Flavivirus[‡]

Flaviviridae

Edwin G. Westaway

■ Kunjin virus. Fig. 1
negative stain. Length of bar [nm]: 50 [previously unpublished by E. G. Westaway]

Virion

Morphology:	spherical, possibly icosahedral
Envelope:	yes
Diameter [nm]:	45–50
Length [nm]:	-
Structural components:	core particle enclosed in envelope (a lipid bilayer)
Buoyant density [g/mL]:	1.22–1.24
Additional information:	sediments at about 200 S; spikes appear on virion at low pH

[‡]This chapter was reprinted from the first edition of the Springer Index of Viruses. Taxonomy and classification of the virus species described in this chapter may have changed.

Genome

Nucleic acid:	RNA
Strandedness:	single-stranded
Polarity:	positive-sense
Configuration:	linear
Segments:	1
Size [kb]:	11
G + C content [%]:	48
Transcription units:	1
Additional information:	5' cap; gene order C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5; no poly(A) tail; conserved 5' and 3'-terminal stem loops

Replication Strategy

Entry mechanism:	receptor-mediated endocytosis, fusion with endosomal membrane
Site of transcription:	cytoplasm
Transcriptase:	viral replicase copies RNA(+) into full length RNA(–)
Site of genome replication:	induced membranes (vesicle packets) in cytoplasm
Replicase:	virus-encoded RNA-dependent RNA polymerase (NS5)
Replication intermediate:	double-stranded RNA with nascent RNA (+) strand
Site of virion assembly:	in endoplasmic reticulum and accumulation in vesicles
Egress mechanism:	cytoplasmic vesicles released by exocytosis (budding rarely observed)
Additional information:	the single open reading frame of genomic RNA is translated as a polyprotein, co- and post-translationally cleaved by cell signal peptidase and at dibasic sites by the viral protease; replicase complex: NS1, NS2A, NS3, NS4A, NS5

History

Year	Event/Discovery	Reference
1900	Transmission of yellow fever by mosquitoes	Reed W, Carroll J (1902) Amer Med 3:301–305
1959	Infectious RNA extracted from virions (Murray Valley encephalitis virus)	Anderson SG, Ada GL (1959) Aust J Exptl Biol Med Sci 37:353–364
1960	Dengue virus associated with dengue haemorrhagic fever	Hammon WMCD, et al. (1960) Science 131:1102–1103
1968	IgM has greater specificity than IgG antibody in flavivirus hemagglutination-inhibition tests	Westaway EG (1968) Nature 219:78–79
1968	Electron microscopy of membranes induced in cells during flavivirus infections	Murphy FA, et al. (1968) Lab Invest 19:656–662
1969	Flavivirus structural proteins first defined (dengue type 2, Kunjin viruses)	Stollar V (1969) Virology 39:426–438; Westaway EG, Reedman BM (1969) J Virol 4:688–693

Year	Event/Discovery	Reference
1970	Dengue haemorrhagic fever associated with dengue serotype cross reactive antibodies	Halstead SB, et al. (1970) Yale J Biol Med 42:311–328
1977	All virus-specified proteins recognized in cell lysates were unrelated (Kunjin virus)	Wright PJ, et al. (1977) J Virol 24:651–661; Wright PJ, Westaway EG (1977) J Virol 24:662–672
1977	Absence of subgenomic RNA in infected cells (Kunjin virus)	Boulton RW, Westaway EG (1977) Arch Virol 55:201–208
1981	Replicative intermediate (RI) and replicative form (RF) RNAs identified (dengue type 2 virus)	Cleaves GR, et al. (1981) Virology 111:73–83
1985	RF identified as recycling template for asymmetric semi-conservative RNA synthesis (Kunjin virus)	Chu PWG, Westaway EG (1985) Virology 140:68–79
1985	New virus family Flaviviridae created	Westaway EG, et al. (1985) Intervirology 24:183–192
1985	Nucleotide sequence of the yellow fever virus genome, the gene order and predicted 3'-terminal stem loop	Rice CM, et al. (1985) Science 229:726–733
1986	Evidence that an acidic environment promotes rapid uncoating of cell-associated West Nile virus	Gollins SW, Porterfield JS (1986) J Gen Virol 67:1941–1950
1988	Translation strategy defining all correct cleavages in the polyprotein (Kunjin virus)	Coia G, et al. (1988) J Gen Virol 69:1–21; Speight G, et al. (1988) <i>ibid</i> 69:23–34
1988	Characteristic 5'-terminal stem loop structure predicted for several flaviviruses	Brinton MA, Dispoto JH (1988) Virology 162:290–299
1989	Antigenic structure of envelope protein at the molecular level (tick-borne encephalitis virus)	Mandl CW, et al. (1989) J Virol 63:560–571
1989	Infectious yellow fever virus RNA transcribed from ligated cDNA	Rice CM, et al. (1989) New Biologist 1:285–296
1990	Role of N-terminal domain of NS3 established as serine protease cleaving viral polyprotein at dibasic sites	Preugschat F, et al. (1990) J Virol 64:4364–4374; Chambers TJ, et al. (1990) Proc Natl Acad Sci USA 87:8898–8902
1991	NS3 serine protease and co-factor NS2B are required for cleavages at dibasic sites in the viral polyprotein	Falgout BJ, et al (1991) J Virol 65:2467–2475; Chambers TJ, et al. (1991) <i>ibid</i> 65:6042–6050
1992	Active replicase complex purified with induced membranes and separated from structural proteins (Kunjin virus)	Chu PWG, Westaway EG (1992) Arch Virol 125:177–191
1993	Carboxy terminal domains of NS3 contain NTPase and RNA triphosphatase activities (West Nile virus)	Wengler G, Wengler G (1991) Virology 184:707–715; Wengler G, Wengler G (1993) Virology 197:265–273
1995	Crystal structure solved for envelope protein (tick-borne encephalitis virus)	Rey F, et al. (1995) Nature 375:291–298
1996	NS5 shown to copy RNA non-specifically in vitro (dengue type 1 virus)	Tan B-H, et al. (1996) Virology 216:317–325
1996	Putative sites of viral RNA synthesis and protease activities identified by cryo-immuno-electron microscopy	Mackenzie JM, et al. (1996) Virology 220:232–240; Westaway EG, et al. (1997) J Virol 72:823–829
1997	Subgenomic non-cytopathic self-replicating RNA (Kunjin virus replicon)	Khromykh AA, Westaway EG (1997) J Virol 71:1497–1505
1998	Apoptosis in the mouse central nervous system during infection with dengue viruses	Despres P, et al. (1998) J Virol 72:823–829
1998	Consensus composition of the replicase complex: NS1, NS2A, NS3, NS4A, NS5 with dsRNA (Kunjin virus)	Mackenzie JM, et al. (1998) Virology 245:203–215
1999	Crystal structure solved for NS3 protease domain (dengue type 2 virus)	Murthy MHK, et al. (1999) J Biol Chem 274:5573–5580; Brinkworth RI, et al. (1999) J Gen Virol 80:1167–1177
1999	Helicase and NTPase activities of NS3 localized to amino acids 160 to 180 (dengue type 2 virus)	Li H, et al. (1999) J Virol 73:3108–3116

Genus Members

Species	Abbr.	Synonym(s)	Wild-type isolates	Host range	Membership status
Yellow fever virus	YFV		Asibi, French viscerotropic	mosquitoes, ticks, humans, monkeys	type species
Apoi virus	APOV			rodents	approved member
Aroa virus	AROAV		Bussuquara, Iguape, Naranjal	mosquitoes, rodents	approved member
Bagaza virus	BAGV		DakArb209	mosquitoes, mammals	approved member
Banzi virus	BANV		SAH336	mosquitoes, rodents	approved member
Bouboui virus	BOUV		DakArb409	mosquitoes, mammals	approved member
Bukalasa bat virus	BBV		UgBP111	bats	approved member
Cacipacore virus	CPCV		BeAn327600	birds	approved member
Carey Island virus	CIV		P70–1215	bats	approved member
Cowbone Ridge virus	CRV		W-10956	rodents	approved member
Dakar bat virus	DBV		Dak249	bats, humans	approved member
Dengue virus	DENV		DENV-1, DENV-2, DENV-3, DENV-4	mosquitoes, humans, monkeys	approved member
Edge Hill virus	EHV		C281	mosquitoes, marsupials, humans (rare)	approved member
Entebbe bat virus	ENTV		Sokuluk, IL-30	bats	approved member
Gadgets Gully virus	GGYV		CSIRO-122	ticks, birds, mammals	approved member
Ilheus virus	ILHV		Rocio	mosquitoes, birds, mammals	approved member
Israel turkey meningoencephalomyelitis virus	ITV			mosquitoes, birds	approved member
Japanese encephalitis virus	JEV		Nakayama, Beijing, JaOArS982	mosquitoes, birds, pigs, humans	approved member
Jugra virus	JUGV		P9–314	mosquitoes, bats (possibly)	approved member
Jutiapa virus	JUTV		JG-1281	rodents	approved member
Kadam virus	KADV		AMP6640	ticks, mammals	approved member
Kedougou virus	KEDV		DakAar D1470	mosquitoes, humans	approved member
Kokobera virus	KOKV		MRM32, Stratford (C338)	mosquitoes, marsupials, humans (rare)	approved member
Koutango virus	KOUV		DakAnd5443	ticks, rodents	approved member
Kyasanur Forest disease virus	KFDV		W371, IP9605	ticks, birds, mammals	approved member
Langat virus	LGTV		TP21	ticks, rodents	approved member
Louping ill virus	LIV		Irish, British, Spanish, Turkish subtypes	ticks, birds, mammals	approved member

Species	Abbr.	Synonym(s)	Wild-type isolates	Host range	Membership status
Meaban virus	MEAV		Brest/Ar/T-707	ticks, seabirds	approved member
Modoc virus	MODV		M544	rodents	approved member
Montana myotis leukoencephalitis virus	MMLV		USA-B-310, A564	bats	approved member
Murray Valley encephalitis virus	MVEV		1/51, MRM66, Alfuy, MRM3929	mosquitoes, birds, mammals	approved member
Ntaya virus	NTAV			mosquitoes, birds, mammals	approved member
Omsk hemorrhagic fever virus	OHFV		157, Kubrin, Bogolukoba, Gubriev	ticks, mammals	approved member
Phnom Phenb bat virus	PPBV		A38/69, Batu Cave virus	bats	approved member
Powassan virus	POWV		LB, Byers	ticks, mammals	approved member
Rio Bravo virus	RBV		M64	bats	approved member
Royal Farm virus	RFV		Art371, Karshi	ticks, birds, mammals	approved member
Saboya virus	SABV		DakAnD4600, Potiskum	sandfly, mammals	approved member
Sal Vieja virus	SVV		78TWM-106	rodents	approved member
San Perlita virus	SPV		71 V1251	rodents	approved member
Saumarez Reef virus	SREV		CSIRO-4	ticks, seabirds	approved member
Sepik virus	SEPV		MK7148	mosquitoes, humans (rare)	approved member
St Louis encephalitis virus	SLEV		Hubbard, MSI.7, Parton	mosquitoes, ticks, birds, mammals	approved member
Tembusu virus	TMUV		MM1775	mosquitoes, birds, mammals	approved member
Tick-borne encephalitis virus	TBEV		European, Far Eastern, Siberian subtypes	ticks, birds, mammals	approved member
Tyuleniy virus	TYUV		LEIV6C	ticks, seabirds, mammals	approved member
Uganda S virus	UGSV			mosquitoes, birds, mammals	approved member
Usutu virus	USUV		SAAr1776	mosquitoes, birds, humans	approved member
Wesselsbron virus	WESSV		van Tonder, SAH177	mosquitoes, ticks, mammals	approved member
West Nile virus	WNV		Nigeria (Wengler), NY, Egypt, Sarafend, Kunjin, MRM61C, MRM16	mosquitoes, ticks, birds, mammals	approved member
Yaounde virus	YAOV		DakArY276	mosquitoes, birds, mammals	approved member
Yokose virus	YOKV			mammals	approved member
Zika virus	ZIKV		MR766, Spondweni	mosquitoes, monkeys, humans	approved member
Cell fusing agent virus	CFAV			mosquitoes	tentative member
Tamana bat virus	TABV			mosquitoes, bats	tentative member

■ **Flavivirus genome organization. Fig. 2**
in the polyprotein, upper arrows indicate cleavage sites in the cytosol by the viral serine protease NS3 and cofactor NS2B, and lower arrows cleavages in the lumen of the endoplasmic reticulum; signal sequences are shown as shaded bars. [figure prepared from data in Coia G, et al. (1988) *J Gen Virol* 69:1–21; Speight G, Westaway EG (1989) *J Gen Virol* 70:2209–2214]

Nucleotide Sequences

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	Dengue virus type 1	Singapore S275/90	10717	M87512	Fu J, et al. (1992) <i>Virology</i> 188:953–958
complete genome	Dengue virus type 2	Jamaica	10723	M20558	Deubel V, et al. (1988) <i>Virology</i> 165:234–244
complete genome	Dengue virus type 3	H87	10664	M93130	Osatomi K, Sumiyoshi H (1990) <i>Virology</i> 176:643–647
5' untranslated sequence and structural genes	Dengue virus type 4	Caribbean 814669	2429	M14931	Zhao B, et al. (1986) <i>Virology</i> 155:77–88
non-structural genes and 3' untranslated sequence	Dengue virus type 4	Caribbean 814669	8215	M17255	Mackow E, et al. (1987) <i>Virology</i> 159:217–218
complete genome	Japanese encephalitis virus	JaORS982	10976	M18370	Sumiyoshi H, et al. (1987) <i>Virology</i> 161:497–510
5' and 3' untranslated sequences	Kunjin virus	MRM61C	724	L24511	Khromykh AA, Westaway EG (1994) <i>Virology</i> 68:4580–4588
complete coding sequence	Kunjin virus	MRM61C	10664	D00246	Coia G, et al. (1988) <i>J Gen Virol</i> 69:1–21
structural genes	Langat virus	TP21	2328	M73835	Mandl CW (1991) <i>Virology</i> 185:891–895
non-structural genes	Langat virus	TP21	7917	S35365	Iacono-Connors LC, Schmaljohn CS (1992) <i>Virology</i> 188:875–880
complete genome	louping ill virus	369/T2	10871	Y07863	Gritsun TS, et al. (1997) <i>Virus Research</i> 49:27–39
5' untranslated sequence and C to NS3 genes	Murray Valley encephalitis virus	1–51	5436	X03467	Dalgarno L, et al. (1986) <i>J Mol Biol</i> 187:309–323
NS3 to NS5 genes and 3' untranslated sequence	Murray Valley encephalitis virus	1–51	5525		Lee E, et al. (1990) <i>Virus Genes</i> 4:197–213

Genomic region	Virus species	Strain	Nucleotides	Accession number	Reference
complete genome	Murray Valley encephalitis virus	1–51	11104	AF161266	Hurrelbrink RJ, et al. (1999) J Gen Virol 80:3115–3125
complete genome	Powassan virus	LB	10838	L06436	Mandl CW (1993) Virology 194:173–184
complete genome	Tick-borne encephalitis virus	Neudoerfl	11141	M27157	Mandl CW (1995) (direct submission)
complete genome	West Nile virus	Wengler	10960	M12294	Castle E (1986) Virology 149:10–26 (and unpublished)
complete genome	Yellow fever virus	French viscerotropic	10862	U21056	Wang E, et al. (1995) J Gen Virol 76:2749–2755
complete genome	Cell fusing agent virus		10695	M91671	Cammisa-Parks H, et al. (1992) Virology 189:511–524
C to NS2B genes	St. Louis encephalitis virus	MSL7	4673	M16614	Trent DW, et al. (1987) Virology 156:293–304
complete genome	Yellow fever virus	17D (vaccine)	10862	NC002031	Rice CM, et al. (1985) Science 229:726–733

Proteins

Protein	Abbr.	MW [kDa]	Time of expression	Accession numbers	Additional information
capsid or core	C	13.5	continuous	M87512, M20588, M93130, M14931, M17255, M18370, L24511, D00246, M73835, S35365, Y07863, X03467, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	binds to virion RNA in core; basic, poorly conserved; nuclear localization signal near C-terminus
precursor to M protein	prM	21–23	continuous	M87512, M20588, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	transmembrane glycoprotein; in envelope of immature virions
minor envelope protein	M	8.2–8.5	continuous	M87512, M20558, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	cleaved from prM by furin during maturation of virion
major envelope protein	E	54–59	continuous	M87512, M20558, M93130, M14931, M18370, D00246, M73835, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	glycosylated; as dimers in virion; crystal structure known
non-structural glycoprotein	NS1	45–47	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	forms dimers, secreted as hexamers; in replicase complex

Protein	Abbr.	MW [kDa]	Time of expression	Accession numbers	Additional information
non-structural protein 2A	NS 2A	24–25	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; in replicase complex
cofactor of viral protease NS3	NS2B	14.5	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, X03467, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; conserved C-terminal octapeptide
serine protease/helicase	NS3	69–70	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF16126, L06436, M27157, M12294, X03700, M91671, M16614, U21056	N- terminal protease; C-terminal helicase, NTPase; in replicase complex
non-structural protein 4A	NS4A	16	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF16126, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; membrane anchor role in replicase complex?
non-structural protein 4B	NS4B	26.0–27.5	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	hydrophobic; some nuclear localization (KUNV)
RNA-dependent RNA polymerase	NS5	104	continuous	M87512, M20558, M93130, M17255, M18370, D00246, S35365, Y07863, AF161266, L06436, M27157, M12294, X03700, M91671, M16614, U21056	C-terminal RdRp, N-terminal methyltransferase; variable phosphorylation

Biology

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Aroa virus	Vero, LLC-MK2	blood, brain	cell necrosis, plaques	CPE 6–9 days
Dengue virus types 1, 2, 3, and 4	BHK21, Vero, LLC-MK2, PS, BSC1, C6/36	blood, mononuclear phagocytes	cell necrosis, plaques, apoptosis (variable)	Dengue virus group; CPE 3–8 days (PS cells)
Japanese encephalitis virus	BHK, Vero, LLC-MK2, PS, mosquito	blood, brain, kidney, and others	cell necrosis, plaques	JEV group; mosquito-pig cycle; CPE 3–4 days
Alfuy virus	Vero, LLC-MK2, PS	blood	cell necrosis, plaques	JEV group; CPE 7–9 days
Kunjin virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood	cell necrosis, plaques	JEV group; CPE 2–4 days
Murray Valley encephalitis virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood, brain, spinal cord, skeletal muscle	cell necrosis, plaques	JEV group; CPE 2–5 days
St Louis encephalitis virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood, brain, CNS, liver, spleen, kidney	cell necrosis, plaques	JEV group; CPE 2–4 days
West Nile virus	BHK, Vero, LLC-MK2, PS	blood, spleen, liver, lymph nodes, brain (rare)	cell necrosis, plaques	JEV group; CPE 2–4 days

Virus species	Permissive cell lines	Tissue tropism	Cytopathic effects	Additional information
Kokobera virus	BHK21, Vero, LLC-MK2, PS, HeLa	blood	cell necrosis or plaques	KOKV group; CPE 3–8 days
Stratford virus	BHK21, Vero, LLC-MK2, PS	blood	plaques (PS, LLC-MK2 cells)	KOKV group; CPE 4–8 days
Ntaya virus	BHK21, LLC-MK2	blood	cell necrosis, plaques (LLC-MK2 cells)	NTAV group; CPE 4 days
Ilheus virus	BHK21, Vero, LLC-MK2, PS	blood	cell necrosis, plaques	NTAV group; CPE 3–5 days
Rocio virus	BHK, Vero, PS	blood, brain, CNS	cell necrosis, plaques	NTAV group; CPE 2–4 days
Israel turkey meningo-encephalomyelitis virus	Vero, LLC-MK2, PS	blood, brain, CNS, liver, spleen	cell necrosis, plaques	NTAV group; CPE 3–5 days
Zika virus	LLC-MK2	blood	plaques (also in primary CEF, DEF)	Spondweni virus group; CPE 4 days
Yellow fever virus	BHK21, Vero, PS, mosquito	blood, liver, kidney	cell necrosis, plaques	YFV group; CPE about 7 days
Banzi virus	BHK21, LLC-MK2, PS	blood, liver	cell necrosis, plaques	YFV group; CPE 3–6 days
Edge Hill virus	BHK21, Vero, LLC-MK2, PS, mosquito	blood	cell necrosis, plaques	YFV group; CPE 3–15 days
Wesselsbron virus	BHK21, Vero, LLC-MK2, PS	blood, spinal cord	cell necrosis, plaques	YFV group; CPE 3–6 days
Kyasanur Forest disease virus	hamster, MK, HeLa, tick	blood, liver, kidney, spleen	cell necrosis, plaques	mammalian tick-borne group; CPE variable
Langat virus	Vero, LLC-MK2	blood, liver, kidney, spleen	cell necrosis, plaques	mammalian tick-borne group; CPE 4–9 days
Omsk haemorrhagic fever virus	BHK21, HeLa, PS	blood, CSF, kidney, spleen	cell necrosis, plaques (PS cells)	mammalian tick-borne group; CPE 2–5 days
Powassan virus	MK	blood, brain	cell necrosis, plaques	mammalian tick-borne group; CPE 5–15 days
Tick-borne encephalitis virus	Vero, HeLa, Hep2, Detroit 6	blood, brain, spinal cord	variable	mammalian tick-borne group; CPE about 6 days
Louping ill virus	Vero, LLC-MK2, PS, HeLa, Detroit 6	blood, CSF, CNS, spleen, skeletal muscles	cell necrosis, plaques	mammalian tick-borne group; CPE 4–15 days
Saumarez Reef virus	BHK21, PS	blood	cell necrosis, plaques (PS cells)	sea-bird tick-borne group; CPE 3–7 days
Entebbe bat virus	BHK21, Vero, LLC-MK2	brain, salivary gland	plaques (LLC-MK2, Vero cells)	ENTV group; no known vector; CPE 4–16 days
Modoc virus	LLC-MK2, Vero	blood, heart, liver	cell necrosis, plaques	MODV group; no known vector; CPE 2–4 days
Rio Bravo virus	LLC-MK2, Vero	blood, salivary gland	plaques	RBV group; no known vector; CPE 2–7 days
Dakar bat virus	BHK21, Vero, LLC-MK2, PS	blood, salivary gland	plaques	RBV group; no known vector; CPE 2–7 days

Diseases

Disease	Causative agent	Affected organism	Characteristics	Route of transmission	Geographic distribution
dengue fever	Dengue virus types 1, 2, 3, and 4	man; monkeys if zoonotic	2 to 7 days incubation; febrile headache, joint pain, rash	Aedes mosquitoes	tropical and temperate
dengue haemorrhagic fever/shock	Dengue virus secondary infections, 3% of primary	man when sensitized	capillary leakage, haemorrhage, shock; 1 to 10% deaths	Aedes mosquitoes	tropical and temperate
Ilheus fever	Ilheus virus	man	mild, febrile headache, myalgia	mosquitoes	Brazil, Central America
Japanese encephalitis	Japanese encephalitis virus	man, pigs, birds	usually mild, febrile headache; if severe approx. 20% fatal	mosquitoes	Asia, New Guinea
Kyasanur Forest disease	Kyasanur Forest disease virus	man, small mammals, monkeys	acute, febrile headache, myalgia, haemorrhage; 4% deaths	ticks	Mysore State in India
Kunjin disease	Kunjin virus	man, birds	mild febrile illness; mild encephalitis (very rare)	mosquitoes	Australia, New Guinea
louping ill	Louping ill virus	mainly sheep, rarely man	neurotropic in sheep	ticks; occupat. in man	British Isles
Murray Valley encephalitis	Murray Valley encephalitis virus	man, birds	fever, headache, myalgia, coma, paralysis; 20% deaths	mosquitoes	Australia, New Guinea
Omsk haemorrhagic fever	Omsk haemorrhagic fever virus	man, rodents, birds	diphasic fever, haemorrhagic mucous membranes; 2% deaths	ticks	Siberia
Powassan disease	Powassan virus	wild mammals, rarely man	fever, encephalitis; neurological sequelae in 35% of cases	ticks	Canada, USA, Russia
Rocio encephalitis	Rocio virus	man; unknown animal host	acute, febrile headache, encephalitis; 4% deaths	mosquitoes	Brazil
St. Louis encephalitis	St. Louis encephalitis virus	man, birds	febrile headache, myalgia, meningo-encephalitis; 7% deaths	culicine mosquitoes	mainly North America
tick-borne encephalitis	Tick-borne encephalitis virus	man, rodents, insectivores	febrile headache, drowsiness, encephalitis; to 20% deaths	ticks; cow/goat's milk	Europe and Russia
Wesselsbron disease	Wesselsbron virus	sheep, goats, cows	fever, myalgia, rash; abortion in ewes; lethal in goats	mosquitoes	Africa and Thailand
West Nile fever	West Nile virus	man, birds	usually mild, fever and rash, rarely encephalitis	mosquitoes, ticks	Eurasia, Africa, New York
yellow fever (urban and jungle)	Yellow fever virus	man, monkeys	febrile headache, myalgia, vomiting, jaundice; 30% deaths	Aedes mosquitoes	tropical Africa, America
Zika disease	Zika virus	man, monkeys	rare in man, fever, headache, rash	mosquitoes	Central Africa, Indonesia

Vaccine Strains

Strain	Attenuation procedure	Additional information	Reference
Yellow fever virus 17D (attenuated Asibi strain)	many serial passages in chick embryo	68 point mutations compared to wild type virus	Theiler M, Smith HH (1939) J Exp Med 65:787–800
Japanese encephalitis virus strain Nakayama	formalin inactivated tissue extract	BIKEN vaccine, purified from infected mouse brain	Poland JD, et al. (1990) J Infect Dis 161:878–882
Japanese encephalitis virus strain SA14–14–2	serial passages in primary hamster kidney cells	vaccine produced in primary hamster kidney cells	Liu Z-L, et al. (1997) J Infect Dis 176:1366–1369
Tick-borne encephalitis virus Western subtype	formalin inactivation	purified vaccine grown in chick embryos	Kunz C, et al. (1980) J Med Virol 6:103–109
Louping ill virus	formalin inactivation	for sheep; grown in sheep kidney cell cultures	Brotherstone JG, Boyce JB (1970) J Comp Pathol 80:377–388

Vector Constructs

Vector	Backbone strain	Application	Insertion capacity [kb]	Additional information	Reference
Kunjin replicon RNA	Kunjin virus strain MRM61C	expression	>3	non-cytopathic self-replicating subgenomic RNA	Khromykh AA, Westaway EG (1997) J Virol 71:1497–1505

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