

Virus Name: Dengue 4		Abbreviation: DENV
Status Arbovirus	Select Agent No	SALS Level 2
SALS Basis Results of SALS surveys and information from the Catalogue.		
Other Information DOC Permit Required		
Antigenic Group B		

SECTION I - Full Virus Name and Prototype Number

Prototype Strain Number / Designation H-241 (1,2)	Accession Number	Original Date Submitted 1/27/1985
Family Flaviviridae	Genus Flavivirus	
Information From W.McD. Hammon	Address Grad. Schl. of Public Health, Univ. of Pittsburgh, Pittsburgh, PA 15213	
Information Footnote Reviewed by editor		

Section II - Original Source

Isolated By (name) G. Sather and W.McD. Hammon	Isolated at Institute Grad. Schl. of Public Health, Univ. of Pittsburgh, Pittsburgh, PA 15213	
Host Genus Man	Species	Host Age/Stage 10 years
Sex Female		
<u>Isolated From</u>	<u>Isolation Details</u>	
Serum/Plasma		
Signs and Symptoms of Illness Sudden onset, fever, headache, muscle and joint pain, rash*	Arthropod	
Time Held Alive before Inoculation		
Collection Method Venipuncture	Collection Date 8/28/1956	
Place Collected (Minimum of City, State, Country) San Lazaro Hospital, Manila		
Latitude 14° 35' N	Longitude 121° E	
Macrohabitat Quezon City, Manila, Philippines	Microhabitat	Method of Storage until Inoculated Dry ice, then Revco freezer at -55dC or lower
Footnotes		

Section III - Method of Isolation

Inoculation Date
4/15/1957

Animal (Details will be in Section 6)
nb mice

Route Inoculated Intracerebral	Reisolation Yes
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Other Reasons
Subsequent isolations from other patients with antibody rise.

Homologous Antibody Formation by Source Animal
Not tested

Test(s) Used

Footnotes

Section IV - Virus Properties

Physicochemical

Pieces (number of genome segments)	Infectivity	Sedimentation Coefficients(s) (S)
Percentage wt, of Virion Protein	Lipid	Carbohydrate
Virion Polypeptides: Number	Details	
Non-virion Polypeptides: Number	Details	
Virion Density	Sedimentation Coefficients(s) (S)	
Nucleocapsid Density	Sedimentation Coefficients(s) (S)	

Stability of Infectivity (effects)

pH (infective range)

Lipid Solvent (ether - % used to test)	After Treatment Titer	Control Titer
Lipid Solvent (chloroform)	After Treatment Titer	Control Titer
Lipid Solvent (deoxycholate) 1:1000	After Treatment Titer <2.0 dex	Control Titer 6.5 dex (5)

Other (formalin, radiation)
Probably similar to types 1 and 2.

Virion Morphology

Shape Spherical	Dimensions 45-50 nm	
Mean nm	Range nm	
Measurement Method EM thin-sections of LLC-MK2 cells (3)	Surface Projections/Envelope Envelope spikes present; spherical incrystalline f	Nucleocapsid Dimensions, Symmetry Core size - 25.28 nm (4)

Morphogenesis

Site of Constituent Formation in Cell	Site of Virion Assembly Membranes of endoplasmic reticulum	Site of Virion Accumulation Cisternae of endoplasmic reticulum
Inclusion Bodies	Other	

Hemagglutination

Hemagglutination Yes	Antigen Source SMB ext. by sucrose-acetone	Erythrocytes (species used) Goose
pH Range 6.4-7.4	pH Optimum 7.0	
Temperature Range 24dC and 37dC.	Temperature Optimum 24dC (5)	

Remarks
See DEN 1 and 2 for HA and CF antigen fractions. * Seen during epidemic of Philippine hemorrhagic fever (incomplete clinical record).

Serologic Methods Recommended
PRNT, immunodiffusion, CF, HI

Footnotes
See DEN 1 and 2 for HA and CF antigen fractions. * Seen during epidemic of Philippine hemorrhagic fever (incomplete clinical record).

Section V - Antigenic Relationship and Lack of Relationship to Other Viruses

See DEN 1 and 2 for general antigenic relationships with other Group B viruses and dengue viruses.

Type 4 had the same early association with hemorrhagic fever as type 3, having been isolated first during an epidemic of Philippine hemorrhagic fever. Subsequent isolations elsewhere during epidemics without hemorrhagic fever cases places it in the same position as the other three types - found both in hemorrhagic fever patients and epidemics and in classical dengue fever patients and epidemics.

Section VI - Biologic Characteristics

Virus Source (all VERTEBRATE isolates)
 Blood (M), liver (M)

Lab Methods of Virus Recovery (ALL ISOLATIONS)
 Newborn mice; LLC-MK2 and mosquito cell cultures;
 inoculation of adult mosquitoes.

Cell system (a)	Virus passage history (b)	Evidence of Infection						
		CPE			PLAQUES			Growth Without CPE +/- (g)
		Day (c)	Extent (d)	Titer TCD50/ml (e)	Day (c)	Size (f)	Titer PFU/ml (e)	

Forms plaques in Vero and and LLC-MK2 (CL)(15); RMK (PC) and PS-Y-15 (CL) (16); MA-104 (CL) and MA-111 (CL) (17); forms plaques and produces CPE in PS (CL) (18); produces CPE in BHK-21 (CL) (19); multiplies and/or produces CPE in C6/36 (CL) Aedes albopictus (CL) (20) and AP-61 (CL) (21,22). Forms plaques in Aedes albopictus (23).

Section VII - Natural Host Range (Additional text can be added below table)

Vertebrate (species and organ) and arthropod	No. isolations/No. tested	No. with antibody/No. tested Test used	Country and region
Man *	Many		SE Asia(1,2), India(6), Philippine Is. (1,2), Indonesia, New Guinea
Aedes aegypti	Many		SE Asia, Philippine Is., India (7)

* Numerous isolations from acute phase blood, days 1-5. Principal source of mosquito infection.

Note: Aedes niveus and Anopheles (Cel) balabacensis introlatus most likely jungle canopy vectors for dengue in Gunong Besout Forest, Malaysia (25).

Experimental host and age	Passage history and strain	Inoculation Route-Dose	Evidence of infection	AST (days)	Titer log ₁₀ /ml
Mice (nb)	P >21	ic 0.01	Death	3	7.0-8.5
Mice (nb)		ip 0.03	Death	10-17	<1.0
Mice (nb)		sc			
Mice (wn)		ic 0.03	Death	8-20	7.5
Mice (wn)		ip 0.1	None		
hamster (ad)	P >21	ic 0.1	None		
guinea pig (yg)		ic 0.1	None		
rabbit (yg)		ic	None		
monkey (yg)	P 21	ic	NT antibody only		
(yg)	P >21	sc, intracut	NT antibody only		

Section IX - Experimental Arthropod Infection and Transmission

Arthropod species & virus source(a)	Method of Infection log ₁₀ /ml (b)		Incubation period (c)		Transmission by bite (d)		Assay of arthropod, log ₁₀ /ml (e)		
	Feeding	Injected	Days	°C	Host	Ratio	Whole	Organ	System

Parenteral passage in *Aedes albopictus* demonstrated.

Cannot be passed in *Blattella germanica*, *Cimex lectularis*, *Attagenus piceus*, *Plodia interpunctella*, *Culex tritaeniorhynchus*, or *Ornithodoros savignyi* (8).

Aedes aegypti readily infected by intrathoracic inoculation or feeding on viremic mice (10).

Natural transovarial transmission of DEN-4 virus in *Aedes aegypti* (26).

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Section X - Histopathology

Character of lesions (specify host)

In man: (See DEN-1). sm: varying degrees of neuronolysis, and chromatolysis. Lesions generally more severe in cerebral cortex. Vascular endothelium changes noted. No prominent perivascular infiltration (9).

Inclusion Bodies

Intranuclear

Organs/Tissues Affected

Brain (LV), spinal cord (LV), lungs (M), liver (M), heart (M), blood vessels (M), marrow (M); no consistent lesions noted in viscera of suckling mice.

Category of tropism

Neurotropic in mouse

Section XI - Human Disease

In Nature
Significant

Residual

Death
Significant

Subclinical

Overt Disease

Clinical Manifestations

Fever, headache, prostration, myalgia, arthralgia, CNS signs (including encephalitis), hemorrhagic signs, leukopenia, rash, lymphadenopathy, vomiting; abdominal pain, shock, thrombocytopenia, petechiae, positive tourniquet test in hemorrhagic fever of SE Asia

Number of Cases

Many; classical dengue fever and hemorrhagic fever

Category (i.e. febrile illness, etc.)

Febrile illness with rash, hemorrhagic fever

Section XII - Geographic Distribution

Known (Virus detected)

Essentially all countries of SE Asia; incl. Philippine Islands; Sri-Lanka; India, Rep. of China, S. Pacific, Cent. America, Surinam, Mexico, Colombia, Venezuela, Brazil, Caribbean,Guatamala, Honduras, W. Africa

Suspected (Antibody only detected)

Section XIII - References

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Remarks

Two recent series of articles relating to extensive studies made in Bangkok, Thailand after 1962 on dengue hemorrhagic fever by Halstead, S.B., et al. will be found in 1969, Amer. J. Trop. Med. Hyg. 18:954-1033, and 1970, Yale J. Biol. Med. 42:261-362. See also following Seminars: Symposium on Hemorrhagic Fever, SEATO Medical Res. Mono. No. 2, Bangkok, 1961, WHO Seminar on Mosquito-borne Hemorrhagic Fevers in the South-east Asia and Western Pacific Regions, Bangkok, 1964. Reports on the Second Regional Seminar on Virus Diseases; Mosquito-borne Virus Diseases, WHO Regional Office for the Western Pacific, Manila, 1969.