

The Clinical Spectrum of Herpesvirus Infections

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Objectives

- **Recognize the herpesviruses that cause disease in humans**
- **Understand the clinical presentations of herpesvirus infections**

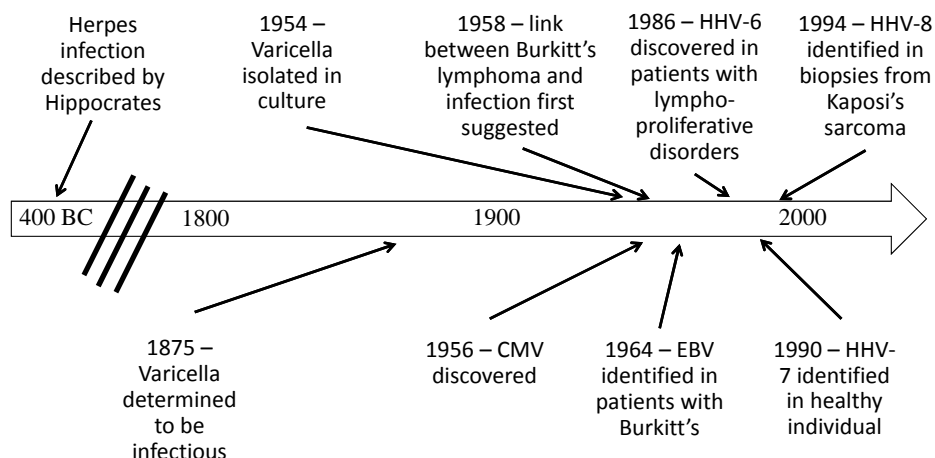
Herpesviruses overview

- > 100 known herpesvirus
 - 8 human herpesviruses
- Greek word *herpein* – "to creep or crawl"
 - referring to the latent, recurring nature
- All herpesviruses can establish latent infection within specific tissues, characteristic for each virus



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History of herpesviruses



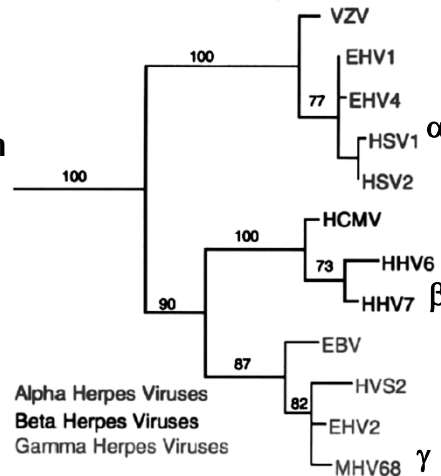
Herpesviridae Subfamilies

Alphaherpesvirinae (HSV-1, HSV-2, VZV)

- Broad host range
- Rapid reproductive cycle,
- Cytopathic effect and spread in culture
- Latent infections: Neuronal (sensory ganglia)

Betaherpesvirinae (HCMV, HHV-6,7)

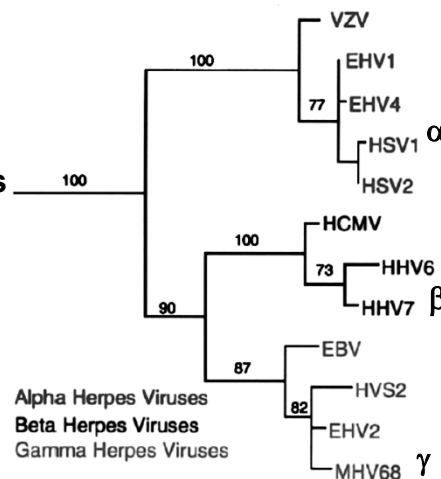
- Restricted host range
- Slow reproductive cycle
- Latent virus: Leukocytes (CD34+), Hematopoietic stem cells, and secretory glands (Salivary glands, and renal tubule).



Herpesviridae Subfamilies

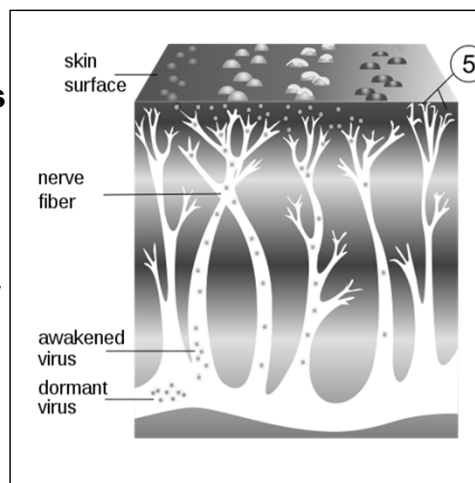
Gammaherpesvirinae (EBV, KHSV)

- Most Restricted Host Range
- Replicate in lymphoblastoid Cells
- Viruses specific for B or T cells
- Latent or lytic infection



Shared properties of human herpesviruses

- Code for unique enzymes involved in the biosynthesis of viral nucleic acids
- Synthesis and assembly of viral DNA is initiated in the nucleus
- Release of progeny virus from the is accompanied by cell death
- Establish latent infection within tissues



HHVs can cause severe and atypical disease in immunocompromised patients

Immunosuppression

- Medications
- HIV
- Cancer/ Transplant

Host Barrier defects (MUCOSITIS, Eczema, Burns)

Immune defects

- Neonates
- Pregnancy
- Elderly
- Cellular defects

Diagnosis of Herpesviruses

- Isolation virus through culture and/or detection of viral genes or gene products
- Direct visualization
- Serology
- Polymerase chain reaction



Case #1

- A 4 year old F presents to your office with a swollen, painful, right index finger. You notice multiple fluid-filled lesions on the finger, as well as some small ulcers on her tongue and bleeding around her gums. What's the diagnosis?



Image courtesy of
Dwight Powell

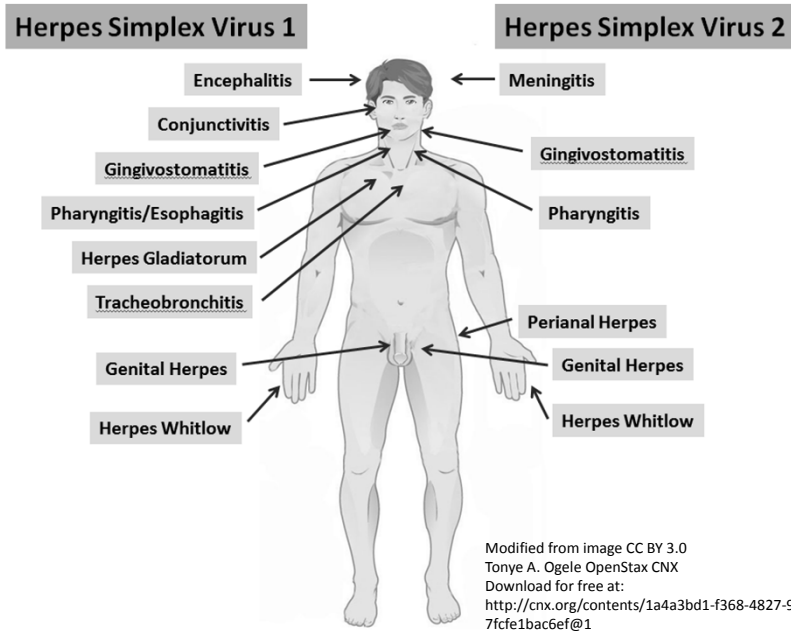
HSV - Pathogenesis

Primary infection: high titer and prolonged infection

Establish Latency: provide reservoir and viral template for future secondary infections

Secondary Reactivation: lower titer and shorter duration but there are some who have more prolonged disease

Clinical Manifestations of HSV



Diseases Caused by HSV: Oral & Cutaneous



Images courtesy of
Dwight Powell

HSV Gingivostomatitis in Immunocompromised

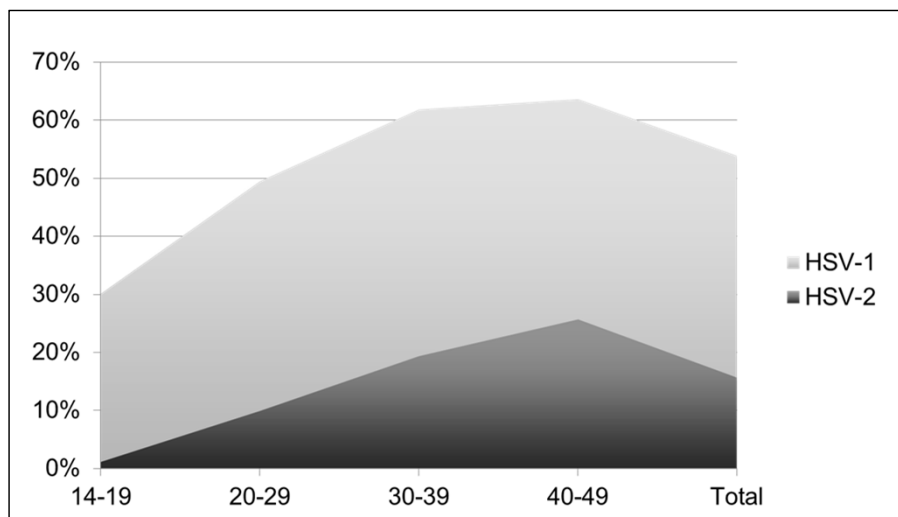


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The National Center for Immunization and Control



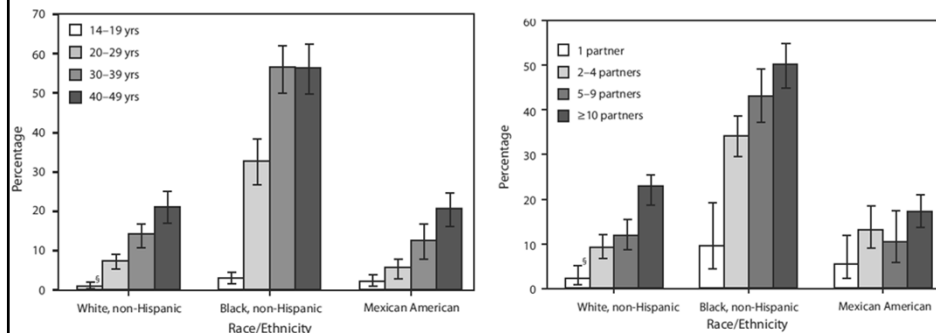
Images courtesy of
Dwight Powell

Percent of U.S. population positive for herpes viruses: 2005-2010



Bradley et al, JID 2013

HSV-2 seroprevalence by race & sexual partners



**Centers for Disease
Control and Prevention**

Case #2

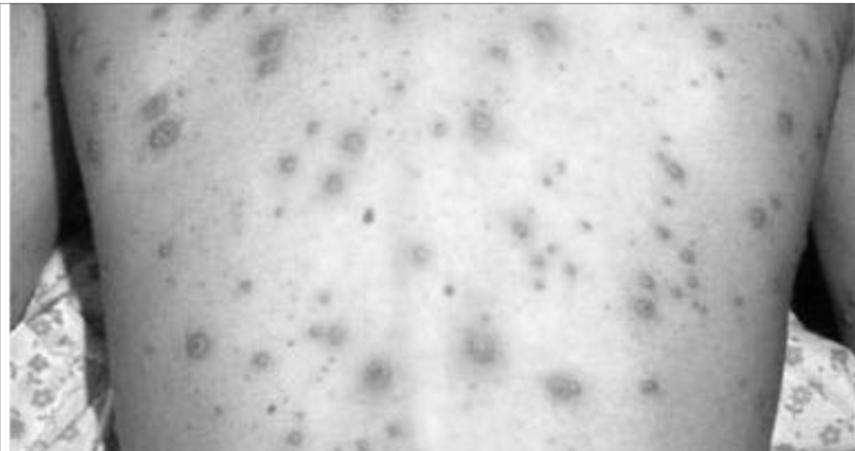
- **An unimmunized, previously healthy 25-year-old woman presents to your office with a 24-hour history of fever, malaise, and a generalized pruritic rash. Physical examination reveals a temperature of 38.6°C, respiratory rate of 25 breaths/min, heart rate of 88 beats/min, and blood pressure of 110/62 mm Hg. She has a papulovesicular rash over her face, trunk, and extremities that involves her scalp but spares her palms and soles. The remainder of her exam is normal. What is your diagnosis?**

Case #2: Papulovesicular Facial Rash*

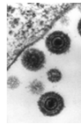


*Courtesy of Red Book Online.® 2009

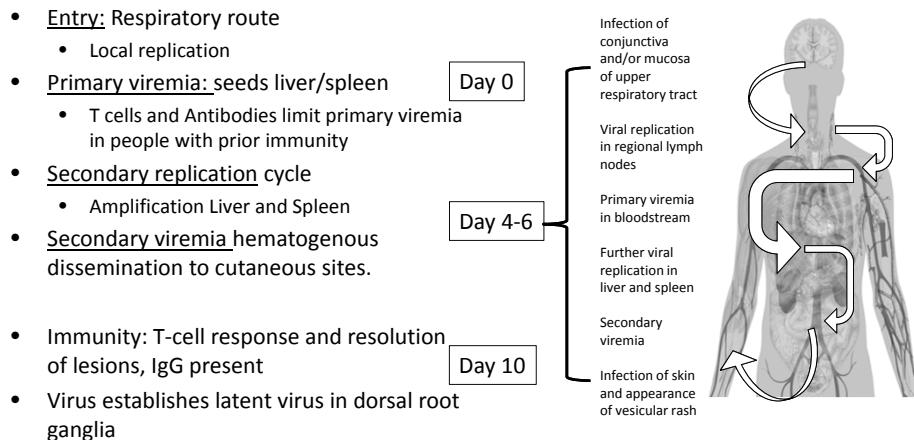
Case #2: Papulovesicular Truncal Rash*



*Courtesy of Red Book Online.® 2009



Varicella-Zoster Virus (VZV) Pathogenesis Primary infection



Varicella-Zoster Virus

- **Transmission: direct contact or aerosol**
- **Incubation**
 - Mean 14-16 days (10-21 days)
 - Contagious 1-2 days before rash and until lesions crusted
- **Increased severity**
 - Immune compromised
 - Older age
 - Pregnancy
- **250-500 lesions wild-type infection; in immunized, ≤ 50 lesions**



© David Clark, MD



Herpes Zoster



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GABHS periorbital cellulitis and necrotizing fasciitis complicating varicella



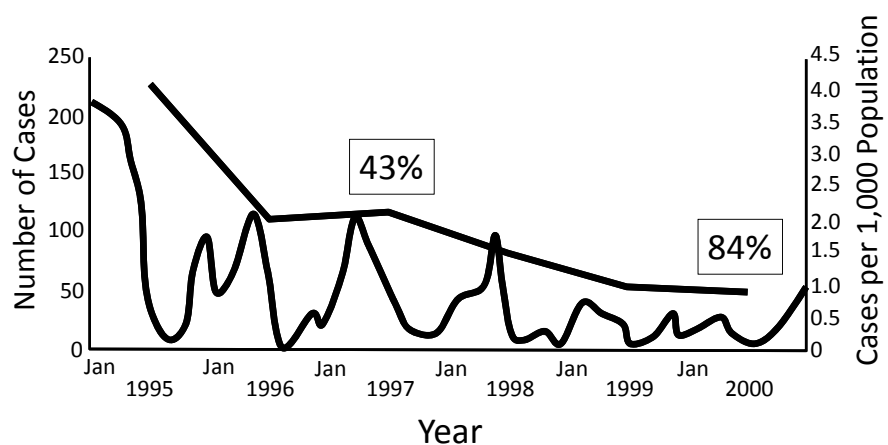
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Necrotizing Fasciitis



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The Report of the Committee on Infectious Diseases

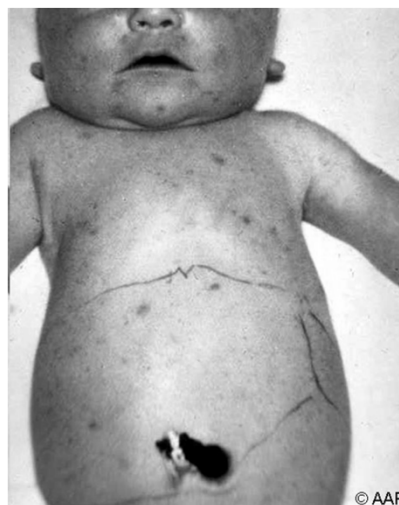
Varicella disease after introduction of Varicella vaccine in West Philadelphia 1995-2000





Case #3

- A 1 day old male is born to a mother with no significant prenatal history. Delivery is uncomplicated but initial examination reveals hepatosplenomegaly and a “blueberry muffin” rash. Labs show thrombocytopenia and elevated liver enzymes. What’s your diagnosis?



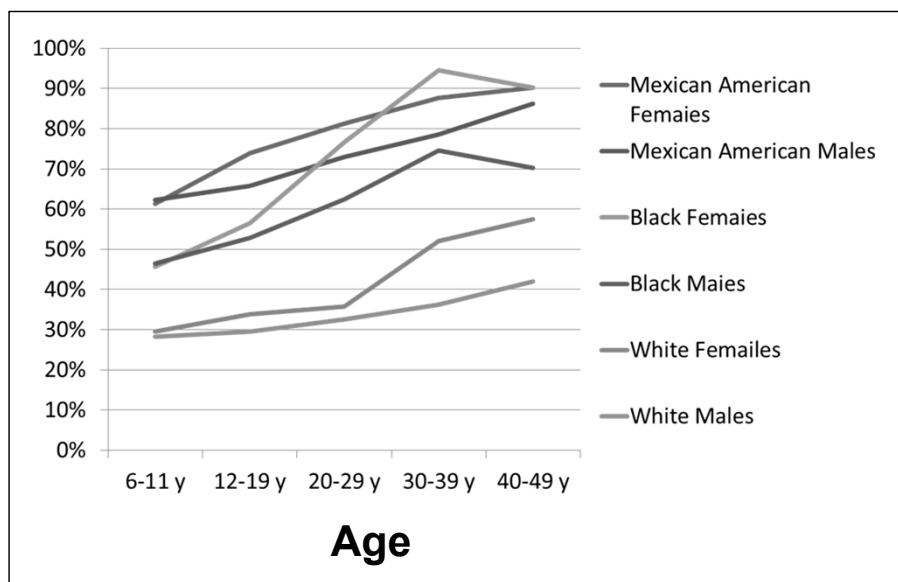
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Cytomegalovirus Clinical Syndromes

- Congenital infection
- Mononucleosis syndrome
- Immunocompromised hosts: may develop life-threatening disseminated disease

CMV Seroprevalence



Clin Infect Dis. 2010 Jun 1;50(11):1439-47

Congenital CMV

- **Hepatosplenomegaly**
- **Retinitis**
- **Rash**
- **Central nervous system involvement**

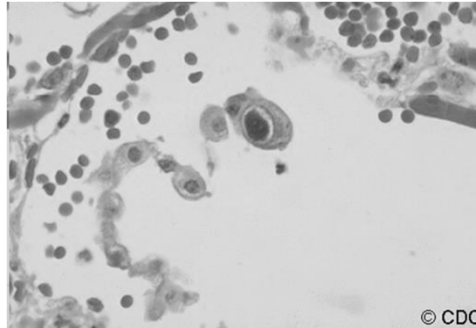
- **Leading nongenetic cause of sensorineural hearing loss in US**
 - **Up to 50% of symptomatic infants**
 - **Up to 15% of asymptomatic infants**

CMV Clinical Manifestations

- **90% asymptomatic**
- **Mononucleosis syndrome (20-50% cases)**
 - **Fever - most prominent**
 - **Increased SGOT/SGPT (90%)**
 - **Rash, particularly following ampicillin (EBV>CMV)**
 - **Atypical lymphocytosis**
 - **Exudative pharyngitis (EBV >> CMV)**
 - **Hepatosplenomegaly (EBV > CMV)**
 - **Adenopathy (EBV > CMV)**
 - **Aseptic meningitis, encephalitis, G B Syndrome**

CMV – Immunocompromised Hosts

- Arthralgia
- Leukopenia
- Pneumonitis
- Retinitis
- Enterocolitis
- Polyradiculopathy
- Deterioration of graft function

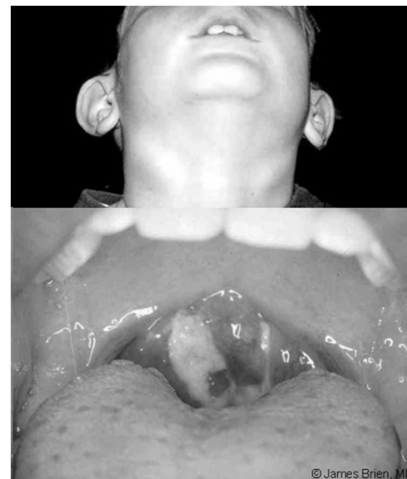


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Case #4

- A 15yo male presents to your office with fever, sore throat, and swollen glands in the neck. Exam reveals exudative pharyngitis, bilateral cervical adenopathy, and mild hepatosplenomegaly. What's your diagnosis?



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Epstein-Barr Virus

- **Present in human populations from all part of the world**
- **Acquisition occurs at an earlier age in underdeveloped countries**

Adolescent seroprevalence:

- **Undeveloped: >90%**
- **Developed: 40-50%**

EBV

Clinical Manifestations - Acute

- **Asymptomatic (frequency inversely related to age)**
- **Mononucleosis syndrome**
- **Neurologic/Neuropsychiatric**
 - **Nerve palsy, esp. Bell's palsy**
 - **Guillain-Barré Syndrome**
 - **Aseptic meningoencephalitis**
 - **Transverse myelitis**
 - **"Alice-in-Wonderland" Syndrome**
- **Thrombocytopenia/purpura**

EBV Mononucleosis Syndrome

- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis
- Skin rash
- Pneumonitis
- Neurologic
- Myocarditis/pericarditis
- Thrombocytopenia
- Anemia
- Granulocytopenia



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EBV Complications

- **Splenic rupture**
- **Airway obstruction**
- **Fulminant hepatitis**
- **Myopericarditis**
- **Meningoencephalitis**
- **Thrombocytopenia**
- **Hemolytic anemia**
- **Orchitis**

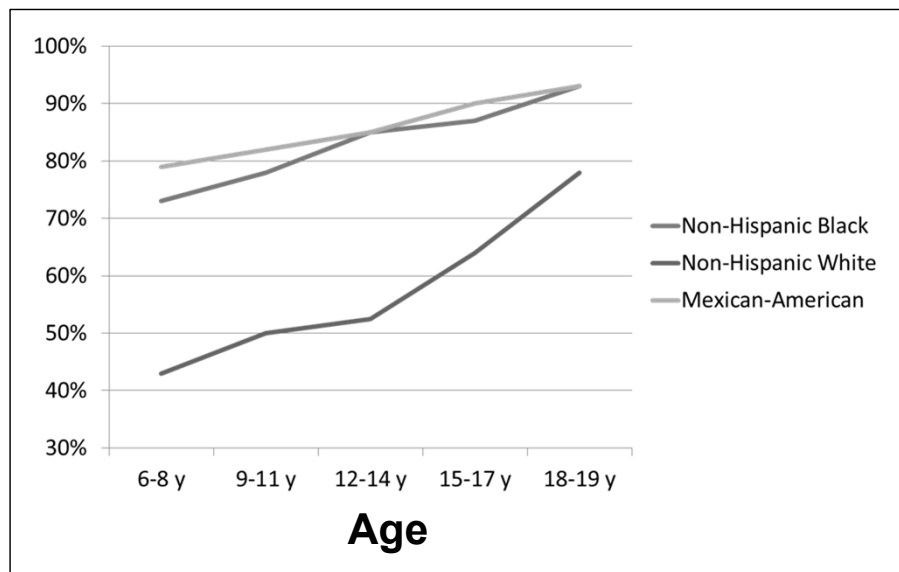
EBV in Immunocompromised Hosts

- **X-linked lymphoproliferative syndrome**
- **Post-transplant B cell lymphoproliferative disorders**
- **HIV-associated B cell lymphoma**
- **HIV-associated oral “hairy” leukoplakia**
- **HIV-associated LIP**
- **HIV-associated leiomyosarcoma**

EBV-associated malignancies

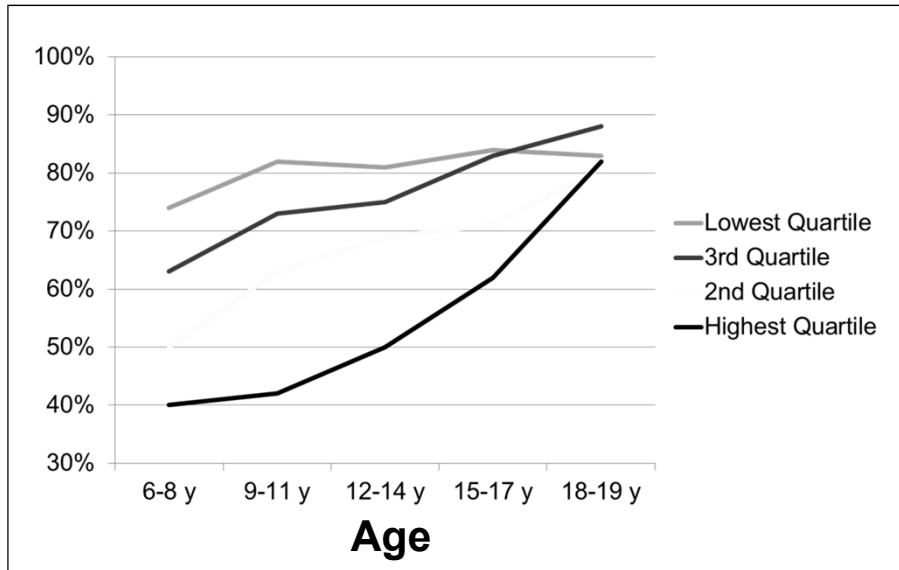
- Burkitt lymphoma
- Nasopharyngeal carcinoma
- Hodgkin's disease (some are EBV-associated)
- HIV-associated
 - B cell, non-Hodgkin lymphoma
 - Smooth muscle (leiomyoma, and leiomyosarcoma)
- Lymphoma

EBV Seroprevalence



PLoS One. 2013; 8(5): e64921

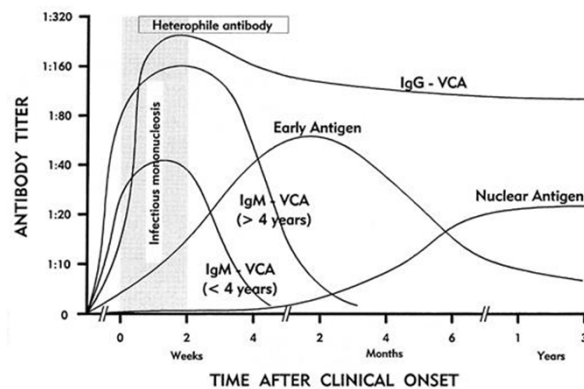
EBV Seroprevalence



PLoS One. 2013; 8(5): e64921

Diagnosis of EBV

- Direct visualization
- Serology
- Polymerase chain reaction



*Courtesy of Red Book Online.® 2009

Case #5

- A 13-month-old female developed high fever that persisted for 4 days without recognized cause. The child appeared relatively well and the fever subsided to be followed by a maculopapular rash that began on the trunk and spread to involve the face and extremities. What's your diagnosis?



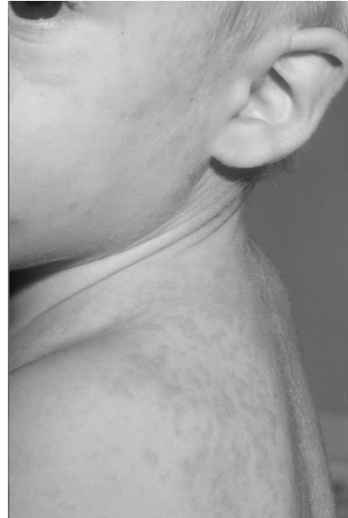
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Human Herpesvirus 6 & 7

- Human herpes viruses 6 and 7 are associated with exanthem subitem (roseola) and rejection of transplanted kidneys
- Antibodies to this HHV-6 present in almost everyone by age 5
- HHV-7 ubiquitous: >95% of adults seropositive
- HHV-6 can also be recovered in vivo from a broad range of tissues

HHV-6 Clinical Manifestations

- High fever
- Irritability
- Adenopathy (cervical and occipital)
- Maculopapular rash
- Inflamed tympanic membranes
- URI symptoms
- GI symptoms: vomiting and diarrhea
- Bulging anterior fontanelle
- Febrile seizures (15%)



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HHV-6 Less Common Manifestations

- Arthritis
- Hepatitis
- Heterophile - negative mononucleosis (primarily adults)
- Intussusception
- Thrombocytopenia
- Neurologic (aseptic meningitis, meningoencephalitis, multiple sclerosis)
- Syndromes in immunocompromised patients
 - Suppression of marrow in BMT
 - Interstitial pneumonitis in BMT/HIV
 - Organ dysfunction/graft rejection
 - Skin rash

HHV-7 Clinical Manifestations

- Fever
- Maculopapular rash
- Irritability
- Lymphadenopathy
- Mild diarrhea
- Hepatitis

Case #6

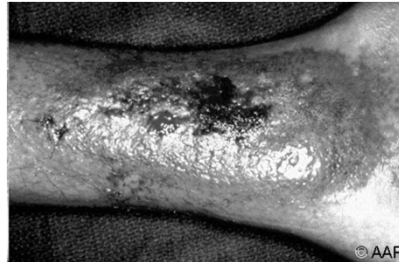
- A 34 year old HIV+ male presents to your office with complaints of a lump in his mouth. He has been noncompliant with medications, his viral load is >2 million copies/ml and his CD4 lymphocyte count is 143 cells/mm³. Exam reveals a firm, fleshy lump on the hard palate.
- What's your presumptive diagnosis?



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Human Herpesvirus 8

- Kaposi's sarcoma-associated herpesvirus (KSHV)
- Manifestations of 1° infection not well characterized
- HHV-8 is implicated as the etiologic agent of:
 - Kaposi's sarcoma (HIV+/HIV-) (found in 95%)
 - Monoclonal B cell lymphomas in HIV
 - Multicentric Castleman's disease



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HHV-8 Epidemiology

<u>Population</u>	<u>Seropositivity Rate</u>
US Children	2 - 8%
US adults	25%
US HIV+ IVDU	23%
US HIV+ women	21%
US HIV+ homosexual men	90%
US HIV+/KS+	96%
African endemic KS	100%

The take-home message...

