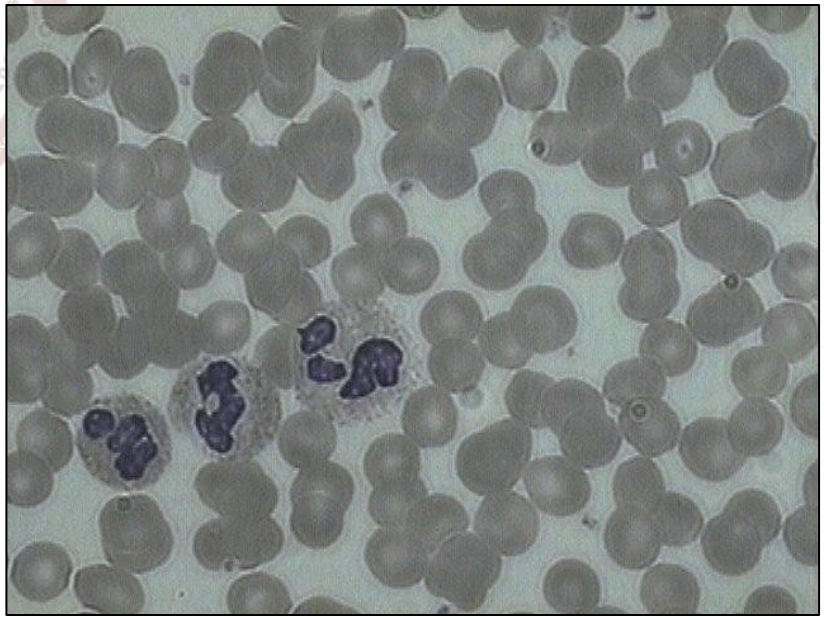
⇑ occasionally or mildly increased
⇑⇑ commonly increased, may be marked
⇑⇑⇑ characteristically increased and usually marked

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

Overview of VHFs



- **Lab Abnormalities**
  - Leukopenia
    - Esp. South American HF
    - Lassa with low, normal or increased WBC
    - Hantavirus: leukemoid counts
  - Anemia
  - Hemoconcentration
    - Extreme: hantavirus
  - Thrombocytopenia
  - Elevated liver enzymes
  - May have renal dysfunction
  - Coagulation abnormalities
    - Modestly abnormal



Operational Medical Infectious Disease Capability
OCID
DoD Global Emerging Infections Surveillance and Response

Overview of VHFs

- **Lab Abnormalities**
  - Coagulation abnormalities
    - No patterns diagnostic
    - Prolonged bleeding time
    - Prothrombin time
    - Activated PTT
    - ↑ fibrin degradation (i.e. increased D-dimer)
    - ↓ fibrinogen
    - DIC: CCHF, filovirus, severe RVF, early HFRS
  - AST, amylase
  - Urinalysis: reflects circulatory status
    - Proteinuria: reflecting capillary leak?
    - Hematuria
    - Oliguria
    - Azotemia

Overview of VHFs

- **Lab Abnormalities and Disease Presentations**
  - **These are <u>not</u> hard and fast rules.**
  - **There will be overlap with many of these infections**
  - **Nonspecific initial presentations**
    - **Mimic many common syndromes**
    - **Must have SA**
    - **Ask the question!**

Overview of VHFs

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

- Malaria
- Typhoid fever (*Salmonella*)
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
- Other rickettsioses
- Leptospirosis
- Meningococci
- Q fever (*Coxiella burnetti*)
- Plague
- Influenza

- Differential Diagnosis

- Viral meningitis / encephalitis
  - Henipaviruses
- HIV / co-infection
- Hemorrhagic smallpox
- Vasculitis (i.e. autoimmune diseases)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Hemophagocytic syndrome
- Shigella

The Walter Reed Army Institute of Research
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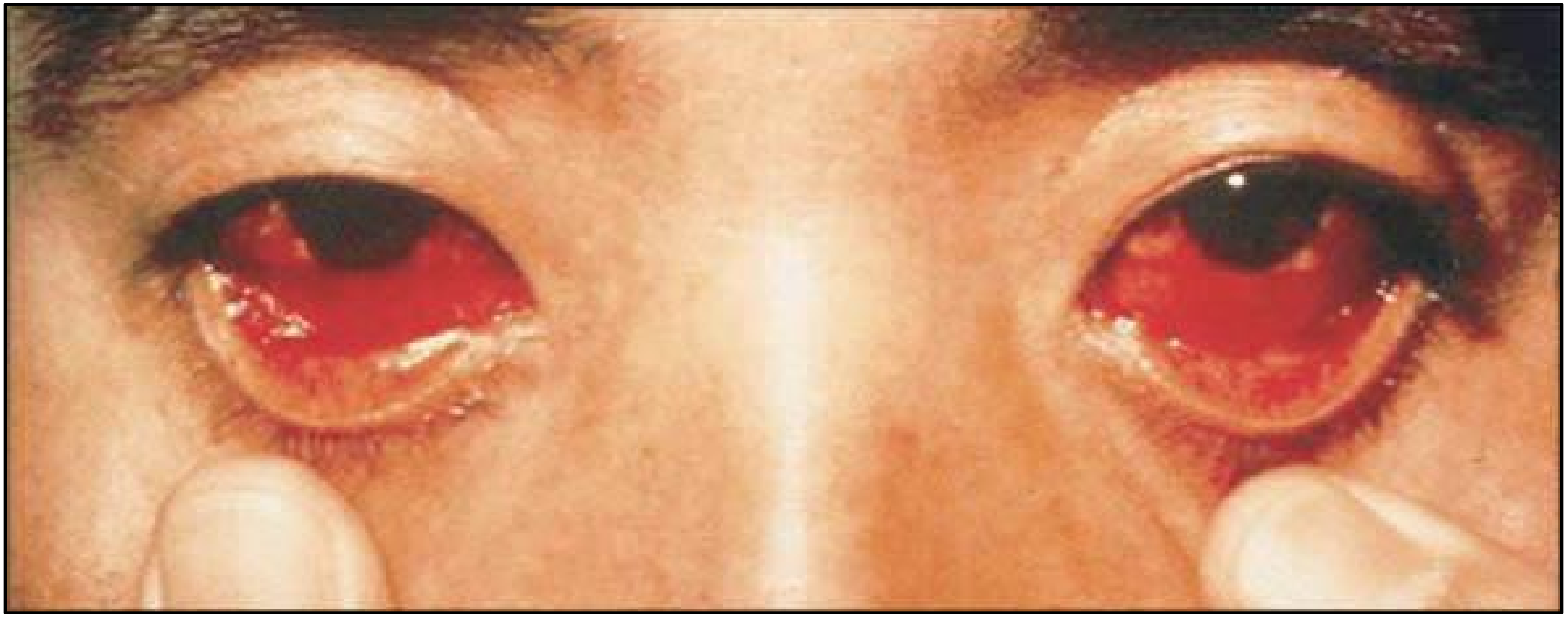
Bolivian Hemorrhagic Fever (Machupo virus – New World Arenavirus)



Conjunctival injection & subconjunctival hemorrhage

Source: 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.

Crimean-Congo Hemorrhagic Fever (CCHF)

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

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

Crimean-Congo Hemorrhagic Fever (CCHF)

Source: healthierpakistan.com

Crimean-Congo Hemorrhagic Fever (CCHF)

Source: glogster.com

Crimean-Congo Hemorrhagic Fever (CCHF)

Source: data.fao.org

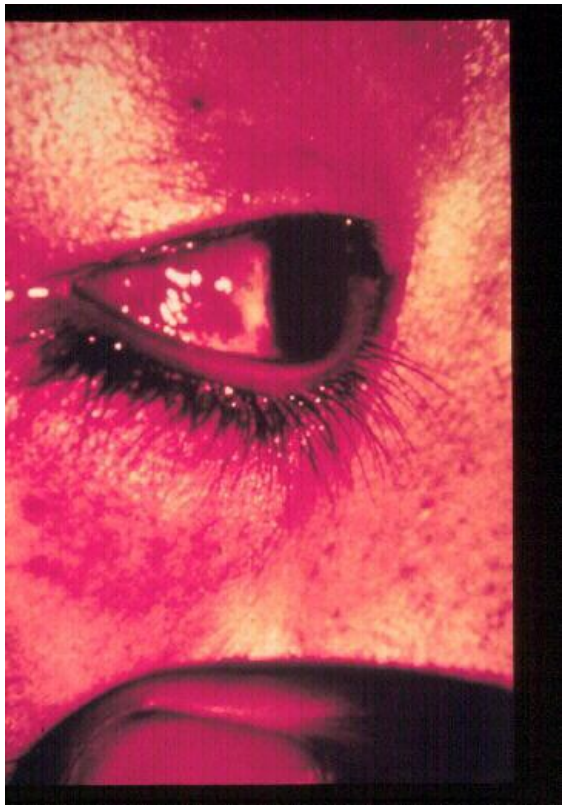
BOLIVIAN HEMORRHAGIC FEVER (MACHUPO)

Source: histopathology-india.net

KOREAN HEMORRHAGIC FEVER (HANTAAN)

Source: emedecine.medscape.com

Argentine Hemorrhagic Fever



Source: telemedicine.org

Dengue Hemorrhagic Fever

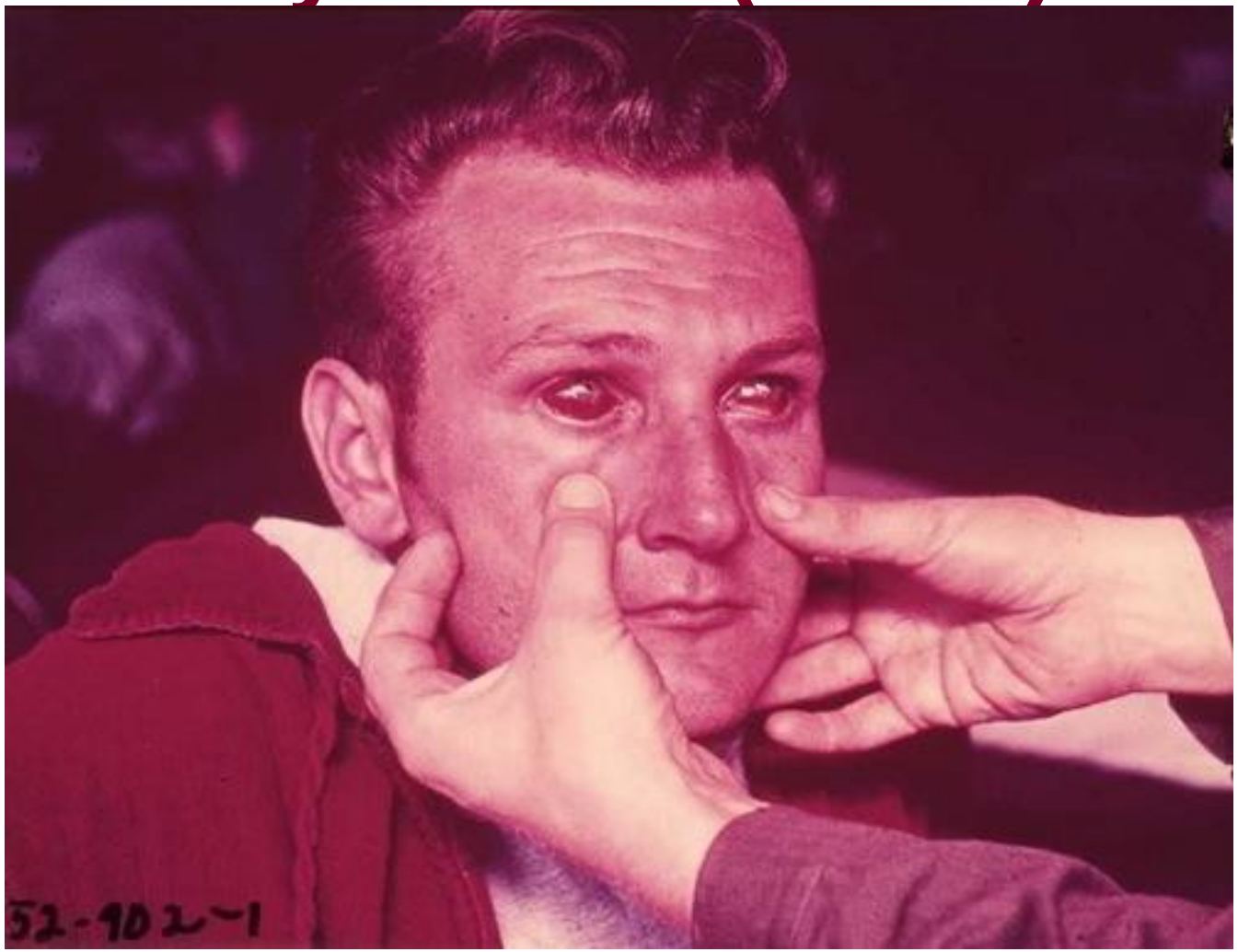
Source: magnustoday.net

Marburg Infection Human

Maculopapular rash

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

Hemorrhagic Fever with Renal Syndrome (HFRS)



Source: lookfordiagnosis.com

Overview of VHFs

- Diagnosis
  - **<u>High index of suspicion</u> (know what is in your AO)**
  - Lab findings
    - Thrombocytopenia , low WBC, anemia, transaminitis, increased bilirubin, prolonged PT, PTT, increased D-dimer, decreased fibrinogen
    - Acute phase: detection of RNA by RT-PCR, finding viral proteins by ELISA, or viral isolation (BSL-4)
    - As patients improve, markers of acute infection disappear and IgM appears
      - Hantaviruses: antibodies present in serum at time of onset of disease (IgM capture ELISA)

Lab Diagnosis

- 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

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

Overview of VHFs

- **Treatment**
  - **Rapid atraumatic hospitalization**
  - **ICU admission if available**
  - **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 cardiotonic 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
    - **<u>No aspirin, NSAIDs, anticoagulant therapies, or IM injections</u>**
      - Use acetaminophen for pain or fevers

Operational Clinical Infectious Disease Course
OCID

Overview of VHFs

- **Treatment**
  - Ribavirin
    - Investigational drug, compassionate use
    - **<u>Contraindicated in pregnancy</u>**
    - All Arenaviridae (**Lassa, Junin, Sabia, Lujo**)
    - Consider for 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 VHFs

- 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 VHFs

	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

JAMA 2002;287:2391

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
  - **<u>NOT AVAILABLE IN THE UNITED STATES</u>**

OCID

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 <u>post-exposure treatment</u> w/ recombinant VSV-GP Marburg vaccine

Experimental Products in the Pipeline

- Recombinant human monoclonal antibodies
  - MB-003, ZMAb, ZMapp
- Vaccines mostly in pre-clinical stage (few human studies)
  - DNA vaccines
  - Live viral vector vaccines
  - Virus-like particles vaccines
- Drugs:
  - Pyrazinecarboxamide derivative, T-705 (favipiravir)
  - Broad-spectrum nucleoside analogue (BCX4430)
  - Recombinant nematode anticoagulant protein (NAP)
  - AVI-6002 (antisense oligomers)
  - Clomiphene/Toremiphene
  - Retanizone (Vit A derivative)

Source: sites.psu.edu

Experimental Products

- 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

vVSV-ZEBOV

- Attenuated, replication-competent, recombinant VSV-based vaccine expressing the glycoprotein of a Zaire strain of ZEBOV
- Two Phase 1 trials (26 x 2 participants)
  - WRAIR and NIH
- Placebo-controlled, double-blind, dose escalating studies
  - 20 million PFU vs. 3 million PFU
- Adverse events
  - Injection site pain, myalgias, fatigue
- Seroconversion (Day 28): 100%
  - GMT 4079 (20 million) vs 1300 (3 million); P<0.001
- VSV viremia detected for short duration

Source: Regules JA, Beigel JH, Paolino KM et al, A Recombinant Vesicular Stomatitis Virus Ebola Vaccine — Preliminary Report, New. Engl. J. Med., DOI: 10.1056/NEJMoa1414216

Overview of VHFs

- **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

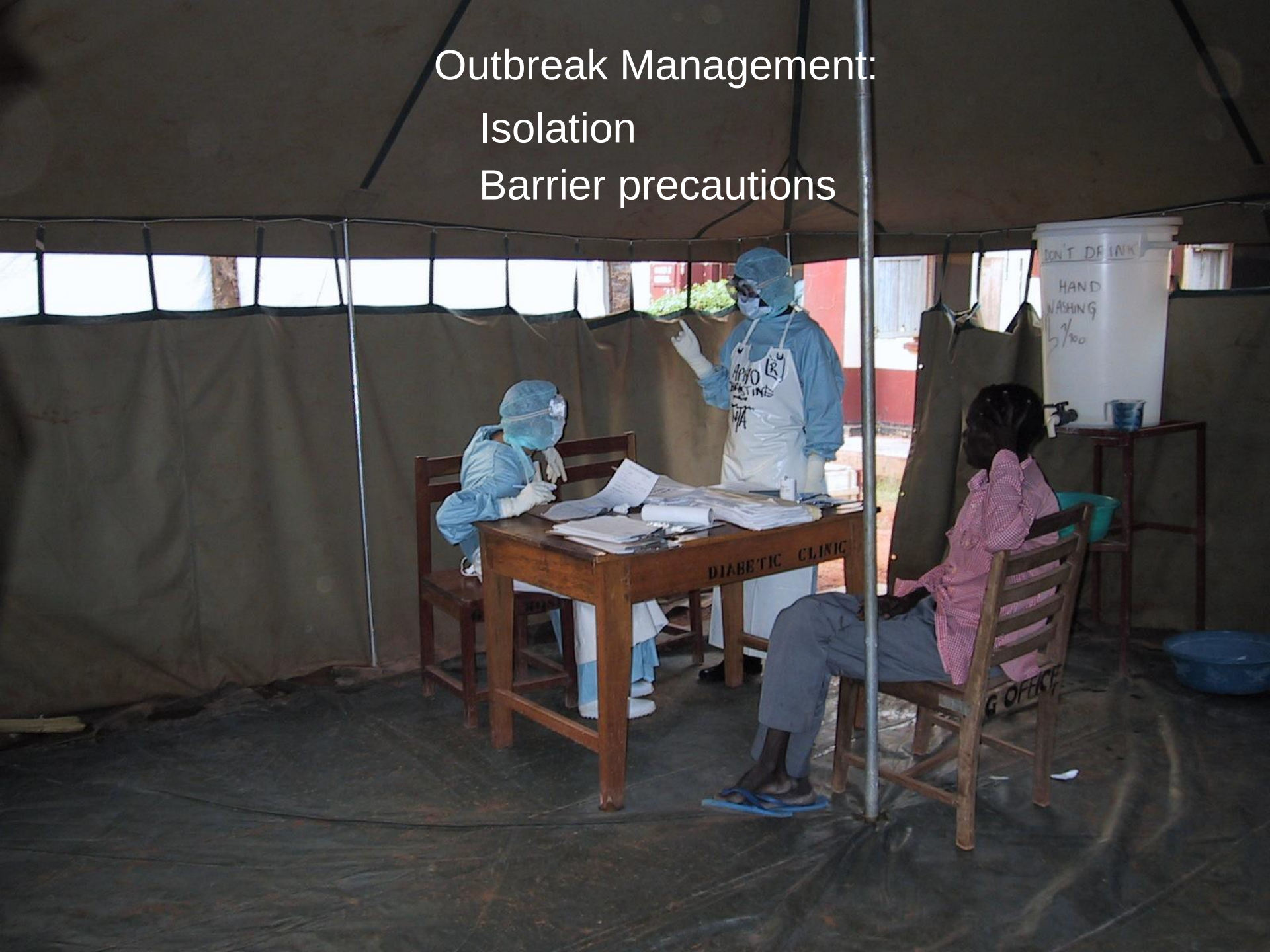
Overview of VHFs

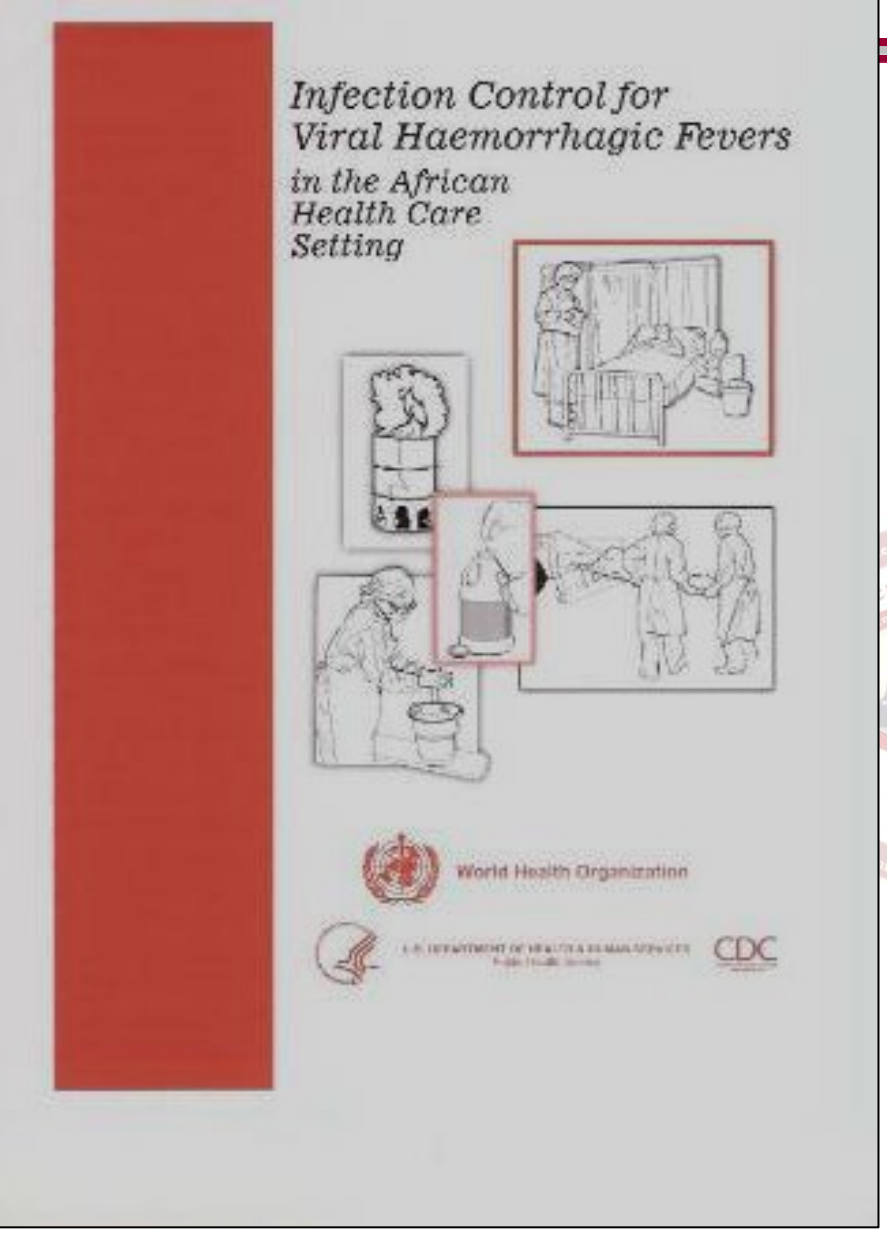
- CDC Recommendations - when to go "hot"
  - Standard Precautions in initial assessments
  - Private room upon initial hospitalization
    - "Barrier precautions" – including face shields, surgical masks, eye protection **within 3 feet** of patient (double glove, impermeable gown)
      - Have your VHF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

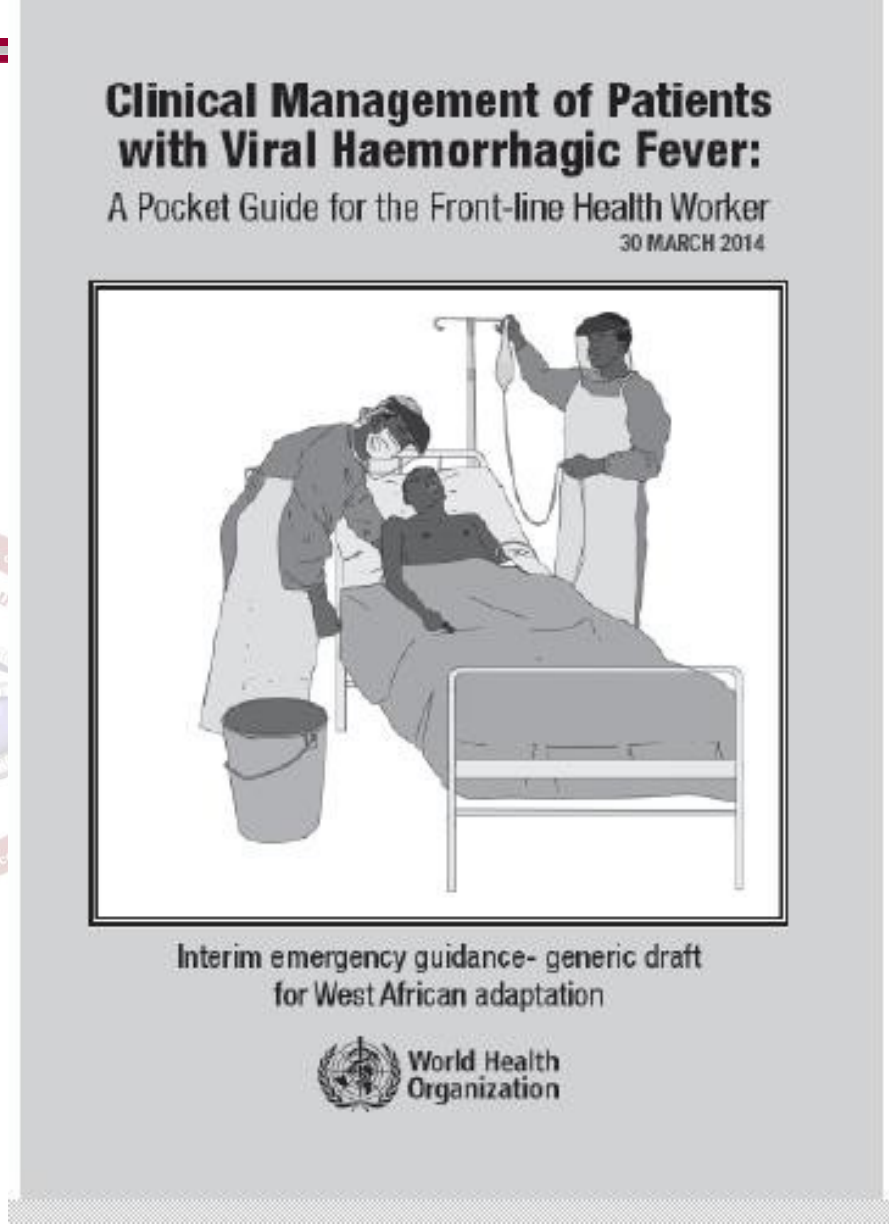
MMWR 1988;37(S-3):1-16. MMWR 1995;44(25):475-79.

Outbreak Management:

- Isolation
- Barrier precautions







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

WHO VHF Africa Manual

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

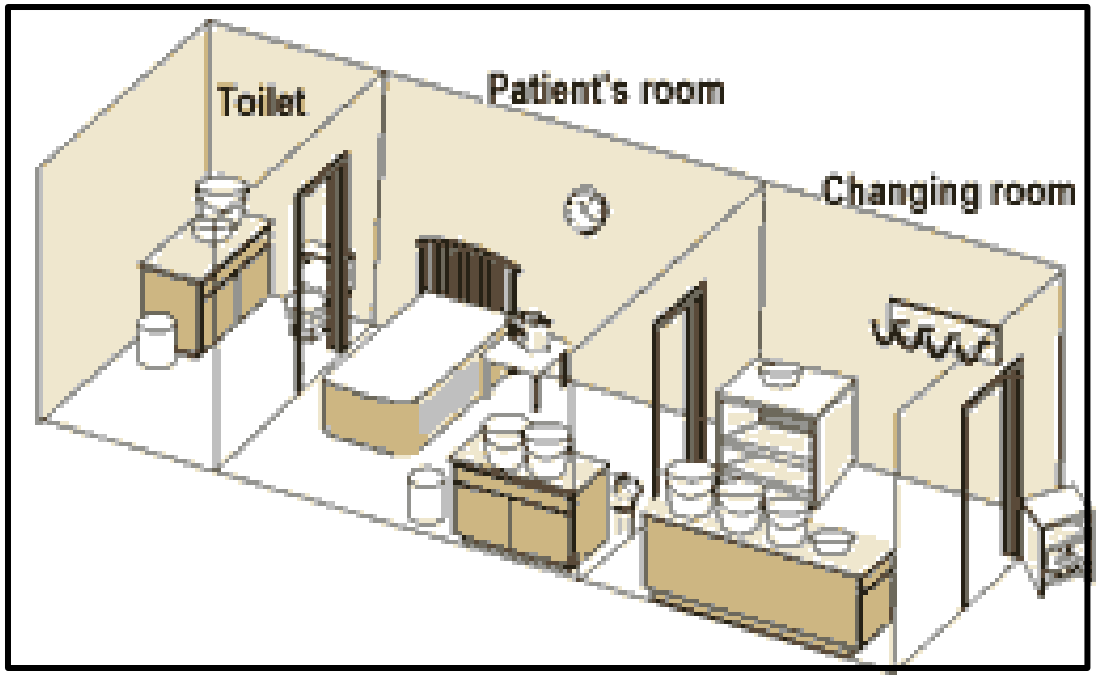
WHO VHF Africa Manual

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

WHO VHF Africa Manual

Overview of VHFs



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

WHO VHF Africa Manual

Overview of VHFs

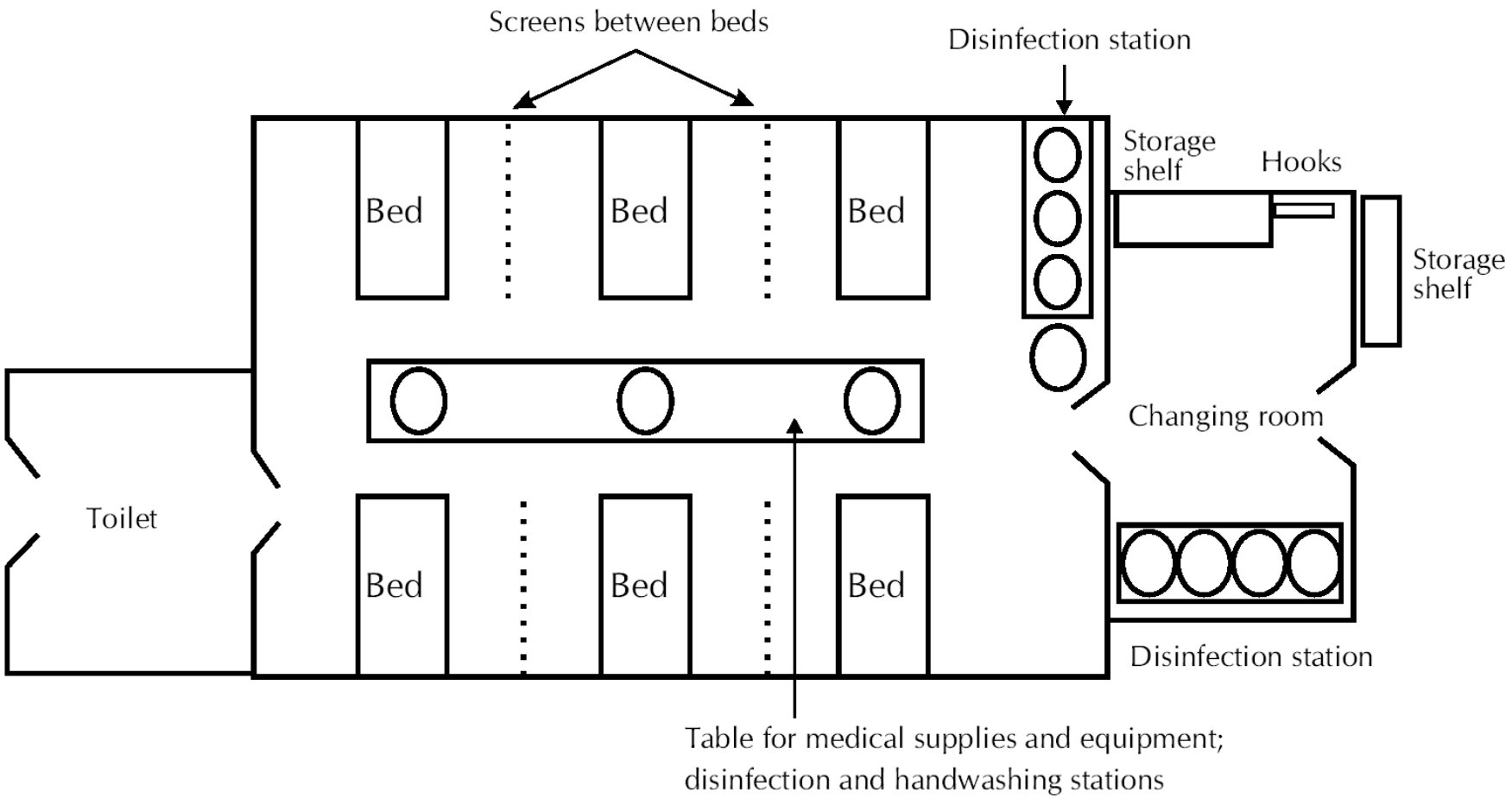


Fig. 10. A sample layout for several patients

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

Overview of VHFs

- 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 VHFs

- 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 >=100.4^{0}F
- 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 >= 100.4^{0}F

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)

Summary

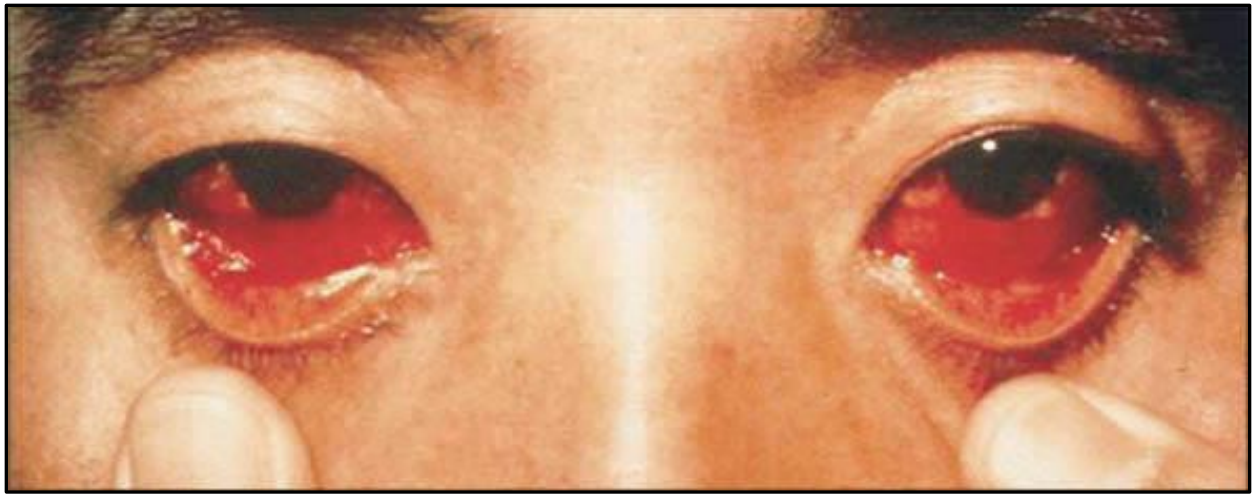
- VHF will start as flu-like illness and progress to organ failure (**bleeding may not be evident**)
- Have high concern for the nosocomial risk as the treating provider
- Masks, gloves, gowns, and eye protection at a minimum
- Have isolation plan, post-exposure plan, and evac plans ready
- Ribavirin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



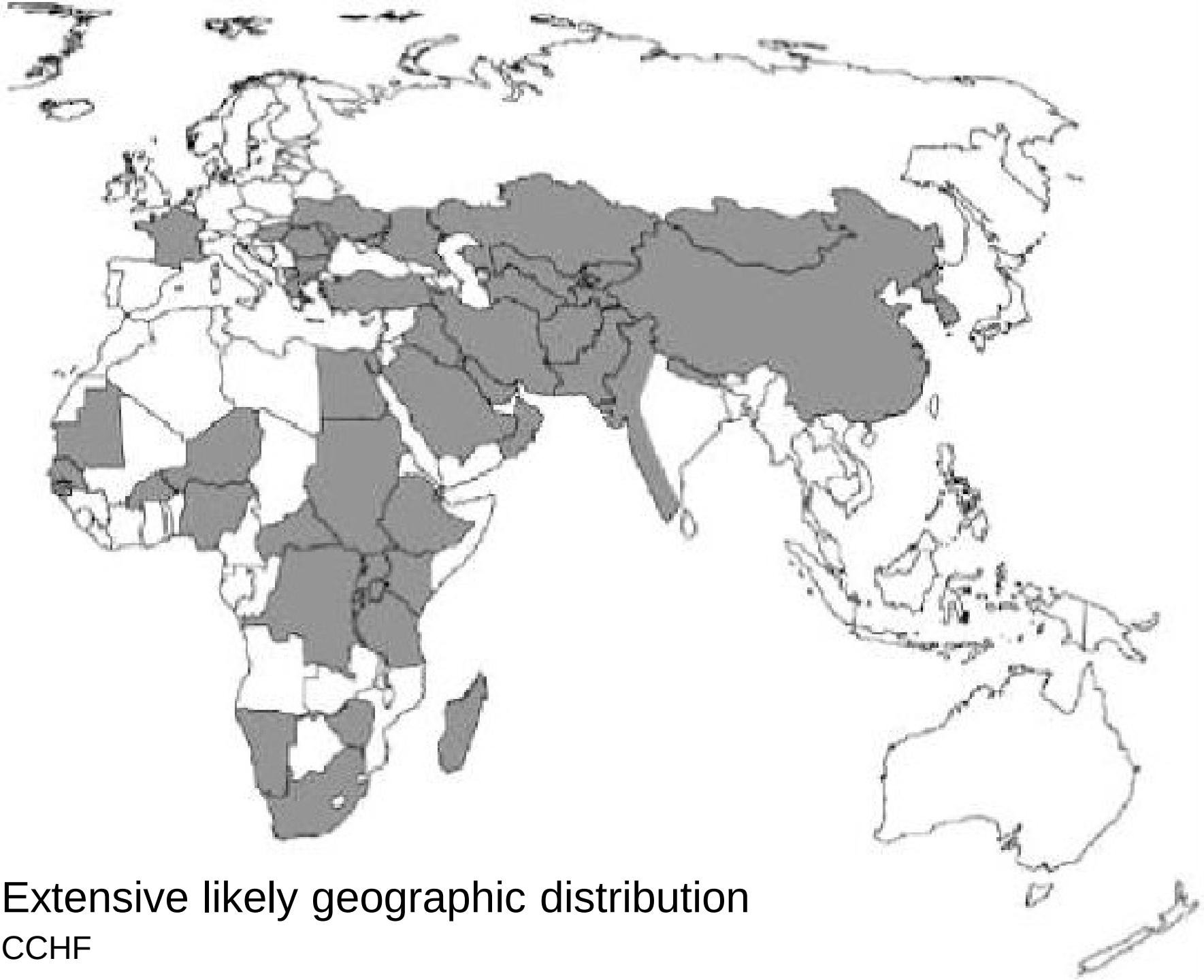
- Any traveler with fever **AND** bleeding out of their eyeballs is VHF until proven otherwise

YOU HAVE MUCH TO LEARN, GRASSHOPPER!
BUBONIC PLAGUE
EBOLA

Crimean-Congo Hemorrhagic Fever

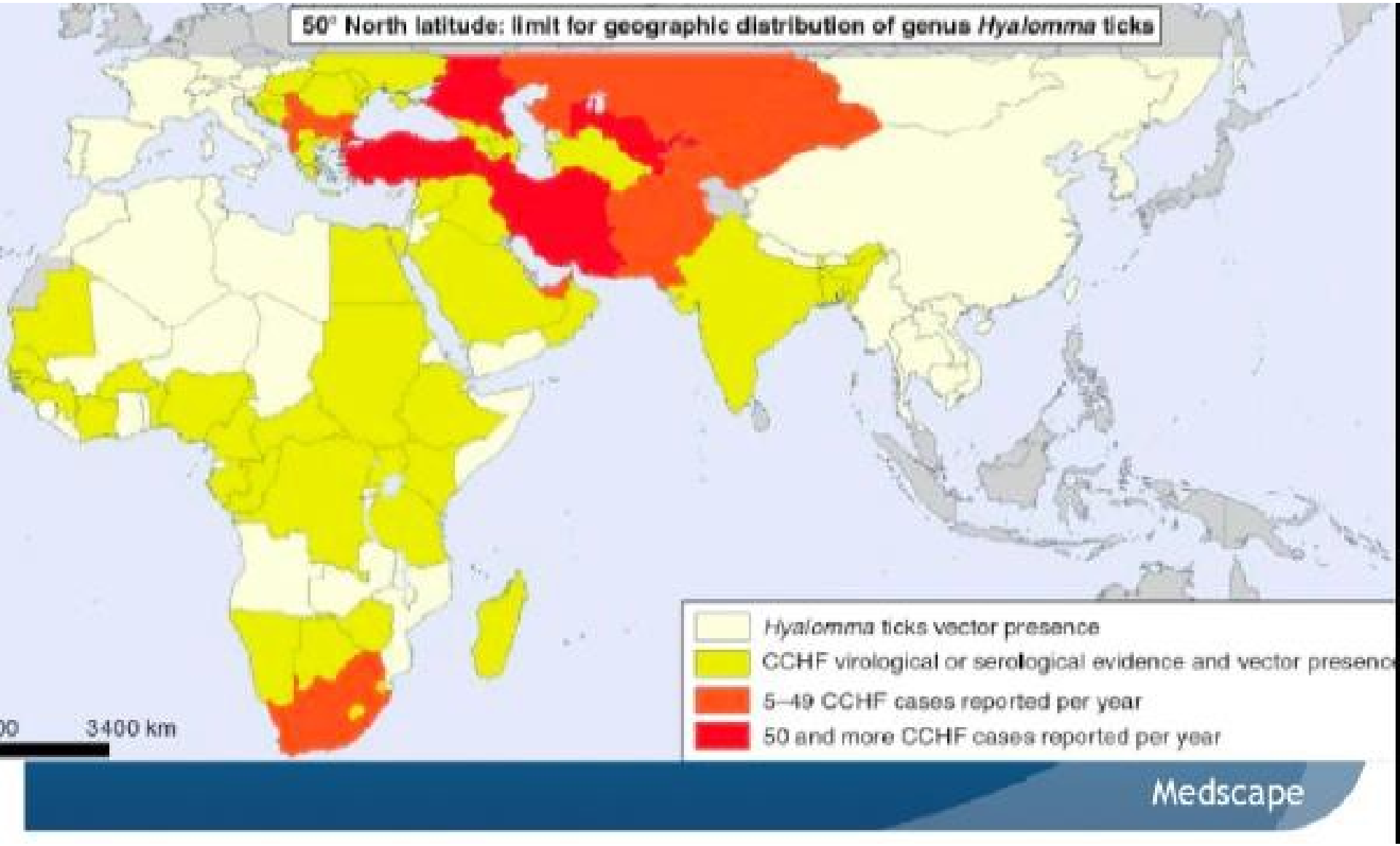
Crimean-Congo Hemorrhagic Fever

- 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

CCHF


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
3400 km
Medscape

CCHF

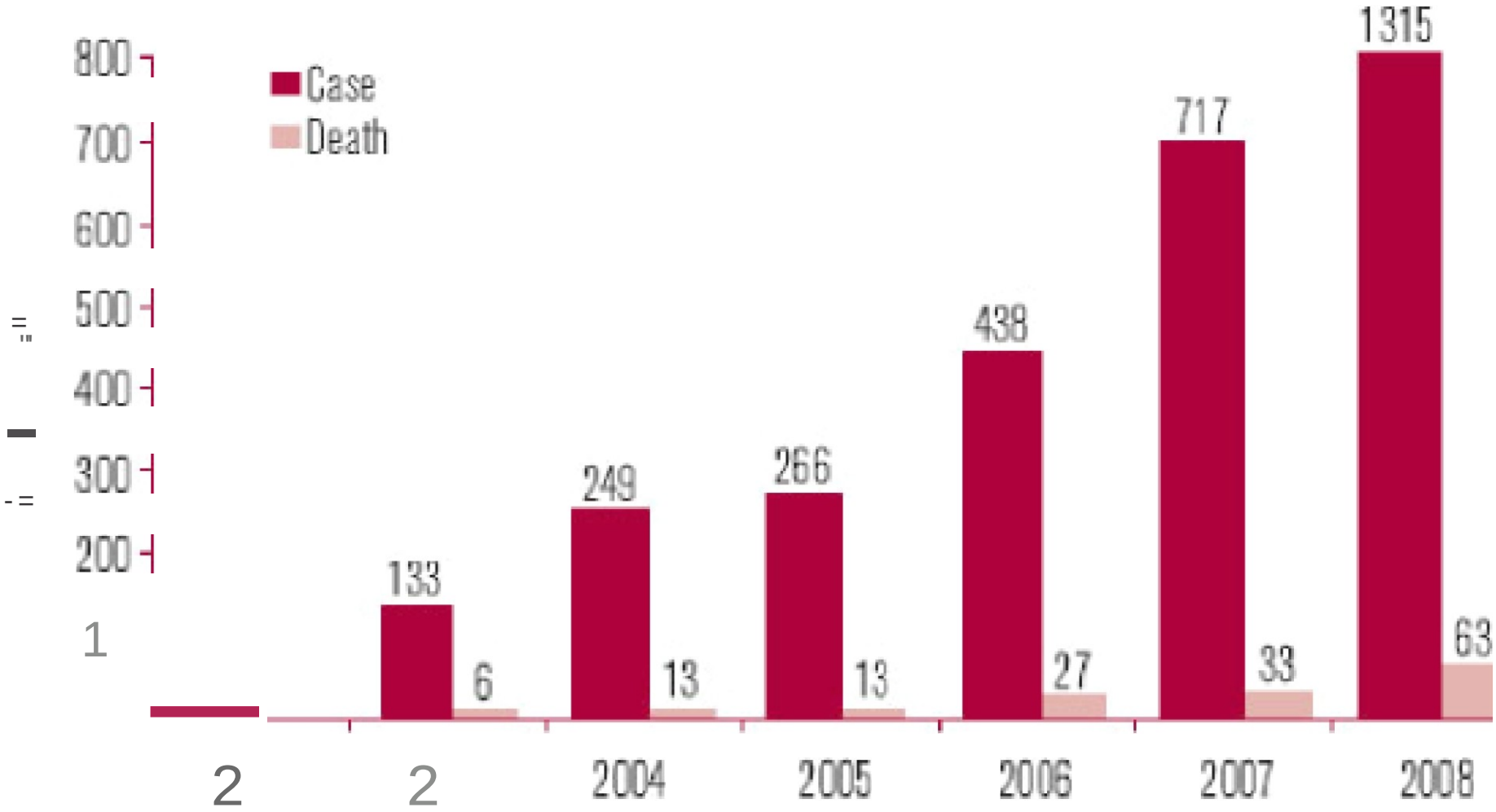
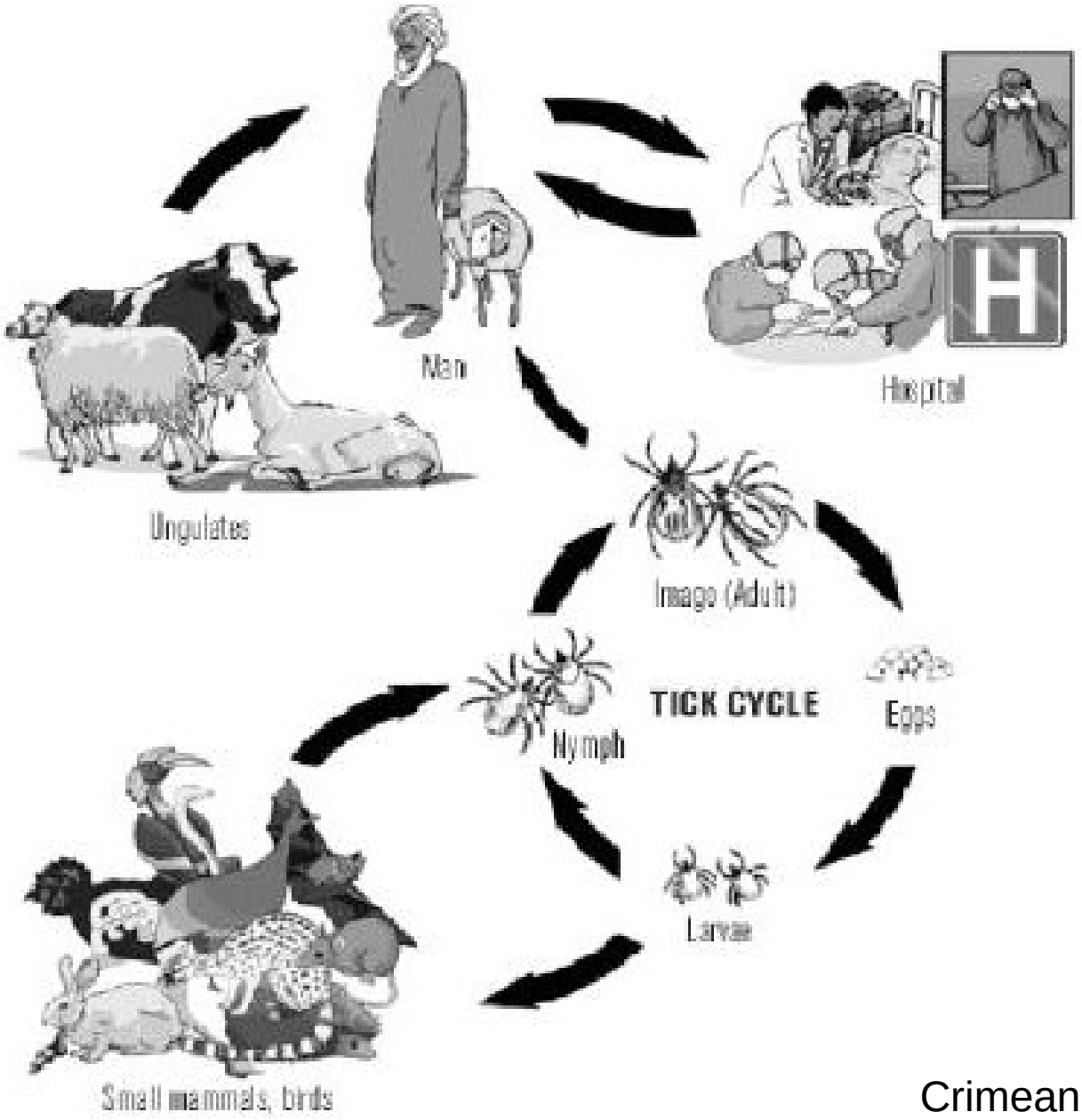


Figure 5. Number Crieman-Con...p hemorrhagic ...d deaths i between 20

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

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

Operational Clinical Infectious Disease Consortium
OCID

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 fever virus [LFV] is endemic in Nigeria, and multi-mammate mice (_Mastomys_ spp.) are the rodent hosts. Lassa fever is now a **serious problem** in **23** of the 36 states of that country." -*Nigeria Centre for Disease Control (NCDC), Federal Ministry of Health Weekly Epidemiology Report Vol. 5, No. 7 2015*

Lassa

BMJ VOLUME 327 29 NOVEMBER 2003 bmj.com

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

OCID

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

Photo by F. Jacquerioz

Aniru Conteh
1942–2004

Dr. Conteh attempted femoral venipuncture and sustained a needlestick.

(WHO, Weekly Epi Record, MAR 2005)

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 2002[15])	
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

PLoS Med 2005; 2(6): e183

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

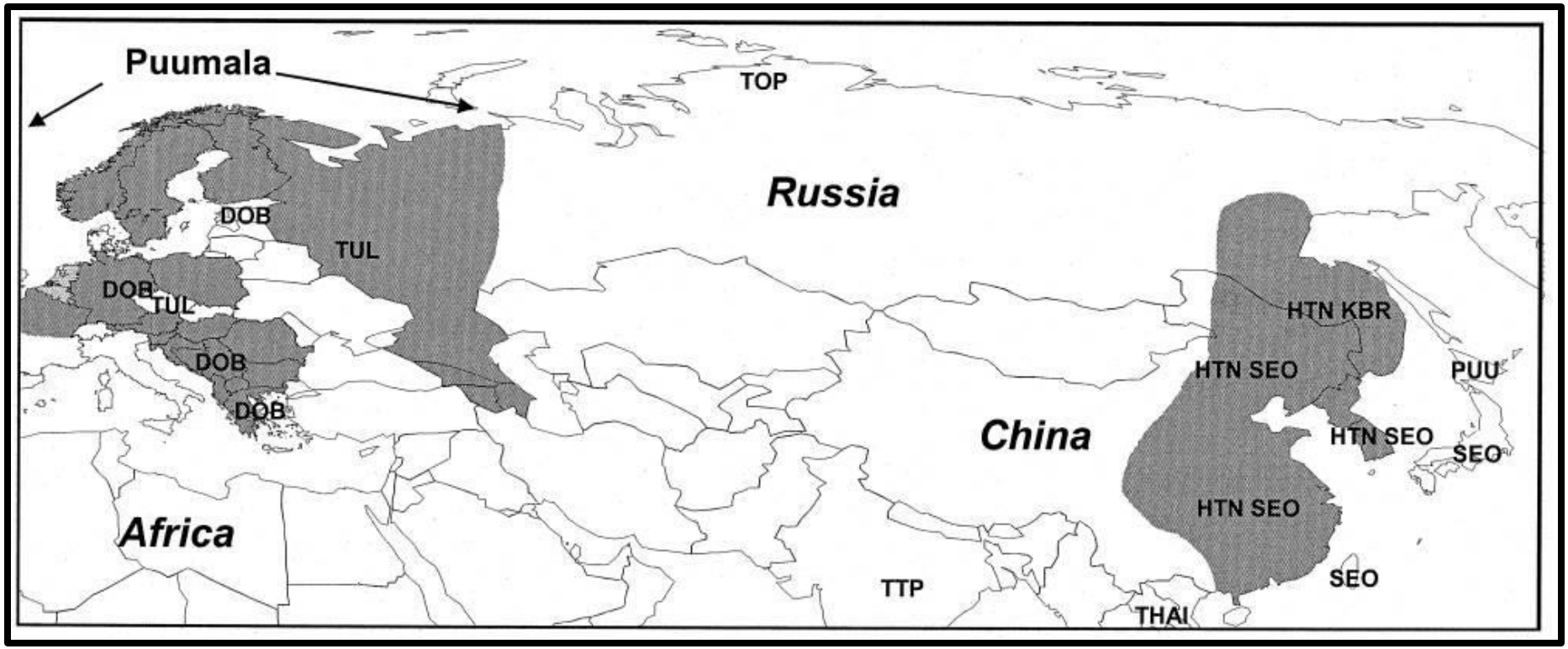
Hantaviruses

- 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

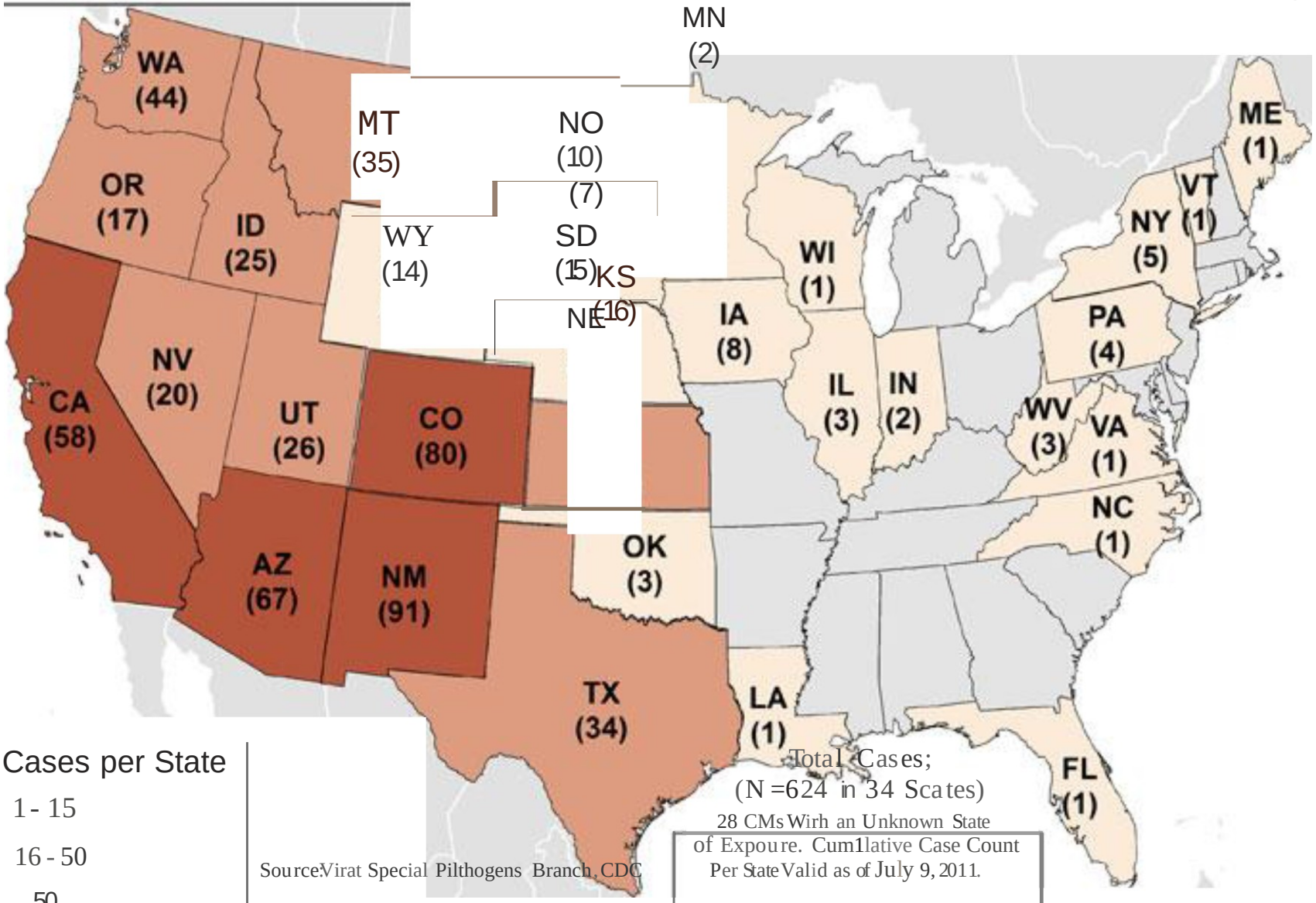
Hantaviruses

- 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



Field's Virology, 4th Ed. Chapter 48

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



HPS Cases per State

1 - 15

16 - 50

50

Zern Cases

Source: Virat Special Pilthogens Branch, CDC

Total Cases;
(N =624 in 34 Scates)

28 CMs Wirh an Unknown State of Expoure. Cum1lative Case Count Per State Valid as of July 9, 2011.

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

- 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

EID 2009; 15(10): 1598-1602

Emerging Threats

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

PLoS Pathog 2008; 4(4): 1-6

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Questions?