Virus Name: Yellow fever	Abbreviation: YFV

Status
Arbovirus

Select Agent
No

SALS Level
3

SALS Basis
Results of SALS surveys and information from the Catalogue.

Other Information
DOC Permit Required, Hepa Filtration, Vaccination Recommended

Antigenic Group
B

SECTION I - Full Virus Name and Prototype Number

Prototype Strain Number / Designation
Asibi

Accession Number

Original Date Submitted
2/1/1985

Family
Flaviviridae

Genus
Flavivirus

Information From
R.M. Taylor

Address
National Institute for Medical Research, Mill Hill, NW7 1AA

Information Footnote
Revised by J.S. Porterfield. Reviewed by editor.

Section II - Original Source

Isolated By (name)
A. Stokes, et al. (1)

Isolated at Institute
Yellow Fever Res. Inst., Lagos, Nigeria

Host Genus
Man

Species

Host Age/Stage
28 years

Sex
Male

Isolated From	Isolation Details
Whole Blood	

Signs and Symptoms of Illness
"Mild case of yellow fever"; 15 hours after onset.(a)

Arthropod

Time Held Alive before Inoculation

Collection Method
Venepuncture

Collection Date
6/29/1927

Place Collected (Minimum of City, State, Country)
Kpeve Village, Ghana

Latitude
6° N

Longitude
0°

Macrohabitat
Tropical West Africa

Microhabitat
Village

Method of Storage until Inoculated
Citrated blood, 6 hrs. room temperature

Footnotes

Section III - Method of Isolation

Inoculation Date
6/29/2027

Animal (Details will be in Section 6)
Rhesus

Route Inoculated
Intraperitoneal

Reisolation
Not tried

Other Reasons
First successful isolation. Subsequent isolations and laboratory infections.

Homologous Antibody Formation by Source Animal
Yes

Test(s) Used
NT

Footnotes

Section IV - Virus Properties

Physicochemical
RNA, Single Strand

Pieces (number of genome segments)	Infectivity	Sedimentation Coefficients(s)
	Yes	**RNA=3.75 x 106 daltons (24)**(S)

Percentage wt, of Virion Protein	Lipid	Carbohydrate

Virion Polypeptides: Number
3

Details
Nucleocapsid; major virion envelope protein (usually glycosolated); nonglycosolated virion envelope protein (24).The complete nucleotide sequence for the RNA genome of yellow fever virus has been determined (24).

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
25%	**Reduced 3 dex**	

Lipid Solvent (chloroform)	After Treatment Titer	Control Titer

Lipid Solvent (deoxycholate)	After Treatment Titer	Control Titer
1:1000	**2.8 dex**	**6.9 dex**

Other (formalin, radiation)
Inactivated by trypsin

Virion Morphology

Shape	Dimensions
	22-38; 30-40 nm

Mean nm	Range nm	
Measurement Method **Filtration, electon microscopy**	Surface Projections/Envelope **Envelope observed**	Nucleocapsid Dimensions, Symmetry

Morphogenesis

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

Hemagglutination

Hemaggiutination **Yes**	Antigen Source **SMB; monkey serum; tissue cultures ext. by sucrose-acetone; acetone-ether; fluorocarbon-borate saline**	Erythrocytes (species used) **Goose**
pH Range **5.8-6.6**	pH Optimum **6.2**	
Temperature Range **4dC - 37dC**	Temperature Optimum **22dC**	

Remarks
(a) Fever = 103/F, severe headache, backache, prostration; symptoms subsided after 48 hours.

Serologic Methods Recommended
HI, CF, NT, IFA

Footnotes
(a) Fever = 103/F, severe headache, backache, prostration; symptoms subsided after 48 hours.

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

Yellow fever virus is the type species of the Group B arboviruses, or flavi- viruses. The type strain is the Asibi strain [b](reference [1]), a viscerotropic strain which has been maintained by serial passage in rhesus monkeys in which it produces a fatal illness [1] , [2] . The 17-D vaccine strain is derived from the Asibi strain by serial passage in tissue culture and in embryonated eggs [3] . The 17-D derivative appears to have an extra antigen not present in the parent strain nor in other yellow fever strains. Avian leukosis virus contaminated early 17-D vaccines, but leukosis-free vaccine is now prepared.
The French or Dakar viscerotropic strain [4] was adapted, after a few monkey passages, to mouse brain [5] . The resulting French Neurotropic strain (FN) is widely used in mouse neutralization tests. A high mouse passage FN strain has been used by the French for vaccination. 17-D virus passaged in mice has also been used as a vaccine.
Strains of yellow fever virus isolated in America lack an antigen present in African strains [6] .

For further reading on the early history of yellow fever see References [7] , [8] , [9] , [10] . For a more recent discussion see Reference [11] .
[12] not only confirmed the contention of Carlos Finlay that yellow fever was transmitted by Aedes aegypti but also demonstrated that the causative agent was filterable and thus were the first to show that a disease in man was due to a virus infection. However, the strain of yellow fever virus that was passed by Reed, et al., from man to man was not transferred to lower animals and was not retained. It would, therefore, seem appropriate to assign the first ""isolation"" of the virus to its continuous passage in monkeys by Stokes, et al. [1] and to designate Asibi as the prototype strain (R.M.T.).
[b] Reed, et al.

Section VI - Biologic Characteristics

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

Lab Methods of Virus Recovery (ALL ISOLATIONS)
Newborn and weanling mice, rhesus monkeys, monkey kidney and mosquito cell lines, inoc. of mosquitoes

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

Will propagate in a variety of cell cultures of vertebrate and invertebrate origin. Hamster, pig and monkey kidney cell lines most useful for CPE and plaque formation.

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	Numerous from blood	NT+, 90% in highly endemic or following severe epidemic	
Primates: Virtually all from blood and Africa	Infrequent	NT+, high % in highly endemic areas and following recent epizootics.	
Monkey (blood) (Bitten by A. variegatum larvae)	1		Central African Rep.(18)
Marsupials; some species		NT+ in some localities	
Aedes, aegypti, Ae simpsoni	Found infected in nature (8)		
Ae africanus	Found infected in nature (8)		
Hemagogus leucocelaenus	Found infected in nature (8)		
Haemagogus species and Sabethes chloropterus	Found infected in nature (13)		
Aedes africanus + Ae opok	4		Central African Rep.(15)
Aedes africanus	1		Central African Rep.(15)
Amblyomma variegatum eggs, larvae	1 ea		Central African Rep.(18)

Two epidemiological patterns recognized: urban, man-mosquito-man, usually transmitted by Aedes aegypti; and jungle or sylvan, involving forest vertebrates, usually if not exclusively primates and forest mosquitoes, mainly Haemagogus in the western hemisphere and Ae africanus in Africa.Man tangentially infected. Ae simpsoni important intermediate vector in human infections in Africa.

Section VIII - Susceptibility to Experimental Infection (include viremia)

Experimental host and age	Passage history and strain	Inoculation Route-Dose	Evidence of infection	AST (days)	Titer log10/ml
Mice [a]		ic 0.02	Paralysis, death	5-7	8.0
Mice (nb)		ip 0.03	Paralysis, death	5-7	7.0
Mice (nb)		sc			
Mice (wn)		ic 0.03	Paralysis, death	7-8	6.0
Mice (wn)		ip 0.5	Paralysis, death	8-12	4.0+
Vertebrates:	All primates susceptible to infection but fatality depends upon species and manner of inoculation and strain. Most susceptible species found in India and S. America. African species circulate virus but rarely die. Some species of Marsupials circulate virus. Wild rodents generally resistant, as well as avian species tested. Only mosquitoes found susceptible. The following mosquitoes will tramsmitt infection; African: Aedes aegypti, Ae luteocephalus, Ae stokesi, Ae vittatus, Ae taylori, Ae metallicus, Eretmapodites chrysogaster, Mansonia africana and Culex thalassius. American: Aedes scapularis, Ae fluviatilis, Hemagogus leucocelaenus, Runchomyia frontosus, Sabethes chloropterus and various members of the genus Haemagogus. (8,14).				

[a] Susceptibility depends largely upon strain and passage.

Section IX - Experimental Arthropod Infection and Transmission

Arthropod species & virus source(a)	Method of Infection log10/ml (b)		Incubation period (c)		Transmision by bite (d)		Assay of arthropod, log10/ml (e)		
	Feeding	Injected	Days	°C	Host	Ratio	Whole	Organ	System
Transovarial trans. of YF virus demonstrated in three colonized geog.strains of Ae aegypti following intrathoracic inoculation, in Ae aegypti(Santo Domingo) following oral infection, and in Ae mascarensis following intrathoracic inoculation (17).									
Exp. trans. of YF virus from monkey to monkey by the tick Amblyomma variegatum (18). Transstadial passage from nymph to adult stage also.									
YF virus isolated from 55 pools of female, 3 pools of male Aedes (Dic) furcifer-taylori in Kedougou, Senegal (23). An example of natural transovarial transmission.									

Section X - Histopathology

Character of lesions (specify host)
Primates: unmodified strains occuring in nature are pantropic, affecting a variety of organs, tissues, and producing striking changes in liver, characterized by midzonal necrosis. The distinctive hyaline degeneration has been referred to as Councilman bodies.

Inclusion Bodies
Intranuclear
Man, Lower Vertabrates

Organs/Tissues Affected
Liver, (M)(LV), kidney (M)(LV), blood vessels (M)(LV). Encephalitis in mice

Category of tropism
Pantropic; liver and kidneys especially involved.

Section XI - Human Disease

In Nature
Significant

Residual

Death
Significant

Subclinical
Reported

Overt Disease
Significant

Clinical Manifestations
Fever(S), headache (S), prostration (S), conjunctival inflammation (S), hemorrhagic signs(S), respiratory involvement(R), leukopenia (S), jaundice (S), vomiting (S). Other significant symptoms: "black vomit".

Number of Cases
Many thousands

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

Section XII - Geographic Distribution

Known (Virus detected)

Endemic in rain forests of Africa and S. America, usually within 12/ N and S. of equator. At intervals epidemic extensions occur N. and S. in both Africa and S. America.

Suspected (Antibody only detected)

Recent severe epidemics in Ethiopia (1960-62) and Northern Nigeria (1969); also Brazil (1972-73) and The Gambia (1978). See References 19-22.

Section XIII - References

1. STOKES, A., et al. 1928. Am. J. Trop. Med. 8:103, 164.
2. TIGERTT, W.D., et al. 1959. Trans. New York Acad. Sci., Series 11, 22, 323-333.
3. THEILER, M. Les Prix Nobel en 1951. "The development of vaccines against yellow fever". Stockholm, 1952. 174-182.
4. MATHIS, E., et al. 1928. C.R. Acad. Sci. (Paris) 186:604-606.
5. THEILER, M. 1930. Ann. Trop. Med. Parasitol. 29:249-272.
6. CLARKE, D.H. 1960. J. Exp. Med. 111:1-20.
7. CARTER, H.R. "Yellow fever: an epidemiological and historical study of its place of origin". Williams and Wilkins Co., Baltimore, 1931.
8. STRODE, G.K. "Yellow fever". McGraw-Hill Book Co., New York, 1951.
9. BAKER, T.H. 1968. Bull. Hist. Med. 42:241-264.
10. BLAKE, J.B., et al. 1968. Bull. N.Y. Acad. Med. 44:673-727.
11. World Health Organization Technical Report, 479, 1971.
12. REED, W., et al. 1901. JAMA 36:431 and U.S. Senate Doc. 822, 1911.
13. DE RODANICHE, E. and Galindo, P. 1957. Am. J. Trop. Med. Hyg. 6:232.
14. DE RODANICHE, E., et al. 1959. Am. J. Trop. Med. Hyg. 8:190.
15. Rapport Annuel de l'Institut Pasteur de Bangui. 1974.
16. AITKEN, T.H.G., et al. 1979. Am. J. Trop. Med. Hyg. 28:119-121.
17. BEATY, B.J., et al. 1980. Am. J. Trop. Med. Hyg. 29:125-132.
18. CORNET, J.P., et al. 1982. Bull. Soc. Pathol. Exot. Filiales (France). 75:136-140.
19. PINHEIRO, F.P., et al. 1978. Am. J. Trop. Med. Hyg. 27:125-132.
20. PINHEIRO, F.P., et al. 1981. Ibid. 30:204-211.
21. SALAUN, J.J., et al. 1980. Med. Trop. 41:45-51.
22. CHIPPAUX, A., et al. 1981. Ibid. 41:53-61.
23. Cornet, M. et al. 1979. Med. Mal. Infect. 9:63-66.
24. RICE, C.M., et al. 1985. Science 229:726-733.
25. MONATH, T.P. 1985. Science 229:734-735.

Remarks

Endemically maintained by wandering epizootics principally if not wholly among primates and transmitted by forest mosquitoes. Endemic and epidemic areas have been defined mainly by serological methods but frequently can be verified by virus isolation. With the exception of former urban outbreaks in North America and Southern Europe, transmitted from man to man by Aedes aegypti, yellow fever as far as is known has been confined to Africa, South America and parts of Central America. In 1948 an extension northward of jungle yellow fever began in the Panama Canal Zone and by 1959 had reached the southern border of Mexico. Monkeys were mainly affected but there were also some tangential human infections. In 1960 a severe outbreak with many deaths was reported in Ethiopia. In the past, epidemics occurred in North America and Southern Europe.