The Cytomegalovirus Group

- Cytomegaloviruses – CMV
- Produce giant cells with nuclear and cytoplasmic inclusions
- Transmitted in saliva, respiratory mucus, breastmilk, urine, semen, cervical secretions
- Commonly latent in various tissues
- Most infections are asymptomatic.
- 3 groups develop a more virulent form of disease: fetuses, newborns, immunodeficient adults.

Cytomegalovirus

- Newborns may exhibit enlarged liver and spleen, jaundice, capillary bleeding microcephaly, and ocular inflammation; may be fatal.
  - Babies who survive develop neurological sequelae, hearing, visual disturbances and mental retardation.
- Perinatal CMV infection – mostly asymptomatic, or pneumonitis, and a mononucleosis-like syndrome
- AIDS patients – CMV mononucleosis, disseminated CMV, retinitis,
- Transplant patients - pneumonitis, hepatitis, myocarditis, meningoencephalitis
- Treatment reserved for immunocompromised - ganciclovir, foscarnet

Epstein-Barr Virus (EBV)

- Ubiquitous virus; infects lymphoid tissue and salivary glands
- Transmission – direct, oral contact and contamination with saliva
- In industrialized countries, college-age population is vulnerable to infectious mononucleosis (mono or kissing disease).
- By mid-life, 90-95% of all people are infected.
- Infectious mononucleosis – sore throat, high fever, cervical lymphadenopathy; develop after 30-50 day incubation
- Dormancy in B cells; reactivated; may be asymptomatic

Tumors and Other Complications Associated with EBV

- Burkitt lymphoma – B cell malignancy; usually develops in jaw and grossly swells the cheek; central African children 4-8 years old; may be associated with chronic coinfections with malaria, etc.
- Nasopharyngeal carcinoma – malignancy of epithelial cells; occurs in older Chinese and African men
- Anyone with an immune deficiency is highly susceptible to EBV.

Diagnosis, Treatment and Prevention

- Differential blood count shows lymphocytosis, neutropenia, and large atypical lymphocytes; serological assays to detect antibodies and antigen.
- Treatment directed at relief of symptoms of fever and sore throat
- Disseminated disease may be treated with IV gamma globulin, interferon, acyclovir, and monoclonal antibodies.

Other Herpesviruses and the Cancer Connection

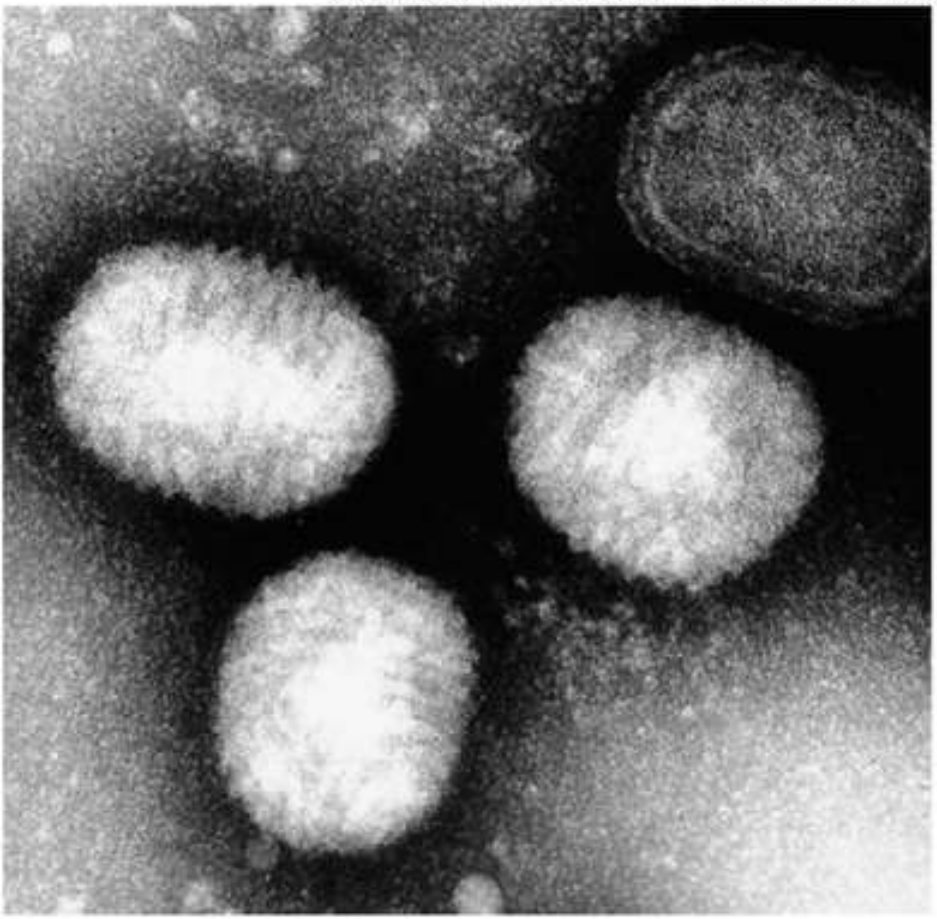
- Human herpes virus 6 (HHV-6)-human T-lymphotropic virus
- Transmitted by close contact with saliva and other secretions; very common
- Causes roseola, an acute febrile disease in babies 2-12 months; begins with fever, followed by a faint maculopapular rash; usually self-limited
- Adults may get mono-like symptoms, lymphadenopathy and hepatitis
- Over 70% of MS patients show signs of infection.
- Can cause encephalitis, cancer–Hodgkin lymphoma, oral carcinoma, certain T-cell leukemias

- HHV-7 is closely related to HHV-6 and causes similar diseases.
- Kaposi's sarcoma-associated virus or HHV-8 is linked with common tumor of AIDS patients; also may be involved in multiple myeloma.

The Viral Agents of Hepatitis

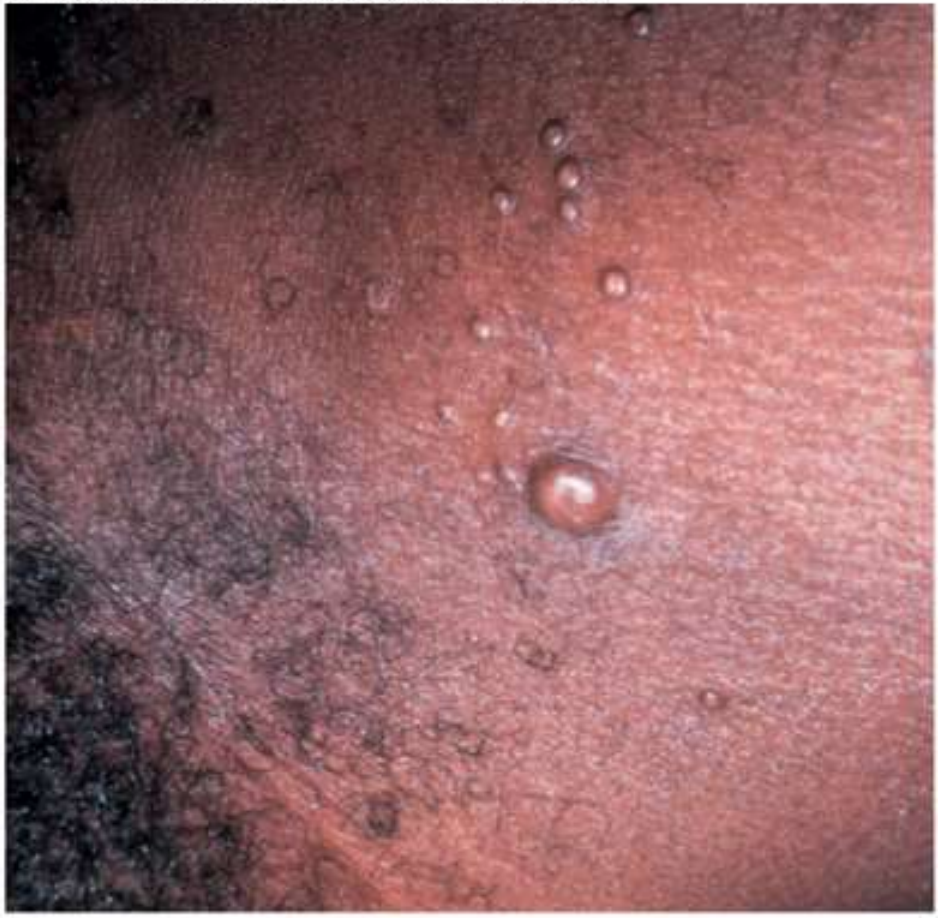
- Hepatitis – an inflammatory disease of liver cells that may result from several viruses
- Interferes with liver's excretion of bile pigments, bilirubin accumulates in blood and tissues causing jaundice, a yellow tinge in skin and eyes
- 3 principal viruses involved in hepatitis:

hepatitis B, hepatitis A (RNA virus), hepatitis C – (RNA virus)



(a)

© Kathy Park Talaro



(b)

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Hepadnaviruses

- Enveloped DNA viruses
- Never been grown in tissue culture
- Unusual genome containing both double and single stranded DNA
- Tropism for liver
- Hepatitis B virus causes hepatitis and can be a factor in liver cancer.
- Other members cause hepatitis in woodchucks, ground squirrels, and Peking ducks.

Hepatitis B Virus and Disease

- Multiplies exclusively in the liver, which continuously seeds blood with viruses - chronic
- 10^7 virions/mL blood
- Minute amounts of blood, blood products can transmit infection; sexually transmitted
- High incidence among homosexuals and drug addicts
- Can become a chronic infection
- Increases risk of liver cancer – hepatocellular carcinoma

Pathogenesis of Hepatitis B Virus

- Virus enters through break in skin or mucous membrane or by injection into bloodstream.
- Reaches liver cells, multiplies and releases viruses into blood; average 7 week incubation
- Most exhibit few overt symptoms and eventually develop HBV immunity.
- Some experience malaise, fever, chills, anorexia, abdominal discomfort and diarrhea.
- Fever, jaundice, rash, and arthritis are common.
- Small number of patients develop chronic liver disease – necrosis and cirrhosis.

Diagnosis and Management of Hepatitis B

- Diagnosis based on examination of risk factors, serological tests to detect viral antibodies or antigen; radioimmunoassay and ELISA tests for surface antigens
- Screening of blood for transfusion, semen for sperm banks, organs for transplant, and routine prenatal testing of all pregnant women
- Mild cases managed by treatment of symptoms and supportive care; chronic infections treated with interferon

- Passive immunization with HBIG for persons exposed, or possibly exposed, including neonates born to infected mothers
- Primary prevention is vaccination for high risk individuals and encouraged for all newborns and infants.

vaccines derived from surface antigen from – cloned yeast – 3 doses with boosters

vaccine derived from purified sterile antigen – extracted from carrier blood; mainly for people who have yeast allergies

The Adenoviruses

- Nonenveloped, ds DNA
- 30 types associated with human disease
- Infect lymphoid tissue, respiratory and intestinal epithelia and conjunctiva
- Oncogenic in animals, not in humans
- Spread by respiratory and ocular secretions
- Causes colds, pharyngitis, conjunctivitis, keratoconjunctivitis, acute hemorrhagic cystitis
- Severe cases treated with interferon
- Inactivated polyvalent vaccine

Papilloma and Polyoma Viruses

- Small, nonenveloped dsDNA
- Circular DNA
- Cause persistent infections and tumors

Human Papillomavirus

- Papilloma – benign, squamous epithelial growth, wart or verruca
- Caused by 100 different strains of HPV
- Common seed warts – painless, elevated, rough growth; on fingers, etc.
- Plantar warts – deep, painful; on soles of feet
- Genital warts – most common STD in U.S.; morphology ranges from tiny, flat, inconspicuous bumps to extensive, branching, cauliflower-like masses
- Transmissible through direct contact or contaminated fomites; incubation – 2 weeks to more than a year

- Nine HPV types increase risk for developing reproductive cancer; 2 account for 70% of metastatic tumors.
- Early detection through inspection of genitals, women Pap smear to screen for abnormal cervical cells
- Most common warts regress over time; they can be removed by direct chemical application of podophyllin and physical removal by cauterization, freezing, or laser surgery.
- Warts can recur.
- Two vaccines scheduled to be released in 2007

Polyomaviruses

- Induce tumors in experimental animals
- JC and BK viruses most important human polyomas
- Common throughout the world
- Majority of infections are asymptomatic or mild
- Not much is known.
- BK infection in renal transplants causes complications in urinary function.
- Progressive multifocal leukoencephalopathy (PML) is an uncommon fatal infection by JC.

Parvoviruses

- Nonenveloped icosahedral, ssDNA
- Small diameter and genome size
- Causes distemper in cats, enteric disease in dogs, fatal cardiac infection in puppies
- B19 cause of erythema infectiosum (fifth disease); rash of childhood
  - Children may have fever and rash on cheeks.
  - Severe fatal anemia can result if pregnant woman transmits virus to fetus.
- Adeno-associated virus (AAV) is a defective virus; it cannot replicate in host cell without adenovirus.

INFLUENZA A VIRUS H1N1 (Swine – Origin Influenza Virus)

Previous Influenza Pandemics

- During 20th century, three influenza pandemics occurred .

Table 1: Antigenic Shifts and Pandemics*

	Designation	Resulting Pandemic	Death Toll
1889	H3N2	Moderate	?
1918	H1N1 ("Spanish")	Devastating	50–100 million
1957	H2N2 ("Asian")	Moderate	1 million
1968	H3N2 ("Hong Kong")	Mild	1 million
?			

* H = haemagglutinin; N = neuraminidase

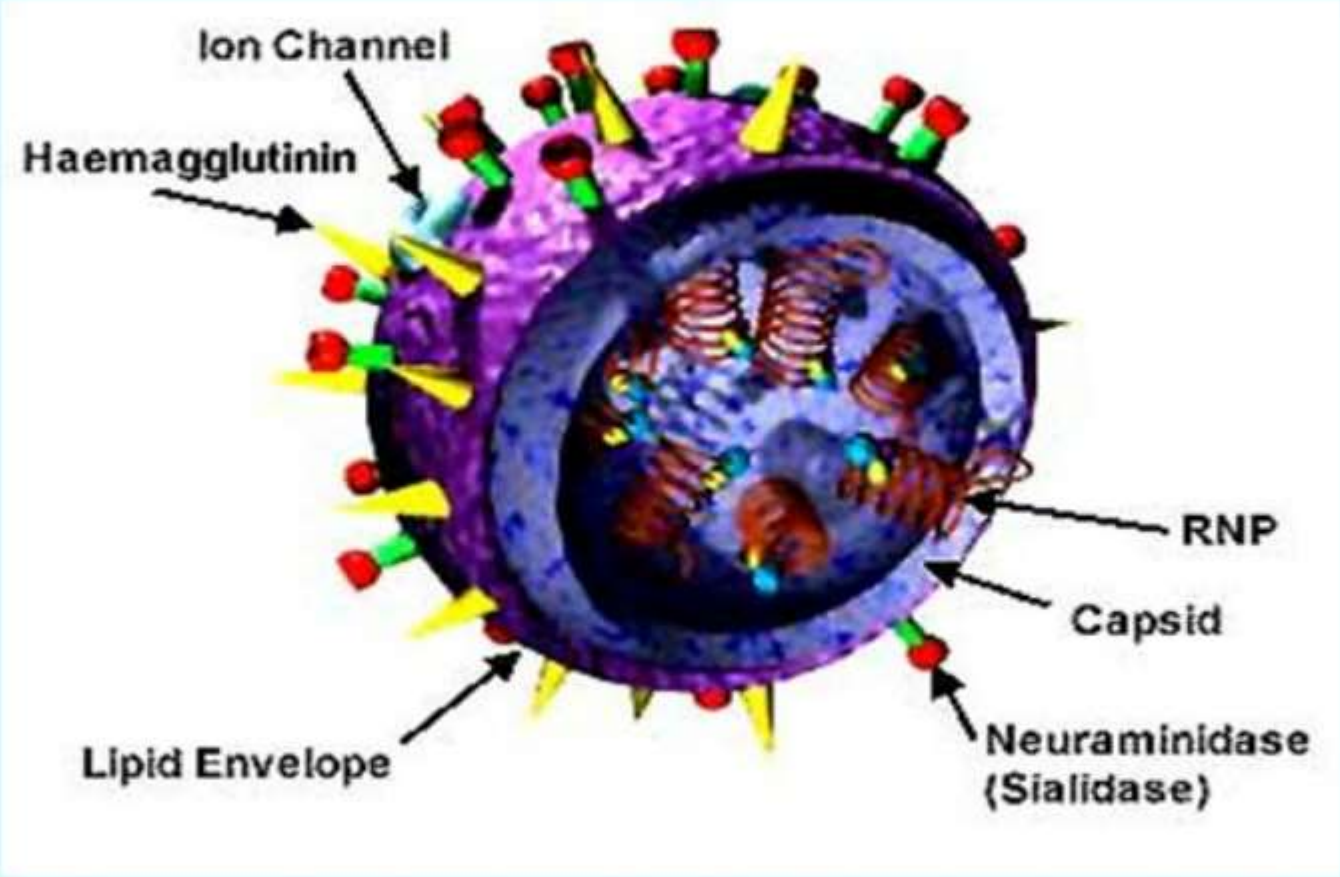
The 1918 Influenza Pandemic

Figure 3. Emergency hospital during influenza epidemic, Camp Funston, Kansas. Images from the 1918 Influenza Epidemic. Image copyright by National Museum of Health & Medicine, Washington, D.C. http://InfluenzaReport.com/link.php?id=19

Microbiology

- Influenza viruses belong to Orthomyxoviridae family.
- Influenza viruses : enveloped,8 single-stranded RNA.
- Divided into 3 genera : A ,B, C
  - Influenza C rarely causes disease in man
  - Both A & B can cause “severe human disease”
  - Remarkably, Influenza A with its continuing mutation can stay below human immunity radar.

Antigens : H & N (Surface glycoproteins)



cont

- H: Hemagglutinin, Subtypes : H1 – H16
  - Major antigen
  - Neutralize antibodies
  - Bind virus to host cell receptors

- N: Neuraminidase, Subtypes: N1 –N9
  - Release the progeny virions from the host cell surface

"Antigenic drift": small changes in antigenicity of Influenza A viruses:recurrent influenza epidemics

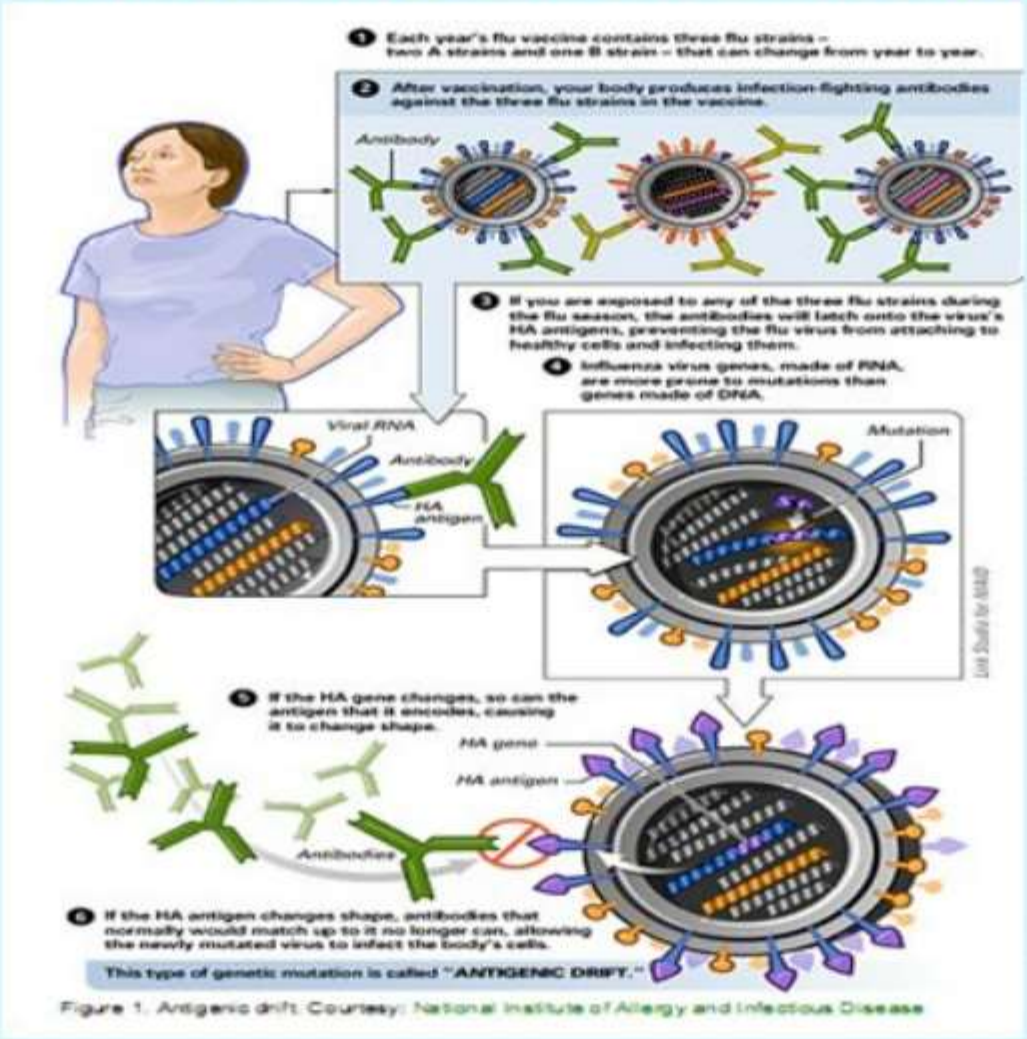


Figure 1. Antigenic drift Courtesy: National Institute of Allergy and Infectious Disease

"Antigenic shift": major changes in antigenicity of Influenza A viruses : recurrent pandemics

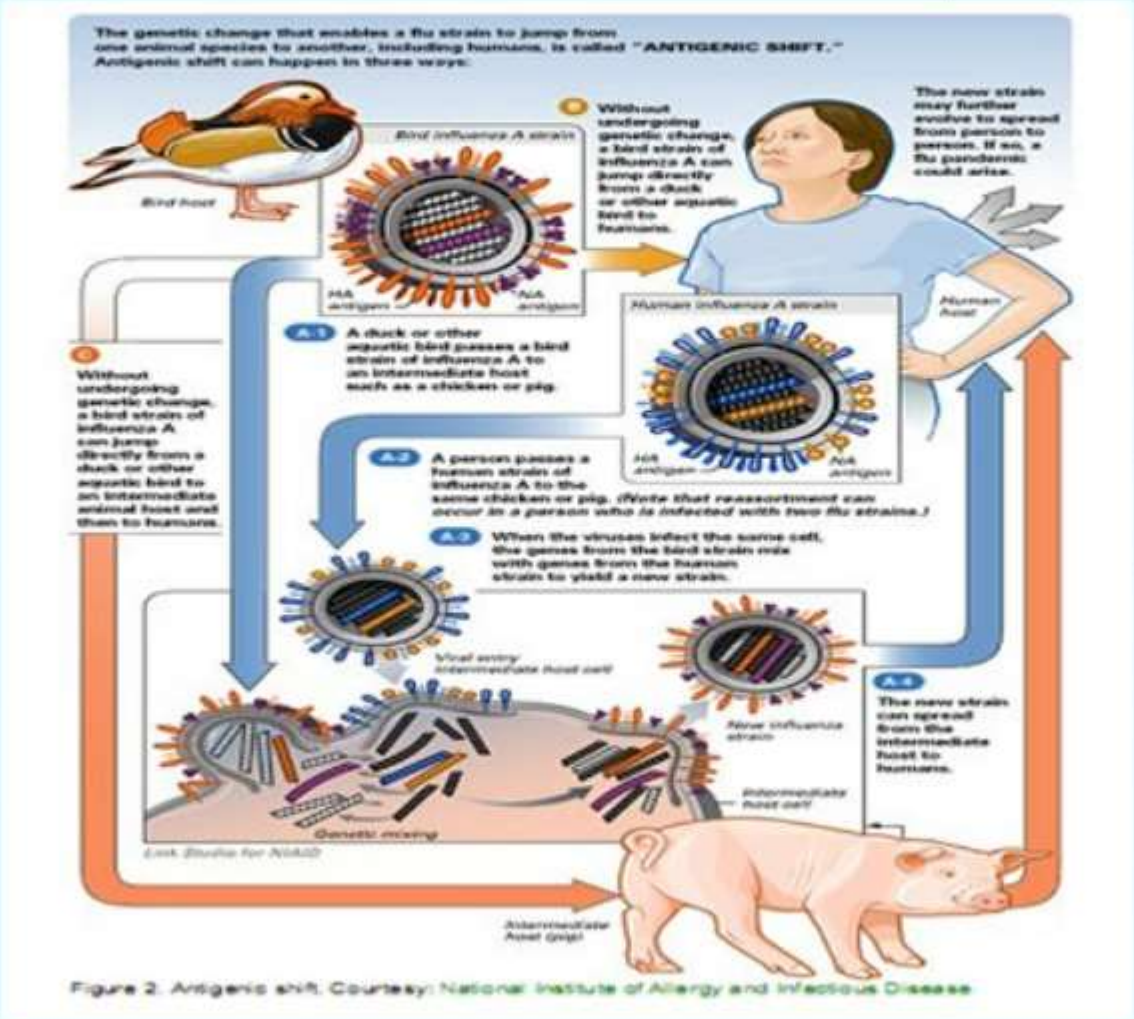
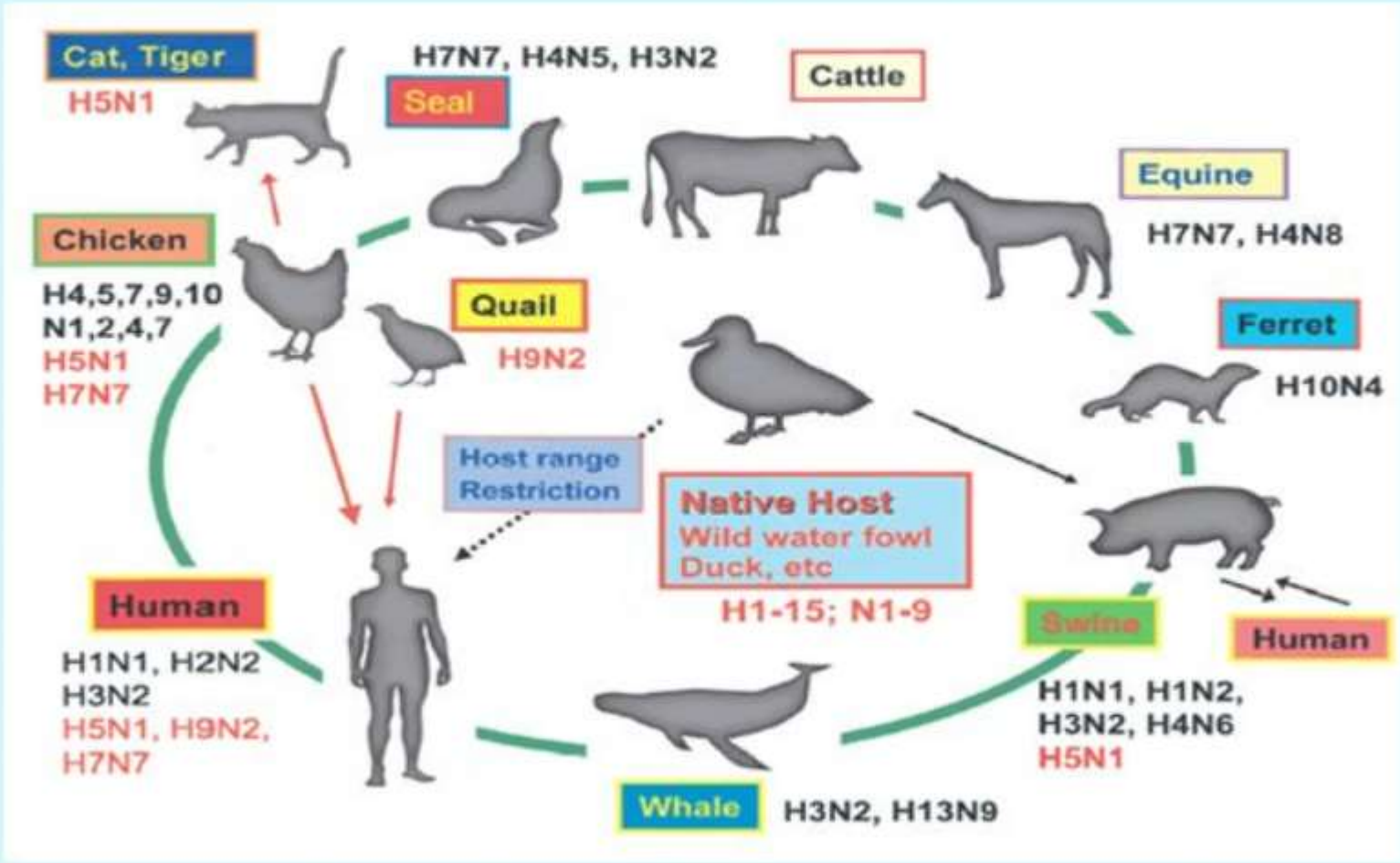


Figure 2. Antigenic shift. Courtesy: National Institute of Allergy and Infectious Disease

Natural reservoirs: a large variety of species



Swine-origin influenza viruses

- Most commonly , H1N1 subtype
- Other subtypes are also circulating in pigs: H1N2,H3N1,H3N2.
- Pigs can also infected with avian (bird) influenza viruses or human seasonal influenza viruses .
- At once, Pigs can be infected with >= 1 types of influenza virus ➡ an influenza virus can contain a number of sources called "Reassortant Virus"

➡ Currently circulating Influenza Virus A H1N1, which has 6 RNA from "Swine flu" + 1 RNA from "Bird flu" + 1 RNA from "Human flu".

Pathogenesis

- Incubation period: is unknown, maybe range from 1-7 days , more likely 1-4 days.
- Infectious period: is not clearly known , current available data show that the duration of shedding with H1N1 is from the day prior to illness onset until resolution of symptoms .
- Children ,esp younger children might be contagious for long periods.

Transmission of Influenza A virus H1N1

- Being studied, current available data show that the transmission of this virus is similar to other influenza virus.
  - Respiratory droplets (when coughing or sneezing, short distance : < 1 metre)
  - Indirect contact with respiratory secrete or other bodily fluids (diarrhea stool), eg touching contaminated surfaces then touching eyes, noses, mouths.

Clinical findings

- Be similar to human seasonal influenza.
- Clinical presentation may range from asymptomatic infection to severe pneumonia → resulting in death.
- Typically, patients present :
  - Abrupt onset of high fever, fatigue, paroxysmal cough, headache, myalgia .
  - Upper respiratory tract symptoms : sore throat, running nose, cough + burning watery eye ,ear ache, hoarseness.

Young children & Influenza A virus H1N1

- Children younger than 5 years old have high risks of influenza-related complications.
- Young children are less likely to have typical influenza symptoms .They may not have respiratory symptoms or signs (eg cough, fever).
- Infants with Influenza A are usually referred to physicians with " fever and lethargy" .

cont

- Symptoms of severe influenza in children include:
  - Tachypnea
  - Dyspnea
  - Apnea
  - Cyanosis
  - Altered mental status
  - Extreme irritability
  - Dehydration

Complications

- So far, there have been insufficient information about this Influenza A virus H1N1. However, clinicians expect complications to be similar to seasonal human influenza:
  - Exacerbation of underlying chronic disease
  - Upper respiratory tract diseases (otitis media, croup)
  - Lower respiratory tract diseases (pneumonia, status asthmaticus)
  - Secondary bacterial pneumonia
  - Cardiac (myocarditis, pericarditis)
  - Muscle (myositis, rhabdomyolysis)
  - Neurologic (encephalitis, status epilepticus)
  - Toxic shock syndrome

Laboratory/Diagnostic tests (WHO, 27 april 2009 Guidance)

- Real-time RT-PCR: time for results : 1-2days

(Influenza A virus H1N1 PCR Testing kit)

- Viral culture : time for results: 5-10 days
  - Be considered as diagnostic test
  - However , viral culture is not timely enough to impact patient care
- Besides , there are other tests such as “rapid antigen test”, “ immunofluoresence” .But they are not recommended by WHO due to low sensitivity and false negative results.

CDC Guidance on specimen collection 29- april, 2009

- Obtaining upper respiratory specimen to test for Influenza A virus H1N1:
  - Nasopharyngeal swab/aspirate
  - Nasal wash/aspirate
  - If the above are impossible, a combination of nasal swabs with oropharyngeal swabs is acceptable.
  - With incubated patients, collect endotracheal aspirate
- Then specimen is immediately placed on ice / cold pack at 4° c (refrigerator) for transport to laboratory.

Case definitions for infection with Influenza A virus H1N1,CDC guidance

- Close contact : within 6 feet (about 2 metres) of an ill person who is confirmed or suspected case of Influenza A virus H1N1 during the case's infectious period.
- Acute febrile respiratory illness : fever > 38 ° c with the spectrum of disease from influenza-like illness to pneumonia.

cont

- A suspected case : is defined as a person with an acute febrile respiratory illness with onset of:
  - Within 7 days of close contact with confirmed case person.
  - Within 7 days of travelling to community either within USA or internationally where there are confirmed cases .
  - Reside in community where there are one or more confirmed cases.

cont

- A confirmed case: is defined as a person with an acute febrile respiratory illness + Laboratory confirmation for Influenza A virus H1N1 by one or more the following tests:
  - Real-time RT-PCR
  - Viral culture
- A probable case : is defined as a person with an acute febrile respiratory illness and :
  - Positive for influenza A by "Rapid antigen test" or "Immunofluorescence" + meet criteria for a suspected case .
  - Positive for influenza A, but negative for H1,H3 by RT-PCR method

Antivirals approved by FDA for the prevention or treatment of Influenza

- Active at the M2 transmembrane Ion channel sites :
  - Amantadine
  - Rimantadine
- Neuraminidase inhibitors:
  - Oseltamivir (Tamiflu)
  - Zanamivir (Relenza)

CDC & WHO recommendations for antivirals against Inluenza A virus H1N1

- Influenza A virus H1N1 (S-OIV) :
  - Sensitive to: Oseltamivir (Tamiflu) ,Zanamivir (Relenza)
  - But, resistant to: amantadine ,remantadine
- Antiviral agents are used as treatment and chemoprophylaxis in cases of:
  - Confirmed case
  - Suspected case
  - Close contact
- Antivirals should be started within 48 hours of illness onset.
- Recommended duration of treatment is 5 days
  However ,Vietnamese health care Ministry : 7 day duration
- With pregnant women : Antivirals belong to "Pregnancy category C" , Used only when the potential benefitsjustifies the potential risk to the fetus.

Antiviral chemoprophylaxis is recommended for following individuals:

- Household close contacts with a confirmed or suspected case.
- School children who had close contact (face to face) with a confirmed or suspected case.
- Travelers to Mexico who are at high risk for influenza complications (eg Elderly,Person with chronic medical conditions).
- Health care /Public health workers who had unprotected close contact with an ill confirmed case during case's infectious period.

Recommended doses of Oseltamivir and Zanamivir for treatment and prevention

Table 1. Swine-origin influenza antiviral medication dosing recommendations.

(Table extracted from IDSA guidelines for seasonal influenza (http://www.journals.uchicago.edu/doi/full/10.1086/598513) (#linkPolicy).)

Agent, group		Treatment	Chemoprophylaxis
Oseltamivir			
Adults		75-mg capsule twice per day for 5 days	75-mg capsule once per day
Children (age, 12 months or older), weight:	15 kg or less	60 mg per day divided into 2 doses	30 mg once per day
	15–23 kg	90 mg per day divided into 2 doses	45 mg once per day
	24–40 kg	120 mg per day divided into 2 doses	60 mg once per day
	>40 kg	150 mg per day divided into 2 doses	75 mg once per day
Zanamivir			
Adults		Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children		Two 5-mg inhalations (10 mg total) twice per day (age, 7 years or older)	Two 5-mg inhalations (10 mg total) once per day (age, 5 years or older)

With children less than 1 year of age : Treatment dose of antiviral agents (CDC)

Because infants typically have high rates of morbidity and mortality from influenza, infants with swine-origin influenza A (H1N1) infections may benefit from treatment using oseltamivir.

Table 2. Dosing recommendations for antiviral treatment of children younger than 1 year using oseltamivir.

Age	Recommended treatment dose for 5 days
<3 months	12 mg twice daily
3-5 months	20 mg twice daily
6-11 months	25 mg twice daily

With children less than 1 year of age : Prophylaxis dose of antiviral agents (CDC,29-april)

Table 3. Dosing recommendations for antiviral chemoprophylaxis of children younger than 1 year using oseltamivir.

Age	Recommended prophylaxis dose for 10 days
<3 months	Not recommended unless situation judged critical due to limited data on use in this age group
3-5 months	20 mg once daily
6-11 months	25 mg once daily

Medications for supportive therapy

- Fever-reducing agents: Acetaminophen, NSAIDs (Ibuprofen, Naproxen) . Avoiding using Aspirin to children or teenagers who have flu due to Reye's syndrome.
- With secondary bacterial infection /flu patients : Antibiotics
- Dehydration : rest and take plenty of fluids ,rehydration therapy when it's necessary.

CDC guidance: Steps to reduce the spread of Flu at home with influenza patients

- Keep the patient away from other people as much as possible.
- Remind the patient of covering his coughs or sneezings and cleaning his hands with soap and alcohol-based hand rub often .
- Also, other members in the household need to clean hands often with soap or alcohol-based rub .
- Consult with the medical staff if person in family with Influenza patient who have chronic health conditions should have antiviral medication (Tamiflu ,Relenza) to prevent the flu.

VIRAL HAEMORRAGHIC FEVERS

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

Viral Hemorrhagic Fever viruses

- Filoviruses
  - Hemorrhagic fever (EHF) Ebola
  - Marburg virus
- Arenaviruses
  - Lassa fever
  - "New World Arenaviruses"
- Bunyaviruses
  - Rift Valley fever (RVF)
  - Crimean Congo Hemorrhagic fever (CCHF)

Differential Diagnosis

Febrile tropical illnesses: •

Malaria –

Typhoid fever –

Bacterial gastro-enteritis –

Rickettsial diseases –

Laboratory Diagnosis

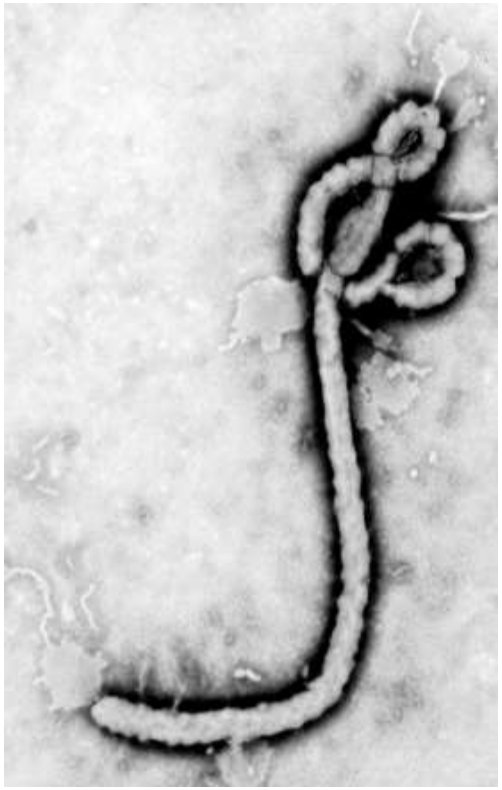
- Malaria smears
- Blood cultures (closed system)
- CBC, especially platelet count
- Transaminases (prognostic value)

VHF: Viruses

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

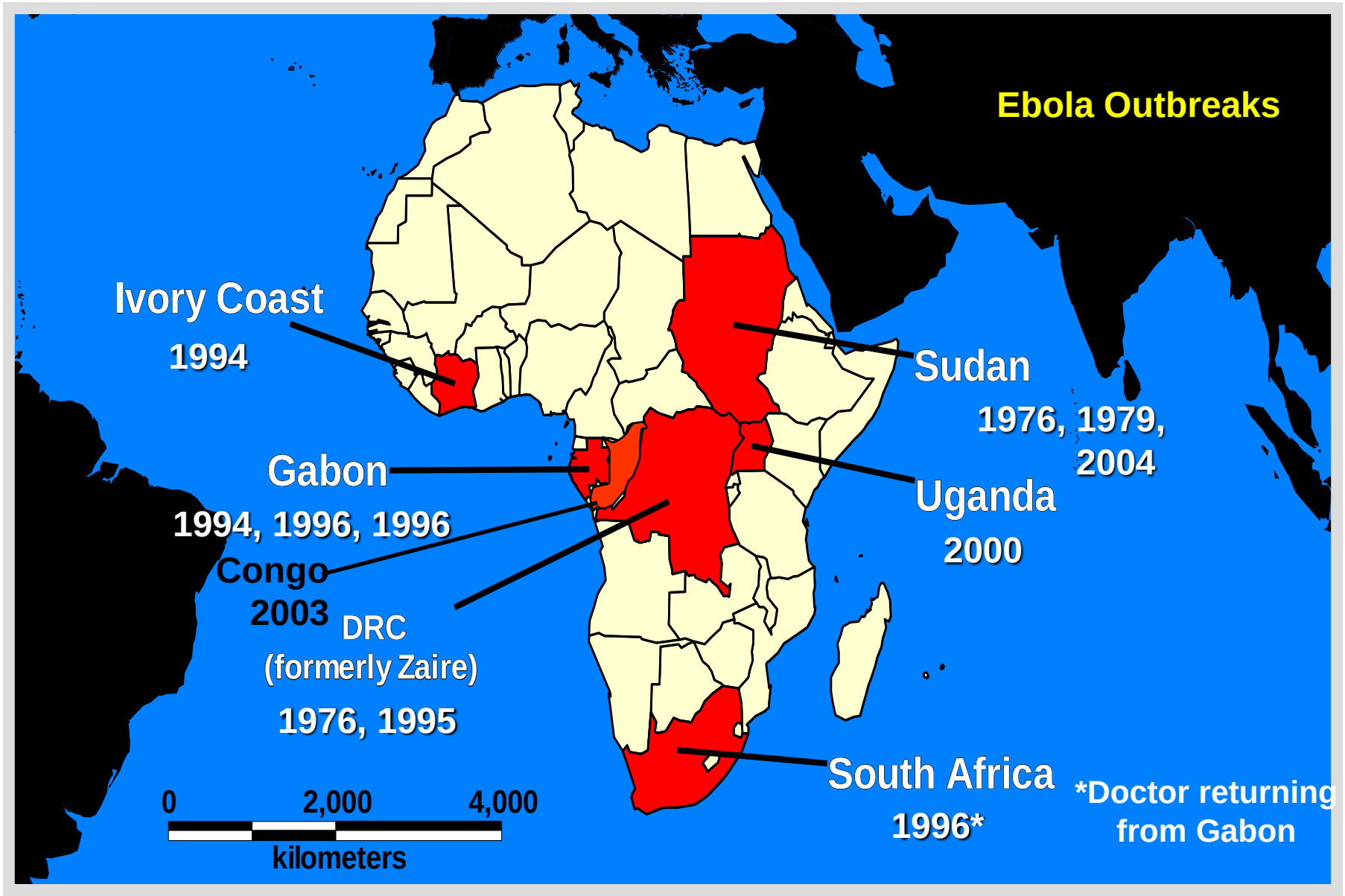
Filoviruses

- Ebola
- Zaire –
- Sudan –
- Marburg



Ebola

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


Ebola Outbreaks
Ivory Coast
1994
Gabon
1994, 1996, 1996
Congo
2003
DRC
(formerly Zaire)
1976, 1995
Sudan
1976, 1979,
2004
Uganda
2000
South Africa
1996*
*Doctor returning
from Gabon
0
2,000
4,000
kilometers

1995 Zaire

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

EHF Risk Factors

2º attack rate of 16%

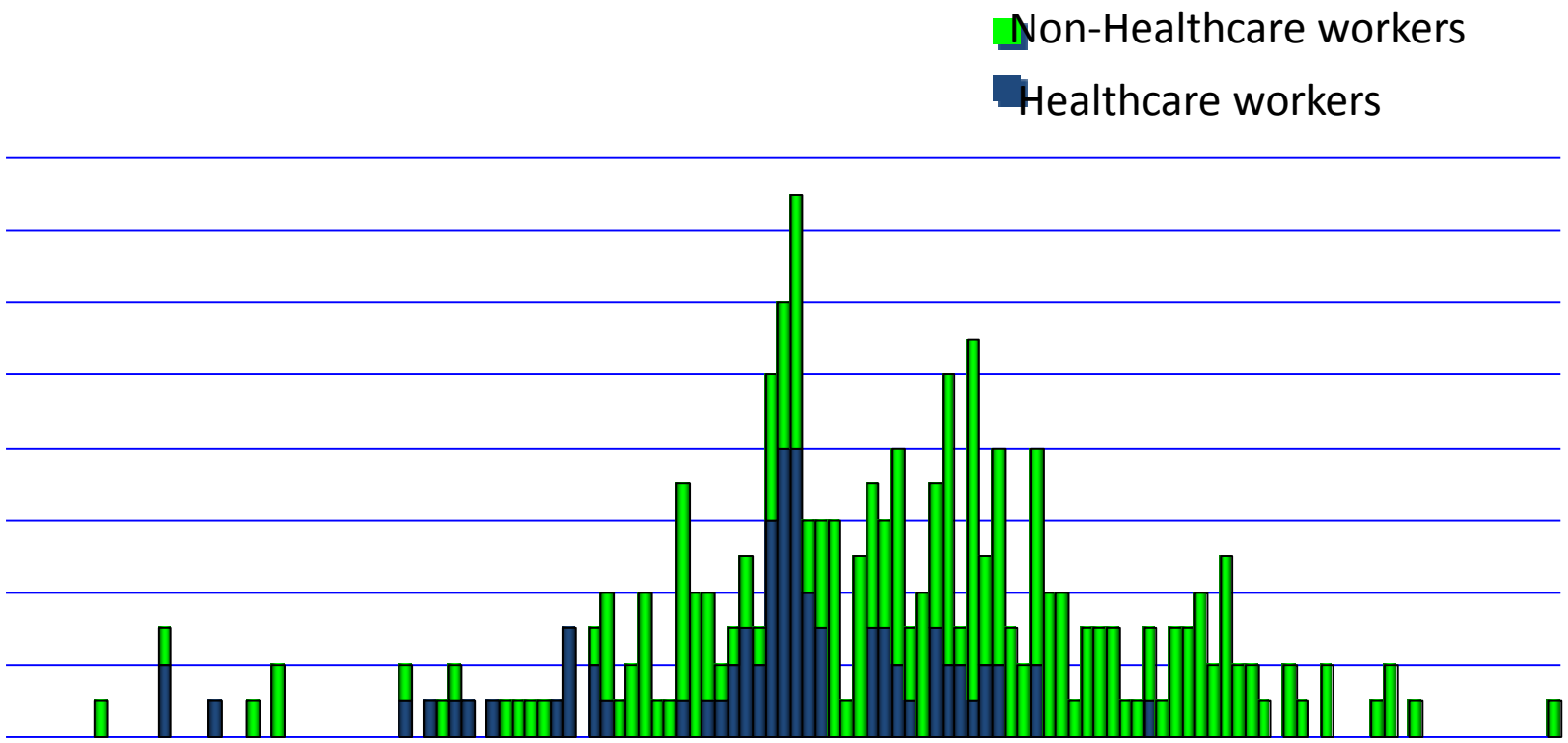
Direct physical contact •

OR = undefined, p<0.01

Body fluids •

OR = 3.8, 95%CI (1.9-6.8)

No contact = no disease •


Non-Healthcare workers
Healthcare workers

Marburg

1967 •

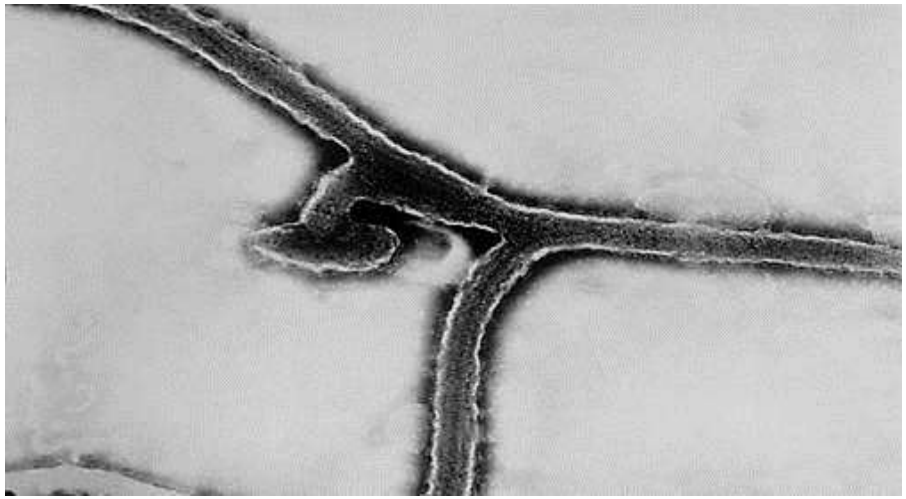
Marburg, Frankfurt, & Belgrade •

25 primary •

6 secondary •

7 deaths •

African green monkeys from Uganda •



1975 •

Australian traveller •

Zimbabwe •

1 primary •

2 secondary •

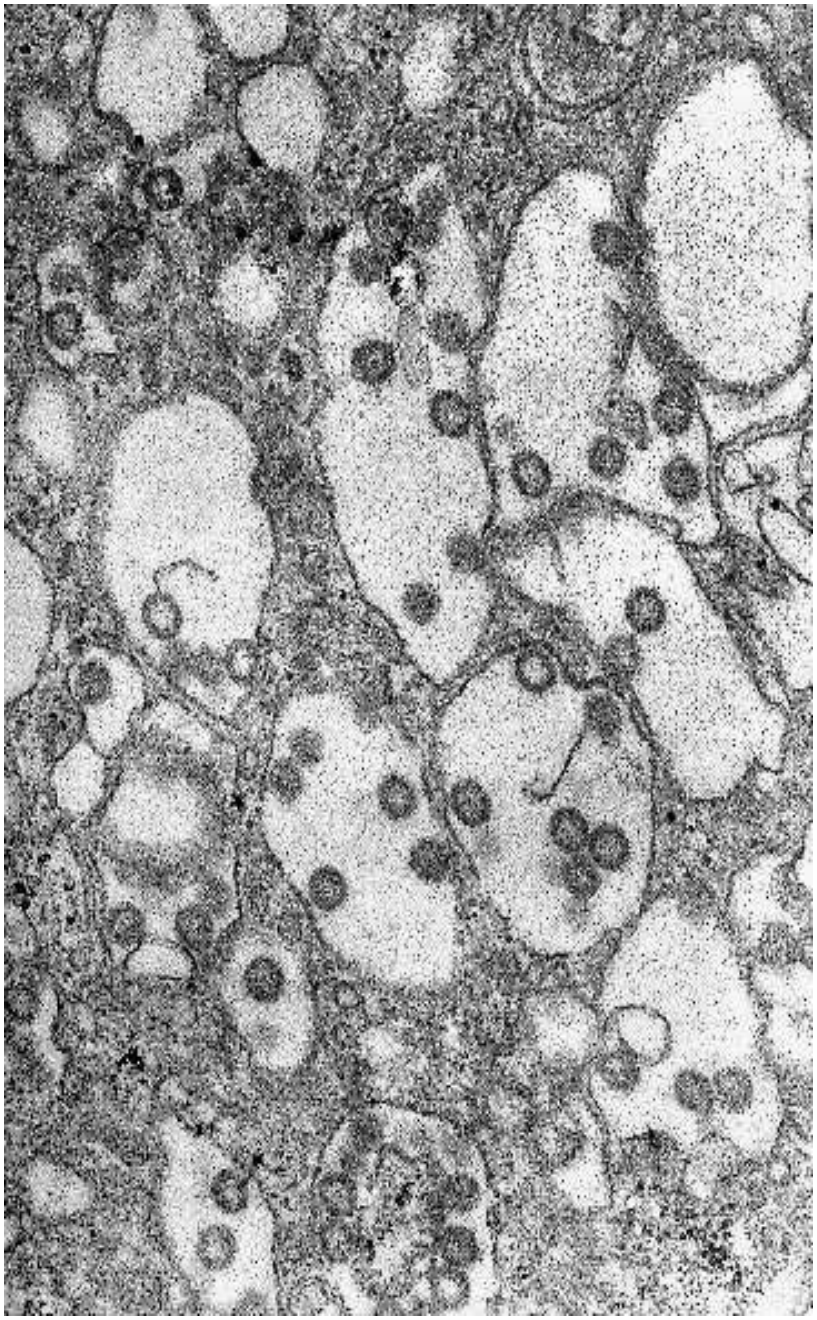
1 death •

Marburg

1980
- Engineer
- N.W. Kenya
- 1 primary
- 1 secondary
- 1 death

1987
- Danish traveller
- W. Kenya
- 1 primary
- 1 death

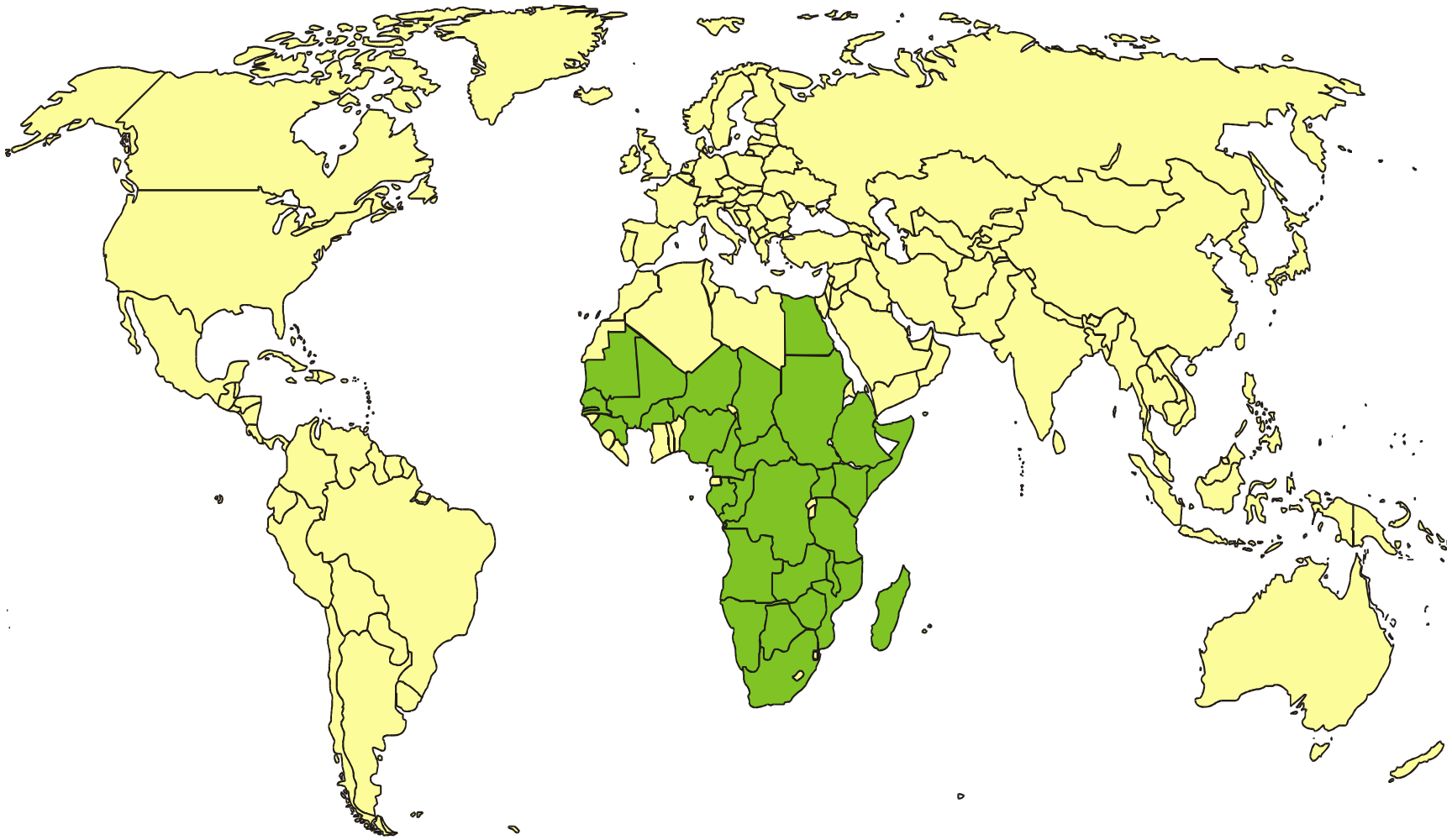
1998-200
- Gold mine
- N.E. DRC
- 76 cases
- 52 deaths
- >150 cases through follow-up



Bunyaviruses

- Rift Valley fever
- Crimean Congo hemorrhagic fever

Distribution of Rift Valley Fever (RVF) Virus



Rift Valley Fever

- Disease of sheep and cattle
- Humans: Asymptomatic-to-mild
- Rare VHF, encephalitis, retinitis

Rift Valley Fever

Mosquito-borne (*Aedes* spp.) •

vertical transmission in mosquitos

Transmission: •

Animal contact (birthing or blood) –

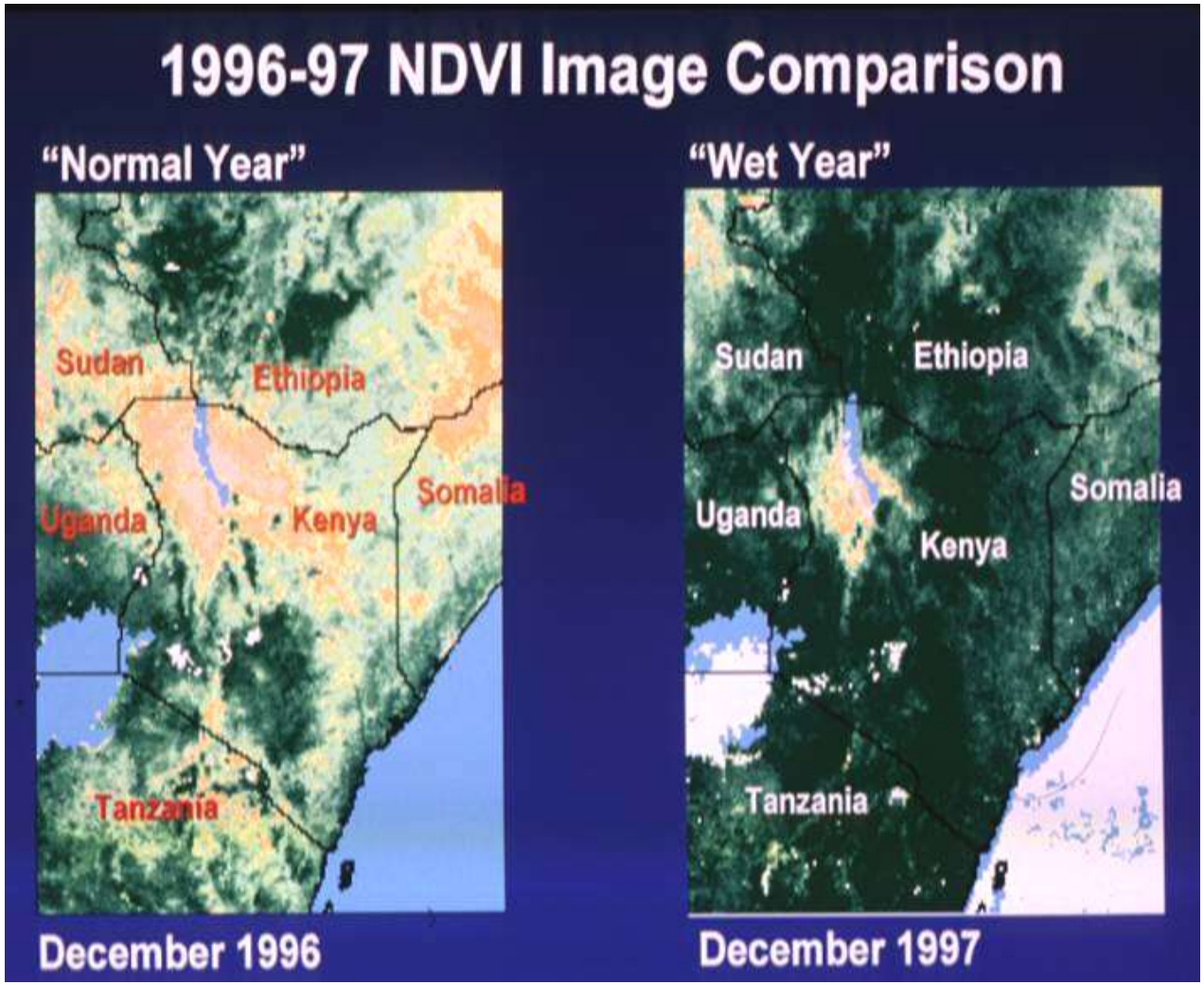
Laboratory aerosol –

Mortality 1% overall •

Ribavirin? Therapy: •

Live-attenuated vaccine (MP-12) undergoing trials •

1997-1998 East Africa Outbreak



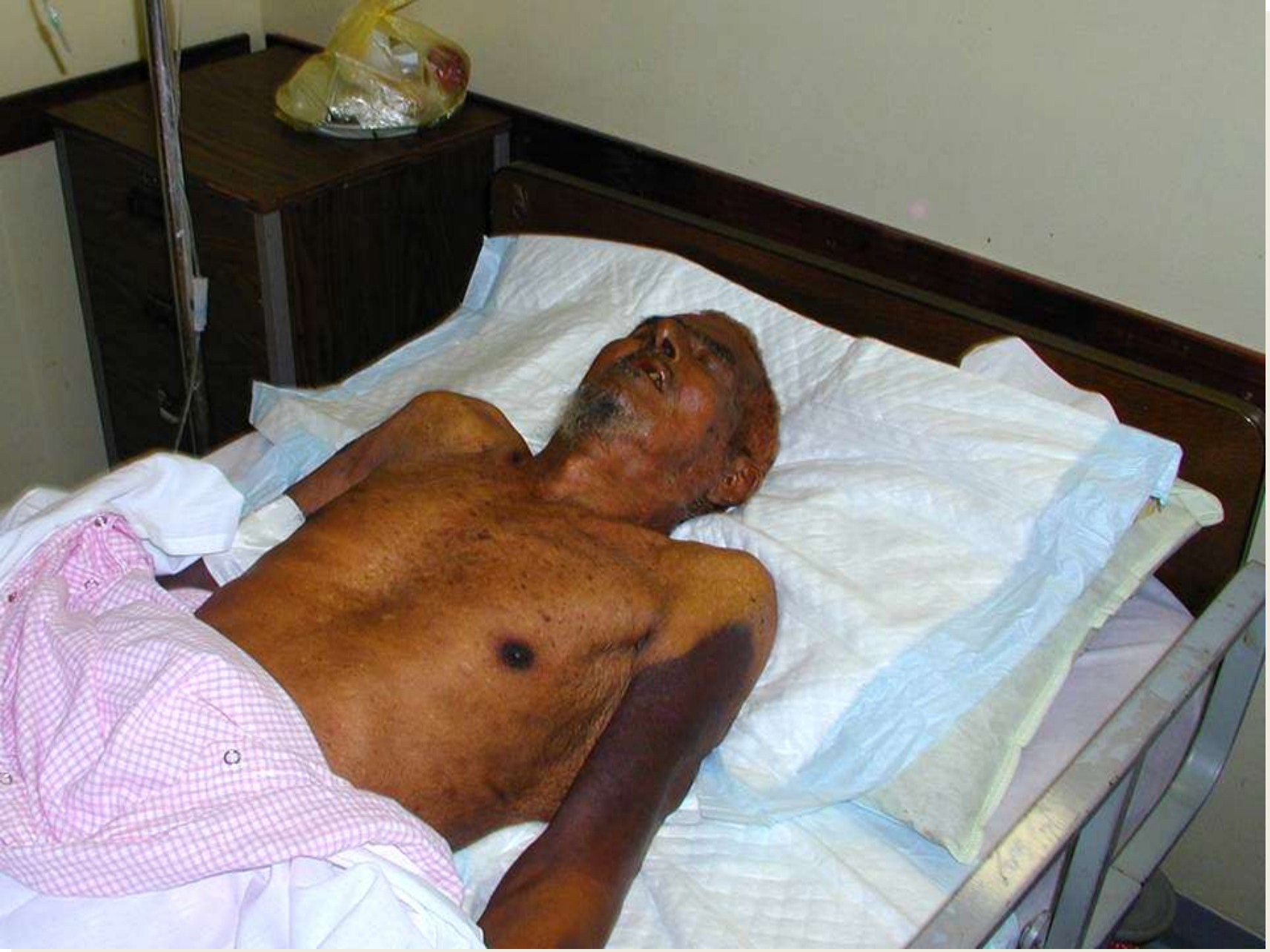
- 478 deaths
- 115 VHF deaths
- 9% IgM+
- ~89,000 cases
- 70% animal loss

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)



RVF: Encephalitis

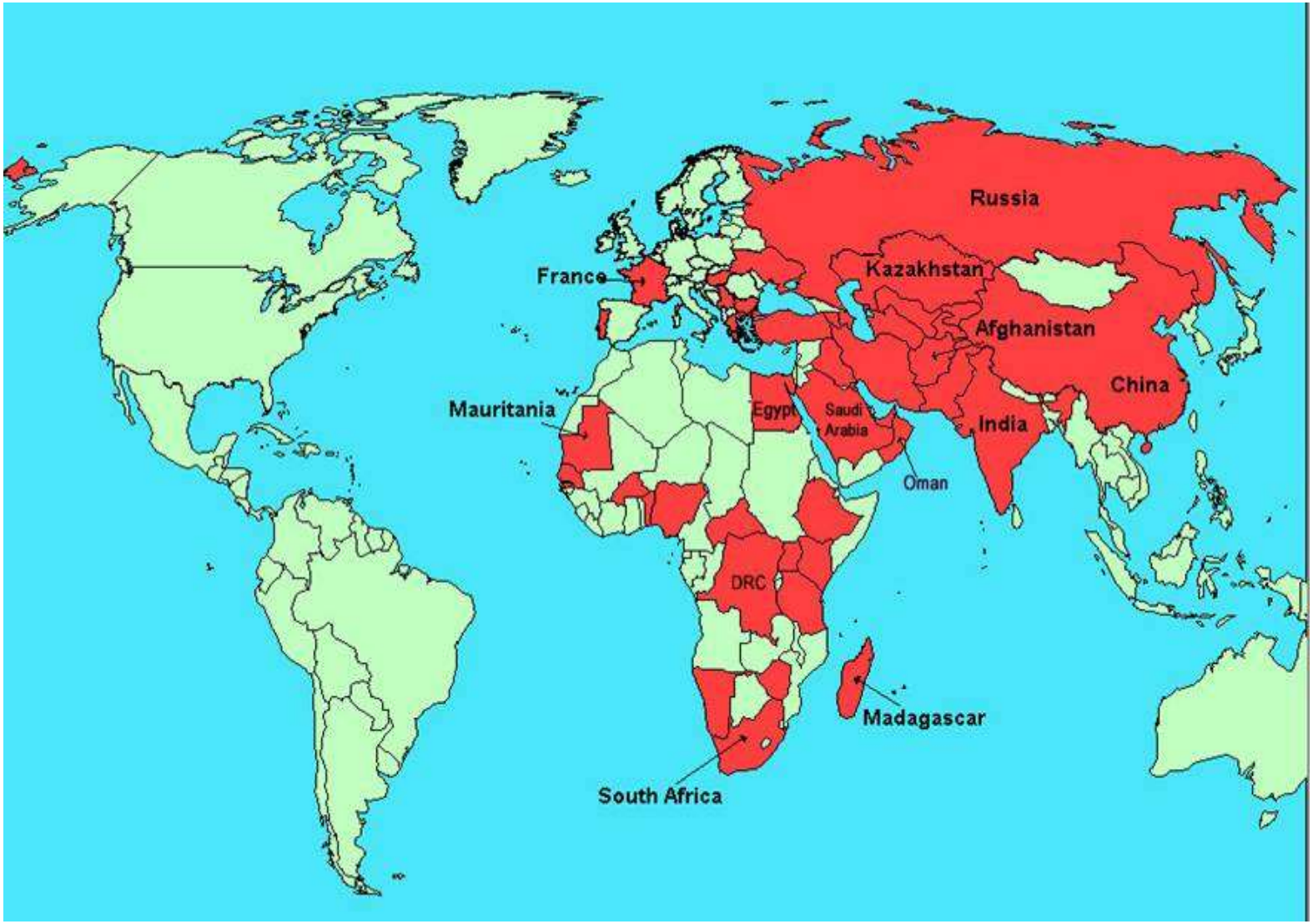
%*	
67	Meningeal signs
81	Confusion
78	Stupor or coma
11	Hypersalivation and teeth grinding
43	Hallucinations
5	Hemiparesis
27	Focal Signs
86	CSF pleocytosis
57	CSF protein > 40 mg%
11	Fatal outcome
7	Residua

* Percent of total from a series of 37 reported cases

CRIMEAN CONGO HEMORRHAGIC FEVER (CCHF)

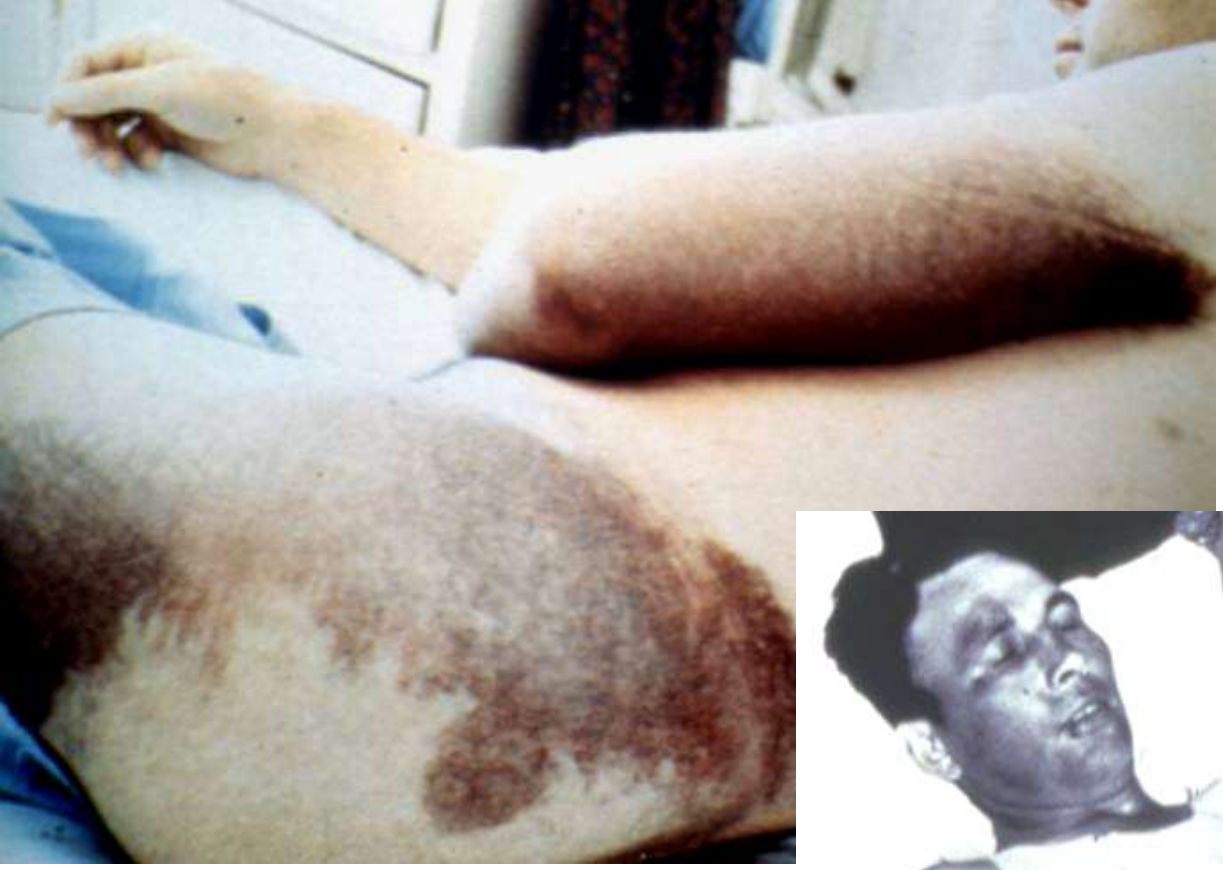
- Extensive geographic distribution (Africa, Balkans, and western Asia)
- Transmission:
  - Tick-borne (*Hyalomma* spp.)
  - Contact with animal blood or products
  - Person-to-person transmission by contact with infectious body fluids
  - Laboratory worker transmission – documented
- Mortality 15-40%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

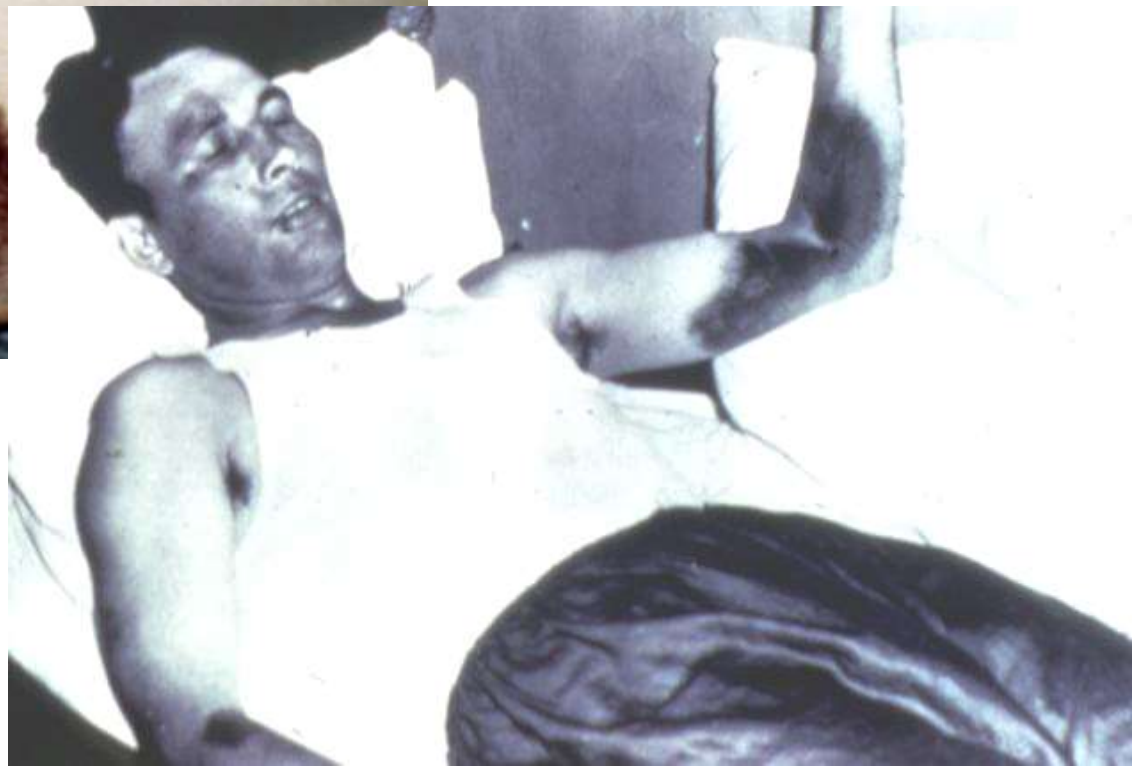
Distribution of CCHF virus



CCHF: Clinical features

- 4-12 day incubation after tick exposure
- 2-7day 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)





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.

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

CCHF: Slaughterhouses

- Sheep and cattle become viremic without disease
- Blood and fresh tissues infective by contact
- Possibility of establishing transmission of CCHF in holding pens by *Hyalomma* or other tick vectors