HUMAN BIOLOGY of VIRAL INFECTIONS

Virus [Strain]	Molecular Classification	Disease Entities **Pathophysiology**	Diagnosis	Epidemiology	Treatment

GENERAL FEATURES OF THE VIRAL LIFE CYCLE

The one-step growth curve

Initial drop in titre (viral uncoating and dismantling) → eclipse period (replication and synthesis of particles) → release period → increase in extracellular titres

Latent period: time from inoculation to rise in extracellular tire (EP + RP)

THE VIRAL LIFE CYCLE

Attachment: capsid proteins (naked) or glycoproteins (enveloped)

behaves as typical ligand-receptor interaction (reversible, saturable, specific)

Cellular entry: direct fusion (enveloped), RME

Direct Fusion: glycoproteins are retained on the plasma membrane

RME: requires fusion with lysosomes → acidification (conformational change + activation of lysosomal protease)

Uncoating;: dependent on genome type

RNA: genome delivered to cytoplasm EXCEPT influenza and Retroviruses

DNA: genome delivered to nucleus EXCEPT poxvirus

Picronaviruses do not require uncoating

Gene Expression and Replication:

DNA: expression of early genes (regulatory, replicative)

RNA: requires expression or packaging of viral RNA polymerase

Retroviruses: RT is a structural protein ; these are SS+ve RNA viruses ; integration ; host transcription from 5' LTR

Monocistronic: mRNA splicing, polyprotein, separate mRNAs via transcription start sequence, segmented genome, ribosomal frameshifting, IRES

Encapsulation: direct elongation (helical) ; scaffolding (icosahedral; requires formation of capsomers)

Release: cellular lysis (naked) or budding (enveloped)

GENERAL FEATURES OF VIRAL PATHOGENESIS

TMX: respiratory > GI > mucosal > vector-borne

Vertical TMX: requires viremia ; must be transmitted across the placenta (thus, prenatal) ; Rubella, CMV

Localized: HPV warts, most respiratory viruses, influenza results in systemic symptoms

Disseminated infection: requires migration past basement membrane (MMPs, transport via dendritic cells)

Persistent Infection: Latent (virus cannot be isolated) or Chronic (virus may be isolated at any time; HBV, HCV)

VIRAL DAMAGE
Apoptosis: activated in early infection and blocked in late infection
HIV-1 results in T-cell and neuronal apoptosis (via soluble GP120)
Direct Lysis: host-shutoff via replication ; may interfere with host processes before gene expression
Cytopathic Effect: nuclear pyknosis, inclusion bodies, cellular sphericity, cellular sloughing, vacuolization, syncytium formation (seen with enveloped viruses)

NEOPLASTIC TRANSFORMATION: Seen with retroviruses
Insertional mutagenesis
Integration of viral gene within cellular oncogene
Tumors are clonal ; develops slowly
Requires additional mutation
Chronc transforming retroviruses ; e.g. HPV
OR
Host oncogene mRNA integrates with viral genome → integration into genome
Tumors are polyclonal
May have concurrent tumors
Develop rapidly
Acute transforming retroviruses ; e.g. HHV-8

GENERAL FEATURES OF THE HOST RESPONSE
INNATE IMMUNITY
Skin: keratinized layer, inactivating secretory products
Mucosa: secrete sialic acid, defensins (antimicrobials), lactoferrin, ciliary ladder
GI: acidity, preoteases, bile salts, lipase, mucosal layer

RECOGNITION of VIRAL INFECITON
Extracellular: CMV can trigger synthesis of IFN I (α, β) without viral entry or replication
Intracellular: this is the main pathway of IFN activation
RIG-1: detects RNA structures (typically dsRNA)
MDA-5: detects dsRNA
TLRs and PRRs (cypoplasmic and endosomal: TLR 3, 7, 8, 9): activated by viral nucleic acids (CpG repeats in DNA viruses)
Activates NFκB → increased expression of Type I IFN + IL-6
Results in recruitment of inflammatory cells and increasedAg presentation
APOBEC: inhibits HIV uncoating

INTERFERON (IFN)
Most somatic cells: Type I IFN (α, β)
Immune cells: Type II IFN (γ)
Upregulates expression of the major antiviral systems:

1. PKR : inhibits all host protein synthesis ; requires activation by dsRNA
2. RNAase L: hydrolyze sall mRNA ; requires activation by Oligo-2A Synthetase
3. Oligo-2A Synthetase: synthesizes a 2'-5' oligonucleotide chain →activates RNAase L
4. MXA: specific inhibition of influenza virus (binds to polymerase)

PKR, RNAaseL, and O2AS are synthesized in the inactive form!

VIRAL RESISTANCE TO IFN
EBV and adenovirus: short RNAs prevent activation of PKR and O2AS
HSV: phosphorylates PKR
May inhibit transduction pathway, inhibit IFN receptor, dephosphorylate STATs

CELLULAR IMMUNE RESPONSE
Infected cells secrete IL-6, IL-8, MIP-1α
Also secrete IL-1 after infection
IL-1 + IFN → fever
First cells at site of infection: neutrophils and APCs
CD4+ cells result in activation of CD8+ cells → attack cells with MHC I + bound viral antigen (perforins)
ALSO result in DTH: secrete IFN-γ and activate macrophages

ANTIBODY RESPONSE
Generally the basis of immunity from vaccination: polio, MMR, HepA, HBV, YFV, HPV

VIRAL RESISTANCE TO HOST DEFENSE
Soluble cytokine receptors
Secretion of immunosuppressive cytokine analogs (IL-4, IL-10): EBV
Glycoprotein Fc receptors: results in antipolar binding of Abs ; prevents complement activation
Suppression of T-cells (Measles, HIV)
Prevent degradation of peptides for presentation MHC-I: EBV (EBNA-1 latency protein)
Prevention of peptide loading onto MHC: HSV
Trigger endocytosis and destruction of MHC I: HIV
This increases cellular killing by NK cells
CMV encodes NK receptor inhibitor

Escape variants: HIV and HCV (main mechanism for persistent infection)

HYPERSENSITIVITY IN VIRAL INFECTIONS
Type I: Skewed IgE production and increased eotaxin secretion (seen with respiratory viruses)
Type II: damage to infected cells by complement and granular cells (express Fc) ; may also result in damage to surrounding cells
Type III: HIV vasculitis (immune complexes with soluble GP120), glomerulonephritis with HBV
Type IV: HSV keratitis, granuloma formation

ENTEROVIRUSES

General Features
All *enteroviruses* are classified into the Picronaviridae family.
TMX: Fecal-oral. All viruses demonstrate post-symptomatic shedding into the feces.
Stable to acid, alcohol, Lysol, and detergents
Susceptible to formaldehyde and chlorine (pools)

Lifecycle of Poliovirus
THM via F/O → replication in GI mucosa → Peyer's Patches and M cells → primary viremia → dissemination → replication and secondary viremia → involvement of CNS (1 – 2%) → replication within, and destruction of, anterior horn LMNs

Poliovirus	Small non-enveloped RNA	**Paralysis** Most commonly in young adults Post-Polio Syndrome Symptoms may reappear with age, in the absence of latent infection **Aseptic Meningitis** **Undifferentiated Febrile illness**	Clinical Dx May be cultured from throat washings and feces PCR No specific therapy, so ID is not informative	Eradicated from North America due to polio vaccine	Vaccination Oral Attenuated IM inactivated The OPV may convert to the wild-type strain
Echovirus Coxsackievirus Enterovirus 68 – 72 Hepatitis A Virus		**Rash** **Aseptic Meningitis** Develops after secondary viremia **Pericarditis** **Myocarditis** Associated with Coxsackie virus **Hepatitis** **Undifferentiated Febrile illness** Peak incidence in the late summer		Typically, these are self-limiting illnesses with low mortality	Vaccination: **HepA only** IM surface antigen IV HepA immunoglobulin (passive immunization) No antivirals Viral myocarditis is exacerbated by exercise

VIRUSES causing GASTROENTERITIS

General Features

These viruses all result in diarrhea (the prominent syndrome)

ALL TMX via F/O. All viruses demonstrate post-symptomatic shedding into the feces.
- Astrovirus may be transmitted via emesis
- Norovirus may be transmitted via respiratory droplets

Gut Bx typically reveals no major structural pathologic changes (EXCEPT coronavirus)
- Replication is not sufficient for diarrheal symptoms
- May have shortening of µvilli
- Rotavirus → secretory toxin (similar to cholera)
- Astrovirus capsid → disruption of actin filaments

There are no anivirals: thus, ID is typically not informative

Rotavirus	Nakes Icosahedral dsRNA Segmented genome	**Diarrhea** **Low-grade fever** Leading cause of diarrheal mortality (in infants) in underdeveloped nations Toxin results in osmotic diarrhea	Clinical Dx (age, symptoms, duration, season) Rotavirus stool ELISA Only used for epidemiological studies Latex agglutination	Most common etiology of diarrhea in peds (U.S) **Peak incidence in winter** Most infection < 2 yrs Incubation: 1 – 3 d.	Rehydration Rotavirus Vaccine: Live Attenuated Strains
Norovirus	Naked Icosahedral SS+ve RNA	Diarrhea Nausea Vomiting Abdominal cramps	Clinical Dx RT-PCR EM on stool samples	2^{nd} – 3^{rd} leading cause of diarrheal illness in U.S 30% of gastroenteritis in adults Affects peds > 6 yrs No seasonality Highly infectious	Rehydration Decontamination

				Occurs in epidemic outbreaks Within communal settings (e.g. cruise ships, stadiums, nursing homes, schools) Incubation: 48 hrs.	
Astrovirus	Naked Icosahedral dsDNA	A unique syndrome: ND + headache + malaise Duration of 2 -4 d.		2^{nd} – 3^{rd} leading cause of diarrheal illness in U.S 20 – 30% of gastroenteritis Slightly higher incidence in winter Incubation: 3 – 5 d.	
Adenovirus	Naked Icosahedral SS+ve RNA **Enteric serotypes!** (38, 40, 41)	No tropism for respiratory tract or eye **NVD** **Low-grade fever**	Clinical Dx Indirect IF	5 – 15% of gastroenteritis in children No seasonality	Rehydration
Coronavirus	Enveloped SS+ve RNA	**Dysenteric illness** (stool with occult blood, pus, and mucus) **Concurrent respiratory infection**	Clinical Dx	Typically seen in peds< 1 yr	Rehydration

RESPIRATORY VIRUSES

General Features

EPIDEMIOLOGY

Rhinovirus (30 – 40%), RSV (10 – 15%), CoV (10%), Metapneumovirus (10%), Adenovirus (5%), PIV (5%), WU Virus (5%)

SEASONALITY

This is NOT useful for diagnosis!

Adenovirus: non-seasonal; epidemics in communal environments (military barracks)
Enterovirus: late summer and early autumn
CoV, Influenza, RSV: winter
Parainfluenza, Rhinovirus: biseasonal (autumn and spring)

SYNDROMES

The immune response is not robust and quickly become anergic: results in recurrent infection (progressively less severe)

DIAGNOSIS

Age: suspect RSV with LRT and < 1 yr
Shell culture (direct IF): requires 24 – 48 hrs
Cytopathic effect
PCR

PATHOGENESIS

Replication within epithelial cells of URT
Ciliary paralysis with some cytotoxicity
Dyspnea due to mucus production and sloughing of epithelium
Rhinovirus + CoV: stimulate release of eosinophil chemotactic protein → exacerbate asthma and COPD
Fever: IL-1 + IFN

Influenza A – C	Enveloped Helical SS –ve RNA Segmental Genome	**Influenza Syndrome** Fever, headache, myalgia, malaise, pharyngitis, dry cough Due to systemic cytokines (Il-1 and IFN-γ) **Viral Pneumonia** Bilateral infiltrates without consolidation on XCR **RF**: extremes of age, pregnant, chronic lung disease, CVD **Secondary Bacterial Pneumonia** Due to *pneumococcus*	Clinical Hx	Peaks in winter **Pandemic strains** generated by antigenic shift and assortment of novel **hemagglutinin (H)** genes Resistance to host response: antigenic drift due to point mutations in RNA genome (N	**Vaccine** Live attenuated and killed virus vaccines are trivalent

		S. aureus *H. influenzae* **Myositis** **Myocarditis** Infection does not disseminate Respiratory symptoms resolve 3 – 4 d. after systemic illness		and H) This explains vaccine strain updates Type A is most common infecting strain	
Respiratory Synctitial Virus (RSV)	Enveloped Helical SS –ve RNA	**Bronchiolitis/Febrile Pneumonitis** **Viral Otitis Media + Sinusitis** **Bacterial AOM + Sinusitis + Pneumonia** May have reinfection due to poor immunity Typically a limited illness in adults	**CXR:** bilateral interstitial infiltrates + hyperinflation	Peaks in winter **Affects peds** 6 mos. – 1 yr. Also affects > 65 yrs and pts with COPD Hospitalization is more frequent in males	**Aerosolized Ribavarin**: hospitalized infants nucleoside analogue **RSV Immunoglobulin** Premature infants < 1 yr **Palivizumab** Ab to fusion protein. Used in peds with increased risk of infection **Breast Feeding** Confers passive immunity via maternal IgG
Parainfluenza Virus	Enveloped Helical SS –ve RNA	**Common Cold + Bronchitis** **Croup** Occurs with Types 1 and 3 PIV Obstructive airway disease characterized by wheezing cough **Pneumonia** Occurs more frequently with Type 3 No significant pathology is seen with Type 4		Peaks in summer and spring (similar to Rhinovirus)	
Metapneumovirus	Enveloped Helical SS –ve RNA	**Limited URT infection** **Bronchiolitis + Bronchitis** < 5 yrs, > 65 yrs, immunocompromised		10% of RTIs Ubiquitous in environment	

		Viral Pneumonia Typically requires ventilation		RF: < 5 or > 65 yrs	
Adenovirus	Naked Icosahedral dsDNA	Site of infection is determine by serotype: **Respiratory** Infants: pharyngitis with cough Peds: pharyngitis + tracheitis Adults: common cold **GI** Simple gastroenteritis **Ocular** Keratoconjunctivitis (epidemic) **Hemorrhagic cystitis** (seen in peds)		Pan-seasonal incidence Epidemics in congregate settings **Latent Infection**	
Rhinovirus	NAked Icosahedral SS +ve RNA	**"Common Cold"** Headache, rhinorrhea, pharyngitis, congestion NO fever, myalgia, or fatigue DOES NOT cause croup, pneumonia, or bronchiolitis **Exacerbation ob asthma, chronic bronchitis** Replication within bronchial epithelium → recruitment of eosinophils (IL-5, ECP) **AOM, Sinusitis** **Secondary Bacterial AOM, Sinusitis**		> 30% of RTIs (leading viral cause) Peaks in summer and spring	
Coronavirus	Enveloped Helical SS +ve RNA	**"Common Cold"** **Gastroenteritis** Typically results in dysentery due to mucosal inflammation		15% of RTIs 2 – 3 yr cycle of epidemics Re-infection is likely due to rapid decline in Ab titre	

		Exacerbation ob asthma, chronic bronchitis **Severe Acute Respiratory Syndrome (SARS-CoV)** Benign URT infection (2 – 7 d) Progressive fever, dry cough, dyspnea, headache, malaise Results in hypoxemia		Peaks in winter	
Enterovirus		**Primarily result in non-respiratory syndromes:** Viral exanthem (EXCEPT polio) Aseptic meningitis Pericarditis, Myocarditis (Coxsackie), Paralysis Hepatitis (HepA) **Undifferentiated Febrile Illness** (Summer Grippe) Similar to common cold: pharyngitis, cough, fever Complicated by acute myocarditis		Peaks in late summer Ubiquitous in the environment	
Human Bocavirus	Naked Icosahedral	Paroxysmal cough (similar to pertusses) Diarrhea Maculopapular rash		Ubiquitous in the environment Infants typically require hospitalization 3 – 6% of LRT viral infections	
WU Virus	Naked Icosahedral	Bronchitis **Croup** Pneumonia		86% of hospitalizations in peds < 3 yrs 3% of total	

HERPESVIRIDAE

General Features

STRUCTURE

Envelope harbors a vast array of GPs

Also contains a **tegument** layer interposed between the envelope and nucleocapsid

- Contain transcription enhancers
- These allow for host cell takeover and **early phase** gene expression
- CMV includes four mRNAs within the tegument (only virus with coexistent DNA and RNA)

LIFE CYCLE

All maintain latency via **episomal elements**

Neurotropic: LAT mRNA is expressed in infected neurons; prevents apoptosis

Lymphotropic: requires expression of several proteins involved in genomic replication.

- Antigenicity of these proteins results in evolution of immunosuppressive characteristics
  - (MHC downregulation, IL-4 + IL-10, false cytokine receptor, stabilizing protein sequences → prevent Ag presentation)

Reactivation of neurotropic strains: fever, stress, nerve trauma, steroids (menstruation), UV

EPIDEMIOLOGY

TMX: close contact; lymphotropic strains also via breast milk and GI shedding; respiratory secretions (VZV only)

Most in general population are seropositive (including CMV)

HSV-1	Neurotropic dsDNA Enveloped Icosahedral Nucleocapsid	**Gingivostomatitis** (prodrome of tingling and pain) **Herpetic Whitlow** (seen in dentists without gloves) **Herpes Gladiatorum** (seen in wrestlers) **Keratitis** Conjunctivitis → invasion of corneal epithelium (reactivation → progressive scarring and vascularization) **Encephalitis** Liquefactive necrosis of the temporal lobes	**Tzank Prep** Detects cytopathic effect in ulcer scrapings **Indirect IF** On cultured infected cells Typically, HSV-1 and HSV-2 are not differentiated by IHC Dx of herpes encephalitis may be achieved by PCR on CSF	50% of primary infections are subclinical Keratitis is leading cause of blindness in US HSV-1 is the leading etiology of spontaneous encephalitis TMX: contact with vesicular fluid	Nucleoside analogs (Idoxuridine, Foscarnet, Acyclovir) may be used for treatment and prophylaxis. All drugs EXCEPT foscarnet require activation by viral thymidine kinase TX encephalitis empirically!

		Pharyngitis **Cutaneous ulcers**			
HSV-2		**Genital herpes** (onset with primary infective prodrome) Disseminated ulceration is seen in HIV Females: dysuria Infection with HSV-1: decreased reactivation frequency **Neonatal Herpes** High mortality. May develop into disseminated disease. Neurological deficits. Occurs during primary maternal infection due to lack of immunizing antibodies. **Aseptic meningitis** **Gingivostomatitis** **Phasryngitis**		60% of asymptomatic hosts may shed viruses	
VZV		**Varicella** Disseminated infection affecting the cutis. Ulcers are identical to HSV on pathology. **Shingles** Reactivation results in autograde transport to sensory nerve terminals along a dermatome **RF**: age (decreased immunity) **Post-herpetic neuralgia**	Clinical Dx	TMX: **respiratory droplets** + contact	

EBV	Lymphotropic dsDNA Enveloped Icosahedral Nucleocapsid	If immunocompetent: no disease is seen with reactivation **Heterophile-Positive Mononucleosis** Fever, malaise, pharyngitis, tonsilar exudates, patatine petichiae, lymphadenopathy, splenomegaly Most infection is asymptomatic Used in diagnosis **Burkitt's Lymphoma** B-cell tumor affecting jaw and longbones. Infection of B cells causes ectopic *rag* expression and extended VDJ recombination → translocation of IgH or λ/κ promoter to *c-myc* → proliferation **American Burkitt's** **Nasopharyngeal Carcinoma** Infection of epithelial cells **EBV lymphoma** *Post-transplant lymphoproliferative disease* (PTLD) Seen in HIV or other immunocompromised state **Oral Hairy Leukoplakia** Non-tender plaque on lateral tongue	Monospot: rapid latex agglutination Hemagglutination may be used to detect heterophile Abs Histology: Downy cells; cytopathic effect seen in circulating lymphocytes	Increased incidence in peds due to childcare facilities Burkitt's lymphoma is only seen in the Subsaharan belt (endemic malaria) Nasopharyngeal carcinoma is seen in southern China	
HCMV		**Latent within monocytes** **Cytomegalic Inclusion Disease**	In post-transplant with severe disease: PCR, IF, IHC	Leading etiology of birth defects in US.	

		(Neonatal CMV) Affects salivary glands on infants. May result in hemolytic anemia, thrombocytopenia, hepatitis, splenomegaly, petechial rash, retinitis, MR Occurs with primary maternal infection If immunocompetent: no disease is seen with reactivation **Heterophile-Negative Mononucleosis** Fever, malaise, lymphadenopathy, hepatitis **Post solid-organ transplant + ISD:** Graft destruction Severe hepatitis and mononucleosis **In HIV:** CMV retinitis **Post allogenic bone marrow transplant:** Interstitial pneumonitis (IP)	CPE: Cells with **dense inclusions**	IP is second leading cause of death in marrow transplant pts.	
HHV-6		**Roseola Infantum** Macular rash with low-grade fever Typically a self-limiting illness May see reactivation with solid organ transplant → severe disease		Acquired < 6 years Most infection is asymptomatic TMX: contact	
HHV-8 (KSHV)		**Kaposi's Sarcoma** Affects vascular endothelium		KS is endemic in Med region, affecting elderly males Sexual TMX	

VECTOR-TRANSMITTED VIRUSES

General Features
ALL are RNA viruses

VIRAL TRANSMISSION PATTERNS
Urban: mosquito ↔ human
YFV, DV, SLEV
Involves high viral titrs and prolonged viremia
Mutiple Sylvan (wild): small mammals, birds → mosquito → overwinter in host or eggs → mosquito
WEEV, VEEV, LaCrosse, WNV
Involves lowerviral titres and shorter viremia
Simple Sylvan (wild) : monkey ↔ mosquito → human (incidental)
YFV in non-urban environment
Arthropod-Sustained: small mammal ↔ tick ↔ another tick → humans
Colorado Tick Fever

ANIMAL-BORNE VIRUSES
Must have capacity to replicate within animal vector
Leading endemic host: bats
Endemic animal infection is typically asymptomatic
Humans are **incidental hosts**: cannot re-infect endogenous animal
(However, the virus may be spread by horizontal TMX: WNV via blood transfusions, and hemorrhagic fever viruses via local hospitals)
Most infectious are severe due to immunologic naiveté

TREATMENT of VIRAL SYNDROMES
Encephalitis

Rabies Virus	Enveloped Helical SS-ve RNA	**Rabies Encephalitis** Local replication in skeletal muscle near bite wound → invasion of peripheral nerves → transport to CNS → replication within gray matter If inhaled: replication in nasopharyngeal mucosa and transport through olfactory nerve	**Negri body**: proteinacious inclusions within infected neurons	TMX: animal bites, inhalation of viral particles in dried bat urine (caving) Nearly universal mortality	**Treat within incubation period!** Disease is fatal once symptomatic Rabies immunoglobulin Rabies diploid vaccine: killed virus

		May also disseminate **via nerves** to other tissues! Results in lysis and inflammation			Interferon Ribavarin Must be introduced at different sites Veterinary vaccine: live attenuated
Sin Nombre Virus	Enveloped Icosahedral SS-ve RNA Semented genome	**Hantavirus Pulmonary Syndrome (HVPS)** Results in pulmonary edema without marked inflammation, necrosis, or CPE **Febrile Uremic Syndrome**	Serology	TMX: inhalation of viral particles in dried animal urine + feces HCPS mortality is 76%	
Lassa Virus Marburg Virus Ebola Virus		**Hemorrhagic Fever** Caused by cytopathic effect on endothelium. Ebola encodes a toxic envelope glycoprotein.	Serology (BL-4)		Passive immunization with Ebola antiserum from convalesced pts. Interferon Ribavarin
Western Equine Encephalitis Virus (WEEV)	Enveloped Icosahedral SS+ve RNA	**Encephalitis** Seeding of CNS during the secondary viremia → replication within neurons and meninges Confusion, lethargy, ataxia, dysarthria **Fever** **West Nile Virus:** Aseptic Meningitis West Nile Fever Severity of symptoms is related to age (more severe if older).	Serology with acute and convalescent titres	Most infection is asymptomatic! RF for severe illness: age Endemic to U.S	
Eastern Equine Encephalitis Virus (EEV)	Enveloped Icosahedral SS+ve RNA			Endemic to U.S	Veterinary vaccine
St. Louis Encephalitis Virus (SLEV)				Endemic to U.S	
California Group LaCross Encephalitis Virus (CGEV)	Enveloped SS-ve RNA Segmented genome			Endemic to U.S	

West Nile Virus (WNV)	Enveloped SS+ve RNA	Replication within the RES before primary viremia (febrile illness) If immunocompromised,may have secondary ciremia with CNS dissemination		Endemic to U.S	Screen blood supply to prevent transfusion infection
Venezuelan Equine Encephalitis Virus (VEEV)				Occasionally seen in U.S	Veterinary vaccine
Dengue Virus (DV)	Enveloped SS+ve RNA	**Dengue Fever** **Arthralgia** **Dengue Hemorrhagic Fever** Occurs with second infection with a new serotype. Immune Enhancement Non-neturalizing Abs bind to virus and expose Fc → results in formation of active immune complexes (endothelial damage due to complement activation) AND increased cell tropism → infection of macrophages → secretion of TNF-α May result in DIC		Endemic to southeast Asia	
Yellow Fever Virus		**Hemorrhagic Fever** Results in massive hepatic injury → loss of coagulation factors → bleeding		Endemic to Brazil, Central America	Vaccine: live attenuated Recommended for travel to endemic areas
Rubella Virus		**Self-limited rash** with **febrile illness** **Congenital Rubella** Primary infection during pregnancy		**NOT transmitted by vectors**	

IDIOSYNCRATIC DNA VIRUSES					
Human Papilloma Virus (HPV)	Naked DNA genome	**Verucous wart (benign)** Typically occur on hands and feet **Epidermodysplasia veruciformis** Occurs with immunodeficiency Flat macular erythematous warts May convert to **squamous cell carcinoma** with exposure to UV **Condyloma Acuminta** Typically occur on cervix and penis. Difficult to detect May be TMX to newborn → laryngeal papilloma **Anal Warts** **Cervical Carcinoma** **Anal Carcinoma** **Head and Neck Cancers** Infection of basal keratinocytes and epithelial cells → enters nucleus → episome (latent) → activates as epithelial cells undergo mitosis and apical growth → expression of Large T Ag (early protein) → increased proliferation and hyperkeratosis → formation of wart → expression of late genes → complete viral particles in upper layers **Carcinogenesis** Immortalizes cells but does not immediately result in malignancy HPV is a chronic cancer virus: requires multiple mutations and propagating factors (UV, smoking, X-rays)	Dx based on inspection of lesion Colposcopy Acetowhite staining PAP smear (cytopathic effect)	Nearly universal infection Virus is ubiquitous in the environment TMX: contact with fomites	**Prevention** Vaccine: HPV serotypes 6, 11, 16, 18 Covers 70 – 80% of strains causing cervical carcinoma and warts Susceptible to acid and bleach Cesarean delivery (not usually practiced) **Treatment** Cryotherapy Chemical removal IFN-α (inject) Ablation via laser therapy May result in inhalation of vaporized particles Tape

		Integration into host genome → disruption of E2 → derepression of E6 and E7 → E6 inhibits Rb and E7 inhibits p53 HPV 6, 11 : warts HPV 16, 18: warts and cervical carcinoma			
Molluscum Contagiosum Virus (MCV)	Poxvirus	**Umbilicated papillary rash** May generalize with immunocompromise	Dx based on appearance Bx: typical CPE May resemble SCC	TMX: sexual and close contact The only Poxvirus naturally infecting humans	NO vaccine Ablation via laser therapy Electrodessication Cryotherapy Cidofovir With AIDS: restore CMI with ART
Parvovirus B19		**In Peds** **Erythema Infectiosum** **In Adults** **Acute symmetric polyarthropathy** **Apalstic crisis** ion background of chronic hemolysis Congential anemia Hydrops Fetalis Infection may be more severe if immunocompromised	Acute: IgM Ag capture (remain seropositive for 3 mos.)	Ubiquitous in environment TMX: respiratory secretions , close contact, transfusion Peak incidence: late winter, spring, early summer	Arthralgia: NSAIDs Aplasia: transfusion IVIG if immunosuppressed