

# The Japanese Encephalitis Serological Group of Flaviviruses: a Brief Introduction to the Group

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## 1 Introduction

Japanese encephalitis (JE) and West Nile (WN) viruses are two of the four major encephalitic flaviviruses of public health importance in the Japanese encephalitis serological group, the other two being St. Louis encephalitis (SLE) virus in North America and Murray Valley encephalitis (MVE) virus in Australasia. JE and WN share a number of similarities, including natural transmission cycles involving avian reservoir hosts and culicine mosquitoes and their ability to cause fatal infections in horses. The two viruses also differ in aspects of their transmission cycles and in their host range. Thus, unlike WN virus, JE virus also has a major mammalian amplifying host in the pig, and indeed most epidemic activity is driven by mosquito–pig transmission cycles. Some strains of WN virus, on the other hand, can cause a fatal disease in both domestic geese and various species of wild birds. However, most importantly, they also share a propensity to emerge and become established in new

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geographic areas. The recent spread of JE virus into western Asia and Australasia has probably been through natural mosquito–vertebrate host cycles, possibly assisted by changes in land use. However, the most recent example of the emergence of WN virus in New York and its subsequent spread in the eastern seaboard of the United States, was almost certainly due to inadvertent human involvement through transportation of either a viraemic human or bird, or an infected mosquito, from Israel or the Middle East. Although JE virus appears to have become established in New Guinea, it has not yet done so in Pakistan or in mainland Australia (Mackenzie et al., this volume). WN virus, however, appears to have now become well established in the eastern seaboard of the United States (Roehrig et al., this volume). Thus in 1999, the original incursion and subsequent epidemic activity was centred on New York city and adjacent counties in New York, New Jersey and Connecticut. In 2000, the virus spread throughout New York State and infected birds were found in 11 other states and in Washington DC. The spread has gathered momentum in 2001, and at the time of writing (beginning of September 2001) has spread south into Alabama, Florida, Georgia, and Louisiana; west into Kentucky, Indiana, Michigan and Ohio; and north into Ontario. Indeed, a total of 99 counties/parishes in 16 states and the District of Columbia have had confirmed findings of WN virus in a mosquito, bird, horse, or human, since 1 January 2001 (PROMED 2001a,b). Of additional interest, a concurrent outbreak of SLE has been reported from Louisiana, thus potentially complicating the diagnoses in that State (PROMED 2001c).

The two viruses are major causes of disease in their respective geographic areas. JE virus is responsible for more than 50,000 cases of encephalitis annually in eastern, south-eastern and southern Asia, with a fatality rate of about 25%. In addition, increasing tourism and travel are placing greater numbers of people at risk of infection. WN virus has been responsible for major outbreaks of human encephalitis in Algeria in 1994, Romania in 1996, Tunisia in 1997, south-western Russia in 1999, and Israel in 2000, and equine encephalitis in Morocco in 1996, Italy in 1998, and France in 2000. Indeed, there has been a change in the spectrum of human disease due to WN virus over the past decade, with the emergence of an increased incidence of encephalitic infections. Thus, with their recent spread into new areas, and the severity of the disease they can cause, there has been a greater public health awareness of both viruses. This paper describes the Japanese encephalitis serological group and its members as a prelude to the remainder of the volume, which explores aspects of the ecology, epidemiology and pathobiology of JE and WN (and its newly classified subtype, Kunjin virus).

## 2 The *Flavivirus* Genus

The *Flavivirus* genus in the family *Flaviviridae* comprises approximately 70 antigenically related members. Most members are arboviruses, transmitted by

arthropod vectors, either ticks or mosquitoes, and usually replicate alternately in susceptible vertebrate and arthropod hosts. A few viruses have no known vectors. The most recent classification, as listed in the 7th Report of the International Committee on Taxonomy of Viruses (ICTV), has assigned members of the genus into species, with some members demoted to strains or serotypes (HEINZ et al. 2000). Thus there are now 27 mosquito-borne species, 12 tick-borne species, and 14 species with no known vector. The current classification of the mosquito-borne flaviviruses, their major vectors and hosts, their geographic range, and their virulence for humans, is shown in Table 1. The major criteria for determining the groupings of species, strains and serotypes within the genus are nucleotide and deduced amino acid sequence data, antigenic relationships, vector association and geographic incidence. The interpretation of the criteria for assigning a species level, and the definition of what constitutes a 'strain' or 'serotype' may be controversial in some instances, and indeed changes may be necessary as more information becomes available. Perhaps a more useful indication of relationships between flaviviruses can be obtained from phylogenetic studies which tend to agree with antigenic and vector/host relationships (e.g., KUNO et al. 1998; ZANOTTO et al. 1996; BILLOIR et al. 2000; JENKINS et al. 2001; GOULD et al. 2001).

### 3 The Japanese Encephalitis Serological Group

The Japanese encephalitis virus serological group currently comprises eight species and two strains or subtypes (Table 1), as listed in the 7th Report of the ICTV (HEINZ et al. 2000). It is perhaps the most important *Flavivirus* group on a global scale, with members endemic to all continents except the Antarctic. They cause diseases ranging from febrile illness, with or without a rash and with or without myalgia, to a meningo-encephalitis with significant mortality, although most infections are subclinical or inapparent. All members of the group are believed to have natural maintenance cycles alternating between birds and mosquitoes, and in many cases, ardeid birds and culicine mosquitoes. The only member that has not been isolated from an arthropod is Cacipacore virus. Isolations of some members of the group have occasionally been reported from ticks, including SLE virus (MCLEAN et al. 1985), WN virus (reviewed in HUBÁLEK and HALOUZKA 1999; RAPPORT ANNUEL 1998), JE virus (LVOV 1978), and Koutango virus (RAPPORT ANNUEL 1998). Indeed Koutango virus has been isolated more frequently from ticks than from mosquitoes (see below). JE virus has also been isolated from a midge, *Lasiohelea taiwana*, collected while biting humans in China (C.-J. Wu and S.-Y. Wu, cited by ROSEN 1986). The ecology and epidemiology of members of the group, other than JE and WN (and its subtype Kunjin virus) viruses, the subjects of this volume, are summarised briefly below.

Table 1. Mosquito-borne members of the *Flavivirus* genus in the family *Flaviviridae*

Group <sup>a</sup>	Species <sup>a</sup>	Subtype/strain/serotype <sup>a</sup>	Major vector <sup>b</sup>	Vertebrate hosts <sup>b</sup>	Geographic range <sup>b</sup>	Human disease <sup>b,c</sup>
Aroa virus group	Aroa virus		None known	(Sentinel hamster) <sup>d</sup>	Venezuela	-
	Bussuquara virus		<i>Culex</i> sp.	Rodents	Brazil	±
	Iguape virus		Not known	Rodents?	Brazil	-
	Naranjal virus		<i>Culex</i> species	(Sentinel hamster) <sup>d</sup>	Ecuador	-
Dengue virus group	Dengue virus					
	Dengue virus type 1		<i>Aedes aegypti</i>	Humans	All tropical/subtropical regions	+ + ± / + + + ± <sup>e</sup>
	Dengue virus type 2		<i>Ae. aegypti</i>	Humans	All tropical/subtropical regions	+ + ± / + + + ± <sup>e</sup>
	Dengue virus type 3		<i>Ae. aegypti</i>	Humans	All tropical/subtropical regions	+ + ± / + + + ± <sup>e</sup>
	Dengue virus type 4		<i>Ae. aegypti</i>	Humans	All tropical/subtropical regions	+ + ± / + + + ± <sup>e</sup>
Japanese encephalitis virus group	Cacipacore virus		None known	Birds	Brazil	-
	Koutango virus		<i>Culex</i> sp.?, ticks	Gerbils?	Western and central Africa	+
	Japanese encephalitis virus		<i>Cx. tritaeniorhynchus</i>	Birds and pigs	Eastern and southern Asia	+ + +
	Murray Valley encephalitis virus		<i>Cx. annulirostris</i>	Birds	Australasia/eastern Indonesia?	+ + + ±
St. Louis encephalitis virus group	St. Louis encephalitis virus		<i>Cx. annulirostris</i>	Birds	Australia	-
	Usutu virus		<i>Cx. pipiens/Cx. tarsalis</i>	Birds	North and South America	+ + + ±
	West Nile virus		<i>Culex</i> sp.	Birds	Eastern, central, southern and western Africa	+ + + ±
	West Nile virus		<i>Cx. species</i>	Birds	Africa, southern and eastern Europe, Middle East, India	+ + + ± ( + + + ± ) <sup>f</sup>
Kokobera group	Yaounde virus		<i>Cx. annulirostris</i>	Birds	Australasia/Malaysia	+ + ±
	Kokobera virus		<i>Culex</i> sp.	Birds?/rodents?	Central and western Africa	-
	Stratford virus		<i>Cx. annulirostris</i> <i>Ochlerotatus vigilax</i>	Marsupials? Marsupials?	Australasia Australasia	± -

Ntaya virus group	Bagaza virus				Central and western Africa	-
	Ilheus virus			Not known Birds, bats?	Southern and central America	+ +
Israel turkey meningo- encephalomyelitis virus	Ntaya virus	Rocio virus	<i>Culex</i> species <i>Psorophora ferox</i>	Birds	South America	+ + + ±
			Mosquito sp./ <i>Culisicoides</i>	Birds (turkeys)	Israel, Southern Africa	-
			<i>Culex</i> sp.	Not known	Eastern, central and western Africa	-
Tembusu virus			<i>Culex gelidus</i>	Not known	Malaysia/Thailand	-
			<i>Aedes</i> sp.	Monkeys?	Eastern, central and western Africa/south-east Asia	+ +
Spondweni virus group	Zika virus	Spondweni virus	<i>Aedes</i> sp. and various	Not known	Southern and western Africa	+ +
Yellow fever virus group	Banxi virus		<i>Cx. rubinotus</i>	Not known	Southern and eastern Africa	+ +
	Edge Hill virus		<i>Oc. vigilax</i>	Marsupials	Australasia	±
Potiskum virus	Jugra virus		<i>Aedes</i> species	Not known	Malaysia	-
	Saboya virus		None known	Gerbils, rodents	Western Africa	-
			None known	Rodents?	Western Africa	-
	Sepik virus		<i>Ficulbia</i> sp., various	Not known	Australasia (New Guinea)	±
	Uganda S		<i>Aedes</i> sp.	Birds, monkeys?	Africa	-
	Wesselsbron virus		<i>Aedes</i> sp.	Domestic animals	Africa	+ +
Yellow fever virus		<i>Haemagogus</i> sp.	Primates, humans	Western, central and eastern Africa, South America	+ + + +	

<sup>a</sup> Based on HEINZ et al. (2000).

<sup>b</sup> Based on KARABATSOS (1985), with additional data from FIGUEIREDO (2000), RAPPORT ANNUEL (1998), and RUSSELL (1995).

<sup>c</sup> Severity scored as: - , no known disease; ± , possible disease or mild very occasional disease; + , mild disease; + + , moderate disease; + + ± , moderate disease with some cases of greater severity; + + + , severe disease, usually requiring hospitalisation; + + + ± , severe disease, with some fatalities; + + + + , severe disease with significant mortality.

<sup>d</sup> Isolates only from sentinel animals.

<sup>e</sup> Dengue fever (DF);dengue haemorrhagic fever (DHF).

<sup>f</sup> Severity score in parentheses relates to severity of recent strains in the elderly.

### 3.1 St. Louis Encephalitis Virus

The ecology and epidemiology of SLE have been reviewed extensively by TSAI and MITCHELL (1988) and by DAY (2001). The geographic range of SLE extends from southern Canada to Argentina, although human cases have occurred almost exclusively in the United States, and particularly in the central and eastern states (MONATH 1980). Humans are the only host to suffer disease and death following natural infection by SLE virus. The major vertebrate maintenance and amplifying hosts of SLE are birds, especially members of the Passeriformes and Columbigiformes, but water birds may be important in Central America (MCLEAN and BOWEN 1980; SPENCE 1980). The major vector species in different areas are *Culex tarsalis*, *Cx. pipiens*, *Cx. p. quinquefasciatus*, and *Cx. restuans* (MITCHELL et al. 1980). Although SLE has been reported to infect a number of mammals, as demonstrated by serological studies or virus isolation, mammals are not thought to play a major role in natural transmission cycles in North America, although they may be involved in Central and South America (TSAI and MITCHELL 1989; SPENCE 1980). SLE virus has been isolated from racoons, opossums, an impala, and Mexican free-tailed bats in North America, and from a three-toed sloth, monkeys and rodents in South America.

### 3.2 Cacipacore Virus

Cacipacore virus was first included in the Japanese encephalitis serological group in the 7th Report of the ICTV (HEINZ et al. 2000). Cacipacore virus was isolated in 1977 from a bird in Pará State in the Amazon area of Brazil (TRAVASSOS et al. 1998). No further isolates have been reported from any source (L.T. Figueiredo, personal communication), so the vector remains unknown. It has not been associated with human disease. Phylogenetic studies show that although it is one of the most divergent members of the group, it is the closest New World member (KUNO et al. 1998; JENKINS et al. 2001; GOULD et al. 2001; BATISTA et al. 2001).

### 3.3 Yaounde Virus

Yaounde virus was first included in the JE serological group in the 7th Report of the ICTV. It has been isolated from mosquitoes, a bird and mammals (rodents) in Cameroun, Central African Republic, Congo, and Senegal (RAPPORT ANNUEL 1998). It has not been associated with human disease. Little information is available about properties of the virus.

### 3.4 Koutango Virus

Koutango virus is closely related to WN virus. It was first isolated from a Kemp's gerbil (*Tatera kempi*) in 1969 in Senegal. Only one isolate has been reported from

mosquitoes (*Culex neavei*) in Senegal, but with a further 10 isolates from ticks, 21 isolates from mammals (rodents), and one human isolate (KARABATSOS 1985; RAPPORT ANNUEL 1998). Most isolates have been obtained from Senegal, with a few from Central African Republic. It has been associated with occasional human infections resulting in fever, rash and arthralgia.

### 3.5 Usutu Virus

Usutu virus was first isolated from *Cx. neavei* mosquitoes in Natal, South Africa in 1969. Subsequent isolates have been reported from Uganda, Nigeria, Central African Republic, Cameroun, and Senegal from mosquitoes, rodents and birds, and from one human serum specimen (KARABATSOS 1985; RAPPORT ANNUEL 1998). The single human infection presented with fever and rash. Phylogenetically, *Usutu virus* is closely related to JE virus, and indeed groups more closely with JE, MVE and Alfuy viruses than it does to the other African viruses – WN, Yaounde, and Koutango viruses (JENKINS et al. 2001; GOULD et al. 2001; KUNO et al. 1998).

### 3.6 Murray Valley Encephalitis Virus

MVE virus is the major encephalogenic flavivirus in Australasia (Australia and Papua New Guinea). It was first isolated in 1951 from a human case during a major outbreak in south-eastern Australia, and from *Culex annulirostris* mosquitoes in 1959 at Kowanyama, Cape York, northern Queensland. Natural transmission cycles are believed to be between ardeid water birds and *Cx. annulirostris* mosquitoes (MARSHALL 1988). Indeed more than 90% of all MVE isolations have been made from this mosquito species (MACKENZIE et al. 1994; RUSSELL 1995). Although serological studies have shown that various mammals can also be infected, they are not believed to play a significant role in natural transmission cycles. The virus is believed to be enzootic in the north of Western Australia and the Northern Territory, and possibly in northern Queensland (SPENCER et al. 2001). It is also enzootic in Papua New Guinea and parts of the eastern Indonesian archipelago (MACKENZIE et al. 1994). Epidemics of MVE occurred in south-eastern Australia in 1951 and 1974, with a few cases in 1956 and 1971, but all cases since 1974 have been from northern Australia (MARSHALL 1988; MACKENZIE et al. 1993, 1998; CORDOVA et al. 2000).

### 3.7 Alfuy Virus

Alfuy virus was first isolated from a swamp pheasant (*Centropus phasianinus*) in 1966 at Kowanyama, Cape York, northern Queensland. All subsequent isolations have been from mosquitoes, including *Aedeomyia catasticta*, *Cx. annulirostris*, and *Cx. pullus*, trapped in northern Western Australia and Queensland. Phylogenetically,

Alfuy virus falls between MVE and JE viruses, but is slightly closer to MVE. There have been no confirmed cases of human disease due to Alfuy virus.

#### **4 Comments on the Classification of the JE Serological Group Viruses**

Although membership of the group has been defined using a number of criteria, including nucleotide sequence analyses (e.g. KUNO et al. 1998; BILLOIR et al. 2000; JENKINS et al. 2001) and antigenic cross-reactivity (DE MADRID and PORTERFIELD 1974; CALISHER et al. 1989), as well as vector and vertebrate host similarities, there are inconsistencies that need to be addressed. One such inconsistency is SLE virus which is listed as a member of the JE serological group based largely on antigenic cross-reactivity (DE MADRID and PORTERFIELD 1974; CALISHER et al. 1989) and ecology, but from nucleotide sequence analyses, it is clearly closer to two South American viruses in the Ntaya virus serological group, Rocio and Ilheus viruses (KUNO et al. 1998; GOULD et al. 2000; JENKINS et al. 2001). In addition, Alfuy virus has been classified as a subtype of MVE virus, but recent sequencing and biological data would suggest that this may have been premature (MAY et al. 2001; F.J. May, R.A. Hall, J.S. Mackenzie, unpublished results). Conversely, Kokobera and Stratford viruses, two Australian viruses that had been included in the JE serological group in the 6th report of the ICTV (WENGLER et al. 1995), have been removed on genetic (POIDINGER et al. 1996; KUNO et al. 1998) and, to a lesser extent, antigenic (WESTAWAY 1968; CALISHER et al. 1989) grounds, and placed into a new group of their own in the 7th Report of the ICTV (HEINZ et al. 2000).

The other inconsistency that needs to be considered is the wide nucleotide sequence variation between WN virus isolates. Berthet and colleagues (BERTHET et al. 1997) clearly demonstrated that there were two distinct genetic lineages of WN viruses. This was confirmed and extended in other studies (JIA et al. 1999; LANCIOTTI et al. 1999; SAVAGE et al. 1999; SCHERRET et al. 2001). One lineage, lineage I, comprises four major clades including most isolates from Africa, Europe and India, as well as the New York isolates and the Australian Kunjin viruses; the second lineage comprises the original prototype strain, and isolates from West, Central and East Africa, and from Madagascar. Interestingly, human disease is rarely recognised from lineage II WN viruses. The maximum nucleotide divergence between members of the two lineages was shown to range from 29% (BERTHET et al. 1997) and 31% (SCHERRET et al. 2001) for sequences within the E gene, to 36.5% for sequences in the NS5–3' untranslated region (SCHERRET et al. 2001), which would suggest that the lineages may represent two distinct viruses. We therefore propose that they should be re-named West Nile subtype 1 and West Nile subtype 2, rather like the dengue viruses, or alternatively, that the name West Nile be retained for the viruses in lineage II, as this lineage contains the prototype strain, and that viruses in lineage I be renamed. Finally the majority of West Nile strains



from India are classified as a distinct clade within lineage I, yet there is low bootstrap support for this conclusion. Further studies are warranted to confirm their inclusion in lineage I/West Nile subtype 1, or whether they should also be considered to represent a different lineage.

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