

A short history of TBE

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Key Points

- TBE virus is a flavivirus and a prominent tick-borne human pathogen occurring in parts of Asia and Europe.
- The virus was discovered by Lev A. Zilber and co-workers in the former USSR during an expedition in the Far Eastern taiga under the most difficult conditions in 1937.
- They and members of a second expedition under the leadership of the Academician Evgeny N. Pavlovsky 1938 elucidated the basic eco-epidemiology of the virus.
- In their natural foci, TBE virus circulates between vectors, certain ixodid ticks, and some of their hosts, so-called reservoir hosts, mostly small mammals.
- Five different subtypes of TBE virus have been described to date.

Introduction

Tick-borne encephalitis virus (TBEV) is an arthropod-borne human pathogen, ecologically known as an arbovirus.¹ Taxonomically, it is a member of the genus *Flavivirus* together with other medically relevant arboviruses (e.g., Yellow fever virus, Dengue virus). The virus is endemic in Asia and Europe where it circulates between its principal vectors, usually hard ticks of the genus *Ixodes*, and certain small mammals, referred to as 'reservoir hosts', fed on by virus-infected vector ticks. The bite of infected vector ticks is also the common route of infection for humans. Each year several thousand people fall ill with TBE. Long before Smith and Kilbourne² discovered that ticks can transmit pathogens to their hosts and before TBEV was discovered, the disease had been mentioned in the literature. Parish records from the Åland islands (Finland) contain case descriptions of a disease at least similar to TBE in the 18th century.³ 'Taiga encephalitis' or 'biphasic meningoencephalitis' had been observed in eastern parts of the former USSR mostly in soldiers, railway workers and loggers, as the region began to develop in the 19th century.

Schneider⁴ was the first to give a medical description of the 'Epidemische akute Meningitis serosa' (also known as 'Schneidersche Krankheit' in Austria), which was in fact TBE. Panov⁵ gave the first detailed description of the clinical picture of the so-called 'summer encephalitis' in the Far East.

This chapter presents a brief synopsis of the major milestones in TBE and TBEV research, beginning with the discovery of the virus in the former USSR.

Discovery of TBEV in different regions of Eurasia

Molecular biological data indicate that TBEV has its origins in Western Siberia approximately 3100 [1800–4900] years ago.⁶ From there the eastern TBEV groups spread to the east through Asia and the western TBEV groups to the west, and they might have reached central Europe approximately 2000 years ago. However, the first isolation of TBEV succeeded only in 1937.

In the 1930s, a large number of people living in the taiga in the Far East and Soviet troops located in that region fell ill with a serious neurological disease, with a frequently fatal outcome. The etiology of the disease was unknown, and first attempts to identify the pathogen failed. In 1937, the USSR Ministry of Health sent out an expedition, which was led by Lev A. Zilber, the head of the first medical virological laboratory in the country. Zilber put together a group of very capable and highly motivated young researchers and technical assistants. They worked in two teams at two different remote places in the taiga under extremely difficult conditions. The northern team was working in the Khabarovsk Territory (leader: Elizabeth N. Levkovich) and the southern team in Primorsky Territory (leader: Alexandra D. Sheboldaeva). No infrastructure for scientific research existed in the area of the taiga where the disease occurred, so the teams had to find simple, practical solutions for establishing what they called a scientific campus.

The teams started their practical work in mid-May 1937, and very soon the first relevant results were available. When investigating local people, they found numerous cases with neurological symptoms. Twelve out of 64 hospitalized patients died. The virus was isolated from 29

febrile patients, from diseased mice (after they had been infected with a tick suspension), and from ticks feeding on them. When team members warned local people to avoid tick bites, the number of new cases distinctly decreased. So there was compelling evidence at the end of that mission in mid-August that the team had found the causative viral agent, with *Ixodes persulcatus* ticks as the vectors.

Unfortunately, some team members became infected with TBEV and developed disease symptoms. Fortunately, nobody died – which appears almost unavoidable when taking into consideration the highly unsafe conditions and the highly contagious nature of the virus. As an example, Dr. Chumakov, who became a famous virologist later on, fell ill with a severe form of TBE after cutting his finger during an autopsy. Residual effects were right-arm paralysis and hearing loss. However, this did not prevent him from finding new TBEV foci in the Ural and Transural regions, far away from the Far East.⁷

Scientifically, the expedition was a great success. Zilber and the other team members had isolated the causative virus, elucidated the basic eco-epidemiology of the disease, and provided some effective prophylactic information on how to avoid an infection. Further expeditions were sent out to the Far East to learn more about the virus and the disease and its prophylaxis.⁸

The first cases of TBE in China were reported in 1943, and the causative virus was isolated in 1944 from brain samples of patients who had died (reviewed in Yoshii et al., 2017).⁹ The discovery of TBE in Europe started with the clinical-epidemiological description of 24 cases of aseptic meningitis in the district of Neunkirchen (Lower Austria) by Schneider in 1931.⁴ Although the outcome was described as benign, the convalescence of many patients was prolonged. In the early 1940s scientists of the Rockefeller Institute for Medical Research in New York showed serological cross-reactions between hyperimmune sera of Louping ill virus and Russian Spring Summer encephalitis virus.

The first documented TBEV isolation in Europe was made from *Ixodes ricinus* ticks (strain 256) in Belarus in 1939¹⁰, and the second isolation was reported in former Czechoslovakia in 1948 (strain *Hanzalova*, isolated near Prague).¹¹ In 1952, a virus strain (*KEM I*) was isolated during an alimentary outbreak in Hungary. Other eastern European countries followed shortly after, and TBEV strains were isolated in Slovenia in 1953, in Poland in 1954, in Austria in 1954 (strain *Scharl*), and in Slovakia in 1958. The first TBEV strain in Finland was detected in 1959 (*Kumlinge* strain).¹² Sweden reported the first detection of TBEV in 1954, and Denmark reported the first clinical cases of TBE from Bornholm Island, also in the 1950s. In Norway, however, the first described human case of TBE occurred only in 1997.¹⁴ In Germany, the first descriptions of TBE and the first virus isolations resulted from the late 1950s in the former German Democratic Republic.¹⁵

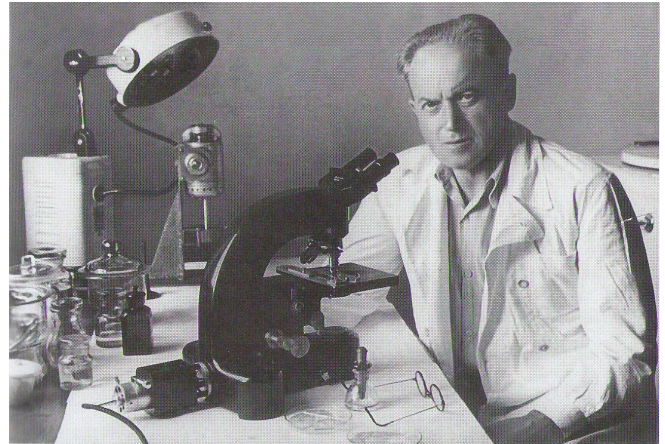


Photo of Lev Zilber from the book “Lev Alexandrovich Zilber” written by his son L.L. Kisselev and E.S. Levina, published in 2005 by the publishing house “Science” in the series “Scientific biographies”

Rehse-Küpper et al. (1978)¹⁶ were probably the first who isolated TBEV strains in the former Federal Republic of Germany as the two virus strains isolated by Müller et al. (1970) were to the best of our knowledge never confirmed as being TBEV.¹⁷

France followed with the first isolation of TBEV from the Alsace region in 1970.¹⁸ It was only in 2016 that the first autochthonous human cases of TBE were described in The Netherlands and a TBEV strain (strain *Sallandse*) was detected in ticks.¹⁹

The detection of the TBEV natural transmission cycle

Due to the pioneering research work by the Zilber expedition in the Far East, the basic outlines of TBEV eco-epidemiology were elucidated within a few months in 1937. They found that the pathogen is a virus that can be transmitted through the bite of *Ixodes persulcatus*, a hard tick (family Ixodidae).

Another expedition was sent out by the USSR Ministry of Health to the Far East under the leadership of E.N. Pavlovsky in 1938 to learn about the circulation of TBEV in the field and the involved reservoir hosts. Largely based on the findings during that expedition, Pavlovsky^{20,21} developed the famous concept of ‘The Natural Nidality of Transmissible Diseases’, where he described the ecology of zoonoses. Arthropod vectors (ixodid ticks) that become infected with TBEV through a blood meal on an infective host carry the virus to the following life stage(s) and transmit it during the following blood meal(s) to a host. So-called reservoir hosts become infected through the bite of an infected tick, and in turn transmit the virus to other feeding ticks. Long-term virus circulation exists only in definite types of landscape with suitable abiotic conditions where all the necessary biotic partners (vectors, reservoir hosts) are present in sufficient densities.

Chumakov & Naidenova²² (cited after²³) found the hard tick *Ixodes ricinus*, a close relative of *I. persulcatus*, to be a vector of a milder form of TBE in some European areas of the former USSR. This was later confirmed by various European researchers. Rampas & Gallia²⁴ from Czechoslovakia were the first outside the former USSR to isolate TBEV from field-collected ticks.

An alternative alimentary route of human TBE infection became apparent in the European part of the former USSR from 1947 to 1951.²⁵ Groups of people contracted TBE after consuming unpasteurized goat milk or goat milk products (e.g., cheese) from viremic goats. Similar alimentary TBE epidemics occurred also in other TBE endemic countries, e.g., in Rožňava (south-eastern Slovakia) with more than 600 cases in 1951²³ and in Niesky (former German Democratic Republic) in 1961.²⁶

Field work on TBEV decreased in several European countries in the 1970s and 1980s. TBEV ecology seemed to be well understood. The main interest of researchers focused more on the molecular biology of TBEV and also on the newly discovered *Borrelia burgdorferi*, the causative agent of human Lyme borreliosis. Interestingly, this coincided with the first European TBE vaccine becoming available in 1976,²⁷ and the TBE problem seemed to be solved.

Jones et al.²⁸ made the significant finding in the laboratory that guinea pigs can infect feeding *Rhipicephalus appendiculatus* with *Thogoto virus*, another tick-borne virus, without showing an apparent viremia. Encouraged by this finding, Alekseev & Chunikhin²⁹ and Labuda et al.³⁰ demonstrated non-viremic transmission of TBEV from small mammals (infected through tick bite) to uninfected feeding ticks. This was a major step forward in our understanding of the field ecology of the virus, and reactivated interest in TBEV ecology. Milan Labuda and various co-workers made a number of further relevant contributions to this topic.³¹⁻³³ They found (i) that TBEV is transported in Langerhans' cells in infected hosts, (ii) that non-viremic transmission also occurs in immune hosts, and (iii) that this kind of transmission happens in small, but not in larger mammals. The most commonly used term now is 'co-feeding transmission', although non-viremic transmission might technically be the better term.

The detection of different TBEV subtypes

Based on general viral properties such as viral morphology, physical and chemical properties, virion structure, arthropod carriers, and serological cross-reactions, the genus *Flavivirus* including TBEV was considered to be part of the family *Togaviridae*. This term was first offered by Lwoff and Tournier (1966).³⁴

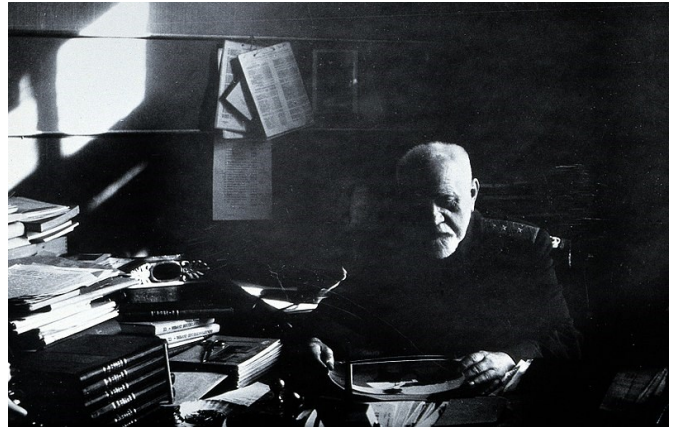


Photo of Evgeny N. Pavlovsky

Credit: LJ Bruce-Chwatt from the Wellcome Collection

The family *Togaviridae* consisted of the genera *Alphavirus* (former arbovirus group A), *Flavivirus* (former arbovirus group B) with *Dengue virus, type 1*, and some other viruses.^{35,36}

De Madrid and Porterfield³⁷ divided the genus *Flavivirus* into 7 subgroups according to plaque reduction neutralization test (PRNT). The first subgroup includes tick-borne viruses such as TBEV, *Omsk hemorrhagic fever virus*, *Louping ill virus*, *Langat virus*, *Negishi virus*, and *Kyasanur forest disease virus*. Along with the above-mentioned viruses, the TBEV complex included *Alma Arasan*, *Apoi*, *Royal-Farm*, *Kadam*, *Powassan* viruses, and according to Gaidamovich and Loginova³⁸ also *Gadgets Gully*, *Saumarez Reef*, *Karshi*, and *Tyuleniy* viruses.

These viruses share some antigenic similarity but have different geographic distributions, associations with different ticks and vertebrate hosts, and a different pathogenic potential for humans. Due to a difference in the replication strategies of alpha- and flaviviruses, the family *Flaviviridae* was established as an independent family that comprises the genus *Flavivirus* with more than 70 species dividing into 10 serocomplexes.³⁹ According to modern classification, the family *Flaviviridae* comprises the genera *Flavivirus*, *Pestivirus*, and *Hepacivirus*. TBEV belongs to the mammalian tick-borne flavivirus group and comprises 3 subtypes: European, Far Eastern, and Siberian.⁴⁰

Two geographic and antigenic variants of TBEV (Eastern and Western) had been known for 40 years.^{1,41-44} Clarke⁴³ divided 28 strains in 2 antigen variants by the gel precipitation test with cross-absorbed sera. She concluded that there are 2 antigen subtypes: Eastern and Western (Central European). Chumakov et al.⁴⁵ considered that Eastern and Western subtypes differ within the species TBEV; they proposed a classification into 'Persulcatus' and 'Ricinus' antigen variants according to viral ecology. Votyakov et al.^{44,46} argued that the infectious agents of Eastern and Western TBE are different species according to differences in antigen profiles, geography, clinical and pathological features in animals and humans.

Pletnev et al.^{47,48} and Mandl et al.^{49,50} decoded the complete genomes of Eastern (*Sofjin*) and European (*Neudoerfl*) strains and thereby started a new phase of intraspecific TBEV classification. The obtained data proved that the genetic differences between the Western and Eastern variants are significant with 16.8–16.9% of nucleotide substitutions and 6.9–7.2% of amino acid substitutions. Two Eastern strains in contrast have 3- and 4-times lower differences in nucleotide (4.6%) and amino acid (1.8%) substitutions, respectively.

Rubin and Chumakov⁵¹ published the first results of the Siberian subtype. They demonstrated some peculiarities of the strain *Aina* isolated in the Irkutsk region, USSR, from a child with TBE. Pogodina et al.^{52,53} described a group of strains isolated in Eastern Siberia from *I. persulcatus*, from rodents and patients serologically closely related to the strain *Aina*. Gritsun et al.^{25,54} were the first to genotype strains of the Siberian subtype by gene E and complete genome sequencing. Two strains – *Vasilchenko* (L40361) and *Zausaev* (AF527415) – became prototype strains of 2 Siberian subtype clusters (reflecting their geographic localization).

Sequencing a gene E fragment (160 bp length) of 8 and thereafter 29 strains isolated in different geographic regions, carried out by Zlobin et al.⁵⁵⁻⁵⁷ enabled the identification of 3 major genotypes (subtypes): (1) Far Eastern, (2) Western, and (3) Ural-Siberian (Siberian). According to Ecker,⁵⁸ TBEV consists of 3 subtypes corresponding to 3 major genotypes: European, Far Eastern, and Siberian. However, Grard⁵⁹ reinterpreted the data of the genetic relationships among arthropod-borne viruses. She suggested that TBEV should include 4 subtypes: (1) Louping ill virus (Spanish, British, and Irish subtypes), (2) TBEV (European subtype), (3) TBEV (Far Eastern and Siberian subtype), and (4) Turkish sheep encephalitis virus and its subtype, Greek goat encephalitis virus.

Beside the 3 described and accepted subtypes, 2 different strains – 178/79 and 886/84 – have been described by Russian researchers. These 2 strains have been shown not to be closely related to any of the 3 known subtypes.⁶⁰ Additional studies are needed to demonstrate whether these strains can be classified as new TBEV subtypes. These results mean also that further TBEV subtypes may be detected in future.

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