

Virus Name: Dengue 1		Abbreviation: DEN IV
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 Hawaii	Accession Number	Original Date Submitted 3/19/1985
Family Flaviviridae	Genus Flavivirus	
Information From W. McD. Hammon	Address Grad. Sch. Public Health, Univ. of Pittsburgh, Pittsburgh, PA 15213 USA	
Information Footnote Reviewed by editor		

Section II - Original Source

Isolated By (name) A.B. Sabin (1,2)	Isolated at Institute Cincinnati, Ohio	
Host Genus Man	Species	Host Age/Stage Adult
Sex Male		
<u>Isolated From</u>	<u>Isolation Details</u>	
Serum/Plasma		
Signs and Symptoms of Illness Compatible with dengue during extensive epidemic in Hawaii	Arthropod	
Time Held Alive before Inoculation		
Collection Method Blood of 6 patients 24-48 hrs after onset; pooled	Collection Date 2/20/1944	
Place Collected (Minimum of City, State, Country) Hawaii, USA		
Latitude 21° N	Longitude 155° W	
Macrohabitat	Microhabitat	Method of Storage until Inoculated Frozen on dry ice and transported to Cincinnati, Ohio
Footnotes		

Section III - Method of Isolation

Inoculation Date
3/23/1944

Animal (Details will be in Section 6)

Man*

Route Inoculated
Intracutaneous

Reisolation
Yes

Other Reasons

Homologous Antibody Formation by Source Animal

Not tested

Test(s) Used

Footnotes

Section IV - Virus Properties

Physicochemical
RNA, Single Strand

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 <2.0 dex	Control Titer 6.2 dex (8)
Lipid Solvent (chloroform)	After Treatment Titer	Control Titer
Lipid Solvent (deoxycholate) 1:100	After Treatment Titer <2.0 dex	Control Titer 6.9 dex (9)

Other (formalin, radiation)

Sens. to trypsin, chymotrypsin, papain, pancreatic lipase, sodium lauryl sulfate

Virion Morphology

Shape Spherical	Dimensions 50-55 nm	
Mean nm	Range nm	
Measurement Method Electron microscopy, negative staining (A)	Surface Projections/Envelope Enveloped, spiked particles	Nucleocapsid Dimensions, Symmetry

Morphogenesis

Site of Constituent Formation in Cell	Site of Virion Assembly	Site of Virion Accumulation
Inclusion Bodies	Other	

Hemagglutination

Hemagglutination Yes	Antigen Source SMB ext. by borate-KCl, pH 9; acetone-ether; sucrose-acetone	Erythrocytes (species used) Goose
--------------------------------	---	---

pH Range 5.8-6.8	pH Optimum 6.2
----------------------------	--------------------------

Temperature Range 4dC, 25dC, 37dC	Temperature Optimum 4dC, 24dC
---	---

Remarks

After exp. human passage virus adapted to wn mice by ic inoc. (2). 3 HA fractions and at least 3 CF's (4-6)

Serologic Methods Recommended

HI, CF, PRNT, immunodiffusion

Footnotes

After exp. human passage virus adapted to wn mice by ic inoc. (2). 3 HA fractions and at least 3 CF's (4-6)**Section V - Antigenic Relationship and Lack of Relationship to Other Viruses**

DEN 1 is antigenically closely related to other types of DEN virus. Currently, the dengue viruses are considered to be related more closely to each other than to other flaviviruses. The dengue viruses comprise a separate complex in Group B ([24], [25]). The concept of a complex or subgroup also exists partially on a disease, vector and epidemiologic basis. All DEN viruses possess one or more antigens common to others in Group B.

There appears to be considerable strain variation within types and a number of strains have been found difficult to type by standard methods ([11] - [13]).

TH-Sman, previously listed in the Catalogue (No. 163) was suggested as a possible type 6 since it was isolated from one of the early Thai hemorrhagic fever cases in Bangkok in 1958 ([11], [12], [14], [15]) and was found eventually to differ antigenically to a significant degree from type I Hawaii. Differences have been shown by CF ([11], [12]), plaque neutralization, [16] immunodiffusion and immunoelectrophoresis [18], and by the soluble CF (SCF) antigen [19] but not by antibody absorption in the HI test [20]. It is generally accepted that strain differences among DEN viruses may be rather prominent. Their significance is as yet unknown.

Section VI - Biologic Characteristics

Virus Source (all VERTEBRATE isolates)
Blood (M)(LV)

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

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)	

Cell cultures of many types, primary and continuous from monkeys; KB of man; primary hamster, and BHK-21, Ae albopictus cell lines

Vertebrate (species and organ) and arthropod	No. isolations/No. tested	No. with antibody/No. tested Test used	Country and region
Man:Very large number of isolations from acute phase blood days 1-5. Principal source of mosquito infection	Many		Hawaii, Southern Japan, SE Asia, India, Nigeria, New Guinea
Man		Many	Previously, not presently: Guam, Panama, French Oceana Australia. Currently: Indonesia, Ceylon
Monkeys	0	Numerous	SE Asia, Philippine Islands, etc., but type uncertain
Sentinel monkey (blood)	1		Malaysia (21)
Mosquitoes: Aedes aegypti	Many		SE Asia
Aedes niveus and Anopheles (Cel) balabacensis introlatus most likely jungle canopy vectors for dengue in Gunong Besout Forest, Malaysia (26).			

Experimental host and age	Passage history and strain	Inoculation Route-Dose	Evidence of infection	AST (days)	Titer log ₁₀ /ml
Mice (nb)	High pass. MB	ic 0.01	Paralysis and death	6-15	7.5-9
Mice (nb)		ip 0.1	Usually none		
Mice (nb)		sc			
Mice (wn)		ic 0.03	Paralysis and death	10-20	6-7.5
Mice (wn)		ip 0.25	None		
Mice (nb)	Low pass. MB	ic 0.01	Irregular illness and death		
Mice (nb)		ip 0.1	Relatively rare		
Mice (nb)		ic 0.01	None		
hamster (nb)	High pass. MB	ic 0.02	Irregular deaths		
hamster (3-4 wk)		ic 0.05	Usually none		
monkey (yg ad)		ic 0.5	Encephalitis and death		
monkey	Low pass. MB	ic,sc,iv	Viremia only		Undil. -3.0
gibbons monkey		sc	Viremia		
man		sc,intracut.	Dengue fever; nonfatal		
rabbits, guinea pigs (yg)	High or low pass. MB	ic,sc	None		
embryonated eggs	High pass. MB		Adaption after many passages; low titer only		

Section IX - Experimental Arthropod Infection and Transmission

Arthropod species & virus source(a)	Method of Infection log10/ml (b)		Incubation period (c)		Transmission by bite (d)		Assay of arthropod, log10/ml (e)		
	Feeding	Injected	Days	°C	Host	Ratio	Whole	Organ	System
Aedes aegypti, Ae albopictus, Ae scutellaris complex									
Transmission readily effected after feeding on infective man, monkey, mouse, mouse brain suspension. Extrinsic incubation essential									

Section X - Histopathology

Character of lesions (specify host)
In man: Classical dengue fever; focal vascular lesion at sight of rash. DEN hem. fever of SE Asia; petechial hemorrhages throughout most organs and skin, frequently a few liver lesions closely resembling those of yellow fever, interstitial pneumonia, fluid in various body cavities. (Councilman bodies in liver)

Inclusion Bodies Intranuclear
Man

Organs/Tissues Affected
Lungs (M), liver (M), heart (M), blood vessels (M), marrow (M) (these are for SE Asian hemorrhagic fever only. See texts for dengue fever).

Category of tropism
Vascular without necrosis or inflammation

Section XI - Human Disease

In Nature	Residual	Death
Significant		Significant
Subclinical	Overt Disease	
Reported	Reported	

Clinical Manifestations
Fever, headache, prostration, stiff neck, myalgia, arthralgia, CNS signs (including encephalitis), hemorrhagic signs, respiratory involvement, leukopenia, CNS pleocytosis, rash, lymphadenopathy, jaundice, vomiting, melena, hematemesis, hemoptysis, etc. (SE Asian hem. fever)

Number of Cases	Category (i.e. febrile illness, etc.)
Probably millions but type specificity	Febrile illness; with rash; hemorrhagic

Section XII - Geographic Distribution

Known (Virus detected)

Caribbean basin, Central America, Mexico, southern USA, Colombia, Nigeria, Senegal, India, Bangladesh, SE Asia, including Philippines, various Pacific island groups, Australia (In addition to above) Past : Panama NA-CA-PM-00 Australia. AU-00-AS-00

Suspected (Antibody only detected)

Probably currently and endemic: Indonesia

Section XIII - References

1. Sabin, A.B. 1950. Bact. Reviews 14:225-232.
2. Sabin, A.B. and Schlesinger, R.W. 1945. Science 101:640-642.
3. Sabin, A.B. 1952. Am. J. Trop. Med. Hyg. 1:30-50.
4. Yoshinaka, Y. and Hotta, S. 1971. Proc. Soc. Exp. Biol. Med. 137:1047-1053.
5. Smith, T.J., et al. 1970. J. Virol. 5:524-532.
6. Matsumura, T., et al. 1967. Kobe J. Med. Sci. 13:273-293.
7. Ada, G.L. and Anderson, S.B. 1959. Aust. J. Sci. 21:259-260.
8. Hotta, S. and Evans, C.A. 1956. Virology 2:704-706.
9. Hammon, W.McD. and Sather, G.E. Unpublished data.
10. Cheng, P.Y. 1958. Virology 6:129-136.
11. Hammon, W.McD., et al. 1961. SEATO Med. Res. Monograph No. 2:30-35.
12. Hammon, W.McD. and Sather, G.E. 1964. Mil. Med. 129:130-135.
13. Halstead, S.B., et al. 1970. Yale J. Biol. Med. 42:261-275.
14. Hammon, W.McD., et al. 1960. Science 131:1102-1103.
15. Hammon, W.McD., et al. 1960. Trans. Assoc. Am. Phys. 73:140-155.
16. Ibrahim, A.N., et al. 1968. Proc. Soc. Exp. Biol. Med. 128:80-83.
17. Ibrahim, A.N. and Hammon, W.McD. 1968. J. Immunol. 100:86-92.
18. Ibrahim, A.N. and Hammon, W.McD. 1968. J. Immunol. 100:93-98.
19. McCloud, T.G., et al. 1971. Am. J. Trop. Med. Hyg. 20:964-968.
20. Clarke, D.H. Personal communication.
21. Brandt, W.E. 1970. J. Virology 6:500-506.
22. UC ICMR, San Francisco, CA. 1973. Unpublished data.
23. Halstead, S.B. 1984. Rev. Inf. Dis. 6:251-264.
24. De Madrid, A.T. and Porterfield, J.S. 1974. J. Gen. Virol. 23:91-96.
25. Calisher, C.H., et al. Personal communication. 1983.
26. Rudnick, A. et al. 1975. Unpublished data.

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. Am. J. Trop. Med. Hyg. 18:954-1033. and 1970. Yale J. Biol. and 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. Report on the Second Regional Seminar on Virus Diseases; Mosquito-borne Virus Diseases, WHO Regional Office for the Western Pacific, Manila, 1969.