Emerging Infectious Diseases & Viral Hemorrhagic Fevers

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Emerging Infectious Diseases

• Newly evolved strains of pathogens

• Pathogens with recently increased human incidence or dramatic changes in their geographic host range

• Pathogens recently entering the human population
Burden of EID

• Societal Costs
  – Investigation
  – Increased hospitalizations
  – Additional/new diagnostics or therapeutic procedures
  – Additional antibiotic/antiviral use
  – Loss of productivity
  – Long-term disability

• Containment Costs
  – School closures
  – Closing of public places
  – Infection control and/or quarantine measures

• Individual Costs
  – Increased morbidity and mortality
Causes of Pathogen Emergence

• Human
  - Changes in human demographics and society
  - Hospitals and medical procedures
  - International travel
  - Poor population health (e.g. HIV, malnutrition)

• Pathogen
  - Capacity to adapt to humans
  - Acquisition of virulence factors and antibiotic resistance
  - Failures of disease control programs

• Environmental
  - Land use and agricultural practices
  - Trade in animals and animal products
  - Production and supply of food and water
  - Climate Change

Profile of an Emerging Pathogen

• RNA virus
• Zoonotic
• Ability to use a receptor that is conserved across species
• Found in areas undergoing ecological, demographic, or social change
• Number of EID events has been steadily increasing

Recent Novel EIDs

• NIPAH (1999)
  – Disease: fever and encephalitis
  – Initial outbreak in Malaysia
    • 265 human cases, 105 fatal
    • Case fatality rate ~ 40%
  – Have been recurrent outbreaks with documented human to human spread
  – Virus originated: bats → pigs → humans
PNEUMONIA - CHINA (GUANGDONG): RFI
*************************************************************************
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

[1]
Date: 10 Feb 2003
From: Stephen O. Cunnion, MD, PhD, MPH <cunnion@erols.com>

This morning I received this e-mail and then searched your archives
and found nothing that pertained to it. Does anyone know anything
about this problem?

"Have you heard of an epidemic in Guangzhou? An acquaintance of mine
from a teacher's chat room lives there and reports that the
hospitals there have been closed and people are dying."

--
Stephen O. Cunnion, MD, PhD, MPH
International Consultants in Health, Inc
Member ASTM&H, ISTM
<cunnion@erols.com>
Recent Novel EIDs

• SARS (2003)
  – First pandemic of the 21st century
  – Severe respiratory disease (~10% case fatality rate)
  – > 8000 cases in 28 countries
  – Pandemic was stopped primary through quarantine efforts and international collaborative efforts of public health personnel, clinicians, and laboratory scientists
  – Caused by a novel coronavirus, SARS-CoV, which originated in BATS
Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia


October 17, 2012
Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

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Truly Emerging — A New Disease Caused by a Novel Virus
Heinz Feldmann, M.D.
Severe Fever with Thrombocytopenia Syndrome (SFTS)

• First seen in March-April 2009 in Hubei and Hunan provinces in China
• Major clinical symptoms:
  – Fever
  – Gastrointestinal symptoms
  – Thrombocytopenia
  – Leukocytopenia
• Case fatality rate: 30%
Figure 1. Geographic Distribution of SFTS in Mainland China. Areas where SFTS surveillance was carried out and SFTS bunyavirus was isolated from patients are shown in red.
Novel PHLEBOVIRUS, member of the BUNYAVIRIDAE FAMILY
Called: SFTS bunyavirus (SFTSV)
Epidemiology of SFTS

- From June 2009 through September 2010, detected SFTS bunyavirus in 171 patients among 241 hospitalized patients who met the case definition for SFTS.
- No human to human transmission.
- 5900 mosquitoes tested (all RNA negative).
- 10 of 186 ticks (5.4%) of the species *Haemaphysalis longicornis* RNA positive.
A New Phlebovirus Associated with Severe Febrile Illness in Missouri

“Two men from northwestern Missouri independently presented to a medical facility with fever, fatigue, diarrhea, thrombocytopenia, and leukopenia, and both had been bitten by ticks 5 to 7 days before the onset of illness. *Ehrlichia chaffeensis* was suspected as the causal agent but was not found on serologic analysis, (PCR), or cell culture.

EM revealed viruses consistent with members of the Bunyaviridae family. Next-generation sequencing and phylogenetic analysis identified the viruses as novel members of the phlebovirus genus.

Although Koch’s postulates have not been completely fulfilled, we believe that this phlebovirus, which is novel in the Americas, is the cause of this clinical syndrome.”
VIRAL HEMORRHAGIC FEVERS
VHFs

• Viruses
  – All enveloped viruses with single stranded RNA genomes
  – Vary greatly in their morphology
  – 4 families:
    • Arenaviridae
    • Bunyaviridae
    • Filoviridae
    • Flaviviridae
VHF

• **Clinical Syndrome**
  – Fever
  – bleeding diathesis
  – N/V/D
  – Circulatory shock
  – Multi-organ failure
  – High case-fatality rates

• **Laboratory Findings**
  – Thrombocytopenia
  – Leukopenia
  – Elevated LFTs
  – Prolonged PT, PTT, INR
  – Evidence of DIC
VHFs

• Pathogenesis
  – Not fully understood
  – Early target cells: dendritic cells, monocytes, macrophages, and vascular endothelial cells (but have a broad tissue tropism)
  – Viruses evoke an intense cytokine response with severe inflammatory tissue damage
    • LN
    • Liver (decreased production of clotting factors)
    • Adrenal Gland (impaired synthesis of steroids)
  – Failure of effective immune responses
    • Inhibition of IFN host responses
    • Depletion of lymphocytes
  – Obtain quickly extremely high levels of viremia
  – Can induce profound immunosuppression
Unregulated virus spread and replication

Dysregulation of host immune responses

Coagulation abnormalities

Impairment of vascular system

Hypotension

Shock & Multi-Organ Failure
## Table 1 Hemorrhagic fever viruses

<table>
<thead>
<tr>
<th>Element or feature</th>
<th>EHF</th>
<th>MHF</th>
<th>AHF</th>
<th>BHF</th>
<th>Lassa fever</th>
<th>CCHF</th>
<th>RVF</th>
<th>Yellow fever</th>
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<tbody>
<tr>
<td>Virus family</td>
<td>Filoviridae</td>
<td>Filoviridae</td>
<td>Arenaviridae</td>
<td>Arenaviridae</td>
<td>Arenaviridae</td>
<td>Bunyaviridae</td>
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<td>Etiological virus</td>
<td>Ebola</td>
<td>Marburg</td>
<td>Junin</td>
<td>Machupo</td>
<td>Lassa</td>
<td>CCHF</td>
<td>RVF</td>
<td>Yellow fever</td>
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<td>Natural distribution</td>
<td>Africa</td>
<td>Africa</td>
<td>South America</td>
<td>South America</td>
<td>West Africa</td>
<td>Africa, Central Asia, Europe, Middle East</td>
<td>Africa, Yemen, Saudi Arabia</td>
<td>Africa, tropical Americas</td>
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<td>Source</td>
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<td>Unknown</td>
<td>Rodent</td>
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<td>Tick</td>
<td>Mosquito</td>
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<td>Incubation (days)</td>
<td>2–21</td>
<td>2–14</td>
<td>7–14</td>
<td>9–15</td>
<td>5–16</td>
<td>3–12</td>
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<td>Fever</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NE</td>
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<td>Hepatocellular necrosis (biochemical evidence)</td>
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<td>Rare</td>
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<td>Infection of lymphocytes</td>
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<td>No</td>
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<td>Infection of macrophages</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Infection of dendritic cells</td>
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<td>NE</td>
<td>NE</td>
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<td>Cytokines/chemokines (increased circulating levels)</td>
<td>IFN-α, IL-6, IL-10, IL-18, MIP-1α, MIP-1β, MCP-1, TNF-α</td>
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<td>IFN-α, IL-6, IL-8, IL-10, TNF-α</td>
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<td>IFN-γ, IL-8, IL-10, IP-10, TNF-α</td>
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<td>NE</td>
<td>IL-6, IP-10, MCP-1, TNF-α, IL-1RA</td>
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<tr>
<td>Other mediators (increased circulating levels)</td>
<td>TF, NO</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
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</tbody>
</table>
EBOLA and MARBURG

family: Filoviruses
Ebola and Marburg

• Filamentous, single-stranded, negative-sense RNA viruses
• First recognized in 1967
• Sporadic cases and outbreaks in equatorial Africa
• Causes severe disease in apes and humans
• Case fatality rate: 25-90% depending on strain
Figure 1: Locations of Ebolavirus infections and outbreaks

(A) Regions in Africa (approximate distribution 10° north and south of the equator) with reported outbreaks of Ebola haemorrhagic fever caused by the three central African species of Ebola virus, Zaire Ebola virus (ZEBOV), Sudan Ebola virus (SEBOV), and Bundibugyo Ebola virus (BEOBV). The Tai Forest region in Côte d’Ivoire reported the only case so far of Ebola virus in western Africa caused by the species Côte d’Ivoire Ebola virus (CIEBOV). (B) Reston ebolavirus REBOV has been introduced several times through imported macaques into USA from 1989 to 1996 (Philadelphia, PA; Reston, VA; San Antonio, TX) and into Italy (Siena) in 1992 (C). The source of the introduction in all cases of REBOV has been a primate export facility in the Philippines (Ferlite farm) (D). Animals of this farm have been diagnosed with REBOV infection several times in the 1990s. REBOV has been detected in pigs on two farms in the Philippines (Pangasinan, Bulacan). DRC-Democratic Republic of the Congo.
2012 update

• Uganda outbreak
  – 24 cases
  – 17 fatal (70% case fatality rate)
  – Ebola Sudan

• Democratic Republic of Congo outbreak
  – 51 cases to date
  – 20 fatal (40% case fatality rate)
  – Ebola Bundibugyo
Routes of Infection

- Enters host via mucosal surfaces, breaks and abrasions in the skin, or by parenteral introduction
- Infectious virus particles have been detected in: blood, semen, genital secretions, skin, nasal secretions, and other body fluids
- Most human infections in outbreaks occur by direct contact with infected patients or cadavers
- Outbreaks associated with
  - Butchering of chimpanzees for food
  - Handling and consumption of freshly killed bats
  - Reuse of contaminated needles
Clinical Disease

- **Incubation period:** 2-21 days (mean 4-10 days)
- **Abrupt onset:** fevers, conjunctival injection, HA, myalgias, arthralgias
- **Multisystem involvement:**
  - GI: abd pain, N/V/D, anorexia
  - Resp: cough, chest pain, SOB, nasal discharge
  - CNS: HA, confusion
  - Derm: maculopapular rash common
  - Hemorrhagic manifestations (seen in about ½ of pts):
    - petechiae, bruising, oozing from venopuncture sites, nosebleeds
- Around DOI 3-4 pts begin to deteriorate suddenly
- Around DOI 6-9 develop shock and multiorgan failure
- Asymptomatic infections (except for Ebola Reston) have not been reported
Crimean-Congo Hemorrhagic Fever (CCHF)

genus: Nairovirus
family: Bunyaviridae
Epidemiology and Ecology

• Single stranded, negative-sense, segmented RNA genome
• First recognized in Russia in 1945 and in the DRC in 1956
• Arbovirus
  – 1ºvector = ticks of the Hyalomma genus
  – Ticks found throughout Africa, Middle East, eastern Europe, Asia, and Far East
• Main reservoirs: livestock (cattle, goats, sheep, horses, donkeys, pigs), small wild animals (hares, hedgehogs), small rodents, and birds (ostriches)
Adult Hyalomma tick
Worldwide Distribution of CCHF

1. Geographic range of CCHF virus is the most extensive of all the medically important tickborne viruses
2. Second most widely spread arboviruses after dengue
Risk factors for Infection

• Natural routes of infection
  – Direct contact of damaged skin with blood and tissues of infected animal
  – Inoculation by infected ticks

• High risk groups/activities
  – Farmers, herdsmen, veterinarians, abattoir workers
  – Hiking, camping, rural recreational activities

• Nosocomial human-human transmission
  – Exposure to hemorrhages from nose, mouth, gums, vagina, injection sites
  – Needlestick injuries
CCHF – Clinical Disease

- **Incubation period:** 1-13 days (mean 2-5 days)
- **Abrupt onset:** fevers, myalgias, HA, N/V/D, severe abdominal pain, conjunctivitis, eye pain, photophobia
- **Differs from other VHF:** shorter clinical course, but has early-onset and extremely severe hemorrhage phase
- **DOI 3-4:** hemorrhagic phase begin (70% of pts) = petechial rash, bleeding from nose, GI system (haematemesis, melena), uterus, urinary tract (hematuria), and respiratory tract (hemoptysis)
- **Case fatality rate:** ~ 30% (varies by strain)
- **High seropositivity in endemic areas suggests mild illness occurs**
Lassa Fever Virus
family: Arenaviruses
Epidemiology and Ecology

- First recognized in 1969 in Lassa, Nigeria in several American missionary nurses
- Single stranded, negative-sense RNA genome
- Endemic in Western Africa
- Reservoir: multimammate RATS (*Mastomys natalensis*)
  - Breed frequently
  - Most common rodent in tropical Africa, distributed widely through west, central, and east Africa
  - Found predominately in rural dwellings
  - Persistently infected and shed virus in excreta
MULTIMAMMATE RATS
(Mastomys natalensis)
Risk Map of Lassa Fever in West Africa
red = higher risk, stars = known outbreaks
Highest correlation of risk – associated with rainfall
Figure 1. West and Central Africa mean annual rainfall (1951–1989 [28]), Lassa fever nosocomial outbreaks (stars) and human seroprevalence (numbers in %).
doi:10.1371/journal.pntd.0000388.g001
Transmission

• **RAT to HUMAN**
  – African grain crops and stores are commonly contaminated with the virus and serve as a direct source of human infections
    • Inhalation of aerosolized virus
    • Direct contact and entry of virus through damaged skin
    • Ingestion of contaminated food
  
  – Catching, preparing, and eating rats (considered a delicacy and eaten by 90% of people in some endemic areas)
Transmission

• **HUMAN to HUMAN**
  – Direct contact with blood, tissues, secretions or excretions of infected humans
  – Needle stick or cut
  – Inhalation of aerosolized virus
  – Spread during traditional burial ceremonies of infected corpses
Clinical Disease

- Incubation period: 3-21 days (mean 5-10 days)
- **Gradual onset**: fever, HA, myalgias, N/V/D, abdominal pain
- Distinguishing features: Sore throat with exudative tonsillitis, cough, retro-sternal pain
- 80% of people infected have asymptomatic or mild disease; 20% have severe disease
- More severe in pregnancy
- Case fatality rate < 2% overall, but ~20% for untreated hospitalized cases
- Long term complication: deafness
  - 30% of patients, not related to severity of illness
Clinical Signs and Symptoms

- Fever
- Headache
- Arthralgias/Myalgias
- Retro-sternal Pain
- Weakness
- Dizziness
- Sore throat/Pharyngitis
- Cough
- Vomiting
- Abdominal Pain/Tenderness
- Diarrhea
- Conjunctivitis/Sub-conjunctival Hemorrhage
- Chills
- Deafness
- Lymphadenopathy
- Bleeding
- Confusion
- Swollen Neck or Face

Percent
# Clinical Stages of Lassa Fever

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (days 1-3)</td>
<td>General weakness and malaise. High fever, &gt;39°C, constant with peaks of 40-41°C</td>
</tr>
<tr>
<td>2 (days 4-7)</td>
<td>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 &lt;100 mm Hg); anaemia</td>
</tr>
<tr>
<td>3 (after 7 days)</td>
<td>Facial oedema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation</td>
</tr>
<tr>
<td>4 (after 14 days)</td>
<td>Coma and death</td>
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## Other Old and New World HF Arenaviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Origin of name</th>
<th>Reservoir</th>
<th>Year</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>Lassa</td>
<td>Town, Nigeria</td>
<td>Rodents</td>
<td>1969</td>
<td>West Africa</td>
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<tr>
<td>Junin</td>
<td>Town, Argentina</td>
<td>Rodents</td>
<td>1957</td>
<td>South America</td>
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<tr>
<td>Machupo</td>
<td>River, Bolivia</td>
<td>Rodents</td>
<td>1962</td>
<td>South America</td>
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<td>Guanarito</td>
<td>Area, Venezuela</td>
<td>Rodents</td>
<td>1989</td>
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<td>Sabia</td>
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<td>Rodents</td>
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<td>Chapare</td>
<td>River, Bolivia</td>
<td>Rodents</td>
<td>2004</td>
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<td>Lujo</td>
<td>Towns in Zambia and South Africa</td>
<td>Rodents</td>
<td>2008</td>
<td>Southern Africa</td>
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</tbody>
</table>

Not a cause of VHF, but most well known arenavirus:

| LCMV        | Clinical disease                | Rodents   | 1933 | worldwide          |
Rift Valley Fever Virus

genus: Phlebovirus
family: Bunyaviridae
Epidemiology and Ecology

• First recognized as a viral zoonosis in Kenya in 1930
• Endemic in Africa (primarily Eastern Africa)
• In 2000 – spread for first time beyond African continent to Saudi Arabia and Yemen
• Concerns regarding further geographic spread
Epidemiology and Ecology

- Outbreaks tend to follow heavy rainfalls and floods
- Pathogenic to both livestock and humans
- $1^\circ$ vector = *aedes* mosquito
  - Other vectors = *culex* mosquitos
- Amplifying hosts = animals, primarily livestock (cattle, sheep, goats, camels)
Transmission

• Direct or indirect contact with blood or organs of infected animals
  – handling of animal tissue during slaughtering or butchering
  – assisting with animal births
  – conducting veterinary procedures
  – disposal of carcasses or fetuses.

• Modes of transmission
  – Inoculation: contact through broken skin, wound from infected knife
  – Inhalation: aerosols produced during slaughter

• Drinking of unpasteurized milk
• Directly from mosquitoes or blood-feeding flies

• **NO human to human transmission has been reported**
Clinical Disease

- **Incubation period: 2-6 days**
- **Abrupt onset, usually lasts 4-7 days**
- **Majority of human infections are asymptomatic or have a “flu-like” illness: fever, HA, myalgias, photophobia**
- **Severe disease**
  - **Ocular (2-10%)**
    - 50% can develop blindness
  - **Meningoencephalitis (1-8%)**
  - **Hemorrhagic fever (~1%)**
    - Case-fatality rate ~ 50%
DIAGNOSIS & TREATMENT
Diagnosis

- Antigen detection ELISA
- Serology
- RT-PCR

- Diagnosis is generally done in national or international reference labs
- For any suspected case contact them immediately regarding proper advice on sampling, sample preparation, and sample transport
Treatment

• Supportive Care (ICU)
• Ribavirin (IV better than PO)
  – YES: Lassa and CCHF
    • [for Lassa – best results if given before DOI 6]
  – NO: filoviruses, flaviviruses
  – NO: CNS dz -- does not cross blood-brain barrier
• Passive immunization – benefits correlate with level of neutralizing antibody
• Treatment of coagulation problems
  – Nematode-derived anticoagulation protein rNAPc2 (33% efficacy in EBOV primate studies)
  – Activated protein C
Box 1: recommended dosage regimens for treating CCHF or Lassa fever with ribavirin

**Intravenous regimen (preferred)**
- **Loading dose:** 33 mg/kg by infusion in normal saline
- **Continuation dose:** begin 6 h after loading dose and give 16 mg/kg 6 h for four days
- **Completion dosing:** 8 mg/kg 8 h for a further six days

**Oral regimen (commence if intravenous ribavirin is not available)**
- **Loading dose:** 2 g
- **Continuation dose:** begin 6 h after loading dose and give 1 g 6 h for four days
- **Completion dosing:** 0.5 g 6 h for a further six days

**Observe for adverse reactions:**
- Nausea, sleeplessness, intrusive dreams
- Dose-related haemolytic anaemia, which may require blood replacement
- Jaundice, transamminaemia, rare pancreatitis
Differential Diagnosis

- Difficult to recognize during first 3-7 days of illness b/c present with influenza like syndromes (fever and myalgias)
- At initial stages of disease, pts may not look that ill or have significant bleeding until severe disease develops abruptly
- Diseases to consider (common things being common):
  - Malaria
  - Dengue
  - Meningococcal bacteremia
  - Gram-positive and Gram-negative bacteremia
  - Rickettsial infections
  - Leginelloses
  - Leptospororosis
  - Brucellosis
  - Salmonella
  - Q fever
  - Influenza
Consider a VHF diagnosis…

• **Epidemiological Risk Factors**
  – Consider incubation period
  – Consider areas of exposure and “high risk” factors
    • Generally no risk in cities or modern hotels
    • Travel without stops for rural excursions is usually safe

• **Clinical warning signs**
  – Failure to improve on antimalarial and/or antibiotic therapy
  – Failure of “dengue” fever to improve after 7 days
  – Rapid rise in AST
  – Rapid fall in platelet count
  – Onset of epistaxis or bloody diarrhea
Infection Control

• Put suspected patient with VHF in a separate room, cubicle, or resuscitation area
• Use available PPE
  – Water repellent gown and/or apron
  – Disposable gloves
  – Surgical face mask
  – Wrap-around eye protection
• Have appropriate sharp containers and waste containers nearby for direct disposal
• Immediately notify local infection specialist and infection control team of any suspected case
Infection Control

• Casual contact, household contact, sharing public transport – not shown to carry any risk of infection
• Can be spread by percutaneous exposure, mucosal splash, or inadvertent ingestion of infected body fluids
• Aerosol transmission has not been confirmed outside of a laboratory setting
Another VHF virus?

- Associated with VHF outbreak in DRC in 2009
- 3 people with severe fever and mucosal hemorrhages (2 died)
- Bas-Congo Virus
  - Novel rhabdovirus (also SS RNA virus)
  - Virus found in recovering patient
  - 1 pt and 1 HCW developed convalescent antibodies
  - Adds a 5th class of viruses as a cause of VHF

Grard, et al. Plos Pathogens 2012;8:e1002924
Figure 1. Map of Africa showing countries that are affected by viral hemorrhagic fever (VHF) outbreaks. Ebola VHF is pictured in orange, Marburg VHF in green, Crimean-Congo HF in violet, Lujo VHF in pink, and Lassa VHF in blue. Yellow fever and dengue VHF, which exhibit a wide geographic distribution throughout Sub-Saharan Africa, are not shown. Mangala village, located in the Bas-Congo province in DRC, is represented by a red star.
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>15</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td><strong>Village</strong></td>
<td>Mangala</td>
<td>Mangala</td>
<td>Mangala</td>
</tr>
<tr>
<td><strong>Neighborhood</strong></td>
<td>Tshela</td>
<td>Tshela</td>
<td>Tshela</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td>Schoolboy</td>
<td>Schoolgirl</td>
<td>Nurse</td>
</tr>
<tr>
<td><strong>Disease onset</strong></td>
<td>May 24</td>
<td>June 4</td>
<td>June 13</td>
</tr>
<tr>
<td><strong>Time until death</strong></td>
<td>2 days</td>
<td>3 days</td>
<td>survived</td>
</tr>
<tr>
<td><strong>Fever (T&gt;39°C)</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Malaise</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Epistaxis (nose bleeding)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ocular hemorrhage/conjunctival injection (eye bleeding)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Oral hemorrhage (mouth bleeding)</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hemorrhagic vomiting</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hemorrhagic diarrhea</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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