

## Viral Hemorrhagic Fevers



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## VHF

- Acute infection:  
fever, myalgia, malaise; progression to prostration
- Small vessel involvement:  
increased permeability, cellular damage
- Multisystem compromise (varies with pathogen)
- Hemorrhage may be small in volume  
(indicates small vessel involvement, thrombocytopenia)
- Poor prognosis associated with:  
shock, encephalopathy, extensive hemorrhage



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## Differential Diagnosis

- Febrile tropical illnesses:
  - Malaria
  - Typhoid fever
  - Bacterial gastro-enteritis
  - Rickettsial diseases



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## Laboratory Diagnosis

- Malaria smears
- Blood cultures (closed system)
- CBC, especially platelet count
- Transaminases (prognostic value)
- Creatinine, BUN
- Coagulation factors

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## VHF: Viruses

- Enveloped, single stranded RNA viruses
- Similar syndromes; different pathogenesis & treatment
- Persistent in nature: rodents, bats, ticks, mosquitoes
- Geographically restricted by host
- Potential infectious hazards from laboratory aerosols

Filoviruses	Ebola Hemorrhagic fever (Z, S, R, IC, B) Marburg Hemorrhagic fever
Arenaviruses	Lassa fever "New World Arenaviruses"
Bunyaviruses	Rift Valley fever (RVF) Crimean Congo Hemorrhagic fever (CCHF)

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## Ebola

- 1-2 week incubation
- Abrupt onset fever, headache, myalgia
- GI symptoms, chest pain, delirium
- 53-88% case-fatality
- ~ 45% hemorrhage
- Person-to-person transmission
- African rainforest
- Unknown reservoir (bat most probable)

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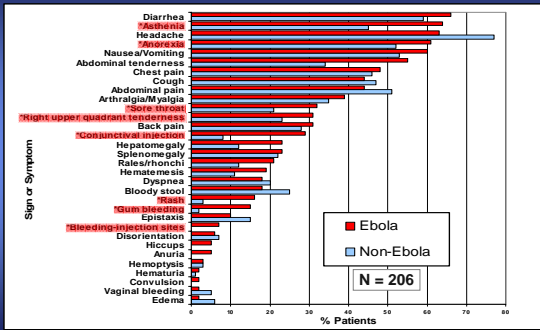
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## Ebola Signs and Symptoms on Presentation




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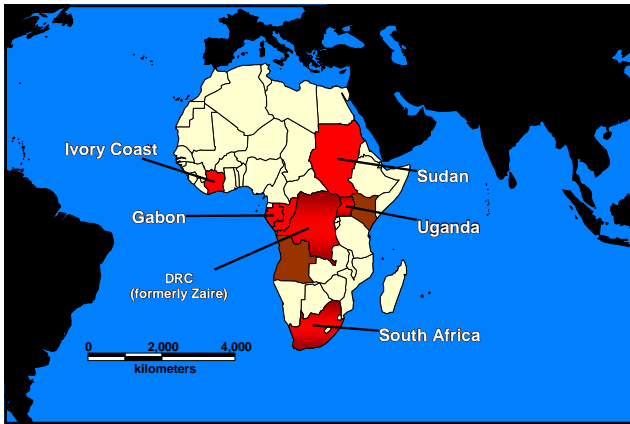
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## 1995 Zaire



- 315 cases
- 81% case-fatality
- Point source outbreak
- Unrecognized 3 months
- 25% health care workers
- 2 "super-spreaders"

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## VIRUS EBOLA FIEVRE HEMORRAGIQUE DE KIKWIT

**EHF Risk Factors**

- 2° attack rate of 16%
- Direct physical contact  
OR = undefined,  $p < 0.01$
- Body fluids  
OR = 3.8, 95%CI (1.9-6.8)
- No contact = no disease

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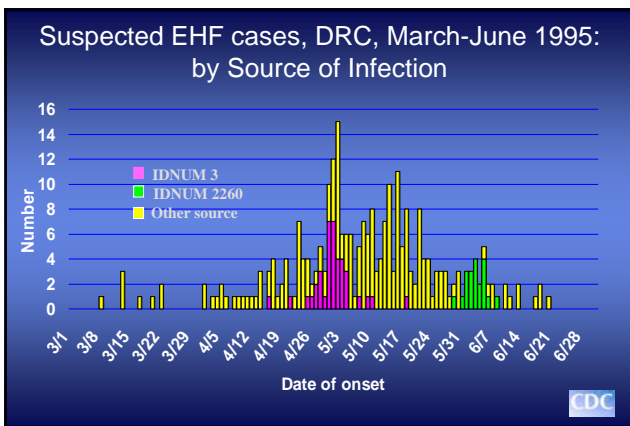
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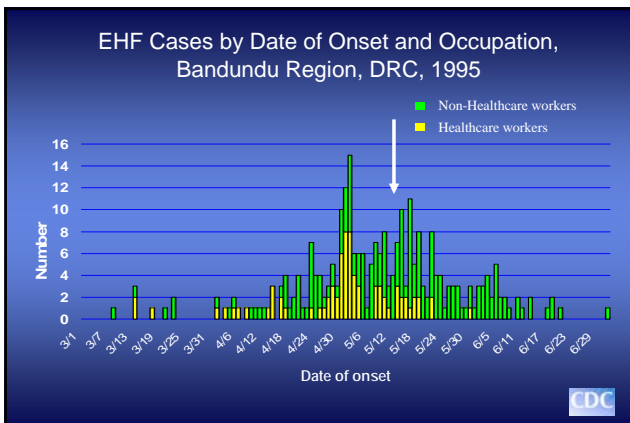
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## Marburg: Past Outbreaks

- 1967  
Marburg, Frankfurt, & Belgrade  
25 primary  
6 secondary  
7 deaths  
African green monkeys from Uganda
- 1975  
Australian traveler  
Zimbabwe  
1 primary  
2 secondary  
1 death



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## Marburg: Past Outbreaks

- 1980  
Engineer  
N.W. Kenya  
1 primary  
1 secondary  
1 death
- 1987  
Danish traveler  
W. Kenya  
1 primary  
1 death
- 1998-2000  
Gold mine  
N.E. DRC  
76 cases  
52 deaths  
>150 cases through follow-up



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## Marburg: Past Outbreaks

- 2005  
Uige, Angola  
Largest and deadliest on record  
374 cases  
329 deaths  
88% CFR  
Home-based injection use
- 2007  
4 cases  
Kitaka mine, Uganda  
Reservoir studies
- 2008  
Fatal case Netherlands  
mild case USA



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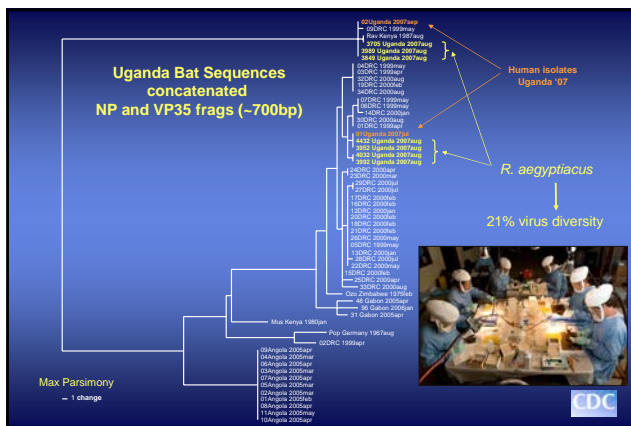
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### Bunyaviruses

- Rift Valley fever
- Crimean Congo hemorrhagic fever
- Hemorrhagic fever with renal syndrome

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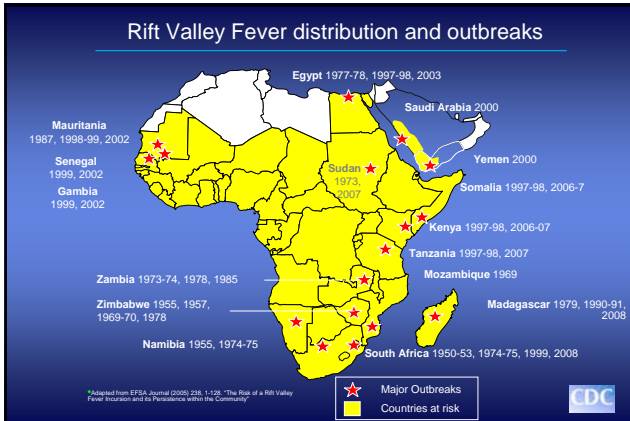
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### Rift Valley Fever

- Mosquito-borne (*Aedes* spp.) vertical transmission in mosquitoes
- Disease of sheep and cattle
- Transmission:
  - Animal contact (birthing or blood)
  - Laboratory aerosol
- Mortality 1% overall
- Therapy: Ribavirin not recommended
- Live-attenuated vaccine (MP-12) undergoing trials

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### Rift Valley Fever: Clinical features

- 3-7 day incubation, 3-5 day duration
- Asymptomatic or mild illness
- Fever, myalgia, weakness, weightloss
- Photophobia, conjunctivitis
- Encephalitis
- <5% hemorrhagic fever
- 1-10% vision loss (retinal hemorrhage, vasculitis)

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### CLINICAL FEATURES RVF IN SAUDI ARABIA, 2001

VARIABLE	n/N	(%)
Fever	499/539	(92.6)
Nausea	315/530	(59.4)
Vomiting	280/532	(52.6)
Abdominal pain	202/532	(38.0)
Diarrhea	118/530	(22.1)
Jaundice	96/530	(18.1)
CNS manifestations	81/475	(17.1)
Hemorrhagic findings	35/494	(7.1)
Vision loss or scotomas	10/683	(1.5)
Vision loss	8/683	(1.2)
Scotomas	2/683	(0.3)

From Madani, et al.  
CID, 2003;37:1084




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### RVF: Encephalitis

	%*
Meningeal signs	67
Confusion	81
Stupor or coma	78
Hypersalivation and teeth grinding	11
Hallucinations	43
Hemiparesis	5
Focal Signs	27
CSF pleocytosis	86
CSF protein > 40 mg%	57
Fatal outcome	11
Residua	7

\* Percent of total from a series of 37 reported cases




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### 1997-1998 East Africa Outbreak

#### 1996-97 NDVI Image Comparison



- 478 deaths
- 115 VHF deaths
- 9% IgM+
- ~89,000 cases
- 70% animal loss




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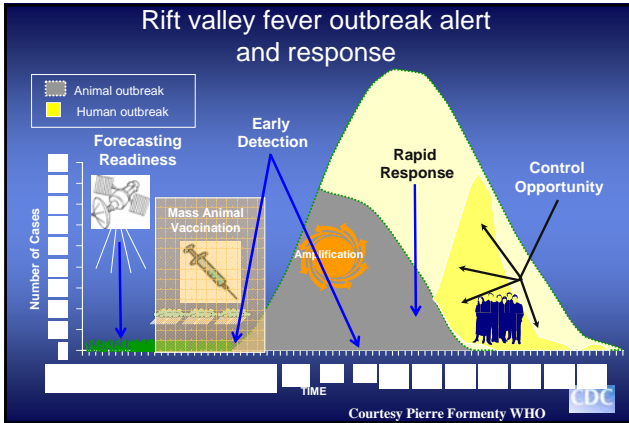
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### CRIMEAN CONGO HEMORRHAGIC FEVER (CCHF)



- Extensive geographic distribution (Africa, Balkans, and western Asia)
- Transmission:
  - Tick-borne (*Hyalomma* spp.)
  - Contact with animal blood or products
  - Person-to-person transmission by contact with infectious body fluids
  - Laboratory worker transmission documented
- Mortality 15-40%
- Therapy: Ribavirin

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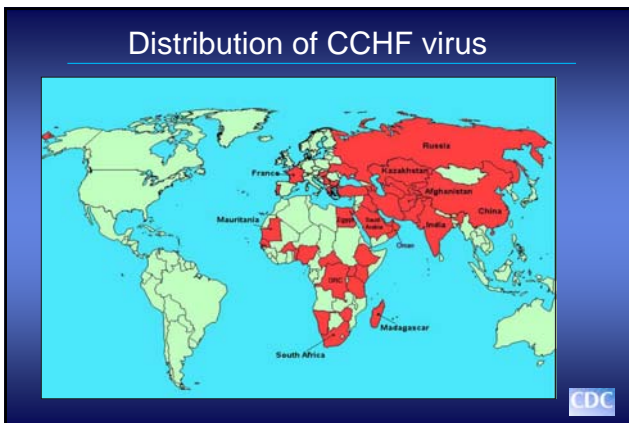
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## CCHF: Clinical features



- 4-12 day incubation after tick exposure
- 2-7 day incubation after direct contact with infected fluids
- Abrupt onset fever, chills, myalgia, severe headache
- Malaise, GI symptoms, anorexia
- Leukopenia, thrombocytopenia, hemoconcentration, proteinuria, elevated AST
- Hemorrhages may be profuse (hematomas, ecchymoses)



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## PREVENTION OF CCHF

- DEET repellents for skin
- Permethrin repellents for clothing – (0.5% permethrin should be applied to clothing ONLY)
- Check for and remove ticks at least twice daily.
- If a tick attaches, do not injure or rupture the tick.  
Remove ticks by grasping mouthparts at the skin surface using forceps and apply steady traction.



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## CCHF: Pathogenesis



- Viremia present throughout disease
- IFA becomes positive in patients destined to survive days 4-6, often simultaneously with viremia
- Recovery may be due to CMI or neutralizing antibodies
- Patients that die usually still viremic
- Virus grows in macrophages and other cells
- DIC often present
- Poor prognosis signaled by early elevated AST and clotting



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## Arenaviruses

- Old world
  - Lassa
  - Lujo
- New world
  - Junin
  - Machupo
  - Guanarito
  - Sabia
  - Chapare

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## Lassa Fever



- West Africa
- Rodent-borne (*Mastomys natalensis*)
- Person-to-person transmission
  - Direct contact
  - Sex
  - Breast feeding
- Mortality 1-3% overall, 20% among hospital patients
- Therapy: Ribavirin

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## Lassa: Clinical features

- 80% asymptomatic
- Fever
- Retro-sternal pain
- Exudative pharyngitis
- Myalgias, headache
- Abdominal pain, vomiting
- Facial edema and conjunctivitis
- Mucosal bleeding
- Proteinuria



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### Junin (Argentine hemorrhagic fever)

- Argentine pampas, autumn grain harvest
- Rodent borne (*Calomys musculinus*)
- Person-to-person transmission uncommon, sexual transmission documented.
- Mortality 15-30%
- Therapy: Immune plasma, Ribavirin(?)

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### Machupo (Bolivian Hemorrhagic Fever)

- Bolivia, Beni Department
- Rodent borne (*Calomys callosus*)
- Person-to-person transmission probable
- Mortality 25%
- Therapy: Ribavirin(?)

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## Guanarito (Venezuelan Hemorrhagic Fever)

- Venezuela, central plains
- Rodent borne (*Zygodontomys brevicauda*)
- Person-to-person transmission not documented
- Mortality 20-30%
- Therapy: Ribavirin(?)



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## South American Hemorrhagic Fevers: Clinical features

- 1-2 week incubation
- Gradual onset fever, malaise, myalgias, anorexia
- Headache, abdominal pain, nausea, vomiting, orthostasis
- Petechiae (axillae, palate), gingival hemorrhage
- Neurologic signs (hyporeflexia, tremor, lethargy, hyperesthesia)
- Leukopenia, thrombocytopenia, proteinuria



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## South American Hemorrhagic Fevers: Clinical features

- 70% Recovery in 7-8 days without sequelae, prolonged fatigue and weakness common.
- Severe disease
  - Severe hemorrhage
  - Delirium, coma, convulsions
  - Combined hemorrhagic/neurologic disease
  - High mortality



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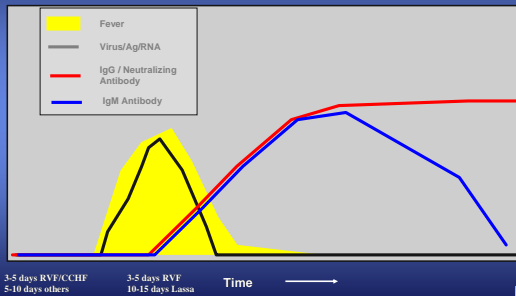
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## VHF - Diagnosis



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## VHF: Supportive therapy

- Rule out or treat febrile illnesses: malaria, rickettsia, leptospirosis, typhoid, dysentery
  - Early hospitalization
  - Distant medical evacuation associated with high mortality
  - Cautious sedation and analgesia
  - Careful hydration
  - Pressors, cardiotonic drugs
  - Support of coagulation system
- CDC

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## Ribavirin

- Guanosine nucleoside analog: blocks viral replication by inhibiting IMP dehydrogenase
  - Licensed for treatment of RSV and HCV
  - Potential adverse effects:
    - Dose dependent reversible anemia
    - Pancreatitis
    - Teratogen in rodents
  - Same regimen: loading dose 30mg/kg (max of 2 grams)
    - 16 mg/kg every 6 hours for 4 days
    - 8 mg/kg every 8 hours for 6 days
  - Post-exposure treatment
- CDC

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## Ribavirin: indications

- Filoviruses No
- Rift Valley No...
- CCHF Yes
- Lassa Yes
- Argentine HF Yes
- Other New/Old world Arena Maybe



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## Ebola Treatment

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

Thomas M. Scobey, Lisa E. Hensley, Peter A. Jahrling, Tom Larsen, Isaac F. Davidson, Jason Flanagan, Vincent P. Frangi, Hans H. Borchers, Andrew F. Sills, George F. Pascoe

#### Summary

**Background:** Infection with the Ebola virus causes hemorrhagic fever and causes the acute respiratory, the cardiovascular, and neurological symptoms associated with Ebola virus infection. The pathogenesis of Ebola virus infection is not fully understood, but it is thought that the virus enters the body through the skin, and spreads to the liver and spleen, where it replicates and spreads to other organs. The virus then enters the bloodstream, where it causes the characteristic hemorrhagic fever and causes the acute respiratory, the cardiovascular, and neurological symptoms associated with Ebola virus infection.

**Methods:** We used a rhesus monkey model of Ebola hemorrhagic fever and assessed the safety, efficacy, and antiviral activity of recombinant activated protein C (rAPC) in the treatment of Ebola virus infection in a study that included 10 rhesus monkeys. The study was a randomized, controlled trial that compared rAPC to placebo. The study was conducted in a biosafety level 4 laboratory.

**Conclusions:** Treatment of Ebola virus infection with rAPC was safe and effective in a rhesus monkey model of Ebola virus infection. The study was a randomized, controlled trial that compared rAPC to placebo. The study was conducted in a biosafety level 4 laboratory.

#### Introduction

The disease caused by infection with Ebola virus is a severe, often fatal, hemorrhagic fever and is caused by infection with Ebola virus. The disease is characterized by fever, muscle pain, and hemorrhagic fever. The pathogenesis of Ebola virus infection is not fully understood, but it is thought that the virus enters the body through the skin, and spreads to the liver and spleen, where it replicates and spreads to other organs. The virus then enters the bloodstream, where it causes the characteristic hemorrhagic fever and causes the acute respiratory, the cardiovascular, and neurological symptoms associated with Ebola virus infection.

### Recombinant Human Activated Protein C for the Postexposure Treatment of Ebola Hemorrhagic Fever

Lisa E. Hensley, Thomas M. Scobey, E. Holly Cox, Isaac F. Davidson, William S. Greene, Tom Larsen, Andrew F. Sills, George F. Pascoe, Vincent P. Frangi, Hans H. Borchers, Andrew F. Sills, George F. Pascoe

**Background:** Infection of primates with Zaire ebolavirus (ZEBV) leads to hemorrhagic fever, shock, and an average case-fatality rate of 50%. Recombinant human activated protein C (rhAPC) is a natural blood anticoagulant and is thought to be involved in the pathogenesis of Ebola virus infection. We conducted a study to evaluate the safety and efficacy of rhAPC in the treatment of Ebola virus infection in a rhesus monkey model of Ebola virus infection.

**Methods:** All 10 rhesus monkeys that were challenged with a moderate titer dose of ZEBV (10<sup>6.5</sup> TCID<sub>50</sub>) survived. The study was a randomized, controlled trial that compared rhAPC to placebo. The study was conducted in a biosafety level 4 laboratory.



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## Filovirus Vaccines

Experimental only, require NHP protection

### Ebola vaccines

DNA Vaccine +Boost Adenovirus (phase II)

Adenovirus (phase I)

VSV

Parainfluenza

### Marburg vaccines

VEE Replicon

VSV



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## VHF: Human-to-Human transmission

- None: Yellow fever, Dengue, Rift Valley fever, Kyasanur, Omsk (arboviruses), hantaviruses
- Low: Lassa and South American Arenaviruses
- High: Ebola, Marburg, Crimean-Congo HF

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## Standard Precautions

- **Constant** use of gloves and handwashing (plus face-shields, masks or gowns if splashes are anticipated) for any contact with blood, moist body substances, mucous membranes or non-intact skin.
- **Additional**, Transmission-based Precautions

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## Standard Precautions

### Transmission-based Precautions

- **Airborne** (TB, Chicken pox, Measles, Smallpox)
- **Droplet** (Diphtheria, Pertussis, Meningococcus, Influenza, Mumps....)
- **Contact** (Enteric infections, Respiratory infections, Skin infections, Conjunctivitis....)

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## VHF: Contact management

- Casual contacts: e.g., shared airplane or hotel, No surveillance indicated
- Close contacts: Direct contact with patient and/or body fluids during symptomatic illness. Fever watch during incubation period
- High risk contacts: Needle stick, mucosal exposure to body fluids, sexual contact. Fever watch, consider inpatient observation.

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## Outbreak response Ebola - Marburg



### ISOLATION – PPE

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*Sometimes a woman would clutch his sleeve, crying shrilly: "Doctor, you'll save him, won't you?" But he wasn't there for saving life; he was there to order a sick man's evacuation. How futile was the hatred he saw on faces then! "You haven't a heart!" a woman told him on one occasion. She was wrong; he had one. It saw him through his twenty-hour day, when he hourly watched men dying who were meant to live.*

(Albert Camus, *The Plague*, 1947)

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