Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

8

Single-Stranded RNA Viruses

8.1 FAMILY BUNYAVIRIDAE

The Bunyaviridae family was named after the prototypical Bunyamwera virus (BUNV) isolated in 1943 from mosquitoes (*Aedes* spp.) in Bunyamwera, Uganda.[1] Currently, the Bunyaviridae family includes four genera of animal viruses (*Orthobunyavirus*, *Phlebovirus*, *Nairovirus*, and *Hantavirus*) and one genus (*Tospovirus*) of plant viruses.[2] Bunyavirus virions are spherical in shape (size, about 80–120 nm) and have an outer lipid bilayer with the viral envelope glycoproteins Gn and Gc exposed on the surface. The genome consists of three segments of single-stranded, negative-sense RNA with a total length from 11,000 to 19,000 nt. Depending on the size, the segments are designated L (large), M (medium), and S (small). The viral proteins are synthesized on the mRNA that is produced during replication and that is complementary to the genomic RNA. The length of segments varies for different genera, but in general, they have a common structure. The L-segment, whose length is from 6,400 nt (*Phlebovirus*) to 12,200 nt (*Nairovirus*), has a single open reading frame (ORF) encoding RNA-dependent RNA polymerase (RdRp). The M-segment of all of the genera also has a single ORF, which encodes a polyprotein precursor of envelope glycoproteins Gn and Gc. The length of the M-segment ranges from 3,288 nt for some of the phleboviruses to 4,900–5,366 nt for the nairoviruses. The mature glycoproteins Gn and Gc of the bunyaviruses are derived during complex endoproteolytic events leading to cleavage of the polyprotein precursor by cellular proteases. The S-segment of the bunyaviruses encodes a nucleocapsid protein. Additional nonstructural (NSs) protein is encoded by the S-segment of viruses of the *Phlebovirus*, *Tospovirus*, and *Orthobunyavirus* genera.[2,3]

The bunyaviruses are widely distributed in the world and are one of the most numerous known zoonotic viruses. Most of the zoonotic bunyaviruses are transmitted to animal or humans by bloodsucking arthropod vectors, usually mosquitoes or ticks. Viruses of the *Hantavirus* genus are the exception, being transmitted mainly by aerosol formed from virus-laden urine, feces, or saliva of infected rodents or insectivores that are their natural hosts.[4–6]

8.1.1 Genus *Hantavirus*

The genus *Hantavirus* consists of those bunyaviruses of vertebrates which do not have the ability to replicate in an arthropod's cell

Zoonotic Viruses of Northern Eurasia.
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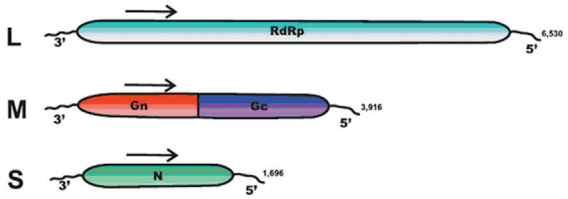


FIGURE 8.1 Structure of the genome of HTNV, the prototypical virus of the genus *Nairovirus* (family Bunyaviridae). The genome of the hantaviruses consists of three segments of negative-sense ssRNA. The L-segment encodes RdRp, the M-segment a polyprotein precursor of envelope proteins Gn/Gc), and the S-segment a nucleocapsid protein (N). *Drawn by Tanya Vishnevskaya.*

and which are transmitted by respiratory route through the formation of aerosols from urine or feces containing the virus.[1] The morphology of the virion and the genome structure of the hantaviruses are common to all bunyaviruses. The size of the negative-sense ssRNA genome of the prototypical Hantaan virus (HTNV) is 6,533 nt for the L-segment, 3,616 nt for the M-segment, and 1,696 nt for the S-segment (Figure 8.1).[1]

In nature, hantaviruses persist asymptomatically in rodents and insectivores, with each type of hantavirus associated predominantly with one host species. The phylogenetic relationships of hantaviruses enable virologists to divide them into three lineages, which correspond in general to their main hosts. In the S-segment of some hantaviruses carried by Arvicolinae and Sigmodontinae rodents, there is an additional ORF-encoded nonstructural protein NSs. But NSs is absent in the hantaviruses of the Murinae rodents.[2–4]

8.1.2 Hemorrhagic Fever with Renal Syndrome Virus and Related Viruses

History. Hemorrhagic fever with renal syndrome (HFRS) was originally described as a separate nosological category (called "endemic (epidemic) hemorrhagic nephroso-nephritis" at that time) by Anatoly Smorodintsev (Figure 2.11) during 1935–1940 in the Far East. Later, Japanese scientists described HFRS in northeastern China as "Songo fever" and Swedish scientists as "epidemic nephropathy"; a similar disease was described in 1960 in China.[1] The abbreviation "HFRS" was suggested by Mikhail Chumakov (Figure 2.10) in 1954 and was recommended for adoption at a World Health Organization (WHO) Expert Meeting in 1982.

The viral nature of the HFRS etiological agent was established by Anatoly Smorodintsev (Figure 2.11) in 1940 during his experiments inoculating volunteers. The first historical and prototypical strain, Hantaan 76-118, was isolated by H.W. Lee in 1976 from a striped field mouse (*Apodemus agrarius coreae*) caught on the banks of the Hantaan River in South Korea.[2]

Hantaviruses. The hantaviruses are members of the *Hantavirus* genus of the Bunyaviridae family. The first serotype, —HTNV, included strains isolated from mouselike rodents (Muridae) in South Korea, China, and the southern part of the Russian Far East (Primorsky Krai).[2–4] The second serotype, Puumala virus (PUUV), was isolated from hamsterlike rodents (Cricetidae), mainly the bank vole (*Myodes glareolus*) in Finland and then in other European countries and the western part of Russia, as well we from Maximowicz's vole (*Microtus maximoviczii*) in the Far East).[5–8] The third serotype, Seoul virus (SEOV), was isolated from brown rats (*Rattus norvegicus*), black rats (*Rattus rattus*), and laboratory albino rats (*Rattus norvegicus f. domestica*) in South Korea and elsewhere, including the United States.[3,4] The fourth serotype, Dobrava–Belgrade virus (DOBV), was isolated from the striped field mouse (*Apodemus agrarius*) in Slovenia[9] and Yugoslavia.[10] The fifth serotype, Sin Nombre virus (SNV), literally "nameless virus" in Spanish, was isolated from the meadow vole (*Microtus pennsylvanicus*).[8]

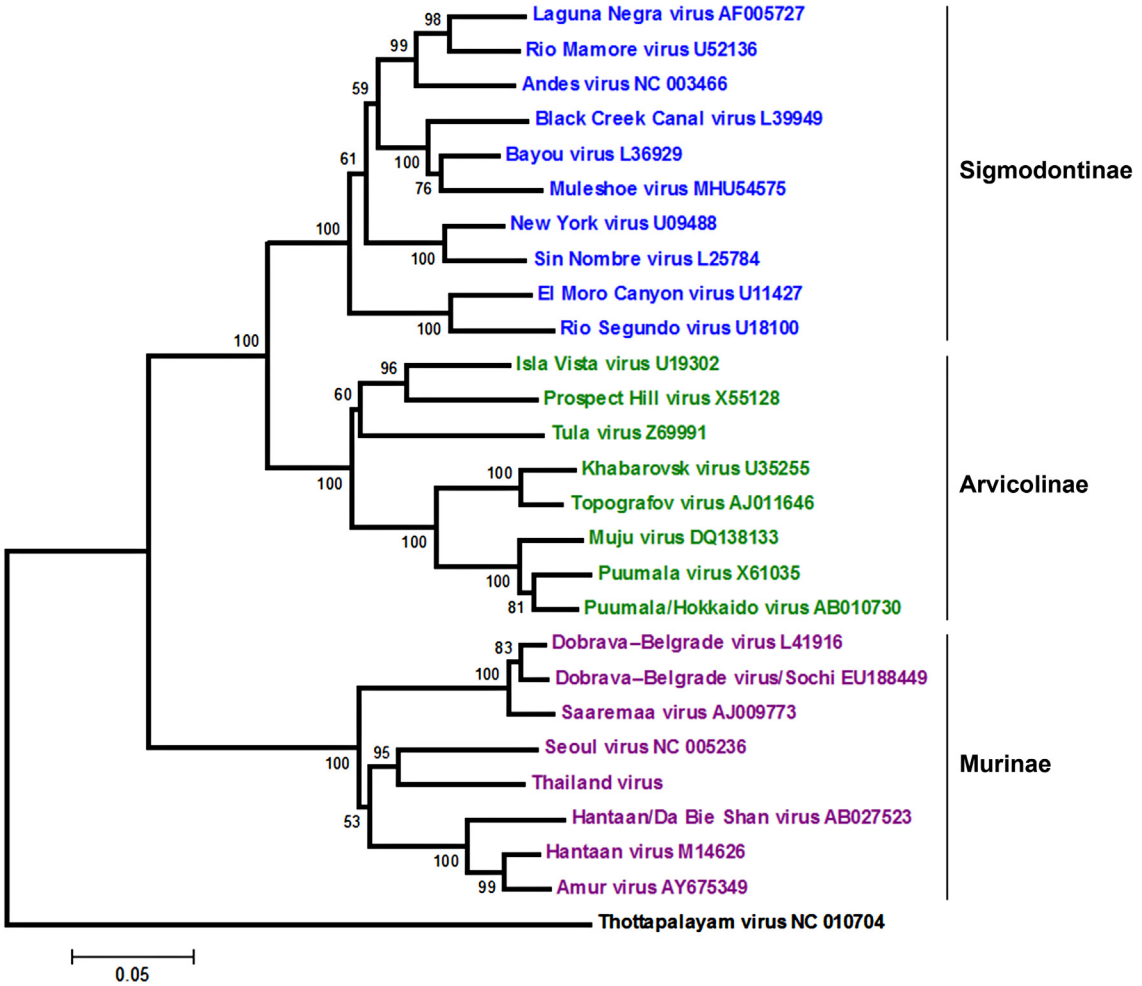


FIGURE 8.2 Phylogenetic analysis of S-segment sequences of certain hantaviruses (family Bunyaviridae, genus *Hantavirus*).

In addition to the 5 main serotypes, 15 other serotypes are known today, including 6 in Eurasia: Amur virus (AMRV), isolated from Asiatic forest mice (*Apodemus peninsulae*) in the Far East of Russia[11] and in China[12]; Tula virus (TULV), from common voles (*Microtus arvalis*) in central Russia[13,14]; Khabarovsk virus (KHAV), from from reed voles (*Microtus fortis*) and Siberian brown lemmings (*Lemmus sibiricus*) in the Far East[15]; Thottapalayam virus (TPMV), from Asian musk shrews (*Suncus murinus*) in India[16]; Thailand virus (THAIV), from bandicoots (*Bandicota indica*) in Thailand[17]; and a newfound hantavirus, from Chinese mole shrews (*Anourosorex squamipes*) in Vietnam.[18]

Virion and Genome. The size of the negative-sense ssRNA genome of the prototypical HTNV is 6,533 nt for the L-segment, 3,616 nt for the M-segment, and 1,696 nt for the S-segment (Figures 8.1 and 8.2).

Epizootiology. Rodents (order Rodentia) are the main natural reservoir of hantaviruses. Nevertheless, strains have been isolated from birds in the Far East[19] and from bats in China.[20] Infection in rodents is asymptomatic, but the virus is expelled with saliva, urine, and excrement, most intensively during the first month after inoculation. (During this period, virus antigen can be detected in the lungs.)[4]

The evolution of hantaviruses is closely related to that of its rodent host (Figure 8.2).[4,6,21] At least 34 species of rodents (Rodentia), 2 species of lagomorphs (order Lagomorpha), 7 species of insectivores (order Insectivora), 1 species of predators (order Carnivora), and 1 species of artiodactyls (order Artiodactyla) are known to take part in hantavirus circulation on the territory of Northern Eurasia.[8,21,22] The main species of rodents, which are the hosts of hantaviruses in Russia, are presented in Table 8.1. The infection rate of mouselike rodents and insectivores lies within the limits $3.3 \pm 0.5\%$.[23] Hantavirus antigens have been detected in birds as well: the Oriental turtle dove (*Streptopelia orientalis*), coal tit (*Parus ater*), marsh tit (*Parus palustris*), Daurian redstart (*Phoenicurus auroreus*), nuthatch (*Sitta europaea*), black-faced bunting (*Emberiza spodocephala elegans*), Eurasian jay (*Garrulus glandarius*), hazel grouse (*Tetrastes bonasia*), pheasant (*Phasianus colchicus*), Ural owl (*Strix uralensis*), green-backed heron (*Butorides striatus*), and grey heron (*Ardea cinerea*).[19] Hantavirus (Magboi virus, or MGBV) was isolated in 2012 from the hairy slit-faced bat (*Nycteris hispida*) in Africa (Sierra Leone),[24] but the role of bats in the circulation of hemorrhagic fever with renal syndrome virus (HFRSV) is yet to be investigated in detail.

In western Siberia, the main natural reservoir of HFRSV is rodents of the hamsterlike (Cricetidae) family—in particular, bank voles

TABLE 8.1 Hantaviruses: Etiological Agents of Hemorrhagic Fever with Renal Syndrome in Russia

Virus	Rodents—Natural reservoirs	Distribution
Amur virus (AMRV)	Asiatic forest mouse (*Apodemus peninsulae*)	Far East of Russia, China
Dobrava–Belgrade virus (DOBV)	Yellow-necked field mouse (*Apodemus flavicollis*)	Balkans, central part of Russia, Slovenia, Yugoslavia
	Field mouse (*Apodemus agrarius*), small forest mouse (*A. uralensis*)	Central sector of European part of Russia
	Black Sea field mouse (*Apodemus ponticus*)	South of European part of Russia
	Unidentified	Western Siberia
Hantaan virus (HTNV)	Field mouse (*Apodemus agrarius*)	Far East of Russia, China, Japan, North and South Korea
Khabarovsk virus (KHAV)	Reed vole (*Microtus fortis*)	Far East of Russia, China
Puumala virus (PUUV)	Bank vole (*Myodes glareolus*)	Northern and central Europe, Russia, Balkans
Seoul virus (SEOV)	Brown rat (*Rattus norvegicus*), black rat (*Rattus rattus*)	Far East of Russia, China, Japan, North and South Korea
Tula virus (TULV)	Common vole (*Microtus arvalis*), Russian common vole (*Microtus rossiaemeridionalis*)	European part of Russia, Czech Republic, Slovenia

(*Myodes glareolus*), with a susceptibility up to 70%; red-backed voles (*Myodes rutilus*), susceptibility 9%; and, in the north, Siberian brown lemmings (*Lemmus sibiricus*), 14%. The infection rate of other rodents and insectivores is about 0.4–3.0%.[8,22]

In eastern Siberia, the maximum susceptibility is demonstrated in grey red-backed voles (*Myodes rufocanus*), 70%; house mice (*Mus musculus*), 15%; water voles (*Arvicola terrestris*), 8%; and tundra voles (*Microtus oeconomus*), 8%.[8]

In the Far East, HFRSV was revealed to circulate among field mice (*Apodemus agrarius*) with a susceptibility of about 35%; Asiatic forest mice (*A. peninsulae*), susceptibility 30%; reed voles (*Microtus fortis*), 4–18%; grey red-backed voles (*Myodes rufocanus*), 12%; and other rodents (Rodentia), 0.7–4.3%.[21,22,25]

Epidemiology. HFRSV infection starts by aerogenic penetration of the virus during the inhalation of waste products (saliva, urine, excrement) of latently infected animals. An alimentary pathway (with contaminated food and water) of the infection is also possible.[4,8,22,26,27]

HFRS is distributed over Eurasia (Russia, Belarus, Ukraine, Moldova, the Baltic countries, the Czech Republic, Slovakia, Bulgaria, Romania, Serbia, Slovenia, England, France, Germany, Belgium, Hungary, Denmark, Fennoscandia, Kazakhstan, Georgia, Azerbaijan, China, North and South Korea, Japan), as well as American and African countries.[7,28,29]

During 2000–2009, in 58 of 83 regions in Russia, 74,890 cases of HFRS were registered (Table 8.2).[8] Annual morbidity of HFRS in Russia is in the range from 2,700 to 11,400 cases (1.3–7.8%) and is decreasing. About 95% of cases take place in European forest landscapes. PUUV associated with the bank vole (*Myodes glareolus*) provokes about 90% of HFRS cases in Russia (especially in Bashkortostan, Udmurtia, Mari El, Tatarstan, the Chuvash Republic, Orenburg, Ulyanovsk, and the Penza region).[8,30] Morbidity in the urban population is higher (65%) than in the rural one. The peak of the disease occurs during July–October in forests and in gardens and kitchens closely situated to the forests.[4,31–33] DOBV associated mainly with field mice (*Apodemus agrarius*) and small forest mice (*A. uralensis*) is of leading epidemiological significance in the central and southwestern sectors of the European part of Russia (the Voronezh, Lipetsk, Orel, and Belgorod regions), as well as in Georgia.[8,31,34,35] PUUV and TULV are associated with the common vole (*Microtus arvalis*) and the bank vole (*Myodes glareolus*) and are also distributed over this territory.[4,8,36] A similar situation is observed in other regions of the Central Federal District: in the Moscow, Yaroslavl, Ryazan, Tver, Kaluga, Vladimir, Ivanov, Kostroma, Smolensk regions. HFRS morbidity in the Moscow region is associated with PUUV,[31] the infection rate of which is 12–57% among bank voles (*Myodes glareolus*), 10–20% in the common vole (*Microtus arvalis*), 11% in Major's pine vole (*Microtus majori*), and in 4–6% other rodent species.[1] In Krasnodar Krai, the Black Sea field mouse (*Apodemus ponticus*) and Major's pine vole (*Microtus majori*) play the main role in human morbidity.[31,37]

TABLE 8.2 Hemorrhagic Fever with Renal Syndrome in Russia (2013)

Federal District	Number of cases (%)	Infection rate per 100,000 of population
Central	624 (14.5)	1.62
Northwestern	134 (3.1)	0.98
Southern	1 (0.02)	0.04
North Caucasian	0	0
Lower Volga	3,378 (78.6)	11.32
Ural	49 (1.2)	0.40
Siberian	1 (0.02)	0.01
Far Eastern	110 (2.6)	1.75
Total	4,297 (100)	

Human morbidity in the European part of Russia is registered beginning at a relatively low level in March–April, decreasing to yet a lower level in May–August, increasing in September–November, and then increasing again during December–January.[1] The hyperendemic territory is the southwestern Ural region (especially the Bashkortostan Republic and the Chelyabinsk and Orenburg regions), the Volga-Vyatka economic region (especially the Udmurt Republic), the Chuvash Republic, and the Tatarstan, Mari El, Samara, Penza, Saratov, and Ulyanovsk regions.[4,8]

The main human morbidity occurs among those 20–40 years old (chiefly men). In Russia, HFRS represents a significant part of all natural-foci zoonotic diseases. The immune layer to HFRSV in the European part of Russia is a mean 4.7%; in the Bashkortostan Republic, it reaches up to 40% (mean, 17%).[4]

The immune layer among the populations of western and eastern Siberia is about 2% for the entire region, 0.2% in Krasnoyarsk Krai, 1.1% in the Irkutsk region, 3.1% in the Omsk region, and 12.6% in the Tyumen region.[1,4]

The Far East provides about 2% of all HFRS cases in Russia.[23] The highest morbidity was revealed in Khabarovsk Krai, Primorsky Krai, and the Amur region.[1] In Khabarovsk Krai and Primorsky Krai, las in China and Japan, — HTNV is associated with grey red-backed voles (*Myodes rufocanus*).[2,3,21,37] The morbidity of SEOV (the third serotype) associated with the synanthropic brown rat (*Rattus norvegicus*) and black rat (*R. rattus*) was examed in both the Far East and the European part of Russia. The researchers found that SEOV provoked HFRS more often among the urban population, whereas HTNV did so more often among the rural population, of Primorsky Krai.[21] Morbidity in the Far East has a small uptick in May–July and reaches its main peak in November–December. The immune stratum in the Far East is about 1% (ranging from 0.3% in the Amur region to 1.5% in Primorsky Krai).[1,21]

Pathogenesis. Capillary damage is the basis of HFRS pathogenesis. In the first part of the disease, toxicoallergic phenomena predominate, caused by viral infection of the walls of vegetative centers, venules, and arterioles. Lesions on the sympathetic nodes of the neck are followed by hyperemia of the face and neck. Irritation of the vagus nerve leads to bradycardia and a fall in arterial pressure. Damage to the vascular permeability is accompanied by hemorrhages in mucous membranes and the skin. The cause of death is cardiovascular insufficiency, massive hemorrhages into the vital organs, plasmorrhea into the tissues, collapse, shock, swelled lungs, spontaneous rupture of the kidneys, a hypertrophied brain, and paralysis of the vegetative centers.[4,22]

Clinical Features. The incubation period is 4–30 days. HFRS starts with fever, headache, muscular pain, dizziness, nausea, vomiting, hyperemia of the face and neck, bradycardia, and a fall in arterial pressure. Abnormalities of the central nervous system (CNS) in the form of block, excitement, hallucinations, meningeal signs, and visual impairments often occur. Hemorrhagic syndrome becomes apparent as plasmorrhea into the tissues, together with microthrombosis; exanthema; petechial skin rash; nasal, pulmonary, and uterine bleeding: vomiting blood, hematuria, and visceral bleeding. In some cases, Pasternatsky syndrome, pain in the kidneys, oliguria, and albuminuria become morphologically apparent as interstitial and tubular nephritis. The duration of fever is 3–9 days. Two-wave temperature dynamics is possible.[22,38] Analyses of 5,282 cases of HFRS etiologically linked with PUUV in Sweden during 1997–2007 found 0.4% mortality in the first three months of the disease.[39,40] Defense immunity remains for at least 30 years.[8,22]

Diagnostics. Laboratory diagnostics are based on the fluorescent antibody method (FAM), enzyme-linked immunosorbent assay (ELISA), and reverse transcription polymerase

chain reaction (RT-PCR) testing. The virus can be isolated with the use of Vero E6 (green monkey kidney cell line), 2Bs (diploid human embryo lung cell line), A-549 (human lung carcinoma cell line), or RLC (rat lung tissue primary cell culture).[8,22]

Control and Prophylaxis. Treatment of HFRS can be symptomatic, pathogenetic, or etiotropic (or any combination thereof). During the fever period, early hospitalization, disintoxical therapy, and strengthening of the walls of vessels are necessary. During the oliguria period, transfusion with desalinated human albumin, hemodes, a 5% glucose solution, and an isotonic NaCl solution (under the control of the emitted volume of urine) are given. In case of shock, antishock therapy is applied, and hemodialysis is prescribed for kidney insufficiency.[4,22]

Vaccination is the most effective approach to the prophylaxis of HFRS. The efficacy of vaccination was demonstrated in China and in North and South Korea. Nevertheless, it must be mentioned that vaccines in these countries are produced from HTNV and SEOV stains and do not defend against PUUV infection, which is the main etiological agent of HFRS in the European part of Russia (where 98% of all Russian morbidity occurs)[8].

For a long time, anti-HFRS vaccine was difficult to produce because there were no sensitive cell lines to accumulate hantavirus. However, the recent adaptation of PUUV and DOBV to the certified Vero E6 cell line affords an opportunity to produce candidate vaccines against HFRS. Experimental series of "Combi-HFRS-Vac" vaccine have passed compliance tests for medical immunoglobulin preparations for use in humans.[8,41,42]

8.1.3 Genus *Nairovirus*

The genus *Nairovirus* includes the tick-transmitted bunyaviruses, whose genome is the largest in the family Bunyaviridae. The size of L-segments of the Dugbe virus (DUGV), a prototypical species of the nairoviruses, is 12,255 nt. The M- and S-segments are 4,888 and 1,716 nt, respectively (Figure 8.3). As with other bunyaviruses, the L-segment of the nairoviruses encodes an RdRp, the M-segment encodes a polyprotein precursor of the envelope glycoproteins Gn and Gc, and the S-segment encodes the nucleocapsid (N) protein.[1,2]

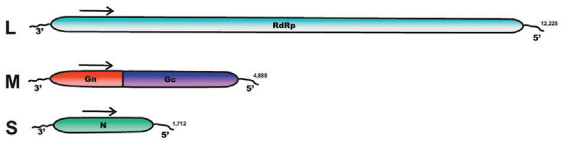


FIGURE 8.3 Genome structure of nairoviruses (Family Bunyaviridae, genus *Nairovirus*). *Drawn by Tanya Vishnevskaya*

The genus *Nairovirus* was established on the basis of antigenic relationships among viruses of the six antigenic groups of arthropod-borne viruses: the Crimean–Congo hemorrhagic fever (CCHF), Nairobi sheep disease (NSD), Qalyub (QYB), Sakhalin (SAK), Dera Ghazi Khan (DGK), and Hughes (HUGV) groups.[3–6] Subsequently, a seventh, Thiafora (TFA), group was assigned to the genus.[7,8] Currently, about 35 viruses are assigned to the genus *Nairovirus*, now united in the aforementioned seven groups.[1] Sequence analysis of previously unclassified bunyaviruses revealed that the nairoviruses actually number much more than 35. Three additional groups of nairoviruses—Issyk-Kul (ISK), Artashat (ARTSV), and Tamdy (TAM)—were established on the basis of phylogenetic analysis (Table 8.3).

8.1.3.1 Crimean–Congo Hemorrhagic Fever Virus

CCHFV belongs to the *Nairovirus* genus of the Bunyaviridae family and is the etiological agent of Crimean–Congo hemorrhagic fever (CCHF).

TABLE 8.3 Viruses of the *Nairovirus* Genus (Family Bunyaviridae) Isolated in Transcaucasia, Central Asia, Kazakhstan, and High Latitudes of Northern Eurasia

Serogroup	Virus	GenBank ID	Type of Biome	Source of isolation	Distribution
CCHFV	Crimean–Congo hemorrhagic fever (CCHFV)	NC005300–NC005302	Pasture	Ticks *Hyalomma* spp., predominantly *H. marginatum*; Hedgehogs; hares; rodents; farm animals; humans	Central Asia, Middle East, China, Kazakhstan, Transcaucasus, south of Europe, Africa
	Hazara (HAZV)	M86624, DQ076419		Ixodidae ticks	Central Asia
Qalyub	Chim (CHIMV)	KF801656	Burrows	Ticks *Ornithodoros tartakovskyi*, *O. papillipes*, *Rhipicephalus turanicus*, *Hyalomma asiaticum*; Great gerbil, *Rhombomys opimus*	Central Asia
	Geran (GRNV)	KF801649		*Ornithodoros verrucosus* ticks	Transcaucasus
Sakhalin	Sakhalin (SAKV)	KF801659	Seabird colony	*Ixodes uriae* ticks	High latitudes
	Paramushir (PMRV)	KF801657			
Tamdy	Tamdy (TAMV)	KF801653	Pasture	Ticks *Hyalomma asiaticum* and *H.* spp., *Rhipicephalus turanicus*, *Haemophysalis concinna*, gerbils, birds, human	Central Asia, Kazakhstan, Transcaucasus
	Burana (BURV)	KF801651		Ticks *Haemaphysalis punctate*, *Haem. concinna*	Central Asia
Hughes	Caspiy (CASV)	KF801659	Seabird colony	Ticks *Ornithodoros capensis*; seagull *Larus argentatus*	Eastern and western coasts of Caspian Sea
Issyk-Kul	Issyk-Kul (ISKV)	KF801652	Burrows	Bats (Vespertilionidae); ticks Argasidae; birds; human	Central Asia, Malaysia
	Uzun-Agach (UZAV)	KJ744032		Bat *Myotis blythii*	Central Asia
Artashat	Artashat virus (ARTSV)	KF801650	Burrows	Ticks *Ornithodoros alactagalis*, *O. verrucosus*	Transcaucasus

History. CCHF was first mentioned as "hunibini" and "hongirifta" by Tajik physician Abu-Ibrahim Djurdjani in the twelfth century. The viral nature of CCHF was originally established in 1945 during an expedition to Crimea headed by Mikhail Chumakov at the time of an outbreak.[1–3]

The modern history of CCHFV investigation starts in June 1944 with an epidemic of the disease in the northwestern steppe part of the Crimean Peninsula. More than 200 severe cases of the disease broke out, all exhibiting hemorrhagic syndrome, known in that time as "severe infectious capillary toxicosis." Mikhail Chumakov headed an expedition to the region, and much research revealed that the disease is transmitted by *Hyalomma plumbeum* (*marginatum*) ticks of the Ixodidae family. The disease

was named Crimean hemorrhagic fever. A viral etiology was demonstrated by experimental infection of volunteers by an ultrafiltrated homogenate of *H. marginatum* nymphs collected in 1945 from local hares.[1] In 1963, the historical Hodzha strain was isolated from a patient with hemorrhagic fever in Uzbekistan, as was a set of strains from *H. marginatum* larvae and nymphs in the Astrakhan region, near the Caspian Sea.[2,3] In 1967, the similarity between the etiological agent of Crimean hemorrhagic fever and that of Congo virus, isolated from a patient in 1966 in Zaire (Congo), was demonstrated, so the virus was renamed CCHFV.[4,5]

Genome and Taxonomy. Like the genomes of all nairoviruses, that of CCHFV consists of three segments of negative ssRNA: a signed small (S) (1,672 nt) segment, a medium (M) (5,366 nt), and a large (L) (12,108 nt) segment. Each segment has a single ORF that encodes the nucleocapsid protein (N, 482 aa, S-segment), a polyprotein precursor of envelope glycoproteins Gn and Gc (1,684 aa, M-segment), and RdRp (3,945 aa, L-segment).

Genetic diversity among CCHFV strains may reach 31% nt and 27% aa differences for M-segment sequences, a reflection of pressure on the immune system and adaptation to various ecologic zones with different prevalences of *Hyalomma* tick species. The S- and L-segments are more conservative: The level of divergence of S-segment sequences is 20% nt and 8% aa, and that for L-segment sequences is 22% nt and 10% aa.

Phylogenetic analysis based on sequence data comparisons of S-segments shows that CCHFV isolates from different regions can be clustered into seven phylogeographic groups: West African isolates (group I), as well as isolates from Central Africa (Uganda and the Democratic Republic of the Congo) (group II); South Africa and West Africa (group III); the Middle East and Asia (group IV) (the Asian strain can be divided to two distinct subgroups: Asia 1 (IVa) and Asia 2 (IVb)); Europe and Turkey (group V); and Greece (group VI), a separate group detached from the rest of Europe (Figure 8.4).[6–8] In general, the genotypic structure defined on basis of the S-segment analysis is correlated strictly with geography. Cases of isolation of strains not typical for a given territory were attributed to possible transmission of the virus by infected ticks carried by migratory birds. The tree topology based on the L-segment comparison is, on the whole, similar to that generated on the basis of the S-segment. Exceptions are the viruses from Senegal, which represent a separate lineage in the S-segment analysis, and those clustered within group III in the L-segment analysis. Similarly, the division of group IV into group IVa (Asia 1) and IVb (Asia 2) is not clear (Figures 8.5 and 8.6).

In Russia, most of the strains of CCHFV that were isolated were isolated in the country's southern regions (Astrakhan, Volgograd, and Stavropol districts). Phylogenetic analysis showed that all of them are closely related to European and Turkish strains (group V).[9–12]

Epizootiology. Up to today, CCHFV has been found to circulate in 46 countries in Europe, Africa, and Asia.[4,13–15]

CCHFV was isolated from at least 27 species of mainly Ixodidae ticks, but their roles in maintaining virus circulation are different (Tables 8.4 and 8.5). The main significance for CCHFV reservation and transmission belongs to ticks of the *Hyalomma* genus: *H. marginatum* in the south of he European part of Russia, *H. anatolicum* and *H. detritum* in the Middle East and Asia, and *H. asiaticum*in Kazakhstan. According to our data, the viral load among imagoes of *H. marginatum* in the Astrakhan region in 2001–2005 was 1.33%; among nymphs, the load was 0.2%. The presence of transphase and transovarial transmission of CCHFV provides a reservation for viruses during the interepidemic period. Three hosts—for larvae (ground birds, mainly Corvidae;

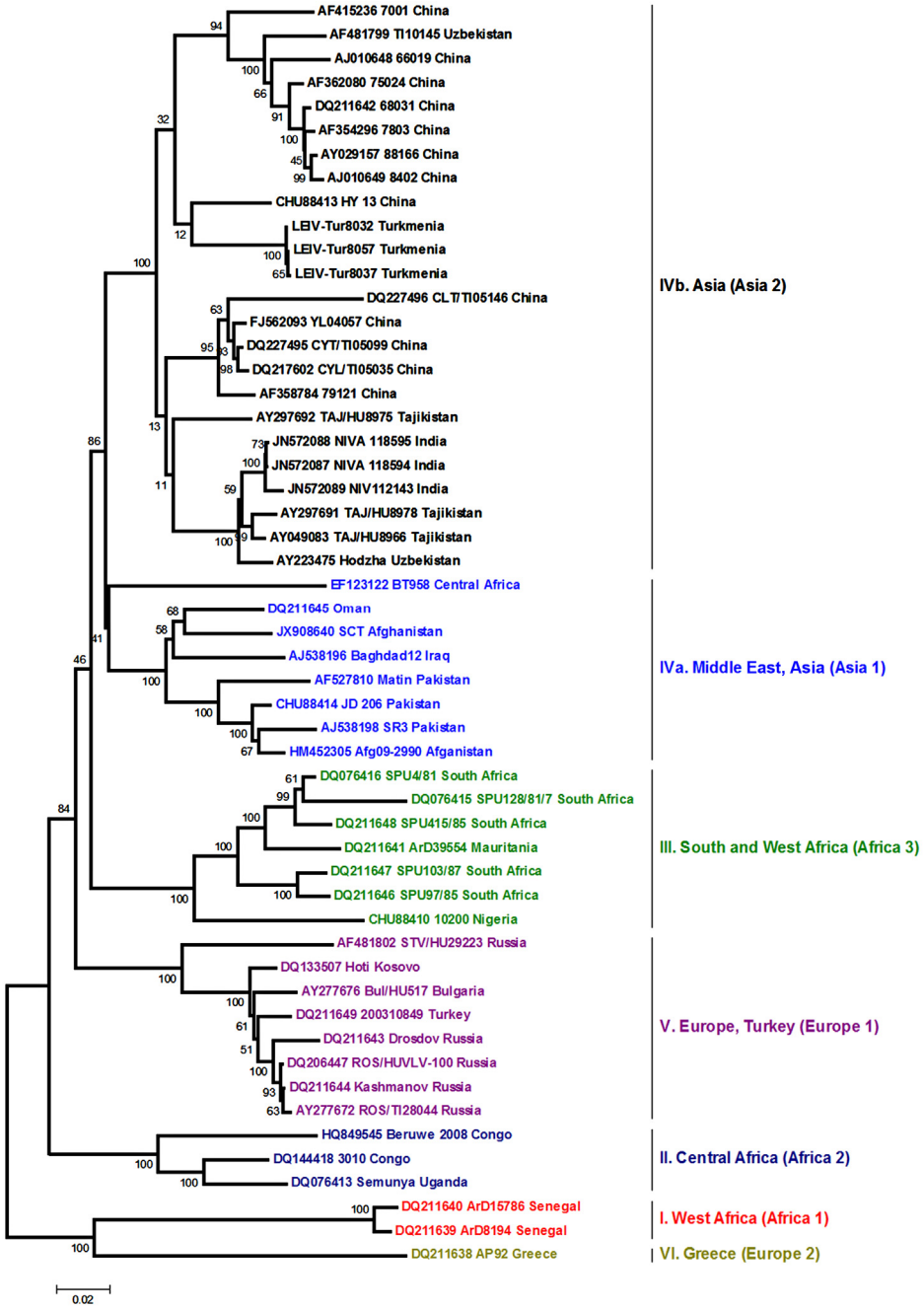


FIGURE 8.4 Phylogenetic relationship between CCHFV strains isolated in different geographical regions, based on comparison of the full-length sequences of the S-segment. I—West Africa (Africa 1); II—Central Africa (Africa 2); III—Southern and Western Africa (Africa 3); IV—Middle East/Asia, divided into groups IVa and IVb, respectively, corresponding to groups Asia 1 and Asia 2; V—Europe/Turkey (Europe 1); VI—Greece (Europe 2).

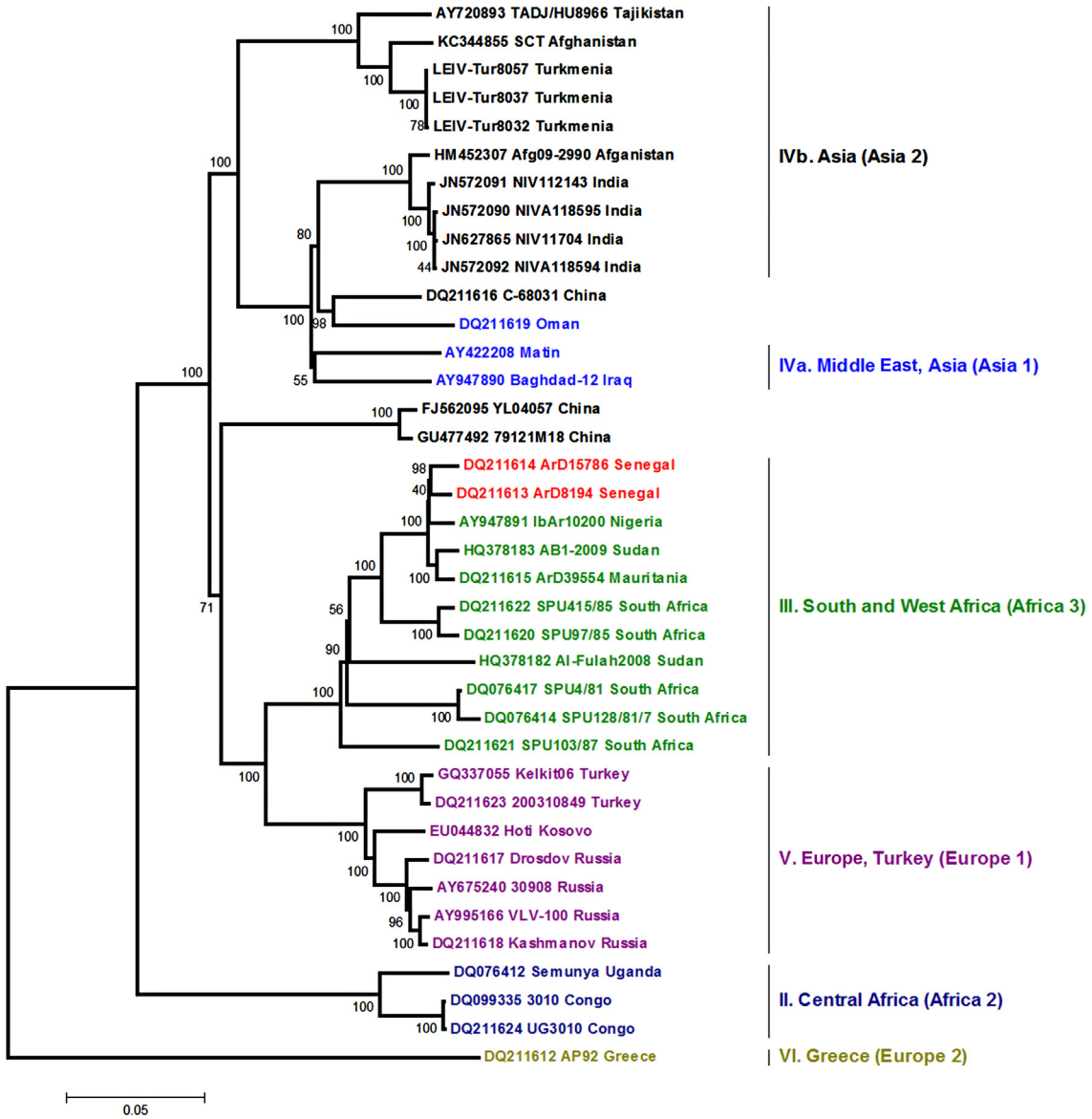


FIGURE 8.5 Phylogenetic relationship between CCHFV strains isolated in different geographical regions, based on comparison of the full-length sequences of the M-segment. I—West Africa (Africa 1); II—Central Africa (Africa 2); III—Southern and Western Africa (Africa 3); IV—Middle East/Asia, divided into groups IVa and IVb, respectively, corresponding to groups Asia 1 and Asia 2; V—Europe/Turkey (Europe 1); VI—Greece (Europe 2).

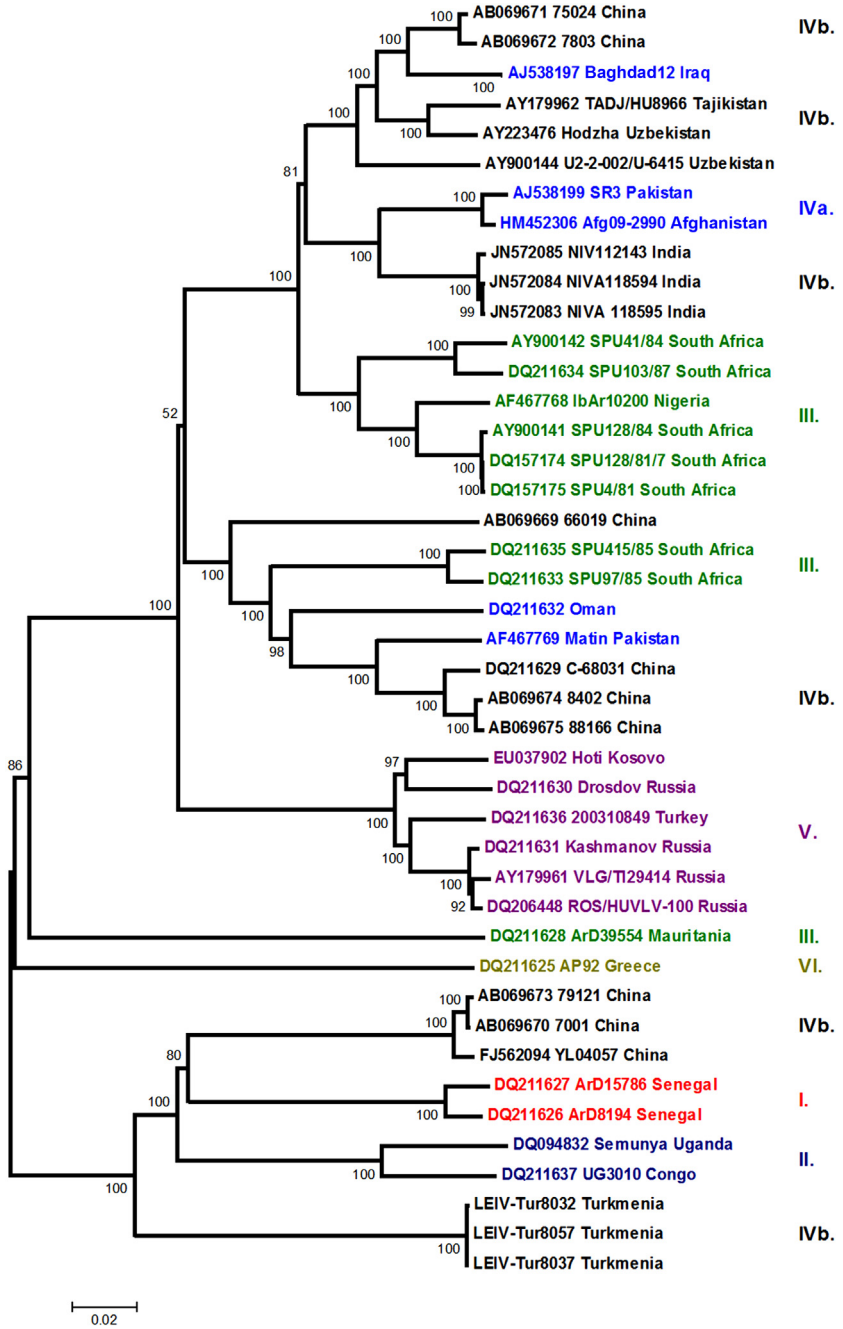


FIGURE 8.6 Phylogenetic relationship between CCHFV strains isolated in different geographical regions, based on comparison of the full-length sequences of the L-segment. I—West Africa (Africa 1); II—Central Africa (Africa 2); III—Southern and Western Africa (Africa 3); IV—Middle East/Asia, divided into groups IVa and IVb, respectively, corresponding to groups Asia 1 and Asia 2; V—Europe/Turkey (Europe 1); VI—Greece (Europe 2).

TABLE 8.4 Isolation of CCHFV from Ixodidae Ticks

Species of ticks	Place of collection
Alveonasus lahorensis	Armenia, Uzbekistan, Iran
Argas persicus	Uzbekistan
Hyalomma marginatum	Moldova, south of Ukraine, south of European part of Russia, central Asian countries, Kazakhstan
H. m. turanicum	Central Asian countries, Kazakhstan
H. m. rufipes	Africa (Nigeria, Senegal, Somali)
H. anatolicum	Central Asian countries, Kazakhstan, Pakistan, Africa (Nigeria)
H. an. excavatum	Africa (Nigeria)
H. asiaticum asiaticum	Central Asian countries, Kazakhstan, China
H. detritum	Europe (Spain)
H. impeltatum	Africa (Senegal, Nigeria, Ethiopia)
H. impressum	Africa (Senegal)
H. lusitanicum	Europe (Spain)
H. nitidum	Africa (Central African Republic)
H. punctatum	Europe (Spain)
H. truncatum	Africa (Senegal, Nigeria)
Amblyomma variegatum	Africa (Nigeria, Senegal, Uganda, Kenya)
B. annulatus (*calcaratus*)	Central Asian countries, Kazakhstan, Bulgaria, Africa (Senegal, Nigeria)
B. decoloratus	Pakistan
B. geigyi	Pakistan
B. microplus	Pakistan, Nigeria
Haemaphysalis punctata	Moldova, south of Ukraine
Dermacentor marginatus	South of Russia, Moldova, Uzbekistan
D. daghestanicus	Kazakhstan
Rhipicephalus sangnineus	Central Asian countries, south of Ukraine, Africa (Guinea)
Rh. turanicus	Central Asian countries
Rh. pumilio	Central Asian countries, Bulgaria
Rh. bursa	Central Asian countries, Azerbaijan, Greece
Rh. rossicus	South of Russia
Rh. pulchellus	Africa (Kenya)
I. ricinus	South of Russia, Moldova, Bulgaria, Hungary

TABLE 8.5 Infection Rate (%)[a] for CCHFV of Some Ixodidae Ticks[b]

	Ixodidae ticks										
	Hyalomma				*Rhipicephalus*		*Dermacentor*	*Boophilus*	*Ixodes*	*Alveonasus*	
Region	*Marginatum*	*Anatolicum*	*Asiaticum*	*Detritum*	*Turanicus*	*Bursa*	*Marginatus*	*Annulatus*	*Ricinus*	*Lahorensis*	*Argas vesperti-lionis*
South Europe	0.110	–	–	–	–	0.001	0.001	SI	–	0.108	–
Central Asia	0.100	0.011	0.013	SI	SI	–	–	–	SI	0.103	SI
Total	0.100	0.011	0.013	SI	SI	0.001	0.001	SI	SI	0.105	SI

[a] *Abbreviations: SI, solitary isolations.*
[b] *According to data on monitoring conducted by the Center of Virus Ecology of the D.I. Ivanovsky Institute of Virology during 1972–1992.*

mouselike rodents; and hares), nymphs (also ground birds, mouselike rodents, and hares), and imagoes (large mammals—mainly cattle, sheep, and camels)—provide a variety of ecological links of CCHFV to vertebrates.[1,16–19] In Nigeria, CCHFV was isolated from midges (*Culicoides* sp.)[4] The distribution of *H. marginatum* is limited by the isotherm of effective temperatures such that sum ($\Sigma_{T \geq 10^{\circ}C}$) = 3,000°C, or 120 days with mean temperature ≥20°C per year.[20] So, the northern boundary of the distribution of CCHFV in the south of the European part of Russia lies in the dry steppe subzone.[1]

In Russia and South Africa, CCHFV is often isolated from hares.[1,21] CCHFV was isolated from hedgehogs (*Atelerix spiculus*) in Nigeria. Hares and mouselike rodents play the main role in CCHFV circulation.[1,21,22] Viremia in birds is not sufficient for vector transmission (although specific antibodies appear); nevertheless, ground birds are an important element of CCHFV transmission because they are the hosts for the preimaginal phases of *H. marginatum* development.[16,18,23] During field investigations of Chatkalsky Ridge in Kirgizia, nymphs and larvae of *H. marginatum* dominated among field-collected materials from birds. The highest number of ticks was found on rollers (*Coracias garrulus*), crested larks (*Galerida cristata*), tree sparrows (*Passer montanus*), and black-billed magpies (*Pica pica*). In the Astrakhan region, rooks (*Corvus frugilegus*) are the main hosts for *H. marginatum* preimaginal phases.[16]

During migrations, birds can take part in dispersing preimago ticks that carry the virus. For example, in Spain in 2010, CCHFV of African origin (probably introduced by migrating birds) was isolated from *H. lusitanicum*.[24] European birds overwintering in Africa were also found to harbor ticks that carried the virus.[25]

CCHFV infection rates found as the result of an investigation of 40,711 domestic animal sera are presented in Table 8.6.[20] Domestic animals are one of the main reservoirs of CCHFV among vertebrates. Viremia (2.6–3.7 ($\log_{10}LD_{50}$)/20 mcL) sufficient for the infection of ticks was detected 5–8 days after experimental inoculation of sheep. Viremia after up to 10 days post inoculation was detected in small gophers (*Citellus pygmaeus*), long-eared hedgehogs (*Hemiechinus auritus*), and wood mice (*Apodemus sylvaticus*). Experimental infection was revealed only in nymphs, and that is why hares and Corvidae birds—the main hosts for nymphs—play the chief role in CCHFV circulation.

TABLE 8.6 Detection of Specific Anti-CCHFV Antibodies Among Humans and Domestic Animals (1968–1992)

Region	Administrative unit, landscape	Number of tested sera: humans/cattle–sheep–horses–camels–birds	Positive results, %
Crim peninsula	Crimea, steppe	0/442	ND/1.4[a]
North Caucasian	Rostov region	1,519/4,154–893–12–0–65	6.5/4.3–1.8–33.3–ND–0
	Krasnodar Krai, steppe	1,035/2,567	0/1.2
	Stavropol Krai	0/350–2,748	ND/0.3–0.5
Lower Volga	Kalmyk Republic, steppe	573/7,966–185	0/0.4–0
Kazakhstan	Southern deserts	0/1,688–2,782–136–181–0	ND/2.6–3.7–8.8–3.8–ND
Uzbekistan	Deserts	334/2,095–156–0–0–0	0.9/2.5–5.1–ND–ND–ND
Turkmenistan	Deserts	304/103–509–0–0–0	0/4.9–7.9–ND–ND–ND
Kirgizia	Mountain steppes, intermountain depression deserts	0/357–489–0–0–0	ND/12.6–7.4–ND–ND–ND
Tajikistan	Mountain steppes, intermountain depression deserts	7339/2,402–1,341–71–38 (donkeys)–506 (other)	1.0/1.3–1.5–2.8–39.5 (donkeys)–0 (other)

[a]*Abbreviation: ND, no data.*

Epidemiology. CCHF distribution correlates with that of the main vector and natural reservoir of CCHFV—*H. marginatum* ticks—placing the virus within the limits of steppe, semidesert, and desert landscapes. CCHFV strains were have been isolated many times from patients in Russia,[1–3] Pakistan, Iraq, Iran, China, Greece, Bulgaria,[26] Turkey,[27,28] Romania, Yugoslavia, the United Arab Emirates, Senegal, Nigeria, the Republic of South Africa, Kenya,[29] Uganda, Tanzania, Ethiopia, Egypt, Burkina Faso, Mauritania, and Zimbabwe.[4] According to serological data, CCHFV is active in the south of France, Hungary, and India.[30] Figure 8.7 presents modern data about the known and predicted distribution of the virus.[4,31,32] CCHF outbreaks and sporadic cases of the disease were revealed on the territory of the former USSR in Ukraine, Moldova, Turkmenistan, Uzbekistan, Tajikistan, Kazakhstan,[20,33] Azerbaijan, the Rostov region, Krasnodar Krai, Stavropol Krai, the Kalmyk Republic, the Dagestan Republic, and the Ingush Republic.[1,34]

After 2006 until today, CCHFV is continuing to circulate in southeastern Europe (Greece and Bulgaria,[26]); in Asia (Turkey,[35,36] Iran,[37] Kazakhstan,[38] Pakistan, Afghanistan,[39] and China; and in all arid territories of Africa.[25,29,40,41] Cases of CCHF were revealed in Georgia.[42]

CCHFV infection rates found as the result of an investigation of 11,676 human sera are presented in Table 8.6.[20] CCHF mortality among humans was 12–16% in 1953–1967, 2.0% in 2006–2010, 3.6% in 2011–2013, and 5.1% in 2013. Starting in 1999, the epidemiological situation for CCHF worsened in the south of the European part of Russia, including Rostov, Astrakhan, the southern regions of Volgograd, the Kalmyk Republic, and the northern part of Dagestan, especially Stavropol Krai (Tables 8.7 and 8.8).[34,43] The deterioration may be explained by an increase in the population

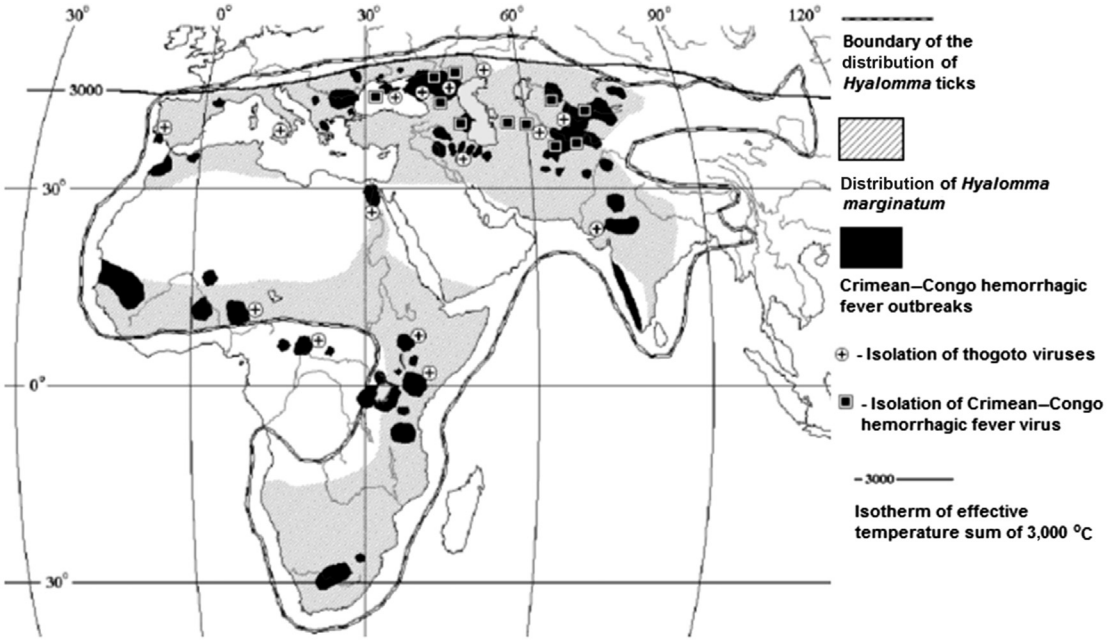


FIGURE 8.7 Distribution of *Hyalomma* ticks, Crimean–Congo hemorrhagic virus, and Thogotoviruses.

TABLE 8.7 Morbidity Due to CCHFV in Russia

	Number of CCHF cases															
Territory	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
Astrakhan	1	5	11	13	9	4	37	16	20	5	6	7	10	7	1	152
Volgograd	0	18	9	3	3	2	6	16	30	7	2	3	0	0	6	105
Dagestan	0	6	10	7	3	1	3	3	2	2	1	3	2	0	2	45
Ingush	0	0	0	0	0	4	0	0	1	0	0	0	0	0	0	5
Kalmyk	0	8	3	13	23	15	38	69	64	16	17	10	11	3	0	290
Karachaevo-Cherkessiya	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Rostov	27	0	5	7	9	9	16	55	53	83	27	16	48	41	38	434
Stavropol	10	48	21	54	30	41	38	41	63	80	66	28	26	24	32	602
Krasnodar	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Total	38	85	59	97	77	76	139	200	234	193	119	67	97	75	79	1,635

TABLE 8.8 CCHF in Russia in 2013[51]

Federal District	Number of cases (%)	Infection rate per 100,000 of Population
Central	1[a] (1.25)	0.01
Northwestern	0	0.00
Southern	45 (56.25)	0.32
North Caucasian	34 (42.50)	0.36
Lower Volga	0	0.00
Ural	0	0.00
Siberian	0	0.00
Far Eastern	0	0.00
Total	80 (100)	

[a]*Imported case.*

of Ixodidae (at first, *H. marginatum*) ticks in this region as the result of climatic changes.

During 1999–2010, 13,838 cases of CCHF[44] were recorded in Russia, including 520 in Stavropol Krai,[45] 307 in the Rostov region,[46] 276 in the Kalmyk Republic,[47] 134 in the Astrakhan region,[48] 99 in the Volgograd region,[49] 41 in the Dagestan Republic, 5 in the Ingush Republic, and 1 in the Karachaevo–Cherkesskaya Republic[50] (Table 8.7). In 2013, 80 cases of CCHF were recorded on the territory of the Southern Federal District and the North Caucasian Federal District (Table 8.8, Figure 8.8). The absence of any recorded cases of CCHF in Krasnodar Krai could be explained by a lack of attention to CCHF diagnostics.

A decrease in the proportion of severe clinical forms with hemorrhagic syndrome occurred after

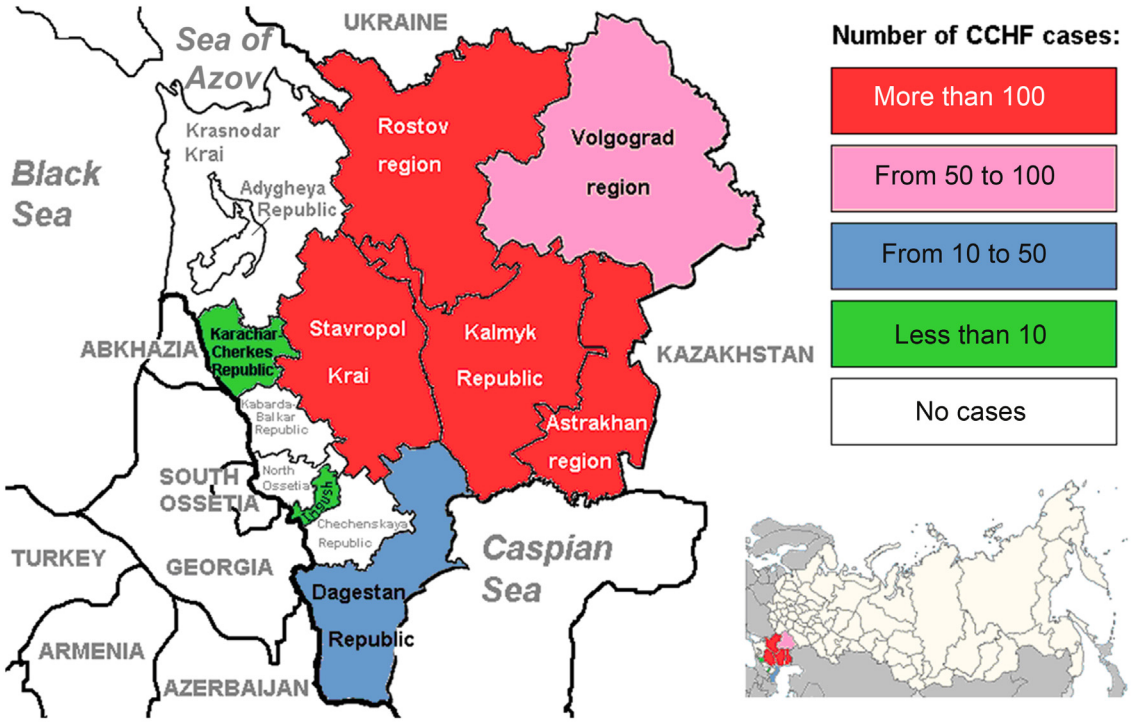


FIGURE 8.8 Distribution of CCHF in Russia (1999–2013).

2006. The drop could have been due to the introduction of high-grade express diagnostics methods into clinical practice and an intensification in seeking out and diagnosing those suspected of having CCHF. At the same time, the disease extended its incidence into the new territories of the Volgograd region, with nosocomial CCHF cases recorded there once again.[52] A warming of the climate promotes an expansion in the distribution of CCHFV to the north and the widening of endemic territory. Starting in 2002, CCHF was registered regularly in all of the units units of the Astrakhan region, accompanied by a mean morbidity of 3.7 per 100,000 population. More than 90% of CCHF cases occurred in the May–July period, and about 85% of the inhabitants of the rural area fell victim to the disease. Morbidity reached 26 units and three towns in the Rostov region. In the Volgograd region, CCHF was originally reported in 2000 in dry steppe on the boundary between that region and the Kalmyk Republic. Morbidity in the Kotelnichesky unit of the Volgograd region reached 37.5 per 100,000 people. Sporadic cases (with 16.7% lethality) were found in six units in the southwestern part of the Volgograd region, where the modern northern boundary of the distribution of CCHFV lies. During 2000–2006, 170 cases of CCHF were reported in the Kalmyk Republic. CCHF morbidity was found in 26 rural units of Stavropol Krai, mainly in dry steppes, where the highest infection rate from *H. marginatum* existed.

Pathogenesis. Pathogenesis is defined by lesions of the vascular and nervous systems.[17,51,53]

Clinical Features. The incubation period after transmissive CCHFV inoculation (as the result of a tick bite) is 2–7 days, whereas that after contact inoculation is 3–4 days. The difference is due to a much higher quantity of virus entering the system during contacts inoculation.[17,50,53] CCHF starts rapidly, with the temperature increasing to 39–40°C and the appearance of fever, skin hyperemia in the top half of the trunk, headache, lumbar pain, abdominal and epigastric pains, generalized arthralgia, conjunctivitis, pharingitis, and diarrhea. About 50% of cases have two obvious waves of increasing temperature, with the temperature decreasing in 6–7 days after the end of the incubation period. Petechial rash appears in the majority of all CCHF patients in 3–4 days after the incubation period and is a marker of the second increasing-temperature wave. Hemorrhagic diathesis with nasal bleeding (in two-thirds of cases), bloody vomiting, blood in the sputum, and hematuria, all starting 3–5 days after the end of incubation period, are characteristic in 85% of cases. The duration of the hemorrhagic period is 8–9 days. Meningitis symptoms and signs of psychosis (depression, sleepiness, lassitude, photophobia) could develop as well. Lethality is 16–20% for transmissive inoculation and up to 50% for contact inoculation. Nevertheless, lethality is decreasing as the result of the introduction of modern testing systems and treatment with ribavirin. The convalescent period is about a month.[17,50,51,53]

E.V. Leshchinskaya has suggested the following clinical classification of CCHF: (i) severe form with hemorrhagic syndrome (1.a. without band bleeding; 1.b. with band bleeding); (ii) without hemorrhagic syndrome (2.a. medium-severe form; 2.b. light form).[50,53]

Diagnostics. Diagnosis is based on the detection of both specific antibodies via ELISA (IgM after 8 days post disease progression and IgG) and virus RNA via RT-PCR testing (earlier than 8 days post disease progression).[43,54] Both tests must be conducted for a definitive diagnosis of CCHF to be made. During the first week of infection with CCHF, positive results via RT-PCR are obtained in 93% of cases; during the second week, the percentage is 40%. During the second week of the disease, positive results in IgM via ELISA are obtained in 93% of cases; during the third week, the percentage of positive reults in IgG via ELISA is 80%.[55–58]

Control and Prophylaxis. Ribavirin is the most effective drug prescribed today.[53,59–61] Ribavirin is used for 5 days after symptoms first

appear: 2,000 mg (10 capsules) or 30 mg/kg for the first time, then 600 mg × 2 times a day if the weight of the patient is more than 75 kg or 500 mg × 2 times a day if the weight of the patient is is less than 75 kg). The duration of treatment is 4–10 days. Ribavirin must not be used by pregnant women, except when the disease is considerd life threatening.

Vaccine development is currently just in the experimental stages,[62–64] so prophylaxis involves early detection of sick humans and the prevention of further contact infections. Nonspecific prophylaxis includes the eradication of Ixodidae ticks on livestock and acaricide treatment of locations inhabited by domestic animals. In pastures with large numbers of Ixodidae ticks, animals have to be led into box stalls and the humans leading them there must use special suits.

8.1.3.2 Artashat Virus

History. Artashat virus (ARTSV, strain LEIV-2236Ar) was originally isolated from *Ornithodoros alactagalis* ticks (family Argasidae) collected in the burrows of a small five-toed jerboa (*Allactaga elater*) near Arevashat village (40°02′N, 44°32′E; Artashat district, Ararat province), Armenia (Figure 8.9) in 1972 (authors: D.K. Lvov, V.A. Zakaryan, V.L. Gromashevsky, T.M. Skvortsova). A second strain of ARTSV was isolated at the same location and source in 1983. Later, in 1984–1985, 10 strains (topotypical strain, LEIV-9000Az) were isolated from *O. verrucosus* ticks, collected in the burrows of a Persian jird (*Meriones persicus*) in Azerbaijan (Figure 8.9, Table 8.9). On the basis of the morphology of the virion, ARTSV was classified as a member of the family Bunyaviridae, and because of the

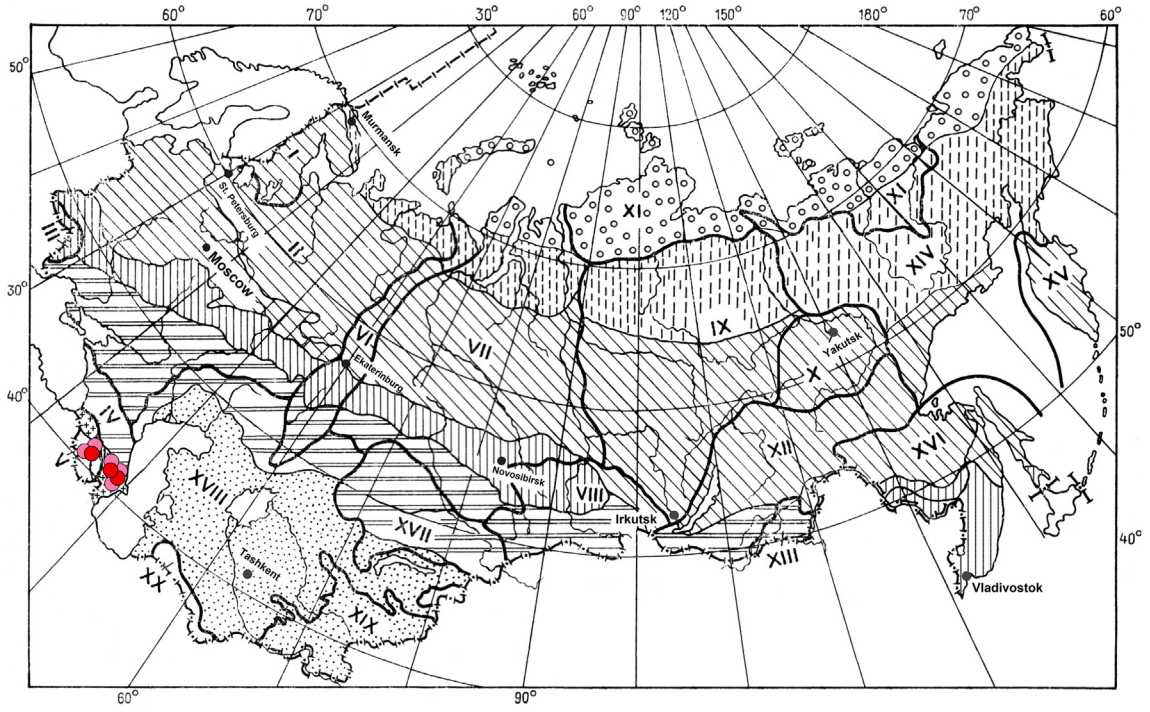


FIGURE 8.9 Places of isolation of ARTSV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: strains of ARTSV with completely sequenced genome; Pink circles: strains of ARTSV identified by serological methods. (See other designations in Figure 1.1.)

TABLE 8.9 Isolation of ARTSV (Family Bunyaviridae, Genus *Nairovirus*)

Place of field material collection	Source	Date of isolation	Number of strains isolated
Armenia, Ararat province	*Ornithodoros alactagalis* ticks from burrows of small five-toed jerboa (*Allactaga elater*)	October 1972	1
Armenia, Ararat province	*Ornithodoros alactagalis* ticks from burrows of small five-toed jerboa (*Allactaga elater*)	July 1983	1
Azerbaijan, Ordubad district	*Ornithodoros verrucosus* ticks from a Persian jird (*Meriones persicus*)	September 1984	2
Azerbaijan, south part of Gobustan	*Ornithodoros verrucosus* ticks from a Persian jird (*Meriones persicus*)	September 1984	1
Azerbaijan, Goranboy District	*Ornithodoros verrucosus* ticks from a Persian jird (*Meriones persicus*)	September 1985	6
Azerbaijan, Yevlax District, near Mingachevir city	*Ornithodoros verrucosus* ticks from a Persian jird (*Meriones persicus*)	September 1985	1

absence of antigenic relationships with any known viruses, it was referred to as an "unclassified bunyavirus."[1–3]

Taxonomy. Three strains of ARTSV were sequenced.[4] A full-length genome comparison revealed that ARTSV has 42–60% nt similarity to other nairoviruses. Phylogenetic analysis revealed that the virus is a new species in the *Nairovirus* genus and forms a distinct genetic lineage on the nairovirus tree, which was constructed for all three segments of the genome (Figures 8.10–8.12).

The phylogeny of the nairoviruses is based mainly on analyses of the partial sequence of the conservative catalytic core domain of RdRp.[5,6] The similarity of this domain of ARTSV to other nairoviruses is 42–65% nt and 58–70% aa. The phylogenetic tree constructed by the maximum-likelihood method on the basis of the amino acid alignment of the RdRp catalytic core domain of nairoviruses confirms the topology of ARTSV on a newly formed genetic lineage (Figures 8.10–8.12). The nairoviruses on the tree can be divided into two main phylogenetic groups. The first group includes the nairoviruses, which are transmitted predominantly by ixodids: the Crimean–Congo hemorrhagic fever group (*Hyalomma* and *Haemaphysalis*, as well as *Dermacentor*, *Rhipicephalus*, and *Ixodes*), the Dugbe group (mainly *Amblyomma*, but also *Hyalomma*, *Rhipicephalus*, and *Haemaphysalis*), the Sakhalin group (*Ixodes*), and the Tamdy group (*Hyalomma*). The first group also includes Erve virus (ERVEV), whose vectors are unknown.[7,8] The second phylogenetic lineage includes the nairoviruses from the Hughes, Issyk-Kul, Dera Ghazi Khan, and Qalyub groups, whose vectors are argasids: *Argas* and *Ornithodoros*. The tree topology of ARTSV shows that the virus is in the lineage of the nairoviruses transmitted predominantly by Ixodidae ticks, although all isolations of ARTSV were obtained from the Argasidae ticks *O. alactagalis* and *O. verrucosus* (Table 8.9). It can be assumed that the adaptation of ARTSV to argasids is the result of the the narrow ecologic niche occupied by those ticks, which are ticks of the subgenera *Theriodoros* and *Pavlovskyella*. Note that, although ERVEV, a European nairovirus, is phylogenetically close to the nairovirus transmitted by ixodids, the association of ERVEV with *Ixodes* spp. ticks has not been established in endemic areas (southern Europe).[8]

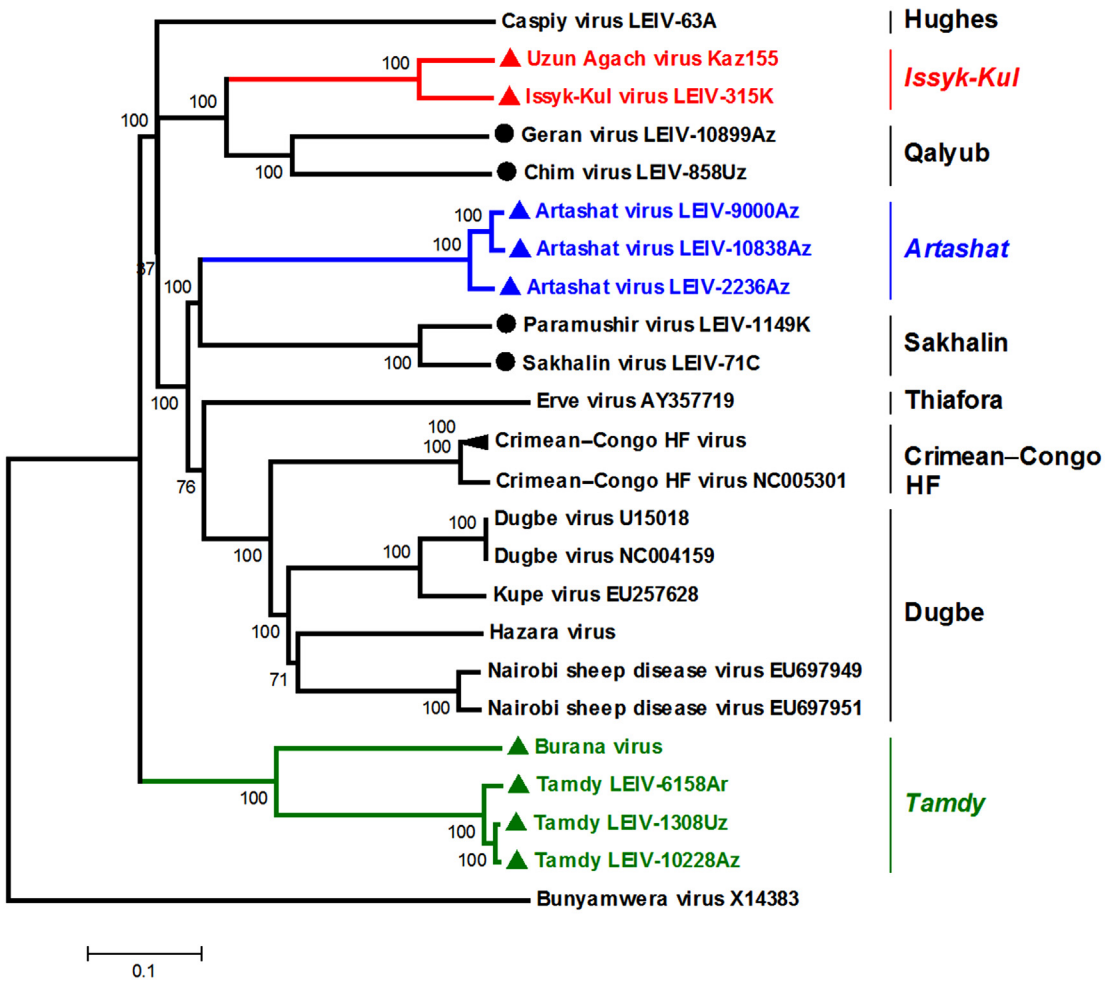


FIGURE 8.10 Phylogenetic structure of RdRp proteins of *Nairovirus* genus members.

ERVEV has been isolated from shrews (*Crocidura russula*).[9]

Arthropod vectors. The adaptation of viruses to Argasidae ticks facilitates the possibility of survival of viral populations in winter at low temperatures and in dry periods. The ability of argasids to fast (up to 9 years and more), the long life cycle of these ticks (up to 20–25 years), and their polyphagia and ecological plasticity determine the stability of the natural foci of arboviruses transmitted by argasids. These foci are confined mainly to the arid regions of the southern part of the temperate and subtropical zones.[1,2,10] The northern border of the range of argasids coincides with isolines denoting a frost-free period of 150–180 days per year and an average daily temperature above 20°C for no less than 90–100 days per year.[11]

Tick species from the subgenera *Theriodoros* (*Ornithodoros alactagalis*, *O. nereensis*) and *Pavlovskyella* (*O. papillipes*, *O. verrucosus*,

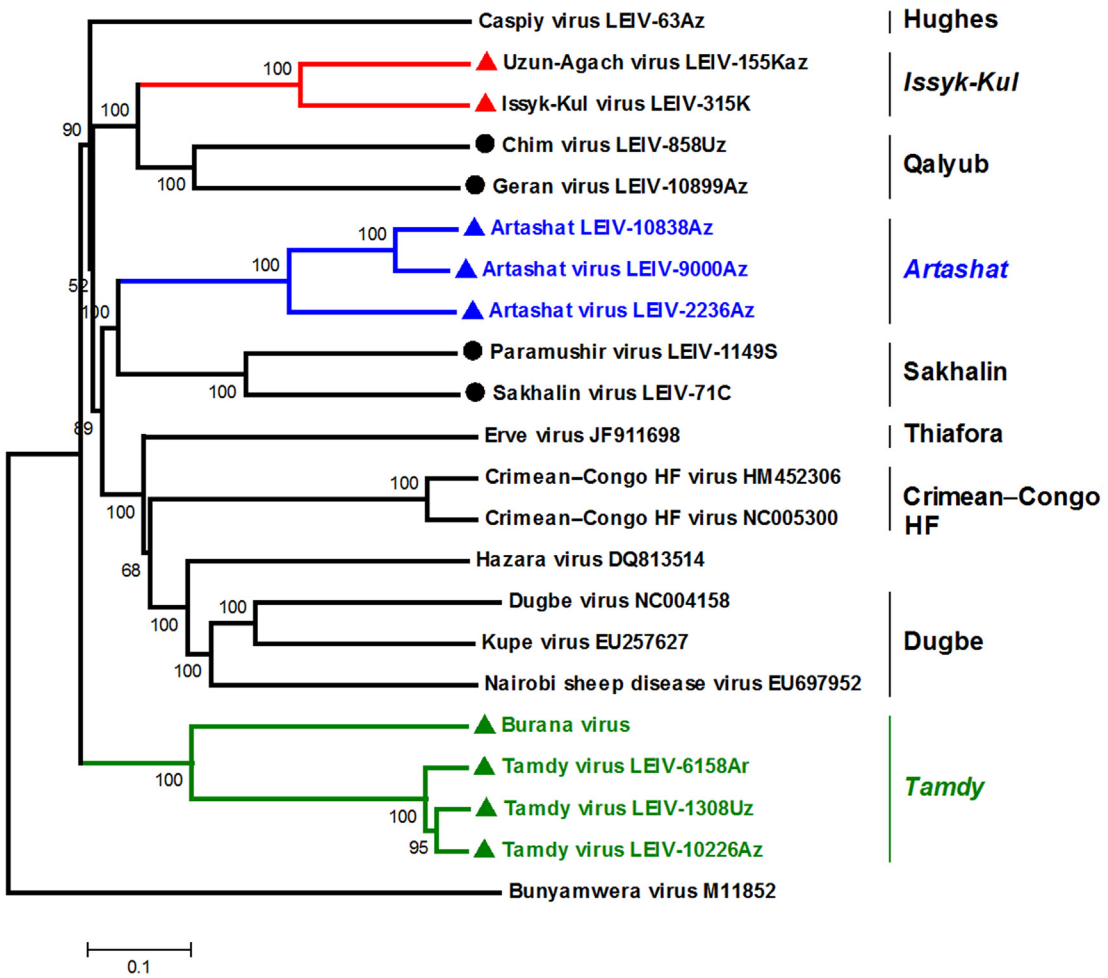


FIGURE 8.11 Phylogenetic structure of Gn/Gc precursor proteins of *Nairovirus* genus members.

O. cholodkovskiy, *O. tartakovskiy*) are associated mainly with burrows of rodents.[11] This ecological peculiarity narrows the possibility of the spread of viruses that are adapted to ticks from the *Theriodoros* and *Pavlovskyella* subgenera.[2] It also applies to ARTSV associated with burrow–shelter biomes and found only in Transcaucasia.

8.1.3.3 *Caspiy Virus*

History. Caspiy virus (CASV, prototypical strain LEIV-63Az) was originally isolated from the blood of a sick herring gull (*Larus argentatus*) caught on Gil Island in the Baku archipelago, off the western coast of Azerbaijan in the Caspian Sea (40°17′N, 49°55′E; Figure 8.13) in 1970.[1–4] On the basis of electron microscopy, CASV was classified as a member of the Bunyaviridae family, but antigenic relationships with known bunyaviruses have not been found. Thus, CASV was categorized into the unclassified bunyaviruses.[5,6–8] At the same time, and in the same place, three strains of CASV were isolated from *Ornithodoros capensis* (family Argasidae) ticks

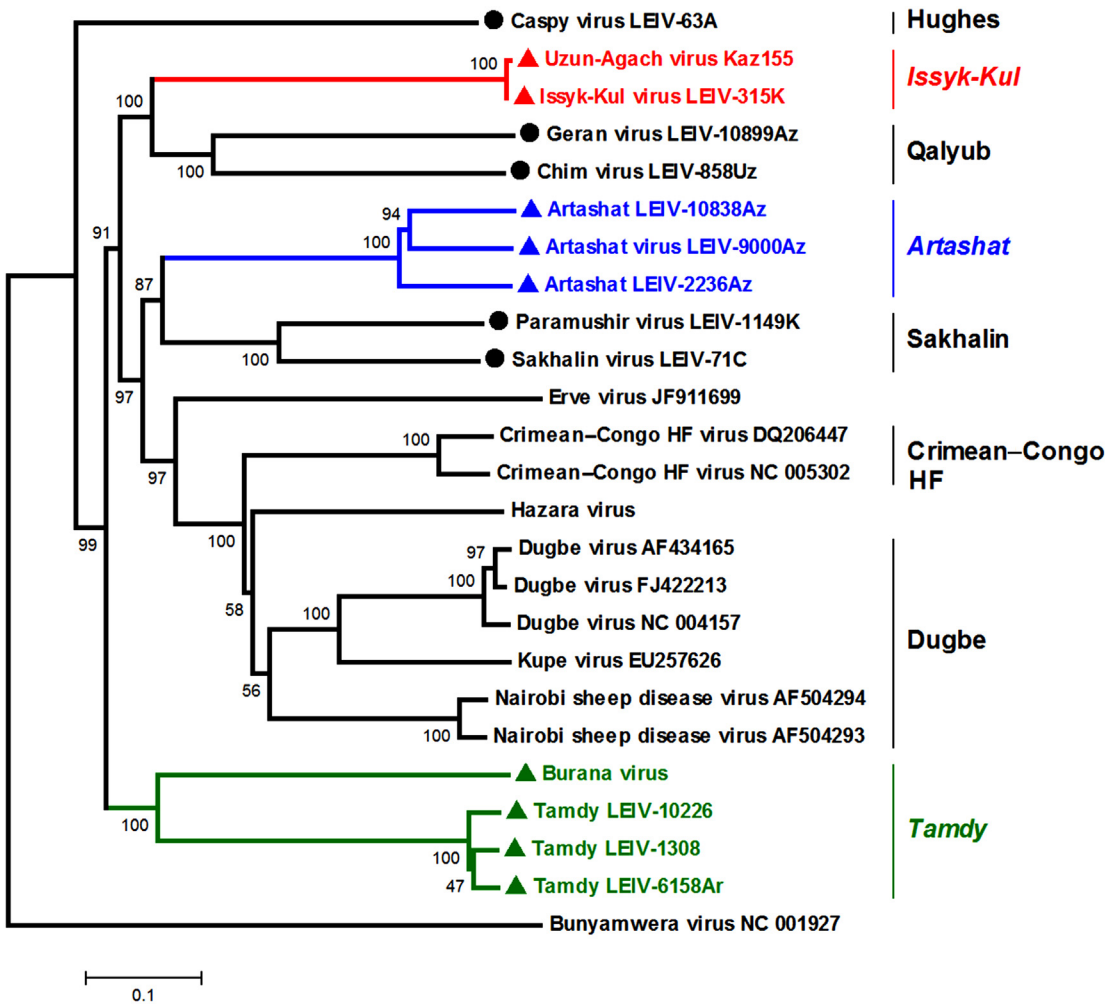


FIGURE 8.12 Phylogenetic structure of nucleocapsid protein of *Nairovirus* genus members.

(1,479 ticks were examined). Later, two more strains were isolated from *O. capensis* ticks (2,019 ticks were examined) collected in colonies of common terns (*Sterna hirundo*) nesting on islands in the Kara-Bogaz-Gol Bay in Turkmenistan, off the eastern coast of the Caspian Sea (41°02′N, 52°53′E; Figure 8.13) in 1974. In total, five strains of CASV were isolated from *O. capensis* ticks. (The rate of infected ticks was 0.21% in Azerbaijan and 0.1% in Turkmenistan.)[8–10]

Taxonomy. The genome of the prototypical strain LEIV-63Az of CASV was sequenced, and it has been shown that CASV is a member of the HUGV group of the *Nairovirus* genus.[11] The S-segment of CASV is about 1,594 nt in length and has a single ORF that encodes the nucleocapsid protein (N, 497 aa). The second start codon, in position 7, is located in the N-protein ORF of CASV. The identity of the amino acid sequence of the N-protein of CASV with those of other nairoviruses is only 28%, on average.

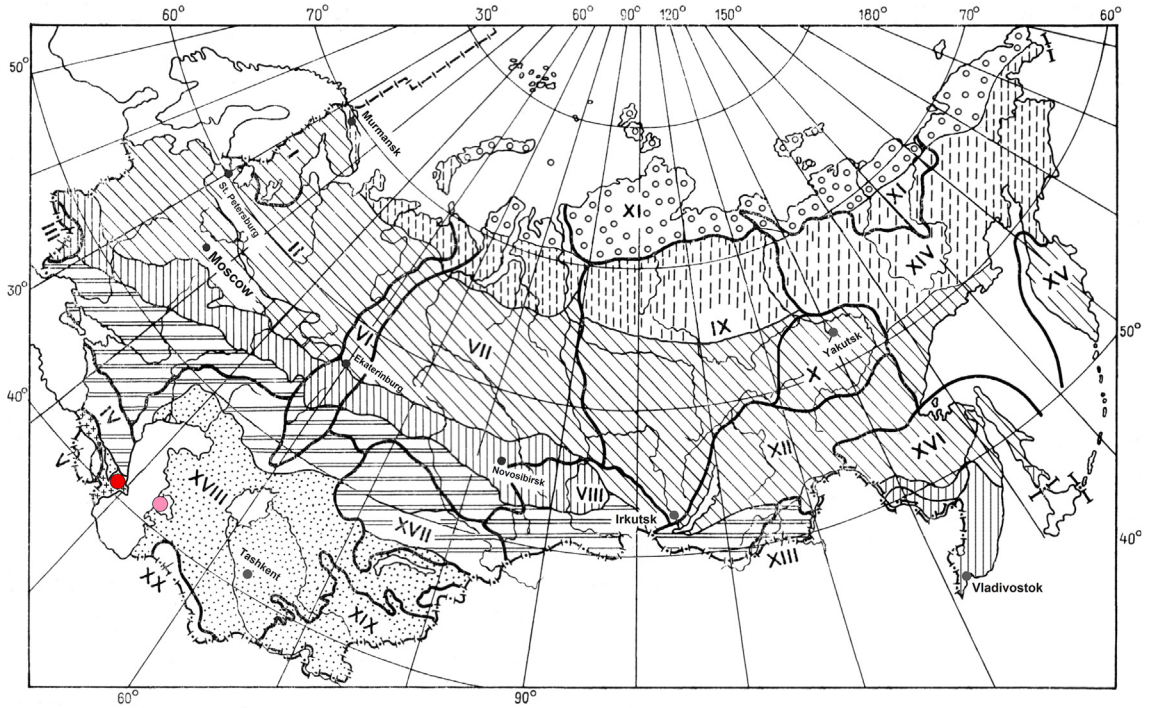


FIGURE 8.13 Places of isolation of CASV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: prototype strains of CASV/LEIV-63Az with completely sequenced genome; Pink circle: two strains of CASV identified by serological methods (See other designations in Figure 1.1.)

The cleavage site for caspase-3 (D285EVD288) that has been found in the N-protein of CCHFV is absent in CASV. Cleavage of N by caspase-3 is required for effective replication of CCHFV.[12] Note that caspase cleavage sites in the nucleocapsid protein are also necessary for replication of human influenza A viruses.[13] The M-segment of CASV, like that of the other nairoviruses, has a single ORF-encoded polyprotein precursor of the envelope glycoproteins Gn and Gc. The length of the Gn/Gc precursor of CASV is 1,376 aa. According to the results of an analysis of polyprotein in the program SignalP server 4.1, the first 32 aa constitute the signal peptide that is cleaved on the SSA/SY site. The cleavage site between pre-Gn and pre-Gc is in position 699 (VSG/IK). These data are confirmed by the location of transmembrane domains in mature proteins Gn and Gc that was defined with the use of the program TMHMM server 2.0. Six potential sites of N-glycosylation are predicted in the mature Gn protein of CASV, only one in the Gc protein. In general, the level of identity of polyprotein in CASV is 25–27% aa with that of other members of the *Nairovirus* genus (Table 8.3). The L-segment of CASV has an ORF (4,001 aa) that encodes the viral enzyme RdRp, which is the most conservative viral protein. The similarity of the RdRp of CASV to that of other nairoviruses for which complete genome sequences were available is 38.8–43.0% aa.

Phylogenetic analysis based on the predicted full-length amino acid sequences revealed that CASV is equidistant from other nairoviruses, and forms a distinct branch, on the trees

(Figures 8.10–8.12). For many nairoviruses, only short sequences of the catalytic core domain of RdRp are available in GenBank. This domain of RdRp is very conservative and relevant to phylogenetic analysis.[1,14,15] The highest level of similarity (80% aa) that the RdRp core domain of CASV has is with the same sequences in viruses of HUG. On the dendrogram, constructed on the basis of a comparison of RdRp core domains, CASV is located on the branch of the HUG group (Figures 8.10–8.12). Note that viruses of this group (as well as CASV) have been isolated from *Ornithodoros* (*Carios*) ticks that are associated with seabirds on the coasts and islands of the world's oceans.[2,16] Thus, the phylogenetic relationship of CASV with HUG group viruses reflects the ecological features of those coasts and islands.

Arthropod Vectors. *Ornithodoros capensis* ticks inhabit the coasts and islands of the Atlantic, Indian, and Pacific Oceans from the southern part of the temperate zone to the equator, as well as some large inland ponds.[3,4] Ticks of the *O. capensis* group (*O. amblus*, *O. capensis*, *O. denmarki*, *O. maritimus*, *O. muesebecki*, *O. sawaii*) are obligate parasites of seabirds and replace *Ixodes (Ceratixodes) uriae* ticks in the south temperate, subtropical, tropical, subequatorial, and equatorial zones. *Ixodes (Ceratixodes) uriae* ticks remain common in the north temperate, subarctic, and subantarctic zones.[3,4,17] *O. capensis* ticks feed on many bird species, mainly those of the order Charadriiformes: gulls (family Laridae) and terns (Sturnidae), but also cormorants (Phalacrocoracidae) and pelicans (Pelecanidae).[4,17] These argasid ticks have a life cycle made up of six to eight stages: egg, larva, three to five stages of nymphs, and imago. According to laboratory study, the cycle is from 43 to 83 days and so can be completed during a single breeding season. These ecological peculiarities provide stability to the natural foci of the viruses, which are adapted to the *O. capensis* tick viruses and their transcontinental transfer by migrating birds.[5]

Vertebrate Host. In 1970, during the collection of field material on islands in the Baku archipelago, an epizootic among herring gulls was observed. The first strain of CASV was isolated from sick birds. Migrations in search of food, including migration between the western and eastern coasts of the Caspian Sea, result in a sharing of the argasids and viruses ranging over the area.

8.1.3.4 Chim Virus

History. The prototypical strain LEIV-858Uz of the Chim virus (CHIMV) was isolated from *Ornithodoros tartakovskyi* ticks collected in July 1971 in the burrows of great gerbils (*Rhombomys opimus*) in the vicinity of the town of Chim in the Kashkadarinsky region of Uzbekistan) (38°47′N, 66°18′E; Figure 8.14).[1–3] Isolation of CHIMV was carried out during monitoring of these arboviruses' foci on the territory of central Asia and Kazakhstan. CHIMV was investigated through serological testing with viruses from different families and with unclassified viruses isolated earlier in the USSR. Because no antigenic relationships of CHIMV were (and still have not been) found, CHIMV was assigned to the category of unclassified viruses.[3,4] Later, four strains of CHIMV were isolated from the ticks *O. tartakovskyi*, *O. papillipes*, and *Rhipicephalus turanicus* (*Rhipicephalinae*) respectively collected in the burrows of great gerbils in the Kashkadarya, Bukhara, and Syrdarya districts of Uzbekistan in 1972–1976.[5,6] Three strains of CHIMV also were isolated from *Hyalomma asiaticum* (*Hyalomminae*) ticks and from the livers of great gerbils, which were collected in the floodplains of the Or River and Karatal River (Dzheskazgan district, Kazakhstan) in April 1979 (Figure 8.14).[7,8]

Taxonomy. The genome of the prototypical strain LEIV-858Uz of CHIMV was sequenced, and, on the basis of sequence analysis, the virus was classified as a novel member of the *Nairovirus* genus.[9] Phylogenetic analysis based

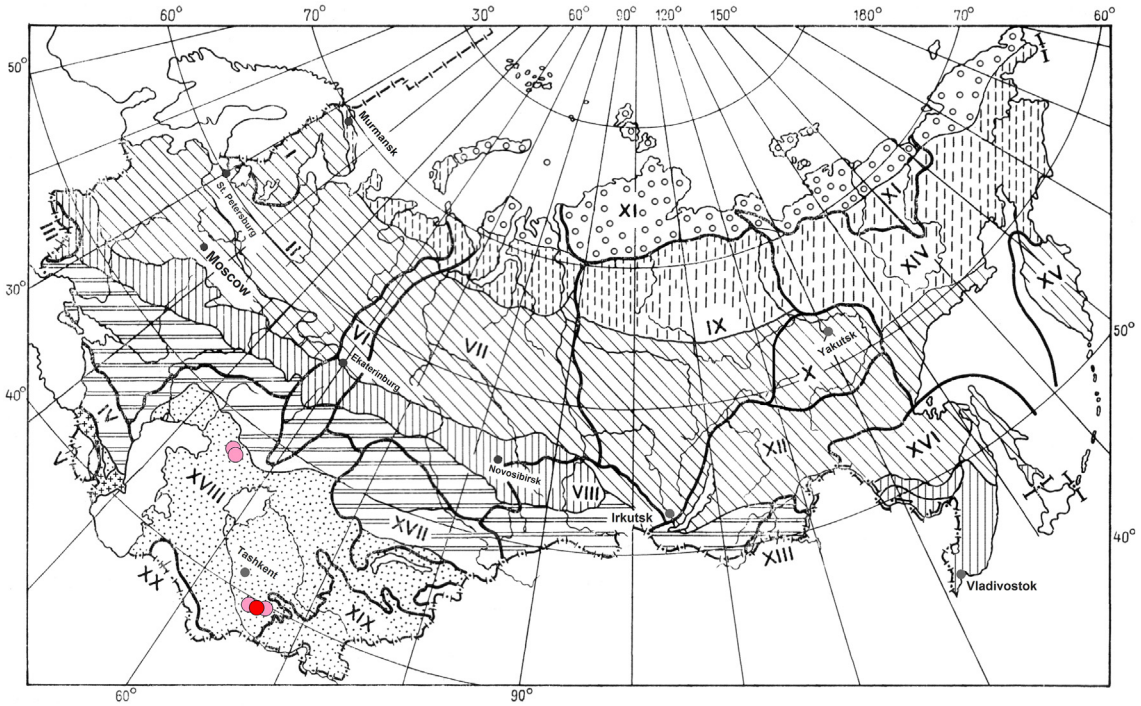


FIGURE 8.14 Places of isolation of CHIMV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: prototype strains of CHIMV/LEIV-858 Uz with completely sequenced genome; Pink circles: strains of CHIMV identified by serological methods. (See other designations in Figure 1.1.)

on a partial sequence of a catalytic center of RdRp placed CHIMV on the genetic branch of the QYBV group.[9,10] The amino acid sequence of this domain of CHIMV has an 87% identity with QYBV, Geran virus (GERV), and Bandia virus (BDAV), the other members of the QYBV group.[11–14] All these data are consistent with the fact that viruses of the QYBV group, as well as CHIMV, have an environmental connection to ticks of the *Ornithodoros* genus and to the burrows of rodents. QYBV has repeatedly been isolated from *O. erraticus* ticks, collected in burrows of the African grass rat (*Arvicanthis niloticus*) in the Nile valley and the Nile delta in Egypt.[13] To date, only short sequences of the RdRp of QYBV are available in GenBank, but recently we gave a genetic characterization of GERV, isolated in Transcaucasia and, apparently, closely related to QYBV.[11] The full-length amino acid comparison of CHIMV with GERV showed that their nucleocapsid proteins N (S-segment) have only a 55.6% identity. The similarity of complete amino acid sequences of RdRp (L-segment) is 74.8%. The similarity of the polyprotein precursor of Gn/Gc is 55.6%. The proteins of CHIMV have 30.3–42.4% aa (N-protein), 27.5–45.1% aa (Gn/Gc precursor), and 48.1–62.3% aa (RdRp) identities with their counterpart proteins in other nairoviruses. Among these nairoviruses, CHIMV has the highest level of similarity with ISKV, which is associated with bats in Central Asia (Figures 8.10–8.12).[15]

Arthropod Vectors. Most isolations of CHIMV were obtained from *Ornithodoros tartakovskyi* ticks. These ticks are common in the Irano-Turanian and mountain provinces of

Asia (Kazakhstan, the central Asian republics, northeastern Iran, and China (Xinjiang)). The western border of the area in question is the eastern shore of the Caspian Sea (53–54°E), the eastern border is in Xinjiang (87°E), and the northern border is 44–47°N. The typical biotopes that *O. tartakovskyi* ticks inhabit are the foothills of dry steppes with loess soils. The ticks also inhabit meadow steppes and deserts (floodplain terraces and canals). *O. tartakovskyi* ticks prefer burrows of small diameter (inhabited by rodents, including jerboas, ground squirrels, small predators, and hedgehogs, as well as by turtles and birds). Synanthropic biotopes are rarely inhabited.[16]

Vertebrate Hosts. The great gerbil (family Muridae, subfamily Gerbillinae, genus *Rhombomys*) is distributed from the shores of the Caspian Sea on the plains of central Asia and southern Kazakhstan, to the deserts of central Asia, Iran, and Afghanistan, and on eastward to northern China and Inner Mongolia. Great gerbils are typical inhabitants of sandy deserts and form a colony with complex multistory burrows that have a large number of entranceways and egresses (up to 200–500). These burrows are a specific biotope that exists for many decades, and they maintain natural foci (in particular, of plague) in arid areas.[6,8]

Animal Infection. The significance of CHIMV in the pathology of humans is unknown. Antibodies to CHIMV have been found in camels (9.5%) in the Kashkadarya region in Uzbekistan.[5] This finding shows the ability of CHIMV to infect camels, as does QYBV, but additional studies are necessary to clarify the pathogenicity of CHIMV in humans and cattle.[17]

8.1.3.5 Geran Virus

History. GRNV (strain LEIV-10899Az) was isolated from *Ornithodoros verrucosus* (family Argasidae, subfamily Ornithodorinae) ticks collected in a burrow of red-tailed gerbils (*Meriones* (*Cricetidae*) *erythrurus*) near Geran Station, Goranboy district, Azerbaijan; Figure 8.15). Serological methods have failed to identify GRNV, but the virus has been sequenced and classified into the *Nairovirus* genus (family Bunyaviridae).[1]

Taxonomy. The genome of GRNV was sequenced by a next-generation sequencing approach.[1] Full-length genome analysis revealed that the genetic similarity of GRNV to other known nairoviruses is, on average, 30–40% aa for the nucleocapsid protein (N, S-segment), 27–33% aa for the polyprotein precursor of the proteins Gn and Gc (M-segment), and 48.0–74.8% aa for RdRp (L-segment). The highest level of similarity all three proteins of GRNV have is to that of CHIMV (54.2–74.8% aa identity) and that of ISKV (42.4–62.3% aa identity).[2,3] Further analysis based on a comparison of partial sequences of the conservative core domain of RdRp of the nairoviruses showed that GRNV and CHIMV were most closely related to QYBV, which is the prototypical virus of the group of the same name.[4] The nucleotide sequence of the RdRp core domain of GRNV has 74.3% nt and 97.1% aa identities with the counterpart sequence of QYBV. The data obtained allow GRNV to be classified as a virus of the QYBV group (Figures 8.10–8.12). The phylogenetic relationship between GRNV and QYBV corresponds to their similar ecological characteristics. QYBV was first isolated in 1952 by R. Taylor and H. Dressler from argasid *Ornithodoros erraticus* ticks collected in a rodent burrow in the Nile River delta near Qalyub village, Egypt (30°N, 32°E).[5–7] Complement-binding antibodies to QYBV were found in humans (1.5%), camels, donkeys, pigs, buffalos, dogs, and rodents.[1,7] The antigenic group of Qalyub, a group that includes QYBV and antigenic-related BDAV, is one of the prototypical groups of the *Nairovirus* genus.[5,8] Previously, QYBV had been repeatedly isolated from *O. erraticum* collected in the burrows of rodents (*Arvicanthis*) in Africa. The second

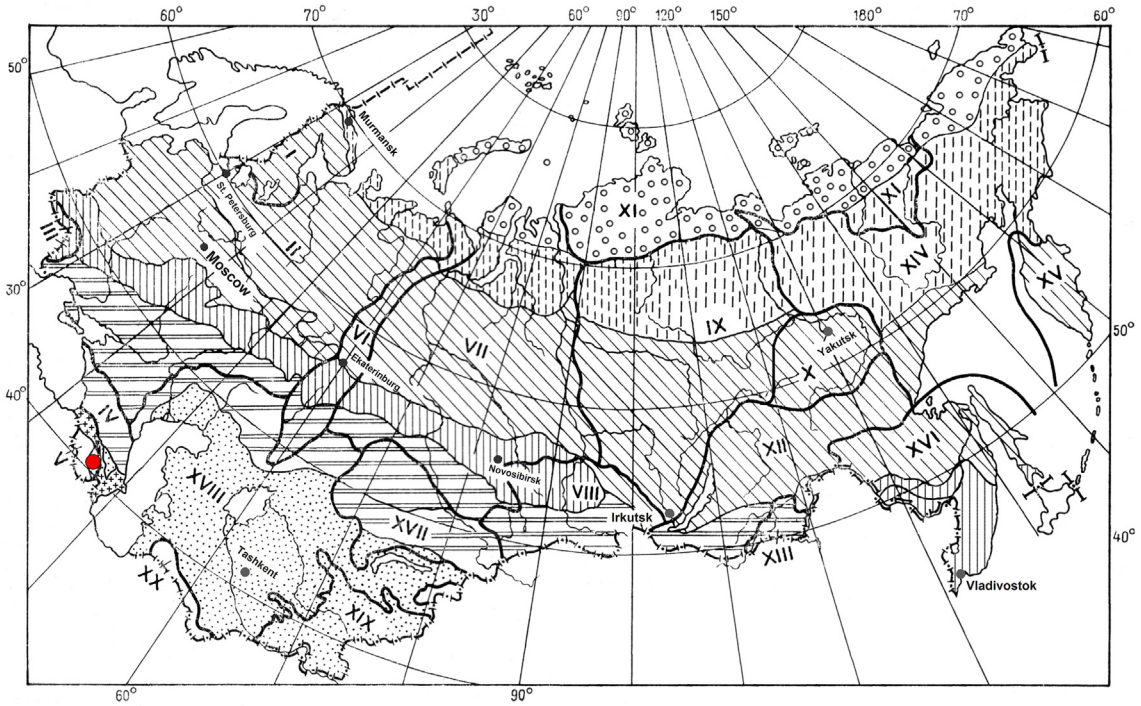


FIGURE 8.15 Place of isolation (red circle) of GRNV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

member of the QYBV group, BDAV, was isolated from *O. sonari* (a member of the *O. erraticus* group) collected in the burrows of rodents (mainly *Mastomys*) in Senegal.[9,10] The isolation of GERV, which is closely related to QYBV, is the first confirmation of the circulation of QYBV group viruses in Transcaucasia.

Arthropod Vectors. The area of distribution of *O. verrucosus* ticks covers the southern part of Moldova as well as Ukraine and the Caucasus region, and is limited by 47°30′N latitude. The area includes the southern part of Russia (the Krasnodar and Stavropol regions), the northern and eastern foothills of Dagestan, the foothills and lowland hills of Georgia, the valleys of the Hrazdan River in Armenia, the foothills of the Lesser Caucasus Mountains in Azerbaijan, and the Gobustan Plateau and the Absheron Peninsula, also in Azerbaijan. *O. verrucosus* ticks inhabit shelter biotopes—in particular, the burrows of red-tailed gerbils (*Meriones* (*Cricetidae*) *erythrurus*), animals that are common in central Asia, southern Kazakhstan, and eastern Transcaucasia. Red-tailed gerbils tends to inhabit desert and semi-desert landscapes. Their burrows are deep and may have 5–10 entranceways and egresses.

8.1.3.6 Issyk-Kul Virus

History. ISKV (prototypic strain, LEIV-315K) was originally isolated from a pool of internal organs (liver, spleen, brain) of *Nyctalus noctula* bats, and their ticks (*Argas (Carios) vespertilionis*) were collected near Issyk-Kul Lake in Kyrgyzstan in 1970 (Figure 8.16).[1,2] Subsequently, ISKV was isolated from other bat species of the Vespertionidae family (*Vespertilio serotinus*, *Vespertilio pipistrellus*, *Myotis blythii*,

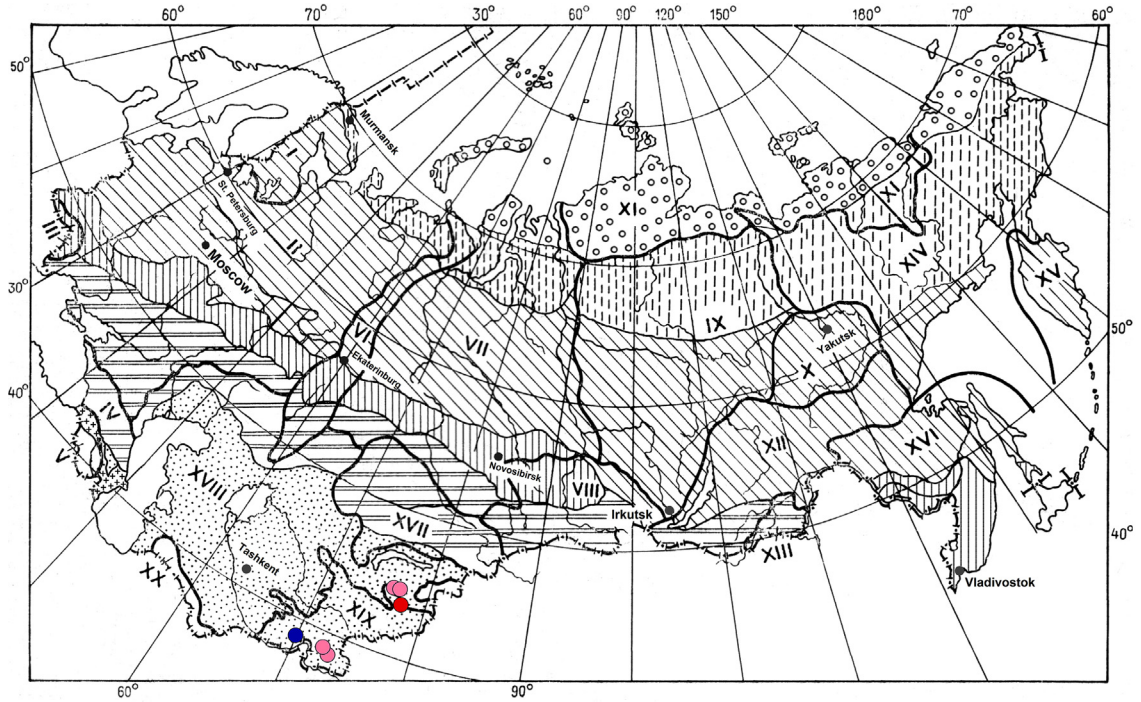


FIGURE 8.16 Places of isolation of ISKV and Garm virus (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: prototype strains of ISKV/LEIV-315K with completely sequenced genome; Pink circles: two strains of ISKV identified by serological methods; Dark-blue circle: strain LEIV-218 Taj of Garm virus. (See other designations in Figure 1.1.)

Rhinolophus ferrumequinum), and from birds, in different regions of Kyrgyzstan and Tajikistan.[3–11] Two strains were isolated from *Anopheles hyrcanus* mosquitoes and *Culicoides schultzei* biting midges, respectively (Figure 8.16, Table 8.10).[3,12,13] Complement-fixation testing showed that ISKV is closely related or identical to the Keterah virus, which was isolated from *Scotophilus temminckii* bats and *A. pusillus* ticks in Malaysia in 1960.[14,15] A strain that has a close, one-sided antigenic relationship to ISKV, LEIV-218Taj (named Garm virus), was isolated from a common redstart (*Phoenicurus phoenicurus*) caught in the village of Garm, Tajikistan, 39°10′N, 70°30′E (Figure 8.16) in the spring (migratory period) of 1976.

Morphological studies by electron microscopy characterized ISKV as a member of the Bunyaviridae family, and because no antigenic relation to any known viruses was found, it was assigned to the unclassified bunyaviruses.[16]

Taxonomy. The genome of the prototypical strain of ISKV, LEIV-315K, was sequenced, and, on the basis of sequence analysis, the virus was classified into the *Nairovirus* genus.[17] Like the genomes of other nairoviruses, that of ISKV consists of three segments of RNA (in negative polarity), each of which has a single ORF-encoded nucleocapsid protein (N, 485 aa, S-segment), a polyprotein precursor of the envelope glycoproteins Gn and Gc (1,631 aa, M-segment), and a RdRp (3,950 aa, L-segment). A pairwise comparison of the full-length nucleotide and deduced amino acid sequences of the ISKV ORFs with those of other nairoviruses revealed 48.2–51.1% nt

TABLE 8.10 Isolation of ISKV (Family Bunyaviridae, Genus *Nairovirus*)

Source of isolation		Place of isolation
Bats (Chiroptera)	*Nyctalus noctula*	Kirgizstan
	Myotis blythi	Kirgizstan
	Vespertilio serotinus	Kirgizstan
	V. murinus	Tajikistan
	V. pipistrellus	Tajikistan
	Rhinolopus ferrumequinum	Tajikistan
	Scotophilus temmencki	Malaysia
Birds (Aves)	Spanish sparrow (*Passer hispaniolensis*)	Kirgizstan
	White wagtail (*Motacilla alba*)	Kirgizstan
	Grey wagtail (*M. cinerea*)	Tajikistan
	Common redstart (*Phoenicurus phoenicurus*)	Tajikistan
	House swallow (*Hirundo rustica*)	Kirgizstan
	Wryneck (*Jynx torquilla*)	Tajikistan
	Common kingfisher (*Alcedo atthis*)	Kirgizstan
Ticks (Ixodidae)	*Argas* (*Carios*) *vespertilionis*	Kirgizstan, Tajikistan
	A. pusillus	Kirgizstan, Tajikistan
	Ixodes vespertilionis	Kirgizstan
Mosquitoes (Diptera: Culicidae)	*Aedes caspius*	Kirgizstan
	Anopheles hyrcanus	Kirgizstan
Horseflies (Diptera: Tabanidae)	*Tabanus agrestis*	Kazakhstan

(39.0–42.1% aa), 37.3–39.7% nt (23.2–26.5% aa), and 43.1–47.0% nt (31.9–34.5% aa) identity for RdRp, the precursor of Gn and Gc, and the N protein, respectively (Table 8.10). Phylogenetic analysis carried out for the full-length amino acid sequences by the maximum-likelihood nearest-neighbor method showed that ISKV occupies a new and distinct branch on the phylogenetic trees relevant to all three nairovirus proteins (RdRp, Gn/Gc, and N) (Figures 8.10–8.12).

For the many known nairoviruses (i.e., QYBV, DGKV, and HUGV, as well as for a new nairovirus that was found in European bats by a metagenomics approach), there are only partial sequences of the conservative catalytic core domain of RdRp.[16,18,19] The level of identity for this domain of ISKV with other nairoviruses ranged from 59.6–66.1% for the nucleotide sequence and 64.8–75.2% for the amino acid sequence (Table 8.10). The ISKV RdRp core domain has the highest level of identity with QYBV (66.6% nt and 74.5% aa). The phylogenetic tree constructed on the basis of the amino acid alignment of the RdRp core domain of nairoviruses confirms the topology of ISKV on a new genetic branch of the nairoviruses (Figures 8.10–8.12).

Arthropod Vectors. Most isolates of ISKV were obtained from *Argas vespertilionis* ticks, and we can assume that these ticks are the main natural reservoir of the virus. The range of ticks of the *A. vespertilionis* group covers territory in central Asia, Africa, Oceania, and Australia (Figure 8.17).

Vertebrate Hosts. The natural vertebrate hosts of ISKV are apparently bats—specifically, the genera *Nyctalus*, *Vespertilio*, *Rhinolophus*, and *Myotis* (family Vespertilionidae). These bats are common in the temperate and subtropical zones of Europe, Asia, and North Africa, and widespread ISKV transmission and the appearance of an emergency are possible in all of their territories.

Human Pathology. The first case of Issyk-Kul fever was registered in Tajikistan in August 1975 when a staff member became ill after catching bats during surveillance for arbovirus. ISKV was isolated from his blood on the second

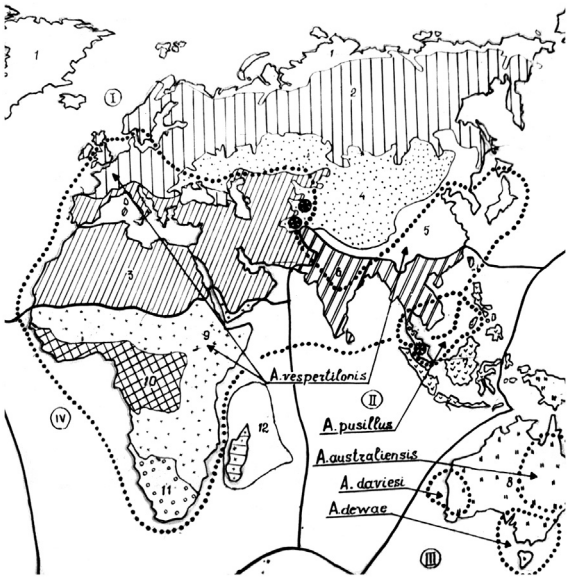


FIGURE 8.17 Geographical distribution of Argasidae ticks: vectors of ISKV (family Bunyaviridae, genus *Nairovirus*).

day of the disease.[20] Later, one case of Issyk-Kul fever was registered in 1978 in Dushanbe, Tajikistan.[20] Local outbreaks of Issyk-Kul fever occurred in Tajikistan in 1982. That year, 22 patients with laboratory-confirmed Issyk-Kul fever were registered.[21] The disease occurs with fever (39–40°C), headache (94%), dizziness (50%), hyperemia of the throat (48%), cough (25%), and nausea (31%). The outcome is generally favorable, and no deaths have been registered.[18] Most of the cases were associated with the presence of bats in the attic of the residence. The primary route of human infection was apparently by argasid ticks, but respiratory or alimentary routes (via the feces and urine of bats) could not be excluded. Furthermore, a laboratory experiment showed that ISKV can be transmitted by *Aedes caspius* mosquitoes.[22] The percentage of the population immune to ISKV in the southern part of Tajikistan is 7.8%. In Kyrgyzstan, antibodies to ISKV have been found in 0.7–3.2% of the human population. The highest percentage (9%) with antibodies to ISKV was found in the southeastern part of Turkmenistan.[12]

8.1.3.7 *Uzun-Agach Virus*

History. Uzun-Agach virus (UZAV), strain LEIV-Kaz155, was isolated from the liver of a *Myotis blythii oxygnathus* (order Chiroptera, family Vespertilionidae) bat caught in the vicinity of the village of Uzun-Agach, Alma-Ata district, Kazakhstan, during the virological sounding of territory in central Asia and Kazakhstan in 1977 (Figure 8.18).[1–3] On the basis of virion morphology, UZAV was classified into the Bunyaviridae family. No serological study of UZAV was ever conducted, but the place of UZAV isolation, Uzun-Agach, is close to where ISKV was originally isolated, namely, near Issyk-Kul Lake, and the source of both viruses is the same: bats.[4,5]

Taxonomy. The full-length genome of UZAV was sequenced, and, on the basis of phylogenetic analysis, the virus was classified into the *Nairovirus* genus.[6] The genome of UZAV, like those of other nairoviruses, consists of three segments of ssRNA with negative polarity. The L-segment encodes RdRp (3,988 aa), the M-segment encodes a polyprotein precursor of the envelope glycoprotein Gn and Gc (1,621 aa), and the S-segment encodes the nucleocapsid protein N (485 aa). A pairwise comparison of the sequence of the UZAV genome with those of other nairoviruses showed that the virus is related most closely to ISKV. Full-length sequences of the L- and M-segments of UZAV have, respectively, 69.3% nt and 64.1% nt identities with those of ISKV. Amino acid sequences of RdRp (S-segment) of UZAV and ISKV have 76.2% aa similarity. The similarity of the amino acid sequences of the precursor of Gn and Gc for UZAV and ISKV is 66.7% aa. A comparison of the S-segments of UZAV and ISKV revealed that they are almost identical (99.6%). Thus, we can conclude that UZAV is a reassortant virus that got an

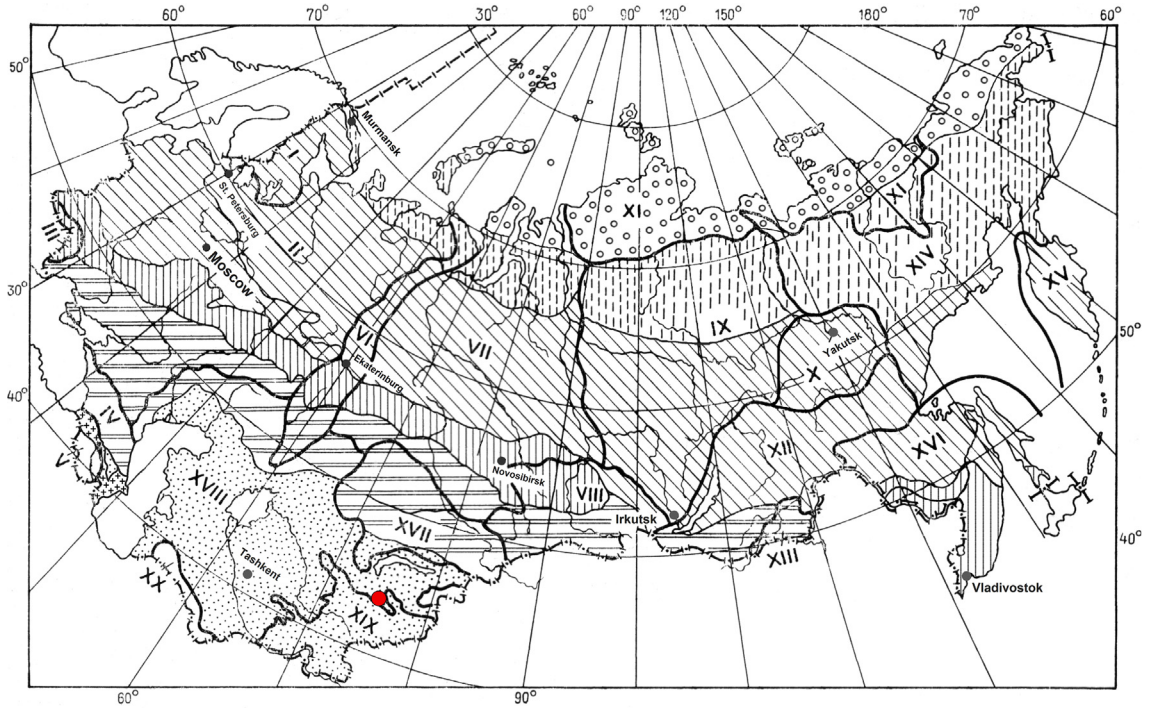


FIGURE 8.18 Place of isolation (red circle) of UZAV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

S-segment from ISKV. Phylogenetic analysis based on L- and M-segments placed UZAV in the lineage of ISKV (Figures 8.10–8.12).[6,7]

Vertebrate Hosts. The vertebrate host of UZAV is apparently bats, but because only a single isolation was obtained, this assertion is speculative. The finding that UZAV is a reassortant virus closely related to ISKV suggests that UZAV occupies the same ecological niche as ISKV and therefore is associated with bats and their argasid ticks. *Myotis blythii oxygnathus*, the bat from which UZAV was isolated, is common in the southern parts of the Russian Plain and in western Siberia, Caucasia, Kazakhstan, southern Europe, northern Africa, Middle and Central Asia, Iran, and Iraq. Bats are important natural reservoir of emerging viruses.[8–11] ISKV and UZAV are the first nairoviruses that appear to be associated with bats.

8.1.3.8 Sakhalin Virus and Paramushir Virus

Sakhalin virus (SAKV) has been isolated from *Ixodes* (*Ceratixodes*) *uriae* (family Ixodidae, subfamily Ixodinae) ticks, which are obligate parasites of auks (family Alcidae). The prototypical strain of SAKV (LEIV-71C) was isolated in 1969 from *I. uriae* ticks collected in a colony of the common murre (*Uria aalge*) on Tyuleniy Island near the southeastern coast of Sakhalin Island in the Sea of Okhotsk (48°29′N, 144°38′E; Figure 8.19).[1–4] Subsequently, 52 strains of SAKV were isolated from *I. uriae* ticks on Tyuleniy Island and Iona Island in the Sea of Okhotsk, the Commander Islands in the Barents Sea, and the southeastern coast of the Chukotka Peninsula in the Bering Strait (Table 8.11).[4–7] On the basis of virion morphology, SAKV has been classified into the Bunyaviridae family.

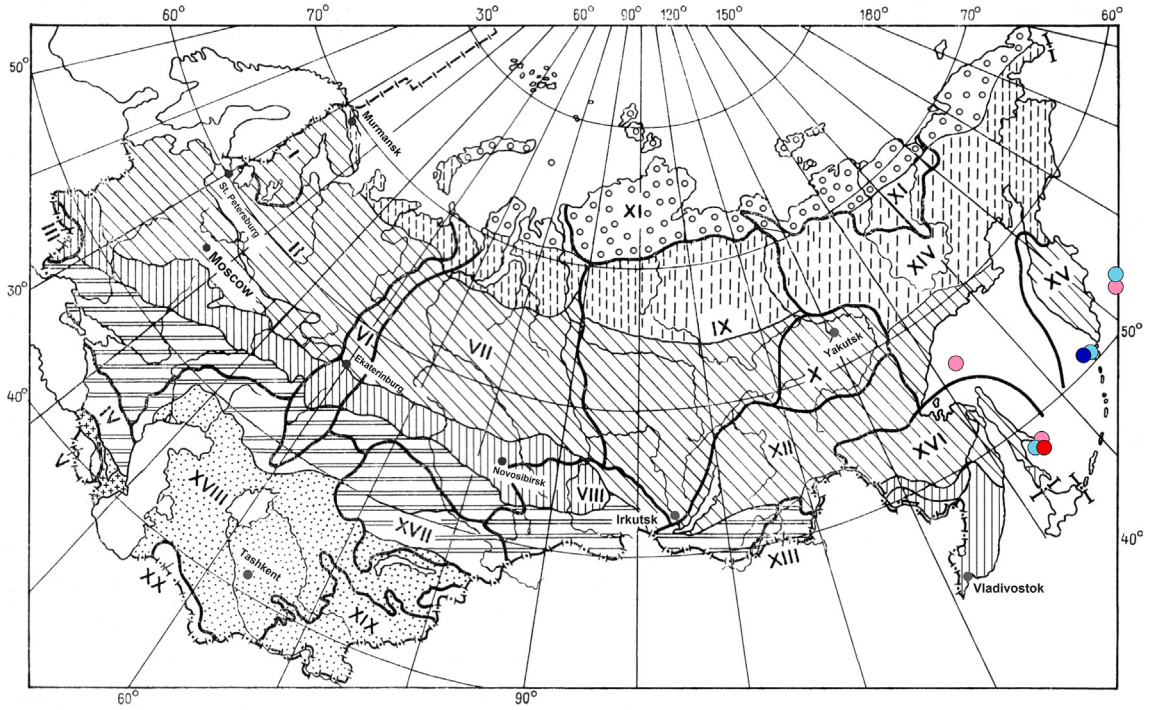


FIGURE 8.19 Places of isolation of SAKV and PMRV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: strain of SAKV with completely sequenced genome; Pink circles: a number of strains of SAKV identified by serological methods; Dark-blue circle: strain of PRMV with completely sequenced genome; Light-blue circles: a number of strains of PRMV identified by serological methods. (See other designations in Figure 1.1.)

SAKV was the first of the eponymous viruses, which together have formed a basis for the *Nairovirus* genus.[8]

Paramushir virus (PMRV), prototypical strain, LEIV-2268, a virus of the SAKV group, was originally isolated from *Ixodes signatus* ticks collected in 1972 in a colony of cormorants (*Phalacrocorax pelagicus*) on Paramushir Island (in the Kuril Islands) (50°23′N, 155°41′E; Figure 8.19).[9,10] Later (in 1972–1987), 18 strains of PMRV were isolated from *I. uriae* ticks, collected in the nests of auks (family Alcidae) on Tyuleniy Island in the Sea of Okhotsk and on the Commander Islands in the Bering Sea (Table 8.11).[11–14]

At least five nairoviruses are included in the SAKV group.[3,10,15–17] Avalon virus (AVAV), which was isolated from engorged imagoes and nymphs of *I. uriae* collected in *L. argentatus* nests on Great Island, Newfoundland, , in 1972, is apparently identical to PMRV.[15,18] Several strains of AVAV were isolated in 1979 in Cap Sizun, Brittany, France.[19] Clo Mor virus (CMV) was isolated in 1973 from nymphal *I. uriae* ticks collected in a *Uria aalge* colony of Clo Mor, Cape Wrath, Scotland.[20] CMV was found to be closely related to SAKV in a complement-fixation test. Two strains of CMV were isolated from *I. uriae* collected in seabird colonies on Lundy Island (England) and the Shiant Isles (Scotland) (Table 8.12).[18,20] Rukutama virus (RUKV) (strain LEIV-6269S), which previously had been included in the SAKV group, is now classified into the Uukuniemi virus (UUKV) group in the *Phlebovirus* genus.[9,21]

Taxonomy. Complete genomes of SAKV (strain LEIV-71C) and PMRV (LEIV-1149K)

TABLE 8.11 Isolation of SAKV and PRMV From *Ixodes* (*Ceratixodes*) *Uriae* Ticks (Obligate Parasites of Alcidae Birds) in the Basins of the Sea of Okhotsk and Bering Sea

		Far East				European part
		Sakhalin District		Kamchatka	Chukotka	Murmansk District
Virus		Tyuleniy Island (48°29′N, 144°38′E)	Iona Island (56°24′N, 143°23′E)	Ari Kamen Island (Commander Islands) (55°13′N, 165°48′E)	Bering Strait Coast (64°50′N, 173°10′E)	Kharlov Island near Kola Peninsula (68°49′N, 37°19′E)
SAKV	Number of strains	42	2	10	3	0
	% of infected ticks	0.307	0.103	0.033	0.26	—
Total	**Number of strains**	**57**				0
	Number of ticks examined	**35,725**				**8,994**
	% of infected ticks	**0.160**				—
PMRV	Number of strains	10	0	8	0	0
	% of infected ticks	0.073	—	0.042	—	—
Total	**Number of strains**	**18**[a]				**0**
	Number of ticks examined	**35,725**				**8,994**
	% of infected ticks	**0.050**				—

[a]*One strain was isolated from* I. signatus *ticks in a Bering cormorant colony on Paramushir Island in the Sea of Okhotsk (50°23′N, 155°41′E).*

were sequenced.[9] Also, partial sequences of RdRp of Tillamook virus (TILLV, identical to SAKV), isolated from *I. uriae* ticks on the Pacific coast (Oregon) of the United States, are available (Table 8.12).[18] A full-length genome comparison showed that SAKH and PMRV respectively share 75.6% nt and 88.0% aa identities in RdRp (L-segment), 59.7% nt and 57.9% aa in the precursor of Gn and Gc (M-segment), and 62.3% nt and 62.2% aa in the nucleocapsid protein (S-segment). SAKV N-protein ranges from 30% (CASV, HUGV) to 43% (CCHFV) similarity to other nairoviruses. The similarity of RdRp and the precursor of Gn and Gc proteins of SAKV to other nairoviruses ranges from 42.8% (CASV, HUGV) to 50.8%

TABLE 8.12 Viruses of the SAKV Group (Family Bunyaviridae, Genus *Nairovirus*) Isolated from *Ixodes* (*Ceratixodes*) *Uriae* Ticks and Penguins (*Spheniscidae*)

Virus	Place of material collection	Biome
Sakhalin (SAKV)	Sea of Okhotsk, Barents Sea (1969–1971)	Nests of common murre (*Uria aalge*), *Ixodes uriae* ticks
Paramushir (PMRV)	Sea of Okhotsk, Barents Sea (1969–1971)	Nests of common murre (*Uria aalge*) and pelagic cormorant (*Phalacrocorax pelagicus*), *Ixodes uriae* ticks
Taggert (TAGV)	Macquarie Island in southern part of Pacific Ocean (54°30′S, 159°00′E) (1972)	Nests of penguins (*Eudyptes schlegeli*), *Ixodes uriae* ticks
Clo Mor (CMV)	Cape Wrath (Scotland) (58°36′N, 04°53′W) (1973)	Nests of common murre (*Uria aalge*), *Ixodes uriae* ticks
Avalon (AVAV)	Avalon Peninsula, Newfoundland island, Labrador Province, Canada (52°46′N, 47°11′W) (1972)	Nests of common murre (*Uria aalge*), *Ixodes uriae* ticks
	France, Brittany	Nests of common murre (*Uria aalge*), *Ixodes uriae* ticks

(CCHFV), respectively, and from 25.9% (ERVEV, TFAV) to 28.9% (NSDV, DUGV), respectively.[9]

Arthropod Vectors. It has been shown that the infection rate of infected *Ixodes uriae* imagoes is 2 times higher than of the species' nymphs and 10 times higher than that of the larval stage. Transovarial transfer of SAKV has been found to be 10%. The infection rates of male and female ticks are approximately the same. The hypostome of male *I. uriae* ticks is vestigial; therefore, they cannot be infected by breeding on infected birds. The infection rate of *I. uriae* imagoes is at least 20 times higher than that of *I. signatus* imagoes.[4–6,22,23] Some other species of *Ixodes* ticks are parasites of seabirds and may be an additional reservoir of SAKV. *I. auritulus* and *I. zealandicus* ticks are distributed from Alaska to Cape Horn in South and North America.[24]

Laboratory experiments have demonstrated that *Aedes aegypti* and *Culex pipiens molestus* mosquitoes can be infected by SAKV as they suck blood. The virus was found in mosquitoes on 9, 14, and 19 days after infection in titers 1.0, 1.5, and 2.0 $\log_{10}(LD_{50})/10\,\mu L$, respectively. However, it was shown that infected mosquitoes could not transmit the virus to mice through a bite.[6,22]

Vertebrate Hosts. *Ixodes uriae* ticks and their host, the common murre (*Uria aalge*), are a natural reservoir of SAKV. Pelagic cormorants (*Phalacrocorax pelagicus*) and their obligate parasites (*I. signatus*) likely have only an additional influence. Antibodies to SAKV have been found in the common murre (*U. aalge*), pelagic cormorants (*P. pelagicus*), fulmars (*Fulmarus glacialis*), tufted puffins (*Lunda cirrhata*), and black-legged kittiwakes (*Rissa tridactyla*) in the Far East.[4–6,22] A serological examination of birds via an indirect complement-fixation test revealed that the northern boundary of the range of SAKV is the Commander Islands, where antibodies have been found in 2.2% of birds. The southernmost place where antibodies have been detected (1.1% birds) is Kunashir Island in the Kuril Islands. Antibodies were found most often (in 4.1–17.8% of birds) in the central part of the basin of the Sea of Okhotsk (on Sakhalin Island, Tyuleniy Island, and Iona Island). Antibodies were also found in the red-necked phalarope (*Phalaropus lobatus*), sanderling (*Calidris alba*), the long-toed stint (*C. subminuta*) (up to 8.4% of the population), fulmars (*F. glacialis*) (4.9%), Leach's petrels (*Oceanodroma leucorhoa*), tufted puffins (*L. cirrhata*) (4.6%), the common murre (*U. aalge*) (3.8%), Japanese

cormorants (*Phalacrocorax filamentosus*) (1.0%), and black-legged kittiwakes (*R. tridactyla*) (0.6%). No antibodies were detected in other species of birds in the Alcidae family or in geese, ducks, or poultry. In the Arctic zone (Novaya Zemlya and Wrangel Island in the Arctic Ocean) and in the northern part of the subarctic (the Pacific coasts of Chukotka and the Kamchatka Peninsula), as well as on Moneron Island and Furugelm Island in the Sea of Japan, no antibodies to SAKV have been found in birds.[5,6,22]

Neutralizing antibodies to AVAV, a virus closely related to PMRV, have been found in 27.6% of puffins (*Fratercula arctica*), petrels (*Calonectris leucomelas*), and herring gulls (*Larus argentatus*) in Canada.[24,25]

Findings of antibodies to SAKV in seabirds carrying out their annual seasonal migration to the Southern Hemisphere suggest the possibility of transcontinental transfer of the virus to the Southern Hemisphere. The closely related Taggert virus (TAGV) was isolated from *Ixodes uriae* ticks in penguin colonies on Macquarie Island, a phenomenon that may indicate a transfer of viruses by birds and their ticks between the Northern and Southern Hemispheres.

Human Infection. Three human cases of cervical adenopathy associated with AVAV were described in France.[25] Serological examination of farmers in Cap Sizun, Brittany, France, found only 1% of the population positive.[18]

8.1.3.9 Tamdy Virus

History. TAMV (prototypal strain, LEIV-1308Uz) was originally isolated from *Hyalomma asiaticum asiaticum* (family Ixodidae, subfamily Hyalomminae) ticks collected from sheep in the arid landscape near the town of Tamdybulak (41°36′N, 64°39′E; Figure 8.20) in the Tamdinsky

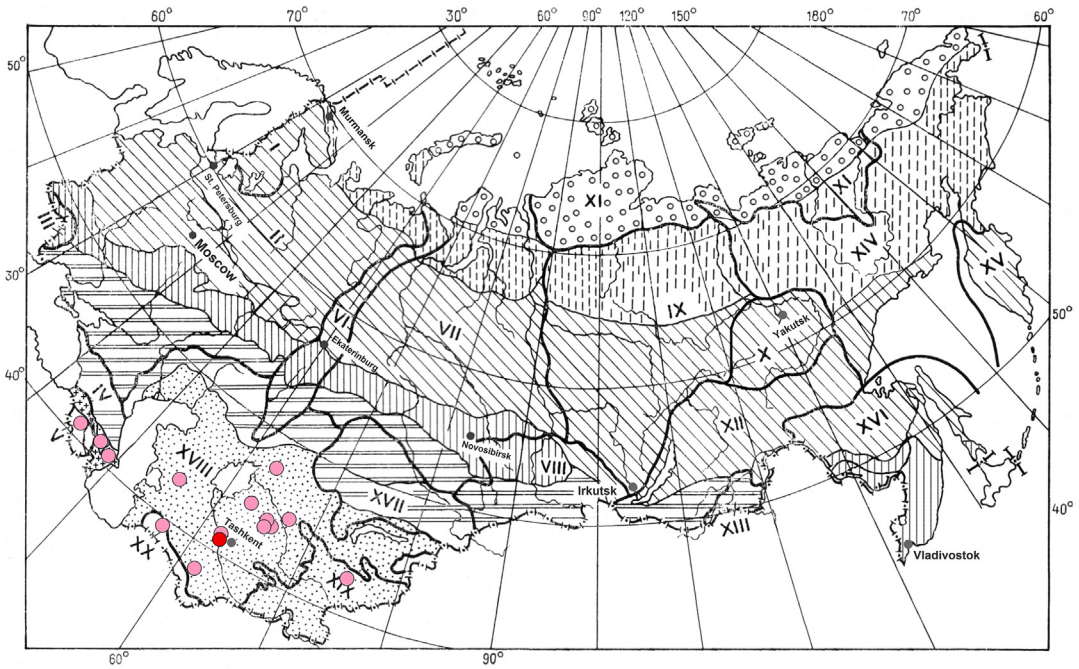


FIGURE 8.20 Places of isolation of TAMV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. Red circle: strain of TAMV with completely sequenced genome; Pink circles: strains of TAMV identified by serological methods. (See other designations in Figure 1.1.)

district of the Bukhara region of Uzbekistan in 1971.[1–3] Subsequently 52 strains of TAMV were isolated in Uzbekistan,[4–7] Turkmenistan,[8–11] Kyrgyzstan,[12,13] Kazakhstan,[11,14,15] Armenia,[6,16] and Azerbaijan[8,17–19] in 1971–1983 (Table 8.13). Most of the strains were obtained from *H. asiaticum* ticks, but several were isolated from birds, mammalians (including bats), and sick humans. On the basis of virion morphology, TAMV has been classified into the Bunyaviridae family. Serological studies by complement-fixation and neutralization tests revealed no antigenic relationships of TAMV with any known viruses.[2]

Taxonomy. Three strains of TAMV isolated in Uzbekistan (LEIV-1308Uz), Armenia (LEIV-6158Ar), and Azerbaijan (LEIV-10226Az) were completely sequenced.[20] Phylogenetic analysis of the full-length sequences showed that TAMV is a novel member of the *Nairovirus* genus, forming a distinct phylogenetic lineage (Figures 8.10–8.12). The similarity of the amino acid sequence of TAMV RdRp (L-segment) with those of other nairoviruses is 40% aa, on average. The similarity of the RdRp of TAMV with that of the nairoviruses associated predominantly with ixodid ticks (CCHFV, Hazara virus (HAZV), and DUGV) is higher (40% aa) than that with viruses associated with argasid ticks (ISKV and CASV) (38% aa). The similarity of the TAMV polyprotein precursor of Cn and Gc with that of other nairoviruses is less than 25% aa. The similarity of the amino acid sequence of the nucleocapsid protein (S-segment) of TAMV is 33% aa with ixodid nairoviruses and 28% aa with argasid nairoviruses. Phylogenetic analysis of the catalytic core domain of the RdRp of the nairoviruses confirms that TAMV forms a novel group in the *Nairovirus* genus (Figures 8.10–8.12).[20]

Genetic diversity among the three sequenced strains of TAMV is low. The prototypic strain LEIV-1308Uz, isolated in central Asia, has 99% nt identity in the L-segment with LEIV-10226Az from Transcaucasia. The L-segment of the strain LEIV-6158Ar has 94.2% nt and 96.3% aa identity with the L-segment of LEIV-1308Uz. The similarity of the M-segment of LEIV-1308Uz with those of LEIV-10226Az and LEIV-6158Ar is 93% nt and 89% aa, respectively. The similarity of the S-segment among the three strains is 93–95% nt.[20]

Arthropod Vectors. *H. asiaticum* ticks are apparently a main reservoir of TAMV. More than half (57%) of TAMV isolations were obtained from *H. asiaticum asiaticum* ticks, 6% from *H. asiaticum*, 8% from *H. anatolicum*, 6% from *H. marginatum*, 6% from *Rhipicephalus turanicus*, and 2% from *Haemaphysalis concinna*. The infection rates of male and female ticks in endemic territory were 1:210 and 1:200, respectively. The infection rate of *H. asiaticum* nymphs was 20 times lower.[7,10,14,16] Furthermore, TAMV was isolated from larvae of *H. asiaticum*, which were hatched from eggs in the laboratory, indicating transovarial transmission of the virus. *H. asiaticum asiaticum* ticks are the most xerophilous subspecies of the *Hyalomma* genus (Ixodinae subfamily),[21] a characteristic that allows TAMV to be distributed over the Karakum desert in Turkmenistan, the Moinkum desert in Kazakhstan, and the central part of the Kyzyl Kum desert in Kazakhstan and Uzbekistan.[7].

Animal Hosts. The larvae of *H. asiaticum* feed on ruminants, hoofed animals, small predators, hedgehogs, birds, and reptilians. One of the major hosts of *H. asiaticum* preimagoes is the great gerbil (*Rhombomys opimus*). Wild animals, as well as sheep and camels, are the hosts for *H. asiaticum* imagoes and may be involved in the circulation of TAMV (Table 8.13).

Human Pathology. Sporadic cases of the disease associated with TAMV was registered in Kyrgyzstan in October 1973, when TAMV was isolated from the blood of a patient with fever (39°C), headache, arthralgia, and weakness.[16] *H. asiaticum asiaticum* ticks rarely attack humans, and no outbreaks of TAMV fever have been registered; however, human infection by *H. asiaticum* ticks is still possible

TABLE 8.13 Isolations of TAMV (Family Bunyaviridae, Genus *Nairovirus*)

Place of isolation					Date of collection	Number of strains isolated
Region	**Country**	**Location**	**Biotope**	**Source of isolation**		
Central Asia	Uzbekistan	Buhara province, near Tamdy village	Sandy desert	*H. as. asiaticum* ticks	August 1971	3
					April 1972	6
					April 1973	1
					May 1974	1
					May 1983	1
					Total	12
	Turkmenistan	Near Karakum kanal (Sakar chaga village), Zahmet village, Sarygamysh lake)	Sandy desert	*H. as. asiaticum* ticks from camel	январь-May 1973	4
				H. marginatum ticks from sheep	June 1973	1
				H. as. asiaticum ticks from camel	June 1973	1
				H. as. asiaticum ticks from camel	Jule 1981	1
		Kyzyl Arvat village	Foothill desert	*H. as. asiaticum* ticks from sheep	April 1984	1
					Total	8
	Kyrgyzstan	Chu valley	Near desert	Human	May 1973	1
				Bat sp. (*Chiroptera*)	May 1973	1
				Pied wagtail (*Motacilla alba* Linnaeus, 1758)	May 1973	2
				European roller (*Coracias garrulus* Linnaeus, 1758)	May 1973	1
				Hoopoe (*Upupa epops* Linnaeus, 1758)	May 1973	1
				Starling (*Sturnus vulgaris* Linnaeus, 1758)	May 1973	1
				Red-tailed shrike (*Lanius meridionalis* Temminck, 1820)	May 1973	1
				Steppe polecat (*Mustela eversmanni* Lesson, 1827)	May 1973	1
				Rh. turanicus	May 1973	3
				Haem. concinna	May 1973	1
					Total	13

(*Continued*)

TABLE 8.13 (Continued)

Region	Country	Place of isolation: Location	Place of isolation: Biotope	Source of isolation	Date of collection	Number of strains isolated
Central Asia (*Continued*)	Kazakhstan	Suzak district	Near desert	*H. as. asiaticum* ticks from sheep	April 1979	1
		Kazaly district		*H. as. asiaticum* ticks from cows	April 1979	1
		Aral district		*H. as. asiaticum* ticks from camel	April 1979	1
		Kzyl-Orda district		*H. as. asiaticum* ticks from camel	May 1979	5
					Total	8
Transcaucasia	Armenia	Ashtrac district	Rocky desert	*H. as. caucasium* ticks from sheep	May 1976	1
					Total	1
	Azerbaijan	Qusar district	Near desert	*H. as. asiaticum* ticks from sheep	April 1985	1
		Apsheronsky district		*H. marginatum* ticks from sheep	May 1985	2
				H. as. caucasium ticks from sheep	May 1985	2
				H. anatolicum ticks from sheep	May 1985	4
				H. as. asiaticum ticks from sheep	May 1986	1
					Total	10

through contact with livestock necessitated by economic activities (e.g., sheep shearing).

8.1.3.10 *Burana Virus (BURV)*

History. The Prototypical strain LEIV-Krg760 of Burana virus (BURV) was originally isolated from *Haemaphysalis punctata* (family Ixodidae, subfamily Haemaphysalinae) ticks collected from cows in Tokmak Wildlife Sanctuary in the eastern part of the Chu valley (43°10′N, 74°40′E; Figure 8.21) in the foothills of the Kyrgyz Ala-Too Range near the village of Burana, Kyrgyzstan, in April 1971. Six strains of virus were isolated from 9,377 ticks of the species *Haem. punctata* and *Haem. concinna* (Ixodidae, Haemaphysalinae) during 1971–1975.[1,2] According to preliminary information, BURV is not able to agglutinate erythrocytes of birds and mammals and has no antigenic relationships with 59 arboviruses from different groups of the Togaviridae,

Flaviviridae, Bunyaviridae, Reoviridae, Orthomyxoviridae, and Arenaviridae families or with 35 unclassified viruses as well.

Taxonomy. The genome of BURV was sequenced, and the virus was classified into the *Nairovirus* genus, family Bunyaviridae. The genome consists of three segments: an L-segment (ORF, 11,919 nt; encodes RdRp); an M-segment (ORF, 4,035 nt; encodes a polyprotein precursor of the envelope proteins Gn and Gc); and an S-segment (ORF, 1,482 nt; encodes the nucleocapsid protein N).[3,4]

A comparison of RdRp sequences of BURV with those of other nairoviruses demonstrated that the virus is distantly related to TAMV (59% aa similarity). The similarity of the RdRp catalytic core domain of BURV to that of TAMV is 82% aa, compared with about 60% aa for viruses in other phylogenetic groups. The level of similarity for the nucleotides sequences of this part of the RdRp of BURV is 68% nt with those of TAMV and 45–50% nt with those of other viruses (Figure 8.10).[3]

The M-segment of BURV has a long ORF and encodes a polyprotein precursor of the envelope glycoproteins Gn and Gc.[4] The size of the polyprotein precursor is 1,344 aa. The mature Gn and Gc proteins of nairoviruses are formed by complex processes involving cellular peptidases. By the NetNGlyc 1.0 server, 11 potential glycosylation sites were predicted, with only 5 within mature Gn or Gc proteins.[5,6] The level of similarity of the amino acid precursor of Gn and Gc in BURV is 45% with that of TAMV and no more than 27% with viruses of other phylogenetic groups. Phylogenetic analyses based on a comparison of the full-length polyprotein precursor

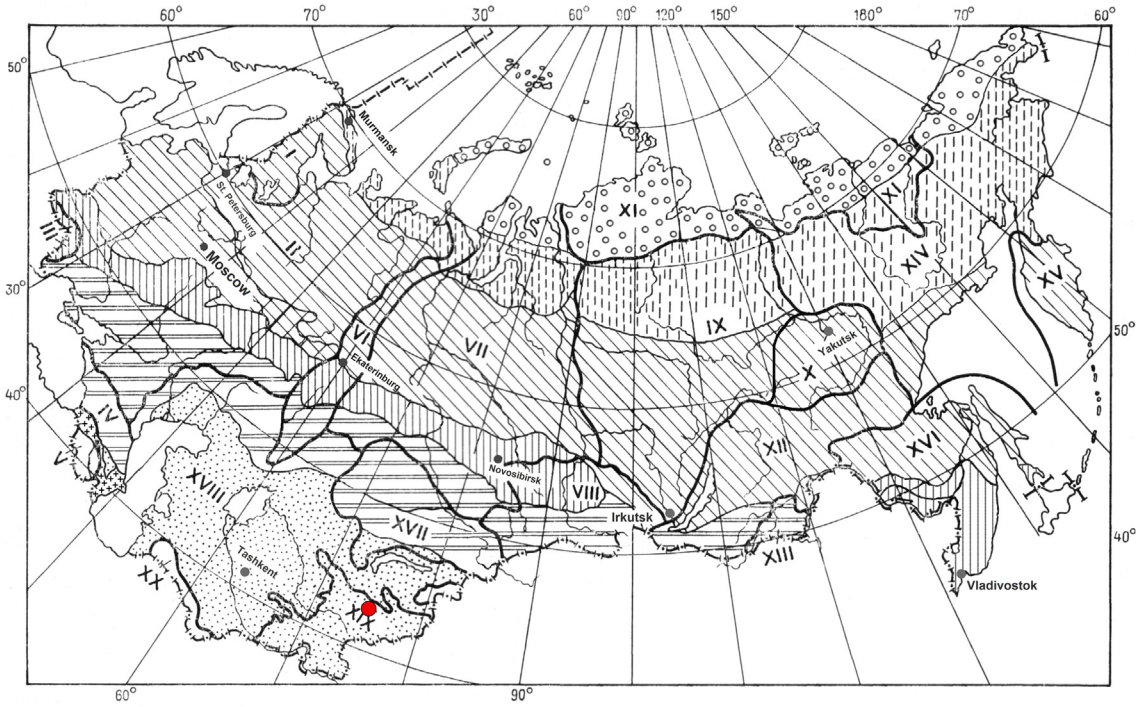


FIGURE 8.21 Place of isolation (red circle) of BURV (family Bunyaviridae, genus *Nairovirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

demonstrated the position of BURV on the TAMV branch and was consistent with the RdRp data (Figure 8.11).[3]

The S-segment of nairoviruses encodes a nucleocapsid protein (N).[4,7] The size of the BURV nucleocapsid protein is 493 aa, corresponding to the average size of the N protein of other nairoviruses (480–500 aa). The level of similarity of the amino acid sequence of BURV N protein with that of TAMV is 44%, and that with the amino acid sequences of other nairoviruses is30–32%. Phylogenetic analyses of BURV N protein are represented in Figure 8.12. The phylogenetic position of BURV is on the TAMV branch, despite the virus's having the lowest level of similarity of the N protein compared with that of other virus proteins.

Arthropod Vectors. As mentioned earlier, six strains of BURV were isolated from the ticks *Haemaphysalis punctata* (five strains) and *Haem. concinna* (one strain) in 1971–1975. The rate of infected ticks was 2.2–2.6%. BURV is associated with *Haem. punctata* and *Haem. concinna* ticks in pasture biocenoses. The virus is phylogenetically close to TAMV, which is also associated with ixodes ticks in pasture and desert biocenoses.[8]

8.1.4 Genus *Orthobunyavirus*

The *Orthobunyavirus* genome consist of three segments of single-stranded negative-sense RNA designated as large (L), medium (M), and small (S) (Figure 8.22).[1] The L-segment of the prototypical BUNV (6,875 nt in length) encodes the viral RdRp.[2] The M-segment (4,458 nt) encodes two surface glycoproteins (Gn and Gc) and a nonstructural protein (NSm).[3,4] The S-segment (961 nt) encodes the nucleocapsid protein (N) and a nonstructural protein (NSs). The NSs protein is considered a pathogenic factor for vertebrates, because it may act as an antagonist of interferon, which is involved in blocking the host's innate immune responses.[5–7] The genus *Orthobunyavirus* is subdivided into multiple serological groups.[8]

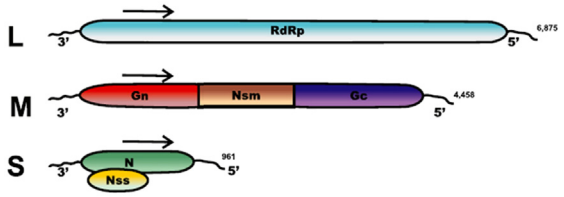


FIGURE 8.22 Scheme of genome organization of BUNV, a prototypical virus of the *Orthobunyavirus* genus. *Drawn by Tanya Vishnevskaya.*

8.1.4.1 Batai Virus and Anadyr Virus

Batai virus (BATV) belongs to the BUNV group (family Bunyaviridae, genus *Orthobunyavirus*), which to date includes 22 viruses (Table 8.14). Among them the African Ilesha virus (ILEV), as well as the North American Northway virus (NORV), Cache Valley virus (CVV), and Tensaw virus (TENV), are the viruses most closely related to BATV.[1–3]

History. BATV was originally isolated by B. Elisberg (US Army Medical Research Unit) from *Culex gelidus* collected in 1988 on the outskirts of Kuala Lumpur, Malaysia.[4,5] BATV is identical to Chalovo virus, isolated in 1960 from *Anopheles maculipennis* (*An. messeae*) mosquitoes collected in Slovakia;[6,7] to Olyka virus, isolated in 1973 from *An. maculipennis* mosquitoes collected in western Ukraine;[8–11] and to Chittoor virus, isolated in 1957 from *An. barbirostris* mosquitoes collected in Brahmanpally, Chittoor district, Andhra Pradesh state, India.[12] The African Ngari virus (NRIV) is reassortant between BATV and BUNV.[12,13] In Russia, BATV was repeatedly isolated in different regions (Figure 8.23).

Anadyr virus (ANADV), strain LEIV-13395, was isolated by S.D. Lvov from a pool of *Aedes* mosquitoes collected in September 1986 in a swamp tundra landscape near the village of

TABLE 8.14 Viruses of the Bunyamwera Group (Family Bunyaviridae, Genus *Orthobunyavirus*)

	Distribution							Vertebrate hosts				Disease of humans	
		America							Mammals				
Virus	Africa	North	South	Asia	Europe	Northern Eurasia	Mosquito vector	Birds	Wild	Domestic	Humans	Clinical symptom	Epidemiology
Batai virus (BATV)	+	–	–	+	+	+	+	+	A	A	+	F	S, O
Birao virus (BIRV)	+	–	–	–	–	–	+	–	–	–	–	–	–
Bozo virus (BOZOV)	+	–	–	–	–	–	+	–	A	A	–	–	–
Bunyamwera virus (BUNV)	+	–	–	–	–	–	+	A	A	A	+	E	S, O
Fort Sherman virus (FSV)	–	–	+	–	–	–	+	–	–	–	+	F	S
Germiston virus (GERV)	+	–	–	–	–	–	+	–	+	A	+	E	S
Iaco virus (IACOV)	–	–	+	–	–	–	+	–	–	–	–	E	S
Ilesha virus (ILEV)	+	–	–	–	–	–	+	–	–	–	–	F	S
Cache Valley virus (CVV)	–	+	+	–	–	–	+[a]	–	A	+	A	F	S
Lokern virus (LOKV)	–	+	–	–	–	–	+[b]	–	+	A	A	F	S
Maguari virus (MAGV)	–	–	+	–	–	–	+	–	A	+	A	F	S
Mboke virus (MBOV)	+	–	–	–	–	–	+	–	–	–	–	–	–
Ngari virus (NRIV)	+	–	–	–	–	–	+	–	–	–	–	–	–
Northway virus (NORV)	–	+	–	–	–	–	+	–	–	–	A	F	S
Playas virus (PLAV)	–	–	+	–	–	–	+	–	–	–	–	–	–
Potosi virus (POTV)	–	–	+	–	–	–	+	–	–	–	–	–	–
Santa Rosa virus (SARV)	–	+	–	–	–	–	+	–	–	–	–	–	–
Tensaw virus (TENV)	–	+	–	–	–	–	+	A	+	+	+	F	S
Tlacotalpan virus (TLAV)	–	+	–	–	–	–	+	–	–	A	A	F	S
Tucunduba virus (TUCV)	–	–	+	–	–	–	+	–	–	–	–	F	S
Shokwe virus (SHOV)	+	–	–	–	–	–	+	–	–	+	–	F	S
Xingu virus (XINV)	–	–	+	–	–	–	+	–	–	–	+	E	S

[a] *Designations: +, virus isolation; A, specific antibodies detection; F, fever; E, encephalitis, meningoencephalitis; S, sporadic cases; O, outbreak.*
[b] *Also isolated from midges.*

Krasneno (64°37′N, 174°46′E) in the Anadyr District of the Chukotka Autonomous Okrug, Russia (Figure 8.23). On the basis of weak serological relationships, V.L. Gromashevsky classified the virus as a Batai-like virus. Sequence analysis then revealed that strain LEIV-13395 was a novel representative virus in the Bunyamwera group, and the virus was designated ANADV.[14]

Taxonomy. Phylogenetic analysis (Figures 8.24–8.26) revealed that the different strains of BATV can be divided into three groups according to their geographic spread: strains from China, Malaysia, Japan, and India form the Asian group; strains from Uganda and NRIV (to which BATV is considered to be a donor of the M-segment) belong to the African group; and strains isolated in Italy, Germany, the former Czechoslovakia, western Ukraine, and Russia are members of the European group. Two strains of BATV—LEIV-Ast04-2-315 and LEIV-Ast04-2-336—isolated in Russia were completely sequenced and placed into the cluster of the European strains.[14] Within this group, they are phylogenetically close to strain 42, isolated in the Volgograd region in 2003 from *Anopheles messeae* (*maculipennis*) mosquitoes, for which the partial nucleotide sequences of the L- and M-segments are known. Between the strains LEIV-Ast04-2-315 and LEIV-Ast04-2-336, there is very high level of nucleotide and amino acid identity of three segments of the genome: 99.6/99.0% (L-segment/RdRp), 99.9/100.0% (M-segment/polyprotein predecessor), and 99.7/100.0% (S-segment/nucleocapsid). The levels of nucleotide identity of strain 42 with these strains on partial sequences of L- and M-segments are

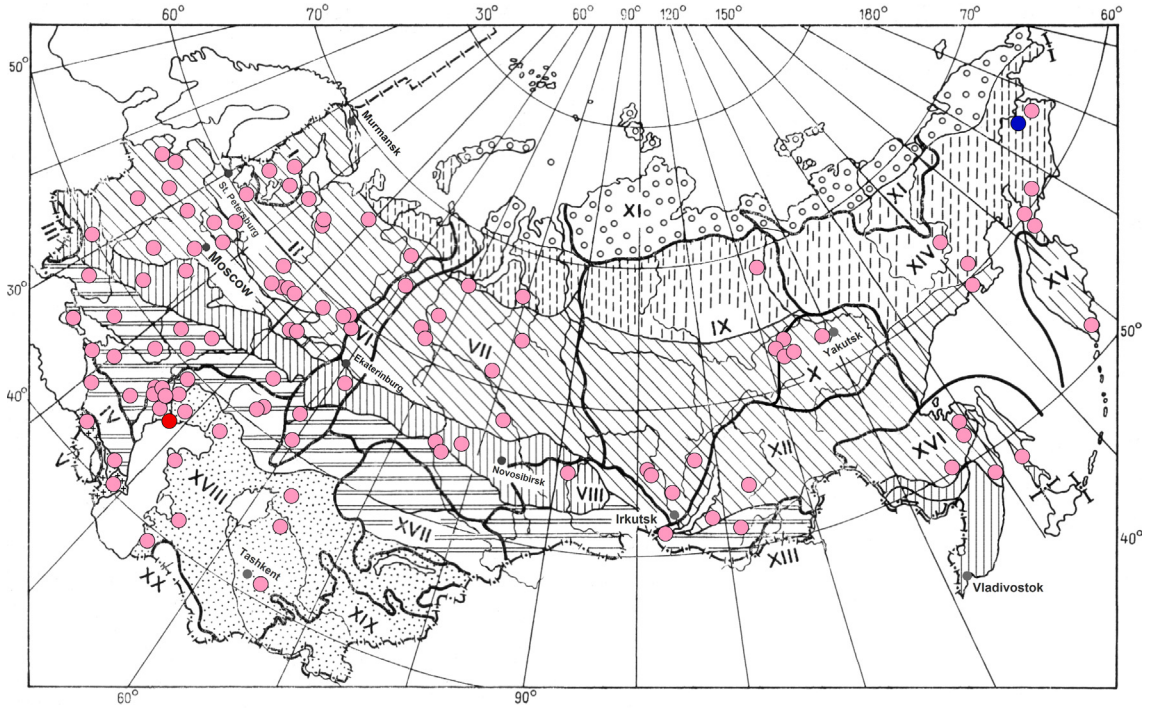


FIGURE 8.23 Places of isolation of viruses from the Bunyamwera group (family Bunyaviridae, genus *Orthobunyavirus*) in the former USSR. Red circle: strains of BATV with completely sequenced genome; Pink circles: strains of BATV identified by serological methods; Dark-blue circle: ANADV. (See other designations in Figure 1.1.)

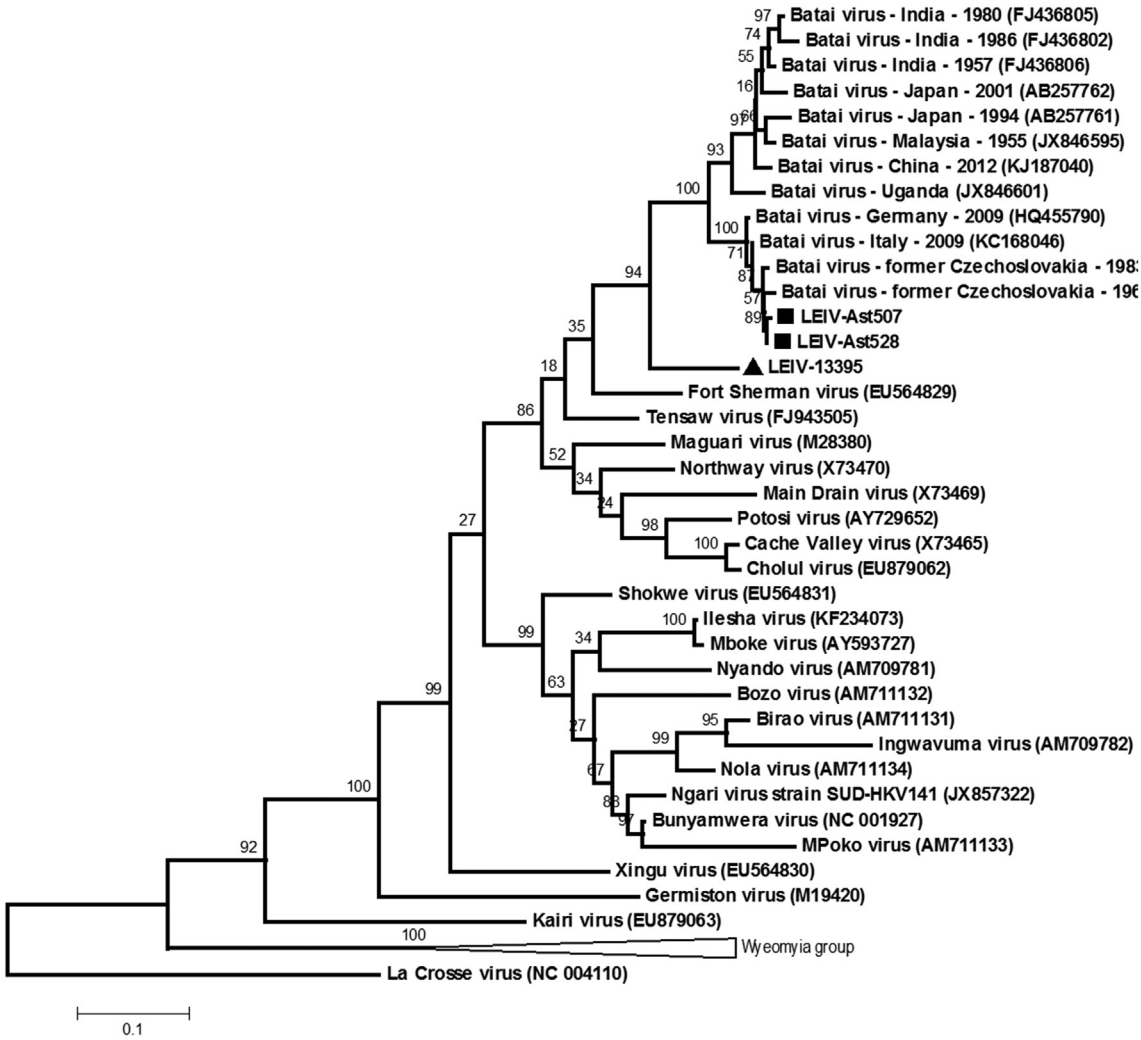


FIGURE 8.24 Phylogenetic analysis of S-segment of Bunyamwera group viruses (family Bunyaviridae, genus *Orthobunyavirus*). The trees were constructed by the maximum-likelihood method with thousandfold bootstrap analysis.

98.6/98.8% and 100/100%, respectively; that is, for the M-segment, all available nucleotide polymorphisms are synonymous. The lowest observed genetic differences and the temporal and geographical proximities of the various strains of these viruses suggest a common origin as different isolates of the same strain of BATV circulating in the southern part of Russia.

Phylogenetic analysis of ANADV (strain LEIV-13395) revealed its similarity to BATV. The L-segment of ANADV is from 76.5% to 79.7% identical with those of the different BATV strains (Figure 8.26, Table 8.15). The identity of the L-segment of ANADV with the L-segments of other viruses of the Bunyamwera group is 73.5% (BUNV), 74.1% (CVV), and 73.9% (TENV). The amino acid

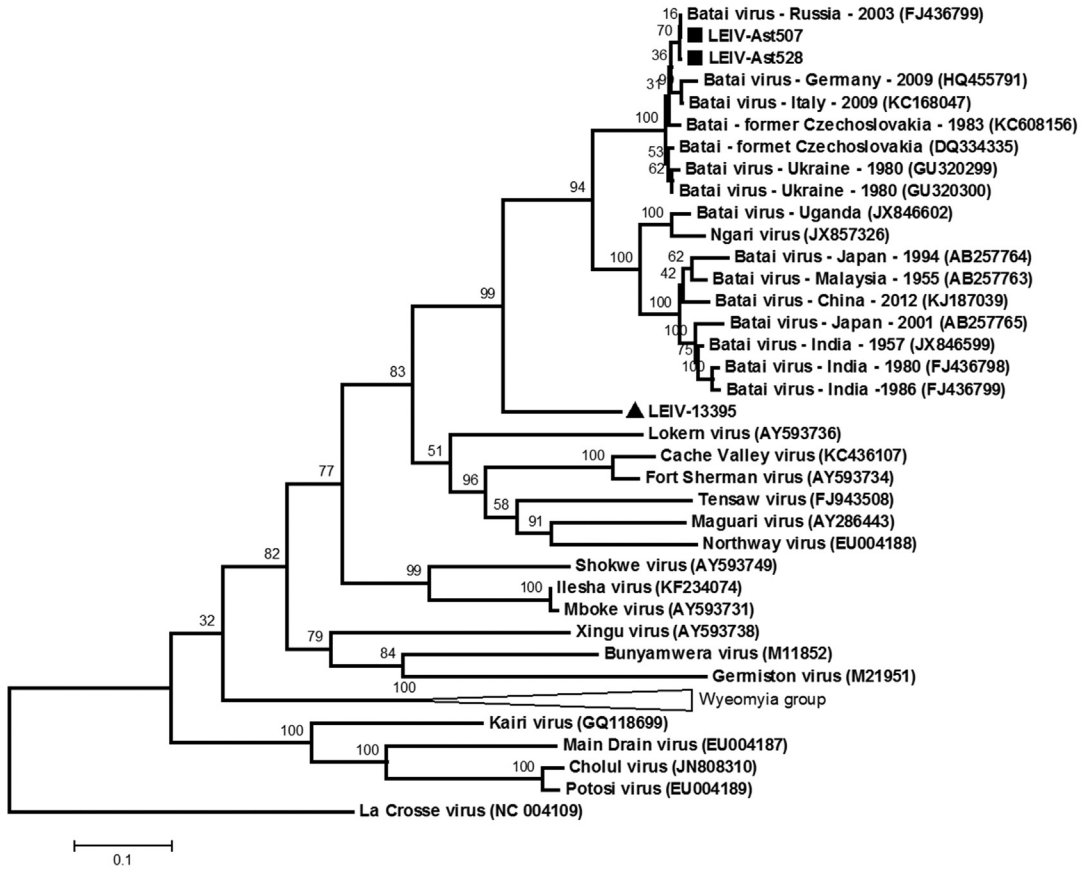


FIGURE 8.25 Phylogenetic analysis of M-segment of Bunyamwera group viruses (family Bunyaviridae, genus *Orthobunyavirus*). The trees were constructed by the maximum-likelihood method with thousandfold bootstrap analysis.

sequence of RdRp of ANADV is 91% similar to the various strains of BATV. The M-segment sequence of ANADV has the greatest similarity (76.9–80.8% nt and 83.1–84.4% aa) to the different strains of BATV. The identity of the S-segment sequence of ANADV with different strains of BATV ranges from 85.8% to 86.9% and is about 82.5% with TENV and CVV. The amino acid similarity of the nucleocapside protein is 98.7% with that of BATV from Uganda.

Phylogenetic analysis of the nucleotide sequences of the S-, M-, and L-segments conducted with the use of a maximum-likelihood algorithm placed ANADV (LEIV-13395) on a distinct branch of the dendrogram that considers it a new representative of the Bunyamwera group.

Arthropod Vectors. BATV has been reported in Sudan, Africa.[15] The distribution of BATV in southeastern Asia includes Malaysia, India, Sri Lanka, Thailand, Cambodia, and Japan,[5,16] while in Europe BATV is distributed over Austria, Germany, Yugoslavia, Moldova, Ukraine, Belarus, and other countries.[2,17–19] In central Europe, BATV was isolated from *Anopheles claviger*, *An. maculipennis* (*An. messeae*), *Coquillettidia*

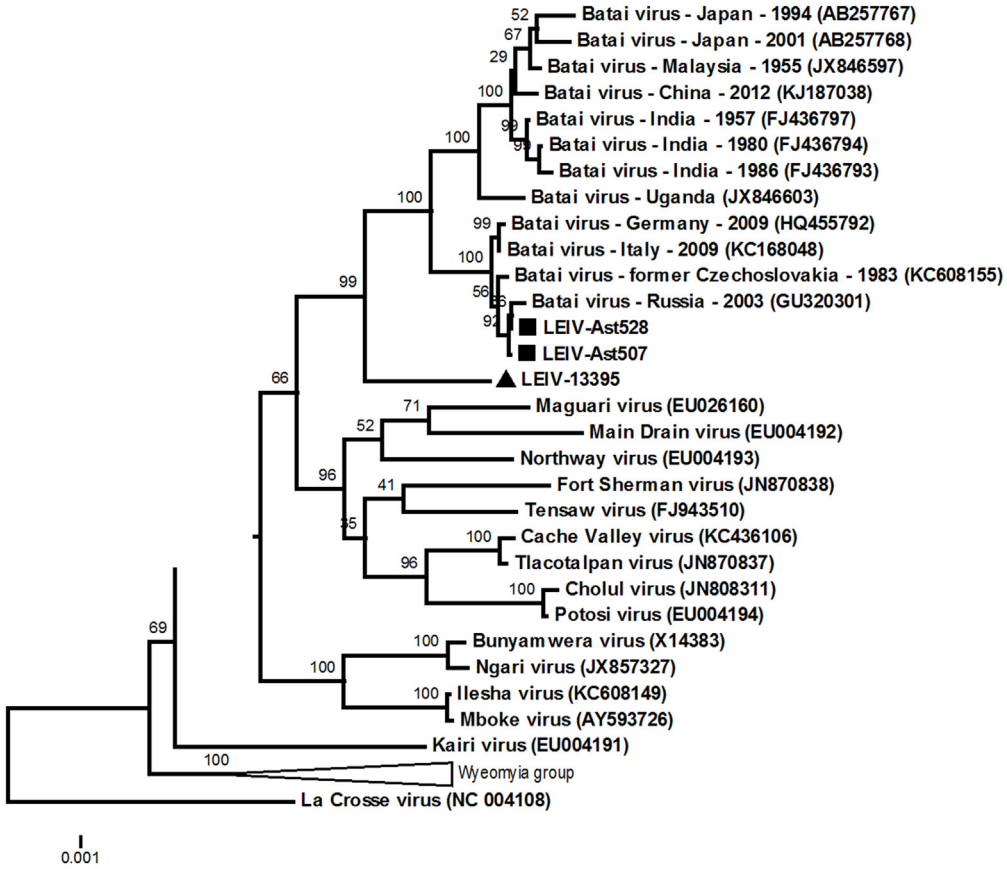


FIGURE 8.26 Phylogenetic analysis of L-segment of Bunyamwera group viruses (family Bunyaviridae, genus *Orthobunyavirus*). The trees were constructed by the maximum-likelihood method with thousandfold bootstrap analysis.

richiardii, *Aedes* (*Ochlerotatus*) *punctor*, and *Ae. communis*.[6,7,20] A wide distribution of BATV in different landscape belts of the European part of Russia, as well as in Siberia and the Far East, was demonstrated: In the temperate belt the main source of BATV isolation was the zoophilic *Anopheles* genus, whereas in high latitudes (tundra, northern taiga) it was the *Aedes* genus.[18,21–24]

In the European part of Russia, BATV has been isolated in the northern (Komi Republic), middle (Vologda region), and southern (Leningrad, Yaroslavl, and Vladimir regions; Udmurt Republic); in the taiga and in deciduous forests (Kaliningrad, Nizhny Novgorod, Moscow, Smolensk, and Kaluga regions; Tatarstan Republic, Chuvash Republic, Mordovia Republic, Mari El Republic, and Bashkortostan Republic); and in forest–steppe and steppe landscape belts (practically everywhere; the Voronezh, Belgorod, Ulyanovsk, Kursk, Rostov, Volgograd, Saratov, Penza, and Lipetsk regions, as well as Stavropol Krai and Krasnodar Krai, are representative). BATV is widespread in western Siberia, from the northern taiga to the forest–steppe

TABLE 8.15 Pairwise Comparison of Full-Length Nucleotide and Amino Acid Sequences of the Viruses of the Bunyamwera Serogroup

L-SEGMENT (RDRP)[a]							
Virus	**LEIV-13395**	**BATV**	**BUNV**	**CVV**	**TENV**	**WYOV**	**LACV**
LEIV-13395		90.6	81.4	83.1	83.0	67.8	55.3
BATV	79.5		81.6	83.1	83.2	68.1	56.1
BUNV	73.5	73.5		82.1	81.6	67.3	56.6
CVV	74.1	74.7	73.0		87.9	67.3	56.1
TENV	73.9	74.2	72.9	77.0		67.0	55.7
WYOV	67.5	67.3	66.9	66.7	66.4		56.1
LACV	60.9	59.3	59.3	58.7	59.1	60.3	
M-SEGMENT (CN/GC POLYPROTEIN PRECURSOR)[b]							
LEIV-13395		84.2	64.0	75.2	74.0	51.2	41.3
BATV	77.5		64.3	75.5	74.5	51.4	42.0
BUNV	65.8	64.4		64.2	64.0	51.2	41.6
CVV	70.5	70.8	63.9		80.6	51.9	41.3
TENV	71.2	69.9	64.4	74.0		52.0	41.6
WYOV	58.8	58.0	58.0	57.3	58.7		40.7
LACV	52.9	53.0	52.1	53.0	53.4	52.9	
S-SEGMENT (NUCLEOCAPSID PROTEIN)[c]							
LEIV-13395		97.8	93.1	94.0	95.3	62.7	42.9
BATV	86.3		92.6	93.9	94.3	62.6	43.5
BUNV	80.3	81.3		90.6	93.1	63.5	42.9
CVV	82.6	83.9	81.2		95.3	63.9	44.2
TENV	82.5	83.2	80.9	84.7		63.5	44.6
WYOV	56.8	57.2	58.5	58.4	58.3		48.5
LACV	51.3	51.2	49.0	50.3	49.9	51.8	

Nucleotide identities (%) are shown below diagonal. Amino acid similarity (%) is shown above diagonal.

[a]*GenBank numbers of RdRp amino acid sequences: Batai virus BATV (AGM40000), Bunyamwera virus BUNV (P20470), Cache Valley virus CCV (KC436106), Tensaw virus TENV (FJ943510), Wyeomyia virus WYOV (JN801038), La Crosse virus LACV (NC_004108). GenBank numbers of nucleotide sequences of L segments: Batai virus BATV (KC168048), Bunyamwera virus BUNV (X14383), Cache Valley virus CCV (AGI03946), Tensaw virus TENV (ACV95629), Wyeomyia virus WYOV (AEZ35278), La Crosse virus LACV (NP_671968).*

[b]*GenBank numbers of Gn and Gc polyprotein amino acid sequences: Batai virus BATV (AGM39999), Bunyamwera virus BUNV (AAA42777), Cache Valley virus CCV (AAF33115), Tensaw virus TENV (ACV95627), Wyeomyia virus WYOV (AEZ35274), La Crosse virus LACV (NP_671969). GenBank numbers of nucleotide sequences of M segments: Batai virus BATV (KC168047), Bunyamwera virus BUNV (M11852), Cache Valley virus CCV (KC436107), Tensaw virus TENV (FJ943508), Wyeomyia virus WYOV (JN572081), La Crosse virus LACV (NC_004109).*

[c]*GenBank numbers of N protein amino acid sequences: Batai virus BATV (ADX97411), Bunyamwera virus BUNV (NP_047213), Cache Valley virus CCV (ADG62277), Tensaw virus TENV (ACV95624), Wyeomyia virus WYOV (AEZ35279), La Crosse virus LACV (NP_671970). GenBank numbers of nucleotide sequences of S segments: Batai virus BATV (KC168046), Bunyamwera virus BUNV (NC_001927), Cache Valley virus CCV (X73465), Tensaw virus TENV (FJ943505), Wyeomyia virus WYOV (FJ235921), La Crosse virus LACV (NC_004110).*

(Tyumen region); in eastern Siberia, from the Arctic Ocean shoreline (Sakha–Yakutia Republic) to the middle and southern taiga (Irkutsk region, Sakha–Yakutia Republic, Republic of Buryatia); and in the Far East, in tundra (Magadan region, Chukotka Autonomous Okrug) and in northern and southern taiga and mixed forests (Khabarovsk Krai and Primorsky Krai).[18,21–24]

BATV is transmitted to vertebrates only by mosquitoes: in southeastern Asia (*Culex gelidus*, *Cx. bitaeniorhynchus*, *Anopheles subpictus*, *An. tessellatus*, *Aedes vexans*); in Czechoslovakia (*An. messeae*, *Ae. punctor*); and in Belarus, Ukraine, and other European countries (*An. Messeae*).[2,6,17,18,20] In the southern hyperendemic regions of Russia, the main vector of BATV is *An. messeae*. According to our data, the infection rate of *An. messeae* in the middle belt of the Volga delta (Astrakhan region) reaches 0.188% (approximately 1 infected mosquito out of 500). Because this species of mosquito attacks mainly domestic animals, it serves as a biological barrier, reducing risk of infection to humas. In the northern areas (the subarctic, the northern taiga), BATV circulation is due mainly to *Aedes* mosquitoes: *Ae. communis* complex and *Ae. punctor*. Under experimental conditions, BATV was isolated from hibernating females of *An. messeae*. Hibernation is one of the mechanisms by which BATV survives during the winter.[20,25]

Vertebrate Hosts. In anthropogenic biocenoses of the southern regions of Russia, domestic animals are the main vertebrate reservoir, because they (especially cattle) are the main hosts for *An. messeae*. BATV-neutralizing antibodies were found in India among rodents (*Mus cervicolor* (55.2%), *Rattus exulans* (36.4%), *Rattus rattus* (19.5%), *Bandicota indica* (15.5%)) and bats (*Cynopterus sphinx*) (2.6%).[2,5] This indicator is significantly higher in India among domestic animals: goats (41.8%), camels (100%), cows (60.9%), and buffalos (23.3%). In Finland, anti-BATV antibodies occasionally were found among cows (0.9%), but not among reindeers.[19] The Chittoor strain is associated with mild illness, but is pathogenic to sheep and goats.[12] BATV was isolated from birds: crows (*Corvus corone*), coots (*Fulica atra*), and grey partridges (*Perdix perdix*).[9] Persistent avian infection was established experimentally with reactivation of viremia by cortisone six months after the acute infection period.[10]

An investigation of 5,000 sera of domestic animals in Russia during 1982–1992 revealed anti-BATV antibodies among these animals significantly more often than among people (Table 8.16). The largest immune layer was found in populations of horses (up to 80%), cattle (35–60%), sheep (up to 80%), and camels in forest–steppe, semidesert, and desert landscape belts. In contrast to the situation in Finland, antibodies were found in reindeer sera in a tundra landscape belt of the Chukotka Peninsula. No examinations of vertebrates in natural biocenoses were conducted.

Epidemiology. Epidemic outbreaks and sporadic cases caused by BATV, as well as outbreaks of hemorrhagic infection caused by Ngari virus, have been reported.[13,15,18,26,27] To date, no cases of laboratory infection are known. According to a serological examination of 10,000 people in the endemic regions of Russia, about 3–10% withstand BATV infection in an asymptomatic form. The highest infection rate was established in forest–steppe and steppe belts. (However, as a rule, the rate is higher for domestic animals than humans.) Some northern areas in Russia became hyperendemic for no apparent reason.[18,21,22]

Pathogenesis. No pathogenetic mechanism during BATV infection in humans has yet been described in detail. There are experimental data, however, on BATV infection in primates:[28] Green monkeys (*Chlorocebus sabaeus*) were found to be carriers of the virus 50 days after inoculation (the observation period); the virus was pantropic, destroying small vessels and producing vasculitis and perivascular focal lymphohistiocytic infiltrates.

TABLE 8.16 Detection of BATV-Neutralizing Antibodies Among Domestic Animals in Russia (1982–1992)[a]

Territory	Federal subject	Number of sera tested		
		Total	Positive Number	%
Northern	Komi Republic, Karelia Republic, Vologda, Murmansk, Arkhangelsk regions	634/566	4/2	0.6/0.4
		2,171/180[b]	257/37	11.8/20.6
Northwestern	Leningrad, Novgorod, Pskov regions	206/0	1/–	0.4/–
Central	Ivanovo, Kostroma, Ryazan regions	285/0	2/–	0.3/–
	Vladimir, Smolensk, Tverskaya, Tula, Kaluga regions	357/0	5/–	1.4/–
		274/0	8/–	2.2/–
	Moscow, Bryansk, Oryol regions	228/0	10/–	4.4/–
		59/0	6/–	10.2/–
Central Chernozemny	Tambov, Kursk, Voronezh, Belgorod, Lipetsk regions	350/0	5/–	1.4/–
		296/32[b]	15/15	5.1/40.9
North Caucasian	Krasnodar Krai, Kabardino-Balkaria Republic, Chechen Republic	212/0	4/–	1.9/–
Volga	Penza, Ulyanovsk, Samara, Saratov, Astrakhan, Volgograd regions, Tatarstan Republic	466/70	2/13	0.4/18.6
		370/159[b]–24[c]–30[d]	9/36–13[c]–12[d]	2.4/22.6–54.2[c]–40.0[d]
Volga-Vyatka	Nizhny Novgorod, Kirov regions, Chuvashia Republic, Mordovia Republic, Udmurtia Republic	488/162[b]	8/57	1.6/35.2
		85/174[b]	50/56	58.8/32.2
Ural	Bashkortostan Republic, Perm, Orenburg regions	286/256[b]	3/9	1.0/3.5
		116/56[b]	12/6	10.3/10.7
Western Siberian	Altai Krai	125/0	0/–	0/–
Eastern Siberian	Irkutsk, Chita regions, Krasnoyarsk Krai, Sakha-Yakutia Republic, Buryatia Republic	1,760/1,360[b]	15/19	0.8/1.4
		40/1,845[b]	3/63	1.5/3.4
Far Eastern	Magadan, Sakhalin regions, Khabarovsk Krai, Kamchatka Krai	486/133[b]–62[e]	7/0–5[e]	1.4/0–8.1[e]
		460/0	3/–	0.7/–

[a] *Human/domestic animal.*
[b] *Cattle.*
[c] *Sheep.*
[d] *Camels.*
[e] *Reindeers.*

Clinical Features. The disease etiologically linked with BATV proceeds mainly as influenzalike disease complicated by meningitis, malaise, myalgia, and anorexia.[13,15,18,26,27] At the same time, Ngari virus (reassortant between BATV and BUNV) infection in east Africa appears as outbreaks of hemorrhagic fever.[13] Diseases associated withtheclosely related ILEV in Africa and Madagascar also proceed with hemorrhagic phenomena and with lethal outcomes.[29,30]

Diagnostics. A highly specific test based on RT-PCR has been developed, as have ELISA tests for the detection of specific anti-BATV IgM and IgG.[24,31]

8.1.4.2 California Encephalitis Complex Viruses: Inkoo Virus, Khatanga Virus, Tahyna Virus

California encephalitis (CE) and related diseases are etiologically linked with 13 currently known viruses of the CE serocomplex (family Bunyaviridae, genus *Orthobunyavirus*). Eight viruses from the CE serocomplex are distributed in North America, three in South America, three in Eurasia, and one in Africa (Table 8.17).[1,2]

History. The prototypical member of the CE serocomplex, California encephalitis virus (CEV), was originally isolated in 1943 by W.M. Hammon from mosquitoes of the genus *Aedes*. Tahyna virus (TAHV) was isolated in 1958 by V. Bardos and V. Danielova from *Ae. vexans* and *Ae. Ochlerotatus* mosquitoes collected in the vicinity of the village of Tahyna in eastern Slovakia. (TAHV is identical to Lumbo virus,[3] isolated in 1960 in Mozambique in the southeastern part of Africa.) Snowshoe hare virus (SSHV) was isolated in 1959 by W. Burgdorfer from the snowshoe hare (*Lepus americanus*). La Crosse virus (LACV) was isolated in 1960 by W.H. Thompson from the brain of a patient who died as the result of meningoencephalitis. Jamestown Canyon virus (JCV) was isolated in 1961 by L.C. La Motte et al. from the *Culiseta inornata* mosquito. Inkoo virus (INKV) was isolated in 1964 by M. Brummer-Korvenkontio from *Ae. communis* and *Ae. punctor* mosquitoes in the south of Finland. Khatanga virus (KHTV) was isolated in 1982 from *Aedes* mosquitoes by D.K. Lvov.[2,4–10]

Genome and Taxonomy. The genome of the CE group of viruses consists of three segments of ssRNA with negative polarity. The L-segment of LACV, a prototypical virus of the group, is 6,980 nt in length, the M- and S-segments 4,527 and 984 nt, respectively. As in other bunyaviruses, the L-segment encodes RdRp, the M-segment a polyprotein precursor of the envelope glycoproteins Gn and Gc, and the S-segment nucleocapsid protein (N). Two nonstructural proteins are found in infected cells: NSs, which encodes by adding an ORF in the S-segment; and NSm, which forms during the maturation of the Gn and Gc proteins from the precursor.[11] Phylogenetic relationships of viruses of the CE serogroup are presented in Figures 8.27–8.29.

Arthropod Vectors. On the territories located to the West of Russia, arthropod vectors of CE serocomplex viruses are mosquitoes (subfamily Culicinae): *Aedes vexans*, *Ae. trivittatus*, *Ae. triseriatus*, *Ae. dorsalis*, *Ae. caspius*, *Ae. cantans*, *Ae. punctor*, *Ae. communis*, *Ae. flavescens*, *Ae. excrucians*, *Culiseta annulata*, *Culex modestus*, *Cx. pipiens*, *Anopheles hyrcanus*, *An. crucians*, and *An. punctipennis*.[4,12–24] *Ae. triseriatus* is the main vector in North America,[25,26] but viruses of the CE serocomplex were isolated from *Ae. albopictus* (a known vector for at least 22 arboviruses), which was imported from southeastern Asia and spread into 30 states of the United States.[27,28] Transovarial transmission was established in *Ae. vexans*[29] and *Cs. annulata*.[16] Overwintering of TAHV was documented in *Cx. modestus* and *Cs. Annulata* females.[16]

Mosquito species have been defined and classified only partially in connection with the huge volume of this laborious work.

TABLE 8.17 Viruses of the CE Serocomplex[a]

	Distribution							Vertebrate hosts				Disease of humans	
		America							Mammals				
Virus	Africa	North	South	Asia	Europe	Northern Eurasia	Mosquito vector	Birds	Wild	Domestic	Humans	Clinical symptoms	Epidemiology
California encephalitis virus (CEV)	–	+	–	–	–	–	+	–	+	+	+	F, E	S, O
Guaroa virus (GROV)	–	+	+	–	–	–	+	–	+	–	+	F	S
Inkoo virus (INKV)	–	–	–	–	+	+	+	–	+	–	–	F, E	S
Jamestown Canyon virus (JCV)	–	+	–	–	–	–	+	–	+	+	A	F, E	S
Keystone virus (KEYV)	–	+	–	–	–	–	+	–	+	–	–	–	–
Khatanga virus (KHTV)	–	–	–	+	+	+	+	–	A	A	A	F, E	S, O
La Crosse virus (LACV)	–	+	–	–	–	–	+	–	+	+	+	F, E	S, O
Melao virus (MELV)	–	–	+	–	–	–	+	–	–	–	–	–	–
San Angelo virus	–	+	–	–	–	–	+	–	A	A	A	–	–
Snowshoe hare virus (SSHV)	–	+	–	–	–	–	+	–	A	+	+	F, E	S
Serra do Navio virus (SDNV)	–	–	+	–	–	–	+	–	A	–	A	–	–
Tahyna virus (TAHV)	+	–	–	+	+	+	+	A	+	–	+	F, E	S, O
Trivittatus virus (TVTV)	–	+	–	–	–	–	+	–	A	–	A	–	–

[a]*Designations: +, virus isolation; A, specific antibodies detection; F, fever; E, encephalitis, meningoencephalitis; S, sporadic cases; O, outbreak.*

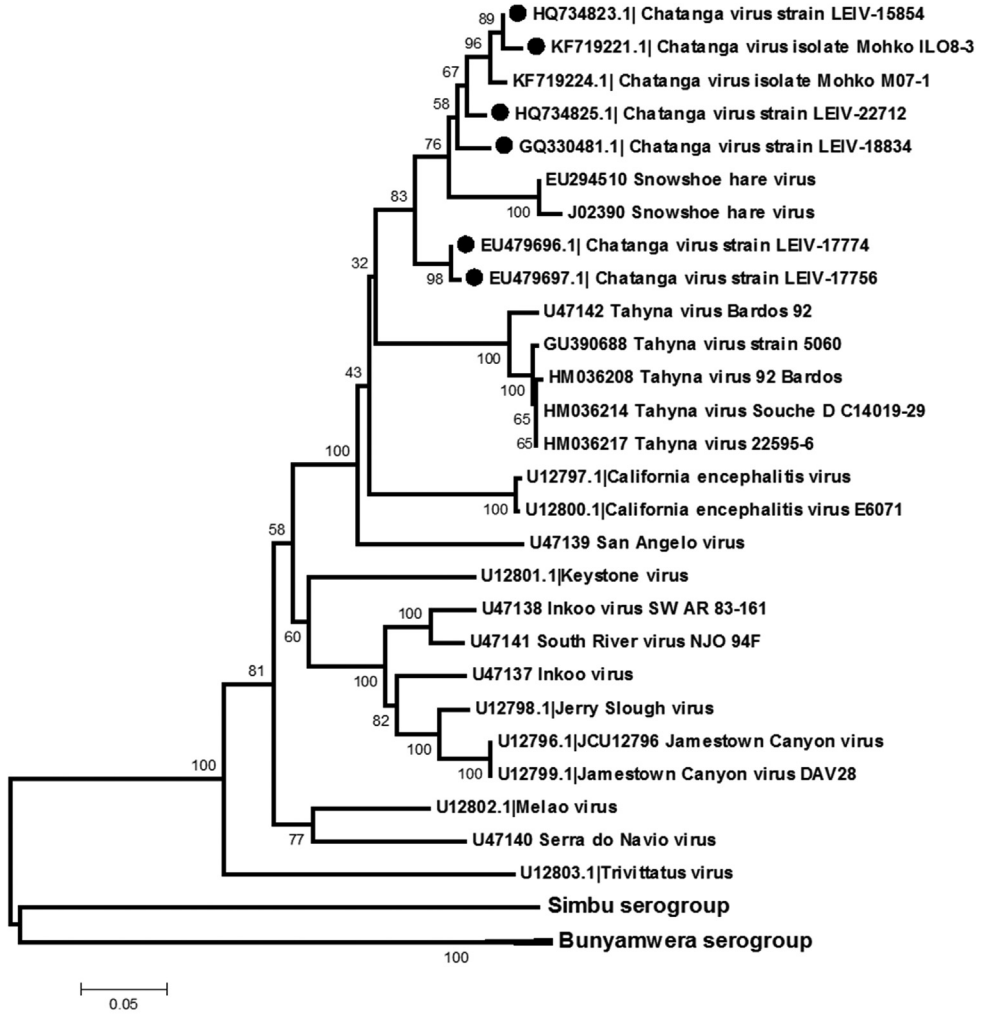


FIGURE 8.27 Phylogenetic analysis of full-length amino acid sequences of nucleocapsid (S-segment) of the California group viruses.

The majority of strains were isolated from pools of mosquitoes belonging to different species. Of 250 strains that were isolated (1 strain was isolated from a wild population of the common house mouse, *Mus musculus*), only 112 were isolated from strictly defined species (Table 8.18). The other 138 strains were isolated from *Aedes* mosquitoes of unidentified species: 34% of strains were from *Ae. communis*, 18% from the mixed pools, in which *Ae. communis* prevailed. Strains were isolated from other species significantly less often. Only one strain was isolated from *Anopheles maculipennis* (*An. messeae*) and *Culiseta alaskaensis*.[30]

The dynamics of the seasonal infection rate of mosquitoes was investigated for two years on the model of the northern part of the

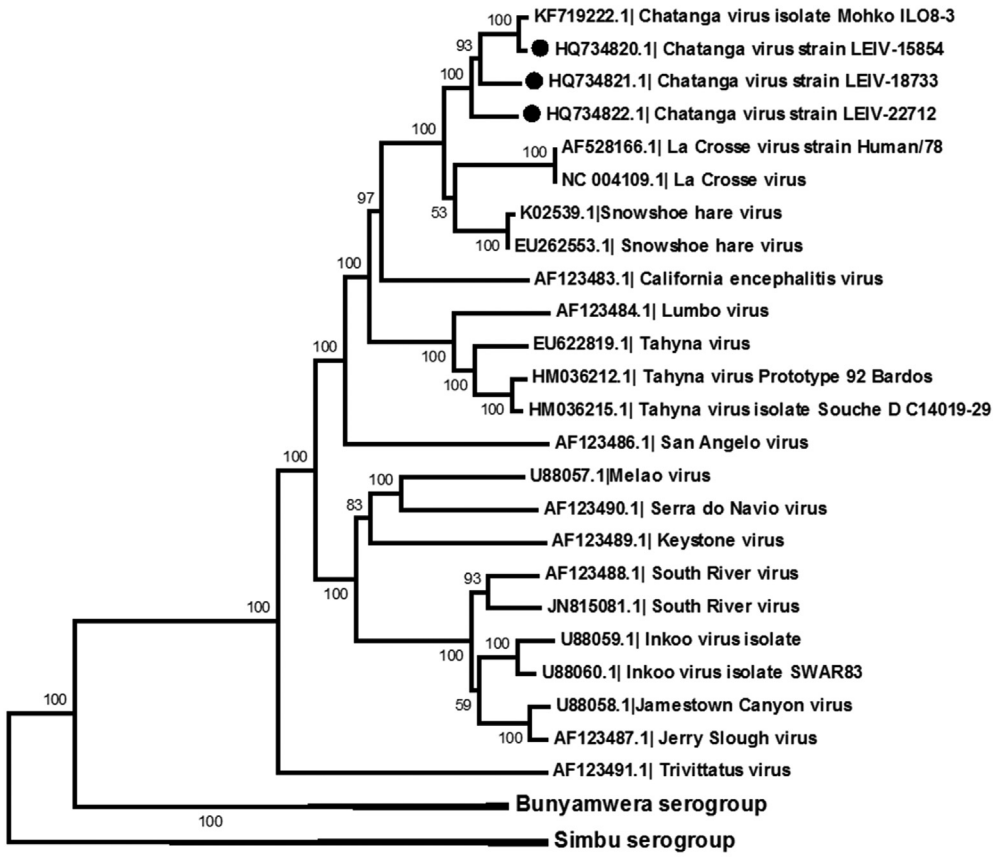


FIGURE 8.28 Phylogenetic analysis of full-length amino acid sequences of Gn/Gc precursor (M-segment) of the California group viruses.

Russian Plain and the eastern part of Fennoscandia. In tundra, the epizootic period begins with the second decade of July and proceeds to the beginning of August, when the activity of mosquitoes comes to an end. In forest tundra, the epizootic period begins with the first decade of July and proceeds for 1.5 months; in the northern taiga, this period lasts at least 2 months (July–August); in the middle and southern taiga, the first strains began to be isolated in the second decade of June. The mosquito infection rate increases significantly in the third decade of July and reaches a maximum in the middle to end of August, when the total number of mosquitoes decreases.[30,31]

The data collected testify to an almost universal distribution of CE serocomplex viruses in all landscape belts, except the Arctic, in all six physicogeographical lands examined in the north of Russia,[32] located on a territory of more than 10 million km^2.

The infection rate of mosquitoes increases ($p < 0.01$) in moving from the subarctic (tundra) ($0.0090 \pm 0.0018\%$) to the landscape belt of the middle taiga ($0.0196 \pm 0.0020\%$).

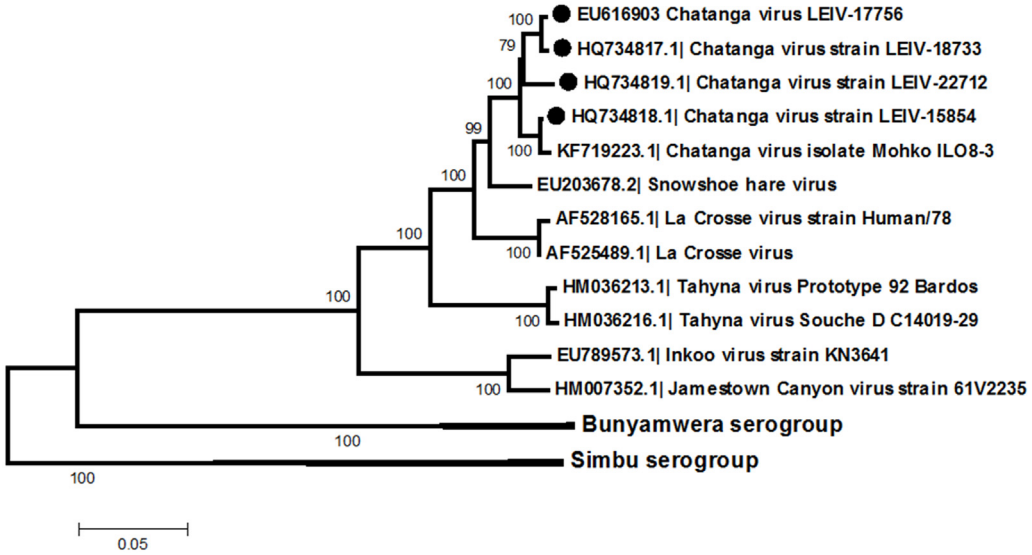


FIGURE 8.29 Phylogenetic analysis of full-length amino acid sequences of RdRp (L-segment) of the California group viruses.

This indicator in tundra and in the forest tundra is close to that in the southern taiga of the Russian Plain (0.0122%), in North America (0.01%), and in the forest steppes of the Russian Plain (0.0100−0.0017%). In the steppe belt of the Russian Plain, the infection rate of mosquitoes appeared to be the smallest (0.001%). In the leaf forests of the Russian Plain (0.0148%) and of the former Czechoslovakia (0.0210%), the infection rate of mosquitoes is comparable to that for landscape belts of the northern and middle taiga.

To date, at least s63 CE serocomplex virus strains were isolated from mosquitoes in the central and southern parts of the Russian Plain. Among them, 4 strains were isolated from the blood and spinal fluid of patients, and 3 strains from the internal parts of rodents (2 from the bank vole, *Myodes glareolus*; and 1 from the wood mouse, *Apodemus sylvaticus*). The infection rate of mosquitoes depends on the landscape belt and the particular season in which field material was collected. The rate decreases, as a rule, from the north to the south. Data indicating an absence of viruses in semideserts can be explained by an insufficient quantity of mosquitoes collected, but in wet subtropical zones in Azerbaijan CE serocomplex viruses were isolated from *Anopheles hyrcanus*.[33]

In the southern taiga belt and mixed forests, the infection rate of mosquitoes was defined to be from the third week of May to the second week of August and two peaks were noted: at the end of June (the emergence of the first generation of *Aedes* mosquitoes) and at the end of July to the beginning of August (the emergence of the second generation of *Aedes* mosquitoes). In the majority of the southern belts, the infection rate was registered from the second week of June until the end of August with a small peak in the first week of August caused by the emergence of the second generation of *Aedes* mosquitoes and by the peak of activity of *Culex*, *Coquillettidia*, and *Anopheles* mosquitoes.[17]

TABLE 8.18 Isolation of CE Serocomplex Viruses From *Aedes* Mosquitoes in High Latitudes of Russia

		Collected		Strains isolated[b]					
Physicogeographical land	**Landscape belt**	**Places**	**Mosquitoes, thousands**	**TAHV**	**INKV**	**KHTV**	**CE complex**	**Total[a]**	**Susceptibility, %**
Fennoscandia	Tundra	3	10.6	0	0	0	0	0	0
	Forest–tundra	2	5.7	0	0	0	0	0	0
	Northern taiga	19	25.8	0	2	2	2	6	0.023
	Middle taiga	8	99.4	0	0	0	18	18	0.018
	Total	32	141.5	0	2	2	20	24	0.017
Russian Plain	Tundra	11	26.3	0	1	1	0	2	0.0076
	Forest–tundra	5	23.8	0	0	0	0	1	0.0042
	Northern taiga	11	63.6	0	6	1	3	10	0.0167
	Middle taiga	14	70.2	0	2	2	0	3	0.0114
	South taiga	1	5.3	0	1	7[c]	0	9[c]	0.0589
	Total	42	189.2	0	10	11[c]	4	25[c]	0.013
Western Siberia	Tundra	19	81.0	0	9	1	1	11	0.0148
	Forest–tundra	12	40.1	0	13	1	0	14	0.0349
	Northern taiga	13	52.8	1	1	2	1	5	0.0095
	Middle taiga	32	91.4	0	4	6	17	27	0.0031
	South taiga	24	53.5	0	2	2	4	8	0.0156
	Forest–steppe	13	43.3	1	1	2	7	11	0.0255
	Steppe	12	41.6	0	2	11	29	42	0.0966
	Total	**125**	**390.6**	**3**	**32**	**25**	**59**	**118**	**0.03**
Central Siberia	Tundra	9	56.1	0	0	1	4	5	0.0089
	Forest–tundra	7	57.4	0	0	0	4	4	0.008
	Northern taiga	4	14.8	0	0	0	0	0	0.0068
	Middle taiga	14	53.1	0	0	3	5	8	0.0151
	South taiga	2	6.2	0	0	0	0	0	0.016
	Total	36	187.6	0	0	4	13	17	0.009

(*Continued*)

TABLE 8.18 (Continued)

Physicogeographical land	Landscape belt	Collected		Strains isolated[b]					Susceptibility, %
		Places	Mosquitoes, thousands	TAHV	INKV	KHTV	CE complex	Total[a]	
Northeastern Siberia	Tundra	10	46.1	0	0	3	2	5	0.0108
	Forest–tundra	8	31.2	0	0	2	0	2	0.0064
	Northern taiga	26	85.1	0	0	12	9	21	0.0247
	Middle taiga	36	130.9	0	0	19	10	29	0.0222
	Total	80	293.3	0	0	36	21	57	0.01
North Pacific land	Tundra	14	76.4	0	0	2	2	4	0.0052
	Forest–tundra	10	30.0	0	0	1	1	2	0.0067
	Northern taiga	11	30.7	0	0	2	2	4	0.013
	Middle taiga	5	19.6	0	0	0	0	0	0.0051
	Total	40	156.7	0	0	5	5	10	0.0064
All lands	Tundra	66	296.5	0	10	8	9	27	0.0091
	Forest–tundra	44	188.2	0	13	4	6	23	0.0122
	Northern taiga	84	272.8	1	9	19	17	46	0.0169
	Middle taiga	109	464.6	0	6	35[c]	50	91[c]	0.0196
	South taiga	27	65.0	0	3	4	4	11	0.0169
	Forest–steppe	13	43.2	1	1	2	7	11	0.0255
	Steppe	12	41.6	0	2	11	29	42	0.0966
	Total	355	1371.9	2	44	83[c]	122	251[c]	0.0183

[a]*Identification of virus strains was carried out with a neutralization test.*
[b]*Abbreviations: TAHV, Tahyna virus; INKV, Inkoo virus; KHTV, Khatanga virus; CE, California encephalitis.*
[c]*Virus strain was isolated from a wild population of house mice* (M. musculus).

In steppe and forest–steppe belts, CE serocomplex viruses were isolated from mosquitoes collected in the Rostov and Orenburg regions, as well as in the foothills of the Caucasus Mountains (Krasnodar Krai). Most of the strains were obtained from *Aedes* mosquitoes, which play the leading role in virus circulation. In these regions, *Anopheles* mosquitoes join the virus population maintenance (three strains were isolated), being ecologically connected with agricultural animals and, because of that connection, playing an important role as an indicator species in anthropogenic biocenoses. In the center and south of the Russian Plain, there is a mix of populations of INKV, TAHV, KHTV.[31,32]

Vertebrate Hosts. The principal vertebrate hosts of TAHV in Europe are Lagomorpha

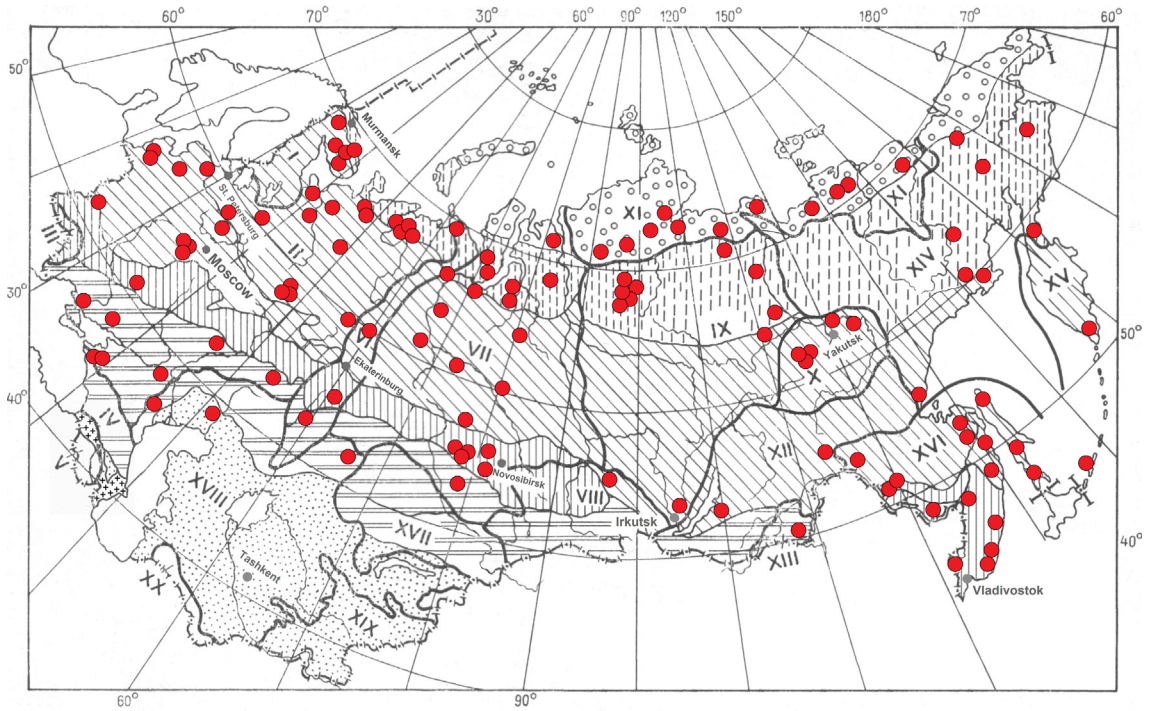


FIGURE 8.30 Places of isolation of CE complex viruses (●) in the former USSR. (See other designations in Figure 1.1.)

(hares (*Lepus europaeus*), rabbits (*Oryctolagus cuniculus*), hedgehogs (*Erinaceus roumanicus*), and rodents (Rodentia)). Experimental viremia has been established in lagomorphs, hedgehogs, ground squirrels (*Citellus citellus*), muskrats (*Ondatra zibethicus*), squirrels (*Sciurus vulgaris*), martens (*Martes foina*), polecats (*Putorius eversmanni*), foxes (*Vulpes vulpes*), badgers (*Meles meles*), bats (*Vespertilio murinus*), piglets, and puppies.[14,15,34,35]

In total, 251 strains of CE serocomplex viruses were isolated within all landscape belts of all physicogeographical lands (Figure 8.30, Table 8.19). According to our data, the susceptibility of mosquitoes increased from the tundra to the northern and middle taiga; however, the highest indicators were noted to be in the forest–steppe and the steppe of western Siberia (in Altai Krai). Identification of these strains revealed at least three viruses of the CE complex: 2 strains of TAHV, 44 of INKV, and 183 strains of KHTV.[30]

In all landscape belts east of the Yenisei River (central and northeast Siberia and the physicogeographical lands bordering the North Pacific Ocean), only KHTV strains have been isolated. West of the Yenisei River, INKV strains predominated in the tundra and the forest–tundra of western Siberia, whereas KHTV prevailed in other landscapes located to the south. In the eastern part of Fennoscandia and in the north of the Russian Plain, INKV and KHTV strains were isolated in about equal proportions.[30]

The pattern of distribution of TAHV, INKV, and KHTV over Northern Eurasia suggests that the emergence of the ancestor of CE serocomplex viruses probably is connected to Oligocene Chinese–Manchurian fauna of the deciduous forests of eastern

TABLE 8.19 Isolation of CE Serocomplex Viruses from Different Species of *Aedes* Mosquitoes in Russia

Species of *Aedes* genus		Strains isolated	
Dominating	**Attendant**	**Number**	**%**
Communis		38	(33.9)
	Nigripes	7	
	Vexans	4	
	Cinereus	1	
	Cantans, excrucians, cinerius	4	
	Cantans, punctor	1	
	Excrucians, nigripes, ciprius	1	
	Intrudens, punctor	1	
	Riparius	1	
	Alaskaensis[a]	1	
	Total	58[a]	51.75
Excrucians		4	(3.5)
	Nigripes, cinerius, vexans	2	
	Mercurator, flavescens, cataphylla, nigripes, cinereus	1	
	Punctor, communis, nigripes, cataphylla	1	
	Cataphylla	1	
	Nigripes	1	
	Total	9	8.0
Cantans		7	6.25
Flavescens		4	(3.5)
	Cinereus, mercurator, hexodontus, nigripes	1	
	Excrucians, mercurator, nigripes, communis	1	
	Nigripes, mercurator	1	
	Total	7	6.25
Ciprius	*Excrucians, communis*	4	
	Cantans, caspius, cinereus	2	
	Nigripes, excrucians, flavescens	1	
	Total	7	6.25
Punctor		1	
	Intrudens, nigripes	4	
	Total	5	4.5
Vexans		4	
	Communis	1	
	Total	5	4.5
Cataphylla		3	
	Punctor, communis	1	
	Total	4	3.6
Nigripes	*Flavescens*	2	
	Mercurator	1	
	Impiger, communis, punctor	1	
	Total	4	3.6
Hexodontus		3	2.6
Eudes		1	0.9
Mercurator, nigripes, excrucians		1	0.9
Maculipennis[b]		1	0.9
	Total	112	100

[a]*One strain was isolated from the genus* Culiseta.
[b]*One strain was isolated from the genus* Anopheles.

Siberia evolving into Okhotsk fauna during the Upper Tertiary period. The Okhotsk fauna, in its turn, extended in early glacial times to the north, the west, and partially to the east in tundra through ancient Beringia and on into North America. The ancestral virus could then penetrate into North America together with this fauna and gradually extend in the southern direction, in the process laying the foundation for the appearance of some other viruses of the CE serocomplex now circulating mainly in North America.

The introduction of the virus population to the Western Hemisphere probably occurred through two pathways around the Central Siberian Plateau: (i) through the tundra lying to the north of the plateau and (ii) through southern taiga and forest–steppe territories. These pathways can explain the modern predominance of KHTV in the forest–steppe belt of Siberia and in a taiga belt west of the Yenisei River. In moving to other ecological systems further to the west, KHTV could have been transformed partially to INKV and TAHV. The INKV population penetrated into the western part of the Eurasian subarctic through the taiga belt and occupied that part of Eurasia, whereas TAHV proceeded into the deciduous forests of Europe, where it now prevails.[36]

Epidemiology. CEV is endemic in the United States in California, New Mexico, Texas, the southwestern part of Virginia, Tennessee, and Kentucky.[26,37] Sporadic morbidity with CNS lesions occurs in those states, but the main morbidity is linked to LACV, which is endemic in 20 states, predominantly the U.S. Census Bureau–defined East North Central states (Ohio, Wisconsin, Minnesota, Iowa, and Indiana), where morbidity reaches 0.1–0.4%.[26] Cases of LACV-associated encephalitis are within the distribution of the main vector—*Aedes triseriatus*—eastward from the Rocky Mountains.[38] During the last few decades, natural foci in West Virginia, North Carolina, and Tennessee, with sporadic cases occurring in Louisiana, Alabama, Georgia, and Florida, joined with previously known ones in Wisconsin, Illinois, Minnesota, Indiana, and Ohio. Thus, having traversed the distance from southeastern Asia to North America, *Ae. triseriatus* is now part of the North American virus circulation.[39] The clinical picture varies from an acute fever syndrome (in some cases with pharyngitis and other symptoms of acute respiratory disease) to encephalitis. Lethality is about 0.05%. From 40 to 100 cases occur annually. Generally, the virus attacks children age 10 and under (60%), a phenomenon that may be explained by the existence of a layer of immunity in up to 40% of adults.[40] JCV (in the United States and Canada) and SSHV (in the northern part of the United States and in Canada) are associated with sporadic cases of fever and encephalitis.[26] Domestic dogs are susceptible to LACV, which provokes encephalitis.[21,34,41,42] The role of deer in virus circulation has been established as well. Horizontal and vertical transmission of viruses provides an active circulation of the virus, a high rate of infection in mosquitoes, and stability of natural foci under the relatively rough conditions of the central and northern parts of the temperate climatic belt.[43]

All three viruses (INKV, KHTV, and TAHV) of the CE serocomplex distributed in Eurasia have significance in human pathology.[43,44] These viruses were found in Czechoslovakia in 1959,[4,45] Austria in 1966,[13] Finland in 1969,[6,46] Romania in 1974,[12] Norway in 1978,[24] the former USSR(in Transcaucasia) in 1972,[47] and elsewhere in the European and Asian parts of Russia.[9,30,32,33,36,44,48–50] In Europe, human disease associated with TAHV presents as an influenzalike illness mainly in children with sudden-onset fever, headache, malaise, conjunctivitis, pharingitis, myalgia, nausea, gastrointestinal symptoms, anorexia, and (seldom) meningitis and other signs of CNS lesions.[16,42,51–56] The circulation of CE serocomplex viruses was established in China,[57] where they provoke human diseases with encephalitis[58] as well as acute respiratory disease, pneumonia, and acute arthritis.[59] In North America (the United States and Canada), LACV is the most important of these viruses,[60] but SSHV also is associated with human disease.[61] Between 1963 and 1981 in the United States, 1,348 cases of CE were reported.[60,62] So, CE serocomplex viruses have circumpolar distribution. In Russia, these viruses are found from subarctic to desert climes (Figure 8.30, Table 8.18).[32,44]

According to our summary data for 8,732 sera, the number of people with specific antibodies to CE serocomplex viruses in the tundra and forest–tundra belts (27.8%) is significantly lower than the number in the north and middle taiga belts (48% and 47%, respectively). These data correlate with the infection rate of mosquitoes in those landscape belts.[31,49]

Results obtained from serological investigation of the human population correlate with those obtained from virological investigation of the mosquitoes (Figure 8.31). The maximum immune layer of the healthy population is registered in the southern taiga. In the landscape and geographical zones located south of that landscape, a gradual decrease in this indicator takes place. Specific antibodies to INKV are seen everywhere that this virus circulates. In forest–steppes, specific antibodies to TAHV and INKV are marked out with an identical frequency. In semideserts, anti-TAHV antibodies are found twice as often as anti-INKV ones. The small number of strains isolated in these natural zones precludes establishing a relationship between the circulation of viruses and an immune layer of the population. Active circulation of CE serocomplex viruses on the territory of Russia results in regular registration of the diseases caused by these viruses. More than 7% of all seasonal fevers are etiologically linked to such viruses, and in some natural zones (the southern taiga and the mixed forests), this indicator increases to 10–12%.

In mixed forests, the main etiological role most often belongs to INKV (50.4%), and in semideserts (Astrakhan region) to TAHV (76.5%). The diseases caused by CE serocomplex viruses in the center and south of the Russian Plain start appearing during the middle of May and reach a maximum in

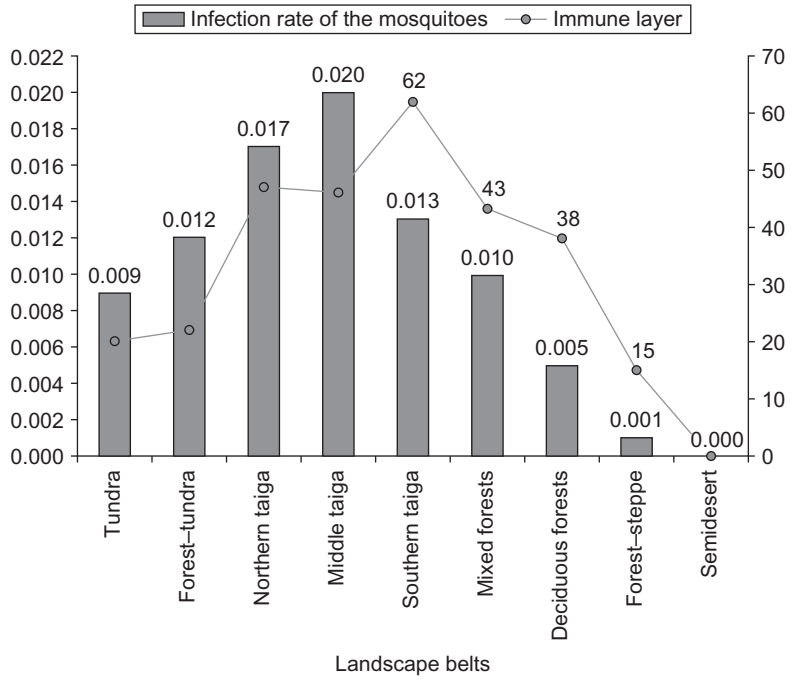


FIGURE 8.31 Immune layer among population and infection rate of mosquitoes for CE serocomplex viruses in different landscape belts in the north of Russia.

July–August. Cases are seen in September as well. The seasonal dynamics of the incidence of TAHV in various landscape zones correlate with the seasonal dynamics of the infection rate of mosquitoes. The etiological role of CE serocomplex members was confirmed in 183 (7.47%) of 2,451 patients with unstated fevers in the summertime . The etiological role of INKV was established in 64 cases (35%), TAHV in 40 (21.9%), and KHTV in 14 (7.6%). Almost equal titers of specific antibodies to more than one virus were revealed in 65 patients (35.5%) in a neutralization test.[31,43,49]

Diseases were registered from May to September: in May, 22 cases (12.02%); in June, 35 (19.13%); in July, 67 (36.61%); in August, 54 (29.51%); and in September, 5 (2.73%). The seasonal dynamics in all landscape zones were identical: The maximum number of diseases is noted in July–August. Diseases were registered everywhere in the form of sporadic cases and small outbreaks, but more often in the taiga and the deciduous forests of the European part of Russia and western Siberia. Most patients were 15–40 years old, with those up to 30 years making up 52.5% of all people infected.[9]

Pathogenesis. A systematic destruction of small vessels, together with the development of vasculitis and perivascular focal lymphohistiocytic infiltrates, underlies the pathogenesis of the diseases caused by CE serocomplex viruses. Lesions in the lungs, brain, liver, and kidneys are the most frequent complications.[31,49]

Clinical Features. The incubation period lasts from 7 to 14 days, but in some cases is only 3 days. Three main forms of disease linked with CE serocomplex viruses have been proposed: (i) influenzalike; (ii) with primary compromise of the bronchiopulmonary system; (iii) neuroinfectious, which proceeds with a syndrome of serous meningitis and encephalomeningitis.

Analysis of the clinical picture of cases examined showed that 79.8% of cases proceeded without signs of CNS lesion, 20.2% with a syndrome of acute neuroinfection, and 8.9% with radiologically uncovered signs of changes in the bronchi–lung system. A comparison of clinical forms and etiologic agents showed that INKV and TAHV often cause disease without CNS lesions (65.6% and 92.5%, respectively) and that INKV plays the leading role in acute neuroinfection (34.4%). The etiological role of KHTV was established in 14 cases without CNS symptoms of lesions.[63]

Eighty-three patients had an influenzalike form of the disease etiologically linked to CE serocomplex viruses. The incubation period was 7–14 days. The disease began abruptly, with a high temperature that reached a maximum of 39–40°C in 98.9% of patients on the first day. The duration of the fever was 4.48 ± 0.30 days. One of the main symptoms was an intensive headache (3.62 ± 0.26 days in duration) that developed in the first few hours and was often accompanied by dizziness, nausea (31.3%), and vomiting (21.7%).[43,63–66]

A survey of patients revealed infection of the sclera ($59.0 \pm 3.4\%$), hyperemia of the face and the neck ($10.8 \pm 3.4\%$), and, in some cases (3.6%), a spotty and papular rash on the skin of the trunk and the extremities. Violations of the upper respiratory airways were characterized by hyperemia of the mucous membranes of the fauces ($95.2 \pm 2.3\%$)and congestion of the nose and a dry, short cough ($13.2 \pm 3.7\%$). With regard to the lungs, $26.5 \pm 4.8\%$ of patients exhibited rigid breathing a dry, rattling cough during auscultation, and a strengthening of the bronchovascular picture on roentgenograms. Among CNS symptoms, the most common were a decrease in appetite, a stomachache without accurate localization and with liquid stool, and a small increase in the size of the liver with a short-term increase in aminotransferase activity in the blood. Inflammatory changes in the bronchi–lung system (bronchitis and pneumonia) occurred as well. In all cases in which it appeared, pneumonia had a focal character with full

regression of inflammatory changes through 14.44 ± 1.36 days after the first symptoms appear. High fever ($39.2 \pm 0.21^{\circ}$C), nausea and vomiting (53.8%), and meningism phenomena (30.7%) also attracted attention.

The etiological role of different CE serocomplex viruses has been established in 8% of 463 cases with acute diseases of the nervous system (serous meningitis, encephalomeningitis, arachnoiditis, acute encephalomyelitis, and seronegative tick-borne encephalitis (TBE)): INKV ($56.7 \pm 8.1\%$), TAHV ($8.1 \pm 4.5\%$), and unidentified ($35.1 \pm 7.8\%$). The age of patients with CNS lesions was from 3 to 61 years, with the majority (51.5%) from age 21 to 30. Serous meningitis was observed in 29 patients who arrived at the hospital a mean 3.3 days after symptoms appeared. The disease began abruptly. The majority (58.6%) of patients complained of a high temperature that reached a maximum the first day, The duration of the fever was 4.54 ± 0.05 days, with a critical (37.9%) or steplike (62.1%) decrease. Headache was noted in 100% of patients and was accompanied by dizziness in 31%. Vomiting developed on the first (53.6%) or the second (46.4%) day and continued in 67.7% of patients. Meningeal signs appeared in 96.5% of patients but were weak and dissociated in most cases, with only 37.9% of patients exhibiting rigidity of the occipital muscles. The duration of the meningeal signs was 3.50 ± 0.4 days. The cells of the spinal fluid (investigated on the $4.57\text{th} \pm 0.54$ day of the disease) was lymphocytic, mostly reaching three digits and up to 500 cells (55.6%); the protein concentration was reduced (0.15 ± 0.02 g/L) in 41.4% of cases but was within the normal range (0.31 ± 0.01 g/L) in other cases. In 34.5% of patients exhibiting acute neuroinfection symptoms of bronchitis and focal pneumonia, their condition was confirmed radiologically.

Encephalomeningitis caused by INKV was characterized by an abrupt beginning and fast development of focal symptomatology (ataxy, horizontal nystagmus, and discoordination) against a background of common infectious and meningeal syndromes, including inflammatory changes to the spinal fluid.[43,63–66]

The variability of the clinical picture of the diseases caused by CE serocomplex viruses and its similarity—especially at early stages—to that of other infections suggest the necessity of carrying out differential clinical diagnostics with a number of diseases. The influenzalike form needs to be differentiated, first of all, from influenza, especially in the presence of symptoms of neurotoxicity, as well as from other acute respiratory diseases (parainfluenza, adenoviral and respiratory–syncytial diseases), pneumonia (including a mycoplasma and chlamydia etiology), and enteroviral diseases. The main epidemiological features and clinical symptoms that lend themselves to carrying out differential clinical diagnostics for the influenzalike diseases described here are presented in Table 8.20. Note that considerable difficulties arise in implementing differential clinical diagnostics of the diseases that proceed with acute neuroinfection syndrome (serous meningitis, encephalomeningitis), especially when those diseases occur in the same season (Tables 8.20 and 8.21).[31,44,66]

The main criteria in differential clinical diagnostics of the disease etiologically linked with CE serocomplex viruses are as follows (see Tables 8.20 and 8.21): acute onset; high short-term fever (4–8 days, on average) reaching a maximum on the first day and decreasing critically at the end of the feverish period; and intensive headache, nausea, vomiting, and weakness. Also observed are insignificant catarrhal phenomena (nose congestion, rare dry cough) or their complete absence. A radiograph of the chest reveals signs of bronchitis and focal pneumonia with poor clinical symptomatology. An examination of the liver shows that its size, as well as its aminotransferase activity, has increased. Changes in urine, such as albuminuria and, in some cases, cylindruria,

are frequently reported. Finally, symptoms relating to the vegetative nervous system (hyperemia of the face and the neck, subconjunctival hemorrhage, bradycardia, and persistent tachycardia) can be observed, as can both CNS lesions in the form of serous meningitis and encephalomeningitis in combination with compromise of the bronciopulmonary system, liver, and kidneys.

Diagnostics. Specific diagnostics of the diseases etiologically linked with CE serocomplex viruses could be based on virological testing (using sensitive biological models of newborn mice or cell lines to isolate the strains) or on serological testing.

In the presence of the sera taken from patients during the acute period of the disease (the first 5–7 days) and in 2–3 weeks, the best method of retrospective inspection is a neutralization test. A hemagglutination inhibition test is considerably less sensitive. Both complement-binding reactions and diffuse precipitation in agar have no diagnostic value today. For serological reactions, it is necessary to utilize HKTV, TAHV, and INKV antigens simultaneously. (In reference labs, SSHV antigen should be used as well.) A quadruple (or greater) increase in the titers of specific antibodies or the detection of specific antibodies in the second serological test in their absence in the first test are diagnostic criteria. ELISA for IgG indication and monoclonal antibody capture ELISA (MAC-ELISA) for IgM indication provide good diagnostic opportunities.

Control and Prophylaxis. Supervision of morbidity and of the activity of natural foci linked with CE serocomplex viruses offers the following instructions: (i) Monitor the patient clinically and the disease epidemiologically. (ii) Provide well-timed diagnostics and seroepidemiological investigations. (iii) Track the number and specific structure of mosquito vectors and possible vertebrate hosts.

8.1.4.3 Khurdun Virus

History. Khurdun virus (KHURV), strain LEIV-Ast01-5 (deposition certificate N 992, 04.11.2004, in the Russian State Collection of Viruses), was isolated from a pool of internal parts of the coot (*Fulica atra*; order Gruiformes, family Rallidae), collected August 3, 2001, in natural biomes in the western part of the Volga River delta, in Khurdun tract, Ikryaninsky District, Astrakhan region.[1] Later, nine more strains of KHURV were isolated from *F. atra* and the cormorant *Phalacrocorax pygmaeus*; order Pelecaniformes: family Phalacrocoracidae) in 2001–2004 (Figure 8.32).

At least six viruses associated with birds have been shown to circulate in the Volga River estuary.[2,3] KHURV has not been identified by any serological method,[1] including sera against viruses of the Flaviviridae, Togaviridae, Bunyaviridae, and Orthomyxoviridae families.[4]

Taxonomy. The genome of KHURV was sequenced, and phylogenetic analysis revealed that it is a new representative of the *Orthobunyavirus* genus (Figures 8.33–8.35).[5] The genome consists of three segments of ssRNA with negative polarity—an L-segment (6,604 nt), an M-segment (3,161 nt), and an S-segment (950 nt)—and has only 25–32% identity with those of other orthobunyaviruses. The terminal 3′- and 5′-sequences of KHURV genome segments, determined by rapid amplification of cDNA ends, are canonical for the orthobunyavirus (3′-UCAUCACAUG and CGTGTGATGA-5′).[6]

The L-segment of KHURV has a single ORF (6,526 nt) that encodes RdRp (2,174 aa). The similarity of KHURV RdRp with those of the orthobunyaviruses is 32%, on average. The similarity of the conservative polymerase domain III (A, B, C, D, and E motifs) [7] in RdRp reaches 62% (in BUNV).

The M-segment of KHURV is shorter than those of the orthobunyaviruses (3,161 nt vs. 4,451 nt for BUNV). The M-segment of KHURV

TABLE 8.20 Basic Differential Features of the Influenzalike Diseases Caused by CE Serocomplex Viruses, Enteroviruses, and Acute Respiratory Viruses

Symptom	Influenzalike form of the diseases caused by CE serogroup viruses	Diseases caused by enteroviruses	Influenza	Parainfluenza	Respiratory–syncytial disease
1	2	3	4	5	6
Epidemiological peculiarities	Sporadic morbidity during summer period (July–August)	Sporadic cases and outbreaks in organized collectives during summer–autumn period	Wide outbreaks and epidemics during autumn–winter period	Increased morbidity during autumn–spring period	Sporadic cases during autumn–spring period (often with worsening of chronic respiratory–syncytial disease against the background of an influenza epidemic)
Period of epidemiological activity[a]					
Onset of the disease	Acute	Acute	Acute, often sudden	Gradual, starting with catarrhal phenomena	Gradual, in some cases acute
Leading symptom	Toxicosis	Toxicosis	Toxicosis	Catarrh	Bronchitis, bronchiolitis
Level of toxicosis	Expressed	Expressed, sometimes moderate	Expressed, sometimes hypertoxicosis	Insignificant or absent	As a rule, poorly expressed
Temperature	High from the very beginning, but short term	High, often two waves	High, short term	Subfebrile, seldom high	More often subfebrile
Meningism	Often expressed from the very beginning	Possible	Could be expressed, as a rule, in severe cases	Absent	Absent
Cough	Dry, rare	As a rule, absent	Dry, painful, tracheitis	Dry, with laryngitis phenomena	Dry, paroxysmal, unproductive
Rhinitis	Nose congestion	Is not characteristic	Dryness of a mucous membrane, poorly serous separated	Swelling of a mucous membrane, plentifully separated	As a rule, absent
Scleritis	Moderate	Moderate	Moderate with cyanosis starting from second to third day of the disease	Moderate	Absent
		Hyperemia			Moderate hyperemia

(*Continued*)

TABLE 8.20 (Continued)

Symptom	Influenzalike form of the diseases caused by CE serogroup viruses	Diseases caused by enteroviruses	Influenza	Parainfluenza	Respiratory–syncytial disease
1	2	3	4	5	6
Change of a mucous membrane of fauces	Hyperemia with pharyngitis phenomena		Hyperemia with cyanosis, discrete hemorrhages	Diffuse hyperemia	
Bronchitis	Often expressed	Absent	Seldom expressed at the early stage	Often expressed	Leading symptom
Pneumonia	Lobular pneumonia at the early stage	Not described	Complications	Complications	Complications
Radiological data from researching lungs	Strengthening of vascular and bronchi–lung outlines	Not described	Strengthening of vascular outlines	As a rule, absent	Strengthening of bronchi–lung outlines with cellular structure
Stomachache	Moderate, seldom	For the majority of patients	Absent	Absent	Absent
Liquid stool	Possible, not often	Possible, not often	Absent	Absent	Absent
Increase in size of liver	Minor, seldom	Minor, seldom	Absent	Absent	Absent
Increase in size of spleen	Absent	Minor	Absent	Absent	Absent
Peripheral blood	Normocytosis, rapid erythrocyte sedimentation speed	Normocytosis, turn to leukopenia, rapid erythrocyte sedimentation speed	Normocytosis, turn to leukopenia	Normocytosis	Normocytosis, moderate leukocytosis
Changes in the urine	Moderate albuminuria, cylinderuria, changed erythrocytes in the beginning of the disease	Seldom in case of severe disease	Albuminuria, cylinderuria in case of severe disease	Absent	Absent

[a]*Designations:*


Winter;


Spring;


Summer;


Autumn.

TABLE 8.21 Basic Differential Features of Serous Meningitis Caused by CE Serocomplex Viruses and Other Viruses

Symptom	Serous meningitis caused by CE serocomplex viruses	Serous meningitis caused by enteroviruses	Meningitis form of TBE	Meningitis caused by parotitis	Lymphocytic choriomeningitis
1	2	3	4	5	6
Epidemiological peculiarities	Sporadic morbidity during summer, with July–August peak	Sporadic outbreaks (more often among children) during summer–autumn period	Sporadic cases and outbreaks on natural-foci territories during spring–summer	Sporadic morbidity during winter–spring period	Sporadic cases (outbreaks are possible) during winter–spring period
Period of epidemiological activity[a]					
Transmission	Mosquito borne	Airborne and fecal–oral	Tick borne, alimentary	Airborne	Airborne and fecal–oral
Leading syndrome	Intracranial hypertension	Intracranial hypertension	Meningitis	Intracranial hypertension	Meningitis, intracranial hypertension
Temperature	High, starting from the first day of the disease	High	High, often in two waves	High	High, wavelike
Headache	Expressed	Expressed	Sharp	Expressed	Excruciating
Meningeal signs	As a rule, moderate (often dissociated)	Moderately expressed	Clearly expressed	Expressed	Expressed
Emesis	Repeated, but not frequent	Frequent	Frequent	Frequent	Frequent
Bronchitis	Often expressed	Absent	Seldom expressed	Absent	Possible
Pneumonia	Lobular pneumonia at the early stage is possible	Absent	Lobular pneumonia during the acute period, hypostatic pneumonia during the late period	Absent	Possible
Increase in size of liver	Often	In some cases	Often	Seldom	In some cases
Increase in size of spleen	Absent	Seldom	Absent	Absent	Seldom
Rash	Papular, seldom	Polymorphic, spotty–papular (10–25% of patients), often rich	Not typical	Not described	Not described

(*Continued*)

TABLE 8.21 (Continued)

Symptom	Serous meningitis caused by CE serocomplex viruses	Serous meningitis caused by enteroviruses	Meningitis form of TBE	Meningitis caused by parotitis	Lymphocytic choriomeningitis
1	2	3	4	5	6
Stomachache	Seldom	Rarely	Rarely	Rarely	In a few cases
Spinal liquid	Normal or decreased protein concentration, lymphocytosis (often in three-digit range, up to 500 cells)	Normal or decreased protein concentration, lymphocytic pleocytosis during the early stage, mixed and not high	Increased protein concentration, mixed cytosis	Increased protein concentration, high lymphocytic cytosis	Increased protein concentration, high lymphocytic cytosis
Changes in conjunctiva of eye	Plethora of expanded veins during acute period (about 30% of cases)	More than seldom	Typical	More than seldom	Hypostasis of optic nerve (about 50% of cases)
Peripheral blood	Normocytosis, rapid erythrocyte sedimentation speed	Normocytosis, shift to the left	Leukocytosis; more rarely, leukopenia	Normocytosis turning to leukopenia, lymphocytosis, rapid erythrocyte sedimentation speed	Lymphocytosis, rapid erythrocyte sedimentation speed

[a]*Designations:*

 *Winter;*  *Spring;*  *Summer;*  *Autumn.*

has a single ORF (2,997 nt), which encodes a polyprotein precursor (998 aa) of the envelope glycoproteins Gn and Gc. Apparently, the M-segment of KHURV does not contain a nonstructural protein NSm, which is common in most of the orthobunyaviruses.[8,9] The putative cleavage site between Gn and Gc of KHURV was found in position 319/320 aa (ASA/EN). This site corresponds to the cleavage site between NSm/Gc of the orthobunyaviruses and the conservative amino acid A/E (VAA/EE in BUNV). The size of the Gn protein of KHURV is the same as that of the other orthobunyaviruses, 320 aa. The similarity of KHURV Gn is 23–29% aa, on average, to that of the other orthobunyaviruses (28.5% aa to BUNV). The size of the Gc protein of KHURV, 679 aa, is shorter than that of the other orthobunyaviruses (cf. 950 aa for the Gc protein of BUNV). The C-part (approx. 500 aa) of the Gc protein, which includes the conservative domain G1 (pfam03557), has about 30% aa similarity to the C-part in the other orthobunyaviruses, whereas the N-part (approximately 170 aa) has no similarity to that of any proteins in the Genbank database.

The S-segment of KHURV is 950 nt in length and encodes a nucleocapsid protein (227 aa). The similarity of the N protein to that of the orthobunyaviruses is 22–26 aa%. Most orthobunyaviruses have an additional ORF that encodes

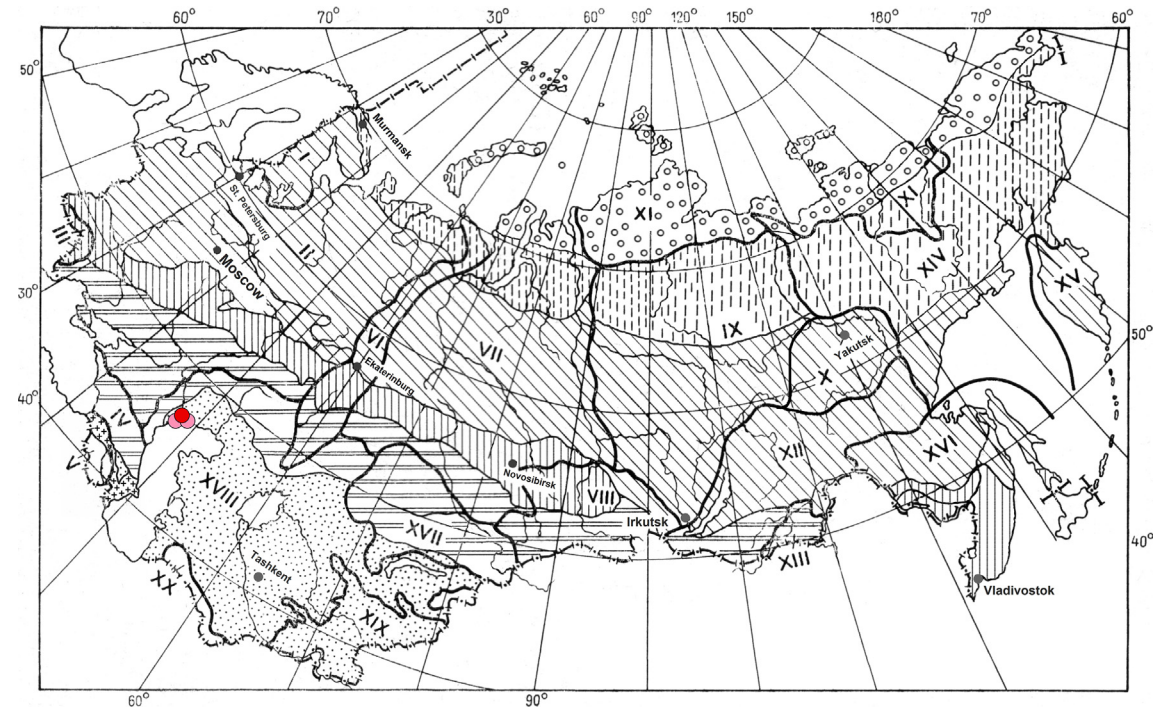


FIGURE 8.32 Places of isolation of KHURV (family Bunyaviridae, genus *Orthobunyavirus*) in Northern Eurasia. Red circle: strains LEIV-Ast01-5 of KHURV with completely sequenced genome; Pink circles: strains of KHURV identified by serological methods. (See other designations in Figure 1.1.)

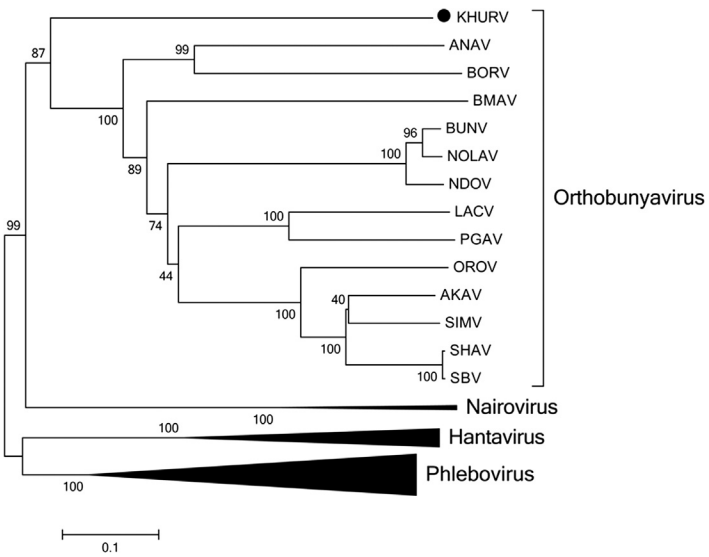


FIGURE 8.33 Phylogenetic tree for nucleocapsid protein (S-segment) of the viruses belonging to the *Orthobunyavirus* genus.

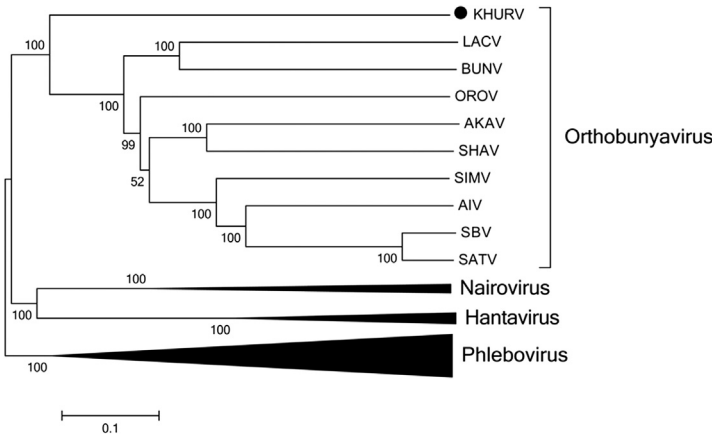


FIGURE 8.34 Phylogenetic tree for Gn/Gc precursor protein (M-segment) of the viruses belonging to the *Orthobunyavirus* genus.

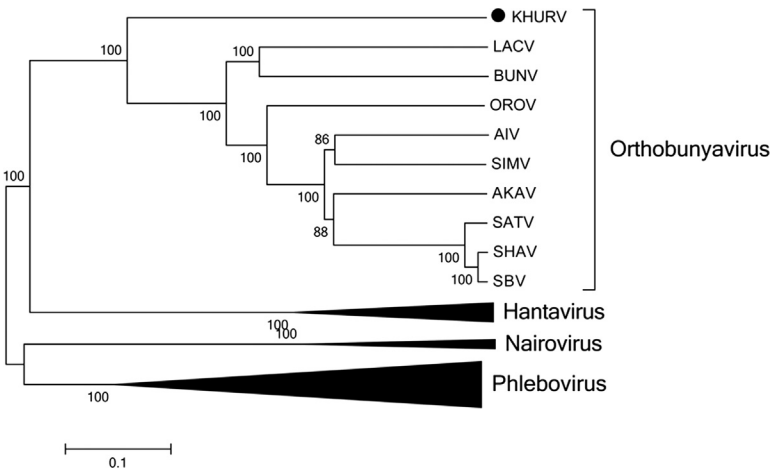


FIGURE 8.35 Phylogenetic tree for RdRp-protein (L-segment) of the viruses belonging to the *Orthobunyavirus* genus.

the nonstructural protein NSs. This protein is considered to be a factor in the pathogenicity of the orthibunyaviruses to vertebrates, because it has the ability to block the action of the interferon pathway. Some orthobunyaviruses (Anopheles A, Anopheles B, Tete serogroups) do not encode any NSs protein.[9] Phylogenetic analysis of full-length sequences showed that KHURV forms a distinct external lineage of the *Orthobunyavirus* genus (Figures 8.33–8.35).

Arthropod Vectors. There are no known arthropod vectors of KHURV; the virus has been isolated only from birds. More than 20,000 *Aedes*, *Culex*, and *Anopheles* mosquitoes were examined during the survival period for arboviruses in this region, and no KHURV isolations were obtained. The family Ceratopogonidae of biting midges is a potential vector of KHURV, but these insects have not been surveyed.

Vertebrate Hosts. All isolations of KHURV were obtained from birds. Nine strains of the virus were isolated from coots (*Fulica atra*). (One hundred seventeen birds were examined and were found to have an infection rate of 8.5%.) One strain was isolated from the pygmy cormorant (*Phalacrocorax pygmaeus*). (Two hundred eighty-nine cormorants, mostly *Ph. carbo*, were examined and were found to have an infection rate of 0.3%.)

8.1.5 Genus *Phlebovirus*

The *Phlebovirus* genus comprises about 70 viruses that are divided into two main groups based on their ecological, antigenic, and genomic properties: mosquito-borne viruses and tick-borne viruses.[1,2]

The genome of the phleboviruses consists of three segments of ssRNA with negative polarity: L (about 6,500 nt), M (about 3,300–4,200 nt), and S (about 1,800 nt) (Figure 8.36). In general, the structure of the genome is the same for mosquito-borne and tick-borne phleboviruses, but the M-segment is shorter in tick-borne viruses and it does not encode the nonstructural protein NSm.[3] Phylogenetically, the phleboviruses can be divided into two branches in accordance with their ecological features. The tick-borne phleboviruses comprise viruses of the Uukuniemi group, the Bhanja group, and the two novel related viruses severe fever with thrombocytopenia syndrome virus (SFTSV) and Heartland virus (HRTV), which form separate clusters and are unassigned to any group

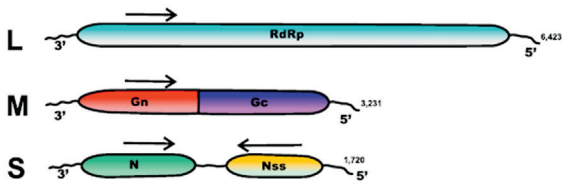


FIGURE 8.36 Structure of genome of UUKV (family Bunyaviridae, genus *Phlebovirus*). *Drawn by Tanya Vishnevskaya*

(Figures 8.37–8.39). The UUKV serogroup currently comprises 15 viruses, but the status of some of them may be revised with the accumulation of more genomic and serological data.

8.1.5.1 Bhanja Virus and Razdan Virus (var. Bhanja virus)

History. Bhanja virus (BHAV) was originally isolated from *Haemaphysalis intermedia* ticks that were collected from a paralyzed goat in the town of Bhanjanagar in the Ganjam district in the state of Odisha, India, in 1954 and was assigned to the unclassified bunyaviruses.[1] In Europe, the first isolation of BHAV was obtained from adult *Haem. punctata* ticks collected in Italy (1967) and then in Croatia and Bulgaria.[2,3,4] Palma virus (PALV), a virus closely related to BHAV, was isolated from *Haem. punctata* ticks in Portugal.[5] Two viruses—Kismayo virus (KISV) and Forécariah virus (FORV)—antigenically related to BHAV were isolated in Africa.[6,7] These viruses have been merged into the Bhanja group on the basis of their serological cross-reactions.[8,9] In Transcaucasia, BHAV (strain LEIV-1818Az) was isolated from Ixodidae ticks *Rhipicephalus bursa* collected from cows in Ismailli District, Azerbaijan, in 1972 (Figure 8.40). Closely related to BHAV, RAZV (strain LEIV-2741Arm) was isolated from ixodid ticks *Dermacentor marginatus* collected from sheep near the village of Solak in the Razdan district of Armenia (Figure 8.40).[10,11] Serological methods (detection of antibodies in animals and humans) have shown that BHAV circulates in many Mediterranean countries, the Middle East, Asia, and Africa.[12,13]

Taxonomy. Viruses of the BHAV group are not antigenically related to any of the other bunyaviruses, but they were assigned to the *Phlebovirus* genus on the basis of a genetic analysis of their full-length genome sequences.[14,15,16] Weak antigenic relationships were found between BHAV and SFTSV, a novel phlebovirus isolated in China.[16,17,18] SFTSV, in its turn, is antigenically related to viruses of the Uukuniemi group.[19] The genomes of certain viruses of the

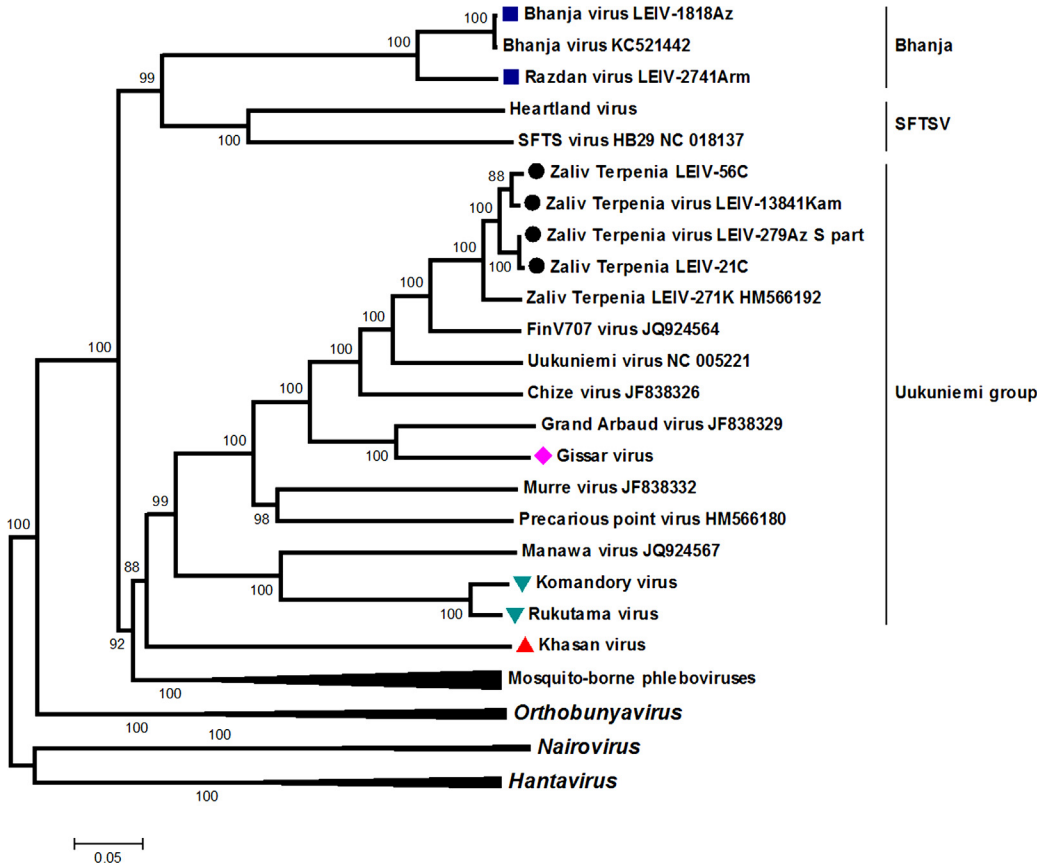


FIGURE 8.37 Phylogenetic analysis of S-segment of viruses belonging to the *Phlebovirus* genus.

Bhanja group were sequenced;[14,15,16] the size and structure of their genomes correspond to those of the tick-borne phleboviruses. The L-segment of BHAV (6,333 nt) encodes RdRp, which has a 34.8% aa identity with that of UUKV and 31.8% aa with that of Rift Valley fever virus (RVFV) (Table 8.22). The structure of the RdRp of the viruses with a negative genome includes three main domains. Domains I and II are formed around the conservative dipeptides HD and PD, respectively.[20] These dipeptides in the RdRp of BHAV are located in positions HD82 and PD113. (They were respectively found to be located in positions HD80 and PD111 in both UUKV and RVFV.)

The third, catalytic, domain, Domain III, consists of preA, A, B, C, D, and E motifs. The preA motif is formed around the conservative position K924 in BHAV (K919 and K922 in RVFV and UUKV, respectively) and includes the site of binding of genomic RNA (R941MIQFSIELLAR in BHAV; conservative positions R941, Q944, E948, and R952 are bolded). The A motif includes the dipeptide KW, which is conservative for viruses with a negative RNA genome.[20] Viruses of the Bhanja group in this position contain a substitution (TW1000) (Figure 8.41). Substitutions in this site are also found in Gouleako virus, an unclassified bunyavirus.[21]

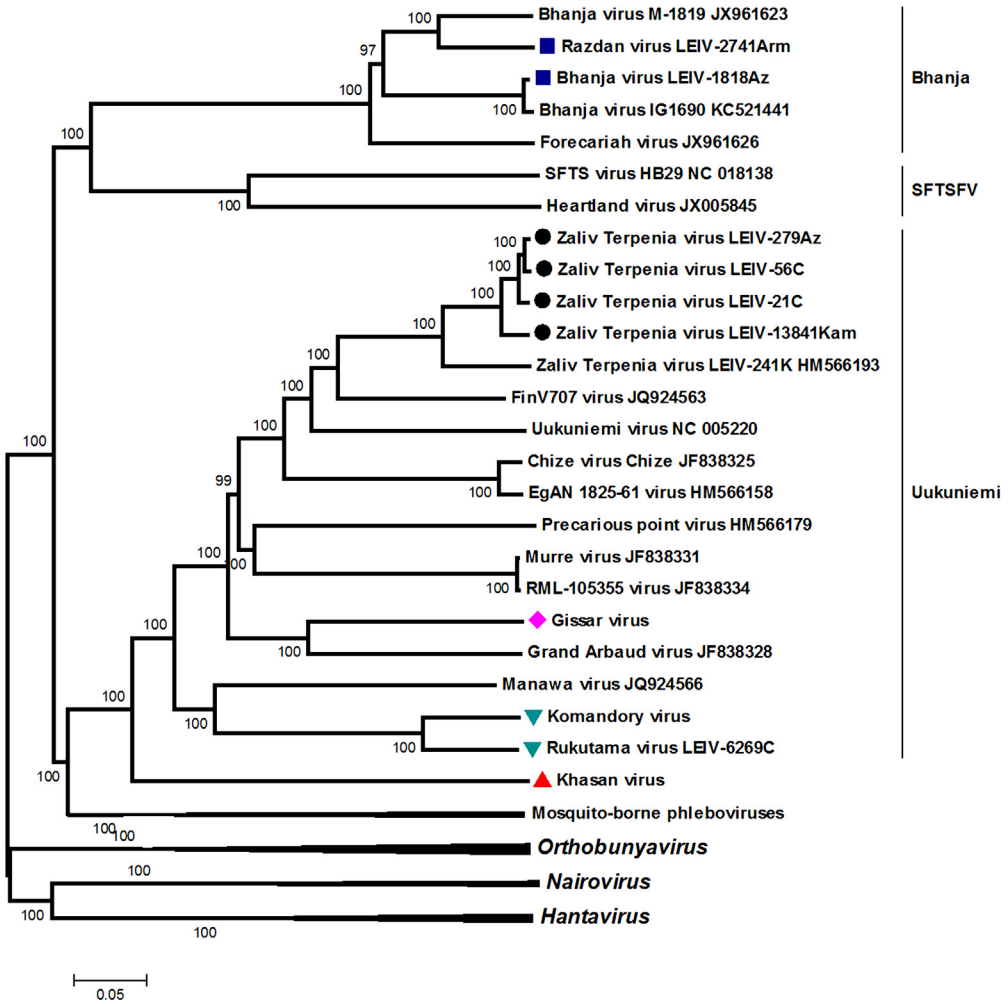


FIGURE 8.38 Phylogenetic analysis of M-segment of viruses belonging to the *Phlebovirus* genus.

The M-segment of BHAV (3,307 nt) encodes a polyprotein precursor (1,069 aa) of the envelope glycoproteins Gn and Gc. Like the M-segments of other tick-borne phleboviruses, that of BHAV has no NSm proteins that are common to mosquitoes-borne phleboviruses. The predicted cleavage site between Gn and Gc proteins has been found by Signal IP software (http://www.cbs.dtu.dk/services) to be in position 559/560 of the polyprotein precursor (motif MHMALC/CDESRL). A dipeptide CD in the cleavage site is also typical for SFTSV and HRTV, which were associated with human disease in China and the United States, respectively.[17,18,22] Other phleboviruses, including UUKV and RVFV, contain a dipeptide CS in this position.

The S-segment (1,871 nt) of BHAV has two ORFs (N and NSs proteins) disposed in opposite orientations (an ambisense expression strategy) and separated by an intergenic spacer (139 nt). The similarity of the nucleocapsid

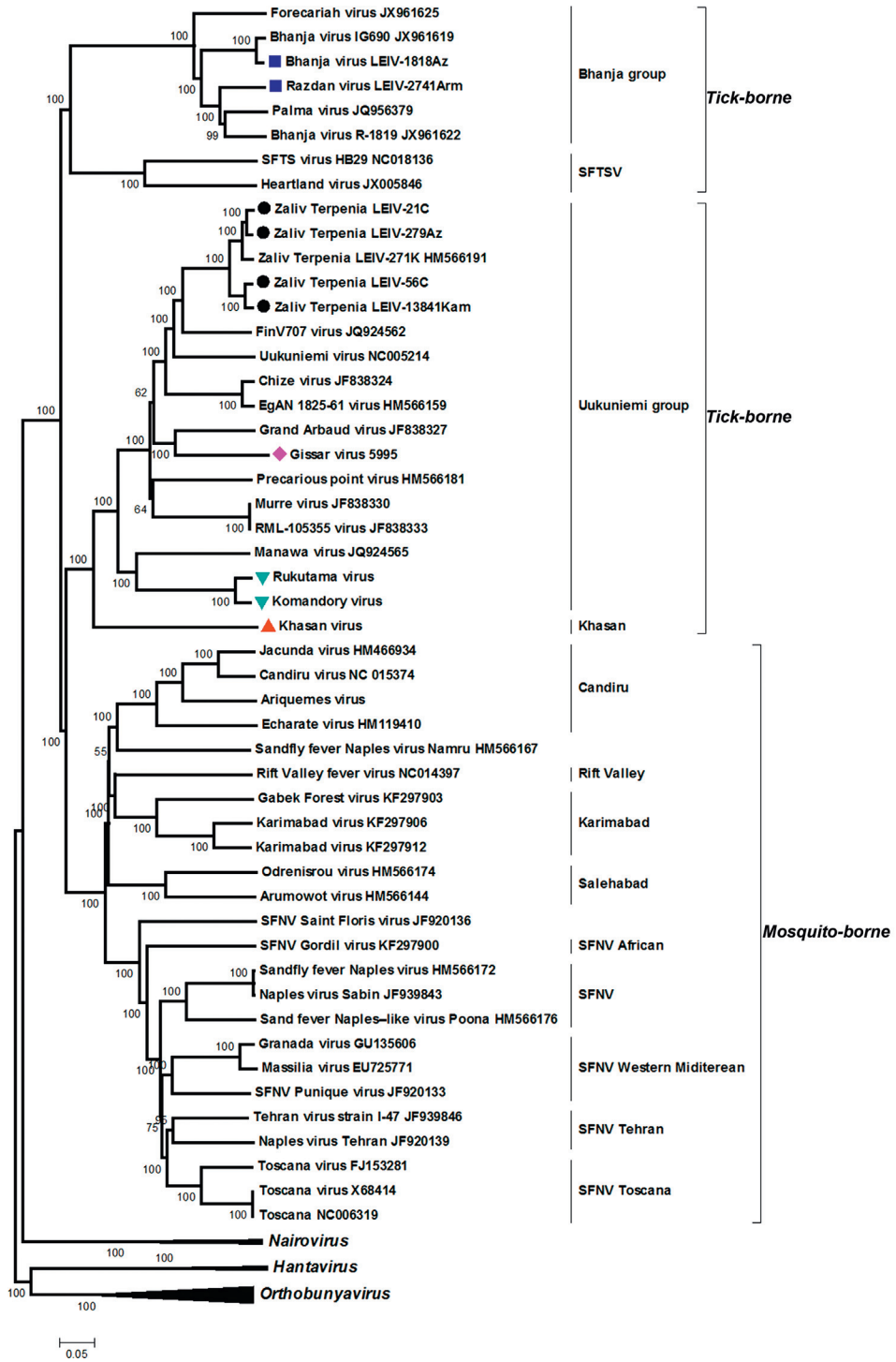


FIGURE 8.39 Phylogenetic analysis of L-segment of viruses belonging to the *Phlebovirus* genus.

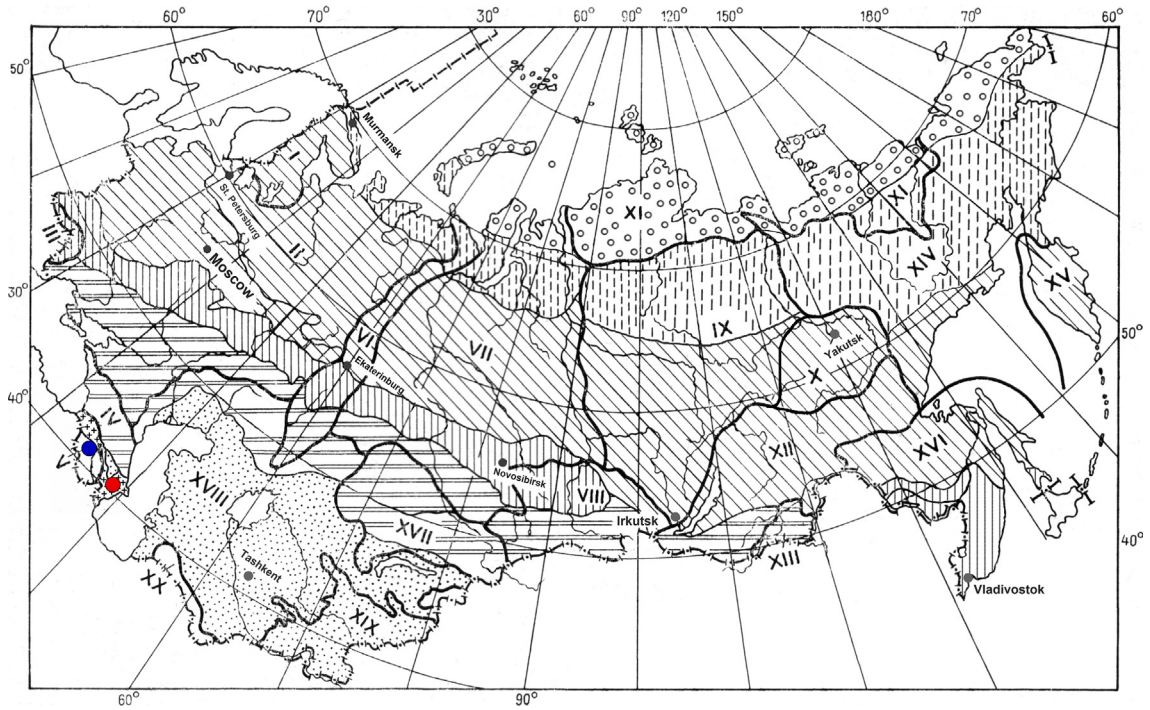


FIGURE 8.40 Places of isolation of BHAV and RAZV (family Bunyaviridae, genus *Phlebovirus*) in Northern Eurasia identified by complete genome sequencing. Red circle: strain LEIV-1818Az of BHAV; Dark-blue circle: strain LEIV-2741Arm of RAZV. (See other designations in Figure 1.1.)

protein (N-protein) of BHAV to that of UUKV is 29.3% and to that of RVFV is 37.4% (Table 8.22).

Phylogenetic analysis has shown that the Bhanja group forms a new separate lineage in the *Phlebovirus* genus (Figures 8.37–8.39).

Arthropod vectors. The main vector of BHAV is Ixodidae ticks. In Europe, BHAV was repeatedly isolated from *Haemaphysalis punctata*, *Haem. sulcata*, and *Dermacentor marginatus*; elsewhere, it has been isolated from *Haem. intermedia*, *Boophilus decoloratus*, *B. annulatus*, *B. geigy*, *Amblyomma variegatum*, *Hyalomma marginatus*, *H. detritum*, *H. dromedarii*, *H. truncatum*, *Rhipicephalus bursa*, and *Rh. appendiculatus*.[12,23]

Vertebrate Hosts. The ungulates, including domestic cows, sheep, and goats, are apparently involved in the circulation of BHAV.[24] Usually, BHAV infection in adult animals is asymptomatic, but it is pathogenic to young ones (lamb, calf, suckling mouse), causing fever and meningoencephalitis.[13,25–27] Experimental infection of rhesus monkeys by BHAV induced encephalitis.[28] Several strains of BHAV were isolated from the four-toed hedgehog (*Atelerix albiventris*) and the striped ground squirrel (*Xerus erythropus*) in Africa. Antibodies have been detected in dogs, roe deer (*Capreolus capreolus*), and wild boars (*Sus scrofa*).[12]

Human Pathology. BHAV infection in human is mainly asymptomatic, but several cases of fever and meningoencephalitis caused by BHAV have been described.[29–31]

8.1.5.2 Gissar Virus

History. Gissar virus (GSRV) was isolated from *Argas reflexus* ticks collected in a dovecote in the town of of Gissar in Tajikistan (38°40′N,

TABLE 8.22 Similarity of Amino Acid Sequences of RAZV and BHAV (Strain LEIV-1818Az) to Those of Certain Phleboviruses (%)

	RdRp (L-segment)		G (M-segment)		N (S-segment)		NSs (S-segment)	
Virus	**RAZV**	**BHAV**	**RAZV**	**BHAV**	**RAZV**	**BHAV**	**RAZV**	**BHAV**
RVFV	32.1	31.8	18.4	19.4	34.3	37.4	13.2	13.2
TOSV	34.4	34.1	16.5	16.8	32.3	35.9	13.9	11.9
AGUV	34.8	34.8	17.3	17.9	33.5	39.8	10.7	11.1
UUKV	34.8	34.8	19.0	19.0	26.3	29.3	13.6	14.0
SFTSV	40.4	40.7	25.3	25.7	40.5	43.2	20.0	19.3
BHAV_IG690	95.9	99.3	89.0	99.2	92.5	99.0	88.8	99.0
BHAV_ibAr2709	94.7	93.7	84.5	86.2	93.2	94.9	87.2	84.0
BHAV_M3811	98.3	96.3	94.9	90.7	94.7	97.1	92.3	86.6
BHAV_R1819	98.2	96.0	93.7	90.1	93.6	96.3	91.7	86.9
PALV	98.1	96.5	92.5	90.5	92.5	96.2	92.7	86.3
FORV	93.9	93.6	84.9	86.2	92.8	95.6	87.5	83.7
BHAV_LEIV-Azn1818	95.8	–	90.3	–	92.5	–	87.9	–
RAZV LEIV-Arm2741	–	95.8	–	90.3	–	92.5	–	87.9

Abbreviations: VFV, Rift Valley Fever virus; TOSV, Toscana virus; UUKV, Uukuniemi virus; AGUV, Aguacate virus; SFTSV, Severe fever with thrombocytopenia syndrome virus; BHAV, Bhanja virus; PALV, Palma virus; FORV, Forécariah virus.

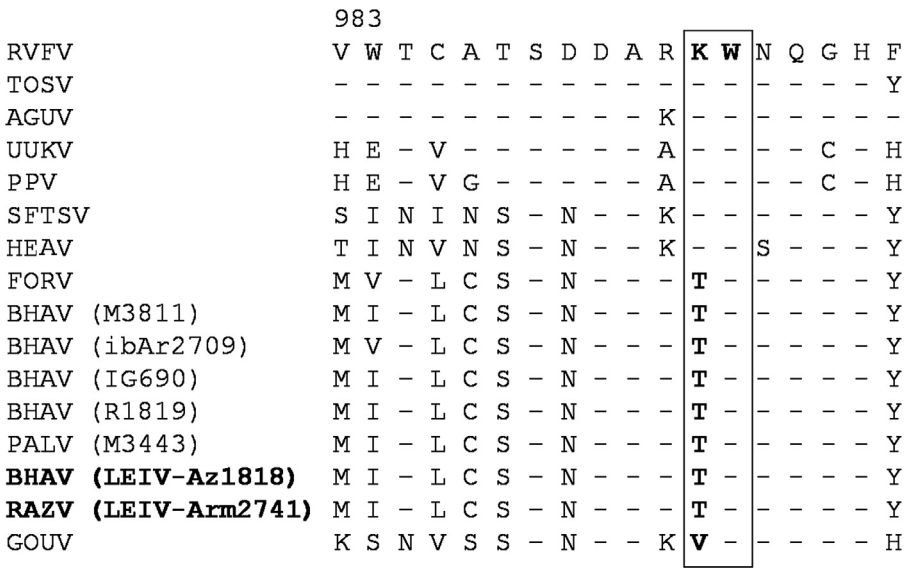


FIGURE 8.41 Alignment of the partial aa sequence of motif A of RdRp of certain phleboviruses. Conservative dipeptide KW is in frame. (RVFV, Rift Valley fever virus; TOSV, Toscana virus; UUKV, Uukuniemi virus; AGUV, Aguacate virus; PPV, Precarious Point virus; SFTSV, Severe fever with thrombocytopenia syndrome virus; HRTV, Heartland virus; BHAV, Bhanja virus; PALV, Palma virus; FORV, Forécariah virus; GOUV, Gouleako virus.)

68°40′E; Figure 8.42). With the use of electronic microscopy, GSRV has been classified into the Bunyaviridae family.[1–3]

Taxonomy. The genome of GSRV (strain LEIV-5995Taj) has been sequenced.[4] Phylogenetic analysis shows that GSRV is a member of the *Phlebovirus* genus of the Uukuniemi group (Figures 8.37–8.39). GSRV is closely related to Grand Arbaud virus (GAV), which was isolated from a pool of *Argas reflexus* ticks collected in a dovecote near Gageron in Arles in the Rhône River delta in the Camargue region of France in 1966.[5] GAV is classified as virus belonging to the Uukuniemi group.[6] The identity of the nucleotide and amino acid sequences of GSRV and GAV is 76% nt for the S-segment (94% aa for the nucleocapsid protein), 73% nt for the M-segment (82% aa for the polyprotein precursor of Gn/Gc), and 76% nt for the L-segment (87.5% aa for RdRp).

Arthropod Vectors. Regardless of their geographical distribution, GSRV and GAV occupy a narrow ecological niche associated with ticks (*Argas reflexus*) and birds (most likely, pigeons (Columbidae)). In laboratory experiments, GSRV reproduced in *A. reflexus* ticks in 30 days with titers up to 2.0 $\log_{10}(LD_{50})/20$ mcL.[7]

The distribution of *Argas reflexus* ticks is limited between 51°N on the north and 31°N on the south. The *A. reflexus* metamorphosis cycle is about three years. The ticks inhabit pigeons' habitats, which are also used by other birds, such as swallows and swifts. *A. reflexus* larvae were found in Europe on a rock swallow (*Ptyonoprogne rupestris*), in Egypt on a little owl (*Athene noctua*), in Israel on a rock dove (*Columba livia*) and a fan-tailed raven

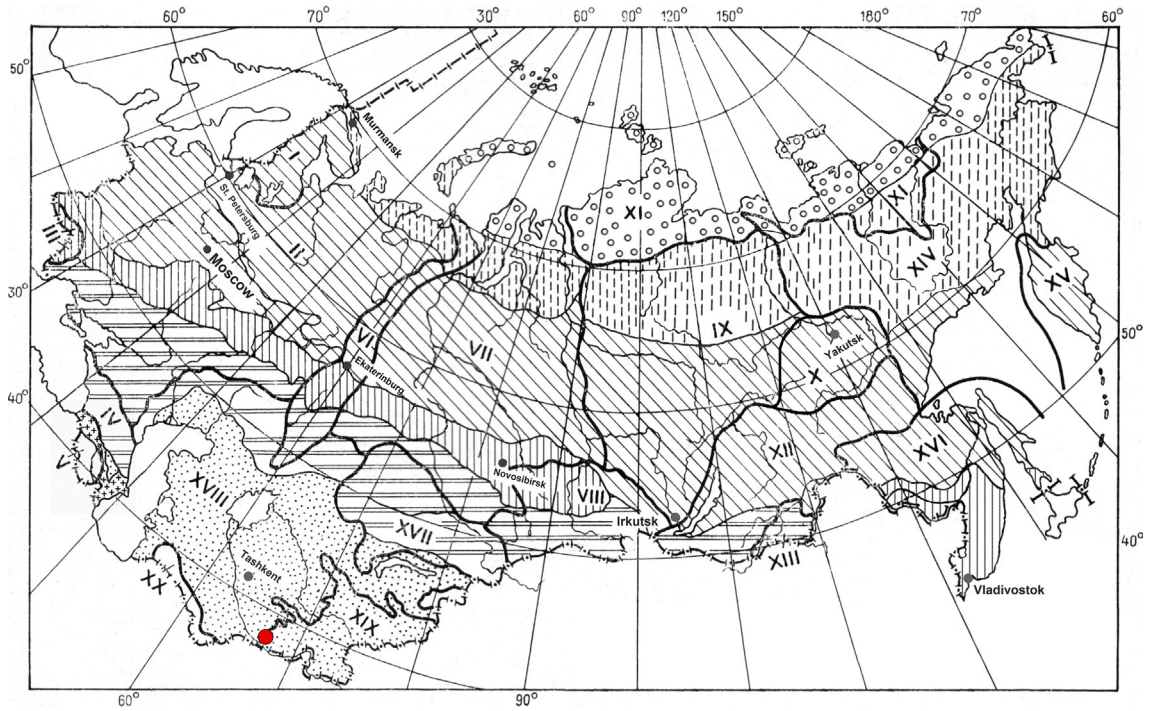


FIGURE 8.42 Place of isolation of GSRV (family Bunyaviridae, genus *Phlebovirus*) in Northern Eurasia. Red circle: prototype strain of GSRV/LEIV-5295-Taj with completely sequenced genome. (See other designations in Figure 1.1.)

(*Corvus rhipidurus*), and in Crimea on the western jackdaw (*Corvus monedula*). The mass reproduction of mites in a dovecote has a negative impact on pigeons' bereeding behavior. Worse, at night the ticks can go down to the living space and bite people if the dovecote is built into a house.[8]

Vertebrate Hosts. The main vertebrates involved in the circulation of GSRV are apparently birds, particularly the Columbidae. In laboratory experiments, GSRV was isolated from the blood of small doves (*Streptopelia senegalensis*) 5, 9, 22, and 30 days after infection. The virus titer in the blood was 1.5–2.5 $\log_{10}(LD_{50})/20$ mcL, on average. Serological examination of birds in Tajikistan found antibodies to GSRV 2% of doves (*Columba livia*).[7]

8.1.5.3 Khasan Virus

History. Khasan virus (KHAV) was isolated from *Haemaphysalis longicornis* ticks collected from spotted deer (*Cervus nippon*) in 1971 in the forest in Khasan District in the south of Primorsky Krai, Russia (Figure 8.43).[1] Morphologic studies showed that KHAV belongs to the Bunyaviridae family. The virion of KHAV has structural elements (filaments up to 10 nm) that are typical for UUKV, but no antigenic relationships between KHAV and UUKV (as well as Zaliv Terpeniya virus, ZTV) have been found.[1,2] In a complement-fixation test, KHAV did not react with serum used in the identification of certain bunyaviruses, so it was categorized in with the unclassified bunyaviruses.[3]

Taxonomy. The genome of KHAV (strain LEIV-Prm776) was sequenced, and the virus

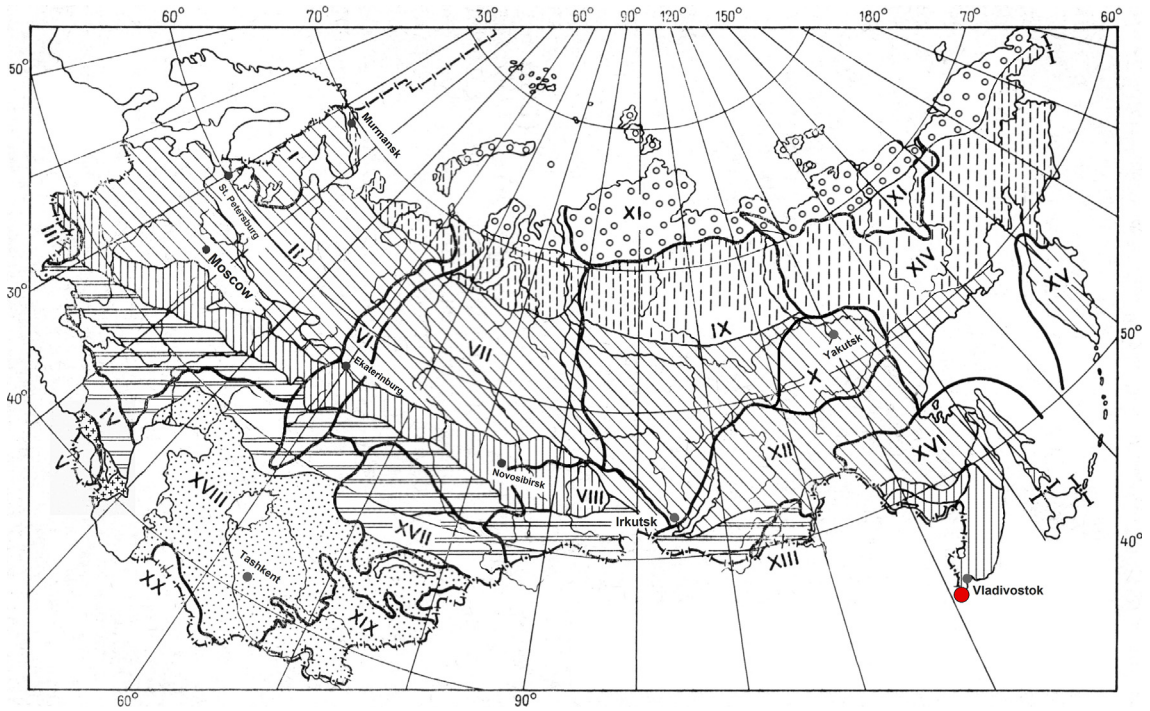


FIGURE 8.43 Place of isolation of KHAV (family Bunyaviridae, genus *Phlebovirus*) in Northern Eurasia. Red circle: prototype strain KHAV/LEIV-Prim776 with completely sequenced genome. (See other designations in Figure 1.1.)

was classified into the *Phlebovirus* genus of the Bunyaviridae family.[4] The genome of KHAV consists of three segments of ssRNA whose size and ORF structure correspond to the size and ORF structure of the other tick-borne phleboviruses. A full-length pairwise comparison of L-segments revealed a 53.1% nt identity between KHAV and UUKV and 45.3% between KHAV and RVFV. The predicted amino acid sequence of RdRp of KHAV has 48.6% and 35.3% aa identities with UUKV and RVFV, respectively. As in other tick-borne phleboviruses, the M-segment of KHAV does not contain any NSm protein. The similarity between the M-segments of KHAV and UUKV is 45.6% nt, and that between the polyprotein precursors of KHAV and UUKV is 35.9% aa. The S-segment of KHAV has 35% nt (25.5% aa for the N-protein) identity, on average, with that of the Uukuniemi group viruses and 35% nt (27.8% aa), on average, with the mosquito-borne phleboviruses.

On phylogenetic trees constructed on the basis of the alignment of full-length genome segments, KHAV forms a distinct branch external to the Uukuniemi group viruses (Figures 8.37–8.39). At least 14 viruses with unsettled taxonomy are included in the Uukuniemi group.[5] Some of them can be considered variants of the species UUKV, Manawa virus (MWAV), Precarious Point virus (PPV), and GAV. Two tick-borne phleboviruses, SFTSV and HRTV, are more closely related to the Bhanja group than the Uukuniemi group.[6,7]

Arthropod Vectors. Only a single isolation of KHAV was ever obtained, and the ecology of the virus has not been studied. *Haemaphysalis longicornis* ticks, from which KHAV was isolated, are distributed in the Far East of Russia, the northeastern part of China, the northern islands of Japan, Korea, Fiji, New Zealand, and Australia.[8] *Haem. longicornis* ticks also are the main vector of SFTSV (oterwise called Huaiyangshan virus, HYSV), which caused a large outbreak of febrile illness with a high mortality rate (30%) in 2009 in China.[9]

Vertebrate Hosts. The principal vertebrate host of KHAV is unknown. KHAV was isolated from ticks collected on deer.[1] *Haemaphysalis longicornis* ticks are repeatedly found on cows, goats, horses, sheep, badgers, and dogs.[8]

8.1.5.4 Sandfly Fever Naples Virus and Sandfly Fever Sicilian Virus

History. The sandfly fever virus group includes Naples and Sicilian subtypes.[1] Epidemics of the comparatively mild acute febrile disease of short duration brought on by these viruses in countries bordering the Mediterranean have been known since the Napoleonic Wars.[2] The same disease was common among newly arrived Austrian soldiers on the Dalmatian coast each summer.[3] Experiments conducted by an Austrian military commission proved that the disease was caused by a filterable agent in the blood of patients and that the sandfly *Phlebotomus papatasi* can serve as a vector to transmit the disease.[4] During World War II, epidemics occurred among troops in the Mediterranean and two antigenically distinct strains were isolated from the blood of patients in 1943 in Sicily and Naples. These strains have been designated the sandfly fever Sicilian virus (SFSV) and sandfly fever Naples virus (SFNV), with prototype virus TOSV.[5,6] Dr. A. Sabin gave a clinical description of the disease and demonstrated that immunity developed to one type of virus does not protect from infection caused by the other type. Later, several viruses related to SFNV (Anhanga (ANHV), Bujaru (BUJV), Candiru (CDUV), Chagres (CHGV), Icoaraci (ICOV), Itaporanga (ITPV), and Punta Toro (PTV)) were isolated from humans and rodents in South America.[2,3,7] To date, viruses related to TOSV have been found in all regions of the world, including the Palearctic, Neotropical, Ethiopian, and Oriental zoogeographical regions.[2] The prototype strain of TOSV was

isolated from *Phlebotomus papatasi* sandflies in 1971 in Monte Argentario in central Italy.[8] Two viruses antigenically related to TOSV—Karimabad virus (KARV) and Salehabad virus (SALV)—were isolated from *Phlebotomus* flies collected in 1959 near Karimabad village and Salehabad village, respectively, in Iran.[9,10] Several related viruses were isolated in the Mediterranean: sandfly fever Cyprus virus (SFCV;[11] Adria virus (ADRV, Salehabad-like), isolated in Saloniki (alternatively, Thessaloniki), Greece;[12] and Massilia virus, isolated near Marseilles, France.[13] Epidemic outbreaks of sandfly fever whose agents could not be typified occurred in some central Asian countries and in Crimea during and after World War II and in Turkmenistan after the devastating earthquake of 1948. Antibodies to SFSV, SFNV, and KARV were found in the blood of humans in Tajikistan, Azerbaijan, and Moldova.[14] Antibodies were also found in wild animals in Turkmenistan: the great gerbil (*Rhombomys opimus*), the long-clawed ground squirrel (*Spermophilopsis leptodactylus*), and the hedgehog (*Erinaceus auritus*). Three strains of SFNV and two strains of SFSV were isolated in 1986–1987 from the blood of patients in Afghanistan.[14,15]

Taxonomy. The genome of TOSV consists of three segments of negative-polarity ssRNA: L-segment (6,404 nt in length), M-segment (4,214 nt) and S-segment (1,869 nt). Phylogenetic analysis revealed that viruses of the SFNV complex are divided into five genetic clades that differ in their geographical distribution: (i) from Africa (Saint Floris virus and Gordil virus (GORV)); (ii) from the western Mediterranean (Punique virus (PUNV), Granada virus (GRV), and Massilia virus); (iii) TOSV; (iv) viruses from Italy, Cyprus, Egypt, and India; (v) strains from Serbia and Tehran virus.[16]

Distribution. SFNV and SFSV are distributed over those areas of the southern parts of Europe and Asia, and over those areas of Africa, which are within the range of the vector.[15,17–22] TOSV is distributed over Italy; Spain; Portugal; the south of France; Slovenia; Greece, including the Ionian Islands: Cyprus; Sicily; and Turkey.[13,17,23–32] Both the Naples and Sicilian strains were isolated from the blood of patients with febrile illness in the vicinity of Aurangabad, Maharashtra state, in northern India. Sandfly virus fever also circulates in western India, as well as in Pakistan.[33] The cocirculation of two TOSV genotypes was uncovered in the southeast of France.[13,15,33] A case of disease associated with TOSV befell a tourist returning from Elba to Switzerland in 2009, and another struck an American tourist returning from Sicily the same year.[27] TOSV from France is genetically different from that in Spain.[3,13,33,34] Periodic outbreaks of sandfly fever occurred in the first half of the twentieth century in some central Asian republics, Transcaucasia, Moldova, and Ukraine.

Arthropod Vectors. The primary vector of SFNV and SFSV is *Phlebotomus Papatasi*; for TOSV, the primary vectors are *Ph. perniciosus* and *Ph. perfiliewi*. The viruses can be transmitted by the transovarial route and therefore may not require amplification in wild vertebrate hosts.[35] The infection rate of sandflies can reach 1:220.[36] The active period of *Phlebotomus* in the southern part of Europe lasts from May to September. Sandflies are peridomestic; the immature stages feed on organic matter in soil and do not require water, but are sensitive to desiccation and therefore are often found in association with humid rodent burrows.

Vertebrate Hosts. The main vertebrates involved in the circulation of SFNV are rodents, particularly the great gerbil (*Rhombomys opimus*) and the long-clawed ground squirrel (*Spermophilopsis leptodactylus*), as well as a hedgehog (*Erinaceus auritus*). The great gerbil is distributed over areas ranging from near the Caspian Sea to the arid plains and deserts of central Asia. The northern border of the animal's distribution is from the

mouth of the Ural River on northward to the Aral Karakum and Betpak-Dala deserts, to the southern coast of Lake Balkhash, and thence to northern China and Inner Mongolia. The habitats of *Rh. opimus* are sandy and clayey deserts. TOSV was isolated from the brain of the bat *Pipistrellus kuhlii*.[8]

Animal and Human Pathology. Sandfly virus fever does not cause disease in domestic or wild animals. The hosts of *Phlebotomus* sandflies are usually rodents, which may develop antibodies. Over 100 human experimental volunteers were infected at the time of World War II.[36,37] The incubation period is between 2 and 6 days, and the onset of fever and headache in those patients was sudden. Nausea, anorexia, vomiting, photophobia, pain in the eyes, and backache were common and were followed by a period of convalescence with weakness, sometimes diarrhea, and usually leucopenia. Viremia was present 24 h before and 24 h after the onset of fever.[37] TOSV was established as the cause of one-third of previously undiagnosed human aseptic meningitis and encephalitis cases examined in central Italy. SFCV was associated with a large outbreak in the Ionian Islands of Greece.[28] ADRV is associated with serious illness with tonic muscle spasms, convulsions, difficulty urinating, and temporary loss of sight. Human disease frequently goes unrecognized by local health-care workers. Studies of antibodies in people indicate that the most infections occur in children. When large numbers of unimmunized adults are introduced into an endemic area, the incidence of disease can be high. Human exposure to sandflies can be reduced by repellents, air-conditioning, and screens on windows. Because sandflies have a flight range of not more than 200 m, human habitats can be constructed at a distance from potential domestic sandflies' breeding places, such as chicken houses and quarters for other farm animals.[19]

8.1.5.5 Uukuniemi virus and Zaliv Terpeniya virus

History. UUKV was originally isolated from *Ixodes ricinus* ticks collected in 1959 from cows in southeastern Finland.[1,2] Antigenically similar isolates (strains LEIV-540Az and LEIV-810Az) have been obtained from blackbirds (*Turdus merula*) and *I. ricinus* ticks collected in the foothills of the Talysh Mountains in the southeast of Azerbaijan in 1968 and 1969, respectively.[3–5] UUKV is distributed in the mid- and southern boreal zones of Fennoscandia and adjacent areas of the Russian Plain. Twelve strains of UUKV were isolated from *I. ricinus* ticks (the infection rate was 0.5%), and one strain from *Aedes communis* mosquitoes, in landscapes in the mideastern region of Fennoscandia.[6,7] Three strains were isolated from *I. persulcatus* ticks collected in Belozersky District, Vologda Region, Russia, in 1979.[8,9] UUKV was also isolated from the mosquitoes *Ae. flavescens* and *Ae. punctor* in the west of Ukraine, as well as at the border between Poland and Belarus.[10,11] Twenty-eight strains of UUKV were isolated from *I. ricinus* ticks collected in Lithuania and Estonia in 1970–1971.[6,7,12–14] UUKV was isolated as well from birds and *I. ricinus* ticks in western Ukraine and Belarus.[11,15,16] In central Europe, UUKV was found in the Czech Republic, Slovakia, and Poland.[17–20]

The prototypical strain LEIV-21C of ZTV was isolated from *Ixodes uriae* ticks collected in 1969 in a colony of common murres (*Uria aalge*) in Tyuleniy Island in Zaliv Terpeniya Bay in the Sea of Okhotsk).[21,22] In accordance with the results of electron microscopy, ZTV was assigned to the Bunyaviridae family. Complement-fixation testing revealed that ZTV is most closely related to UUKV, but the two viruses are easily distinguishable in a neutralization test.[21,22] More than 60 strains of ZTV were isolated from *I. uriae* ticks collected in colonies of seabirds on the shelf and islands

of the Sea of Okhotsk, the Bering Sea, and the Barents Sea (Table 8.23, Figure 8.44).[9,21,23,24] Two strains of ZTV were isolated from *I. signatus* ticks collected on Ariy Kamen Island in the Commander Islands, but their infection rate was less than 1:10,000 (<0.01%).[9] A similar virus was found in Norway.[25] One strain of ZTV (LEIV-279Az) was isolated from the mosquito *Culex modestus* collected in 1969 in a colony of herons (genus *Ardea*) in the district of Kyzylagach in the southeastern part of Azerbaijan (Figure 8.44).[3] Natural foci of ZTV and UUKV associated with bloodsucking mosquitoes (subfamily Culicinae) are found in continental areas in the European part of Russia, particularly Murmansk region.[7]

Taxonomy. The viruses of the *Phlebovirus* genus can be divided into two main ecological groups: those transmitted by bloodsucking mosquitoes (subfamily Culicinae) and midges (subfamily Phlebotominae), together called mosquito borne, and those transmitted by ticks (tick borne). UUKV is a prototypical virus of the Uukuniemi antigenic group, which includes at least 15 related tick-borne phleboviruses (Figures 8.37–8.39).[26] The genome of UUKV consists of three segments of ssRNA: an L-segment 6,423 nt long, an M-segment 3,229 nt long, and an S-segment 1,720 nt long. The M-segment of UUKV, and indeed, that of all tick-borne phleboviruses, is shorter than the M-segment of mosquito-borne phleboviruses, owing to the absence of the nonstructural protein NSm, which is common in the mosquito-borne phleboviruses. Originally, ZTV was described as a virus closely related to UUKV. A full-length sequence comparison showed that the similarity of ZTV to UUKV is 77.3% nt identity of the L-segment (90.9% aa of RdRp) and 70.9% nt identity of the M-segment (81.5% aa).

Arthropod Vectors. Most isolations of UUKV and ZTV were obtained from *Ixodes*

TABLE 8.23 Isolation of Zaliv Terpeniya Virus (ZTV) (Family Bunyaviridae, Genus *Phlebovirus*) from *Ixodes* (*Ceratixodes*) *Uriae* Ticks, Obligate Parasites of Alcidae Birds in the Basins of the Sea of Okhotsk, the Bering Sea, and the Barents Sea

		Far East				European part
		Basin of Sea of Okhotsk		Basin of the Bering Sea		Basin of Barents Sea
		Sakhalin District		Kamchatka	Chukotka	Murmansk District
Results of examination		Tyuleniy Island (48°29′N, 144°38′E)	Iona Island (56°24′N, 143°23′E)	Ari Kamen Island (Commander Islands) (55°13′N, 165°48′E)	Bering Strait Coast (64°50′N, 173°10′E)	Kharlov Isl., Near Kola Peninsula (68°49′N, 37°19′E)
Number of strains isolated		3	2	20	0	41
Infecion rate (%)		0.022	0.103	0.096	< 0.087	0.456
Total	Number of strains	25				41
	Number of ticks tested	35,725				8,994
	Infection rate total (%)	0.070				0.456

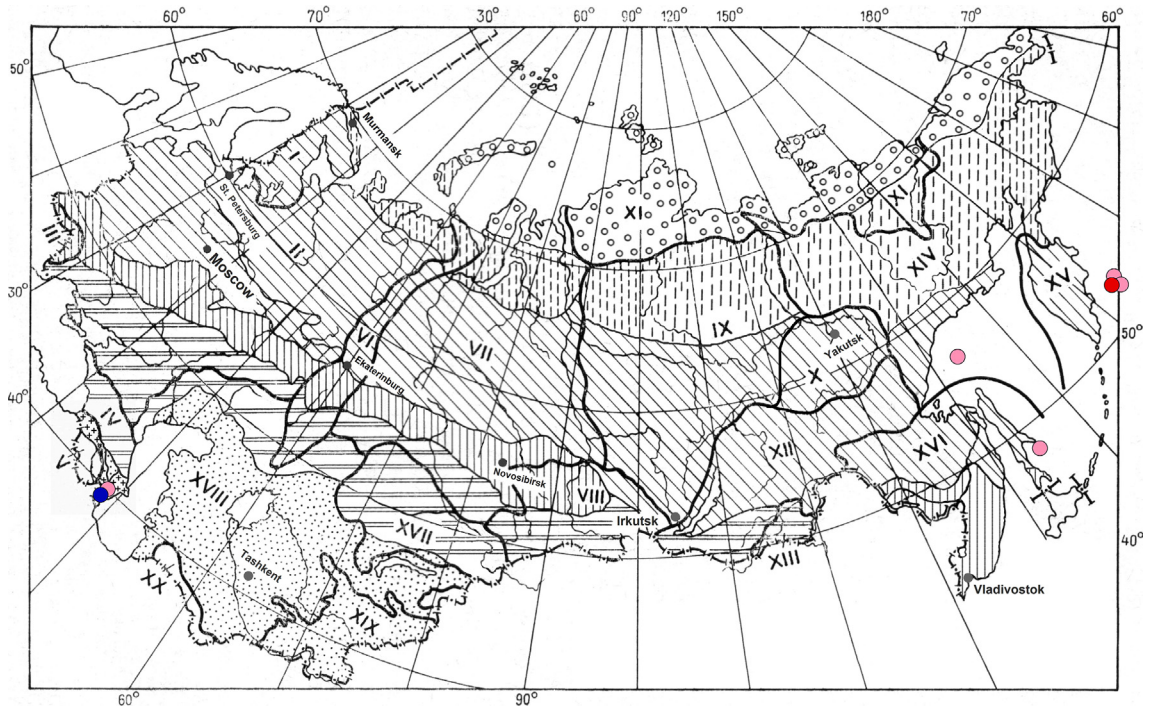


FIGURE 8.44 Places of isolation of ZTV (family Bunyaviridae, genus *Phlebovirus*) in Northern Eurasia. Red circle: strain of ZTV/LEIV-13841Kam with completely sequenced genome; Pink circles: strains of ZTV/LEIV-279Az identified by complete genome sequencing; Dark-blue circle: strains of ZTV identified by serological methods. (See other designations in Figure 1.1.)

ricinus and *I. uriae* ticks, respectively. The infection rates of nymphs and larvae of *I. uriae* are 5 and 13 times lower, respectively, than that of the imago. These rates indicate a high frequency (8–10%) of transovarial transmission of ZTV.[7,9] Probably, ZTV has a more pronounced ability to replicate in mosquitoes that are active in the subarctic climate zone (tundra landscapes) in July through the first half of August at temperatures sufficient for the accumulation of virus in the salivary glands.[7,9] During this period, circumpolar species predominate: *Aedes communis*, *Ae. punctor*, *Ae. hexodontus*, *Ae. impiger*, and *Ae. nigripes; Culiseta alaskaensis* is rarer. *I. ricinus*, together with *I. persulcatus*, *I. pavlovskyi*, *I. nipponensis*, *I. kashmiricus*, *I. kazakstani*, *I. granulatus*, *I. nuttallianus*, and *I. hyatti*, forms a single phylogenetic branch within the genus *Ixodes*.[7,9] The origin of this group of species is said to be southeast Asia. Currently, *I. ricinus* inhabits mixed and deciduous forests of the eastern coast from the Atlantic Ocean to the Middle Volga, but zoogeographical data show that the tick emerged in the Paleocene epoch in a belt of mesophilic forests.[27] Comparative ontogenetic analysis revealed a relation of *I. ricinus* to the southern group of *I. persulcatus* (*I. kazakstani*, *I. kashmiricus*, *I. nipponensis*, and *I. hyatti*) and, through that group, with *I. pavlovskyi*.

Vertebrate Hosts. Complement-binding antibodies to ZTV were found in 1% of common murres (*Uria aalge*) on the Commander

Islands. In the Murmansk Region, which lies to the north of the European part of Russia, antibodies were found in 6% of common murres (*U. aalge*), 4% of black-legged kittiwakes (*Rissa tridactyla*), and 1% of voles (*Microtus oeconomus*).[7,9] Apparently, ruminants could be infected by mosquitoes or by eating fallen birds. On the north coast of the Kola Peninsula, antibodies were found in 6% of thick-billed murres (*U. lomvia*), in 7% of black-legged kittiwakes, and in 1% of voles.[7,9]

In central and eastern Europe, a number of vertebrate hosts are involved in the circulation of UUKV: forest rodents (*Myodes glareolus*, *Apodemus flavicollis*) and terrestrial passerine birds—the blackbird (*Turdus merula*), pale trush (*T. pallidus*), ring ouzel (*T. torquatus*), European robin (*Erithacus rubecula*), hedge sparrow (*Prunella modularis*), wheatear (*Oenanthe oenanthe*), European starling (*Sturnus vulgaris*), carrion crow (*Corvus corone*), magpie (*Pica pica*), brambling (*Fringilla montifringilla*), hawfinch (*Coccothraustes coccothraustes*), yellow bunting (*Emberiza sulphurata*), turtle dove (*Streptopelia turtur*), and ring-necked pheasant (*Phasianus colchicus*).[20,28–32] Viremia and long-term persistence of the virus were demonstrated in experimentally infected birds of many species. Specific antibodies were detected in cows and reptiles.

Human Pathology. An association was revealed between UUKV and different forms of disease, including neuropathy.[33,34] A serological survey of 1,004 people in Lithuania concluded that antibodies existed in 1.8–20.9% of the population. Human antibodies to UUKV were detected in less than 5% of the human population in central Europe[33–35] and 13–14% in Belarus.[16] The people living in the tundra landscape had antibodies to ZTV in 3.3% of cases, while in the forest no such antibodies were detected (via a neutralization reaction).[7]

8.1.5.6 Komandory Virus and Rukutama Virus (var. Komandory virus)

History. Komandory virus (KOMV), strain LEIV-13856, was isolated in 1986 from *Ixodes* (*Ceratixodes*) *uriae* ticks in Ari Kamen Island (54°30′N, 166°20′E; Figure 8.45), a part of the Commander Islands archipelago in the Bering Sea.[1] RUKV, strain LEIV-6269, was isolated from *I. uriae* ticks collected in September 1976 in a colony of common murres (*Uria aalge*) on Tyuleniy Island.[1] RUKV was named for the Rukutama River, which flows into Zaliv Terpeniya Bay, off Sakhalin Island, near the place of first isolation of the virus (Figure 8.45). Later, two additional strains of RUKV were isolated from the same source and place (Table 8.24). In previous studies, RUKV was mistakenly included in the Sakhalin serogroup in the *Nairovirus* genus.[1]

Taxonomy. The genome of KOMV (strain LEIV-13856) and RUKV (strain LEIV-6269) were completely sequenced, and the two viruses were classified into the *Phlebovirus* genus.[2,3] A full-length comparison showed that the genetic similarity between KOMV and RUKV is 93.0–95.5% nt. Among other tick-borne phleboviruses, KOMV and RUKV are most closely related to MWAV, which was isolated from *Argas abdussalami* ticks in 1964 in Pakistan.[4] The similarities of the genomes of KOMV and RUKV to that of MWAV are 67.1% nt for the L-segment (73.0% aa for RdRp), 59.6% nt of the M-segment (58% aa for the polyprotein precursor), and 66.8% nt for the S-segment (58.4% aa for the N-protein). In phylogenetic trees, KOMV and RUKV were placed into the Uukuniemi group (Figures 8.37–8.39).[5]

The ecology and area of distribution of KOMV and RUKV are the same as those of ZTV, which is closely related to UUKV. Several strains of ZTV isolated on the Commander Islands were sequenced, and no reassortants of ZTV with KOMV were found.[6,7]

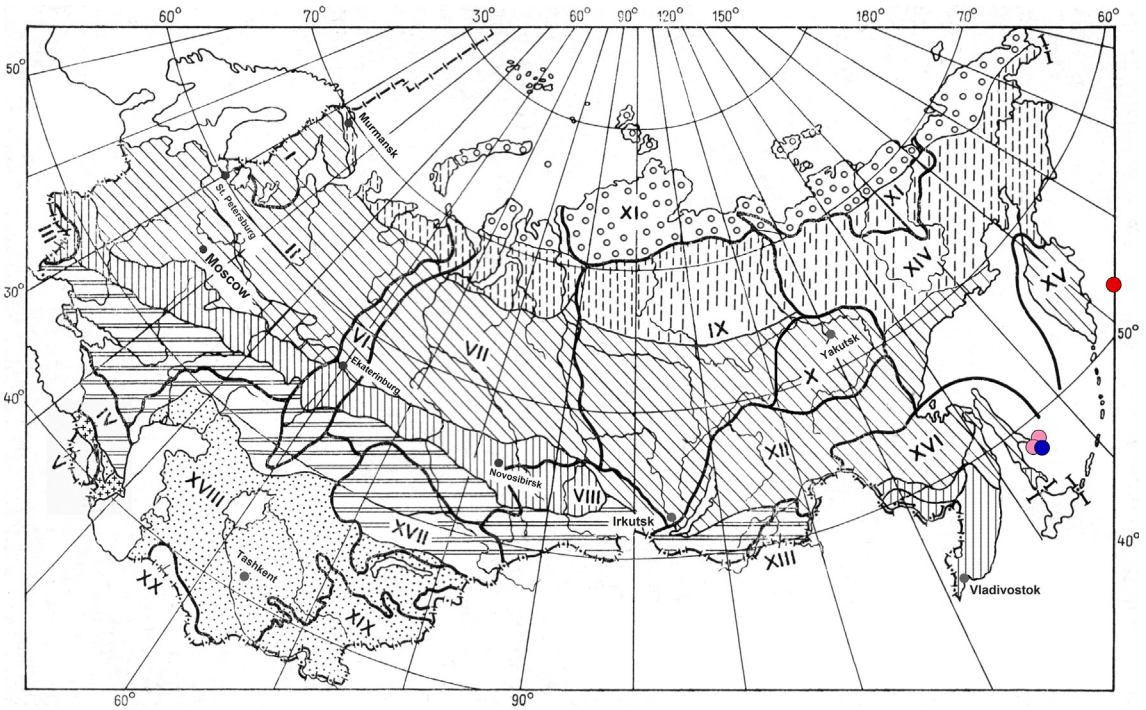


FIGURE 8.45 Places of isolation of KOMV and its variant RUKV (family Bunyaviridae, genus *Phlebovirus*) in Northern Eurasia. Red circle: strain of KOMV/LEIV-13856 identified by complete genome sequencing; Pink circles: strains of KOMV identified by serological methods; Dark-blue circle: strain of KOMV/LEIV-6269 (RUKV) identified by complete genome sequencing. (See other designations in Figure 1.1.)

Arthropod vectors. All isolations of KOMV and RUKV were obtained from *Ixodes uriae* ticks, the obligate parasite of Alcidae birds. The Commander Islands are located on the border of the temperate and subarctic climatic zones, and many different viruses belonging to the Bunyaviridae (ZTV, SAKV, PMRV), Flaviviridae (Tyuleniy virus, TYUV), and Reoviridae (OKHV) families have been isolated from *I. uriae* ticks collected from birds living in colonies there.[8–11] Note that the KOMV infection rate of the *I. uriae* ticks in the Commander Islands is 10 times less than the ZTV (1:900) and TYUV (family Flaviviridae, genus *Flavivirus*) infection rates of the same ticks.

Vertebrate Hosts. The main vertebrate host of KOMV and RUKV is apparently Alcidae birds, especially the common murre (*Uria aalge*), but their involvement in the circulation of KOMV and RUKV has not been studied sufficiently.

Human Pathology. UUKV group viruses, in general, do not play a role in human infectious pathology, although serological studies have detected antibodies to various viruses of this group in people.

8.2 FAMILY FLAVIVIRIDAE

The Flaviviridae family (from the Latin *flavus*, "yellow," as well as from yellow fever virus (YFV)) includes three genera: *Flavivirus*, *Pestivirus*, and *Hepacivirus*.[1] The Flaviviridae are small (40–60 nm) enveloped viruses. The genome is represented by ssRNA

TABLE 8.24 Isolation of KOMV, or Synonymous RUKV, from *Ixodes Uriae* Ticks in Colonies of Alcidae Birds in the Basin of the Sea of Okhotsk.

		Far East	
		Sakhalin district	Kamchatka
Virus		Tyuleniy Island (48°29′N, 144°38′E)	Ari Kamen Island (55°13′N, 165°48′E)
Commander Islands	Number of strains	3	1
	% of infected ticks	0.022	0.005
Total	Number of strains	4	
	Number of ticks examined	35,725	
	% of infected ticks	0.011	

(9,100−12,300 nt) with positive polarity. The genomic RNA is infectious and acts as mRNA in the cytoplasm of infected cells.[2] Members of the the *Flavivirus* genus are zoonotic viruses infecting a wide range of vertebrate and arthropod hosts.

8.2.1 *Flavivirus* Genus

The *Flavivirus* genus includes more than 70 viruses classified into 15 antigenic groups.[1,3] The *Flavivirus* virion is spherical (50 nm) and consists of a nucleocapsid (30 nm) and a lipid bilayer envelope covering it. The lipid envelope contains two transmembrane glycoproteins: M (matrix protein, 8 kD) and E (envelope protein, 50 kD). The genome of the flaviviruses is a single molecule of RNA about 11,000 nt in length and capped on the 5′ terminus. The genomic RNA encodes a long ORF of a polyprotein precursor flanked by 5′ and 3′ untranslated regions. Mature viral proteins are produced during a complex process of proteolytic cleavage of the polyprotein precursor by cellular and viral proteases. Structural proteins (core, M, and E) occupy one-third of the RNA (the N part of the polyprotein) on the 5′ part of the genome, followed by nonstructural proteins (NS1-NS5b) (Figure 8.46).[2,4]

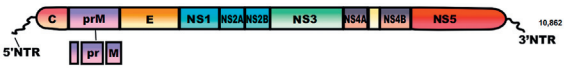


FIGURE 8.46 Genome organization of YFV (family Flaviviridae, genus *Flavivirus*). *Drawn by Tanya Vishnevskaya.*

Most of the flaviviruses are arboviruses; that is, they can be transmitted to vertebrate hosts by bloodsucking arthropod vectors (Figure 8.47). Approximately 50% of known flaviviruses are transmitted by mosquitoes, about 30% by ticks. The arthropod vectors of some flaviviruses are unknown. There is also a group of flaviviruses that infect only insects and not vertebrates. Some flaviviruses (e.g., West Nile virus, WNV) have ecological plasticity and can be transmitted either by mosquitoes or by ticks. Flaviviruses are distributed over all continents, with mosquito-borne viruses found mainly in regions with an equatorial and tropical climate And tick-borne viruses found mostly in regions with a temperate climate zone. Many flaviviruses are associated with birds, which can transfer them during the birds' seasonal migration. Flaviviruses belongs to natural foci zoonoses. Certain flaviviruses, such as YFV, dengue virus (DENV), and West Nile virus (WNV), pose a serious threat to humans.[5–7]

8.2.1.1 *Omsk Hemorrhagic Fever Virus*

History. The first hint that Omsk hemorrhagic fever (OHF) was etiologically linked

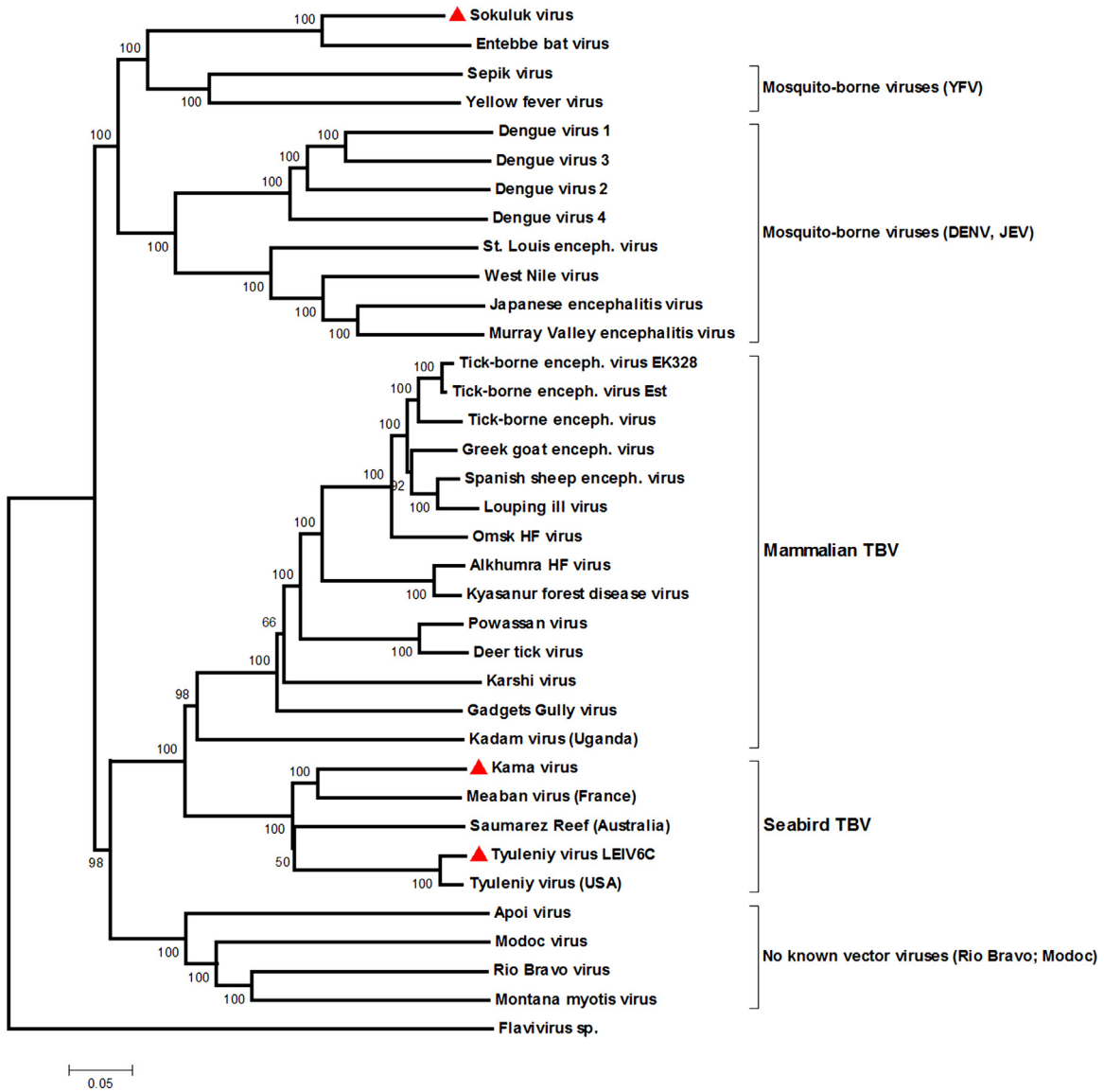


FIGURE 8.47 Phylogenetic analysis of viruses belonging to the *Flavivirus* genus, based on full-length genome comparison.

with Omsk hemorrhagic fever virus (OHFV) (family Flaviviridae, genus *Flavivirus*, antigenic complex of TBE) came in 1940–1945.[1,2] The disease arose in the spring–summer in the northern forest–steppe landscape zone in the region around Omsk, western Siberia; Figure 8.48) an area with a wide network of lakes. About 200 cases with two lethal outcomes ("atypical tularemia" and "atypical leptospirosis") were investigated (without

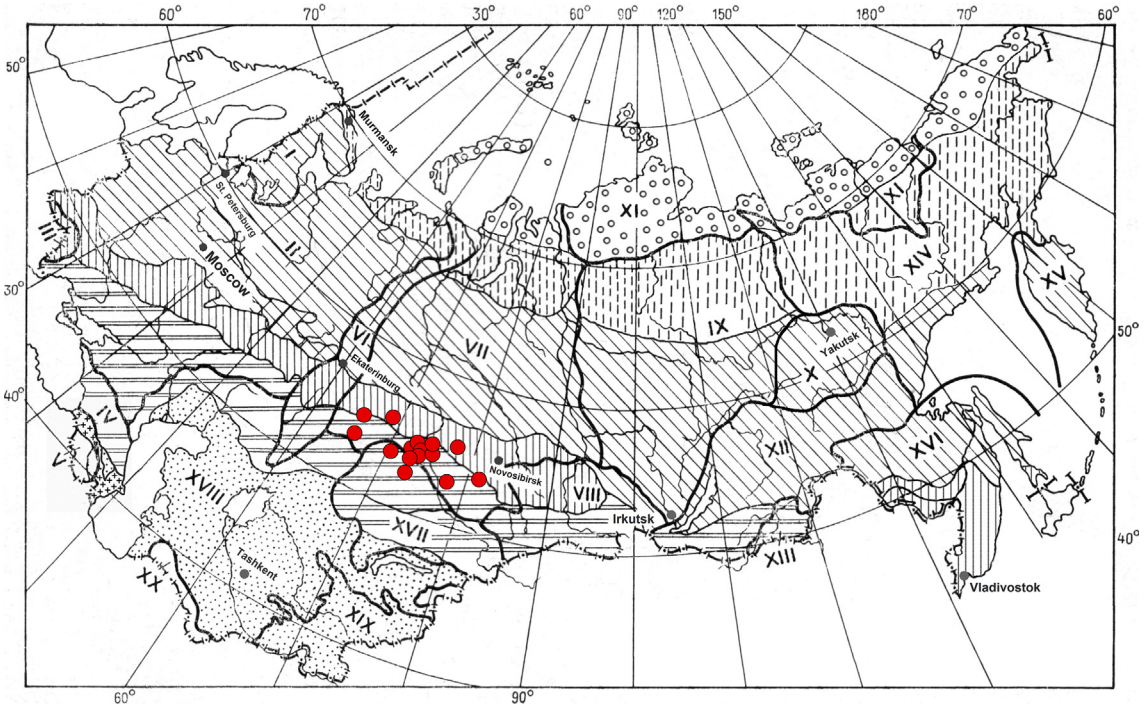


FIGURE 8.48 Places of isolation of OHFV (family Flaviviridae, genus *Flavivirus*) strains (●) in the former USSR. (See other designations in Figure 1.1.)

laboratory confirmation) from the end of April to the beginning of October in 1945. In the spring–summer of 1946, the endemic territory enlarged and the number of cases increased to 623, with 4 lethal outcomes.[3,4] In 1947, a large expedition (about 50 members) under the leadership of Mikhail Chumakov (Figure 2.10) began to work in the Omsk region; the virus etiology of OHF was proven, and the disease acquired its modern name: OHF.[3,5–7] The expedition produced prodigious results: The prototype strain OHFV/Kubrin was isolated from the blood of one patient; the mechanism of transmission of the virus by the Ixodidae tick *Dermacentor reticulatus* was established; the epidemiological and clinical features of OHF, as well as its pathogenesis and pathomorphology, were described; and inactivated vaccine from mouse brain was developed and prepared for epidemiological trials.[5] Later, the role of another species of Ixodidae ticks (*D. marginatus*) as an OHFV vector was revealed.[8,9]

Taxonomy. OHFV belongs to the phylogenetic branch of the mammalian tick-borne virus group (Figure 8.47). The OHFV genome has a length of 10,787 nt, and its organization is common to the flaviviruses. Two genotypes of OHFV are known today: Prototypical strains for the first one are OHFV/Kubrin and OHFV/Bogolubovska, which have an extremely small genetic distance between them; the prototypical strain for the second genotype is OHFV/uve.[10–12] Only six nucleotide substitutions, which encode four amino acids, have been found in the entire genome.

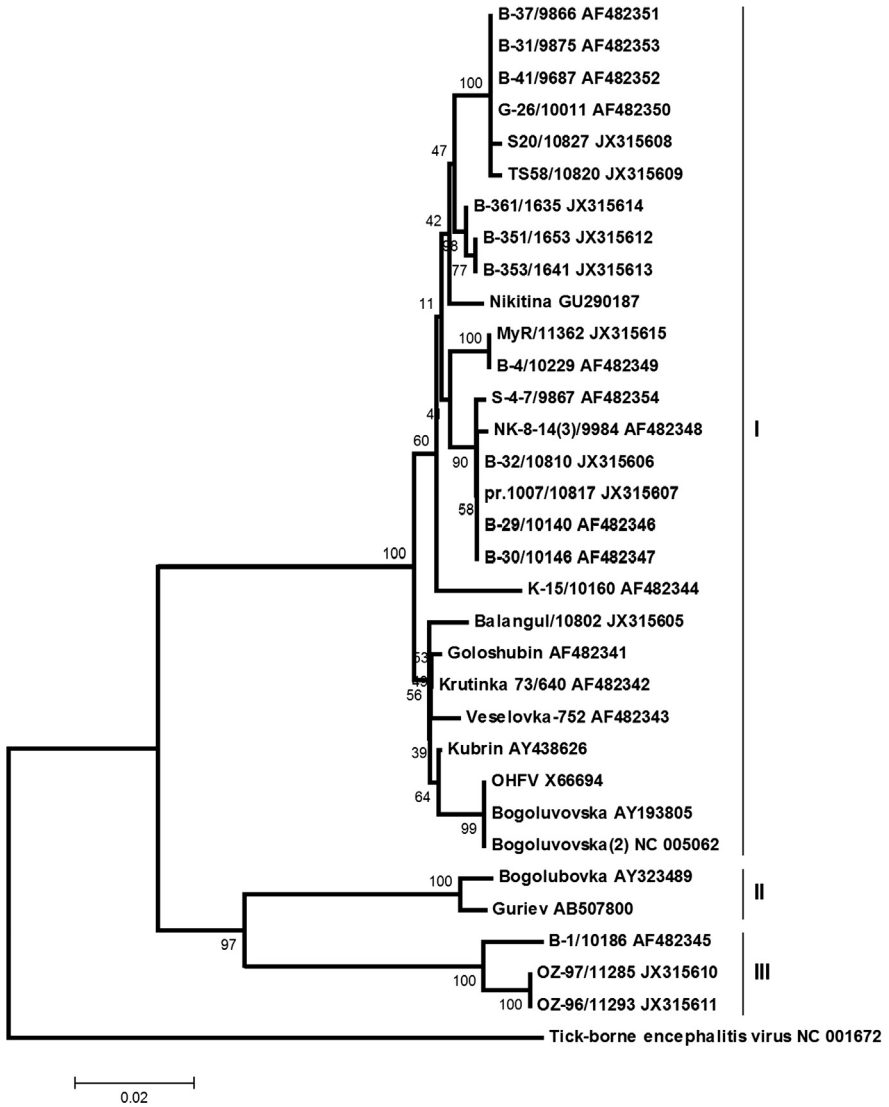


FIGURE 8.49 Phylogenetic analysis based on comparison of partial sequences of E protein of OHFV (family Flaviviridae, genus *Flavivirus*, TBEV group). Alignment of OHFV sequences available in GenBank were analyzed by neighbor-joining method and rooted on the corresponding sequence of TBEV.

Three of four amino acid changes were located in the envelope glycoprotein E.[11]

Phylogenetic analysis based on a comparison of partial sequences of the E gene available in GenBank showed that OHFV isolates can be divided to three genetic lineages (Figure 8.49). The genetic diversity among strains of different lineage is up to 11.8%.

Arthropod Vectors. The natural foci of OHFV are found in the forest–steppe landscape zone of western Siberia, an area with numerous bogs and a wide network of lakes

within the Omsk, Novosibirsk, Kurgan, and Tyumen regions (Figure 8.48). The natural foci border the area of distribution of TBEV, and the two virus's natural foci are intermingled.[13–15]

The principal Ixodidae tick vectors for OHFV are *Dermacentor pictus* (in the northern forest–steppe subzone) and *D. marginatus* (in the southern forest–steppe subzone).[3,8,9] The infection rate of *D. pictus* in epidemic years reaches 8%, in interepidemic years 0.1–0.9%. The main host for preimago phases of *D. pictus* is the narrow-headed vole (*Microtus gregalis*). This species of rodent is host to 70–90% of *D. pictus* nymphs and larvaein the northern forest–steppe subzone. In 1959–1962, when the number of *Microtus gregalis* voles fell significantly, there was a concomitant decrease in the number of *D. pictus* ticks in the center of an epidemic zone that was accompanied by a sharp decrease in the infection rate of ticks and an attenuation of the meadow natural foci of OHFV. In some of those years, however, a high number of *Ixodes apronophorus*, all phases of which feed on the water vole (*Arvicola terrestris*), become involved in the virus's circulation on a par with *D. pictus* ticks. *Ar. terrestris* makes fodder migrations in June–August from damp locales (where their infection takes place) to coastal meadows (where peak activity of the larvae and nymphs of *D. pictus* is observed during those months). Small animals living in those meadows become infected as they feed on the *D. pictus* larvae and nymphs. In damp locales, *I. apronophorus* could infect muskrats. Also, *D. marginatus*, whose optimum zone lies in a steppe landscape belt, plays some (though largely insignificant) role in the lake areas of the southern forest–steppe subzone.[16]

During epizootic and epidemic activity of OHF natural foci, Gamasidae ticks, as well as aquatic organisms belonging to the Hydracarinae, take part in OHFV circulation. Their involvement is confirmed by the identity of isolated strains with those isolated from muskrats and sick humans. Experiments with experimentally and spontaneously OHFV-infected Gamasidae ticks testify to the ability of longitudinal (more than six months) virus preservation.[17]

Vertebrate Hosts. The principal vertebrate host of OHFV, which is able to directly infect humans, is the muskrat (*Ondatra zibethicus*). This species was introduced into western Siberia from Canada in 1928. Their population density reached a modern-day high in the 1940s. Close interactions among *O. zibethicus* and local populations of *Arvicola terrestris* emerged. *Ar. terrestris* has periods of rapid population growth followed by epizootics of tularemia, leptospirosis, and OHFV. Muskrats suffered these epizootics together with other local species of rodents: *Microtus oeconomus*, *M. gregalis*, *Myodes rutilus*, *Apodemus agrarius*, and *Ar. terrestris*.[13] The OFV infection rate among muskrats is about 15% in both the autumn–winter and the spring–summer periods.[16] Latent infection was established in all rodents except the muskrat.[18]

OHFV was detected in birds and in mosquitoes, but the role of these two animals in virus circulation is not clear.[18–21]

Epidemiology. OHFV is transmitted both by Ixodidae tick bites and as the result of direct contact with infected muskrats, their flesh, and fresh fells.[1,5]

OHF morbidity during 1945–1949 reached 1.5–5.0%. Then there was a gradual decrease down to single cases. Most OHF cases (96.8%) were detected in the lake forest–steppe, in the south of the forest–steppe landscape zone, which occupies 14.5% of the territory where 15.3% of country people in the Omsk region live. The northern forest–steppe landscape zone is the youngest landscape of western Siberia, having evolved in place of the former southern taiga landscape zone.[22,23] In the south of western Siberia, the following territorial zones can be marked out: (i) the

preferred territory of Tick-borne encephalitis virus (TBEV) (the southern taiga); (ii) intermediate territory (the boundary of the southern taiga with the northern forest–steppe); (iii) the preferred territory of OHFV (the northern and southern forest– steppe); and (iv) the territory of sporadic cases of OHF (part of the southern forest–steppe and steppe).[13,23] In the first zone, more than 90% of all cases of TBE in western Siberia are registered and only single OHF cases are found; in the second zone, 1% each of cases of TBE and OHF; in the third zone, 4% of TBE and 96% of OHF; and in the fourth zone, 4% of TBE and single cases of OHF.[13]

The seasonal incidence of OHF distinctly correlates with the activity of the principal Ixodidae tick vectors. Cases (a few) of OHF acquired by direct contact with muskrats occur mainly during the season in which the animals are hunted, in October–January. In the spring–summer season, OHF cases occur chiefly in rural areas. The age of patients ranges from 5 to 70 years, but cases occur mainly among middle-aged persons (40–50 years old). In the autumn–winter period, OHF occurs mainly among muskrats trappers (60%), adult members of their families (28%), and children (12%). It appears that all patients infected directly from muskrats develop symptomatic illness. Seroprevalence ranges from 0 to 32% in populations of endemic regions.[3,7,23] In the last decade of the twentieth century, an increase in OHF natural foci activity took place in the Tyumen (1987), Omsk (1988, 1999–2007), Novosibirsk (1989–2002; regular epidemic activity took place on the territory of only four administrative districts), and Kurgan (1992) regions. In the absolute majority of laboratory-confirmed cases, the nontransmissive pathway (direct contact with muskrats) of the infection dominated.[17]

Pathogenesis is determined first of all by the destruction of capillaries, the vegetative nervous system, and the adrenal glands.[16,24]

Clinical Features. The incubation period of OHFV is 2–4 days long. The disease begins abruptly, with fever, head and muscular pain, hyperemia, and injection in the sclera. The body temperature increases up to 39–40°C and stays that way for 3–4 days, then decreases a little and critically falls on the 7th to 10th day after symptoms appear. From the first days of the illness, there are diapedetic bleedings, especially in the nose. Recovery is usually complete, without any residual phenomena; lethal outcomes are possible, but are rare.[16,24–26]

Control and Prophylaxis. OHFV survives up to 20 days in lake water. Water can be contaminated by urine and feces of the infected muskrats or some other rodents. The water pathway in human infection has been discussed in the literature.[13,14]

Prevention of the infection depends on the use of protective respirators and rubber gloves in processing muskrat pelts and on personal protective measures against tick bites. TBE vaccine offers a high degree of protection against OHF.[10,23] Cases of laboratory-acquired OHF have been reported in unvaccinated persons, and TBE vaccine is recommended for laboratory personnel working with either virus.[23]

Interferon and its inductors have shown a high efficiency in preventing OHF in experiments using animal models.[27]

8.2.1.2 *Powassan Virus*

History. Powassan virus (POWV) (family Flaviviridae, genus *Flavivirus*, antigenic complex of TBE) was originally isolated by D.M. McLean and W.L. Donohue in September 1958 from the brain of a five-year-old child who was admitted to the hospital with blinking, tremors, and dizziness in the small town of Powassan in the north of Ontario, Canada.[1] The child later died of encephalitis. Subsequent virological and serological surveys carried out in the Powassan–North Bay and

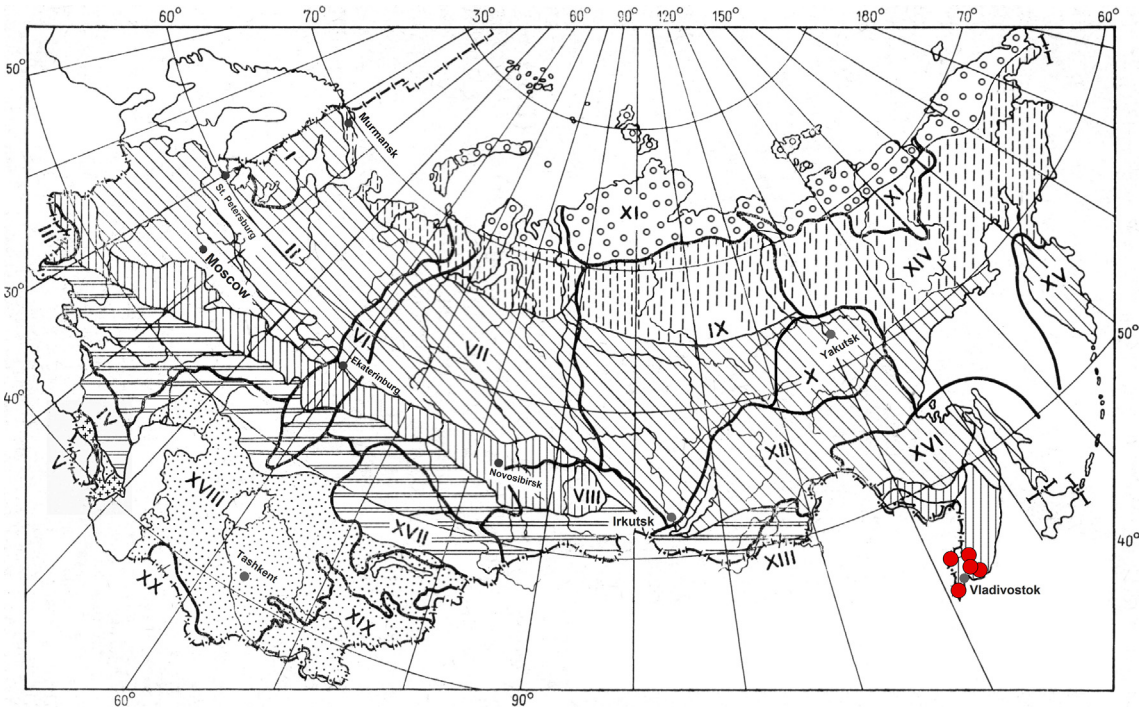


FIGURE 8.50 Places of isolation of POWV (family Flaviviridae, genus *Flavivirus*) strains (●) in the former USSR. (See other designations in Figure 1.1.)

Manitoulin Island areas of northern Ontario during 1959–1966 elucidated a summer transmission cycle involving Ixodidae ticks and small wild mammals.[2] Neutralizing antibodies were found in 1.1% of humans.[3] A virus strain isolated from a pool of *Dermacentor andersoni* collected in Colorado was identified as POWV.[4] In Russia, POWV was isolated in 1972 in Primorsky Krai from *Haemaphysalis neumanni* collected from spotted deer (*Cervus nippon*) (Figure 8.50).[5]

Taxonomy. POWV belongs to the tick-borne group of mammalian flaviviruses, together with TBEV, OHFV, Kyasanur Forest disease virus (KFDV), Alma-Arasan virus (AAV), Alkhurma fever virus (AHFV), Langat virus (LGTV), Gadgets Gully virus (GGYV), Louping ill virus (LIV), and Royal Farm virus (RFV).[6,7]

The genome of POWV is a about 10,835 nt in length. The virus comprises two genetic lineages, formed by POWV (lineage I) and the closely related deer tick virus (DTV, lineage II) (Figure 8.51).[8] Phylogenetic analysis based on partial sequences of the E gene showed that the population of POWV in Russia has a low genetic diversity.[9] The strains of POWV isolated in Russia have a high genetic similarity to the strains of lineage I isolated in North America. A full-length genome comparison revealed that Far Eastern isolates (LEIV-3070Prm, Spassk-9, and Nadezdinsk-1991) have a 99.5% identity with strain POWV/LB from Canada (Figure 8.51).

Arthropod Vectors. POWV was isolated from Ixodidae ticks collected in the Russian Far East and in the U.S. states of California,

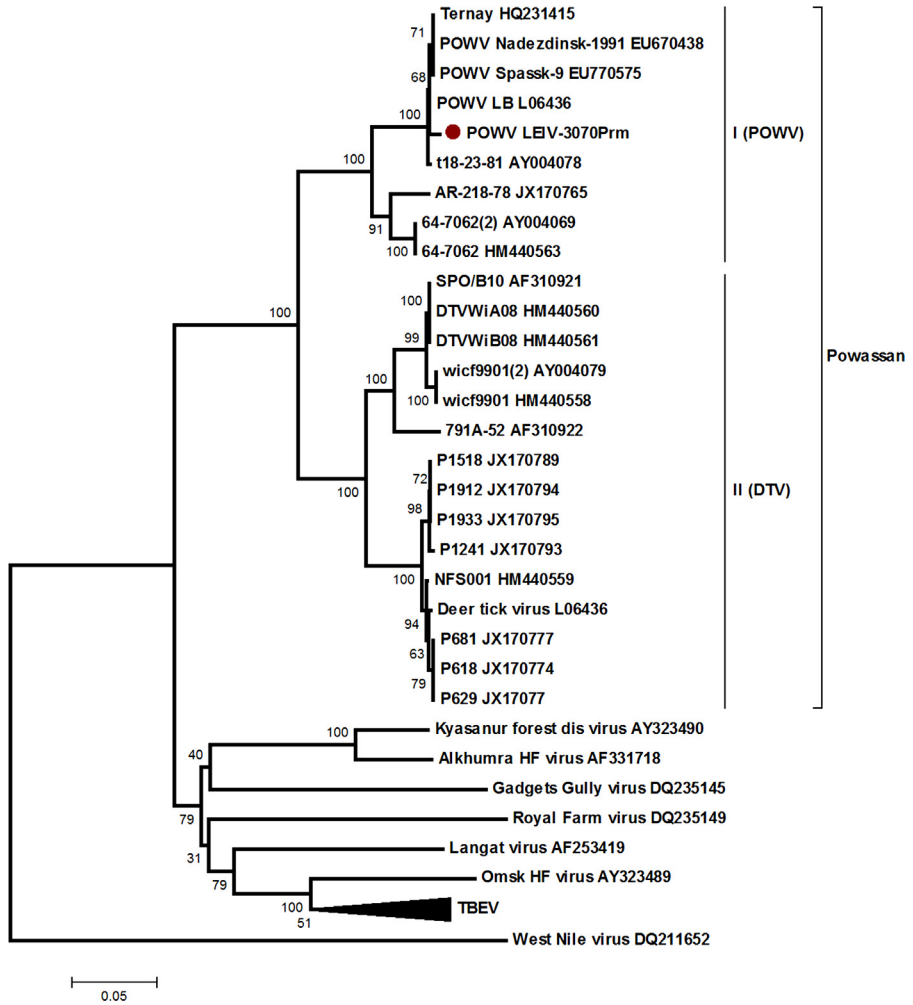


FIGURE 8.51 Phylogenetic analysis of the Eurasian and North American isolates of POWV (family Flaviviridae, genus *Flavivirus*) based on the partial sequences of E gene.

Colorado, Connecticut, Massachusetts, South Dakota, and West Virginia. Serological investigations of wild mammals indicate that POWV also circulates in the Canadian provinces of Alberta, British Columbia, and Nova Scotia.[3,10–12]

In North American natural foci, POWV was isolated from *Ixodes cookei*, *I. spinipalpus*, *I. marxi*, and *Dermacentor andersoni* ticks.[3,10,11] In the Far East, known vectors of POWV are *Haemaphysalis longicornis*, *Haem. concinna*, *Haem. japonica*, *D. silvarum*, and *I. persulcatus* ticks.[5,9,13,14] Transphase and transovarial transmission of POWV in Ixodidae ticks has been established.

Vertebrate Hosts. In North America, POWV was isolated from wild mammals: the woodchuck (*Mormota monax*, the main reservoir), American red squirrel (*Tamiasciurus hudsonicus*), deer mouse (*Peromiscus maniculatus*), red fox (*Vulpes fulva*), eastern gray squirrel

(*Sciurus carolinensis*), North American porcupine (*Erethizon dorsatum*), striped skunk (*Mephitis mephitis*), raccoon (*Procyon lotor*), long-tailed weasel (*Mustela frenata*), and gray fox (*Urocyon cinereoargenteus*).[2,4,15] Infection of wild vertebrates most often is inapparent.[2,10] In the south of the Russian Far East (in Primorsky Krai), POWV was isolated from aquatic birds: the common teal (*Anas crecca*) and the mallard (*Anas platyrhynchos*).[9,13,14,16]

Epidemiology. Human infections of POWV were reported in Canada (Ontario and Quebec), the United States (New York and Pennsylvania),[2] and Russia (Primorsky Krai).[14,17,18] Nevertheless, human infection rarely develops.

Clinical Features. The clinical picture of developing meningitis and encephalomeningitis includes high temperature, dryness in the gullet, drowsiness, headache, disorientation, convulsions, vomiting, difficulty breathing, coma, and paralysis, with 11% lethality in the severe phase of the disease. Autopsy has revealed widespread perivascular and focal parenchymatous infiltration. In 50% of recoveries, consequent damage to the CNS develops, which could lead to death in 1–3 years.[2,18]

Control and Prophylaxis. The vaccine against TBEV is not effective against POWV.[2,17,19]

8.2.1.3 Tick-Borne Encephalitis Virus and Alma-Arasan Virus (var. Tick-borne encephalitis virus)

TBEV (family Flaviviridae, genus *Flavivirus*, TBEV antigenic group) is the natural foci for neuroinfection transmitted by Ixodidae ticks.

History. In 1931–1934, the Russian military medical doctor–neuropathologist A.G. Panov, together with his colleagues A.N. Shapoval and D.A. Krasnov, described a neuroinfection with a high level of mortality in the Far East. This neuroinfection later was called "spring–summer encephalitis."[1,2] During field expeditions in 1937–1940, the historical strain TBEV/Sofjin was isolated from the brain of a patient with encephalitis who died in Khabarovsk Krai (Figure 8.52). In that period, the main vector of TBEV—*Ixodes persulcatus* ticks—was established, epidemiological peculiarities of TBE were studied, and the first anti-TBEV vaccine was developed on the basis of intracerebrally infected mouse brain and was successfully used in medical practice.[2] Complex expeditions were undertaken by a number of prominent virologists (L.A. Zilber (Figure 2.9), M.P. Chumakov (Figure 2.10), A.A. Smorodintsev (Figure 2.11), E.N. Levkovich (Figure 2.14), A.D. Sheboldaeva, and A.K. Shubladze (Figure 2.15)), bacteriologists (V.D. Soloviev (Figure 2.13) and N.V. Ryzhkov), parasitologists (Ye. N. Pavlovsky (Figure 2.12), A.V. Gutsevich, B.I. Pomerantsev, A.S. Monchadsky, and A.N. Skrynnik), and clinicians (A.G. Panov, A.N. Shapoval, and Z.I. Finkel).

Taxonomy. The antigenic complex of TBEV includes TBEV proper (with three genotypes; see next paragraph); GGYV (Australia, Oceania); KFDV (Hindustan) and the closely related AHFV (Arabian Peninsula); LGTV (Malay Peninsula); LIV (Europe), with British (LIV-Brit), Irish (LIV-I), Spanish (LIV-Spain), Turkish (Turkish sheep encephalitis virus (TSEV)), and Greek (Greek goat encephalitis virus (GGEV)) subtypes; OHFV; POWV and the closely related DTV; RFV; and Karshi virus (KSIV).[3–10]

The three genotypes of TBEV were established by antigenic or phylogenetic analysis: Far Eastern (TBEV-FE) (prototypical strain, TBEV/Sofjin; KC806252), Siberian (TBE-Sib) (TBEV/Aina; JN003206; TBEV/Vasilchenko; L40361), and European (TBE-Eur) (TBEV/Neudoerfl; U27495) (Figure 8.53). Genetic diversity among strains of different genotypes is about 32–33% nt and for the polyprotein precursor is 25–26% aa.

Strain TBEV/LEIV-1380Kaz (the former AAV) was isolated from *Ixodes persulcatus* in the low-mountain part of southeastern Kazakhstan (Alma-Ata Region) in 1977.[11]

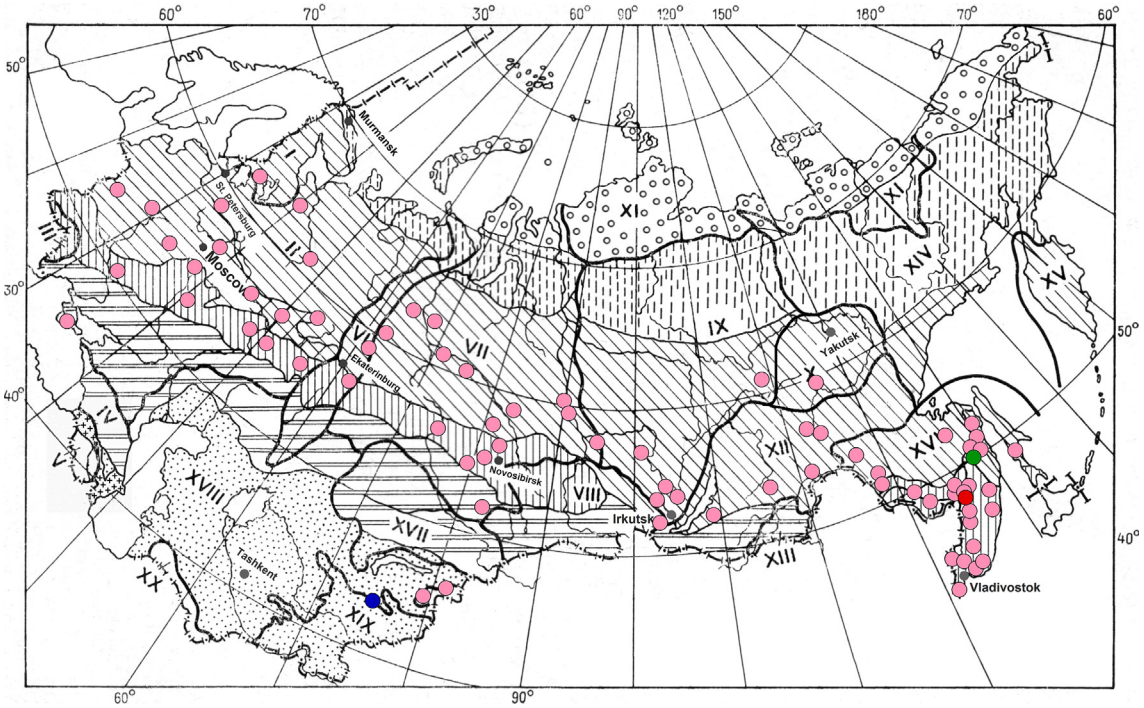


FIGURE 8.52 Places of isolation of TBEV (family Flaviviridae, genus *Flavivirus*) in the former USSR. (See other designations in Figure 1.1.)

Preliminary investigation revealed a one-sided antigenic relation between AAV and POWV.[12] AAV was associated with human cases of meningitis. Specific antibodies to AAV were found among ground squirrels (*Citellus fulvus*), agricultural animals, and humans. Later, the AAV genome was sequenced (GenBank ID: KJ 744033).[13] A full-length genome comparison showed that AAV has the highest similarity (94.6% nt and 98.3% aa identities) to the TBEV/Chita-653, TBEV/Irkutsk-12, TBEV/Aino, and TBEV/Vasilchenko strains belonging to the Siberian genotype (Figure 8.53).

Recent genetic studies of TBEV revealed two additional genotypes of this virus on the territory of eastern Siberia (Irkutsk Region): for the first one, only a single strain is known today; for the latter, there are five strains in Mongolia.[14] Thus, TBEV has a high level of genetic diversity in Northern Eurasia. TBEV-Sib genotype dominates in Europe, western Siberia, and eastern Siberia, TBEV-FE in the Far East.[15,16] The TBEV-FE genotype, which was widely distributed in Siberia and northeastern Europe, is now being displaced by TBEV-Sib. TBEV-FE strains are often pathogenic to laboratory mice, whereas TBEV-Sib frequently provokes severe and lethal disease.[15] Local populations of all genotypes of TBEV could be stable for a long time.[16]

Distribution. TBEV is distributed within the areas of distribution of its main vectors: *Ixodes persulcatus* and *I. ricinus* ticks (Figure 8.54—see details in the detailed work of E.I. Korenberg[17]). In Russia, those areas are the Far East, Siberia, the Ural region, and the European part of Russia[18–24] (Tables 8.25 and 8.26); in Fennoscandia, Finland,[20,25,26] Sweden,[19,27,28] and

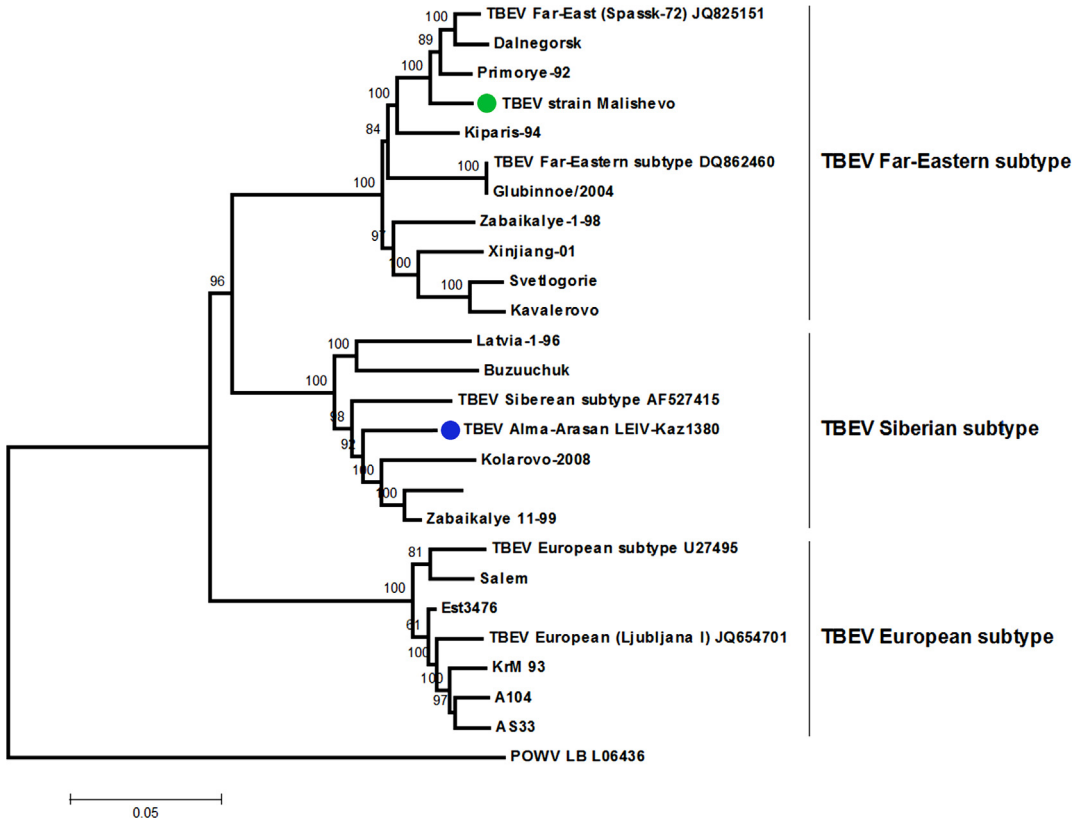


FIGURE 8.53 Phylogenetic analysis of the complete genome nucleotide sequences of certain strains of TBEV (family Flaviviridae, genus *Flavivirus*).

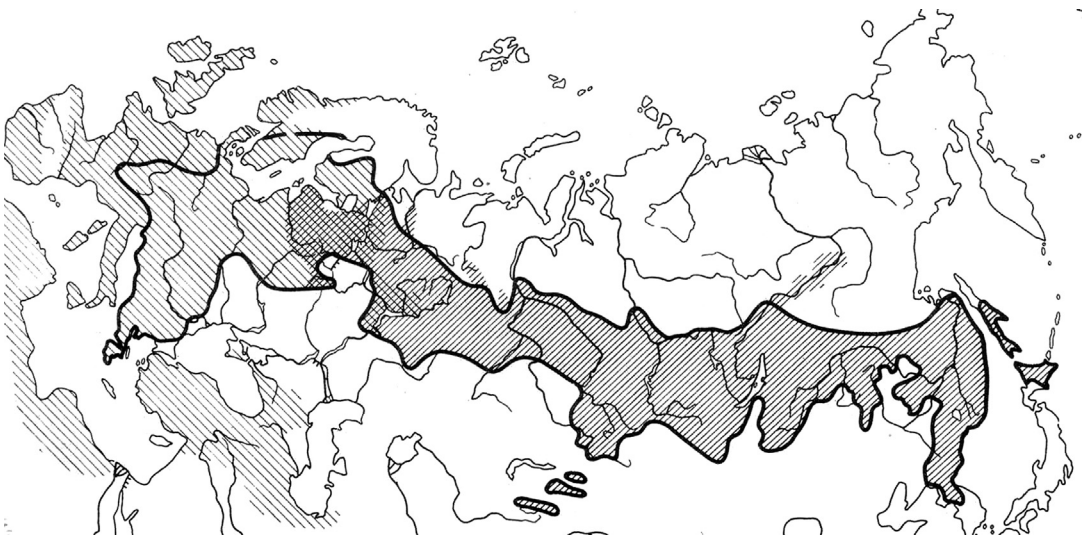


FIGURE 8.54 Coincidence of areas of distribution of TBEV (family Flaviviridae, genus *Flavivirus*) and its arthropod vectors *Ixodes persulcatus* and *I. ricinus* in Northern Eurasia. (See other designations in Figure 1.1.)

TABLE 8.25 Incidence of TBE in Europe

Year	Austria	Hungary	Germany	Denmark	Italy	Latvia	Lithuania	Norway	Poland	Slovakia	Slovenia	Finland	France	Croatia	Czech Republic	Sweden	Switzerland	Estonia
1996	128	224	114	0	8	309	716	0	257	101	406	10	1	57	571	44	62	177
1997	99	99	211	0	8	874	645	0	201	76	274	19	1	25	415	76	123	404
1998	62	84	148	1	11	1,029	548	1	209	54	136	17	2	24	422	64	68	387
1999	41	51	115	4	5	350	171	1	101	57	150	12	5	26	490	53	112	185
2000	60	45	133	3	15	544	419	2	170	92	190	41	0	18	719	133	91	272
2001	54	76	253	1	19	303	298	1	205	76	260	33	0	27	411	128	107	215
2002	60	80	226	1	6	153	168	2	126	62	262	38	2	30	647	105	53	90
2003	82	114	278	4	14	365	763	1	339	74	275	16	6	36	606	105	116	237
2004	54	89	274	8	23	251	425	3	262	70	204	31	7	38	500	160	138	182
2005	100	52	431	4	22	142	242	3	174	28	297	17	0	28	642	130	206	164
2006	84	56	546	0	14	170	462	3	316	91	373	18	6	20	1029	163	259	171
2007	45	62	238	2	4	171	234	13	233	46	199	20	7	12	542	190	113	140
2008	86	70	285	1	34	181	220	9	202	77	246	23	10	20	630	224	127	90
2009	79	64	313	1	32	328	617	8	335	71	307	26	0	0	816	211	118	179

TABLE 8.26 TBE Cases in Russia in 2013

Federal District	Number of TBE cases/portion (%)	Infection rate per 100,000 population
Central	40/1.8	0.10
Northwestern	288/12.8	2.11
Southern	0	0.00
North Caucasian	0	0.00
Volga	272/12.0	0.91
Ural	315/13.9	2.60
Siberian	1,307/58.0	6.79
Far Eastern	33/1.5	0.53
Total	2,255/100.0	

Norway;[29–31] in the rest of Europe, the Czech Republic,[8,32] Slovakia,[6,33,34] Bulgaria,[35] Hungary,[36,37] Poland,[38,39] Croatia,[40] Latvia,[41] Lithuania,[42] Estonia,[43,44] Denmark,[31] Germany,[45–48] Austria,[49] Slovenia,[50] France,[51] Italy,[52,53] and Spain[54] (Table 8.25); And in Asia, the Russian Far East and Siberia,[1,16,55] Japan (Hokkaido),[55] North and South Korea,[56,57] China,[58] Mongolia,[59] Kazakhstan,[13] and Kyrgyzstan.[60]

Arthropod Vectors. Natural TBEV infection has been observed in 16 species of Ixodidae ticks. The principal arthropod vectors for TBEV in Russia are the Ixodidae ticks *Ixodes persulcatus* (in the Far East, Siberia, and the north of the European part of the country) and *I. ricinus* (in the south of the European part) (Figure 8.54).

The infection rate in *I. ricinus* is about 0.2% in the northwestern part of the Russian Plain, 0.4% in Lithuania, and 3.8% in Crimea. The infection rate in *I. persulcatus* is, as a rule, higher, ranging from 0.6% to 4.8%. Occasional vectors are *I. hexagonus*,[61] *I. pavlovskii*,[17,62] *Haemaphysalis inermis*, *Haem. concinna*, *Haem. punctata*, *Haem. longicornis*, *Haem. japonica*, and *Dermacentor reticulatus*.[35,63–66] The main TBEV vector in Japan (Hokkaido) is *I. ovatus*.[67,68] In the Korea Peninsula, where both *I. ricinus* and *I. persulcatus* are absent, the main TBEV vector is *Haem. longicornis* and *Haem. flava*.[69]

The northern boundary of *I. persulcatus* and *I. ricinus* lies within the limits of an effective temperature sum isoline of about 1,000–1,300°C (the middle taiga landscape belt). The most suitable climatic conditions for these ticks are within the south taiga. Imago tick activity begins in the third d decade of April and reaches a maximum in the second and third decades of May or in the first and second decades of June, with activity beginning to decrease in the third decade of June. This time frame correlates with morbidity dynamics having an 8- to 10-day lag (Figure 8.55).[70]

The ecological links of TBEV during its circulation in natural foci are extremely diverse as the result of wide distribution of this virus (Figures 8.52 and 8.54). Ixodidae ticks, mainly *I. persulcatus*, are the natural reservoir of TBEV and the core of natural foci.[12,62,71,72]

From the very beginning of the tick's larval stage, a suctional, tarlike liquid appears around the hypostome and becomes rosin.[62,73] The quantity of virus in this rosin plug is comparable to that in the tick's body (10^3–10^4 PFU/mcL).[74] The place of suction on the body of the host is significant for the development of infection; for example, suction in the axillary hollow results in the highest lethality (16.1%, 1.5 times more in comparison to suction in the neck and in the head.[73]

Ticks become infected as they suck blood from a vertebrate host with a level of viremia that is equal to or higher than the threshold required for infection. Ticks can also become infected from an *uninfected* vertebrate host as they suck blood together with infected ticks.[73,75] Transovarial and transphase transmission of TBEV has been described in the literature; nevertheless, the effectiveness of vertical transmission of TBEV is low. (About 1% of progeny turn out to be infected).[52,76] The sexual pathway of TBEV transmission from male to female is quite effective (about 50%).[77–79] The aggressiveness and activity of TBEV-infected Ixodidae ticks increases with the TBEV titer in their bodies.[62,75] Infected ticks have been found on the clothing of

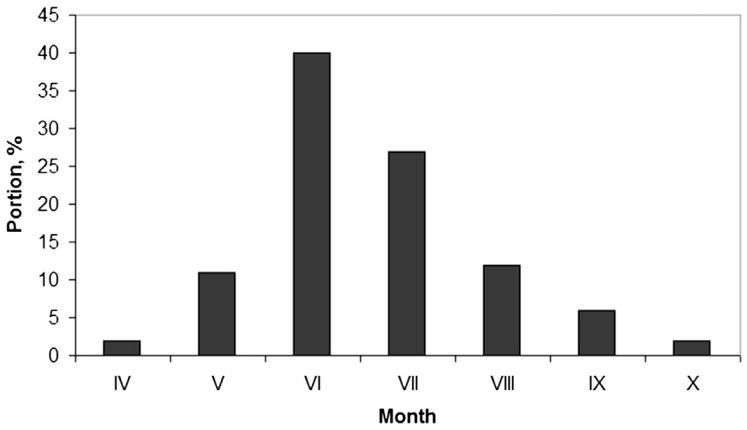


FIGURE 8.55 Trends in the incidence of TBE in Russia, by month (as a percentage of the amount of disease for the year, according to long-term data).

humans at a fequency 5–20 times higher than uninfected ticks have been found.[48,62,75]

TBEV has been isolated from the mosquitoes *Anopheles hyrcanus* in Kyrgyzstan[80] and *Aedes* sp. in western Siberia.[81] The strain TBEV/Malyshevo was isolated from *Aedes vexans nipponii* mosquitoes collected in 1978 on the coast of Petropavlovskoe Lake in Khabarovsk Krai in the Russian Far East (48°40′N, 135°41′E).[82–84] A preliminary investigation[82] concluded that this strain belonged to Negishi (NEGV) virus,[85] and later the possibility was discussed that the strain belonged to a separate, Malyshevo virus. Then, phylogenetic analysis using a next-generation sequencing approach revealed that Malyshevo is a strain of TBEV and is closely related to TBEV strains isolated in the Far East: TBEV/1230, TBEV/Spassk-72, TBEV/Primorye-89.[13]

TBEV has been isolated many times from ticks and fleas of the superfamily Gamasoidea living in nests of rodents and birds (Table 8.27), even during the winter period.[2,47,86–89]

Vertebrate Hosts. Hosts for the preimago stage of Ixodidae ticks—Asian chipmunks (*Tamias sibiricus*), shrews (members of the Soricidae family), bank voles (*Myodes glareolus*), field voles (*Microtus agrestis*), mountain hares (*Lepus timidus*), and 74 species of birds (Table 8.28)—have great significance in TBEV circulation.[10,12,62,64,71,72,90,91] Persistent TBEV infection in bank voles and field voles has been found during the winter period.[26]

Infection among vertebrates occurs mainly by tick bites. In rare instances, alimentary transmission of TBEV through milk containing viruses is possible.[34,92]

Epidemiology. There are two basic modes of human infection by TBEV: (i) as the result of being bitten by infected Ixodidae ticks (the main mode); and (ii) as the result of consuming infected raw goat, sheep, and cow meat, milk, or dairy products (mainly in natural foci linked to *Ixodes ricinus*).[23,32,93] The latter pathway of TBEV distribution often involves whole families. As much as 70% of cases in Belarus have been alimentary.[70] TBEV can persist in milk at 60°C for more than 10 min, and some of the viruses can remain viable even after pasteurization at 62°C for 20 min. Nor is TBEV inactivated after 24 h at 4°C and pH 2.8. Many laboratory infection cases (usually by aerosol) have been described.

Several hundred cases are recorded in Europe (Table 8.25) and in Russia (Table 8.26) each year, with considerable interannual variation.[17,70,94–96] The highest level of TBE morbidity is registered in the Baltic states (Latvia, 6.2–10.8 per 100,000 population); Lithuania, 6.5–13.5; and Estonia, 10.4–13.5) and in Slovenia (10.2–18.6) and the Czech Republic (5.0–10.0). In neighboring Austria, where the vaccination rate is higher, the index is lower (0.6–1.2).[97] Seasonal TBE morbidity in Russia is connected with seasonal activity of the Ixodidae tick vectors (Figure 8.55).

The risk of infection depends upon the frequency of tick bites, which is different for populations living in the different landscape belts. Results of an investigation of almost 200,000 people demonstrate that the highest risk is for the population living in the southern taiga belt, where about 20% of adults were found to have tick bites during one epidemic season (Table 8.29).

In rural localities of the southern taiga belt, about half of schoolchildren and about 80% of adults have antibodies to TBEV. For comparison, only 14–20% of adult citizens of Kemerovo, a city of about half a million in western Siberia, and 2–3% of citizens of Moscow have antibodies specific to TBEV (Table 8.29).[98]

A mathematical model for evaluating the infection rate and the probability of developing the disease as a function of the density of the tick population, its infection rate and biting activity, and the level of the immune human layer was developed by D.K. Lvov and coauthors.[98–102] The same approach, which is also suitable for other arboviral infections, was

TABLE 8.27 TBEV Isolation from Birds and their Ectoparasites in Northern Eurasia

Taxonomy of birds				Place of collection	
Order	**Family**	**Genus**	**Species**	**Physicogeographical land**	**Region of Russia**
1	**2**	**3**	**4**	**5**	**6**
Anseriformes	Anatidae	*Clangula*	Long-tailed duck (*C. hyemalis*)	Russian Plain	European part
		Melanitta	White-winged scoter (*M. fusca*)	Russian Plain	European part
		Anas	Garganey (*An. querquedula*)	Russian Plain	European part
Falconiformes	Accipitridae	*Accipiter*	Goshawk (*A. gentilis*)	Eastern Siberia	Irkutsk region
		Butastur	Buzzard eagle (*B. indicus*)	Southern part of the Far East	Primorsky Krai
Galliformes	Phasianidae	*Tetrastes*	Grouse (*T. bonasia*)	Western Siberia, southern part of the Far East	Tomsk region, Khabarovsk Krai
			Black grouse (*T. tetrix*)	Eastern Siberia, southern part of the Far East	Irkutsk region, Primorsky Krai
Ralliformes	Rallidae	*Crex*	Corn crake (*C. crex*)	Eastern Siberia	Irkutsk region
Charadriiformes	Charadriidae	*Charadrius*	Little ringed plover (*C. dubius*)	Eastern Siberia	Irkutsk region
		Scolopax	Woodcock (*S. rusticola*)	Eastern Siberia	Irkutsk region
Columbiformes	Columbidae	*Streptopelia*	Oriental turtle dove (*S. orientalis*)	Southern part of the Far East	Primorsky Krai
		Columba	Pigeon (*C. livia*)	Eastern Siberia	Irkutsk region
Mesostigmata	Dermanyssidae	*Dermanyssus*	Mites *D. gallinae* from pigeons (*C. livia*)	Eastern Siberia	Irkutsk region
			Mites *D. hirundintis* from common starling (*S. vulgaris*)	Eastern Siberia	Irkutsk region
Cuculiformes	Cuculidae	*Cuculus*	Himalayan cuckoo (*C. saturatus*)	Eastern Siberia, southern part of the Far East	Irkutsk region, Primorsky Krai
			Lesser cuckoo (*C. poliocephalus*)	Eastern Siberia, southern part of the Far East	Irkutsk region, Primorsky Krai
Piciformes	Picidae	*Jynx*	Eurasian wryneck (*J. torquilla*)	Eastern Siberia	Irkutsk region
		Picoides	Three-toed woodpecker (*P. tridactylus*)	Eastern Siberia	Buryatia Republic
		Dendrocopos	Great spotted woodpecker (*D. major*)	Ural	Perm region
			Lesser spotted woodpecker (*D. minor*)	Eastern Siberia, southern part of the Far East	Buryatia Republic, Primorsky Krai
			White-backed woodpecker (*D. leucotos*)	Southern part of the Far East	Primorsky Krai

(*Continued*)

TABLE 8.27 (Continued)

Taxonomy of birds				Place of collection	
Order	**Family**	**Genus**	**Species**	**Physicogeographical land**	**Region of Russia**
1	**2**	**3**	**4**	**5**	**6**
Coraciiformes	Meropidae	*Merops*	European Bee-eater (*M. apiaster*)	Central Asia	Kyrgyzstan
Ixodida	Ixodidae	*Ixodes*	Ticks *I. persulcatus* from the nests of sand martins (*R. riparia*)	Northern part of the Far East	Yakut Republic
Siphonaptera	Ceratophyllidae	*Ceratophyllus*	Fleas *C. maculates* from the nests of house martins (*Delichon urbicum*)	Ural	Perm region
Passeriformes	Alaudidae	*Alauda*	Eurasian skylark (*A. arvensis*)	Eastern Siberia, central Asia	Buryatia Republic, Kyrgyzstan
	Hirundinidae	*Riparia*	Sand martin (*R. riparia*)	Eastern Siberia	Irkutsk region
	Motacillidae	*Anthus*	Tree pipit (*A. trivalis*)	Western Siberia, eastern Siberia	Tomsk region, Buryatia Republic
			Pechora pipit (*A. gustavi*)	Southern part of the Far East	Khabarovsk Krai
		Motacilla	Pied wagtail (*M. alba*)	Eastern Siberia	Irkutsk region
			Yellow wagtail (*M. flava*)	Southern part of the Far East	Khabarovsk Krai
	Campephagidae	*Pericrocotus*	Rosy minivet (*P. roseus*)	Southern part of the Far East	Primorsky Krai
	Laniidae	*Lanius*	Brown shrike (*L. cristatus*)	Southern part of the Far East	Primorsky Krai
			Chinese grey shrike (*L. sphenocercus*)	Eastern Siberia	Irkutsk region
	Troglodytidae	*Troglodytes*	Northern wren (*T. troglodytes*)	Southern part of the Far East	Primorsky Krai
	Turdidae	*Turdus*	Siberian thrush (*T. sibirica*)	Eastern Siberia	Irkutsk region
			Song thrush (*T. philomelos*)	Eastern Siberia, western Siberia	Tomsk region, Buryatia Republic
			Naumann's thrush (*T. naumanni*)	Southern part of the Far East	Primorsky Krai
			Red-throated thrush (*T. ruficollis*)	Western Siberia	Tomsk region
			Grey-backed thrush (*T. hortulorum*)	Southern part of the Far East	Khabarovsk Krai
			Pale thrush (*T. pallidus*)	Southern part of the Far East	Primorsky Krai
			Common blackbird (*T. merula*)	Western European part	Kaliningrad region
			Eyebrowed thrush (*T. obscurus*)	Southern part of the Far East	Khabarovsk Krai

Passeriformes (*Continued*)	Muscicapidae	*Monticola*	White-throated rock thrush (*M. gularis*)	Southern part of the Far East	Primorsky Krai
		Tarsiger	Red-flanked bluetail (*T. cyanurus*)	Southern part of the Far East	Primorsky Krai
		Luscinia	Siberian blue robin (*L. cyane*)	Southern part of the Far East	Khabarovsk krai
	Bombycillidae	*Bombycilla*	Bohemian waxwing (*B. garrulus*)	Eastern Siberia	Buryatia Republic
	Sylviidae	*Sylvia*	Lesser whitethroat (*S. curruca*)	Eastern Siberia	Buryatia Republic
	Muscicapidae	*Ficedula*	Mugimaki flycatcher (*F. mugimaki*)	Eastern Siberia	Buryatia Republic
		Muscicapa	Brown flycatcher (*M. latirostris*)	Southern part of the Far East	Primorsky Krai
	Acrocephalidae	*Acrocephalus*	Blyth's reed warbler (*A. dumetorum*)	Ural	Perm region
	Paridae	*Parus*	Great tit (*P. major*)	Western European part of Russia, Eastern Siberia	Kaliningrad region, Buryatia Republic
		Periparus	Coal tit (*P. ater*)	Eastern Siberia	Buryatia Republic
	Remizidae	*Remiz*	Black-headed penduline tit (*R. macronyx*)	Eastern Siberia	Buryatia Republic
	Aegithalidae	*Aegithalos*	Long-tailed tit (*Ae. caudatus*)	Eastern Siberia	Buryatia Republic
	Sittidae	*Sitta*	Eurasian nuthatch (*S. europaea*)	Southern part of the Far East	Khabarovsk Krai
	Emberizidae	*Emberiza*	Yellowhammer (*E. citrinella*)	Western Siberia	Tomsk region
			Chestnut-eared bunting (*E. fucata*)	Southern part of the Far East	Khabarovsk Krai, Primorsky Krai
			Yellow-breasted bunting (*E. aureola*)	Eastern Siberia	Irkutsk region
			Meadow bunting (*E. cioides*)	Eastern Siberia, Southern part of the Far East	Buryatia Republic, Primorsky Krai
			Little bunting (*E. pusilla*)	Southern part of the Far East	Primorsky Krai
			Yellow-throated bunting (*E. elegans*)	Southern part of the Far East	Primorsky Krai
			Tristram's bunting (*E. tristrami*)	Southern part of the Far East	Primorsky Krai
			Black-faced bunting (*E. spodocephala*)	Southern part of the Far East	Primorsky Krai

(*Continued*)

TABLE 8.27 (Continued)

Taxonomy of birds				Place of collection	
Order	**Family**	**Genus**	**Species**	**Physicogeographical land**	**Region of Russia**
1	**2**	**3**	**4**	**5**	**6**
Passeriformes (*Continued*)	Fringillidae	*Acanthis*	Common redpoll (*A. flammea*)	Eastern Siberia	Irkutsk region
		Eophona	Chinese grosbeak (*E. migratoria*)	Southern part of the Far East	Primorsky Krai
			Japanese grosbeak (*E. personata*)	Southern part of the Far East	Primorsky Krai
		Pyrrhula	Eurasian bullfinch (*P. pyrrhula*)	Eastern Siberia	Buryatia Republic
		Uragus	Long-tailed rosefinch (*U. sibiricus*)	Southern part of the Far East	Primorsky Krai
		Pinicola	Pine grosbeak (*P. enucleator*)	Eastern Siberia	Buryatia Republic
		Loxia	Common crossbill (*L. curvirostra*)	Eastern Siberia	Buryatia Republic
		Fringilla	Brambling (*F. montifringilla*)	Western Siberia	Tomsk region
	Passeridae	*Passer*	Tree sparrow (*P. montanus*)	Western European part of Russia	Ukraine
	Sturnidae	*Sturnus*	Common starling (*S. vulgaris*)	Eastern Siberia	Irkutsk region
	Corvidae	*Nucifraga*	Spotted nutcracker (*N. caryocatactes*)	Eastern Siberia	Irkutsk region
		Garrulus	Eurasian jay (*G. glandarius*)	Eastern Siberia	Irkutsk region
		Perisoreus	Siberian jay (*P. infaustus*)	Eastern Siberia	Buryatia Republic
	13	**33**	**53**	**76**	**Within the boundaries of distribution of *I. persulcatus* and *I. ricinus* ticks**

TABLE 8.28 Number (Thousands) of Humans Investigated /Frequencies (%) of Ixodidae Tick Bites in the Various Western Siberian Landscape Belts (One Epidemic Season)

	Age groups (years)				
Landscape belt	**<3**	**3–7**	**8–17**	**≥18**	**Sum**
Southern taiga	2.6/5.0	6.2/12.9	13.4/19.9	32.2/18.2	54.4
Mountain taiga	0.7/0.9	2.1/1.4	5.6/3.2	9.9/3.9	18.3
Forest–steppe	7.0/0.6	15.1/4.5	31.2/7.9	67.7/8.0	121.0
Total	10.3	23.4	50.2	109.8	193.7

TABLE 8.29 Specific Antibodies ((Number of Samples Investigated)/(Portion (%) of Positive Results) to TBEV Among Populations Living in the Various Landscape Belts of Western Siberia and in Moscow (As An Outside Point)

Landscape belt	**Setting**	**Serological method**[a]	**Age groups (years)**		
			≤7	**8–17**	**≥18**
Southern taiga	Rural	HIT	25/16	100/53	274/78
		NT	90/12	146/60	376/88
	Urban	HIT	–	–	568/59
		NT	–	–	476/60
Mountain Taiga	Rural	HIT	81/10	191/26	422/64
		NT	76/17	64/20	121/44
	Urban	HIT	–	–	80/20
		NT	–	–	92/20
Forest–steppe	Rural	HIT	64/11	138/17	746/47
		NT	–	–	15/47
	Urban	HIT	–	–	296/21
		NT	–	–	103/32
Steppe	Rural	HIT	34/12	49/12	111/21
Kemerovo	Urban	HIT	–	–	454/14
		NT	–	–	54/9
Moscow	Urban	HIT	–	–	266/3
		NT	–	–	49/2
Total		**HIT**	**204/11**	**478/28**	**3,217/42**
		NT	**166/14**	**210/48**	**1,286/58**
Sum		**HIT**	**3,899/38**		
		NT	**1,662/52**		

[a] *Abbreviations: HIT, hemagglutination inhibition test; NT, neutralization test; –, no data.*

used for landscape-epidemiological zoning of TBEV natural foci in Altai Krai in the southern part of western Siberia: More than 10,000 residents living in the different landscape belts on a territory about 250,000 km^2 were tested by serological methods (Figure 8.56). The tests produced a good fit between calculated and registered morbidity data (Table 8.30).

Pathogenesis. TBE can be realized in several pathogenetic variants. An inapparent clinical form is characterized by short-term localization of TBEV in lymph nodes and immune cells, as well as by extranervous reproduction without viremia. Infection is terminated by the development of stable immunity. About 95% of cases of infection are inapparent.[102] Clinical fever is expressed as a common infectious process, but both the central and the peripheral nervous system are involved in the pathology.[103] Neuroinfection is characterized by lesion of the envelope and substance of the spinal cord and CNS.

Clinical Features. The incubation period ranges from 1 to 30 days, but usually is 7–12 days. The onset of illness in typical cases is abrupt and with a headache. The temperature

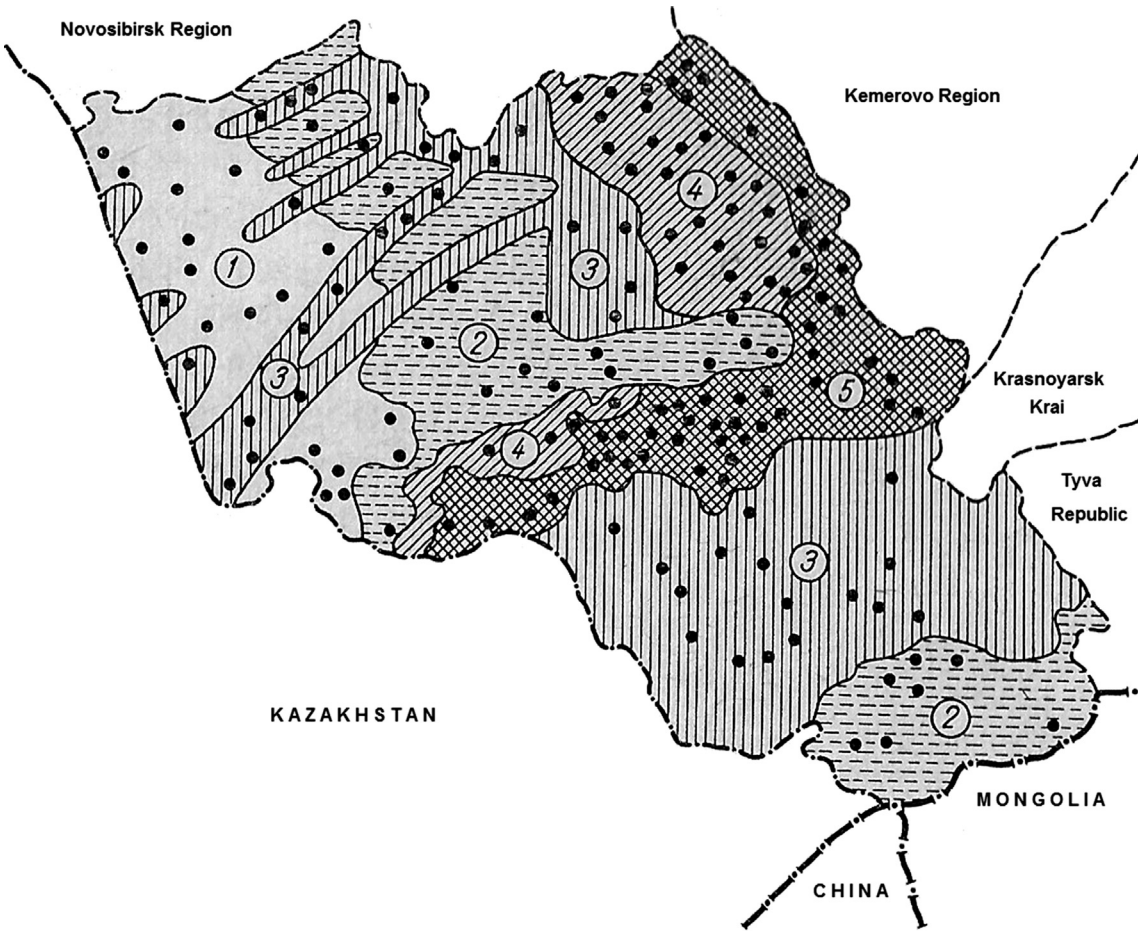


FIGURE 8.56 Landscape-epidemiological zoning of the territory of Altai Krai for TBE. Designations for epidemiological regions in respect to the level of immune layer: 1. 0-5%; 2. 6-10 %; 3. 11-20%; 4. 21-40%; 5. 41-60%.

TABLE 8.30 Calculated and Registered Tick-Borne Encephalitis Morbidity Per 100,000 in a Rural Population of Western Siberia

	Age groups (years)					
	8–12		13–22		23–57	
Landscape belt	Registered	Calculated	Registered	Calculated	Registered	Calculated
Southern taiga	99	107	84	93	53	48
Forest-steppe	41	47	42	38	39	45

rises to 38–40°C. Malaise, vomiting, general hyperesthesia, and photophobia develop.

Clinical symptoms of TBE, as well as the severity of the disease, are at least partially determined by biological properties of the virus.[104] There are two main clinical forms of TBE: the Far Eastern variety, associated with Far Eastern and Siberian strains of the virus, and the European variety (also known as Western biphasic meningoencephalitis or biphasic milk fever), associated chiefly with European strains. Human disease of the first type is usually clinically more severe in the acute phase, but is associated with a lower rate of chronic CNS sequelae.

The first phase starts with sudden fever, flulike symptoms (pronounced headache, weakness, nausea, myalgia, arthralgia), and conjunctivitis. The second phase appears after 4–7 days of apparent recovery, but then the CNS is affected (meningoencephalitis appears), accompanied with fever, retrobulbar pain, photophobia, stiff neck, sleeping disorders, excessive sweating, drowsiness, tremors, nystagmus, meningeal signs, ataxia, pareses of the extremities, dizziness, confusion, psychic instability, excitability, anxiety, disorientation, and/or memory loss. TBEV produces diffuse degenerative changes in neurons, perivascular lymphocytic infiltration, and damage to Purkinje cells in the CNS. Mortality ranges from 1% (TBEV-Eur), to 8% (TBEV-Sib), to 20–40% (TBEV-FE). Convalescence is prolonged, and neurological and psychotic sequelae often include paresis and atrophic paralysis of the neck and shoulders.[27,45,104] A chronic form of the disease occasionally combines with a progressive course (called Kozhevnikov's epilepsy), in which progressive neuritis of the shoulder plexus, multiple sclerosis, and progressive muscle atrophy often develop.[105,106] The chronic form is registered in 1–2% of all TBE cases and is said to be the result of virus–immunity interactions.[19]

Many authors have noted a decreasing number of severe TBE cases.[103]

Diagnostics. Laboratory diagnosis of TBE involves both serological (ELISA, hemagglutination inhibition test (HIT), neutralization testing) and virological methods (virus isolation using a biological model of intracerebrally inoculated newborn mice, 5–6 g mice, cell culture), as well as highly sensitive RT-PCR and real-time RT-PCR.

Control and Prophylaxis. Specific and nonspecific prophylaxis tools are highly efficient if they are utilized correctly. Personal safety includes protection against ticks. Vaccination against TBEV has a long history of success. Mass vaccination of populations in the endemic territory is necessary. A full course of vaccination provides 98% safety.[102] All vaccines produced in Russia are effective in the entire area of distribution of TBEV, independently of the strain used to prepare the vaccine. Vaccination has reduced TBE morbidity down to single cases in Austria, the Czech Republic, and Slovakia.[107]

Single cases of TBEV among vaccinated persons need to be investigated because possible causes are personal peculiarities of the immune system and errors in the control of vaccine production.[108] The presence of brain tissue in vaccines produced on the basis of intracerebrally inoculated newborn mice was a source of danger for a long time: Demyelinating encephalitis could develop. This danger was eliminated after vaccines were developed which used TBEV strains that reproduced in cell cultures. In the 1960s, cell culture vaccines against TBEV were developed by E.N. Levkovich and G.D. Zasukhina, and their high efficiency was demonstrated during 1961–1964 in controlled epidemiological trials carried out by D.K. Lvov in Kemerovo Region, western Siberia (Figure 2.36). The total number of people tested was 1,779,000.[101] Wide use of vaccination is the most effective instrument for reducing TBE morbidity.[109–111]

Etiotropic treatment includes three groups of antivirals: (i) serological (specific anti-TBEV immunoglobulin, immune blood plasma); (ii) enzymes (ribonuclease); and (iii) interferon.[27,103,104]

8.2.1.4 *Japanese Encephalitis Virus*

History. Japanese encephalitis virus (JEV) was originally isolated by H. Hayashi in 1933 from a patient who died with encephalitis and then, again, in 1935 from a patient who died with a fever in Tokyo.[1,2] Before that, however, Japanese encephalitis (JE) epidemics was documented in Japan in 1903 and onward as "Ioshiwara cold." In the south of the Russian Far East, strains of JEV were known since the end of the 1930s (Figure 8.57).

JE played a role in the historical events of World War II. American military personnel massed on Okinawa and preparing to invade

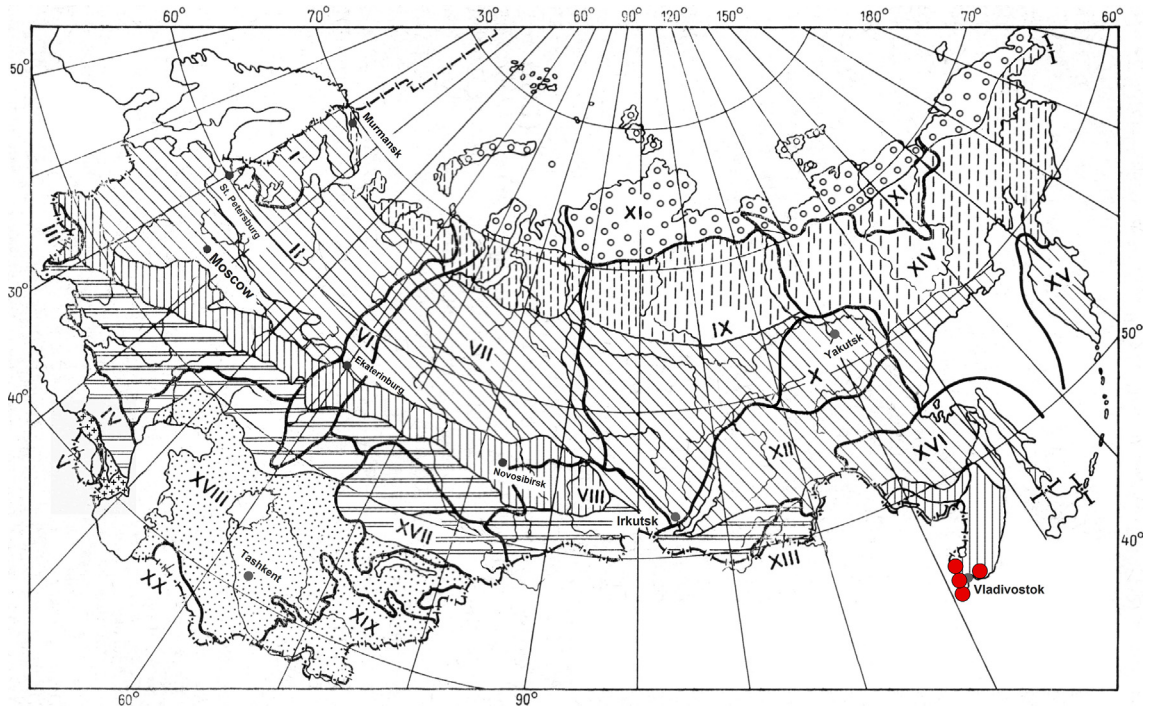


FIGURE 8.57 Places of isolation of Japanese encephalitis virus (JEV) (family Flaviviridae, genus *Flavivirus*) strains (●) in the former USSR. (See other designations in Figure 1.1.)

Japan were demoralized by an outbreak of encephalitis among the indigenous people. A fictionalized account of the risk from JE for American soldiers during World War II underscores the military risk.[3]

Taxonomy. Phylogenetic studies indicated that JEV isolates be divided into five genotypes, the distributions of which overlapped (Figure 8.58). Genotypes I, II, and III are most prevalent and are spread throughout Asia (Japan, China, India, Korea, Malaysia, and Vietnam), the Far East of Russia, and northern Australia. Genotypes IV and V are rarer and were isolated in Indonesia and India, respectively. Genotypes I and III are found mostly in temperate zones, whereas genotypes II and IV predominate in tropical zones.[4–6] Genetic diversity between strains of the different genotypes ranges from 9.1% to 16.6%.

Arthropod Vectors. JEV circulation in the equatorial and subequatorial climatic zones is year-round and is seasonal in the tropical, subtropical, and temperate belts, with a peak at the end of summer and the beginning of fall. JEV is brought from the equatorial and tropical climatic belts to the subtropical and temperate belt during the spring migration of birds.

About 30 species of mosquitoes are able to transmit JEV; nevertheless, only some of them are effective vectors. The main vector in Japan, the Philippines, the Korean Peninsula, China, the Indochinese Peninsula (except Malaysia), Indonesia, Sri Lanka, India, and Nepal is

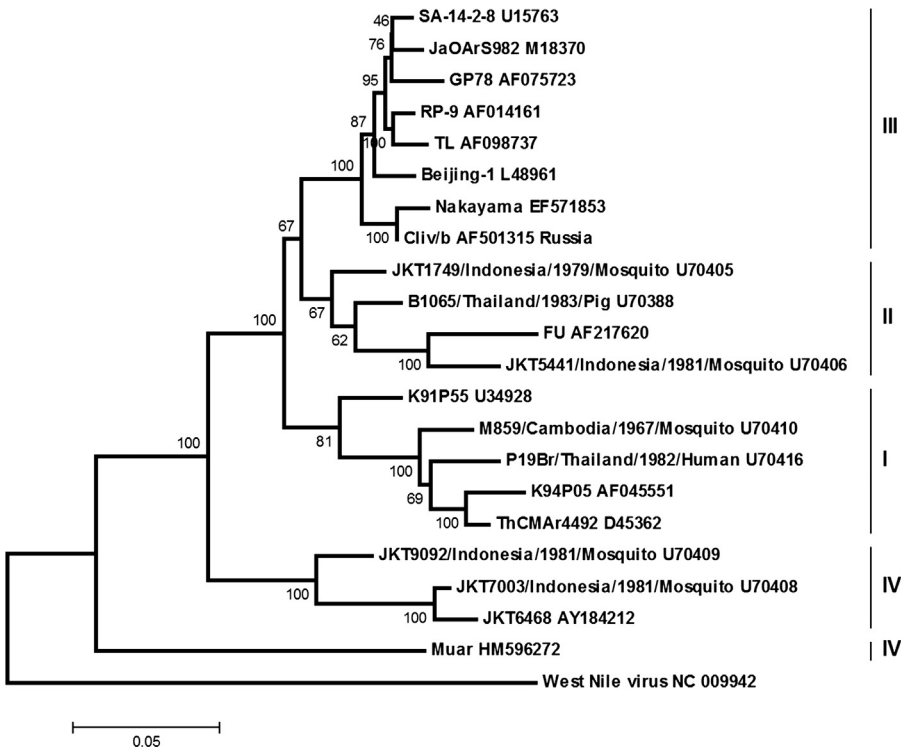


FIGURE 8.58 Phylogenetic analysis of E gene sequences of different isolates of JEV (family Flaviviridae, genus *Flavivirus*).

mosquitoes belonging to the *Culex vishnui* group (in particular, *Cx. tritaeniorhynchus*). Additional vectors are *Cx. vishnui* in India, Thailand, and southern China; *Cx. fuscocephala* in Malaysia, Thailand, and southern China; *Cx. gelidus* in Indonesia, Thailand, and Vietnam; and *Cx. annulus* —in southern China. The JEV contamination index reaches 1:200 among *Cx. tritaeniorhynchus* imagoes, 1:30,000 among *Cx. vishnui* larvae, and 1:550 among *Cx. gelidus* imagoes. Epidemics usually develop after plentiful precipitation and a long rise in environmental temperatures until they are no less than 25°C (but within the range 25−32°C).[7]

For a long time, the main vector for JEV in the south of Primorsky Krai in Russia was *Culex tritaeniorhynchus*. In the 1940s, as a result of both improvements in agriculture and meteorological changes, this species of mosquitoes consisted about 80% of all field collections. In subsequent years, however, their numbers abruptly declined, and by the 1960s the species represented only 0.15−0.75% of all mosquitoes collected. *Cx. pipiens* is an accessory vector, and *Aedes togoi* transmits JEV in seashore areas. JEV was also isolated in 1989 from *Ae. vexans*.[8,9]

Vertebrate Hosts. Aquatic and semiaquatic birds (especially herons) have the main significance in the natural cycle of JEV circulation. Regular transfer of JEV in migratory birds from endemic territories with year-round circulation of the virus to regions of the southern part of the temperate climatic belt (in particular, the southern part of Primorsky Krai, to the south from Lake Khanka[11]) is likely.[10] JEV transfer over hundreds of kilometers by infected mosquitoes is possible as well, especially in areas with a monsoonal climate (e.g., in Australia through the Torres Strait[12−14]). Birds transfer JEV from natural to synantropic biocenoses, where, thanks to *Culex tritaeniorhynchus* mosquitoes willingly attacking wild birds, pigs, persons, synantropic birds, and domestic animals (chiefly pigs), these all join into JEV circulation.[7] Infection in pigs could be inapparent, or it could be clinically expressed with encephalitis and a lethal outcome. The level of viremia in infected pigs is enough to infect mosquitoes. Such epizootics among pigs are, in effect, amplifiers for JEV, serving as prerequisites for the development of epidemics, first of all among people living in the countryside, but then among city dwellers as well.

Antibodies to JEV specifically were revealed among wild boars (83%), raccoons (59%),[14] and dogs (17%).[7] In the south of China, JEV was isolated from both Leschenault's Rousette (*Rousettus leschnaulti*), a species of fruit bat, and the little tube-nosed bat (*Murina aurata*),[15] and anti-JEV antibodies were identified in the blood of those animals.[16] JEV preservation in bats could be one of the mechanisms of the year-round circulation of the virus in its natural foci, with activation in the spring and subsequent replication and spreading in the summer and autumn.

In natural foci, birds are the principal vertebrate hosts contributing to transmission of the virus; in synantropic foci, pigs are the most important vertebrate hosts.[10,11] JEV has been isolated from the grey-headed bunting (*Emberiza fucata*), great cormorant (*Phalacrocorax carbo*), Japanese thrush (*Turdus cardis*), azure-winged magpie (*Cyanopica cyana*), Japanese wagtail (*Motacilla grandis*), barn swallow (*Hirundo rustica*), and night heron (*Nicticorax nicticorax*). Natural foci are situated in meadows. Of late, *Culex tritaeniorhynchus* has become more abundant in connection with intensive rice cultivation, portending the possibility of increased JEV circulation and epidemics.[17,18]

Epidemiology. All the territory of Japan, except for northern part of Hokkaido,[7] is endemic, but most diseases are registered near islands in a closed sea, as well as in Tokyo and adjacent prefectures.[3] Before 1966, outbreaks of JE emerged in Japan practically every year, with 1,200−2,700 patients seen.

Later, morbidity began to decrease to tens of cases per year. In the 1970a and 1980s, morbidity fell to the level of single cases per year. The main cause of the decrease was a significant drop in the population of the main JEV vector—*Culex tritaeniorhynchus* mosquitoes—as the result of a reduction in the acreage of rice fields as well as water pollution in places of mosquito habitation. In addition, the program of mass vaccination carried out annually among children of school age and a change in the structure of pork farms lessening the availability of pigs played a significant role in the falloff in the mosquito population.

JE is a serious problem in 20 countries of southeast Asia and Oceania.[19] During the last few years, more than 50,000 cases per year were registered, with about 20% lethality.[19] Morbidity increases annually in Bangladesh, Indonesia, Laos, Myanmar, North Korea, and Pakistan.[19,20] In addition, , the occurrence of an epidemic in southeastern Asian countries is becoming more and more likely because those countries are now seeking to increase their production of rice. The greatest risk of JE is said to be in China, Nepal, Sri Lanka, Thailand,[21] Laos, and Vietnam. JE is of the highest importance among all kinds of endemic encephalitis, potentially threatening nearly 50% of the population of our planet.[3] The disease especially affects military contingents, as it did the American army during the concentration of armies in Okinawa[3] and the Soviet army during the Battle of Lake Khasan (also called the Changkufeng Incident) in the south of Primorsky Krai.

Precursors of JEV circulated in Indonesia and then evolved into six genotypes.[22] Genotype III is widespread in a moderate climatic belt and often provokes epidemic outbreaks in eastern and southeastern Asia. Genotype I originated in Indonesia, circulated in Thailand and Cambodia in the 1970s and in South Korea and Japan in the 1990s, and has now completely replaced genotype III.[23] Genotype I got into Japan in two ways: from southeastern Asia and from mainland China.[24,25] Two island territories—the Philippines and Taiwan, in both of which genotype III circulates—were free of genotype I—and the Philippines remains free—but the genotype appeared in Taiwan in 2008.[26] The evolution of JEV led to the emergence of two new subclusters in 2009–2010; the two together have replaced genotype III. Until recently, the Qinghai-Tibet Plateau, in China, was free of JEV, but in August 2009 the virus was isolated from *Culex tritaeniorhynchus* mosquitoes there.[27] During an epidemic in September–November 2009, genotype I circulated in Japan.[28] In Nepal, on the northern border of India, JE has been known since 1978, after which outbreaks were observed annually.[9] JEV circulates in the north of Australia as well.[12,21]

JE claimed morbidity in the south of the Russian Far East (in Primorsky Krai) in 1938 during an expedition headed by P.G. Sergiev and I.I. Rogosin. Epidemics of JEV broke out in the region in 1938, 1939, and 1943. More than 800 cases were recognized between 1938 and 1943, with 68% reported in the extreme south of Primorsky Krai. The northern extent of this area is limited by the southern part of the Ussuri Lowland (about 42–43°N, 130–133°E). Enzootic JEV circulation without human morbidity has been documented, with the seroprevalence of residents estimated at about 10–20%.[11,18,29,30] JE cases occur mainly in August–September (but also when heavy rains are combined with high temperatures from April to September: ≥21°C in April, ≥23°C in June, ≥25°C in August, and ≥21°C in September).

Clinical Features. The clinical picture of JE varies from asymptomatic and easy feverish forms to an encephalitis syndrome. The ratio of clinical to asymptomatic forms is from 1:300 to 1:1,000, although the ratio in India in the 1970s and 1980s was from 1:20 to 1:30.[31–33]

The start of the disease is sudden, with fever (80%), headache, vomiting (24%), and symptoms of CNS destruction (most often, hemiplegia and articulation lesions)—in 12% of cases, and at the height of the illness in 65% of cases. About one-third of patients with CNS lesions recover completely.[34] Lethal outcomes are preceded by unconsciousness and then coma (20–44% of the total number of patients). Death comes in two-thirds of cases during the first week, in one-fourth during the second week, and in the rest of the cases in one month, from the onset of symptoms. After the disease, residual phenomena in the form of paralysis and mental issues are quite often observed.[28,32]

Control and Prophylaxis. Inactivated vaccines are used to immunize people,[19,29,33,35–37] live vaccines to immunize pigs and horses.[31] Vaccination and protection of pigs from mosquito attack and protection of humans from mosquitoes (through the use of repellents, mosquito nets, bed curtains, etc.) are recommended during epidemics among people. Mass vaccination has been carried out successfully in Japan, South Korea, China, and India.[19,28,33,35–37] Live vaccine manufactured on the basis of the Chinese strain SA 14–22 is is given in China, South Korea, and other countries in government programs aimed at expanding immunization of children.[19,20,33,35–37]

8.2.1.5 Tyuleniy Virus and Kama Virus

History. The prototypical strain LEIV-6C (deposition certificate 526 in the Russian State Collection of Viruses; authors: D.K. Lvov, V.L. Gromashevsky) of TYUV was isolated from Ixodidae ticks *Ixodes* (*Ceratixodes*) *uriae* collected from nests of Alcidae birds in August 1969 in the territory of the Russian Far East on Tyuleniy Island in the Sea of Okhotsk (48°29′N, 144°38′E) (Figure 8.59).[1–5] On the basis of electron microscopy, TYUV was classified as a member of the Flaviviridae family.[6] Subsequently, serological investigation of Tyuleniy antigenic complex revealed that TYUV belonged to the *Flavivirus* genus,[2,5] which includes (1) Meaban virus (MEAV), isolated from *Ornithodoros* (*Alectorobius*) *maritimus* ticks collected in July 1981 from the nests of herring gulls (*Larus argentatus*) in Meaban Bay in the French province of Brittany (47°31′N, 02°56′W);[7–9] (2) Saumarez Reef virus (SREV), isolated from *O. capensis* ticks collected in August 1974 from the nests of sooty terns (*Sterna fuscata*) on Saumarez Reef, a chain of coral islands in the Australian state of Queensland (22°00′S, 153°30′E)[10,11]; and (3) GGYV, isolated from *I. uriae* ticks collected in December 1976 in a nesting colony of penguins on Macquarie Island (a part of the Australian state of Tasmania) in the southern Pacific Ocean between New Zealand and Antarctica (54°30′S, 159°00′E).[12] Later, MEAV and SREV were categorized into the seabird tick-borne virus group whereas GGYV was classified into the mammalian tick-borne virus group.[13–15] Subsequently, TYUV was multiply isolated in the basins of the Sea of Okhotsk and the Bering and Barents Seas.[16–23]

Kama virus (KAMV) was isolated from *Ixodes lividus* ticks—obligatory parasites of the sand martin (*Riparia riparia*)—collected in August 1989 on islands of the Volga–Kama stretch of the Kuibyshev Reservoir in the Republic of Tatarstan in the central part of the Russian Plain (55°20′N, 49°40′E) (Figure 8.59).[24]

The complete genomes of TYUV and KAMV (GenBank ID: KF815939 and KF815940, respectively) were presented in a 1973 article in the *Journal of Medical Entomology*,[25] and it was established that KAMV was a new virus within the TYUV group of the *Flavivirus* genus.

Virion and Genome. TYUV is a prototypical virus of the Tyuleniy antigenic complex. The viruses of that complex belong to the ecological group of seabird tick-borne flaviviruses, which forms a distinct branch on the

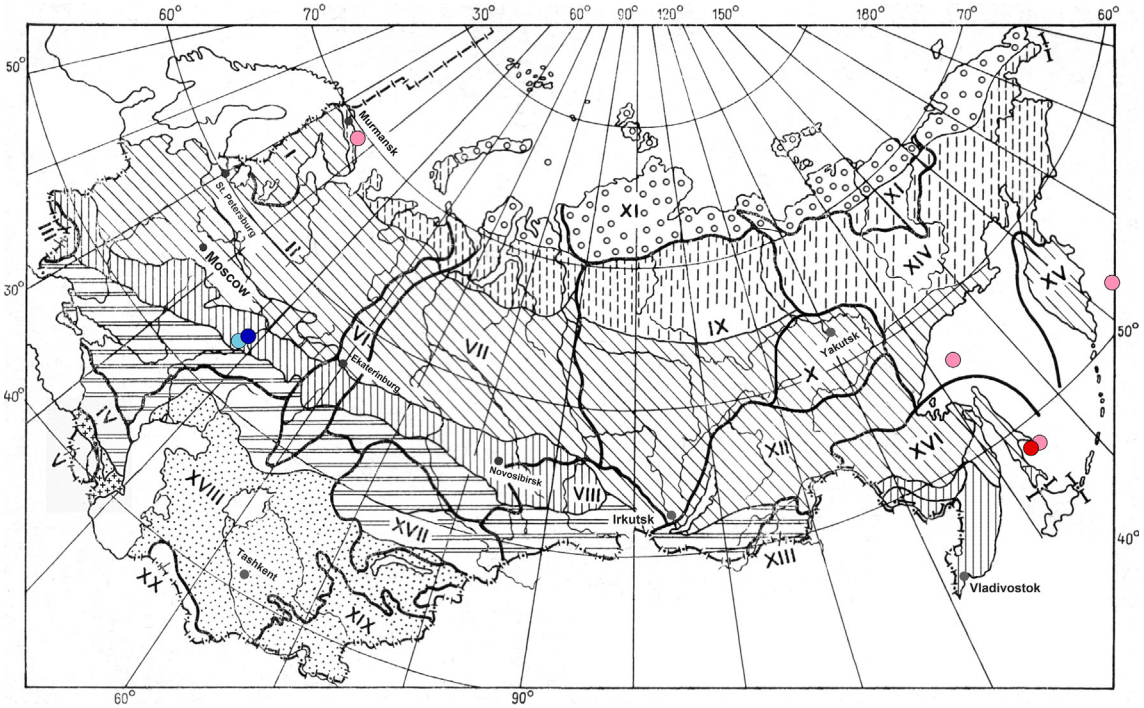


FIGURE 8.59 Places of isolation of TYUV and KAMV (family Flaviviridae, genus *Flavivirus*) in Northern Eurasia. Red circle: prototype strain TYUV/LEIV-6C identified by complete genome sequencing; Pink circles: strains of TYUV identified by serologic method; Dark-blue circle: prototype strain KAMV/LEIV - 20776 Taj identified by complete genome sequencing; Light-blue circle: strain of KAMV identified by serologic methods. (See other designations in Figure 1.1.)

phylogenetic tree.[26] Four species are known in the Tyuleniy antigenic complex: TYUV (in Russia and the United States), MEAV (in Europe), SREV (in Oceania) and KAMV (in Russia). The genetic similarity between the seabird tick-borne flaviviruses and the mammalian tick-borne flaviviruses is about 42% nt. A full-length genome comparison showed that the similarity among the four viruses in the Tyuleniy antigenic complex is 70% nt and 85% aa, on average. TYUV LEIV-61C, isolated in the Russian Far East, has 86% nt and 97% aa identities with TYUV isolated on the Pacific coast of the United States. Kama virus (strain LEIV-Tat20776) has 70% nt identity with the other viruses of the Tyuleniy antigenic complex (MEAV, SREV, TYUV). The similarity of the polyprotein precursor of KAMV is 74% aa with each of TYUV and SREV, 78% aa with MEAV.[25]

Arthropod Vectors. TYUV is distributed over the basins of the Sea of Okhotsk and the Bering and Barents Seas. The infection rate of *Ixodes uriae* in the Pacific part of the virus's distribution is 4.5 times greater than in the Atlantic part (Table 8.31).[16,18–23] Outside of Northern Eurasia, TYUV is distributed over the west coasts of the United States (chiefly in Oregon) and Canada.[27,28] The infection rate of nymphs and larvae of *I. uriae* is one-twentieth to one-half the infection rate of the imago. The infection rates of *I. uriae* females and males (the males have only a rudimentary hypostome and do not feed) are practically the same.[21] These data testify to the transphase and transovarial transmission of TYUV. (The efficiency of this type of

TABLE 8.31 Infection Rate of TYUV (Family Flaviviridae, Genus *Flavivirus*) Among *I. Uriae* in Nesting Colonies of Alcidae Birds in the Basins of the Sea of Okhotsk and the Bering and Barents Seas

	Far East				Europe
	Okhotsk Sea Basin		Bering Sea Basin		Barents Sea Basin
	Sakhalin Region		Kamchatka Krai	Chukotka Okrug	Murmansk Region
Results of investigation	Tyuleniy Island (48°29′N, 144°38′E)	Iona Island (56°24′N, 143°23′E)	Ariy Kamen Island (Commander Islands) (55°13′N, 165°48′E)	Bering Strait Coast (64°50′N, 173°10′W)	Kharlov Island Near Kola Peninsula (68°49′N, 37°19′E)
Number of strains	9	4	22	0	2
Infection rate (%)	0.066	0.205	0.116	0	0.022
Total Number of strains			35		2
Number of ticks tested			34,569		8,994
Infection rate (%)			0.101		0.022

transmission is about 5%.) Attempts to isolate TYUV from *I. signatus* ticks were unsuccessful.

The presence of antibodies to TYUV among local cows and indigenous people of the Commander Islands[19,21] indicates the possible role of sanguivorous mosquitoes (e.g., *Aedes communis*, *Ae. punctor*, and *Ae. excrucians*) in infection. Mosquitoes could also take part in virus circulation: Their infection rate from the end of July to the beginning of August reaches 0.3% in nesting colonies of seabirds and 0.1% on the seacoast.

Experimental infection of TYUV on the model of *Aedes aegypti* demonstrated the presence of the virus 4–31 days after inoculation, with 1.5–2.0 lg LD_{50}/10 mcL on days 4–17; 3.0–3.5 lg LD_{50}/10 mcL on days 23–27; and 1.5 lg LD_{50}/10 mcL on day 31. The transmission of TYUV during the feeding of infected mosquitoes on mice was established 7–19 days after infection of the mosquitoes. In *Culex pipiens molestus*, TYUV was detected 5–21 days (the period of observation) after infection, with 1.0–2.0 lg LD_{50}/10 mcL.[20]

Vertebrate Hosts. Migratory seabirds play a role in the exchange of TYUV group flaviviruses between the Northern and Southern Hemispheres.[18,29]

Investigation with the help of indirect complement-binding reactions of sera samples from 2,500 birds collected in the Far East revealed that the maximum TYUV infection rate takes place in Brünnich's guillemots (*Uria lomvia*), common murres (*U. aalge*), and tufted puffins (*Fratercula cirrhata*). Lower rates were seen in pelagic cormorants (*Phalacrocorax pelagicus*), red-faced cormorants (*Ph. urile*), glaucous-winged gulls (*Larus glaucescens*), kittiwakes (*Rissa tridactyla*), northern fulmars (*Fulmarus glacialis*), and sandpipers (Scolopacidae).[17,18,20,21,23,30] The presence of specific anti-TYUV antibodies among sandpipers—red-necked phalaropes

(*Pholaropus lobatus*) and ruffs (*Philomachus pugnax*)—testifies to the possibility that *Ixodes uriae* ticks have penetrated into the Southern Hemisphere, whereas Alcidae birds could transfer the virus through circumboreal routes .[27,28,31] Considering the annual migrations of these birds, TYUV can be found within the *I. uriae* area of distribution in nesting colonies of puffins.

About 90% of adult and 10% of juvenile northern fur seals (*Callorhinus ursinus*) on the Commander Islands have specific anti-TYUV antibodies, implying that these animals are involved in the circulation of that virus. A TYUV strain was isolated from the Arctic ground squirrel (*Citellus* (*Urocitellus*) *parryii*) on the southeastern coast of the Chukotka Peninsula (63°N, 180°E). This event is one more argument for virus splash into the continent, with rodents included in virus circulation.

In the tundra of the Kola Peninsula seacoast, antibodies specific to TYUV were detected among cattle (28.1%) as well as red-necked phalaropes (*Phalaropus lobatus*), snow buntings (*Plectrophenax nivalis*), ruffs (*Philomachus pugnax*), and rodents: tundra voles (*Microtus oeconomus*).[21] Thus, in the Atlantic part of its distribution, TYUV also tends to penetrate into the continent.

Experimental infection of kittiwakes (*Rissa tridactyla*), herring gulls (*Larus argentatus*), and Brünnich's guillemots (*Uria lomvia*) was followed by the development of clinical features with CNS lesions and lethal outcomes.[32]

Epidemiology. The indigenous population in the Far Eastern part of TYUV distribution has specific anti-TYUV antibodies: 8.4% in tundra on the coast of the Chukotka Peninsular, 4.2% in forest–tundra on the coasts of the Sea of Okhotsk and the Bering Sea, 7.4% —in taiga on Sakhalin island, and 9.1% in tundra on the coast of the Kola Peninsula.[21]

The development of fever in humans visiting nesting colonies of seabirds on the coast of the Barents Sea has been described in the literature.[33]

Ecological Peculiarities of TYUV and KAMV Distribution. Penetration of TYUV from the Northern to the Southern Hemisphere is carried out by about 20 species of birds, mostly turnstones (*Arenaria interpres*), that nest in the north of Asia and overwinter in Australia and New Zealand. Wedge-tailed shearwaters (*Puffinus pacificus*) nest in the Southern Hemisphere and carry out an annual migration along the coasts of the Pacific Ocean up to Northern Eurasia and North America.[23,34]

Close genetic relations found between TYUV and KAMV have not been explained yet because information is lacking about ecological links between Alcidae birds in the north and bank swallows in the central part of the Russian Plain. Nontheless, the closeness demonstrates an ancient link between the flaviviruses and Ixodidae ticks—obligatory parasites of colonial and burrow-shelter birds not only on the ocean coast, but also on the continental part of the distribution of those viruses.[19,20,23,35,36]

MEAV and SREV, which are genetically close to TYUV,[25,26] could be intermediate evolutionary branches between tick-borne viruses of seabirds and later mammalian viruses transmitted by ticks.[13,15]

The main vector of TYUV in subarctic regions—*Ixodes Uriae*, adapted to seabirds—is replaced by the *Ornithodoros capensis* complex or *Argas* spp. in the subtropics and tropics.[18,27] The northern boundary of the *Argas* genus distribution is limited by a July isotherm of 15–20°C and of the *Ornithodoros* genus by 20–25°C in Europe and 25–30°C in Asia.[37] The vector of KAMV—the *I. lividus* tick—has transpaleoarctic distribution, from the British Isles in the west to Japan in the east and from 62°N down to 43°S. This species of tick has an extrazonal distribution in the diggings of bank swallows (*Riparia riparia*) made in the soft ground of steeps along the banks of rivers and lakes in taiga, leaf forest, forest–steppe and

steppe climatic belts. *I. lividus* ticks are typical parasites of—burrow-shelter birds and relate strictly to the life cycle of the host: After the appearance of birds in the nesting areas in May, larvae begin to feed. In June, nymphs feed on the nestlings; female imagoes also feed on the nestlings, but male imagoes do not.[38]

Given the presence of KAMV—a virus closely related to TYUV—in the central part of the Russian Plain, it is worthwhile, and even necessary, to carry out a wider search for TYUV analogues on the continental part of Northern Eurasia.

8.2.1.6 Dengue Virus (imported)

History. Dengue fever (DENF), etiologically linked to Dengue virus (DENV) (family Flaviviridae, genus *Flavivirus*), has been known in Asia, Africa, and America since the end of the eighteenth century.[1,2] Wide epidemics of DENF appeared in southeastern Asia after World War II.[3] According to WHO data, DENF morbidity, including imported cases, has been detected in more than 100 countries of Asia, Africa, and Europe. More than 2.5 billion people on Earth are under the threat of DENF. About 50 million people fall victim to DENF annually.[4] American armies sustained heavy losses as the result of DENF during World War II,[3] as well as during 1960–1990 in Vietnam, the Philippines, Somalia, and Haiti.[5] Simultaneous outbreaks of DENF and Chikungunya fever often occur.[6]

The virus etiology of DENF and its transmission by mosquitoes was established by P.M. Ashburn and C.F. Craig in experiments using volunteers at the beginning of the twentieth century.[7] DENV-1 was isolated in 1944 from the blood of patients with fever on the Hawaiian Islands,[8] DENV-2 in 1944 from the blood of patients with fever on New Guinea,[8] DENV-3 in 1956 from the blood of patients with fever in the Philippines,[9] and DENV-4 in 1956 from the blood of patient with fever during epidemics in Manila.[9]

Taxonomy. Four different serotypes of DENV form a distinct phylogenetic lineage on the mosquito-borne flavivirus lineage (Figure 8.47). Genetic variation among different strains suggested that DENV be divided into distinct genetic clusters considered as genotypes. The genetic diversity of DENV is best exemplified in DENV-2, the different strains of which are divided into four genotypes: Asian 1, Asian 2, American/Asian and so-called Cosmopolitan.[10] DENV-3 strains are divided into five genotypes (I–V),[11] and DENV-4 strains form three genotypes.[12] In general, a particular genotype is linked to specific geographical regions and that genotype may be used in describing imported cases of DENV infection.

Arthropod Vectors. DENF belongs to natural-foci diseases. Its vectors are anthropophilic species of mosquitoes: *Aedes aegypti* and *Ae. albopictus* in synantropic natural foci. Humans are the only vertebrate hosts in synantropic natural foci, whereas wild mammals are involved in virus circulation in sylvatic natural foci. Vectors in equatorial Africa are *Ae. furcifer*, *Ae. vittatus*, *Ae. tailori*, and *Ae. luteocephalus*.

Vertebrate Hosts. In southastern Asia, the vertebrate hosts of DENV are macaques (genus *Macaca*) and surilis (genus *Presbytis*) living in the rain forests of equatorial climatic belts; the main vector is *Aedes niveus*; a circulation of DENV-{1, 2, 4} has been identified. Natural foci of DENV were also found in the eastern part of equatorial Africa, in Senegal and Nigeria. The vertebrate hosts are patas monkeys (*Erythrocebus patas*); wild strains are considered possible precursors of epidemic ones. Among humans, wild strains provoke slight clinical forms of Dengue fever.[13–15]

Epidemiology. DENF has an epidemic character involving tens of thousands of people in southeastern Asia, Oceania, the Caribbean basin, Central and South America, and Africa. The transmission pathway is a mosquito bite,

mainly by members of the *Aedes* genus. These mosquitoes are able to transmit DENV in 8–10 days after feeding on a sick person. About 60–70% of the human population falls victim to DENF during epidemics.[15]

DENV continues to circulate actively and to provoke wide epidemics. For example, all four types of DENV exist in Sri Lanka, with new clades replacing old ones, accompanied by a severe clinical picture.[16,17] In the 1980s, a new wave of DENF epidemics began to develop in Sri Lanka, India, Pakistan, and Central and South America.[18,19] These epidemics were linked mainly to the relatively new DENV-3, but to DENV-1 and DENV-2 as well.[20] In some cases—for instance, in Myanmar[21] and China[1]—all four types of DENV circulated simultaneously.

Clinical Features. The incubation period is 2–7 days. The start of the disease is quick, with fever and with frontal and retroorbital headache. Lymphadenopathia, rash in macule and papule forms (not always), leukopenia, skin hyperesthesia, changes in taste, loss of appetite, and muscle and joint pains gradually develop. Then, after 1–2 days of normal body temperature, the second wave of fever develops, accompanied by a measleslike rash. The palms and soles are rash free. Severe CNS complications have been described to arise in endemic regions (e.g., Brazil).[3]

The hemorrhagic clinical form of DENF, with shock and a high level of lethality (especially among children), was originally seen in the Philippines in 1953. Later, this clinical form was registered in India, Malaysia, Singapore, Indonesia, Vietnam, Cambodia, and Sri Lanka, as well as on islands in the Pacific. According to WHO data, more than 1.3 million patients had hemorrhagic DENF from 1956 to 1992, with 14,000 lethal outcomes. Starting from 1975, hemorrhagic DENF has become the main cause of hospitalization and deaths among children in the countries of southeastern Asia.[1]

The hemorrhagic form of DENF usually develops after a secondary infection by a type of DENV different from the primary one. The primary type of DENV is not neutralized, but fragments antigen binding (Fab)-associated enhancement of the infection occurs. For example, in French Polynesia in 2000, two years after epidemics of DENV-2, an outbreak etiologically linked to DENV-1 emerged and hemorrhagic DENF was detected among children 6–10 months and 4–11 years old.[16] Five symptoms are characteristic of the hemorrhagic clinical form of dengue: high temperature, rash, hemorrhagia, hepatomegalia, and insults to the circulatory system. Thrombocytopenia with blood condensation also occurs.[4] Hemorrhagic DENF can be without shock or can precede it. Shock develops in 3–7 days of the disease, wheninsults to the circulatory system appear: The skin becomes cold, sticky, and cyanochroic; the pulse rate increases; and drowsiness appears. In the absence of antishock actions, patients die within 12–24 h. The severity of the disease depends on a number of factors: the infection titer in the blood, the type of DENV, its biological properties, and more.[22–24]

Imported Cases of Dengue. There is a high risk of DENV infection for visitors to endemic regions, with consequent penetration of the virus into nonendemic regions.[1,25]

DENF has occurred in Spain in the past (e.g., in Cádiz in 1778). Several tens of human cases are introduced into the country each year from equatorial and subequatorial regions. DENV-1 and DENV-2 caused a huge outbreak in Greece in August–September of both 1927 and 1928: in those periods, about 650,000 of 700,000 inhabitants of Athens and Piraeus contracted DENF, including hemorrhagic forms and about 1,000 lethal outcomes.[26] Penetrations of DENV also took place in the Netherlands in 2006–2007[27] and in Japan,[28] France,[29] northern Italy,[30] and Germany in 2010.[31]

During 2002–2011 in Russia, among patients with fever from the risk group that visited tropical–equatorial countries, 48 cases of DENF were identified with the help of serological investigation (22 cases arrived from Indonesia; 11 from Thailand; 3 each from Vietnam and India; 2 each from Venezuela and the Dominican Republic; and 1 each from Sri Lanka, Malaysia, Singapore, Sierra Leone, and Costa Rica).[32–34] In 2013 in Russia, 30 cases of DENF were identified in Moscow, 8 in St. Petersburg, and 8 imported strains of DENV were isolated.

The risk of DENF for Europe has appeared again with the introduction of *Aedes albopictus* and *Ae. aegypti* mosquitoes in the countries of the Mediterranean and Black Sea basins.[35] Stable populations of both these species were found on the southeastern coast of the Black Sea (in Krasnodar Krai, Russia, as well as in Abkhazia).[36–38]

Control and Prophylaxis. The main approach to prophylaxis is to struggle against mosquito vectors. During the 1950s and 1960s, a program against *Ae. aegypti* mosquitoes that was unprecedented in terms of scale and expense was conducted in America, but it was stopped in 1970; as a result, in 1995 the number of *Ae. aegypti* mosquitoes was estimated to be same as that before the program began.[39] The struggle against mosquito vectors in Singapore turned out to be more successful, but still did not prevent DENF morbidity.[40]

Investigations into four-component vaccines are far from completion today.[22,41]

Express methods of DENF diagnostics are used in airports.[42] WHO issues a reference guide for the diagnosis, treatment, prophylaxis, and control of DENF.[43]

8.2.1.7 Sokuluk Virus

History. Prototypical strain LEIV-400K of Sokuluk virus (SOKV) (family Flaviviridae, genus *Flavivirus*, Entebbe bat antigenic complex) was isolated from internal parts of the bat *Vespertilio pipistrellus* collected in 1970 in the garret of a house in Sokuluk District, Kyrgyzstan (42°30′N, 74°30′E) (Figure 8.60).[1–4] Later, in 1971–1973, SOKV was isolated from Argasidae and Ixodidae ticks, as well as from birds, in Fergana Valley and Chuysky Valley in central Asia (Table 8.32, Figure 8.60). Further serological investigations with the help of HIT revealed that SOKV belongs to the Flaviviridae family, and with the help of complement-fixation testing (but not neutralization testing), to the Entebbe bat serogroup.[1–3] A prototypical strain of this serogroup was isolated from a Kenyan big-eared free-tailed bat (*Tadarida lobata*) collected near Entebbe, Uganda, in July 1957.[5]

Taxonomy. The genome of SOKV was sequenced, and genome analysis showed that the virus is related most closely (71% nt and 79% aa identities) to Entebbe bat virus (ENTV). SOKV has about 50% nt and 55% aa identities with other flaviviruses, except viruses of the Rio Bravo (RBV) and Modoc (MODV) groups (<50% similarity).[6] No arthropod vector of ENTV and SOKV has been established; however, phylogenetic analysis based on a full-length genome comparison placed SOKV and ENTV together on a distinct branch of mosquito-borne flaviviruses related to YFV and Sepik virus (SEPV) (Figure 8.47).

Arthropod Vectors. According to serological data, domestic animals do not take part significantly in SOKV circulation, although antibodies to SOKV were detected among cows and sheep. Isolation of SOKV from birds that were known not to have made contact with obligatory parasites of bats, as well as the presence of positive sera from humans and domestic animals, suggest the participation of mosquitoes in SOKV circulation. Transmission of the virus by bats could be carried out by *Argas vespertilionis* and *Ixodes vespertilionis*.[7–10]

Vertebrate Hosts. More than 20 flaviviruses were isolated from bats (order Chiroptera); about half are unique to these mammals.[11]

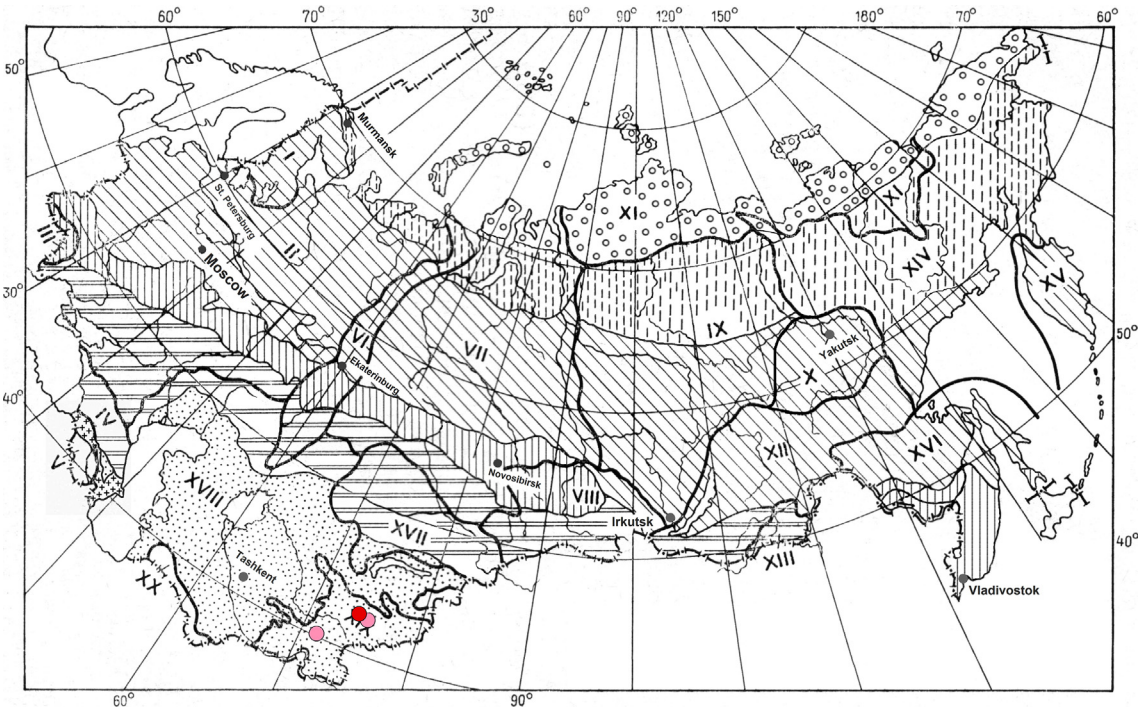


FIGURE 8.60 Places of isolation of SOKV (family Flaviviridae, genus *Flavivirus*) in Northern Eurasia. Red circle: prototype strain SOKV/LEIV-400K identified by complete genome sequencing; Pink circles: strains of SOKV identified by serological methods. (See other designations in Figure 1.1.)

TABLE 8.32 Isolation of SOKV on the Territory of Kyrgyzstan (1971)

Source of isolation			Location of material collection		Number of strains
Class	**Family**	**Species**	**Territory**	**Station**	
Mammalia	Vespertilionidae	Bat (*Vespertilio pipistrellus*)	Fergana Valley	House garret	2
Avis	Motacillidae	White wagtail (*Motacilla alba*)	Chuysky Valley	Settlement	1
	Hirundinidae	Barn swallow (*Hirundo rustica*)	Chuysky Valley	Nesting colony in the house	1
	Alcedinidae	Common kingfisher (*Alcedo atthis*)	Chuysky Valley	Natural biocenosis, nest near the bank of the river	1
Arachnida	Argasidae	*Argas vespertilionis* ticks	Fergana Valley	Collected from *Vespertilio pipistrellus*	2
		Argas vulgaris ticks	Chuysky Valley	Digging colony of birds	2
	Ixodidae	*Hyalomma marginatum* ticks	Fergana Valley	Collected from the cattle	1

Bats of the suborder Microchiroptera are susceptible to a number of flaviviruses: JEV[12]; Dakar bat virus (DBV)[13–16]; Bukalasa bat virus (BBV)[17]; ENTV[18]; RBV,[19,20] closely related to MODV, from the deer mouse (*Peromyscus maniculatus*), in the north of California[21]; Montana Myotis leukoencephalitis virus (MMLV)[22,23]; Carey Island virus (CIV)[17]; Phnom Penh bat virus (PPBV)[24]; and Yokose virus (YOKV).[25]

The insectivorous bats *Vespertilio pipistrellus*, from which SOKV was isolated, belong to the evening bats family (Vespertilionidae), which is active during the evening and at night. Their daylight shelters are situated mostly in house garrets. *V. pipistrellus* is distributed over Europe, the Mediterranean, the Caucasus region, and central Asia. A part of the population overwinters in Africa, where infection by local viruses (e.g., BBV, DBV, ENTV) could occur.

Experimental infection of sparrows (*Passer montanus*) resulted in SOKV being detected in internal parts of infected birds on the 8th and 25th days after inoculation.[26]

Epidemiology. There are no laboratory-confirmed human cases of SOKV infection. Nevertheless, the proximity of SOKV hosts (bats) to human habitats, as well as the presence of encephalitis and hemorrhagic fever agents among the flaviviruses, suggest that SOKV may be dangerous to humans.

Complement-binding specific anti-SOKV antibodies were detected among humans in Kyrgyzstan and Turkmenistan (6.2% and 4.0%, respectively), testifying to recent infection events.[1–4,7,9,10,16,27–31]

8.2.1.8 West Nile Virus

History. WNV (family Flaviviridae, genus *Flavivirus*), theetiological agent of West Nile fever (WNF), was first isolated during research on YFV in 1937 from the blood of a native of Uganda who was suffering a mild fever.[1] The strain isolated, B956, belongs to genetic lineage II. (See "Taxonomy" next.) Strain Eg101, isolated from the sera of a child without clinical signs in Egypt,[2] is the prototype for African genetic lineage I, widely used for investigations. WNV belongs to the JEV group, has the broadest antigenic properties, and, on theoretical grounds, appears to be the most ancient member of the *Flavivirus* genus.[3] Low-passaged WNV strains are known by many investigators to be common causes of laboratory infection, apparent or inapparent.[4]

Taxonomy. Phylogenetic analysis revealed that different geographic isolates of WNV could be grouped into two major genetic lineages (Figure 8.61). Lineage I includes strains from Africa, southern and eastern Europe, India, and the Middle East. Lineage II includes isolates from west, central, and east Africa, as well as Madagascar. Lineage 1 can be subdivided into three clades: Clade 1a consists of strains from Europe, Africa, the United States, and Israel. The topotypic isolates of WNV in Australia—Kunjin virus (KUNV)—belong to clade 1b, and clade 1c is formed by isolates from India.[5] Subsequently, two genetically divergent Rabensburg strains—97–103 (isolated in the Czech Republic) and LEIV-Krnd88-190 (isolated in Russia)—were proposed to form novel lineages III and IV, respectively.[6–8] A fifth lineage was formed by strains from India.[9] Phylogenetic analyses based on complete genomic sequences revealed that the various lineages differed from each other by 20–25%. A putative novel sixth lineage has been detected in Spain in 2006, but only a partial sequence of the NS5 gene of this isolate is available in GenBank.[10]

World Distribution. The distribution of WNV in Northern Eurasia, and indeed, in the whole world, covers vast territories within the equatorial, tropical, and temperate (the southern part) climatic belts in Africa, Europe, Asia, Australia, and North America (the last starting from 1999).

In Africa, it is very difficult to find a country or landscape in which WNV has not been

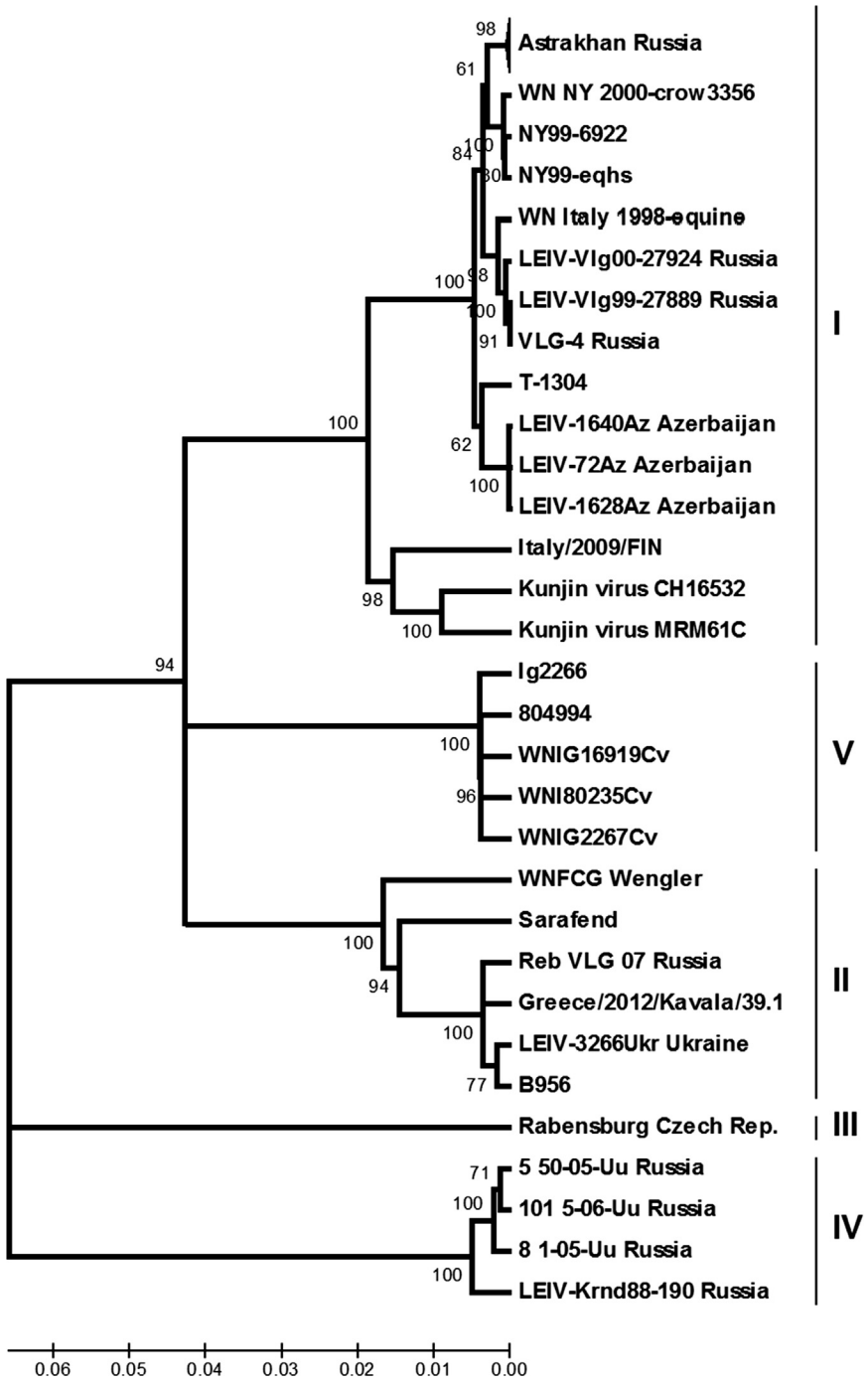


FIGURE 8.61 Phylogenetic tree constructed on the basis of a complete genome analysis of different strains of WNV.

detected by either a virological or serological approach. The isolation of this virus from a wide array of species of birds, mosquitoes, Ixodidae and Argasidae ticks, and domestic animals as well as humans testifies to the ecological plasticity of the virus and therefore to its ability to adapt to different ecological conditions. Two genetic lineages circulate in Africa: the first, which dominates, and the second.

Sporadic morbidity and epidemic outbreaks permanently take place in a number of African countries, especially the Republic of South Africa, where a wide outbreak with at least 3,000 human cases occurred in 1974 after an active period of rain. According to a report from the Pasteur Institute, during the last 10–15 years alone, epidemic outbreaks were registered in Algeria (in 1994, with more than 50 cases and 8 deaths, and in 1997, with 173 cases), in Tunisia (during 1997–2003, with 173 cases), Morocco (in 1996 and 2002; the epidemic reached both humans and horses), in Senegal (in 1993), and in Kenya (in 1998).[11] New centers of infection continue to be arise in Africa—for example, in 2009 in Morocco, where morbidity among people and horses was observed and 3.5% of birds had specific anti-WNV antibodies,[12] and in 2010 in the Republic of South Africa, where there were a number of lethal outcomes.[13]

The wide distribution of WNV in Africa and its circulation among populations of the majority of the continent's species of local and migrating birds indicates that the virus is able to penetrate to southern Europe and western Siberia through the birds' migration pathways. Most of the birds nesting in or migrating through the Volga delta overwinter in Africa.[14] Thus, Africa is the main source of penetration of WNV genotypes I and II into southern Europe and western Siberia.

In Asia, a peculiar third genotype of WNV appears to be circulating in the Indian subcontinent.[11] A prototypical strain of WNV genotype 3 was isolated from *xCulex vishnui* mosquitoes in southeastern India, and human morbidity was identified in India, Pakistan, and Israel. Taking into account the fact that most of the birds from western Siberia and many from eastern Siberia overwinter in India and other countries of southern Asia, there is a high probability that WNV genotype 3 has penetrated into Siberia. Also in Asia, both epidemics and sporadic cases etiologically linked with the first genotype of WNV have arisen regularly in Israel since at least1958. One such outbreak was observed in 1999–2000.[15] Surveillance in South Korea does not indicate any WNV circulation in that country.[16]

In Australia and Oceania, the Kunjin variant of the first genotype of WNV appears to be circulating.[17–19] KUNV could be introduced into Northern Eurasia (in eastern Siberia and the Far East) by migrating birds overwintering in southeastern Asia and Australia.[11,14] In 2011, an outbreak among horses in New South Wales, Australia, was identified.[20]

In central Europe, for a long time only two strains of WNV were known: one isolated in from *Aedes cantans* in 1972 in western Slovakia and the other isolated from *Ae. vexans*, *Ae. cinereus*, and *Culex pipiens* in 1997 in the Czech Republic, near the Austrian border. Anti-WNV antibodies were identified in the Czech Republic among 1.4–9.7% of birds, including crows, daws, turtle doves, common kestrels, ducks, coots, and thrushes. Later, two strains of the so-called Rabensburg genotype of WNV were isolated from *Cx. pipiens* in 1997 and 1999 in the Czech Republic.[21–23] The strain belonging to the second lineage of WNV was isolated from a goshawk in Hungary.[7]

In 1996 in Tuscany, Italy, Usutu virus (USUV), which is closely related to WNV, was isolated during an epizootic episode among birds, especially thrushes (*Turdus merula*), and then, again, in 2001 in Austria. Later, this virus was found in Hungary, Switzerland, and Germany.[24]

Practically all of the southern European countries are endemic for WNV.[25,26] Especially tragic events unfolded in Romania, where there was an epidemic in July–October 1996 with a peak at the end of August to the beginning of September in the southeastern part of the country, downstream of the Danube River. Six administrative units and Bucharest were affected, among other jurisdictions. Human morbidity reached 12.4%, and 835 patients with CNS insult were hospitalized. The number of patients with fever was at least 10 times more, and the number of infected individuals 100–300 times more. The outbreak, which dragged on until 2000,[27] testifies to the development of a city epidemic form of WNF. The virus belonged to the first genotype of WNV and probably was brought to Romania by birds from Africa.

WNV distribution in Europe indicates an especially high risk of a WVF outbreak in deltas of the large rivers—the Rhône in France and the Danube in Romania—through which the main migratory paths of birds overwintering in Africa lie.[14] In the recent past, WNV has been active in Europe in Italy,[28,29] Greece,[30,31] Spain,[10] Poland,[26] the Czech Republic,[3,22] and France.[22] Infected mosquitoes were imported into Great Britain from the United States by airplane travel.[32]

As for North America, before 1999 that continent was free of WNV. Penetration of WNV into America most likely happened by infected mosquitoes in the holds of ships from ports in the Mediterranean Sea or Black Sea.[11] Fifty-six cases of human WNF were revealed in New York City and its surroundings at the end of July–September 1999, with a peak in the second half of August. Seven cases (12.5%) had a lethal outcome. The virus was found in *Culex* sp. and *Aedes vexans* mosquitoes caught in September–October in New York City and in the states of New Jersey and Connecticut. Positive results were obtained by RT-PCR during an investigation of brain tissues of dead birds: crows, seagulls, storks, herons, ducks, cuckoos, pigeons, jays, robins, hawks, and eagles. The genomes of the strains that were isolated were found to belong to the first genotype and were close to the strains isolated in 1996 in Romania and in 1998 in Israel.[33] In 1999, WNV was registered in the United States, probably translocated there by migrating birds or by infected mosquitoes inhabiting the holds of visiting ships. WNV was found in Florida and on the Cayman Islands. In the spring of 2002, WNV extended its coverage to the eastern part of the United States through the central and Mississippi migratory pathways. Also in 2002, the virus reached the central regions of the United States and southern Canada and, in the fall of that year, Mexico, Jamaica, other Caribbean countries and Central and South America (Cuba, Guatemala, and the archipelago of the Lesser Antilles islands). Then, in 2004, WNV penetrated to California through the Pacific migratory pathway.

By 2003–2004, practically all the territory of the United States, southern Canada, and Latin America became endemic with high morbidity and mortality.[34] The greatest morbidity in the United States was found in the states of NorthDakota, South Dakota, and Nebraska.[27,35] The number of diseased individuals reached 4,000–9,000 cases in separate years. During 1999–2006 in the United States, more than 16,000 WNF cases were identified, with more than 600 (4%) succumbing to the disease. The economic damage was estimated in billions of dollars.[36,37] Today, WNV continues to circulate in the United States.[38,39] Morbidity grew in the states of Louisiana and Mississippi after Hurricane Katrina.[40] In Montana, the infection rate of people living in close proximity to a colony of pelicans (*Pelecanus erythrorhynchos*) is five times higher than in other regions of the state.[41] In a sea park in Texas, grampuses (*Orcinus orca*) contracted encephalitis and died,[42] and previous episodes of polyencephalomyelitis

were revealed among seals (*Phoca vitulina*). Also in Texas, three new genetic clades of WNV were found, testifying to rapid evolution of the virus on the American continent.[43] In 2012, an epidemic arose again, accompanied by a large number of lethal outcomes. In Texas, a state of emergency was declared.

Northern Eurasia. In Northern Eurasia, on the basis of the results of multiple investigations, the distribution of WNV includes Moldova, Ukraine, Belarus, Armenia, Azerbaijan, Georgia, Kazakhstan, Tajikistan, Kyrgyzstan, Uzbekistan, Turkmenistan, the south of the European part of Russia (the desert, semidesert, steppe, and forest–steppe landscape belts), and western Siberia.[11,35,44]

The first data on WNV isolation were obtained from *Hyalomma marginatum* ticks collected in the Astrakhan region in 1963. Data were also obtained in Azerbaijan from a blackbird (*Turdus merula*) and a European nuthatch (*Sitta europaea*) and, later, from a herring gull (*Larus argentatus*) and *Argasidae* ticks (*Ornithodoros coniceps*) parasitizing it.[14] WNF morbidity is now a permanent feature in the Astrakhan region, Kazakhstan, central Asian countries (republics of the former USSR), Ukraine, and Azerbaijan.

Virological, entomological, zoologico-ornithological, and epidemiological investigations of WNV in the Astrakhan region and the Kalmyk Republic were conducted especially actively.[8,39,45–61] Virus activity in the Volga River delta was found at least as far as 50 years ago.[11,35,60] But interactions between WNV, on the one hand, and animal and vector populations, on the other, were not investigated in detail as well as genetic characteristics of the virus; indeed, the latter began to be studied well only during the first decade of twenty-first century, when suckling mice and Vero-E6 cell culture were used to isolate the virus and serological investigations were employed to detect viral RNA (neutralization testing, ELISA, HIT) and to sequence genes (RT-PCR).

WNV endemic territories in southern Russia were known from the moment the virus was isolated in the Astrakhan region in 1964. (The number of cases confirmed by ELISA in the southof the European part of Russia is presented in Table 8.33.) Sporadic cases with a moderate clinical picture and minor outbreaks were observed in the area practically annually, as well as in other southern regions of the former Soviet Union. The immune structure to WNV among humans in the USSR was also known, with the most immunity occurring in the south of Russia, mainly the Astrakhan region (Figure 8.62, Table 8.34).

All this familiarity with WNF is why an outbreak in 1999 in Volgograd was not exactly unexpected,[62] even though it originally was identified by regional experts as an enterovirus infection. Still, laboratory-confirmed WNF cases reached more than 500 that year, and according to our estimations, the number of

TABLE 8.33 WNF Cases Confirmed By ELISA in the South of the European Part of Russia (1968–2001)

	WNF morbidity/mortality (%)						
Region	**1968**	**1990–1996**	**1997**	**1998**	**1999**	**2000**	**2001**
Lower Volga (Volgograd region)	–	–	5	35	380/40 (10.5)	32/3 (9.4)	15
Volga–Akhtuba, Volga delta (Astrakhan region)	12	10	8	9	95/5 (5.3)	24	49/1 (2.0)
Total	12	10	13	44	475/45 (9.5)	56/3 (5.4)	64/1 (1.6)

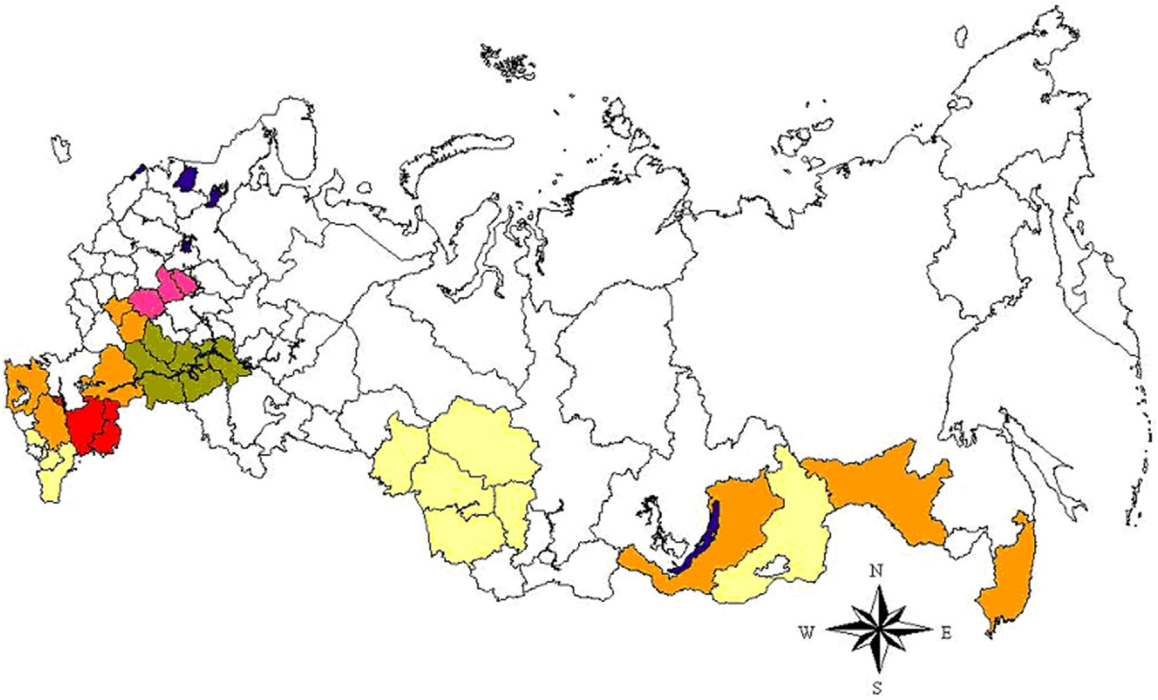


FIGURE 8.62 Immune structure of human population to WNV on the territory of Russia.

infected patients exceeded 200,000 (Table 8.35). Mortality (about 10%) was also unusually high.

Large deltas of European rivers such as the Rhône, Danube, and Volga Rivers are known to be transit hubs for migrating birds and places of introduction of viruses linked with birds.[14] The main natural focus in Russia is the Volga delta.

The Volga delta and contiguous territories around the northern Caspian basin have been endemic for WNF for many years (Tables 8.33–8.35), and other arboviruses have been ecologically linked with aquatic and semiaquatic birds frequenting the region. Ninety percent of these species of birds overwinter on the African continent. Up to 100,000 birds pass over the region daily during their seasonal migrations via the Volga delta main line of the eastern Europe migratory route. (See Figure 3.2.) The problem is that the Volga delta is the place from which viruses are introduced into anthropogenic biocenoses in close vicinity to human habitation. One consequence of this scenario was epidemic outbreaks in the Astrakhan and Volgograd regions in 1999–2001.

The Volga delta consists of three basic belts, each with its own unique ecosystem features (Figure 8.63).

The lower Volga delta borders the Caspian Sea and is characterized by extensive exposed spaces with water. The water depth usually does not exceed 1.0–1.5 m, a situation that is highly conducive to the mass propagation of mosquitoes and one that also provides nesting opportunities for aquatic and semiaquatic birds. Near where it empties into the Caspian Sea, the Volga bed turns significantly to the west, so the western part of the delta,

TABLE 8.34 Distribution of Antibodies to WNF Virus Among Humans and Domestic Animals in Russia (1986–1990)

Physicogeographical country	Landscape zone	Economic territory	Regions investigated	Category	Total	Positive number	%
Russian Plain	Northern, middle taiga, southern taiga	Northern	Vologodsk region; Komi Republic	Humans	1,740	9	0.5
				Cattle	325	0	0.0
				Deer	141	0	0.0
	Leaf-bearing forests	Central	Vladimir, Ivanov, Ryazan regions	Humans	692	12	1.7
	Forest–steppe, steppe	Central Chernozemny	Lipetsk, Tambov regions	Humans	694	5	0.7
		Povolzhsky	Volgograd, Samara, Saratov, Penza, Ul'yanov regions; Tatarstan Republic[a]	Humans	1,884	17	0.9
				Cattle	547	5	0.9
				Rodents	240	3	1.3
Central Asian Plain	Steppe, semidesert, desert	Povolzhsky	Astrakhan region; Kalmykiya Republic	Humans	722	61	8.4
				Cattle	178	6	3.4
				Camels	30	10	33.3
				Horses	41	1	2.4
				Sheep	60	0	0.0
Russian Plain	Steppe	Northern Caucasian	Rostov region; Stavropol, Krasnodar territories	Humans	1,132	8	0.7
Crimean–Caucasian mountain country	Mountain deciduous forests	Northern Caucasian	Kabardino-Balkaria, Chechnya Republics	Humans	461	1	0.2
				Cattle	211	1	0.5
				Sheep	59	0	0.0
Ural	Southern taiga	Ural	Orenburg region; Bashkortostan Republic	Humans	356	25	7.0
				Cattle	56	2	3.6
				Pigs	76	0	0.0
Western Siberia	Southern taiga, forest–steppe	Western Siberian	Altai territory; Omsk, Novosibirsk, Kemerovo, Tomsk regions	Humans	1,824	9	0.5
				Cattle	1,807	8	0.4
Eastern Siberia	Southern taiga, forest–steppe	Eastern Siberian	Chita region; Krasnoyarsk territory; Buryatiya Republic	Humans	936	4	0.4
				Cattle	25	0	0.0
				Deer	100	0	0.0
Amuro-Sakhalin country	Southern taiga, deciduous forests	Far Eastern	Amursk region; Primorsky Krai, Khabarovsk territory	Humans	2,917	21	0.7
				Cattle	1,539	6	0.4
				Pigs	1,667	23	1.4
Total	**8 landscape belts from northern taiga to desert**	**9 economic territories**	**33 regions**	**Humans**	**13,358**	**172**	**0.2–8.4**
				Animals	**7,102**	**65**	**0–33.3**

[a]*Southern taiga and deciduous forests.*

TABLE 8.35 Detection of Antibodies to WNV Before and After Epidemic Outbreak (1999)

		Year			Population (1999)		
Region	**Parameter**	**1988–1989**	**1998**	**2000**	**Total**	**Urban population**	**Evaluation of WNV-Infected/WNF (1999)**
Lower Volga (Volgograd region)	Number tested	544	–	608	2,494,000	2,454,000	**~95,700/~960**
	Percentage positive	1.6	–	5.3 **(+3.9)**			
Volga–Akhtuba	Number tested	383	310	162	931,000	637,000	**~117,000/~2,130**
Volga delta (Astrakhan region)	Percentage positive	13.8	31.6 **(+17.8)**	50.0 **(+18.4)**			
Total	Percentage positive	6.7	31.6 **(+24.9)**	14.7	3,425,000	3,091,000	**~212,700/~3,090**

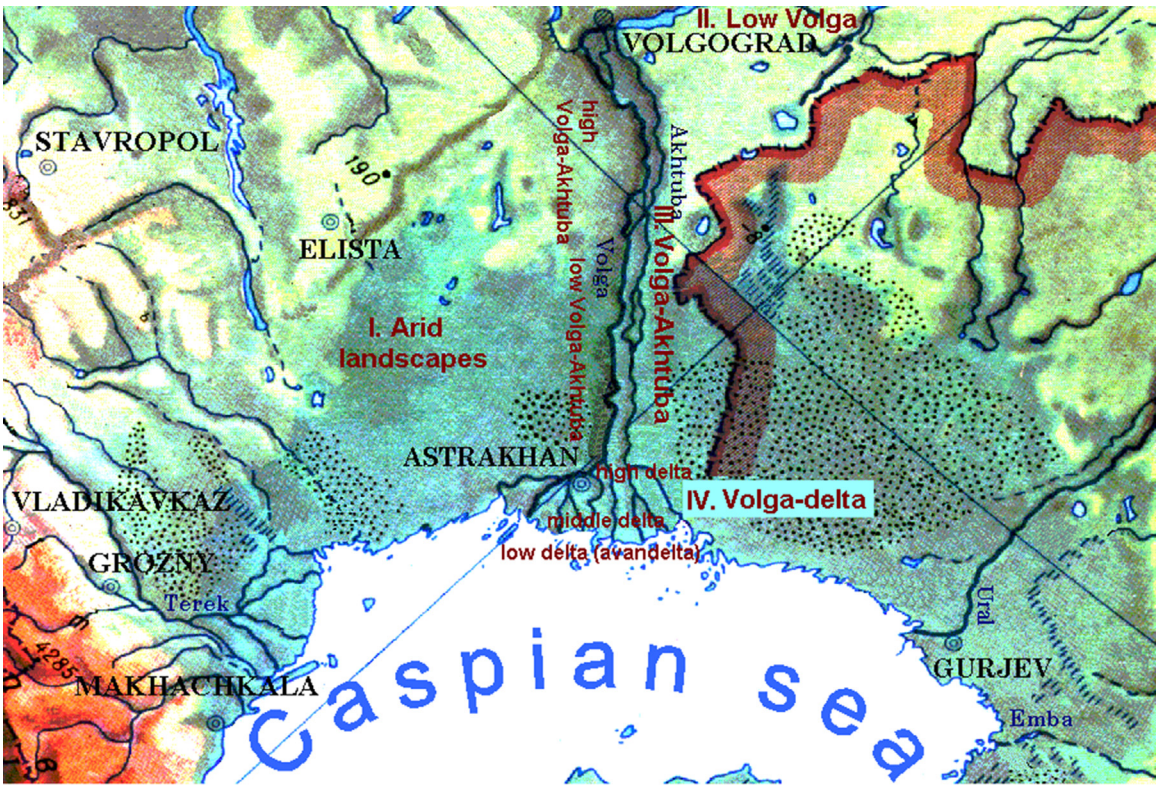


FIGURE 8.63 Ecosystem division of the northern Caspian Sea basin. I. Arid belt (semi-deserts and deserts); II. Low Volga (steppe); III. Volga Akhtuba (arthropodgenic-biocenosis); III.1. High Volga Akhtuba (semi-desert water ecosystems); III.2. Low Volga Akhtuba (desert) water ecosystems); IV. Volga delta; IV.1. High delta of Volga (anthropogenic biocenoses); IV.2. Middle delta of Volga (wild anthropogenic biocenoses); IV.3. Low delta of Volga (wild biocenoses).

including both the reed bed of the northwestern Caspian coast (up to Lagan in the Kalmyk Republic) and some flooded islands, is more extensive than the central and eastern parts. The extreme eastern part of the delta lies in Kazakhstan. A number of hunters and fishermen could be infected in the lower delta of the Volga.

The middle Volga delta is more distant from the sea, has powerful currents, and consists of shallow lake ecosystems with reeds and shrubs. Water ecosystems adjoin semidesert ones. Within the limits of this zone, wild biocenoses combine with anthropogenic areas around a number of settlements, whose inhabitants keep cattle, sheep, and camels. WNF is widely registered among the native population.

The upper Volga delta adjoins the Volga–Akhtuba lowlands and semideserts. Large cities, including Astrakhan, are located within the limits of this zone. Some species of wild birds that are common in the middle delta also occur in this zone, coming into close contact with domestic animals and synanthropic birds.

Analysis of retrospective data collected before 1999 revealed that the main locus of native-population morbidity by WNF is in the Volga delta (Table 8.35). Viruses could be introduced into the northern part of the Volga–Akhtuba lowland up to Volgograd and maybe even higher. Thus, in the future it will be necessary to control the introduction of the virus into the Volga–Akhtuba lowland from Astrakhan to Volgograd.

Arid landscapes occupying contiguous terrian to the west of the Volga–Akhtuba system and the Volga delta are situated within the boundaries of the Caspian Sea–Turanian Basin physicogeographical area (Figure 8.63).

Every year at the end of July, a group of specialists from the D.I. Ivanovsky Institute of Virology in Moscow has traveled to the Astrakhan region and the Kalmyk Republic to organize and conduct a joint scientific expedition with local Centers of Sanitary–Epidemiological Inspection for ecologo-virological monitoring of the northwestern Caspian region (Figures 8.64–8.66). The main goal of the expedition is to contain the ecological and epidemiological situation after suppression of WNV circulation in the previous epidemiological season as the result of a combination of natural factors.

The plan for the collection of field material took into account the results of previous expeditions, when key milestones and marker species of mosquitoes and wild and domestic animals were identified. In particular, the researchers planned to investigate the role of the Ixodidae tick *Hyalomma marginatum* (Figure 8.67) in WNV and other arbovirus circulation in anthropogenic and wild biotopes.

Both federal and local heads of various services, as well as virologists, epidemiologists, veterinarians, hunters, and frontier guards, were supplied with materials containing evaluations of ecologo-virological monitoring of their respective territories in the previous epidemiological season. Practical recommendations were given for prophylaxis of WNF, CCHF, and other arboviral diseases.

Field materials—bloodsucking mosquitoes, Ixodidae ticks, internals (blood, serum, liver, spleen, and brain) of wild birds and mammals, and sera from donors and domestic animals—were collected on the territory of the Astrakhan region and the Kalmyk Republic from the end of July to the beginning of August 2000–2004 within the boundaries of the Volga delta, the Volga–Akhtuba valley, and adjacent arid landscapes. Field materials were collected in the biotopes of the west Volga coast and the east Akhtuba coast, including internal water–meadows of the upper and lower Volga–Akhtuba zones, hydromorphic and adjacent meadow–steppe biotopes of the upper and meddle belts of the Volga, the Volga avandelta, the territory of the Sarpa Lakes, and the east side of Ergeny (see Figures 8.64–8.66).

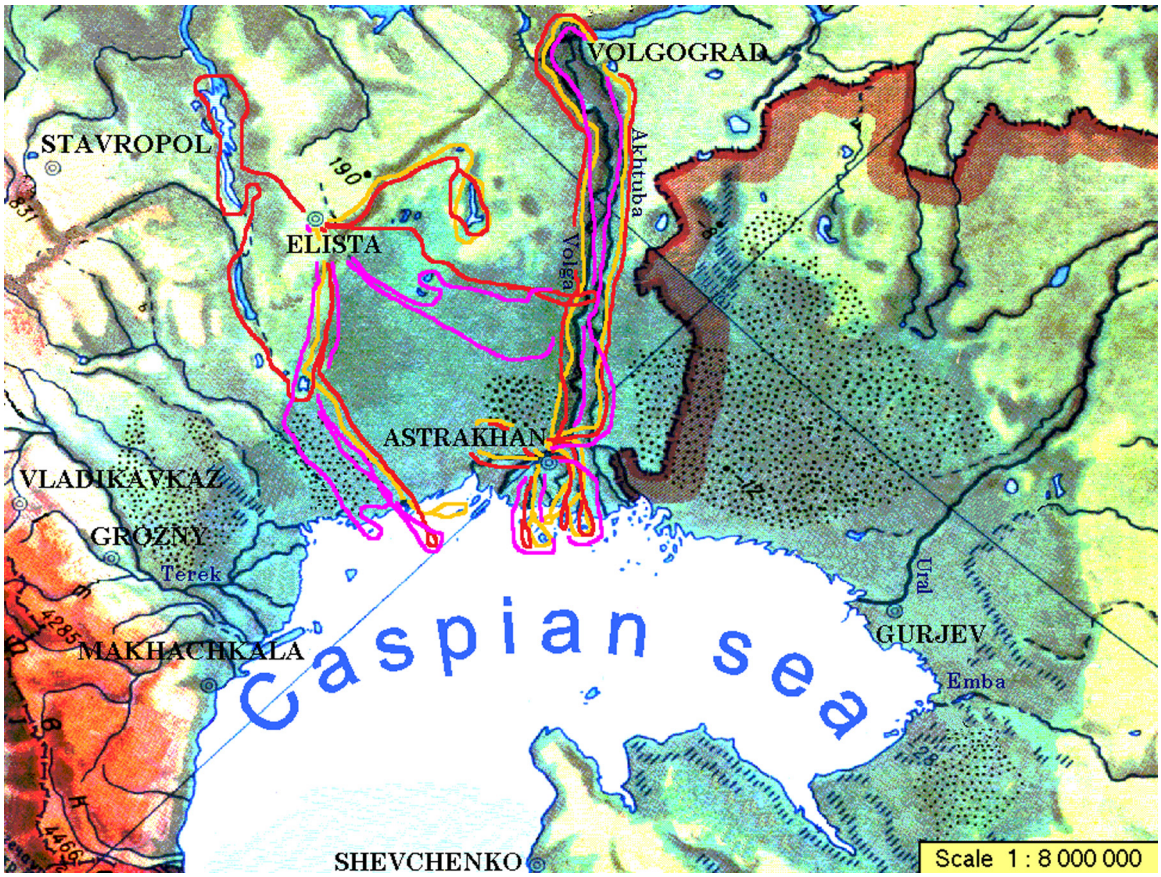


FIGURE 8.64 Pathway of the expedition mounted for the collection of field material for WNV investigation on the territory of the northwestern Caspian region during the 2004 epidemiological season. (Different-colored lines denote different expedition groups.)

During 2000–2004, the expedition collected 504,731 bloodsucking mosquitoes (of the order Diptera and family Culicidae: genera *Culex*, *Aedes*, *Coquillettidia*, and *Anopheles*); 11,266 Ixodidae ticks (of the taxon Acari and family Ixodidae: genera *Hyalomma*, *Rhipicephalus*, and *Dermacentor*), mainly *H. marginatum*; internal parts of 2,794 birds and 67 hares (*Lepus europaeus*); sera from 4,500 human donors (2,500 in the Astrakhan region and 2,000 in the Kalmyk Republic); and sera from 5,300 domestic animals (2,900 in the Astrakhan region and 2,400 in the Kalmyk Republic) (Figure 8.68).

The field materials that were collected were stored and transported to the D.I. Ivanovsky Institute of Virology in liquid nitrogen in dewars, in accordance with all requirements for the handling and transport of infectious samples.

Internal parts of 2,794 wild birds were investigated by virological methods (Table 8.36). Twelve WNV strains (Tables 8.36 and 8.37) were isolated. According to the bioprobe method used, the total WNV infection rate among wild birds is about 0.4%, with the highest level (0.7%) reached in the middle and

FIGURE 8.65 (A) D.K. Lvov, head of the scientific expedition. (B) Field laboratory deployed at the stern of the expedition ship. (C) One of the channels in the middle belt of the Volga. (D) Light traps at the head of the expedition ship. (E) Scientific researcher D.N. Lvov and senior technician E.I. Vakar are preparing mosquito-collecting materials on a small island in the lower belt of the Volga delta. (F) Scientific researcher M. Yu. Shchelkanov during the scientific collection of birds on the western hill—il'men territory in the upper Volga delta. A Ber hill can be seen in the distance on the right and a dug-up Ber hill on the left.

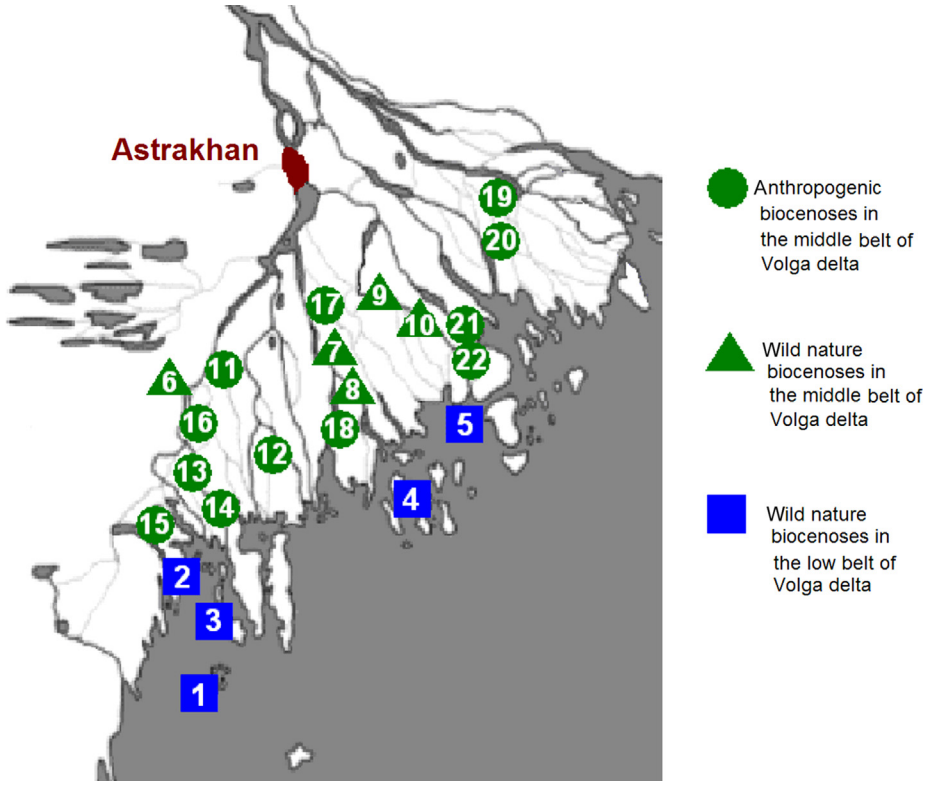


FIGURE 8.66 The places where field material was collected in the middle and lower belts of the Volga delta in 2000–2004.

FIGURE 8.67 Preimago of the Ixodidae tick *Hyalomma marginatum* on the head of a rook (*Corvus frugilegus*).

upper belts of the Volga delta. The highest intensity of WNV circulation was among cormorants (3.4% in the middle and lower Volga delta) and Corvidae (3.3% in the upper and middle Volga delta); among other birds of this terrestrial ecological complex, the intensity was 1.4%, on average.

RT-PCR testing was performed on 5,080 pools containing 504,731 individual mosquitoes (order Diptera, family Culicidae) (Tables 8.37 and 8.38) and 892 pools containing 11,266 individual *Hyalomma marginatum* ticks (taxon Acari, family Ixodidae; 4,923 imagoes from cattle, horses, and sheep, as well as 6,343 preimagoes mainly from Corvidae birds) (Tables 8.37 and 8.39). Two WNV strains were

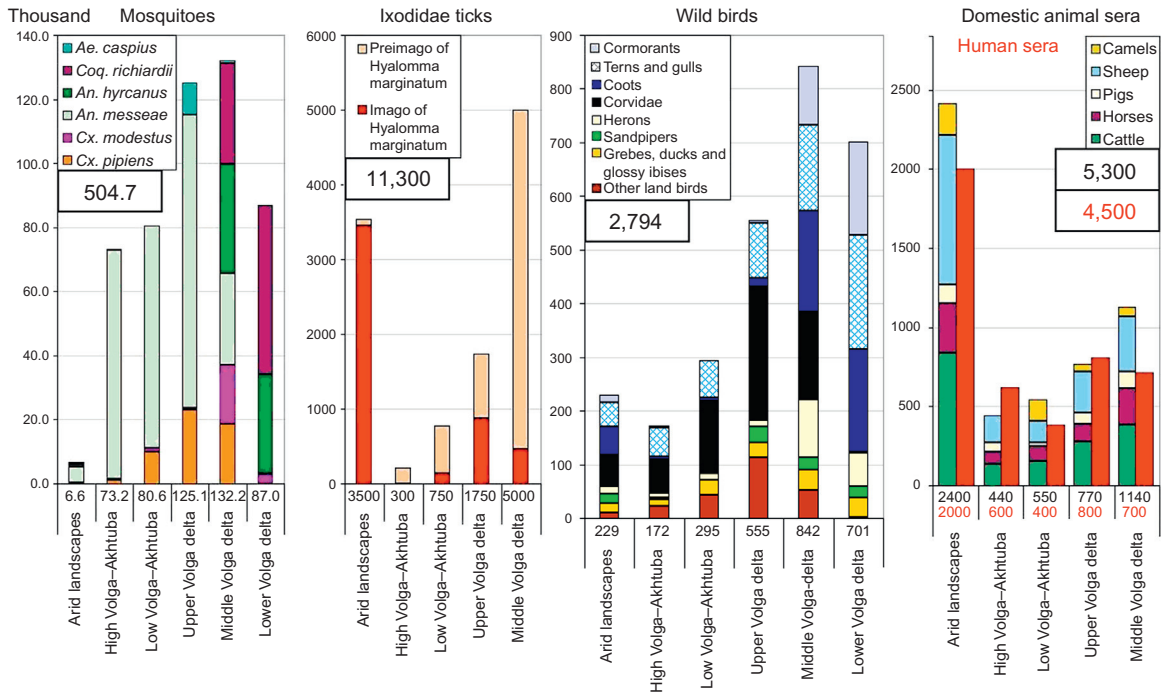


FIGURE 8.68 Field material collected during 2000–2004 in the lower Volga region for WNV investigations.

isolated from mosquitoes and 11 WNV strains from ticks.

With the help of RT-PCR, 2,794 samples of internal parts fromwild birds were collected on the territory of the nothwestern Caspian region and were tested for any indication of WNV RNA. Positive results are presented in Tables 8.40 and 8.41. The total WNV infection rate among wild birds during 2001–2004 was established to be 4.8%. The highest WNV infection rate was found for cormorants (*Phalacrocorax carbo*) (10.6%; 22.0% in the middle belt of the Volga delta, 20.0% in the upper belt), Corvidae birds (6.1%; 12.0% in the upper belt of the Volga delta, 3.7% in the middle belt), and coots (*Fulica atra*) (5.0%; 6.4% in the middle belt of the Volga delta, 4.7% in the lower belt); the lowest WNV infection rate was discoverded in ducks and grebes (*Podiceps*): 1.3% (Figures 8.69–8.71). The most intensive WNV circulation takes place in the middle (7.0%) and upper (7.4%) belts of the Volga delta. The highest portion of positive results was obtained from internal parts of wild birds in 2001 and was decreasing until 2004 (Figure 8.72).

RT-PCR testing for any indication of WNV RNA was carried out on 108 samples of internal parts collected from wild mammals on the territory of the northwestern Caspian region. Positive results are presented in Tables 8.42 and 8.43.

RT-PCR testing for WNV RNA was done on 3,066 pools containing 305,064 samples of mosquitoes (order Diptera, family Culicidae). Positive results are presented in Table 8.44. During 2001–2004, the highest WNV infection rate was detected in *Culex pipiens* (0.036%) living mainly in basements of human houses. A significant WNV infection rate was also

TABLE 8.36 Number of Internal Parts of Wild Birds Collected in Different Natural Belts of the Northwestern Caspian Region (2000–2004) and Investigated with a Bioprobe Approach

Kinds of birds	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Corvidae	59	63	135	249	164	2	**672**
				4 strains	**3 strains**		**7 strains**
Other land birds	10	22	43	114	52	2	**243**
	1 strain				**1 strain**		**2 strains**
Cormorants	13	3	0	5	109	173	**303**
					2 strains	**1 strain**	**3 strains**
Coots	52	5	6	15	188	191	**457**
Terns and gulls	45	54	70	103	160	213	**645**
Sandpipers	19	4	0	29	23	20	**95**
Herons	14	9	13	13	107	63	**219**
Ducks, podiceps, and glossy ibises	17	12	28	27	39	37	**160**
Total	**229**	**172**	**295**	**555**	**842**	**701**	**2,794**
	1 strain			**4 strains**	**6 strains**	**1 strain**	**12 strains**

TABLE 8.37 Number of Mosquitoes Collected in Different Natural Belts of the Northwestern Caspian Region (2001–2004) and Investigated by a Bioprobe Approach

Species of mosquitoes	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Culex pipiens	0	1,140	9,818	23,109	18,622	0	**52,689**
Culex modestus	300	200	1,200	380	18,504	2,933	**23,517**
Anopheles messeae	4,900	71,709	69,378	91,766	28,436	132	**266,321**
				2 strains			**2 strains**
Anopheles hyrcanus	900	0	0	0	34,216	31,149	**66,265**
Coquillettidia richiardii	0	0	0	0	31,528	52,834	**84,362**
Aedes caspius	500	100	214	9,830	933	0	**11,577**
Total	**6,600**	**73,149**	**80,610**	**125,085**	**132,239**	**87,048**	**504,731**
				2 strains			**2 strains**

TABLE 8.38 Number of *Hyalomma marginatum* Ticks Collected in Different Natural Belts of the Northwestern Caspian Region and Number of WNV Strains Isolated by a Bioprobe Method

Ontogenesis stage of *H. marginatum*	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Imago	3,448	0	140	877	458	0	**4,923**
Preimago	89	216	638	863	4,537	0	**6,343**
				9 strains	**2 strains**		**11 strains**
Total	3,537	216	778	1,740	4,995	0	**11,266**
				9 strains	**2 strains**		**11 strains**

TABLE 8.39 WNV Strains from Field Materials Collected in Different Natural Zones of the Northwestern Caspian Region (2000–2004)

Strains code	Source of isolation	Place of material collection	Identification approach
ARID LANDSCAPES (1 STRAIN)			
Ast02-2-558	Internals of pigeon (*C. livia*)	Narimanovsky department	ELISA, HIT, NT
UPPER VOLGA–AKHTUBA (0 STRAINS)			
LOWER VOLGA–AKHTUBA (0 STRAINS)			
UPPER VOLGA DELTA (15 STRAINS)			
Ast02-2-25	Internals of crow (*C. cornix*)	Vicinity of Astrakhan	ELISA, HIT, NT
Ast02-2-26	8 preimagoes of *H. marginatum* from crow (*C. cornix*)	Vicinity of Astrakhan	ELISA, HIT, NT
Ast02-2-173 (Dhori + WNV)	20 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-176 (Dhori + WNV)	13 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-188	10 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-205	Internals of rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-208	Internals of rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-209 (Dhori + WNV)	12 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-218	8 preimagoes of *H. marginatum* from crow (*C. cornix*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-239 (Dhori + WNV)	19 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT

(*Continued*)

TABLE 8.39 (Continued)

Strains code	Source of isolation	Place of material collection	Identification approach
Ast02-2-298	Internals of rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-326	6 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Privolzhsky department	ELISA, HIT, NT
Ast02-2-2045	10 preimagoes of *H. marginatum* from rook (*C. frugilegus*)	Krasnoyarsky department	ELISA, HIT, NT
Ast02-2-691	*An. messeae* mosquitoes (100 insects pooled)	Privolzhje city near Astrakhan	ELISA, RT-PCR
Ast02-2-692	*An. messeae* mosquitoes (100 insects pooled)	Privolzhje city near Astrakhan	ELISA, RT-PCR
MIDDLE VOLGA DELTA (8 STRAINS)			
Ast01-66	Internals of cormorants (*Ph. carbo*)	Ikryaninsky department	ELISA, HIT, RT-PCR
Ast01-182	20 preimagoes of *H. marginatum* from crow (*C. cornix*) and rook (*C. frugilegus*)	Limansky department	ELISA, HIT, NT
Ast01-183	20 preimagoes of *H. marginatum* from crow (*C. cornix*) and rook (*C. frugilegus*)	Limansky department	ELISA, HIT, NT
Ast01-187	Internals of crow (*C. cornix*)	Limansky department	ELISA, HIT, NT, RT-PCR
Ast02-3-146	Internals of pigeon (*C. livia*)	Ikryaninsky department	ELISA, HIT, NT
Ast02-3-165	Internals of cormorants (*Ph. carbo*)	Ikryaninsky department	ELISA, HIT, NT
Ast02-3-570	Internals of magpie (*P. pica*)	Limansky department	ELISA, HIT, NT
Ast04-2-824-A	Internals of crow (*C. cornix*)	Limansky department	ELISA, RT-PCR
LOWER VOLGA DELTA (1 STRAINS)			
Ast02-3-717	Internals of cormorants (*Ph. carbo*)	Limansky department	ELISA, HIT, NT
TOTAL: 25 WNV STRAINS			
	From the internals of wild birds		**12**
	From mosquitoes (Diptera, Culicidae)		**2**
	From preimago of ticks (Acari, Ixodidae)		**11**

detected in *Anopheles messeae* (0.028%), a common visitor to houses with domestic animals in anthropogenic biocenoses, as well as in *An. hyrcanus* (0.026%) in rushes in natural biocenoses. As is illustrated in Figure 8.73, the highest intensity of WNV circulation takes place among sanguivorous mosquito populations in anthropogenic biocenoses on the territory of the Volga delta (Figure 8.74).

RT-PCR testing was carried out for the detection of WNV RNA in 11,266 samples of *Hyalomma marginatum* ticks (taxon Acari,

TABLE 8.40 Positive Results Obtained from RT-PCR Testing for WNV RNA in Wild-Bird Internals Collected in the Northwestern Caspian Region (2001–2004)

Kinds of birds	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Corvidae	59	63	135	249	164	2	**672**
		1 (1.6%)	**3 (2.2%)**	**30 (12.0%)**	**6 (3.7%)**	**1**	**41 (6.1%)**
Other land birds	10	22	43	114	52	2	**243**
		1 (4.5%)		**5 (4.4%)**	**2 (3.8%)**		**8 (3.3%)**
Cormorants	13	3	0	5	109	173	**303**
				1 (20.0%)	**24 (22.0%)**	**7 (4.0%)**	**32 (10.6%)**
Coots	52	5	6	15	188	191	**457**
	2 (3.8%)				**12 (6.4%)**	**9 (4.7%)**	**23 (5.0%)**
Terns and gulls	45	54	70	103	160	213	**645**
	1 (2.2%)	**2 (3.7%)**	**1 (1.4%)**	**4 (3.9%)**	**8 (5.0%)**	**3 (1.4%)**	**19 (2.9%)**
Sandpipers	19	4	0	29	23	20	**95**
		1				**1 (5.0%)**	**2 (2.1%)**
Herons	14	9	13	13	107	63	**219**
				1 (7.7%)	**5 (4.7%)**	**1 (1.6%)**	**7 (3.2%)**
Ducks, podiceps, and glossy ibises	17	12	28	27	39	37	**160**
					2 (5.1%)		**2 (1.3%)**
Total	**229**	**172**	**295**	**555**	**842**	**701**	**2,794**
	3 (1.3%)	**5 (2.9%)**	**4 (1.4%)**	**41 (7.4%)**	**59 (7.0%)**	**22 (3.1%)**	**134 (4.8%)**

family Ixodidae). Positive results are presented in Table 8.45 and Figure 8.75.

The total WNV infection rate for *Hyalomma marginatum* during 2001–2004 on the territory of the northwestern Caspian region was 0.5% (0.22% for the imago, 0.71% for the preimago). The maximum value was detected in the upper delta of the Volga (1.84%) and the lower Volga–Akhtuba (1.16%).

Thirty-three laboratory-confirmed WNF cases were identified in the Astrakhan region in 2002, with 16 (48.5%) of the cases seen in the rural population and 17 (51.5%) in the urban population. The transmission pathway was established in all cases: Patients confirmed that they had been bitten by mosquitoes numerous times. Inoculations took place in the fields where much of the rural population worked; however, 76.5% of infected patients from Astrakhan did not leave the town. The percentage of patients who were younger than 14 years old was 15.2%, while 30.3% of patients were 18–40 years old, 36.4% 41–60 years old, and 18.1% 61–76 years old. Of sick patients, 63.6% were male, 36.4% female.

WNF cases began to be registered starting in June 2001, with the maximum reached in August (Figure 8.76). Durint the first three

TABLE 8.41 Positive Results Obtained from RT-PCR Testing for WNV in Wild Birds Collected on the Territory of the Northwestern Caspian Region (2001–2004)

Ecological complex	Order	Family	Genus	Species	Positive	
					Number	Portion, %
Waterbirds	Podicipediformes	Podicipedidae	*Podiceps*	Great crested grebe (*P. cristatus*)	2	1.4
	Suliformes	Phalacrocoracidae	*Phalacrocorax*	Great cormorant (*Ph. carbo*)	33	23.7
				Pygmy cormorant (*Ph. pygmaeus*)	1	0.7
	Pelecaniformes	Ardeidae	*Ardea*	Grey heron (*A. cinerea*)	1	0.7
			Egretta	White egret (*E. alba*)	2	1.4
				Little egret (*E. garzetta*)	1	0.7
			Nicticorax	Night heron (*N. nicticorax*)	3	2.2
	Gruiformes	Rallidae	*Fulica*	Coot (*F. atra*)	26	18.7
	Charadriiformes	Charadriidae	*Philomachus*	Ruff (*Ph. pugnax*)	1	0.7
			Tringa	Redshank (*T. totanus*)	1	0.7
		Laridae	*Larus*	Herring gull (*L. argentatus*)	4	2.9
				Common gull (*L. canus*)	1	0.7
		Sternidae	*Chlidonias*	Whiskered tern (*Ch. hybrida*)	7	5.0
			Sterna	Common tern (*S. hirundo*)	5	3.6
				Little tern (*S. albifrons*)	2	1.4
Subtotal	5	7	*11*	15	90	64.7
Terrestrial birds	Columbiformes	Columbidae	*Columba*	Pigeon (*C. livia*)	2	1.4
	Galliformes	Phasianidae	*Perdix*	Grey partridge (*P. perdix*)	1	0.7
	Cuculiformes	Cuculidae	*Cuculus*	Common cuckoo (*C. canorus*)	1	0.7
	Coraciiformes	Upupidae	*Upupa*	Hoopoe (*U. epops*)	1	0.7
	Passeriformes	Laniidae	*Lanius*	Great grey shrike (*L. excubator*)	1	0.7
		Sylviidae	*Locustella*	Warbler (*L. fluviatilis*)	1	0.7
		Motacillidae	*Motacilla*	Pied wagtail (*M. alba*)	1	0.7
		Corvidae	*Corvus*	Hooded crow (*C. cornix*)	14	10.1
				Rook (*C. frugilegus*)	23	16.5
				Jackdow (*C. monedula*)	1	0.7
			Pica	Magpie (*P. pica*)	1	0.7
			Garrulus	Jay (*G. glandarius*)	2	1.4
Subtotal	5	8	10	12	49	35.3
Total	10	15	21	27	139	100.0

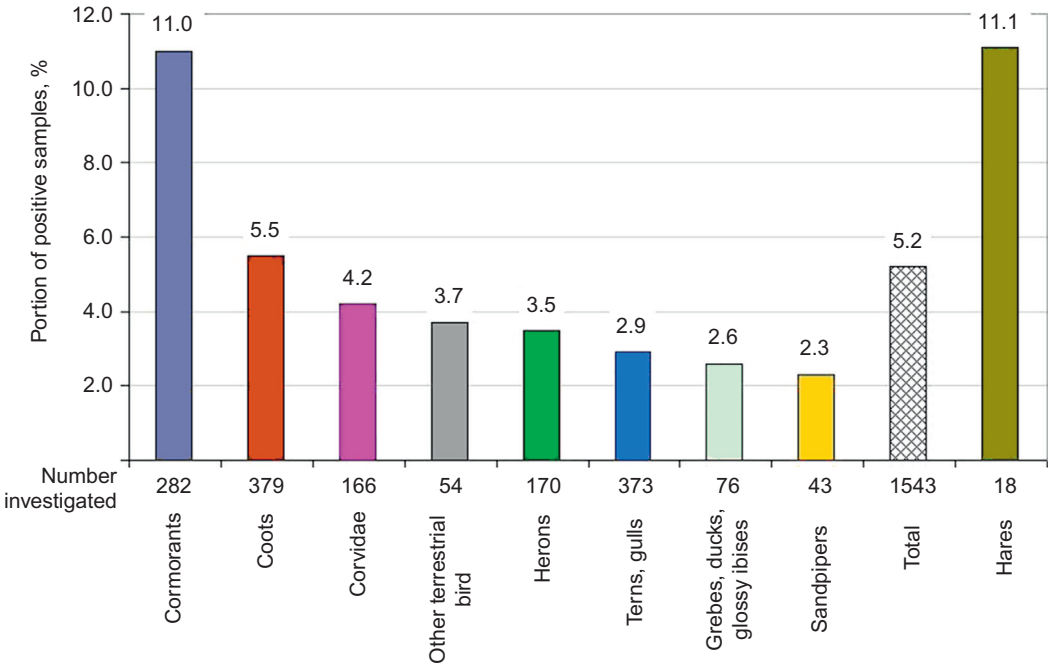


FIGURE 8.69 WNV infection rate obtained from RT-PCR testing of different species of wild vertebrates (2001–2004) in the middle and lower belts of the Volga River.

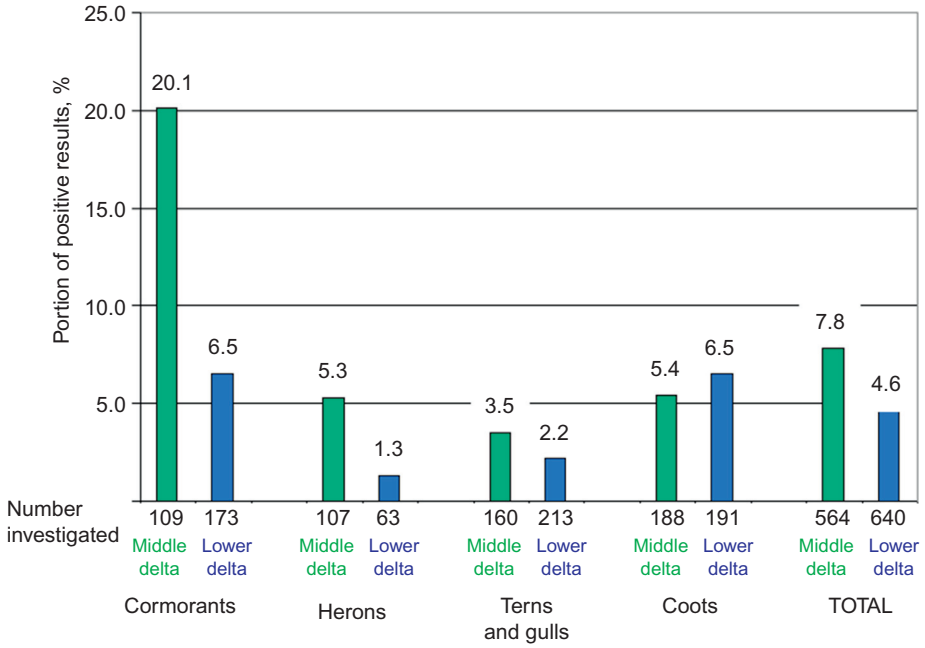


FIGURE 8.70 WNV infection rate obtained from RT-PCR testing of wild birds (2001–2004) in natural biocenoses of different ecosystems in the Volga delta.

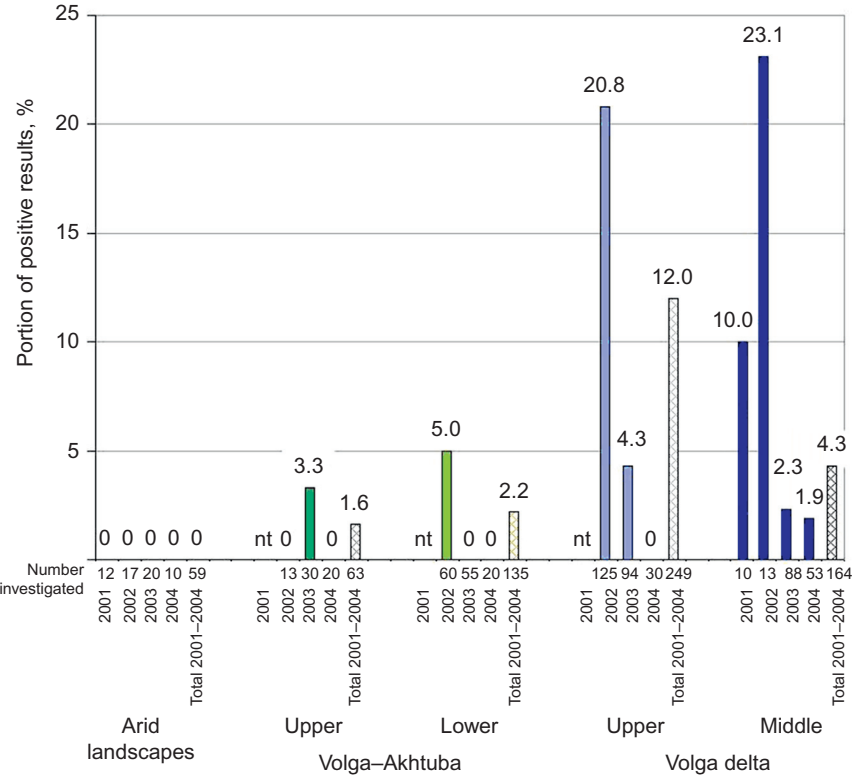


FIGURE 8.71 WNV infection rate obtained from RT-PCR testing of Corvidae birds (2001–2004) in different ecosystems.

days, 21 (63.4%) of patients appealed for medical aid; from the fourth to the sixth day, 9 patients (24.2%) did so. Twenty-six (78.8%) of the patients were hospitalized during the first five days of the disease.

Patients were hospitalized with the following initial diagnoses: adenovirus infection (33.3%), viral meningitis (36.4%), and a combined 30.3% for other diagnoses (acute respiratory viral infection, pneumonia, Q-fever, and Astrakhan fever). Thus, it would have been impossible to establish WNF without laboratory diagnostics. Seven patients (21.2%) demonstrated acute neuroinfection syndrome, whereas another 26 patients (78.8%) had no CNS insults. However, 27.0% of patients in the latter group had intracranial hypertension syndrome. There were two cases of severe disease: a 71-year-old patient with seromeningitis and an 8-year-old child with neurotoxic syndrome during the acute period. All of the cases had a favorable result: No lethal cases were registered.

Sera from 2,884 farm animals collected in the Astrakhan region during 2001–2004 were tested by HIT and neutralization testing in order to detect specific anti-WNV antibodies. In addition, HIT-positive sera underwent neutralization testing. Anti-WNV antibodies were found by HIT in all species investigated: horses (mean positive result for the entire observation period, 9.8%; coincidence with neutralization testing, 94.1%), cattle (6.4%; 72.0%), camels (5.2%; 41.7%), pigs (3.1%;

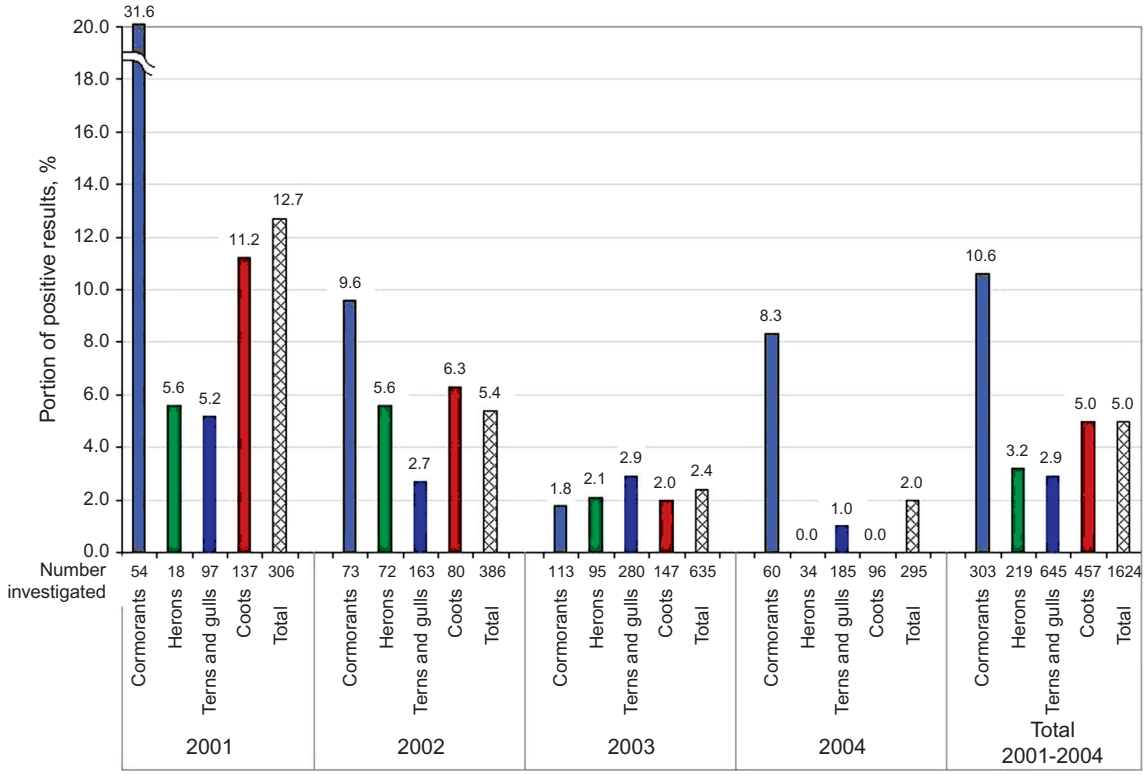


FIGURE 8.72 WNV infection rate obtained from RT-PCR testing of wild birds in natural biocenoses during different years (2001–2004).

TABLE 8.42 Positive Results Obtained from RT-PCR Testing for WNV RNA on Internal Parts Collected from Wild Mammals in the Northwestern Caspian Region (2001–2004)

Kinds of wild mammals	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Hare	2	13	13	9	14	4	**55**
					2 (14.3%)		**2 (3.6%)**
Hedgehog	1	1	3	0	0	0	**5**
Fox	0	1	0	0	0	0	**1**
Dog	0	0	1	0	0	0	**1**
Rodents	23	17	3	2	0	0	**45**
		1 (5.9%)					**1 (2.2%)**
Saiga	0	0	0	0	1	0	**1**
Total	**26**	**32**	**20**	**11**	**15**	**4**	**108**
							3 (2.8%)

TABLE 8.43 List of Positive Samples Obtained from RT-PCR Testing for WNV on Internal Parts Collected from Wild Mammals on the Territory of the Northwestern Caspian Region (2001–2004)

Field material code	Species of mammals	Place of field material collection
UPPER VOLGA DELTA (1)		
Ast02-2-622	*Pygeretmus pumilio*	Narimanovsky department of Astrakhan region, western hill–il'men region
MIDDLE VOLGA DELTA (2)		
Ast02-3-564	*Lepus europaeus*	Limansky department of Astrakhan region
Ast02-3-920	*Lepus europaeus*	Limansky department of Astrakhan region

75.0%), and sheep (2.2%; 57.1%). Results obtained are presented in Table 8.46.

Cattle are the main host of *Anopheles messeae*, and cowsheds offer favorable conditions for the mosquitoes to reproduce. Cattle-specific antigens could often be found in the intestines of *Culex pipiens* females (but not *An. Messeae* females), which inhabitat damp basements. Town utilities adjoin with farm utilities in all settlements of the Astrakhan region, so cattle are the hosts both for *An. messeae* and for *Cx. pipiens*. Both species of mosquitoes are active vectors of WNV in anthropogenic biocenoses.

Horses were the only species of farm animals with clinically expressed WNF. In contrast to cattle, whose pastures are situated close to human settlements, horses browse far from settlements, often grazing in natural biocenoses. A significant portion of horse livestock in the Astrakhan region are of the Kushum breed, bred for meat and racing, and browse freely all year. Pedigree horses (Don, Akhaltekinsky and Arabian race horses) are kept in bloodstock farms in a stall, or they browse locally. Draft horses are kept in settlements. Horse-specific antigens have been found in the intestines of replete females of all mosquitoes species (except for *Culiseta annulata*, which are relatively fewer). The total (2001–2004) distribution of HIT-positive horses increases from the upper Volga–Akhtuba to the lower, with the highest number found in the middle belt of the Volga delta (where the epicenter of the natural foci is located).

Pigs are the animals closest to human settlements, so pig-specific antigens are often found in the intestines of replete females of the anthropogenic mosquito species *Anopheles messeae* and *Culex pipiens*. Pigs are kept in individual yards or on pig farms. The latter are situated far from human settlements. As they are in cattle housing, *An. messeae* are the main mosquito species on the pig farm; nevertheless, all mosquitoes collected here by probe were negative for WNV. In 2003, we collected sera on the pig farms, and all probes were HIT negative. In 2004, we collected sera both on pig farms and in individual yards.

Sheep are the most numerous species of farm animal in the Astrakhan region. Sheep pastures are in the dry steppe, where conditions are favorable for the Ixodidae tick *Hyalomma marginatum*. Only a couple of species of mosquito could live in the saltish, dry steppe il'mens: *Aedes caspius* and *Cx. modestus*. The latter is an active vector for WNV. A stable and low level of infection rate among sheep (about 2%) reflects the low level of intensity of WNV circulation in arid landscapes of the Astrakhan region.

Kalmyk racing camels inhabit more arid landscapes than sheep inhabit; consequently, one might expect a lower level of seropositive camels. However, HIT often demonstrates a high percentage of positive results: 33.3% in 1989 and 13.9% in 2001. So, we instead collected sera from camels during 2002–2004 in semiwild pastures, and the percentage of seropositive results decreased. The coincidence between the results of HIT testing and neutralization testing is presented in Table 8.46.

TABLE 8.44 Results of Testing for the Detection of WNV RNA in Mosquitoes (Order Diptera, Family Culicidae) (2001–2004)[a]

Species of mosquitoes	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Aedes caspius	5/500	0	0	2/200	8/720	0	**15/1,420**
					1		**1**
Aedes flavescens	0	0	1/38	0	0	0	**1/38**
Aedes vexans	0	1/100	0	0	6/600	0	**7/700**
Anopheles hyrcanus	9/900	0	0	0	318/31,645	297/29,421	**624/61,966**
					10 (0.032%)	**6 (0.020%)**	**16 (0.026%)**
Anopheles messeae	49/4,900	161/16,100	121/12,100	406/40,672	216/21,335	1/132	**954/95,239**
	1 (0.020%)	**1 (0.006%)**	**3 (0.025%)**	**13 (0.032%)**	**9 (0.042%)**		**27 (0.028%)**
Culex modestus	3/300	2/200	11/1,100	3/240	60/5,970	151/14,933	**230/22,743**
			1 (0.091%)	**1**	**1 (0.017%)**	**1 (0.007%)**	**4 (0.018%)**
Culex pipiens	0	9/840	81/8,100	180/18,085	177/17,622	0	**447/4,4647**
		1	**2 (0.025%)**	**6 (0.033%)**	**7 (0.040%)**		**16 (0.036%)**
Culiseta annulata	0	0	0	1/4	0	0	¼
				1			**1**
Coquillettidia richiardii	0	0	0	0	294/29,300	493/49,007	**787/78,307**
					13 (0.044%)	**14 (0.029%)**	**27 (0.034%)**
Total	66/6600	173/17240	214/21338	592/59201	1079/107192	942/93493	**3066/305064**
	1 (0.015%)	**2 (0.012%)**	**6 (0.028%)**	**21 (0.035%)**	**41 (0.038%)**	**21 (0.022%)**	**92 (0.030%)**

[a]*Data format: number of pools/number of mosquitoes.*

Horses are the best marker of WNV circulation, because they have the largest percentage of HIT-positive results and the greatest coincidence between HIT and NT results. Kushum race horses are the most significant marker. Monitoring the infection rates among farm animals will be continued, taking into account the relationships and phenomena described.

It has been found that WNV can remain viable during interepidemiological periods in overwintering imagoes of sanguivorous mosquitoes (e.g., *Anopheles messeae*, *Culex pipiens* and *Culiseta annulata*) as well as overwintering imagoes of the Ixodidae tick *Hyalomma marginatum*. The scheme of WNV circulation on the territory of the northwestern Caspian region is presented in Figure 8.77.

After the 1999–2006 outbreak of WNF in four administrative units in southern Russia, a significant outbreak with more than 500 cases arose in the summer and autumn of 2010. The disease spread up to 500 km to the north and northeast from an earlier known endemic area and now includes an additional two administrative units (Tables 8.47 and 8.48, Figure 8.78).

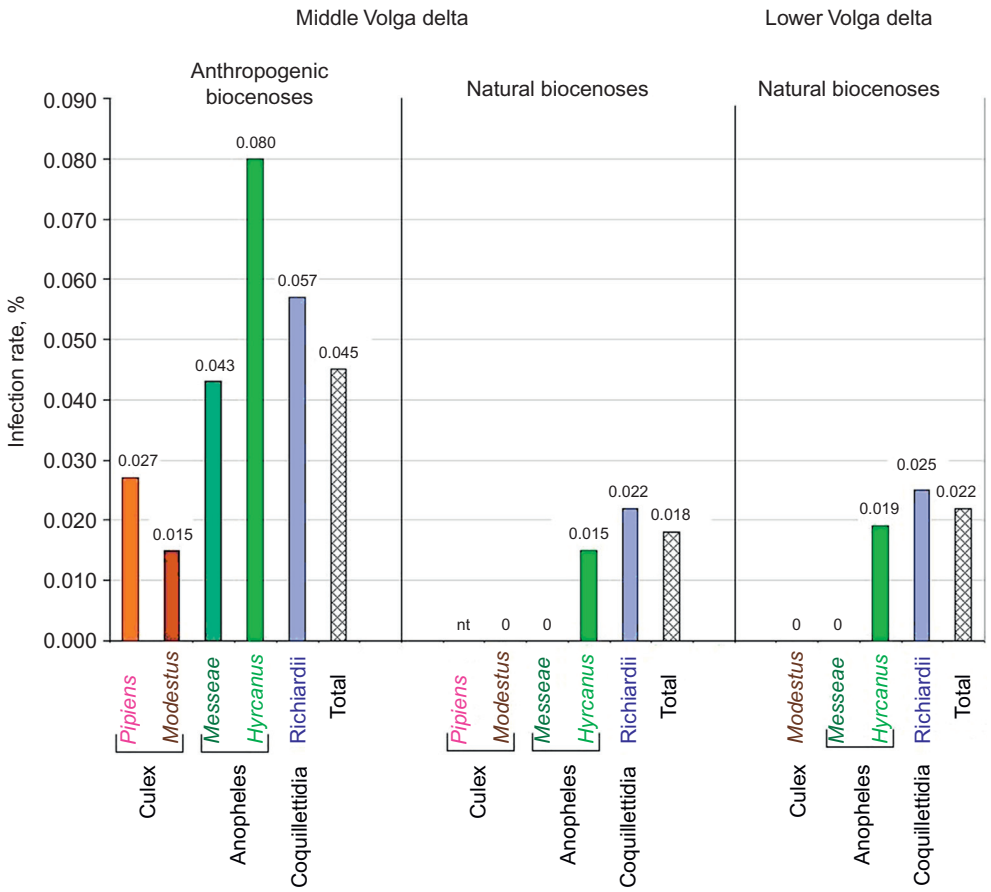


FIGURE 8.73 WNV infection rate of mosquitoes (order Diptera, family Culicidae) in natural and anthropogenic biocenoses of the middle and lower belts of the Volga delta.

8.3 FAMILY ORTHOMYXOVIRIDAE

The Orthomyxoviridae includes six genera of enveloped viruses with a segmented, negative-polarity ssRNA genome. The genome of the orthomyxoviruses consists of six (*Thogotovirus* and *Quaranjavirus*), seven (*Influenza C virus*), or eight (*Influenza A virus*, *Influenza B virus* and *Isavirus*) segments.[1,2] All orthomyxoviruses encode three enzymes formed of viral RdRp: PB1 (Figure 8.79), PB2, and PA. These proteins are about 30% similar among viruses of different genera. Common structural proteins are NP, associated with genomic RNA; matrix protein; and two envelope proteins: hemagglutinin, or HA (possesses hemagglutinating activity) and neuraminidase, or NA (also called sialidase) in the influenza viruses.

Viruses of the *Thogotovirus* and *Quaranjavirus* genera are transmitted by arthropod vectors, predominantly Ixodidae and Argasidae ticks, respectively. Viruses of the *Influenza A virus*, *Influenza B virus* and *Influenza C virus* genera are important human pathogens transmitted by a respiratory route.[1,2]

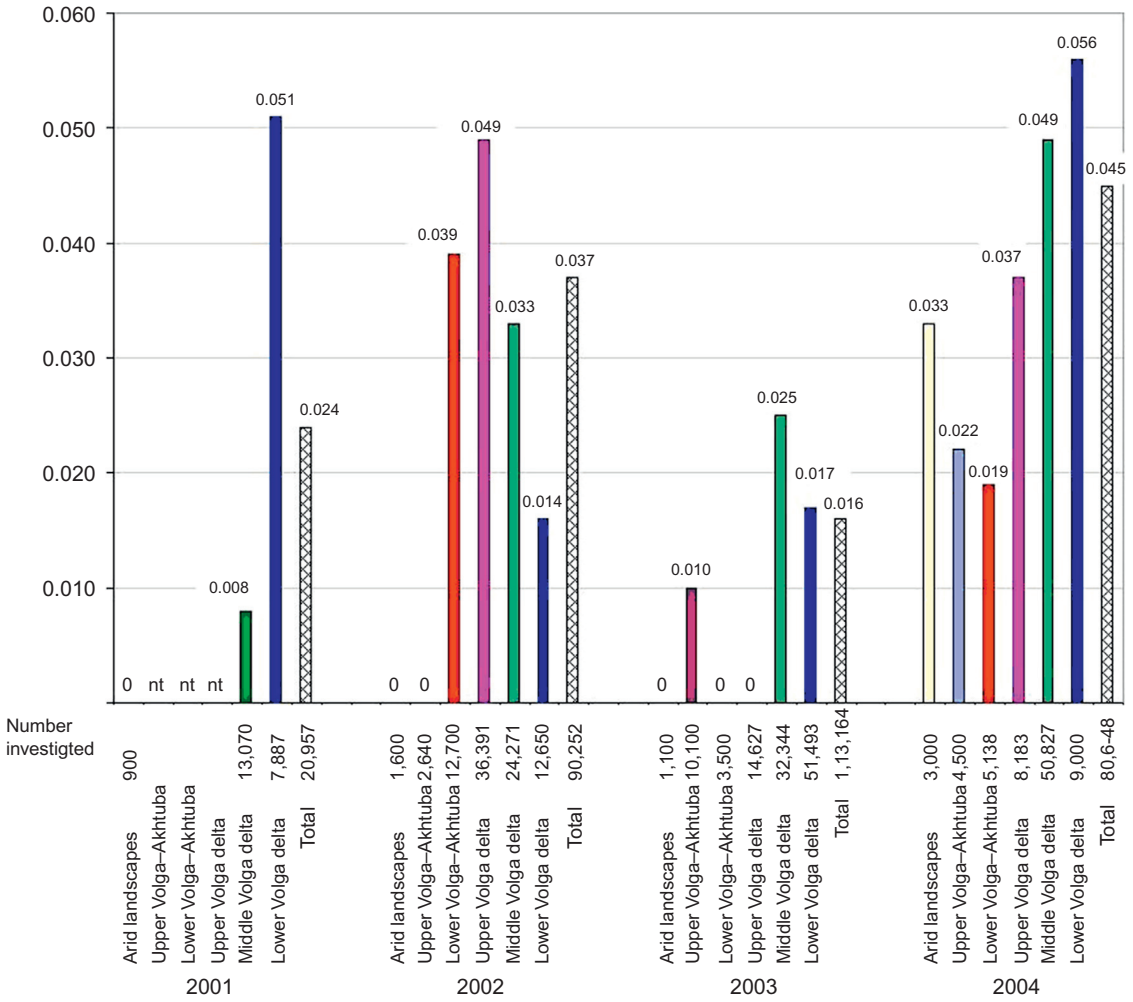


FIGURE 8.74 RT-PCR testing for WNV infection rate of mosquitoes in different ecosystems of the northern Caspian Sea basin in different years (2001–2004).

Genus *Isavirus* has only one species: infectious salmon anemia virus, which strikes fish in the Salmonidae family.

8.3.1 Genus *Influenza A Virus*

Genus *Influenza A virus* has just one named species: Influenza A virus, represented by numerous antigenic and genetic subtypes. The genome of Influenza A virus consists of 8 segments of ssRNA that encode 11 or more proteins.[1–5] Influenza A viruses are divided into distinct subtypes based on the antigenic and genetic properties of their HA and NA proteins. Sixteen subtypes of HA (HA1–16) and 9 subtypes of NA (NA1–9) have been found worldwide in aquatic birds. Two additional subtypes of HA (HA17 and HA18) and NA (NA10 and NA11) are seen in New World bats.[4,6,7] H17 and HA18 form a clade distinctly

TABLE 8.45 Positive Results Obtained from RT-PCR Testing for WNV RNA in the Ixodidae Tick *Hyalomma Marginatum* (2001–2004)

Stage of development of *H. Marginatum*	Arid landscapes	Upper Volga–Akhtuba	Lower Volga–Akhtuba	Upper Volga Delta	Middle Volga Delta	Lower Volga Delta	Total
Imago	3,448	0	140	877	458	0	**4,923**
	1 (0.03%)		**1 (0.71%)**	**4 (0.46%)**	**5 (1.09%)**		**11 (0.22%)**
Preimago	89	216	638	863	4,537	0	**6,343**
		1 (0.46%)	**8 (1.25%)**	**28 (3.24%)**	**8 (0.18%)**		**45 (0.71%)**
Total	**3,537**	**216**	**778**	**1,740**	**4,995**	**0**	**11,266**
	1 (0.03%)	**1 (0.46%)**	**9 (1.16%)**	**32 (1.84%)**	**13 (0.26%)**		**56 (0.50%)**

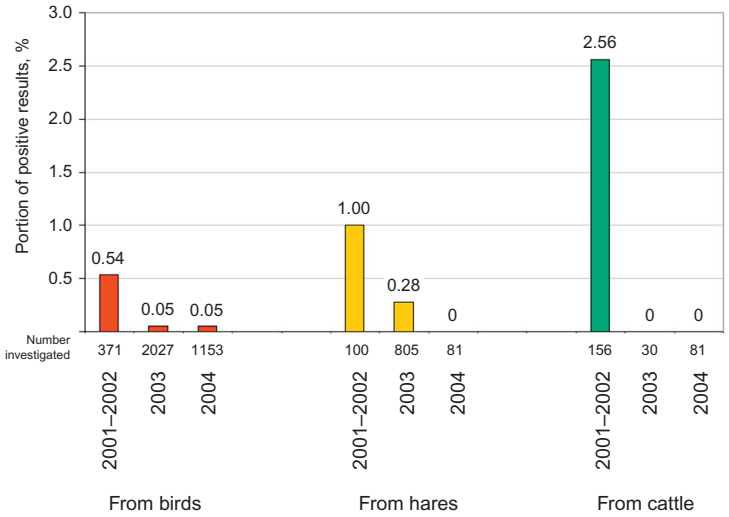


FIGURE 8.75 RT-PCR testing for WNV infection rate of *Hyalomma marginatum* ticks in the middle belt of the Volga delta (2001–2004).

related to the other Influenza A subtypes, but NA10 and NA11 form a new phylogenetic branch external to the Influenza A and Influenza B viruses (Figures 8.80 and 8.81).

8.3.1.1 *Influenza A Viruses (H1–H18)*

History. Influenza as a human disease was originally described in 412 B.C. by Hippocrates (Figure 8.82) in his book *Epidemics*, but the "father of medicine" did not consider influenza to be an infectious disease. Instead, the famous English physician Thomas Sydenham (Figure 8.83) was the first who suggested the infectious nature of the disease.[1,2]

The term "influenza" has been around since the first half of eighteenth century and derives

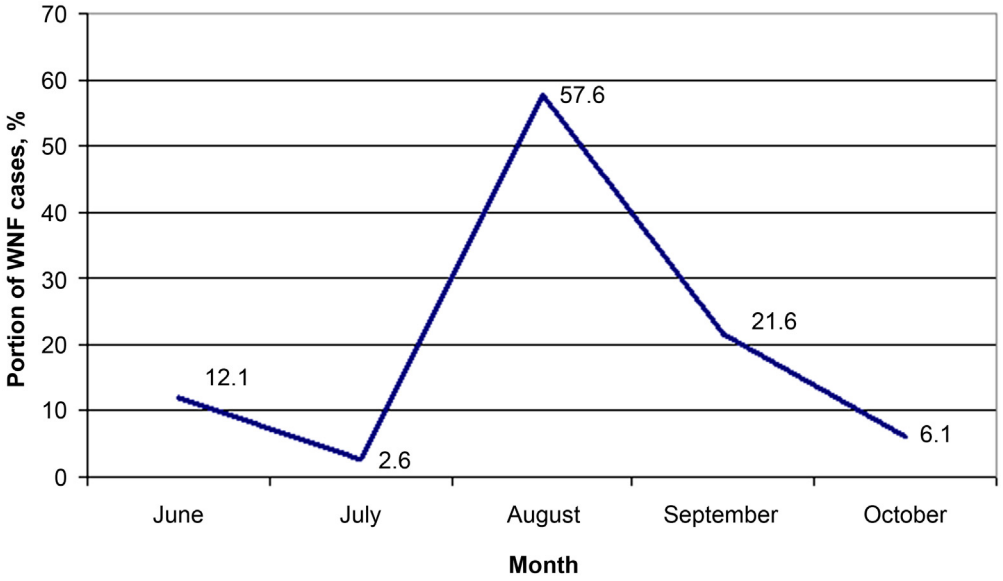


FIGURE 8.76 Seasonal dynamics of WNF in the Astrakhan region.

from the Italian "influenza di freddo" ("influence of the cold") or from Spanish "influencia de las estrellas" ("influence of the stars"), the latter reflecting the contemporaneous belief in astrological reasons for the emergence of disease.[3] Up to the nineteenth century, the archaic terms "catarrhus epidemicus," "cephalgia contagiosa," "febris catarrhalis" and "febris comatose" had wide currency.[4] The English word "grippe" (related to the Russian "грипп") is related to the German "greifen" ("to catch hold") and derived from the French "gripper" ("to catch hold," "paralyze"); the word gained currency at the beginning of nineteenth century. (Cf., e.g., the passage from Volume 1, Chapter 1 of Tolstoy's famous novel *War and Peace*: "She was, as she said, suffering from la grippe; grippe being then a new word in St. Petersburg, used only by the elite.").[5]

Before the nineteenth century, influenza A epidemics were described only qualitatively. Subtypes of the etiological agent were retrospectively revealed for the 1889–1892 epidemic (H2N2), the 1897–1900 epidemic (H3N8), and the 1918–1919 pandemic (H1N1, the so-called Spanish flu)[5–9]—retrospectively only because Influenza A virus wasn't found until 1930 by Richard Shope (Figure 8.84) on the model of swine (*Sus scrofa*) flu.[10,11] Human flu was found two years later[12,13] by a group of English scientists: Wilson Smith (Figure 8.85), Christopher Andrewes (Figure 8.86) and Patrick Laidlaw (Figure 8.87). During the pandemic of 1918–1919, it was suggested that the etiological agent of influenza A was the so-called Afanasiev–Pfeiffer bacillus,"[14–16] named after the Russian bacteriologist Mikhail Afanasiev (Figure 8.88) and the German bacteriologist Richard Pfeiffer (Figure 8.89)—the modern *Haemophilus influenzae* bacillus.[17,18] Three Influenza A pandemics were described after the discovery of the etiological agent: the

TABLE 8.46 Results of HIT Testing of Farm Animal Sera in the Astrakhan Region (2001–2004)[a]

Natural-territory unit		2001		2002		2003		2004		Total (2001–2004)	
		HIT	R	HIT	R	HIT	R	HIT	R	HIT	R
CATTLE											
Volga–Akhtuba	Upper	6/44		2/30		1/30		0/29		9/133	
		13.6%	**66.7%**	**6.7%**	**100%**	**10.0%**	–	**0%**	–	**6.8%**	**75.0%**
	Lower	1/41		6/35		0/40		0/40		7/156	
		2.4%	**100%**	**17.1%**	**83.3%**	**0%**	–	**0%**	–	**4.5%**	**85.7%**
Volga delta	Upper	1/43		16/80		9/71		0/81		26/275	
		2.3%	**100%**	**20.0%**	**62.5%**	**12.7%**	–	**0%**	–	**9.5%**	**64.7%**
	Middle	5/90		7/112		1/106		6/74		19/382	
		5.6%	**80.0%**	**6.3%**	**85.7%**	**0.9%**	–	**8.1%**	**50.0%**	**5.0%**	**72.2%**
Total		13/218		31/257		11/247		6/224	**50.0%**	61/946	
		6.0%	**76.9%**	**12.1%**	**74.2%**	**4.5%**	–	**2.0%**		**6.4%**	**72.0%**
HORSES											
Volga–Akhtuba	Upper					3/40		1/40		4/80	
		–	–	–	–	**7.5%**	–	**2.5%**	**100%**	**5.0%**	**100%**
	Lower			0/17		1/40		8/37		9/94	
		–	–	**0%**	–	**2.5%**	–	**21.6%**	**75.0%**	**9.6%**	**75.0%**
Volga delta	Upper					0/40		0/73		0/113	
		–	–	–	–	**0%**	–	**0%**	–	**0%**	–
	Middle			15/68		17/60		6/105		38/233	
		–	–	**22.1%**	**93.3%**	**28.3%**	–	**5.7%**	**100%**	**16.3%**	**95.2%**
Total				15/85		21/180		15/255		51/520	
		–	–	**17.6%**	**93.3%**	**11.7%**	–	**5.9%**	**86.7%**	**9.8%**	**94.1%**
PIGS											
Volga–Akhtuba	Upper					0/30		0/30		0/60	
		–	–	–	–	**0%**	–	**0%**	–	**0%**	–
	Lower							0/20		0/20	
		–	–	–	–	–	–	**0%**	–	**0%**	–
Volga delta	Upper					0/42		2/30		2/72	
		–	–	–	–	**0%**	–	**6.7%**	**100%**	**2.8%**	**100%**
	Middle					0/65		6/42		6/107	
		–	–	–	–	**0%**	–	**14.3%**	**66.7%**	**5.6%**	**66.7%**
Total						0/137	–		**75.0%**		
		–		–	–	**0%**	**6.6%**	8/122	**3.1%**	8/259	**75.0%**

(*Continued*)

TABLE 8.46 (Continued)

Natural-territory unit		2001		2002		2003		2004		Total (2001–2004)	
		HIT	R	HIT	R	HIT	R	HIT	R	HIT	R
SHEEP											
Volga–Akhtuba	Upper	1/37		1/71		0/30		0/30		2/168	
		2.7%	**100%**	**1.4%**	**100%**	**0%**	–	**0%**	–	**1.2%**	**100%**
	Lower	0/25		0/55		0/40		1/20		1/140	
		0%	–	**0%**	–	**0%**	–	**5.0%**	–	**0.7%**	–
Volga delta	Upper	2/53		4/75		1/91		0/40		7/259	
		3.8%	**0%**	**5.3%**	**33.3%**	**1.1%**	–	**0%**	–	**2.7%**	**20.0%**
	Middle	2/89		3/130		3/80		2/45		10/344	
		2.2%	**100%**	**2.3%**	**66.7%**	**3.8%**	–	**4.4%**	**50.0%**	**2.9%**	**71.4%**
Total		5/204		8/331		4/241		3/135		20/911	
		2.5%	**60.0%**	**2.4%**	**57.1%**	**1.7%**	–	**2.2%**	**50.0%**	**2.2%**	**57.1%**
CAMELS											
Volga–Akhtuba	Upper	–	–	–	–	–	–	–	–	–	–
	Lower	2/48		0/35		1/40		0/10		3/133	
		4.2%	**50.0%**	**0%**	–	**2.5%**	–	**0%**	–	**2.3%**	**50.0%**
Volga delta	Upper			0/22		0/20		1/9		1/51	
		–	–	**0%**	–	**0%**	–	**11.1%**	**100%**	**2.0%**	**100%**
	Middle	8/24		1/30		0/10				9/64	
		33.3%	**37.5%**	**3.3%**	**0%**	**0%**	–	–	–	**14.1%**	**33.3%**
Total		10/72		1/87		1/70		1/19		13/248	
		13.9%	**40.0%**	**1.1%**	**0%**	**1.4%**	–	**5.3%**	**100%**	**5.2%**	**41.7%**

[a] *Abbreviations: HIT, hemagglutination inhibition test; R, coincidence coefficient between hemagglutination inhibition test (HIT) and neutralization test (NT); –, no data.*

so-called Asian flu (1957–1959) (H2N2),[19–21] Hong Kong flu (1968–1970) (H3N2),[21–23] and swine flu (2009–2010) (H1N1 pdm09).[24–29] (The large epidemic of "Russian flu" (1977–1978) (H1N1)[21,23,30] did not reach pandemic scale.)

Avian flu has been known under the name "Lombardian disease" since the beginning of the nineteenth century.[31–34] In 1878, the Italian veterinarian Edoardo Perroncito (Figure 8.90) described a highly contagious disease (previously named "exsudative typhus of chickens") among chickens, with 100% lethality in the vicinity of Turin.[35] The terms "classic fowl plague" and "bird pest" came

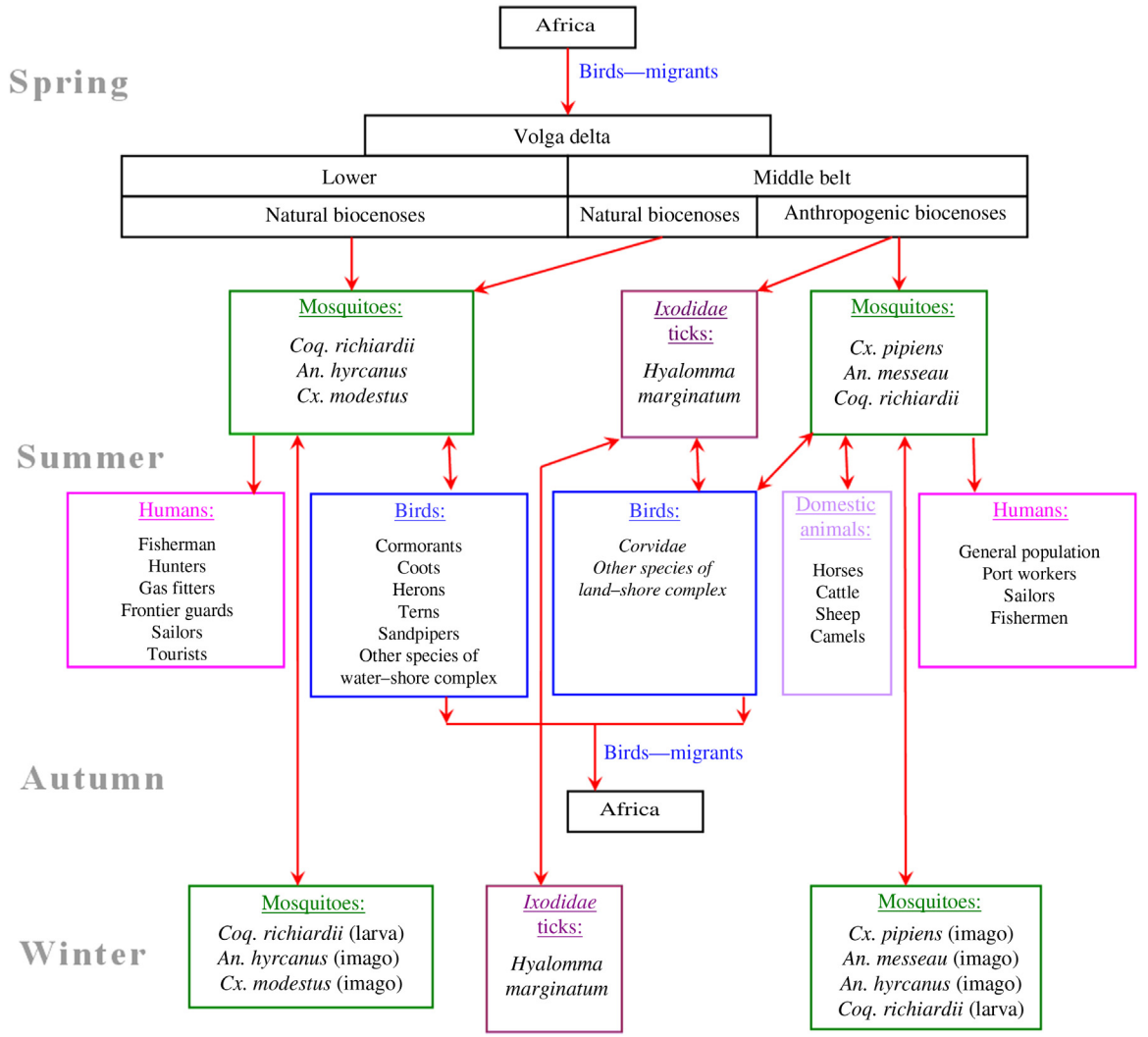


FIGURE 8.77 Circulation pattern for WNV on the territory of North-Western Caspian region.

into wide use in 1901, when a large epizootic outbreak in Tyrol province, Italy, did away with the population of farm birds there.[33] The term "Braunschweig disease" was used to identify an analogous disease among guinea fowls in Europe.

In 1901, the Italian scientists Eugenio Centanni and Ezio Savonuzzi demonstrated that the etiological agent of classic fowl plague is a filtrated substance.[34] Nevertheless, classic fowl plague wasn't identified as Influenza A virus until 1955, by Werner Shäfer (Figure 8.91) on the example of the historical strain A/chicken/Brescia/1/1902 (H7N7).[36,37] W.B. Becker was the first who identified Influenza A virus among wild birds when he

TABLE 8.47 WNF Morbidity in Russia (1999–2013)[a]

	Number of cases per year															
Administrative unit	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
Astrakhan region	95	24	49	31	11	25	73	16	1	1	5	22	18	67	70	508
Volgograd region	380	32	15	15			3	12	63	2	5	411	57	210	48	1,253
Voronezh region												27	34	36	6	103
Krasnodar Krai	85						2		7	2		5	3			104
Rostov region		7	5		3	7	18	13	18	1	2	63	16	48	11	212
Saratov region												2			28	30
Samara region															9	9
Lipetsk region														35	2	37
Belgorod region															2	2
Total	560	63	69	46	14	32	96	41	89	6	12	530	128	396	176	2,258

[a]*WNF mortality in 1999 was 0.9%, in 2010, it was 1.2%.*

TABLE 8.48 WNF Cases in Russia in 2013

Federal District	Number of cases	Portion, %	Infection rate per 100,000 population
Central	15	7.2	0.04
Northwestern	1	0.5	0.01
Southern	147	70.3	1.06
North Caucasian	0	0.0	0.00
Lower Volga	42	20.1	0.14
Ural	1[a]	0.5	0.01
Siberian	3[a]	1.4	0.02
Far Eastern	0	0.0	0.00
Total	209	100.0	

[a]*Imported cases.*

described antigenic relations between A/tern/South Africa/61 and A/chicken/Scotland/59 strains and developed the hypothesis that wild birds played a role in disseminating the virus.[38] Then, during 1960–1970, Gram Laver (Australia), Dmitry Lvov (Figure 2.36) (former USSR, Russia), and Robert Webster (Figure 2.20) (USA) independently formulated the more general idea that there were natural foci f Influenza A virus and that wild aquatic birds were a natural reservoir for the virus.[39–42]

Subtypes of Influenza A Virus in Northern Eurasia. At present, we know that numerous avian influenza viruses are abundant in the bird populations of Northern Eurasia. However, until the end of the 1960s, these data were absent. At that time in the former USSR, avian Influenza A virus was being isolated only from poultry. One of the first avian viruses isolated in the USSR—A/duck/Ukraine/1/1963—was destined to play an important role in the development of the theory of influenza virus evolution.[43]

In 1960–1964, a group of researchers in the Ukrainian Soviet Republic isolated several influenza virus strains from ducklings affected with sinusitis. The first three strains were isolated in 1960 in Crimea and in the Kharkov

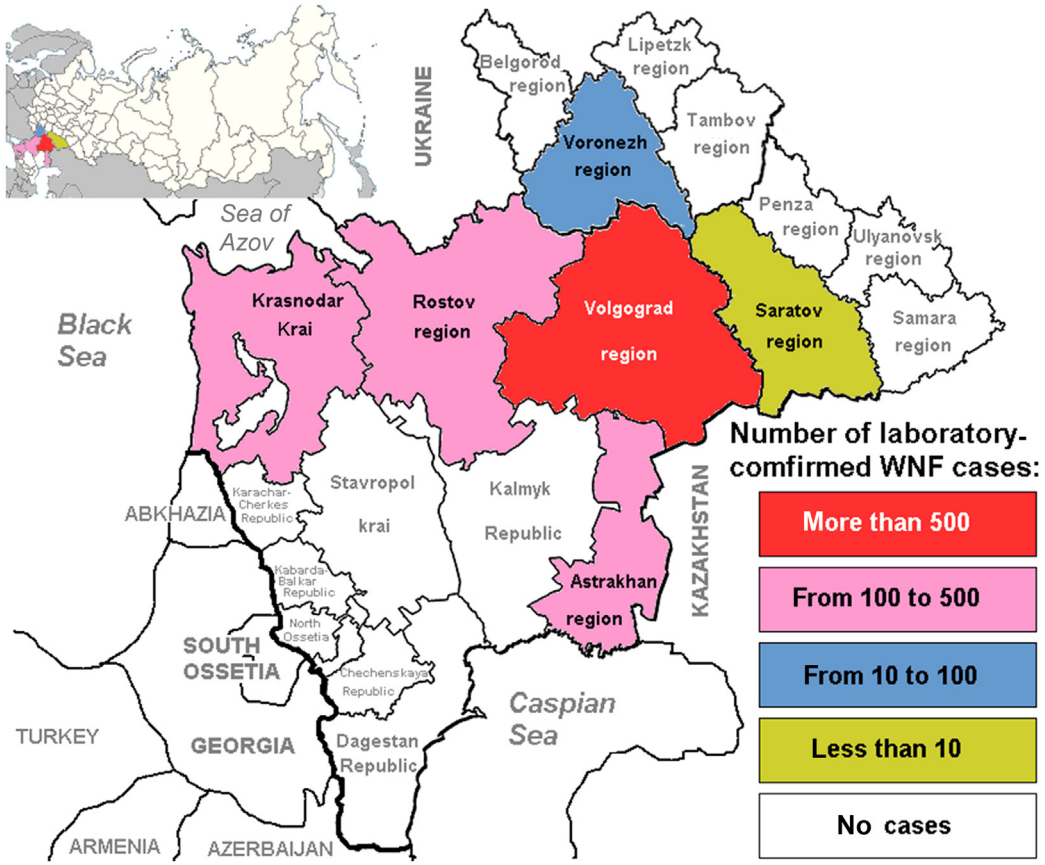


FIGURE 8.78 Present distribution of WNF in Russia.

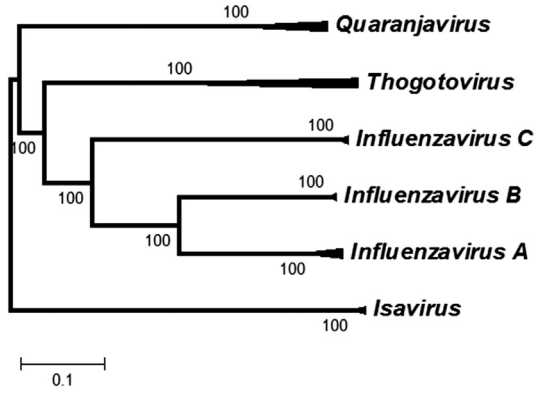


FIGURE 8.79 Phylogenetic structure of the Orthomyxoviridae family, constructed for PB1 amino acid sequences.

region.[44] These prototypical strains were Ya-60, B-60, and S-60. [45] Several other strains (Z-61, C-61, N-62, D-62, D-62, Z-62, S-64, and BV1) were isolated from ducks and chickens[46] in 1961–1964. The most peculiar features of these isolates were revealed in comparative studies performed at the D.I. Ivanovsky Institute of Virology in Moscow. As early as 1964, the duck strains Ya-60, B-60, Z-61, and C-61 were analyzed with respect to their antigenic specificity by HIT and were found to be antigenically distinct from the human H1 and H2 viruses.[47] After the appearance of the H3 pandemic virus in 1968, some of the Ukrainian duck strains were shown to be antigenically

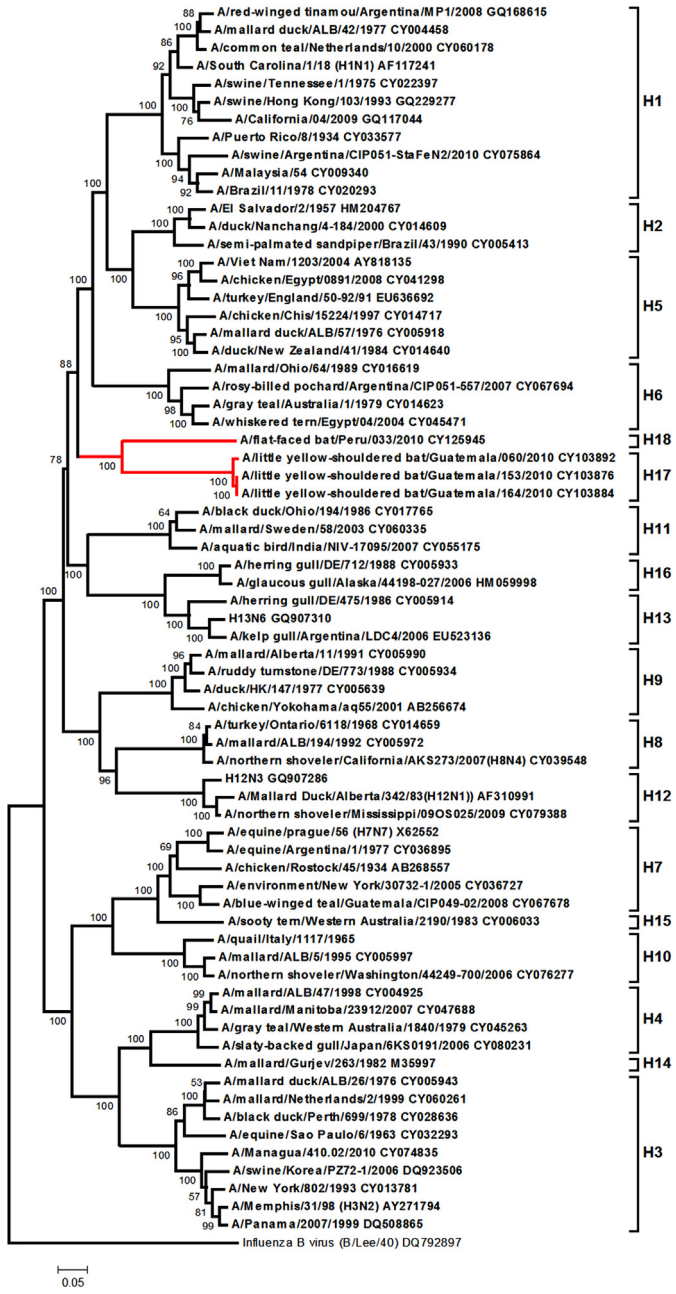


FIGURE 8.80 Phylogenetic structure of the *Influenza A virus* genus, constructed for HA amino acid sequences.

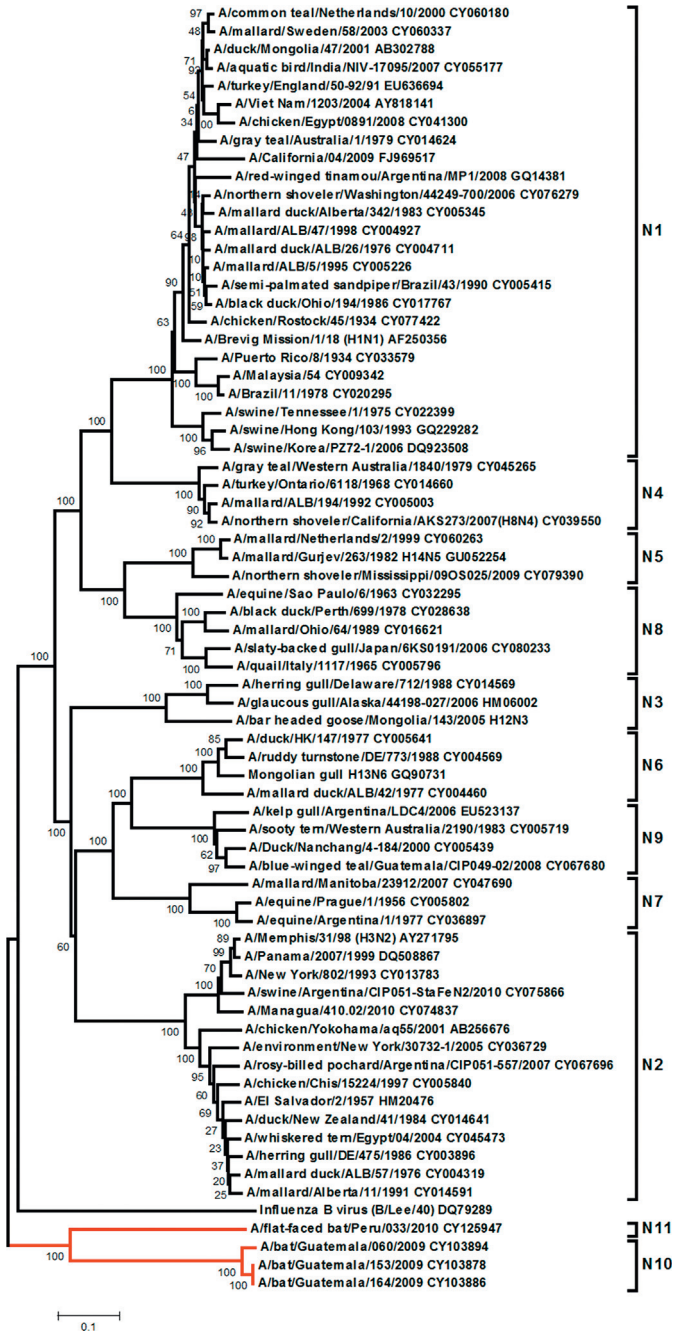


FIGURE 8.81 Phylogenetic structure of the *Influenza A virus* genus, constructed for NA amino acid sequences.

FIGURE 8.82 Hippocrates (Ἱπποκράτης) (460 B.C.–377 B.C.).

FIGURE 8.83 Thomas Sydenham (1624–1689).

FIGURE 8.84 Richard Shope (1901–1966).

FIGURE 8.85 Wilson Smith (1897–1965).

FIGURE 8.86 Christopher Andrewes (1896–1988).

FIGURE 8.87 Patrick Laidlaw (1881–1940).

FIGURE 8.88 Mikhail Ivanovich Afanasiev (1850–1910).

FIGURE 8.91 Werner Shäfer (1913–2000).

FIGURE 8.89 Richard Pfeiffer (1858–1945).

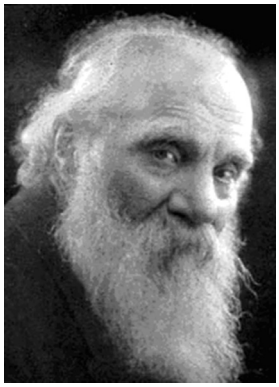


FIGURE 8.90 Edoardo Perroncito (1847–1936).

related to the new subtype. In 1969, L.Ya. Zakstelskaya et al. used HIT to demonstrate that duck strains B-60 and BV1 cross-reacted with the A/Hong Kong/1/1968 pandemic strain and other human strains isolated in 1968, whereas the strain Ya-60 exhibited a negligible cross-reaction with the human viruses.[48,49] Moreover, HIT testing also showed that the B-60 and BV1 strains of the virus reacted with human sera, including those collected in 1881–1886 and in 1905–1908. On the basis of this phenomenon, the authors suggested that an avian virus similar to the strains B-60 and BV1 was the precursor of the human pandemic strain and that this antigenic variant had appeared in humans several times in the past.[48] Formerly known as Ya-60, strain A/duck/Ukraine/1/1960 was shown[50] to belong to the H11N2 subtype, whereas A/duck/Ukraine/2/1960 was identified as H3N6 and A/duck/Ukraine/1/1963 as H3N8.

The highly pathogenic H5N2 and H7N2 strains were isolated from chickens in the Moscow region.[51,52]

Several virus strains producing enteritis in chickens were isolated in 1972 and in 1974 in chicken farms and identified as H6N2 strains,[51,53,54] an unusual antigenic formula for a pathogenic virus affecting poultry.

Six H3N2 isolates were obtained in a chicken farm in Kamchatka from chickens affected with rhinitis, conjunctivitis, and laryngotracheitis.[51,55]

In 1977, isolates identified as H3N1 viruses were isolated from sick chickens and ducks in the Russian Federation[25] and Uzbekistan in the former USSR.[26]

In 1984, H8N4 strains were isolated in the western part of the Ukrainian Soviet Republic from the lungs of ducklings affected with pneumonia. The isolation was the only one of an H8 influenza virus in the USSR (Lvov DK, unpublished data).

In 1970, a large-scale series of virus isolations from wild birds, combined with some serological studies, was initiated as a part of the Coordinated Program of the National Committee on the Studies of Viruses Ecologically Linked to Birds together with the Virus Ecology Center of the D.I. Ivanovsky Institute of Virology. By the end of the 1970s, the pattern of circulation of avian viruses in the territory of the USSR was identified.[3,11,26,30] In the ensuing years, the pattern of the Influenza A virus subtypes (including H15 and H16) circulating in Northern Eurasia was amplified (Figure 8.92).

Blood sera collected in the spring and autumn of 1970 near Lake Khanka and Peter the Great Bay (both in Primorsky Krai) from 262 birds—mainly mallards (*Anas platyrhynchos*), common teals (*An. crecca*), Baikal teals (*An. formosa*), garganeys (*An. querquedula*), falcated ducks (*An. falcata*), pintails (*An. acuta*), grey herons (*Ardea cinerea*), coots (*Fulica atra*), black guillemots (*Cepphus grylle*) and black-tailed gulls (*Larus crassirostris*)—were HIT-tested against H1, H4, H5, H6, H10, and H11 avian influenza viruses. No antibodies were found in the sera of grey herons and coots, nor were any found against H11 in any species. Antibodies against all the other subtypes tested were encountered occasionally

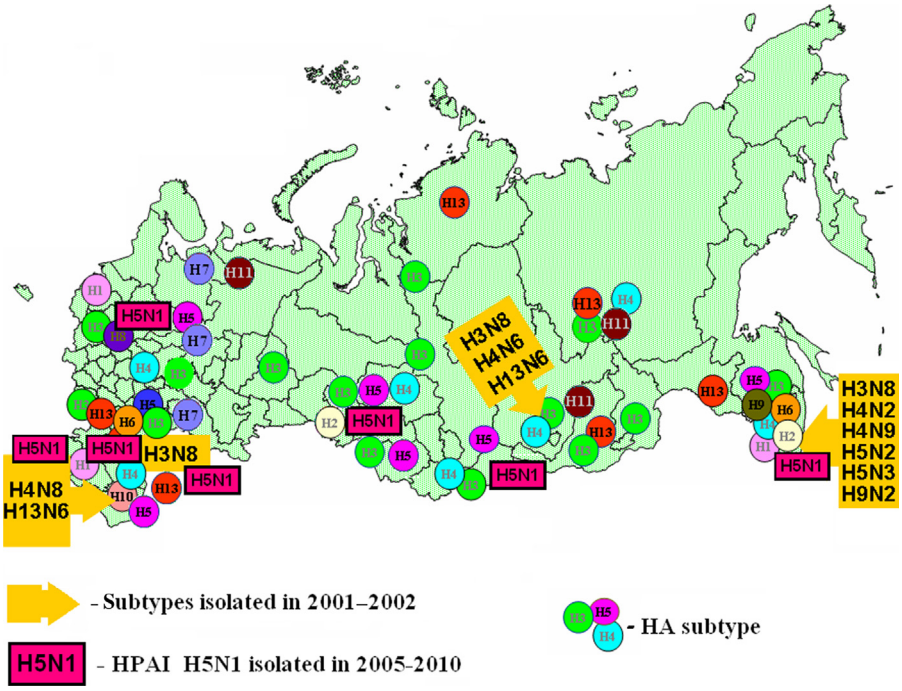


FIGURE 8.92 Avian Influenza A virus subtypes isolated in Russia (1962–2013).

in the sera of gulls, black guillemots, and ducks. In some species, such as teals, falcated ducks, and black guillemots, antibodies against several subtypes were detected.[27]

In 1972, sera were collected from gulls, cormorants, murres, and tufted puffins in the Commander Islands. Antibodies against H2, H3, H5, and H7 viruses were detected.[28] In 1970–1972, sera from gulls, cormorants, and murres were collected in the Kamchatka, Sakhalin, and Magadan regions and antibodies to H1, H2, H3, H5, H6, and H7 viruses were detected.[30] Antibodies against H1, H3, H4, H5, and H7 were identified in sera taken from Arctic terns (*Sterna paradisaea*), black-throated loons (*Gavia arctica*), mallards (*Anas platyrhynchos*), common teals (*Anas crecca*), tufted ducks (*Aythya fuligula*), greylag geese (*Anser anser*), skuas (*Stercorarius* sp.), and a blue whistling thrush (*Myophonus caeruleus*) collected in the White Sea Basin in the estuary of the Pechora River in the Arkhangelsk region of Russia in 1969–1972.[56] The serologic studies suggested a wide range of avian influenza viruses circulating in wild birds in Northern Eurasia. This suggestion was confirmed and extended by the isolation of virus strains from other wild birds.

Many avian species proved to be hosts of H1 viruses. A virus belonging to the H1N3 subtype was isolated in 1977 from a tern in the southern part of the Caspian Sea basin.[57] In 1978, an H1N4 strain was isolated from a common teal (*Anas crecca*) in the Russian Republic of Buryatia in eastern Siberia.[41] Several H1N1 viruses were isolated in Kazakhstan in 1979 from waterfowl, including the common teal (*An. crecca*), garganey (*An. querquedula*), shoveler (*Spatula clypeata*), and coot (*Fulica atra*),[58] as well as in 1980 from tree sparrows (*Passer montanus*) and hooded crows (*Corvus cornix*).[41] In 1979, an H1N1 virus was isolated from a hawfinch (*C. coccothraustes*) in Mongolia.[59] In the same year, an H1N2 strain was isolated from a black-headed gull (*Larus ridibundus*) on an island in the northern part of the Caspian Sea.[41]

The avian viruses belonging to the H2 subtype seem not to be abundant in Russia. In fact, for a long time the only virological evidence of the presence of this subtype in Russia was the isolation of an H2N3 virus in 1976 from a pintail (*Anas acuta*) in Primorsky Krai.[60] However, serological data suggested that H2 viruses circulated in wild birds not only in Primorsky Krai, but also in other regions of the Far East, including the Commander Islands as well as the Kamchatka, Sakhalin, and Magadan regions.[54,61]

Avian influenza A viruses belonging to the H3 subtype are widespread in Northern Eurasia. An H3N2 virus was isolated from a common murre (*Uria aalge*) in 1974 on Sakhalin Island,[62] and another H3N2 strain was isolated in 1976 from a pintail (*Anas acuta*) in Primorsky Krai.[63] Two H3N2 strains were isolated in 1974 in the Ukrainian Soviet Republic from unusual hosts for avian viruses: the white wagtail (*Motacilla alba*) and the European turtle dove (*Streptopelia turtur*).[64] H3N2 strains were also isolated from grey crows (*Corvus cornix*) in 1972 in the Volga basin and from a shelducks (*Tadorna ferruginea*) in 1979 in Kazakhstan.[65] An H3N2 virus was isolated from a tree sparrow (*P. montanus*) in 1983 in the Ukrainian Soviet Republic.[66] In 1972–1973, H3N3 and H3N8 viruses were isolated from ducks and herons in Khabarovsk Krai. One of the viruses closely resembled a strain isolated a year later in central Asia. This resemblance demonstrated that H3N3 viruses circulated in regions fairly distant from one another.[67] In 1972–1973, H3N8 viruses were isolated in Khabarovsk Krai from wild ducks (*Anas* sp.), tufted puffins (*Fratercula cirrhata*), and horned puffins (*F. corniculata*)[65] and in the Arkhangelsk region in the Pechora River estuary (White Sea basin) from Arctic terns (*Sterna paradisaea*) and black-throated loons (*Gavia arctica*).[68] In 1978, H3N8 strains were

isolated in the Republic of Buryatia from a mallard (*An. platyrhynchos*) and a pintail (*An. acuta*),[65] as well as in Khabarovsk Krai from the common murre (*U. aalge*)[67] and from black-headed gulls (*Larus ridibundus*).[69]

Avian viruses of the H4 subtype were isolated in 1970–1980 mostly in a narrow belt stretching from the lower Volga, through Kazakhstan, and on to the south of eastern Siberia. Several H4N6 strains were isolated in 1976 from slender-billed gulls (*Chroicocephalus genei*) in the Volga delta[70] and from great black-headed gulls (*Ichthyaetus ichthyaetus*) on the islands in the northern part of Caspian Sea.[41] In 1977, H4N8 virus was isolated from the black tern (*Chlidonias niger*) in Central Kazakhstan.[71] In the Republic of Buryatia, H4N6 strains were isolated in 1978 from the common goldeneye (*Bucephala clangula*).[41]

Isolations of H5 influenza viruses from wild birds were scarce. In 1976, several H5N3 strains were isolated from terns (common terns and little terns) and a slender-billed gull in the Volga River delta.[70] A detailed description of the penetration of the H5N1 strain of of highly pathogenic avian influenza (HPAI) A into Northern Eurasia and its further dissemination is presented shortly.

The strains belonging to the H6 subtype seem not to be abundant, but their geographic distribution is wide. An H6N2 strain was isolated in 1972 from the Arctic tern (*Sterna paradisaea*)[68] in the Arkhangelsk region (White Sea basin). One H6N4 strain was isolated in 1978 from the pintail (*Anas acuta*) in Primorsky Krai,[41] and an H6N8 strain was isolated from the common tern (*S. hirundo*) in 1977 in the Caspian Sea basin.[57] In 2010, two H6N2 strains were isolated on Kunashir Island (the southernmost of the Kuril Islands) and four were isolated on Sakhalin Island.

An H7N3 strain was isolated in 1972 from a sandpiper (a member of the Scolopacidae family) in the Arkhangelsk region of Russia.[68]

One strain of H8N4 was isolated in 2001 in the Republic of Buryatia, and one strain in 2003 in Mongolia.

An H9N2 strain was isolated from a mallard (*Anas platyrhynchos*)[72] in Primorsky Krai in 1982 and in Khabarovsk Krai in 2013.

Over 40 H10N5 strains were isolated from a wide array of bird species near Alakol Lake in east central Kazakhstan in 1979. The strains were isolated from several species of ducks (*Anas* sp.), from shorebirds (members of the order Charadriiformes), to passerine birds (members of the order Passeriformes), to coots (*Fulica atra*), plovers (members of the family Charadriidae, subfamily Charadriinae), and chukars (*Alectoris chukar*).[41] This situation is a rare case of an isolation of closely related viruses from an extremely wide array of avian species.

The viruses identified as H11N8 strains were isolated in 1972 from the Arctic tern (*Sterna paradisaea*) and the red-throated diver (*Gavia stellata*) in the estuary of the Pechora River in the northern part of European Russia.[54] Several H11N6 strains were isolated from the common teal (*Anas crecca*), the European widgeon (*An. penelope*), and the European golden plover (*Pluvialis apricaria*) in 1979 in eastern Siberia.[41] In 1987, H12N2 strains were isolated from mallards, a pintail, and European widgeons south of Issyk-Kul Lake in Kyrgyzstan.[72]

Two strains of H12N2 were isolated from wild ducks (subfamily Anatinae) in Kyrgyzstan.

The results of virus isolation and serological studies in the territory of the USSR in 1970–1980 suggested a wide circulation of avian influenza viruses in wild birds and enabled researchers to construct a map of avian influenza viruses encountered in different regions of Northern Eurasia. The general pattern of distribution of influenza virus subtypes in wild birds was fairly evident by the end of the decade. Virus isolation was continued in the ensuing years, and it brought

several major results. Isolations were performed mostly in the central and southern parts of European Russia, in western and eastern Siberia, and in the Russian Far East.[72] Overall, 1,005 strains were isolated from wild birds in Russia in 1980–2013 (Table 8.49). About 250 samples were taken yearly from 50 to 100 birds in each geographic region. The mean percentage of successful isolations ranged from 3.5% to 5.7%. Over 50% of the isolates were H13 viruses (H13N2, H13N3, H13N6, and H13N8) isolated mostly from gulls and shorebirds in the northern part of the Caspian Sea. The viruses of the H3 subtype (over 25% of the total number of isolates) were isolated in several regions.

Many strains isolated in 1979–1985 from great black-headed gulls (*Ichthyaetus ichthyaetus*), herring gulls (*Larus argentatus*) and Caspian terns (*Hydroprogne caspia*) on the island of Maly Zhemchuzhny in the northern part of the Caspian Sea were not identified at the time of isolation with respect to the subtype of their HA. As it turned out, the strains belonged to the subtype H13, was first described in 1982,[73] and in 1989 the mysterious Caspian isolates were identified[74] as H13N2, H13N3, and H13N6. To characterize the H13 subtype molecularly and antigenically, the complete nucleotide sequence of the HA of the strain A/great black-headed gull/Astrakhan/277/84 was used for comparison with the HAs

TABLE 8.49 Isolation of Influenza A Strains from Birds in Northern Eurasia (1980–2014) (According to Data from the Russian State Collection of Viruses in the D.I. Ivanovsky Institute of Virology)

		NA subtype									Total	
HA Subtype		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Number**	**%**
1		59		6			4				**69**	**6.87**
2			2	1							**3**	**0.30**
3		2	18		3		38		177		**238**	**23.68**
4		3	2	3	2		36		7	1	**54**	**5.37**
5		57	3	9							**69**	**6.87**
6			8		1				1		**10**	**1.00**
7		8		1				2			**11**	**1.09**
8					1						**1**	**0.10**
9			10		4						**14**	**1.39**
10					12				7		**19**	**1.89**
11			1				6		1	5	**13**	**1.29**
12			2								**2**	**0.20**
13			99	78			311		10		**498**	**49.55**
14						3	1				**4**	**0.40**
Total	Number	**129**	**145**	**98**	**23**	**3**	**396**	**2**	**203**	**6**	**1,005**	
	%	**12.84**	**14.43**	**9.75**	**2.29**	**0.30**	**39.40**	**0.20**	**20.20**	**0.60**		

of two American strains isolated from a gull and a pilot whale.[75]

Virus isolation studies in the northern Caspian basin were continued in the 1990s and 2000s. Materials were collected from wild birds in the area of the northern coast of the Caspian Sea (including Maly Zhemchuzhny Island) from the delta of the Terek River in the north Caucasus region to the Emba River in western Kazakhstan. Most of the strains that were isolated belonged to the H13 subtype, including H13N2, H13N3, H13N6, and H13N8 isolates; besides these strains, only single isolates belonging to the H4N3, H4N6, H6N2, and H9N2 subtypes were isolated.[76,77]

In 1990, a new, previously unrecognized, subtype of influenza virus H14 HA was described[78] on the basis of the characterization of two strains isolated in 1982 from mallards (*Anas platyrhynchos*) in the Ural River delta. The H14N5 and H14N6 subtypes were isolated from mallards and gulls in Astrakhan.[76] A partial sequencing revealed that NS gene of the H14 strains isolated from the gulls was closely related to the NS gene of H9 and H13 strains isolated previously from gulls and terns in the Caspian Sea basin and to the H9N4 strain isolated in the Russian Far East. The NS gene of an H14N5 strain isolated from a mallard was much more distantly related to the NS gene of the viruses isolated from gulls.[76] The results suggest that reassortment events play a significant role in the evolution of H14 viruses, with the NS gene being an important determinant of the range of the host.

A large-scale isolation of avian influenza viruses from fecal samples was performed in 1995–1998 in eastern Siberia and the Far East by a group that included both Russian and Japanese researchers.[79] Scientific contacts between Russian and Japanese researchers of avian Influenza A virus were ongoing during the eighth Russian–Japanese Consultations at a conference titled "Protection of Migratory Wild Birds in the Asia–Pacific region" held at the Russian Ministry of Natural Resources in Moscow April 01–05, 2011. At the conference, the D.I. Ivanovsky Institute of Virology took the initiative to renew the international meetings on medical ornithology at the level of experts of Asia–Pacific countries that had been taking place regularly during the 1970 and 1980s. As a result, the First International Meeting for Medical Ornithology in the Asia–Pacific Region was held in Tokyo, Japan, on June 23, 2011. The meeting was devoted to the topic of HPAI H5N1 distribution in Asia. A second meeting was conducted in Moscow at the D.I. Ivanovsky Institute of Virology March 15–16, 2012 (Figure 8.93).[80]

In the summer of 2000 in a valley in the Sayan Mountains in southeastern Siberia, the strains H3N8, H7N1, H7N8, H13N1, and H13N6 were isolated.[81] The H3N8 and H7N8 strains were isolated from ruddy shelducks (*Tadorna ferruginea*) and common redshanks (*Tringa totanus*), the H7N1 strains from common pochards (*Aythya ferina*), and the H13N1 strains from northern shovelers (*Anas clypeata*) and great crested grebes (*Podiceps cristatus*). The H13N6 strains were isolated from all of the aforementioned species, as well as from teals, ducks, and terns. In 2000–2002, the subtypes H3N8, H4N2, H4N6, H4N8, H4N9, H5N2, H5N3, H9N2, and H13N6 were isolated in the same region; 1,750 samples were taken from 48 bird species.[72] A strain isolated from the muskrat (*Ondatra zibethicus*)[81] in 2000 in the Republic of Buryatia was identified as an H4N6 virus closely resembling the H4N6 strains isolated from ducks in the same year and the same region.[72] The HAs of the H4 strains (including the muskrat strain) isolated in Buryatia formed a separate group of the Eurasian–Australian branch in the phylogenetic tree of H4 HA (Figure 8.94). They had a C-terminal proline residue in their HA1 subunit, in contrast to the serine residue of most Eurasian strains. The HA genes of the H5N2 isolates turned out[82] to have cleavage peptides LRNVPQRETR/GL identical to the ones of the

FIGURE 8.93 (A) Official emblem of the Second International Meeting for Medical Ornithology in the Asia–Pacific Region (Moscow, Russia, D.I. Ivanovsky Institute of Virology, March 15–16, 2012). (B) Chairman Dmitry Lvov opening the plenary session of the meeting. From left to right: Dr. Yasuko Neagari (Ministry of the Environment, Tokyo, Japan), Dr. Mikhail Shchelkanov (D.I. Ivanovsky Institute of Virology, Moscow, Russia), and Dr. Dmitry Lvov (D.I. Ivanovsky Institute of Virology, Moscow, Russia). (C) Organizing Committee of the Second International Meeting for Medical Ornithology in the Asia–Pacific Region, held at the D.I. Ivanovsky Institute of Virology. (D) Closing of the meeting. From left to right: Dr. Yoshihiro Sakoda (Hokkaido University, Sapporo, Japan), Dr. Mikhail Shchelkanov (D.I. Ivanovsky Institute of Virology, Moscow, Russia).

low-pathogenic strains isolated from ducks in Hong Kong and Malaysia. In contrast, the HAs of H3 and H4 strains isolated from teals in 2002 and from mallards in 2003 near Lake Chany in Novosibirsk Region western Siberia, were related to the HAs of the European H3 and H4 strains.[83,84] Interestingly, the HAs of the H3 strains were closely related to the HA of A/duck/Ukraine/1/1963 (H3N8).[83] However, unlike the Has of H3 and H4, the HAs of H2 strains isolated in the same area in 2003 from mallards resembled the HAs of H2 strains isolated in 2001 in Japan from mallards (*Anas platyrhynchos*).[84]

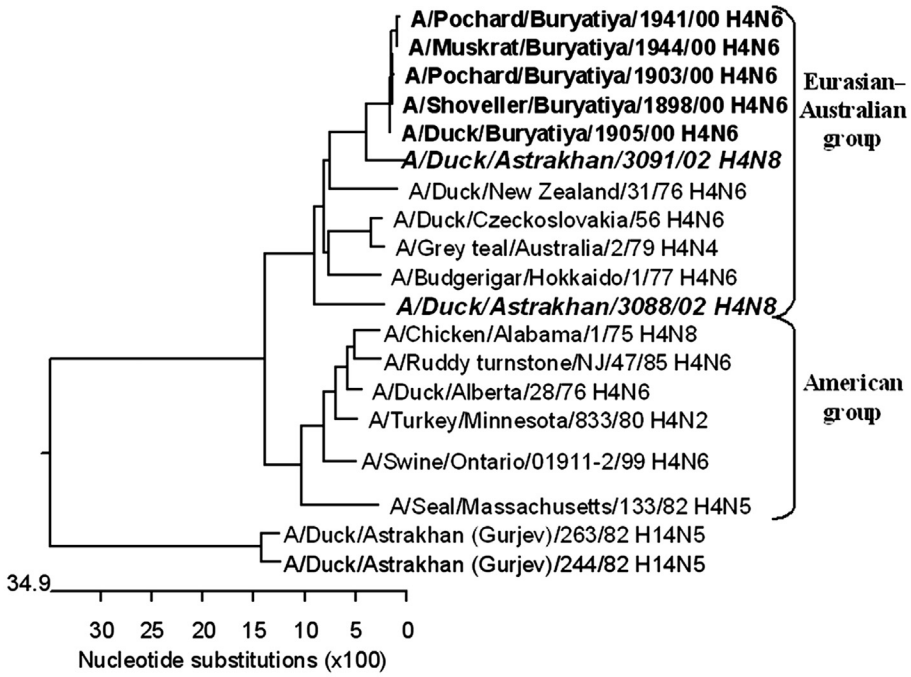


FIGURE 8.94 Phylogenetic tree for the HA gene of Influenza A H4 subtype.

In 2003, influenza A virus strains belonging to a rare subtype H8N6 were isolated in Mongolia from the great cormorant (*Phalacrocorax carbo*), white wagtail (*Motacilla alba*), and magpie (*Pica pica*).[85]

Penetration of HPAI H5N1 into Northern Eurasia: Reasons and Consequences. During longitudinal wide-scale monitoring of Influenza A viruses among wild bird populations in Northern Eurasia, several H5N2 and H5N3 strains were isolated in 1976 and 1981 in the Caspian Sea basin.[70,74] More recently, in 1991–2001, strains belonging to the same subtypes were isolated in Siberia, and their features proved to be relevant to H5 virus circulation. Onn the one hand, the HAs of the strains isolated from teals in 2001 in Primorsky Krai, as well as the HAs of strains isolated from a mallard in Lake Chany in western Siberia in 2003, were shown to be closely related to HAs of H5 strains isolated in 1997 in Italy from poultry.[79,82] On the other hand, the HA of the H5N3 strain isolated from a wild duck as early as 1991 in Altai Krai in southwest Siberia was closely related to the HA of A/duck/Malaysia/F119-3/1997 (Figure 8.95). The HA of the Altai (1991) and Lake Chany (2003) viruses had a monobasic HA1–HA2 cleavage site, and, accordingly, it had a low-pathogenic avian influenza (LPAI) phenotype.[72,79,82,86]

Besides the amino acid sequence of the HA, the sequences of other genes of the H5 viruses isolated in Russia proved to be relevant. The NP genes of the H5N2 and H5N3 strains isolated in Primorsky Krai in 2001 formed a separate cluster in the phylogenetic tree, together with the NP genes of the H4N6 strains isolated from common shelducks (*Tadorna ferruginea*) and common pochards (*Aythya ferina*) in the Republic of Buryatia in 2000, the H2N3 strain isolated from the northern pintail (*Anas acuta*) in Primorsky Krai in 1976, and the

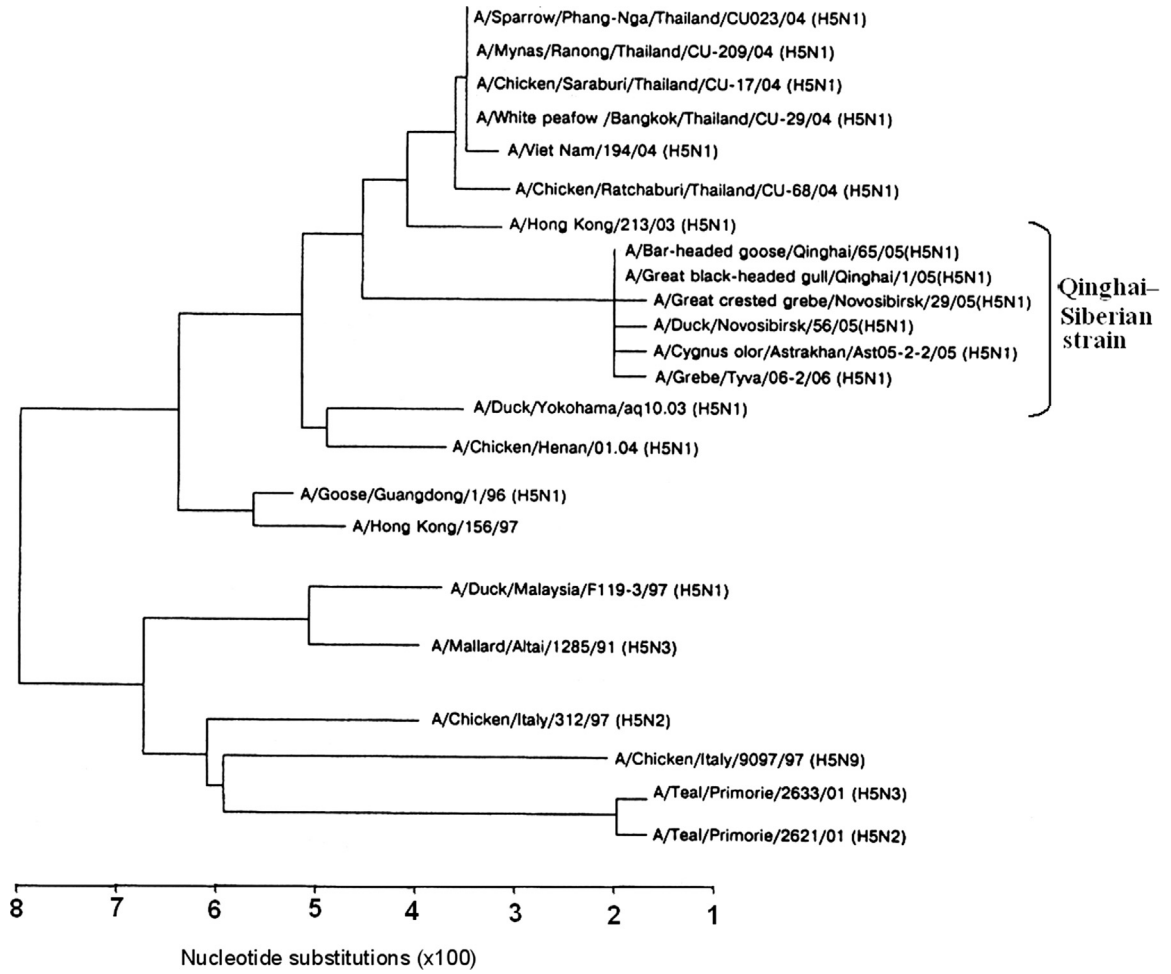


FIGURE 8.95 Phylogenetic tree for the HA gene of Influenza A H5 subtype.

H14N5 strain isolated from a wild duck in the Caspian Sea basin in 1982 (Figure 8.96).[43,72] However, they were very distantly related to the NP genes of H3N8, H6N1, and H5N1 strains isolated from poultry and humans in southeast Asia in 1996–2001 and to the NP genes of H4N8 viruses isolated from wild ducks in the Caspian Sea basin in the European Russia in 2002. By contrast, unlike the NP genes, NS genes of the strains from Primorsky Krai were closely related to the NS genes of the H5N1 and H4N8 viruses isolated in southeastern Asia in 1997–2001, as well as to the NS genes of an H4N8 virus isolated in the Caspian Sea basin in 2002 (Figure 8.97).[43,72]

An abundance of influenza A subtypes in the avian populations of Northern Eurasia provides excellent conditions for gene exchange. The extent of the exchange is demonstrated by the relatedness of different genes of the Russian isolates to the genes of European

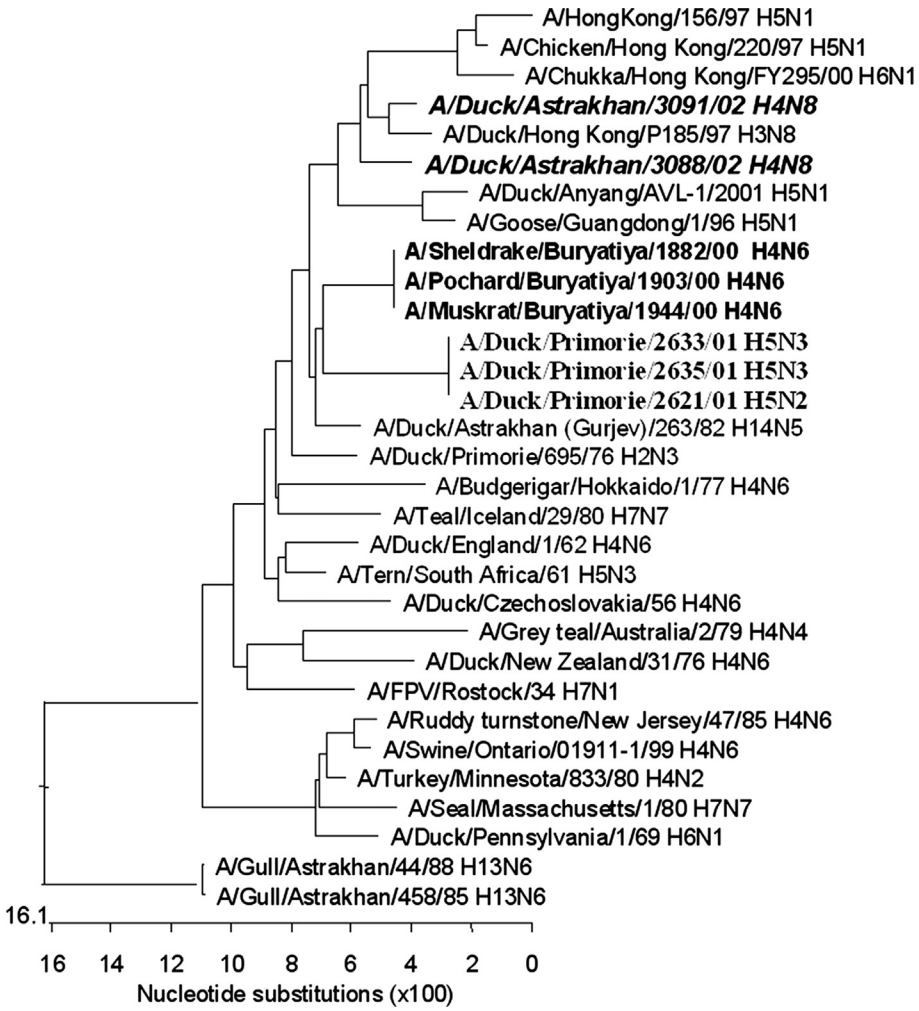


FIGURE 8.96 Phylogenetic trees for the NP gene (1,027–1,415 nt fragments) of Influenza A viruses.

strains, on the one hand, and South Asia isolates, on the other.[72,76,83,84] The exchange is to a certain extent restricted by host specificity, but this restriction is not rigid, and the virus genes frequently traverse interspecies barriers. Avian migration routes crossing Russian territory are an important factor in the gene flow. The extensive intra- and interspecies contacts in the natural habitats of wild birds in Russia stimulate rapid virus evolution and the appearance of new variants through reassortment events and, presumably, through the postreassortment adjustment of genes, thereby restoring the functional intergenic match.[87,88] Another factor may be the occurrence of avian influenza viruses in lake water, first registered in 1979 in eastern Siberia.[41] This phenomenon might provide a means for the temporal as well as territorial transfer of genes, as suggested by the recent detection of influenza

FIGURE 8.97 Phylogenetic trees for the NS gene (600–852 nt fragments) of Influenza A viruses.

viral RNA in the ice of high-latitude lakes in the Lena River basin in the Sakha–Yakutia Republic.[89]

Thus, the sequencing data suggest that there exists an extensive exchange of genes of the avian influenza viruses circulating in Europe, Siberia, and southeast Asia along the avian migration routes connecting Europe, through the Russian territory, with southeastern Asia, the cradle of potentially pandemic reassortant viruses. After the highly pathogenic H5N1 viruses began disseminating from southeastern

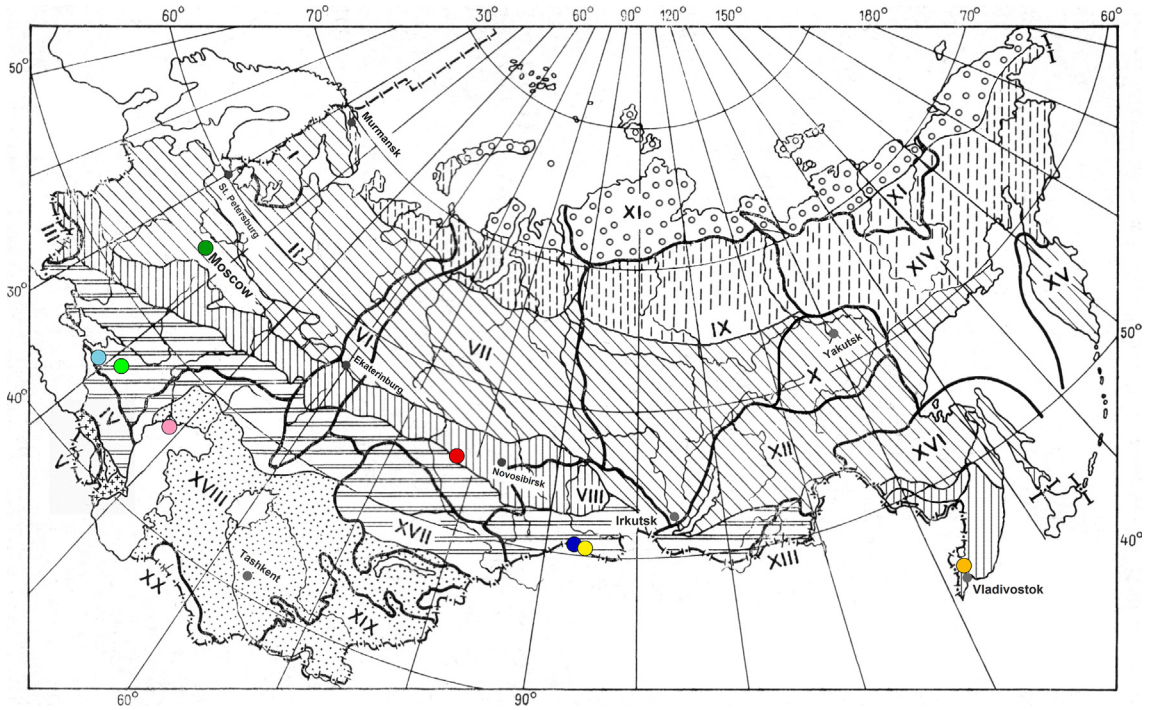


FIGURE 8.98 Places of isolation of HPAI H5N1 (family Orthomyxoviridae, genus *Influenza A virus*) in Northern Eurasia. (See other designations in Figure 1.1.)

Asia westward in 2004, their transfer to Russia by migrating birds was to be expected. On the eve of an HPAI H5N1 epizootic in southeastern Asia starting in the autumn of 2003, we warned about the likelihood of outbreaks with the Asian lineage HPAI H5N1 at the international conference titled "Options for the Control of Influenza V," held in Okinawa, Japan, October 04–13, 2003).[82]

Our second prediction was that overwintering migrating birds could transmit the HPAI virus into Northern Eurasia during their spring migration. We discussed two possible routes by which the birds might introduce the virus: the Dzungarian (Indian–Asian) migration route and the Asian–Pacific route. Preparing for these two possibilities, we increased our surveillance in the southern part of western Siberia (through the Russian Foundation for Basic Research Project 03-a04-49158) and in Primorski Krai (through the International Science–Technical Center Project 2800) in the spring of 2004. In April of 2005, a wide epizootic outbreak emerged at Kukunor Lake (also called Qinghai Lake) in Qinghai Province, China, and from this location the virus could spread through the Dzungarian Gate, which links the northwestern mountain ranges of Tibet with the western Siberian lowland. Our second prediction was confirmed as well, when HPAI H5N1 first appeared in Northern Eurasia, in western Siberia (Novosibirsk Region, Russia) in the summer of 2005 (Figure 8.98). Although the official start of the epizootic among poultry was dated July 10, 2005 (Table 8.50), that one occurred among wild birds about 2 weeks before was retrospectively established.[5] The outbreak spread

TABLE 8.50 Coverage by the Subjects of Russia of the Epizootic Provoked by HPAI H5N1 in the Southern Part of Western Siberia

	Official start of the epizootic		Coverage of epizootic			Official mortality[a] among poultry	
Subject of Russia	Date	Settlement	Districts	Settlements	Homesteads	Number of birds	Portion of the entire poultry population
Novosibirsk region	July 10, 2005	Suzdalka	11	37	268	5,031	1%
Omsk region	July 15, 2005	Pervotarovka	13	15	47	1,763	2%
Tyumen region	July 25, 2005	Peganovo	4	8	30	428	1%
Altai Krai	July 30, 2005	Titovka	12	22	78	2,454	1%

[a]*In the period from October 7 to October 31, 2005.*

quickly and caused over 90% lethality among poultry.

The virus isolations in the area were performed independently by two groups of researchers. A number of strains were isolated in Zdvinsky District, Novosibirsk Region, by a group of researchers from the D.I. Ivanovsky Institute of Virology in Moscow. The materials for isolation (cloacal and tracheal swabs, pools of internal organs, and blood) were taken from dead, sick, and healthy birds at the farm where the epizootic occurred and from wild birds in the vicinity.[90,91] Three strains were isolated from dead chickens (*Gallus gallus domesticus*), two strains from sick or dead ducks (*Anas platyrhynchos domesticus*), and one strain from a healthy great crested grebe (*Podiceps cristatus*). All of the strains were deposited into the Russian State Collection of Viruses functioning under the auspices of the D.I. Ivanovsky Institute of Virology (Table 8.51). Sequencing of the HA gene of two strains (Table 8.52)[92] revealed a close relationship to the HA of the H5N1 strains isolated at Qinghai Lake, China, and belonging to genetic group 2.2. Nevertheless, the Qinghai strains formed a so-called Qinghai genetic subgroup, whereas the strains isolated in Russia belonged to the western Siberian genetic subgroup within clade 2.2 clade (Figure 8.99). Still, the close relationship to H5N1 could be the consequence of a "bottleneck" type of genetic selection during transfer of the virus from Qinghai Lake to western Siberia by migrating wild birds.

The sequencing of the other genes of the western Siberian isolates (Table 8.52) confirmed their close relationship to the H5N1 viruses isolated in China: A/great black-headed gull/Qinghai/1/2005 (H5N1) and A/bar-headed goose/Qinghai/65/2005 (H5N1).[93] Several features of the primary structure of virus proteins, such as Lys627 residue in PB2 and Glu92 residue in NS1, characteristic of highly virulent variants of H5N1 viruses, correlated with the high pathogenicity of the Novosibirsk isolates. A deletion in the NA gene in amino acid positions 49–60 indicated that the strains belonged to the genotype Z, which dominated in 2004 in southeastern Asia.[94] The other group of strains was isolated by a team of researchers from the State Research Center of Virology and Biotechnology VECTOR (also known as the Vector Institute) in Koltsovo, Novosibirsk Region. Two strains were isolated from chickens and one strain from a turkey in the village of Suzdalka, Dovolnoe District, in July 2005. The viruses were isolated from homogenates

TABLE 8.51 Infection Activity *In Vitro* of HPAI H5N1 Strains Isolated in Natural and Anthropogenic Ecosystems of Northern Eurasia (2005–2010)

Month, Year	Region	Ecological group of birds	Strain[a]	Number of deposition certificate in Russian State Collection of Viruses	Clinical features[b]	Log_{10} $TCID_{50}$/mL for SPEV
July 2005	Southern part of western Siberia (Novosibirsk region)	Wild	**A/grebe/Novosibirsk/29/2005**	2,372	∅	5.7
					Mean value	5.7
		Poultry	**A/duck/Novosibirsk/56/2005**	2,371	⊗	7.7
			A/duck/Novosibirsk/67/2005	2,376	⊕	10.2
			A/chicken/Novosibirsk/64/2005	2,373	⊕	11.2
			A/chicken/Novosibirsk/65/2005	2,374	⊕	10.7
			A/chicken/Novosibirsk/66/2005	2,375	⊕	10.7
					Mean value	10.1
November 2005	Mouth of Volga River (Astrakhan region, Kalmyk Republic)	Wild	**A/Cygnus olor/Astrakhan/Ast05-2-1/2005**	2,379	⊗	3.7
			A/Cygnus olor/Astrakhan/Ast05-2-2/2005	2,380	⊗	4.2
			A/Cygnus olor/Astrakhan/Ast05-2-3/2005	2,381	⊗	4.2
			A/Cygnus olor/Astrakhan/Ast05-2-4/2005	2,382	⊗	3.7
			A/Cygnus olor/Astrakhan/Ast05-2-5/2005	2,383	⊗	5.2
			A/Cygnus olor/Astrakhan/Ast05-2-6/2005	2,384	⊗	5.2
			A/Cygnus olor/Astrakhan/Ast05-2-7/2005	2,385	⊗	5.7
			A/Cygnus olor/Astrakhan/Ast05-2-8/2005	2,386	⊗	4.2
			A/Cygnus olor/Astrakhan/Ast05-2-9/2005	2,387	⊗	3.2
			A/Cygnus olor/Astrakhan/Ast05-2-10/2005	2,388	⊗	4.7
					Mean value	4.4
June 2006	Uvs-Nuur Lake (Tyva Republic)	Wild	**A/grebe/Tyva/Tyv06-1/2006**	2,393	⊗	8.0
			A/grebe/Tyva/Tyv06-2/2006	2,394	⊗	8.5
			A/cormorant/Tyva/Tyv06-4/2006	2,396	∅	5.0
			A/coot/Tyva/Tyv06-6/2006	2,397	⊗	5.0
			A/grebe/Tyva/Tyv06-8/2006	2,395	⊕	8.0
			A/tern/Tyva/Tyv06-18/2006	2,399	∅	5.0
					Mean value	6.6
February 2007	Vicinity of Moscow (Moscow and Kaluga regions)	Poultry	A/chicken/Moscow/1/2007	2,403	⊕	4.0
			A/chicken/Moscow/2/2007	2,404	⊕	4.5
			A/chicken/Moscow/3/2007	2,405	⊕	4.0

(*Continued*)

TABLE 8.51 (Continued)

Month, Year	Region	Ecological group of birds	Strain[a]	Number of deposition certificate in Russian State Collection of Viruses	Clinical features[b]	Log_{10} $TCID_{50}$/mL for SPEV
February 2007 (*Continued*)			A/chicken/Moscow/4/2007	2,406	⊕	4.0
			A/goose/Moscow/5/2007	2,407	⊕	4.0
			A/chicken/Moscow/6/2007	2,408	⊕	4.5
			A/chicken/Moscow/7/2007	2,409	⊕	4.5
			A/chicken/Moscow/8/2007	2,410	⊕	4.0
			A/chicken/Moscow/9/2007	2,414	⊕	4.0
					Mean value	4.2
September 2007	North-Eastern part of Sea of Azov basin (Krasnodar krai)	Wild	**A/Cygnus cygnus/Krasnodar/329/2007**	2,421	⊗	3.5
					Mean value	3.5
		Poultry	**A/chicken/Krasnodar/300/2007**	2,418	⊗	3.5
			A/chicken/Krasnodar/301/2007	2,419	⊗	3.0
			A/chicken/Krasnodar/302/2007	2,420	⊗	3.5
					Mean value	3.3
December 2007	Southwestern part of Russian Plain (Rostov region)	Wild	**A/pigeon/Rostov-on-Don/6/2007**	2,423	∅	6.5
			A/pigeon/Rostov-on-Don/7/2007	2,424	∅	5.5
			A/heron/Rostov-on-Don/11/2007	2,425	∅	6.0
			A/pigeon/Rostov-on-Don/21/2007	2,426	∅	6.0
			A/rook/Rostov-on-Don/26/2007	2,427	∅	6.5
			A/rook/Rostov-on-Don/27/2007	2,428	∅	6.0
			A/tree sparrow/Rostov-on-Don/28/2007	2,429	∅	6.0
			A/starling/Rostov-on-Don/39/2007	2,435	∅	6.0
					Mean value	6.1
		Poultry	A/chicken/Rostov-on-Don/31/2007	2,430	⊗	7.5
			A/chicken/Rostov-on-Don/32/2007	2,431	⊗	7.0
			A/chicken/Rostov-on-Don/33/2007	2,432	⊕	7.0
			A/chicken/Rostov-on-Don/34/2007	2,433	⊕	7.5
			A/chicken/Rostov-on-Don/35/2007	2,434	⊕	7.0
			A/muscovy duck/Rostov-on-Don/51/2007	2,436	⊕	7.0
			A/chicken/Rostov-on-Don/52/2007	2,437	⊕	7.5
					Mean value	7.2

(*Continued*)

TABLE 8.51 (Continued)

Month, Year	Region	Ecological group of birds	Strain[a]	Number of deposition certificate in Russian State Collection of Viruses	Clinical features[b]	Log_{10} $TCID_{50}$/mL for SPEV
April 2008	Suifun-Khanka Lowland (Primorsky Krai)	Wild	A/*Anas crecca*/Primorje/8/2008	2,441	∅	4.0
					Mean value	4.0
		Poultry	**A/chicken/Primorje/1/2008**	2,440	⊕	4.5
			A/chicken/Primorje/11/2008	2,442	⊕	4.0
			A/chicken/Primorje/12/2008	2,443	⊕	4.5
					Mean value	4.3
June 2009	Uvs-Nuur Lake (Tyva Republic)	Wild	**A/grebe/Tyva/3/2009**	2,461	⊕	3.0
			A/grebe/Tyva/5/2009	2,462	⊕	2.0
			A/grebe/Tyva/8/2009	2,463	⊕	2.5
			A/bean goose/Tyva/10/2009	2,464	⊕	2.5
			A/grebe/Tyva/15/2009	2,465	⊕	3.0
			A/grebe/Tyva/16/2009	2,466	∅	2.0
					Mean value	2.5
June 2010	Uvs-Nuur Lake (Tyva Republic)	Wild	**A/grebe/Tyva/2/2010**		⊗	2.0
			A/grebe/Tyva/4/2010		⊕	1.7
			A/teal/Tyva/5/2010		⊕	1.8
			A/grebe/Tyva/6/2010		⊕	2.1
			A/grebe/Tyva/7/2010		⊕	1.9
			A/grebe/Tyva/8/2010		⊕	1.7
			A/grebe/Tyva/11/2010		⊕	2.0
			A/grebe/Tyva/13/2010		⊕	2.1
			A/grebe/Tyva/14/2010		⊕	1.5
					Mean value	1.9

[a]*Strains with complete genome sequences are marked by bold font.*
[b]*Description: ∅, Birds without clinical features; ⊗, birds with clinical features; ⊕, birds that died.*

of turkey spleen and chicken kidneys. The isolated viruses belonged to subtype H5N1, and their HA gene was closely related to the HA gene of the viruses isolated near Qinghai Lake in China in 2003. The sequences of the internal genes (PB1, PB2, PA, and NS) revealed a similarity to the avian H5N1 viruses isolated in Hong Kong in 2004 and in 2005 in Shantou,

TABLE 8.52 GenBank Identification Numbers of HPAI H5N1 Strains Isolated in Natural and Anthropogenic Ecosystems of Northern Eurasia (2005–2010) with Complete Nucleotide Sequences of Genomes

Strain	HA genotype	Source of isolation	Complete nucleotide sequences							
			PB2	PB1	PA	HA	NP	NA	M	NS
A/grebe/Novosibirsk/29/05	2.2	Great crested grebe (*Podiceps cristatus*)	DQ232607	DQ232605	DQ234075	DQ230521	DQ232609	DQ230523	DQ234077	DQ234073
A/duck/Novosibirsk/56/05	2.2	Domestic duck (*Anas platyrhynchos domesticus*)	DQ232608	DQ232606	DQ234076	DQ230522	DQ232610	DQ230524	DQ234078	DQ234074
A/Cygnus olor/Astrakhan/Ast05-2-1/05	2.2	Mute swan (*Cygnus olor*)	DQ389161	DQ394578	DQ394579	DQ389158	DQ394577	DQ389159	DQ394576	DQ389160
A/Cygnus olor/Astrakhan/Ast05-2-2/05	2.2	Mute swan (*Cygnus olor*)	DQ343506	DQ343505	DQ343504	DQ343502	DQ359694	DQ343503	DQ359692	DQ359693
A/Cygnus olor/Astrakhan/Ast05-2-3/05	2.2	Mute swan (*Cygnus olor*)	DQ358750	DQ358749	DQ358748	DQ358746	DQ358751	DQ358747	DQ358739	DQ358752
A/Cygnus olor/Astrakhan/Ast05-2-4/05	2.2	Mute swan (*Cygnus olor*)	DQ363916	DQ363915	DQ363917	DQ363918	DQ363929	DQ363919	DQ363925	DQ363926
A/Cygnus olor/Astrakhan/Ast05-2-5/05	2.2	Mute swan (*Cygnus olor*)	DQ365011	DQ365008	DQ365007	DQ365004	DQ365006	DQ365005	DQ365009	DQ365010
A/Cygnus olor/Astrakhan/Ast05-2-6/05	2.2	Mute swan (*Cygnus olor*)	DQ365001	DQ365000	DQ364999	DQ364996	DQ364998	DQ364997	DQ365002	DQ365003
A/Cygnus olor/Astrakhan/Ast05-2-7/05	2.2	Mute swan (*Cygnus olor*)	DQ363921	DQ363920	DQ363922	DQ363923	DQ363930	DQ363924	DQ363928	DQ363927
A/Cygnus olor/Astrakhan/Ast05-2-8/05	2.2	Mute swan (*Cygnus olor*)	DQ386305	DQ386304	DQ399537	DQ399540	DQ399539	DQ399541	DQ399542	DQ399538
A/Cygnus olor/Astrakhan/Ast05-2-9/05	2.2	Mute swan (*Cygnus olor*)	DQ399543	DQ406738	DQ406737	DQ399547	DQ399545	DQ399546	DQ400912	DQ399544
A/Cygnus olor/Astrakhan/Ast05-2-10/05	2.2	Mute swan (*Cygnus olor*)	DQ434890	DQ423612	DQ434891	DQ434889	DQ440580	DQ440579	DQ434888	DQ434887
A/grebe/Tyva/Tyv06-1/06	2.2	Great crested grebe (*Podiceps cristatus*)	DQ914807	DQ914810	DQ978999	DQ914808	DQ916293	DQ914809	DQ914805	DQ914806
A/grebe/Tyva/Tyv06-2/06	2.2	Great crested grebe (*Podiceps cristatus*)	DQ852607	DQ852606	DQ852603	DQ852600	DQ852602	DQ852601	DQ852604	DQ852605
A/grebe/Tyva/Tyv06-8/06	2.2	Great crested grebe (*Podiceps cristatus*)	DQ863510	DQ863509	DQ863508	DQ863503	DQ863506	DQ863507	DQ863504	DQ863505
A/chicken/Moscow/2/07	2.2	Chicken (*Gallus gallus domesticus*)	EF474443	EF474444	EF474445	EF474450	EF474447	EF474448	EF474449	EF474446
A/chicken/Krasnodar/300/07	2.2	Chicken (*Gallus gallus domesticus*)	EU163436	EU163435	EU163434	EU163431	EU163432	EU163433	EU163429	EU163430
A/Cygnus cygnus/Krasnodar/329/07	2.2	Whooper swan (*Cygnus cygnus*)	EU257707	EU257636	EU257637	EU257631	EU257635	EU257632	EU257633	EU257634
A/pigeon/Rostov-on-Don/6/07	2.2	Rock dove (*Columba livia*)	EU441930	EU441931	EU441932	EU441937	EU441933	EU441936	EU441935	EU441934
A/rook/Rostov-on-Don/26/07	2.2	Rook (*Corvus frugilegus*)	EU814510	EU814509	EU814508	EU814503	EU814506	EU814505	EU814504	EU814507
A/starling/Rostov-on-Don/39/07	2.2	Starling (*Sturnus vulgaris*)	EU486848	EU486849	EU486850	EU486855	EU486851	EU486854	EU486853	EU486852
A/chicken/Rostov-on-Don/35/07	2.2	Chicken (*Gallus gallus domesticus*)	EU414265	EU420032	EU408333	EU401751	EU401754	EU401753	EU401752	EU401755
A/muscovy duck/Rostov-on-Don/51/07	2.2	Muscovy duck (*Cairina moschata*)	EU441922	EU441923	EU441924	EU441929	EU441925	EU441928	EU441927	EU441926
A/chicken/Primorje/1/08	2.3.2.1	Chicken (*Gallus gallus domesticus*)	EU672455	EU672456	EU672457	EU676174	EU672458	EU672460	EU676173	EU672459
A/grebe/Tyva/3/2009	2.3.2.1	Great crested grebe (*Podiceps cristatus*)	GQ386146.1	GQ386147.1	GQ386145.1	GQ386142.1	GQ386144.1	GQ386143.1	GQ386148.1	GQ386149.1
A/bean goose/Tyva/10/2009	2.3.2.1	Taiga bean goose (*Anser fabalis*)	GQ386154.1	GQ386155.1	GQ386153.1	GQ386150.1	GQ386152.1	GQ386151.	GQ386156.1	GQ386157.1
A/grebe/Tyva/2/2010	2.3.2.1	Great crested grebe (*Podiceps cristatus*)	HQ630841.1	HQ630842.1	HQ630840.1	HQ630838.1	HQ630839.1	HQ630837.1	HQ630843.1	HQ630844.1

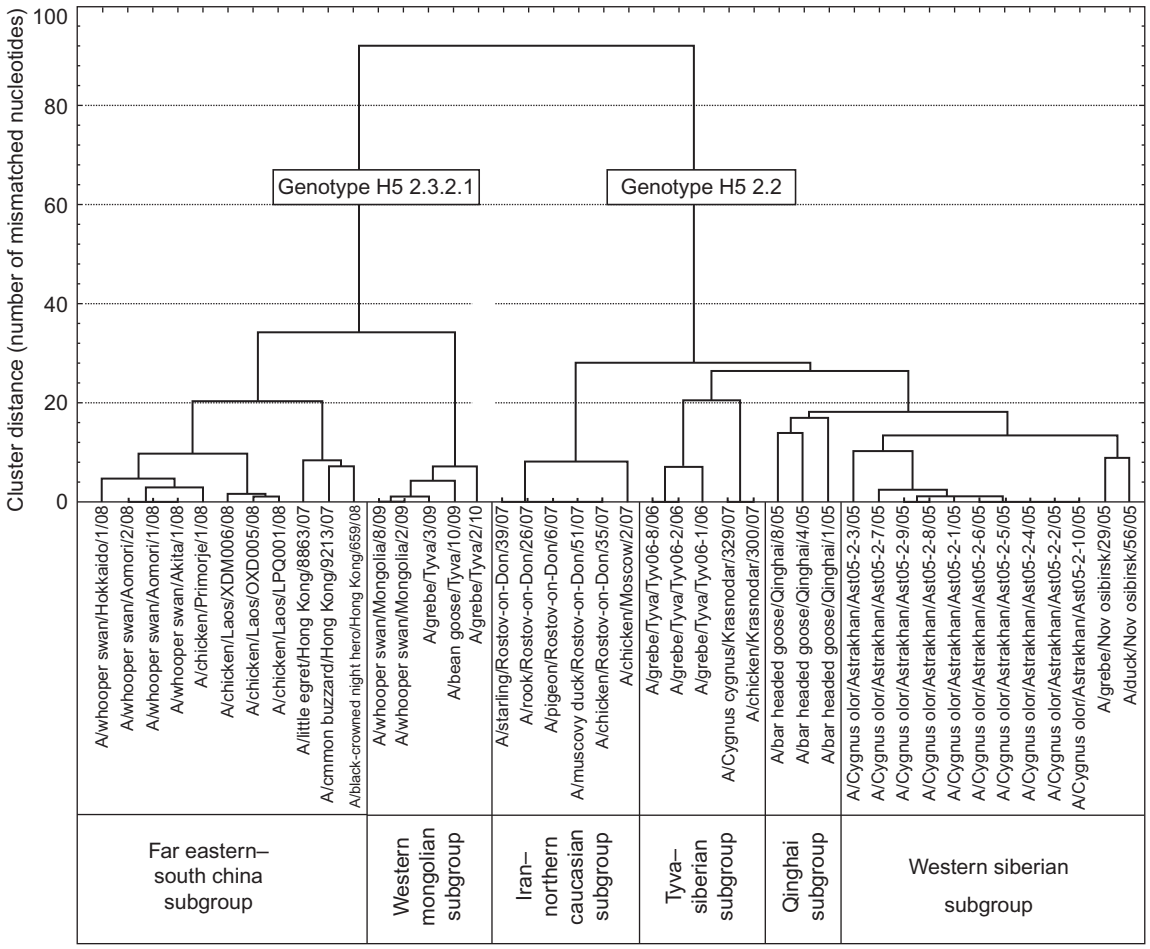


FIGURE 8.99 Phylogenetic analysis of complete nucleotide sequences of ORFs for HPAI H5N1 HA.

Guangdong Province, China.[95] The viruses were highly pathogenic to chickens in a laboratory test.[96]

Our third prediction was that the virus would move with the migrating birds to their overwintering locations. As it turned out, coincident with this prediction, epizootic outbreaks occurred along the main migration routse in the Urals, the Russian Plain, Europe, Africa, central Asia, and India (Figure 8.100).[97–103] In November 2005, an epizootic with mass deaths emerged in the downstream part of the mouth of the Volga River (Figure 8.98) among a local population of mute swans (*Cygnus olor*).[102] Many of the swans contracted neurological disorders, including the inability to keep their neck or head raised, paralysis of the extremities (mainly the legs), and depression. Because there are no human settlements in this part of the Volga, no infections were detected among poultry. Migrating tufted ducks (*Aythya fuligula*), among which no clinical features were detected, are suspected to be the source of the infection, because the start

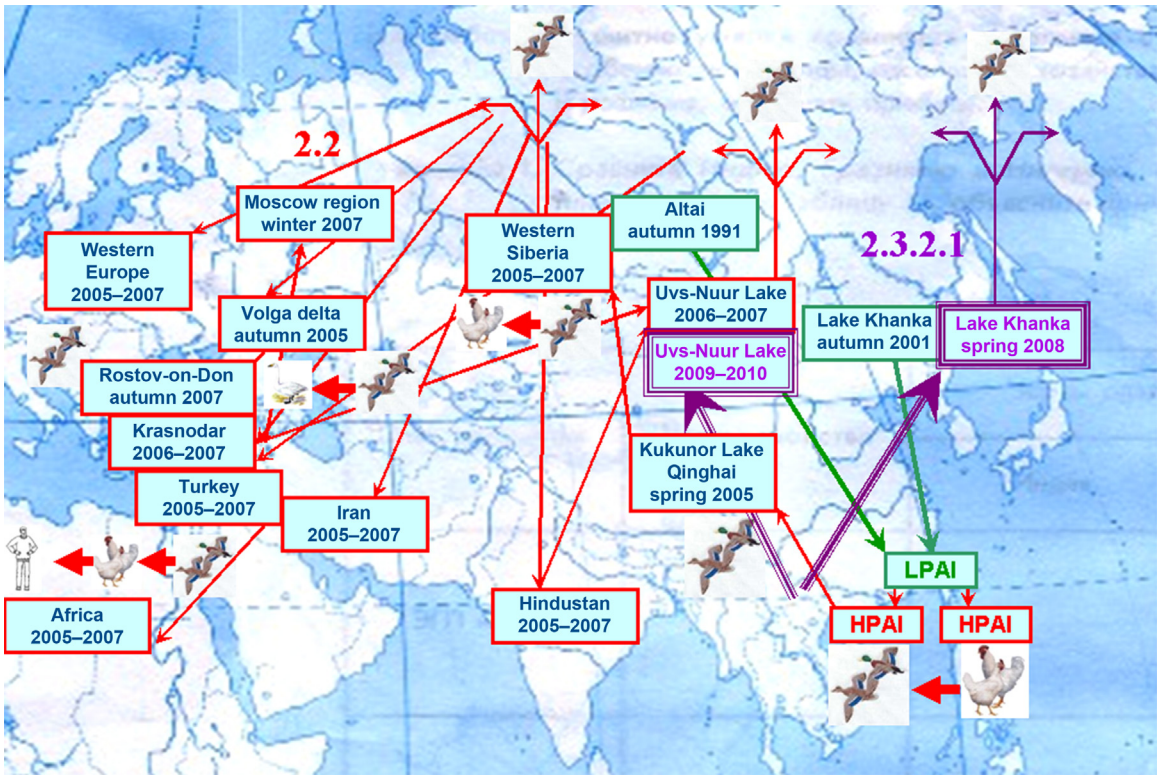


FIGURE 8.100 Reasons and consequences of HPAI H5N1 (clades 2.2 and 2.3.2) virus penetration into Northern Eurasia.

of the epizootic coincided with the appearance of the ducks. Sequencewise, the swan viruses, including A/Cygnus olor/Astrakhan/Ast05-2/2005, were closely related to the western Siberian strains (Tables 8.51 and 8.52, Figure 8.99),[102] indicating the distribution of the virus through the eastern European flyway of birds (Figure 8.100), connecting western Siberia, the Russian Plain, eastern Europe, the Middle East, and Africa.[54]

Our fourth prediction was that the virus would return in birds migrating from their overwintering places to Northern Eurasia in the spring of 2006, with a widening of the epizootic. Dramatic events occurred June 10–28, 2006, at Uvs-Nuur Lake, which is situated on the boundary between the Great Lakes Depression of Mongolia and the Tyva Republic of Russia (Figure 8.98). An estimated 3,000-plus birds died in the Russian part of this lake, which is only about 1% of the total area of the lake. The species most affected was the great crested grebe (*Podiceps cristatus*); as also affected were coots (*Fulica atra*) and cormorants (*Phalacrocorax carbo*). Terns and gulls were involved in the epizootic to a significantly less extent. The absence of poultry farms in the vicinity of Uvs-Nuur Lake precluded outbreaks among poultry. The Tyva strains appeared to be the beginning of a new genetic lineage in the Qinghai–Siberian genotype 2.2. The lineage was designated as a Tyva–Siberian subgroup[104] (Figure 8.99) that was isolated not only in Siberia, but also in Europe. It is believed

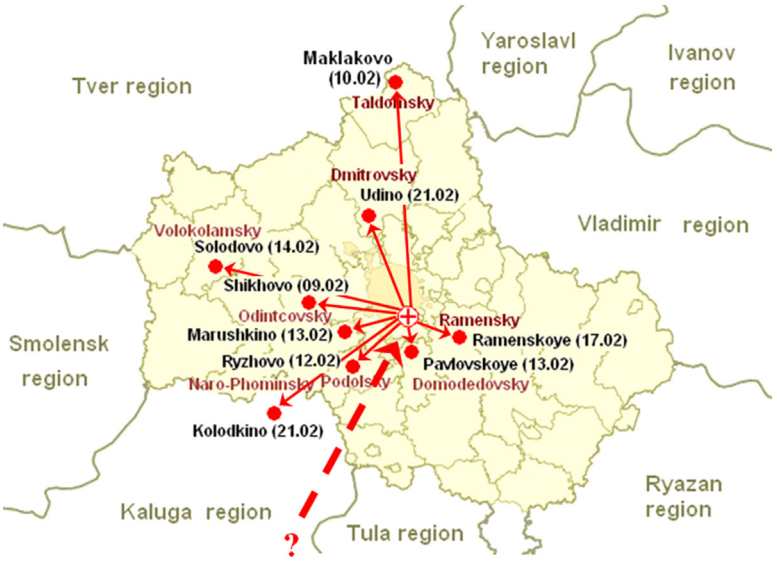


FIGURE 8.101 Dynamics of epizootic provoked by HPAI H5N1 in the Moscow region in February 2007.

that the Tyva–Siberian subgroup emerged in 2006 on nesting grounds of wild ducks in western Siberia. These birds were thought to have been infected in 2005 at the Great Lakes Depression in Mongolia and at their overwintering grounds in India. After the virus was introduced into the nesting places of Northern Eurasia, it spread through the region.

A series of nine outbreaks occurred on the outskirts of Moscow beginning in February 2007 (Figures 8.98 and 8.101). The occurrence of the outbreak at that time of the year seems to preclude the participation of wild waterfowl in introducing or spreading the virus; in addition, terrestrial wild birds tested negative by RT-PCR. The virus was isolated (Table 8.51) from dead and sick poultry, and all the isolates were identified as HPAI H5N1 (Table 8.52) with a high level of sequence similarity to the Qinghai–Suberian genotype 2.2 (Figure 8.99). This outcome implied a common source of infection for all the local outbreaks (Figure 8.101), and subsequent epidemiologic investigation demonstrated a link to live-bird markets in Moscow, where the affected farmers had purchased poultry several days before. A complete genome analysis of the prototype A/chicken/Moscow/2/2007 revealed[105] that the highest similarity occurred for the strains isolated in the Caucasus region during the winter of 2005–2006: A/cat/Dagestan/87/2006, A/Cygnus cygnus/Iran/754/2006, A/chicken/Krasnodar/01/2006, A/chicken/Adygea/203/2006 (the similarity for nucleotide sequences of PB2 was 99.5%; PB1, 99.3%; PA, 99.7%; HA, 99.1–99.4%; NP, 99.4%; NA, 99.1–99.6%; M1, 99.5–99.9%; and NS1, 99.9%). The closest neighbor for A/chicken/Moscow/2/2007 was found to be A/Cygnus cygnus/Iran/754/2006. Later, this genetic subgroup of HPAI/H5N1/2.2 was designated as "Iran–North Caucasian" (Figure 8.99). Nevertheless, A/chicken/Moscow/2/2007 differed significantly from other Qinghai–Siberian strains: In four genes—PB2, PB1, HA, and NP—there were 12 unique amino acid substitutions (Table 8.53), and all 8 amino acid substitutions in PB1 were unique at that time, affording evidence of active circulation of the virus before 2007. However, the specific origin of A/chicken/Moscow/2/2007 has not been officially identified, and it is suspected that the virus was circulating in a small intermountain

TABLE 8.53 Point Mutations in the Proteins of HPAI/H5N1/2.2 Strains Isolated in Northern Eurasia (2005–2007)

Strains *	Amino acid substitutions **					
	NP	NA	M1	M2	NS1	NS2
A/{*}/05	Y_{10} N_{397}				D_{202}	M_{50} I_{60}
↓	↓ ↓	no	no	no	↓	↓ ↓
A/{*}/{06–07}	**H_{10}** **S_{397}**				**G_{202}**	**V_{50}** **T_{60}**
A/duck/Novosibirsk/56/05	**T_{403}**	M_{29} **L_{143}**				
↓	↓	↓ ↓	no	no	no	no
A/grebe/Novosibirsk/29/05	A_{403}	**I_{29}** V_{143}				
A/duck/Novosibirsk/56/05	**T_{403}**	**L_{143}**				
↓	↓	↓	no	no	no	no
A/Cygnus olor/Astrakhan/Ast05-2-{1-10}/05	A_{403}	V_{143}				
A/duck/Novosibirsk/56/05	Y_{10} N_{397} **T_{403}**	**L_{143}** P_{320}			D_{202}	M_{50} I_{60}
↓	▼ ↓	↓ ▼	no	no	▼	▼ ▼
A/grebe/Tyva/Tyv06-{1,2,8}/06	**H_{10}** **S_{397}** A_{403}	V_{143} **L_{320}**			**G_{202}**	**V_{50}** **T_{60}**
A/duck/Novosibirsk/56/05	Y_{10} K_{90} A_{373} N_{397} **T_{403}**	R_{44} **L_{143}**			D_{202}	M_{50} I_{60}
↓	▼ ▼ ▼ ▼ ↓	↓ ↓	no	no	▼	▼ ▼
A/chicken/Moscow/2/07	**H_{10}** **R_{90}** **T_{373}** **S_{397}** A_{403}	**C_{44}** V_{143}			**G_{202}**	**V_{50}** **T_{60}**
A/duck/Novosibirsk/56/05	Y_{10} N_{397} **T_{403}**	Q_{39} G_{41} **L_{143}** P_{320} K_{412}			I_{64} D_{202}	M_{50} I_{60}
↓	▼ ▼ ↓	↓ ↓ ↓ ▼ ↓	no	no	↓ ▼	▼ ▼
A/{*}/Krasnodar/{*}/07	**H_{10}** **S_{397}** A_{403}	**L_{39}** **R_{41}** V_{143} **L_{320}** **E_{412}**			**M_{64}** **G_{202}**	**V_{50}** **T_{60}**
A/duck/Novosibirsk/56/05	Y_{10} K_{90} A_{323} A_{373} N_{397} **T_{403}**	A_{46} V_{63} I_{102} **L_{143}** Q_{288}		V_{68} Q_{81}	D_{202}	M_{50} I_{60}
↓	▼ ▼ ↓ ▼ ▼ ↓	↓ ↓ ↓ ↓ ↓	no	↓ ↓	▼	▼ ▼
A/{*}/Rostov-on-Don/{*}/07	**H_{10}** **R_{90}** **T_{323}** **T_{373}** **S_{397}** A_{403}	**V_{46}** **L_{63}** **V_{102}** V_{143} **R_{288}**		**I_{68}** **R_{81}**	**G_{202}**	**V_{50}** **T_{60}**

[a]Group of strains is shown with the use of braces: Designations common to all strains in the given group are shown outside the braces; the variable part of the designations is cited inside the braces; the asterisk "*" means "any designation." Only mutations that are found in all the strains of the given group are listed in the table.

[b] **Bold font** indicates substitutions with respect to HPAI/H5N1/2.2 consensus; the frame—substitutions unique to Northern Eurasian strains (Tables 1–2)—that is, they did not occur among Northern Eurasian strains previously; the frame with grey background—substitutions unique to all HPAI/H5N1/2.2 genotypes (strains isolated in both Northern Eurasia and other places); «↓»—substitution that takes place in the strains of the given epizootic outbreak only; «▼»—substitution that takes place in the strains of both the given and later or previous epizootic outbreaks.

valley ecosystem in the north or south Caucasus in the winter of 2007 and was introduced into the live-bird market through contaminated poultry cages or contaminated grain.

In September 2007, an outbreak was detected in the northeastern part of the basin of the Sea of Azov on a chicken farm called "Lebyazhje-Chepiginskaya" in the Krasnodar region of Russia (Figure 8.98). The virus isolates—A/chicken/Krasnodar/300/2007 from poultry and A/Cygnus cygnus/Krasnodar/329/2007 from a sick whooper swan (*Cygnus cygnus*) found in a "liman" (shallow gulf) near the farm—were closely related to each other (they had two synonymous nucleotide substitutions in PB1, two synonymous in PB2, one nonsynonymous in M1, two nonsynonymous in NA, and one nonsynonymous in NS1) and belonged to the Iran–North Caucasian subgroup of Qinghai–Siberian genotype 2.2 (Figure 8.99). The isolated strains contained 10 unique amino acid substitutions with respect to a Qinghai–Siberian consensus in PB2, PA, HA, NA, and NS1, suggesting that regional variants were continuing to emerge.[106]

In December 2007, a poultry farm called "Gulyai-Borisovskaya" in the Rostov region became infected (Figure 8.98). Unfortunately, the infection was not reported in time, and infected poultry manure was spread on adjacent fields, where wild terrestrial birds could be infected.[107] This exposure is thought to have contributed to the infection of a number of species. including rooks (*Corvus frugilegus*), jackdaws (*Corvus monedula*), rock doves (*Columba livia*), common starlings (*Sturnus vulgaris*), tree sparrows (*Passer montanus*), house sparrows (*Passer domesticus*), and more. Surveillance of these species by RT-PCR detected H5 virus in 60% of pigeons and crows, in around 20% of starlings, and in 10% of tree sparrows, all without clinical features. These results were confirmed by viruses isolated from wild birds and poultry (Table 8.51). Birds whose infection was confirmed by RT-PCR and virus isolation seemed reluctant to move and had ruffled feathers. On necropsy, the birds were observed to have had conjunctivitis; hemorrhages on the lower extremities and in muscle, adipose, intestine, mesentery, and brain tissue; and changes in the structure of the pancreas and liver. Wide involvement of wild terrestrial birds in virus circulation, presumably from the exposure to infected chicken manure, distinguished this outbreak from others. Genome analysis (Table 8.52) revealed that the strains which were isolated belonged to the Iran–Northern Caucasian subgroup of the Qinghai–Siberian genotype (Figure 8.99). They were phylogenetically similar to A/chicken/Moscow/2/2007 and 13 unique amino acid substitutions with respect to Qinghai–Siberian consensus in PB2, PA, HA, NP, NA, and M2 (Table 8.53).

The main genetic characteristics of the Qinghai–Siberian clade[5,43,92,108] persisted as the virus lineage extended into the western part of Northern Eurasia and Africa (2005–2008). The other genes of the Qinghai–Siberian genotype are associated with group Z, which has dominated among poultry in southeastern Asia since 2003–2004.[93,94] The group Z genotype has several unique genetic markers, including a 20-mer amino acid fragment deletion C_{49}NQSIITYENNTWVNQTYVN_{68} in the N1 gene, compared with the genotype of A/goose/Guangdong/1996. The HA cleavage site—P_{337}QGERRRKKRGLF$_{349}$—has multiple basic amino acid insertion. Three types of silent nucleotide substitutions are known in the coding region of the cleavage site among members of the Qinghai–Siberian clade: $G\overset{1020}{\rightarrow}A$ (A/chicken/Volgograd/236/2006), $G\overset{1028}{\rightarrow}A$ (A/pied magpie/Liaoning/7/2005), and $A\overset{1044}{\rightarrow}G$ (A/chicken/Crimea/04/2005). In addition, four types of amino acid substitutions are known: $G\overset{339}{\rightarrow}R$ (A/bar-headed goose/Qinghai/{1,3}/2005; A/brown-headed gull/Qinghai/1/2005; A/great black-headed gull/Qinghai/3/2005; A/great

cormorant/Qinghai/3/2005; A/whooper swan/Mongolia/13/2005), $R^{341}\rightarrow G$ (A/chicken/Sudan/1784-{7,10}/2006), $R^{343}\rightarrow K$ (A/pied magpie/Liaoning/7/2005), and $K^{344}\rightarrow R$ (A/whooper swan/Mongolia/7/2005). The presence of consensus G339 makes the Qinghai–Siberian clade different from other HPAI/H5N1 variants from southeastern Asia containing consensus R339. The highest portion of R339, 5/15 (33.3%), was detected in the initial outbreak at Kukunor Lake, suggesting that the Qinghai–Siberian strains which originated from southeastern Asia were under a "bottleneck" selection at an early stage of their evolution. The NS1 protein has E92, instead of the more common D92 in virus variants from birds,[109,110] and a 5 aa deletion.

The Qinghai–Siberian clade includes viruses that have infected and caused severe disease and mortality in humans, but currently they do not appear to be transmitted efficiently in humans. Upon analyzing representative viruses in our collection for their potential to replicate in mammals, we found that isolated strains replicated effectively in mammalian cell culture lines BHK-21, LECH, Vero E6, MDCK, and SPEV.[5,108,111] PB2 has consensus K627 that promotes virulence in mammalian cells.[93,112] Six representative isolates from the Qinghai–Siberian clade have E627: A/bar-headed goose/Qinghai/2/2005, A/ruddy shelduck/Qinghai/1/2005, A/duck/Novosibirsk/02/2005, A/duck/Kurgan/08/2005, A/Cygnus olor/Astrakhan/Ast05-2-4/2005, and A/Cygnus olor/Italy/808/2006. These strains are uniformly distributed over time and territory as the result of the stochastic nature of E627 and the absence of any tendency for K627 elimination. Amino acid substitutions that are correlated with virus tropism in mammals include $D^{701}\rightarrow N$ and $S^{714}\rightarrow R$ in PB2, $L^{13}\rightarrow P$ and $S^{678}\rightarrow N$ in PB1, and $K^{615}\rightarrow N$ in PA. In the viruses of the Qinghai–Siberian clade, proline is present in all the genomes in the 13th aa position of PB1 and asparagine at position 701 of the PB2 protein was found only in A/ruddy shelduck/Qinghai/1/2005.

On the basis of the amino acid sequence of HA receptor-binding sites of Qinghai–Siberian isolates containing E202, Q238, and G240, its affinity of Qinghai Siberian isolates for α2′-′–3′-sialic acids was predicted. However, a double mutation $Q^{238}\rightarrow L$ and $G^{240}\rightarrow S$ or just a single mutation $E^{202}\rightarrow D$ could switch HA receptor-binding affinity from avian to human receptors.[113]

All the Qinghai–Siberian isolates are sensitive to amantadine, rimantadine, and oseltamivir, as has been confirmed by both direct biological experiments *in vitro*[114] and the presence[5,92,102,104–108] of marker substitutions in M and NA virus proteins.

Genetic stratification of the Qinghai–Siberian (2.2) genotype of HPAI/H5N1 virus in Northern Eurasia appeared to occur in accordance with the following ecological model: In the summer of 2005, western Siberian cluster variants selected during an epizootic outbreak at Kukunor Lake, Qinghai province, China, spread to the summer nesting places of birds. In winter, 2005–2006, HPAI/H5N1/2.2 was under selection in two main overwintering areas: (1) Africa, Transcaucasia, and the Middle East (penetrating along eastern and western European flyways); and (2) India and central Asia (penetrating along the Indian–Asian flyway).[54] The first overwintering area could be the source for the Iran–North Caucasian subgroup, the second for the Tyva–Siberian subgroup. Returning to their nesting areas in Northern Eurasia in the spring of 2006, wild birds afforded a mixed virus population the opportunity to spread (Figure 8.100).[5,24,28,42,43,108] A decrease in the potential of isolated strains to reproduce *in vitro* (Figure 8.102) is more evident in poultry ($TCID_{50} = 11.847 - 0.272 \times t$) than in to wild birds ($TCID_{50} = 6.185 - 0.066 \times t$)[115] (Time t is time expressed in months starting from the beginning of 2005.) Tables 8.53 and 8.54 facilitate a comparison of phenotypical changes

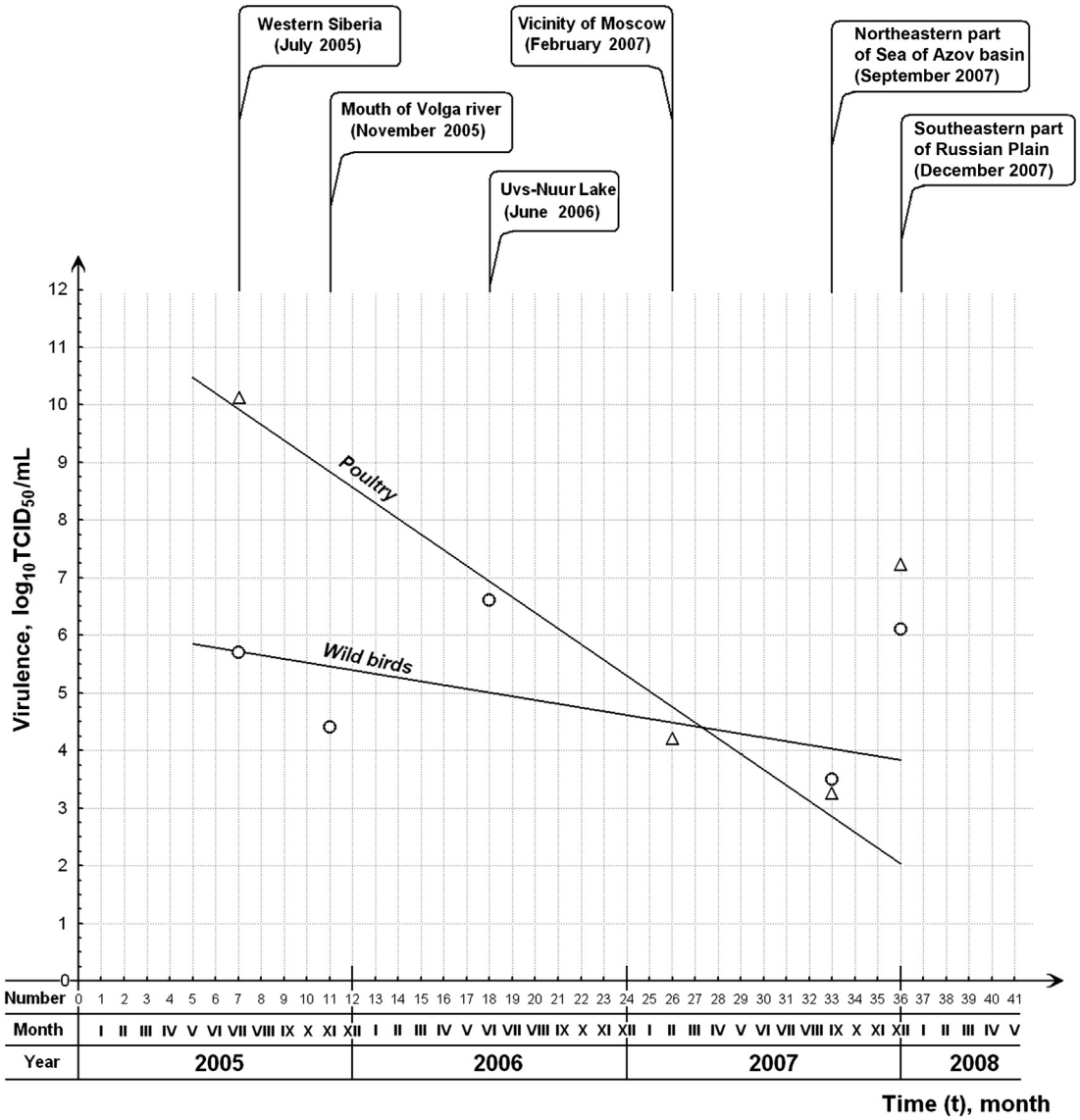


FIGURE 8.102 Virulence dynamics of HPAI/H5N1/2.2 strains isolated in Northern Eurasia (July 2005–September 2007; epizootic episode in December 2007 was excluded from the calculation of the trend because of its ecologically distinctive features described in the text).

with point mutations in the proteins of HPAI/H5N1/2.2 strains isolated in Northern Eurasia.

Although HPAI H5N1 has penetrated into Northern Eurasia through the Dzungarian flyway of wild birds, this fact did not exclude the possibility of the virus transferring through other flyways —(e.g., through the Far East–Pacific flyway).[54] Indeed, in April

TABLE 8.54 Possible Influence of Amino Acid Substitutions on the Virulence of HPAI/H5N1/2.2 Strains Isolated in Northern Eurasia (2005–2007)

		Virulence			
Protein	**Position**	**Increased**	**Decreased**	**Function region of the protein**	**Influenced process of virus life cycle**
PB2	69	E	A	Domain of uncovalent binding with C-terminus of PB1	Formation and functioning of polymerase complex PB2–PB1–PA
	73	Q	R		
	221	A	T		
	473	M	T	NLS	Import of RNP into the nucleus
PB1	212	L	M	NLS	Import of RNP into the nucleus
	294	Q	H	Enzyme polymerase center	Functioning of polymerase complex PB2–PB1–PA
	451	V	L		
	618	E	K	Domain of uncovalent binding with N-terminus of PB2	Formation and functioning of polymerase complex PB2–PB1–PA
	678	S	G		
	741	A	N		
PA	213	R	K	NLS	Import of RNP into the nucleus
HA	512	A	S	Elongation fragment during fusion peptide disengage	Virion and endosome membrane fusion
	545	L	M	C-terminus transmembrane domain	
NP	10	Y	H	NLS	Import of RNP into the nucleus
	323	A	T		
	373	A	T		
	397	N	S		
	403	T	A		
NA	29	M	I	N-terminus transmembrane domain	Assembling of new virions
M2	68	I	V	C-terminus cytoplasm domain	Interaction between M2 and M1
	81	R	Q		
NS1	64	I	M	Unknown	Interaction with signal systems of infected cell
	202	D	G		
NS2	50	M	V	Terminus of α-helix N2	Export of RNP from the nucleus
	60	I	T	Base of α-helix C1	

2008, a second breach of HPAI H5N1 into Northern Eurasia emerged in the Russian Far East[116] and was linked with another genotype: 2.3.2.1 (Figure 8.99, Table 8.52). The epizootic originated from unvaccinated poultry in the outermost backyard of Vozdvizhenka, a village in Primorsky Krai surrounded by a small river and meadow where poultry often interacted

with wild waterfowl. One initial theory of the introduction of the virus to poultry was from the birds' exposure to hunted ducks, but the direct interaction of wild birds with poultry seems more likely. The isolates (see Table 8.51) from dead chickens and the common teal (*Anas crecca*) collected in the vicinity of epizootic farms were identical and indicated a direct role of migrating birds in the introduction of the virus. The teal, which appeared to be the most likely source of infection of poultry, had no obvious behavior changes but did have hemorrhagic lesions in the intestines on necropsy. It is interesting to underline the fact that common teals were the source of isolation of H5 strains in Primorski Krai in autumn 2001. The teals migrate for long distances, so, the operative hypothesis is that HPAI/H5N1/2.3.2.1 variants may have migrated from the Far East to southern China, Vietnam, or Laos. The HPAI/H5N1 virus was widely distributed in Primorski Krai in the spring of 2008: According to RT-PCR testing, 26% of wild ducks in the Suifun River–Lake Khanka lowland were infected.[116] However, during monitoring in the autumn of 2008, we were not able to find HPAI/H5N1. Nevertheless, the emergence of the HPAI/H5N1 virus in Primorski Krai creates a new type of HPAI stratification in Northern Eurasia (genotype 2.2 in the eastern portion of the subcontinent, genotype 2.3.2.1 in the western portion), as well as the threat of introducing HPAI into North America. The closest neighbors of Primorski Krai 2008 strains are A/chicken/Viet Nam/10/2005 (the nucleotide sequence similarity for the HA gene is 97.5%), A/chicken/Guandong/178/2004 (97.3%), and A/duck/Viet Nam/12/2005 (97.2%). The cleavage site of HA—P_{337}QRERRRKRGLF$_{348}$—contains a multiple basic amino acid motif, which is typical for HPAI but differs from the Qinghai–Siberian HA cleavage site. The 2008 isolates also belong to group Z for internal genes, have avian-type receptor specificity, and are sensitive to M2-channel formation and neuraminidase inhibitors. Nevertheless, in contrast to the HPAI/H5N1/2.2 strains, which contain K627 (an amino acid that promotes virulence in mammalian cells), the Far Eastern 2008 isolates contains E627, typical for avian-adaptive variants. Finally, direct experiments *in vitro* verified that the 2008 isolates had a reduced tropism for mammalian cell lines.[116]

A comparison of the biological microchip of a representative isolate from the clade 2.2 and 2.3.2.1 isolates shows a clear difference in hybridization pattern in the HA and neuraminidase genes (Figure 8.103). The sequence similarities of the HA/H5/2.2 strains to A/chicken/Primorje/1/2008 and A/*Anas crecca*/Primorje/8/2008 are 92.9–95.3% nt for the HA gene and 94.1–95.3% nt for the NA gene. The nucleotide differences lead to different hybridization patterns for HA/H5/2.2 and 2.3.2.1on the biological microchip, as shown in Figure 8.103.

In June 2009 and 2010, epizootics provoked by HPAI H5N1 reoccurred in Uvs-Nuur Lake in the Tyva Republic, Russia (Figures 8.98 and 8.100). Although the HPAI H5N1 viruses that affected the area in June 2006 belonged to the 2.2 clade, the viruses that appeared in 2009 and 2010 belonged to the 2.3.2.1 clade. (See Tables 8.51 and 8.52.) Nevertheless, these viruses differed from viruses isolated in Primorsky Krai in 2008. Thus, taking into account the fact that the epizootic included Great Lake Depression territory in western Mongolia, researchers classified the Uvs-Nuur strains of 2009–2010 into a new so-called western Mongolian genetic subgroup[5] (Figure 8.99).[117,118]

Fortunately, both clades (2.2 and 2.3.2.1) of HPAI H5N1 that had penetrated into Northern Eurasia had low epidemic potential because their receptor specificity did not switch from $\alpha 2'-3'$- to $\alpha 2'-6'$-sialoside affinity, a fact that was revealed by the primary structure of the HA receptor-binding region and direct testing in sialoside-based experiments *in vitro*.[5,80]

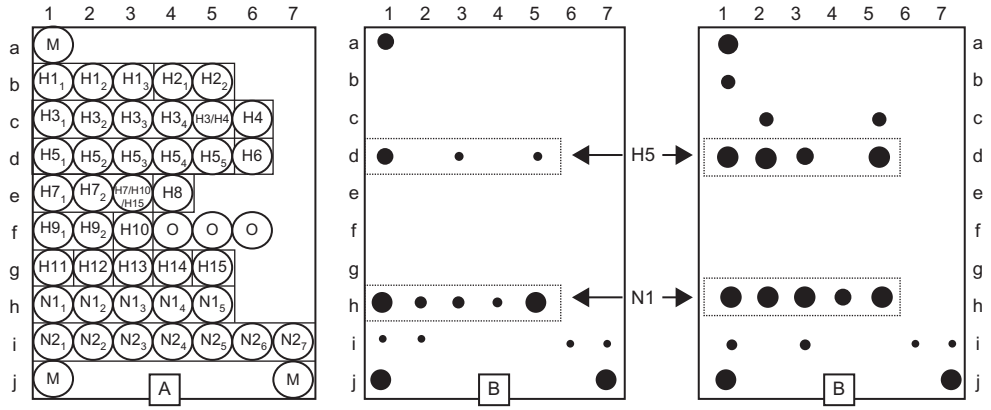


FIGURE 8.103 Subtyping of the HPAI/H5/2.2 and 2.3.2 virus strains by using biological microchips: (A) biological microchip structure; (B) hybridization pattern for A/chicken/Novosibirsk/64/2005 belonging to the HA/H5/2.2 (Qinghai–Siberian) genotype; (C) hybridization pattern for A/chicken/Primorje/1/2008 belonging to the HA/H5/2.3.2 genotype.

Thus, we discuss the epizootic event provoked by HPAI H5N1 in Northern Eurasia during 2005–2010 as a model of an emerging–reemerging situation in need of permanent ecologo-virological monitoring.

Influenza A Viruses Among Mammals. The circulation of Influenza A viruses among swine (order Artiodactyla: family Suidae, genus *Sus*) was originally established in 1930 by Richard Shope (Figure 8.84): His investigations not only established the viral etiology of swine flu and isolated the first historical strain A/swine/Iowa/15/1930 (H1N1), but also serologically demonstrated the close relation between human infection agents and those of swine.[11]

Shope's findings gave rise to a number of isolations of swine respiratory disease agents. Many of these agents later turned out not to be Influenza A virus; for example, "Köbe porcine influenza virus," isolated in Germany;[119] "infectious pneumonia of pigs;"[120,121] "Beveridge–Betts virus"[122] (more often, these pathogens belonged to *Chlamydia* sp.); and "Hemagglutinating virus of Japan,"[123,124] which initially was named "Influenza D virus" and was later identified as Sendai virus (SeV) (family Paramyxoviridae, genus *Respirovirus*).[125] Nevertheless, a number of strains isolated at the end of 1940s in Korea (strain Oti),[126] and in the 1950s and 1960s in Lithuania (prototype A/swine/Kaunas/353/1959),[127] Estonia,[128] Poland,[129] and Russia[130] were identified as Influenza A (H1N1) virus. Also, in the middle of twentieth century, Influenza A strains closely related to A/swine/Iowa/15/1930 (H1N1) were isolated in Czechoslovakia[131,132] and Hungary.[133] Finally, after the beginning of the "Asian flu" pandemic in 1957, swine Influenza A (H2N2) virus strains were isolated initially in China[134] and later in Czechoslovakia[135] and Moldova (prototype A/swine/Moldova/1/1964).

For a long time, the close relationship between swine and human Influenza A virus strains was held to be the consequence of laboratory contamination. A change in this situation came after the "Hong Kong flu" (H3N2) pandemics in 1968, when a great number of Influenza A (H3N2) strains were isolated all over the world. It then became clear that Influenza A virus is able to penetrate from humans to pigs and, conversely, from pigs to humans.

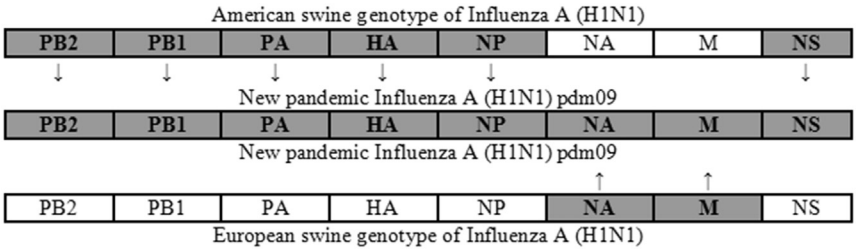


FIGURE 8.104 Reassortation scheme of the emergence of pandemic Influenza A (H1N1) pam09.

The principal peculiarity of pigs is the presence of both α2′−6′-sialosides (typical of human cells) and α2′−3′-sialosides (typical of avian cells) on the surface of respiratory tract cells. This feature permits both human (or adapted swine) and bird Influenza A virus strains to circulate simultaneously, giving rise to conditions favorable to the reassortment and emergence of virus variants with suddenly appearing new properties.[42,136–143] Avian Influenza A virus strains have been demonstrated to initiate productive infection in swine under experimental conditions.[31,144–147]

The great number of reassortment forms of Influenza A viruses isolated from swine constitute evidence of the extremely high reassortment potential of the swine viral population. Thus, A/swine/England/191973/1992, isolated from nasal swabs of sick pigs in Great Britain in 1992, belongs to the unique H1N7 subtype, which was formed by the reassortment of A/USSR/90/1977 (H1N1) (the source of PB2, PB1, PA, HA, NP, and NS segments) and A/equine/Prague/1/1956 (H7N7) (the source of NA and M segments).[148,149] Another swine reassortant virus, of the subtype H1N2 (A/swine/Ehime/1/1980),[150] was originally isolated in Ehime Prefecture, Japan, in 1980. It was formed by the strains A/swine/Hong Kong/1/1974 (H1N1) and A/swine/Taiwan/7310/1970 (H3N2), a close relative of A/Taiwan/1/1969 (H3N2).[150,151] According to serological data, subtype H1N2 did not circulate in Japan before 1980,[150] but it was isolated after 1980 from A/swine/Miyagi/5/2003 (H1N2) and A/swine/Miyazaki/1/2006 (H1N2).[151]

The most evident illustration of the reassortment potential of swine populations is the emergence of the pandemic "swine flu" H1N1 pdm09 in 2009 as the result of the reassortment of two swine genotypes of the H1N1 subtype: the "American swine genotype" (the source of PB2, PB1, PA, HA, NP, and NS segments) and the "European swine genotype" (the source of NA and M segments) (Figure 8.104).[24–29] Using different receptor-mimicking sialosides (Table 8.55), we investigated the evolution of receptor specificity in Influenza A (H1N1) pdm09 virus during pandemic and postpandemic epidemiological seasons. Different types of sialoside specificity spectra are presented in Figure 8.105.

To compare α2′−3′- and α2′−6′-sialoside specificities, we introduced the special parameter $W_{3/6}$, which is the ratio of the optical density for flat α2′−3′-sialosides (3′SL and 3′SLN) to the optical density for flat α2′−6′-sialosides (6′SL and 6′SLN): $W_{3/6} = (d[3'SL] + d[3'SLN])/(d[6'SL] + d[6'SLN])$. If $W_{3/6}$ is <1 ($W_{3/6} < 1.00$), then α2′−6′-specificity dominates. In contrast, if $W_{3/6} > 1.00$, then α2′−3′-specificity dominates. (Strains with $W_{3/6} \approx 1.00$ have approximately equal α2′−3′- and α2′−6′-specificities.)[152]

The sialoside specificity of the first pandemic strains isolated in our study, A/California/04/2009 (H1N1) pdm09,

TABLE 8.55 Receptor-Mimicking Oligosaccharides (Sialosides) Used in the Detection of Receptor Specificity of the Influenza A (H1N1) pdm09 Virus

Type of covalent bond	Brief designation	Chemical composition
2′−3′	3′SL	3′-sialyllactose: Neu5Acα2-3Galβ1-4Glcβ
	3′SLN	3′-sialyllactosamine: Neu5Acα2-3Galβ1-4GlcNAcβ
	6Su-3′SLN	6-Su-3′-sialyllactose: 6-Su-Neu5Acα2-3Galβ1-4Glcβ
	SLe^a	Neu5Aα2-3Galβ1-3(Fucα1-4)GlcNAcβ
	SLe^x	Neu5Acα2-3Galβ1-4 (Fucα1-3)GlcNAcβ
	SLe^c	Neu5Acα2-3Galβ1-3GlcNAcβ
2′−6′	6′SL	6′-sialyllactose: Neu5Acα2-6Galβ1-4Glcβ
	6′SLN	6′-sialyllactosamine: Neu5Acα2-6Galβ1-4GlcNAcβ
	6Su-6′SLN	6-Su-6′-sialyllactose: 6-Su-Neu5Acα2-6Galβ1-4Glcβ

demonstrates dual affinity to both α2′−3′- and α2′-6′-sialosides (Figure 8.106). Therefore, such strains might be able to effect swine−human and human−human transmission, and their pathogenicity is higher than that of seasonal influenza viruses ($W_{3/6} \approx 1$). The other strains isolated during the epidemic seasons of 2009−2011 in Russia have a different value for the *W* parameter. Most strains were isolated from nasopharyngeal swabs and had the value $W_{3/6} < 1$. These strain had D222 and Q223 in the receptor-binding site of HA1 and usually did not cause any severe complication of the disease, such as pneumonia. The strains with $W_{3/6} \approx 1$ were isolated from autopsies of patients who died of primary viral pneumonia. About 10% of these strains had the substitutions D222N/G and Q223R in HA1 (Tables 8.56 and 8.57). The third group of strains had a $W_{3/6} > 1$ multiple substitution in the receptor-binding site and caused the majority of viral pmeumonias and deaths of patients (Tables 8.56 and 8.57).[153−160]

Pigs could be the source of Influenza A virus not only in humans, but also in synantropic animals. S. Agapov published an article on the pathogenic properties of Influenza A virus specimens isolated from brown rats (*Rattus norvegicus*) in pigsties.[161] Experimental infection of swine influenza A virus strains in rodents—mice (subfamily Murinae) and hamsters (subfamily Cricetinae)—has been described in a number of publications.[3,133,146,161−163]

Rodents have become a widely used laboratory model for Influenza A virus. Productive infection in laboratory mice (order Rodentia: family Muridae, genus *Mus*) was revealed in a pioneer publication[13] of W. Smith (Figure 8.85), C. Andrewes (Figure 8.86) and P. Laidlaw (Figure 8.87). Adapted to mice, Influenza A virus strains are widely used to investigate infectious process, pathology, and the efficiency of antivirals.[161,164−168]

In 2000, the strain Influenza A/muskrat/Buryatia/1944/2000 (H4N6) was isolated from muskrat (*Ondatra zibethicus*) hunted in the Selenga River delta, near where it empties into Lake Baikal. Despite mountain relief along the lake coast, the delta represents a sandbank wedge overgrown with low reeds where the conditions are conducive to a mass nesting of ducks and a high density of population of muskrats. As a result, there is a high level of interaction between the populations of aquatic birds and muskrats. In particular, A/muskrat/Buryatia/1944/2000 (H4N6) has the highest homology with A/pochard/Buryatia/1903/2000 (H4N6). The strain from muskrat turned out to be virulent to mice without any preliminary adaptation, like the majority of H4 strains from Siberian ducks. It was suggested that virulence was promoted by an R220G mutation in HA.[72,81]

The Russian State Collection of Viruses contains the Influenza A/*Sciurus vulgaris*/

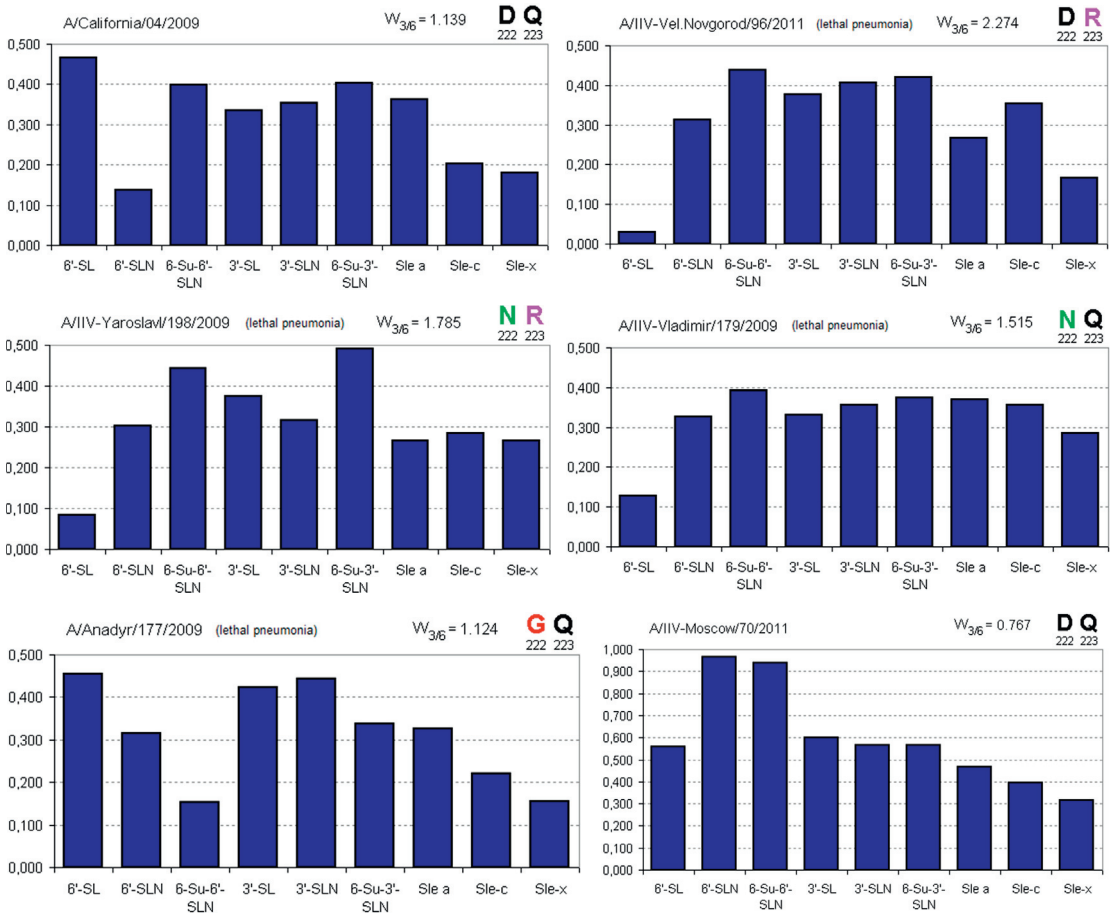


FIGURE 8.105 Different types of sialoside specificity spectra with $W_{3/6}$ parameter value and amino acid substitution in the limits of the receptor binding site of HA.

Primorje/1004/1979 strain with an undetermined subtype isolated from a red squirrel (*Sciurus vulgaris*).[5]

Weasels (order Carnivora: family Mustelidae) are another sensitive group of hosts for Influenza A viruses. The sensitivity of the domestic ferret (*Mustela putorius furo*), an albino form of the forest polecat (*Mustela putorius*), to the virus was explored even in the earliest scientific publications devoted to Influenza A virus.[13,14] Today, ferrets are the best animal model of Influenza A virus infection. In particular, sera of infected ferrets (as well as infected rats) are widely utilized for Influenza A virus subtype identification.

In 1985, Japanese scientists demonstrated that the epidemic strain A/Kumamoto/22/1977 (H3N2) was able to provoke disease in the European mink (*Mustela lutreola*),[169] and perhaps it was this virus that caused a respiratory disease epizootic on Japanese fur farms during 1977–1978. In 1984–1985, during an epizootic among minks in Sweden, six strains of Influenza A (H10N4) virus (prototype A/

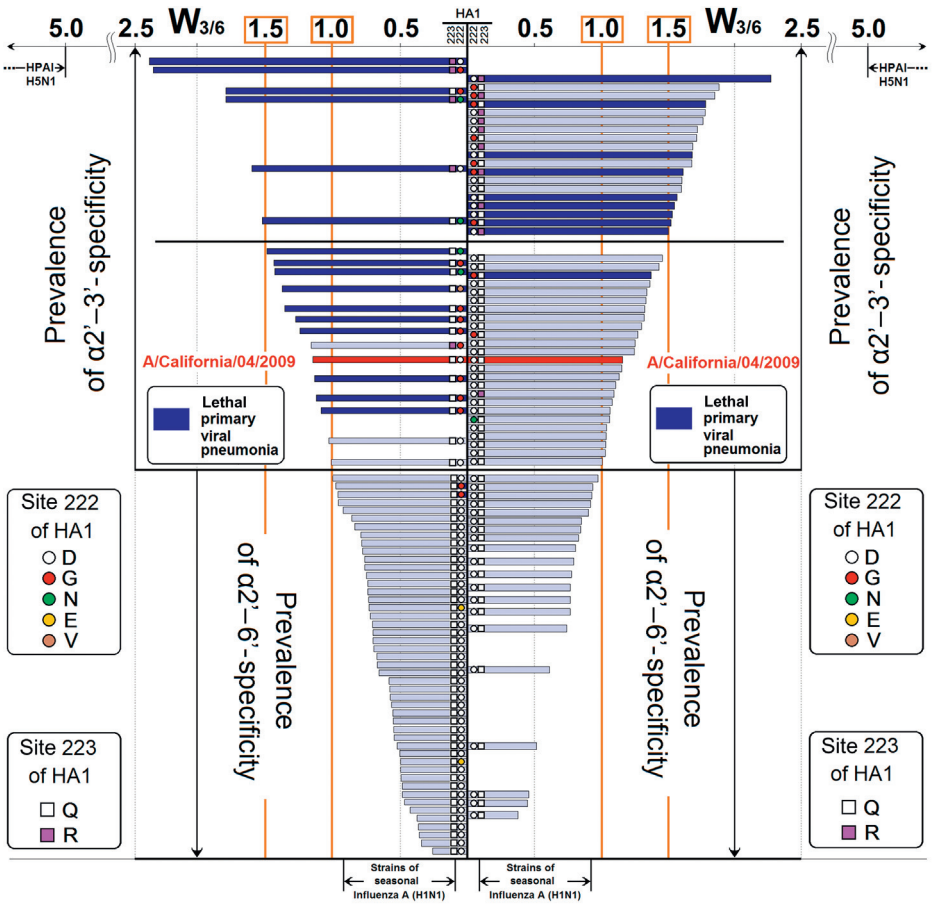


FIGURE 8.106 Receptor specificity toward α2′−3′/α2′−6′-sialosides and the structure of 222−223 sites of HA in pandemic Influenza A (H1N1) pdm09 isolated from hospitalized patients during epidemiological seasons 2009−2010 and 2010−2011.

mink/Sweden/E12665/1984) were isolated and turned out to have an avian origin.[170] In 2007, an Influenza A/stone marten/Germany/R747/06 (H5N1) strain was isolated from the internals of a stone marten (*Martes foina*) that was found dead in a place where there was mass mortality of birds in Germany.[171,172]

The circulation of Influenza A virus among cats (order Carnivora: family Felidae) was originally established in 1942 by the Japanese virologists J. Nakamura and T. Iwasa: Strain A/cat/Fusan/1/1942 (known as "Chiba virus")[173] turned out to be an avian strain of the H7N7 subtype.[168] In 1970, C.K. Paniker and C.M. Nair described the successful experimental infection of adult cats and eight-month-old kittens by A/Hong Kong/1/1968 (H3N2), of the "Hong Kong flu" pandemic strain.[174] A number of H5N1 strains from Felidae members—tigers (*Panthera tigris*),[175−177] leopards (*P. pardus*),[176] and domestic cats (*Felis catus*)[178−180]—were described after 2005.

The first experiment involving the infection of dogs (order Carnivora: family

TABLE 8.56 Correlation Between Receptor Specificity of Pandemic Influenza A (H1N1) pdm09 Strains from Hospitalized (2009–2011) Patients, the Structure of Those Strains' Receptor-Binding Site of HA, and the Probability of Patients Developing Lethal Primary Viral Pneumonia (LPVP)

Strains			Prevalence of α2′–6′-specificity	Prevalence of α2′–3′-specificity		Total
			$W_{3/6} \leq 1.0$	$1.0 < W_{3/6} \leq 1.5$	$1.5 < W_{3/6}$	
Number			67	37	25	129
From patients with LPVP			0	11 (29.7%)	15 (60.0%)	26 (20.2%)
Amino acid substitutions in the receptor-binding site	D222	G	2 (3.0%) 4 (6.0%)	10 (27.0%) 14 (37.8%)	9 (36.0%) 11 (44.0%)	21 (16.3%) 29 (22.5%)
		N	0	3 (8.1%)	2 (8.0%)	5 (3.9%)
		E	2 (3.0%)	0	0	2 (1.6%)
		V	0	1 (2.7%)	0	1 (0.8%)
	Q223	R	0	2 (5.4%)	13 (52.0%)	15 (11.6%)
	D222Q223		4 (6.0%)	15 (40.5%)	20 (80.0%)	39 (30.2%)

TABLE 8.57 Detection of Amino Acid Substitutions in the Limits of the HA Receptor-Binding Site of Influenza A (H1N1) pdm09 Virus Strains from Hospitalized Patients (2009–2011) with Lethal and Favorable Outcomes

Outcome of the disease	Amino acid substitutions in the receptor-binding site of HA												Strains with amino acid substitutions in the limits of the receptor-binding site	
	D222										Q223			
	G		N		E		V		Total		R			
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Lethal (26 patients)	13	50.0	4	15.4	0	0	1	3.8	18	69.2	8	30.8	23	88.5
Nonlethal (103 patients)	8	7.8	1	1.0	2	1.9	0	0	71	10.7	7	6.8	16	15.5

Canidae, genus *Canis*) was carried out by S.M. Titova[181] in 1954. Then, in 1959, an analogous experiment was conducted by A.D. Ado and S.M. Titova.[182] In 1968, J.D. Todd and D. Cohen[183] repeated Ado and Titova's 1959 experiment. Isolation of Influenza A virus from dogs—A/dog/Vladivostok/1/1970 (H3N2)—under natural conditions was originally performed by T.V. Pysina[31,184,185] in Vladivostok, Primorsky Krai, Russia, in the winter of 1970. A year later, one more canine strain—A/dog/Vladivostok/110/1971 (H3N2)—was isolated in Vladivostok.[31,184,185] The Russian State Collection of Viruses in the D.I. Ivanovsky Institute of Virology contains the strain Influenza A/Canis lupus albus/Chukotka/1320/1976 (H6N2), isolated from a tundra wolf (*Canis lupus albus*) in Chukotka in

the Russian Far East. The strain A/dog/Thailand/KU-08/2004 was isolated from a dog in Thailand;[178] this strain had an avian origin, but provoked lethal pneumonia in dogs.[186] It is noteworthy that Influenza A virus can be isolated from nasal swabs of dogs during inapparent infection,[187] so this virus might be more widely distributed among dogs than is usually considered. Influenza A virus is often the cause of pericarditis in dogs.[188]

The circulation of Influenza A viruses among horses (order Perissodactyla: family Equidae, genus *Equus*) was originally explored in 1956 by a group of Czechoslovakian scientists headed by Bella Tumova (Figure 8.107). In that year, a widespread epizootic emerged among horses (*Equus ferus caballus*) and the historical strain A/equine/Prague/1/1956 was isolated.[189] A subtype of this strain was given an initial designation $H_{eq1}N_{eq1}$ and later was identified as H7N7 (but, for a long time, veterinarians designated this subtype as equine influenza type 1).[146] Later, Influenza A (H7N7) strains were isolated in other European countries[190] and the United States.[191]

During the "Asiatic flu" pandemic of 1958–1961, a number of strains of Influenza A (H2N2) were isolated from sick horses in the Moscow region of the former USSR[192] and in Hungary.[133,163] It was shown that these strains were significantly different from A/equine/Prague/1/1956 (H7N7), belonged to the H2N2 subtype, and had a human origin.

Equine Influenza A type 2 was originally found in 1963 in Miami, Florida, in the United States, when the prototypical strain A/equine/Miami/1963 was isolated and designated as subtype $H_{eq2}N_{eq2}$.[193] Later, this subtype was identified as H3N8 and was multiply isolated[194–196] in both North and South America. In the former USSR, Influenza A (H3N8) virus strains were isolated from horses in the Ukrainian Soviet Republic during a widespread epizootic in 1970 in the vicinity of Kiev.[31]

The Russian State Collection of Viruses contains the Influenza A/equine/Mongolia/3/1975 (H5N3) strain, which originates from birds and over came the interspecies barrier to penetrate into the equine population.

The circulation of Influenza A virus among camels (suborder Tylopoda: family Camelidae, genus *Camelus*) was originally established by D. K. Lvov[59] (Figure 2.36) in 1980. In December 1979, an epizootic of "contagious cough" among Bactrian camels (*Camelus bactrianus*) emerged in Mongolia. Thirteen strains were isolated from nasal swabs;[59] prototypical strains were A/camel/Mongolia/1/1980, A/camel/Mongolia/1/1981, and A/camel/Mongolia/7/1983. Later, these strains were identified[197] as belonging to H1N1, a virus closely related to the epidemic strain A/USSR/90/1977 (H1N1).

The first Influenza A virus strains from cattle (order Artiodactyla: family Bovidae, subfamily Bovinae) were isolated by J. Romváry[133,163] in 1958 from domestic cows (*Bos taurus taurus*). During 1958–1961, about a hundred epizootic outbreaks emerged in Hungary. Together with his coauthors, Romváry isolated Influenza A2 virus strains (the modern H2N2) from calves. During the "Hong Kong flu" (H3N2) pandemic of 1968–1970, a number of strains were isolated from cattle in the Russian Federation,[145,198] Tajikistan,[199] and the Ukrainian Soviet Republic

FIGURE 8.107 Bella Tumova (1929–2007).

in the former USSR.[31] The circulation of Influenza A viruses among cattle has been confirmed by multiple serological data.[31,200–204]

The first isolation of Influenza A strain from sick sheep (*Ovis aries*) (order Artiodactyla: family Bovidae, subfamily Caprinae) was carried out in 1959 by a group of Hungarian scientists under the direction of G. Takatsy during an epizootic among farm animals.[133,163] The Strain A/sheep/Hungary/B111/59 (H2N2) isolated by Takatsy was later utilized by J.L. McQueen and F.M. Davenport for experimental infection in lambs, but they observed no clinical symptoms.[205]

The circulation of Influenza A viruses among deer (order Artiodactyla: family Cervidae) was originally established by T.V. Pysina and D.K. Lvov when they isolated the A/*Rangifer tarandus*/Chukotka/1254/77 (H6N2) strain from slowed reindeer (*Rangifer tarandus*) in the Chukotka Peninsula.[206] The Russian State Collection of Viruses in the D.I. Ivanovsky Institute of Virology contains the strains A/deer/Primorje/1201/78 (H1N1), isolated from red deer (*Cervus elaphus*) in Primorsky Krai, and A/*Rangifer tarandus*/Yamal/865/90 (H13N1), isolated from reindeer (*R. tarandus*) on the coast of the Barents Sea. Specific antibodies towards Influenza A (H1N1) and A (H3N2) were detected in the sera of red deer (*C. elaphus*) and elks (*Alces alces*) in the north of Germany.[207,208] S.Q. Li established the presence of about a 10% immune layer toward Influenza A (H1N1) and A (H3N2) among Cervidae in the northeastern provinces of China.[209]

The strain Influenza A/whale/Pacific Ocean/19/1976 (H1N3) (or, alternatively, A/whale/PO/19/1976) from a whale belonging to the Balaenopteridae family (order Cetacea, suborder Mysticeti) and bagged in the South Pacific Ocean was isolated by a group of Soviet virologists under the direction of D.K. Lvov[210] (Figure 2.36) in 1976. This strain turned out to be reassortant between human and avian virus variants.[211]

Two strains of Influenza A virus were isolated by a group of American virologists under the direction of R. Webster[212] (Figure 2.20) from slowed long-finned pilot whales (*Globicephala melaena*) near Portland, Maine, in the United States in 1984: A/whale/Maine/1/84 (H13N9) (from periapical lymph nodes in the lungs) and A/whale/Maine/2B/84 (H13N2) (from the lungs). Further molecular genetic investigation, carried out by a Russian–American group of scientists, revealed that Influenza A variants in gulls (family Laridae) were the source of these strains.[75]

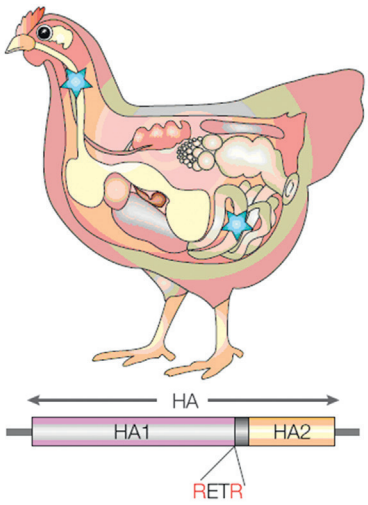
A number of Influenza A virus strains were isolated on the coast of North America: H4N5,[213] H4N6,[214] and H7N7.[215,216] Thus, one could expect to find Influenza A viruses among seals in Northern Eurasia as well.

Pathogenesis. Epithelial cells of mucous membranes are the main targets of Influenza A viruses. Degeneration, necrosis, and further apoptosis, followed by tearing away of the epithelial cell layer take place as a result of the infection. Nevertheless, the main element of Influenza A virus–induced pathogenesis is lesions on the system of vessels; the lesions emerge as the result of the toxic effect of the virus, an effect that includes the multiple formation of active oxygen forms. The latter provoke the generation of hydroperoxides, which interact with lipids and phospholipids of the cell wall to oxidize their peroxide, thereby hindering transport across the cell membrane.[217–219] A subsequent increase in the permeability of vessels, the fragility of their walls, and a violation of the body's microcirculation result in hemorrhagic manifestations, from nasal bleeding to hemorrhagic hypostasis of the lungs and hemorrhages in the substance of the brain.[219,220] Frustration of the circulation, in turn, defeats the nervous system. The pathomorphological picture is characterized by the existence of lymphomonocytic infiltrates around small and average-size veins, hyperplasia of glial elements, and a focal

demyelinization that testifies to the toxic and allergic nature of the pathological process in the CNS during influenza.[219,221,222]

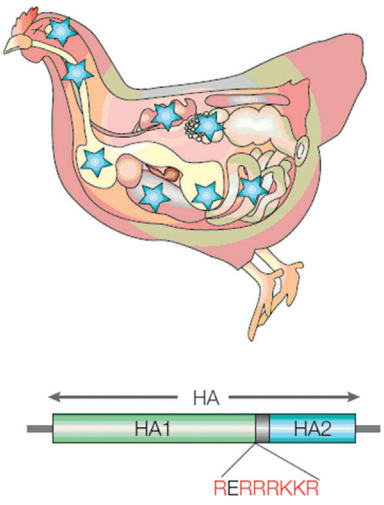
The most significant factors involved in cell tropism of the Influenza A virus are the receptor assembly on the surface of the potential target cell and the ability of cell proteases to cleave HA into two subunits (HA1and HA2) followed by fusion peptide rescue.[223–227] For example, for avian Influenza A virus variants, there is an obvious threshold in the virulence level: so-called LPAI and HPAI. HPAI strains strike vascular endothelial and perivascular parenchymal cells as well as the cardiovascular system, quickly reproduce high titers in practically all internal organs, and cause systemic disease leading to death of a bird 1–7 days after infection. LPAI strains, to the contrary, reproduce in low titers, have a narrow tropism toward mucous in the digestive and respiratory tracts (Figure 8.108), and cause enteritis or rhinitis with low mortality. (However, bird diseases connected with LPAI also cause significant damage to agriculture and can break the interspecies barrier, resulting in diseases that are dangerous to people). Wild aquatic and semiaquatic birds, which are natural reservoirs of Influenza A viruses, can have inapparent disease during either LPAI or HPAI infection.[5,24,27,28,39,41–43,53,226,228–230]

The ability of HA to be cleaved by proteases depends on the amino acid composition of the proteolytic cleavage site: LPAI strains contain only one or two positively charged basic amino acids (K or R), whereas HPAI strains have an enriched amount of basic amino acids.[5,24,27,28,39,41,228–230] Nevertheless, pandemic strains with extremely high virulence in humans have only single basic amino acids within the limits of the proteolytic cleavage site (Table 8.58). Still, it is noteworthy that LPAI could provoke human disease as well.



LPAI — low-pathogenic avian influenza

HA cleavage could be performed by attachment to mucous cells of the digestive and respiratory tracts



HPAI — highly pathogenic avian influenza

HA cleavage could be performed by cells of practically all tissues

FIGURE 8.108 Comparative characteristics of LPAI and HPAI. Blue stars designate localization of proteases, which cleave HA.

TABLE 8.58 Amino Acid Sequences of the Proteolytic Cleavage Site of HA in LPAI and HPAI (Positively Charged Residues are Marked in Bold on the Blue Backspace; "."—Deletions for the Alignment; "|"—Point of Proteolytic Cleavage)

AVIAN STRAINS OF INFLUENZA A VIRUS	
Nonvirulent (LPAI H5)	PQ....RETR|G
Nonvirulent (LPAI H7)	PEXP...KXR|G
Virulent (HPAI H5)	PQ..RKRKKR|G
Virulent (HPAI H7)	PEPSKKRKKR|G
PANDEMIC STRAINS OF INFLUENZA A VIRUS	
≪Spanish flu≫ (1918–1919) (H1N1)	PS....IQSR|G
≪Asian flu≫ (1957–1958) (H2N2)	PQ....IESR|G
≪Hong Kong flu≫ (1968–1970) (H3N2)	PE....KQTR|G
≪Russian flu≫ (1977–1978) (H1N1)	PS....IQSR|G
≪Swine flu≫ (2009–2010) (H1N1 pdm09)	PS....IQSR|G
AVIAN STRAINS OF INFLUENZA A VIRUS ISOLATED FROM HUMANS	
Hong Kong 1997 (HPAI H5N1)	PQRERRRKKR|G
Hong Kong 1999 (LPAI H9N2)	PQ....RSSR|G
Netherlands 2003 (HPAI H7N7)	PEIP.KRRRR|G
Southeastern Asia 2003 (HPAI H5N1)	PQRERRRKKR|G

Except for the amino acid composition of the proteolytic cleavage site of HA, the efficiency of the cleavage process depends on glycosylation of HA in the vicinity of this site.[231,232]

Amino acid substitutions that switch virus tropisms from avian to mammalian cells in different Influenza A virus proteins have been described: E627K,[112,233] D701N,[100,233] S714R[234] in PB2; L13P,[234] K615N,[234] and S678N[234] in PA.

Clinical features. The clinical features of Influenza A virus infection among birds vary with the virulence level, the subtype of the virus, and the species of the host. Symptoms of disease in poultry have been investigated more than those in wild birds. Four basic clinical forms (listed in order of increasing severity) are distinguishable in birds: sinusitis, enteritis, catarrhal disease, and systemic disease. The last is linked with HPAI and with only two type of HA: H5 and H7. It was the systemic form of the disease that was historically designated "classical avian plaque." A comparison of clinical characteristics of the different forms of avian influenza is presented in Table 8.59. The most massive epizootics provoked by HPAI systemic disease are given in Table 8.60. Clinical symptoms of sick birds are shown in Figure 8.109.

TABLE 8.59 Comparison of Clinical Characteristics of Different Forms of Avian Influenza

Clinical form	Subtype of Influenza A virus	Level of virulence	Type of transmission	Typical level of lethality (with forced slaughter)
Sinusitis	H3N1, H3N2, H3N6, H3N8, H4N1, H4N8, H6N1, H6N3, H6N6, H6N7, H10N1, H10N5, H10N9, H11N2, H11N6, H11N9	LPAI	Aerosol	1–%
Enteritis	H6N2, H6N4, H6N8, H8N2, H8N4, H11N3, H11N8, H12N2	LPAI	Alimentary	2–30%
Catarrhal disease	H5N2, H7N1, H7N2, H7N3, H7N9, H8N4, H9N2, H9N4, H10N7	LPAI, HPAI	Aerosol	5–80%
Systemic disease (classical avian plague)	H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N3, H7N4, H7N7	HPAI	Aerosol and alimentary	100%

TABLE 8.60 Large Epizootics Provoked by HPAI

Year	Country	Subtype	Prototype strain	Scale of epizootic
1959	Scotland	H5N1	A/chicken/Scotland/59	5,000 chickens died on two farms
1963	Great Britain	H7N3	A/turkey/England/63	29,000 turkeys became ill
1966	Canada	H5N9	A/turkey/Ontario/7732/66	8,000 turkeys became ill
1967	USSR	H5N1	A/chicken/USSR/314/67	5,000 chickens became ill
1976	Australia	H7N7	A/chicken/Victoria/76	40,000 chickens and 16,000 ducks became ill
1979	Germany	H7N7	A/chicken/Germany/79 A/goose/Leipzig/187-7/79	600,000 chickens and geese became ill
	Great Britain	H7N7	A/turkey/England/199/79	3 farms with turkeys
1983	Ireland	H5N8	A/turkey/Ireland/1378/83	270,000 ducks, 28,000 chickens, 9,000 turkeys
1983–1985	USA	H5N2	A/chicken/Pennsylvania/1370/83	17,000,000 chickens and turkeys
1985	Australia	H7N7	A/chicken/Victoria/85	220,000 chickens
1991	Great Britain	H5N1	A/turkey/England/50-92/91	8,000 turkeys
1992	Australia	H7N3	A/chicken/Victoria/1/92	13,000 chickens, 6,000 ducks
1994	Australia	H7N3	A/chicken/Queensland/667-6/94	22,000 chickens
	Pakistan	H7N3	A/chicken/Pakistan/447/95	3,200,000 chickens
1994–1995	Mexico	H5N2	A/chicken/Puebla/8623-607/94	360 farms with poultry
1997	Hon Kong	H5N1	A/chicken/Hong Kong/220/97	1,400,000 chickens
	Italy	H5N2	A/chicken/Italy/330/97	6,000 poultry
	Australia	H7N4	A/chicken/New South Wales/1651/97	160,000 chickens, 300 emus
1999–2000	Italy	H7N1	A/turkey/Italy/1265/99	14,000,000 poultry
2002	Chili	H7N3	A/chicken/Chile/1/02	15,000 chickens
2003	Netherlands, Belgium, Denmark, Germany	H7N7	A/chicken/Netherlands/1/03	255 farms in Netherlands (30,000,000 chickens), 8 farms in Belgium (3,000,000 chickens), 1 farm in Germany (80,000 chickens)
2004	Canada	H7N3	A/chicken/Canada-BC/1/04	19,000,000 chickens
	USA	H5N2	A/chicken/USA-TX/1/04	7,000 chickens
	South Africa	H5N2	A/ostrich/South Africa/1/04	24,000 emus, 5,000 chickens
2003–2009	Southeastern Asian countries	H5N1	A/duck/China/E319-2/03	More than 300,000,000 poultry
2005–2010	Russia and European countries	H5N1	A/duck/Novosibirsk/56/05	3,000,000 chickens
	Transcaucasian countries	H5N1	A/chicken/Turkey/986/06	500,000 chickens and turkeys
	African countries	H5N1	A/chicken/Egypt/1/06	500,000 chickens, turkeys, and ducks
	Middle East countries	H5N1	A/chicken/Gaza/450/06	300,000 chickens and turkeys
	India	H5N1	A/chicken/Navapur/Nandurbar/India/7966/06	150,000 chickens and ducks

FIGURE 8.109 Sick birds as the result of HPAI/H5N1/2.2 virus infection. A - sick domestic duck (Anas platyrhynchos domesticus) (south of Western Siberia, July, 2005); B - sick mute swan (Cygnus olor) (mouth of Volga river, November, 2005); C - sick great crested grebe (Podiceps cristatus) (Uvs-Nur Lake; June, 2006); D - sick coot (Fulica atra) (Uvs-Nur Lake; June, 2006); E - rooks (Corvus frugilegus) on the mixed fodder ground in the poultry farm "Gulyai-Borisovskay" (Rostov region; December, 2007); F - intestine vessel plethohora and changes in pancreas structure of infected rook (Corvus frugilegus) from poultry farm "Gulyai-Borisovskay" (Rostov region; December, 2007).

Diagnostics. Avian Influenza A (family Orthomyxoviridae, genus *Influenza A virus*) is to be differentiated from Newcastle disease (family Paramyxoviridae, genus *Avulavirus*), avian rhinotracheitis (family Herpesviridae, genus *Iltovirus*), avian bronchitis (family Coronaviridae, genus *Coronavirus*), ornithosis (*Chlamydia psittaci*), and mycotoxicosis[32,144,146,235–238]; similarly, mammalian Influenza A is to be distinguished from other respiratory diseases, mainly parainfluenza (family Paramyxoviridae, genus *Paramyxovirus*), coronavirus disease (family Coronaviridae, genus *Betacoronavirus*), torovirus disease (family Coronaviridae, genus *Torovirus*), respiratory syncytial disease (family Paramyxoviridae, genus *Pneumovirus*), and arboviruses with influenzalike symptoms.[144,146,219,221]

The classic diagnostic approach is to isolate the virus with the use of sensitive biological models (ferrets, developing chicken embryoa, and cell lines). Influenza A virus infection could be retrospectively detected by HIT[239] or neutralization testing, but the most effective diagnostic methods are RT-PCR and biological microchips.

Control and Prophylaxis. Vaccination, together with the forced slaughter of livestock. is the most effective and accessible approach to Influenza A prophylaxis among domestic animals. Each country chooses its own strategy for combining these methods. For example, in Russia only livestock in small and individual farms is to be vaccinated whereas birds in poultry farms are not vaccinated, but are killed if either HPAI or LPAI is detected.[32,144,146,235]

8.3.2 Genus *Quaranjavirus*

In 2013, the Quaranfil group, which includes Quaranfil virus (QRFV), Johnston Atoll virus (JAV), and Lake Chad virus (LCV), was allocated to the separate *Quaranjavirus* genus of the Orthomyxoviridae family. Tyulek virus (TLKV) (see Section 8.3.2.1) is a new member of this genus.

The genome of the quaranjaviruses consists of six segments of negative ssRNA. Segments 1–3 encode the proteins of a replicative polymerase complex (polymerase basic protein 2, or PB2; polymerase acidic protein, or PA; and polymerase basic protein 1, or PB1, respectively). The PB1 protein (polymerase 1 basic protein, RdRp) is one of the most conservative proteins of all viruses with a segmented RNA genome. The amino acid sequence similarity of the PB1 protein among the viruses of different genera in the Orthomyxoviridae family is 25–30%, on average, but the similarity of the functional domains of RdRp (pre-A, A, B, C, D, and E motifs) is 40–50% (Figure 8.110).

The envelope glycoprotein GP (HA, segment 5) of the quaranjaviruses has a very low similarity to the homologous protein (HA, segment 4) of influenza viruses. However, it has some similarities tgo the surface glycoprotein of the baculoviruses.[1] The amino acid sequences of *Thogotovirus* genus members have about 20% identity with QRFV and TLKV.

Two other segments of the genome (segments 4 and 6) of the quaranjaviruses encode two proteins whose function is unknown. These proteins are probably structural proteins, which act as nucleocapsid (N) and matrix protein (M), respectively, but currently their function is not well known.

Other viruses of the *Quaranjavirus* genus have been found in South Africa, Nigeria, Egypt, Iran, Afghanistan, and Oceania. The quaranjaviruses are associated with Argasidae ticks (*Argas arboreus*, *A. vulgaris*, *Ornithodoros capensis*), which are obligate parasites of birds.[2–7]

8.3.2.1 Tyulek Virus

History. Tyulek virus (TLKV), prototypical strain LEIV-152Arg, was isolated from Argasidae ticks *Argas vulgaris* collected in the burrows of a colony of birds in the floodplain of Aksu River near the village of Tyulek (43°N, 74°E), in the northern part of the Chu Valley in Kyrgyzstan; Figure 8.111) in 1978.[1,2] Subsequently, a total of

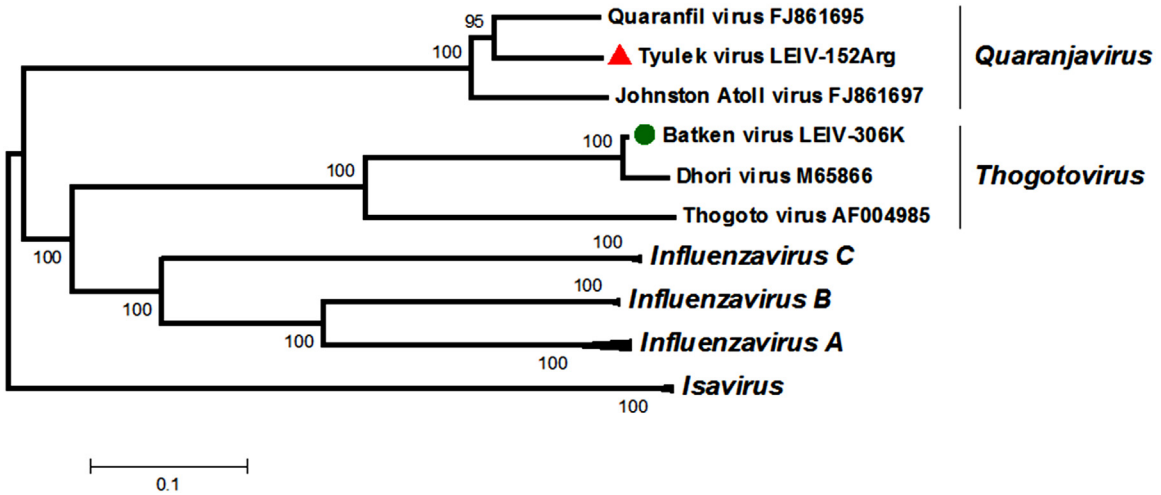


FIGURE 8.110 Phylogenetic analysis of the Orthomyxoviridae family based on PB1 protein sequence comparison.

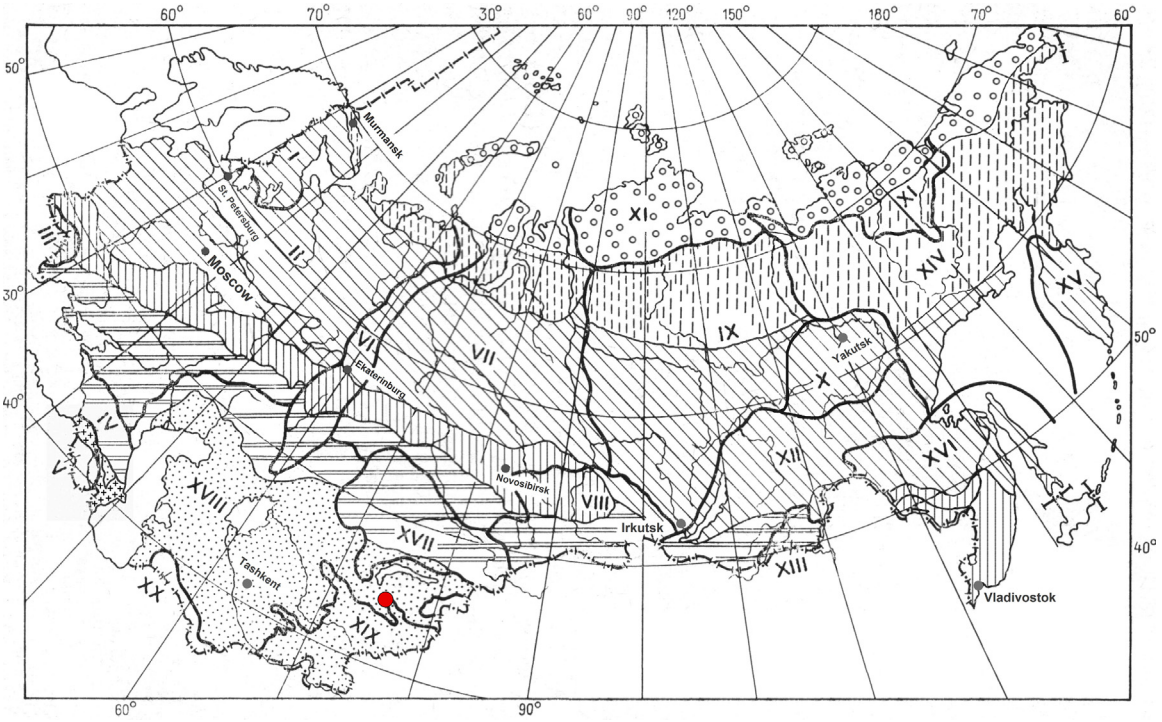


FIGURE 8.111 Place of isolation (red circle) of Tyulek virus (TLKV) (family Orthomyxoviridae, genus *Quaranjavirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

42 strains of TLKV was isolated in 1981, 1984, and 1986.[3] TLKV has been classified into the Quaranfil group of the Orthomyxoviridae family on the basis of its antigenic reactions.[4–14]

Taxonomy. Like the other members of the *Quaranjavirus* genus, TLKV has a genome that consists of six ssRNA segments.[13] The PB1 protein amino acid sequence of TLKV has 86% and 84% identities with QRFV and JAV, respectively (Table 8.61). The similarity of the PB2 and PA proteins of TLKV to those of Orf virus (ORFV) is 70%, on average.

The envelope glycoprotein (GP, segment 5) of the quaranjaviruses has very low similarity to the homologous protein (HA) of influenza viruses. However, it has some similarities to the surface glycoprotein of the baculoviruses.[4] The similarity of the GP of TLKV to that of QRFV is 72% nt and 80% aa (Table 8.62). Segment 5 of TLKV has one ORF and encodes a protein with unknown function (524 aa). Its similarity to the same protein of QRFV is 85% aa. Segment 6 encodes a protein 266 aa long, which has no homology with any of the virus's proteins that are deposited in the database GenBank. The similarity of this protein in TLKV and the same protein in QRFV is 60%.

Figures 8.110 and 8.112 show the results of phylogenetic analysis based on a comparison of PB1 and the envelope protein (GP and HA, respectively). On the phylogenetic trees, TLKV is grouped with QRFV and JAV within the *Quaranjavirus* genus.[13]

Arthropod Vectors. Natural foci of TLKV associated with *Argas vulgaris* ticks in Kyrgyzstan are located below the northern border of the area of distribution of Argasidae ticks (43ǫN). This boundary coincides with the line of a frost-free period of 150–180 days a year and an average daily temperature above 20° for no less than 90–100 days per year. The ability of these ticks to withstand prolonged starvation (up to 9 years), as well as their long life cycle (25–30 years), polyphagia, and ability to transfer viruses transovarially, provides stability of the virus's natural foci.[1–3,15–18]

Animal Hosts. TLKV was isolated from Argasidae ticks collected in the nesting burrows of birds. Complement-fixation testing of the birds from these colonies revealed that

TABLE 8.61 Divergence of PB1 (Segment 3) of the Orthomyxoviridae

			Differences (%)									
Genus	**Virus**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Quaranjavirus	Tyulek LEIV-152Arg	**1**		0.28	0.33	0.67	0.65	0.60	0.74	0.68	0.75	0.71
	Quaranfil virus	**2**	0.20		0.32	0.67	0.66	0.61	0.75	0.70	0.76	0.69
	Johnston Atoll virus	**3**	0.31	0.27		0.65	0.64	0.60	0.75	0.68	0.74	0.72
Thogotovirus	Batken LEIV-306K	**4**	0.82	0.85	0.82		0.20	0.59	0.71	0.72	0.74	0.74
	Dhori virus 1313/61	**5**	0.85	0.87	0.85	0.09		0.60	0.73	0.73	0.74	0.73
	Thogoto virus	**6**	0.82	0.81	0.81	0.71	0.71		0.73	0.68	0.71	0.73
Influenza A virus	Influenza A virus PR8	**7**	0.91	0.92	0.95	0.89	0.90	0.90		0.61	0.72	0.71
Influenza B virus	Influenza B virus	**8**	0.94	0.95	0.94	0.93	0.93	0.89	0.79		0.67	0.68
Influenza C virus	Influenza C virus	**9**	0.95	0.95	0.93	0.93	0.93	0.90	0.88	0.89		0.69
Isavirus	Infectious salmon anemia virus	**10**	0.95	0.92	0.95	0.92	0.92	0.92	0.91	0.90	0.90	

Nucleotide differences (%) are shown above the diagonal, and amino acid differences (%) are shown below the diagonal.

TABLE 8.62 Divergence of HA (Segment 4) of the Orthomyxoviridae

			Differences (%)									
Genus	**Virus**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Quaranjavirus	Tyulek LEIV-152Arg	**1**		0.28	0.33	0.67	0.65	0.60	0.74	0.68	0.75	0.71
	Quaranfil virus	**2**	0.20		0.32	0.67	0.66	0.61	0.75	0.70	0.76	0.69
	Johnston Atoll virus	**3**	0.31	0.27		0.65	0.64	0.60	0.75	0.68	0.74	0.72
Thogotovirus	Batken LEIV-306K	**4**	0.82	0.85	0.82		0.20	0.59	0.71	0.72	0.74	0.74
	Dhori virus 1313/61	**5**	0.85	0.87	0.85	0.09		0.60	0.73	0.73	0.74	0.73
	Thogoto virus	**6**	0.82	0.81	0.81	0.71	0.71		0.73	0.68	0.71	0.73
Influenza A virus	Influenza A virus PR8	**7**	0.91	0.92	0.95	0.89	0.90	0.90		0.61	0.72	0.71
Influenza B virus	Influenza B virus	**8**	0.94	0.95	0.94	0.93	0.93	0.89	0.79		0.67	0.68
Influenza C virus	Influenza C virus	**9**	0.95	0.95	0.93	0.93	0.93	0.90	0.88	0.89		0.69
Isavirus	Infectious salmon anemia virus	**10**	0.95	0.92	0.95	0.92	0.92	0.92	0.91	0.90	0.90	

Nucleotide differences (%) are shown above the diagonal, and amino acid differences (%) are shown below the diagonal.

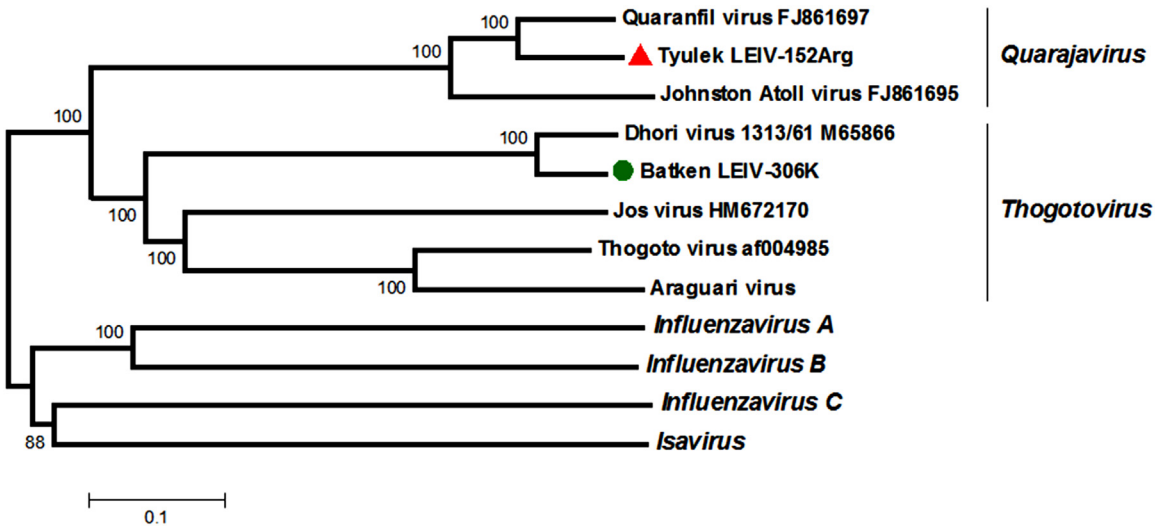


FIGURE 8.112 Phylogenetic analysis of the Orthomyxoviridae family based on HA protein sequence comparison.

some of them had anti-TLKV antibodies. But all attempts to isolate TLKV from birds, Ixodidae ticks, and mosquitoes ended in failure.[2,3,17,18] Antibodies to QRFV have been found in camels, cows, swine, and donkey.

Human Pathology. No cases of disease caused by TLKV have been registered. Two strains of QRFV were isolated from children bitten by ticks in the village of Quaranfil, Egypt. In and around this village, antibodies to

QRFV have been found in 2.6% of the human population.[11]

8.3.3 Genus *Thogotovirus*

The genus *Thogotovirus* currently includes four viruses: Thogoto virus (THOV), Dhori virus (DHOV), Araguari virus (ARGV), and Jos virus (JOSV).[1,2] The viruses of *Thogotovirus* are arboviruses, transmitted mainly by Ixodidae ticks; therefore, the genus had previously been called *Orthoacarivirus*, to emphasize these viruses' association with ixodids (taxon Acari: order Parasitiformes, family Ixodidae). THOV was originally isolated from the ticks *Rhipicephalus* (*Boophilus*) *decoloratus* and *Rh. evertsii* collected from cattle in Thogoto forest, Nairobi, Kenya, in 1960. Subsequently, it was isolated from human, cows, camels, and ticks in many countries in Africa.[3,4]

The genome of the thogotoviruses consists of six segments of negative-polarity ssRNA that encode seven proteins. (Segment 6 encodes two forms of matrix protein.)[1,2] The most conservative proteins of the replicative complex (PB1, PB2, PA) of thogotoviruses have 25–30% identity with those of the *Influenza A virus* genus.

8.3.3.1 Dhori Virus and Batken Virus (var. Dhori virus)

History. Dhori virus (DHOV) was originally isolated from *Hyalomma dromedarii* ticks collected from camels in India.[1] DHOV has also been isolated in Egypt, Portugal, Russia, and Transcaucasia.[2–7] In Russia, several strains of DHOV were isolated from *H. plumbeum* ticks, *Anopheles hyrcanus* mosquitoes, and *Lepus europaeus* hares, all in the Volga River estuary.[5,7] One strain of DHOV was isolated from the cormorant *Phalacrocorax carbo* in Maly Zhemchuzhnyi Island in the Caspian Sea (45°00′N, 48°18′E; Figures 8.113 and 8.114).[4]

The prototypical strain of Batken virus (BKNV), LEIV-K306, was isolated from *Hyalomma marginatum* ticks collected from sheep near the town of Batken in Kyrgyzstan in April 1970.[8] Other strains of BKNV were isolated from a mixed pool of *Aedes caspius* and *Culex hortensis* mosquitoes in Kyrgyzstan[9] and from *Ornithodoros lahorensis* and *Dermacentor marginatus* ticks in Transcaucasia.[10] Antigenic studies showed that BKNV is closely related to DHOV, but differs from it.[8]

Taxonomy. The similarity of the structural homologous proteins of the thogotoviruses (THOV, DHOV, ARGV, and JOSV) ranges from 25% (M-protein, segment 6) to 45% (NP, segment 5). The envelope protein HA (segment 4) has 35–45% identity, on average. The similarity of the nonstructural proteins (PB1, PB2, and PA) ranges from 60% to 74%.

BKNV has a high similarity to DHOV. The proteins are 96% (PB2, PA, NP, M) and 98% (PB1) identical. The similarity of the envelope protein HA of BKNV to that of DHOV is 90%, a percentage that explains the antigenic differences between these two closely related viruses. Because the homology of the other structural and nonstructural proteins of BKNV and DHOV is 96–98%, it can be concluded that BKNV is a variant of DHOV, typical to central Asia and Transcaucasia. A phylogenetic analysis based on a comparison of the PB1 and HA proteins is presented in Figures 8.110 and 8.112.

Arthropod Vectors. Apparently, the main arthropod vector of DHOV and BKNV is *Hyalomma* sp. ticks—in particular, *H. marginatum*. DHOV has also been isolated from *H. dromedarii*, *Dermacentor marginatus*, and *Ornithodoros lahorensis* ticks. Rare isolations of DHOV and BKNV from mosquitoes (*Anopheles hyrcanus*, *Aedes caspius*, and *Culex hortensis*) suggest that they play some role in the circulation of these viruses.[9]

Vertebrate Hosts. Antibodies to DHOV were found in 100% of camels, 19% of horses, and 2% of goats in the Indian state of Gujarat, where the virus was first isolated. Antibodies

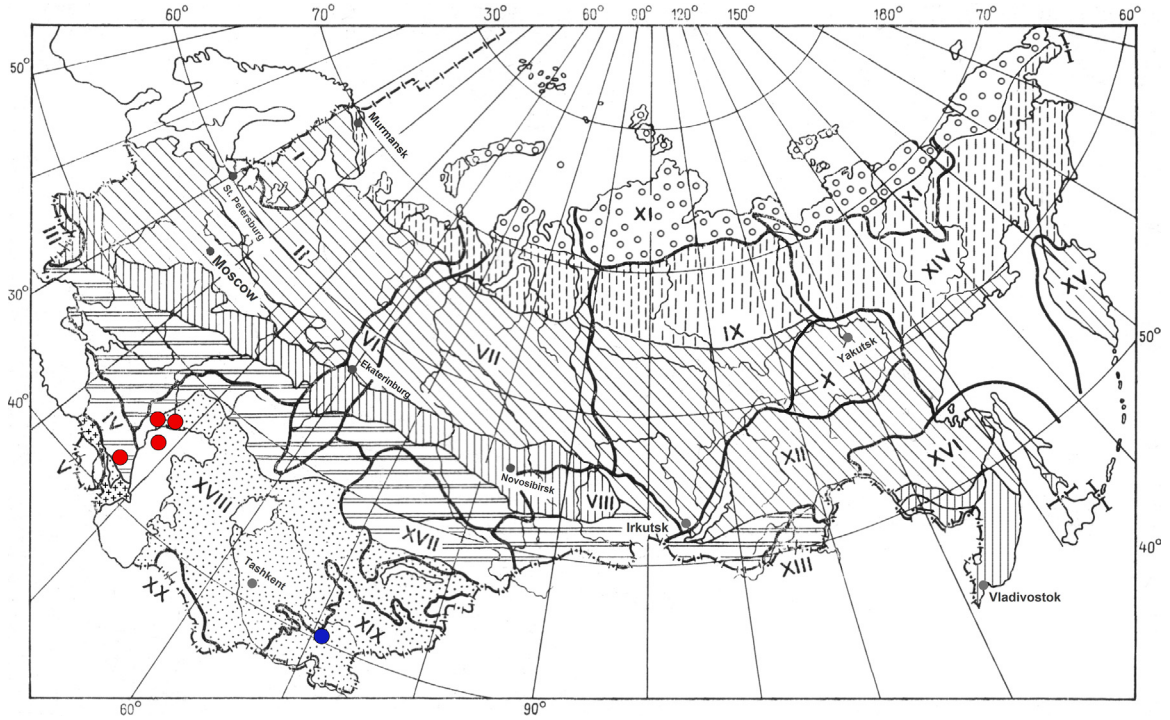


FIGURE 8.113 Places of isolation of Dhori virus (DHOV) (red circles) and Batken virus (BKNV) (dark-blue circle) (family Orthomyxoviridae, genus *Thogotovirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

to BKNV were found in 1.0% of sheep and 1.3% of cattle in Kyrgyzstan.[9] Two strains of DHOV were isolated from a hare (*Lepus europaeus*) and a cormorant (*Phalacrocorax carbo*) in natural foci of the virus.[4,5] The bird, from which DHOV was isolated on Maly Zhemchuzhnyi Island, was ill with respiratory failure, inability to fly, and loss of coordination[4] (Figure 8.114C).

Human Disease. Several cases of disease caused by DHOV have been registered.[11] The disease occurred with fever, encephalitis (40%), headache, and weakness. Antibodies to DHOV were found in 4–9% of the population in the Volga River delta (in the south of Russia) and in 0.8% in the south of Portugal.[12] Antibodies to BKNV were found in the sera of 0.3% of the human population of Kyrgyzstan. Five cases of laboratory infection were identified.[11]

8.4 FAMILY TOGAVIRIDAE

The Togaviridae family consists of two genera (*Alphavirus* and *Rubivirus*) of enveloped RNA viruses. The virion of the togaviruses (70 nm) contains a core particle (40 nm) formed by a capsid protein and comprising a single-stranded, positive-sense genomic RNA 11,400–11,800 nt long. The lipid bilayer contains the heterodimers of two surface glycoproteins E1 and E2, which form an icosahedral surface of the virion. The genomic RNA has a cap structure at the 5′- and poly-A tail at the 3′-end, as well as two ORFs encoding

FIGURE 8.114 Maly Zhemchuzhny Island (45°00′N, 48°18′E) in the northwestern part of the Caspian Sea: (A) Terns and gulls in a nesting colony; (B) A group of fledglings of Pallas's gull (*Larus ichthyaetus*); (C) A sick great cormorant (*Phalacrocorax carbo*), a source of DHOV isolation; (D) The expedition team (from left to right): Stepan Lvov (researcher); Dmitry Lvov (director); captain and sailor of the expedition ship; (E) Chief sanitary physician officer of the Kalmyk Republic Konstantin Yashkulov during scientific hunting; (F) Mikhail Shchelkanov (researcher) during sample collection near the mortheastern extremity of the island; in the background is a group of Caspian seals (*Phoca caspica*) surrounded by terns and gulls.

nonstructural and structural proteins. The nonstructural proteins are encoded by the 5′-ORF (which occupies two-thirds of the genome), whereas the structural proteins are encoded by the subgenomic 3′-ORF.[1]

Most viruses of the *Alphavirus* genus are arboviruses and can replicate in either a vertebrate host and or an invertebrate vector.[2,3] The *Rubivirus* genus consists of one species—*Rubella virus*—that is transmitted by aerosol and is the causative agent of disease known as rubella.[4,5]

8.4.1 Genus *Alphavirus*

The genome of the alphaviruses is a single-stranded RNA with positive polarity about 11,500 nt in length. The viral RNA has a cap at the 5′-end and a poly-A tail at the 3′-end. A large part of the genome of the alphaviruses (about two-thirds, beginning from one-third into the genome and extending to the 5′-end) encodes nonstructural proteins that form the viral replicative complex nsP1, nsP2, nsP3, and nsP4). Structural proteins (core, E3, E2, 6K, and E1) are translated from subgenomic RNA (26S RNA), which is formed in the process of replicating the virus and corresponds to the other one-third of the genome (Figure 8.115).[1]

The alphaviruses can infect a wide range of vertebrates. Most of the alphaviruses are arboviruses and are associated with mosquitoes (genera *Culex*, *Culiseta*, *Aedes*, *Coquillettidia*, and *Haemogogus*) and birds, the latter of which can transfer viruses during migration.[2–4] Other vertebrate hosts of the alphaviruses are ruminants, reptiles, amphibians, and fish.[5,6] The

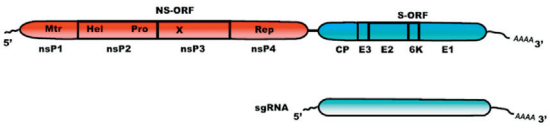


FIGURE 8.115 Scheme of the genome organization of SINV (*Togaviridae*, *Alphavirus*). *Drawn by Tanya Vishnevskaya.*

alphaviruses are divided into 10 antigenic complexes. Among the alphaviruses are dangerous pathogens of humans or animals, such as Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Sindbis virus (SINV), Chikungunya virus (CHIKV), and others.[7,8]

8.4.1.1 Chikungunya Virus (imported)

History. CHIKV (family Togaviridae, genus *Alphavirus*, Semliki Forest group) is the etiological agent of a fever that is mortally dangerous to humans. This disease is accompanied by joint and muscle pains (right up to complete immobilization of the patient) and a two-wave course of the fever, together with a macular–papular rash emergency (usually during the second wave).[1] The etymology of the name "Chikungunya" is ≪chee-kungunyala≫, which, in the Makonde local language, means "doubled up," owing to the severe joint pains.

CHIKV was originally isolated by R.W. Ross from the serum of a patient with fever during the decoding of an epidemic outbreak in Tanzania in February–March 1956.[2–4] The close relation of CHIKV to Mayaro virus (MAYV), from the Semliki Forest group, was demonstrated in 1957 by serological methods.[5,6]

Distribution. CHIKV was also isolated in Cambodia in southeastern Asia in 1963,[7] in Hindustan in 1964,[8,9] and in the eastern part of New Guinea in 2012.[10] The basic area over which CHIKV is distributed (Table 8.63) comprises (1) the sub-Saharan region of Africa bounded by the equatorial and subequatorial climatic belts (only the southern parts of Africa and Madagascar are in the tropical belt) (Angola, Burundi, the Central African Republic, Kenya, Namibia, Nigeria, Senegal, the Republic of South African, Tanzania, Uganda, Zimbabwe, Madagascar, Sierra Leone, and Guinea); (2) southeastern Asia (Myanmar, Malaysia, Cambodia, India, Hong Kong, Laos, Sri Lanka, Thailand, Vietnam, the southern provinces of China, and Pakistan); and (3)

TABLE 8.63 Laboratory-Confirmed Epidemic Outbreaks of Chikungunya Fever Since the Middle of the 1980s

Year	Country	Region	Genotype [a]	Relation to the basic area of distribution
1985	Uganda[18]	Africa	CESA	Basic area
1985	Philippines[19]	Malay Archipelago	A	Basic area
1987	Malawi[20]	Africa	CESA	Basic area
1988	Thailand[21]	Southeastern Asia	A	Basic area
1990	Australia[22]	Australia	A	**Imported cases**
1991	Thailand[21]	Southeastern Asia	A	Basic area
1992	Guinea[23]	Africa	WA	Basic area
1995	Thailand[21]	Southeastern Asia	A	Basic area
1996	Senegal[24]	Africa	WA	Basic area
1998	Indonesia[25]	Southeastern Asia	A	Basic area
1998	Malaysia[26]	Southeastern Asia	A	Basic area
1999	Congo[27]	Africa	CESA	Basic area
1999	Central African Republic[13]	Africa	CESA	Basic area
2000	Indonesia[25]	Southeastern Asia	A	Basic area
2003	Timor[13]	Malay Archipelago	A	Basic area
2004	Kenya[28]	Africa	CESA	Basic area
2005	United States[29]	North America	CESA	**Imported cases**
2005	Reunion[30]	Islands near the eastern coast of Madagascar	CESA	Basic area
2005	Mauritius[30]		CESA	Basic area
2005	Seychelles[30]		CESA	Basic area
2006	Comoro Islands[30]	Islands in the Mozambique Channel	CESA	Basic area
2006	Madagascar[30]	Madagascar	CESA	Basic area
2006	Cameroon[31]	Africa	CESA	Basic area
2006	India[32]	Hindustan	CESA	Basic area
2006	Australia[33]	Australia	CESA	**Imported cases**
2006	Malaysia[34]	Southeastern Asia	CESA	Basic area
2006	Canada[13]	North America	CESA	**Imported cases**
2006	Belgium[35]	Europe	CESA	**Imported cases**
2006	Czech Republic[35]	Europe	CESA	**Imported cases**
2006	Germany[35]	Europe	CESA	**Imported cases**

(*Continued*)

TABLE 8.63 (Continued)

Year	Country	Region	Genotype [a]	Relation to the basic area of distribution
2006	Norway[35]	Europe	CESA	**Imported cases**
2006	Switzerland[35]	Europe	CESA	**Imported cases**
2006	France[35]	Europe	CESA	**Imported cases**
2006	Hong Kong[36]	Southeastern Asia	CESA	**Imported cases**
2006	United States[35]	North America	A	**Imported cases**
2007	Japan[37]	Eastern Asia	CESA	**Imported cases**
2007	Italy[38]	Europe	CESA	**Imported cases**
2007	Spain[39]	Europe	CESA	**Imported cases**
2009	South Korea[40]	Eastern Asia	CESA	**Imported cases**
2009	Malaysia[41]	Southeastern Asia	A	Basic area
2009	Japan[42]	Eastern Asia	CESA	**Imported cases**
2010	France[43]	Europe	CESA	**Imported cases**
2010	Brazil[44]	South America	Unknown	**Imported cases**
2011	Japan[45]	Eastern Asia	CESA	**Imported cases**

[a]*Chikungunya virus (CHKV) genotypes: A, Asian genotype; CESA, centre, east, and south African genotype; WA, west African genotype.*

Oceania (Indonesia, Malaysia, the Philippines, Singapore, and a number of Pacific Ocean islands).[1–4,10–17]

Taxonomy. CHIKV belongs to the Togaviridae family, Alphavirus genus, Semliki Forest group. On the basis of comparative analysis of the E1 gene, CHIKV was classified into three genotypes: A (Asian), CESA (centre, east, and south African), and WA (west African)[1,12–14] (Table 8.64).

Vertebrate Hosts. Rodents, bats, and monkeys are the natural reservoir of CHIKV.[1,11–14,46] There is substantial evidence, that, in Africa, wild primates play an important role in the natural transmission cycle, but it is not clear whether infection in primates is incidental to or necessary for the maintenance of the virus. In Uganda, CHIKV was frequently isolated from *Aedes africanus* mosquitoes, which preferto feed on monkeys in the forest canopy.[47] Specific anti-CHIKV antibodies were found among chimpanzees (*Pan troglodytes*) in equatorial and savanna forests in the Democratic Republic of the Congo (Kinshasa)[48] and in savannas in southern Africa. Antibodies were found over a wide area in vervet monkeys (*Cercopithecus aethiops*) and baboons (*Pipio ursinus*), and in both species the virus could circulate in the blood for two to three days at high concentrations without evidence of illness.[49] So, wild animals could play an important role as amplifying hosts.[49] CHIKV was isolated in Dakar< Senegal, from bats, which developed viremia after experimental infection. But in India, inoculation of the virus into two species of fruit-eating bats was followed by low virulence.[50,51] Antibodies were found among donkeys, bats,

TABLE 8.64 Members of the Semliki Forest Group (Family Togaviridae, Genus *Alphavirus*), to which CHIKV Belongs

Group	Virus		Distribution of natural foci	Prototype strain	GenBank ID
Semliki Forest	Bebaru virus (BEBV)		Malaysia	MM2354	AF339480
	Getah virus (GETV)		Asia	M1	EU015061
	Semliki Forest virus		Africa	42S	X04129
	Mayaro virus (MAYV)		South America, Trinidad	Brazil	AF237947
	O'nyong-nyong virus (ONNV)		Africa	SG650	AF079456
	Ross River virus (RRV)		Australia, Oceania	NB5092	M20162
	Una virus (UNAV)		South America	BeAr 13136	AF339481
	Chikungunya virus (CHIKV)	A	Asia	Gibbs 63-263	AF192901
		CESA	Centre, east, and south Africa	Ross	AF192905
		WA	West Africa	37997	AY726732

and wild rodents in Africa[52] and among domestic animals in Asia.[49,50]

Inoculation of African strains into cattle, sheep, goats, and horses failed to produce viremia. Apart from chickens, adult fowl and several species of wild birds did not develop viremia after experimental infection. But experimental infection of vervet monkeys and baboons led to high viremia (up to 8 $\log_{10}$ PFU/mL) during six days, which is sufficient for the infection of mosquitoes.[53]

Arthropod Vectors. CHIKV is transmitted by bloodsucking mosquitoes. The main vectors for this virus during epidemics are *Aedes aegypti* and *Ae. albopictus* in urban regions and mosquitoes from the *Aedes*, *Culex*, and *Coquillettidia* genera in rural landscapes.[1,11–14,46] CHIKV has been multiply isolated from *Ae. africanus*, *Ae. luteocephalus*, *Ae. furcifer–taylori*, *Cx. fatigans*, and *Coq. fuscopenatta*, all of which could preserve the virus and realize virus circulation in natural foci.[1,54,55]

Epidemiology. A high level of viremia in humans (up to 8 $\log_{10}$ PFU/mL) makes it possible for mosquitoes to transmit CHIKV from human to human[1]—a plausible reason that large epidemic outbreaks have been known in big cities of southern and southeastern Asia since the 1960s.[11,13,56–58] Beginning in the middle of the 1980s, epidemiological processes linked to CHIKV have intensified (Table 8.63), although this fact could be explained by improvements in laboratory diagnostics: Previously, Chikungunya fever was often confused with dengue. In any event, CHIKV-provoked lethality has increased, in some cases up to 4.5%).[1,59]

Increases in the frequency of imported Chikungunya fever cases seen at the beginning of the twenty-first century (Table 8.63) are most dangerous, especially when the possibility of CHIKV penetration into local mosquito populations is taken into account. Since 2006, imported cases of Chikungunya fever have become more frequent in Europe (Italy,[15,38,60,61]

Spain,[39] France,[35,44,62] Belgium,[35] Switzerland,[35] Germany,[35] the Czech Republic,[35] Norway[35]); the Americas (Canada,[13] the United States,[35,63] Brazil[44]); eastern Asia (Hong Kong,[36] South Korea,[40] Japan[37,45]); and Australia.[33] Outbreaks in Brazilian cities emerged with infections from *Aedes aegypti*, whereas in rural regions *Aedes albopictus* was the vector, introduced from south-eastern Asia,[44] including Japan.[64]

Imported Cases of Chikungunya Fever in Russia. A 59-year-old patient arrived in Russia September 22, 2013, and suddenly fell ill, with a body temperature of 38.7°C. Antipyretic drugs were not effective. Early in the morning on September 24, 2013, the patient was delivered to a Moscow infection hospital with a diagnosis of "fever with unknown etiology." The fever had mid-level severity, and the patient complained of shivering, headache, and asthenia. Hyperemia of the conjunctivae, papular–hemorrhagic rash on the abdomen, and cruses were found.

A medical radiolograph (Figure 8.116) of the lungs of the patient revealed decreased clarity at the back of the lung field and diffuse reticular pneumosclerosis in the right lower lobe pyramid, as well as local changes with expressed peribronchial and perivascular alterations. A round shadow was detected near (i.e., peribronchially to) the intermediate bronchus. The roots were intensified. The heart was enlarged at the left. Thus, the medical radiography portrait was consistent with right-side pneumonia with lymphadenopathy. Several peculiarities of the case were the bareness of clinical symptoms (pneumonia was diagnosed only via medical radiography), a rapid progression of changes in the lungs, and the absence of inflammation markers in the peripheral blood. Three days later, positive dynamics were detected: The basal parts of the right lung were restored to their previous level of clarity, although the shadow indicating a hypertrophic lymph node and right root broadening remained.

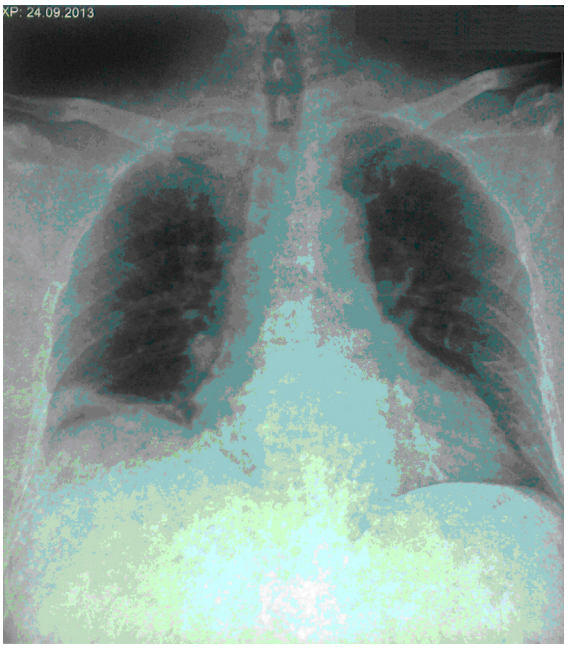


FIGURE 8.116 Medical radiological photograph of the lungs of a patient with Chikungunya fever on the first day of the disease.

Bioprobes (blood swabs and nasopharyngeal swabs) were delivered to the D.I. Ivanovsky Institute of Virology. The absence of Influenza A and B viruses was established by RT-PCR. The strain CHIKV/LEIV-Moscow/1/2013 was isolated with the use of intracerebrally inoculated newborn mice and was identified with the help of a complete-genome (GenBank ID: KF872195) next-generation sequence approach. Phylogenetic analysis (Figure 8.117, Table 8.64) revealed that the CHIKV/LEIV-Moscow/1/2013 strain belonged to an Asian genotype. This strain was deposited into the Russian State Collection of Viruses (deposition certificate N 1239 with a priority of November 11, 2013).[65]

Serological methods revealed eight cases of imported Chikungunya fever that had previously been described in Russia:[66] from Indonesia, Singapore, India, the island of Réunion, and the

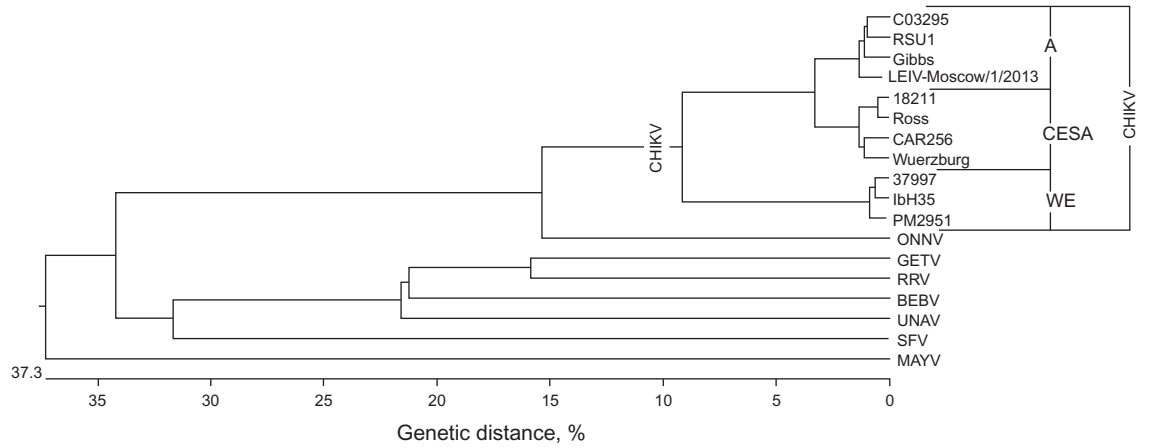


FIGURE 8.117 Phylogenetic tree for nucleotide sequences of the E1 gene (1,044 nt) of the Semliki Forest group viruses. Three genotypes of CHIKV are presented: A (Asian), CESA (centre, east, and south African), and WA (west African).

Maldives Islands. The CHIKV/LEIV-Moscow/1/2013 strain was found to belong to the A-genotype, whereas most of the cases imported into Europe belong to the CESA genotype, reflecting the "bridge" role of Russia between Europe and Asia. The modern-day intensification of both international links and transport flows among countries increases the probability of imported cases of infection emerging. The penetration of *Aedes aegypti* and *Aedes albopictus* to the Russian Black Sea coast[1,67,68] suggests the emergence of seasonal outbreaks in the dynamically developing greater Sochi region as well.

8.4.1.2 *Getah Virus*

History. Getah virus (GETV) was originally isolated in western Malaysia from *Culex gelidus* and *Cx. tritaeniorhynchus* mosquitoes.[1–3] This virus is widespread in southeastern Asia and in Australia.[3–5] The first isolation of GETV in Northern Eurasia was carried out by M.P. Chumakov[6] (Figure 2.10) in 1972.

Taxonomy. GETV belongs to the Togaviridae family, Alphavirus genus, Semliki Forest group, which also includes subtypes of GETV—Ross River virus (RRV) (Australia, Oceania) and Sagiyama virus (SAGV) (Japan)—as well as other viruses: Bebaru virus (BEBV), CHIKV, MAYV, O'nyong-nyong virus (ONNV), Semliki Forest virus (SFV), and Una virus (UNAV)[7].

The Genome of GETV is 11,598 nt long. The strains of GETV, circulating in different geographical regions of northeastern and southeastern Asia, have a high level of similarity.[8–11] A pairwise comparison of complete genome sequences revealed that isolates from Malaysia, South Korea, China, Mongolia, Japan, and Russia have 96–98% nt identities, suggesting that the rate of GETV evolution is low. Phylogenetic analysis of the E2 gene (Figure 8.118) is not conducive to dividing the GETV strains into distinct clusters.

Analyses of numerous strains isolated in Japan showed that genetic differences were determined by the time of isolation more than the place of isolation.[8] An analysis of 21 strains of GETV isolated in different regions of Russia revealed their high degree of similarity, but still, they could be divided into three groups on the basis of minimal differences. The first group comprises strains from tundra and forest–tundra in the Magadan region and the Sakha–Yakutia Republic in the north of Asia. The second group encompasses strains

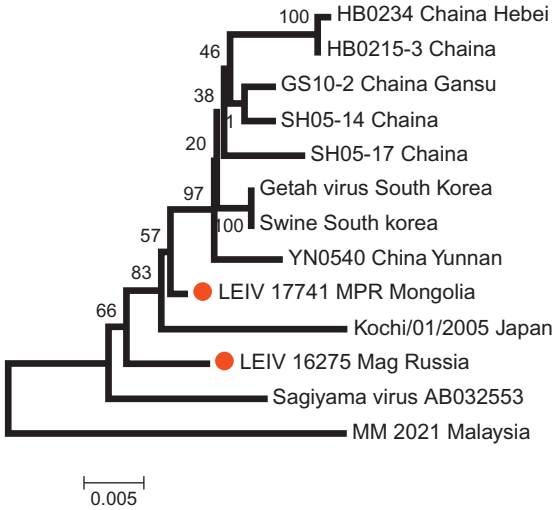


FIGURE 8.118 Phylogenetic tree based on the E2 sequences of different isolates of GETV.

from leaf-bearing forests of Khabarovsk Krai. The third group consists of isolates from forest–steppe and steppe landscape belts of Khabarovsk Krai, the Republic of Buryatia, and Mongolia.[10,12]

Distribution. According to our data,[6,10,12–22] GETV is distributed over eastern Siberia and North Pacific physicogeographical lands (Figure 8.119). The most intensive virus circulation was revealed in the steppe landscape belt of Mongolia, as well as in the mixed forests of Khabarovsk Krai and in the northern taiga of the Magadan region and the Sakha–Yakutia Republic. GETV circulation intensity is significantly lower in tundra and forest–tundra landscapes, a phenomenon that could be explained by the temperature there.

GETV is the only member of the *Alphavirus* genus whose distribution extends to the rough

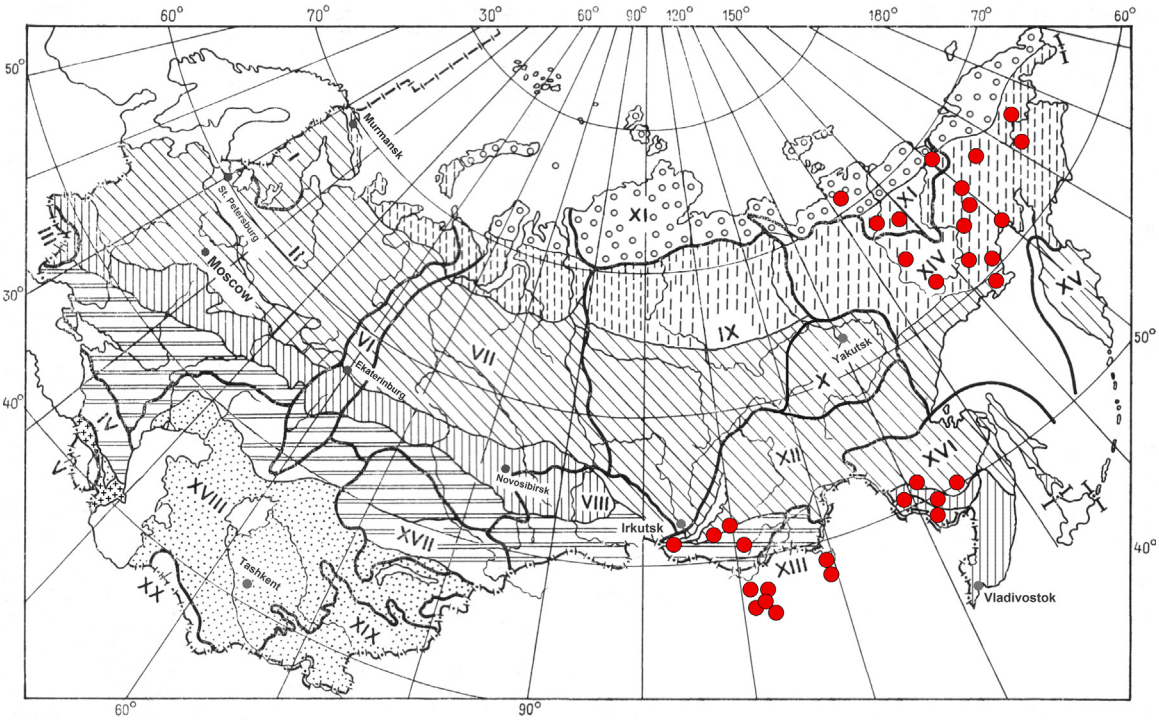


FIGURE 8.119 Places of isolation (red circles) of GETV (family Togaviridae, genus *Alphavirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

climatic conditions of the high latitudes of Northern Eurasia.[18,19] GETV has penetrated to the north of Asia from the overwintering places of birds, which regularly migrate by the east Asian flyway[17,23] (Figure 3.2). The distribution of the virus in the north coincides with that of *Aedes* mosquitoes, which are the effective vector of GETV.

GETV and closely related viruses are known outside of Northern Eurasia in Japan, various countries in southeastern Asia, and Australia.[1–3,5,24–29]

Human Infection. The pathogenicity of GETV to humans has not yet been described. Nevertheless, the antigenically close RRV has been associated with large epidemic outbreaks of polyarthritis in Australia and Sarawak.[2,4]

Vertebrate Animal Infection. Symptomatic and subclinical infections of animals were reported in 1998 in Japan, where there was a large outbreak involving 722 racehorses.[30,31] Among the clinical features seen were fever, rash on various parts of the body, and edema on the hind legs. Virus isolates were more similar to the prototypical Malaysian strain than to the Japanese Sagiyama strain. GETV has been implicated in illness and abortion or stillbirths in pigs.[32,33] Disease among horses was described in India.[34] Infection in cattle is usually subclinical.[3]

Arthropod Vectors. GETV has been isolated from *Culex gelidus*, *Cx. tritaeniorhynchus* (Malaysia, Cambodia, China), *Cx. bitaeniorhynchus*, *Anopheles amictus* (Australia), *Cx. vishnui* (Philippines); the Sagiyama subtype of GETV was isolated from *Cx. tritaeniorhynchus* and *Aedes vexans*, as well as from pigs with fever, in Japan.[27,35]

Although their natural transmission cycle is not known in details, mosquitoes acquire GETV mainly while feeding on domestic mammals and fowl. There may also be a jungle cycle involving wild vertebrates.[5] The Bebaru subtype was isolated from *Culex lophoceratomyia* and *Aedes* spp. mosquitoes collected in mangrove swamp forests of western Malaysia.[32]

The main vectors in Russia (i.e., in Northern Eurasia) are *Aedes nigripes*, *Ae. communis*, *Ae. impiger*, *Ae. punctor*, and *Ae. excrucians*.[18,21]

8.4.1.3 Sindbis Virus and a Set of Var. Sindbis Virus: Karelian Fever Virus, Kyzylagach Virus ()

History. SINV was first isolated from the ornithophilic mosquitoes *Culex univittatus* collected in 1952 in the Sindbis district near Cairo, Egypt.[1] Subsequently, SINV has been found in many regions of Africa, Europe, the Middle East, central and southeastern Asia, Australia, New Zealand, and the Philippines.[2–10] In the Old World, SINV is widely distributed and has several geographical variants: Karelian fever virus (KFV), Ockelbo virus (OCKV), Babanki virus (BBKV), Kyzylagach virus (KYZV), and Whataroa virus.[4,11–14] SINV was categorized into the western equine encephalomyelitis complex.[4,13]

KFV was first noted in the summer of 1981 in the central and southwestern parts of Fennoscandia, including Russia, Finland, Sweden, and southern Norway (Figure 8.120).[14]

The prototypical strain LEIV-65A of KYZV was first isolated from *Culex modestus* mosquitoes collected in a colony of Ardeidae birds (herons) in Kyzylagach Reservation, located on the coast of Kyzylagach Bay in the Caspian Sea (39°10′N, 48°58′E; Figure 8.120).[15]

Taxonomy. On the basis of a comparison of a partial sequence of the E2 gene, isolates of SINV can be divided into five genotypes (Figure 8.121).[9] Genotype I includes viruses from Europe and Africa, genotype II isolates from Australia and Oceania, and genotype III viruses from India and the Philippines. Together with the Chinese strain SINV XJ-160, KYZV was assigned to genotype IV. Genotype V consists of only the strain M78 from New Zealand.

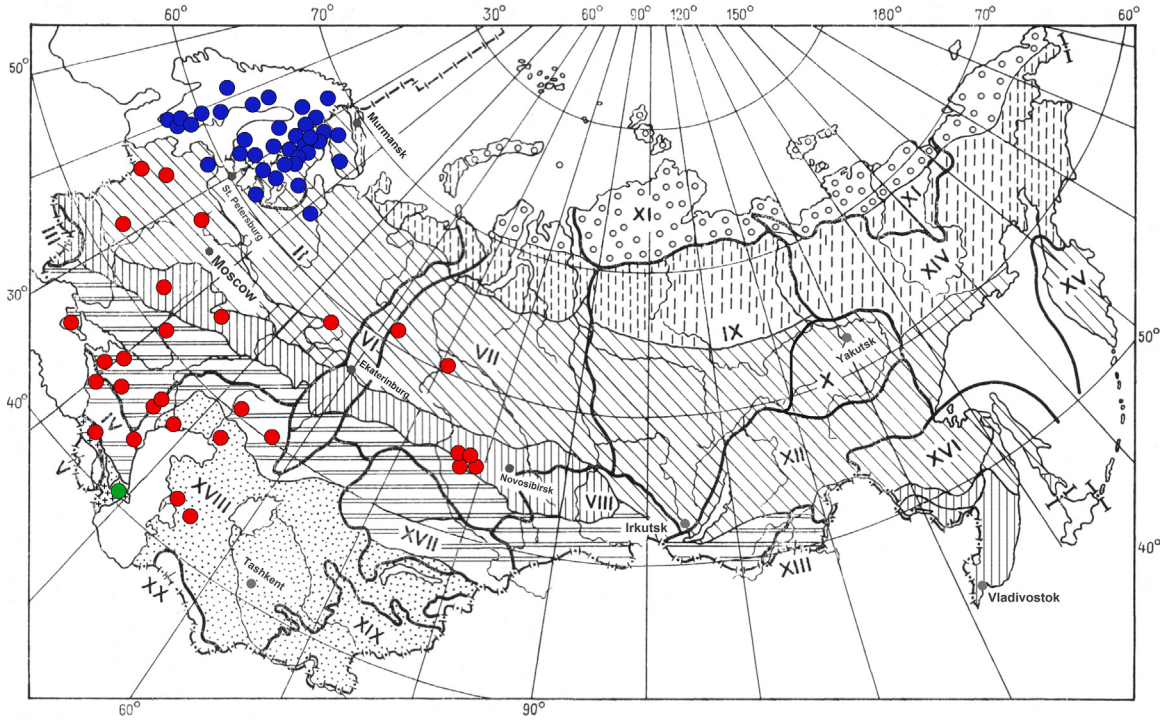


FIGURE 8.120 Places of isolation of SINV (red circles), KFV (blue circles), and KYZV (green circle) (family Togaviridae, genus *Alphavirus*) in Northern Eurasia. (See other designations in Figure 1.1.)

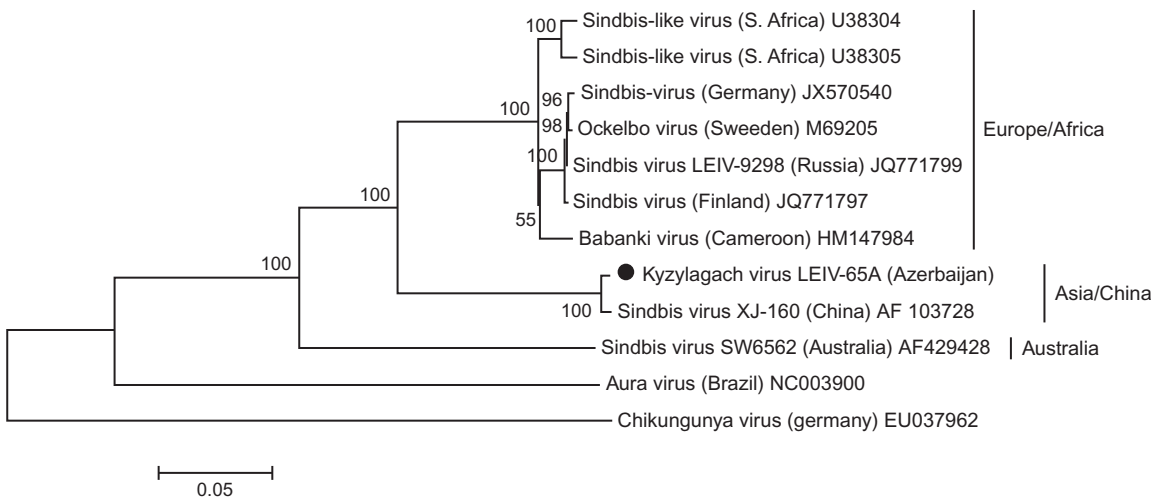


FIGURE 8.121 Phylogenetic tree of different isolates of SINV based on sequences of 26S subgenomic RNA (structural proteins) rooted in Aura virus (AURAV) and CHIKV sequences.

The strains of genotype I form two subclusters, one of which comprises SINVs from northern Europe and sub-Saharan Africa and the second of which consists of strains from the Mediterranean region (southern Europe, northern Africa, and the Middle East).[9] The genetic distance between the viruses of the different genotypes of SINV (e.g., between the European and Australian isolates) is not more than 23% nt (Table 8.65). At the same time, SINVs isolated in the same geographic region are characterized by a high degree of similarity (Figure 8.122). Thus, SINV strains isolated in Russia, Germany, Sweden(OCKV), and Finland have about 99% similarity (Table 8.65).[3,5,6,11] Babanki virus, which is from Cameroon, has 98% similarity to the European strains of SINV.

Despite the high degree of similarity among the different genotypes of SINV, known cases of human disease are caused only by strains of the European−African subcluster of genotype I (Karelian fever, a disease of Ockelbo, a disease of Babanki). KYZV has a high similarity (99%) to the Chinese isolate SINV XJ-160, isolated from *Anopheles* sp. mosquitoes in the Xinjiang Uighur Autonomous Region in the northwest of China.[16] The divergence of KYZV and XJ-160 from the European isolates of SINV is 18% nt and 7% aa of the entire genome sequence (Table 8.65). The geographic isolation of KYZV and XJ-160 and their genetic divergence from the European and Australian isolates suggest that KYZV is a variant of SINV that is typical to Central Asia.

Distribution. SINV has been isolated in many regions of southern Europe, the Middle East, Africa, southeastern Asia, the Philippines, and Australia.[2,17,18] The African continent is almost all endemic for SINV: Strains are known from Egypt, the Republic of South Africa, Uganda, the Central African Republic, Sudan, Nigeria, and Zimbabwe. As for Asia, there are strains from Turkey, India, Malaysia, and the Philippines. In Australia, SINV strains were multiply isolated in the north of the continent. In Europe, SINV has been isolated in Sicily (Italy) and Slovenia. On

TABLE 8.65 Genetic Divergence (Percent of Differences in the Entire Genome Sequences) Among Different Isolates of SINV

SINV strains		1	2	3	4	5	6	7	8	9	10	11
Kyzylagach_virus_LEIV-65A	**1**		0.01	0.19	0.19	0.19	0.19	0.18	0.19	0.25	0.37	0.42
Sindbis_virus_XJ-160_AF103728	**2**	0.01		0.19	0.18	0.18	0.18	0.18	0.18	0.25	0.37	0.42
Sindbis_virus_LEIV-9298_(Russia)_JQ771799	**3**	0.07	0.07		0.01	0.01	0.01	0.03	0.03	0.23	0.36	0.41
Sindbis_virus_(Germany)_JX570540	**4**	0.07	0.07	0.01		0.01	0.01	0.03	0.03	0.23	0.36	0.41
Ockelbo_virus_(Sweden)_M69205	**5**	0.07	0.07	0.01	0.01		0.01	0.03	0.03	0.23	0.36	0.41
Sindbis_virus_(Fennoscandia)_JQ771797	**6**	0.07	0.07	0.01	0.01	0.01		0.03	0.03	0.23	0.36	0.41
Babanki_virus_(Cameroon)_HM147984	**7**	0.07	0.07	0.01	0.01	0.01	0.01		0.03	0.23	0.37	0.41
Sindbis-like_virus_(S._Africa)_U38305	**8**	0.07	0.07	0.01	0.01	0.01	0.01	0.01		0.23	0.36	0.41
Sindbis_virus_SW6562_(Australia)_AF429428	**9**	0.12	0.13	0.11	0.11	0.11	0.11	0.11	0.11		0.36	0.42
Aura_virus_(Brazil)_NC003900	**10**	0.32	0.32	0.31	0.31	0.31	0.31	0.31	0.31	0.31		0.43
Chikungunya_virus_EU037962	**11**	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.41	0.41	

Nucleotide differences (%) are shown above the main diagonal; amino acid differences (%) are shown below the main diagonal.

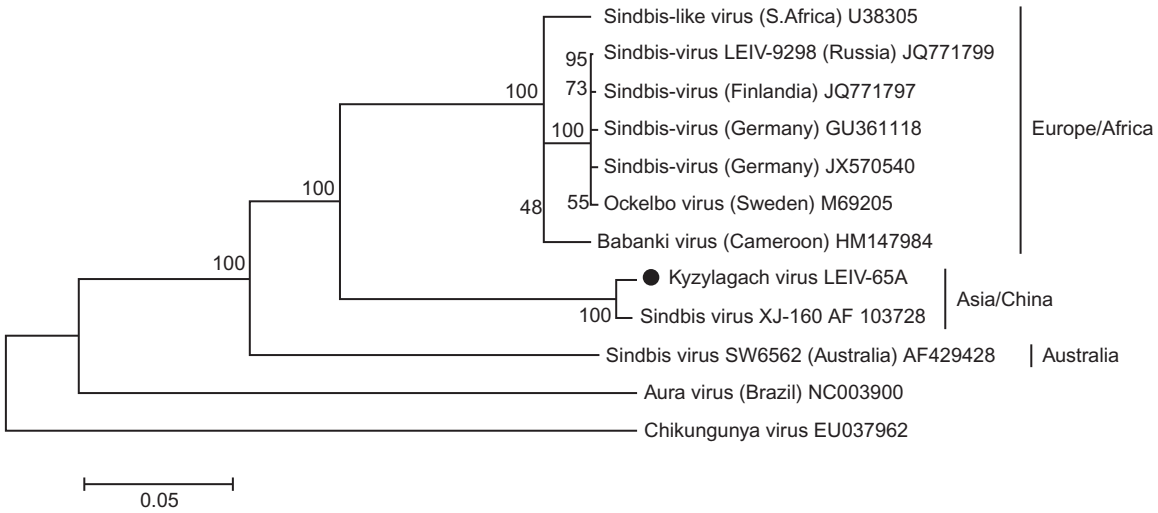


FIGURE 8.122 Phylogenetic tree of different isolates of SINV based on sequences of genomic RNA encoding structural proteins, rooted in AURAV and CHIKV sequences.

the territory of the former USSR, SINV strains were multiply isolated in Belarus, Ukraine, Azerbaijan, Tajikistan, and western Siberia (in the areas around the central region of the Ob River valley).[17–19].

Vertebrate Hosts. The main vertebrate hosts of SINV are different species of birds, predominantly of the orders Passeriformes, Pelecaniformes, Ciconiiformes, and Anseriformes. SINV infection in birds can chronic, allowing them to transfer the virus during their seasonal migration.[17–20] Migratory birds play an important role in the wide distribution of this virus. SINV has been known to persist for as much as two months after experimental infection.

SINV strains have been multiply isolated from aquatic and semiaquatic birds in the delta of the Nile River in Egypt, from the white wagtail (*Motacilla alba*) and the common hill myna (*Gracula religiosa*) in India, and from the reed warbler (*Acrocephalus scirpuceus*) in the western part of Slovakia.

In Zimbabwe, SINV has been isolated from insectivorous bats of the Rhinolophidae and Hipposideridae families.[2] Occasionally, SINV has been isolated from rodents and amphibians.

On the territory of the former Soviet Union, SINV was originally isolated from a yellow herons (*Ardeola ralloides*) caught out of a bird colony in the southeastern part of Azerbaijan in 1968. Serological methods have revealed SINV circulation in the Astrakhan region among aquatic and semiaquatic birds, especially those of the orders Pelecaniformes (18%), Ciconiiformes (15%), and Anseriformes (11%). Neutralizing antibodies to SINV were found in coots (*Fulica atra*) (16.7%) from natural foci of the middle belt of the Volga River delta. In the Kuban River delta in Krasnodar Krai, specific anti-SINV antibodies were found among eight species of aquatic and semiaquatic birds, most frequently mallards (*Anas platyrhynchos*) and purple herons (*Ardea purpurea*). In Belarus, anti-SINV antibodies were detected in 4% of birds in the summer and in 0.4% in the fall.[21]

Antibodies to SINV have been detected among farm animals (Table 8.66). For example, neutralizing antibodies were found among

TABLE 8.66 Detection of Antihemagglutinating Antibodies to SINV Among Humans and Farm Animals in the Russian Federation (1982–1992)

				Positive	
Federal district	**Federal subject**	**Species**	**Tested**	**Number**	**%**
Northern	Volgograd, Arkhangelsk regions, Komi Republic, Karelia Republic	Humans	2,278	21	0.9
		Farm animals	3,042	493	16.2
Northwestern	Novgorod, Kaliningrad, Leningrad, Pskov regions	Humans	894	2	0.2
		Farm animals	2,291	37	1.6
Central	Moscow, Tver, Vladimir, Ivanovo, Kostroma, Bryansk, Kaluga, Tula, Ryazan, Orel, Smolensk regions	Humans	2,417	0	0
		Farm animals	415	2	0.5
Central–Chernozem	Belgorod, Kursk, Lipetsk, Tambov regions	Humans	1,152	0	0
North Caucasian	Krasnodar, Rostov regions, Stavropol krai, Kabardino-Balkar Republic	Humans	1,312	1	0.1
		Farm animals	281	6	2.1
Volga	Astrakhan, Volgograd, Penza, Saratov, Samara, Ulyanovsk regions, Kalmyk Republic, Tatarstan Republic	Humans	1,152	41	3.6
		Farm animals	2,213	1	0.05
Volga–Vyatka	Kirov, Nizhny Novgorod regions, Chuvash Republic, Mordva Republic, Udmurtia Republic, Mari El Republic	Humans	1,384	4	0.3
		Farm animals	681	10	1.5
Ural	Chelyabinsk, Orenburg, Perm, Sverdlovsk regions, Bashkortostan Republic	Humans	1,665	5	0.3
		Farm animals	175	18	10.3
Western Siberian	Tyumen, Novosibirsk, Kemerovo, Omsk, Tomsk, Kurgan regions, Altai Krai	Humans	4,826	3	0.06
		Farm animals	660	8	1.2
Eastern Siberian	Irkutsk, Chita regions, Krasnoyarsk Krai, Sakha-Yakutia Republic	Humans	3,308	4	0.1
		Farm animals	1,130	17	1.5
Far Eastern	Amur region, Kamchatka Krai, Khabarovsk Krai, Primorsky Krai	Humans	2,554	4	0.2
		Farm animals	638	22	3.4

cattle (17.5%) and horses (15.0%) in the middle belt of the Volga River delta.

Arthropod Vectors. SINV is closely associated with ornithophilic mosquitoes. In Egypt, this virus was isolated from *Culex univittatus*, *Cx. antennatus*, and *Anopheles pharoensis*; in Uganda, from *Coquillettidia* spp.; in Sarawak, (Malaysia), from *Cx. bitaeniorhynchus*; in Australia, from *Cx. annulirostris*, *Aedes normanensis*, and *Ae. vigilax*; in India, from *Coq. fuscopennata*; in Sudan, from *Cx. quinquefasciatus*; and in Europe, from *Cx. pipiens*, *Cx. torrentium*, *Culiseta morsitans*, *Coq. richiardii*, *Ochlerotatus communis*, *Oc. excrucians*, *Ae. cinereus*, and *An. hyrcanus*.[22,23]

According to our data, in the Volga River delta SINV is transferred by *Culex pipiens* in anthropogenic biocenoses and by *Anopheles hyrcanus* and *Coquillettidia richiardii* in natural ones. In the natural foci of the middle belt of

the Volga delta, 1 strain can be isolated from approximately 3,800 *An. hyrcanus* or 3,300 *Coq. Richiardii* mosquitoes; in the low belt of the delta the ratio is 1 in about in a power less, and in anthropogenic biocenoses it is 1 strain per 1,500 *Cx. pipiens* mosquitoes.

SINV strains from Gamasidae ticks (*Ornithonyssus bacoti*) in India and from Ixodidae ticks (*Hyalomma marginatum*) in Sicily (Italy) are known.[2] Productive experimental infections were described in the Argasidae ticks *Ornithodoros savignyi* and *Argas persicus* (although infected ticks did not transmit the virus during feeding).[23] Most likely, ticks do not play an important role in SINV circulation or as a reservoir for this virus.

Human Pathology. SINV causes acute fever in humans but has a favorable outcome. Antibodies to SINV are widely detected in human sera (Table 8.66), although in eastern Siberia and the Far East cross-reactions with GETV (another member of the Semliki Forest serogroup) can take place.

The start of the disease is sudden. Clinical symptoms include fever, muscle and joint pain, and rash. Severe progressive arthritis of large joints could develop several years after the disease and could lead to disability. This pathology appears in 6–20% of citizens of endemic territories. Outbreaks of Sindbis fever in Egypt and Israel emerged at the same time as West Nile fever; hence, it is necessary to distinguish these infections in the laboratory.

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8.4.1.3 Sindbis Virus and a Set of Var. Sindbis Virus: Karelian Fever Virus, Kyzylagach Virus ()

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