

DENGUE


Dengue in Latin America



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The Discussion

- History and epidemiology
 - Virology and pathogenesis
 - Clinical manifestations/presentations
 - Diagnosis
 - Laboratory diagnosis
 - Management/prevention and control
 - Current topics regarding research
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History and Epidemiology

- 1635 The first outbreak of a disease compatible with classic dengue fever (DF) in Latin America and the Caribbean took place in the French West Indies.
 - 1699 Panama.
 - 1799 Panama epidemic often reported as the first dengue epidemic.
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History and Epidemiology

- 1940's paralleling Asian and Pacific epidemics DF occurred in the Caribbean Basin during WWII.
 - 1953 Trinidad DEN-2 serotype isolated.
 - 1946-1963 no record of epidemic dengue. Possible success of *Aedes aegypti* mosquito eradication programs.
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History and Epidemiology

- 1963-1964 DEN-3 Jamaica and Puerto Rico.
 - 1968-69 DEN-2 Caribbean islands.
 - 1970 Pan American Health Organization *Aedes aegypti* program discontinued.
 - 1978 cases reported in Mexico
 - 1980 cases reported in Texas
 - 1980's geographic expansion to South American countries that had been free of dengue for decades.
 - 1981 DEN-4 introduced
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History and Epidemiology

- 1977-1980 >700,000 cases PAHO
approximately (5 million) individuals infected.
 - Cuba 42% of 10 million infected with DEN-1
 - 1990's dengue traveled to last two countries
that had been free of dengue for decades
(Costa Rica and Panama).
 - 1994 DEN-3 detected in Nicaragua and
Panama (coinciding with increased DHF)
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History and Epidemiology

- 1981 first out break of DHF/DSS new strain of DEN-2 introduced to Cuba from South East Asia. 4 years after DEN-1 epidemic. Results:
 - 344,203 cases of DF reported
 - 10,312 cases met WHO criteria for DHF/DSS in 3 months
 - 116,143 hospitalizations
 - 11,400 cases reported in 1 day
 - 158 deaths (101 children and 57 adults)
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History and Epidemiology

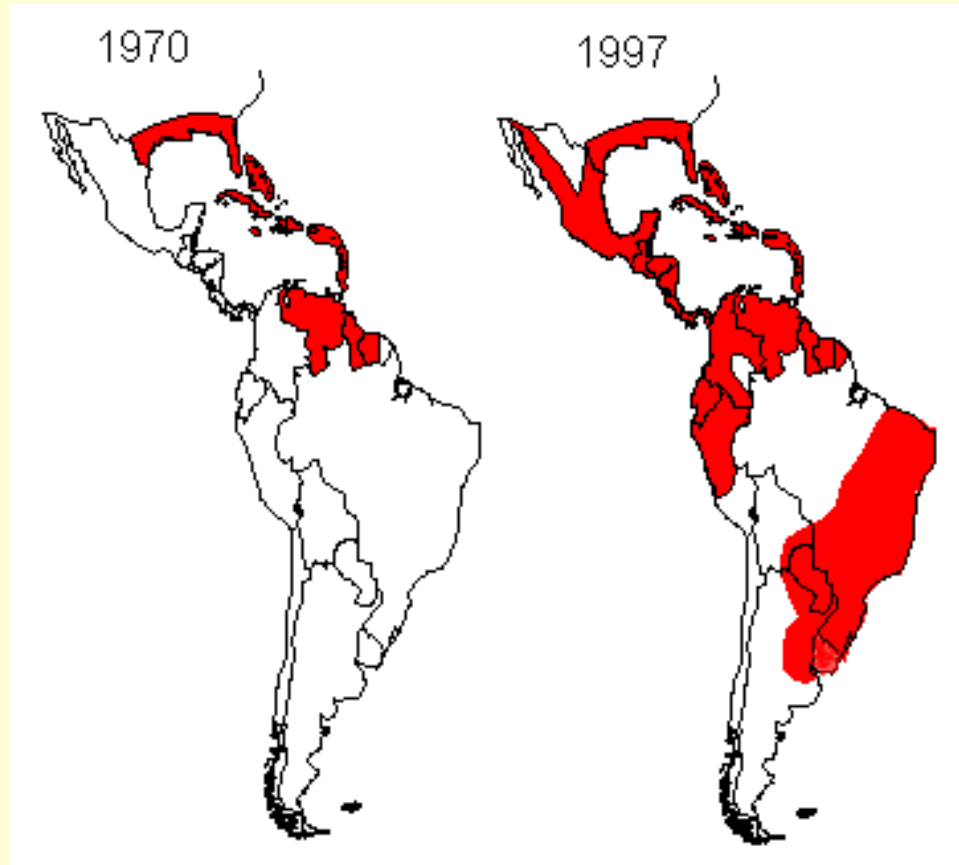
- 1989-1990 second major outbreak Venezuela.
 - 1990 another epidemic in Venezuela disease reported yearly to date.
 - 1981 to 1999 67,362 cases of DHF and 894 fatalities in the Americas (PAHO unpublished data 1999)
 - DHF is now endemic in the region with 24 countries reporting confirmed cases.
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History and Epidemiology

- News Desk “Tackling dengue in Central America” The Lancet Infectious Diseases Volume 2 Number 9 September 2002. Stated:
 - An epidemic of Dengue has spread from Guatemala to Costa Rica.
 - By 1970 Dengue had been virtually eradicated in Central America and Mexico, but has since returned with vengeance affecting 60,000 annually across the region.
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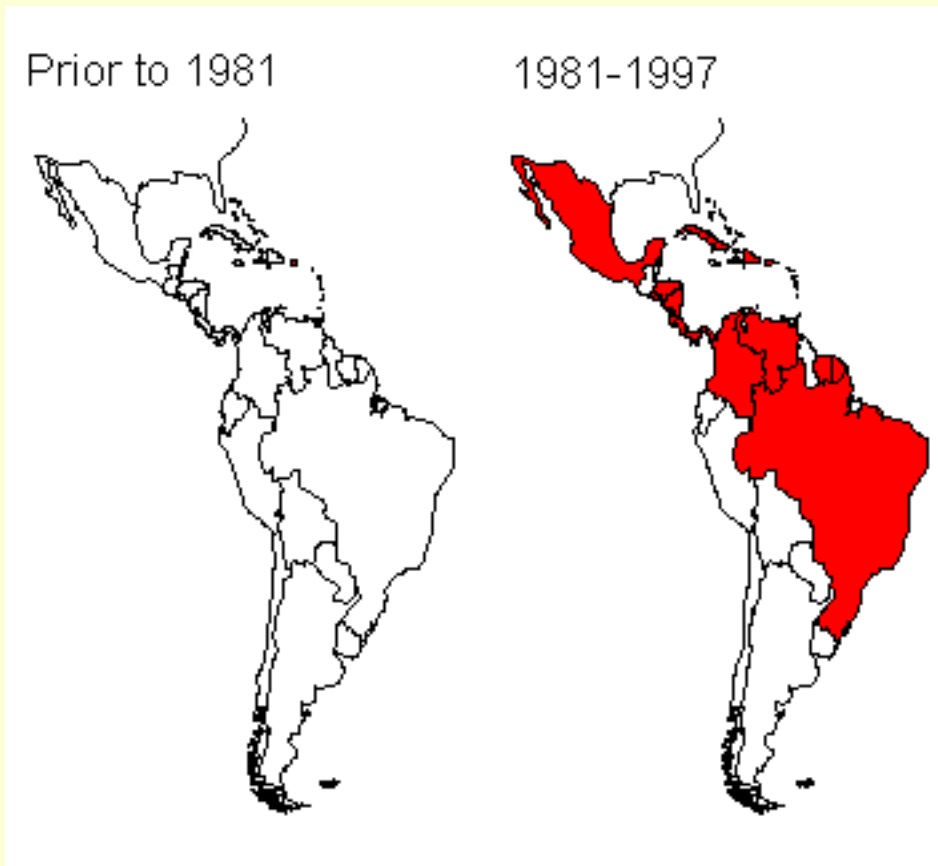
Aedes aegypti distribution after the end of
eradication program 1970 to 1997



**American countries with lab confirmed
hemorrhagic dengue prior to 1981 and from**

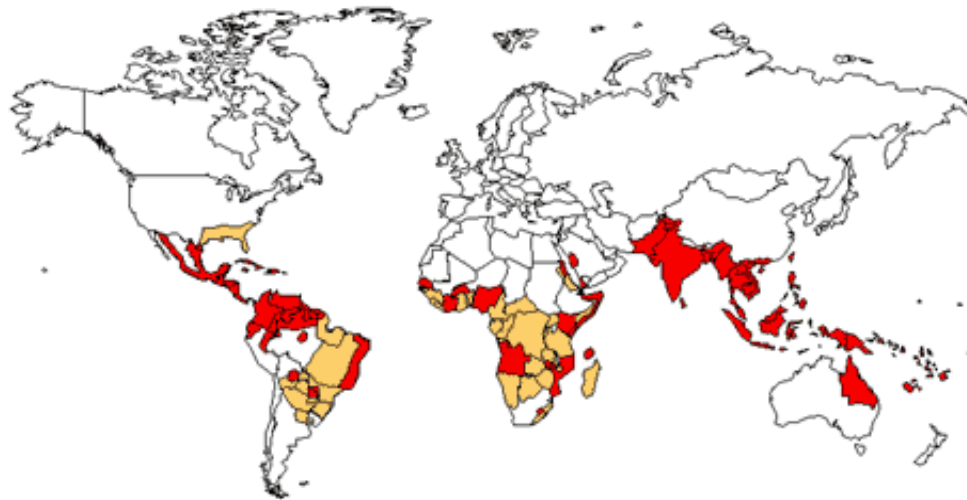


1981 to 1997



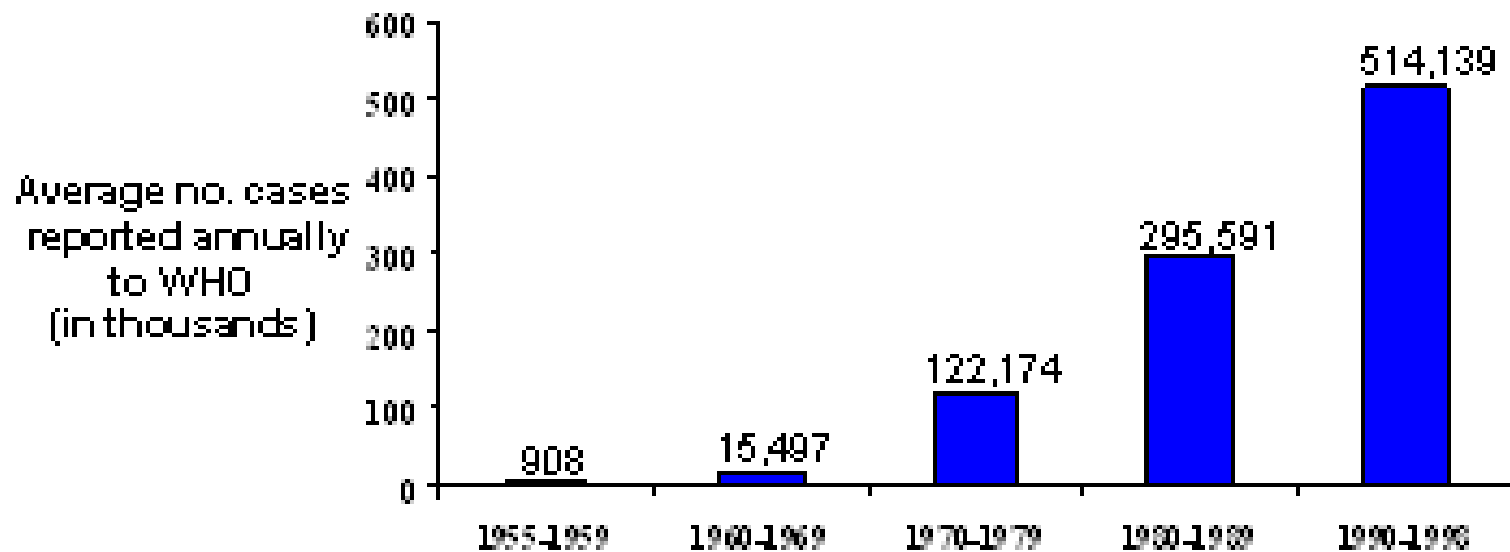
World distribution of Dengue and primary vector *Aedes Aegypti*

World Distribution of Dengue - 2000

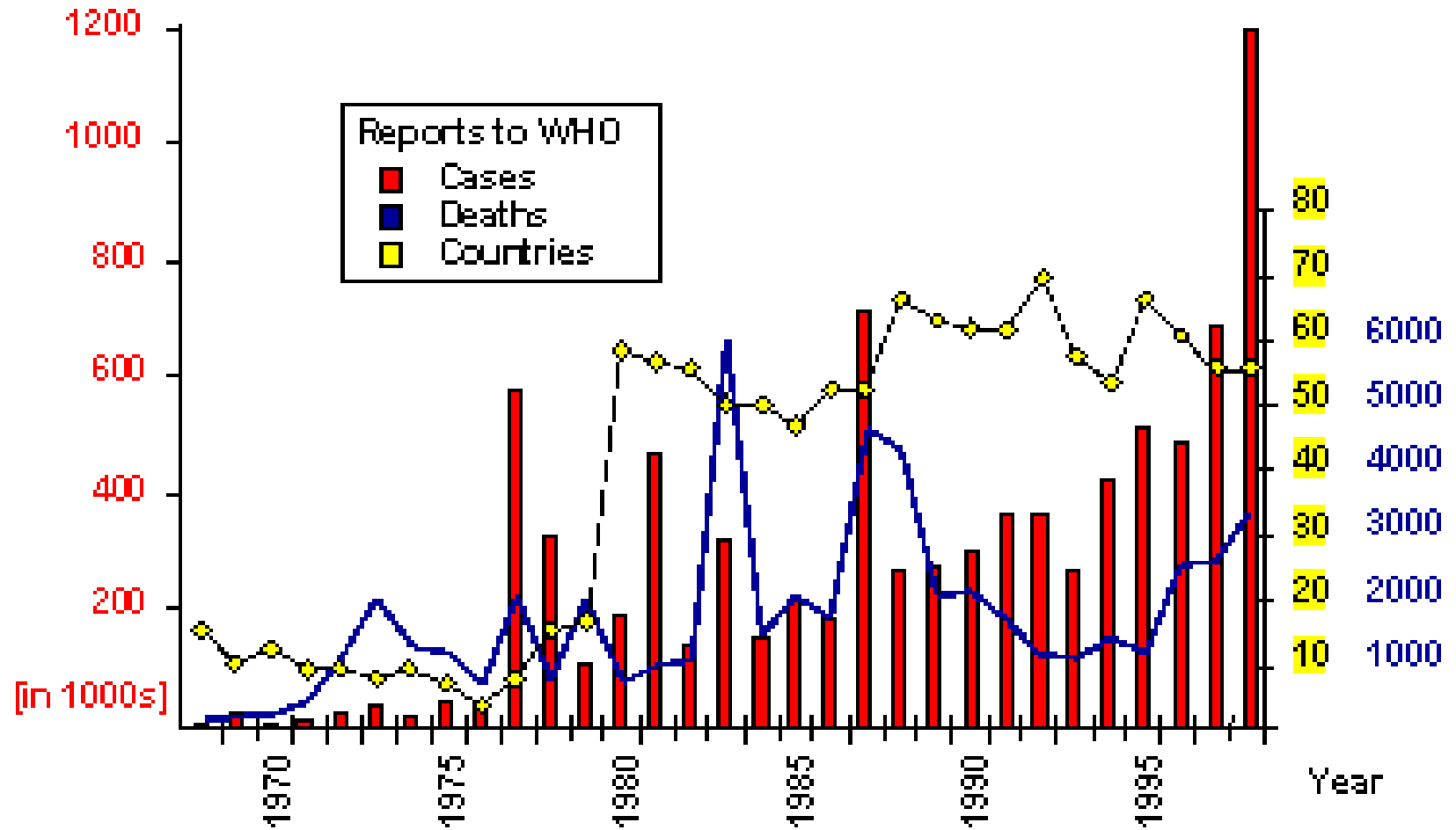


- Areas infested with *Aedes aegypti*
- Areas with *Aedes aegypti* and dengue epidemic activity

Rapid Increase of Dengue/Dengue Hemorrhagic Fever




Dengue/Dengue Haemorrhagic fever World-wide (1968 - 1998)






Virology and pathogenesis

- Family Flaviviridae (flavivirus)
 - 40-50 nm single stranded RNA viruses
 - Spherical lipid envelope from host cell membrane
 - 7 proteins make up the genome which are formulated from 11,000 bases.
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Virology and pathogenesis

- Flavivirus family: Yellow fever, Japanese Encephalitis, St. Louis Encephalitis, West Nile, Murray Valley, Kayanapur Forrest Disease, and tick born encephalitis.
 - Similarities entail common epitopes on envelope proteins resulting in cross reaction of serologic tests.
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Virology and pathogenesis

- 4 serological types of Dengue
 - DEN-1, DEN-2 (5 genotypes)
 - DEN-3 (4 genotypes)
 - DEN-4 (2 genotypes)
 - Genetic variance a correlation to epidemic transmission? (Has not been studied)
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Virology and pathogenesis

- Infection with one dengue virus serotype results in specific lifelong homotypic immunity, but cross protective heterotypic immunity may last 2-12 months exposed individuals can theoretically be infected with all 4 serotypes.
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Virology and pathogenesis

● Transmission variables:

- Human behavior
 - Prevention/control
 - Education campaigns
 - Susceptible human population
 - Chronic preexisting co morbidities
 - Previous infection
 - Risk Factors for hemorrhage in severe Dengue infections Journal of pediatrics Volume 140 Number 5 Sept 2002
 - Passive acquired maternal antibodies
 - Concept of antibody dependent enhancement
 - Environment
 - Rainfall, Temperature variation
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Virology and pathogenesis


● Transmission variables

- Viral virulence hypotheses
- Primary Vectors
 - *Aedes aegypti*
 - *Aedes albopictus*
 - Mosquito life cycle and habits
 - Peak feeding hours
 - After 8-10 days with infected blood meal mosquito is infective for life
 - Females nervous feeders (single mosquito infection)






Virology and pathogenesis

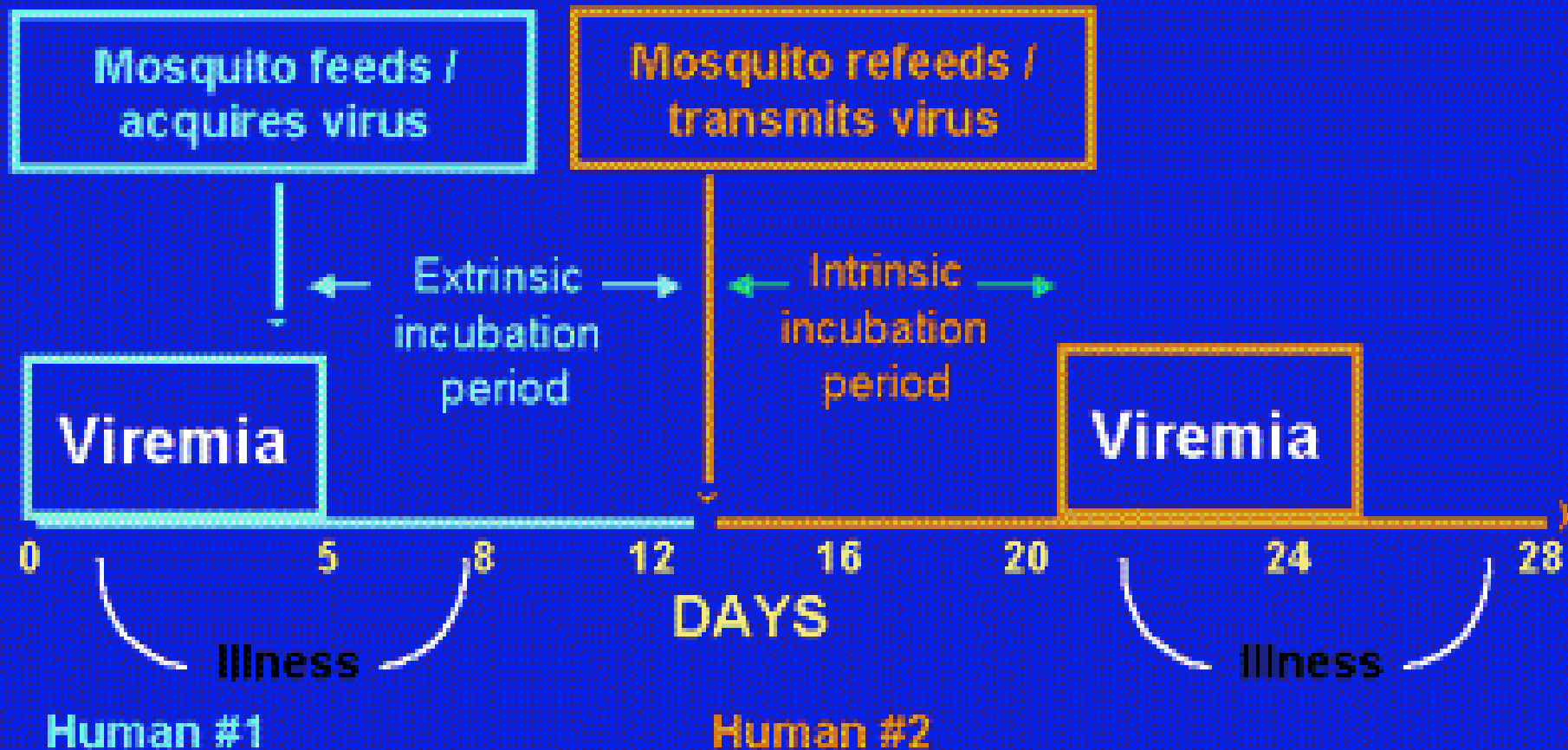
- Mosquito has blood meal inoculates human with virus.
 - Viral incubation 4-7 days (Symptoms depend on age, strain, immune status etc.)
 - Viremia peaks around onset of symptoms may last 2-12 days.
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Virology and pathogenesis


- In Some secondary infections, viremia may not be detected due to virus complex with heterologous antibodies.
 - Principal site of replication of the virus is in the cells of mononuclear phagocyte lineage.
 - Viral antigens have been found in kidney, liver, spleen, thymus, lung, saliva and skin.
Isolates have also been found in brain
BBB passage?
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Dengue transmission





Virology and pathogenesis

- Antibody dependent enhancement suggests that preexisting nonneutralizing heterologous dengue antibodies developed as a consequence of prior infection or acquired transplacentally enhance the infection and replication of a second virus.
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Virology and pathogenesis

- Subsequent to antibody enhancement there is an increased number of infected cells.
 - Increased production of cytokines
 - Increased vascular permeability
 - Hypovolemia
 - Shock
 - Hemostatic abnormalities






Cytokine production and pathology


● CD4: IFN- α , IL-2, TNF- α and TNF- β

● CD8: IFN- α

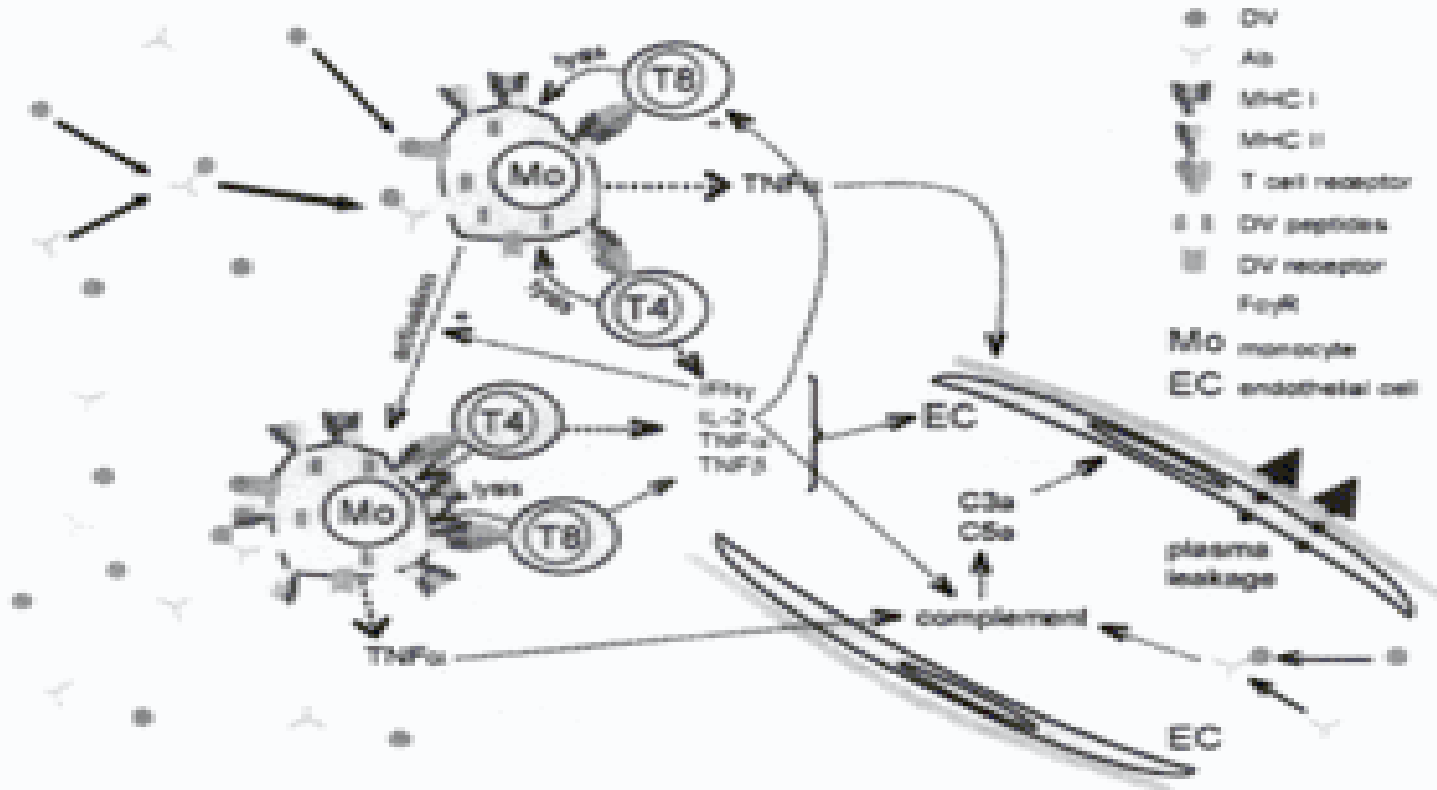




Indirect and direct effects on vascular endothelium

- TNF- α and IL-2: plasma leak
 - IFN- α Stimulation production of TNF- α as well as enhancement of antigen presentation.
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Model for immunopathogenesis of plasma leakage in DHF





Virology and pathogenesis

- Increased viral virulence hypotheses
 - Selective pressure
 - Invertebrate and vertebrate host
 - Genomic variation
 - Confer enhanced virulence
 - Epidemic potential



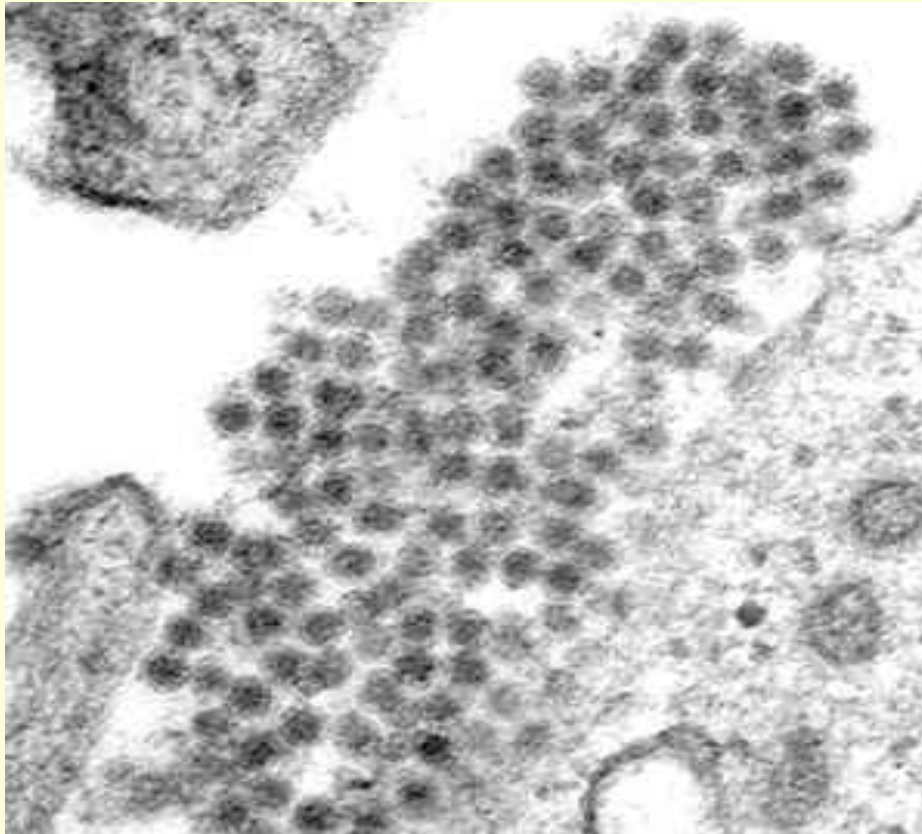


Gross pathology

- Petechial hemorrhages and ecchymoses
 - Pleural and Peritoneal effusions
 - Pulmonary edema
 - Vasculitis of small vessels
 - Midzonal Hepatic Necrosis
 - Subendocardial left ventricle and gastric mucosal hemorrhages
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Electron microscopy

Dengue viral particles






Clinical manifestations

- Clinical Manifestations of Dengue may be categorized in any one of five typical presentations.
 - Nonspecific febrile illness
 - Classic Dengue Fever
 - Dengue Hemorrhagic Fever
 - Dengue Shock Syndrome
 - Other severe Dengue syndromes
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Classic Dengue

- Older children, adults effected
 - Less virulent infection
 - Fever
 - Malaise
 - Rash
 - Dx often unreported Rx symptomatic
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Classic Dengue

- More severe infection
 - Erythematous mottling, chills (5-7 Days)
 - High fever first 2 days (may be preceded by above) *in young children biphasic temperature curve with paradoxical bradycardia during fever.*
 - Concomitant findings will be discussed:
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Classic Dengue

- Severe frontal, orbital/retroorbital headaches.
 - Myalgias: arms, legs, lower back, leg pains, arthralgias (shoulders, knees).
 - Prostrating weakness, anorexia.
 - Macular/macular papular rash appears around third day over (thorax, face, and flexure surfaces lasts 2-3 days).
 - Altered taste sensation, mild sore throat, cough, facial flushing and conjunctival injection.
 - Defervescence heralded by erythematous or itching sensation palmar or plantar surface followed by desquamation.
 - Hemorrhagic manifestations may appear petehiae, purpura, gingivorrhagia, epistaxis, metrorrhagia, and GI bleeding.
 - Death GI hemorrhage.
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Dengue Hemorrhagic

- Sudden Elevation Fever frequently (39-41 degrees) for 2-7 days
 - Fall in platelets with rising hematocrit
 - Febrile seizures in children
 - Ultra sound: peritoneal fluid accumulation, acalculous cholecystitis, hepatic ptosis.
 - Petechiae at venipuncture site, subcutaneous hemorrhage, purpura, ecchymoses, epistaxis, gingivorrhagia, GI bleeding, and less common hematuria.
 - Effusions right sided pleural and pericardial
 - Ascites
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**Typical erythematous skin lesion
“white islands in a sea of red”**



Typical skin lesion



Hemorrhagic erythema



Scleral bleeding conjunctival hemorrhage from DHF






Dengue Shock Syndrome

- Criteria for DHF plus signs of circulatory failure:
 - Narrowing pulse pressure ≤ 20 mm Hg
 - Hypotension or shock
 - Circulatory failure is rapid profound shock and death in 12-24 hours.
 - Poor prognosis with GI hemorrhage recurrent hypotension, complicated metabolic acidosis.
 - Profound shock
 - Recurrent shock
 - Respiratory Failure
 - High Level leukocytosis in absence of secondary bacterial infection
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Other Dengue syndromes


● Encephalopathy:

- Headache, seizure, stupor and coma
 - Meningeal irritation with lack of inflammatory response in CSF
 - Pathophysiology
 - Vascular leak
 - Metabolic consequences
 - Invasion of Dengue virus
- 



Other Dengue syndromes

● Cardiomyopathy

- Sinus tachycardia during febrile phase.
 - Sinus Bradycardia with various conduction defects.
 - Myocarditis and heart failure are rare
 - Pericardial effusions during vascular leak phase
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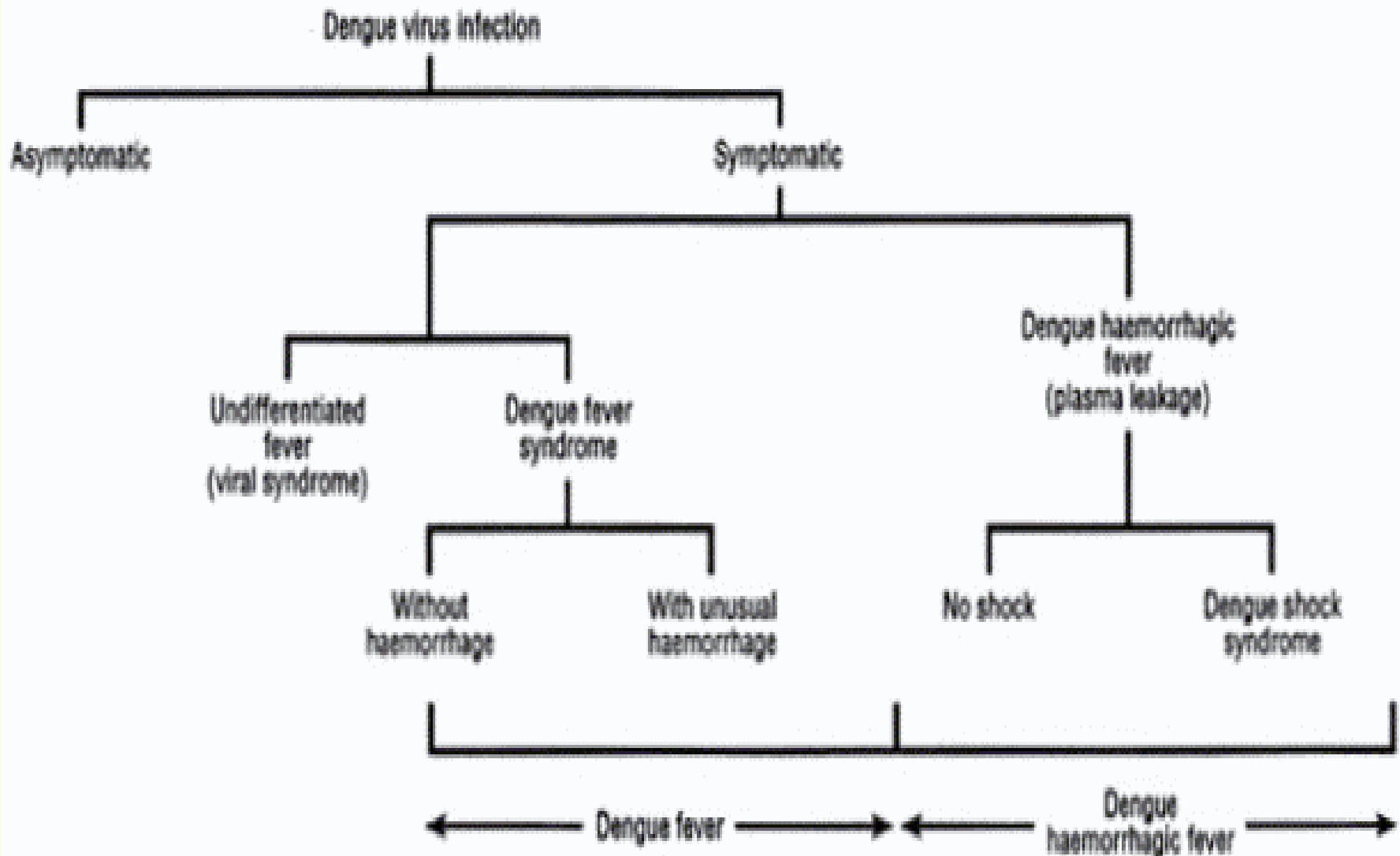


Other Dengue syndromes

● Renal complication

- Microscopic or macroscopic hematuria
 - More severe renal involvement due to renal hypoperfusion.
 - Acute glomerulonephritis has been associated with Dengue.
 - Other aspects
 - Gallbladder thickening
 - Splenic enlargement
 - Ascites
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Clinical symptoms






Differential Diagnosis

- Influenza (fever myalgia)
 - Rubella, Measels, Meningococemia (rash)
 - Typhoid fever (Headache, prostration, paradoxical bradycardia)
 - Malaria (preceding rigors)
 - Monocytic and granulocytic erlichiosis (leukopenia and thrombocytopenia)
 - Viral hepatitis or leptospirosis elevated liver enzymes
 - Yellow fever
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Diagnosis/Laboratory Diagnosis

- Diagnosis can be made clinically with an appropriate understanding of signs and symptoms. However in more complicated cases and for purposes of surveillance, confirmation, and designation of virus type a number of laboratory methods can be utilized.
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Laboratory Diagnosis

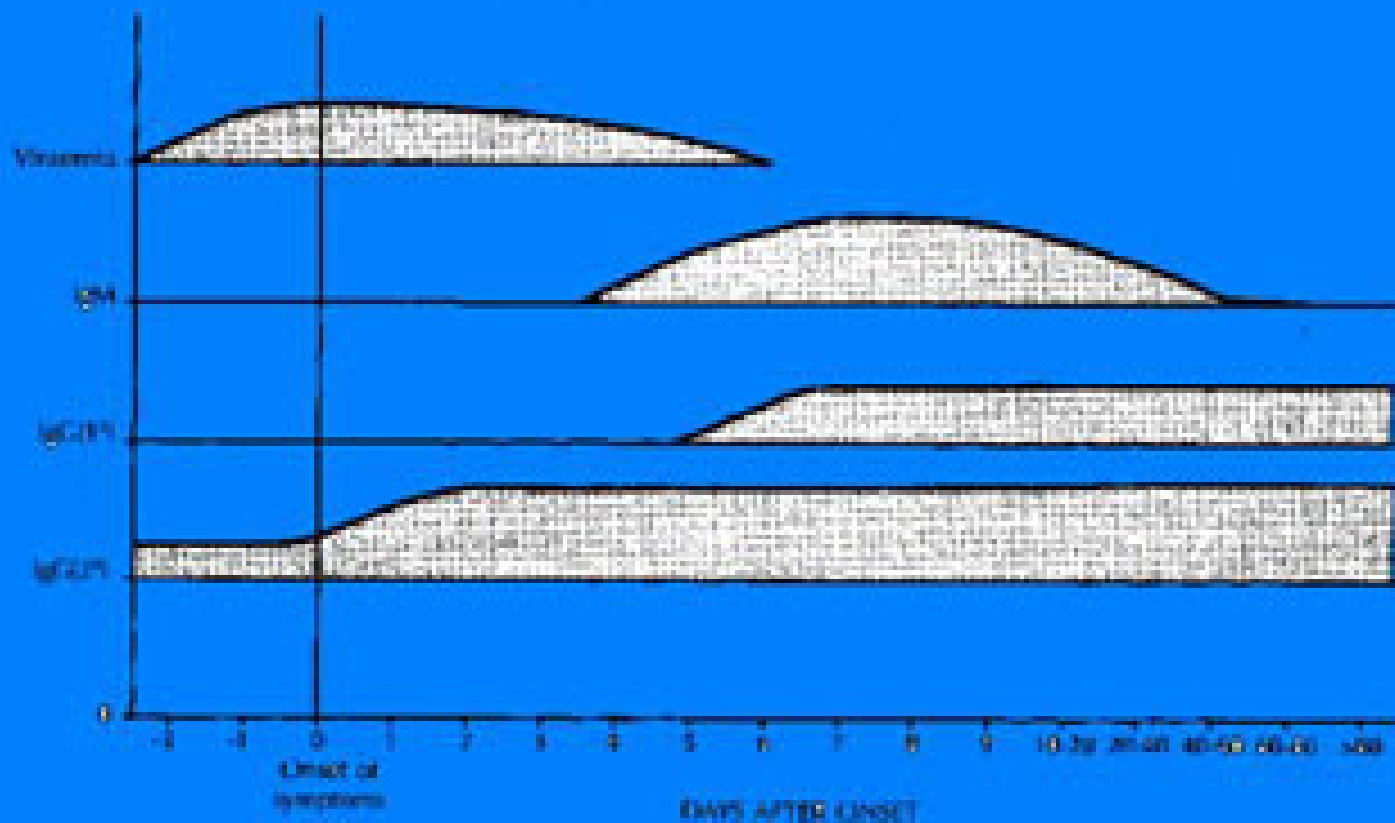
- 1) Intracerebral inoculation of baby mice.
 - 2) Mammalian Cell Culture
 - 3) Mosquito inoculation (most sensitive method)
 - Time consuming, slow, insensitive and expensive
 - 4) Culture in Mosquito cell lines
 - Best compromise for sensitivity, convenience and cost effectiveness
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Procedures for diagnosing Dengue cases

- Antibody detection
 - IgG and or IgM (a four fold increase IgG correlates with infx)
 - isolation identification of virus
 - Immunofluorescence
 - Cytopathic effect and immunofluorescence in mammalian cells
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Representation of the temporal appearance of virus, IgM, and IgG antibodies in persons infected with dengue virus.



Shaded areas represent approximate time periods when virus or antibody can be detected using current methods. 1 = primary infection; 2 = secondary infection. Cubán LR 1991, unpublished, prepared for Scientific Publication No. 548, WHO GJ 1994. --



Serological tests

- Hemagglutination-Inhibition test (HI)
 - Complement Fixation test
 - Enzyme linked Immunosorbent assay
ELISA
 - Immunochromatographic Card Test
 - Immunochromatographic Strip Test
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Laboratory diagnosis of Dengue Fever 1

- Complement fixation test
 - It is only suitable to detect primary infection
 - Needs highly trained personnel
 - Hemagglutination inhibition test
 - Highly sensitive
 - Based on inhibition of goose RBC agglutinating (property of Dengue virus by antibody in the serum)
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Laboratory Diagnosis of Dengue Fever 2

● Enzyme Linked Immunosorbent assay ELISA

- Widely used to detect IgG and IgM
 - Slightly less sensitive (88%) and high specificity (96%) when compared with (HI)
 - This can only be used in large hospital and labs
 - Time consuming and needs trained personnel
- 



Laboratory Diagnosis of Dengue Fever 3

- Immunochromatographic Strip test
 - Recombinant Dengue antigen used
 - Sensitivity 99.3% and specificity 92%
 - Immunochromatographic Card Test
 - Most widely used test, quick and easy.
 - Whole Dengue virus is used for detection of antibody.
 - Detects both IgG and IgM
 - Sensitivity 98.7% and specificity 82%
 - Both tests are used at Field level
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Significance of IgG and IgM


● Dengue

- Primary mostly IgM rarely IgM and IgG
- Secondary mostly IgG and/or IgG and IgM
- Only IgG cases can be considered as secondary or previous infection with Dengue

● IgG

- Appears late 10th day and remains for several months.

● IgM

- It is apparent by 5th day and fades away (30th day) early.
- 



Management

- Decision to admit the patient
 - Reliable IV line
 - Monitor over 24 hours
 - BP
 - HCT
 - Plt
 - Urinary output
 - Level of consciousness






Management

- Most dangerous period is vascular leakage 12-48hours
 - Similar to treating mild isotonic dehydration.
 - 0.9% NaCl are administered as maintenance
 - 10 to 20 mL/kg boluses every 30-60 minutes
 - Hct every 2-4 hours
 - Hourly urinary output
 - Massive leakage use colloid






Prevention and control

- Dengue Vaccine? (progress)
 - Mosquito Control
 - Public Education
 - Governmental agencies and specific strategy related to study of the virus and local and association with human behavior.
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Current topics/Research

- Host Reservoir?
 - Where does the virus reside between epidemics?
 - How does Human behavior correlate to epidemics and how does this effect economics.
 - Economic effects of dengue
 - Human behavior
 - Seasonality and agrarian societies (The Impact)
 - Increased Travel ... How is the US involved?
 - Immigrants, Vacationers etc...
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Conclusion

- The incidence Dengue/DHF has increased significantly over the last decades.
 - Yearly 50-100 million cases of DF and 250,000 - 500,000 cases of DHF occur world wide.
 - A vaccine and aggressive prevention strategies to curb the current trend of the disease is in dire need to reduce the significant increase in morbidity and mortality in Latin America and abroad.
 - The epidemiological situation of Latin America resembles that of South East Asia. It is my contention with an ever interdependent global economy this virus will influence economic progress in a number of countries and eventually the US if not already...
- 